Consultee comments on the Appraisal Consultation Document:

SHTAC critique of studies

March 2014

Summary

In response to concerns raised by the manufacturers and consultees, SHTAC has critiqued two trials (RethinQ, EchoCRT) and a meta-analysis (Cleland et al 2013).

The RethinQ and EchoCRT trials compared CRT-D with ICD in people with a narrow QRS duration (<130 ms). Both trials had a low risk of bias; EchoCRT was stopped early for futility and potential harm. Around 70-80% of the population in each trial had a QRS interval <120 ms, and 92-100% had NYHA class III symptoms. Both trials found higher all-cause mortality with CRT-D, however this was statistically significant only in the larger EchoCRT trial. RethinQ did not explore the effects of QRS duration on mortality, and although benefit was seen in the primary outcome with QRS 120-130 ms and not with QRS <120 ms, the statistical significance of the interaction was not reported. Subgroup analysis in EchoCRT found increased mortality with CRT-D in people with QRS <120 and no benefit in those with QRS 120-130, however the treatment-by-subgroup interaction was not statistically significant. The subgroup analyses should be viewed with caution

The Cleland meta-analysis of five CRT trials suggested benefit of CRT (with or without a defibrillator) when QRS duration was greater than 126 ms, however there was some uncertainty surrounding this until QRS duration reached around 140 ms. The Cleland meta-analysis appeared to be well conducted but did not include a large proportion of the relevant evidence. The meta-analysis combined the intervention groups (CRT-D or CRT-P), and the control groups (ICD or OPT). These factors limit comparison with the ABHI analysis.

Introduction

At the Appraisal Committee meeting on 20th November 2013, some participants raised concerns regarding the suitability of cardiac resynchronisation therapy in patients with slightly prolonged QRS intervals. Two trials (RethinQ[1] and EchoCRT[2]) and one individual patient meta-analysis (Cleland et al. 2013[3]) were mentioned. In their responses to the Appraisal Consultation Documentation, the manufacturers (ABHI) and a consultee (British Heart Rhythm Society) have raised some concerns regarding interpretation of these studies. This document presents a brief critique of these studies, as requested by NICE, to enable the Committee to hold an informed discussion.

RethinQ RCT

RethinQ (2007) was a multicentre (34 centres) RCT of 172 participants and had a follow-up of six months. A summary of the inclusion criteria, baseline characteristics and risk of bias is presented in Appendix 1.

RethinQ was included in the ABHI individual patient data (IPD) network meta-analysis (NMA) and the independent SHTAC technology assessment report (TAR) systematic review. The TAR noted that RethinQ differed from the other CRT-D trials in the criteria used to define cardiac dyssynchrony, recruiting people with a narrow QRS interval (<130 ms) and evidence of intraventricular mechanical dyssynchrony on echocardiography. Mean QRS interval at baseline was 107 ms in RethinQ; most (71-76%) participants had a QRS interval < 120 ms and 24-29% of participants had a QRS interval 120-130 ms. The participants in this trial had NYHA class III symptoms, and LBBB was not reported.

Participants who had undergone successful implantation of a CRT-D device and baseline evaluation 14 days post-implantation were randomised to CRT-ON or CRT-OFF (with defibrillator). The study was powered to detect a 23% difference in the proportion of participants who achieved the primary endpoint (an increase of ≥1.0 ml/kg body weight / min in peak oxygen consumption during cardiopulmonary exercise testing); the study was not powered for mortality. The trial was judged to have generally a low risk of bias.

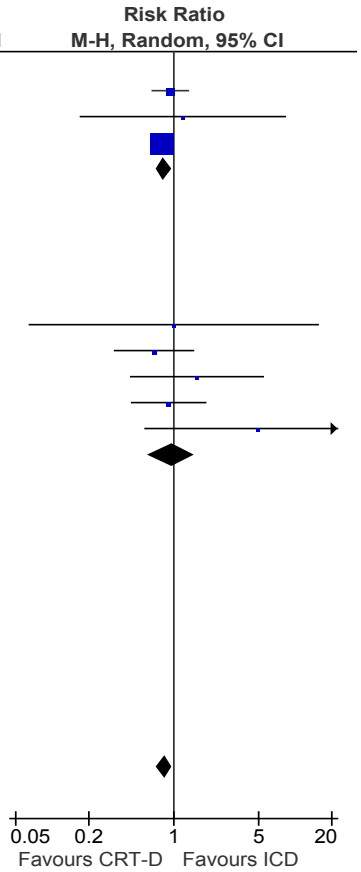
Of 172 successfully implanted participants randomised, 3 crossed from CRT-OFF to CRT-ON due to worsening heart failure. No crossover occurred from the CRT-ON group.

All-cause mortality

All-cause mortality was higher in the CRT-D group (5.7% vs 1.2%), however this was not statistically significant (Figure 1).

Figure 1 All-cause mortality: CRT-D vs ICD (Fig 19, p208 of TAR)

Study or Subgroup	CRT-D Events	CRT-D Total	ICD Events	ICD Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Class II						
MADIT CRT	74	1089	53	731	17.7%	0.94 [0.67, 1.32]
MIRACLE ICD II	2	85	2	101	0.5%	1.19 [0.17, 8.26]
RAFT	186	894	236	904	71.9%	0.80 [0.67, 0.94]
Subtotal (95% CI)		**2068**		**1736**	**90.1%**	**0.82 [0.71, 0.96]**
Total events	262		291			
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 2.51 (P = 0.01)						
1.1.2 Class III						
Pinter 2009	1	36	1	36	0.3%	1.00 [0.07, 15.38]
CONTAK-CD	11	245	16	245	3.7%	0.69 [0.33, 1.45]
RHYTHM ICD	9	83	3	43	1.3%	1.55 [0.44, 5.44]
MIRACLE ICD	14	187	15	182	4.2%	0.91 [0.45, 1.83]
RethinQ	5	87	1	85	0.5%	4.89 [0.58, 40.95]
Subtotal (95% CI)		**638**		**591**	**9.9%**	**0.95 [0.60, 1.50]**
Total events	40		36			
Heterogeneity: Tau² = 0.00; Chi² = 3.64, df = 4 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.21 (P = 0.83)						
1.1.3 Class IV						
Piccirillo 2006	0	16	0	15		Not estimable
Subtotal (95% CI)		**16**		**15**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2722**		**2342**	**100.0%**	**0.84 [0.73, 0.96]**
Total events	302		327			
Heterogeneity: Tau² = 0.00; Chi² = 4.82, df = 7 (P = 0.68); I² = 0%						
Test for overall effect: Z = 2.45 (P = 0.01)						
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.56), I² = 0%						



Primary outcome

There was no statistically significant difference in the primary outcome (proportion of participants with an increase of ≥1.0 ml/kg body weight / min in peak oxygen consumption); CRT-D 46% vs CRT-OFF 41%, p=0.63.

Subgroup analysis

RethinQ presented prespecified stratified analysis according to QRS interval (≥ 120 ms or <120 ms), reproduced in Appendix 2. A statistically significant improvement in the proportion of people with an increase of at least 1 ml/kg body weight/min in peak oxygen consumption was found with CRT-D for people with QRS 120-130 ms (58.9% vs 19.7%. p=0.02), but not for those with QRS <120 (42.2% vs 51.2%, p=0.45). However, the statistical significance of the interaction was not investigated. There was a statistically significant improvement in the proportion with improvement in NYHA class with CRT-D for both QRS ≥120 ms (70.7% vs 28.0%, p=0.01) and <120 ms (49.4 vs 29.3%, p=0.04) subgroups. There was no statistically significant difference between CRT-D and ICD in QoL or distance walked in 6 minutes for either QRS interval subgroup. Subgroup analysis to explore the effect of QRS duration on mortality was not undertaken. The general limitations of subgroup analysis, for example the lack of statistical power, and the absence of an appropriate statistical test for interaction, mean that these results should be viewed with caution.

EchoCRT RCT

EchoCRT (2013) was a multicentre RCT of 809 participants and had a follow-up of almost 20 months at trial termination. The trial was noted as ongoing at the time of the TAR systematic review. A summary of the inclusion criteria, baseline characteristics and risk of bias is presented in Appendix 1.

EchoCRT aimed to evaluate the effect of CRT in people with symptomatic heart failure, a narrow QRS complex (<130ms), and echocardiographic evidence of left ventricular dyssynchrony. The mean QRS interval was about 106 ms; and the majority (about 80%) had a QRS duration <120 ms. Most (92-95%) participants in this trial had NYHA class III symptoms, and LBBB was not reported.

Participants with a successful implantation of a CRT-D device were randomised to CRT-ON or CRT-OFF (defibrillator active). The primary outcome was the combination of death from any cause or first hospitalization for worsening heart failure. The trial was stopped early on the basis for futility with a potential for harm. The trial was judged to have a low risk of bias.

30/405 (7.4%) of successfully implanted participants crossed over from CRT-OFF to CRT-ON, and 7/404 (1.7%) in the CRT-ON group had the CRT capability switched off.

All-cause mortality

All-cause mortality was higher in the CRT-ON group (11.1% vs 6.4%, adjusted HR 1.81, 95% CI 1.11 to 2.93, p=0.02), see Table 1. There was an excess of deaths due to cardiovascular causes in this group (9.2% vs 4.2%, adjusted HR 2.26 (1.27 to 4.01, p=0.004).

Primary outcome

There was no significant difference between CRT-ON and CRT-OFF in the primary composite outcome of death from any cause or hospitalization for heart failure (28.7% vs 25.2%, adjusted HR 1.20, 95% CI 0.92 to 1.27, p=0.15).

Subgroup analysis

The effects of treatment on nine pre-specified subgroups (including QRS duration <120 ms or 120-130 ms) for the primary composite outcome and each of the component outcomes, all-cause mortality and hospitalisation for worsening heart failure, were examined. Subgroup analyses for all-cause mortality are reproduced in Appendix 3. There was only one statistically significant treatment-by-subgroup interaction; this was for all-cause mortality and suggested greater harm with CRT in patients less than 65 years of age (HR 4.05, 95% CI 1.65 to 9.95). For QRS duration, the 95% confidence interval does not cross 1.0 (HR 2.08, 95% CI 1.16 to 3.73) for those with QRS < 120 ms indicating harm, whereas no effect is seen for those with QRS ≥ 120 (HR 1.01, 95% CI 0.35 to 2.90); however the interaction was not statistically significant (p=0.33). The subgroup analyses are limited by lack of statistical power and the multiple comparisons increase the probability of a false positive finding, therefore the results should be viewed with caution.

Table 1 Results from EchoCRT

Outcome *no. of patients with event (%)*	**CRT-D** **n=404**	**ICD** **n=405**	**Adjusted Hazard Ratio** **(95% CI)**	**p-value**
Primary composite outcome				
Death from any cause or hospitalization for heart failure	116 (28.7)	102 (25.2)	1.20 (0.92–1.57)	0.15
Components of primary outcome				
Hospitalization for heart failure	99 (24.5)	90 (22.2)	1.16 (0.87–1.55)	0.25
Death from any cause	45 (11.1)	26 (6.4)	1.81 (1.11–2.93)	0.02
Causes of death				
Cardiovascular event	37 (9.2)	17 (4.2)	2.26 (1.27–4.01)	0.004
-Heart failure	17 (4.2)	10 (2.5)	1.74 (0.80–3.81)	0.15
-Arrhythmic events	14 (3.5)	4 (1.0)	not reported	<0.05

Hazard ratios were calculated by means of the Cox model with adjustment for country, and P values were calculated by the stratified log-rank test.

Cleland et al meta-analysis

Cleland et al (2013) undertook an IPD meta-analysis with the aim of identifying pre-implantation variables that predict the response to CRT. Five trials for which individual patient data (IPD) could be supplied by Medtronic were included in the analysis, with a total of 3872 participants:

1. MIRACLE
2. MIRACLE ICD (including Miracle ICD II)
3. CARE-HF
4. REVERSE
5. RAFT

Cleland at al noted that two relevant large CRT trials were not included as the authors did not have access to IPD. These trials were included in the ABHI IPD NMA and have a combined total of 3340 participants:

1. COMPANION
2. MADIT-CRT

Six smaller CRT trials identified by the SHTAC systematic review that would also be relevant but were not included in the Cleland et al meta-analysis totalled about 1000 participants. In particular, the two trials of people with a narrow QRS duration discussed above, RethinQ and EchoCRT, were not included in the meta-analysis. The Cleland et al meta-analysis therefore excludes a large proportion of the relevant evidence. A summary of baseline characteristics from all relevant CRT trials is presented in Appendix 4.

1. CONTAK-CD (also included in ABHI NMA)
2. RethinQ (also included in ABHI NMA)
3. Picirillo
4. Pinter

5. Rhythm ICD
6. MUSTIC

Quality assessment of the five included trials was not undertaken by Cleland et al. The interventions and comparators in the five trials differed; MIRACLE ICD and RAFT compared CRT-D versus ICD; MIRACLE and CARE-HF compared CRT-D with OPT; and in REVERSE participants were randomised to receive CRT (with or without an ICD) or a device with CRT switched off. The IPD analysis therefore compared CRT (with or without defibrillator) versus control (ICD or OPT); this is in contrast to the ABHI NMA which examined the devices separately.

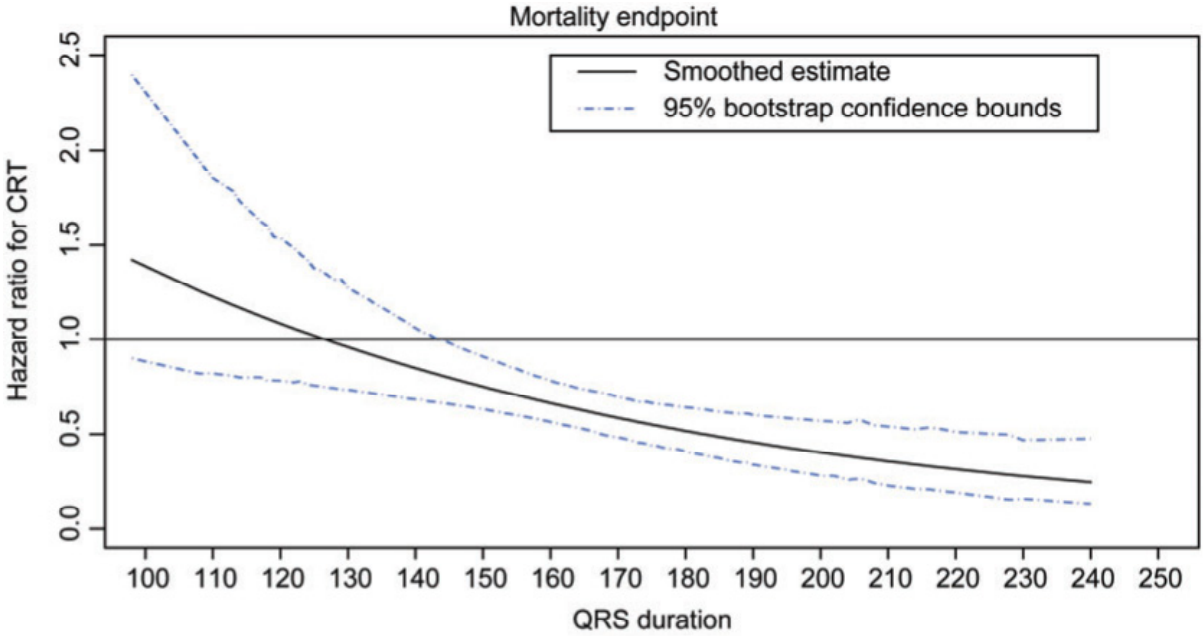
To create a more homogeneous population some patients were excluded (107 with NYHA class I from REVERSE; 338 in atrial fibrillation or with pre-existing pacemaker from RAFT). Cleland et al state that statistical analyses were undertaken using the intention-to-treat principle. Statistical methods are not fully described, although the general approach taken appears reasonable. QRS duration was treated as a continuous variable in the model, whereas in the ABHI model QRS duration was categorised as 0-120 ms, ≥120-<150 ms, and ≥150 ms.

For the whole IPD population, the HR for all-cause mortality was 0.66 (95% CI 0.57 to 0.77). A significant interaction between CRT and QRS duration was observed for all-cause mortality (p=0.0013). Further analysis to investigate the relationship between QRS duration and CRT estimated an HR which crossed 1.0 at 126 ms for all-cause mortality (
Figure 2), suggesting benefit from CRT when QRS duration exceeds this value. However the confidence intervals indicate that some uncertainty remains until about 140 ms, where the upper 95% confidence interval crosses 1.0.

Interactions between CRT and other covariates (including LBBB) were not significant in a multivariate 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, LVEF, LBBB, aetiology, systolic blood pressure, or use of beta-blockers.

For comparison, the unadjusted HR for all-cause mortality from the ABHI IPD NMA was 0.72 (95% CrI 0.63 to 0.80) for CRT-P vs OPT, and 0.58 (95% CrI 0.50 to 0.68) for CRT-D vs OPT. The predicted treatment effects for each subgroup are displayed in Table 2.

Figure 2 The relationship between the effect of CRT on all-cause mortality and QRS (reproduced from Cleland et al)



Model 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. 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.

Table 2 Updated hazard ratios (95% confidence intervals) for all-cause mortality from NMA with covariables for the comparisons between the different devices and OPT following revised analysis by ABHI

Non-LBBB					
QRS	**Device**	**Sex and Age Groups**			
		Male <60yrs	**Male ≥60yrs**	**Female <60yrs**	**Female ≥60yrs**
<120	ICD	[redacted]	[redacted]	[redacted]	[redacted]
≥120 to <150	ICD	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-D	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-P	[redacted]	[redacted]	[redacted]	[redacted]
≥150	ICD	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-D	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-P	[redacted]	[redacted]	[redacted]	[redacted]
LBBB					
QRS	**Device**	**Sex and Age Groups**			
		Male <60yrs	**Male ≥60yrs**	**Female <60yrs**	**Female ≥60yrs**
≥120 to <150	ICD	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-D	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-P	[redacted]	[redacted]	[redacted]	[redacted]
≥150	ICD	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-D	[redacted]	[redacted]	[redacted]	[redacted]
	CRT-P	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 1 Inclusion criteria, baseline characteristics and risk of bias for RethinQ and EchoCRT

Appendix 1a Inclusion criteria

	RethinQ	**EchoCRT**
Study design	RCT	RCT
Intervention	CRT-D + OPT	CRT-D + OPT
Comparator	CRT-OFF + OPT	CRT-OFF + OPT
Country (no. of centres)	USA (34)	USA (56), Canada (2), Israel (5), Australia (5), Europe (47) (total 115 centres)
Number randomised	172	809
Length of follow-up	6 months	To study termination (mean 19.4 months for all, 19.8 months for survivors).
Key inclusion criteria:	Evidence of intraventricular mechanical dyssynchrony on echocardiography, ischemic or non-ischemic cardiomyopathy	Symptomatic heart failure, a narrow QRS complex and echocardiographic evidence of left ventricular dyssynchrony
- NYHA Class	III	III or IV
- LVEF	≤35	≤35
- QRS interval, ms	<130	<130
- LBBB	not reported	not reported
- ICD indication requirement	'standard indication for an ICD'	'standard indication for an ICD'

Appendix 1b Baseline characteristics

	RethinQ		**EchoCRT**	
	CRT-D	ICD	CRT-D	ICD
Sample size, n	87	85	404	405
Age, mean (SD)	60 (12)	58 (14)	57.6 (12.9)	58.3 (12.6)
Sex, % male	71	58	72.8	71.9
NYHA I, %	0	0	0.5	0.7
NYHA II, %	0	0	1.7	3.0
NYHA III, %	100	99	95.3	92.3
NYHA IV, %	0	0	2.5	4.0
LVEF %, mean (SD)	25 (5)	26 (6)	27 (5.7)	27 (5.4)
QRS interval ms, mean (SD)	107 (12)	106 (13)	106.1 (13.1)	105.5 (12.1)
- < 120, % - ≥ 120, %	76 24	71 29	not reported not reported	not reported not reported
LBBB/RBBB, %	not reported	not reported	not reported	not reported

Appendix 1c Risk of bias

Judgement[a]	RethinQ	EchoCRT
Selection bias		
Random sequence generation	Low	Low
Allocation concealment	Low	Low
Performance bias		
Blinding of participants & personnel	Unclear	Low
Detection bias		
Blinding of outcome assessment	Low	Low
Attrition bias		
Incomplete outcome data addressed	Primary outcome[b]- Low Other outcomes - High	Primary outcome - Low Other outcomes - Low
Reporting bias		
Selective reporting	Low	Low
Other bias		
Other sources of bias	Low	Low

[a] 'Low risk', 'high risk' or 'unclear risk' of bias. [b] Also QoL, NYHA and mortality.

Appendix 2 RethinQ subgroup analysis according to QRS interval

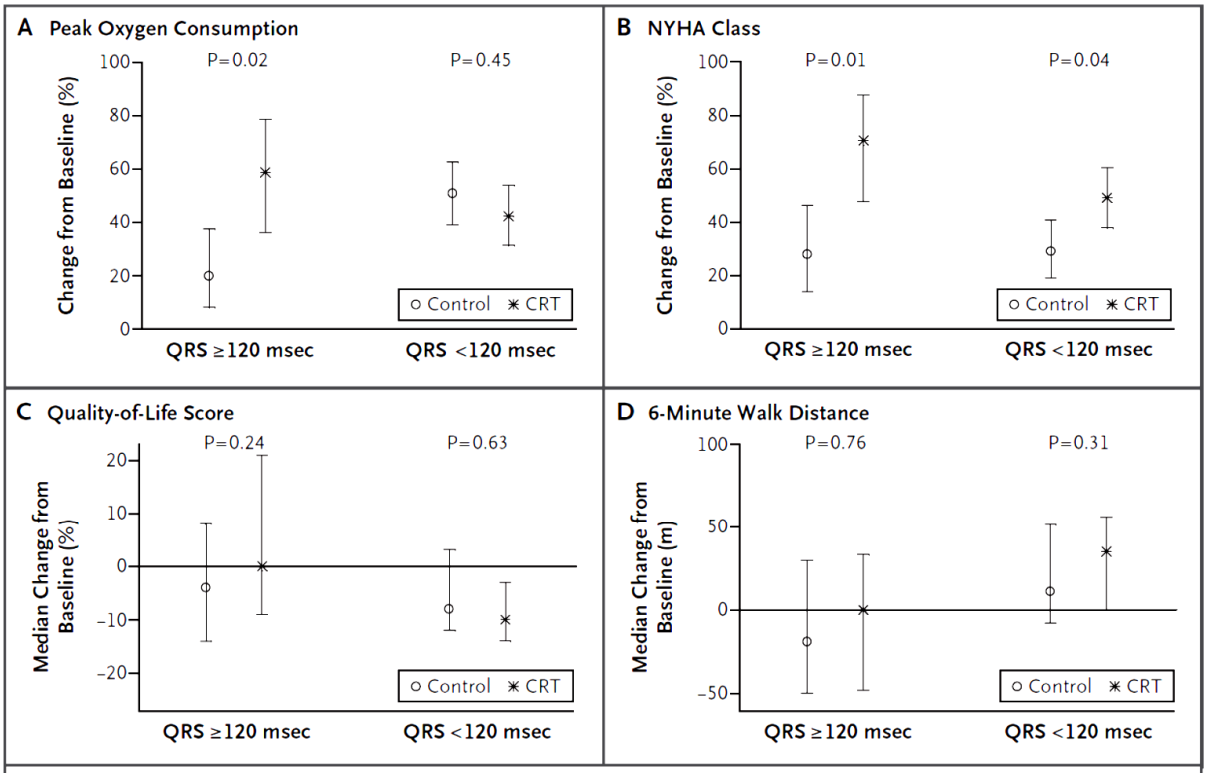


Figure 2. Subgroup Analysis According to the QRS Interval at 6 Months.

For the peak oxygen consumption, the primary end point was an increase of at least 1 ml per kilogram of body weight per minute from baseline (Panel A). For New York Heart Association (NYHA) class, shown are the proportions of patients whose condition improved by at least 1 class from baseline (Panel B). For the quality-of-life score (Panel C) and 6-minute walk distance (Panel D), shown are the median changes from baseline. In the CRT group, the QRS interval was 120 msec or more in 17 patients and less than 120 msec in 59 patients. In the control group, the QRS interval was 120 msec or more in 25 patients and less than 120 msec in 55 patients. P values are for the comparison between groups, and I bars indicate 95% confidence intervals.

Appendix 3 EchoCRT subgroup analyses for all-cause mortality

SUBGROUPS	CRT=OFF	CRT=ON	Hazard ratio (95% CI)	P(interaction)
OVERALL	26/405 (6.4%)	45/404 (11.1%)	1.81 (1.11, 2.93)	
NYHA Class				
III (N=759)	23/374 (6.1%)	44/385 (11.4%)	1.88 (1.13, 3.11)	
IV (N=26)	1/16 (6.2%)	1/10 (10.0%)	1.73 (0.11, 27.89)	0.69
QRS width				
< 120ms (N=661)	17/328 (5.2%)	35/333 (10.5%)	2.08 (1.16, 3.73)	
≥ 120ms (N=123)	9/68 (13.2%)	8/55 (14.5%)	1.01 (0.35, 2.90)	0.33
LVESV				
< 131ml (N=400)	13/199 (6.5%)	19/201 (9.5%)	1.86 (0.90, 3.87)	
≥ 131ml (N=406)	13/205 (6.3%)	25/201 (12.4%)	1.71 (0.86, 3.43)	0.89
Age				
< 65 years (N=542)	6/264 (2.3%)	25/278 (9.0%)	4.05 (1.65, 9.95)	
≥ 65 years (N=267)	20/141 (14.2%)	20/126 (15.9%)	1.04 (0.54, 2.00)	0.024
Qualification				
TDI only (N=202)	4/106 (3.8%)	11/96 (11.5%)	3.23 (0.98, 10.69)	
Speckle Radial strain only (N=185)	7/100 (7.0%)	11/85 (12.9%)	1.66 (0.64, 4.31)	
Both (N=421)	15/199 (7.5%)	23/222 (10.4%)	1.30 (0.67, 2.50)	0.40
Gender				
Female (N=224)	5/114 (4.4%)	5/110 (4.5%)	0.99 (0.28, 3.45)	
Male (N=585)	21/291 (7.2%)	40/294 (13.6%)	1.83 (1.08, 3.12)	0.56
Etiology of heart failure				
Non-Ischemic (N=376)	4/190 (2.1%)	12/186 (6.5%)	3.64 (1.11, 11.98)	
Ischemic (N=432)	22/214 (10.3%)	33/218 (15.1%)	1.54 (0.89, 2.67)	0.25
Lead Placement				
Optimal (N=136)	3/71 (4.2%)	7/65 (10.8%)	2.10 (0.51, 8.70)	
Sub-optimal (N=521)	18/263 (6.8%)	32/258 (12.4%)	1.90 (1.06, 3.41)	0.63
Mitral regurgitation				
None/Trace (N=280)	5/147 (3.4%)	14/133 (10.5%)	3.02 (1.06, 8.58)	
Mild (N=317)	11/154 (7.1%)	22/163 (13.5%)	1.98 (0.94, 4.17)	
Moderate or worse (N=204)	9/101 (8.9%)	8/103 (7.8%)	0.84 (0.31, 2.25)	0.12

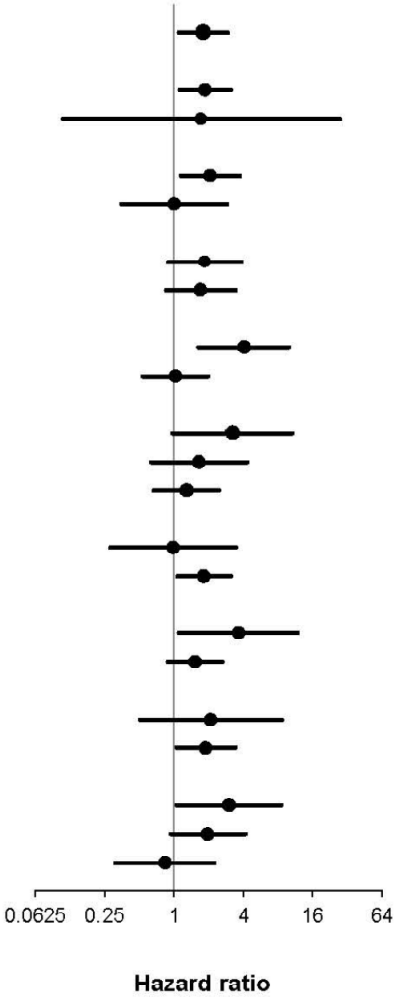


Figure S1c: Display of hazard ratios and 95% confidence intervals for CRT=ON relative to CRT=OFF for each pre-specified subgroup, with tabulation of corresponding numbers of subjects with all-cause mortality endpoint(percentage), hazard ratio and P-value for the interaction between the effect of CRT=ON relative to CRT=OFF across the subgroup categories.

Appendix 4 Summary of baseline charecterisics from CRT trials

	Intervention & comparator	Sample size, n	NYHA Class, %				LVEF %, mean (SD)	QRS interval, ms	LBBB/RBBB
			I	II	III	IV		mean (SD)	%
1. MIRACLE	CRT-P ON	228	0	0	90	10	21.8 (6.3)	167 (21)	
	CRT-P OFF	225	0	0	91	9	21.6 (6.2)	165 (20)	
2. MIRACLE ICD	CRT-D	187	0	0	88.2	11.8	24.2 (6.5)	165 (22)	nr/13
	ICD	182	0	0	89.6	10.4	23.9 (6.0)	162 (22)	nr/13
MIRACLE ICD II	CRT-D	85	0	100	0	0	24.4 (6.6)	166 (25)	nr/12
	ICD	101	0	100	0	0	24.6 (6.7)	165 (23)	nr/21
3. CARE-HF	CRT-P	409	0	0	94	6	25 [a]	160 [a], (152-180) [b]	
	OPT	404	0	0	93	7	25 [a]	160 [a,] (152-180) [b]	
4. REVERSE	CRT- ON	419		82			26.8 (7.0)	153 (21)	
	CRT- OFF	191		83			26.4 (7.1)	154 (24)	
5. RAFT	CRT-D	894	0	83	20.8	0	22.6 (5.4)	157 (23.6)	73/8
	ICD	904	0	80.8	19.2	0	22.6 (5.1)	158.3 (24.0)	71/10
Cleland meta-analysis total		**3872**		**48.5**	**47.8**	**3.8**	**24 (6)**	**161 (23)**	**78.4/8.9**
COMPANION	CRT-P	617	0	0	87	13	20 [a]	160 [a]	69/12
	CRT-D	595	0	0	86	14	22 [a]	160 [a]	73/10
	OPT	308	0	0	82	18	22 [a]	158 [a]	70/9
MADIT-CRT	CRT-D	1089	14.0	86	0	0	24 (5)	QRS ≥ 150 64.2**%**	70/13
	ICD	731	15.5	84.5	0	0	24 (5)	QRS ≥ 150 65.1%	71/13
CONTAK-CD (included in ABHI NMA)	CRT-D	245	0	32	60	8	21 (7)	160 (27)	54/14
	ICD	245	0	33	57	10	22 (7)	156 (26)	55/12
RethinQ (included in ABHI NMA)	CRT-D	87	0	0	100	0	25 (5)	107 (12)	
	ICD	85	0	0	99 [c]	0	26 (6)	106 (13)	
Picirillo	CRT-D	16	0	0	31.3	68.8	23 (4)	160 (4)	
	ICD	15	0	0	33.3	66.7	22 (8)	159 (8)	
Pinter	CRT-D	36	nr	nr	nr	nr	21.2 (7.9) [d]	nr	
	ICD	36	nr	nr	nr	nr	24.0 (8.3) [d]	nr	
Rhythm ICD	CRT-D	119	0.8	5.0	87.4		25.6 (8.3)	169 (16)	
	ICD	59	3.4	6.8	84.7	5.1	23.3 (6.4)	167 (15)	
MUSTIC	CRT-P ON	29	0	0	100	0		172 (22)	
	CRT-P OFF	29	0	0	100	0		175 (19)	

nr, not reported. [a] Median, [b] Range, [c] NYHA class of one participant not reported, [d] Measured by echocardiogram; also measured by quantitative resting radionuclide angiogram (MUGA): CRT-D 24.2 (SD 7.5), ICD 26.8 (SD 8.4).

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