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# Association between vectorcardiographic QRS area and incident heart failure diagnosis and mortality among patients with left bundle branch block: A register-based cohort study

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ABSTRACT

*Background:* QRS duration and morphology including left bundle branch block (LBBB) are the most widely used electrocardiogram (ECG) markers for assessing ventricular dyssynchrony and predicting heart failure (HF). However, the vectorcardiographic QRS area may more accurately identify delayed left ventricular activation and HF development.
*Objective:* We investigated the association between QRS area and incident HF risk in patients with LBBB.
*Methods:* By crosslinking data from Danish nationwide registries, we identified patients with a first-time digital LBBB ECG between 2001 and 2015. The vectorcardiographic QRS area was derived from a 12-lead ECG using the Kors transformation method and grouped into quartiles. The endpoint was a composite of HF diagnosis, filled prescriptions for loop diuretics, or death from HF. Cause-specific multivariable Cox regression was used to compute hazard ratios(HR) with 95% confidence intervals(CI).
*Results:* We included 3316 patients with LBBB free from prior HF-related events (median age, 72 years; male, 40%). QRS area quartiles comprised Q1, 36–98 μVs; Q2, 99–119 μVs; Q3, 120–145 μVs; and Q4, 146–295 μVs. During a 5-year follow-up, 31% of patients reached the composite endpoint, with a rate of 39% in the highest quartile Q4. A QRS area in quartile Q4 was associated with increased hazard of the composite endpoint (HR:1.48, 95% CI:1.22–1.80) compared with Q1.
*Conclusions:* Among primary care patients with newly discovered LBBB, a large vectorcardiographic QRS area (146–295 μVs) was associated with an increased risk of incident HF diagnosis, filling prescriptions for loop diuretics, or dying from HF within 5-years.



## Introduction

Patients with left bundle branch block (LBBB) have a poor prognosis due to increased risks of heart failure (HF) and mortality [1–4]. LBBB causes ventricular dyssynchrony that leads to insufficient cardiac contractility and abnormal left ventricular filling, resulting in reduced cardiac function [5,6]. Current clinical guidelines recommend using QRS morphology and duration based on the standard 12lead electrocardiogram (ECG) for assessment of ventricular dyssynchrony and thereby patient selection for cardiac resynchronization therapy (CRT) implantation in case of ongoing HF symptoms [7]. Although wider QRS duration (≥150 ms), strict LBBB morphology, and T-wave discordance have all

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been associated with adverse outcome, these ECG markers are still not optimal for predicting future HF burden [8–10].

Recently, attention has been drawn to the possible prognostic value of vectorcardiographic QRS area derived from the standard 12-lead ECG. Evidence suggests that the QRS area accurately identifies delayed activation of the left ventricular lateral wall, response to CRT, and survival following CRT implantation [8,11–15]. However, to our knowledge, no studies have assessed whether the QRS area may adequately predict HF development in patients with newly discovered LBBB.

Therefore, using a large contemporary primary care clinical database including digital ECGs from approximately 450,000 patients, we sought to investigate the association between vectorcardiographic QRS area and risk of developing a composite HF endpoint in LBBB patients.

## Methods

### *Study design and population*

In this Danish registry-based retrospective cohort study, we obtained standard 12-lead ECGs from a large contemporary population of primary care patients referred to the central core facility Copenhagen General Practitioners' Laboratory (CGPL), as described prevoiusly [16], for ECG recording between use of loop diuretics who were free of prior HF-related events who had a clinically obtained ECG demonstration LBBB for the first time. See section 'Outcome measure' for HF definition.

Corresponding demographic data and data on causes of death and death date were obtained from the Danish Civil Registration System [17] and the Danish Registry of Causes of Death, respectively [18]. Patients were excluded in case of missing demographic data, age < 16 years, or a registration error (i.e. death date prior to ECG recording date).

### *Electrocardiography and vectorcardiographic QRS area*

All ECG data were analyzed using the 12 SL algorithm, version 23 in the MUSE Cardiology Information System (GE Healthcare, Wauwattosa, WI). The complete LBBB definition is available elsewhere [19]. It has been favorably validated, with a specificity from 99.9% to 100% and sensitivity from 78% to 90.9% when compared to diagnosis by cardiologists using traditional LBBB guidelines [20].

We further excluded patients with interfering ECG abnormalities including atrial fibrillation or flutter, second- and third-degree atrioventricular blocks, left ventricular hypertrophy (any of the following: Sokolow Lyon, Cornell Product, Romhilt-Estes or amplitude of the R-wave in aVL > 110 mV), paced rhythms, delta waves, as well as tachycardia and bradycardia with heart rates >120 and < 50 bpm, respectively.

Vectorcardiograms were derived from the digitally stored standard 12-lead ECGs by use of the Kors transformation method [8,21,22]. The Kors method has prognostic value regarding HF development, response to CRT [8,14,15], and all-cause mortality [23].

Vectorcardiographic QRS area was calculated, using the median beat, as described previously.: QRS area $= (QRS_x^2 + QRS_y^2 + QRS_z^2)^{1/2}$, where $QRS_{x/y/z}$ represent the integrals between the deflection and baseline of each lead between onset and offset (J point) of the QRS complex (Fig. 1) [8,14,15,24]. ECG with QRS area > 300 μVs were excluded, as done previously [15]. The final cohort was grouped into quartiles (Q1, 36–98 μVs; Q2, 99–119 μVs; Q3, 120–145 μVs; and Q4, 146–295 μVs).

### *Comorbidities, procedures, and prescription drugs*

Baseline variables were obtained from the Danish National Patient Registry [25] to identify International Classification of Diseases (ICD) codes for ischemic cardiomyopathy, atrial fibrillation or flutter, valvular heart disease, hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease prior to LBBB ECG (Supp. Table 1). Furthermore, we obtained procedure codes for pacemaker and implantable cardioverter-defibrillator implantations prior to first ECG with LBBB configuration and excluded patients with these registered codes (Supp. Table 2).

Finally, the Danish National Prescription Registry [26] was used to identify Anatomical Therapeutic Chemical (ATC) codes for filled prescriptions for cardiovascular drugs within 180 days prior to LBBB ECG (Supp. Table 3). Generally, hypertension, hyperlipidemia, diabetes, and chronic obstructive pulmonary disease are managed in primary care, and patients may not necessarily have ICD codes registered in the Danish National Patient Registy. As such, ACT codes for filled prescriptions for antihypertensives (at least dual therapy), lipid-lowering drugs, antidiabetics, and beta adrenergic or anticholinergic inhalants were further used to define these specific conditions.

### *Outcome measure*

The primary endpoint was a composite of a HF diagnosis (ICD-10: I11.0, I13.0, I13.2, I42, I50, and J81), filled prescriptions for loop diuretics (ATC: C03C and C03EB), or death from HF (similar ICD-10 codes as the HF diagnosis). The secondary outcome was all-cause mortality. Patients

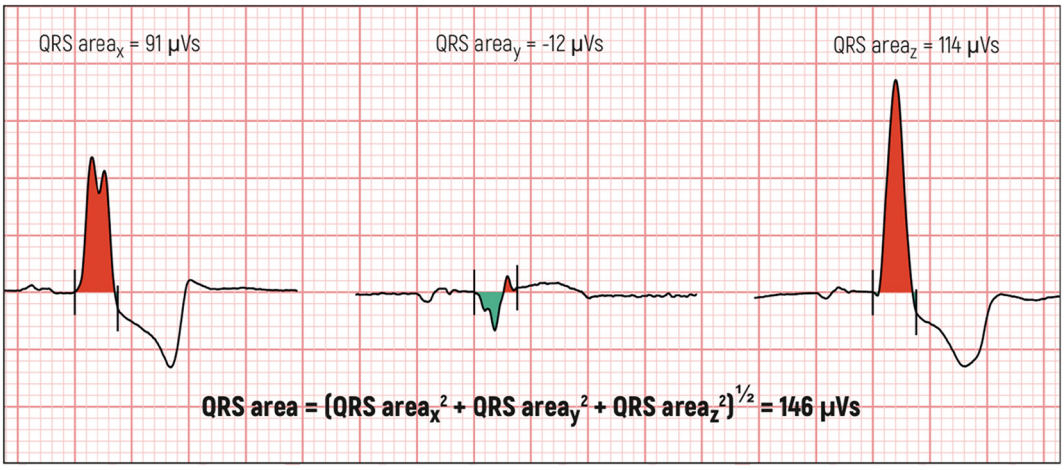


**Fig. 1.** Example of vectorcardiographic QRS area calculation where $QRS_{x/y/z}$ represents the integral between the deflection and the baseline of each lead between onset and offset (J point) of the QRS complex.

were followed for a period of 5 years from first ECG with LBBB configuration or until the occurrence of primary or secondary endpoint, censoring in case of emigration or at the end of study on December 31, 2017, whichever came first. We accounted for death from other causes as a competing risk.

### *Statistical analysis*

Continuous variables were reported as medians with 25th–75th percentiles and categorical variables as counts with percentages. Differences were compared using Kruskal-Wallis and chi-squared tests, as appropriate.

We reported the cumulative incidence of the composite HF endpoint stratified by QRS area quartiles using the Aalen Johansen method. We used multivariable cause-specific Cox regression, yielding cause-specific hazard ratios (HRs) with 95% confidence intervals (CIs) for assessing the risk of composite HF associated with QRS area quartiles. The lowest quartile Q1 served as reference.

The proportional hazard assumption was tested by plotting cumulative Martingale residuals and was not violated. Interaction testing was based on introducing an interaction term in a Cox regression model and using a likelihood ratio test to compare this model to one without an interaction term. A two-sided *P*-value <0.01 was considered statistically significant for interactions and < 0.05 for all other analyses. No significant interactions were present. Linearity of continuous variables was also assessed using a likelihood ratio test comparing a linear description to a categorical one. Age was observed to violate linearity and was included as a categorical variable based on quartiles.

We used a restricted cubic spline to depict how the QRS area was associated with outcome if considered on a continuous scale. Knots were placed at the 10th, 50th, and 90th percentile, and the median value 119 μVs served as reference (HR 1.00).

All analyses were adjusted for QRS duration ≥150, age quartiles, sex, ischemic cardiomyopathy, atrial fibrillation or flutter, valvular heart disease, hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease.

Data management and analysis were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R, version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

### *Ethics*

In Denmark, registry-based studies do not require ethical committee approval or individual patient consent if the study is conducted for the sole purpose of statistics and scientific research, as defined in the Data Protection Act. Approval to use the data sources for research purposes was granted by the institute responsible for the data in the Capital Region of Denmark in accordance with the General Data Protection Regulation (approval number: P-2019-191).

## Results

### *Patient characteristics*

Based on 978,855 ECGs from 449,979 patients, we included 3316 first-time LBBB ECG recordings of patients free from prior HF-related events (Fig. 2). Median age at the time of ECG recording was 72 (62–80) years, and 1319 patients (40%) were men.

Overall, patients in the highest vectorcardiographic QRS area quartile (146–295 μVs) more often demonstrated QRS duration >150 ms (70%) and prolonged QTc interval (473 [460–488] ms). Patients in the lowest quartile Q1 (36–98 μVs) had a higher cardiovascular comorbidity burden, and they also more frequently filled the prescriptions for angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and beta blockers (Table 1).

### *Association between QRS area and composite HF endpoint*

The total incidence of the composite HF endpoint, with death from non-HF causes as a competing risk, was 31% during the 5-year follow-up period. When stratifying by QRS area quartiles, 39% of patients in the highest quartile Q4 (146–295 μVs) reached the composite HF endpoint (Fig. 3) versus 27% in Q1.

After multivariable adjustment, patients with the highest QRS area (146–295 μVs) had increased rate of composite HF endpoint (HR: 1.48, 95% CI: 1.22–1.80). The remaining quartiles Q2 (99–119 μVs) and Q3 (120–145 μVs) were not associated with an increased HR if composite HF compared to the lowest quartile Q1 (36–98 μVs) (Fig. 4). As an additional analysis, QRS area did not confer increased 5-year all-cause mortality (Suppl. Fig. 1).

Furthermore, we observed a non-linear association between greater QRS area and risk of developing a composite HF endpoint, whit adverse outcomes observed in patients with QRS area > 120 μVs ($p < 0.001$) (Fig. 5).

## Discussion

This Danish register-based cohort study based on 3316 first ECGs with LBBB configuration from primary care patients reports findings that may add valuable prognostic information about which patients eith newly discovered LBBB are at increased hazard of developing HF. Our study demonstrated that having a large vectorcardiographic QRS area (> 146 μVs) on the first ECG with LBBB configuration was associated with a significant increased risk of experiencing the composite HF endpoint within 5 years. Furthermore, our study shows a strong non-linear association between greater QRS area and an increased risk of experiencing the composite HF endpoint beyond a QRS area of 119 μVs. Finally, the QRS area was not useful in the prognostication of all-cause mortality during the first 5 years after diagnosis of LBBB.

The ECG plays an essential role when diagnosing and managing patients with LBBB due to its ability to identify and quantify ventricular depolarization. However, ECG markers such as QRS morphology and duration have several important limitations [8–10,27]. While prior studies have investigated the QRS area in relation to CRT, [8,11–15,27,28] no information exists about the usefulness of the QRS area for LBBB risk prediction in a non-CRT setting. Our study suggests that the risk of developing a composite HF endpoint in patients with LBBB can be predicted using the QRS area, a simple marker derived from the standard 12-lead ECG. Early prognostication may facilitate earlier preventive strategies.

The vectorcardiographic QRS area identifies global ventricular activation delay and quantifies the extent of the delay [13,27]. The QRS area changes as a result of changes in both the amplitude and duration of the QRS complex [21]. It is likely that the QRS areas provides better association with long-term outcomes compared to other ECG markers such as QRS duration and morphology because it includes more information about the ventricular activation delay. It can be suggested that QRS area is largely mass dependent and that it captures not only activation delay but also the amount of myocardium that is activated late [13]. Thereby, the QRS area serves as a robust non-invasive summative marker which embraces the complexity that lies within the interplay of the intrinsic electrical substrates and the LBBB activation pattern [13].

Baseline QRS area could be a supportive diagnostic tool when considering patients who would be more likely to benefit from CRT. Overall, studies report that a high QRS area in LBBB patients is associated with better outcomes after CRT. [8,11,14,15,27] Some specifically compared the QRS area with the traditional ECG markers of LBBB and observed that QRS area better predicts LV reverse remodelling and clinical outcome after CRT. [8,12,14] Combined with our findings, that high QRS area is associated with increased risk of HF development, the baseline LBBB QRS area may allow early identification of high-risk patients who may have a good outcome from possible CRT implantation. While

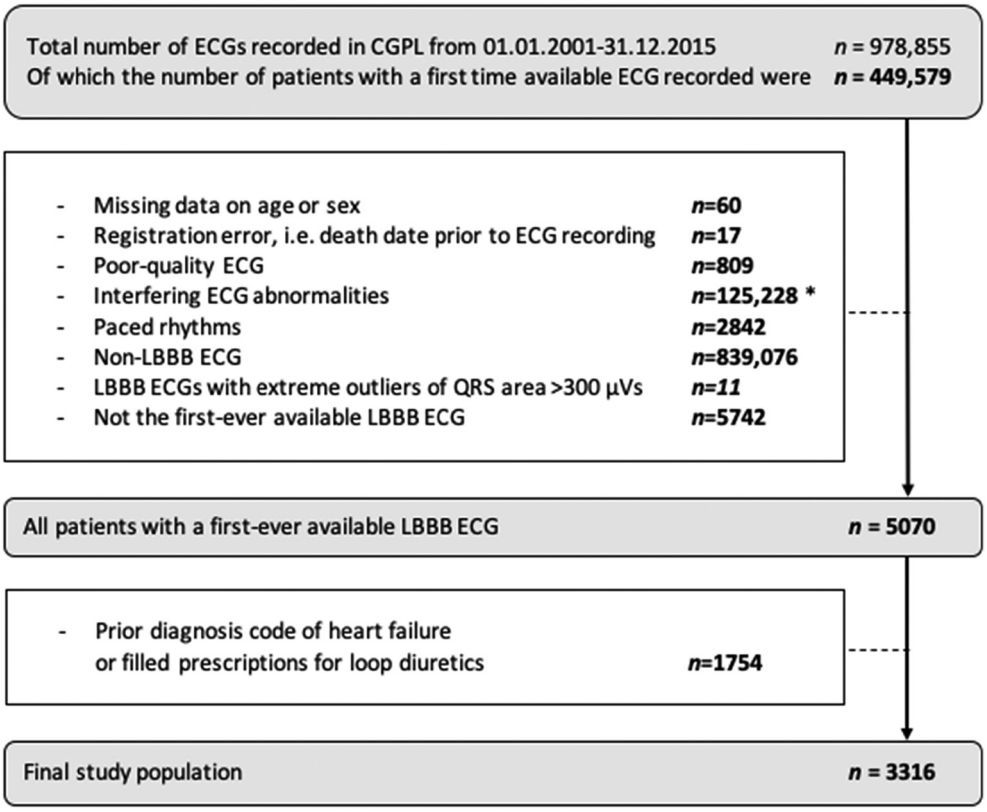


**Fig. 2.** Flowchart of patient selection. *Including atrial fibrillation or flutter, second- or third-degree atrioventricular blocks, delta waves, left ventricular hypertrophy, tachycardia (>100 beats per minute), and bradycardia (<50 beats per minute). Abbreviations: ECG: Electrocardiogram, LBBB: Left bundle branch block, CGPL: Copenhagen general Practitioners' Laboratory

**Table 1**
Baseline clinical characteristics of the total study population after stratification by vectorcardiographic QRS area. Values are presented as *n* (%) or medians [25%tile, 75%tile], *p*-values are based on Kruskal-Wallis tests, as appropriate.

| | Vectorcardiographic QRS area | | | | | |
|---|---|---|---|---|---|---|
| | Q1<br>36–98 µVs<br>*n* = 829 | Q2<br>99–119 µVs<br>*n* = 829 | Q3<br>120–145 µVs<br>*n* = 830 | Q4<br>146–295 µVs<br>*n* = 828 | Total<br>*n* = 3316 | p-value |
| Demographics | 75 [66, 81] | 72 [62, 80] | 70 [60, 79] | 71 [60, 81] | 72 [62, 80] | < 0.001 |
| Age at ECG recording, years | | | | | | |
| Males | 290 (35.0) | 263 (31.7) | 334 (40.2) | 432 (52.2) | 1319 (39.8) | < 0.001 |
| ECG characteristics | 71 [64, 80] | 71 [64, 80] | 72 [65, 81] | 72 [63, 82] | 72 [64, 80] | 0.179 |
| Ventricular rate, bpm | | | | | | |
| P-wave duration, ms | 114 [104, 122] | 112 [102,120] | 112 [102, 120] | 116 [106, 124] | 114 [104, 122] | < 0.001 |
| Missing | 18 | 8 | 11 | 13 | 50 | |
| PR interval, ms | 174 [158, 192] | 170 [154, 186] | 171 [156, 188] | 174 [158, 194] | 172 [156, 190] | < 0.001 |
| Missing | 13 | 7 | 6 | 9 | 35 | |
| QRS duration, ms | 136 [130, 144] | 142 [134, 150] | 148 [140, 154] | 156 [148, 166] | 144 [136, 154] | < 0.001 |
| QRS duration ≥ 150 ms | 109 (13.1) | 223 (26.9) | 342 (41.2) | 575 (69.4) | 1249 (37.7) | < 0.001 |
| QT interval, ms | 430 [408, 450] | 434 [414, 456] | 438 [418, 458] | 446 [424, 468] | 438 [416, 458] | < 0.001 |
| QTc interval, ms | 454 [440, 469] | 461 [448, 475] | 465 [452, 479] | 473 [459.8, 488.0] | 463 [449, 479] | < 0.001 |
| Comorbidities | 142 (17.1) | 130 (15.7) | 107 (12.9) | 107 (12.9) | 486 (14.7) | 0.032 |
| Ischemic heart disease | | | | | | |
| Atrial fibrillation/flutter | 42 (5.1) | 26 (3.1) | 22 (2.7) | 28 (3.4) | 118 (3.6) | 0.046 |
| Valvular heart disease | 9 (1.1) | 12 (1.4) | 15 (1.8) | 19 (2.3) | 55 (1.7) | 0.255 |
| Hypertension | 166 (20.0) | 134 (16.2) | 140 (16.9) | 135 (16.3) | 575 (17.3) | 0.126 |
| Hyperlipidemia | 201 (24.2) | 180 (21.7) | 154 (18.6) | 108 (13.0) | 643 (19.4) | < 0.001 |
| Diabetes | 115 (13.9) | 77 (9.3) | 69 (8.3) | 39 (4.7) | 300 (9.0) | < 0.001 |
| Chronic obstructive pulmonary disease | 82 (9.9) | 79 (9.5) | 64 (7.7) | 63 (7.6) | 288 (8.7) | 0.215 |
| Chronic kidney disease | 12 (1.4) | 12 (1.4) | 17 (2.0) | 17 (2.1) | 58 (1.7) | 0.625 |
| Cardiovascular drugs | 268 (32.3) | 217 (26.2) | 225 (27.1) | 186 (22.5) | 896 (27.0) | < 0.001 |
| ACEIs or ARBs | | | | | | |
| Beta blockers | 144 (17.4) | 130 (15.7) | 113 (13.6) | 113 (13.6) | 500 (15.1) | 0.096 |

Abbreviations: ECG: Electrocardiogram, ACEI: Angiotensin-converting-enzyme inhibitors, ARB: Angiotensin II receptor blockers

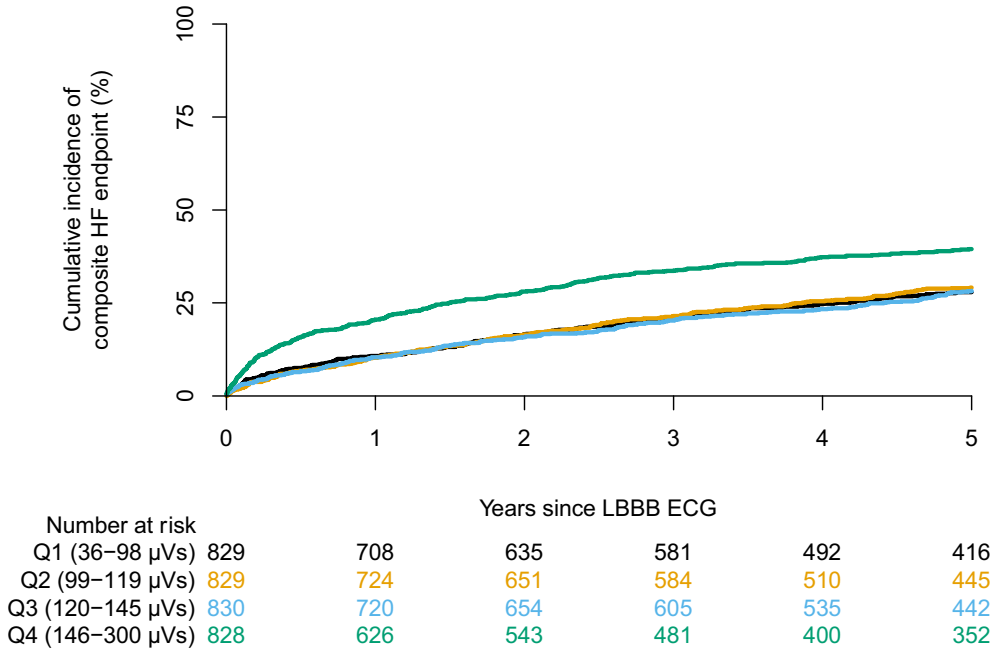


**Fig. 3.** Cumu Cumulative incidence of composite heart failure endpoint based on vectorcardiographic QRS area quartiles over a 5-year follow-up for LBBB patients.Abbreviations: HF: Heart failure, ECG: Electrocardiogram, LBBB: Left bundle branch block

it appears that vectorcardiographic QRS area is related to CRT outcome prediction, studies examining QRS area in relation to heart failure risk are limited. Such knowledge may be helpful in guiding risk stratification, referral and treatment of patients with first time LBBB.

*Clinical implications*

Currently, different LBBB definitions exist and their relation to clinical outcomes have been established [9,29,30].

By considering QRS area as an additional ECG marker to current LBBB guidelines, we may be able to earlier risk stratify and thereby optimize patient selection and improve response to HF therapies including CRT. Our findings suggest that this risk stratification can be done in primary care, which could improve referral to secondary clinical care for earlier diagnostic testing and therapeutic intervention earlier within a patient's disease course. QRS area should be provided as supplementary information next to other automatically computed and well-established markers including heart rate, PR interval, QRS duration and QTc.

*Limitations*

Our study has several limitations. First, the retrospective design of this study introduces biases regarding selection. This only allows us to establish associations and not causation. Second, this study does not

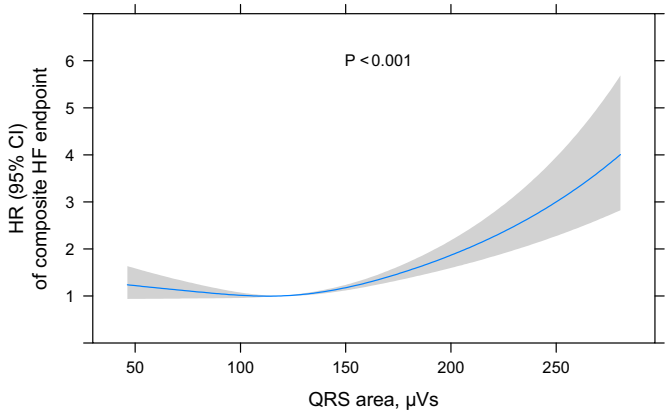


**Fig. 5.** Restricted cubic spline of the association between vectorcardiographic QRS area, as a continuous marker, and incident composite heart failure endpoint. The reference point was set as QRS area as 112 µVs, thereby representing a HR at 1.0. Adjusted for age quartiles, sex, ischemic cardiomyopathy, atrial fibrillation or flutter, valvular heart disease, hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease. Abbreviations: HR: Hazard ratio, CI: Confidence interval. HF: Heart failure, LBBB: Left bundle branch block

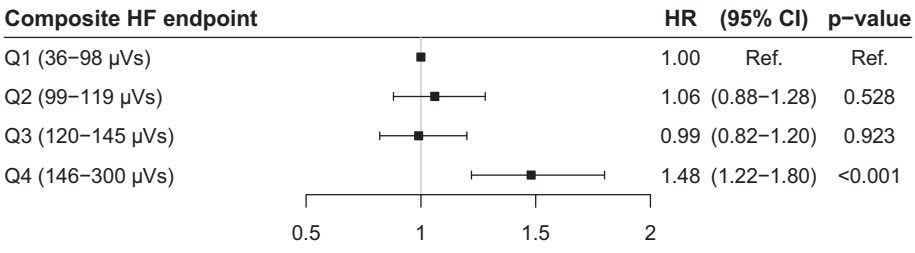


**Fig. 4.** Cox regression for the association between vectorcardiographic QRS area and incident composite heart failure endpoint over a 5-year follow-up for LBBB patients. Adjusted for age quartiles, sex, ischemic cardiomyopathy, atrial fibrillation or flutter, valvular heart disease, hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease. Abbreviations: HR: Hazard ratio, CI: Confidence interval, HF: Heart failure, LBBB: Left bundle branch block

compare outcomes by different LBBB definitions including AHA/ACC/HRS [30], ECS [29], or Strauss et al. [9] Third, we do not compare our results to a control population without LBBB. Fourth, our study does not investigate the association between QRS area and outcome severity such as New York Heart Associations class or echocardiographic data. Baseline and follow-up LVEF were unavailable in our population, preventing us from adjusting for this important covariate and differentiating the development of HFpEF and HFrEF. In addition, we lacked adequate data on CRT and ICD implantations during follow-up, thus we could not account for a potential beneficial effect of CRT on HF prognosis. Finally, we did not have information on the indication for the ECG recording or available data on blood samples in relation to the ECG.

## Conclusions

Among primary care patients with newly discovered LBBB, a large vectorcardiographic QRS area (146–295 μVs) was associated with an increased risk of incident HF diagnosis, filling prescriptions for loop diuretics, or dying from HF within 5-years.

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## Appendix A. Supplementary data

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