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Association of ECG characteristics with clinical and echocardiographic outcome to CRT in a non-LBBB patient population

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Abstract

Purpose Effectiveness of cardiac resynchronization therapy (CRT) in patients without left bundle branch block (non-LBBB) QRS morphology is limited. Additional selection criteria are needed to identify these patients.

Methods Seven hundred ninety consecutive patients with non-LBBB morphology, who received a CRT-device in 3 university centers in the Netherlands, were selected. Pre-implantation 12-lead ECGs were evaluated on morphology, duration, and area of the QRS complex, as well as on PR interval, left ventricular activation time (LVAT), and the presence of fragmented QRS (fQRS). Association of these ECG features with the primary endpoint: a combination of left ventricular assist device (LVAD) implantation, cardiac transplantation and all-cause mortality, and secondary endpoint—echocardiographic reduction of left ventricular end-systolic volume (LVESV)—were evaluated.

Results The primary endpoint occurred more often in non-LBBB patients with with PR interval ≥ 230ms, QRS area < 109μVs, and with fQRS. Multivariable regression analysis showed independent associations of QRS area (HR 2.33 [1.44, 3.77], p = 0.001) and PR interval (HR 2.03 [1.51, 2.74], $p < 0.001$) only. Mean LVESV reduction was significantly lower in patients with baseline RBBB, QRS duration < 150 ms, PR interval ≥ 230 ms, and in QRS area < 109 μVs. Multivariable regression analyses only showed significant associations between QRS area ≥ 109 μVs (OR 2.00 [1.09, 3.66] p = 0.025) and probability of echocardiographic response to CRT.

Conclusions In the heterogeneous non-LBBB patient population, QRS area and PR prolongation rather than traditional QRS duration and morphology are associated to both clinical and echocardiographic outcomes of CRT.

Keywords Cardiac resynchronization therapy · Non-left bundle branch block · Electrocardiography · QRS area

Muhammet Dural and Antonius M. W. van Stipdonk contributed equally to this work.

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1 Introduction

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with heart failure (HF) with a reduced ejection fraction and evidence of dyssynchronous electrical ventricular activation. Typically, patients with left bundle branch block (LBBB) respond well to CRT. Response in patients with non-LBBB is known to be less [1–4]. Current guideline recommendations for CRT are based primarily on the presence of LBBB QRS morphology and then by QRS duration [5]. There is only limited data to support the use of these two ECG parameters together and even less for the use of QRS duration in non-LBBB patients [6, 7]. However, as response and non-response to CRT is almost equally distributed among non-LBBB patients, research should focus on finding additional predictors in this heterogeneous group of patients. Few studies have evaluated additional 12-lead ECG characteristics that may contribute to the characterization of non-LBBB patients and their chance of response to CRT.

Subanalyses of landmark trials suggest significant differences in outcome to CRT in non-LBBB patients with a right bundle branch block (RBBB) conduction pattern, as compared with those with a non-specific interventricular conduction delay (IVCD) [1, 2]. Also PR interval prolongation over 230 ms has been associated with increased benefit from CRT [8, 9]. Furthermore, retrospective cohort studies have identified left ventricular activation time (LVAT), fragmented QRS (fQRS), and vectorcardiographic QRS area as alternative methods in the evaluation of electrical dyssynchrony in patients with HF and predictors of response to CRT [10–13]. However, these parameters have not been specifically studies in a non-LBBB CRT patient population. Overall there is a lack of evidence of the value of known additional ECG parameters in the specific cohort of non-LBBB patients.

In this study we aimed to assess the additional value of these ECG characteristics in a large non-LBBB patient population on the association with both clinical and echocardiographic endpoints in CRT-treated patients.

2 Methods

2.1 Patient population

The Maastricht-Utrecht-Groningen (MUG) cohort consisted of 1946 consecutive patients implanted with CRT in either tertiary centres between 2001 and 2015, with baseline 12-lead ECG available. For the present study, we considered patients selected for de novo CRT device implantation according to at that time prevailing guidelines [14, 15]. Only patients with non-LBBB QRS morphology were considered for the present analysis. For PR interval prolongation analyses, patients with atrial fibrillation on their baseline ECG were excluded.

Baseline data were retrieved from local hospital patient information systems. Patient characteristics like HF etiology and classification, comorbidities, and medication were retrieved from patient history and referral letters. HF etiology was deemed ischemic when there was clear evidence of myocardial infarction or coronary artery bypass grafting (CABG) in the medical history. Device data were retrieved from specific device databases. ICD programming and biventricular pacing were according to treating physicians preference. Left ventricular lead location was judged from the fluoroscopic images or chest X-ray. The Dutch Central Committee on Human-related Research (CCMO) allows for 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.

2.2 Electro- and vectorcardiography

Electrocardiographic analyses were performed blinded to outcomes. Recorded baseline 12-lead ECGs were stored digitally in the MUSE Cardiology Information system (GE Medical System). LBBB morphology was defined according to the presence of accepted criteria, including QRS duration ≥ 130ms, QS, or rS in lead V_1, mid QRS notching or slurring in ≥2 consequetive leads (V_1, V_2, I, aVL, V_5, or V_6) [16], and absent Q waves in leads V_5 and V_6.

Patients classified as non-LBBB were thereafter analysed for QRS morphology, QRS duration, PR interval, QRS area, LVAT and fQRS. RBBB morphology was defined as the presence of any R wave ≥ 50ms or any RSR' pattern (independent of R/R' ratio) in leads V1 or V2. IVCD was defined as the absence of RBBB. QRS duration and PR interval were determined using automated ECG readings. Using a cut-off of 150 ms, non-LBBB patient were divided into two groups, QRS 120–150 ms and QRS > 150ms. PR interval prolongation was defined as PR ≥ 230ms, as suggested previously [8]. QRS area was calculated as described previously [17, 18]. In brief, custom Matlab sortware (MathWorks Inc., Natick, Massachusetts) was used to convert the 12-lead ECG into three orthogonal VCG leads (X-, Y-, and Z-) using the Kors conversion matrix [19]. QRS area was calculated as the sum of the area under the QRS complex in the calculated vectorcardiographic X, Y, and Z lead [$QRSarea = (QRS_{area,x}^2 + QRS_{area,y}^2 + QRS_{area,z}^2)^{1/2}$]. Patient groups were defined by QRS area ≥ or < 109μVs, based on the findings of a previous study in unselected CRT patients [20]. LVAT was measured as the time between first notch in any of the leads V_1, V_2, I, avL, V_5, or V_6 and the end of the QRS complex, as described previously [11, 21]. Patient groups were stratified according to LVAT ≥ or < 125 ms, based on previous analyses in the unselected CRT population [11]. The presence of fQRS was defined as the presence of >2 R' or > 2 notches in the S waves in 2 contiguous leads [22]. Examples of the ECG criteria used are provided in Supplementary Figure 1.

2.3 Study endpoints

The primary endpoint was a combination of all-cause mortality, LV assist device implantation, and cardiac transplantation.

Secondary endpoint was reduction of ≥ 15% in left ventricular end-systolic volume (LVESV) determined by echocardiography at 6 months after implantation. Left ventricular dimensions and ejection fraction measurements were preferably calculated by Simpsons modified biplane method. Information was obtained from hospital records, linked to municipal registries. End of follow-up was defined at December 31st of 2015. Data was considered missing when

follow-up was not in the centre where the implantation was performed.

2.4 Statistical analysis

Statistical analysis was performed using IBM SPSS statistics software version 21 (SPSS Inc., Chicago, IL, USA). Continuous and discrete variables are presented as mean ± standard deviation (SD) and counts (percentages), respectively. Correlations between ECG parameters were tested using a X^2 test or bivariate Pearson correlation when appropriate. Dichotomous variables were compared using a X^2 test. Continuous variables were compared using a Student t-test. Overall differences were evaluated for ECG parameters. Kaplan-Meier survival analyses and cumulative hazard analyses were used when appropriate to evaluate the association between the ECG parameters and the outcomes. The log-rank test was used to determine probability values. Cox regression analyses were used to assess univariable and multivariable effects of ECG parameters, on the association with the primary outcome. Variables included in the multivariable analysis were all variables that significantly differed between the compared groups. Comparison of continuous echocardiographic values was performed using 1-way ANOVA. Logistic regression analyses were used to assess univariable effects of ECG parameters on continuous echocardiographic response variables. Logistic regression analysis was used to assess binary echocardiographic response, in a univariable and multivariable model. Variables included in the multivariable model were all relevant clinical variables that were significantly differed between the compared groups. Hazard ratios (HR) and odds ratio (OR) were calculated for cox and logistic regression analyses, respectively. A two-sided p value < 0.05 was considered statistically significant.

3 Results

3.1 Study population

The final study population consisted of 790 Non-LBBB patients after exclusion of patients with baseline RV pacing (n = 340), baseline QRS duration below 120 ms (n = 114), and patients with LBBB QRS morphology (n = 702). Patient selection is shown in Fig. 1. With respect to PR interval prolongation analyses, patients with atrial fibrillation (n = 168) on their baseline ECG were excluded.

3.2 Baseline characteristics

Baseline characteristics of the 790 non-LBBB patients are shown in Table 1. The study population was evaluated in patient groups stratified according to QRS morphology, QRS duration, PR interval, QRS area, LVAT and fQRS presence. The patient selection process is illustrated in Fig. 1. Patients with baseline IVCD QRS morphology, QRS of duration ≥ 150ms, QRS area of ≥ 109μVs, LVAT of ≥ 125ms, and fQRS had signficantly lower LVEF and larger LV dimensions.

Significant, but generally weak correlations were observed between QRS morphology and QRS area (p < 0.001, r = −0.289), QRS duration and QRS area (p < 0.001, r = 0.492), QRS duration and LVAT (p < 0.001, r = 0.845), QRS duration and fQRS (p < 0.001, r = 0.211), PR interval duration and QRS area (p < 0.001, -r = 0.150), QRS area and LVAT (p < 0.001, r = 0.397), and LVAT and fQRS (p = 0.008, r = 0.102).

3.3 Primary endpoint

Data on primary endpoint was available in all but one patient (99.9%). In a mean follow-up time of 3.7 ± 2.3 years, 308 patients (39%) experienced the primary endpoint.

Figure 2 shows Kaplan-Meier estimates of event-free survival in non-LBBB patient groups stratified to predefined ECG parameters. Occurrence of the primary endpoint was significantly associated with PR interval, QRS area, and fQRS. Primary endpoint occurence was significantly higher in patients with a PR interval of ≥ 230ms (54 vs 34%, HR 2.23 [1.67, 3.00] and in the presence of fQRS (47 vs 26%, HR 1.44 [1.12, 1.85], p = 0.004). On the other hand, the occurrence of the primary endpoint was significantly lower when QRS area was > 109μVs (32 vs 42%, HR 0.64 [0.50, 0.81], p < 0.001). Patient subgroups stratified according to QRS duration, -morphology, and LVAT did not significantly differ with respect to the occurence of the primary endpoint.

A multivariable regression analysis showed independent associations of QRS area (HR 2.33 [1.44, 3.77], p = 0.001) and PR interval (HR 2.03 [1.51, 2.74], p < 0.001) with the primary endpoint but failed to show independent associations of fQRS with the primary endpoint.

3.4 Echocardiographic response

Data on the secondary endpoint of reverse remodelling was available in 470 patients (59.5%). Mean LVESV reduction was 11 ± 29%. Echocardiographic response was present in 207 (44%) of the 470 patients.

Echocardiographic response to CRT in different subgroups is shown in Fig. 3. Mean LVESV reduction was significantly lower in RBBB patients compared with IVCD patients (−1 ± 36 vs 13 ± 27%, p = 0.001), QRS duration < 150ms patients compared with ≥ 150ms (5 ± 29 vs 15 ± 28%, p < 0.001), PR interval ≥ 230ms compared with < 230 ms (6 ± 24 vs 14 ± 29%, p = 0.003), and in QRS area < 109μVs patients compared with ≥ 109μVs (7 ± 27 vs 19 ± 30%, p < 0.001). There

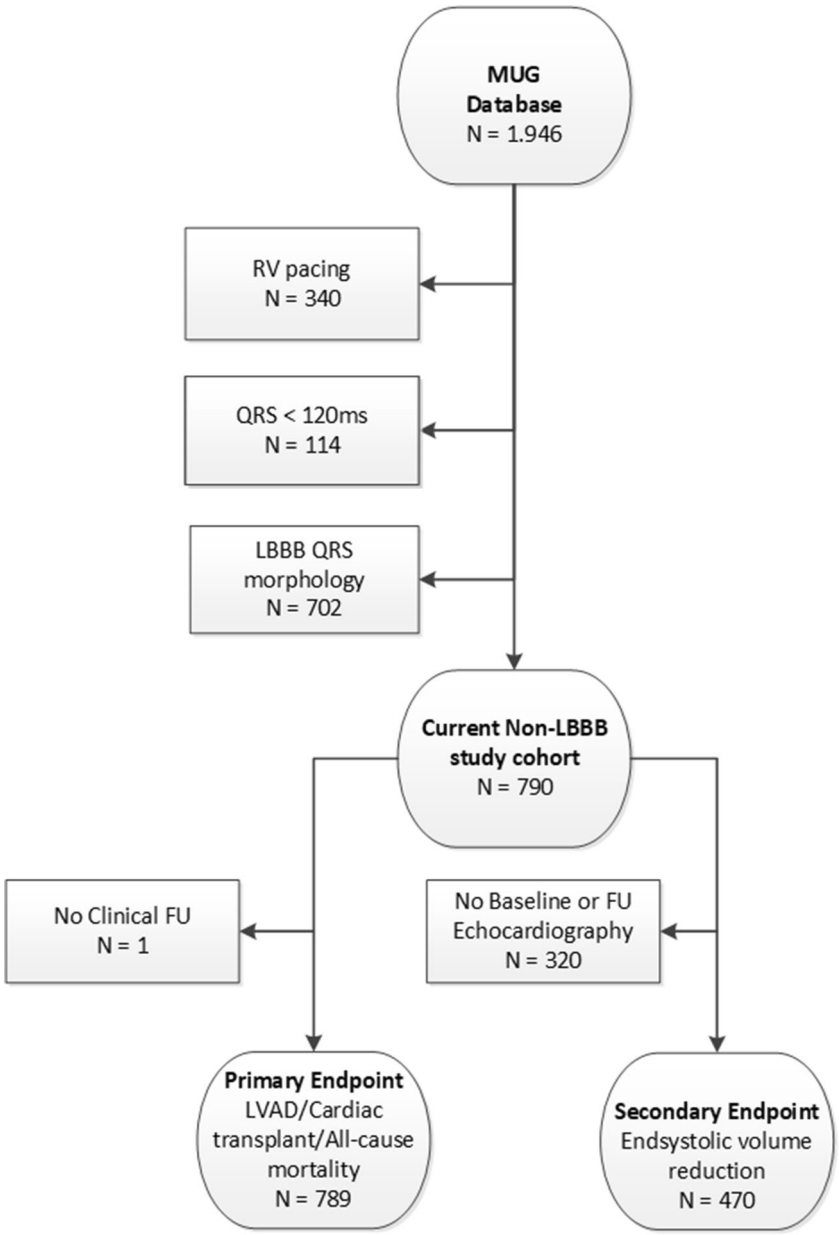

Fig. 1 Patient data selection and availability for analyses. The entire MUG cohort consisted of all patients with a CRT device implanted from January 2001 to January 2015 in 3 university hospitals in the Netherlands. For the present study patients with QRS<120 ms and patienst with LBBB were excluded. Availability of data for analyses on the primary and secondary endpoints is also shown. *BL* baseline, *FU* follow-up, *HF* HF, *LBBB* left bundle branch block, *LVAD* left ventricular assist device, *RV pacing* right ventricular pacing

were no significant differences between echocardiographic outcomes of subgroups stratified according to LVAT and fQRS.

Regression analyses showed significant associations between QRS duration ≥ 150ms (OR 1.86 [1.27, 2.72], p = 0.001) and QRS area ≥ 109 μVs (OR 2.35 [1.60, 3.45], p <0.001) and the probability of echocardiographic response (LVESV reduction ≥ 15%). But did not for QRS morphology, PR interval prolongation, LVAT, or fQRS. Multivariable correction for baseline differences however no longer showed significant associations between echocardiographic response and QRS duration, whereas baseline QRS area ≥ 109 μVs remained significantly associated with echocardiographic remodelling (OR 2.00 [1.09, 3.66] p = 0.025)

4 Discussion

This study shows that QRS area ≥ 109 μVs and PR interval< 230 ms are strongly associated to both the occurrence of LVAD implantation, cardiac transplantation, or all-cause mortality, as well as echocardiographic outcomes in non-LBBB patients treated with CRT. RBBB as opposed to IVCD and QRS duration only showed associations to echocardiographic

remodelling, but were not independently associated with either outcomes.

4.1 QRS area in non-LBBB

There is no study evaluating the association between QRS area and CRT response in non-LBBB patients. QRS area has been shown to be associated to echocardiographic response in the general CRT population. Recently Maass et al. [23] prospectively studied a large set of clinical, electrocardiographic, echocardiographic, and blood biomarkers to predict CRT response in 240 patients. They found that QRS area (as a continuous measure) was the strongest predictor of reverse remodelling as defined by the reduction of indexed LVESV, stronger than currently recommended QRS morphology and duration. This confirmed results from earlier studies [13, 17, 24] and was confirmed in the non-LBBB patient population in the present study. Non-LBBB patients with QRS area ≥ 109 uVs showed significantly higher mean LVESV decrease, resulting in a higher response rate compared with patients with QRS area < 109 uVs. Moreover this study is the first to show the strong association to relevant long-term clinical outcome of all-cause mortality, cardiac transplantation, or LVAD implantation.

The clear additional value of QRS area in this cohort may be explained by the heterogeneity of the non-LBBB cohort and therefore wide range of underlying substrates contributing to the electrical activation displayed on the 12-lead ECG. Whereas this gives rise to uncertainties concerning ECG morphological characteristics determined manually, QRS area is a quantitative semi-automatically determined parameter, not subjected to interpretation. Moreover QRS area has previously been shown to be associated to the presence of scar [13] and may therefore exclude patients with significant scar and therefore lesser benefit from CRT and overall worse outcome.

4.2 PR prolongation in non-LBBB

A recent subanalysis of the MADIT-CRT trial data has shown a prolonged PR interval (≥ 230ms) in non-LBBB patients to be associated to increased benefit from CRT compared with ICD only therapy in terms of HF hospitalization and death (RRR 73%) and all-cause mortality (RRR 81%) [8]. Our study shows that non-LBBB patients with a prolonged PR interval, treated with CRT, have a higher chance of any of the reported endpoints, but this does not state anything about the effect of CRT on these endpoints. In the study by Kutyifa et al. [8], 22% of patients with a normal PR interval and 48% of those with a prolonged PR interval experienced the primary endpoint of HF hospitalization or death. In the CRT-D-treated arms of the study this was 25 versus 10% of patients with a prolonged PR interval versus a normal PR interval in a mean 29-month follow-up. Concordantly, in the present study, in which mean follow-up was 47 months, the primary endpoint occured in 53 vs 34% of non-LBBB with and without prolonged PR interval patients, respectively. However, the greater amenability to CRT found in the subanalyses by Kutyifa et al. in patients with PR prolongation ≥ 230 ms was not reflected by the results on echocardiographic remodelling in this study. As patients with PR prolongation showed significantly lower reduction in LVESV, the contrary could be expected, as is reflected by an overall worse outcome in these patients. In contrast to the results of the MADIT-CRT subanalysis, a subanalysis of the REVERSE-trial showed no significant association of PR prolongation to benefit from CRT at all. That study, however, used a cut off for PR interval prolongation of 180 ms (median of population); possibly, this lower cut off may contribute to the absence of any effect as PR prolongation substantially less than 230 ms may not result in the proposed negative haemodynamic consequenses [9]. Also, in a retrospective CRT study involving 291 LBBB patients, it was found that patients with PR interval > 200 ms had less reduction in QRS duration and QRS area and shorter survival free of heart transplantation or LV assist device implantation [25].

We hypothesize that the overall worse outcome in patients with a significantly prolonged PR interval seen in the present study is due to more extensive cardiac disease, making prolonged PR interval a marker of a worse HF substrate. Although CRT should be able to amend detrimental effects on acute heamodynamics of LV filling in non-LBBB patients with prolonged PR interval, more extensive underlying disease, often accompanied by fibrosis, cannot be corrected by CRT [26]. Baseline characteristics however did not reflect a poorer baseline heart failure status in patients with PR prolongation at baseline.

4.3 QRS morphology and duration

Several subanalyses of landmark trials have shown the reduced likelyhood of benefit from CRT in non-LBBB patients [27–29]. Although some have explored the additional value of RBBB morphology in the non-LBBB patient group, this is the first study specifically adressing the non-LBBB patient subgroup for the evaluation of known baseline 12-lead ECG parameters' association to outcome of CRT.

Subanalyses of the MADIT-CRT, REVERSE, and RAFT trials further stratified non-LBBB patients into RBBB and IVCD QRS morphology [1, 2, 4]. Whereas these analyses conclude that IVCD patients derive no clinical benefit or even harm from CRT, and RBBB patients show intermediate benefit, Zareba et al. [1] did find significant echocardiographic remodelling in both RBBB and IVCD patients treated with CRT compared with those treated with ICD-therapy alone. Furthermore echocardiographic remodelling in the

Table 1 Baseline characteristics. Patient baseline characteristics stratified according to the presence of baseline ECG parameters.

	Total	RBBB	IVCD	QRS ≥ 150	QRS 120–150	PR ≥ 230	PR < 230	QRS area ≥ 109	QRS area < 109	LVAT ≥ 125	LVAT < 125	No fQRS	fQRS
N = (%)	790 (100)	133 (17)	653 (83)	463 (59)	327 (41)	120 (19)	508 (81)	266 (34)	514 (66)	124 (18)	555 (82)	282 (36)	503 (64)
Demographics													
Male (%)	76.5	85.0*	74.7	72.1	68.8	89.2*	71.1	67.2*	74.7	76.6	75.0	81.6*	73.6
Age	66.4	67.0	66.4	66.9	66.3	67.4	65.6	66.0	67.2	65.0	66.7	67.3	65.9
BMI	26.6	27.0	26.5	26.2*	27.1	26.4	26.6	25.4*	27.3	26.4	26.7	26.8	26.4
iCMP (%)	56.1	60.2	55.4	47.9	53.1	58.3	56.8	36.9*	62.3	46.8*	58.4	51.8	58.4
Afib (%)	18.0	24.1*	16.7	12.5	19.3	-	-	9.2*	19.3	14.5	18.2	16.1	21.3
NYHA II-III (%)	92.0	96.2	91.2	92.9	92.3	88.8	93.6	92.4	93.2	92.7	91.5	91.3	92.6
Medication													
B-blok (%)	80.1	81.8*	72.3	82.5	81.8	70.0*	84.7	82.6	81.9	79.8	80.1	84.0*	77.8
ACEi/ARB (%)	89.7	85.4	90.6	90.2	89.9	86.7	91.8	89.9	90.4	92.7	89.8	90.4	89.3
MRA (%)	45.4	37.7	46.7	45.5	44.7	48.8	44.5	40.5	50.3	43.5	47.8	41.0	48.3
Echo													
LVEF (%)	24.0	26.5*	23.5	23.2*	25.2	24.0	23.8	22.8*	24.8	21.4*	24.1	25.1*	23.3
LVESV (ml)	175	153*	179	187*	158	181	180	187*	168	210*	171	160*	184
LVEDV (ml)	228	209*	232	241*	209	239	233	241*	221	268*	223	212*	238
Clear (ml/min)	70.6	70.2	68.2	67.4	70.3	63.2	71.4	68.7	69.0	69.6	68.9	69.1*	68.4
NTproBNP (pmol/L)	366	370	365	419*	290	437.5	313.8	497*	311	402	365	379	357
Device													
ICD	94.8	91.7	95.4	93.2	93.6	95.0	96.1	91.9	94.7	96.0	94.2	91.5*	96.8
LV lead lateral	91.6	86.3*	92.4	92.9	90.7	91.3	92.0	90.2	91.3	89.4	91.6	92.1	91.3

*$p < 0.05$

ACEi/ARB angiotensin converting enzyme inhibitor/angiotensin receptor blockers, *Afib* atrial fibrillation, *B-block* Betablockers, *BMI* body mass index, *Clear* creatinine clearance, *fQRS* fragemented QRS, *ICD* implantable cardioverter defibrillator, *iCMP* ischemic cardiomyopathy, *IVCD* non-specific intraventricular conduction delay, *LVAT* left ventricular activation time, *LVEF* left ventricular ejection fraction, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *LV* lead lateral lateral position of LV lead, *MRA* mineralocorticoid receptor antagonist. *NT-proBNP* N-terminal prohormone of brain natriuretic peptide, *NYHA* New York Heart Association classification of HF, *PR* PR interval, *RBBB* right bundle branch block

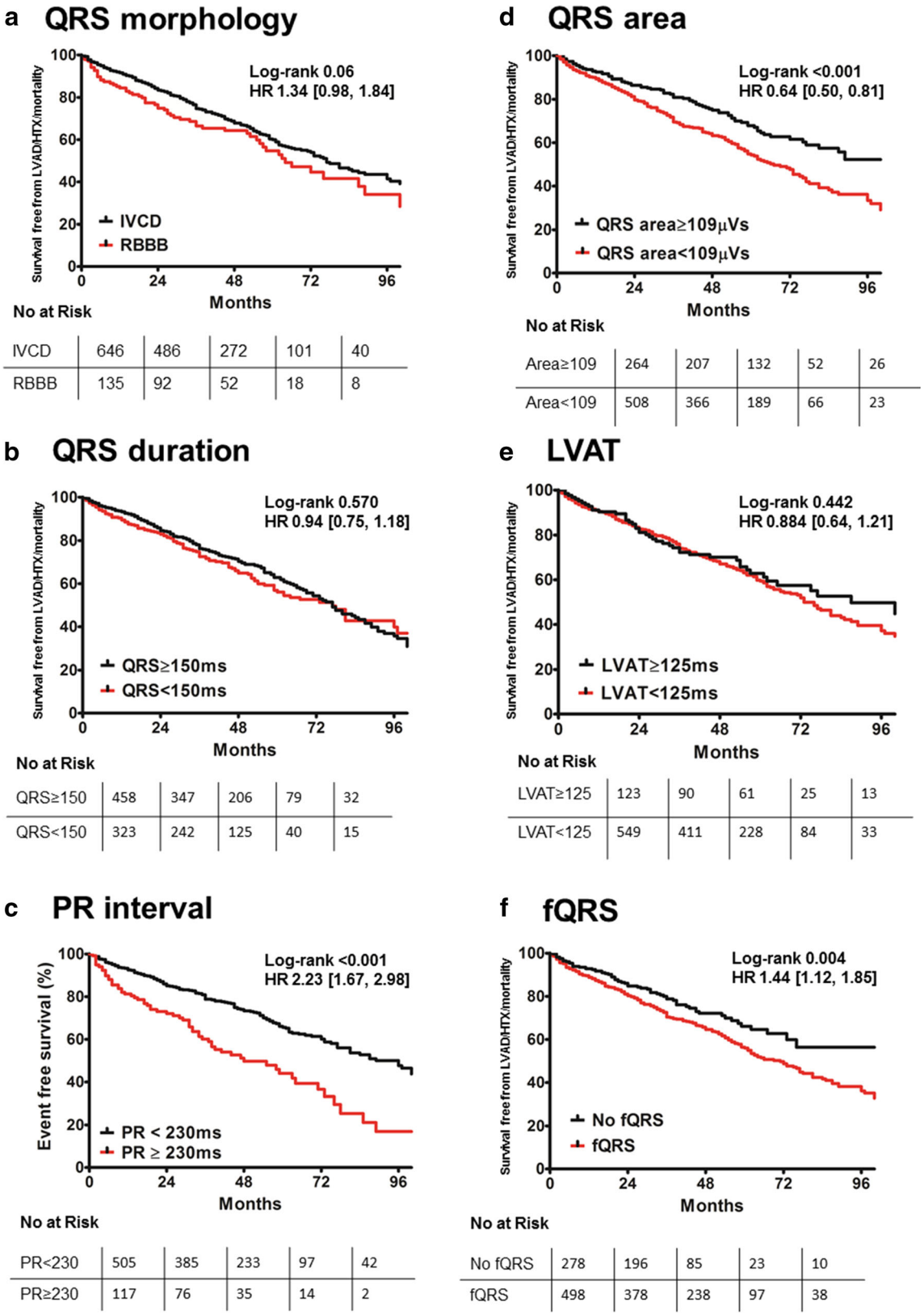

Fig. 2 Kaplan-Meier estimates of survival free of the primary endpoint (combination of LVAD, cardiac transplantation or all-cause mortality). Patients are stratified by (**a**) QRS morphology (RBBB or IVCD). (**b**) QRS duration < or ≥ 150ms , (**c**) PR interval < or ≥ 230 ms, (**d**) QRS area < or ≥ 109 μVs, (**e**) LVAT < or ≥ 125 ms, and (**f**) the presence of fQRS. *fQRS* fragmented QRS, *HR* hazard ratio, *IVCD* non-specific intraventricular conduction delay, *LVAD* left ventricular assist device, *LVAT* left ventricular activation time, *RBBB* right bundle branch block

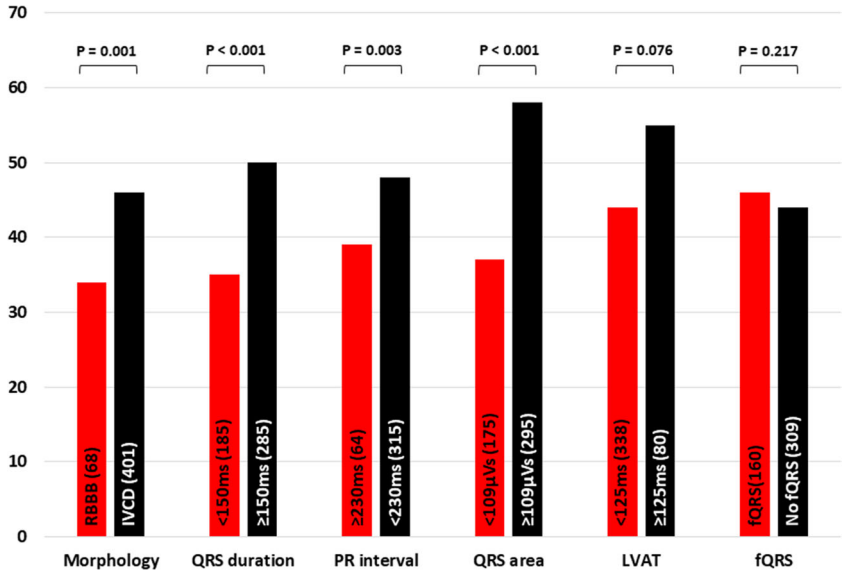

Fig. 3 Echocardiographic reduction in LVESV and response rate. Echocardiographic LVESV reduction in percentage at follow-up echocardiography in patient groups stratified by QRS morphology (RBBB or IVCD), QRS duration < or ≥ 150ms, PR interval < or ≥ 230 ms, QRS area < or ≥ 109 µVs, LVAT < or ≥ 125 ms, and the presence of fQRS. *fQRS* fragmented QRS, *IVCD* non-specific intraventricular conduction delay, *LVAT* left ventricular activation time, *LVESV* left ventricular end-systolic volume, *RBBB* right bundle branch block

REVERSE subanalyses seems to be better in IVCD patients than in RBBB patients (although non-significant). The results of the current study support these echocardiographic findings, showing significantly more benefit from CRT in IVCD than in RBBB patients.

The relation between QRS duration and CRT response has been shown in several studies [2, 4, 6]. However, there is only limited data on QRS duration in non-LBBB patients. Gold et al. [2] assessed the association of QRS duration with LVESV reduction in CRT patients grouped by QRS morphology. They failed to show a significant association; however non-LBBB patients in this study included a large group of narrow QRS patients (24% of 238 patients). A recent study by van der Bijl et al. [30] assessed echocardiographic remodelling in CRT defined by LVESDV and LVESV reduction and LVEF increase in wide QRS patients alone. They showed that in both LBBB and non-LBBB QRS morphology, increasing QRS duration is associated to increase remodelling in CRT. Similarly, in the current study, the group with QRS ≥ 150 ms demonstrated higher reduction in LVESV and improvement in LVEF.

Similarly to a recent retrospective study by Khidir et al. [31], the current study failed to demonstrate a significant survival benefit in patients with a QRS duration ≥ 150ms compared to those with a QRS duration < 150ms. The randomized RAFT population substudy by Birnie et al. [4] also showed that QRS duration has a continuous inverse relation with the hazard ratio for a composite clinical outcome of all-cause mortality or HF hospitalization in both LBBB and non-LBBB subgroups. However, the authors also suggest that a QRS duration cut off of 160 ms might be more appropriate in non-LBBB population. Moreover, as the multivariable regression analyses did not show QRS duration to be independently associated, whereas QRS area and PR prolongation were, these parameters could turn out more valuable in the subgroup of non-LBBB patients.

4.4 Fragmented QRS

Previous studies report contradicting results on the relation between fQRS and CRT response. Rickard et al. [32] evaluated 233 consequetive patients undergoing CRT implantation. This population consisted of almost 60% non-LBBB patients, with only 22% of patients demonstrating fragmented QRS. fQRS was not associated to echocardiographic remodelling or all-cause mortality. In contrast, Celikyurt et al. [12] prospectively evaluated 105 patients with HF undergoing CRT. They found that the number of leads with fQRS was a predictor of echocardiographic response to CRT (odds ratio: 0.61, $p < 0.001$). In the current cohort, patients with fQRS on their baseline 12-lead ECG showed no significant differences in remodelling indices. However, these patients showed a significantly higher occurrence of the combined endpoint of death, cardiac transplantation, or LVAD implantation. The differences between aforementioned and current study may be explained by difficulties in defining fragmentation, as the differentiation of fragmentation and notching/slurring included in some LBBB definitions depends very much on the observer and filter and zoom-settings of the 12-lead ECG. Furthermore, the association is not independent from other electrocardiographic parameters evaluated in the current study and may therefore, especially in light of the variability in interpretation, not be the recommended option for stratification of patients.

4.5 LVAT

LVAT showed a significant association with response to CRT in previous studies including the general CRT population. Eitel et al. [11] evaluated 219 patients treated with CRT. The study included chronically right ventricular (RV) paced and non-paced patients. In the non-paced group, only 21% of patients had non-LBBB QRS morphology. They found LVAT ≥ 125 ms to be associated to death or cardiac transplantation in non-paced group. In contrast, there was no significant association with any of the outcomes in the current evaluation in non-LBBB patients. A reason for this difference may be that in non-LBBB patients, myocardial activation patterns by definition are significantly different than in LBBB patients [33, 34]. As many presume the transseptal activation related 'notching' to be hallmark feature of LBBB QRS morphology [16], this may exclude any value of this pattern and associated markers of the 12-lead ECG, like LVAT in non-LBBB patients.

4.6 Limitations

Because of the retrospective design of our study, the absence of the non-treated control group precludes the definite allocation of the differences found in this study to CRT. However, echocardiographic response is assesed using each patient as his/her own control. Furthermore, attrition bias may be present because of the incomplete data, specifically on echocardiographic outcomes. Prospective randomized controlled trials are needed to clarify the the influence of QRS-area and PR-prolongation on CRT-response in non-LBBB patients.

4.7 Clinical implications

The results of this study may provide further aid in the very heterogeneous group op non-LBBB patients. As depicted by current guideline recommendation levels (IIa and IIb), currently we are not able to tell which non-LBBB patients benefit from CRT. Eventhough the study design makes it unsuited to address benefit from CRT in clinical parameters, it does show that additional ECG parameters separate patients with positive remodelling from those that show non-response, equally, or better that currently recommended QRS duration. The better separation of patients with good from poor clinical outcome could reflect either benefit from therapy or baseline risk of adverse events and is equally valuable in providing prognostic data. Further studies, or rather subanalyses of randomised trials, will be needed to address the value of these ECG parameters to select patients for CRT.

5 Conclusions

In the heterogeneous non-LBBB patient population, QRS area and PR prolongation rather than traditional QRS duration and morphology are associated to both clinical and echocardiographic outcomes of CRT. These 12-lead ECG markers may provide additional information in patient selection for non-LBBB patients.

Figure including normal 12-lead ECG on left and respesentative ECG-parameters evaluated in non-LBBB patients in the current study. ECG parameters included from upper-left to lower right box are (1) QRS morphology with example of lead V1 RSR pattern indicative of RBBB morphology, (2) QRS duration measurement, (3) PR interval measurement with evident PR prolongation in example, and (4) QRS area measurement with vector X-axis displayed. QRS area requiring area measurement in X-, Y- and Z-axis and calculation of total QRS area according to formula: $(\text{QRS area}_X^2 + \text{QRS area}_Y^2 + \text{QRS area}_Z^2)^{1/2}$, (5) fQRS assessment and (6) LVAT measurement from notch or slurring to end of the QRS complex. The 12-lead ECG is representative of the QRS duration, QRS area, and LVAT measurement

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