

REVIEW TOPIC OF THE WEEK

QRS Duration or QRS Morphology

What Really Matters in Cardiac Resynchronization Therapy?



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ABSTRACT

The beneficial effects of cardiac resynchronization therapy (CRT) have been well established in large, randomized trials. Despite the documented success of this treatment strategy, a significant proportion of patients with heart failure do not achieve the desired response. The aim of this review was to delineate factors contributing to a successful CRT response, emphasizing the interrelated roles of QRS morphology and QRS interval duration. More data are available on QRS duration, as this factor has been used as an enrollment criterion in clinical trials. Response to CRT seems to increase as the QRS duration becomes longer, with greatest benefit in QRS duration ≥ 150 ms. Recent data have placed more emphasis on QRS morphology, demonstrating variability in clinical response between patients with left bundle branch block, non-left bundle branch block, and right bundle branch block morphology. Notably, myocardial scarring and cardiac dimensions, among other variables, may alter heterogeneity in ventricular activation. Understanding the electrophysiological underpinnings of the QRS complex has become important not only to predict response but also to facilitate the patient-specific delivery of resynchronization therapy. (J Am Coll Cardiol 2016;67:1104-17)
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Cardiac resynchronization therapy (CRT) has effectively had an impact on the natural trajectory of symptomatic heart failure (HF) in patients with coexisting conduction tissue disease. CRT brings its physiological impact to bear through synchronizing cardiac contraction, resulting in favorable ventricular remodeling and improvement in ejection fraction (EF). Prospective randomized studies of patients with both ischemic and nonischemic causes of HF have shown that this effect of CRT translates into long-term clinical benefits, such as improved quality of life, increased functional capacity, reduction in hospitalization for HF, and overall mortality (1-11). Despite the success of this therapeutic modality, a significant proportion of patients may

not respond sufficiently or in a predictable way to this pacing therapy. There are several determinants of successful response to CRT; QRS duration and QRS morphology are of considerable importance in this response.

Although surface electrocardiographic (ECG) evidence of electrical dyssynchrony due to the presence of an intraventricular conduction delay (IVCD) serves as a surrogate for ventricular mechanical dyssynchrony, its precision in predicting response may be limited by the complexity of electrical and mechanical dyssynchrony in the diseased heart. Dyssynchrony can exist at numerous levels within the heart: within the atria; between the atrium and ventricles; and at different levels within the ventricles (i.e., at the

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interventricular, intraventricular, and intramural levels) (12,13). These factors may operate to greater or lesser degrees in an individual patient, such that a simple approach based on the ECG markers (QRS morphology and QRS duration) may not adequately represent the conduction patterns within any single heart. Nevertheless, these ECG surrogates of electromechanical dyssynchrony are the clinical tools on which we rely to help select patients for CRT. This review focuses on dyssynchrony within the ventricle, the electrical conduction abnormalities that underlie mechanical dyssynchrony, and the clinical trial data defining appropriate patient selection for CRT.

MECHANICS OF ELECTRICAL ACTIVATION

As discussed in detail later, there is a large amount of data confirming the variability in the clinical response between patients with left bundle branch block (LBBB) and non-LBBB morphology. Much of this response is driven not only by the altered electrical activation of the left ventricle but by the current lack of individualized pacing approaches within these variable substrates. Mechanical dyssynchrony due to pure conduction block in the right or left bundles is the easiest to appreciate. Typically, an LBBB is linked with a U-shaped activation pattern that courses through the apex, with delayed activation of the lateral and posterolateral portions of the left ventricle. This spread of electrical activity parallels the mechanical activation and constitutes the basic reasoning behind the conventional left ventricular (LV) lead implantation strategy of targeting the lateral wall.

However, even in a pure LBBB, a high level of heterogeneity remains in the LV activation pattern, accompanied by a wide variance in the line of functional block. Some of this may be linked to the axis of activation, but it can be affected by other underlying characteristics, such as myocardial scarring and cardiac dimensions. Another important factor is that as the QRS duration increases, the band of electrical and mechanical dyssynchrony widens, such that some patients may respond to CRT, even with nonconventional pacing lead locations (14). Patients with HF and impaired left ventricular ejection fraction (LVEF) are complex and may manifest variable degrees of mechanical dyssynchrony due to scarring from infarction/ischemia or primary myocardial disease, even in the situation of an LBBB. Some have suggested that unless a “true” LBBB is present, patients are unlikely to respond to CRT. For instance, Strauss et al. (15) suggested revised ECG criteria for determining if a true LBBB can be confirmed. Risum et al. (16) used echocardiographic longitudinal strain

methods to determine if LV late activation was present in 234 patients with an LBBB ECG pattern. These investigators found that only two-thirds of the patients, those with both an ECG LBBB pattern and late LV activation, were CRT responders.

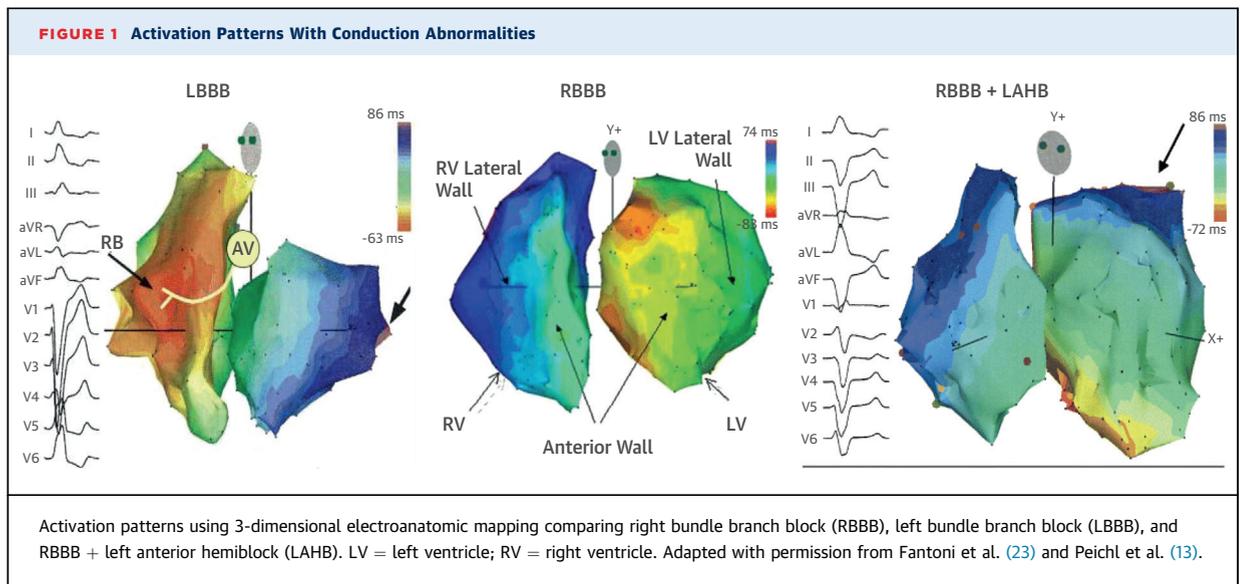
As will be discussed later, patients with non-LBBB morphology generally have responded poorly to CRT, perhaps driven by the abnormal and variable electrical activation pattern of their left ventricle. Some patients with non-LBBB may not manifest mechanical dyssynchrony at all; some do, but late activation does not occur at the lateral LV wall, where LV leads are generally targeted. Non-LBBB has included an examination of nonspecific IVCD patient subsets, who consistently demonstrate outcomes inferior to LBBB patients and to those with a right bundle branch block (RBBB), who generally fare even worse (17-22). Examination of the activation sequence in non-LBBB conduction lends further understanding to the physiology behind CRT response (Figure 1). As shown in the example, the segment of the heart with the most delayed activation can be markedly different in patients with a non-LBBB morphology compared with those with an LBBB (13,23). In the situation of an RBBB, there is delayed right ventricular activation, with relatively early LV activation.

The patterns of activation in the myopathic heart can affect patients manifesting an RBBB pattern. Electroanatomic mapping of such patients has found significant LV conduction delay (especially in very prolonged QRS duration), albeit with wide variability in the degree of mechanical dyssynchrony. There is evidence that in some patients, the presence of an RBBB ECG pattern may mask a coexistent LBBB as an explanation for this finding. This situation may be recognized by the concomitant presence of broad, slurred, and occasionally notched R waves in leads I and aVL, along with left-axis deviation (23-27). Several other proposed explanations for a worse outcome in patients with RBBB include: 1) ventricular dyssynchrony patterns, which are simply not favorable for CRT; 2) concomitant right ventricular dysfunction; and 3) more extensive conduction disease (28).

As will be discussed further, QRS morphology is simply 1 determinant of CRT response. Although areas of delayed activation result in mechanical dyssynchrony, the duration of activation delay also seems to be a critical component.

ABBREVIATIONS AND ACRONYMS

- CRT** = cardiac resynchronization therapy
- CRT-D** = cardiac resynchronization therapy combined with a defibrillator
- CRT-P** = cardiac resynchronization therapy combined with a pacemaker
- ECG** = electrocardiographic
- EF** = ejection fraction
- HF** = heart failure
- ICD** = implantable cardioverter-defibrillator
- IVCD** = intraventricular conduction delay
- LBBB** = left bundle branch block
- LV** = ventricular
- LVEF** = left ventricular ejection fraction
- NYHA** = New York Heart Association
- OR** = odds ratio
- RBBB** = right bundle branch block



THE RANDOMIZED CONTROLLED TRIALS OF CRT

QRS DURATION. QRS duration historically was the primary surrogate for mechanical dyssynchrony determining enrollment into the randomized controlled trials of CRT. Thus, the strength of evidence for or against CRT has primarily rested on QRS duration. A summary of the trials' QRS duration enrollment criteria and percentage of patients enrolled with LBBB morphology (if known) is shown in [Table 1](#).

Whereas the required minimum enrollment QRS interval varied between 120 and 200 ms in these trials, the median QRS duration centered around 150 ms (1-11). Most of the more recent and larger trials reported on the interaction of QRS duration and the primary endpoint ([Table 2](#)). This finding was true in the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) study, which enrolled 1,520 patients with a QRS duration ≥ 120 ms, LVEF $\leq 35\%$, and New York Heart Association (NYHA) functional class III and IV HF symptoms to receive either cardiac resynchronization therapy combined with a defibrillator (CRT-D), cardiac resynchronization therapy combined with a pacemaker (CRT-P) but without a defibrillator, or background optimal HF pharmacological therapy alone (3). The interaction of the primary endpoint of death or all-cause hospitalization with QRS duration at intervals ≤ 147 ms, 148 to 168 ms, and >168 ms was examined. CRT-D was better than optimal HF pharmacological therapy at all QRS durations,

although the effect was greater with increasing QRS duration. CRT-P benefited those with QRS duration ≥ 150 ms. Boehmer et al. (29) reported further on the COMPANION trial, using the QRS duration cutpoints <150 ms and ≥ 150 ms. For the combined CRT-P and CRT-D patients compared with patients receiving optimal HF pharmacological therapy alone, benefit for the primary endpoint was only observed for those with a QRS duration ≥ 150 ms.

The CARE-HF (Cardiac Resynchronization-Heart Failure) study randomized 813 patients with a QRS duration ≥ 120 ms, LVEF $\leq 35\%$, and NYHA functional class III and IV HF to receive CRT-P or optimal HF pharmacological therapy (no CRT-D arm) (2). The primary outcome of mortality plus unplanned cardiovascular hospitalization according to interaction with QRS duration was reported for QRS intervals above or below 160 ms. CRT therapy was better than pharmacological therapy alone at all QRS durations, although the benefit was greater in those with a QRS duration ≥ 160 ms. A unique feature of CARE-HF was to require documentation of echocardiographic dyssynchrony for the patients enrolled with a QRS duration between 120 and 149 ms.

REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction), MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy), and RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial) predominantly enrolled patients with NYHA functional class II (9-11). All 3 trials reported the interaction of CRT benefit on their respective primary composite endpoints with QRS

TABLE 1 Randomized Trials of CRT in Prolonged QRS Duration

Trial (Ref. #)	n	Study Design	Enrollment QRS Duration, ms	Enrollment NYHA Functional Class/Etiology of HF	Enrollment LVEF, %	SR/AF Included?	% LBBB	Primary Endpoint
MUSTIC-SR (5)	58	Single-blinded, crossover CRT pacing on or off	≥150	III Ischemic and nonischemic	≤35	SR	87	6-min walk distance
MUSTIC AF (5)	43	Single-blinded crossover CRT pacing on or VVI pacing	≥200	III Ischemic and nonischemic	≤35	AF	NA*	6-min walk distance
MIRACLE (1)	453	Double-blinded, parallel control CRT pacing on or off	≥130	III, IV Ischemic and nonischemic	≤35	SR	NR	NYHA, QOL, 6-min walk distance
PATH CHF (4)	42	Single-blinded, crossover CRT pacing on or off	≥1,520	III, IV Ischemic and nonischemic (epicardial LV leads)	NA	SR	97	Peak VO ₂ on CPET 6-min walk distance
MIRACLE ICD (6)	369	Double-blinded, parallel control CRT-D with CRT pacing on or off	≥130	III, IV Ischemic and nonischemic	≤35	SR	LBBB/IVCD = 94	NYHA, QOL, 6-min walk distance
CONTAK CD (8)	490	Single-blinded Phase I: crossover CRT-D with CRT pacing on or off Phase II: parallel control	≥120	II, III, IV Ischemic and nonischemic	≤35	SR	46	NYHA, QOL, 6-min walk distance
MIRACLE ICD II (7)	186	Double-blinded, parallel control CRT-D with CRT pacing on or off	≥130	II Ischemic and nonischemic	≤35	SR	LBBB/IVCD = 83.4	Peak VO ₂ on CPET
COMPANION (3)	1520	Randomized CRT-D vs. OPT or CRT-D vs. OPT	≥120	III, IV Ischemic and nonischemic	≤35	SR	86	All-cause mortality or hospitalization
CARE-HF (2)	813	Randomized CRT-P vs. medical therapy	≥120	III, IV Ischemic and nonischemic	≤35	SR	95	All-cause mortality or unplanned cardiovascular hospitalization
REVERSE (9)	610	Single-blinded, parallel control CRT-D with CRT pacing on or off	≥120	I, II Ischemic and nonischemic	≤40	SR	60.5	Clinical composite score improvement
MADIT-CRT (10)	1,820	Randomized CRT-D vs. ICD (single or dual)	≥130	I, II Ischemic and nonischemic	≤30	SR	70.5	All-cause mortality or nonfatal HF event
RAFT (11)	1,798	Double-blinded, randomized CRT-D vs. ICD (single or dual)	≥120	II, III Ischemic and nonischemic	≤30	SR/AF/paced	72	All-cause mortality or HF hospitalization

*Patients were paced.

AF = atrial fibrillation; CARE-HF = Cardiac Resynchronization-Heart Failure; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CPET = cardiopulmonary exercise test; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy combined with a defibrillator; CRT-P = cardiac resynchronization therapy combined with a pacemaker; HF = heart failure; ICD = implantable cardioverter-defibrillator; IVCD = intraventricular conduction delay; LBBB = left bundle branch block; LV = left ventricular; LVEF = left ventricular ejection fraction; MADIT-CRT = Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE ICD = Multicenter InSync ICD Randomized Clinical Evaluation; MIRACLE ICD II = Multicenter InSync ICD Randomized Clinical Evaluation II; MUSTIC = Multisite Stimulation in Cardiomyopathy; NA = not applicable; NR = not recorded; NYHA = New York Heart Association; OPT = optimal pharmacological therapy; PATH-CHF = Pacing Therapies for Congestive Heart Failure; QOL = quality of life; RAFT = Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; REVERSE = Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction; SR = sinus rhythm; VF = ventricular fibrillation; VO₂ = maximal oxygen consumption.

duration. MADIT-CRT, enrolling 1,820 patients with NYHA functional class I or II HF, EF <30%, and QRS duration ≥130 ms, found that the benefit of CRT-D compared with an implantable cardioverter-defibrillator (ICD) alone on the primary endpoint of death or nonfatal HF event was confined to those with QRS duration ≥150 ms (10). When multiple QRS cut-points were considered, male patients who received CRT-D benefited only when the QRS duration was at least 160 ms, although female patients benefited from CRT therapy across all QRS durations <180 ms (17). A long-term follow-up analysis of the MADIT-CRT population showed that among the 1,281 patients with just LBBB QRS morphology, CRT-D compared

with ICD alone was associated with improved all-cause survival, regardless of QRS duration (21).

The REVERSE trial enrolled 610 patients with NYHA functional class I or II HF, EF ≤40%, and a QRS duration ≥120 ms, to receive CRT, either combined with a defibrillator or not, according to clinical indications (9). The randomization was to active CRT or not (i.e., ON vs. OFF function) for 12 months of follow-up, with a primary endpoint defined as a clinical composite score. In REVERSE, remodeling (as measured by change in LV index volume at 12 months) progressively improved with wider QRS duration when cutpoints of <134 ms, 134 to 152 ms, 152 to 167 ms, and 168 to 219 ms were examined (18).

TABLE 2 Effect of QRS Duration and CRT Response

Trial (Ref. #)	QRS, ms	HR, OR, or Interaction With Endpoint	95% CI	p Value	Primary Endpoint	
COMPANION CRT-P (3)	≤147 148-169 >168	No benefit CRT-P Favors CRT-P Favors CRT-P			Death or all-cause hospitalization	
COMPANION CRT-D (3)	≤147 148-169 >168	Favors CRT-D Favors CRT-D Favors CRT-D	NR	NR	Death or all-cause hospitalization	
COMPANION CRT-P (29)	<150 ≥150	0.91 0.70	0.58-1.44 0.48-1.00	0.697 0.053	All-cause mortality	
COMPANION CRT-D (29)	<150 ≥150	0.82 0.61	0.50-1.34 0.42-0.88	0.42 ≤0.01	All-cause mortality	
COMPANION CRT-P + CRT-D (29)	<150 ≥150	0.87 0.52	0.63-1.21 0.39-0.68	0.413 <0.01	All-cause mortality + HF hospitalization	
CARE-HF (2)	<160 ≥160	0.74 0.60	0.54-1.02 0.46-0.79	NR NR	Death or unplanned cardiovascular hospitalization	
MADIT-CRT (17) Men	<140 140-159 160-179 >180	1.69 0.77 0.51 0.50	0.97-2.95 0.52-1.12 0.33-0.79 0.28-0.89	0.63 0.164 0.003 0.19	Death or nonfatal HF event	
MADIT-CRT (17) Women	<140 140-159 160-179 >180	0.20 0.31 0.42 0.33	0.60-0.66 0.51-0.63 0.19-0.94 0.09-1.23	0.008 0.001 0.036 0.100	Death or nonfatal HF event	
MADIT-CRT long-term analysis LBBB patients only (21) (N = 1,281)	<150 ≥150	0.55 (0.31-0.97) 0.65 (0.46-0.90)	NR NR	0.04 0.01	All-cause mortality	
REVERSE (18)	QRS continuous variable 120-151 >151	(OR) 0.831 For each 10-ms interval ≥120ms 1.05 0.42			0.0001 0.87 0.009	Clinical composite score
RAFT (11)	120-149 ≥150 Paced ≥200	0.99 0.59 1.07	0.77-1.27 0.48-0.73 0.63-1.84	0.94 <0.001 0.03	Death or HF hospitalization	

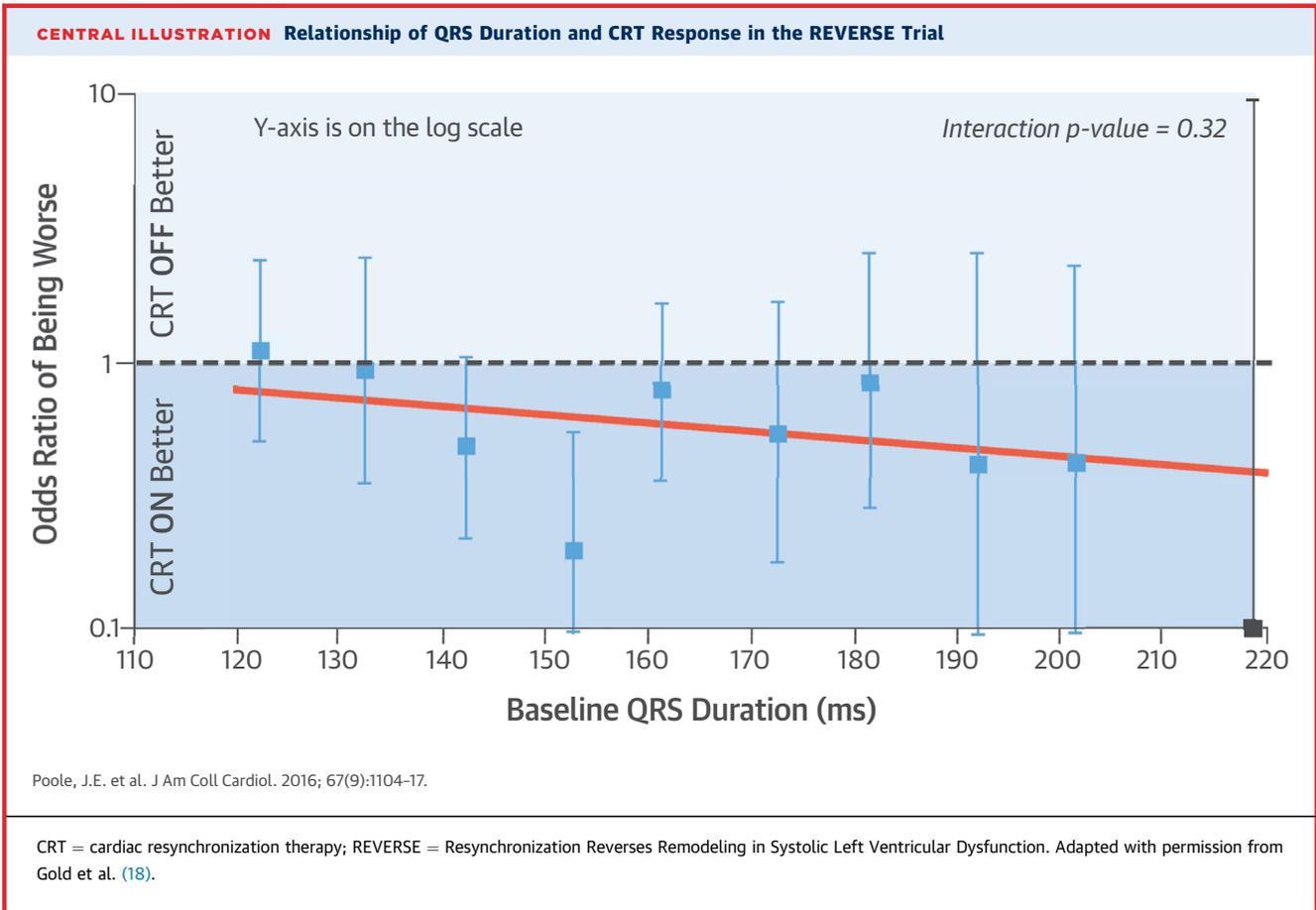
CI = confidence interval; HR = hazard ratio; NR = not recorded; OR = odds ratio; other abbreviations as in Table 1.

Gold et al. (18) further demonstrated a progressive increase in CRT benefit on the primary clinical composite score outcome when QRS duration >120 ms was considered as a continuous variable (odds ratio [OR] 0.831 for each 10-ms increase in the QRS interval; $p < 0.0001$) (Central Illustration). Importantly, at <120 ms, CRT benefit could not be observed.

The RAFT trial enrolled 1,798 patients with NYHA functional class II or III HF, EF ≤30%, and QRS duration ≥120 ms to receive CRT-D or ICD alone, with a primary endpoint of death from any cause or hospitalization for HF (11). A significant interaction between CRT and QRS duration was observed ($p = 0.003$), with CRT benefit observed only in the patients with a QRS duration ≥150 ms compared with patients with a QRS duration <150 ms or with a paced QRS duration ≥200 ms. Several meta-analyses of

these pivotal CRT trials add additional support to the observation that QRS duration is an important factor in determining CRT response and a useful surrogate for electromechanical dyssynchrony (30,31).

However, mechanical dyssynchrony is not the sole determinant of response to CRT. If it were, the duration of QRS would not matter. Four randomized controlled trials specifically examined the question of narrow QRS durations (<120/130 ms) but with echocardiographic evidence of mechanical dyssynchrony (Table 3). Three of these studies showed no benefit of CRT-D compared with the control arms for their primary endpoints (all patients underwent implantation with a CRT device, with randomization to the active CRT function ON versus CRT function OFF) (32-35). Because of futility and safety concerns, the LESSER-EARTH (Evaluation of



Resynchronization Therapy for Heart Failure) trial was terminated after only 85 patients underwent implantation with a CRT-D (32). EchoCRT (Echocardiography Guided Cardiac Resynchronization Therapy), also stopped early for futility, demonstrated a nonsignificant trend toward harm in NYHA functional class III/IV patients with EF <35% and QRS

duration <130 ms who received a CRT-D (33). The RethinQ (Resynchronization Therapy in Normal QRS) study investigators noted an improvement in NYHA functional class and maximal oxygen consumption among the 27% of patients with a QRS interval of 120 to 130 ms versus those with a QRS duration <120 ms. Overall, however, there was no benefit of

TABLE 3 Randomized Trials of CRT in Narrow QRS Duration

Trial (Ref. #)	n	Study Design	Enrollment QRS Duration, ms	Enrollment NYHA Functional Class/HF Etiology	Enrollment LVEF, %	SR/AF Included?	Primary Endpoint
RethinQ (34)	172	Parallel control CRT-D with CRT pacing on or off	<130	NYHA III Ischemic and nonischemic	≤35	SR	Peak VO ₂ on CPET
NARROW CRT (35)	120	CRT-D vs. DDD-ICD	<120	II/III Ischemic only	≤35	SR	HF clinical composite response
EchoCRT (33)	809	Parallel control CRT-D with CRT pacing on or off	<130	III/IV Ischemic and nonischemic	≤35	SR	All-cause or first hospitalization for worsening HF
LESSER EARTH (32)	85	Parallel control CRT-D with CRT pacing on or off	<120	Symptoms of HF and a 6-min walk ≤400 m Ischemic and nonischemic	≤35	SR	Exercise capacity and LV reverse remodeling

DDD-ICD = dual-chamber implantable cardioverter-defibrillator; EchoCRT = Echocardiography Guided Cardiac Resynchronization Therapy; LESSER-EARTH = Evaluation of Resynchronization Therapy for Heart Failure; NARROW CRT = Narrow QRS Ischemic Patients Treated With Cardiac Resynchronization Therapy; RethinQ = Resynchronization Therapy in Normal QRS; other abbreviations as in Table 1.

CRT for the primary endpoint of an increase in peak oxygen consumption >1.0 ml/kg during cardiopulmonary exercise testing at 6 months (34).

In contrast, results of the NARROW CRT (Narrow QRS Ischemic Patients Treated With Cardiac Resynchronization Therapy) trial suggest that some patients may benefit from CRT, despite a narrow QRS interval. NARROW CRT enrolled 120 patients with echocardiographic dyssynchrony who were randomized to receive CRT or a dual-chamber ICD (35). CRT was associated with an improvement in the primary endpoint, which was a HF clinical composite response at 1 year ($p = 0.004$). With a longer follow-up of 16 months, CRT was associated with improved survival from the combined endpoint of HF hospitalization, HF death, and spontaneous ventricular fibrillation ($p = 0.028$).

Collectively, the clinical trial results support QRS duration as a critical, but not the sole, indicator of CRT response. Differences in the outcomes between the trials likely reflect varying endpoints and follow-up times, as well as differences in the patient populations studied.

Another interesting aspect of CRT pacing is that the extent of narrowing of the QRS duration after CRT does not always forecast outcome from CRT. This finding conceivably relates to the fact that a paced QRS complex is the summated signal of right ventricular endocardial and LV epicardial pacing. Furthermore, in several comparative studies, LV-only pacing seems to be as effective as biventricular pacing. Although biventricular pacing often results in a much narrower paced QRS complex than the native QRS complex, LV-only pacing would not decrease QRS duration (36-38). Thus, although the QRS duration provides us with an immediate practical tool, it lacks the finesse to uniformly predict response and enable individualization of the delivery of CRT.

QRS MORPHOLOGY. Although QRS morphology was not the basis on which patients were enrolled in the randomized controlled CRT trials, important observations have nevertheless emerged from post hoc analyses. Patients with LBBB morphology have demonstrated the best response to CRT, whereas those with non-LBBB morphology generally have responded poorly. The majority of patients enrolled in the clinical trials have had an LBBB or nonspecific IVCD, leaving few patients with an RBBB available to draw any conclusion regarding CRT benefit (Table 1). Given that limitation, however, the data that are available are consistent: patients with an RBBB have demonstrated little or no benefit from CRT therapy. These observations have led to a specific emphasis on

QRS morphology, as well as QRS duration, in the updated U.S. and European medical practice guidelines for use of CRT (39,40).

In 2 of the earliest studies reporting on the effect of QRS morphology, MIRACLE (Multicenter InSync Randomized Clinical Evaluation) and CONTAK CD, patients with an RBBB received benefit on some, but not all, outcome measures (1,8). Although the 61 patients with an RBBB showed 6-month improvements in NYHA functional class, 6-min walk distances, and quality of life, LVEF did not improve. Importantly, control patients also improved their NYHA functional class, suggesting a potent placebo effect (19).

In the COMPANION study, patients randomized to receive CRT (CRT-P or CRT-D) had improved outcomes compared with those treated only with optimal pharmacological therapy, regardless of QRS morphology. However, the non-LBBB patients seemed to benefit to a lesser degree (3). In a post hoc analysis of CARE-HF, baseline RBBB and prolonged corrected JT interval (in addition to higher NYHA functional HF class and longer PR and QRS intervals) were predictors of all-cause mortality and hospitalization (20). Only 4.3% of CARE-HF patients had an RBBB. Similarly, Nery et al. (41) identified a total of 259 patients with RBBB in a meta-analysis of 5 trials (MIRACLE, CONTAK CD, CARE-HF, RAFT, and MADIT-CRT). CRT was not associated with benefit in the patients with RBBB.

Data from the recent trials of patients with predominantly NYHA functional class II (REVERSE, MADIT-CRT, and RAFT) demonstrated reduced or absent CRT benefit in those described as having non-LBBB, IVCD, or RBBB QRS morphologies (Table 4) (9-11). For example, whereas REVERSE reported a significant benefit of CRT on the primary clinical composite score outcome for patients with an LBBB (OR: 0.53; $p = 0.0034$), non-LBBB patients, representing 39% of the population, did not show improvement (OR: 0.72; $p = 0.21$; p value for the interaction = 0.35) (18). Similarly, data from the RAFT trial found that the greatest benefit of CRT occurred in patients with an LBBB (42).

In a post hoc analysis of MADIT-CRT, the benefit of CRT-D compared with ICD alone was confined solely to those with LBBB when multiple endpoints were examined, including the primary composite endpoint of HF event, all-cause mortality, the occurrence of ICD-treated ventricular tachycardia/ventricular fibrillation, or death (17). When echocardiographic parameters of reverse remodeling were evaluated, patients with a non-LBBB still exhibited improvement greater than those receiving ICD therapy alone, but the benefit was attenuated compared with those with an LBBB. Over the course of a longer

TABLE 4 Effect of QRS Morphology and CRT Response

Trial (Ref. #)	LBBB	Non-LBBB	RBBB	IVCD	Primary Endpoint
COMPANION (3)	CRT-D and CRT-P better than OPT	CRT-D and CRT-P better than OPT (includes RBBB, IVCD)	NR	NR	Death or all-cause hospitalization
CARE-HF (2,20)	CRT associated with favorable outcome	NA	CRT associated with unfavorable outcome	NR	Death or unplanned cardiovascular hospitalization
MADIT-CRT (17)	HR: 0.47 (95% CI: 0.37-0.61); p < 0.001	HR: 1.24 (95% CI: 0.85-1.81); p = 0.257	HR: 0.99 (95% CI: 0.55-1.79); p = 0.969	HR: 1.44 (95% CI: 0.88-2.36); p = 0.143	Death or nonfatal HF event
MADIT-CRT long-term analysis, LBBB patients only (21) (N = 1,281)	0.59 (0.43-0.80); p < 0.001	1.57 (1.03-2.39) 0.04 (includes RBBB, IVCD)	NR	NR	All-cause mortality
REVERSE (18)	OR: 0.530 (0.35-0.81); p = 0.0034	OR: 0.27 (0.10-0.77)*	0.083 (0.01-0.69)	0.79 (0.40-1.57)	Clinical composite score
RAFT (42)	HR: 0.640 (95% CI: 0.524-0.781); p < 0.001	HR: 0.986 (95% CI: 0.695-1.399); p = 0.937	HR: 0.890 (95% CI: 0.530-1.494); p = 0.659	HR: 1.116 (95% CI: 0.666-1.815); p = 0.657	Death or HF hospitalization

*For all non-LBBB, p = 0.21.

NR = not recorded; RBBB = right bundle branch block; other abbreviations as in Tables 1 and 2.

follow-up (7 years), the benefit continued to be confined to those with LBBB QRS morphology for the outcomes of cumulative probability of all-cause mortality (adjusted p < 0.001) and nonfatal HF events (adjusted p < 0.001). A concerning observation was the trend toward an increased risk of death observed for those with a non-LBBB QRS morphology when a Cox proportional hazards regression analysis was performed. QRS duration had no effect on these findings (QRS ≥150 ms or <150 ms), nor did having IVCD versus RBBB QRS morphology (21).

The data from the individual trials were evaluated in a meta-analysis of COMPANION, CARE-HF, RAFT, and MADIT-CRT. Sipahi et al. (43) found that patients with RBBB or IVCD did not benefit from CRT (relative risk for the composite primary outcome: 0.97; 95% confidence interval: 0.82 to 1.15; p = 0.75). Given the overall paucity of data on non-LBBB patients in the clinical trials, especially those with RBBB, more information may be obtained from population-based studies and registries. Using data from the Medicare ICD registry, Bilchick et al. (28) tested the hypothesis that patients with RBBB would have significantly worse outcomes after CRT-D implantation than those with an LBBB. In 14,946 patients, decreased survival was observed among the 1,638 (11.0%) patients with RBBB compared with the patients with LBBB. Similarly, Peterson et al. (44) noted that among 24,169 patients in the National Cardiovascular Data Registry ICD Registry who underwent CRT-D implantation, 1-year hospital readmission rates and 3-year mortality rates in non-LBBB patients (as well as in LBBB patients with baseline QRS duration <150 ms) were higher than in patients with LBBB QRS morphology and QRS duration ≥150 ms. The difficulty in interpreting these data include: 1) the lack of control groups; 2) the absence of information on whether there was a clinical response to CRT; and 3) the lack of information regarding target site of lead placement.

Observation of a higher mortality rate in non-LBBB cannot necessarily be equated to a complete lack of CRT benefit in patients who may be more ill at baseline and/or have more cardiomyopathic disease, such that CRT response is modulated. A comparison of baseline clinical characteristics between LBBB and non-LBBB patients from several of these trials suggests significant clinical differences, such as a greater likelihood of ischemic HF, diabetes, pulmonary disease, atrial fibrillation, and renal dysfunction (17,18,20,44).

It should be apparent that both QRS morphology and QRS duration are important. Data from the RAFT trial explored the interplay of QRS morphology and

QRS duration. In this study by Birnie et al. (42), 1,483 patients in sinus rhythm with QRS durations ≥ 120 ms were examined. A LBBB was present in 1,175 patients (79.2%), 141 patients had an RBBB (9.5%), and the remainder (11.3%) had an IVCD. Patients with RBBB and IVCD were more likely to have an ischemic etiology of HF. Among the patients with LBBB, the benefit of CRT increased directly as QRS duration increased, although all patients with LBBB improved with CRT. In contrast, the benefit of CRT only began to emerge in the non-LBBB patients once the QRS duration was ≥ 160 ms and only after 2 years of follow-up. These data may be limited by the smaller numbers of patients available to analyze with very prolonged QRS durations in the non-LBBB patient groups.

The MADIT-CRT investigators examined combined factors that favored reverse remodeling, as defined by percent reduction in left ventricular end-diastolic volume, assessed according to echocardiography at 1 year of follow-up (22). Seven independent factors were predictive of reverse remodeling and, when combined into a risk score, were associated with improved prediction of CRT response. The 7 factors were as follows: female sex; nonischemic HF; LBBB; QRS interval ≥ 150 ms; previous hospitalization for HF; left ventricular end-diastolic volume ≥ 125 ml/m²; and left atrial volume < 40 ml/m². Taken together, these data from the clinical trials support a benefit of CRT among LBBB patients once the QRS duration is at least 120 ms, and the longer the QRS duration, the greater the response to CRT.

Patients with a true LBBB are the most likely to respond, plausibly because an LBBB causes a “LBBB-cardiomyopathy,” which may be the sole or dominant cause of HF in some patients. In others, comorbid factors, such as sex, type and extent of the cardiomyopathic disease process, and other medical comorbidities, modify the benefit of CRT.

Considering non-LBBB patients for CRT therapy remains difficult and suggests that a patient- and mechanism-specific approach must be explored. Important factors include the extent of conduction delay within the left bundle and evidence of delayed activation within the left ventricle by using imaging techniques. Attempts to target LV lead placement to sites of electrical and/or mechanical delay may be required when considering CRT in these patients.

CRT RESPONSE IN WOMEN AND MEN

Sex differences affecting CRT response are another important factor to consider. MADIT-CRT specifically analyzed long-term outcomes according to female and male CRT recipients. In an analysis by Arshad

et al. (45), women (25% of those enrolled) were more likely to have a nonischemic cause of HF and to have LBBB QRS morphology. They also had less renal dysfunction. The effect of CRT-D compared with ICD therapy on the primary outcome of all-cause mortality or nonfatal HF event was significantly better in female patients compared with male patients, with a relative risk reduction of 69% (hazard ratio: 0.31; $p < 0.001$). All-cause mortality was reduced by 72% (hazard ratio: 0.28; $p = 0.02$), and significant interactions were noted with LBBB and QRS intervals ≥ 150 ms (p value for the interaction < 0.05). Extending these observations to just the 1,281 patients with LBBB in the MADIT-CRT trial, Biton et al. (46) showed that women (31% of the population) had shorter baseline QRS durations but greater clinical benefit from CRT. Specifically, women with CRT-D had a significant risk reduction in HF or death with both QRS durations < 150 ms and ≥ 150 ms versus ICD therapy only. Men exhibited benefit from CRT-D only when the QRS duration was ≥ 150 ms.

These findings are in line with a recent study by Varma et al. (47), in which echocardiographic response to CRT was assessed on the basis of QRS duration and sex in those with nonischemic cardiomyopathy and LBBB. Overall response to CRT among 105 (49.5%) women was greater than in the men, and the response rate remained high in women whether their QRS duration was < 150 ms or ≥ 150 ms. Examination of the effect of QRS duration within the male cohort showed that they were more likely to respond if the QRS duration was ≥ 150 ms than if it was < 150 ms. It is not clear why women would benefit from CRT at a shorter QRS duration versus men. It has been hypothesized that LBBB in men may be associated with conditions such as LV hypertrophy, which might prolong QRS duration without causing mechanical dyssynchrony (48). One could postulate that women respond better to CRT at more narrow QRS durations because, for a similar degree of electrical delay, mechanical dyssynchrony is greater, but this reasoning is speculative.

TARGETING LATE ACTIVATION AND THE ROLE OF IMAGING TO IMPROVE CRT OUTCOMES

Extending the benefit of CRT to a broader group of patients requires revisiting the complexity of factors necessary to improve outcomes with this therapy in HF. It is well understood that the presence of conduction delay in the failing heart prompts dyssynchronous LV contraction and, therefore, diminishes mechano-energetic efficiency. As a result of this scenario, the ensuing molecular and metabolic

changes further the LV dysfunction. It is the interaction between the native activation sequence and biventricular pacing-induced alterations that dictate the benefit from CRT. The importance of both QRS duration and morphology influence the most optimal pacing site and, therefore, the clinical outcome (49).

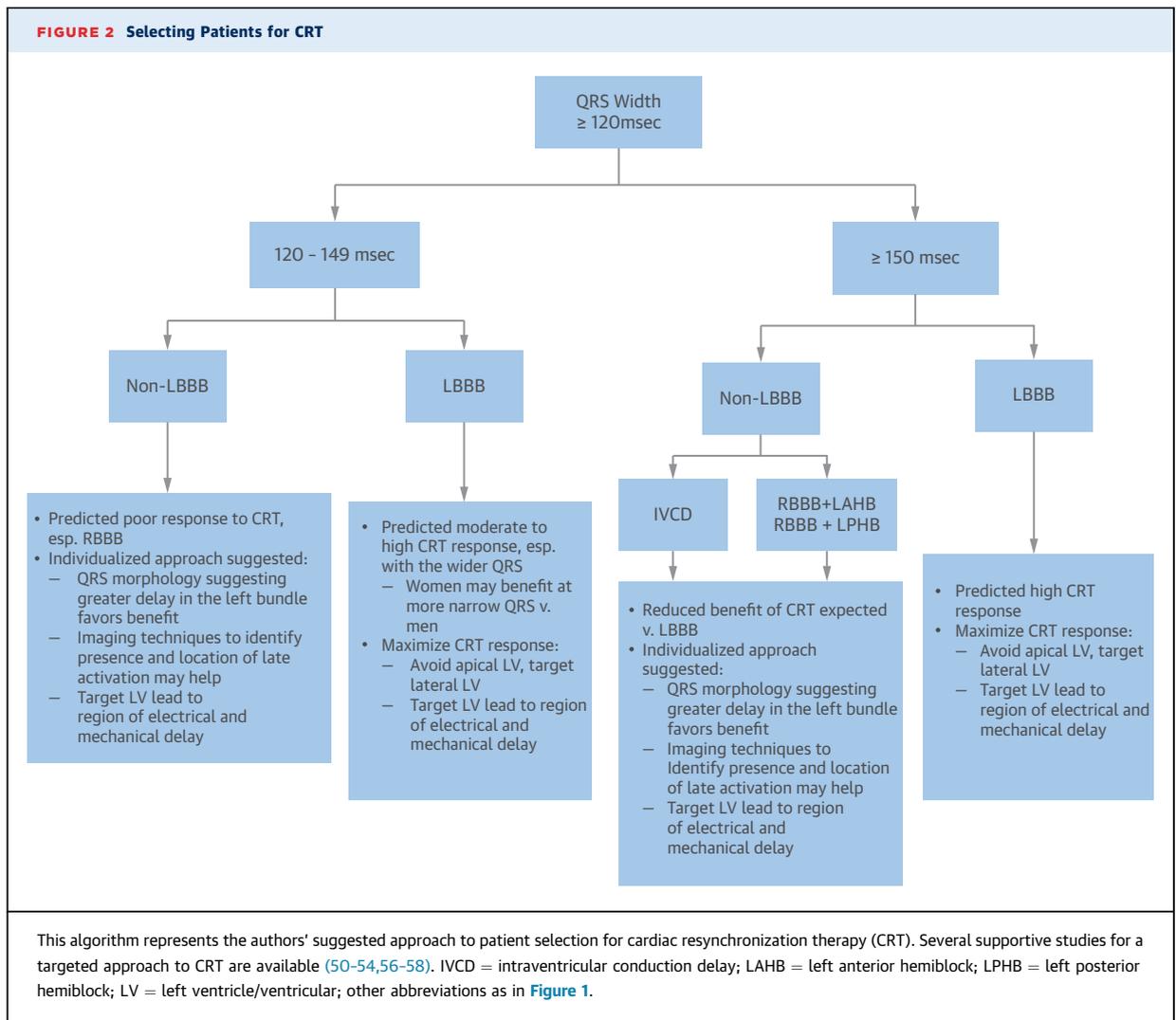
Research has shown that pacing from a site with more delayed electrical activation, as assessed by a LV lead electrical delay greater than one-half the width of the baseline QRS duration (LV lead electrical delay >50%), is associated with a beneficial acute hemodynamic response (measured as percent change in the rate of rise in LV pressure [dP/dt]) and an improved long-term outcome (50). The SMART-AV (SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy) study showed that the measurement of electrical delay is a practical tool for individualizing CRT delivery (51). This prospective substudy of 426 patients (LBBB 75%; IVCD 12%; and RBBB 13%) found that a QLV duration >95 ms was strongly associated with improved reverse remodeling and increased quality of life, even after adjustment for baseline QRS morphology. These data suggest that patients with non-LBBB with underlying cardiomyopathy may benefit from CRT if efforts are made to target the LV lead in a region of significant electrical delay.

Imaging methods have also been used to improve site-specific pacing. Several studies showed that these techniques were associated with improved clinical outcomes. The STARTER (Speckle Tracking Assisted Resynchronization Therapy for Electrode Region) trial randomized 187 patients with HF, QRS duration ≥ 120 ms, and EF $\leq 35\%$ to undergo LV lead placement guided to the site of latest mechanical activation by using speckle-tracking radial strain compared with routine, nonguided LV lead implantation (52). A substudy analysis of 151 patients from this trial who had a QRS duration of 120 to 149 ms or non-LBBB demonstrated that if the LV lead was placed concordant or adjacent to the site of latest mechanical activation, favorable outcomes of CRT were observed, similar to patients with LBBB or QRS durations ≥ 150 ms (53). In TARGET (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronisation Therapy: A Randomised Controlled Trial), 220 patients with standard indications for CRT were randomized to undergo unguided LV lead placement versus placement at the site of latest activation by using speckle-tracking radial strain (54). Targeted LV lead placement yielded a greater proportion of responders at 6 months.

Large, prospective studies are needed to determine the role of echocardiographically guided LV lead placement in non-LBBB patients.

To enhance our understanding of mechanical dyssynchrony, a number of echocardiographic measures (e.g., M-mode, 2-dimensional echocardiogram, 3-dimensional echocardiogram, tissue Doppler imaging) to describe the level of baseline dyssynchrony, acute response, and evidence of favorable remodeling to CRT have emerged. Despite these measures not proving useful for selection of potential patients with narrow QRS intervals who might benefit from CRT, understanding mechanical dyssynchrony and areas of latest activation may still be important for the patient with a prolonged QRS duration and a non-LBBB QRS morphology (18,47,52,55). Existing measures have lacked the necessary refinement and standardization to be of broad clinical utility. Complementary information regarding cardiac structure (e.g., fluoroscopy for coronary venous anatomy) and function (e.g., echocardiography for mechanical dyssynchrony) ought to improve the diagnosis of mechanical dyssynchrony and facilitate planning the treatment and delivery of pacing therapy targeted to areas of activation delay (56). Single imaging modalities, such as computed tomography scanning and cardiac magnetic resonance imaging, have the potential to provide both anatomic and functional information, thereby obviating the need for image integration strategies. Multidetector computed tomography scans also have the potential to provide important information pertinent to: 1) the coronary venous anatomy (i.e., distribution of tributaries, patency, and luminal size of the coronary veins); 2) localization of scarring; 3) mechanical dyssynchrony; and 4) integrated information regarding the relation of the venous branch to the segment of dyssynchrony and/or scarring (57,58). In addition to QRS duration and imaging-based demonstration of anatomic and functional characteristics, many clinical characteristics could affect ventricular remodeling and clinical outcome. Although delving into each of these factors is beyond the scope of the current paper, it is important to recognize that patients with right ventricular dysfunction, end-stage renal disease, high scar burden, and markedly enlarged hearts are liable to have a diminished response to CRT.

An important consideration when examining the data on non-LBBB patients in the randomized CRT trials is that information regarding LV pacing site has not been matched to QRS morphology to further understand the poorer response of these patients. In the simplest example, an LV lead targeting the lateral LV wall would not be expected to alter



hemodynamics in any meaningful way in a patient with a true RBBB. In contrast, the patient with a true LBBB has delayed activation in the lateral LV wall, the usual target for the LV lead and, thus, would be a predicted responder. Substudies of the COMPANION and MADIT-CRT studies provide information for the entirety of the patients who received CRT but were not stratified according to QRS morphology. Saxon et al. (59), in COMPANION, determined that any lead location other than posterior had a similar effect on outcome, whereas Singh et al. (14), in MADIT-CRT, found that only an apical LV lead position was associated with a worse outcome. One explanation for these findings may have to do with a recent school of thought that the wider the QRS interval, the greater the band of dyssynchrony, such that some level of response may be observed, even in a suboptimal LV lead location (i.e., anterior or posterior) (14,59).

However, the practical reality of performing CRT is that finding the “ideal” LV lead-pacing site is often simply limited by coronary sinus venous anatomy. There may not be an acceptable vein in the desired position, whether directed by QRS morphology, electrical activation delay, or by use of advanced imaging techniques.

PUTTING IT ALL TOGETHER

There are a number of critical factors that must be taken into account for CRT to be effective. These include confirmation that: 1) mechanical dyssynchrony is actually present; 2) conduction is sufficiently delayed; 3) the area of late activation can be identified; 4) comorbid conditions are considered; 5) myocardial scarring, possibly altering conduction pattern, is recognized; 6) sex-specific responses may be operative; and 7) placement of the pacing lead

ideally targets the area of late activation. Ultimately, the goal is to achieve reversal of electromechanical dyssynchrony. Although a QRS interval >120 ms is a reasonable starting point for patient selection, those most likely to benefit are patients with an LBBB and delayed activation of the LV lateral myocardium. In patients with a non-LBBB morphology, a more individualized approach may be required when considering patients with a less than “ideal” ECG profile (Figure 2). Recent data from MADIT-CRT also suggests that a subgroup of non-LBBB patients with a prolonged PR interval derived benefit from CRT compared with patients with a normal PR interval and non-LBBB. Therefore, this ECG finding should also be taken into account when considering non-LBBB patients for CRT (60).

An understanding of the clinical trial data is important when considering the current medical practice guidelines for CRT. The 2012 ACCF/AHA/HRS Focused Update of the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines reflects the strength given to QRS morphology and QRS duration after analysis of more recent post hoc data (39). The only remaining Class I recommendation is for patients with a QRS duration ≥ 150 ms in the setting of LBBB (the patient must have an LVEF $\leq 35\%$; sinus rhythm; NYHA functional class II or III, or ambulatory NYHA functional class IV, symptoms; and be undergoing guideline-directed medical therapy). It is important to emphasize that a Class IIa recommendation does not equate to “should not be done.” Class IIa indications suggest that the therapy “can be useful” and, in the case of CRT, this recommendation includes patients with an LBBB and a QRS duration ≥ 120 ms or <149 ms, as well as patients with a non-LBBB and a QRS duration ≥ 150 ms, patients with atrial fibrillation, and those with frequent ventricular pacing. Even a Class IIb indication “may be considered.” This category includes NYHA functional class I and II patients with variable LVEF, QRS morphology, and QRS interval criteria.

Similarly, the 2013 ESC Guidelines on Cardiac Pacing and Cardiac Resynchronization Therapy emphasize QRS morphology and duration when assigning levels of recommendations (40). The primary difference between the U.S. and the European guidelines is that the latter provides for Class Ia and Ib recommendation levels (Class Ia for patients with LBBB and QRS duration ≥ 150 ms, and Class Ib for LBBB and QRS duration <150 ms). The European guidelines specify patients with QRS duration <120 ms as the sole Class III indication (i.e., is not recommended).

The U.S. document differs by noting that CRT is not recommended in the following groups: 1) patients with NYHA functional class I or II symptoms and non-LBBB pattern with QRS duration <150 ms; or 2) patients whose frailty and comorbidities predict <1 year of good functional capacity.

Thus, although both guidelines emphasize that patients with LBBB morphology and the longest QRS duration are the most likely to benefit from CRT, strong support exists for considering many other patients for this important therapy.

CONCLUSIONS

This paper summarizes the clinical trial data regarding QRS morphology and QRS duration as ECG predictors of CRT response. Neither of these QRS criteria can be considered in isolation, as they both reflect the ability of CRT to address LV mechanical dyssynchrony only when considered together. The randomized trials have indicated those patients who may achieve the greatest benefit, and these findings have been appropriately reflected in our current guidelines. If the LV lead is to be placed on the lateral LV myocardium, it is clear that the most favorable candidates for CRT are those with a “true” LBBB, and the longer the QRS duration, the greater the likelihood of response. However, a single QRS duration, above which patients will improve and below which they will not, is too simplistic an approach. To deny patients with borderline indications according to ECG criteria alone a chance for improvement would be unfortunate. An individualized approach, integrating additional strategies (e.g., identification of scarring and areas of late activation), may improve CRT response among those currently demonstrating little or no response. Advancements in LV lead technology and pacing algorithms also have the potential to improve response to CRT. Larger trials are needed to better understand the role of targeted LV placement in patients with non-LBBB QRS morphologies. The ENHANCE-CRT (CRT Implant Strategy Using the Longest Electrical Delay for Non-left Bundle Branch Block Patients) study is an ongoing trial using such a targeted approach (NCT01983293).

CRT has, in many ways, revolutionized the management of HF. Patients receiving CRT have a chance to improve their quality of life, their EF, and their survival, all of which are elusive goals for many other treatment strategies.

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