ORIGINAL RESEARCH

Changes in QRS Area and QRS Duration After Cardiac Resynchronization Therapy Predict Cardiac Mortality, Heart Failure Hospitalizations, and Ventricular Arrhythmias

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***Background*—**Predicting clinical outcomes after cardiac resynchronization therapy (CRT) and its optimization remain a challenge. We sought to determine whether pre- and postimplantation QRS area (QRS_{area}) predict clinical outcomes after CRT.

***Methods and Results*—**In this retrospective study, QRS_{area}, derived from pre- and postimplantation vectorcardiography, were assessed in relation to the primary end point of cardiac mortality after CRT with or without defibrillation. Other end points included total mortality, total mortality or heart failure (HF) hospitalization, total mortality or major adverse cardiac events, and the arrhythmic end point of sudden cardiac death or ventricular arrhythmias with or without a shock. In patients (n=380, age 72.0±12.4 years, 68.7% male) undergoing CRT over 7.7 years (median follow-up: 3.8 years [interquartile range 2.3–5.3]), preimplantation QRS_{area} ≥102 μVs predicted cardiac mortality (HR: 0.36; P<0.001), independent of QRS duration (QRSd) and morphology (P<0.001). A QRS_{area} reduction ≥45 μVs after CRT predicted cardiac mortality (HR: 0.19), total mortality (HR: 0.50), total mortality or heart failure hospitalization (HR: 0.44), total mortality or major adverse cardiac events (HR: 0.43) (all P<0.001) and the arrhythmic end point (HR: 0.26; P<0.001). A concomitant reduction in QRS_{area} and QRSd was associated with the lowest risk of cardiac mortality and the arrhythmic end point (both HR: 0.12, P<0.001).

***Conclusions*—**Pre-implantation QRS_{area}, derived from vectorcardiography, was superior to QRSd and QRS morphology in predicting cardiac mortality after CRT. A postimplant reduction in both QRS_{area} and QRSd was associated with the best outcomes, including the arrhythmic end point. **(*J Am Heart Assoc*. 2019;8:e013539. DOI: 10.1161/JAHA.119.013539.)**

Key Words: cardiac resynchronization therapy • left bundle branch block • QRS area • QRS duration • vectorcardiography

Cardiac resynchronization therapy (CRT) is an established treatment for patients with heart failure (HF), impaired left ventricular (LV) function, and a wide QRS complex.[1] As with any medical therapy, its treatment effect is variable. "Nonresponder" rates range from 9% to 68%, depending on the criteria used to define response.[2] Although no medical therapy can be expected to be 100% effective, there is a consensus view that response to CRT can be improved.[3]

Manifold imaging studies explored mechanical dyssynchrony in relation to patient selection and optimization but, ultimately, no single measure of mechanical dyssynchrony has been adopted by clinical guidelines.[4] In this context, we should consider CRT is an electrical treatment and that its substrate should be electrical rather than mechanical. In this respect, QRS duration (QRSd) has been adopted as a surrogate of electrical dyssynchrony in randomized, controlled trials,[1] and a reduction in QRSd has been shown to predict better long-term outcomes after CRT.[5,6]

Evidence has recently emerged in support of vectorcardiography in the field of CRT. In this respect, QRS area (QRS_{area}) has been shown to correlate with LV lateral wall activation time,[7] the maximum rate of rise of LV pressure ($\Delta LV\ dP/dt_{max}$),[8,9] and LV reverse remodeling[10] after CRT. Crucially, pre-implantation QRS_{area} has also been shown to be superior to pre-implantation QRSd and QRS morphology in predicting total mortality after CRT.[11,12]

Although QRS_{area} and QRSd duration relate to depolarization in a global sense, QRS_{area} also yields the dominant axis of the activation sequence.[13] Given that the objective of CRT is

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Received June 7, 2019; accepted September 5, 2019.

Clinical Perspective

What Is New?

- Pre-implantation QRS_{area} was superior to QRSd and QRS morphology in predicting cardiac and total mortality after cardiac resynchronization therapy.
- Concomitant reductions in QRS_{area} and QRSd after cardiac resynchronization therapy were associated with the best survival and the lowest risk of heart failure hospitalization, major adverse cardiac events as well as ventricular arrhythmias.

What Are the Clinical Implications?

- Reductions in QRS_{area} and QRSd could be a focus for optimization after cardiac resynchronization therapy implantation.

to make depolarization more synchronous, both the pacing location and timing between LV and right ventricular pacing can be used to manipulate activation sequence. In this study, we explored pre- and postimplantation QRS_{area} and QRSd in relation to long-term cardiac mortality, HF hospitalization, and major adverse cardiac events (MACEs) after CRT.

Methods

Patients referred for CRT implantation at the University Hospitals Birmingham, Queen Elizabeth, United Kingdom, were retrospectively evaluated. The study was approved by the local Ethics Committee and local Clinical Audit Department, both of which waived patient consent on the basis that all study tests and interventions had already been undertaken. The study conforms with the Declaration of Helsinki.

Study Population

Patients undergoing CRT implantation from November 2011 to June 2018 were identified. Implantation practice adhered to the United Kingdom's National Institute of Clinical Excellence guidelines, which before 2007 recommended CRT with defibrillation (CRFT-D) only in the context of secondary prevention. After 2014, National Institute of Clinical Excellence recommended cardiac resynchronization therapy with defibrillation rather than CRT-pacing in nonischemic cardiomyopathy.[14]

Inclusion criteria were the following: indications for CRT according to National Institute of Clinical Excellence guidance and availability of a digitizable 12-lead ECG before and after implantation. Exclusion criteria were the following: subjects with technically unsuitable ECGs and patients with congenital heart disease.

Device Therapy

Device implantation was undertaken using standard transvenous techniques with patients under local anesthesia and

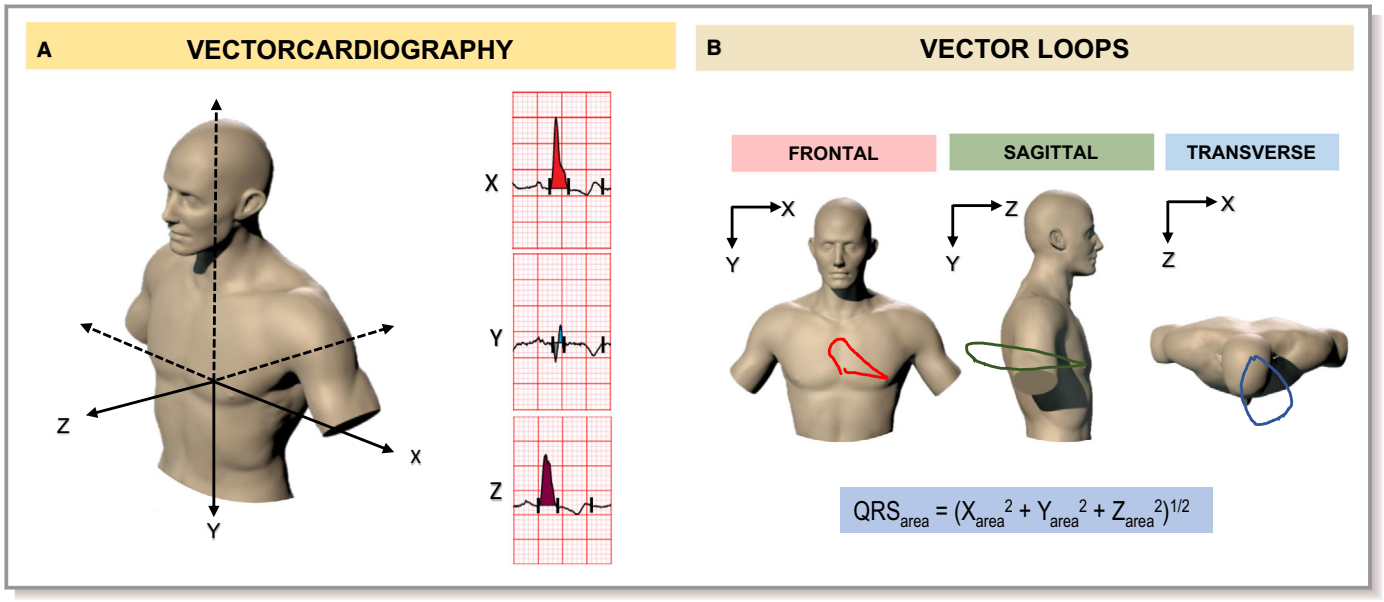

Figure 1. Vectorcardiography in cardiac resynchronization therapy. The vectorcardiogram displays the various features of the ECG, such as the QRS complex, in the form of "loops," which are determined from vectors representing successive, instantaneous mean electrical forces throughout the cardiac cycle. **A**, A representation of the 3 vectorcardiogram leads (X, Y, and Z), according to Frank's orthogonal lead system. **B**, Two-dimensional vector loops in the frontal (X-Y leads), sagittal (Y-Z leads), and transverse (X-Z leads) planes from a patient with a left bundle branch block. The QRS_{area} is calculated as the integral sum of the area bound by the QRS complex and the isoelectric baseline in each vectorcardiogram lead (X, Y, and Z).

Table 1. Characteristics of the Study Group According to Pre-Implantation QRS Area

	All	QRS_{area} ≥102 μVs	QRS_{area} <102 μVs	*P* Value
N	380	197	183	
Age, y	72±12.4	72.2±12.9	71.9±11.7	0.832
Sex (male), n (%)	261 (68.68)	119 (60.41)	142 (77.6)	<0.001
NYHA class, n (%)				
I	26 (7.34)	17 (9.34)	9 (5.23)	0.190
II	87 (24.58)	46 (25.27)	41 (23.84)	
III	225 (63.56)	114 (62.64)	111 (64.53)	
IV	16 (4.52)	5 (2.75)	11 (6.4)	
Cause, n (%)				
Ischemic	182 (47.89)	74 (37.56)	108 (59.02)	<0.001
Nonischemic	198 (52.11)	123 (62.44)	75 (40.98)	
Comorbidities, n (%)				
Diabetes mellitus	89 (23.42)	41 (20.81)	48 (26.23)	0.213
Hypertension	106 (27.89)	57 (28.93)	49 (26.78)	0.639
CABG	64 (16.84)	23 (11.68)	41 (22.4)	0.005
Device type, n (%)				
CRT-D	209 (55.15)	94 (47.96)	115 (62.84)	0.004
CRT-P	170 (44.85)	102 (52.04)	68 (37.16)	
Upgrades, n (%)				
Pacemaker to CRT-D	39 (47.56)	23 (43.40)	16 (55.17)	0.307
Pacemaker to CRT-P	43 (52.44)	30 (56.60)	13 (44.83)	
CRT-D indication*				
Primary prevention	166 (79.4)	76 (80.9)	90 (78.3)	0.645
Secondary prevention	43 (20.6)	18 (19.1)	25 (21.7)	
LVEF, %	25.8±9.9	25.5±9.7	26.0±10.3	0.633
Medication, n (%)				
ACEI/ARA	337 (89.63)	173 (88.72)	164 (90.61)	0.548
β-Blocker	277 (73.67)	140 (71.79)	137 (75.69)	0.391
MRA	167 (44.41)	80 (41.03)	87 (48.07)	0.170
ECG variables				
Sinus rhythm, n (%)	269 (70.79)	152 (77.16)	117 (63.93)	0.005
AF/flutter, n (%)	111 (29.21)	45 (22.84)	66 (36.07)	
PR interval, ms	192.5±54.7	181.6±39.8	207.5±67.5	<0.001
QRSd, ms	153.5±22.7	163.9±20.4	142.2±19.5	<0.001
QRS <150 ms, n (%)	169 (44.47)	45 (22.84)	124 (67.76)	<0.001
LBBB, n (%)	239 (62.89)	151 (76.65)	88 (48.09)	<0.001
RBBB, n (%)	33 (8.68)	1 (0.51)	32 (17.49)	<0.001
NICD, n (%)	59 (15.53)	5 (2.54)	54 (29.51)	<0.001
RV-paced, n (%)	49 (12.89)	40 (20.30)	9 (4.92)	<0.001
Vectorcardiography variable				
QRS_{area}, μVs	113.4±56.5	156.9±41.7	66.6±22.7	<0.001

ACEI indicates angiotensin receptor converting enzyme inhibitor; AF, atrial fibrillation; ARA, angiotensin receptor antagonist; CABG, coronary artery bypass graft; CRT-D, cardiac resynchronization therapy with defibrillation; CRT-P, cardiac resynchronization therapy-pacing; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; NICD, nonspecific conduction delay; NYHA, New York Heart Association; QRS_{area}, QRS area; QRSd, QRS duration; RBBB, right bundle branch block; RV, right ventricular.

*Expressed as a percentage of CRT-D devices.

Table 2. Clinical Outcomes

	All	Pre-CRT		Post-CRT	
		QRS_{area} ≥102 μVs	QRS_{area} <102 μVs	QRS_{area} Reduction ≥45 μVs	QRS_{area} Reduction <45 μVs
N	380	197	183	177	203
Mortality end points					
Cardiac mortality	70 (18.4)	21 (10.7)	49 (26.8)	11 (6.21)	59 (29.1)
Sudden cardiac death*	5 (7.14)	1 (4.76)	4 (8.16)	0	5 (8.47)
Death from pump failure*	63 (90.0)	19 (90.5)	44 (89.8)	10 (90.9)	53 (89.8)
Total mortality	135 (35.5)	55 (27.9)	80 (43.7)	42 (23.7)	93 (45.8)
Total mortality or HF hospitalization	165 (43.4)	66 (33.5)	99 (54.1)	53 (29.9)	112 (55.2)
Total mortality or hospitalization for MACE	185 (48.7)	74 (37.6)	111 (60.7)	59 (33.3)	126 (62.1)
Ventricular arrhythmic events					
All VT/VF	32 (8.42)	12 (6.09)	20 (10.9)	7 (3.95)	25 (12.3)
VT/VF treated with ATP only	6 (15.8)	4 (2.03)	2 (1.09)	3 (1.69)	3 (1.48)
Appropriate shocks (with or without ATP)	19 (5.0)	7 (3.55)	14 (7.65)	2 (1.13)	17 (8.37)
Inappropriate shocks	1 (0.26)	0	1 (0.5)	0	1 (0.5)

Clinical outcomes, expressed as n (%), according to pre-implantation QRS area (QRS_{area}) and postimplantation change in QRS_{area}. ATP indicates antitachycardia pacing; CRT, cardiac resynchronization therapy; HF, heart failure; MACE, major adverse cardiac events; VF, ventricular fibrillation; VT, ventricular tachycardia.
*Expressed as a percentage of cardiac deaths.

intravenous sedation. Following implantation, patients were followed up in combined cardiac device therapy/HF clinics. Devices were programmed according to physician discretion. Generally, backup atrial pacing was set at 60 beats/min, and the pacing mode was set to DDDR. The atrioventricular delay was set at 90 ms and the interventricular delay to between 0 and −20 ms (LV first). In patients in permanent atrial fibrillation, right ventricular and LV leads were deployed, a CRT generator was implanted, and devices were programmed to a ventricular triggered mode. Atrioventricular junction ablation was undertaken according to physicians' discretion. Targeted echocardiographic optimization was only undertaken in symptomatic nonresponders.

Lead positions

The anteroposterior, as well as the left anterior and right anterior oblique fluoroscopic views from coronary sinus venography taken at the time of implantation were used retrospectively to assess the LV lead tip position, as previously described.[15] All LV lead positions were assessed retrospectively by an experienced implanter (F.L.) who was blinded to clinical outcome data.

ECG

Pre-implantation, standard supine 12-lead ECGs (25 mm/s, 10 mm/mV) were used for analysis. A left bundle branch block (LBBB) was defined as a QRSd >120 ms, rS or QS in lead V_1, notched or slurred R-waves in leads I, aVL, V_5 or V_6, with absent q waves in leads V_5 and V_6.[16] We used this definition rather than "strict" Strauss criteria, as the latter is not predictive of clinical outcomes after CRT.[12] Right bundle branch block was defined as a QRS ≥120 ms, with a wide, positive R-wave deflection in lead V_1 and a slurred S wave in leads I and V_6. A nonspecific intraventricular conduction delay was defined as nonpaced QRS >120 ms not fitting these criteria. Postimplantation ECGs were undertaken within 3 months after implantation.

Vectorcardiography

Standard 12-lead ECGs were first converted to an Extensible Markup Language (XML) format using ECGScan (AMPS LLC, New York, USA), a commercially available program approved by the US Food and Drug Administration. A custom-made program was used for generation of 2 vectorcardiographies according to Frank's orthogonal lead system using the Kors transformation. The latter was used given previous evidence that it is superior to other vectorcardiography transformations in predicting clinical outcomes after CRT.[12] The start and end of the QRS complex were defined semi-automatically using digital calipers at 200% magnification. For paced rhythms, the onset and end of the QRS complex was measured manually, excluding the pacing spike. Digitization of ECGs and generation of vectorcardiographies were undertaken by a single investigator (O.O.) who was blinded to clinical outcomes

collected by another investigator (A.Z.). The QRS_{area} was calculated as the integral between the ventricular deflection curve and the isoelectric line in each the 3 orthogonal leads (X, Y, and Z), according to the formula: $(X^2_{area} + Y^2_{area} + Z^2_{area})^{1/2}$ (Figure 1).

End points

The primary end point was cardiac mortality, which included cardiac transplantation or implantation of a ventricular assist device. The secondary end point was total mortality. Ancillary end points included total mortality or unplanned HF hospitalization; total mortality or unplanned hospitalization for MACE; and the combined end point of sudden cardiac death, ventricular tachycardia, ventricular fibrillation, or shock. MACE included unplanned hospitalization for HF, myocardial infarction, acute coronary syndrome, ventricular arrhythmias, and atrial fibrillation. A HF hospitalization was defined as an unplanned admission related to worsening dyspnea, in association with peripheral edema, pulmonary edema on chest radiography, and requirement for intravenous diuretic therapy. Device-treated arrhythmias (appropriately treated with shocks or antitachycardia pacing) not leading to an unplanned hospitalization were not regarded as a hospitalization for MACE. Stroke and pulmonary embolism were not regarded as MACE. In composite end points, the first event was included in statistical analyses. Mortality data were collected through medical record and cross-checked with a national mortality database. Data were collected retrospectively from medical records and entered into an electronic database every 6 months by investigators who were blinded to clinical and imaging data. Events were adjudicated by blinded investigators on a 6-monthly basis.

Mode of death

Sudden cardiac death was defined as a natural, unexpected death because of cardiac causes, heralded by an abrupt loss of consciousness within 1 hour of the onset of acute symptoms. Death from pump failure was defined as "death after a period of clinical deterioration in signs and symptoms of HF despite medical treatment".[17]

Statistical Analysis

Continuous variables are expressed as mean± SD. Normality was tested using the Shapiro–Wilk test. Comparisons between normally distributed continuous variables were made using the Student *t* test. Categorical variables were analyzed using χ^2 tests. Receiver operating characteristic curves were

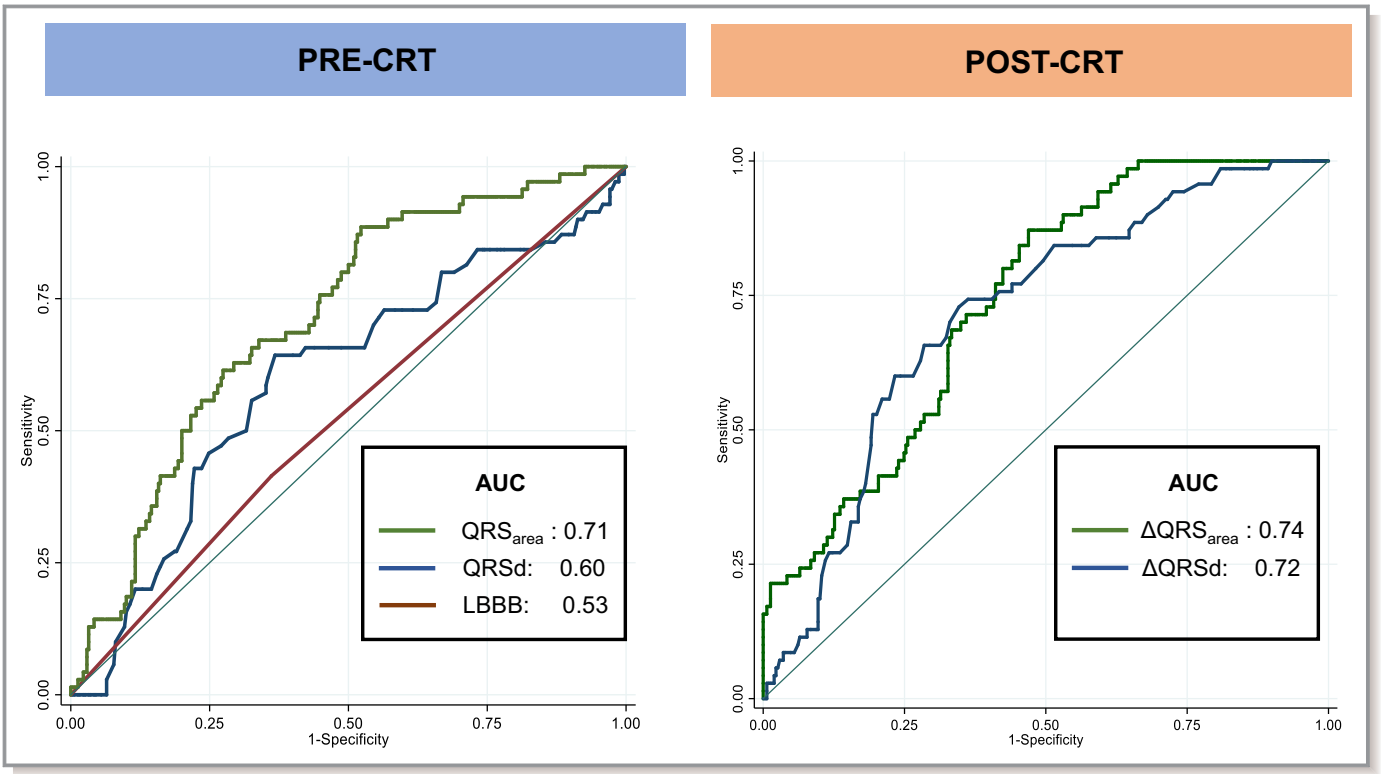

Figure 2. Receiver-operator characteristic curves. Graphs show areas under the receiver-operator characteristic curves (AUC) for QRSd, QRS area, and QRS morphology (LBBB) in the whole cohort. AUC indicates area under the curve; CRT, cardiac resynchronization therapy; LBBB, left bundle branch block.

created to assess the predicted probabilities of ECG and vectorcardiography variables in relation to cardiac mortality. A 10-fold cross-validation was used as the model validation technique for assessing performance, and the average was calculated over 10 repetitions. The measure with largest area under the receiver operating characteristic (area under the curve [AUC]) was used for subsequent analyses. The Liu method was also applied to estimate nonparametrically the optimal cutoffs for ECG and vectorcardiography measures.[18] Kaplan–Meier curves and the log-rank test were used to assess cumulative survival and Cox proportional hazard models were used to assess relative risks. Proportionality hypotheses were verified by visual examination of log (survival) and Schoenfeld residuals. Variables reaching $P<0.10$ as univariate predictors of cardiac mortality were entered in multivariate models. Statistical analyses were undertaken by a biostatistician (T.Q.) who did not partake in data collection. The Stata15 (StataCorp, TX) statistical package was used. The package "cvauroc" was used for cross-validation of the areas under the receiver operating characteristic curve, and package "cutpt" was used for empirical estimation of optimal cutoffs. A 2-sided $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

The analytic sample consisted of 380 patients. As shown in Table 1, baseline characteristics were typical of a CRT population (age 72.0±12.4 years [mean±SD], 68.7% male) with a left ventricular ejection fraction of 25.8±9.9% and a

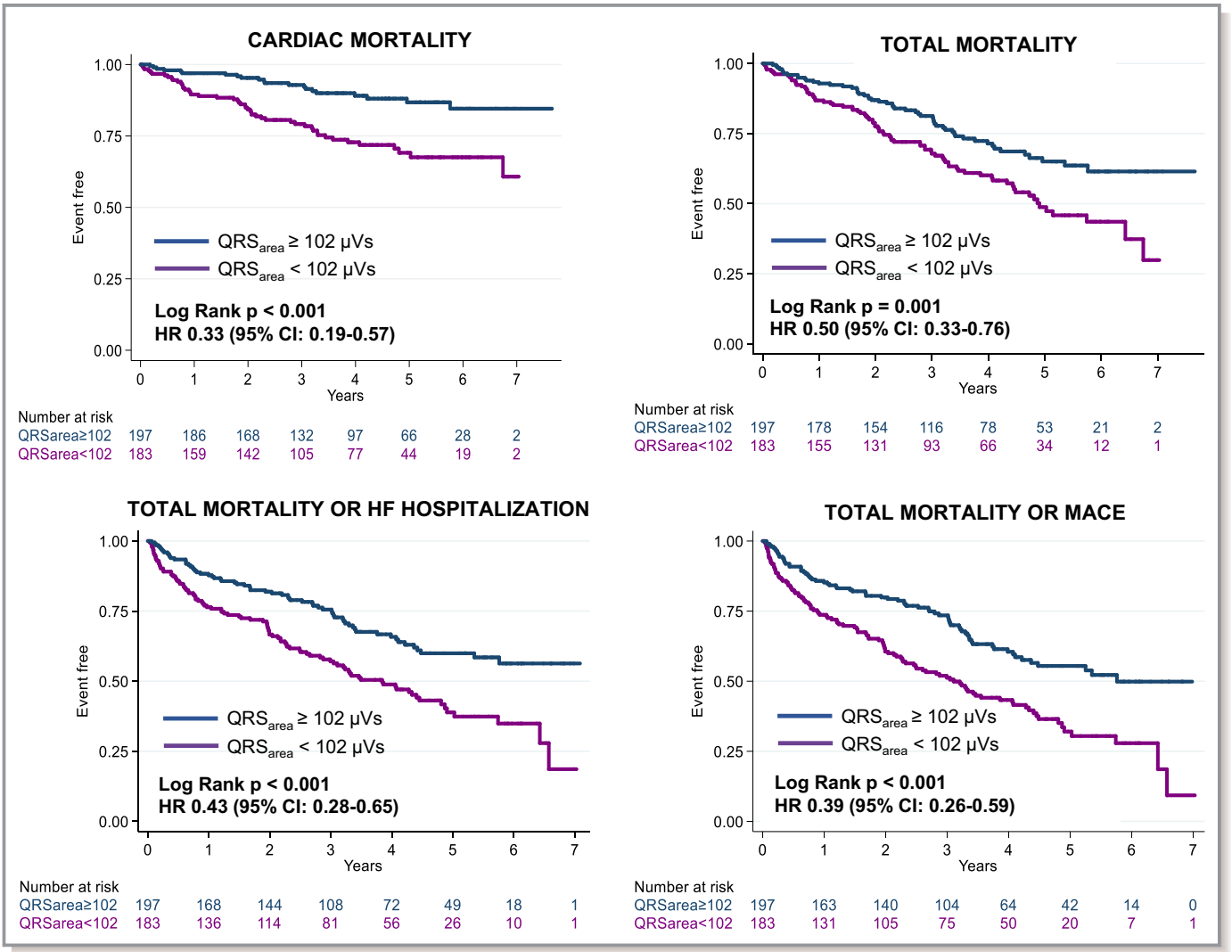

Figure 3. Clinical outcomes according to pre-implantation QRS area. Kaplan–Meier survival curves for the various end points according to precardiac resynchronization therapy QRS_{area}. Results of univariate Cox proportional hazard models are expressed in terms of hazard ratio (HR) (95% CI). HF indicates heart failure; MACE, major adverse cardiac events.

Table 3. Univariable Analyses of Predictors of Clinical Outcomes After CRT

	Cardiac Mortality			Total Mortality			Total Mortality or HF Hospitalization			Total Mortality or MACE			SCD, VT/VF or Shock		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Pre-CRT															
QRS_{area} (≥102 μVs)	0.33	0.19	0.57	<0.001	0.50	0.33	0.76	<0.001	0.43	0.28	0.65	<0.001	0.39	0.26	0.59	<0.001	0.50	0.25	0.98	0.042
QRSd (≥150 ms)	0.37	0.22	0.64	<0.001	0.60	0.39	0.92	0.018	0.60	0.40	0.91	0.016	0.53	0.35	0.80	0.002	0.38	0.19	0.75	0.006
LBBB	0.80	0.47	1.36	0.408	0.75	0.49	1.15	0.192	0.67	0.44	1.02	0.061	0.82	0.54	1.25	0.355	0.69	0.36	1.31	0.251
Post-CRT																				
ΔQRS_{area}, μVs	1.02	1.01	1.02	<0.001	1.01	1.01	1.01	<0.001	1.01	1.01	1.01	<0.001	1.01	1.01	1.01	<0.001	1.01	1.01	1.02	0.003
QRS_{area} reduction ≥45 μVs	0.19	0.10	0.36	<0.001	0.45	0.31	0.65	<0.001	0.44	0.32	0.61	<0.001	0.43	0.31	0.58	<0.001	0.26	0.11	0.58	0.001
ΔQRSd, ms	1.02	1.01	1.03	<0.001	1.01	1.01	1.02	<0.001	1.01	1.01	1.02	<0.001	1.01	1.02	1.02	<0.001	1.01	1.01	1.03	0.003
QRSd reduction*	0.23	0.14	0.39	<0.001	0.48	0.34	0.68	<0.001	0.48	0.35	0.65	<0.001	0.51	0.38	0.68	<0.001	0.33	0.17	0.67	0.018

Results of univariate Cox proportional hazards models, expressed as hazard ratio (HR) and 95% CI, for QRS area (QRS_{area}) and QRS duration (QRSd) using specified cutoffs (in parentheses), and for QRS morphology (LBBB). Results of analyses using continuous and dichotomous variables are shown. CRT indicates cardiac resynchronization therapy; HF, heart failure; LBBB, left bundle branch block; MACE, major adverse cardiac events; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

*Refers to any QRSd reduction below baseline.

QRSd of 153.5±22.7 ms. The cutoff of pre-CRT QRS_{area} derived from the Liu method was 102 μVs (86–119 μVs). The QRS_{area} groups were well matched for age, New York Heart Association class, diabetes mellitus and hypertension status, upgrade status, left ventricular ejection fraction, and medication. In the QRS_{area} <102 μVs group, patients were more likely to be male, to have ischemic cardiomyopathy or a previous coronary artery bypass operation, and a greater proportion received CRT with defibrillation rather than CRT-pacing.

Pre-CRT QRS_{area}

Over a median follow-up period of 3.8 years (interquartile range 2.3–5.3), 135/380 (36%) patients died, 70/380 (18%) from cardiac causes and 31/380 (8%) from noncardiac causes (Table 2). The cause of death was unknown in 34/380 (9%).

The AUC for predicting cardiac mortality was higher for QRS_{area} than for QRSd or QRS morphology (0.71, 0.60, and 0.53, respectively; $P<0.001$ for comparison) (Figure 2) and for QRSd and QRS morphology combined (AUC: 0.66; $P=0.002$). In Kaplan–Meier survival analyses, QRS_{area} ≥102 μVs was associated with a lower cardiac mortality ($P<0.001$), total mortality ($P=0.001$), total mortality or HF hospitalization, and total mortality or MACE (both $P<0.001$) (Table 2 and Figure 3). In univariable Cox proportional hazards analyses, QRS_{area} predicted cardiac mortality, total mortality, total mortality or HF hospitalization, and total mortality or MACE (all $P<0.001$) (Table 3). In multivariate analyses, QRS_{area} (per μVs) predicted cardiac mortality (adjusted hazard ratio [HR]: 0.99 [95% CI]: 0.98–0.99), independent of all baseline variables, including QRSd and QRS morphology (Table 4).

Post-CRT QRS_{area}

The QRS_{area} decreased by 41.0 μVs (interquartile range: −79 to −4) after CRT (Figure 4). The cutoff of ΔQRS_{area} derived from Liu method was −45 μVs ([−60] to [−31] μVs). As shown in Table 5, the ΔQRS_{area} groups were well matched for age, New York Heart Association class, hypertension and diabetes mellitus status, device type, left ventricular ejection fraction, and medical therapy (Table 5). A QRS_{area} reduction ≥45 μVs group had a lower proportion of men ($P<0.001$), and most had nonischemic cardiomyopathy ($P<0.001$). As expected from the ΔQRS_{area} grouping, there were significant differences in ECG and vectorcardiography variables.

Cardiac mortality was 11/177 (6.21%) in patients with QRS_{area} reduction ≥45 μVs and 59/203 (29.1%) in patients with QRS_{area} reduction <45 μVs. (Table 2). The AUC for predicting cardiac mortality for ΔQRS_{area} and ΔQRSd were similar (0.74 versus 0.72; $P=0.425$ for comparison) (Figure 2).

Table 4. Univariate and Multivariate Analysis of Pre-Implantation Variables in Relation to Cardiac Mortality

	Univariate				Multivariate			
	HR	95% CI		*P* Value	HR	95% CI		*P* Value
Age, y	1.02	1.00	1.04	0.044	1.02	1.00	1.05	0.097
Sex (male)	2.25	1.21	4.19	0.011	1.57	0.80	3.07	0.186
NYHA class (I, II)	0.61	0.32	1.14	0.122				
Ischemic cause	1.73	1.07	2.80	0.026	1.07	0.63	1.80	0.813
Comorbidities								
Diabetes mellitus	2.08	1.28	3.38	0.003	1.56	0.95	2.58	0.081
Hypertension	1.25	0.76	2.08	0.380				
CABG	1.46	0.83	2.54	0.187				
CRT-D	0.79	0.49	1.26	0.327				
Upgrades	1.18	0.67	2.09	0.564				
LVEF (%)	0.98	0.96	1.01	0.141				
Medication								
ACEI/ARA	0.56	0.29	1.10	0.092	0.63	0.31	1.27	0.196
β-Blocker	0.80	0.48	1.33	0.389				
MRA	1.24	0.78	1.98	0.371				
ECG variables								
AF/flutter	1.62	1.01	2.62	0.047	1.03	0.60	1.76	0.925
PR interval, ms	1.00	1.00	1.01	0.153				
LBBB	0.79	0.49	1.27	0.331				
RBBB	2.50	1.34	4.65	0.004	0.92	0.42	2.02	0.831
RV-paced	0.56	0.22	1.38	0.207				
NICD	1.08	0.58	2.01	0.806				
QRSd, ms	0.99	0.98	1.00	0.075	1.01	0.99	1.02	0.219
QRS_{area}, μVs	0.99	0.98	0.99	<0.001	0.98	0.98	0.99	<0.001

ACEI indicates angiotensin receptor converting enzyme inhibitor; AF, atrial fibrillation; ARA, angiotensin receptor antagonist; CABG, coronary artery bypass graft; CRT-D, cardiac resynchronization therapy with defibrillation; HR, hazard ratio; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NICD, nonspecific intraventricular conduction delay; NYHA, New York Heart Association; QRS_{area}, QRS area; QRSd, QRS duration; RBBB, right bundle branch block; RV, right ventricular.

In Kaplan–Meier survival analyses, a QRS_{area} reduction ≥45 μVs was associated with a lower cardiac mortality, total mortality, total mortality or HF hospitalization, and total mortality or MACE, compared with a QRS_{area} reduction <45 μVs (all $P<0.001$) (Figures 5 and 6). In univariate analyses, a QRS_{area} reduction ≥45 μVs was a strong predictor of cardiac mortality (HR: 0.19, 95% CI: 0.10–0.36), as well as other end points (all $P<0.001$) (Table 3).

Interaction of ΔQRS_{area} and ΔQRSd

As shown in Figures 2 and 5, ΔQRS_{area} and ΔQRSd were comparable predictors of cardiac mortality. In Cox proportional hazard analyses, a significant interaction between ΔQRS_{area} and ΔQRSd emerged with respect to cardiac mortality (HR: 0.12, 96% CI 0.06–0.26). A similar trend was observed for total mortality, total mortality or HF hospitalization, and total mortality or MACE (Figure 6).

Lead Positions

Most LV leads were deployed in a lateral or posterolateral position (Table 5). As shown in Figure 7, there was considerable interindividual variability in ΔQRS_{area} and ΔQRSd within each LV lead position, but no significant differences emerged in ΔQRS_{area} or ΔQRSd between the different LV lead positions.

Arrhythmic events

As shown in Table 3 and Figure 8, both QRSd and QRS_{area} predicted the combined end point of sudden cardiac death, ventricular tachycardia/ventricular fibrillation or shock, but no

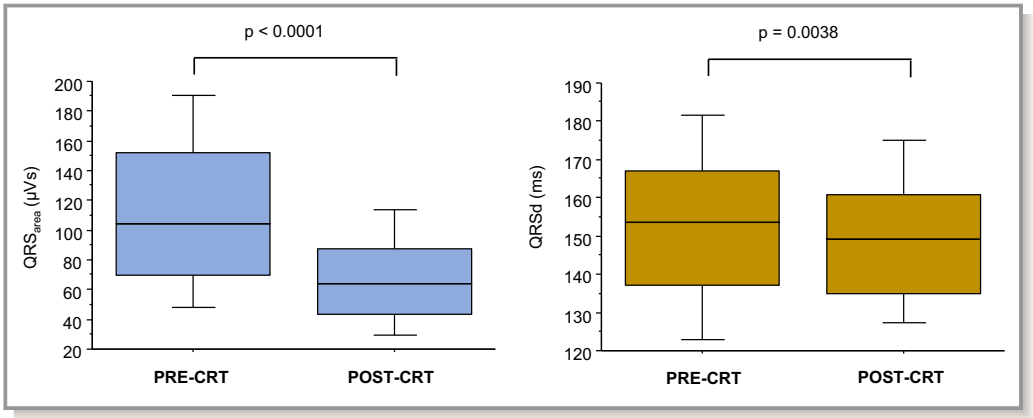

Figure 4. Postimplantation changes in QRS area and QRS duration. Box-and-whisker plots of QRS area (left) and QRS duration (QRSd) (right) before and after CRT implantation. The horizontal line denotes the median, whereas the lower and upper limits of the box denote the first and third quartiles. The limits of the vertical bar denote maximum and minimum. CRT indicates cardiac resynchronization therapy.

such relationship was observed for QRS morphology. A QRS_{area} reduction ≥45 μVs (HR: 0.26, 95% CI 0.11–0.58) and QRSd reduction (HR: 0.33, 95% CI 0.17–0.67) predicted this combined end point. Concomitant reductions in QRS_{area} and QRSd were associated with the lowest risk of the arrhythmic end point (HR: 0.12, 95% CI 0.04–0.41).

Discussion

This is the first study to explore both pre- and postimplantation QRS_{area} in relation to long-term, cause-specific mortality, as well as long-term HF hospitalization, MACE, and ventricular arrhythmias after CRT. Several findings have emerged. First, pre-implantation QRS_{area} was superior to QRSd and QRS morphology in predicting cardiac mortality after CRT. Second, a QRS_{area} reduction after CRT was associated with favorable outcomes, independent of baseline QRSd or QRS morphology. Third, the best outcomes after CRT were observed in patients exhibiting concomitant reductions in QRS_{area} and QRSd.

Pre-CRT QRS_{area}

This study provides an external validation of the findings of 2 observational studies showing that QRS_{area} is superior to QRSd and QRS morphology in predicting total mortality after CRT.[11,12] We found that QRS_{area} (<102 μVs) predicted total mortality, with an AUC of 0.71, which is higher than the AUC of 0.61 identified by van Stipdonk et al using a cutoff of 109 μVs.[11] Emerek et al found that a QRS_{area} ≤95 μVs was associated with a higher total mortality than a QRS_{area} >95 μVs, with an unadjusted HR of 2.11 (P<0.001).[12] Using a cutoff of 102 μVs, we have found an unadjusted HR of 1.73 (P=0.002) for total mortality and 2.77 for cardiac mortality (P<0.001).

Previous studies on QRS_{area}[11,12] did not address cause-specific mortality and only 1 year follow-up data were provided with respect to HF hospitalization.[11] We found that, in addition to predicting total mortality, QRS_{area} predicted cardiac mortality, total mortality or HF hospitalization, and total mortality or MACE. The relation between a high QRS_{area} and better clinical outcomes after CRT is not unexpected, because QRS area correlates with electrical dyssynchrony,[8] the natural substrate of CRT.

Post-CRT ΔQRS_{area}

In an acute hemodynamic study of 25 patients with LBBB, De Pooter et al showed that ΔQRS_{area} correlated with ΔLV dP/dt_{max}.[8] This is consistent with our finding that a reduction in QRS_{area} was associated with a lower cardiac mortality, as well as other end points. While De Pooter et al[8] found that ΔQRS_{area} after CRT was a stronger correlate of ΔLV dP/dt_{max} than ΔQRSd, we found that both ΔQRSd and ΔQRS_{area} were comparable in predicting long-term clinical outcomes. Importantly, the combination of ΔQRSd and ΔQRS_{area} had additive effects in predicting cardiac mortality: patients who exhibited reductions in both variables experienced the best outcomes after CRT, whereas patients who did not exhibit reductions in either experienced the worst outcomes.

QRSd

Randomized, controlled trials of CRT[19,20] adopted a QRSd ≥120 ms as an indication for CRT. In COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure), patients without LBBB and those with QRSd ≤147 ms did not derive a benefit.[19] Similarly, in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–

Table 5. Characteristics of the Study Group According to Post-Implantation Change in QRS Area

	QRS_{area} Reduction ≥45 μVs	QRS_{area} Reduction <45 μVs	*P* Value
N	177	203	
Age, y	72.1±13.1	72±11.7	0.979
Sex (male), n (%)	103 (58.19)	158 (77.83)	<0.001
NYHA class, n (%)			
I	14 (8.48)	12 (6.35)	0.322
II	36 (21.82)	51 (26.98)	
III	110 (66.67)	115 (60.85)	
IV	5 (3.03)	11 (5.82)	
Cause, n (%)			
Ischemic	67 (37.85)	115 (56.65)	<0.001
Nonischemic	110 (62.15)	88 (43.35)	
Comorbidities, n (%)			
Diabetes mellitus	44 (24.86)	45 (22.17)	0.537
Hypertension	50 (28.25)	56 (27.59)	0.886
CABG	17 (9.6)	47 (23.15)	<0.001
Device type, n (%)			
CRT-D	90 (51.14)	119 (58.62)	0.144
CRT-P	86 (48.86)	84 (41.38)	
Upgrades, n (%)			
Pacemaker to CRT-D	14 (35)	25 (59.52)	0.026
Pacemaker to CRT-P	26 (65)	17 (40.48)	
LVEF	25.3±9.1	26.2±10.7	0.429
Medication, n (%)			
ACEI/ARA	154 (88)	183 (91.04)	0.334
β-Blocker	125 (71.43)	152 (75.62)	0.357
MRA	82 (46.86)	85 (42.29)	0.374
ECG variables			
Sinus rhythm, n (%)	139 (78.53)	130 (64.04)	0.002
AF/flutter, n (%)	38 (21.47)	73 (35.96)	
PR interval, ms	178.3±34.5	208.8±67.6	<0.001
QRSd, ms	162.1±20.6	145.9±21.8	<0.001
LBBB, n (%)	134 (75.71)	105 (51.72)	<0.001
RBBB, n (%)	2 (1.13)	31 (15.27)	<0.001
NICD, n (%)	10 (5.65)	49 (24.14)	<0.001
RV-paced, n (%)	31 (17.51)	18 (8.87)	0.012
Vectorcardiography variable			
QRS_{area}, μVs	153.9±47.5	78.1±36.3	<0.001
Circumferential lead positions			
Anterior	6 (3.39)	8 (3.94)	0.498
Anterolateral	28 (15.8)	37 (18.2)	
Lateral	73 (41.2)	86 (42.3)	
Posterolateral	24 (13.6)	16 (9.03)	
Posterior	46 (26.0)	56 (27.6)	
Longitudinal lead positions			
Basal	19 (10.7)	12 (5.91)	0.249
Mid	99 (55.9)	121 (59.6)	
Apical	59 (33.3)	70 (34.5)	

ACEI indicates angiotensin receptor converting enzyme inhibitor; AF, atrial fibrillation; ARA, angiotensin receptor antagonist; CABG, coronary artery bypass graft; CRT-D, cardiac resynchronization therapy with defibrillation; CRT-P, cardiac resynchronization therapy-pacing; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NICD, nonspecific intraventricular conduction delay; NYHA, New York Heart Association; QRS_{area}, QRS area; QRSd, QRS duration; RBBB, right bundle branch block; RV, right ventricular.

Cardiac Resynchronization Therapy) trial, patients with a QRSd <150 ms derived no survival benefit from CRT.[21,22] In the present study, we found that a QRSd ≥150 ms was associated with a lower cardiac mortality, compared with a QRSd <150 ms. The ability of QRSd to predict cardiac mortality, however, was relatively weak (AUC: 0.60).

Meta-analyses of observational studies have shown an inconsistent relationship between post-CRT ΔQRSd[23,24] and "clinical response." In these meta-analyses, however, "clinical response" was defined in terms of symptoms, echocardiographic variables, and/or hard end points, assuming that these are identical, interchangeable measures. On the other hand, studies focusing on hard end points do indeed support a relationship between a QRSd reduction and better outcomes after CRT. The REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) study, the only randomized controlled trial to address ΔQRSd after CRT, explored acute ΔQRSd in the CRT-treated group in relation to the primary end point of the clinical composite score, as well as LV reverse remodeling.[25] Although not designed to address hard end points, REVERSE reported an association between ΔQRSd and total mortality or HF hospitalization over a relatively short follow-up (12 months in North America and for 24 months in Europe) on univariate analyses, but not in a multivariate model that corrected for baseline QRSd. Importantly, however, the CRT-treated group in REVERSE only had 4 deaths over 24 months, raising the possible play of statistical underpowering. In contrast, in an observational study, Appert et al showed that a lack of postoperative QRSd reduction was independently associated with an increased risk of total mortality over a median follow-up period of 48 months.[6] In a similar study, Jastrzebski et al showed that a QRSd reduction predicted death from any cause or urgent heart transplantation and death from any cause/urgent heart transplantation or hospital admission for HF over an average follow-up period of 46 months.[5] In the present study, in which 135 deaths occurred over a median follow-up of 3.8 years, a QRSd

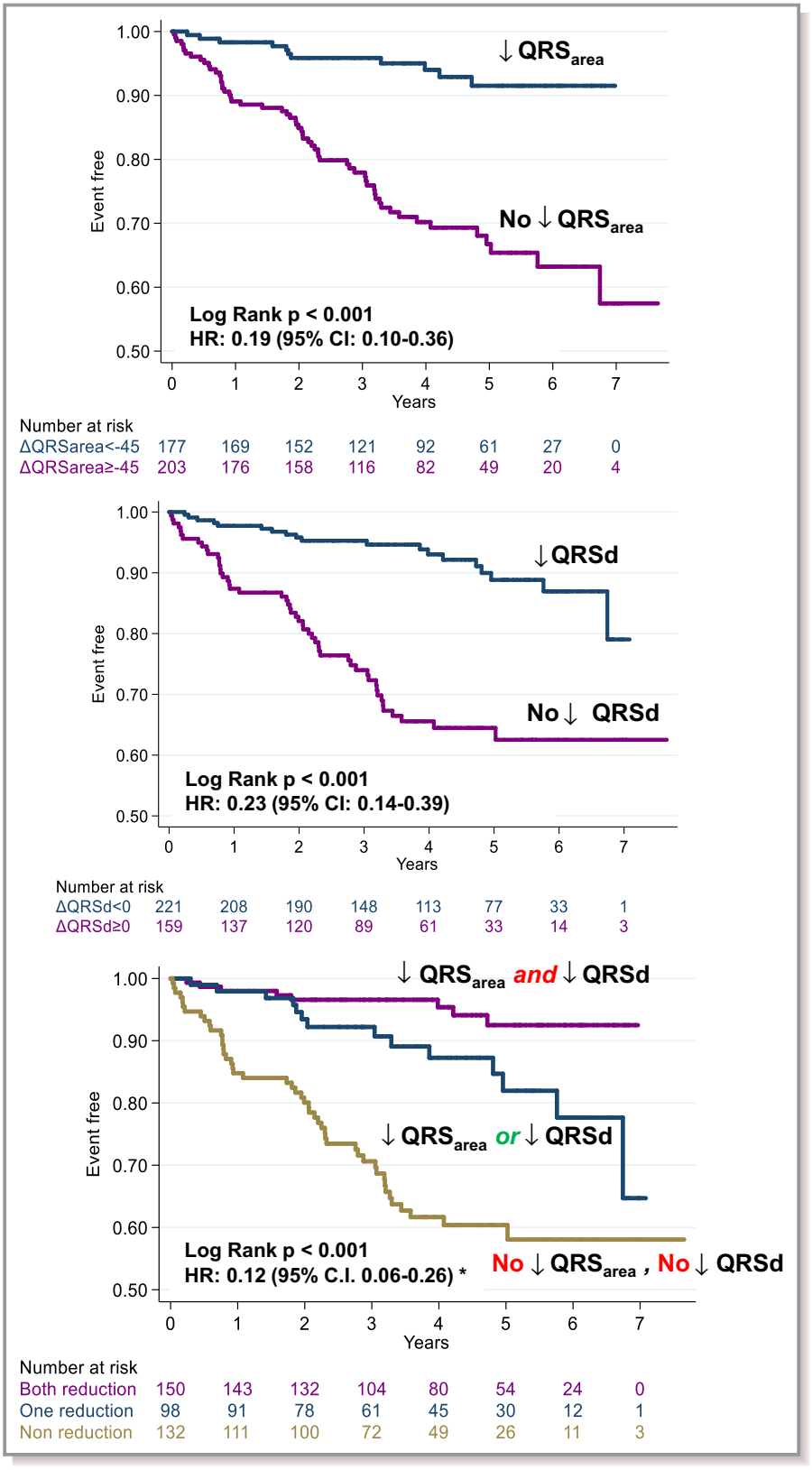

Figure 5. QRS area and QRS duration in relation to cardiac mortality. Kaplan–Meier survival curves and univariate HR and (95% CI for QRS area (QRS_{area}) and QRS duration (QRSd) in relation to cardiac mortality. *Refers to the interaction between changes in QRSarea and QRSd after CRT. HR indicates hazard ratios.

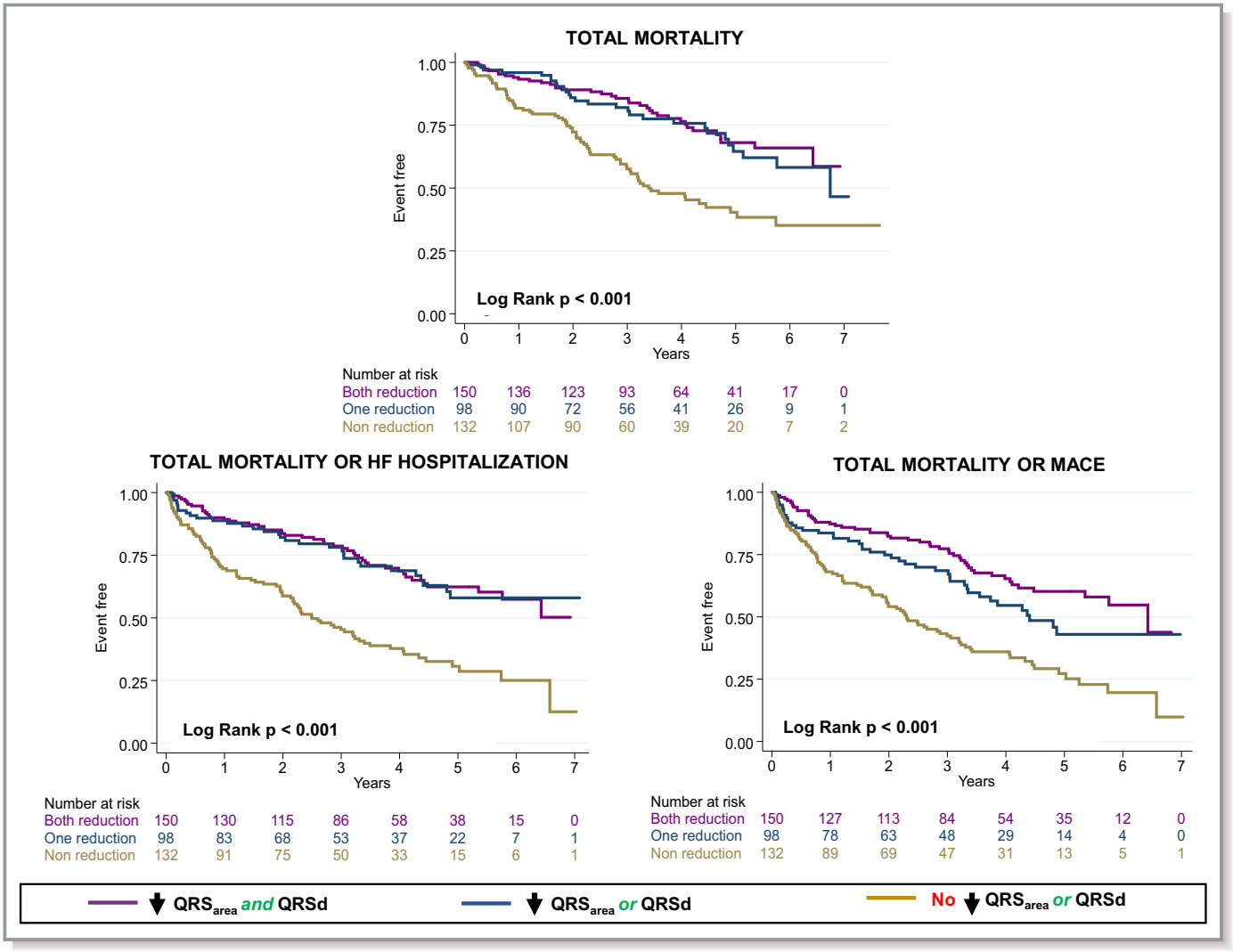

Figure 6. Secondary clinical end points according to changes in QRS area and QRS duration. Kaplan–Meier survival curves for the various end points according to postcardiac resynchronization therapy reductions in QRS_{area} (≥45 μVs) QRS duration (QRSd; to any value below baseline). HF indicates heart failure; MACE, major adverse cardiac events.

reduction below baseline predicted cardiac mortality, total mortality, total mortality or HF hospitalization, and total mortality or MACE.

QRS Morphology

Observational studies[26,27] as well as large registries[28] and subanalyses of randomized, controlled trials[19,22,25,29] have shown that patients with a LBBB morphology derive the most benefit from CRT. While some studies have suggested that a LBBB defined using "strict" criteria, with notching and/or slurring of the QRS complex, is associated with a better left ventricular ejection fraction response to CRT,[10,27] this is not a consistent finding.[30,31] Moreover, Emerek et al found that "strict" (Strauss) criteria of LBBB was not predictive of clinical outcomes after CRT.[12] In the present study, a conventionally defined LBBB did not predict cardiac mortality after CRT (AUC: 0.53).

Lead Position

We have observed a considerable interindividual variability in QRS_{area} at a given LV lead position. In this regard, De Pooter et al also found a similar interindividual variability in QRS_{area} in CRT recipients with a LBBB.[8] Crucially, they also found that QRS_{area} and the acute hemodynamic response to CRT in a given patient could be improved by changing the LV lead position. Together, these findings make the case for optimization of QRS_{area} in CRT recipients. To date, however, no studies have prospectively explored this issue.

Arrhythmic events

Several studies have suggested that QRSd predicts sudden cardiac death.[32,33] In contrast, no studies have explored QRS_{area} or ΔQRS_{area} in relation to sudden cardiac death or ventricular tachycardia/ventricular fibrillation. Although pre-

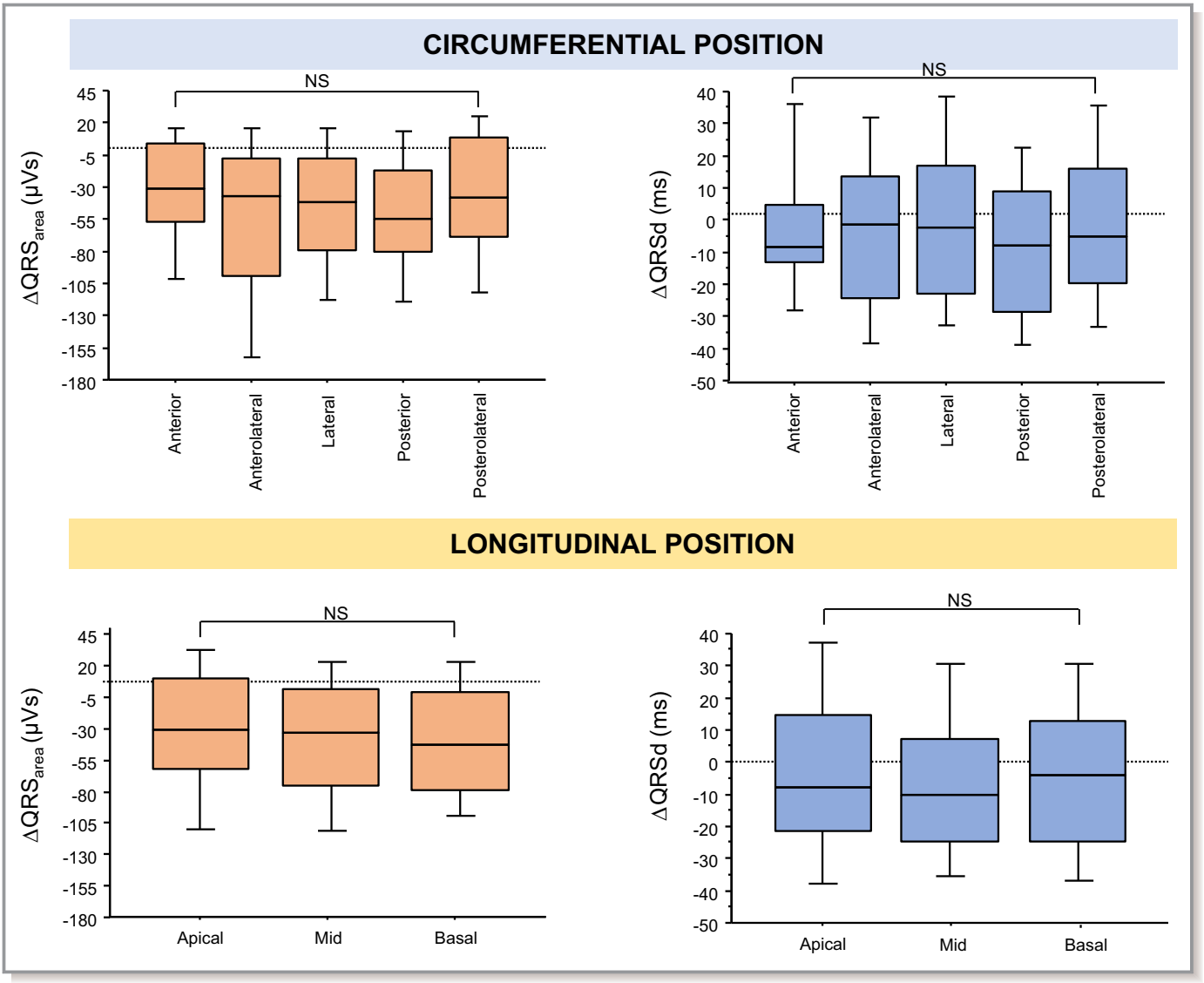

Figure 7. Postimplantation changes QRS area and QRS duration according to left ventricular lead position. The figure shows post– cardiac resynchronization therapy changes in QRS area (ΔQRS_{area}) and QRS duration ($\Delta QRSd$) according to circumferential (upper panel) and longitudinal (lower panel) left ventricular lead positions. In the box-and-whisker plots, the horizontal line denotes the median, whereas the lower and upper limits of the box denote the first and third quartiles. The limits of the vertical bar denote maximum and minimum. NS indicates not significant.

implantation QRS_{area} did not predict this end point, its reduction was associated with a 74% reduction in the end point. Moreover, concomitant with QRS_{area} reduction, a QRd reduction was associated with an 88% lower risk of the combined end point. This novel finding, which was not anticipated, could speculatively relate to a greater dispersion of depolarization in relation to arrhythmic events. The physiological basis for this empirical finding requires further study.

Clinical Perspectives

Attention has recently focused on ECG imaging using body surface mapping as a tool for identifying electrical dyssynchrony and to predict response to CRT.[34,35] Although there is a proof-of-principle and encouraging clinical data to support the use of this technique in CRT, it requires specialized acquisition. Importantly, data on body surface mapping in relation to long-term outcomes after CRT are lacking. In contrast, QRS_{area} can be readily derived from the standard 12-lead ECG and crucially, is now known to predict long-term clinical outcomes. The role of QRS_{area} in patient selection and CRT optimization requires further investigation.

Limitations

This study has all the limitations of an observational study. Although we have corrected for potential confounders using

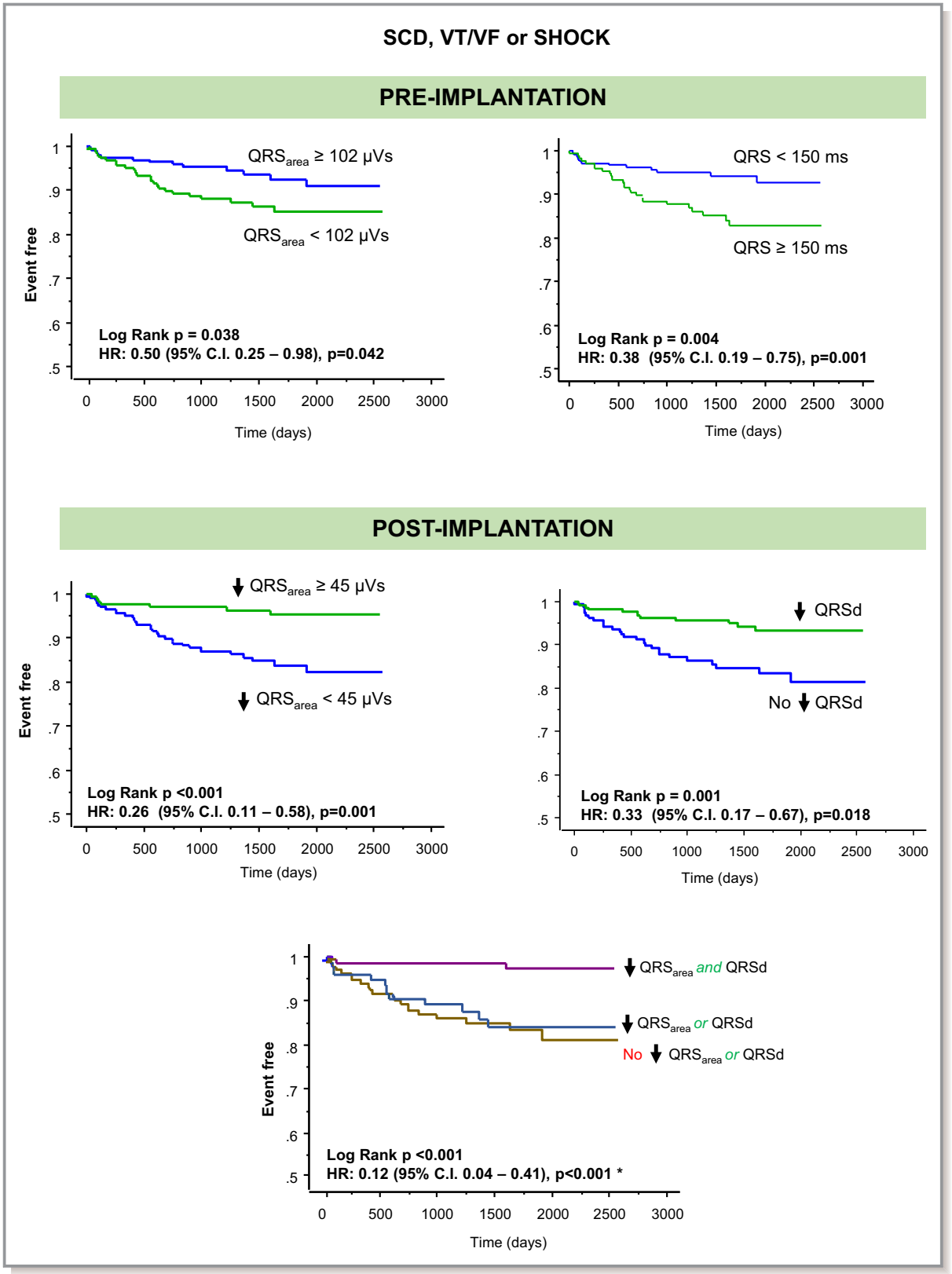

Figure 8. Sudden cardiac death and ventricular arrhythmias according to postimplantation changes in QRS area and QRS duration. Kaplan–Meier survival curves for the combined end point of sudden cardiac death (SCD), ventricular tachycardia (VT)/ventricular fibrillation (VF), or shock according to postimplantation reductions in QRS area (QRS$_{area}$, ≥45 μVs) QRS duration (QRSd to any value below baseline). *Refers to the comparison of the group with concomitant reductions in QRS$_{area}$ (≥45 μVs) and QRSd against the group with no reductions in either variable. HR indicates hazard ratio.

statistical means, unobserved variables may have contributed to outcomes. Importantly, vectorcardiographies were derived retrospectively from 12-lead ECGs undertaken before implantation. Inconsistencies in electrode position could conceivably influence vectorcardiography analysis.[36] Notwithstanding, all ECGs were acquired by trained cardiac technicians using a standardized operating procedure in routine clinical practice. Consequently, our results should be generalizable to a "real-world" environment. Unfortunately, we did not systematically collect data on device programming. In this respect, variable programming at implantation and follow-up could account for variations in ECG and vectorcardiography variables, as well as outcomes. Although the AUCs for pre-implant QRS_{area} and ΔQRS_{area} did not exceed 0.74, these values are comparable to those found in other studies[11] and exceed the AUCs for QRSd and LBBB.

Conclusions

Pre-implantation QRS_{area} was superior to QRSd and QRS morphology in predicting clinical outcomes after CRT. A concomitant reduction in QRSd and QRS_{area} after CRT was associated with the lowest risk of cardiac and total mortality, as well as ventricular arrhythmias. These findings add support for the use of QRS_{area} and QRSd in the risk stratification and optimization of CRT recipients.

Sources of Funding

Okafor was supported by an unrestricted educational grant from Medtronic Plc.

Disclosures

None.

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