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Short Title (3-5 words): LOR Predicts Poor CRT Response

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Abstract:

Background: A low electrocardiogram (ECG) Lead One Ratio (LOR) of the maximum positive/negative QRS amplitudes is associated with lower left ventricular ejection fraction (LVEF) and worse outcomes in left bundle branch block (LBBB); however, the impact of LOR on CRT outcomes is unknown. We compared clinical outcomes and echocardiographic changes after cardiac resynchronization therapy (CRT) implantation by LOR.

Methods: Consecutive CRT-defibrillator recipients with LBBB implanted between 2006-2015 at Duke University Medical Center were included (N=496). Time to heart transplant, left ventricular assist device (LVAD) implantation or death was compared among patients with LOR< vs ≥12 using Cox-proportional hazard models. Changes in LVEF and LV volumes after CRT were compared by LOR.

Results: Baseline ECG LOR<12 was associated with an adjusted hazard ratio (HR) of 1.69 (95% CI: 1.12-2.40, p=0.01) for heart transplant, LVAD or death. Patients with LOR<12 had less reduction of LV end diastolic volume (ΔLVEDV -4 ± 21 vs -13 ± 23%, p=0.04) and LV end systolic volume (ΔLVESV -9 ± 27 vs -22 ± 26%, p=0.03) after CRT. In patients with QRS duration (QRSd) ≥150ms, LOR<12 was associated with an adjusted HR of 2.01 (95% CI 1.21-3.35, p=0.008) for heart transplant, LVAD or death, compared with LOR≥12.

Conclusions: Baseline ECG LOR<12 portends worse outcomes after CRT implantation in patients with LBBB, specifically among those with QRSd≥150ms. This ECG ratio may identify patients with a class I indication for CRT implantation at high risk for poor post-implantation outcomes.

Key Words (5-10): Left Bundle Branch Block, Cardiac Resynchronization Therapy, Electrocardiography, Clinical Outcomes, Echocardiography

Abbreviations:

CI: confidence interval

CRT: cardiac resynchronization therapy

CRT-D: cardiac resynchronization therapy defibrillator

CRT-P: cardiac resynchronization therapy pacemaker

ECG: electrocardiogram

HR: hazard ratio

ICD: implantable cardioverter-defibrillator

LBBB: left bundle branch block

LOR: lead one ratio

LV: left ventricle

LVAD: left ventricular assist device

LVEF: left ventricular ejection fraction

LVEDV: left ventricular end diastolic volume

LVESV: left ventricular end systolic volume

NICM: non-ischemic cardiomyopathy

NYHA: New York Heart Association

Introduction:

Left bundle branch block (LBBB) can precipitate left ventricular (LV) systolic dysfunction in some patients and is independently associated with a higher mortality.[1,2] Cardiac resynchronization therapy (CRT) improves cardiac function, facilitates LV reverse remodeling and reduces mortality in patients with LBBB.[3] Electrocardiogram (ECG) features such as QRS duration, area and morphology have been previously shown to be important predictors of response to CRT.[4-7] Prior work has demonstrated that LBBB patients with a low ECG Lead One Ratio (LOR) of positive/negative amplitudes have lower LV ejection fraction (LVEF) and worse clinical outcomes.[8] The LOR is calculated by dividing the maximum positive and negative amplitudes of the QRS complex in ECG lead I. This ECG metric was hypothesized to identify a more asymmetric LV conduction pattern similar to the asymmetric/dyssynchronous, U-shaped LV contraction pattern (type II LBBB) shown to be a strong predictor of CRT response in prior independent studies.[9,10] LV lateral wall pacing via CRT may allow for correction of both septal-lateral wall dyssynchrony caused by LBBB and anterior-inferior wall dyssynchrony caused by the U-shaped activation pattern. We hypothesized that patients with LBBB and a low LOR would have more LV reverse remodeling and better clinical outcomes after CRT.

Methods:

Study population:

Patients with LBBB who had a CRT-defibrillator (CRT-D) device implanted between April 2006 and September 2015 at Duke University Medical Center were identified for this analysis. Included patients had a digital 12-lead ECG demonstrating LBBB (as defined by Strauss et al.[11]) within 6 months prior to CRT-D implantation. Patients were excluded if they had arrhythmias on their ECG precluding analysis of the QRS complex. For all patients, informed consent was retrospectively waived by the Duke University Institutional Review Board.

Demographic information including age, gender, race, ethnicity, New York Heart Association Class (NYHA), comorbidities, medications and prior cardiac devices were abstracted from data prepared for submission to the National Cardiovascular Disease Registry by the implanting physician or nurse practitioner at the time of the CRT-D procedure.

ECG Analyses:

Digital ECG data were analyzed using the MUSE Cardiology Information System version 8.0.2.10132 with 12SL analysis software version 241 (General Electric Healthcare, Milwaukee, WI, USA). The maximum positive and negative amplitudes within the QRS complex in lead I were extracted from the 12SL measurements from digital ECG XML files exported from MUSE. The ratio of positive/negative amplitudes in lead I (LOR) was calculated for each ECG and patients were divided into those with a LOR≥12 (normal) or <12 (low/abnormal) based on prior work in two independent populations demonstrating that this threshold had the highest sensitivity and specificity for identifying reduced LV systolic function and has been associated with poor prognosis in LBBB (examples in Figure 1).[8,12]

QRS area was derived from the XML files as previously described.[7] Briefly, the vectorcardiogram was derived using the inverse Kors method on the median beat. The integral between the ventricular deflection and the baseline from the onset to the offset of the QRS complex in the x, y and z planes was calculated and QRS area was defined as the vectorial sum of these integrals.

Clinical Outcomes:

The primary study end point was time to heart transplantation, LV assist device (LVAD) implantation, or death. End point ascertainment was performed on May 24, 2017 via a query of the Duke Enterprise Data Unified Content Explorer by incorporating data from billing claims, hospital records, and the Social Security Death Index.[13] Time from CRT-D implantation to death, LVAD or heart transplant was calculated for all included patients.

Echocardiographic Assessment:

A subset of patients had echocardiograms prior to implantation of their CRT-D implantation ("Pre-CRT echo") and after CRT-D implantation ("Post-CRT echo"). Echocardiograms were individually reviewed and analyzed for LV end diastolic volumes (LVEDV), LV end systolic volumes (LVESV) and calculated LVEF using post-processing software (TomTec Imaging Systems GMBH, Unterschleissheim, Germany). The percent change in these variables between the baseline and follow-up echoes was calculated for all patients. Additionally, the proportion of patients whom experienced a ≥15% reduction in LVESV (a measure of reverse remodeling and successful CRT response)[14,15] was calculated.

Statistical Analyses:

Demographic and patient baseline characteristics were compared between patients with LOR<12 and ≥12. All analyzed variables followed a Gaussian distribution and data are presented as mean ± standard deviation or proportions as n (%). Continuous variables were analyzed using two-tailed t-tests and categorical variables were compared using Pearson's chi-squared test.

A Kaplan-Meier curve was generated to compare the hazard of the primary outcome (death, LVAD or heart transplant) between patients with LOR<12 and those ≥12. Cox-proportional hazard models were constructed to quantify this risk in both univariable and multivariable models. The proportionality assumption was confirmed with log(-log) plots. The multivariable model included patient characteristics which were unbalanced between the LOR groups as well as variables known to influence CRT response (QRS duration, QRS area, LVEF, non-ischemic cardiomyopathy [NICM], presence of atrial fibrillation/flutter).[16-18] A subgroup analysis was performed for stratifying patients by QRSd above and below a threshold of 150ms for both the primary outcome and echocardiographic analyses. Analyses were performed using R (R Core Team, 2014) and figures were produced using ggplot2 (Wickam, 2009).

Results:

A total of 496 patients were identified with an available pre-procedure ECG showing LBBB and CRT-D device implantation during the study timeframe. LOR was ≥12 in 383 (77%) patients and <12 in 113 (23%) patients. Table 1 shows the patient characteristics according to LOR. Patients with LOR<12 were younger (63 ± 11 vs 66 ± 12, p=0.003), more often male (79.6% vs 60.8%, p=0.002), more frequently had a prior implantable cardioverter-defibrillator (ICD) (27.4% vs 13.1%, p=0.002), less often had NICM (43.4% vs 62.9%, p=0.0002), and more often had a history of stroke (16.8% vs 8.9%, p=0.04) than patients with LOR ≥12. Patients with LOR<12 had more symptomatic heart failure (8.8% vs 2.1% NYHA class IV, p=0.001) despite similar LVEF (22 ± 9% vs 23 ± 9%, p=0.54) and smaller QRS areas (86 ± 38 μVs vs 108 ± 43 μVs, p<0.001) despite similar QRS durations (156 ± 25 ms vs 156 ± 22 ms, p=0.88) compared to patients with LOR ≥12. Medication use was similar between both groups as was biventricular pacing percentage.

Clinical outcomes:

Clinical outcomes data were available for all patients with a median follow up time of 3.0 years. Kaplan-Meier curves comparing time to death, heart transplant or LVAD by LOR are shown in Figure 2. Patients with a LOR≥12 experienced a total of 143 events (127 deaths, 5 heart transplants, and 12 LVAD implantations) with a median time from CRT implantation to event of 7.6 years. Patients with a LOR<12 experienced 61 events (46 deaths, 11 heart transplants, and 7 LVAD implantations) with a median time from CRT implantation to event of 4.3 years. In a univariable Cox-proportional hazards model, LOR<12 was associated with a hazard ratio (HR) of 1.82 (95% confidence interval [CI] 1.34-2.45, p<0.001) for the outcome of death, heart transplant or LVAD (Table 2). A multivariable Cox-proportional hazard model was created including variables that differed between LOR groups (age, sex, NYHA class, prior ICD, NICM, history of stroke) as well as known predictors of CRT outcomes (QRSd, QRS area, LVEF, presence of atrial fibrillation/flutter). In

the multivariable model, LOR<12 was associated with a HR of 1.69 (95% CI: 1.12-2.40, p=0.01) for the combined clinical outcome. Other variables significantly associated with a higher risk of death, heart transplant or LVAD included age (HR 1.02 [1.00-1.04] per year, p=0.02), history of prior ICD (HR 2.17 [1.46-3.23], p<0.001), and atrial fibrillation (HR 1.76 [1.22-2.54], p=0.002). Lower event rates were seen in patients with larger baseline QRS areas (HR 0.99 [0.98-1.00] per microvolt-second [μVs] increase, p<0.001) and higher baseline LVEF (HR 0.96 [0.94-0.98] per % increase p<0.001).

Echocardiographic response:

Of the 496 included patients, 140 had both baseline and follow-up echocardiogram data available. The median time between acquisition of the baseline echocardiogram and CRT implantation was 42 days and the median time between baseline and follow up echocardiograms was 232 days. Patients had a mean reduction in LVEDV of -11 ± 23%, mean reduction in LVESV of -20 ± 27%, and a relative improvement in LVEF of 52 ± 76% compared to baseline (absolute LVEF change of 8 ± 10%) (Table 3). Eighty-seven out of 140 patients (62%) demonstrated a ≥15% reduction in LVESV. Patients with LOR<12 had less reduction in LVEDV (-4 ± 21% vs -13 ± 23%, p = 0.04), and LVESV (-9 ± 27% vs -22 ± 26%, p=0.03), but relative change in EF was not statistically significant (50 ± 105% vs 52 ± 67%, p=0.91). There was a trend towards lower reverse remodeling rates (≥15% reduction in LVESV) in patients with low (<12) vs normal (≥12) LOR (47% vs 66%, p=0.06).

Subgroup analyses by QRS duration:

Patients were sub-grouped into those with QRSd<150 ms (N=200) and those with QRSd≥150 ms (N=296). LOR<12 occurred in 65/296 (22%) patients with QRSd≥150 ms and in 48/200 (24%) patients with QRSd<150 ms (p=0.66 for difference). LOR<12 was associated with a higher hazard of death, heart transplant or LVAD implantation in patients with QRSd≥150 ms (univariable HR 2.07 [1.37-3.08], p<0.001; multivariable HR 2.01 [1.21-3.35], p=0.008), but not in those with QRSd<150 ms (univariable HR 1.50 [0.94-2.34], p=0.09; multivariable HR 1.18 [0.63-2.22], p=0.61) (Table 2).

Kaplan-Meier curves stratified by both LOR and QRSd show that patients with a QRSd≥150 ms and a LOR<12 had similar event rates as patients with QRSd<150 ms (Figure 3, blue line compared with green and red lines). Kaplan-Meier curves stratified by LOR and dichotomized QRS area (< or ≥69 μVs) demonstrated a similar pattern where patients with QRS area ≥69 μVs and a LOR<12 had similar event rates as patients with QRS area <69 μVs (Supplemental figure, blue line compared with green and red lines)

Discussion:

ECG LOR<12 in LBBB is associated with worse clinical outcomes and less improvement in LV volumes after CRT-D implantation. Among patients with markedly prolonged QRSd (≥150ms), LOR<12 was associated with worse clinical outcomes and similar event rates as patients with QRSd<150 ms. These findings suggest that LOR<12 may identify patients at higher risk for adverse clinical outcomes after CRT implantation including patients with LBBB and QRSd≥150ms who currently have a class I indication for CRT implantation.[19] LOR<12 remains predictive of adverse outcomes after adjustment for other known predictors of poor CRT response including sex, ischemic etiology of cardiomyopathy, QRS duration, QRS area, baseline LVEF, and presence of atrial fibrillation.

While there were numerically more events in the LOR ≥ 12 group, a larger proportion of patients with LOR <12 experienced an endpoint (54% vs 37%) and did so earlier after CRT implantation compared to LOR ≥ 12 (median time to event 4.3 vs 7.6 years). Death was the most common endpoint; however, 17 of the 61 events (28%) in the LOR < 12 group were due to LV failure resulting in heart transplant or LVAD implantation compared to 17 of 143 events (12%) in the LOR ≥ 12 group. Unfortunately, the causes of death are not available in this cohort limiting our ability to fully understand the mechanisms behind the differential event rates between the groups. Examining the Kaplan-Meier curves in Figure 2, we see that the curves separate early and then maintain a

relatively constant hazard rate overtime. This suggests that the clinical trajectories after CRT implantation diverged early and that the LOR < 12 group had an accelerated clinical decline compared to patients with LOR ≥ 12.

The hypothesis of this study was that a low LOR would predict higher response rates to CRT as it was thought to identify a more malignant form of LV dyssynchrony potentially amenable to correction by CRT.[9,10] The results of the study; however, demonstrated that patients with low LOR had *worse* clinical outcomes after CRT-D implantation than those with normal LOR. There are several potential explanations for this result. Low LOR may be a marker of LV scar, which in turn is associated with poor response to CRT.[20] Two prior studies of LOR demonstrated inconsistent results regarding the relationship between LOR and LV scar.[8,12] Larger future studies may clarify this relationship.

Alternatively, low LOR may be a marker of asymmetric LV conduction that is not correctable by current resynchronization strategies. In our center, during the study timeframe, LV leads were placed preferentially in the basal or midventricular posterolateral or anterolateral branch of the coronary sinus based on available literature identifying these locations as most likely to provide benefit from CRT implantation in patients with LBBB.[21] The asymmetric pattern we hypothesized might cause LOR<12 may not be as responsive to stimulation from the lateral wall due to anatomical or functional lines of block. Targeting LV lead placement based on individual LBBB electrical activation or contraction patterns has shown promise in improving CRT outcomes.[22] Patients with LOR<12 may have lines of block that cause asymmetric conduction which may require a targeted LV lead placement approach.

Patients with LOR<12 had significantly lower mean QRS area than patients with LOR≥12. QRS area is a measure of non-opposed electrical forces, and high values suggest more significant dyssynchrony and have also been associated with greater response to CRT.[6,7] When QRS area was

included in multivariable models along with QRS duration, LOR<12 remained strongly predictive of clinical outcomes. When LOR is used in combination with QRS duration and/or QRS area, it is able to identify high risk patients among those with ECG features otherwise associated with favorable response to CRT (prolonged QRS duration and large QRS area). QRS area is a measure of dyssynchrony irrespective of any specific direction or plane; whereas, LOR relies on a single lead and quantifies the balance of rightward and leftward electrical forces. Patients with LOR<12 and large QRS areas may have severe dyssynchrony, but this dyssynchrony is not aligned along the right-left axis. Thus, placing the LV lead in the lateral wall (as is done in the plurality of cases)[23] may not effectively correct dyssynchrony in these patients which may explain the observed poor outcomes. Studies evaluating LOR, LV lead position, and CRT response are ongoing.

The prior studies showing a higher rate of response to CRT among patients with asymmetric contraction patterns may also have identified patients earlier in their disease process when CRT could reverse the pattern.[9,10] LOR<12 may be a phenomenon reflecting irreversible electrical or anatomical LV remodeling that is not correctable by CRT. The patients with LOR<12 had larger LV volumes and were more likely to have a pre-existing ICD than patients with LOR≥12 suggesting that they had more adverse structural remodeling prior to CRT. Rather than being an early sign of dyssynchrony amenable to correction, it may be a marker of more severe disease, which is too advanced to be fully corrected with CRT.[24] Further studies comparing this ECG pattern to contraction patterns and evaluating how it changes over time will help further define the relationship between these metrics.

LOR<12 was noted to be associated with worse clinical outcomes among patients with severely prolonged QRS durations (≥150 ms). This difference was not significant in patients with moderately prolonged QRS durations (130-150 ms); however, this group was smaller in size and did show numerically worse outcomes with low LOR. The data from this study suggest that LOR<12 is a negative prognostic indicator for adverse clinical outcomes after CRT in patients with severely prolonged QRS durations.

Limitations:

This study evaluates longitudinal clinical outcomes and echocardiographic changes in a large dataset of CRT-D patients; however, it has several important limitations. This is a retrospective, single center observational study, which limits any claims of causality between ECG patterns and clinical outcomes. Multivariable models were evaluated; however, many unmeasured variables including lead position, were not available to be included in analyses. While we included QRS duration and QRS area as variables in our multivariable models, other ECG predictors (e.g. left ventricular activation time)[4] were not available in this dataset. Biventricular pacing percentage was only available on slightly more than half of the patients (58.5%, N=290) but appeared to be similar between patients with LOR<12 vs ≥12. The composite outcome of death, LVAD or transplant is non-ambiguous; however, whether these outcomes occurred due to worsened arrhythmias or progressive pump failure cannot be determined from this dataset. As this study evaluated only echocardiograms obtained through routine clinical care, echocardiograms may have been more likely to be ordered in patients with persistent symptoms despite CRT implantation resulting in an underestimation of remodeling rates. Only a subset of patients had available echocardiographic data and these results were designed to be exploratory and hypothesis generating. This study evaluated patients with CRT-D devices and did not include any patients with CRT pacemakers (CRT-P) so conclusions about the effect of this ECG parameter on CRT response cannot be extrapolated to those receiving CRT-P devices. While the clinical importance of using 12 as a threshold for the LOR has been previously studied,[8] the stability of this measure over time is unknown. Current, ongoing longitudinal studies will establish the normal limits for individual variation over time.

Conclusions:

In patients with LBBB receiving a CRT-D device, LOR<12 is associated with worse clinical outcomes and less echocardiographic improvement. This ECG pattern portends a particularly poor

prognosis to those with severely prolonged QRS duration who are traditionally thought of as having a high response rate to CRT. Future work will explore whether these patients may benefit from personalized resynchronization strategies.

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Figure Legends:

Figure 1: LOR examples: 12-lead ECGs with zoomed inset displaying median beat of lead I. The full 12-lead ECG is displayed with standard scale of 10mm/mV with a paper speed of 25mm/sec. The zoomed inset depicts the median beat for lead I displayed at a scale of 20mm/mV and paper speed of 50mm/sec, brackets not to scale. **A**: Patient with LBBB, QRSd 188ms and a maximum positive amplitude of 913μV and maximum negative amplitude of 39μV corresponding to a LOR of 23.4; **B**: Patient with LBBB, QRSd 152 and a maximum positive amplitude of 214μV, maximum negative amplitude of 97μV, and a LOR of 2.21. ECG = electrocardiogram; LBBB = left bundle branch block; LOR = lead one ratio, QRSd = QRS duration.

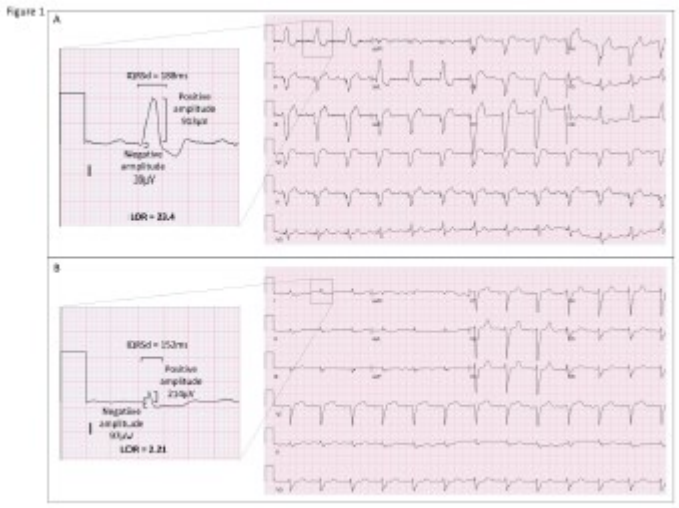

Figure 2: **Clinical outcomes after CRT-D by LOR**. Kaplan-Meier curve demonstrating rates of death, heart transplant or LVAD implantation stratified by LOR. CRT-D = cardiac resynchronization therapy- defibrillator; LOR = lead one ratio; LVAD = left ventricular assist device.

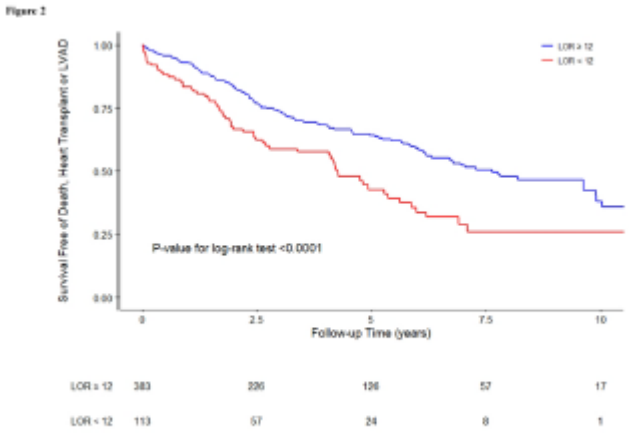

Figure 3: **Clinical outcomes after CRT-D by LOR and QRSd**. Kaplan-Meier curve demonstrating rates of death, heart transplant or LVAD implantation stratified by LOR and QRSd. CRT-D = cardiac resynchronization therapy- defibrillator; LOR = lead one ratio; LVAD = left ventricular assist device; QRSd= QRS duration.

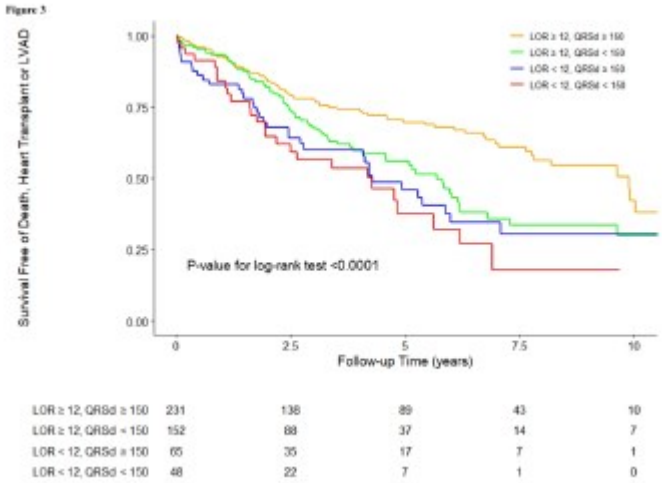

Table 1: Baseline Characteristics:

Table 1	Total	LOR< 12	LOR≥ 12	P-value
N	496	113	383	
Age	63 ± 12	63 ± 11	66 ± 12	**0.003**
Sex (n, % male)	323 (65.1%)	90 (79.6%)	233 (60.8%)	**0.002**
Race				
Black	99 (20.0%)	25 (22.1%)	74 (19.3%)	
Caucasian	246 (49.6%)	53 (46.9%)	193 (50.4%)	
Asian	4 (0.8%)	0 (0.0%)	4 (1.0%)	0.08
Eskimo	1 (0.2%)	1 (0.9%)	0 (0.0%)	
Indian	10 (2.0%)	5 (4.4%)	5 (1.3%)	
Unknown	136 (27.4%)	29 (25.7%)	107 (27.9%)	
Hispanic	2 (0.4%)	0 (0.0%)	2 (0.5%)	0.16
Ejection fraction (%)	23 ± 9	22 ± 9	23 ± 9	0.54
QRSd (ms)	156 ± 22	156 ± 25	156 ± 22	0.88
QRS area (μVs)	103 ± 43	86 ± 38	108 ± 43	**<0.001**
Post-CRT QRSd (ms)	153 ± 23	152 ± 24	153 ± 23	0.96
% Biventricular pacing	99 (95-100)	98 (93-100)	99 (95-100)	0.45
NYHA Class				
I	14 (2.8%)	5 (4.4%)	9 (2.3%)	
II	85 (17.1%)	12 (10.6%)	73 (19.1%)	**0.001**
III	379 (76.4%)	86 (76.1%)	293 (76.5%)	
IV	18 (3.6%)	10 (8.8%)	8 (2.1%)	
Prior ICD	81 (16.3%)	31 (27.4%)	50 (13.1%)	**0.002**
Prior pacemaker	19 (3.8%)	5 (4.4%)	14 (3.7%)	0.49
Ischemic CM	233 (47.0%)	69 (61.1%)	164 (42.8%)	**0.0006**

Non-ischemic CM	290 (58.5%)	49 (43.4%)	241 (62.9%)	**0.0002**
Atrial fibrillation/flutter	125 (25.2%)	34 (30.1%)	91 (23.8%)	0.17
Hypertension	355 (71.6%)	81 (71.7%)	274 (71.5%)	0.98
Diabetes mellitus	161 (32.5%)	39 (34.5%)	122 (31.9%)	0.6
End stage renal disease	14 (2.8%)	5 (4.4%)	9 (2.3%)	0.32
History of stroke	53 (10.7%)	19 (16.8%)	34 (8.9%)	**0.04**
Chronic lung disease	99 (20.0%)	30 (26.5%)	69 (18.0%)	0.07
Medications				
Beta blocker	443 (89.3%)	94 (83.2%)	349 (91.1%)	0.07
ACEi/ARB	404 (81.4%)	84 (74.3)	321 (83.8%)	0.06
AAD	84 (16.9%)	26 (23.0%)	58 (15.1%)	0.06
Digoxin	83 (16.7%)	26 (23.0%)	57 (14.9%)	0.06
Diuretic	406 (81.9%)	87 (77.0%)	319 (83.3%)	0.22

Variables expressed as mean (standard deviation), median (interquartile range), or n (% of population) as appropriate. AAD = antiarrhyhmic drug (includes amiodarone, mexilitine, sotalol); ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CM = cardiomyopathy; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association; QRSd = QRS duration

Table 2: Hazard Models: Hazard ratios for univariable and multivariable Cox-proportional hazard models for the outcome of death, heart transplant or left ventricular assist device implantation.

Table 2	Total population			QRSd<150 ms			QRSd≥150 ms		
N	496			200			296		
Univariable model	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
LOR<12	1.82	1.34-2.45	**<0.001**	1.50	0.94-2.34	0.09	2.07	1.37-3.08	**<0.001**
Multivariable model	HR	95%CI	P-value	HR	95%CI	P-value	HR	95%CI	P-value
LOR<12	1.69	1.12-2.40	**0.01**	1.18	0.63-2.22	0.61	2.01	1.21-3.35	**0.008**
Age	1.02	1.00-1.04	**0.02**	1.01	0.98-1.00	0.48	1.02	0.98-1.05	0.09
Male	1.13	0.75-1.69	0.55	1.77	0.89-3.55	0.11	0.93	0.55-1.60	0.81
NYHA class III/IV	1.26	0.78-2.04	0.34	1.01	0.49-2.06	0.99	1.75	0.88-3.48	0.11
Prior ICD	2.17	1.46-3.23	**<0.001**	2.92	1.69-5.07	**<0.001**	2.03	1.04-3.98	**0.04**
Non-ischemic CM	0.95	0.66-1.37	0.80	0.98	0.57-1.69	0.96	0.88	0.53-1.46	0.63
History of stroke	0.86	0.54-1.38	0.54	0.70	0.33-1.49	0.36	0.92	0.49-1.75	0.81
QRS duration	1.00	0.99-1.01	0.57	1.01	0.99-1.03	0.33	0.99	0.97-1.00	0.12
QRS area	0.99	1.12-2.40	**<0.001**	0.99	0.98-1.00	**0.02**	0.99	0.98-1.00	**0.01**
LVEF	0.96	0.94-0.98	**<0.001**	0.97	0.94-1.00	0.06	0.96	0.93-0.99	**0.006**
Atrial	1.76	1.22-	**0.002**	1.50	0.86-	0.15	2.26	1.38-	**0.001**

fibrillation/flutter	2.54	2.62	3.72

Hazard ratios for age, QRS duration, QRS area and LVEF refer to incremental hazard per unit increase. Hazard ratios for NYHA are hazard compared to NYHA class I/II. CM = cardiomyopathy; ICD = implantable cardioverter defibrillator; LOR = lead one ratio; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

Table 3: Echocardiographic measures before and after CRT

Table 3	Total			LOR<12			LOR≥12			
N	140			30			110			
	Pre	Post	%Change	Pre	Post	%Change	Pre	Post	%Change	P-value *
LVEDV (mL)	227 ± 93	198 ± 88	-11 ± 23	244 ± 89	231 ± 89	-4 ± 21	223 ± 94	190 ± 86	-13 ± 23	**0.04**
LVESV (mL)	179 ± 87	142 ± 81	-20 ± 27	194 ± 84	173 ± 88	-9 ± 27	174 ± 87	133 ± 77	-22 ± 26	**0.03**
LVEF (%)	23 ± 9	31 ± 11	52 ± 76	21 ± 9	27 ± 12	50 ± 105	24 ± 8	33 ± 11	52 ± 67	0.91
≥15% ΔLVESV	87 (62%)			14 (47%)			73 (66%)			0.06

*P-values express difference between patients with LOR<12 and LOR ≥12. CRT = cardiac resynchronization therapy; LVEDV = left ventricular end diastolic volumes; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volumes; LOR = lead one ratio