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Vectorcardiographic QRS Area is Associated with Long-Term Outcome Following Cardiac Resynchronization Therapy

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Abstract

Background: Recent studies have suggested that vectorcardiographic measures predict left ventricular (LV) reverse remodeling and clinical outcome in patients receiving cardiac resynchronization therapy (CRT).

Objective: To compare predictive abilities of different vectorcardiographic measures (QRS area and sum absolute QRS-T integral) and transformation methods (Kors and inverse Dowers), and to assess the independent association between the best predictor and outcomes in CRT recipients.

Methods: Retrospective study including CRT recipients with a digital baseline electrocardiogram, QRS duration 120 ms, and ejection fraction 35%. The end point was a composite of heart transplantation, LV assist device implant, or death. Analyses were performed for the overall cohort and for a pre-specified subgroup of left bundle branch block (LBBB) patients.

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Conflicts of interest

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Results: Of 705 included patients with mean age of 66.6 years, 70% were males, 53% had ischemic heart disease, and 66% had LBBB. QRS area from vectorcardiograms derived via the Kors transformation demonstrated the best predictive value. In multivariable Cox regression, patients with a smaller QRS area ($< 95 \mu\text{Vs}$) had an increased hazard in the overall cohort (adjusted hazard ratio: 1.65, $p < 0.001$) and in the LBBB subgroup (adjusted hazard ratio: 1.95, $p < 0.001$). QRS area was associated with outcome in patients with QRS duration ≤ 150 ms (unadjusted hazard ratio: 3.85, $p < 0.001$), and in patients with QRS duration > 150 ms (unadjusted hazard ratio: 1.76, $p < 0.001$).

Conclusion: Vectorcardiographic QRS area is associated with survival free from heart transplantation and LV assist device implantation in CRT recipients.

Keywords

Cardiac resynchronization therapy; Heart failure; Vectorcardiography; QRS area; Sum absolute QRS-T integral; Left bundle branch block; QRS prolongation

Introduction

Although cardiac resynchronization therapy (CRT) has been an established treatment for patients with prolonged QRS duration and heart failure for several years,^{1–3} a substantial proportion of patients do not benefit from the treatment.^{4,5} In current guidelines, QRS morphology and duration are the two surrogates of dyssynchrony used for patient selection.⁶ Recently, two different vectorcardiographic measures of dyssynchrony have been proposed, namely QRS area and sum absolute QRS-T integral (SAI QRS-T), and these have been shown to identify delayed activation of the left ventricular (LV) lateral wall, predict echocardiographic response to CRT, and in a small, retrospective cohort study to predict survival following CRT.^{7–10} Currently, there are no published comparisons of these two vectorcardiographic measures or the different matrices (the Kors matrix and the inverse Dower matrix) used for the derivation of the vectorcardiogram from the digital 12-lead electrocardiogram (ECG).^{11,12}

The objective of this study was to compare the predictive abilities of the two different vectorcardiographic measures and the two transformation matrices, and to assess the association between the best predictor and long-term outcome in CRT recipients.

Methods

This was a retrospective cohort study performed at Duke University Medical Center. The study was approved by the Duke Institutional Review Board and complies with the Declaration of Helsinki.

Study population

All patients who received a CRT with defibrillator from April 2006 to September 2015 were identified using an institutional dataset prepared for the National Cardiovascular Data Registry. We included patients who received a de novo CRT due to symptomatic heart failure with a LV ejection fraction $\leq 35\%$ and had an available ECG with QRS duration ≤ 120

ms within 180 days before CRT implantation. Patients were excluded if the LV lead could not be implanted, the patient demonstrated 2nd or 3rd degree atrioventricular or had missing follow-up data.

Electro- and vectorcardiographic analyses

The ECG most proximal to CRT implantation was reanalyzed in the GE MUSE Cardiology Information System version 8.0.2.10132 with 12SL analysis software version 241 (GE Healthcare, Milwaukee, WI, USA) and exported in Extensible Markup Language (XML) format. QRS morphology was designated by two readers (DF and KE) blinded to outcome. Left bundle branch block (LBBB) morphology was further divided into strict and non-strict LBBB using the criteria described by Strauss et. al.¹³ QRS onset and offset and thereby QRS duration as detected by the 12SL software were verified or manually corrected if needed.

Vectorcardiograms were derived from the XML files using customized MATLAB software (MathWorks, Inc., Natick, MA, USA) using both the inverse Dower and the Kors matrices.^{11,12} Using the median beat, the QRS area and SAI QRS-T were calculated as described previously by others.^{8,9} The QRS area was calculated as $(QRS_x^2 + QRS_y^2 + QRS_z^2)^{1/2}$, with $QRS_{x/y/z}$ being the integral between the ventricular deflection and the baseline from the onset to the offset of the QRS complex in the x, y, and z leads, respectively (Figure 1A). SAI QRS-T was calculated as the sum of the absolute areas between the deflection and the baseline of the entire QRS-T waveform from the x, y, and z-leads (Figure 1B). Thus, a total of 4 vectorcardiographic measures were derived:

- QRS area (Kors)
- QRS area (inverse Dower)
- SAI QRS-T (Kors)
- SAI QRS-T (inverse Dower)

End points

The study end point was a composite of heart transplantation, LV assist device implantation, or all-cause death. End point ascertainment was performed on May 24, 2017 via a query of the Duke Enterprise Data Unified Content Explorer by incorporating data from billing claims, hospital records, and the Social Security Death Index.¹⁴

Statistical analyses

Continuous, normally distributed variables are reported as means $\pm$ SD and differences were tested using the Student t-test, while non-normally distributed variables are reported as median (25th–75th percentile) and differences were tested using the Wilcoxon rank-sum test. Categorical variables were compared using Fisher's exact test.

Time-dependent receiver operating characteristics (ROC) curves were created to assess the ability of the 4 vectorcardiographic measures to predict the occurrence of the study end point and the vectorcardiographic measurement with the greatest AUC at 3 years after CRT

implantation was used for all subsequent analyses. The median value for the overall cohort was used to separate cohorts into two groups.

Kaplan-Meier plots were used to depict the cumulative hazard of the composite outcome and differences were assessed using log-rank statistics. Cox proportional hazard models were used for assessing univariable and multivariable predictors of the composite outcome. Multivariable models were adjusted for ischemic heart disease, QRS morphology, QRS duration <150 milliseconds, atrial fibrillation/flutter, and univariable predictors with a p-value <0.10. Proportional hazards assumptions were verified graphically using plots of Schoenfeld's residuals. Sensitivity analysis with stepwise removal of the covariates in the model was performed. Analyses were performed for the overall cohort and for the pre-specified subgroups of patients with LBBB and non-LBBB QRS morphologies.

All statistical analysis was performed in RStudio version 1.1.423 (RStudio, Inc, Boston, MA, USA) running R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). The R packages "survival"¹⁵ and "timeROC"¹⁶ were used for survival analyses and time-dependent ROC curves. A two-sided p-value <0.05 was considered statistically significant.

Results

A total of 1001 patients underwent CRT implant at the Duke University Medical Center during the study period. After excluding patients with a missing baseline digital ECG (n=159), prior LV lead (n=12), QRS duration <120 ms (n=56), a LV ejection fraction that was >35% (n=17) or missing (n=7), a failed LV lead (n=8), 2nd/3rd degree AV block (n=34), or missing follow-up data (n=3), a total of 705 patients remained. Of the included patients, 492 (70%) were males, the mean age was 66.6±11.5 years, 374 (53%) had ischemic heart disease, 465 (66%) had LBBB, and the mean QRS duration was 163±27 ms (Table 1).

Predictive ability of vectorcardiographic measurements

The Kors-derived QRS area predicted the probability of reaching the study end point 3 years after CRT implantation better than the inverse Dower-derived QRS area (AUC 0.645 vs 0.620, p=0.005), and the SAI QRS-T derived by either the Kors method (AUC 0.645 vs. 0.625, p=0.03) or the inverse Dower method (AUC 0.645 vs. 0.608, p=0.001) (Figure A.1). Based on these results, the Kors derived QRS area was used for all subsequent analyses.

Patient characteristics by QRS area

The median (25th–75th percentile) QRS area by the Kors method for the overall cohort was 95 (63–127) μ Vs. Patients with a QRS area $\leq$ 95 μ Vs were more often males with ischemic heart disease, more advanced New York Heart Association functional class, a longer PR interval, shorter QRS duration, higher serum creatinine, and were less likely to receive beta-blocker medication. Patients with a QRS area >95 μ Vs were more likely to have a strict LBBB or have right ventricular pacing, whereas all other QRS morphologies were more common in patients with a QRS area $\leq$ 95 μ Vs (Table 1).

Follow-up

Over a median follow-up of 3.1 years (1.8–5.4 years), 312 (44%) patients reached the study end point. The most common reason for reaching the end point was death ($n=263$, 37%) followed by LV assist device implantation ($n=26$, 4%) and heart transplantation ($n=23$, 3%). During follow-up, 194 (55%) patients with a QRS area $\leq 95 \mu\text{Vs}$ experienced an end point, compared with 118 (34%) patients with a QRS area $>95 \mu\text{Vs}$ (Figure 2). QRS area was associated with the likelihood of reaching the study end point in both univariable (unadjusted hazard ratio: 2.11; 95% CI 1.68–2.65; $p<0.001$) and multivariable analyses adjusting for QRS duration and morphology, age, sex, ischemic heart disease, 1st degree atrioventricular block, atrial fibrillation/flutter, LV ejection fraction, New York Heart Association Functional Class, creatinine, cerebrovascular disease, chronic lung disease, angiotensin converting enzyme-inhibitor or angiotensin II-receptor blocker use, and beta-blocker use (adjusted hazard ratio: 1.65; 95% CI: 1.25–2.18; $p<0.001$) (Table 2).

QRS area and outcomes among LBBB and non-LBBB subgroups

The median QRS area for the LBBB subgroup was 101 μVs , while it was 77 μVs for the non-LBBB subgroup ($p<0.001$). In the LBBB subgroup, 260 of the 465 (56%) patients had a QRS area $>95 \mu\text{Vs}$. Baseline characteristics for the LBBB subgroup are described in Table A.1. Among patients with a QRS area $\leq 95 \mu\text{Vs}$, 109 (53%) reached the composite end point, compared to 77 (30%) patients with QRS area $>95 \mu\text{Vs}$ (unadjusted hazard ratio: 2.35; 95% CI: 1.75–3.15; $p<0.001$) (Figure 3A). In the adjusted model including the same covariates as the model for the overall cohort, QRS area remained significantly associated with composite outcome (adjusted hazard ratio: 1.95; 95% CI: 1.38–2.76; $p<0.001$) in patients with LBBB.

Among patients without LBBB, a QRS area $>95 \mu\text{Vs}$ was much more common among patients with right ventricular pacing (68%, 81/119) compared to all other non-LBBB QRS morphologies (9%, 11/121). A QRS area $\leq 95 \mu\text{Vs}$ was associated with the study outcome in univariable analysis (unadjusted hazard ratio: 1.55; 95% CI: 1.07–2.25; $p=0.02$) (Figure 3B). After adjusting for QRS duration and morphology, age, sex, ischemic heart disease, and atrial fibrillation/flutter, QRS area was not significantly associated with the study end point (adjusted hazard ratio: 1.50, 95% CI: 0.94–2.39, $p=0.09$) in patients without LBBB. Among the non-LBBB patients without right ventricular pacing, a QRS area $<95 \mu\text{Vs}$ demonstrated a non-significant association with worsened outcomes (unadjusted hazard ratio: 2.76; 95% CI: 0.86–8.80; $p=0.09$).

Outcome in relation to QRS area in combination with QRS duration

In patients with QRS duration <150 ms, 53 of 239 (22%) had a QRS area $>95 \mu\text{Vs}$. In patients with QRS duration ≥ 150 ms, 167 of 466 (36%) had a QRS area $\leq 95 \mu\text{Vs}$. In the LBBB subgroup, 51 of 185 (28%) patients with QRS duration <150 ms had a QRS area $\leq 95 \mu\text{Vs}$, and 71 of 280 (25%) patients with QRS duration ≥ 150 ms had a QRS area $\leq 95 \mu\text{Vs}$. QRS area $\leq 95 \mu\text{Vs}$ was associated with the study end point in univariable analysis in both patients with QRS duration <150 ms (unadjusted hazard ratio: 3.85, 95% CI: 2.02–7.37, $p<0.001$) (Figure 4A) and in patients with QRS duration ≥ 150 ms (unadjusted hazard ratio: 1.76, 95% CI: 1.32–2.34, $p<0.001$) (Figure 4B). Similar results were found in the LBBB subgroup when stratifying by QRS duration above/below 150 ms (Figure A.2).

Discussion

This study found that a smaller baseline QRS area calculated from derived vectorcardiograms is associated with an increased hazard of death, heart transplant or LV assist device implant after CRT independently of critical baseline characteristics like QRS duration and morphology. Second, the study found that the Kors method is superior to the inverse Dower method for derivation of the vectorcardiogram for prediction of CRT outcome using QRS area. Third, it found that among the two most widely studied vectorcardiographic based measures of LV electrical delay, the QRS area is superior to the SAI QRS-T for prediction of adverse outcomes after CRT implantation. Finally, the study findings suggest that especially in patients with QRS duration <150 ms (i.e. patients without a current class I indication for CRT), QRS area has important prognostic value.

Vectorcardiographic measures as predictors of CRT outcome

Vectorcardiography was developed in the 1950's but has been seldom used clinically for the past 20 years. With the development of digital ECG signal processing, renewed interest in vectorcardiography has emerged, largely as a tool for patient selection in CRT. The digital 12-lead ECG allows for digital derivation of a vectorcardiogram that bears good resemblance and correlation with vectorcardiograms recorded with Frank's method.^{17,18} Prior studies have demonstrated that QRS area identifies delayed LV lateral wall activation in CRT candidates, while SAI QRS-T correlates with a dyssynchrony index determined by non-invasive electrocardiographic mapping.^{7,19} Thus, these measures were proposed to reflect LV electrical dyssynchrony and thereby identify a substrate amenable to CRT. Subsequent studies demonstrated that QRS area and SAI QRS-T predicted LV reverse remodeling and long-term outcome after CRT.⁸⁻¹⁰

Current guidelines for selection of CRT candidates

Currently, QRS duration and morphology are the only ECG measures incorporated in guidelines for selection of CRT candidates.⁶ The presence of LBBB and a QRS duration 150 ms are associated with a high likelihood of a positive outcome following CRT implantation.²⁰⁻²³ However, this study found that within this cohort of patients with a current class I indication for CRT,⁶ about 25% have a QRS area 95 μ Vs and an increased hazard of adverse outcome after CRT implantation. Additionally, this study finds that QRS area is strongly associated with long-term outcome in patients with QRS duration <150 ms both in the overall cohort and in the LBBB subgroup, i.e. patients without a current class I indication for CRT.

Strict versus non-strict LBBB was a predictor of outcomes in unadjusted analyses; however, in adjusted models, strict versus non-strict LBBB was not a significant predictor, in contrast to QRS area, which remained a robust predictor of outcomes. Taken together, these data suggest that QRS area is a more powerful predictor of outcomes than strict versus non-strict LBBB.

In patients without LBBB, a smaller QRS area was also associated with an increased hazard of adverse outcome in the univariable analysis. However, the association was not significant

in the multivariable analysis, albeit the estimated hazard ratio was not changed much (from 1.55 in univariable to 1.50 in multivariable analysis). In patients without LBBB or right ventricular pacing, less than 10% had a QRS area $>95 \mu\text{Vs}$. Nevertheless, there was a trend towards these patients having a substantially better outcome than similar patients with QRS area $>95 \mu\text{Vs}$. As the LV has a significantly larger myocardial mass than the right ventricle, QRS area is mainly determined by the electrical activation in the LV and is thought to reflect LV dyssynchrony. The results of this study suggest that an important minority of patients with a non-LBBB QRS morphology may have LV activation delay, which might be amenable to correction using CRT. However, due to the lack of statistical power in these exploratory analyses, further research is needed.

Limitations

The major limitation of this study is the retrospective nature and absence of a control group. To definitively establish that QRS area effectively identifies CRT candidates, studies that include a control group of patients not receiving CRT are needed. Vectorcardiography may simply identify patients with a high risk of adverse outcomes regardless of whether they benefit from CRT, for example by identifying patients with extensive myocardial scarring. Neither this study nor the previously mentioned studies⁸⁻¹⁰, included a control group who did not receive CRT, and despite efforts to adjust for confounding, the risk of residual confounding is inherent in the study design.

It is possible that the use of transformed 12-lead ECGs rather than vectorcardiograms may have led to patient misclassification. However, a prior study has shown good agreement between these methods¹⁷, and furthermore, 12-lead ECGs (and not vectorcardiograms) are ubiquitous in clinical practice.

Due to the relatively small study cohort, we were unable to separately test and validate the QRS area threshold in separate subpopulations. The findings should be replicated in a prospective study to confirm the predictive value of vectorcardiographic QRS area.

This study only included a clinical end point, and no data on LV reverse remodeling or symptomatic improvement were available. However, previous studies have shown that QRS area is associated with LV reverse remodeling and acute hemodynamic response to CRT.^{8,24} Additionally, the single center nature of the study may decrease generalizability of results.

Data on several device attributes and parameters were not included in our adjusted models, including LV lead type and position, percent biventricular pacing, and whether CRT optimization was performed. Finally, since many patients undergo CRT implant at Duke University Medical Center but have routine longitudinal care via referring providers, comprehensive data on post implantation device programming and management were not available.

Conclusion

Derived vectorcardiographic QRS area is independently associated with survival free from heart transplantation and LV assist device implantation regardless of QRS duration and the

presence of LBBB. QRS area calculated from vectorcardiograms derived with the Kors method is superior to the QRS area derived by the inverse Dower method and to SAI QRS-T from vectorcardiograms derived with either method.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Moss AJ, Hall WJ, Cannom DS, et al.: Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; 361:1329–1338. [PubMed: 19723701]
2. Cleland JGF, Daubert J- C, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L: The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; 352:1539–1549. [PubMed: 15753115]
3. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM: Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; 350:2140–2150. [PubMed: 15152059]
4. Ellenbogen K a Gold MR, Meyer TE, et al.: Primary results from the SmartDelay determined AV optimization: a comparison to other AV delay methods used in cardiac resynchronization therapy (SMART-AV) Trial. *Circulation* 2010; 122:2660–2668. [PubMed: 21098426]
5. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elvik M, Read P a, Begley D, Fynn SP, Dutka DP: Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. *J Am Coll Cardiol* 2012; 59:1509–1518. [PubMed: 22405632]
6. Tracy CM, Epstein AE, Darbar D, et al.: 2012 ACCF/AHA/HRS Focused Update Incorporated Into the ACCF/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. *J Am Coll Cardiol* 2013; 61:e6–e75. [PubMed: 23265327]
7. Mafi Rad M, Wijntjens GWM, Engels EB, Blaauw Y, JGLM Luermans, L Pison, HJ Crijns, FW Prinzen, K Vernooij: 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.
8. van Deursen CJM, Vernooij K, Dudink E, Bergfeldt L, HJGM Crijns, FW Prinzen, L Wecke: Vectorcardiographic QRS area as a novel predictor of response to cardiac resynchronization therapy. *J Electrocardiol* 2015; 48:45–52. [PubMed: 25453196]
9. Tereshchenko LG, Cheng A, Park J, Wold N, Meyer TE, Gold MR, Mittal S, Singh J, Stein KM, Ellenbogen KA: Novel measure of electrical dyssynchrony predicts response in cardiac resynchronization therapy: Results from the SMART-AV Trial. *Heart Rhythm* 2015; 12:2402–2410. [PubMed: 26272523]
10. Jacobsson J, Borgquist R, Reitan C, Ghafoori E, Chatterjee NA, Kabir M, Platonov PG, Carlson J, Singh JP, Tereshchenko LG: Usefulness of the Sum Absolute QRST Integral to Predict Outcomes in Patients Receiving Cardiac Resynchronization Therapy. *Am J Cardiol* 2016; 118:389–395. [PubMed: 27265674]

11. Kors JA, van Herpen G, Sittig AC, van Bommel JH: Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. *Eur Heart J* 1990; 11:1083–1092. [PubMed: 2292255]
12. Edenbrandt L, Pahlm O: Vectorcardiogram synthesized from a 12-lead ECG: superiority of the inverse Dower matrix. *J Electrocardiol* 1988; 21:361–367. [PubMed: 3241148]
13. Strauss DG, Selvester RH, Wagner GS: Defining left bundle branch block in the era of cardiac resynchronization therapy. *Am J Cardiol* 2011; 107:927–934. [PubMed: 21376930]
14. Horvath MM, Winfield S, Evans S, Slopek S, Shang H, Ferranti J: The DEDUCE Guided Query Tool: Providing Simplified Access to Clinical Data for Research and Quality Improvement. *J Biomed Inform* 2011; 44:266–276. [PubMed: 21130181]
15. Therneau TM: Package “survival”: Survival Analysis [Internet]. 2018 [cited 2018 May 11]. Available from: <https://cran.r-project.org/web/packages/survival/survival.pdf>
16. Blanche P: Package “timeROC”: Time-Dependent ROC Curve and AUC for Censored Survival Data [Internet]. 2015 [cited 2018 May 11]. Available from: <https://cran.r-project.org/web/packages/timeROC/timeROC.pdf>
17. Engels EB, Alshehri S, van Deursen CJM, Wecke L, Bergfeldt L, Vernooij K, Prinzen FW: The synthesized vectorcardiogram resembles the measured vectorcardiogram in patients with dyssynchronous heart failure. *J Electrocardiol* 2015; 48:586–592. [PubMed: 25900820]
18. Frank E: An Accurate, Clinically Practical System For Spatial Vectorcardiography. *Circulation* 1956; 13:737–749. [PubMed: 13356432]
19. Tereshchenko LG, Ghafoori E, Kabir MM, Kowalsky M: Electrical Dyssynchrony on Noninvasive Electrocardiographic Mapping Correlates with SAI QRST on Surface ECG. *Comput Cardiol* 2015; 42:69–72.
20. Zareba W, Klein H, Cygankiewicz I, et al.: 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. [PubMed: 21357819]
21. Sipahi I, Chou JC, Hyden M, Rowland DY, Simon DI, Fang JC: Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. *Am Heart J* 2012; 163:260–267. [PubMed: 22305845]
22. Hsu JC, Solomon SD, Bourgoun M, McNitt S, Goldenberg I, Klein H, Moss AJ, Foster E: Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: the MADIT-CRT (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy) study. *J Am Coll Cardiol* 2012; 59:2366–2373. [PubMed: 22698490]
23. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, Sherfese L, Wells G a., Tang ASL: An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J* 2013; 34:3547–3556. [PubMed: 23900696]
24. De Pooter J, El Haddad M, De Buyzere M, et al.: Biventricular Paced QRS Area Predicts Acute Hemodynamic CRT Response Better Than QRS Duration or QRS Amplitudes. *J Cardiovasc Electrophysiol* 2017; 28:192–200. [PubMed: 27885752]

Figure 1. –. Examples of calculation of QRS area and SAI QRS-T from the vectorcardiogram
 QRS area (**A**) is calculated using the integral between the deflection and baseline from the onset to the offset of the QRS complex. SAI QRS-T (**B**) is calculated as the sum of the orthogonal leads' absolute area under the QRS complex and T-wave deflections. The vertical lines mark the on- and offsets of the QRS complex and the T-wave offset.
 SAI QRS-T = sum absolute QRS-T integral.

Figure 2. —. Kaplan-Meier plot of event-free survival for the overall cohort

The curves are in relation to QRS area above (blue) or below (red) the median value (95 μVs). The hazard ratio is unadjusted.

CI = confidence interval; CRT = cardiac resynchronization therapy; LVAD = implantable left ventricular assist device.

Figure 3. - Kaplan-Meier plots of event-free survival for the LBBB (A) and non-LBBB (B) subgroups

The curves are in relation to QRS area above (blue) or below (red) 95 μVs . The hazard ratios are unadjusted.

CI = confidence interval; CRT = cardiac resynchronization therapy; LBBB = left bundle branch block; LVAD = implantable left ventricular assist device.

Figure 4. —. Kaplan-Meier plots of event-free survival for QRS duration below (A) or above (B) 150 ms for the overall cohort

The curves are in relation to QRS area above (blue) or below (red) 95 μ Vs. The hazard ratios are unadjusted.

CI = confidence interval; CRT = cardiac resynchronization therapy; LVAD = implantable left ventricular assist device.

Table 1. –

Baseline characteristics for the overall cohort

	All (N = 705)	QRS area <95 μ Vs (n = 353)	QRS area >95 μ Vs (n = 352)	p-value
Days from ECG to CRT[†]	6(1–23)	7(1–24)	5(1–22)	0.22
Age, years	66.6 $\pm$ 11.5	66.4 $\pm$ 10.9	66.7 $\pm$ 12.2	0.76
Male	492 (70%)	270 (76%)	222 (63%)	<0.001
Ischemic Heart Disease	374 (53%)	216 (61%)	158 (45%)	<0.001
LVEF, %	24 $\pm$ 7	24 $\pm$ 7	24 $\pm$ 7	0.69
NYHA class III/IV	584 (83%)	309 (88%)	275 (78%)	0.001
QRS duration, ms	163 $\pm$ 27	153 $\pm$ 25	174 $\pm$ 26	<0.001
QRS duration < 150 ms	239 (34%)	186 (53%)	53 (15%)	<0.001
QRS morphology				
Strict LBBB	358 (51%)	120 (34%)	238 (68%)	<0.001
Non-strict LBBB	107 (15%)	85 (24%)	22 (6%)	<0.001
RV paced	119 (17%)	38 (11%)	81 (23%)	<0.001
RBBB	27 (4%)	26 (7%)	1 (< 1%)	<0.001
RBBB + LAFB	49 (7%)	44 (12%)	5 (1%)	<0.001
RBBB + LPFB	5 (1%)	5 (1%)	0	0.06
IVCD	40 (6%)	35 (10%)	5 (1%)	<0.001
PR interval, ms	186 $\pm$ 40	193 $\pm$ 44	179 $\pm$ 34	<0.001
1st degree AV block	118 (17%)	78 (22%)	40 (11%)	<0.001
Atrial fibrillation/flutter	243 (34%)	127 (36%)	116 (33%)	0.43
Hypertension	513 (73%)	259 (73%)	254 (72%)	0.74
Diabetes	266 (38%)	144 (41%)	122 (35%)	0.10
Cerebrovascular disease	89 (13%)	51 (14%)	38 (11%)	0.17
Chronic lung disease	151 (21%)	83 (24%)	68 (19%)	0.20
Creatinine, mg/dL[†]	1.2 (1.0–1.6)	1.3 (1.0–1.6)	1.1 (0.9–1.4)	<0.001
Creatinine > 1.2 mg/dL	323 (46%)	186 (53%)	137 (39%)	<0.001
ACE-inhibitor/ARB	540 (77%)	260 (74%)	280 (80%)	0.10
Beta-blocker	627 (90%)	300 (86%)	327 (93%)	0.002
Diuretics	583 (84%)	295 (85%)	288 (82%)	0.41

[†]Median (25th–75th percentile), Wilcoxon rank sum test used for statistical testing.

ACE = angiotensin converting enzyme; ARB = angiotensin II-receptor blocker; AV = atrioventricular; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; IVCD = non-specific interventricular conduction delay; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LPFB = left posterior fascicular block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RBBB = right bundle branch block; RV = right ventricular.

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Table 2. –

Association of QRS area and baseline variables to outcome in univariable and multivariable analyses for the overall cohort

	Univariable Cox Regression			Multivariable Cox Regression		
	HR	95% CI	p-value	HR	95% CI	p-value
Age, per 5-year increase	1.05	1.00–1.10	0.05	0.98	0.93–1.04	0.54
Male	1.61	1.23–2.11	<0.001	1.00	0.73–1.36	0.99
Ischemic heart disease	1.69	1.34–2.12	<0.001	1.35	1.04–1.75	0.03
QRS duration < 150 ms	1.44	1.14–1.81	0.002	1.27	0.91–1.77	0.15
QRS morphology						
Strict LBBB	(1.00)			(1.00)		
Non-strict LBBB	1.66	1.22–2.27	0.001	0.87	0.58–1.31	0.51
RV paced	1.49	1.10–2.02	0.01	1.17	0.82–1.67	0.38
IVCD	2.04	1.33–3.14	0.001	1.06	0.65–1.72	0.83
RBBB + LAFB	1.31	0.83–2.06	0.24	0.49	0.30–0.80	0.005
RBBB + LPFB	19.97	7.91–50.39	<0.001	6.96	2.66–18.20	<0.001
RBBB	2.01	1.13–3.56	0.02	1.19	0.64–2.22	0.59
1 st degree AV block	1.63	1.24–2.13	<0.001	1.79	1.33–2.41	<0.001
Atrial fibrillation/flutter	2.00	1.59–2.50	<0.001	1.64	1.28–2.12	<0.001
LVEF, per 5% increase	0.91	0.84–0.99	0.03	0.91	0.83–1.00	0.05
Hypertension	1.13	0.87–1.45	0.36			
Diabetes	1.18	0.94–1.48	0.15			
NYHA class III/IV	1.90	1.28–2.82	0.001	1.49	0.99–2.26	0.06
Creatinine > 1.2 mg/dL	2.39	1.90–3.00	<0.001	1.86	1.44–2.40	<0.001
Cerebrovascular disease	1.50	1.11–2.02	0.009	1.23	0.90–1.70	0.19
Chronic lung disease	1.72	1.35–2.20	<0.001	1.39	1.07–1.80	0.01
ACE-inhibitor/ARB	0.44	0.34–0.56	<0.001	0.57	0.44–0.74	<0.001
Beta-blocker	0.57	0.41–0.78	<0.001	0.78	0.56–1.10	0.16
Diuretics	1.23	0.87–1.74	0.24			
QRS area < 95 μ Vs	2.11	1.68–2.65	<0.001	1.65	1.25–2.18	<0.001

ACE = angiotensin converting enzyme; ARB = angiotensin II-receptor blocker; AV = atrioventricular; IVCD = non-specific interventricular conduction delay; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LPFB = left posterior fascicular block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RBBB = right bundle branch block; RV = right ventricular.