Aims Cardiac resynchronization therapy (CRT) has been shown to improve symptoms and exercise tolerance in patients with advanced heart failure (HF). However, studies were underpowered to address its effect on overall mortality. To evaluate whether CRT alone (without a combined defibrillator function) reduces overall mortality as compared with optimal pharmacological therapy, and how it affects the mode of death in patients with advanced HF.

Methods and results Public domain databases were systematically searched. Randomized controlled studies that evaluated the effects of CRT alone in patients with advanced HF and a depressed left ventricular systolic performance were selected for this analysis. Trials, which did not independently report data on CRT alone or had a follow-up period of less than 3 months, were excluded. Five studies were identified and analyzed. They included a total of 2371 patients, 1028 controls and 1343 CRT-treated patients. Pooled analysis demonstrated that CRT alone, as compared with optimal medical therapy, significantly reduced all-cause mortality by 29% [16.9 vs. 20.7%; odds ratio (OR), 0.71; 95% confidence interval (CI), 0.57–0.88] and mortality due to progressive HF by 38% (6.7 vs. 9.7%; OR, 0.62; 95% CI, 0.45–0.84). No effect on sudden cardiac death (SCD) was observed with CRT (6.4 vs. 5.9%; OR, 1.04; 95% CI, 0.73–1.22).

Conclusions CRT alone as compared with optimal medical therapy reduces all-cause mortality in patients with advanced HF. It predominantly reduces worsening HF mortality, not affecting SCD.

KEYWORDS
Cardiac resynchronization therapy; Heart failure; Mortality; Mode of death

Introduction
Heart failure (HF) is a growing public health problem in the western world. For instance only in the USA, more than 5 million patients suffer from this disease, and about 500 000 patients are diagnosed with HF yearly.1 Despite the latest achievements of medical therapy,2–8 in patients with advanced stages of the disease, mortality remains high and quality-of-life (QOL) severely impaired.9

Cardiac resynchronization therapy (CRT) has consistently proven to improve symptoms, QOL, and exercise tolerance in patients with a severely depressed left ventricular ejection fraction (<35%) who remain symptomatic (NYHA class III and IV) despite optimal medical therapy.10–16 Early published studies were specifically designed to evaluate the effects of CRT upon these functional endpoints and were underpowered to evaluate its effect on mortality.10,12,14,15 The recently published Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure study11 has shown a survival benefit only in those patients randomized to CRT with a combined defibrillator function (CRT-D). In the CARE-HF trial,13 patients who received CRT alone (without a CRT-D function) had a significant reduction in overall mortality compared with those under optimal pharmacological therapy.

Previously published meta-analyses have corroborated the effects of CRT upon symptoms, QOL, and exercise tolerance.17–19 However, an overall survival benefit of CRT alone has not been addressed. This is true, mainly because in their analysis, trials that also evaluated the effects of CRT-D were included. In this way, the effects of CRT were confounded by the proven life-saving effect of the ICD. Performing a meta-analysis increases the power to see a difference in mortality that was not evident in the majority of individual trials performed. It also allows having a more precise estimation of this effect.20 We designed a meta-analysis with the purpose of establishing whether CRT alone, compared with optimal medical therapy, reduces overall mortality and in which way it affects the different modes of death in patients with advanced HF.
Methods

Search strategy

A comprehensive search of public domain databases was carried out with the purpose of identifying reports of randomized trials comparing CRT alone vs. optimal pharmacological therapy (control) in patients with advanced symptoms of HF due to left ventricular systolic dysfunction. Using the terms HF, pacemaker, pacing, biventricular, biventricular pacing, left ventricular pacing, left ventricular pre-excitation, multi-site pacing, cardiac resynchronization, and cardiac resynchronization MEDLINE (1985–2005) and the Cochrane Central Register of Controlled Trials (third quarter 2005) were searched. The search was limited to English language publications. In addition, the website of the US Food and Drug Administration (www.fda.gov) was searched, and the reference lists of identified papers were examined. Reports presented during the last 5 years at the scientific sessions of the American College of Cardiology, the American Heart Association, the North American Society of Pacing and Electrophysiology later the Heart Rhythm Society, and the European Society of Cardiology were manually or electronically sought. The latest search was carried out in November 2005.

Study selection

Randomized trials performed in patients with advanced symptoms of HF due to left ventricular systolic dysfunction that evaluated the effects of CRT alone vs. optimal pharmacological therapy (control) were included in this analysis. Studies were excluded if they evaluated the effects of CRT-D and did not separately report data on CRT alone. Because we were mainly interested in the chronic effects of CRT, studies with a follow-up of less than 3 months were excluded. To be included, the duration of the first follow-up phase of the randomized cross-over trials had to be at least 3 months. To avoid a carry-over effect, only the first randomized cross-over period was considered for analysis.

Two investigators (M.R.A., D.A.M.J.T.) independently screened all titles and abstracts to determine which studies met the inclusion criteria. Publications for this review were selected if they fulfilled the following criteria: (i) randomized trials performed in humans; (ii) comparing the effects of CRT alone with optimal pharmacological therapy (control); and (iii) reported mortality and mode of death during the randomized period. Discrepancies between investigators were resolved by consensus.

Data analysis

Two investigators using a standardized form independently abstracted data. A meta-analysis of summary statistics from individual trials was performed. ORs from each included trial were pooled using both fixed and random effects model that used weighting based on inverse variance calculated according to DerSimonian and Laird. To check for statistical evidence of heterogeneity among trial-specific ORs, a χ² test was used and it was quantified using the I² statistic. When pooled analysis resulted in a significant heterogeneity, the random effects model was used.

Quantitative analyses were performed on an intention-to-treat basis using the same standardized endpoint definitions [overall mortality, worsening HF mortality, and sudden cardiac death (SCD)] as in the primary studies. For non-worsening HF mortality, all deaths except those due to HF were considered. Data analysis was performed using the Review Manager 4.2.

Results

Search results

A total of 6893 references from all databases were found. A total of 1757 reports were identified as potentially relevant, of which 1719 were excluded based on titles and abstracts. Full-text versions of the remaining 38 reports were retrieved for detailed evaluation. Of these, eight reports of five randomized studies were included for this analysis (Figure 1).

Figure 1 Results evaluated for inclusion in the meta-analysis.

Qualitative findings

Five studies met the criteria for inclusion, the Multisite Stimulation in Cardiomyopathies Study (MUSTIC), the Multicenter InSync Randomized Clinical Evaluation (MIRACLE), the MUSTIC AF, the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) (CRT alone and control arms only) and the Cardiac Resynchronization–Heart Failure (CARE-HF) trials. Although the results of the extension phase of this last trial were recently presented, data from the original study will be considered for this analysis. However, in order to also evaluate the effects of CRT considering the data of the extension phase of this last trial, a sensitivity analysis was performed.

Baseline patient characteristics and design of all trials are summarized in Tables 1 and 2. The mean age of the populations ranged between 64 and 68 years. The majority of patients in each trial were male and presented symptoms of advanced HF (NYHA functional class III and IV). In two studies, ischaemic cardiomyopathy was the main aetiological diagnosis. Although most trials excluded patients with atrial fibrillation, one trial specifically evaluated the effects of CRT in this population. The only trial in which mechanical ventricular dyssynchrony was considered an inclusion criterion was the CARE-HF. In order to be included, patients in whom the QRS duration ranged between 120 and 150 ms were required to present echocardiographic documentation of ventricular dyssynchrony. MUSTIC AF was the only study to include patients with a pacemaker indication. The rest of the studies excluded patients with sinus node dysfunction, AV block, or other indications for permanent pacemaker implantation.
In no trial was overall mortality the primary endpoint. In COMPANION\textsuperscript{11,24} and CARE-HF\textsuperscript{13} all-cause mortality was part of a combined primary endpoint. In all the studies analyzed, mortality was one of the secondary endpoints (Table 2).

All patients underwent implantation of a pacemaker with CRT capabilities through a trans-venous left ventricular lead implantation. In the COMPANION trial,\textsuperscript{11,24} one arm of the study evaluated the effects of CRT-D. In order to establish the effects of CRT alone, this last arm of the study was not included in this analysis. In three trials, all patients received CRT devices and were randomized in a parallel way\textsuperscript{10,23} or crossover design\textsuperscript{12,14} to CRT on or off. In the two largest trials,\textsuperscript{11,13,24} patients were randomized to receive, or not to, a CRT device.

In the COMPANION study,\textsuperscript{11,24} 13% of the patients in the control group received commercially available implants before reaching the primary endpoint; 2% of the patients in the CRT alone group withdrew from the study. In CARE-HF,\textsuperscript{13} only 5% of the patients assigned to receive

<table>
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<tr>
<th>Table 1</th>
<th>Baseline clinical characteristics of patients included in the analysed trials</th>
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<tr>
<td></td>
<td>CARE-HF\textsuperscript{13}</td>
</tr>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>N</td>
<td>404</td>
</tr>
<tr>
<td>Age (mean) (years)</td>
<td>66\textsuperscript{a}</td>
</tr>
<tr>
<td>Men (%)</td>
<td>73</td>
</tr>
<tr>
<td>Ischaemic cause (%)</td>
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</tr>
<tr>
<td>NYHA class III (%)</td>
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<tr>
<td>LVEF (mean) (%)</td>
<td>25\textsuperscript{a}</td>
</tr>
<tr>
<td>QRS duration (mean) (ms)</td>
<td>160\textsuperscript{b}</td>
</tr>
<tr>
<td>Beta-blocker use (%)</td>
<td>74</td>
</tr>
<tr>
<td>ACE-I or ARB use (%)</td>
<td>95</td>
</tr>
<tr>
<td>Spironolactone use (%)</td>
<td>59</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; LVEF, left ventricular ejection fraction; NR, not reported; NYHA, New York Heart Association functional class.

\textsuperscript{a}Reported as median.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Description of the analysed trials</th>
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<tbody>
<tr>
<td></td>
<td>CARE-HF\textsuperscript{13}</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>NYHA III and IV, EF ≥ 35%, PR &gt; 120 ms, CRQ &gt; 120 ms, 6 min-walk ≥ 450 m</td>
</tr>
<tr>
<td>Death as endpoint</td>
<td>Primary (combined with unplanned hospitalizations for major CV events)</td>
</tr>
<tr>
<td>Design</td>
<td>RND parallel</td>
</tr>
<tr>
<td>Intervention Device manufacturer</td>
<td>CRT vs. No CRT Medtronic</td>
</tr>
<tr>
<td>Follow up, months</td>
<td>29.4</td>
</tr>
<tr>
<td>Intention to treat</td>
<td>Yes</td>
</tr>
<tr>
<td>Blinding</td>
<td>Not Blinded\textsuperscript{b}</td>
</tr>
<tr>
<td>End point committee</td>
<td>Blinded</td>
</tr>
</tbody>
</table>

CV, cardiovascular; HF hosp, heart failure hospitalization; NR, not reported; RND, randomized.

\textsuperscript{a}First cross-over phase.

\textsuperscript{b}Reported for adjudication of heart failure hospitalizations.
optimal medical therapy were actively paced with CRT before reaching the primary endpoint. In the MIRACLE study,\textsuperscript{10,23} 10 patients in the control group had their CRT device activated. Only one patient in the MUSTIC\textsuperscript{12} and one in the MUSTIC AF\textsuperscript{14} were switched to active biventricular pacing during the first crossover phase. All results were reported on an intention-to-treat basis.

Weighted mean follow-up was 18.4 months. It ranged from 3 months to 29.4 months depending on the trial. In the COM-PANION trial,\textsuperscript{11,24} the median duration of follow-up for mortality was 14.8 months in the control group and 16.5 months in the CRT group. In CARE-HF,\textsuperscript{13} mean follow-up for all patients enrolled was 29.4 months.

Effects of CRT alone on overall mortality

When pooling data from all five studies together (2371 patients) using a fixed-effect model, CRT alone significantly showed to reduce all-cause mortality by 29\% (OR, 0.71; 95\% CI, 0.57–0.88) with respect to controls (\textsuperscript{Figure 2}). Among the CRT-treated group, 227 patients died (16.9\%) compared with 213 controls (20.7\%). This represents an absolute reduction of 3.8\%; 26 patients need to be treated with CRT in order to save one life during the corresponding follow-up. No evidence of statistical heterogeneity was observed between trials regarding this effect (\(P = 0.54\)).

Mode of death

Data on the mode of death (all-cause mortality, mortality due to worsening HF SCD) was reported in all trials.\textsuperscript{10–14,23–25} When considering mortality due to progressive HF, most studies showed a tendency towards a reduction in this mode of death in patients treated with CRT (\textsuperscript{Figure 3}). The only trial to show a significant 45\% reduction in mortality due to worsening HF was the CARE-HF trial.\textsuperscript{13} When pooling the data of all trials, a significant 38\% relative reduction in this endpoint was observed among patients treated with CRT alone (OR, 0.62; 95\% CI, 0.45–0.84). It was observed that 90 patients (6.7\%) died due to pump failure in the CRT group as compared with 100 patients (9.7\%) randomized to optimal pharmacological therapy. Thirty-three patients need to be treated in order to avoid one death due to worsening HF. No evidence of statistical heterogeneity was observed regarding this effect (\(P = 0.45\)).

However, in CARE-HF,\textsuperscript{13} more SCDs occurred in the control group, whereas in other studies more patients suffering this mode of death were observed among the CRT-treated patients. After the extended phase of the CARE-HF study, a significant reduction in SCD was observed in patients treated with CRT.\textsuperscript{26} However, even after performing a sensitivity analysis including these results, no effect of CRT on SCD was observed (OR, 0.86; 95\% CI, 0.63–1.19).

Of the total amount of deaths in the control group (213 deaths), 47\% were due to progressive HF and 28\% were due to worsening HF.
considered to be sudden, whereas in the CRT-treated patients (227 deaths), these represented 39% and 38%, respectively.

**Discussion**

Our analysis demonstrates that CRT alone reduces all-cause mortality in patients with advanced symptoms of HF refractory to standard pharmacological therapy. It does so predominantly by reducing mortality due to progressive HF not affecting SCD.

CRT has recently emerged as an effective treatment for patients with HF. It improves symptoms, QOL, and exercise tolerance in a selected group of patients with systolic HF who present, as a surrogate sign of ventricular dysynchrony, with a broad QRS complex on the ECG. Improvement in more objective endpoints like a positive ventricular remodelling effect and admissions due to HF, have also been demonstrated. For patients who suffer from chronic diseases, improvement in QOL is an important treatment goal. When this is cost-effective and achieved without significant side effects, acceptance among the medical community is likely. So far, this has been the case for CRT. The implantation rate of CRT devices has importantly expanded in recent years before conclusive evidence of a survival benefit was demonstrated.

It is only recently that the CARE-HF trial demonstrated a significant reduction in overall mortality with CRT alone. Other trials and meta-analyses confounded the benefits that CRT alone might have on this last endpoint by including in their analysis the effects of CRT-D devices. It is mandatory then to definitively establish to what extent, and in which way CRT alone affects survival. By pooling data from randomized trials that evaluated the effects of CRT devices, a significant overall survival benefit of 29% was observed (Figure 4). The predominant modes of death in patients with HF are SCD and death attributed to progression of the disease. Patients who are mildly symptomatic will more likely die suddenly, whereas those with advanced symptoms are more likely to die due to pump failure. All patients included in the analysed studies were in advanced stages of HF. As CRT alone directly affects myocardial function and HF profile, it is not surprising that the survival benefit can almost exclusively be attributed to the significant 38% reduction in HF mortality (Figure 5).

A previous meta-analysis showed a non-significant increase in SCD among patients treated with CRT. In the COMPANION study, CRT-D significantly increased survival compared with control patients. Median time to SCD was shorter in the CRT arm (186 days) than in CRT-D and control patients (253 days). In those studies with shorter follow-up like MUSTIC and MUSTIC AF, most deaths occurred suddenly during active biventricular pacing. CARE-HF reported a non-significant reduction in SCD in patients undergoing CRT compared with controls during follow-up. When pooling data of all studies together, no effect of CRT on the occurrence of SCD was observed (even after considering the data of the extension phase of CARE-HF). Patients whose profile improves after being treated with CRT are less likely of dying due to worsening HF; in this way the relative contribution of SCD to overall mortality increases (Figure 5). This raises the question of what the role of ICD will be in these patients. In the COMPANION study, CRT-D significantly increased survival compared with controls and showed a trend towards a beneficial effect when compared with CRT alone. However, not all patients profited from the addition of an ICD. The patients who derived more benefit were those with somewhat better preserved EF, and who had a better symptom profile. Furthermore, in the SCD-Heft trial, patients in NYHA functional class III did not benefit from the ICD, as did patients with a lower functional class. Having shown an important mortality reduction with
CRT alone, and considering that the benefits of adding a defibrillator to the CRT device have not yet been proven, the question whether which CRT candidates should receive additional defibrillator function gains relevance and remains unanswered. Nonetheless, probability of survival, quality of the life prolonged, and mode of death are important aspects that patients and physicians should consider when discussing treatment options and deciding whether to implant, and which device to select.

Our analysis has some potential limitations that should be addressed. Although overall mortality is a reliable endpoint, determination of the mechanism leading to death is sometimes very difficult and not accurate. Misclassification of deaths due to pump failure is less likely to occur because symptoms of progressive HF are easily recognized and many patients are admitted during the final stages of their disease. In contrast, it is more likely to misclassify deaths when they occur suddenly because they are frequently thought to be arrhythmic in origin even though other cardiovascular causes could be responsible.

Duration of follow-up varied between the analyzed studies. However, most of the patients were followed for at least 1 year (73%) and the mean weighted follow-up was 18.4 months. It is important to highlight that the observed effects of CRT only apply to the limited follow-up period covered by this meta-analysis.

Another potential limitation of this study is the influence of publication bias. This type of bias can never be completely avoided, although performing an extensive search may minimize it. Though funnel plots were performed, the small number of trials included in our analysis reduces its usefulness.

Some of the data used for this analysis was extracted from public domain reports that did not undergo conventional peer review, however, the thorough scrutiny to which these reports were submitted by the US Food and Drug Administration is in favour of their reliability.

Conclusion
This meta-analysis demonstrates that CRT alone reduces all-cause mortality in a selected group of patients with advanced symptoms of HF. It predominantly reduces mortality due to worsening HF and does not affect SCD. This observation raises the need to establishing to what extent and which patients will benefit from combining an additional defibrillator function.

Conflict of interest: none declared.

References


