QRS Area Is a Strong Determinant of Outcome in Cardiac Resynchronization Therapy

van Stipdonk, Antonius M. W.; ter Horst, Iris; Kloosterman, Marielle; Engels, Elien B.; Rienstra, Michiel; Crijns, Harry J. G. M.; Vos, Marc A.; van Gelder, Isabelle C.; Prinzen, Frits W.; Meine, Mathias

Published in:
Circulation. Arrhythmia and Electrophysiology

DOI:
10.1161/CIRCEP.118.006497

Publication date:
2018

Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

QRS Area Is a Strong Determinant of Outcome in Cardiac Resynchronization Therapy

BACKGROUND: The combination of left bundle branch block (LBBB) morphology and QRS duration is currently used to select patients for cardiac resynchronization therapy (CRT). These parameters, however, have limitations. This study evaluates the value of QRS area compared with that of QRS duration and morphology in the association with clinical and echocardiographic outcomes in a large cohort of CRT patients.

METHODS: A retrospective multicentre study was conducted in 1492 CRT patients. LBBB morphology, QRS duration, and QRS area in the baseline 12-lead ECG were evaluated for their association with the occurrence of the combined primary end point of all-cause mortality, cardiac transplantation, and left ventricular assist device implantation. Secondary end points were heart failure hospitalization within the first year after implantation and echocardiographic reduction in left ventricular end-systolic volume.

RESULTS: During a mean follow-up period of 3.4 years, 32% of patients reached the primary end point. The association of QRS area with all outcomes was stronger than that of LBBB morphology and QRS duration separately and at least as strong as their combination. QRS area identified patients who did not experience the primary end point better than QRS morphology and QRS duration (area under the curve, 0.61 versus 0.55 and 0.51, respectively; $P<0.001$). Furthermore, QRS area identifies patients with echocardiographic remodeling in response to CRT better than QRS morphology and duration (area under the curve, 0.69 versus 0.58 and 0.58, respectively; $P<0.001$). QRS area was the only independent electrocardiographic determinant associated with the primary end point; hazard ratio, 0.50 (0.35–0.71). Furthermore, QRS area showed significant association with outcomes in both patients with and without LBBB and QRS ≥150 ms.

CONCLUSIONS: QRS area has a strong association to clinical and echocardiographic response to CRT, at least as strong as current patient selection parameters. QRS area may be particularly useful to predict CRT response in patients without a wide LBBB.

VISUAL OVERVIEW: A visual overview is available for this article.

Antonius M.W. van Stipdonk, MD*
Iris ter Horst, MD, PhD*
Marielle Kloosterman, BSc*
Elien B. Engels, PhD
Michiel Rienstra, MD, PhD
Harry J.G.M. Crijns, MD, PhD
Marc A. Vos, PhD
Isabelle C. van Gelder, MD, PhD
Frits W. Prinzen, PhD
Mathias Meine, MD, PhD
Alexander H. Maass, MD, PhD†
Kevin Vernooy, MD, PhD†

*Dr van Stipdonk, Dr ter Horst, and M. Kloosterman are joint first authors.

†Drs Maass and Vernooy are joint senior authors.

Key Words: bundle-branch block ■ cardiac resynchronization therapy ■ heart failure ■ patient selection ■ stroke volume

https://www.ahajournals.org/journal/circep

WHAT IS KNOWN?

- Cardiac resynchronization therapy offers great benefit to selected heart failure patients.
- Current ECG parameters for patient selection hamper further increase of the rate of patients benefiting from cardiac resynchronization therapy.

WHAT THE STUDY ADDS?

- QRS area is a new, simple ECG-derived parameter.
- In a large patient cohort, QRS area provides equal or better association with clinical and echocardiographic outcomes compared with the combination of QRS duration and morphology.
- QRS area especially improves selection of patients for cardiac resynchronization therapy without a typical left bundle branch block and a QRS duration ≥150 ms.

Cardiac resynchronization therapy (CRT) is an established treatment for patients with heart failure (HF) and ventricular conduction abnormalities. In these patients, CRT has been shown to improve exercise tolerance and quality of life and to reduce HF hospitalizations and mortality.[1,2] However, identification of patients who benefit from CRT remains a challenge.[3] Initial guidelines on patient selection suggested QRS duration as a marker of the degree of electrical dyssynchrony and suitability for CRT.[4] More recent subanalyses of randomized clinical trials showed that left bundle branch block (LBBB) morphology has a strong association with CRT response.[5,6] Current guidelines therefore include QRS duration and LBBB morphology to classify patients referred for CRT to a level of recommendation for implantation, as illustrated by Table I in the Data Supplement.[7] The lower level of evidence of the recommendation for patients not having LBBB and a QRS duration >150 ms illustrates the existence of uncertainties about a significant portion of patients. Uncertainties in using QRS duration and LBBB morphology to properly identify patients who will respond to CRT may lie in caveats of the individual parameters. QRS widening may be caused by many different pathophysiological processes,[5,8] and the value of the QRS duration depends on how it is measured, with up to 20 ms variability.[9] A disadvantage of the use of LBBB is that there are various LBBB definitions,[10] many of which consist of criteria that are sensitive to subjective interpretation.

Vectorcardiography has recently been introduced as an alternative way to assess suitability for CRT. In particular the area under the 3-dimensional QRS complex, QRS area showed a strong association with CRT response.[11–14] The ratio behind this parameter is that it expresses nonopposed electrical forces, and high values of these parameters may therefore indicate dyssynchronous electrical activation. This hypothesis was confirmed in a recent study that showed that a large QRS area corresponds with delayed activation of the left ventricular (LV) posterolateral wall, independently of QRS morphology.[13]

The present study was undertaken to evaluate the value of QRS area in a large patient cohort undergoing CRT implantation on clinical and echocardiographic outcome. Special attention was paid to the added value of the QRS area in patients who do not have an LBBB with QRS duration >150 ms.

METHODS

The MUG (Maastricht-Utrecht-Groningen) study cohort was used for retrospective analysis of consecutive patients implanted with a CRT device in 3 university hospitals in the Netherlands, from January 2001 up to January 2015 (Maastricht University Medical Center, January 2010–December 2015; University Medical Center Utrecht, January 2005–December 2015; and University Medical Center Groningen, January 2001–December 2015). No formal inclusion criteria on LV ejection fraction, New York Heart Association, or QRS duration were set in advance. Patients were included if a baseline digital 12-lead ECG was available and if CRT was continued until end of follow-up. Patient selection, device implantation, lead positioning, as well as device and patient follow-up were according to then prevailing guidelines and local protocols. No formal optimization protocol was conducted to the patient cohort from either hospital, but was up to the discretion of the patients' physician.

Patient Population

The MUG cohort consisted of a total of 1946 patients with baseline 12-lead ECG available and continued CRT during follow-up. For the present study, we considered patients selected for de novo CRT device implantation according to current guidelines.[7] Accordingly, patients were excluded when baseline ECG showed right ventricular pacing (340 patients; 17%) or QRS duration <120 ms (114 patients; 6%). The patient selection process is shown in Figure 1.

Baseline data were retrieved from the local hospital patient information systems. Patient characteristics like HF cause and classification, comorbidity, and medication were retrieved from patient history and referral letters. HF cause was deemed ischemic when there was clear evidence of myocardial infarction or CABG in the medical history. Device data were retrieved from specific device databases. LV lead location was judged from the fluoroscopic images or chest x-ray. The Dutch Central Committee on Human-Related Research (CCMO [Centrale Commissie Mensgebonden Onderzoek]) allows the use of anonymous data without prior approval of an institutional review board provided that the data are acquired for routine patient care. All data used were handled anonymously. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. As ongoing research and analyses on these data prohibit the release of the findings.

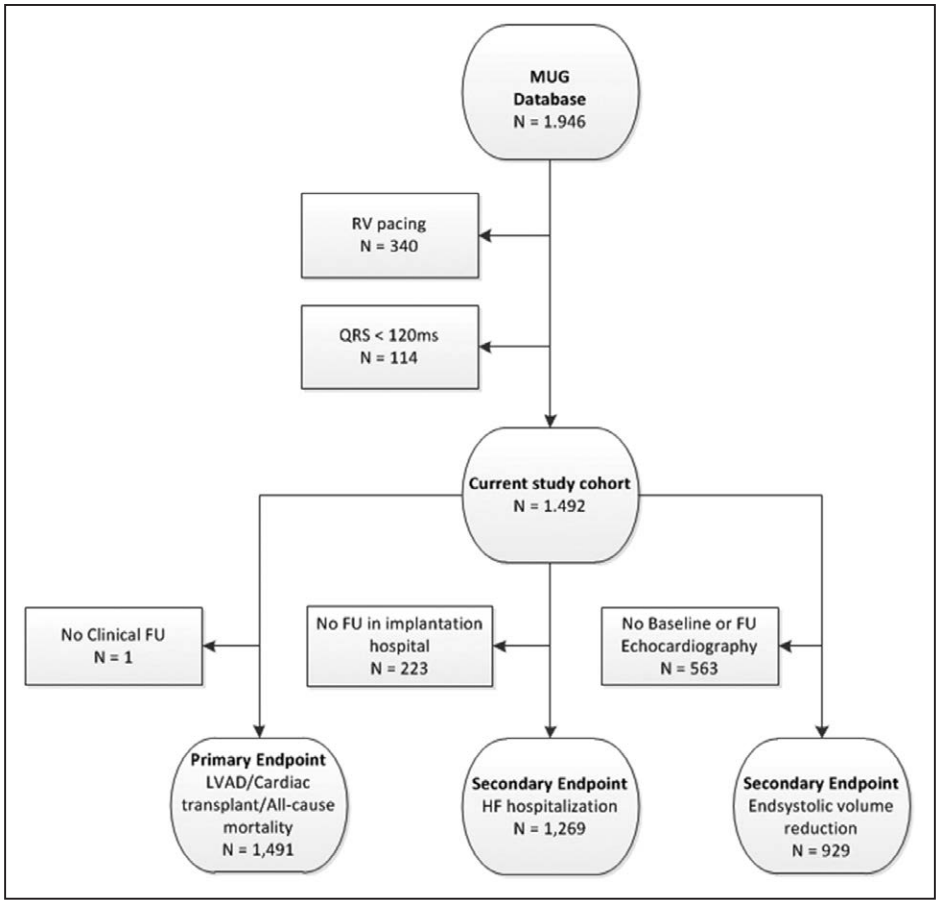

Figure 1. Patient data selection and availability for analyses.
The entire MUG (Maastricht-Utrecht-Groningen) cohort consisted of all patients with a cardiac resynchronization therapy (CRT) device implanted from January 2001 to January 2015 in 3 university hospitals in the Netherlands. For the present study, patients with QRS <120 ms and patients receiving an upgrade to biventricular pacing were excluded. Availability of data for analyses on the primary and secondary end points is also shown. FU indicates follow-up; HF, heart failure; LBBB, left bundle branch block; LVAD, left ventricular assist device; and RV pacing, right ventricular pacing.

Electro- and Vectorcardiography

Recorded baseline 12-lead ECGs were stored digitally in the MUSE Cardiology Information system (GE Medical System) and were evaluated for QRS duration and baseline ECG parameters using the automated ECG readings. LBBB morphology was defined according to accepted criteria.[15] Including QRS duration ≥120 ms, QS or rS in lead V_1, broad (frequently notched or slurred) R waves in leads I, aVL, V_5, or V_6, and absent Q waves in leads V_5 and V_6. Patients were grouped according to the level of indication for CRT according to current guideline recommendations (Table I in the Data Supplement).[7]

QRS area was calculated as described previously.[16,17] In brief, the original digital signals were extracted from the PDF files stored in the MUSE system. Subsequently, custom Matlab software (MathWorks Inc, Natick, MA) was used to convert the 12-lead ECG into the 3 orthogonal vectorcardiography leads (X, Y, and Z) using the Kors conversion matrix.[18] QRS area was calculated as the sum of the area under the QRS complex in the calculated vectorcardiographic X, Y, and Z lead ($QRS\ area=[QRS_{area,x}^2+QRS_{area,y}^2+QRS_{area,z}^2]^{1/2}$). Figure I in the Data Supplement shows 2 examples of 12-lead ECGs converted to QRS area.

Study End Points

Patients were followed for 3.4±2.4 years. The primary end point was a combination of LV assist device implantation, cardiac transplantation, and all-cause mortality. Information was obtained from hospital records, linked to municipal registries.

Secondary end points were HF hospitalization within the first year after CRT device implantation. The cause of hospitalization was considered HF when described as such in discharge forms by responsible physicians. Data were considered missing when follow-up was not in the center where the implantation was performed.

Another secondary end point was the reduction in LV endsystolic volume (LVESV) determined by echocardiography at 6 to 12 months after implantation. LV dimensions and ejection fraction measurements were calculated by Simpsons modified biplane method. Echocardiographic CRT response was defined as a reduction in LVESV ≥15%.

Statistical Analysis

The statistical analysis was performed using IBM SPSS statistics software version 21 (SPSS Inc, Chicago, IL). Continuous and discrete variables are presented as mean±SD and counts

(percentages), respectively. Dichotomous variables were compared using a χ^2 test. Continuous variables were compared using a Student *t* test. Overall differences were evaluated for ECG parameters and QRS area. Stratification of QRS area for presentation purposes and initial analyses was based on median values when dichotomous. QRS area was further stratified into quartiles for the purpose of evaluation of its distinctive value next to that of 4 groups, based on guideline recommendation levels by classification of QRS duration and LBBB morphology. Furthermore, patients with and without a class I guideline indication (LBBB morphology and QRS duration ≥150 ms) were evaluated separately in the same way.

Kaplan-Meier survival analyses and cumulative hazard analyses were used when appropriate to evaluate the association between electrical parameters and the primary outcome. The log-rank test was used to determine the difference in survival probabilities between groups. The diagnostic performance of the electrical parameters for identifying patients without clinical end points or with echocardiographic response to CRT was evaluated using unadjusted receiver operating characteristic curve analysis. Area under the curve (AUC) for tested variables was statistically compared using the Delong method.[19]

Cox and logistic regression analyses were used to assess univariable- and multivariable-adjusted effects of ECG parameters and QRS area, on the association with the primary outcome and secondary outcomes when appropriate. Hazard ratio (HR) and odds ratios (ORs) were reported, respectively. Multivariable regression analyses included parameters known to be associated with outcome to CRT (sex, age at implantation, HF cause, history of atrial fibrillation, device type, LV lead position, baseline New York Heart Association, baseline ejection fraction, and use of a β-blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and mineralocorticoid receptor antagonist). Additional adjustment was done for interaction terms, and proportional hazards assumption was tested graphically. Comparison of continuous echocardiographic values was performed using 1-way ANOVA. Follow-up paired comparisons were made using the Tukey test. A 2-sided *P* value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The 1492 patients included in the current analysis represent a typical CRT population, with a mean age of 67 years and predominantly male (71%). An ischemic cause was present in 50% of patients and most were in New York Heart Association functional class II or III (93%; Table 1). Mean QRS duration was 160±21 ms, LBBB morphology was present in 78% of patients, and 15% of patients showed atrial fibrillation on the baseline ECG.

Vectorcardiographic analysis was not possible in 17 patients (1%) because of frequent extrasystolic beats. Mean QRS area was 116±54 μVs. Fifty-six percent and 23% of patients showed LBBB with QRS duration ≥150 and <150 ms, respectively, and 12% and 9% of patients showed non-LBBB in combination with QRS duration ≥150 and <150 ms, respectively (Table 1).

Table 1. Baseline Characteristics

	Total* n=1492
Age, y	67±11
Female gender, %	29
BMI, m/kg^2	27±5
Atrial fibrillation, %	15
Ischemic CMP, %	50
Diabetes mellitus, %	25
Hypertension, %	42
LVEF, %	25±9
LVEDV, mL	219±88
LVESV, mL	168±78
NYHA I, %	2
NYHA II, %	39
NYHA III, %	54
NYHA IV, %	5
NT-proBNP, pmol/L	334±591
CreatClear, mL/min	71±32
β-Blocker, %	82
ACE inhibitor/ARB, %	90
MRA, %	45
CRT-D, %	93
Anterior, %	1
Anterolateral, %	11
Lateral, %	36
Posterolateral, %	44
Posterior, %	8
QRS duration, ms	160±21
QRS area, μVs	116±54
LBBB morphology, %	78
LBBB/QRS ≥150 ms, %	56
LBBB/QRS<150 ms, %	23
Non-LBBB/QRS ≥150 ms, %	12
Non-LBBB/QRS <150 ms, %	9

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CMP, cardiomyopathy; CreatClear, creatinine clearance; CRT-D, cardiac resynchronization therapy with defibrillator function; LBBB, left bundle branch block; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

*Total population including 17 patients without QRS area calculation.

Primary End Point

Information on the primary end point of LV assist device implantation, cardiac transplantation, or all-cause mortality was available in 1491 patients. One patient was

lost to follow-up because of emigration. During the follow-up time of 3.4±2.4 years, 472 patients (31.7%) reached the primary end point.

Survival free from the primary end point was significantly different in patient groups stratified to LBBB morphology (*P*<0.001), QRS duration (*P*=0.009), and QRS area (*P*<0.001; Figure 2). The association with the combined end point was stronger in patients with QRS area ≥109 µVs compared with patients with QRS area <109 µVs (HR, 0.49 [0.41–0.59]), than in patients with LBBB morphology compared with non-LBBB morphology, and patient with QRS duration ≥150 ms compared with those with QRS duration <150 ms (HR, 0.54 [0.43–0.68], and HR, 0.76 [0.62–0.94], respectively; Figure 2).

Receiver operating characteristic curve analysis showed that QRS area improved identification of patients who did not experience the primary end point, compared with QRS morphology and duration ([AUC], 0.61 versus 0.55 and 0.51, respectively; *P*<0.001 for comparison with both QRS morphology and duration; Figure II in the Data Supplement).

The occurrence of the primary end point was significantly different between patient groups when stratified according to the combination of QRS duration (120–150 ms versus ≥150 ms) and morphology (LBBB versus non-LBBB; *P*<0.001). Figure 3A shows that these differences were most clear between the subgroup of patients with LBBB and QRS duration ≥150 ms (class I indication) and the other subgroups (HR, 0.71 [0.56–0.89]). Pairwise comparison showed that patients with LBBB and QRS duration <150 ms have a significantly higher event free survival than patients with non-LBBB and QRS duration ≥150 ms (HR, 0.72 [0.54–0.96]; *P*=0.025). QRS duration did not affect the association with the primary end point in the non-LBBB subgroups.

A clearer separation in the occurrence of the primary end point was achieved when stratifying patients to quartiles of QRS area. Figure 3B shows significant deviation of the Kaplan-Meier estimates of survival free of events between the quartiles. Pairwise comparison shows a significantly higher event free survival in patients with QRS area ≥150 µVs compared with those with QRS area of 109 to 150 µVs (HR, 0.64 [0.47–0.87]; *P*=0.004). Patients with QRS area between 109 to 150 µVs had a higher event free survival compared with patients with QRS area of 75 to 108 µVs (HR, 0.60 [0.46–0.77]; *P*<0.001). The occurrence of the primary event did not significantly differ between patients with QRS area of 75 to 108 µVs and <75 µVs (Figure 3B).

The analysis of QRS area in patients without a class I indication showed that patients with QRS area ≥109 µVs had a significantly higher event free survival from the primary end point than patients with a QRS area <109 µVs (HR, 0.51 [0.36–0.73]; *P*<0.001; Figure 3C). In the group of patients with a class I indication for CRT, patients with QRS area ≥109 µVs also showed a significantly higher event free survival than those with QRS area <109 µVs (HR, 0.54 [0.41–0.70]; *P*<0.001; Figure 3D).

A multivariable regression model for the entire cohort, including the combination of LBBB and QRS duration and quartiles of QRS area, showed that only QRS area remained significantly associated with the primary end point (HR, 0.75 [0.69–0.83]; *P*<0.001), whereas the combination of LBBB and QRS duration was not independently associated to the occurrence of events (*P*=0.134; Table 2). Also in patients other than those with LBBB and QRS duration ≥150 ms, the association with the primary end point was only significant for QRS area (HR, 0.49 [0.34–0.71]; *P*<0.001) and not for QRS duration or LBBB morphology (*P*=0.094 and *P*=0.671, respectively; Table 2).

HF Hospitalization

Data on HF hospitalization within 1 year after CRT implantation were available for 1269 patients (85%). Eighty-five (5.7%) patients had been hospitalized.

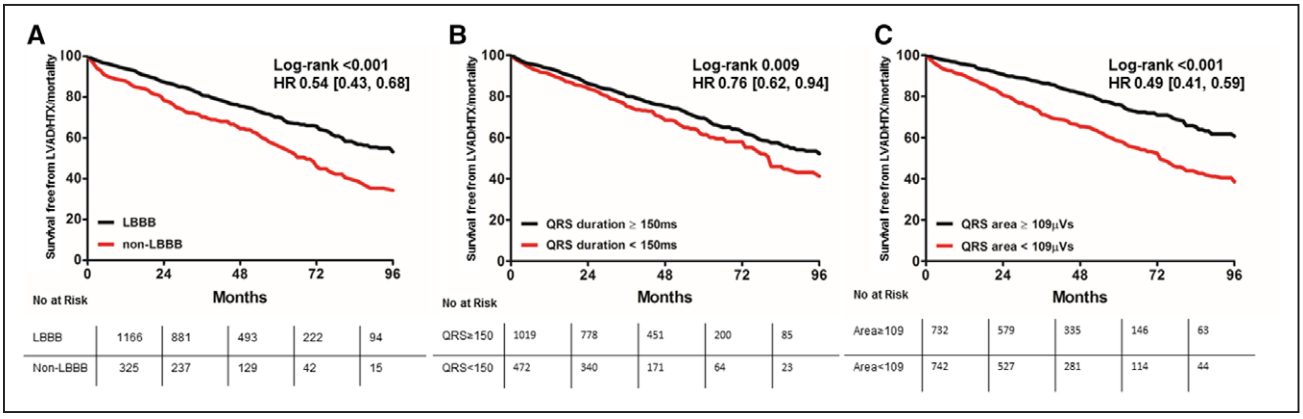

Figure 2. Kaplan-Meier estimates of survival free of the primary end point (combination of left ventricular assist device [LVAD], cardiac transplantation or all-cause mortality).

Patients are stratified to (**A**) left bundle branch block (LBBB) morphology, (**B**) QRS duration (≥150/<150 ms), and (**C**) QRS area (≥109/<109 µVs). HR indicates hazard ratio; HTX, cardiac transplantation; LBBB, left bundle branch block; and LVAD, left ventricular assist device.

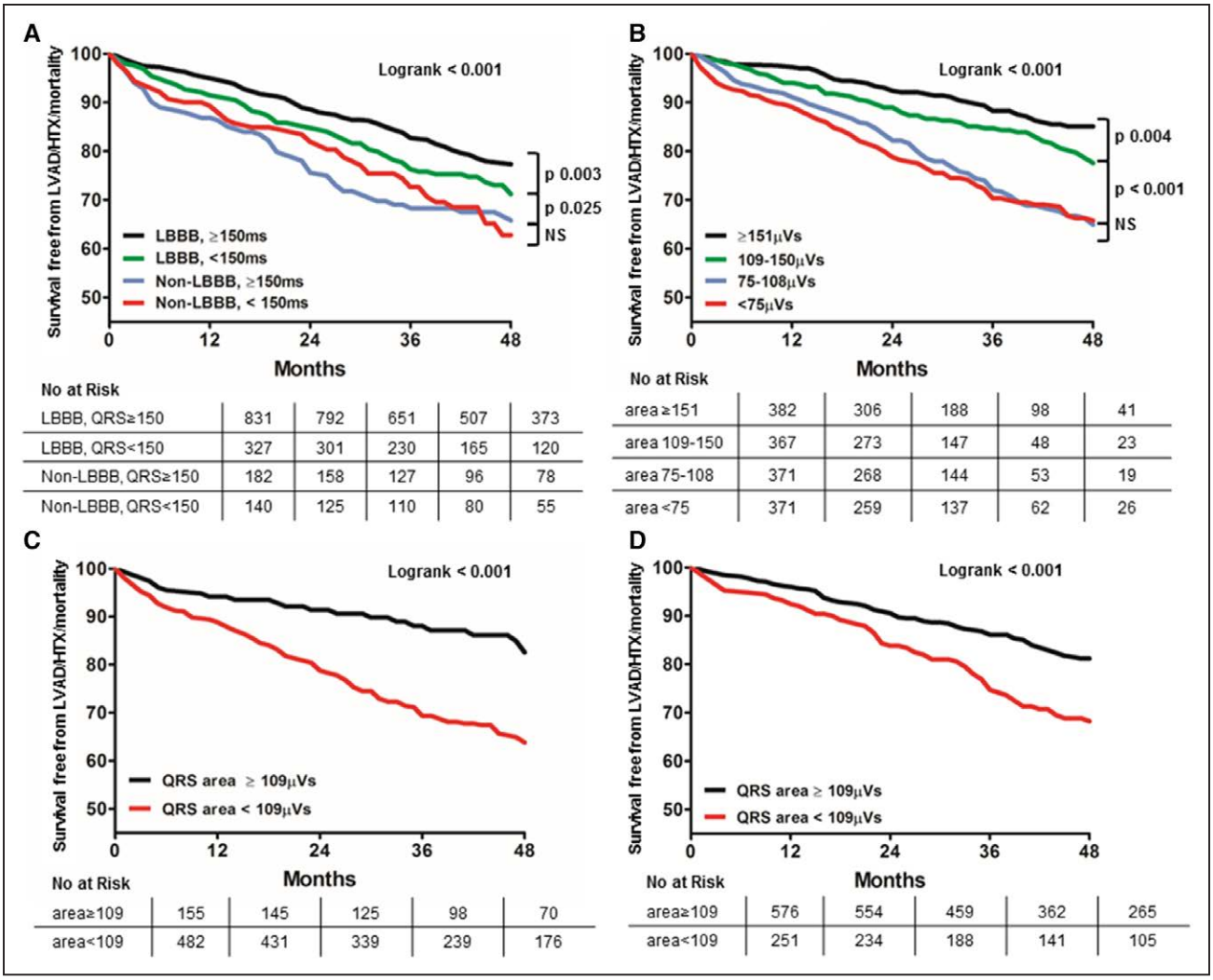

Figure 3. Kaplan-Meier estimates of survival free of the primary end point comparing QRS area and the combination of left bundle branch block (LBBB) morphology and QRS duration.

A, The combination of QRS duration and morphology divides patients into subgroups according to presence of LBBB and QRS duration <150 or ≥150 ms (corresponding to current guideline recommendations). **B**, Subgroups of QRS area are based on quartiles. **C**, Patients without a guideline class I indication[7] (without LBBB and QRS duration ≥150 ms) are stratified to QRS area <109 or ≥109 μVs. **D**, Patients with a guideline class I indication[10] (with LBBB and QRS duration ≥150 ms) are stratified to QRS area <or ≥109 μVs. HTX indicates cardiac transplantation; LBBB, left bundle branch block; LVAD, left ventricular assist device; and NS, nonsignificant.

Patient groups stratified according to the combination of QRS duration and morphology did not significantly differ in the occurrence of HF hospitalization (Figure IIIA in the Data Supplement). Patients stratified according to QRS area differed significantly with respect to the occurrence of HF hospitalization (*P*=0.007). Patients with a QRS area >150 μVs had a significantly lower hospitalization rate compared with those with a QRS area of 109 to 150 μVs (HR, 0.49 [0.34–0.71]; *P*<0.001; Figure IIIB in the Data Supplement).

In patients without a class I indication (LBBB and QRS duration ≥150 ms) stratification according to QRS area (≥109/<109 μVs) showed a trend toward lower HF hospitalization in patients with QRS area ≥109 μVs (*P*=0.085; Figure IIIC in the Data Supplement). The same trend was shown in the subgroup of patients with a class I indication (*P*=0.065; Figure IIID in the Data Supplement).

In the receiver operating characteristic analysis, the AUC was higher for QRS area than for QRS morphology or duration (0.62 versus 0.54 and 0.56, respectively; *P*=0.04 for comparison with QRS duration and *P*=0.01 for comparison with QRS morphology; Figure II in the Data Supplement).

In a multivariable analysis, QRS area remained the only parameter significantly associated with HF hospitalization (HR, 0.76 [0.60–0.96]; *P*=0.019; Table 2).

Echocardiographic Outcome

Paired LVESV measurements at baseline and follow-up were available in 929 patients (62%). The average reduction in LVESV was 19±32%. Echocardiographic

Table 2. Uni- and Multivariable Regression for ECG Parameters and the Association With Clinical Outcomes and Echocardiographic Response to CRT

	Variable	Univariable Regression		Multivariable Regression	
		P Value	OR/HR* (95% CI)	*P* Value	OR/HR* (95% CI)
LVAD, cardiac transplantation, all-cause mortality					
All	LBBB+QRS duration	<0.001	0.80 (0.73–0.86)	0.134	0.93 (0.69–1.02)
	QRS area quartiles	<0.001	0.73 (0.67–0.79)	<0.001	0.75 (0.69–0.83)
Nonclass I	LBBB morphology	0.032	0.76 (0.59–0.98)	0.671	0.93 (0.66–1.30)
	QRS duration	0.049	0.77 (0.59–0.99)	0.094	0.74 (0.52–1.05)
	QRS area	<0.001	0.51 (0.36–0.73)	<0.001	0.49 (0.34–0.71)
Class I	QRS area	<0.001	0.54 (0.41–0.70)	…	…
HF hospitalization within 1 y of implantation					
All	LBBB+QRS duration	0.030	0.81 (0.67–0.98)	0.711	0.96 (0.76–1.21)
	QRS area quartiles	0.004	0.74 (0.61–0.91)	0.019	0.76 (0.60–0.96)
Nonclass I	LBBB morphology	0.483	0.81 (0.45–1.46)	…	…
	QRS duration	0.891	1.05 (0.55–1.99)	…	…
	QRS area	0.085	0.44 (0.17–1.12)	…	…
Class I	QRS area	0.001	0.43 (0.27–0.70)	…	…
Echocardiographic responder					
All	LBBB+QRS duration	<0.001	1.69 (1.47–1.96)	0.002	1.29 (1.09–1.52)
	QRS area quartiles	<0.001	1.82 (1.61–2.07)	<0.001	1.65 (1.43–1.90)
Nonclass I	LBBB morphology	0.004	1.85 (1.22–2.80)	0.02	2.01 (1.12–3.62)
	QRS duration	0.324	0.79 (0.50–1.26)	…	…
	QRS area	0.007	1.90 (1.19–3.03)	0.031	1.70 (1.05–2.76
Class I	QRS area	<0.001	3.54 (2.38–5.28)	…	…

CRT indicates cardiac resynchronization therapy; HF, heart failure; HR, hazard ratio; LBBB, left bundle branch block; LVAD, left ventricular assist device; and OR, odds ratio.

*OR and HR are reported for Logistic and Cox regressions, respectively, used when appropriate for the selected end point.

response to CRT, defined as LVESV reduction ≥15%, occurred in 516 (56%) patients.

LVESV reduction was significantly larger in patients with LBBB with QRS duration ≥150 ms compared with those with QRS duration <150 ms (Figure 4A). Response rate ranged from 31% in non-LBBB with QRS duration <150 ms to 60% in patients with LBBB and QRS duration ≥150 ms.

QRS area provided significant separation in the extent of LVESV reduction between all subgroups, except between quartiles with QRS area of 75 to 108 μVs and <75 μVs (*P*=0.223; Figure 4B). Response rate ranged from 37% in patients with QRS area <75 μVs to 77% in patients with QRS area >150 μVs.

Stratification of patients without a class I indication according to QRS area (≥109/<109 μVs) showed that mean reduction of LVESV was significantly larger in patients with QRS area ≥109 μVs than in those with QRS area <109 μVs (20% versus 7%), resulting in response rates of 54% and 38%, respectively (OR, 1.90 [1.19– 3.03]; *P*=0.009; Figure 4C). In patients with a class I indication, stratification to QRS area also resulted in significant separation of response rates (OR, 3.54 [2.38–5.28]; *P* <0.001) and mean reduction of LVESV (29% versus 12%; Figure 4D).

Identification of echocardiographic responders was better with QRS area than with QRS morphology or duration (AUC, 0.69 versus 0.58 and 0.58, respectively; *P*<0.001 for both comparison with QRS morphology and QRS duration; Figure II in the Data Supplement). Logistic multivariable regression showed a significant independent association of QRS area to LVESV reduction ≥15% (OR, 1.65 [1.43–1.90]; *P* <0.001), as well as the combination of QRS morphology and duration (OR, 1.29 [1.09–1.52]; *P*=0.002; Table 2); In patients without LBBB with QRS duration ≥150 ms, LBBB morphology (*P*=0.02; HR, 2.02 [1.12–3.62]) and QRS area (*P*=0.03; OR, 1.70 [1.05–2.76]), but not QRS duration (*P*=0.449), were significantly associated to echocardiographic response (Table 2).

DISCUSSION

The main findings of this study are that QRS area alone can stratify CRT patients at least as good as the combination of LBBB and QRS duration. In the present study,

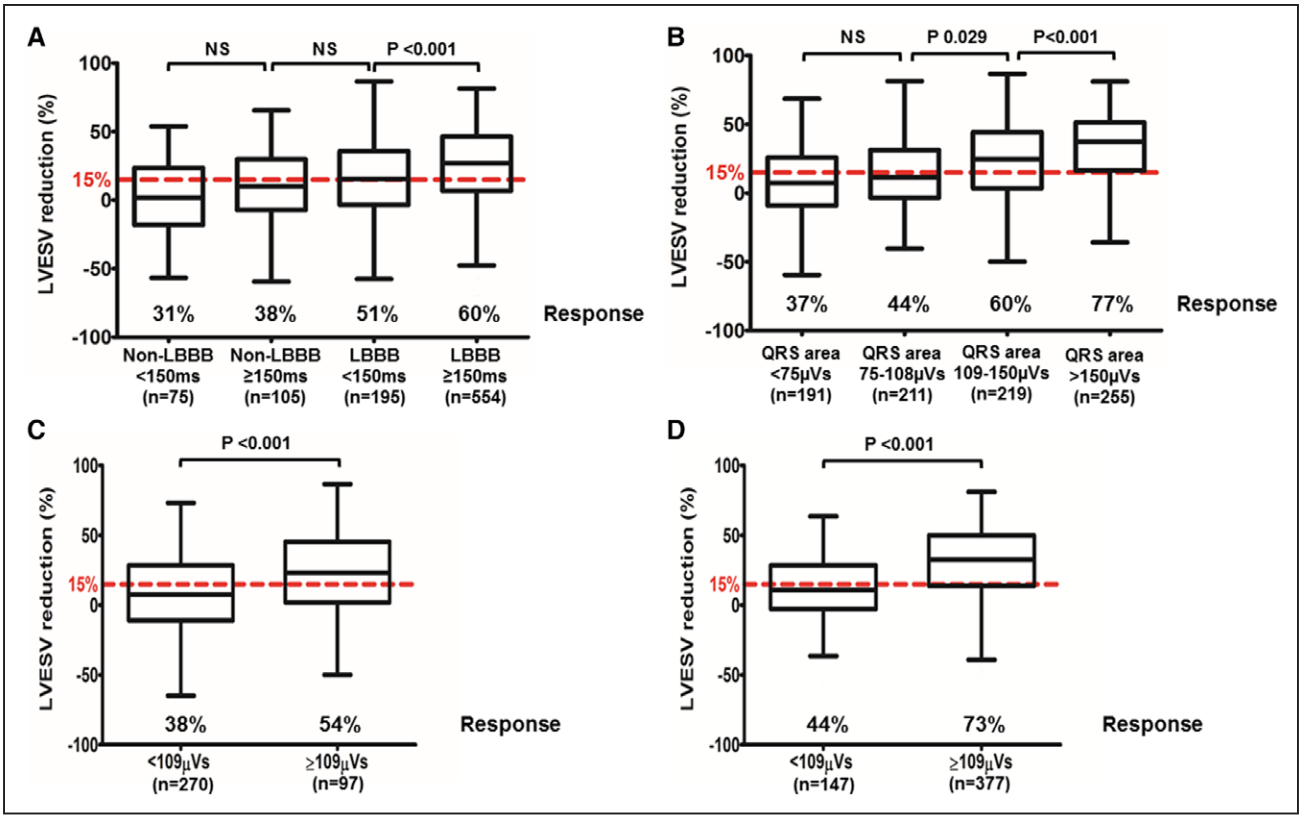

Figure 4. Echocardiographic reduction in left ventricular end-systolic volume (**LVESV) and response rate.**
Echocardiographic LVESV reduction in percentage at follow-up echocardiography in patient groups stratified by (**A**) The combination of QRS duration and morphology divides patients into subgroups according to presence of left bundle branch block (LBBB) and QRS duration <150 or ≥150 ms (corresponding to current guideline recommendations). **B**, QRS area stratified into quartiles. **C**, Patient without a class I indication according to current guidelines[7] (LBBB and QRS duration ≥150 ms) stratified to QRS area <109 or ≥109 µVs. **D**, Patient with a class I indication according to current guidelines[7] stratified to QRS area <109 or ≥109 µVs. Mean and SD are presented. The red reference line represents echocardiographic response, defined as ≥15% reduction of LVESV. In the bottom of the graph, the % of response according to this definition is shown per patient group. NS indicates nonsignificant.

QRS morphology and duration fail to differentiate CRT response in patients without a class I indication for CRT. However, QRS area proves to be an independent electrocardiographic determinant of clinical and echocardiographic outcomes to CRT in these patients.

Because QRS area is a simple and objective measurement, it may be a valuable alternative measure for selection of patients for CRT, especially in those patients who do not have a wide LBBB QRS complex on their baseline 12-lead ECG.

Association of QRS Area With CRT Response

The results on the primary end point and on the secondary end point of HF hospitalization demonstrate that QRS area is stronger related to clinical outcome that QRS duration and LBBB separately. The finding of the strong association of QRS area with reverse remodeling in the present study is in line with previous studies.[11,12,14,16] In a recent prospective study in 240 patients, Maass et al[14] showed that QRS area was the strongest vectorcardiography predictor of echocardiographic response to CRT that also outperformed QRS duration and LBBB morphology. Besides the support of these findings from a considerably larger cohort, the present study compares the association of QRS area to the combination of LBBB morphology and QRS duration in the way it is used in current practice.

Moreover, the present study shows that QRS area is of particular value in the group of patients that is considered to have a class IIa or lower recommendation for CRT: those not having an LBBB and QRS duration >150 ms. Among 637 of these patients, 155 had a QRS area value above the median (109 µVs) of the entire cohort. In this subgroup of 155 patients, clinical outcome was as good as that of patients with a class I (level of evidence A) indication (Figure 3 and Figure III in the Data Supplement), and echocardiographic response was close to that as well (60% versus 54% responders; Figure 4). These observations are supported by uni- and multivariable regression analyses, showing that QRS area is the only ECG parameter, independent of the other ECG parameters, associated to clinical as well as echocardiographic response to CRT. The 50% reduction in relative risk of clinical events and over 90% increase in relative risk of significant echocardiographic response suggest important associations of QRS area

with outcome. Although QRS area provides similar separation in the subgroup of patients with a class I indication for CRT (LBBB and QRS duration ≥150 ms), results in this group are less relevant to clinical practice, as CRT will be instituted in these patients in almost every case, despite the value of QRS area.

The strong association of QRS area with CRT response may be explained by several properties. First of all, QRS area is large in the presence of strong electrical forces pointing in a dominant direction. Although QRS area depends on QRS duration, it is also larger in patients with LBBB than in those with other conduction abnormalities.[12] Moreover, a study using coronary venous electrical maping demonstrated that a large QRS area is predictive of delayed LV activation, the most important electrical substrate of CRT.[13] In that study, 1 patient with right bundle branch block showed a large QRS area and in that particular patient the LV lateral wall was shown to be activated late. Moreover, QRS area is lower in patients with ischemic cardiomyopathy[12] and, more specifically in the presence of focal scar,[19] conditions which are known to reduce response to CRT. Therefore, it seems that QRS area is a comprehensive parameter, reflecting multiple factors that contribute to the benefit of CRT. Though as reflected by the AUC values of the receiver operating characteristic curve analyses for identification of clinical and echocardiographic outcomes, QRS area is limited to identification of the electrical substrate and some properties of the myocardial disease. Clinical, and to less extent echocardiographic, outcomes to CRT are dependent on many more patient, disease, and treatment properties than the electrical substrate alone. Nevertheless, QRS area seems to improve contribution to the prediction of these outcomes compared with conventional ECG parameters.

Performance of Conventional ECG Parameters

Whereas many studies and meta-analyses have evaluated QRS duration and LBBB morphology and their association with outcome to CRT,[5,6,20–22] not many have evaluated their combination in the way these markers are used in current practice.

Individual studies specifically evaluating the combination of QRS morphology and QRS duration have shown significant associations with outcome to CRT for QRS duration as a continuous parameter in QRS morphology subgroups. In a REVERSE study (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) subanalysis, QRS duration as a continuous parameter was associated to echocardiographic LVESV reduction in LBBB and non-LBBB patient subgroups. This showed that in LBBB patients the reduction in LVESV was larger in patients with longer QRS duration, whereas there was no significant reduction in LVESV in non-LBBB patients, regardless of QRS duration.[5] Dichotomous evaluations of QRS duration fail to show any significant associations with outcomes. A recent evaluation by Khidir et al[23] in 973 patients confirmed the association of LBBB morphology with outcome to CRT, but showed no significant differences in QRS duration (≥150/<150 ms) subgroups within the LBBB and non-LBBB subgroups. However, an evaluation of echocardiographic outcomes to CRT from the same groups in 1467 patients showed that, although different, there was a significant correlation between increasing QRS duration and echocardiographic reduction in LVESV and increase in LV ejection fraction both in LBBB and non-LBBB patient subgroups.[24]

A much larger evaluation of 24 169 Medicare beneficiaries in the National Cardiovascular Data Registry ICD (implantable cardioverter defibrillator) Registry between 2006 and 2009 who underwent CRT with defibrillator function implantation, however, did show significant associations of QRS duration with clinical outcomes in QRS morphology subgroups.

In this analysis, the subgroups of LBBB with QRS duration 120 to 149 ms and non-LBBB with QRS duration ≥150 ms failed to show significant differences. The stronger predictive effect of LBBB than of QRS duration, observed in all these studies, seems to be in disagreement with the results from 2 meta-analyses. These studies failed to show an independent association of LBBB to outcome in a model including QRS duration.[25,26] This discrepancy may be caused by the use of different definitions of LBBB in the trials included in these analyses, thus probably creating variability in the non-LBBB and LBBB subpopulations.

The different results of these recent studies reveal the uncertainties in the way these ECG parameters are used for patient selection in CRT in current practice. Although QRS morphology and duration have proven valuable as individual markers of response, their combination has not. The results presented in this study add to this uncertainty. Moreover the conflicting results of previous studies may be the result of the caveats of the individual parameters. Which may be even greater when used in combination. Because of the heterogeneity of underlying causes of QRS broadening in patients other than broad LBBB,[27] strict morphological criteria may not be applicable. Furthermore, QRS duration may be prolonged because of excessive scarring or dilatation, as opposed to conduction delay in a narrow sense.

Clinical Implications

The results from the present study provide important evidence that QRS area is a valuable additional electrocardiographic parameter that can be used to improve patient selection for CRT. Like QRS duration, it can be measured as a continuous variable, whereas the var-

iability in its measurement is likely to be less than in QRS duration. After all, variability in indicating the beginning and end of the QRS complex greatly affects QRS duration, but hardly affects QRS area, because its value is largely determined by the amplitude of the QRS complex.

Although some studies[11,12] used digital ECG recordings, others, including the present study, extracted the original signals from PDF files stored in the ECG database using simple software. For future, wider application, it is possible to program current ECG equipment to automatically calculate QRS area in the way QRS duration is currently calculated. Automated QRS area calculation can be easily implemented in current ECG equipment because signal amplitudes are available, and onset and end of QRS complex are already recognized by the software. Moreover, ECG equipment currently already convert the 12-lead ECG information into a vectorcardiogram, which, however, is not frequently used in clinical practice.

Limitations

Inherent limitations because of the studies' retrospective nature are selection, referral, and attrition biases. The retrospective design of our study prohibited the inclusion of a nontreated control group. Therefore, we do not know the absolute benefit of CRT compared with nontreated patients with respect to the primary clinical end point. However, the echocardiographic response is measured using each patient as his/her own control.

Conclusions

QRS area has a strong association with clinical and echocardiographic outcomes to CRT in this large population. Because the QRS area is a simple and objective measurement, it might be an alternative measure for selection of patients for CRT, especially in those patients who do not show a wide LBBB QRS complex on their baseline 12-lead ECG.

ARTICLE INFORMATION

Received April 11, 2018; accepted November 11, 2018.

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCEP.118.006497.

Affiliations

Department of Cardiology, Maastricht University Medical Centre, The Netherlands (A.M.W.v.S., H.J.G.M.C., K.V.). Department of Cardiology, University Medical Centre Utrecht, The Netherlands (I.t.H., M.M.). Department of Cardiology, University Medical Centre Groningen, University of Groningen, The Netherlands (M.K., M.R., I.C.v.G., A.H.M.). Department of Physiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, The Netherlands (E.B.E., H.J.G.M.C., F.W.P., K.V.). Department of Medical Physiology, University of Utrecht, The Netherlands (M.A.V.). Department of Cardiology, Radboud University Medical Centre, Nijmegen, The Netherlands (K.V.).

Correspondence

Antonius M.W. van Stipdonk, MD, Department of Cardiology, Maastricht University Medical Center, PO Box 5800, 6202AZ Maastricht, The Netherlands. Email twan.van.stipdonk@mumc.nl

Sources of Funding

This research was performed within the framework of the Centre for Translational Molecular Medicine (www.ctmm.nl), project COHFAR (Congestive Heart Failure and Arrhythmias, grant 01C-203), and supported by the Dutch Heart Foundation.

Disclosures

Dr Crijns received research grants from Medtronic. Dr Vos received funding from Centre for Translational Molecular Medicine COHFAR, CVON Predict (CardioVasular Onderzoek Nederland [Cardiovascular Research in the Netherlands]), European Union (EU) TrigTreat, EU, CERT_ICD, and GiLead to perform (pre)clinical studies. Dr Prinzen received research grants from Medtronic, St Jude Medical, Biotronik, Sorin, Biosense Webster, and EBR Systems; and is a member on the Medtronic Advisory Board. Dr Maass received lecture fees from Medtronic and LivaNova. Dr Vernooy is a consultant in Medtronic; received research grants from Medtronic; and received speaker fees from St Jude Medical. The other authors report no conflicts.

REFERENCES

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J; MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845–1853. doi: 10.1056/NEJMoa013168
2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539–1549. doi: 10.1056/NEJMoa050496
3. Daubert JC, Saxon L, Adamson PB, Auricchio A, Berger RD, Beshai JF, Breithard O, Brignole M, Cleland J, DeLurgio DB, Dickstein K, Exner DV, Gold M, Grimm RA, Hayes DL, Israel C, Leclercq C, Linde C, Lindenfeld J, Merkely B, Mont L, Murgatroyd F, Prinzen F, Saba SF, Shinbane JS, Singh J, Tang AS, Vardas PE, Wilkoff BL, Zamorano JL, Anand I, Blomstrom-Lundqvist C, Boehmer JP, Calkins H, Cazeau S, Delgado V, Estes NA, Haines D, Kusumoto F, Leyva P, Ruschitzka F, Stevenson LW, Torp-Pedersen CT; European Heart Rhythm Association; European Society of Cardiology; Heart Rhythm Society; Heart Failure Society of America; American Society of Echocardiography; American Heart Association; European Association of Echocardiography of ESC; Heart Failure Association of ESC. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. *Europace*. 2012;14:1236–1286. doi: 10.1093/europace/eus222
4. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices); American Association for Thoracic Surgery; Society of Thoracic Surgeons. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Circulation*. 2008;117:e350–e408. doi: 10.1161/CIRCUALTIONAHA.108.189742
5. Gold MR, Thébault C, Linde C, Abraham WT, Gerritse B, Ghio S, St John Sutton M, Daubert JC. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results

from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. *Circulation*. 2012;126:822–829. doi: 10.1161/CIRCULATIONAHA.112.097709

6. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichstein E, Pitschner H, Rashtian M, Solomon S, Viskin S, Wang P, Moss AJ; MADIT-CRT Investigators. Effectiveness of cardiac resynchronization therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation*. 2011;123:1061–1072. doi: 10.1161/CIRCULATIONAHA.110.960898
7. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NA III, Ferguson TB Jr, Hammill SC, Karasik PE, Link MS, Marine JE, Schoenfeld MH, Shanker AJ, Silka MJ, Stevenson LW, Stevenson WG, Varosy PD; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Heart Rhythm Society. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines and the heart rhythm society. *J Am Coll Cardiol*. 2013;61:e6–e75. doi: 10.1016/j.jacc.2012.11.007
8. Varma N, Manne M, Nguyen D, He J, Niebauer M, Tchou P. Probability and magnitude of response to cardiac resynchronization therapy according to QRS duration and gender in nonischemic cardiomyopathy and LBBB. *Heart Rhythm*. 2014;11:1139–1147. doi: 10.1016/j.hrthm.2014.04.001
9. De Pooter J, El Haddad M, Timmers L, Van Heuverswyn F, Jordaens L, Duytschaever M, Stroobandt R. Different methods to measure QRS duration in CRT patients: impact on the predictive value of QRS duration parameters. *Ann Noninvasive Electrocardiol*. 2016;21:305–315. doi: 10.1111/anec.12313
10. van Deursen CJ, Blaauw Y, Witjens MI, Debie L, Wecke L, Crijns HJ, Prinzen FW, Vernooy K. The value of the 12-lead ECG for evaluation and optimization of cardiac resynchronization therapy in daily clinical practice. *J Electrocardiol*. 2014;47:202–211. doi: 10.1016/j.jelectrocard.2014.01.007
11. Tereshchenko LG, Cheng A, Park J, Wold N, Meyer TE, Gold MR, Mittal S, Singh J, Stein KM, Ellenbogen KA; SMART-AV Trial Investigators. Novel measure of electrical dyssynchrony predicts response in cardiac resynchronization therapy: results from the SMART-AV trial. *Heart Rhythm*. 2015;12:2402–2410. doi: 10.1016/j.hrthm.2015.08.009
12. van Deursen CJ, Vernooy K, Dudink E, Bergfeldt L, Crijns HJ, Prinzen FW, Wecke L. Vectorcardiographic QRS area as a novel predictor of response to cardiac resynchronization therapy. *J Electrocardiol*. 2015;48:45–52. doi: 10.1016/j.jelectrocard.2014.10.003
13. Mafi Rad M, Wijntjens GW, Engels EB, Blaauw Y, Luermans JG, Pison L, Crijns HJ, Prinzen FW, Vernooy K. Vectorcardiographic QRS area identifies delayed left ventricular lateral wall activation determined by electroanatomic mapping in candidates for cardiac resynchronization therapy. *Heart Rhythm*. 2016;13:217–225. doi: 10.1016/j.hrthm.2015.07.033
14. Maass AH, Vernooy K, Wijers SC, van 't Sant J, Cramer MJ, Meine M, Allaart CP, De Lange FJ, Prinzen FW, Gerritse B, Erdtsieck E, Scheerder COS, Hill MRS, Scholten M, Kloosterman M, Ter Horst IAH, Voors AA, Vos MA, Rienstra M, Van Gelder IC. Refining success of cardiac resynchronization therapy using a simple score predicting the amount of reverse ventricular remodelling: results from the markers and response to CRT (MARC) study. *Europace*. 2018;20:e1–e10. doi: 10.1093/europace/euw445
15. Linde C, Abraham WT, Gold MR, Daubert C; REVERSE Study Group. Cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure patients in relation to etiology: results from the REVERSE (REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction) study. *J Am Coll Cardiol*. 2010;56:1826–1831. doi: 10.1016/j.jacc.2010.05.055
16. Engels EB, Végh EM, Van Deursen CJ, Vernooy K, Singh JP, Prinzen FW. T-wave area predicts response to cardiac resynchronization therapy in patients with left bundle branch block. *J Cardiovasc Electrophysiol*. 2015;26:176–183. doi: 10.1111/jce.12549
17. Engels EB, Alshehri S, van Deursen CJ, Wecke L, Bergfeldt L, Vernooy K, Prinzen FW. The synthesized vectorcardiogram resembles the measured vectorcardiogram in patients with dyssynchronous heart failure. *J Electrocardiol*. 2015;48:586–592. doi: 10.1016/j.jelectrocard.2015.04.001
18. Kors JA, van Herpen G, Sittig AC, van Bemmel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. *Eur Heart J*. 1990;11:1083–1092.
19. Nguyên UC, Claridge S, Vernooy K, Engels EB, Razavi R, Rinaldi CA, Chen Z, Prinzen FW. Relationship between vectorcardiographic QRS area, myocardial scar quantification, and response to cardiac resynchronization therapy. *J Electrocardiol*. 2018;51:457–463. doi: 10.1016/j.jelectrocard.2018.01.009
20. Birnie DH, Ha A, Higginson L, Sidhu K, Green M, Philippon F, Thibault B, Wells G, Tang A. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: results from the resynchronization-defibrillation for ambulatory heart failure trial (RAFT). *Circ Heart Fail*. 2013;6:1190–1198. doi: 10.1161/CIRCHEARTFAILURE.113.000380
21. Selzman K, Shein M. QRS morphology rather than QRS duration for predicting CRT response. *Arch Intern Med*. 2011;171:1859–1860; author reply 1860. doi: 10.1001/archinternmed.2011.516
22. Zusterzeel R, Curtis JP, Caños DA, Sanders WE, Selzman KA, Piña IL, Spatz ES, Bao H, Ponirakis A, Varosy PD, Masoudi FA, Strauss DG. Sex-specific mortality risk by QRS morphology and duration in patients receiving CRT: results from the NCDR. *J Am Coll Cardiol*. 2014;64:887–894. doi: 10.1016/j.jacc.2014.06.1162
23. Khidir MJ, Delgado V, Ajmone Marsan N, Schalij MJ, Bax JJ. QRS duration versus morphology and survival after cardiac resynchronization therapy. *ESC Heart Fail*. 2017;4:23–30. doi: 10.1002/ehf2.12122
24. van der Bijl P, Khidir M, Leung M, Mertens B, Ajmone Marsan N, Delgado V, Bax JJ. Impact of QRS complex duration and morphology on left ventricular reverse remodelling and left ventricular function improvement after cardiac resynchronization therapy. *Eur J Heart Fail*. 2017;19:1145–1151. doi: 10.1002/ejhf.769
25. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bänsch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM; ESC Committee for Practice Guidelines (CPG); Document Reviewers. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J*. 2013;34:2281–2329. doi: 10.1093/eurheartj/eht150
26. Woods B, Hawkins N, Mealing S, Sutton A, Abraham WT, Beshai JF, Klein H, Sculpher M, Plummer CJ, Cowie MR. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. *Heart*. 2015;101:1800–1806. doi: 10.1136/heartjnl-2015-307634
27. Eschalier R, Ploux S, Ritter P, Haïssaguerre M, Ellenbogen KA, Bordachar P. Nonspecific intraventricular conduction delay: definitions, prognosis, and implications for cardiac resynchronization therapy. *Heart Rhythm*. 2015;12:1071–1079. doi: 10.1016/j.hrthm.2015.01.023