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FASTTRACK CLINICAL RESEARCH

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

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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.

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Keywords Cardiac resynchronization therapy • Morbidity • Mortality • Heart failure

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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.[1] 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.[2,3] 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.[4]

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.[5–7] These may be unable to untangle the therapeutic response to CRT from the natural history of the underlying disease.[5] 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.[2,4] 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] REVERSE[11,12]) or CRT-D with ICD (REVERSE,[11,12] MIRACLE ICD,[13,14] RAFT[15]). 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 homogenous 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

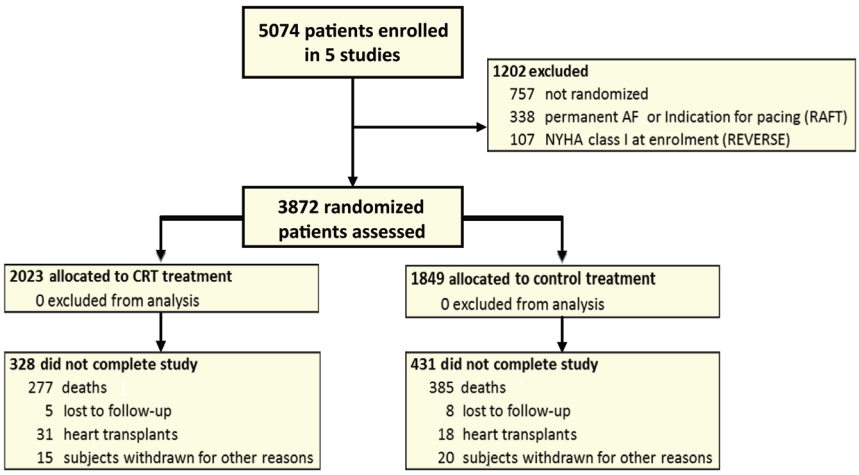

Figure 1 CONSORT flow diagram showing reasons for excluding patients from analysis.

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

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

[a]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.

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 of death/HF hospitalization ($P = 0.0039$), 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 ~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 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 visit					
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 available[a]	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	118	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 block[a]	637 (86.7)	963 (74.8)	596 (85.1)	840 (73.1)	3036[a] (78.4)
Right bundle branch block[b]	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

[a]LBBB status not known for some subjects (15 CRT-P subjects and 22 OMT subjects).
[b]There were 14 subjects reported to have both LBBB and RBBB; these are counted in both groups.

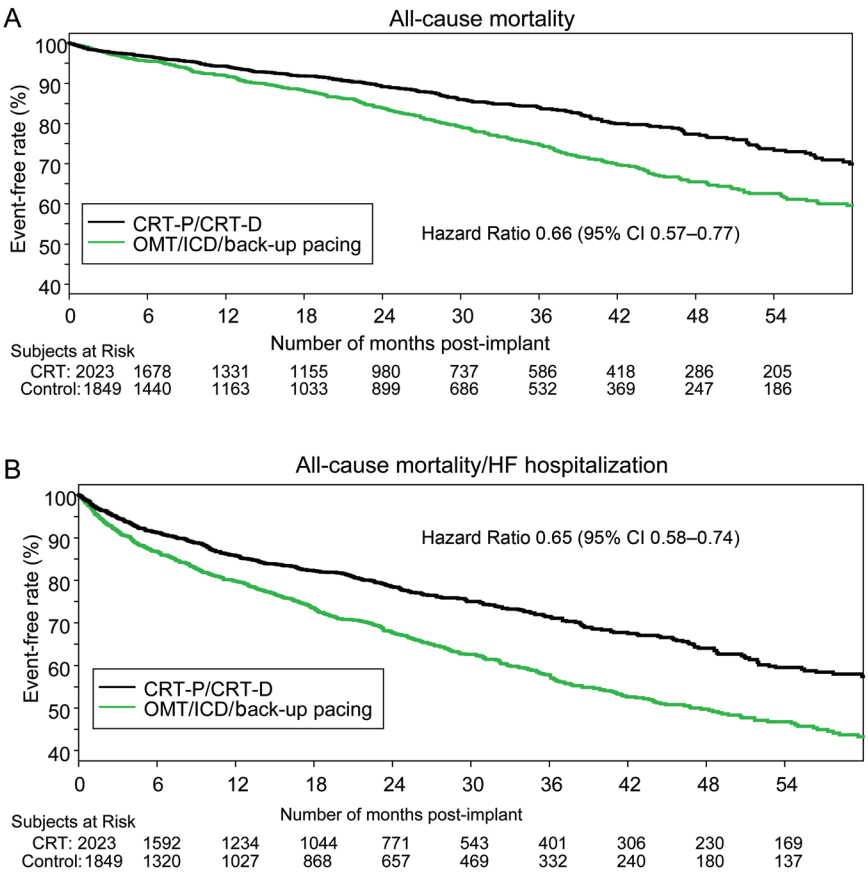

Figure 2 Overall effect of cardiac resynchronization therapy vs. control on all-cause mortality (*A*) and on death or heart failure hospitalization (*B*).

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 trials[21,22] 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 $\leq$35% if the QRS duration is $\geq$150 ms and LBBB is present.[26] The Heart Failure Society of America guidelines[27] strongly recommend CRT only when both QRS is $\geq$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 guidelines[29] strongly recommend CRT only when LBBB is present and QRS is $\geq$130 ms if in NYHA

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
Main effects						
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**
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**
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**
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	0.3832
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**	**0.0013**
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 $P < 0.05$.

class II or ≥120 ms if in NYHA class III, with a weaker recommendation for patients who have a QRS ≥ 150 ms in the absence of LBBB, regardless of NYHA class.

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.[30] 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.[31,32] 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.[5,6] 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,[33] 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.[34–36] However, patients with ischaemic heart disease have substantially less improvement in ventricular function with CRT, presumably because of myocardial scar,[37,38] and yet the benefits of CRT on prognosis are remarkably similar in patients with or without ischaemic heart disease.[12,34,35,39] Improvement in left ventricular function after CRT implantation may indicate that the patient has more viable myocardium and therefore an intrinsically better prognosis[40] 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 by arrhythmia suppression.[41–43] 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.[44] Cardiac

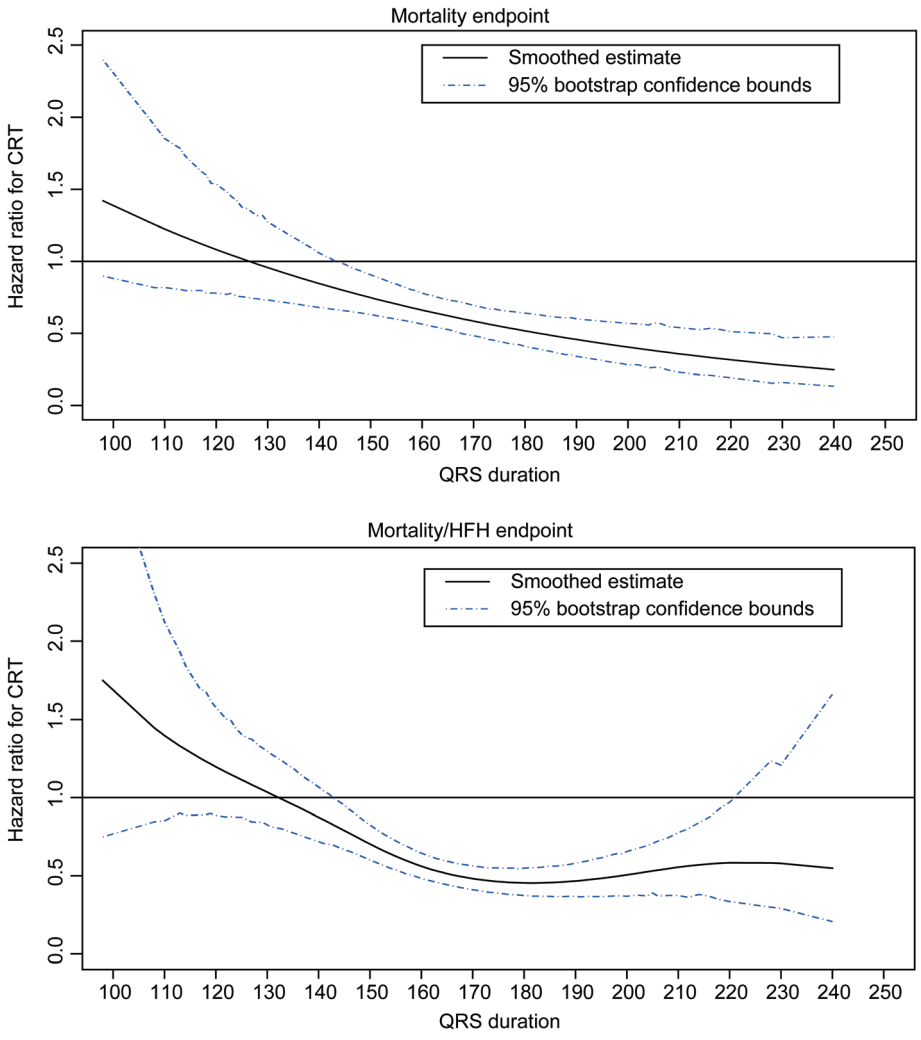

Figure 3 Models showing hazard ratios (*Y*-axis and solid black line) and their 95% confidence intervals (dotted lines) for the effects of cardiac resynchronization therapy vs. control with QRS plotted on the *X*-axis. (*A*) The relationship between the effect of cardiac resynchronization therapy on 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.

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.[6] 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.[6]

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.[45] 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.[46]

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.[47] 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.[48] This compares with 662 deaths and 1082 events of death or first

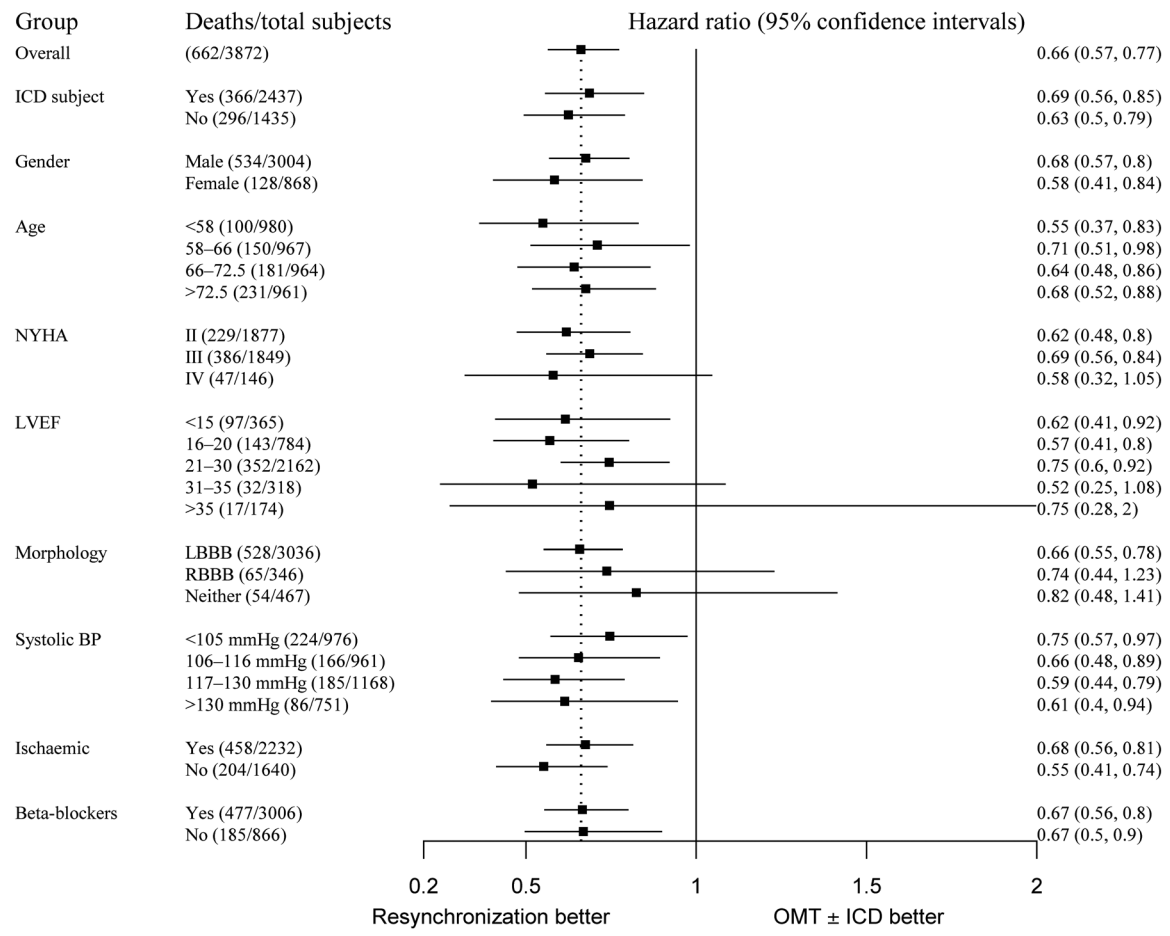

Figure 4 Forest plot for univariate frailty models evaluating the effect of cardiac resynchronization therapy in pre-specified subgroups on all-cause mortality.

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.[16,24,47] 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

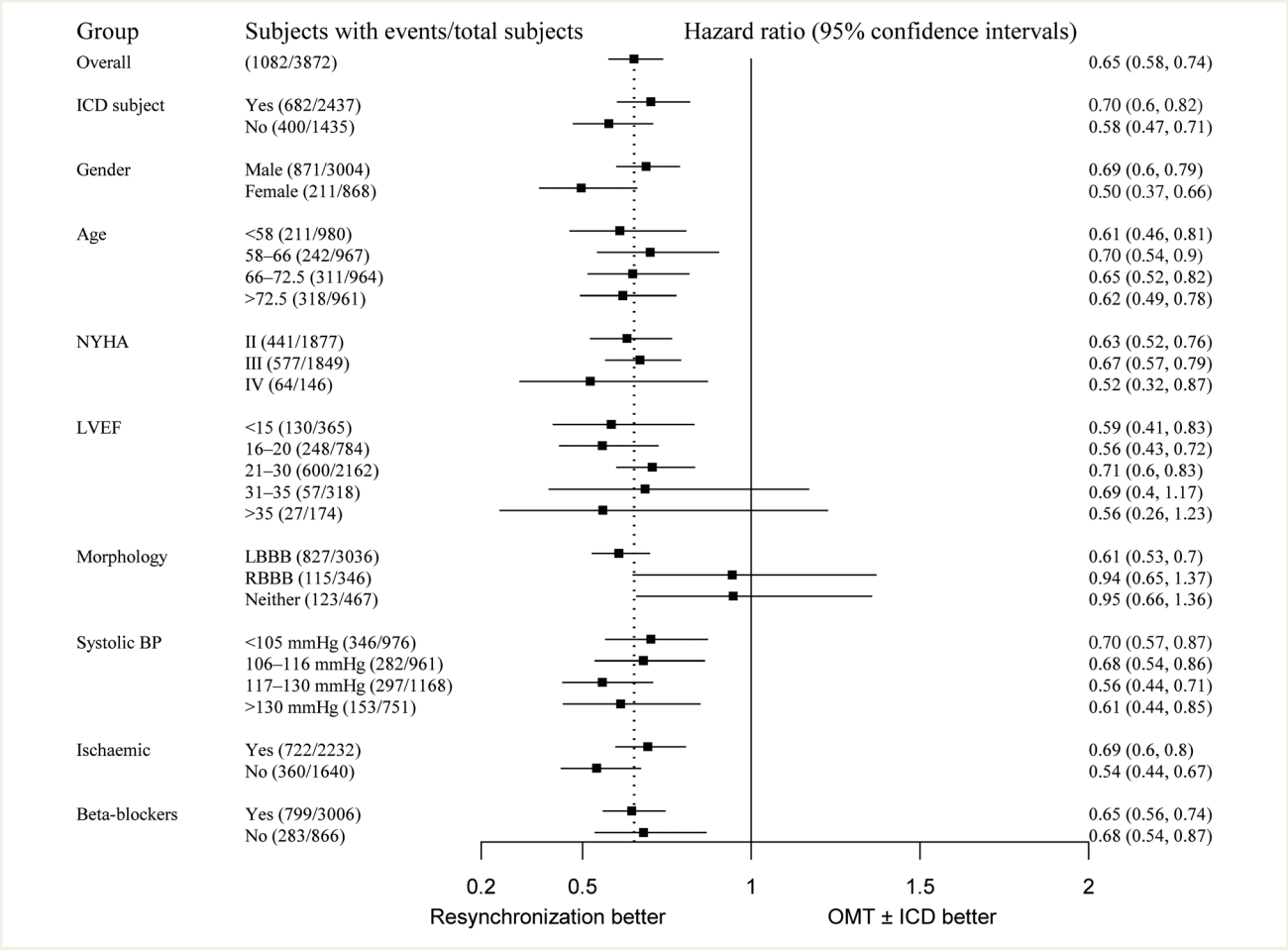

Figure 5 Forest plot for univariate frailty models evaluating the effect of cardiac resynchronization therapy in other pre-specified subgroups on death or heart failure hospitalization. Figures show hazard ratio and 95% confidence intervals.

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.[49] 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.

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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.

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