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Impact of QRS Duration on Clinical Event Reduction With Cardiac Resynchronization Therapy

Meta-analysis of Randomized Controlled Trials

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Background: Cardiac resynchronization therapy (CRT) is effective in reducing clinical events in patients with heart failure and prolonged QRS interval. Studies using surrogate measures and subgroup analysis of large trials suggest that only patients with severely prolonged QRS benefit from CRT. Our objective was to determine whether the effect of CRT on adverse clinical events (eg, death, hospitalizations) is different in patients with moderately (ie, 120-149 milliseconds) vs severely (ie, ≥150 milliseconds) prolonged QRS duration.

Methods: Searches of MEDLINE, SCOPUS, and Cochrane databases were conducted for randomized controlled CRT trials. Trials reporting clinical events according to different QRS ranges were identified. Five randomized trials fulfilling the inclusion criteria (total patients, n=5813) were included in the meta-analysis.

Results: In patients with severely prolonged QRS, there was a reduction in composite clinical events with CRT (risk ratio, 0.60; 95% confidence interval [CI], 0.53-0.67) ($P<.001$). In contrast, there was no benefit of CRT in patients with moderately prolonged QRS (RR, 0.95; 95% CI, 0.82-1.10) ($P=.49$), resulting in a significantly different impact of CRT in the 2 QRS groups ($P<.001$). There was a significant relationship between baseline QRS duration and risk ratio ($P<.001$) with benefit of CRT appearing at a QRS of approximately 150 milliseconds and above. The differential response of the 2 QRS groups was evident for all New York Heart Association classes.

Conclusions: Cardiac resynchronization therapy was effective in reducing adverse clinical events in patients with heart failure and a baseline QRS interval of 150 milliseconds or greater, but CRT did not reduce events in patients with a QRS of less than 150 milliseconds. These findings have implications for the selection of patients for CRT.

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HEART FAILURE CURRENTLY affects approximately 6 million people in the United States and 6.5 million people in Europe.[1,2] Not only does heart failure contribute to death and poor quality of life, but it also contributes to a significant utilization of resources, with costs related to heart failure estimated to be in excess of $39 billion in 2010 in the United States.[1] Over the past decade, in addition to medical therapy, implantable device therapy has become a cornerstone of the treatment for this disease. Cardiac resynchronization therapy (CRT), also known as biventricular pacing, has been shown to improve hemodynamics, promote reverse remodeling, and reduce clinical events including death in patients with prolonged QRS duration on the electrocardiogram.[3-6]

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Traditionally, treatment guidelines endorsed by the American College of Cardiology, American Heart Association, Heart Rhythm Society, European Society of Cardiology (ESC), and Heart Failure Society of America (HFSA) recommended CRT in patients with systolic heart failure, New York Heart Association (NYHA) class 3 or 4 symptoms, and a QRS duration of 120 milliseconds or greater.[7-10] About one-third of patients with systolic heart patients have a QRS duration above this cutoff of 120 milliseconds.[11-13] Soon after CRT became a popular treatment for heart failure, it was

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recognized that one-third to one-half of patients receiving CRT based on the guidelines did not respond to this treatment.[14,15] The recommendation for the QRS cutoff of 120 milliseconds or greater for implantation of CRT devices was based on the entry criteria of 2 major trials.[16,17] Recently, the HFSA[18] and ESC[19] guidelines for management of heart failure were revised in response to the MADIT-CRT trial.[20] These new guidelines introduced a new recommendation for CRT in NYHA 1 and/or NYHA 2 systolic heart failure, but this time with a new QRS cutoff of greater than 150 milliseconds for this population. The new cutoff was based on the subgroup analysis of the MADIT-CRT trial,[20] in which patients with a QRS interval shorter than 150 milliseconds had no reduction in heart failure events with CRT. These updated guidelines continued to recommend CRT for patients with NYHA 3 and 4 heart failure with the old QRS cutoff of 120 milliseconds or greater. However, studies using surrogate measures of response (ie, hemodynamics or peak oxygen consumption) suggest that patients with a QRS duration between 120 and 150 milliseconds do not benefit from CRT, regardless of their NYHA functional class.[3,21] In this context, to our knowledge, the impact of the degree of QRS prolongation on the effect of CRT for reducing adverse clinical events (ie, death and hospitalization) has never been analyzed systematically. Therefore, our objective was to determine whether the impact of CRT on clinical end points is affected by the degree of baseline QRS prolongation by performing a meta-analysis of randomized trials testing CRT in heart failure.

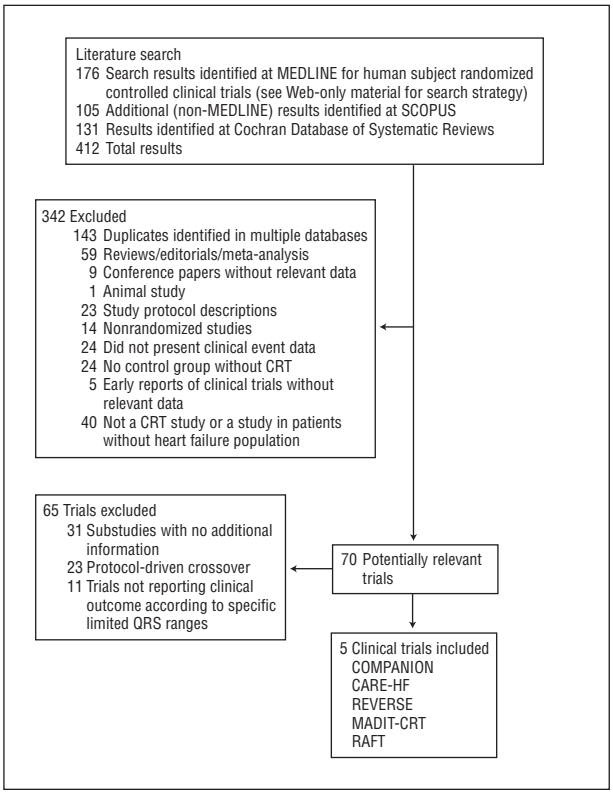

Figure 1. Flowchart of cardiac resynchronization therapy (CRT) trials included in the meta-analysis. Web-only material includes an eTable, eAppendix, and eFigure. CARE-HF indicates Cardiac Resynchronization-Heart Failure[17]; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure[16]; CRT, cardiac resynchronization therapy; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy[20]; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial[22]; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction.[23]

METHODS

LITERATURE SEARCH

Systematic searches were made of MEDLINE, SCOPUS (covering EMBASE), Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews databases to retrieve all published randomized controlled trials of CRT that reported clinical events according to baseline QRS duration. The search terms and other search strategies are described in detail for each database in the eAppendix (available at http://www.archinternmed.com along with eTable and eFigure). The results of the literature search are depicted in **Figure 1**.

STUDY SELECTION

To evaluate the efficacy of CRT in relation to QRS duration, we included trials that reported clinical outcomes of subgroups stratified by QRS duration. Studies were excluded if they (1) were not randomized; (2) did not have a non-CRT control group; (3) enabled implantable cardioverter defibrillator (ICD) implantation only in one study arm and not in the other(s) (trials enabling ICD implantation in both arms were eligible); (4) had cross-over study design; (5) did not report the clinical outcomes of interest such as death and hospitalization; and/or (6) reported clinical outcomes without any relation to specific limited QRS ranges.

DATA EXTRACTION

Data from studies meeting the selection criteria were extracted and verified independently by 2 investigators (I.S. and T.P.C.). In cases where the point estimates and the confidence intervals (CIs) for subgroups were not specifically stated, forest plots were used, if available, to extract this information using electronic calipers. Among the included trials, there were slight differences in the cutoffs used for QRS subgroup reporting. In an attempt to standardize the cutoff, we contacted the corresponding authors of the trials that did not report QRS subgroups with the exact 150-millisecond cutoff (ie, COMPANION[16] reporting with 147 milliseconds, REVERSE[23] with 152 milliseconds, and CARE-HF[17] with 159 milliseconds) and asked for the effect sizes with the 150-millisecond cutoff. However, this information was not provided for any of these trials. Thus, we defined the subgroup with a QRS duration of less than 150 milliseconds in most cases as *moderately prolonged* and those with a QRS duration of 150 milliseconds or greater in most cases as *severely prolonged*. One trial[16] reported 3 subgroups; the "middle" subgroup of this trial (148-168 milliseconds) was included among our severely prolonged QRS subgroups, since the QRS duration was greater than 150 milliseconds for most patients in the subgroup.

STATISTICAL ANALYSIS

We generated funnel plots according to different QRS subgroups to examine the possibility of publication bias. We supplemented testing for publication bias with the Begg Rank Correlation test.[24]

Four of the included trials reported hazard ratios (HRs), and 1 trial reported odds ratios (ORs). The values for ORs are similar to those for HRs (ie, instantaneous risk ratio [RR]) when the outcome is uncommon. Given that the outcome in the trial that reported ORs was less than 20%, we were able to combine

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Table 1. Characteristics of Randomized Controlled Trials of Cardiac Resynchronization Therapy That Were Included in the Meta-analysis

Trial (Sponsor)	Inclusion Criteria: NYHA Class	Inclusion Criteria: EF, %	Inclusion Criteria: QRS Duration, ms	Study Intervention	Control	Average Follow-up, mo	Subgroups by QRS Duration, ms	Composite End Point Reported for QRS Subgroup Analysis
COMPANION[16] (Guidant)	3 or 4	≤35	≥120	CRT (n=617)[a]	Medical therapy (n=308)	16.2 (CRT) and 11.9 (medical therapy)	120-147 (n=324) 148-168 (n=314) >168 (n=287)	All-cause mortality or hospitalization
CARE-HF[17] (Medtronic)	3 or 4	≤35	≥120[b]	CRT (n=409)	Medical therapy (n=404)	29.4	120-159 (n=290) >159 (n=505)	All-cause mortality or hospitalization for major cardiovascular event including heart-failure hospitalization
REVERSE[23] (Medtronic)	1 or 2	≤40	≥120	CRT on (n=419)	CRT off (n=191)	12	120-151 (n=303) >151 (n=307)	All-cause mortality or heart-failure hospitalization or worsened heart failure resulting in cross-over or dropout or worsened NYHA class or moderately or markedly worsened heart-failure symptoms
MADIT-CRT[20] (Boston Scientific)	1 or 2	≤30	≥130	CRT (n=1089)	Medical therapy (n=731)	28.8	130-149 (n=645) >149 (n=1175)	All-cause mortality or heart-failure event (heart-failure hospitalization or outpatient intravenous diuretic therapy)
RAFT[22] (Canadian Institutes of Health Research, Medtronic)	2 or 3	≤30	≥120	CRT (n=894)	No CRT (n=904)	40	120-149 (n=627) >149 (n=1036)[c]	All-cause mortality or heart-failure hospitalization

Abbreviations: CARE-HF, Cardiac Resynchronization-Heart Failure[17]; COMPANION indicates Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure[16]; CRT, cardiac resynchronization therapy; EF, ejection fraction; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy[20]; NYHA, New York Heart Association; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial[22]; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction.[23]

[a] The COMPANION trial[16] had 3 arms (CRT, combined CRT and implantable cardioverter defibrillator, and medical therapy). For the purpose of this meta-analysis, only the CRT and the medical therapy arms were included.

[b] In the CARE-HF trial,[17] patients with a QRS interval of 120 to 149 milliseconds were required to meet 2 of 3 additional echocardiographic criteria for dyssynchrony: (1) an aortic preejection delay of more than 140 milliseconds; (2) an interventricular mechanical delay of more than 40 milliseconds; and (3) delayed activation of the posterolateral left ventricular wall.

[c] The RAFT trial[22] also included 135 patients with baseline right ventricular pacing with a QRS interval of 200 milliseconds or greater, not included in this analysis.

the ORs from this trial with the HRs from the other trials to obtain a meta-analytic RR.[25]

Statistical heterogeneity was tested by the Cochran Q statistic and reported as I^2. Fixed-effect models were used, unless there was evidence of heterogeneity (ie, $I^2 > 40\%$) where random-effects models were used. The difference in the meta-analytic effect size in patients with severely vs moderately prolonged QRS intervals was assessed with heterogeneity analysis. A meta-regression analysis was performed to examine the relationship between the QRS duration (ranked according to the degree prolongation among all subgroups) and log-transformed RR. Statistical tests were considered significant if the 2-sided *P* value was less than .05. Data were analyzed using Comprehensive Meta Analysis software, version 2.2.048 (Biostat Inc, Englewood, New Jersey).

RESULTS

SEARCH RESULTS

The results of the literature search are shown in Figure 1. Of the 412 results, 70 reports without the exclusion criteria were then subjected to a detailed investigation looking for the parameters of interest (ie, reporting of clinical events according to specific baseline QRS ranges). Accordingly, a total of 5 randomized controlled trials enrolling a total of 5813 patients were included in the meta-analysis.

STUDY CHARACTERISTICS

The characteristics of the included trials are summarized in **Table 1**. The COMPANION[16] trial had 3 arms (medical therapy vs CRT only vs CRT-ICD). Data from the medical therapy vs CRT only arms are included in this analysis. In REVERSE,[23] all patients received a CRT device, but the left ventricular lead was turned off in the control arms. The control group patients did not receive a CRT device in COMPANION,[16] CARE-HF,[17] MADIT-CRT,[20] and RAFT.[22] The REVERSE[23] and RAFT[22] trials were double-blind trials, whereas the COMPANION,[16] CARE-HF,[17] and MADIT-CRT[20] trials were not blinded. However, all of the unblinded trials had blinded end points committees. The composite clinical end point reported in subgroup analyses according to different baseline QRS duration ranges always included all-cause mortality and heart failure hospitalization but varied across trials with respect to other included events, as indicated in Table 1. A total of 3624 patients were in the severely prolonged QRS group (62.3%), and 2189 were in the moderately prolonged QRS group (37.7%).

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Table 2. Characteristics of Patients Enrolled in Randomized Controlled Trials of CRT Included in the Meta-analysis[a]

Source	Patient Age, Mean or Median, y	Male	Nonischemic Heart Failure	Diabetes	Mean or Median Baseline EF, %	Conduction Anomaly		Mean or Median QRS Duration at Baseline, ms	Treatment at Baseline			ICD Device Implantation During Trials	
						LBBB	RBBB		ACE Inhibitor or Angiotensin Receptor Blocker	β-Blocker	Spironolactone	CRT Arm	Control Arm
COMPANION[16]	67	68	44	41	21	69	11	159	89	67	54	0[b]	0[b]
CARE-HF[17-27]	67	73	62	41	25	90	5	160	95	72	56	2.0	5.7
REVERSE[23]	63	79	46	23	27	NA	NA	153	96	95	NA	82	85
MADIT-CRT[20]	65	75	45	30	24	70	13	NA	98	93	32	99	97.4
RAFT[22]	66	83	33	34	23	72	9	158	97	90	42	99	99

Abbreviations: ACE, angiotensin-converting enzyme; CARE-HF, Cardiac Resynchronization-Heart Failure[17]; COMPANION indicates Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure[16]; CRT, cardiac resynchronization therapy; EF, ejection fraction; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy[20]; NA, not available; NYHA, New York Heart Association; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial[22]; RBBB, right bundle branch block; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction.[23]

[a] Unless otherwise indicated, data are reported as percentage of patients.

[b] While the COMPANION trial[16] did not allow ICDs in the CRT and medical therapy arms, information about off-protocol ICD use in these arms was not available.

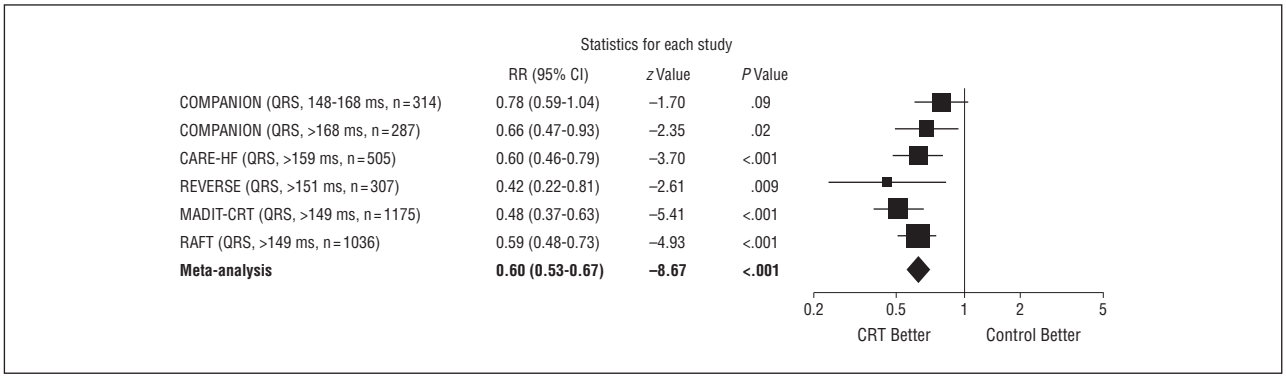

Figure 2. Effect of cardiac resynchronization therapy (CRT) on composite clinical events in patients with severely prolonged QRS interval (n=3624; I^2=32.1%, fixed-effect model). CARE-HF indicates Cardiac Resynchronization-Heart Failure[17]; CI, confidence interval; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure[16]; CRT, cardiac resynchronization therapy; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy[20]; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial[22]; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction[23]; RR, risk ratio.

All 5 trials were analyzed using intention-to-treat principle. In COMPANION,[16] prior to reaching the primary end point, 13% of patients in the medical therapy group withdrew, and 2% in the CRT group (without ICD) withdrew. In REVERSE,[23] 7.3% of patients crossed over from CRT off to CRT on, and 1.4% patients crossed over from CRT on to CRT off at 12 months. In MADIT-CRT,[20] 1% did not receive a device in the CRT-ICD arm, and 2.6% did not receive a device in the ICD only arm. In this trial, 12.4% of patients assigned to ICD only were switched to a CRT-ICD device before study end, whereas in the CRT arm, 7.5% of patients crossed over to ICD only. In RAFT,[22] 4% of patients crossed over and received CRT in addition to an ICD, and in the CRT-ICD group, 6.0% did not receive CRT. In this trial 0.6% and 1.1% either withdrew or were lost to follow-up in the ICD and CRT-ICD arms, respectively. Dropout or cross-over rates were not presented in the CARE-HF trial.

The baseline characteristics of patients enrolled in the trials are listed in **Table 2**. Within each arm of the included trials, there were no statistically significant differences with regard to age, sex, ejection fraction, functional class, QRS duration, or medication use.

No evidence of publication bias was detected with the Begg Rank Correlation method ($P>.50$). Funnel plots examining publication bias according to the QRS groups are presented in the eFigure.

QUANTITATIVE FINDINGS

The impact of CRT on clinical events in patients with severely prolonged QRS is shown in **Figure 2**. For these patients, there was a statistically significant reduction in risk for composite clinical events in each individual trial with the exception of the middle QRS subgroup of COMPANION[16] (ie, the subgroup with the least severely prolonged QRS among the subgroups with severely prolonged QRS), where there was a statistically insignificant benefit (P=.09). On meta-analysis, patients with severely prolonged QRS randomized to CRT had a 40% risk reduction in clinical events (I^2=32.1%; RR, 0.60[95% CI, 0.53-0.67]) ($P<.001$ by fixed-effect model). On the contrary, there was no statistically significant benefit for patients with moderately prolonged QRS in any of the individual trials

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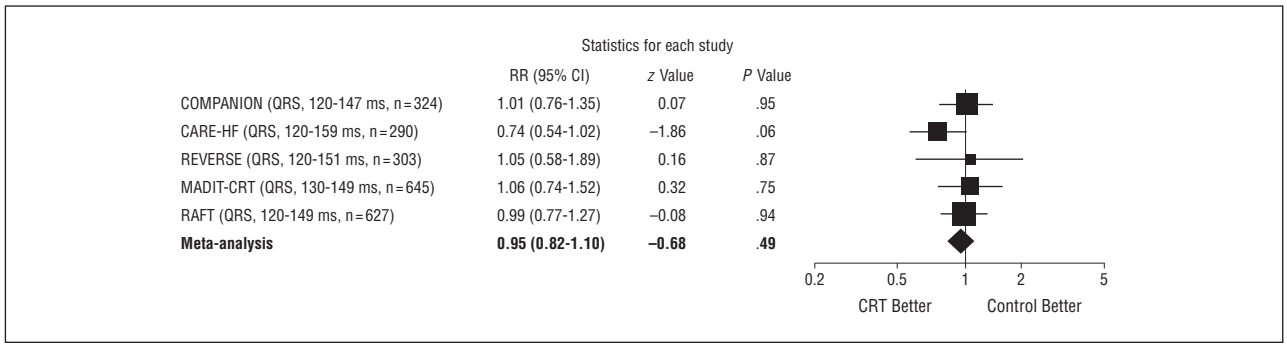

Figure 3. Effect of cardiac resynchronization therapy (CRT) on composite clinical events in patients with moderately prolonged QRS interval (n=2189; I^2=0%, fixed-effect model). CARE-HF indicates Cardiac Resynchronization-Heart Failure[17]; CI, confidence interval; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure[16]; CRT, cardiac resynchronization therapy; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy[20]; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial[22]; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction[23]; RR, risk ratio.

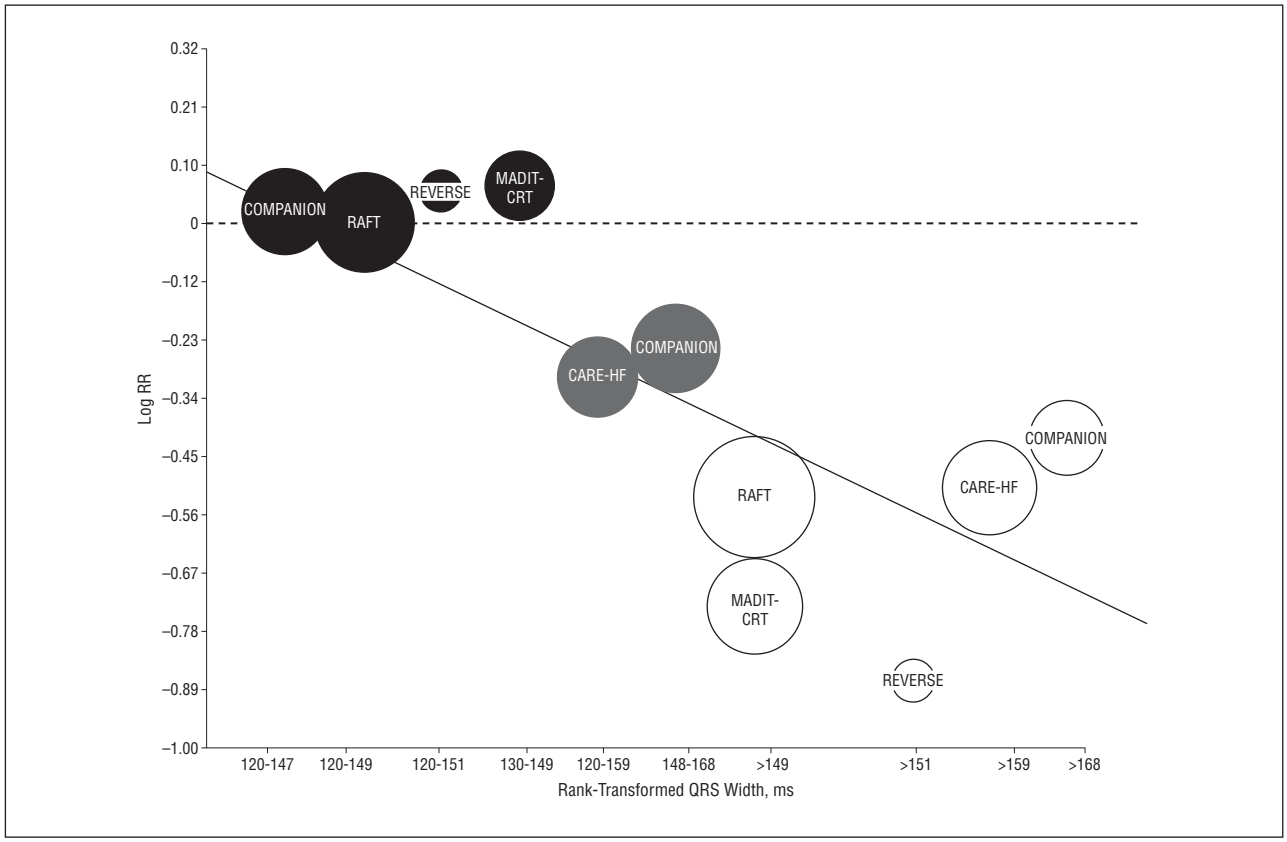

Figure 4. Meta-regression analysis examining the impact of baseline QRS duration on the effect of cardiac resynchronization therapy (CRT) on composite clinical events. Each circle represents a QRS subgroup within a trial. The sizes of the circles are proportional to the sample size in each subgroup. The dashed line corresponds to a log risk ratio (RR) of 0 (ie, RR, 1.00), where there is no net benefit or harm. The further the circles are below the 0 line, the larger the clinical benefit for prevention of composite of adverse clinical events. There was a statistically significant relationship between the QRS duration at baseline and log RR (slope, –0.07 [95% confidence interval, –0.10 to –0.04]; z=–4.60) ($P<.001$). Accordingly, groups with QRS ranges below 150 milliseconds did not benefit from CRT (black circles, log risk ratio close to 0). Clinical benefit appeared when cases with QRS intervals of 150 milliseconds or greater were included (gray circles) and became more prominent with increasing QRS width (white circles). CARE-HF indicates Cardiac Resynchronization-Heart Failure[17]; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure[16]; CRT, cardiac resynchronization therapy; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy[20]; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial[22]; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction.[23]

(**Figure 3**). There was a statistically insignificant benefit in the CARE-HF[17] trial, which had the most prolonged QRS interval within the moderately prolonged QRS subgroups (P=.06). On meta-analysis, there was no significant benefit of CRT for reduction in clinical events in this group of patients (I^2=0%; RR, 0.95 [95% CI, 0.82-1.10]) (P=.49 by fixed-effects model). When directly compared with heterogeneity analysis, the overall effect of CRT on clinical events was significantly different in patients with moderately vs severely prolonged QRS intervals ($P<.001$).

The relationship between the magnitude of QRS prolongation and the impact of CRT on the risk of composite clinical events assessed by meta-regression analysis is pre-

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Table 3. Sensitivity Analyses

Characteristic	I^2, %	Model	Risk Ratio (95% CI)	*P* Value	*P* Value, Moderately vs Severely Prolonged QRS Subgroups
NYHA 3 and 4 only					.06
Severely prolonged QRS (n=1106)	0	Fixed effect	0.67 (0.57-0.80)	<.001	
Moderately prolonged QRS (n=614)	50.6	Random effects	0.87 (0.64-1.18)	.38	
NYHA 1 and 2 only					<.001
Severely prolonged QRS (n=1482)	0	Fixed effect	0.47 (0.37-0.60)	<.001	
Moderately prolonged QRS (n=948)	0	Fixed effect	1.06 (0.78-1.44)	.72	
With background ICD					<.001
Severely prolonged QRS (n=2518)	0.2	Fixed effect	0.54 (0.46-0.63)	<.001	
Moderately prolonged QRS (n=1575)	0	Fixed effect	1.02 (0.84-1.23)	.87	
No Background ICD					.06
Severely prolonged QRS (n=1106)	0	Fixed effect	0.67 (0.57-0.80)	<.001	
Moderately prolonged QRS (n=614)	50.6	Random effects	0.87 (0.64-1.18)	.38	
One Study Out					
COMPANION[16]					<.001
Severely prolonged QRS (n=3023)	0	Fixed effect	0.55 (0.48-0.63)	<.001	
Moderately prolonged QRS (n=1865)	0	Fixed effect	0.93 (0.79-1.10)	.41	
CARE-HF[17]					<.001
Severely prolonged QRS (n=3119)	45.7	Random effects	0.60 (0.49-0.72)	<.001	
Moderately prolonged QRS (n=1899)	0	Fixed effect	1.01 (0.86-1.19)	.86	
REVERSE[23]					<.001
Severely prolonged QRS (n=3317)	35.6	Fixed effect	0.61 (0.52-0.71)	<.001	
Moderately prolonged QRS (n=1882)	0.1	Fixed effect	0.95 (0.82-1.10)	.46	
MADIT-CRT[20]					<.001
Severely prolonged QRS (n=2449)	4.3	Fixed effect	0.63 (0.55-0.72)	<.001	
Moderately prolonged QRS (n=1544)	0	Fixed effect	0.93 (0.80-1.09)	.38	
RAFT[22]					<.001
Severely prolonged QRS (n=2588)	45.6	Random effects	0.60 (0.49-0.73)	<.001	
Moderately prolonged QRS (n=1562)	0	Fixed effect	0.93 (0.78-1.11)	.44	

Abbreviations: CARE-HF, Cardiac Resynchronization-Heart Failure[17]; CI, confidence interval; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure[16]; ICD, implantable cardioverter defibrillator; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy[20]; NYHA, New York Heart Association; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial[22]; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction.[23]

sented in **Figure 4**. There was a statistically significant relationship between the QRS duration and log RR (slope, –0.07 [95% CI, –0.10 to –0.04; z=–4.60) ($P<.001$). Accordingly, groups with QRS durations less than 150 milliseconds did not benefit from CRT. Beneficial effects of CRT on reduction of clinical events became evident when cases with QRS intervals of 150 milliseconds or greater were included, and the magnitude of benefit became more prominent with further increases in QRS duration.

SENSITIVITY ANALYSIS

The findings of the meta-analysis remained robust to sensitivity analysis (**Table 3**). When the analysis was limited to NYHA 3 and 4 cases (COMPANION[16] and CARE-HF[17]), there was still a highly significant benefit of CRT in patients with severely prolonged QRS and no statistically significant benefit in patients with moderately prolonged QRS. The same was observed in NYHA 1 and 2 cases. Similarly, when the analysis was limited to trials with nearly universal use of ICDs in both arms of trials, statistically significant benefit with CRT was seen only in patients with severely prolonged QRS and not in those with moderately prolonged QRS. When the analysis was limited to trials without background ICD therapy, again the benefit of CRT was observed only in the patients with severely prolonged QRS. In each sensitivity analysis performed using the 1-study-out method, there remained a significant difference in the impact of CRT on clinical events according to degree of QRS prolongation. When analysis was limited to trials uniformly reporting HRs (ie, when REVERSE[23] was left out), there was again benefit in patients with severely prolonged QRS and not in patients with moderately prolonged QRS.

COMMENT

This meta-analysis shows that while CRT was very effective in reducing adverse clinical events in patients with systolic heart failure and a baseline QRS duration of 150 milliseconds or greater, it did not reduce such events in patients with a QRS interval less than 150 milliseconds. The difference in benefit between the 2 QRS groups was statistically significant ($P<.001$). These results were consistent among all the randomized trials included in this meta-analysis, regardless of enrollment criteria for functional class.

The lack of benefit of CRT in patients with QRS durations less then 150 milliseconds has been observed in several hemodynamic and echocardiographic studies, as well as in studies using cardiometabolic stress tests and quality of life measures. Auricchio et al[3] observed that

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when the QRS duration was less than 150 milliseconds, biventricular pacing did not improve either the maximum left ventricular pressure derivative or aortic pulse pressure, whereas those with longer QRS intervals had increases in both.[3] In a more recent randomized study, Auricchio et al[21] also showed that peak oxygen consumption as assessed by cardiometabolic stress test did not improve with left ventricular pacing in patients with a QRS duration between 120 and 150 milliseconds. In contrast, both parameters improved significantly in patients with QRS intervals greater than 150 milliseconds. Similarly, distance walked in 6 minutes and quality-of-life score improved only in patients with QRS intervals greater than 150 milliseconds. REVERSE study investigators[26] showed that there was no significant reverse remodeling with CRT in patients with moderately prolonged QRS, contrasting with the remarkable reverse remodeling in those with longer QRS durations. Our meta-analysis extends these previous observations of lack of benefit on surrogate measures in patients with QRS interval less than 150 milliseconds to the lack of reduction in clinical events, including death and hospitalizations in such patients, in the setting of randomized controlled clinical trials. On the other hand, it was observed that there was a trend for benefit in the moderately prolonged QRS subgroup (ie, 120-159 milliseconds) in the CARE-HF trial.[17] In this context, it should be pointed out that CARE-HF mandated the presence of at least 2 predefined echocardiographic criteria for mechanical dyssynchrony if baseline QRS was between 120 and 149 milliseconds, unlike the other included trials. Of the 290 patients with QRS intervals between 120 and 159 milliseconds in this trial, only 92 of them had a QRS between 120 and 149 (32%), and the remaining 198 had a QRS of 150 milliseconds or greater (68%).[27] Therefore, it is not completely clear whether this trend for benefit was driven by the patients with QRS durations between 150 and 159 milliseconds or by the use of echocardiographic criteria in patients with QRS between 120 and 149 milliseconds or both. One recent nonrandomized study[28] suggests that echocardiographic parameters of dyssynchrony (Yu index, radial strain) may help identify patients with moderately prolonged QRS who might respond to CRT.

The initial guidelines advising on the indication for CRT in heart failure were primarily directed by the two trials that reported significant reductions in clinical events in NYHA III and IV patients.[7-10] These two trials used a QRS duration of >120 milliseconds as the enrollment criterion. The writing committees subsequently endorsed the same cutoff of ≥120 milliseconds in their guidelines with the strongest level of recommendation (ie, Class I: procedure should be performed).[16,17] However this cutoff set forth in these trials appears to be arbitrary in that other clinical trials have used different QRS cutoffs such as 130 or 150 milliseconds.[29-31] In contemporary practice, approximately 40% of CRT devices are implanted in patients with a QRS duration <150 milliseconds.[32]

Soon after CRT was approved as a treatment for heart failure, it was recognized that one-third to one-half of patients do not respond to these devices implanted according to the current indications.[14,15] This has led to intense research examining the reasons for non-response and led to the creation of special "non-responder clinics" in some institutions.[33] Predicting response to CRT is complex and is related to both substrate and procedural factors. Sweeney, et al. recently demonstrated that the probability of LV reverse remodeling is linearly related to baseline left ventricular activation time and is <50% with a left ventricular activation time <90 milliseconds (corresponding to a QRS duration of approximately <150 milliseconds according to their regression formula).[34] The current meta-analysis of randomized controlled clinical trials that assessed clinical endpoints, along with the previous studies using surrogate outcomes, suggest that a predominant reason for CRT non-response is a suboptimal patient selection criterion for QRS duration.

Very recently treatment guidelines advising on CRT were updated primarily to incorporate the findings of the MADIT-CRT trial and extended the indication for CRT to NYHA I and/or II patients.[18,19] For these patients a new QRS cutoff of ≥150 milliseconds was advised given the subgroup analysis of the MADIT-CRT trial showing lack of benefit with a QRS<150 milliseconds. However, these guidelines continued to recommend a QRS cutoff of 120 milliseconds for NYHA III and IV patients. Our meta-analysis shows that the lack of benefit in patients with QRS<150 milliseconds is a more pervasive phenomenon and is not limited to only NYHA I and II patients but is also observed in NYHA III and IV patients. It appears that the degree of QRS prolongation is more important than the level of functional impairment for selection of patients for CRT. Modification of the current guidelines that reflect these findings can have important consequences for resource utilization. We think that an individual patient level analysis of existing clinical trials to examine whether a subset of patients with moderately prolonged QRS might benefit from CRT (perhaps offset by another subset with increased risk resulting in a net neutral effect in the moderately prolonged QRS group) will be helpful to further specify the new recommendations.

STUDY LIMITATIONS

Not all randomized CRT trials reported clinical events according to different QRS subgroups, and these trials could not be included in this meta-analysis. However, all the long-term and large-scale trials could be included. For example, the meta-analysis could incorporate QRS-specific data for more than 85% of the total number of deaths recorded in all the randomized CRT trials reporting on this outcome.[35] Therefore, publication bias with regard to reporting according to QRS ranges is highly unlikely to account for the observed differences.

The composite outcome varied across the included trials. However, despite the differences in the inclusion of other events besides all-cause mortality and heart failure hospitalization to the composite outcome, the RR was always lower in the severely prolonged QRS group of all the trials, and there was no statistically significant reduction in any of the composite outcomes in the moderately prolonged QRS subgroup of any trial.

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The exactitude of the 150-millisecond cutoff observed in the current analysis for predicting clinical benefit with CRT is likely to be imperfect for the individual patient. Because we did not have access to individual-level patient data, we used the ranges of QRS durations reported in the publications of clinical trials to determine a cutoff. With this approach, an approximate value of 150 milliseconds emerged as a cutoff, below which clinical events were not reduced by CRT. In this context, Varma[36] has recently shown that despite similar QRS durations, patients with left bundle branch block have left ventricular activation times that are on average 36 milliseconds longer than patients with right bundle branch block. Consequently, the QRS duration above which CRT will be beneficial is probably significantly different with different types of conduction abnormalities. Therefore, we believe that a meta-analysis of individual patient-level data of all relevant clinical trials can further refine the QRS cutoffs for different types of conduction abnormalities.

When performing this meta-analysis, we were faced with the problem of dealing with 2 different types of association measures (ie, HR and OR) reported in different trials. We believed that including only the 4 trials that reported HRs and excluding REVERSE[23] reporting ORs would introduce bias and would be less robust. Given the similarities of the 2 measures in many situations, we combined these measures and reported the meta-analytic effect size as RR. We addressed this limitation using sensitivity analysis (where we excluded REVERSE[23]), which revealed very similar results. It is noteworthy that the REVERSE trial also had a broad clinical end point, not only including mortality and heart failure hospitalization but also worsened heart failure symptoms or NYHA functional class.

CONCLUSIONS

While CRT was very effective in reducing clinical events in patients with systolic heart failure and a baseline QRS duration of 150 milliseconds or greater, it did not reduce such events in patients with QRS intervals less than 150 milliseconds. This finding was observed not only in trials that enrolled patients with NYHA 1 and 2 disease but also in those that enrolled patients with NYHA 3 and 4 disease. These results have implications regarding patient selection for this important treatment technique.

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Authors Contributions: Dr Sipahi had full access to all the data used in the study and takes responsibility for the integrity of the data and accuracy of the analysis. *Study concept and design:* Sipahi and Carrigan. *Acquisition of data:* Sipahi and Carrigan. *Analysis and interpretation of data:* Sipahi, Carrigan, Rowland, Stambler, and Fang. *Drafting of the manuscript:* Sipahi, Carrigan, and Rowland. *Critical revision of the manuscript for important intellectual content:* Sipahi, Carrigan, Rowland, Stambler, and Fang. *Statistical analysis:* Sipahi and Rowland. *Administrative, technical, and material support:* Sipahi and Fang. *Study supervision:* Sipahi and Fang.
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EDITOR'S NOTE

ONLINE FIRST

CRT—Less Is More

Cardiac resynchronization therapy has been a great advance in the treatment of selected patients with congestive heart failure and prolonged QRS interval. However, about one-third to one-half of patients who have a CRT device implanted do not respond. Since all patients with implants incur risk from this procedure, it is important to select those who will benefit from these invasive, high-risk devices, so that the benefits outweigh the risks. Sipahi et al find that patients with a QRS interval shorter than 150 milliseconds do not benefit from CRT, yet patients with QRS in the 120- to 150-millisecond range are currently receiving CRT. This study received our "Less Is More" designation because it identifies patients who do not derive clinical benefit from this invasive, high-risk device.

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Disclaimer: The views expressed herein are those of the author only and are not to be construed as those of the Department of the Army or Department of Defense.
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Correction

Typographical Error in Abstract. In the "Background" section of the abstract of the Original Investigation "Impact of QRS Duration on Clinical Event Reduction With Cardiac Resynchronization Therapy: Meta-analysis of Randomized Controlled Trials" by Sipahi et al, published in the September 12, 2011, issue of the *Archives* (2011;171[16]:1454-1462) and published online June 13, 2011, the reported range for moderately prolonged QRS duration was incorrect. The correct range is 120 to 149 milliseconds.

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