An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure

John G. Cleland1*, William T. Abraham2, Cecilia Linde3, Michael R. Gold4, James B. Young5, J. Claude Daubert6, Lou Sherfesee7, George A. Wells8, and Anthony S.L. Tang9

1National Heart and Lung Institute, Imperial College London (Royal Brompton & Harefield Hospitals) and Department of Cardiology, Castle Hill Hospital, University of Hull, Kingston-upon-Hull, UK; 2Division of Cardiovascular Medicine and the Davis Heart and Lung Research Institute, The Ohio State University, Columbus, OH, USA; 3Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden; 4Medical University of South Carolina, Charleston, SC, USA; 5Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA; 6Departement de Cardiologie, CHU, Rennes, France; 7Medtronic, Inc., Minneapolis, MN, USA; 8The University of Ottawa Heart Institute, Ottawa, Canada; and 9The Island Medical Program, University of British Columbia, Vancouver, Canada

Received 15 May 2013; revised 24 June 2013; accepted 4 July 2013; online publish-ahead-of-print 29 July 2013

Aims Cardiac resynchronization therapy (CRT) with or without a defibrillator reduces morbidity and mortality in selected patients with heart failure (HF) but response can be variable. We sought to identify pre-implantation variables that predict the response to CRT in a meta-analysis using individual patient-data.

Methods and results An individual patient meta-analysis of five randomized trials, funded by Medtronic, comparing CRT either with no active device or with a defibrillator was conducted, including the following baseline variables: age, sex, New York Heart Association class, aetiology, QRS morphology, QRS duration, left ventricular ejection fraction (LVEF), and systolic blood pressure. Outcomes were all-cause mortality and first hospitalization for HF or death. Of 3782 patients in sinus rhythm, median (inter-quartile range) age was 66 (58–73) years, QRS duration was 160 (146–176) ms, LVEF was 24 (20–28)% and 78% had left bundle branch block. A multivariable model suggested that only QRS duration predicted the magnitude of the effect of CRT on outcomes. Further analysis produced estimated hazard ratios for the effect of CRT on all-cause mortality and on the composite of first hospitalization for HF or death that suggested increasing benefit with increasing QRS duration, the 95% confidence bounds excluding 1.0 at ≏ 140 ms for each endpoint, suggesting a high probability of substantial benefit from CRT when QRS duration exceeds this value.

Conclusion QRS duration is a powerful predictor of the effects of CRT on morbidity and mortality in patients with symptomatic HF and left ventricular systolic dysfunction who are in sinus rhythm. QRS morphology did not provide additional information about clinical response.

ClinicalTrials.gov numbers NCT00170300, NCT00271154, NCT00251251.

Keywords Cardiac resynchronization therapy • Morbidity • Mortality • Heart failure

* Corresponding author. Tel: +44 1482 46 1780; fax: +44 1482 46 1779; Email: j.g.cleland@hull.ac.uk

© The Author 2013. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Introduction

Despite the successes of pharmacological therapy for heart failure (HF), many patients remain symptomatic, many relapse after a period of control, the underlying disease often progresses and morbidity and mortality still remain high. For some patients, symptoms and/or prognosis can be improved by implanted devices. Cardiac defibrillators (ICD) are designed to treat malignant ventricular tachyarrhythmias and are highly effective in preventing sudden arrhythmic death. Cardiac resynchronization therapy (CRT) has a broader range of therapeutic benefits in appropriately selected patients, including improvements in cardiac function symptoms and quality of life and reductions in HF-related hospitalizations and death. Devices with both CRT and ICD functions (CRT-D) are often implanted and have been shown to be superior to an ICD alone in improving outcome.

Clinical trials are designed to show the average effect of an intervention in the population enrolled and usually lack the power to assess effects within subgroups. However, from a patient and clinician perspective, estimating risks and benefits on an individual basis is paramount. Clearly, CRT will sometimes fail to improve cardiac function, symptoms, or prognosis. This has spawned many observational studies attempting to identify predictors of success or failure, usually based on surrogate outcomes. These may be unable to untangle the therapeutic response to CRT from the natural history of the underlying disease. Ideally, analyses to predict benefit or lack thereof should be done on data from randomized trials. Several meta-analyses using aggregate data from trials of CRT have been reported but these are limited by variable reporting of subgroup data and cannot reliably investigate potential interactions between variables, for example QRS duration and morphology, conferred by access to individual patient data. Accordingly, we undertook an individual patient meta-analysis on data from five landmark randomized clinical trials of CRT.

Methods

All five randomized controlled trials comparing CRT compared with no CRT with ≥6 months of follow-up for which Medtronic could supply individual patient data were used in this analysis. Two relevant large trials, COMPANION and MADIT-CRT, were not included as the authors did not have access to individual patient data. Data were pooled on 4317 patients comparing either CRT with no active control (no device or back-up pacing; CARE-HF,8,9 MIRACLE,10 REVERSE11,12) or CRT-D with ICD (REVERSE,11,12 MIRACLE ICD,13,14 RAFT15). In order to create a more homogeneous population, patients in New York Heart Association (NYHA) class I (107 patients from REVERSE) and those in atrial fibrillation or with a pre-existing pacemaker (338 patients from RAFT) were excluded.

Statistical analyses were done using the intention-to-treat principle and included patients who failed to receive their assigned treatment. In CARE-HF, 19 (4.6%) patients failed to receive a CRT device after one or more attempts. In RAFT, five patients (0.6%) failed to receive an ICD and 53 (5.9%) a CRT-D. Successful implantation prior to randomization was required in the MIRACLE, MIRACLE ICD, and REVERSE trials. Implant failure rates in these three studies were 7.8, 10.8, and 3.3%, respectively.

The following baseline variables were included in the analyses: age, sex, NYHA class, aetiology, QRS morphology, QRS duration, left ventricular ejection fraction (LVEF), and systolic blood pressure. Core-laboratory values were used for ECG measurements in CARE-HF, REVERSE, and RAFT, and for echocardiographic assessment of LVEF in all studies except RAFT.

The two outcomes of interest specified for this analysis were all-cause mortality and the composite of hospitalization for HF or all-cause mortality. Hospitalizations were adjudicated by committees blind to treatment allocation in each study.

Statistics

Continuously distributed data are shown as both mean and standard deviation and median, inter-quartile range (IQR), and full range (FR). Categorical data are shown as percentages. Because data were pooled from multiple studies which may be heterogeneous for one or more unaccounted factors affecting outcomes, shared frailty models were used for both endpoints with random effects for each study following a gamma distribution. These models included main effects of the covariates defined above as well as corresponding interaction effects with CRT. Quantitative variables (age, LVEF, QRS duration, systolic blood pressure) were treated as continuous variables in the models. QRS duration was normalized by subtracting 120 ms from each QRS value. Patients in NYHA class III were enrolled in all studies except REVERSE and served as the default for calculating hazard rate.

Additional models were fitted for subgroup analyses to estimate CRT effects among specific homogeneous patient groups. Age and systolic blood pressure were split by quartile, whereas LVEF was partitioned by pre-specified cut-offs of ≤15, 16–20, 21–30, 31–35, and >35%. Other subgroups were categorical, including QRS morphology (left bundle branch block (LBBB) or not). For each subgroup, a univariate frailty model was fitted, with CRT as a fixed effect and random study effects accounted for and the corresponding hazard ratio (HR) and 95% confidence bound for the HR of CRT compared with control was calculated.

To investigate the relationship between QRS duration and the effect of CRT, Cox proportional hazards models were fitted for each pre-specified endpoint with all significant main effects from the frailty model, main effects for CRT and normalized QRS duration, and the interaction effect for normalized QRS duration and CRT. The model tested a linear interaction effect for QRS duration and CRT, and a nonlinear interaction effect incorporating a third-order P-spline with 4 degrees of freedom. The latter interaction term was tested to determine whether the HR for CRT changes over different QRS duration subgroups in a nonlinear manner. P-splines allow for fitting complicated curvilinear patterns and so were utilized. The predicted values from each model were used to determine and plot the estimated HR of CRT for QRS duration as a continuous measure. To assess the variability of the results, 95% bootstrap confidence intervals were determined for each set of HRs. While random study effects were not incorporated into these models, sampling with replacement was performed such that each study/treatment arm combination provided the same number of subjects in each sample as in the original cohort.

Results

Altogether, 3872 (76%) patients were included in this analysis (Figure 1; Table 1). The median (IQR) age of patients was 66 (58–73) years, 868 (22%) were women (Table 2). 1995 (52%) were in NYHA class III or IV, and 2232 (58%) had ischaemic heart disease, including 1926 men (64% of men) and 306 women (35% of women). Only 81 patients in REVERSE were assigned to receive CRT or back-up pacing, and, therefore, among NYHA II patients...
who were enrolled, the comparison was predominantly CRT-D vs. ICD. The median value for LVEF (IQR) was 24 (20–28)%; it was 116 (105–130) mmHg for systolic blood pressure and was 160 (146–176) ms for QRS duration, with 78% having LBBB.

Comparing patients assigned to CRT/CRT-D or to the control group in the whole population, the HR for all-cause mortality was 0.66 (95% CI 0.57–0.77), and it was 0.65 (95% CI 0.58–0.74) for death or HF hospitalization (Figure 2A and B).

A significant interaction between CRT and QRS duration (Table 3) was observed, for both the composite outcome ($P = 0.0001$) and all-cause mortality alone ($P = 0.0013$), suggesting that patients with longer QRS durations derive greater benefit from CRT. Use of P-splines to examine the relationship between the effect of CRT and QRS duration as a continuous variable demonstrated a progressive increase in the benefit of CRT for both endpoints as QRS duration increased (Figure 3). The analyses yielded a significant nonlinear relationship with regard to the composite outcome ($P = 0.0039$), with a plateau of effect beyond 180 ms for the composite outcome, but not for mortality alone ($P = 0.3454$). The estimated HR crossed 1.0 at 126 ms for all-cause mortality and at 132 ms for the composite, suggesting possible benefit from CRT when QRS duration exceeds these values. The 95% confidence bounds excluded 1.0 beginning at $\approx 140$ ms for each endpoint, providing robust evidence of benefit from CRT when QRS duration exceeds this limit.

Interactions between CRT and other covariates were not significant in a multivariable model that included QRS duration. Similar reductions in all-cause mortality were observed with CRT regardless of whether the comparator was or was not an ICD and regardless of age, sex, NYHA class, aetiology, systolic blood pressure, or use of beta-blockers (Figure 4). Subgroup analyses for time to first composite event of HF hospitalization or death showed similar results (Figure 5). Patients who did not have LBBB appeared to have less benefit from CRT, especially in the composite outcome, but differences were not statistically significant. QRS duration was similar in patients with LBBB [median (IQR) 160 (150–180) ms] and RBBB [160 (150–172) ms] but shorter among patients with a non-specific intra-ventricular conduction delay [139 (128–160) ms], which may account for the trend to less reduction in mortality in the latter group. Removal of the QRS duration interaction term strengthened the interaction term between QRS morphology and the composite outcome ($P = 0.031$), but not for mortality alone ($P = 0.63$).

**Table 1** Characteristics of five studies included in the patient-level meta-analysis of cardiac resynchronization therapy

| Study   | Patients                 | Randomization         | Sample | Median follow-up* |
|---------|--------------------------|-----------------------|--------|-------------------|
| MIRACLE | NYHA III–IV, QRS $\geq$ 130 ms, EF $\leq$ 35% | 1:1 (CRT-P vs. VDI-30) | 541    | 6 months          |
| MIRACLE ICD | NYHA II–IV, QRS $\geq$ 130 ms, EF $\leq$ 35%, ICD indication | 1:1 (CRT-D vs. DDI-35) | 555    | 6 months          |
| CARE-HF | NYHA III–IV, QRS $\geq$ 120 ms, EF $\leq$ 35% | 1:1 (CRT-P vs. OMT)   | 813    | 29 months (35 months for mortality) |
| REVERSE | NYHA I–II, QRS $\geq$ 120 ms, EF $\leq$ 40% | 2:1 (CRT ± D vs. VVI-35) | 610    | 12 months (24 months, EU cohort) |
| RAFT    | NYHA II–III, QRS $\geq$ 120 ms (pQRS $\geq$ 200 ms), EF $\leq$ 30% | 1:1 (CRT-D vs. ICD)   | 1798   | 40 months         |

*Follow-up is for median of the randomized period only.

CRT-P, cardiac resynchronization therapy - pacemaker only, with no defibrillator function; OMT, optimal medical therapy.
### Table 2  Patient characteristics

| Patient characteristics | CRT-P (n = 735) | CRT-D (n = 1288) | OMT + back-up pacing (n = 700) | ICD (n = 1149) | Total (n = 3872) |
|-------------------------|-----------------|-----------------|-------------------------------|---------------|----------------|
| Gender, n (%)           |                 |                 |                               |               |                |
| Male                    | 531 (72.2)      | 1050 (81.5)     | 503 (71.9)                    | 920 (80.1)    | 3004 (77.6)    |
| Female                  | 204 (27.8)      | 238 (18.5)      | 197 (28.1)                    | 229 (19.9)    | 868 (22.4)     |
| Age, years at baseline  |                 |                 |                               |               |                |
| Mean ± standard deviation | 65 ± 10         | 65 ± 10         | 65 ± 11                       | 65 ± 10       | 65 ± 10        |
| Median                  | 66              | 66              | 66                            | 66            | 66             |
| 25th percentile–75th percentile | 58–73           | 58–72           | 58–72                         | 58–73         | 58–73          |
| Minimum–maximum         | 33–88           | 23–89           | 28–94                         | 20–89         | 20–94          |
| Baseline left ventricular ejection fraction |          |                 |                               |               |                |
| Mean ± standard deviation | 25 ± 7          | 24 ± 6          | 25 ± 7                        | 23 ± 6        | 24 ± 6         |
| Median                  | 24              | 24              | 25                            | 24            | 24             |
| 25th percentile–75th percentile | 21–29           | 20–28           | 21–30                         | 20–27         | 20–28          |
| Minimum–maximum         | 9–53            | 7–52            | 8–48                          | 6–45          | 6–53           |
| Number (%) of patients with LVEF availablea | 693 (94.3)      | 1287 (99.9)     | 674 (96.3)                    | 1149 (100)    | 3803 (98.2)    |
| Baseline QRS duration   |                 |                 |                               |               |                |
| Mean ± standard deviation | 165 ± 21        | 158 ± 24        | 164 ± 20                      | 159 ± 24      | 161 ± 23       |
| Median                  | 160             | 160             | 160                           | 160           | 160            |
| 25th percentile–75th percentile | 152–180         | 140–174         | 152–180                       | 140–176       | 146–176        |
| Minimum–maximum         | 94–240          | 93–263          | 100–240                       | 80–230        | 80–263         |
| Number (%) of patients with QRS available | 727 (98.9)      | 1288 (100)      | 690 (98.6)                    | 1149 (100)    | 3854 (99.5)    |
| Baseline supine systolic BP |                 |                 |                               |               |                |
| Mean ± standard deviation | 117 ± 18        | 119 ± 18        | 117 ± 18                      | 118 ± 18      | 118 ± 18       |
| Median                  | 115             | 115             | 115                           | 118           | 116            |
| 25th percentile–75th percentile | 105–130         | 106–130         | 105–128                       | 106–130       | 105–130        |
| Minimum–maximum         | 75–184          | 72–205          | 73–180                        | 75–185        | 72–205         |
| Number (%) of patients with measurement | 732 (99.6)      | 1283 (99.6)     | 696 (99.4)                    | 1145 (99.7)   | 3856 (99.6)    |
| Baseline supine diastolic BP |                 |                 |                               |               |                |
| Mean ± standard deviation | 70 ± 10         | 69 ± 11         | 69 ± 11                       | 69 ± 10       | 69 ± 11        |
| Median                  | 70              | 70              | 70                            | 70            | 70             |
| 25th percentile–75th percentile | 60–79           | 60–76           | 60–78                         | 60–76         | 60–77          |
| Minimum–maximum         | 36–101          | 35–112          | 40–110                        | 40–120        | 35–120         |
| Number (%) of patients with measurement | 732 (99.6)      | 1283 (99.6)     | 696 (99.4)                    | 1145 (99.7)   | 3856 (99.6)    |
| NYHA classification, n (%) |                 |                 |                               |               |                |
| NYHA II                 | 60 (8.2)        | 963 (74.8)      | 21 (3.0)                      | 833 (72.5)    | 1877 (48.5)    |
| NYHA III                | 625 (85.0)      | 303 (23.5)      | 624 (89.1)                    | 297 (25.8)    | 1849 (47.8)    |
| NYHA IV                 | 50 (6.8)        | 22 (1.7)        | 55 (7.9)                      | 19 (1.7)      | 146 (3.8)      |
| Morphology, n (%)       |                 |                 |                               |               |                |
| Left bundle branch blocka | 637 (86.7)      | 963 (74.8)      | 596 (85.1)                    | 840 (73.1)    | 3036 (78.4)    |
| Right bundle branch blockb | 37 (5.0)        | 124 (9.6)       | 45 (6.4)                      | 140 (12.2)    | 346 (8.9)      |
| Neither                 | 47 (6.4)        | 205 (15.9)      | 39 (5.6)                      | 176 (15.3)    | 467 (12.1)     |
| Ischaemic heart disease, n (%) | 352 (47.9)      | 829 (64.4)      | 319 (45.6)                    | 732 (63.7)    | 2232 (57.6)    |
| Beta-blocker use at baseline | 509 (69.3)      | 1101 (85.5)     | 454 (64.9)                    | 942 (82.0)    | 3006 (77.6)    |
| Duration of follow-up (months) |               |                 |                               |               |                |
| Mean ± standard deviation | 21.3 ± 15.0     | 28.3 ± 21.4     | 19.7 ± 15.0                   | 28.5 ± 21.4   | 25.5 ± 19.7    |
| Median                  | 23.9            | 23.7            | 16.4                         | 24.1          | 23.7           |
| 25th percentile–75th percentile | 6–35.2          | 11.1–44.7       | 5.8–33.6                     | 6.5–43.8      | 6.2–38.8       |
| Minimum–maximum         | 0.2–51.6        | 0–89.5          | 0.1–52.4                     | 0.3–88.8      | 0–89.5         |

*aLBBB status not known for some subjects (15 CRT-P subjects and 22 OMT subjects).

*bThere were 14 subjects reported to have both LBBB and RBBB; these are counted in both groups.
Discussion

This individual patient data meta-analysis confirms the substantial benefits of CRT on morbidity and mortality in patients with mild, moderate, or severe symptoms of HF who have left ventricular systolic dysfunction, are in sinus rhythm, and have a prolonged QRS. After adjusting for QRS duration, LBBB morphology was not a significant predictor of the benefits of CRT. Patients with non-specific intra-ventricular conduction delay had shorter QRS duration and this may account for reports suggesting that such patients receive less benefit from CRT.7,16–20 Age, sex, aetiology of disease, LVEF, blood pressure, and use of beta-blockers had no important, independent influence on the effects of CRT on morbidity or mortality. Furthermore, the benefits of CRT were similar whether or not the comparator group received an ICD. The failure of most patient characteristics to predict the effect of CRT in this large individual patient meta-analysis contrasts with that from some individual randomized trials21,22 and many smaller observational studies, that variously suggest that older patients, men, those with RBBB, and patients with ischaemic heart disease benefit less than others from CRT.5,7,23,24 Individual randomized trials may lack statistical power to investigate these issues, and observational studies may be unable to untangle the treatment effect of CRT from the natural history of disease.25 Use of individual patient data, analysis of QRS as a continuous variable, and the ability to investigate interactions between QRS duration and QRS morphology allowed a more sophisticated and granular analysis than previous meta-analyses that used only aggregated subgroup data. A more detailed analysis of subtle differences in QRS morphology might have identified patterns that provided prognostic information in addition to QRS duration, but such information was not available. Inclusion of a larger number of patients from additional trials would have increased the power to identify or refute any additional contribution from QRS morphology.

Our analysis may inform and simplify existing guidelines about the selection of patients for CRT. Current joint guidelines from the American Heart Association and American College of Cardiology strongly recommend CRT implantation in patients with an LVEF ≤35% if the QRS duration is ≥150 ms and LBBB is present.26 The Heart Failure Society of America guidelines27 strongly recommend CRT only when both QRS is ≥150 ms and RBBB morphology is absent, with a weaker recommendation when QRS is 120–150 ms regardless of BBB morphology. The 2012 joint European Heart Rhythm Association and Heart Rhythm Society expert consensus statement also suggested that QRS duration ≥150 ms was associated with a more consistent response and that non-LBBB morphology was associated with a poor response or even harm.28 European Society of Cardiology guidelines29 strongly recommend CRT only when LBBB is present and QRS is ≥130 ms if in NYHA
LVEF criterion required for study inclusion. In the current laboratory, perhaps reflecting a bias introduced by the threshold, tors often report a lower LVEF than measured by the central trial. It may also create a dilemma if treatment effects are identified in rather than the overall effect; most clinical trialists would caution other-effect, that guidelines should be based on subgroups within trials rather than on the trial inclusion/exclusion criteria, which has some merit but requires large data sets to explore effects in less prevalent subgroups. Indeed, such recommendations are advocating, in merit but requires large data sets to explore effects in less prevalent subgroups.

Some guidelines have suggested that recommendations should be based on the characteristics of patients actually enrolled in trials rather than on the trial inclusion/exclusion criteria, which has some merit but requires large data sets to explore effects in less prevalent subgroups. Indeed, such recommendations are advocating, in effect, that guidelines should be based on subgroups within trials rather than the overall effect; most clinical trialists would caution otherwise. It may also create a dilemma if treatment effects are identified in patients who do not appear to fit the study inclusion criteria. Investigators often report a lower LVEF than measured by the central trial laboratory, perhaps reflecting a bias introduced by the threshold LVEF criterion required for study inclusion. In the current analysis, patients with an LVEF > 35% measured in the core echocardiography laboratory appeared to derive similar benefit from CRT compared with patients with a lower LVEF even though the entry criteria of most trials might have been expected to exclude such patients.

The precise mechanism(s) by which CRT delivers benefit remains elusive. This analysis suggests that there is something about electrical, and presumably electro-mechanical, delay that is fundamental to the effect of CRT. QRS prolongation is associated with poorer ventricular function, but in contrast with QRS duration, no significant association between the effect of CRT and baseline LVEF was noted across the measured range. Improvement in left ventricular function in the months after CRT implantation is associated with a better prognosis. However, patients with ischaemic heart disease have substantially less improvement in ventricular function with CRT, presumably because of myocardial scar and yet the benefits of CRT on prognosis are remarkably similar in patients with or without ischaemic heart disease. Improvement in left ventricular function after CRT implantation may indicate that the patient has more viable myocardium and therefore an intrinsically better prognosis, rather than providing an overriding mechanism by which CRT delivers clinical benefit. Alternatively, patients with ischaemic heart disease may benefit in ways other than improved LVEF, such as arrhythmia suppression. In some patients, shortened AV conduction and reduction in mitral regurgitation may be an important mechanism of CRT effect. The rise in blood pressure that occurs with successful CRT may exert secondary benefits but could again just be a marker of improved cardiac function.

### Table 3 Main modelling results for time to all-cause mortality/heart failure hospitalization or mortality alone

| Effect                                | All-cause mortality/heart failure hospitalization | All-cause mortality |
|---------------------------------------|--------------------------------------------------|---------------------|
|                                       | Hazard ratio: univariate | Hazard ratio: multivariable | P-value for multivariable | Hazard ratio: univariate | Hazard ratio: multivariable | P-value multivariable |
|---------------------------------------|--------------------------------------------------|---------------------|
| ICD therapy                           | N/A                                              | 1.172               | 0.6283              | N/A                                              | 0.630               | 0.0500              |
| CRT therapy                           | N/A                                              | 1.046               | 0.9452              | N/A                                              | 0.458               | 0.3803              |
| Age at baseline                       | 1.020                                            | 1.018 <0.0001       | 1.030               | 1.030 <0.0001                                   | 1.030               | 0.0001              |
| NYHA II                               | 0.605                                            | 0.687               | 0.0004              | 0.658                                           | 0.658               | 0.0020              |
| NYHA IV                               | 2.771                                            | 2.180 <0.0001       | 2.444               | 2.444 <0.0001                                   | 2.444               | 0.0001              |
| Left Bundle Branch Block              | 0.839                                            | 0.830               | 0.0820              | 0.825                                           | 0.825               | 0.1782              |
| Ischaemic heart disease               | 1.519                                            | 1.394               | 0.0004              | 1.638                                           | 1.638               | <0.0001             |
| Gender: male                          | 1.052                                            | 1.001               | 0.9897              | 1.131                                           | 1.131               | 0.3663              |
| QRS duration                          | 1.000                                            | 1.001               | 0.7061              | 1.004                                           | 1.004               | 0.0941              |
| LVEF                                  | 0.963                                            | 0.965 <0.0001       | 0.956               | 0.956 <0.0001                                   | 0.956               | <0.0001             |
| Beta-blocker use at baseline          | 0.711                                            | 0.774               | 0.0093              | 0.700                                           | 0.700               | 0.0041              |
| Systolic BP at baseline               | 0.988                                            | 0.990               | 0.0001              | 0.987                                           | 0.987               | <0.0001             |

Interaction with effect of CRT

| Age at baseline                       | 0.998                                            | 1.000               | 0.9858              | 1.008                                           | 1.008               | 0.3812              |
| NYHA II                               | 0.959                                            | 0.820               | 0.1499              | 0.777                                           | 0.777               | 0.1654              |
| NYHA IV                               | 0.832                                            | 0.836               | 0.5334              | 0.800                                           | 0.800               | 0.5233              |
| Left bundle branch block              | 0.663                                            | 0.785               | 0.1228              | 0.977                                           | 0.977               | 0.9157              |
| Ischaemic heart disease               | 1.232                                            | 1.080               | 0.5996              | 1.045                                           | 1.045               | 0.8171              |
| Gender: male                          | 1.351                                            | 1.299               | 0.1234              | 1.173                                           | 1.173               | 0.4709              |
| QRS duration                          | 0.989                                            | 0.988 <0.0001       | 0.988               | 0.988 <0.0001                                   | 0.988               | 0.0013              |
| LVEF                                  | 1.025                                            | 1.021               | 0.0625              | 1.016                                           | 1.016               | 0.2667              |
| Beta-blocker use at baseline          | 0.975                                            | 1.034               | 0.8259              | 1.109                                           | 1.109               | 0.5897              |
| Systolic BP at baseline               | 0.998                                            | 0.996               | 0.2735              | 0.998                                           | 0.998               | 0.7583              |

Frailty effect for study

| N/A                                   | N/A                                              | <0.0001             | N/A                                              | N/A                                              | 0.1376              |

Values in bold are statistically significant at P < 0.05.
resynchronization therapy could also prevent brady-arrhythmic death, although this would only be noticed in studies such as CARE-HF and COMPANION where the control group did not receive a device. There may be no single mechanism by which CRT exerts its effects and the dominant mechanism of benefit may vary from one patient to the next and over time within an individual.

This analysis was conducted using common, relatively simple variables that were available from all five trials. It does not preclude the possibility that other markers of cardiac dyssynchrony are superior to QRS duration in predicting benefit from CRT. However, the reduced effect of CRT in patients with QRS duration <140 ms implies either that the individual benefit is small in such patients or that only a few patients respond or that substantial benefit in some patients is negated by harm in others. Whether measures of ventricular dyssynchrony by imaging are able to identify a patient who is more likely to benefit, and if so which measure, remains controversial.

A randomized controlled trial enrolling patients with QRS < 130 ms is addressing this question (enrolment recently stopped); results will be presented at the European Society of Cardiology Congress in 2013.

An important limitation of this analysis was the lack of access to individual patient data from two large trials that were funded by Boston Scientific Incorporated. The COMPANION trial would have added a further 1520 patients (308 assigned to the control group), predominantly with NYHA class III or IV HF, a further 313 deaths, and at least 594 events of death or first HF hospitalization. The MADIT-CRT trials would have added a further 1555 patients (618 assigned to the control group) with NYHA class II HF and up to a further 127 deaths and 372 events of death or first hospitalization. This compares with 662 deaths and 1082 events of death or first

Figure 3  Models showing hazard ratios (Y-axis and solid black line) and their 95% confidence intervals (dotted lines) for the effects of cardiac resynchronization therapy vs. control with QRS plotted on the X-axis. (A) The relationship between the effect of cardiac resynchronization therapy on all-cause mortality and QRS. (B) The corresponding relationship for heart failure hospitalization or death. The intersection of the 95% confidence interval and the line indicating a hazard ratio of 1.0 (no effect) indicates the QRS duration above which there is a high certainty of response.
hospitalization in the current analysis. Review of aggregate data from these two trials reinforces our findings about the relationship of QRS duration and the benefits of CRT and the relationship between QRS morphology and QRS duration. In both COMPANION and MADIT-CRT, longer QRS duration was associated with greater benefit. In a univariate analysis of MADIT-CRT, despite substantial reductions in cardiac volumes and improvement in LVEF, a trend towards an increase in mortality was observed with CRT amongst patients who did not have LBBB. However, there were few deaths in MADIT-CRT amongst such patients, especially in the small number randomized to the control group. This will have increased the risk of a chance finding of an adverse effect of CRT in patients without LBBB. Our univariate analysis also showed less benefit with respect to the composite of mortality or HF hospitalization in patients without LBBB. However, after adjusting for QRS duration, outcomes were similar whether or not LBBB was present. QRS morphology might play a role in predicting the effect of CRT, but QRS duration appears consistently stronger. Individual patient data-sets that include larger representation of subjects with RBBB or non-specific intra-ventricular conduction delay are required to explore how QRS duration and QRS morphology interact with the effects of CRT on morbidity and mortality.

Care should be taken in extrapolating data gathered from patients selected to participate in clinical trials to the wider population of patients with HF who might be considered for CRT. However, the heterogeneity of the studies, in terms of symptom severity, background therapy, and whether the intervention was CRT or CRT-D, may be seen as a strength rather than a limitation of the analysis as these differences did not appear to influence the benefits of CRT. Trials with longer durations of follow-up will have accumulated more events and had a greater influence on the results. Although an absolute benefit of CRT on the composite outcome of first hospitalization for HF or death appeared within 6 months, the absolute benefit for mortality was not obvious until 12–18 months. Short-term trials will have contributed little to this part of the analysis.

In practical terms, this analysis suggests that the chances of a patient benefiting from CRT diminish when QRS is >140 ms. If the choice is between CRT or no device, then renewed efforts at medical management are justified rather than preferring device implantation. If the choice is between CRT-D and ICD, then a lower decision threshold...
of 130 ms may be justified as the patient is already going to have a procedure; there is evidence of benefit in patients with QRS 130–140 ms and QRS duration increases over time. Implanting a CRT-D system initially may prevent the need for a later upgrade with its attendant risk of complications.

In conclusion, this individual patient meta-analysis confirms the benefits of CRT on morbidity and mortality in patients with mild, moderate, or severe symptoms of HF who have moderate or severe left ventricular systolic dysfunction and who are in sinus rhythm with a QRS duration.

140 ms. The clinical benefits of CRT in patients with QRS durations between 120 and 140 ms are, on average, smaller and/or less certain. After adjusting for QRS duration, in this analysis, QRS morphology was not a determinant of the clinical response to CRT. Future analyses of these data will investigate whether QRS duration or other variables can predict which patients obtain symptomatic benefits from CRT.

Authors’ contributions

Each author helped gather the primary information as they have all led Steering Committees of the Medtronic-funded studies that form a large part of the evidence base for CRT. A steering group was formed for this meta-analysis, which jointly formulated the analysis plan. L.S. conducted the analysis. J.G.C. wrote the first draft. All authors contributed to revising the manuscript and have read and approved the final version.

Funding

Medtronic played a role in the design of each of the studies included in the meta-analysis and had representatives (Daniel Schaber and Harrison Hudnall) on the meta-analysis steering group. The steering group invited comments on their analysis plan from Medtronic. L.S., who conducted the statistical analysis, is an employee of Medtronic. G.A.W., an independent academic statistician, provided oversight through the statistical analysis plan. Medtronic was invited to comment. The committee had access to the full data set through Medtronic and direct access to data for each of the studies which they chaired individually. J.G.C. had the final responsibility for submitting the manuscript. The Open Access charge was funded by the Medtronic.

Conflict of interest: J.G.C.: other research support (modest)—Biotronik; consultant/advisory board (modest)—Biotronik, St Jude Medical. W.T.A.: consultant/advisory board (significant)—Biotronik, Medtronic.
References

1. Nanthakumar K, Epstein AE, Kay GN, Plumb VJ, Lee DS. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction. A pooled analysis of 10 primary prevention trials. J Am Coll Cardiol 2004; 44:2166–2172.

2. Wells G, Parkash R, Hesley JS, Talajic M, Arnold JM, Sullivan S, Peterson J, Yestis E, Theoret-Patrick P, Luce M, Tang AS. Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials. CMAJ 2011; 183:421–429.

3. Freeman E, Thamanthan P, Calvert MJ, Abraham WT, Ghosh J, Cleland JGF. Cardiac resynchronization for patients with heart failure due to left ventricular systolic dysfunction. A systematic review and meta-analysis. Eur J Heart Failure 2010; 12:433–440.

4. Bertoldi EG, Polanczyk CA, Cunha V, Ziegelmann PK, Beck-da-Silva L, Rohde LE. Mortality reduction of cardiac resynchronization and implantable cardioverter-defibrillator therapy in heart failure: an updated meta-analysis. Does recent evidence change the standard of care? J Card Fail 2011; 17:860–866.

5. Cielandes JG, Tavazzi L, Daubert JC, Tageldien A, Freeman E, Nanteuil NC. Cardiac resynchronization therapy: Are modern myths preventing appropriate use? J Am Coll Cardiol 2009; 53:608–611.

6. Cielandes JG, Tageldien A, Buga L, Wong K, Gorcsan J. Should we be trying to define responders to cardiac resynchronization therapy? JACC Cardiovasc Imaging 2010; 3:541–549.

7. Bilich KC, Kamath S, D’Marco JP, Stukenberg C. Bundle-branch block morphology and other predictors of outcome after cardiac resynchronization therapy in Medicare patients. Circulation 2010; 122:2022–2030.

8. Cielandes JG, Daubert JC, Erdmann E, Freeman N, Gras D, Kappenberger L, Tavazzi L. For the Cardiac Resynchronization – Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. New Engl J Med 2003; 352:1539–1549.

9. Cielandes JG, Daubert JC, Erdmann E, Freeman N, Gras D, Kappenberger L, Tavazzi L, on behalf of the CARE-HF study investigators. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure (the Cardiac Resynchronization – Heart Failure [CARE-HF] trial extension phase). Eur Heart J 2006; 27:1928–1932.

10. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavel AI, Hayes DL, Ellessad M, Messenger J, for the MIRACLE Study Group. Cardiac resynchronisation in chronic heart failure. N Engl J Med 2002; 346:1845–1853.

11. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert J-C, on behalf of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) Study. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008; 52:1834–1843.

12. Daubert JC, Gold MR, Abraham WT, Ghio S, Hassager C, Goodie G, Sjõli-Torok T, Linde C, on behalf of the REVERSE Study Group. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction. J Am Coll Cardiol 2009; 54:1837–1846.

13. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Carby RC, Schroeder JS, Lien LB, Hall S, Wheeler K. Combined cardiac resynchronization and implantable cardioversion-defibrillation in advanced chronic heart failure. The MIRACLE ICD Trial. JAMA 2003; 289:2685–2694.

14. Abraham WT, Young JB, Leon AR, Adler S, Bank AJ, Hall SA, Lieberman R, Lien LB, O’Connell JB, Schroeder JS, Wheeler KR, on behalf of the Multicenter InSync ICD II study group (MIRACLE ICD II). Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. Circulation 2004; 110:2864–2868.

15. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL. Cardiac-resynchronisation therapy for mild-to-moderate heart failure. N Engl J Med 2010; 363:2385–2395.

16. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom DS, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichtenstein E, Pickering S, Rashian MS, Visan S, Wang P, Moss AJ. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011; 123:1061–1072.

17. Gold MR, Thebault C, Linde C, Abraham WT, Gerrits B, Ghio S, St John SM, Daubert JC. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. Circulation 2012; 126:822–829.

18. Dupont M, Rickard J, Baranowsky B, Varma N, Dresing T, Gabi A, Finucan M, Mullens W, Wilkoff BL, Tang WH. Differential response to cardiac resynchronization therapy and clinical outcomes according to QRS morphology and QRS duration. J Am Coll Cardiol 2012; 60:592–600.

19. Rickard J, Jackson G, Spragg DD, Cronin EM, Baranowsky B, Tang WH, Wilkoff BL, Varma N. QRS prolongation induced by cardiac resynchronization therapy correlates with deterioration in left ventricular function. Heart Rhythm 2012; 9:1674–1678.

20. Saphi I, Chou JC, Hyden M, Rowland DY, Simon DI, Fang JC. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Am Heart J 2012; 163:260–267.

21. Marzio A, Moss AJ, Foster E, Padeletti L, Bartschret A, Goldberger I, Greenberg L, Hall WJ, McNitt S, Zareba W, Solomon S, Steinberg JS. Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. J Am Coll Cardiol 2011; 57:813–820.

22. Goldenberg I, Moss AJ, Foster E, Goldberger JJ, Santucci P, Shinn T, Solomon S, Steinberg JS, Wilber D, Bartschret A, McNitt S, Zareba W, Klein H. Predictors of response to cardiac resynchronization therapy in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011; 124:1527–1536.

23. Zabbarovska S, Gadler F, Braunschweg F, Stahlberg M, Hornsten J, Linde C, Lund LH. Women have better long-term prognosis than men after cardiac resynchronization therapy. Europace 2012; 14:1188–1155.

24. Egozi L, Ho RT, Greenspon AJ, Pivarnik BB. Cardiac resynchronization therapy in patients with right bundle branch block: analysis of pooled data from the MIRACLE and Contak CD trials. Heart Rhythm 2005; 2:611–615.

25. Nijs S, Pabari PA, Stegemann B, Palmieri V, Levy F, Linde C, Freeman E, Davies JF, Hughes AD, Francis DP. The limit of plausibility for predictors of response: application to biventricular pacing. JACC Cardiovasc Imaging 2012; 5:1046–1056.

26. Jessup M, Abraham WT, Casey DE, Feldman AM, Franklin GB, Gañatsas TG, Kontos MC, Manini DM, Milrow KM, Silverman MA, Stevenson LW, Yang CW. 2009 focused update: ACCF/ACCM, ACCF/AHA, ACHA, and ASNC guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119:1977–2016.

27. Stevenson WG, Hernandez AF, Carson PE, Fang JC, Spodias SA, Jutze SR, Swetzer NK, Tang WH, Albert NM, Butler J, Westlake Canay CA, Collins SP, Colvin-Adams M, Ezekowitz J, Givertz MM, Hershberger RE, Rogers JG, Teerlink JR, Walsh MN, Stough WG, Starling RC. Indications for cardiac resynchronization therapy: 2011 update from the Heart Failure Society of America Guideline Committee. J Card Fail 2012; 18:94–106.

28. Daubert JC, Saxon L, Adamson PB, Auricchio A, Berger RD, Beshai JF, Breithardt O, Brignole M, Cleland J, Delurgio DB, Dickstein K, Exner DV, Gold M, Gersh BB, Goldstein S, Grady RA, Grimm RA, Hirsch AT, Kober L, Lip GY, Maggioni AP, Nihoyannopoulos P, Pachucki R, Pfeffer MA, Torp-Pedersen C, van Veldhuisen DJ, Zopp MW, on behalf of the Multicenter InSync ICD II trial extension phase. Multicenter InSync ICD Trial Investigators. Women have better long-term prognosis than men after cardiac resynchronization therapy: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. Circulation 2012; 125:1061–1072.
Maggioni AP, Parkhomenko A, Pieske BM, Pupescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trinidad PT, Voors AA, Zannad F, Zieher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knust J, Koli P, McDonagh T, Moulin C, Pupescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windsheuer S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Gaida GF, Hardman S, Jung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803–869.

Dickstein K, Vardas PE, Auricchio A, Daubert JC, Linde C, McMurray J, Ponikowski P, Oh JK, Pellikka PA, Panza JA, Biernat J, Attisano T, Manahan BG, Wiste HJ, Lin G, Cleland JG, Freemantle N, Ghio S, Fruhwald F, Shankar A, Marijanowski M, Solomon SD, Foster E, Bourgoun M, Shah A, Viloria E, Brown MW, Hall WJ, Bleeker GB, Lamb TA, Boersma E, Steendijk P, De Roos A, Van der Wall EE, St John SM, Ghio S, Plappert T, Tavazzi L, Scelsi L, Daubert C, Abraham WT, van Bommel RJ, Tanaka H, Delgado V, Bertini M, Borleffs CJ, Ajmone MN, van Bommel RJ, Tanaka H, Delgado V, Bertini M, Borleffs CJ, Ajmone MN, Holzmeister J, Ruschitzka F, Schalij MJ, Bax JJ, Gorcsan J III. Association of intravenous ejection fraction on the effectiveness of cardiac resynchronization therapy. Circulation 2012;126:327–336.

Kutyla V, Kloppe A, Zareba W, Solomon SD, McNitt S, Polonsky S, Barsheeth A, Merkely B, Lemke B, Nagy VK, Moss AJ, Goldenberg I. The influence of left ventricular ejection fraction on the effectiveness of cardiac resynchronization therapy. MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). J Am Coll Cardiol 2013;61:936–944.

Khan NK, Goode KM, Cleland JGF, Rigby AS, Freemantle N, Eastaugh J, Clark AL, de Silva R, Calvert MJ, Szwedberg K, Komajda M, Mareev V, Follath F, for the EuroHeart Failure Survey Investigators. Prevalence of ECG abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge. Eur J Heart Fail 2007;9:491–501.

Solomon SD, Foster E, Bourgoun M, Shah A, Vilara E, Brown MW, Hall WJ, Pfeffer MA, Moss AJ. Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: multicenter automatic defibrillator implantation trial: cardiac resynchronization therapy. Circulation 2010;122:985–992.

Cleland JG, Freemantle N, Ghio S, Fruhwald F, Shankar A, Marianiowski M, Verbeken Y, Tavazzi L. Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response: a report from CARE-HF (Cardiac Resynchronization in Heart Failure). J Am Coll Cardiol 2008;52:438–445.

St John SM, Ghio S, Pappert T, Tavazzi L, Scelsi L, Daubert C, Abraham WT, Gold MR, Hassager C, Herre JM, Linde C. Cardiac resynchronization induces major structural and functional reverse remodeling in patients with New York Heart Association class II/III heart failure. Circulation 2009;120:1858–1865.

Bleecker GB, Lamb TA, Boersma E, Steendijk P, De Roos A, Van der Wall EE, Schalji MJ, Bax JJ. Effect of posterior lateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. Circulation 2006;113:969–976.

Blinchik KC, Dimaano V, Wu KC, Helm RH, Weiss RG, Lima JA, Berger RD, Tomaselli GF, Bluemke DA, Halperin HR, Abraham T, Kass DA, Lardo AC. Cardiac magnetic resonance assessment of dysynchrony and myocardial scar predicts function class improvement following cardiac resynchronization therapy. JACC Cardiovasc Imaging 2008;1:561–568.

Barsheshet A, Goldenberg I, Moss AJ, Eldar M, Huang DT, McNitt S, Klein HU, Hall WJ, Brown MW, Goldberger JJ, Goldstein RE, Schuger C, Zareba W, Daubert JP. Response to preventive cardiac resynchronization therapy in patients with ischemic and nonischemic cardiomyopathy in MADIT-CRT. Eur Heart J 2010;31:1622–1630.

Cleland JGF, Pennell DJ, Ray SG, Coats AJ, Macfarlane PW, Murray GD, Dalie Mule, Vered Z, Lahin A, on behalf of the CHRISTMAS (Cardiellated Hibernating Reversible Ischaemia Trial: Marker of Success) investigators. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial. Lancet 2003;362:14–21.

Uretsky BF, Thygessen K, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, Cleland JG. Predictors of mortality from pump failure and sudden cardiac death in patients with systolic heart failure and left ventricular dysynchrony: results of the CARE-HF trial. J Card Fail 2008;14:670–675.

Brenyo A, Link MS, Barsheshet A, Moss AJ, Zareba W, Wang P, McNitt S, Huang D, Foster E, Estes M III, Solomon SD, Goldenberg I. Cardiac resynchronization therapy reduces left atrial volume and the risk of atrial tachyarrhythmias in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). J Am Coll Cardiol 2011;58:1682–1689.

Barsheshet A, Wang P, Moss AJ, Solomon SD, Al-Ahmad A, McNitt S, Foster E, Huang DT, Klein HU, Zareba W, Eldar M, Goldenberg I. Reverse remodeling and the risk of ventricular tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). J Am Coll Cardiol 2011;57:2416–2423.

Raphael CE, Wynnnett ZI, Davies JE, Fontana M, Ferenczi EA, Manisty CH, Mayet J, Francis DP. Quantifying the paradoxical effect of higher systolic blood pressure on mortality in chronic heart failure. Heart 2009;95:56–62.

Fornwal BK, Sprague WW, BeDell P, Suver JD, Gerbrtse B, Merlino JD, Fyde YA, Leon AR, Oshinski JN. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. Circulation 2010;121:1985–1991.

van Bommel RJ, Tanaka H, Deigado V, Bertini M, Barfette CJ, Ajmone MN, Holzmeister J, Ruschitzka F, Schalji MJ, Bax JJ, Gorcsan J III. Association of intraventricular mechanical dyssynchrony with response to cardiac resynchronization therapy in heart failure patients with a narrow QRS complex. Eur Heart J 2010;31:3054–3062.

Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, Dements D, White BG, Devries DW, Feldman AM, for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. New Engl J Med 2004;350:2140–2150.

Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA III, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329–1338.

Tageldien A, Cleland JG, Hurri S, Khaleva O, Cullington D, Clark AL, Rigby AS. Prevalence and incidence of intraventricular conduction delay in patients with heart failure and an implantable cardiac defibrillator. 2008;A102–A103.