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Concomitant Changes in Ventricular Depolarization and Repolarization and Long-Term Outcomes of Biventricular Pacing

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Abstract

BACKGROUND: Biventricular (BiV) pacing increases transmural repolarization heterogeneity due to epicardial to endocardial conduction from the left ventricular (LV) lead. However, limited evidence is available on concomitant changes in ventricular depolarization and repolarization and long-term outcomes of BiV pacing. Therefore, we investigated associations of BiV pacing-induced concomitant changes in ventricular depolarization and repolarization with mortality (i.e., LV assist device, heart transplantation, or all-cause mortality) and sustained ventricular arrhythmia endpoints.

METHODS: Consecutive BiV-defibrillator recipients with digital pre- and post-implantation electrocardiograms recorded between 2006 and 2015 at Duke University Medical Center were included. We calculated changes in QRS duration and corrected JT (JTc) interval and split them by median values. For simplicity, these variables were named $QRS_{decreased}$ (≤–12 ms), $QRS_{increased}$ (>–12

ms), $JTc_{decreased}$ (≤22 ms), and $JTc_{increased}$ (>22 ms) and subsequently used to construct four mutually exclusive groups.

RESULTS: We included 528 patients (median age, 68 years; male, 69%). No correlation between changes in QRS duration and JTc interval was observed (p=0.295). Compared to $QRS_{decreased}/JTc_{increased}$, increased risk of the composite mortality endpoint was associated with $QRS_{decreased}/JTc_{decreased}$ (hazard ratio [HR]=1.62; 95% confidence interval [CI]=1.09–2.43), $QRS_{increased}/JTc_{decreased}$ (HR=1.86; 95% CI=1.27–2.71), and $QRS_{increased}/JTc_{increased}$ (HR=2.25; 95% CI=1.52–3.35). No QRS/JTc group was associated with excess sustained ventricular arrhythmia risk (p=0.400).

CONCLUSION: Among BiV-defibrillators recipients, $QRS_{decreased}/JTc_{increased}$ was associated with the most favorable long-term survival free of LV assist device, heart transplantation, and sustained ventricular arrhythmias. Our findings suggest that improved electrical resynchronization may be achieved by assessing concomitant changes in ventricular depolarization and repolarization.

KEY WORDS: Biventricular Pacing; Cardiac Resynchronization Therapy; Heart Failure; Implantable Cardioverter-Defibrillator; Ventricular Arrhythmias; Ventricular Repolarization.

Abbreviations

ATP = antitachycardia pacing

BiV = biventricular

bpm = beats per minute

CI = confidence interval

ECG = electrocardiogram

eGFR = estimated glomerular filtration rate

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

JTc = corrected JT

LBBB = left bundle branch block

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

RV = right ventricular

VF = ventricular fibrillation

VT = ventricular tachycardia

Introduction

Although biventricular (BiV) pacing remains an established therapy for patients with heart failure and left ventricular (LV) dyssynchrony, around 30% of patients derive no benefit.[1] Current clinical guidelines on BiV pacing recommend using prolonged QRS duration as a marker of dyssynchrony on the standard 12-lead electrocardiogram (ECG),[2] but the change in QRS duration with BiV pacing is inconsistently associated with likelihood of response.[3] Novel ECG dyssynchrony markers including R-wave amplitude in V1–V2, vectorcardiographic QRS area, or time from QRS onset to the intrinsicoid deflection in V1, V5, aVL, and aVF have been shown to predict response to BiV pacing better than prolonged QRS duration.[4-8] However, their clinical implementation is limited largely due to the lack of availability during routine clinical practice making post-implantation prognostication using standard 12-lead ECG challenging.

Assessing the absolute change in QRS duration in combination with the concomitant change in ventricular repolarization following BiV pacing is easy and readily available in real time during device implantation and follow-up using standard 12-lead ECG. BiV pacing increases transmural repolarization heterogeneity due to epicardial to endocardial wavefront propagation from the LV lead,[9-11] but data are inconsistent on its effect on common ECG markers of ventricular repolarization including QT interval, QT dispersion, JT interval, and Tpeak to Tend interval.[12] Furthermore, while some studies have associated BiV pacing-induced increases in QT interval with excess ventricular arrhythmia burden,[13-17] others suggest no association.[18] Although QT prolongation is common with BiV pacing, and most patients benefit despite developing transmural repolarization heterogeneity,[19, 20] little is known about the complex interaction between concomitant changes in ventricular depolarization and repolarization and their association with long-term outcomes of BiV pacing.

As such, using a single-center cohort of recipients of BiV implantable cardioverter-defibrillators (ICDs), we investigated long-term risks of mortality and sustained ventricular arrhythmia endpoints associated with acute concomitant changes in QRS duration and corrected JT (JTc) interval. As prolonged QRS duration may contribute to artificial QT prolongation, thus making true QT assessment difficult, we utilized the JT interval as a more valid marker of ventricular repolarization in this patient population.[21]

Methods

Study Design and Population

This was a single-center retrospective observational cohort study performed at Duke University Medical Center, Durham, NC, United States. Our study was approved by the Duke Institutional Review Board.

Using an institutional data set prepared for the National Cardiovascular Data Registry, first-time recipients of BiV-ICDs were identified between April 01, 2006, and September 30, 2015. We restricted the cohort to patients demonstrating QRS duration ≥120 ms as assessed on digital ECG within 180 days prior to implantation and left ventricular ejection fraction (LVEF) ≤35% as assessed within 365 days prior to implantation. Patients were further required to have a digital follow-up ECG recorded within 90 days following implantation. Patients were excluded if ECG measurements were unmeasurable or they died prior to discharge. If multiple ECGs were available in the allowable pre-implantation and post-implantation period, the ECG closest to the implantation was utilized.

Electrocardiography

Clinically obtained digital ECGs were reanalyzed in the MUSE Cardiology Information System version 8.0.2.10132 using the Marquette 12SL algorithm version 241 (GE Healthcare, WI, USA) and exported in .xml format. QRS morphology was assessed by two authors (DJF and KE) blinded to outcome. P-wave, PR, QRS, and QT onsets and offsets and thereby P-wave duration, PR interval, QRS duration, and QT interval as detected by the 12SL algorithm were over read and manually corrected if needed.

We calculated the JTc interval as the Fridericia-corrected QT interval minus the QRS duration, as done previously.[21] Using pre-implantation and post-implantation ECGs, we calculated changes in QRS duration and JTc interval as post-implantation ECG value minus pre-implantation ECG value and split them by median values. This was done to ensure adequate sample sizes for later analyses. For simplicity, these variables were named $QRS_{decreased}$ (≤–12 ms), $QRS_{increased}$ (>–12 ms), $JTc_{decreased}$ (≤22 ms), and $JTc_{increased}$ (>22 ms) and subsequently used to construct four mutually exclusive groups ($QRS_{decreased}/JTc_{decreased}$, $QRS_{decreased}/JTc_{increased}$, $QRS_{increased}/JTc_{decreased}$, and $QRS_{increased}/JTc_{increased}$).

Echocardiography and Clinical Data

Two-dimensional echocardiography was performed using ImageArena version 4.6 (TomTec Imaging Systems, Unterschleissheim, Germany). We derived LV volumes using a modified Simpson's triplane method included in the software based on apical four-chamber, two-chamber, and long-axis views. We reported pre-implantation LV volumes including LVEF, left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV).

We further reported data on age, sex, race, current ICD indication, prior ICD, prior cardiac arrest, comorbidities, and drug use at discharge. The renal function of patients was assessed using the estimated glomerular filtration rate (eGFR).[22]

Device Interrogation Data

Implantation, programming, and selection of the device were at the discretion of the treating electrophysiologist. Patients were longitudinally followed using remote patient monitoring or in-clinic device interrogation, and all reports obtained within the first 2 years following implantation were retrospectively reviewed in the electronic medical record. Devices were usually programmed to initially treat ventricular tachycardia (VT) with antitachycardia pacing (ATP) followed by high-voltage shocks if ATP failed. Ventricular fibrillation (VF) was treated with high-voltage shocks. Device electrograms from all treated arrhythmias were manually reviewed by two authors (CP and BDA) and classified as appropriate if therapy was delivered for ventricular arrhythmias meeting the preprogrammed detection criteria or inappropriate if delivered for supraventricular arrhythmias or noise.

Endpoints

Patients were followed from implantation to an incident composite mortality endpoint (i.e., LV assist device, heart transplantation, or all-cause mortality). Endpoint ascertainment was performed on May 24, 2017, using a query of the Duke Enterprise Data Unified Content Explorer that incorporates data from billing claims, hospital records, and the Social Security Death Index.[23] We performed an additional analysis using appropriate ICD therapies for sustained ventricular arrhythmias.

Statistical Analysis

Continuous variables were reported as medians with 25th–75th percentiles or means with standard deviations and categorical variables as counts with percentages. Differences in variables were compared using Kruskal-Wallis, one-way analysis of variance, and chi-squared tests as appropriate. For differences in pre-implantation and post-implantation QRS duration and JTc interval, the Wilcoxon rank-sum test was used. We further displayed boxplots and scatterplots for visual comparisons.

Cumulative incidence curves of endpoints by QRS/JTc groups were computed and displayed using the Kaplan-Meier method, and differences were tested using the log-rank test. Cox regression was used to compute hazard ratios (HRs) with 95% confidence intervals (CIs) of the association of QRS/JTc groups with endpoints.

The proportional hazard assumption was tested by displaying cumulative Martingale residuals and was not violated. Interaction testing was performed by introducing an interaction term in a Cox regression model and using a likelihood ratio test to compare this model to one without an interaction term. Specifically, we tested whether the change in JTc interval (decreased vs. increased groups) modified the association of the change in QRS duration (decreased vs. increased groups) with endpoints. Linearity of continuous variables was also assessed using a likelihood ratio test

comparing a linear description with a categorical one. Both age and LVEF were observed to violate the linearity assumption and were therefore included as categorical variables based on quartiles.

All models were adjusted for age quartiles, sex, QRS morphology, LVEF quartiles, ischemic cardiomyopathy, atrial fibrillation, hypertension, diabetes, and eGFR <60 mL/min/1.73 m^2. We additionally adjusted for current ICD indication, prior ICD, prior cardiac arrest, and amiodarone use when assessing risk of appropriate ICD therapies for sustained ventricular arrhythmias.

Data management and analysis were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). A $p<0.05$ was considered statistically significant for all analyses except for during interaction testing where an a prior decision was made to use $p<0.01$ to account for multiple testing.

Results

Patient Characteristics

A total of 1001 patients underwent first-time BiV-ICD implantation during the study period. After excluding patients with missing ECGs (*n*=409), pre-implantation QRS duration <120 ms (*n*=37), LVEF >35% (*n*=18), unmeasurable post-implantation QRS duration (*n*=2), and those not surviving to hospital discharge (*n*=7), 528 patients remained for further analysis.

Patients had a median age of 68 (58–75) years, and most were male (69%), white (71%), had left bundle branch block (LBBB) (64%), and ischemic cardiomyopathy (56%). Median time to pre-implantation ECG was 5 (1–21) days and post-implantation ECG was 1 (1–1) day. Median changes in QRS duration and JTc interval were –12 (–26 to 7) ms and 22 (2–41) ms, respectively. When stratifying by QRS/JTc groups, patients with $QRS_{decreased}/JTc_{decreased}$ demonstrated the highest median intrinsic QRS duration and were more often right ventricular (RV) paced. Patients with $QRS_{increased}/JTc_{decreased}$ more often had atrial fibrillation and were more often discharged with diuretics. Finally, patients with $QRS_{increased}/JTc_{increased}$ demonstrated the highest median intrinsic PR interval (Table 1).

Device Programming Characteristics

Median time to follow-up device interrogation was 562 (143–703) days. Patients were usually programmed DDD or DDDR (88%), with a median pacing % of 99 (96–100). Median paced and sensed atrioventricular delays were 130 (130–170) ms and 100 (100–120) ms, respectively, and ventricular-ventricular delay was most often simultaneous (62%). Quadripolar leads were implanted in 15% of patients, and AdaptivCRT was programmed on in 11% of patients, which was more common in the $QRS_{decreased}/JTc_{increased}$ group. Of note, quadripolar leads and AdaptivCRT programming were not clinically available until later in the study period. Tachycardia therapies did not differ by QRS/JTc groups and were more often programmed as a single-zone device detecting VF at a median rate of

200 (188–200) beats per minute (bpm), with varying detection criteria. For patients programmed with a two-zone or three-zone device, VT was detected at a median rate of 171 (162–181) bpm or 188 (178–197) bpm, respectively (Table 2).

Ventricular Depolarization and Repolarization Changes

Following BiV pacing, median QRS duration decreased (pre, 160 [144–180] ms vs. post, 154 [138–168] ms; $p<0.001$), and median JTc interval increased (pre, 326 [305–343] ms vs. post, 349 [326–369] ms; $p<0.001$) (Figure 1A). Around 70% of patients demonstrated post-implantation decrease in QRS duration, and 60% post-implantation increase in JTc interval. Furthermore, we observed that the change in QRS duration did not correlate with the change in JTc interval ($p=0.295$) (Figure 1B).

Long-Term Outcomes

With a median follow-up of 3 (2–5) years, 47% of patients reached the composite mortality endpoint of LV assist device (3%), heart transplantation (5%), and all-cause mortality (39%). Compared to $QRS_{decreased}/JTc_{increased}$, patients with $QRS_{decreased}/JTc_{decreased}$, $QRS_{increased}/JTc_{decreased}$, or $QRS_{increased}/JTc_{increased}$ experienced shorter event-free survival ($p<0.001$) (Figure 2A). Around 12% of patients received at least one appropriate ICD therapy for sustained ventricular arrhythmias, which did not differ by QRS/JTc groups ($p=0.400$) (Figure 2B). This was also similar when assessing the average number of appropriate ICD therapies for VT or VF and delivered ATP or shocks (Table 3).

We observed that the change in JTc interval tended to modify the association of the change in QRS duration with the composite mortality endpoint ($p=0.011$), whereas the interaction analysis did not reach statistical significance with appropriate ICD therapies for sustained ventricular arrhythmias as endpoint ($p=0.549$).

Following multivariable adjustment, risk of the composite mortality endpoint remained increased for $QRS_{decreased}/JTc_{decreased}$ (HR=1.62; 95% CI=1.09–2.43), $QRS_{increased}/JTc_{decreased}$ (HR=1.86; 95% CI=1.27–2.71), and $QRS_{increased}/JTc_{increased}$ (HR=2.25; 95% CI=1.52–3.35) compared to $QRS_{decreased}/JTc_{increased}$ (Figure 3A). No QRS/JTc group was associated with excess risk of appropriate ICD therapies for sustained ventricular arrhythmias (Figure 3B).

Additional Analyses

We designed various additional analyses to test the consistency and robustness of our findings.

1. We performed an explorative analysis, in which changes in QRS duration and JTc interval were split by tertiles (Q1–Q3) instead of median values (Figure S1, Online Supplementary Material). Particularly, the combination of QRS Q3 (>–2 ms) and JTc Q3 (>34 ms) was associated with highest risk of the composite mortality endpoint (HR=4.12; 95% CI=2.16–

7.84) and appropriate ICD therapies for sustained ventricular arrhythmias (HR=5.07; 95% CI=1.24–20.69).

2. In another explorative analysis, we utilized median values of the change in Fridericia-corrected QT interval (decreased group: ≤12 ms, increased group: >22 ms) and combined these with the prespecified QRS groups (Figure S2A–B, Online Supplementary Material). We observed similar trends as in the main analysis.
3. As the study period may affect findings owing to changes in clinical practice in device implantation and programming, as well as patient selection, we additionally adjusted for implantation year, and findings did not deviate from the main analysis (Figure S3, Online Supplementary Material).
4. Although the change in QRS duration is highly correlated with intrinsic QRS duration, QRS/JTc groups were still associated with adverse outcome in a multivariable model including intrinsic QRS duration ≥150 ms (Figure S4, Online Supplementary Material).
5. We additionally adjusted for heart failure drug therapy at discharge including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta-blockers, and diuretics and observed similar findings to the main analysis (Figure S5, Online Supplementary Material).
6. We performed subgroup analyses of LBBB (*n*=339) and non-LBBB or RV-only pacing (*n*=189) (Figure S6A–B, Online Supplementary Material). Despite sample size limitations, we observed similar trends as in the main analysis.
7. We also performed subgroup analyses of ischemic (*n*=294) and non-ischemic (*n*=234) cardiomyopathy (Figure S7A–B, Online Supplementary Material). Particularly, QRS/JTc groups were associated with more than a 3-fold increased risk of adverse outcomes in non-ischemic cardiomyopathy.

Discussion

In this study of real-life recipients of BiV-ICDs, we report a series of key findings underscoring the long-term prognostic value of a QRS/JTc risk stratification model derived from the standard 12-lead ECG, which can easily be incorporated in clinical care. First, we observed that 70% of patients demonstrated post-implantation decrease in QRS duration, and 60% post-implantation increase in JTc interval. Of note, narrowing of the QRS duration did not correlate with prolongation of the JTc interval with BiV pacing. Second, $QRS_{decreased}/JTc_{increased}$ was associated with the most favorable long-term survival free of LV assist device, heart transplantation, and appropriate ICD therapies for sustained ventricular arrhythmias, which was independent of several critical patient characteristics including intrinsic QRS morphology and duration. Finally, our explanatory analysis revealed that patients demonstrating a decrease in QRS duration of ≤–22 ms and an increase in JTc interval of 11–34 ms with BiV pacing comprised a low-risk group.

As described in animal models and simulation studies, BiV pacing induces a reversed sequence of ventricular depolarization and repolarization due to the epicardial pacing location, thus increasing

transmural repolarization heterogeneity and prolonging ventricular repolarization.[10, 11] However, the effect of BiV pacing on ECG markers of ventricular repolarization is inconsistently reported,[12] and prior studies on the association of BiV pacing-induced concomitant changes in ventricular repolarization with ventricular arrhythmia burden are conflicting.[13-18] This suggests that BiV pacing has differential effects on arrhythmogenic substrate. The proarrhythmic effect of BiV pacing may occur early due to the reversed direction of the activation of the LV wall, thus prolonging the QT interval and increasing intrinsic transmural dispersion of repolarization and creating a substrate for arrhythmias. Over time, an antiarrhythmic effect may develop particularly among responders who benefit from BiV pacing with reduction of myocardial wall stress and correction of intrinsic global dyssynchrony.[19] We observed that QRS/JTc groups were strongly prognostic of LV assist device, heart transplantation, and all-cause mortality rather than appropriate ICD therapies for sustained ventricular arrhythmias. Although the prognostic value of the change in QRS duration or JTc interval as separate markers has been extensively validated, no studies on both markers combined and long-term outcomes of BiV pacing have been performed making comparison of our findings with others difficult.

Concomitant changes in QRS duration and JTc interval following BiV pacing represents a powerful summative marker that incorporates complex information. We speculate that the mechanism behind the favorable long-term event-free survival associated with $QRS_{decreased}/JTc_{increased}$ strongly relates to both optimal electrical resynchronization and LV pacing. Therefore, while $QRS_{decreased}$ is a marker of corrected intrinsic global dyssynchrony, $JTc_{increased}$ is not necessarily a reflection of proarrhythmia but may also indicate contribution of LV pacing to overall LV activation making non-arrhythmic (e.g., heart failure) endpoints very likely to occur. This is further supported by the fact that prolonged ventricular repolarization is associated with diastolic dysfunction.[24] Although $JTc_{increased}$ portends better outcomes among patients with $QRS_{decreased}$, further studies are warranted to explore its role in the $QRS_{increased}$ group. Of note, patients with $QRS_{increased}/JTc_{increased}$ demonstrated by far the highest intrinsic PR interval suggesting overall poor cardiac conduction, and PR prolongation has recently been associated with less intrinsic global dyssynchrony and poor prognosis following BiV pacing.[25]

We studied only the association of acute concomitant changes in ventricular depolarization and repolarization with long-term outcomes of BiV pacing. Recently, cardiac memory where T-wave changes develop following wide QRS complex rhythms is suggested to be an important time-dependent mechanism strongly associated with hemodynamic improvement.[26] Therefore, our finding of a more favorable prognosis for patients with $QRS_{decreased}/JTc_{increased}$ may indicate a short-term effect of reverse electrical remodeling away from the configuration during wide QRS complex rhythm to one adapting better to the activation sequence during BiV pacing. However, further studies are warranted to explore long-term effects of QRS/JTc groups derived from serial ECGs on clinical outcomes of BiV pacing.

Considering that a large minority of patients derive no benefit from BiV pacing,[1] our study suggests that the combination of concomitant changes in QRS duration and JTc interval to a single marker possess incremental prognostic value and may improve discrimination in identifying patients

who are at increased risk of non-response to BiV pacing. Importantly, information on QRS/JTc groups is readily available prior to, during, and following implantation, and further studies are warranted to explore if the groups can assist the electrophysiologist in changing LV lead positions, device programming, or considering an alternative cardiac resynchronization therapy including multipoint pacing, His bundle pacing, or wireless endocardial pacing. Of interest, the latter has recently been associated with a more physiological LV activation, hemodynamic improvement, narrower paced QRS duration, and lesser transmural repolarization heterogeneity, which may reflect an overall improved contribution of LV pacing.[27, 28]

Limitations

The major limitation of our study is the retrospective observational design and lack of causes of death including arrhythmic death. The underlying mechanism of appropriate ICD therapies is also a limiting factor, thus we could not assess whether sustained ventricular arrhythmias developed due to electrolyte disturbances or premature ventricular contractions. Although we used robust statistical methods to account for differences between groups, we cannot rule out the potential for residual confounding. Specifically, we did not have data on follow-up echocardiography or LV scar burden as assessed on cardiac magnetic resonance imaging, which may contribute to ventricular repolarization abnormalities. Furthermore, we were not able to include a control group to compare the clinical efficacy of BiV-ICD versus ICD only by QRS/JTc groups. In addition, selection bias may have been introduced, in that only half of all implanted patients had follow-up ECG data available. Finally, although the median survival of the cohort was comparable to guideline-forming clinical trials, the single-center study design also limits generalizability of our findings.

Conclusion

Among recipients of BiV defibrillators, $QRS_{decreased}/JTc_{increased}$ was associated with the most favorable long-term survival free of LV assist device, heart transplantation, and sustained ventricular arrhythmias. Our findings suggest that improved electrical resynchronization may be achieved by assessing concomitant changes in ventricular depolarization and repolarization.

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Tables and Figures

Table 1: Pre-Implantation Patient Characteristics.

	$QRS_{decreased}$/ $JTc_{decreased}$ (*n*=126)	$QRS_{decreased}$/ $JTc_{increased}$ (*n*=142)	$QRS_{increased}$/ $JTc_{decreased}$ (*n*=138)	$QRS_{increased}$/ $JTc_{increased}$ (*n*=122)	Total (*n*=528)	*p* Value
Demographics						
Age (years)	66.5 [57.2–74.8]	68.0 [58.0–76.0]	68.0 [59.2–75.0]	68.5 [56.0–75.8]	68.0 [58.0–75.0]	0.471
Sex (male)	86 (68.3)	91 (64.1)	101 (73.2)	86 (70.5)	364 (68.9)	0.409
Race						0.967
Black	22 (22.0)	30 (25.4)	25 (24.8)	27 (28.1)	104 (25.1)	
White	73 (73.0)	84 (71.2)	71 (70.3)	65 (67.7)	293 (70.6)	
Other	5 (5.0)	4 (3.4)	5 (5.0)	4 (4.2)	18 (4.3)	
NA	26	24	37	26	113	
NYHA class III/IV	103 (81.7)	120 (84.5)	121 (87.7)	104 (85.2)	448 (84.8)	0.608
ICD indication						0.291
Primary prevention	109 (86.5)	130 (91.5)	116 (84.1)	107 (87.7)	462 (87.5)	
Secondary prevention	17 (13.5)	12 (8.5)	22 (15.9)	15 (12.3)	66 (12.5)	
Prior ICD	32 (25.4)	22 (15.5)	27 (19.6)	27 (22.1)	108 (20.5)	0.229
Prior cardiac arrest	10 (7.9)	11 (7.7)	6 (4.3)	13 (10.7)	40 (7.6)	0.291
ECG characteristics						
Heart rate (bpm)	75.0 [68.0–84.0]	72.0 [65.2–83.0]	74.0 [65.0–84.0]	70.0 [61.0–81.8]	73.0 [64.0–84.0]	0.376
P-wave duration (ms)	116.0 [102.0–126.0]	110.0 [102.0–122.0]	118.0 [104.0–130.0]	116.0 [104.5–130.0]	114.0 [103.5–128.0]	0.024
NA	45	31	52	20	148	
PR interval (ms)	176.0 [152.5–196.0]	174.0 [160.0–198.0]	185.0 [168.0–206.0]	196.0 [178.0–220.0]	182.0 [162.0–206.0]	<0.001
NA	36	21	46	19	122	
QRS duration (ms)	179.0 [160.0–	170.0 [156.0–	144.0 [132.0–	149.0 [136.0–	160.0 [144.0–	<0.001

	199.5]	185.5]	160.0]	162.0]	180.0]	
QTc interval (ms)	514 [485.2–543.8]	487.5 [460.2–509.5]	485.5 [464.2–510.0]	469 [451.2–487.8]	486.5 [463.0–513.2]	<0.001
JTc interval (ms)	336 [315.2–354.2]	316.5 [293.5–332.8]	333 [320.0–355.0]	315 [298.2–334.0]	326 [305.0–343.2]	<0.001
QRS morphology						<0.001
LBBB	59 (46.8)	100 (70.4)	90 (65.2)	90 (73.8)	339 (64.2)	
Non-LBBB	19 (15.1)	15 (10.6)	35 (25.4)	29 (23.8)	98 (18.6)	
RV paced	48 (38.1)	27 (19.0)	13 (9.4)	3 (2.5)	91 (17.2)	
Echocardiographic characteristics						
LVEF (%)	25.0 [20.0–30.0]	21.5 [20.0–27.0]	25.0 [20.0–30.0]	22.5 [17.0–30.0]	25.0 [20.0–30.0]	0.296
LVEDV (mL)	202.0 [148.5–246.5]	181.0 [152.2–238.0]	203.0 [169.0–248.0]	209.0 [172.5–258.0]	199.0 [162.0–252.0]	0.466
NA	31	48	33	27	139	
LVESV (mL)	147.0 [109.0–202.0]	140.0 [109.0–192.0]	158.0 [124.0–205.0]	157.0 [126.5–210.5]	154.0 [118.0–204.0]	0.673
NA	31	48	33	27	139	
Comorbidities						
Ischemic cardiomyopathy	69 (54.8)	77 (54.2)	85 (61.6)	63 (51.6)	294 (55.7)	0.403
Atrial fibrillation	47 (37.3)	36 (25.4)	64 (46.4)	39 (32.0)	186 (35.2)	0.002
Hypertension	84 (66.7)	98 (69.0)	103 (74.6)	92 (75.4)	377 (71.4)	0.328
Diabetes	47 (37.3)	52 (36.6)	58 (42.0)	45 (36.9)	202 (38.3)	0.768
eGFR (mL/min/1.73 m^2)	61.0 [45.0–80.8]	62.0 [46.0–78.0]	57.0 [41.0–70.8]	56.0 [37.0–72.8]	60.0 [42.8–76.0]	0.167
Drug use						
ACEIs or ARBs	97 (77.0)	119 (83.8)	104 (75.4)	91 (74.6)	411 (77.8)	0.239
Beta-blockers	114 (90.5)	127 (89.4)	117 (84.8)	111 (91.0)	469 (88.8)	0.355
Diuretics	101 (80.2)	123 (86.6)	126 (91.3)	99 (81.1)	449 (85.0)	0.039
Amiodarone	23 (18.3)	16 (11.3)	28 (20.3)	25 (20.5)	92 (17.4)	0.146

Values reported as median [25th–75th percentiles] or *n* (%). *p* Values based on Kruskal-Wallis and chi-squared tests as

appropriate.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; JTc, corrected JT; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NA, not available; NYHA, New York Heart Association; RV, right ventricular.

Table 2: Device Programming Characteristics.

	$QRS_{decreased}$/ $JTc_{decreased}$ (*n*=126)	$QRS_{decreased}$/ $JTc_{increased}$ (*n*=142)	$QRS_{increased}$/ $JTc_{decreased}$ (*n*=138)	$QRS_{increased}$/ $JTc_{increased}$ (*n*=122)	Total (*n*=528)	*p* Value
Pacing mode						0.052
DDD or DDDR	105 (84.0)	126 (89.4)	115 (83.3)	112 (94.1)	458 (87.6)	
VVI or VVIR	19 (15.2)	15 (10.6)	20 (14.5)	7 (5.9)	61 (11.7)	
Other	1 (0.8)	0 (0.0)	3 (2.2)	0 (0.0)	4 (0.8)	
NA	1	1	0	3	5	
BiV or LV-only pacing (%)	98.3 [94.9–99.3]	99.0 [96.9–99.9]	97.8 [93.6–99.5]	99.0 [96.4–99.7]	98.6 [95.5–99.7]	0.223
Off	2 (1.6)	4 (2.8)	7 (5.1)	4 (3.3)	17 (3.2)	0.445
NA	25	17	19	22	83	
AT/AF burden (%)	0.1 [0.0–99.4]	0.1 [0.0–1.0]	0.1 [0.0–22.5]	0.1 [0.0–1.0]	0.1 [0.0–1.1]	0.009
NA	46	38	40	39	163	
Lower rate (bpm)	60.0 [50.0–70.0]	60.0 [50.0–60.0]	60.0 [50.0–70.0]	60.0 [50.0–60.0]	60.0 [50.0–60.0]	0.004
NA	1	1	0	3	5	
Upper rate (bpm)	130.0 [120.0–130.0]	130.0 [130.0–130.0]	130.0 [120.0–130.0]	130.0 [120.0–130.0]	130.0 [120.0–130.0]	0.170
NA	1	5	3	6	15	
Paced AV delay (ms)	140.0 [130.0–170.0]	130.0 [130.0–170.0]	130.0 [130.0–170.0]	140.0 [130.0–170.0]	130.0 [130.0–170.0]	0.833
NA	30	22	29	19	100	
Sensed AV delay (ms)	105.0 [100.0–120.0]	100.0 [100.0–120.0]	100.0 [100.0–120.0]	100.0 [100.0–120.0]	100.0 [100.0–120.0]	0.586

NA	38	28	36	21	123	
V-V delay (ms)						0.021
RV, ≥10	2 (2.5)	6 (5.9)	9 (9.5)	7 (8.1)	24 (6.6)	
LV, 0	56 (70.9)	68 (67.3)	58 (61.1)	40 (46.5)	222 (61.5)	
LV, ≥10	21 (26.6)	27 (26.7)	28 (29.5)	39 (45.3)	115 (31.9)	
NA	47	41	43	36	167	
Quadripolar leads	21 (16.7)	18 (12.7)	22 (15.9)	19 (15.6)	80 (15.2)	0.805
AdaptivCRT programming	13 (10.3)	23 (16.2)	7 (5.1)	14 (11.5)	57 (10.8)	0.028
VT therapy zone 1 (bpm)	170.0 [160.5–181.0]	171.0 [165.0–185.0]	171.0 [162.0–180.8]	170.5 [162.0–180.0]	171.0 [162.0–181.0]	0.832
Off	87 (69.0)	107 (75.4)	91 (65.9)	82 (67.2)	367 (69.5)	0.330
NA	1	2	1	2	6	
VT therapy zone 2 (bpm)	188.0 [173.5–191.0]	183.0 [169.5–192.5]	188.0 [188.0–197.0]	183.5 [166.2–197.0]	188.0 [177.5–197.0]	0.635
Off	118 (93.7)	136 (95.8)	131 (94.9)	114 (93.4)	499 (94.5)	0.818
NA	1	2	1	2	6	
VF therapy zone (bpm)	200.0 [188.0–200.0]	200.0 [188.0–200.0]	200.0 [188.0–200.0]	200.0 [188.0–200.0]	200.0 [188.0–200.0]	0.424
NA	1	2	2	2	7	
VF detection criteria						0.254
1.0 s	6 (8.2)	7 (7.3)	2 (2.4)	3 (4.2)	18 (5.5)	
2.5 s	5 (6.8)	6 (6.2)	4 (4.7)	4 (5.6)	19 (5.8)	
12/16 intervals	10 (13.7)	8 (8.3)	13 (15.3)	9 (12.5)	40 (12.3)	
18/24 intervals	16 (21.9)	20 (20.8)	28 (32.9)	28 (38.9)	92 (28.2)	
24/32 intervals	13 (17.8)	19 (19.8)	8 (9.4)	7 (9.7)	47 (14.4)	
30/40 intervals	23 (31.5)	36 (37.5)	30 (35.3)	21 (29.2)	110 (33.7)	
NA	53	46	53	50	202	

Values reported as median [25th–75th percentiles] or *n* (%). *p* Values based on Kruskal-Wallis and chi-squared tests as appropriate.

Abbreviations: AF, atrial fibrillation; AT, atrial tachycardia; AV, atrioventricular; BiV, biventricular; bpm, beats per minute; CRT, cardiac resynchronization therapy; JTc, corrected JT; LV, left ventricular, NA, not available; RV, right ventricular; VF,

ventricular fibrillation; VT, ventricular tachycardia; V-V, ventricular-ventricular.

Table 3: Appropriate Implantable Cardioverter-Defibrillator Therapies For Sustained Ventricular Arrhythmias.

	$QRS_{decreased}$/ $JTc_{decreased}$ (*n*=126)	$QRS_{decreased}$/ $JTc_{increased}$ (*n*=142)	$QRS_{increased}$/ $JTc_{decreased}$ (*n*=138)	$QRS_{increased}$/ $JTc_{increased}$ (*n*=122)	Total (*n*=528)	*p* Value
Total VT or VF therapies	1.3 (9.6)	0.6 (3.4)	0.6 (3.3)	0.4 (1.7)	0.7 (5.4)	0.614
Adjusted for person-years follow-up	0.0 (0.0)	0.1 (1.5)	0.0 (0.4)	0.0 (0.0)	0.0 (0.8)	0.544
Total ATP or shock therapies	1.4 (9.9)	0.8 (4.9)	0.7 (3.5)	0.5 (1.9)	0.8 (5.8)	0.637
Adjusted for person-years follow-up	0.0 (0.0)	0.2 (1.7)	0.1 (0.4)	0.0 (0.0)	0.1 (0.9)	0.518

Values reported as mean (standard deviation). *p* Value based on one-way analysis of variance test.

Abbreviations: ATP, antitachycardia pacing; JTc, corrected JT; VF, ventricular fibrillation; VT, ventricular tachycardia.

Figure 1: Boxplots (A) and correlation plot (B) of QRS duration and JTc interval.

Abbreviations: BiV, biventricular; ECG, electrocardiogram; JTc, corrected JT.

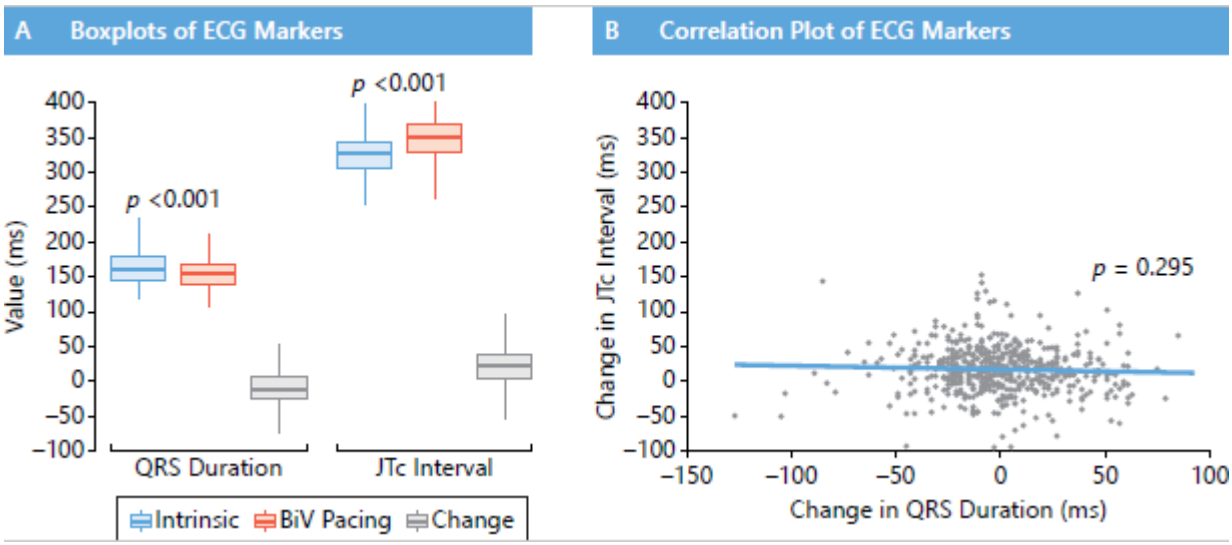


Figure 2: Cumulative incidence of long-term mortality (A) and sustained ventricular arrhythmia (B) endpoints by QRS/JTc groups.

Abbreviations: ICD, implantable cardioverter-defibrillator; JTc, corrected JT; LV, left ventricular.

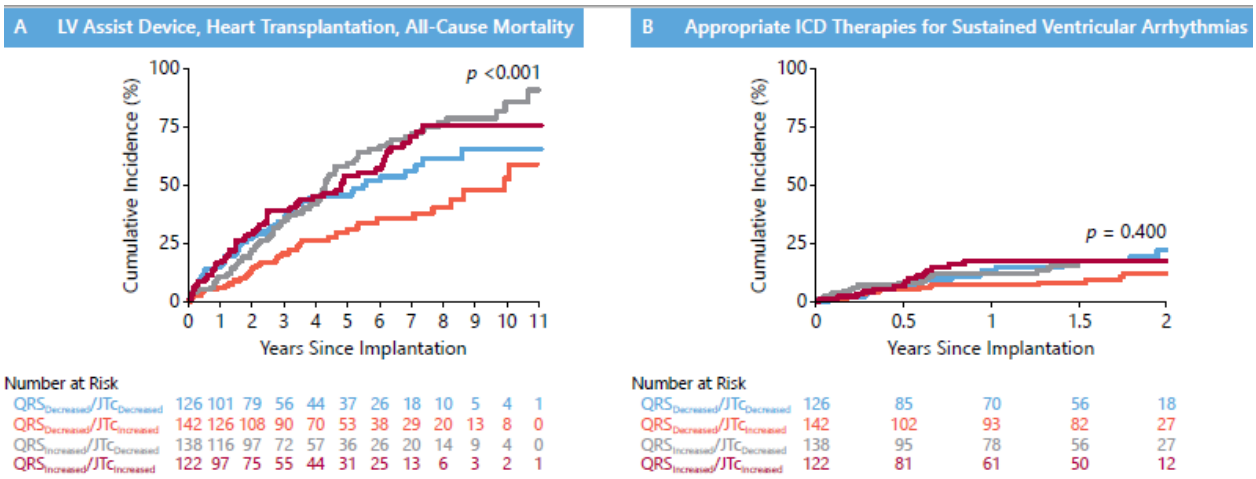
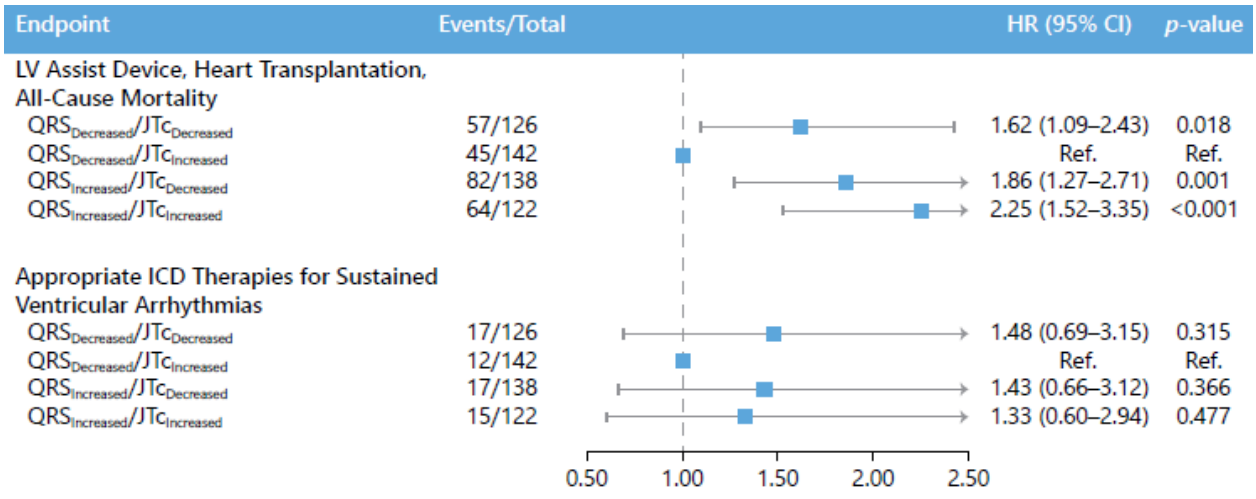


Figure 3: Multivariable Cox regression of the association of QRS/JTc groups with long-term mortality (A) and sustained ventricular arrhythmia (B) endpoints.



Abbreviations: CI, confidence interval; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; JTc, corrected JT; LV, left ventricular.