QRS Duration Criteria to Select Patients for Cardiac Resynchronization Therapy

Cardiac Resynchronization Therapy: 150 Is Not A Magic Number!

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Scope of the Problem

Current American College of Cardiology/American Heart Association/Heart Rhythm Society as well as European Society of Cardiology guidelines recommend the use of cardiac resynchronization therapy (CRT) in patients with symptomatic heart failure (HF) and QRS durations >120 ms. However, 2 recent meta-analyses by Sipahi et al and Stavrakis et al challenged these recommendations. Both studies found that patients with QRS durations between 120 and 150 ms do not benefit from CRT.

Response by Sipahi and Fang on p 435

This is a very important conclusion, from both the clinical and financial standpoints. If the conclusions of these meta-analyses are correct, the guidelines should be revised, and the cutoff for QRS duration indicating the need for CRT should be changed from 120 to 150 ms. From the reimbursement standpoint, these analyses would suggest that the cost of CRT devices implanted in patients with QRS durations shorter than 150 ms should not be covered by insurers. Indeed, the authors of the second meta-analysis state that “the decision to routinely recommend CRT for patients with QRS <150 ms may not be justified.”

Although not in such categorical terms, some societies are already embracing this idea. In fact, in their recently published update, the Heart Failure Society of America, citing one of the abovementioned meta-analyses, definitely recommends CRT only for patients with QRS durations >150 ms (and not because of right bundle-branch block), with severe left ventricular (LV) systolic dysfunction and persistent New York Heart Association (NYHA) functional class II-III symptoms, despite optimal medical therapy. According to the same update, CRT may still be considered for patients with QRS intervals between 120 and 150 ms and severe left ventricular dysfunction who have persistent symptoms on medical treatment. However, the wording “may be considered” reflects the lowest possible strength of recommendation. Despite the high quality of both meta-analyses, as well as of the individual trials included in them, we doubt that such a conclusion is justified.

CRT is a unique therapy for patients with HF and prolonged QRS duration. Not only does it induce reverse LV remodeling, it also improves functional status and increases longevity in these patients. Unlike any other therapy with the exception of ventricular assist devices, CRT interrupts the progression of the disease and reverses the natural course of HF, even in minimally symptomatic or asymptomatic patients with complete left bundle-branch block (LBBB) and systolic dysfunction. In just 1 year of therapy, LV end-systolic and end-diastolic volume decreases and ejection fraction increases in most patients, especially those with nonischemic cardiomyopathy. There is also a subset of super-responders in whom biventricular pacing leads to restoration of cardiac geometry and...
function to a normal or nearly normal state. Although the proportion of super-responders is modest (10% to 22%), the large total volume of CRT procedures means that a significant number of patients receive this benefit of almost complete recovery of ventricular function.

Because of the uniqueness of this therapy, indications for CRT should be worded very carefully, with full consideration of the entire pool of data accumulated to date.

### Evidence for the 150 ms Cutoff

A summary of the CRT clinical trials is presented in Table 2. Almost all of them performed a subanalysis of clinical outcomes in patients with severely prolonged QRS (>150 ms, with some interstudy variability) and moderately prolonged QRS (<150 ms, also with some variability).

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial demonstrated...
that CRT decreased the combined risk of death from any cause or first hospitalization, but provided no benefit if the QRS was <147 ms.

The Cardiac Resynchronization-Heart Failure (CARE-HF) Study was the first to show that biventricular pacing decreased morbidity and mortality, and improved LV ejection fraction as well as symptoms and quality of life. Although patients with QRS durations >120 ms qualified for the study, there were additional requirements of dyssynchrony by echocardiographic criteria for QRS durations between 120 and 149 ms. Patients were categorized into QRS durations above and below 160 ms, and only the latter subgroup did better with CRT. However, during a 3-year extended follow-up, there was benefit for both subsets.

The Multisite Stimulation In Cardiomyopathy (MUSTIC) Study included only patients with QRS durations >150 ms. The Resynchronization-Defibrillation for Ambulatory Heart Failure (RAFT) trial demonstrated that the addition of CRT to an implantable cardioverter defibrillator (ICD) reduced the rates of death and hospitalization for symptomatic HF. CRT was effective in patients with QRS durations >150 ms and ineffective in patients with QRS durations <150 ms.

The REsynchronization reVerses Remodeling in Systolic Left vEntricular Dysfunction (REVERSE) trial demonstrated that CRT in asymptomatic LV dysfunction and in minimally symptomatic HF resulted in major structural and functional reverse remodeling, especially in nonischemic cardiomyopathy. There was no benefit in patients with QRS durations <140 ms, significant benefit in patients with QRS durations from 140 to 160 ms, and even greater benefit in patients with QRS >160 ms. In the European cohort of the REVERSE trial, no benefit was demonstrated in patients with QRS durations <152 ms as opposed to those with wider QRS.

The Multicenter Automatic Defibrillator Implantation Trial/Cardiac Resynchronization Therapy (MADIT-CRT) trial showed that CRT combined with ICD therapy decreased the risk of HF events in relatively asymptomatic patients. In a prespecified subgroup analysis, there was benefit in patients with QRS >150 ms, whereas no benefit was derived in the subset with QRS between 120 and 149 ms.

In summary, almost all of the CRT trials reported no effect in patients with moderately prolonged QRS durations. Indeed, every 1 of the 5 trials included in both of the aforementioned meta-analyses (COMPANION, CARE-HF, MADIT-CRT, REVERSE, and RAFT) demonstrated a beneficial effect of CRT in severely prolonged QRS and no effect in moderately prolonged QRS. Examining this point in greater detail, in both the REVERSE (European cohort) and the RAFT studies, the investigators stated that their cohorts with longer QRS durations derived more benefit than those with shorter QRS durations, implying that patients with shorter QRS durations also benefit, at least somewhat, from CRT. However, the odds ratios with corresponding confidence intervals overlapping one indicate that, in terms of clinical outcomes, CRT, in fact, made no difference in patients with shorter QRS durations.

Flaws in the Evidence for the 150 ms Cutoff

Indeed, there is no need to do a meta-analysis to demonstrate that there is no benefit from CRT in patients with moderately prolonged QRS if each of the included trials already reached the same conclusion individually. However, there is an important problem with this seemingly obvious conclusion. All the above studies share the same feature: the duration of the QRS interval was categorized.

In clinical trials, many continuous variables are categorized for analysis purposes. For instance, LV ejection fraction is a continuous variable. It can theoretically be anywhere between 0% and 100%. But, for the purpose of this analysis, let us say that it is either normal, above 50%, or reduced, below 50%. Now, instead of a continuous set of values, we have 2 categories: normal and reduced. If we use these categories for analysis, all ejection fractions below 50%, whether, for example, 10% or 45%, will be analyzed together, as if there is no difference between them.

Likewise, QRS duration is a continuous variable. But, for the subgroup analyses, the investigators categorized QRS durations into those above 150 ms and below 150 ms (120–149 ms), and thus they obscured all the differences that can exist between 121 and 149 ms. The authors of both meta-analyses reproduced the same strategy. Lo and behold! They found exactly what each of the trials already proved individually.

In other words, outcomes in patients with QRS durations 120 to 149 ms were analyzed as a single group. Meanwhile, better outcomes in patients with QRS durations >160 ms compared with <160 ms, and in QRS durations exceeding 168 ms in comparison with 148 to 168 ms, prompt the extrapolation that longer QRS predicts better response to CRT. It means that QRS durations within the group from 120 to 149 ms must be analyzed as a continuous variable and not as a single category. Only a couple of trials, not included in either meta-analysis, looked at different groups of patients within the range of 120 to 150 ms for QRS duration and did not treat them as a single group. Data from the Pacing Therapies for Congestive Heart Failure (PATH-CHF) I demonstrated that CRT produces symptomatic improvement in patients with HF. Although those with a baseline QRS >150 ms virtually always experienced acute hemodynamic improvement, some patients with QRS durations between 120 and 150 ms also showed improvement. In the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, the only study in which QRS duration was analyzed as a continuous variable, the magnitude of favorable effects was not influenced by baseline QRS duration.

QRS Duration and Dyssynchrony

These results are not surprising, because there is plenty of evidence that the severity and prognosis of HF is dependent on QRS duration. Intraventricular conduction delay resulting in electric and mechanical dyssynchrony occurs commonly in HF. According to different sources, the prevalence of prolonged intraventricular conduction ranges from 20% to 30% in HF with systolic dysfunction. It is well established that a QRS duration above 120 ms is a significant predictor
of LV systolic dysfunction, and moreover, prolonged QRS is associated with a poor prognosis.\textsuperscript{2,3,15} For the purpose of this discussion, studies examining outcomes in HF based on graded duration of QRS are of particular interest. It is important to realize that patients with QRS durations exceeding 120 ms are almost equally distributed between moderately and severely prolonged QRS.\textsuperscript{26} This means that if the cutoff 150 ms is accepted, about half of all patients who currently qualify for CRT would be found ineligible for this therapy.

In a study of nearly 3500 patients with HF, Shenkman et al\textsuperscript{24} found a stepwise increase in the prevalence of systolic LV dysfunction as QRS duration increased progressively above 120 ms. Reduced LV ejection fraction was present in 42.5\% of patients with a QRS duration <120 ms, 60\% of patients with a QRS duration 120 to 129 ms, 61.6\% of patients with a QRS duration 130 to 139 ms, 67.3\% of patients with a QRS duration 140 to 149 ms, and in 75.7\% of patients with a QRS duration >150 ms (\textit{P}<0.05).\textsuperscript{24} In another study, the 3-year mortality rate was 20\% for an intraventricular conduction delay of <120 ms, 61.6\% of patients with a QRS duration 120 to 129 ms, 66.6\% of patients with a QRS duration 130 to 139 ms, 73.7\% of patients with a QRS duration 140 to 149 ms, and in 75.7\% of patients with a QRS duration >150 ms (\textit{P}=0.01). Sandhu and Bahler\textsuperscript{26} reported a progressive decrease in LV ejection fraction and an increase in LV diameter and the severity of mitral regurgitation with incremental prolongation of the QRS from <100 ms to 100 to 119 ms, 120 to 149 ms, and >150 ms (Figure 1). In other words, a moderate degree of QRS prolongation, which, according to the new proposals, should not be corrected with CRT, was associated with significant deterioration of LV systolic dysfunction.

In terms of prognosis, a prolonged QRS duration of 120 to 149 ms was associated with an increased mortality at 60 months (\textit{P}=0.001), even after adjustment for age, sex, and race (\textit{P}=0.001).\textsuperscript{24} In another study, the 3-year mortality rate was 20\% for an intraventricular conduction delay of <120 ms, 36\% for a QRS duration 120 to 160 ms, and 58.3\% for QRS duration >160 ms\textsuperscript{27} (Figure 2).

Stratifying patients according to 2-year event free survival, Kalra et al\textsuperscript{28} found that the optimal QRS duration providing the best demarcation between benign and poor prognosis was 120 ms. Moderate prolongation of QRS duration (120–149 ms) was associated with worse NYHA class, lower peak oxygen consumption, and poorer LV ejection fraction compared with patients with normal QRS durations (all \textit{P}<0.05). Moreover, patients with moderate prolongation of the QRS had similar impairment of NYHA class and peak oxygen consumption compared with patients with QRS >150 ms.

**LBBB and HF**

In particular, LBBB has been found to have a detrimental effect in HF. In 1 study, mean ejection fraction in patients with
HF was 40% in those with normal QRS (<120 ms), 36.3% in those with right bundle-branch block, and 29.6% in those with LBBB. Short-term mortality rates were 46.1%, 56.8%, and 57.7%, respectively (P<0.0001).31

The normal sequence of electric activation is reversed in LBBB, with the direction of septal depolarization proceeding from right to left and the impulse spreading first to the right ventricle and then to the LV. The resulting delay in the inward motion of the lateral wall of the LV depends on the duration of the QRS, with greater duration of the QRS producing more dyssynchronous contraction.32 When patients with LBBB have been compared with control subjects, striking delays were observed in both LV systolic and diastolic events in the LBBB group. The delay was associated with shortening of LV diastole with a resultant increase in the ratio of right to LV diastolic time. Also, the abnormal interventricular septal motion in LBBB corresponded to periods of asynchrony in contraction, ejection, end systole, and end diastole between the right and left ventricles. This loss of septal contribution resulted in a reduction in global ejection fraction in LBBB compared with normals (54±7% compared with 62±5%; P<0.005).33

In the Framingham study, QRS duration was modeled as a continuous and as a categorical variable (<100, 100–119, and ≥120 ms). QRS duration was positively related to LV dimensions but inversely related to fractional shortening (a surrogate of ejection fraction). Importantly, LBBB was associated with greater LV mass and dimensions, and with lower fractional shortening than other types of QRS prolongation.34 In another study, LBBB was an independent predictor of long-term mortality in patients with acute HF.35

In the MADIT-CRT trial, patients with LBBB treated with CRT experienced a 53% reduction (hazard ratio, 0.47; P<0.001) in the risk of a HF event or death compared with patients with LBBB treated with an implantable defibrillator only. This effect was consistent across the whole spectrum of QRS durations, especially for women, indicating that LBBB, per se, with its abnormal activation was responsible for the dyssynchrony to a greater extent than QRS duration alone.36 Therefore, the presence of LBBB by itself, in patients with systolic dysfunction and symptomatic HF, should justify CRT, regardless of the extent of QRS prolongation beyond 120 ms.

Reverse LV Remodeling and QRS Duration

Although all sets of guidelines consistently put NYHA functional class among other criteria for CRT, there is hardly any evidence that the severity of symptoms in HF before biventricular stimulation determines the success of CRT.37 The essence of this treatment is reverse remodeling of the LV with secondary improvement in symptoms.38 Meanwhile, LV systolic dysfunction, per se, is a poor prognostic sign even if completely asymptomatic, and reversal of LV remodeling results in survival benefit. Comparison of reverse LV remodeling with 3 months of biventricular pacing in patients with baseline QRS duration of 120 to 150 ms and above 150 ms showed benefit in both groups, although it was greater in those with longer QRS. Significant reverse remodeling, defined as a reduction of LV end-systolic volume by >15%, was evident in 46% of the moderately prolonged QRS group and in 68% of those with severely prolonged QRS. Similarly, improvement in LV systolic function and in functional status (NYHA class) occurred in all patients with QRS >120 ms. Specifically, LV ejection fraction increased from a baseline value of 28.4±7.3% to 33.9±9.7% (P<0.001) in 3 months in patients with QRS between 120 and 150 ms, and from 26.0±12.9% to 37.0±12.5% (P<0.001) in those with QRS >150 ms, creating a gain of 5.5±7.3% versus 11.0±12.1% (P=0.04), respectively.39

The origin of the currently recommended cutoff for CRT of 120 ms is clear. It is an upper range for normal intraventricular conduction. Beyond that, longer QRS durations mean a higher degree of dyssynchrony (because of greater delay between the arrival of the electric signal at the ventricular septum and the LV free wall), which translates into poorer clinical outcomes. Therefore, the response to CRT will be better in patients with longer QRS durations. However, there is no reason to limit CRT only to patients with QRS durations above 150 ms. There is nothing magical about this number! It is simply an arbitrary cutoff chosen by clinical trial investigators for categorization of QRS into moderately and severely prolonged.

If we really want to know the appropriate cutoff for QRS duration below which the risks of CRT implantation outweigh the benefits, we would need to reanalyze existing data sets from the clinical trials studying QRS as a continuous variable or subdivide QRS durations between 120 and 150 ms into smaller increments. This should be a topic of a separate meta-analysis. But eliminating all the gradations between 120 and 150 ms, and only recommending CRT for patients with very prolonged QRS (>150 ms) will deny a very effective treatment to a substantial number of patients with HF.

Disclosures

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'Super-responders' to cardiac resynchronization therapy: the importance of symptom duration and left ventricular morphology.


Response to Maya Guglin, MD, PhD, and Anne B. Curtis, MD

Ilke Sipahi, MD, FACC; James C. Fang, MD, FACC

Transformation of continuous variables into categorical ones using cutoff values is inherently problematic and weakens the strength of information provided by the variable. Nevertheless, dichotomization of continuous variables is a necessity while practicing medicine. These cutoffs are used universally in every patient encounter, regardless of the medical specialty. The QRS cutoff of 120 ms for cardiac resynchronization therapy used to be one such cutoff. We demonstrated that 120 ms is not a good cutoff value, and that 150 ms is a better one, but inevitably an imperfect one, like all other cutoff values. Accordingly, in their recently revised guidelines, the American College of Cardiology, the American Heart Association, the Heart Rhythm Society, the American Association for Thoracic Surgery, the Heart Failure Society of America, and the Society of Thoracic Surgeons agree with our observations and now recommend cardiac resynchronization therapy as a class I indication only for patients with a QRS duration >150 ms with left bundle-branch block. Nevertheless, no number is a magic number in medicine, regardless of whether you put an exclamation mark after it.
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