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Scar burden assessed by Selvester QRS score predicts prognosis, not CRT clinical benefit in preventing heart failure event and death: a MADIT-CRT Sub-Study

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Abstract

Background—There is a need for improved selection criteria for Cardiac Resynchronization Therapy (CRT). High myocardial scar burden has been associated with worse outcome in CRT patients. It is, however, unclear whether high scar burden ameliorates CRT clinical benefit or is merely predictive of prognosis in heart failure (HF) patients regardless of CRT implantation. We aimed to study the prognostic value of scar burden estimated by electrocardiographic Selvester QRS scoring in determining outcome in the Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT) population.

Method—Selvester QRS scoring was performed on all 1820 ECGs of the MADIT-CRT population by a single observer. In both arms and in their respective LBBB subgroups, QRS score was analyzed in comparison to echocardiographic volumes and in relation to time to HF event or death using Cox Proportional Hazard Ratios. To determine effect on CRT clinical benefit, we

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Author contributions

WZ and JPD acquired data as part of the MADIT-CRT study. DGS, ZL and GSW conceived of this substudy. ZL and SM designed the statistical analysis plan, which was critically reviewed by DGS, WZ and JPD. BW later added complementary analyses to the statistical analysis plan. ZL applied Selvester QRS scoring to all ECGs. DGS scored ECGs that ZL flagged as difficult to analyze. SM conducted all statistical analyses. All co-authors participated in interpretation of results. BW and ZL produced the initial draft of the manuscript, which was then revised and approved by all remaining co-authors.

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tested for interaction between the effects of CRT assignment and QRS score on time to HF event or death.

Results—In the CRT-D arm, a significant correlation was found between higher continuous QRS score and less increase of left ventricular ejection fraction (LVEF) as well as less decrease of left ventricular end systolic volume (LVESV) (multivariate P-values: <0.001). QRS score was significantly correlated with HF event/death in the left bundle branch block (LBBB) subgroup (n=1037, multivariate HR 1.07 per point, P=0.046). Scar extent estimated by QRS scoring was neither predictive of CRT clinical benefit in the total study population (interaction P-value=0.25) nor in the LBBB subgroup (interaction P-value=0.86).

Conclusion—High scar burden estimated by Selvester QRS score is predictive of adverse overall prognosis in LBBB patients regardless of CRT implantation. However, QRS score does not identify patients who benefit clinically from CRT-D compared to implantation of ICD only.

Keywords

Cardiac resynchronization therapy; myocardial scar; heart failure; prognosis; Selvester QRS scoring

Introduction

Cardiac Resynchronization Therapy (CRT) improves prognosis and ameliorates symptoms in selected heart failure (HF) patients. However, up to one third of patients may not benefit from CRT but are still subjected to adverse effects and costs(1). Several factors that may predict favorable CRT response determined by echocardiography parameters and/or event-free survival have been identified, including QRS duration 150 ms(2), non-ischemic heart failure etiology(3), female sex(2), left ventricular (LV) lead placement (non-apical(4), at site of latest activation(5) and away from scar(6)) and left bundle branch block (LBBB) QRS morphology. In addition, newer strict LBBB criteria indicative of complete left bundle branch block(7) have been shown to predict CRT success better than traditional LBBB criteria(8). Finally, low myocardial scar burden either measured by cardiac magnetic resonance imaging with late gadolinium enhancement (CMR-LGE) or estimated by ECG Selvester QRS score have been linked to favorable CRT outcome(9, 10). Importantly, previous studies on the value of both ECG estimation of scar using the Selvester QRS score and scar burden by CMR-LGE in predicting CRT response have not featured any non-CRT-D arm and thus could not evaluate the effect of scar burden on CRT clinical benefit.

We aimed to test whether QRS score was a significant predictor of echocardiographic and clinical benefit after CRT implantation in the MADIT-CRT population. We specifically hypothesized that among CRT recipients, high myocardial scar burden estimated by ECG Selvester QRS score would be predictive of: a) less increase of left ventricular ejection fraction (LVEF), b) less reduction of left ventricular end-systolic volume (LVESV), and c) a smaller improvement in event-free survival compared to implantable cardioverter-defibrillator (ICD).

Methods

Study patients

MADIT-CRT enrolled subjects of either sex who were more than 21 years of age with ischemic cardiomyopathy (New York Heart Association [NYHA] class I or II) or non-ischemic cardiomyopathy (NYHA class II only), sinus rhythm, an LVEF of 30% or less and QRS duration of 130 msec or more as described previously(2, 11). Further exclusion criteria included existing indication for CRT at time of enrollment, previously implanted pacemaker, Implantable Cardioverter Defibrillator (ICD) or CRT, previous coronary-artery bypass grafting among others as previously described(2). Subjects were randomized in a 3:2 ratio to receive either Cardiac Resynchronization Therapy Defibrillator (CRT-D) (n=1089) or ICD (n=731)(2). During analysis, all patients were maintained in their original assignment groups per an intention-to-treat protocol. An overview of the included study patients can be found in figure 1.

ECG Analysis

All subjects enrolled in MADIT-CRT received baseline electrocardiograms (ECGs) before randomization. Standard 12-lead ECGs were evaluated by a single investigator (ZL) blinded to all clinical data aside from age and gender according to a standardized protocol. ECGs were excluded from analysis in the present substudy of the MADIT-CRT population if they were unable to be accurately scored due to poor quality, missing lead information or indeterminate QRS axis prohibiting conduction classification (n=87). Selvester QRS scoring was performed as previously described, each ECG being awarded 0–33 QRS points with each point indicating scar amount of roughly 3% of LV mass (12–14). Briefly, ECGs were first classified by ventricular conduction/hypertrophy type: left bundle branch block (LBBB), left anterior fascicular block (LAFB), left ventricular hypertrophy (LVH), right bundle branch block (RBBB), RBBB+LAFB or no confounders. Left bundle branch block was defined as presence on the ECG of a terminal deflection in V1, QRS $\geq$ 130 ms (women) or 140 ms (men) and mid-QRS notching/slurring in $\geq$ 2 of the leads V1, V2, V5, V6, I or aVL. Conduction-specific QRS-scoring criteria involving Q-, R- and S-wave amplitudes, durations, amplitude ratios and notches in 10 of the 12 standard ECG leads (excluding leads III and aVR) were applied. Electrocardiograms of poor recording quality were flagged for additional review by a second investigator also experienced with Selvester QRS scoring (DGS) and a consensus was achieved.

Echocardiography analysis

Echocardiography was performed at baseline and at the 1-year follow-up on 746 patients in the CRT-D arm and 620 patients in the ICD arm, as described previously(2). Changes in left ventricular volumes and ejection fraction were evaluated.

Outcomes

The primary clinical outcome of the MADIT-CRT trial was defined as whichever came first of either nonfatal HF event or death from any cause as previously described(2). Diagnosis of HF required symptoms and clinical signs that were consistent with those expected in HF

responsive to either intravenous decongestive therapy administered in an outpatient setting or an augmented decongestive regimen with oral or intravenous drugs given during hospitalization. The physicians making the HF diagnosis were aware of study-group assignment. To account for this, all outcomes were adjudicated by both an independent mortality committee and an independent HF committee according to specified criteria. Both committees were blinded to study-group assignment. Two echocardiographic parameters were evaluated, Left Ventricular Ejection Fraction (LVEF) and Left Ventricular End Systolic Volume (LVESV).

CRT clinical benefit analysis

To determine how QRS score affected CRT clinical benefit (compared to the ICD control group), we tested the interaction of assignment to the CRT-D arm of the trial and continuous and dichotomous QRS score (QRS score ≥ 5 was prospectively selected as cut-off point, based on previously published results(15, 16)) in outcomes using Cox-proportional hazards for time to HF hospitalization or death. This was then repeated in the “All LBBB” subgroup (1037).

QRS score vs echocardiographic outcome analyses

The relationship between the predictor variable of QRS score and the outcome variable of time to HF event or death was analyzed by calculating change in Cox Proportional Hazard ratio per incremental QRS score. Linear regression was used to determine the effects of QRS score on change in the echocardiographic variables of LVEF and LVESV at 1-year follow up. Univariate and multivariate analysis was performed in all the above analyses with gender, HF etiology, age and QRS duration also included in all multivariate models. Analyses were then repeated for the LBBB subgroups within both arms. Figure 1 provides an overview of the division of the study population into subgroups.

Results

Study patients

A total of 1733 patients were included in this substudy, 1029 in the CRT-D arm and 704 in the ICD arm. The CRT-D arm and the overall population had similar baseline characteristics and similar use of cardiac drugs at time of enrollment as shown in table 1. Mean follow-up was 2.4 years. There were 441 that reached the clinical endpoint of HF event or death. The average QRS score was 5.2 in the overall study population (4.2 in the LBBB subgroup). The distribution of conduction types in the non-LBBB subgroup was 198 with no confounders, 108 with LVH, 147 with LAFB, 89 with RBBB and 154 with combined RBBB and LAFB.

QRS score and heart failure

In the LBBB subgroups in both arms, but in neither arm as a whole, QRS score as a continuous variable was associated with increased risk of HF event or death (figure 2). In the CRT-D arm, QRS score in the univariate analysis was significantly associated with increased risk of HF event or death during the follow-up time, with a HR of 1.05 per QRS score point ($P=0.010$). However, when accounting for age, gender, HF etiology and QRS duration in the multivariate model, the significance did not persist ($P=0.151$). Similarly, a high QRS score

(≥ 5 points) was associated with an increased risk for HF event or death in the univariate analysis (HR 1.40, $p=0.015$) but not when age, gender and other variables were taken into account in the multivariate analysis (HR 1.26, $p=0.093$). However, when the analysis was repeated in only the LBBB subgroup of the CRT-D arm ($n=601$), QRS score was significantly associated with an increased risk of HF event or death (univariate: HR 1.09 per incremental QRS score, $p=0.01$, multivariate: HR 1.07 per incremental QRS point, $p=0.046$). A QRS score of ≥ 5 points was not a useful cutoff to predict HF event or death among LBBB subjects (univariate: HR 1.44, $p=0.08$, multivariate: HR 1.38, $p=0.12$). Findings were similar in the ICD arm, in which QRS score was not significantly associated with clinically adverse outcome (HR 1.01 per incremental QRS score, $P=0.690$) except in the ICD LBBB subgroup (HR 1.08 per incremental QRS score, $P=0.012$).

QRS score and CRT clinical benefit

The interaction effect of QRS score and CRT-D arm assignment on heart failure hospitalization and overall mortality was assessed to determine how scar burden influences CRT clinical benefit as compared to the ICD control group (table 2). The interaction between QRS score and CRT on these primary outcomes was not statistically significant (continuous score $p=0.25$, dichotomous score $p=0.33$). Limiting analysis to the highly responsive All-LBBB group ($n=1037$) showed similar results (continuous score $p=0.86$, dichotomous $p=0.99$). Thus, QRS score did not modify or prevent the effect of CRT on clinical outcomes.

QRS score and echocardiographic improvement

A higher QRS score was associated with a lesser increase in LVEF and lesser decrease of LVESV at 1-year follow-up in CRT-D arm, but not in the ICD arm (figure 3). This same was true when analyzing only the LBBB subgroups of both arms, as shown in figure 3. In the CRT-D arm, each QRS score point was associated with a lesser increase in LVEF (-0.33% per QRS score point) in the univariate model ($p < 0.001$). This lessened increase in LVEF for patients with higher QRS scores in the CRT-D arm persisted when taking age, gender, QRS duration and HF etiology into account in the multivariate model (-0.24% increase in LVEF per QRS score point $p < 0.001$). In the CRT-D arm, each point increase in QRS score was associated with a 0.97% smaller decrease in LVESV in the univariate model ($P < 0.001$) and 0.69% smaller decrease in the multivariate model ($P < 0.001$). These findings persisted when analyzing only the LBBB subgroup within the CRT-D arm ($n=601$), as shown in figure 3.

Discussion

The major finding of the present study was that in the LBBB subgroup, scar burden estimated by ECG using the Selvester QRS score did not predict CRT clinical benefit, but rather prognosis regardless of CRT implantation.

Interestingly, QRS score predicted echocardiographic outcome in the CRT-D arm as a whole but predicted clinical outcome only in the LBBB subgroups of both arms. This may indicate that QRS score may predict echocardiographic (but not clinical) benefit by CRT in LBBB patients. Over the last decade, there has been a growing number of studies supporting the

notion that increased scar burden estimated by several modalities, including QRS scoring, is associated with adverse echocardiographic outcome after CRT implantation (10, 17–21). However, none to date have included a non-CRT-D arm to assess whether scar burden influences CRT clinical benefit compared to a control group. Further, several of these studies have only evaluated CRT response by echocardiography after a certain follow-up time, typically 6 months, which may not translate into clinical outcomes such as self-reported health improvement, decreased mortality and lowered risk of heart failure events. For instance, one study by Veersteg et al(22) found that 54 out of 104 consecutive CRT recipients had a discrepancy between echocardiographic response (defined as 15% reduction in end-systolic volume) and self reported health improvement.

Because CRT has been shown to be most effective in LBBB, coupled with the notion that scar extent could prevent CRT effect, one may readily hypothesize that scar burden would be most important prognostically in the CRT-LBBB subgroup. However, we found that CRT was equally beneficial in high (5 points) and low (0–4 points) QRS score subgroups within the “All LBBB” subgroup (n=1037), with a CRT-D vs ICD hazard ratio of exactly 0.44 for both the high and low QRS score subgroups. Further, interaction between QRS score and CRT-D arm assignment was far from significant in the overall cohort and even less so in the “All LBBB” subgroup (n=1037). Thus, QRS score identified adverse outcome in the “All LBBB” subgroup regardless of device assignment, but did not predict who would benefit clinically from CRT. These results are analogous to those found by Wikstrom et al in the CARE-HF population (23), in that benefit of CRT was similar in patients with ischemic and non-ischemic HF etiology, despite ischemic patients in general tending to have higher scar burden and have poorer outcome in general. The notion that ischemic etiology is a prognostically adverse sign but does not prevent any CRT benefit is supported by a separate substudy of the MADIT-CRT population(24) as well as a meta-analysis by Chen et al in 2014 (25). Interestingly, scar burden by QRS scoring was predictive of clinical prognosis in the “All LBBB” subgroup independently of HF etiology.

The ability of the Selvester QRS score to accurately quantify scar in presence of various conduction abnormalities such as RBBB, LBBB and LAFB has been initially validated(13), but further studies in larger cohorts should be undertaken to confirm the validity of the modified QRS score for each separate conduction abnormality. There is also a possibility that the QRS score criteria could be improved through future research efforts in order to more accurately quantify scar. Interestingly, amount of QRS score points did not predict prognosis in non-LBBB patients in the present study. It seems unlikely that scar burden would only be relevant to prognosis in LBBB patients. This could be due to multiple reasons, including the smaller number of non-LBBB patients or that most non-LBBB patients, especially those with RBBB, referred for CRT have a very large scar burden(26) and the QRS score cannot further discriminate risk. Further improvements in the QRS score in RBBB and LAFB may improve its prognostic utility.

Clinical implications

Although prior results have shown that QRS score predicts echocardiographic outcome after CRT implantation, the results of the present study show that patients with LBBB and high

scar burden estimated by Selvester QRS scoring still derive similar CRT clinical benefit over ICD alone. Further study of additional scar estimation techniques, such as CMR-LGE are required to determine if scar burden can serve as a useful tool in predicting clinical response to CRT. Such imaging studies may provide more accurate approximations of scar burden, which may prove useful in predicting CRT prognosis and clinical benefit.

Interestingly, the present results suggest that QRS score is a more powerful predictor of echocardiographic LV remodeling than of clinical outcomes. It may be that there are factors beyond only remodeling that affect risk of HF event/death and that the ability of the QRS score to predict remodeling does not translate into predicting clinical outcomes.

Limitations

Scar burden as estimated by Selvester QRS scoring likely does not reflect actual scar burden with perfect accuracy. However, although scar burden by Selvester QRS scoring has had individual variability in a previous validation study, the accuracy has been found to be relatively good in a population with <35% LVEF(13), and the population in the present study was large. Despite the large sample size however, the ICD-arm was notably smaller than the CRT-D arm as a consequence of the 3:2 randomization strategy in favor of CRT-D assignment. Thus, potential predictiveness of QRS scoring of echocardiographic outcome may have been missed in the ICD arm (figure 3). The sample size is also limited in the non-LBBB subgroups of both arms.

Conclusion

In the LBBB subgroup, myocardial scar estimated by electrocardiographic Selvester QRS scoring predicts prognosis in heart failure patients and may identify echocardiographic responders to CRT. However, QRS score cannot be used to determine who will benefit clinically from CRT-D over implantation of ICD only. Future research should determine if these finding are also present with other markers of myocardial scar, such as cardiac magnetic resonance imaging.

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Figure 1.
Overview of the division of the study population into subgroup.

Figure 2.

A Shows how Cox Proportional Hazard of the clinical endpoints of HF event or death are affected by QRS score per point (adjusted for gender, age, heart failure etiology and QRS duration) in each respective subgroup. **B** Shows the Hazard ratios for HF event or death between the low (0-4) vs high (≥ 5) QRS score subgroups.

Abbreviations: HR: Hazard ratio. CI: Confidence interval.

Figure 3.

A Shows the beta coefficients derived from linear regression (with 95 % confidence intervals) showing the effect on percentage points of LVEF change, at 1 year follow up, per incremental QRS score (adjusted for gender, age, heart failure etiology and QRS duration) in each respective subgroup. **B** Shows the effect on percentage point LVESV change, at 1 year follow up, per incremental QRS score.

Abbreviations: CI - Confidence intervals. LVEF - Left ventricular ejection fraction. LVESV - Left ventricular end systolic volume.

Table 1

Baseline characteristics

Characteristic	CRT-D arm LBBB (n=601)	Non-LBBB (n=428)	Overall population LBBB (n=1037)	Non-LBBB (n=696)
Age at enrollment – yrs $\pm$ std	63.6 $\pm$ 10.5	65.4 $\pm$ 11.2	63.8 $\pm$ 10.7	65.2 $\pm$ 10.9
Female gender – no. (%)	209 (35)	56 (13)	335 (32)	102 (15)
Cardiac history – no. (%)				
Ischemic HF etiology				
NYHA class I	56 (9)	84 (20)	102 (10)	142 (20)
NYHA class II	186 (31)	237 (55)	327 (32)	378 (54)
Non-ischemic HF etiology				
NYHA class II	359 (60)	107 (25)	605 (59)	179 (26)
Baseline echocardiography variables				
Baseline LVEF – % $\pm$ std	23.6 $\pm$ 5.3	24.3 $\pm$ 5.1	23.3 $\pm$ 5.4	24.5 $\pm$ 4.9
Baseline LVEDV – ml $\pm$ std	250.0 $\pm$ 63.4	240.1 $\pm$ 52.4	253.9 $\pm$ 66.7	239.6 $\pm$ 52.6
Baseline LVESV – ml $\pm$ std	179.1 $\pm$ 51.1	170.0 $\pm$ 42.3	182.2 $\pm$ 54.0	169 $\pm$ 41.9
Cardiac medications				
ACE inhibitor – no. (%)	460 (77)	334 (78)	792 (77)	546 (78)
ARB	130 (22)	83 (19)	223 (22)	131 (19)
B-blocker – no. (%)	567 (94)	395 (92)	974 (94)	646 (92)
Diuretic – no. (%)	397 (66)	299 (70)	695 (67)	471 (67)
Amiodarone – no. (%)	39 (6)	36 (8)	69 (7)	54 (8)
QRS duration – mean ms $\pm$ std	165 $\pm$ 17	147 $\pm$ 16	166 $\pm$ 18	147 $\pm$ 15

LBBB – Left Bundle Branch Block. CRT – Cardiac Resynchronization Therapy. Yrs – Years. Std – Standard Deviation. HF – Heart Failure. NYHA – New York Heart Association. LVEF – Left Ventricular Ejection Fraction. LVESV – Left Ventricular End-Systolic Volume. ACE – Angiotensin Converting Enzyme. RBBB – Right Bundle Branch Block. LAFB – Left Anterior Fascicular Block.

Table 2

QRS score and CRT clinical benefit.

Variable	All LBBB subgroup (n=1037)	Overall population (n=1733)
Hazard ratio for HF event/death (CRT vs ICD arm)		
QRS score 0-4 - HR (95%CI)	0.44 (0.30 – 0.63)	0.58 (0.44 – 0.77)
QRS score 5 - HR (95%CI)	0.44 (0.30 – 0.65)	0.70 (0.54 – 0.90)
Interaction in regression model analyzing risk of HF event/death		
CRT x continuous QRS score - P-value	0.855	0.246
CRT x QRS score 5 - P-value	0.986	0.327

CI – Confidence Interval. LBBB – Left Bundle Branch Block. CRT Cardiac Resynchronization Therapy. HF – Heart Failure. HR – Hazard Ratio.