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Association between T-wave Discordance and the Development of Heart Failure in Left Bundle Branch Block Patients: Results from the Copenhagen ECG Study

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Abstract

Background: In left bundle branch block (LBBB), discrepancies between depolarization and repolarization of the heart can be assessed by similar direction (concordant) or opposite direction (discordant) of the lateral T-waves compared to the direction of the QRS complex and by the QRS-T angle. We examined the association between discordant T-waves and high QRS-T angles for heart failure development in primary care LBBB patients.

Methods: Between 2001-2011, we identified 2,540 patients from primary care with LBBB without overt heart failure. We examined the development of heart failure in relation to two ECG measures: (1) LBBB as either discordant (two or three monophasic T-waves in the opposite direction of the QRS complex in leads I, V5 or V6) or concordant, and (2) the frontal plane QRS-T angle in quartile groups.

Results: In total, 244 of 913 patients (26.7%) with discordant LBBB developed heart failure compared to 302 of 1,627 patients (16.7%) with concordant LBBB. Multivariable Cox regression comparing discordant with concordant LBBB showed a hazard ratio (HR) of 2.58 (95% Confidence interval[CI] 1.71-3.89) for heart failure development within 30 days of follow-up and a HR of 1.45 (95%CI 1.19-1.77) after 30 days. For QRS-T angle, comparing the highest quartile (160° - 180°) with the lowest quartile (0° - 110°) we found a HR of 2.25 (95%CI 1.26-4.02) within 30 days and a HR of 1.67 (95%CI 1.25-2.23) after 30 days.

Conclusion: T-wave discordance in lateral ECG leads and a high QRS-T angle are associated with heart failure development in primary care LBBB patients.

Keywords: Heart Failure, Left Bundle Branch Block, Discordance, Concordance, QRS-T angle,

Introduction

Left bundle branch block (LBBB) is associated with increased morbidity and mortality in healthy individuals and in HF patients close to 25% have LBBB[1–5]. Routine electrocardiogram (ECG) recordings have reported LBBB in 0.1 to 1.2 % of all patients, and the rate increases with age.[3,4,6,7] LBBB on routine ECGs entails diagnostic challenges and the clinical approach to these patients, including the need for specialist referral and additional examination, warrants further investigation.[3,8]

LBBB is classified as discordant LBBB if there are two or more monophasic discordant T-waves in leads I, V5 or V6 or concordant if these conditions are not met (see Figure 1)[9]. Moreover, LBBB patients may also have varying degrees of T-wave discordance in the limb leads seen as discrepancy between the frontal plane QRS-axis and the frontal plane T-axis measured by the corresponding QRS-T angle. [10] T-wave discordance arises when the repolarization sequence and the depolarization sequence follow the same direction. This is usually seen with wider QRS complexes as in LBBB, but the clinical significance of T-wave discordance in LBBB is unclear.[11,12] However, recent evidence suggests that discordant LBBB is a marker of poor prognosis in HF patients with LBBB[9,13] and may be associated with worse systolic function.[9,10,13–15] LBBB is often associated with cardiac disease, but may also be observed in apparently healthy people. T-wave discordance in LBBB could be a sign of underlying or developing HF, but this has not yet been studied.

We hypothesized that T-wave discordance may be associated with the development of HF in LBBB patients without HF. Using Danish registries, we examined the association between T-wave discordance or concordance observed on an LBBB ECG and the development of HF. Two approaches were used, the dichotomous subdivision of LBBB into

concordant LBBB and discordant LBBB as well as a continuous marker of T-wave discordance given by the frontal plane QRS-T angle.

Methods

Study population and electrocardiograms

We had access to a total of 345,278 patients who had 655,345 12 lead ECGs recorded at the Copenhagen General Practitioners Laboratory between January 2001 to September 2011. Patients were followed for up to two years after first ECG recording with LBBB or until a HF event, death from other cause, emigration or end of study at December 2012.

The Copenhagen General Practitioners Laboratory performed paraclinical procedures including ECG recordings for General practitioners in the Greater Copenhagen Region. The recorded ECGs were digitally stored in MUSE Cardiology Information System (GE Healthcare, Wauwatosa, WI) and analyzed using version 21 of the Marquette 12 SL algorithm. All first time ECGs identified with LBBB were included in the study. The use of this algorithm to diagnose LBBB has been favorably validated with high specificity (ranging from 99.9% and 100%) and sensitivity (ranging from 78% and 90.9%) when compared to diagnosis by cardiologist using a traditional definition of LBBB.[16] The criteria used by the algorithm includes a QRS duration > 120 ms, Q or S wave > 80 ms in lead V1 and V2, the absence of Q waves in two of I, V5 and V6, and a R duration + R' duration of > 100 ms in any of I, V5 or V6 among other criteria. The specific algorithm used to define LBBB can be found the GE Marquette 12SL Analysis Program Physician's Guide in the section regarding diagnosis.[17]

We excluded patients with HF registered prior to ECG recording. To ensure high sensitivity, HF was defined as either (1) a hospital admission, outpatient contact or emergency room contact with a HF diagnosis in the Danish National Patient Registry[18], or (2) dispensation of loop diuretics Definitions of HF based on both loop diuretics and

diagnosis have been described previously.[19,20] We further excluded patients with previous pacemaker or ICD implantation registered by procedure code in the Danish National Patient Registry [18] and patients with ECGs showing pace-rhythm. Furthermore, we excluded patients with arrhythmia, heart rate above 120 beats per minute (bpm) or below 50 bpm, and PR intervals below 120 milliseconds (ms) or above 400 ms. Excluded arrhythmias were atrial fibrillation, atrial flutter, Wolf-Parkinson White and 2nd and 3rd degree atrioventricular blocks. Exclusions based on PR interval and heart rate were to ensure that patients did not have an arrhythmia undetected by the ECG algorithm.

Baseline variables

Baseline data was obtained from Danish national registries. We retrieved baseline disease information up to five years prior to ECG recording including previous myocardial infarction, other ischemic heart disease, valvular heart disease, hypertension, diabetes, chronic pulmonary disease, and chronic renal disease. We retrieved baseline medication data up to 180 days prior to the ECG recording for beta-blockers, ACE-inhibitors, cardiac glycosides and spironolactone. The use of Danish registries is described in detail in supplementary materials.

Hypertension and diabetes were defined by either diagnosis or prescription of treatment for the conditions as done previously.[20] All data used to define these conditions was recorded for up to five years prior to ECG recording. Further details about the definitions of these conditions can be found in supplementary materials.

Exposure

Patients were classified as having either concordant or discordant LBBB, the latter defined as two or more monophasic T-waves with direction opposite that of the QRS complex in leads I,

V5 or V6.[9,13,14] Additionally, the frontal plane QRS-T angle was calculated as the absolute difference between the frontal plane QRS axis and frontal plane T axis and patients were divided in four groups using the quartiles of the difference in angle.

Outcome

HF was the primary outcome of interest. A HF event was defined as either (1) a hospital admission, outpatient contact, or emergency room contact with a HF diagnosis (ICD-10: I50), (2) incident dispensation of prescribed loop diuretics, or (3) death from HF. Death from other causes was a competing risk.

We also assessed the number of patients having a second ECG recorded during follow up and reported any change in LBBB type from discordant to concordant or vice versa.

Statistical Analysis

When summarizing descriptive statistics, categorical variables were presented as frequencies and proportions and continuous variables as median values with 25-75th percentiles.

Accordingly, Chi-square and Mann-Whitney U tests were used test for differences between groups. We reported Aalen Johansen cumulative incidences of the HF event with death as a competing risk for the LBBB classification as either concordant or discordant and for the frontal plane QRS-T angle stratified according to quartile values.

To assess the association between T-wave discordance and development of HF, multivariable Cox regression analyses were used to compare the risk of HF events based on concordant or discordant LBBB type and the frontal plane QRS-T angle. The covariates used

in the multivariable regression analyses were sex, age, hypertension, diabetes, and ischemic heart disease. Due to non-linearity, age was divided into quartiles: 22.6-62.7, 62.7-74.5, 74.5-80.1, and 80.1-100.7. The analysis of concordant and discordant LBBB type used concordant LBBB as reference. For analysis of the frontal plane QRS-T angle two separate approaches were taken. First, the QRS-T angle divided into quartiles was analyzed using the narrowest QRS-T angle quartile as reference. Second, the results of the Cox regression analysis on QRS-T angle as a continuous variable were visualized using a restricted cubic spline with 3 knots at the 10th, 50th and 90th percentile. In this analysis, the median value was used as reference. To further assess the impact of the QRS axis and the T axis, which make up the QRS-T angle, a subdivided analysis stratified into tertiles of QRS axis and tertiles of T axis was performed and the result were illustrated with the use of a heatmap. In this analysis, the group with the lowest QRS axis and T axis was used as reference. One outlier with a QRS axis of 170 degrees was excluded in the analysis.

All Cox regression models were analyzed for statistical interaction between the main exposure and each of the covariates. In these analyses, a p-value < 0.01 was considered statistically significant. No interactions were found. In all other analysis, a two-sided p-value < 0.05 was considered statistically significant. Furthermore, all Cox regressions were evaluated for the proportional hazards assumption using cumulative Martingale residuals which was found to be violated for concordant and discordant LBBB. To account for this, we used time-dependent coefficients for analysis of LBBB as either concordant or discordant and for the quartile QRS-T angle groups. We chose a cut-off point at 30 days for the coefficient and as a result, the analysis yielded separate hazard ratios for the first 30 days and the remaining time of the follow-up period. For other covariates where the proportional hazards assumption was violated, the covariates were included as stratified in the Cox regression model.

All analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA) and R statistical software (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>).

Ethics

The use of registry data was approved by the Danish Data Protection Agency (2008-58-0028). Registry-based studies do not require ethical approval in Denmark.

Results

Patients and characteristics

We included 2,540 patients with LBBB (see Figure 2 for details). Of these, 1,627 (64.1 %) patients had concordant and 913 (35.9%) discordant LBBB. Baseline characteristics according to concordant and discordant LBBB types are available in Table 1. Baseline characteristics for LBBB divided into quartile groups by QRS-T angle can be found in Supplementary Table 2. A histogram showing the distribution of QRS-T angle based on discordant and concordant LBBB can be found in Supplementary Figure 1.

Outcomes

A total of 516 patients (20.3 %) developed HF during the two-year follow up period and 146 (5.8 %) patients died from other cause than HF. Within the first 30 days, 97 patients were diagnosed with HF and 11 died. No patients were lost to follow-up within the first 30 days. The median follow-up time was 700.5 days (Q1-Q3: 553.0-700.5); 114 cases free from event

at the end of study follow-up on December 31, 2012, had incomplete 2-year follow-up information.

1048 patients had a second ECG recorded during follow up. A total of 41 patients had a change in LBBB type; 19 patients had a change from concordant to discordant LBBB and 22 patients had a change from discordant to concordant LBBB.

Cumulative incidence of heart failure

The cumulative incidence of HF with death as a competing risk is illustrated for concordant and discordant LBBB types in Figure 3. The cumulative incidence of HF with death as a competing risk for LBBB subdivided by the groups of the QRS-T angle can be found in Supplementary Figure 2.

Association between LBBB type and heart failure

Results based on LBBB type as either concordant or discordant are shown in Figure 4. Patients with discordant type LBBB have an increased hazard of HF both within 30 days (hazard ratio [HR] 2.58, 95% confidence interval [CI] 1.71-3.89) and the 2-year follow-up (HR 1.45, 95% CI 1.19-1.77) compared to those with concordant type LBBB.

Association between QRS-T angle and heart failure

Patients with the widest QRS-T angle (160° to 180°) had a HR of 2.25 (95% CI 1.26-4.02) for a HF event within the first 30 days when compared to those with a QRS-T angle in the lowest quartile group (0° to 110°). Moreover, Figure 5 shows that the highest quartile of the

QRS-T angle had higher risk of HF events with a HR of 1.67 (95% CI 1.25-2.23) for the 2-year follow-up compared to the lowest quartile group.

A larger angle was associated with a greater hazard of HF and the relation seems to follow an exponential curve as seen from the restricted cubic spline curve (Figure 6) and the heatmap (Figure 7) identified a leftward QRS axis of -114° to -37° and a T axis of 117° to 180° to be associated with the greatest hazard of HF.

Sensitivity Analyses

Sensitivity analysis of discordant LBBB compared to concordant LBBB with a composite endpoint of a HF event or death yielded a HR of 2.58 (95% CI: 1.75-3.82) within the first 30 days and 1.54 (95% CI: 1.30-1.82) for the remaining 2-year follow-up. For quartiles of QRS-T angle the HR of the composite endpoint for the highest QRS-T quartile compared to the lowest quartile was 2.43 (95% CI: 1.37-4.29) within the first 30 days and 1.88 (95% CI: 1.46-2.43) for the 2-year follow-up.

In a second sensitivity analysis the condition of incident loop diuretic prescription was omitted from the HF outcome. In this analysis, discordant LBBB showed a HR of 2.70 (95% CI: 1.63-4.48) within the first 30 days and 1.43 (95% CI: 1.12-1.82) for the 2-year follow-up compared to concordant LBBB and the highest QRS-T angle quartile showed a HR of 2.28 (95% CI: 1.14-4.57) within the first 30 days and 1.95 (95% CI: 1.38-2.77) for the 2-year follow-up compared to the lowest quartile.

Discussion

This study investigated the association between concordant and discordant types of LBBB as well as the QRS-T angle and the development of HF in LBBB patients. We showed that the discordant LBBB type as well as a very wide QRS-T angle are associated with increased risk of short and long-term HF.

A cross sectional study of LBBB patient showed that discordant LBBB was associated with more severe HF when compared to patients with concordant LBBB.[14] These findings are further supported by patient characteristics in studies of HF patients with discordant LBBB.[9,13] In our study we observed an increased short-term risk of HF development when comparing discordant to concordant LBBB. The prevalence of discordant LBBB in our population was lower (39%) compared to previous studies (62-72 %).[9,13,14] A likely explanation is that we selected primary care patients without known HF in contrast to previous studies including hospitalized patient with HF.

Concomitant with the acute impact of discordant LBBB on the development of HF, we also showed that this remained predictive of HF on longer term. We speculate that this is because discordant LBBB is associated with more electro-mechanical dyssynchrony. This greater dyssynchrony would lead to alignment of the vectors of repolarization and depolarization, causing lateral T-wave inversion. However, Padeletti et al. (2017)[9] failed to show superior impact of cardiac resynchronization therapy (CRT) discordant LBBB compared to concordant LBBB. Thus, it is more likely that discordant LBBB represent impaired myocardial performance due to structural abnormalities rather than an electro-mechanical substrate amenable to CRT.[9] Structural abnormalities such as higher left ventricular volumes and pressure or ischemic heart disease can cause endocardial damage affecting the normal transmural sequence of repolarization reflected as T-wave inversion. [14] As such, it is possible that discordant lateral T-waves in LBBB simply reflect strain on

the left ventricle as also seen in non LBBB patients. This strain could in turn be caused by the dyssynchrony seen in LBBB, explaining the high prevalence seen in this condition.

The role of left ventricular strain in discordant LBBB may be further elucidated by studies of cardiac memory. Cardiac memory describes the phenomena where discordant t-waves persist following abolishment of wide QRS rhythms.[21] It has been shown that ventricular stretch rather than just the altered activation pattern in wide QRS rhythms is obligatory for cardiac memory to occur.[22] This further illustrates that structural ventricular properties must be considered when addressing T-wave changes in LBBB.

The initiation of cardiac memory can be identified during wide QRS rhythms. A study has shown that the amplitude of the T-wave vector reduces during DDD pacing, indicative of cardiac memory, although they did not show altered direction.[23] This clearly illustrates that secondary T-wave changes are not fixed and may change over time. In this study 41 patients had a documented change in LBBB type during follow-up. We found that patients changed to either LBBB type from the other. Cardiac memory may play a role in these changes, but the exact mechanism is not yet known. Neither has the prognostic impact of a change in LBBB type been studied and thus, there is a need for further research to fully understand these changes.

The QRS-T angle is a measure of discordance between depolarization (the QRS axis) and repolarization (the T axis). In the general population, a wider QRS-T angle has been associated with mortality including sudden cardiac death, incident coronary heart disease, and incident HF.[24–26] In LBBB patients, the QRS-T angle may represent a different mechanism than in the background population, as the QRS-T angle is widened by the right-to-left sequence of depolarization. Therefore, very little is known about the importance of the QRS-T angle in LBBB patients. Results from the Atherosclerosis Risk in Communities Study

revealed that a wide QRS-T angle in both right (R-) and (L-) bundle branch block (BBB) patients was a strong predictor of incident HF, however the study had a much larger proportion of RBBB patients in the narrow QRS-T angle group (51.6%) than in the wide QRS-T angle group (13.8%).[10,15]

We showed that a wide QRS-T angle was associated with development of HF. We further analyzed the components of the QRS-T angle: the QRS axis and the T axis. In this analysis, a leftward QRS axis in conjunction with discordance of the T-axis was the strongest predictor of incident HF. This implies that when looking at QRS-T angle as a predictor of HF in LBBB attention should be paid to the specific direction of both the depolarization compared with the subsequent repolarization and not just the absolute difference between the two. Specifically, studies have indicated the importance of the QRS axis in CRT.[27,28] Here, left axis deviation lead to worse prognosis in CRT compared to no axis deviation. It has also been shown that LBBB patients with left axis deviation had more myocardial scarring by the use of a ECG scar score, giving a plausible explanation for the worse response to CRT.[29] Nonetheless, further research is necessary to fully understand the importance of the QRS-T angle in LBBB as well as the nature of its relationship with the QRS axis and T axis.

The use of the QRS-T angle as well as discordant LBBB in a clinical setting provides an advantage as they have been shown to be among the least influenced factors regarding lead placement in a small study of HF patients with interventricular conduction defects including LBBB.[30]

A limitation of this study is its observational nature, meaning that the associations found may not necessarily be causal. Furthermore, our study is limited by lack of data on patient symptoms as well as echocardiography data on ventricular function at baseline that might have been related to the ECG recording being performed. Nor did we have access to

echocardiographic data or cardiac magnetic resonance imaging during follow-up. However, this study utilized ECG recording from a primary care setting where echocardiography is not accessible without specialist referral. As such, this study reflects the clinical reality wherein physicians can use our results in combination with other clinical data at hand to gauge the need for referral and further examination. Consequently, the implication of this study is that readily accessible and assessable ECG parameters in a primary care setting can be used for risk stratification and referral purposes when a LBBB ECG is encountered. In particular, recognizing a discordant pattern on ECG is very simple and can be easily taught and implemented at the level of primary care.

Conclusion

In this primary care registry-based study, we found that two ECG parameters including discordant LBBB relative to concordant LBBB as well as a very large QRS-T angle were associated with an increased hazard of heart failure in both short- and long-term follow-up periods. These findings suggest that these readily accessible and assessable ECG parameters can be used for risk stratification and referral to secondary care evaluation.

Conflicts of interest

PS; Consultant; Biotronik, Astra-Zeneca; Honararia, Biotronik, Astra-Zeneca, and GE Health CARE. KK; Research grant, The Laerdal Foundation; Honararia, Novartis. SMH significant Research grants; The Danish Heart foundation, and The Laerdal foundation. CTP; Research grants, Bayer, Biotronik; Personal fee, Bayer. CP; Honararia, Lundbeck. No other conflicts of interest to disclose.

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Figure Legends

Figure 1. Left bundle branch block type.

Figure shows LBBB type based definition as either concordant or discordant. Discordant LBBB is defined as two or more monophasic discordant T-waves in leads I, V5 or V6 and concordant if these conditions are not met. A.1: Concordant LBBB due to T-waves in the same direction as the QRS-complex in more than two of the respective leads. A.2: Concordant LBBB due biphasic T-waves in more than two of the respective leads. B: Discordant LBBB due to T-waves facing the opposite of the QRS-complex in more than two of the respective leads.

Figure 2. Patient selection flow-chart

Figure shows study population selection. Abbreviations: LBBB: left bundle branch block.

Figure 3. Cumulative incidence of heart failure based on type of LBBB

Figure shows cumulative incidence of heart failure (solid lines) over a two-year follow up period for LBBB classified as either concordant or discordant with death as a competing risk (dashed lines). Abbreviations: HF: heart failure.

Figure 4. Hazard of heart failure according to LBBB type.

Figure shows the results of Cox regressions for LBBB type (i.e. concordant and discordant LBBB classification) and its association with the development of heart failure both during the first 30 days of follow-up and the remaining time of follow-up. The analysis was adjusted for age, sex, hypertension, diabetes, and ischemic heart disease. Abbreviations: HR: hazard ratio, CI: confidence interval, HF: heart failure.

Figure 5. Hazard of heart failure according to QRS-T angle.

Figure shows the results of Cox regressions for the QRS-T angle and its association with the development of heart failure both during the first 30 days of follow-up and the remaining time of follow-up. The analysis was adjusted for age, sex, hypertension, diabetes, and ischemic heart disease. Abbreviations: HR: hazard ratio, CI: confidence interval, HF: heart failure, Q1: 0-25% percentile, Q2: 25-50% percentile, Q3: 50-75% percentile, Q4: 75-100% percentile.

Figure 6. Hazard of heart failure based on QRS-T angle.

Figure shows a restricted cubic spline of the results of multivariate Cox regression frontal plane QRS-T angle and development of heart failure. There knots were placed at the 10%, 50% and 90% percentile and the 50% percentile was used as reference. The regression was

adjusted for age, sex, hypertension, diabetes, myocardial infarction, other ischemic heart disease, and renal disease. Abbreviations: Ref.: reference.

Figure 7. Hazard of heart failure based on QRS and T axes.

Figure shows a heatmap of hazard ratio of heart failure for groups divided by tertiles of QRS axis and T axis. One outlier with a QRS axis of 170 degrees was excluded in the analysis.

The group with the lowest QRS axis and T axis was used as the reference in the analysis.

Abbreviations: HR: hazard ratio, HF: heart failure.

Tables

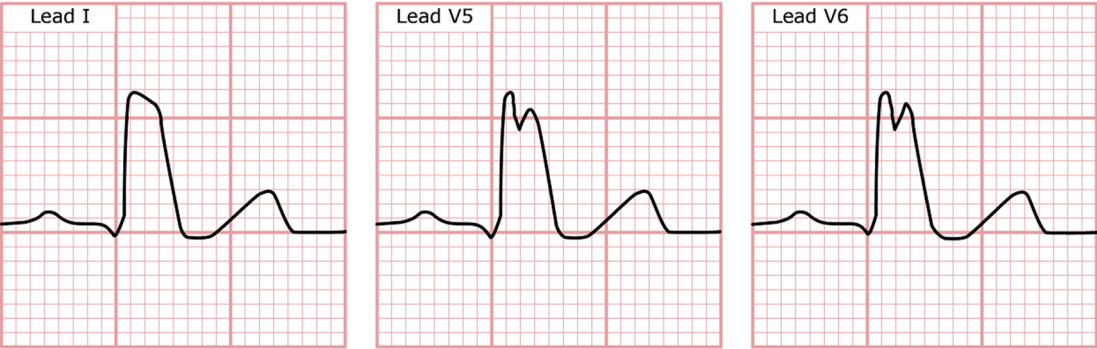
Table 1. Baseline characteristics based on LBBB type.

| Parameter | cLBBB (No. 1,627) | dLBBB (No. 913) |
|-----------------------------|-------------------|-------------------|
| Age, median, Q1-Q3 | 71.0 (61.2, 79.6) | 74.5 (65.7, 82.5) |
| Male Sex, No. (%) | 568 (34.9) | 400 (43.8) |
| QRS-T Angle, median, Q1-Q3 | 127 (96, 148) | 158 (143, 170) |
| QRS-Duration, median, Q1-Q3 | 144 (136, 154) | 148 (138, 158) |
| Hypertension, No. (%) | 543 (33.4) | 349 (38.2) |
| Diabetes, No. (%) | 104 (6.4) | 89 (9.7) |
| MI, No. (%) | 18 (1.1) | 11 (1.2) |
| Other IHD, No. (%) | 94 (5.8) | 53 (5.8) |
| VHD, No. (%) | 11 (0.7) | < 4 |
| CPD, No. (%) | 43 (2.6) | 23 (2.5) |
| Renal Disease, No. (%) | 5 (0.3) | < 4 |
| Cardiac glycosides, No. (%) | 12 (0.7) | 15 (1.6) |
| Beta-Blockers, No. (%) | 241 (14.8) | 117 (12.8) |
| ACE-Inhibitors, No. (%) | 229 (14.1) | 138 (15.1) |
| Spironolactone, No. (%) | 11 (0.7) | 12 (1.3) |

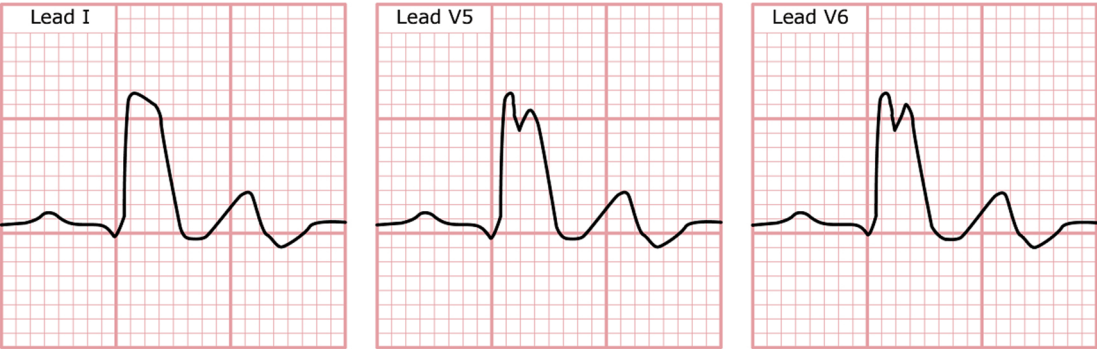
Table shows characteristics based on left bundle branch block (LBBB) type, with discordant

LBBB being defined by the presence of two or more monophasic T-waves in opposite direction to the QRS complex in leads I, V5, V6. Continuous variables are represented by median values with 25-75% percentiles (Q1-Q3) and categorical variables by frequencies and proportions. Abbreviations: cLBBB: concordant LBBB, dLBBB discordant LBBB, MI: myocardial infarction, IHD: ischemic heart disease, VHD: valvular heart disease, CPD: chronic pulmonary disease.

(A.1) Concordance between QRS complex and normal T wave in LBBB ECG



(A.2) Concordance between QRS complex and biphasic T wave in LBBB ECG



(B) Discordance between QRS complex and inverted T wave in LBBB ECG

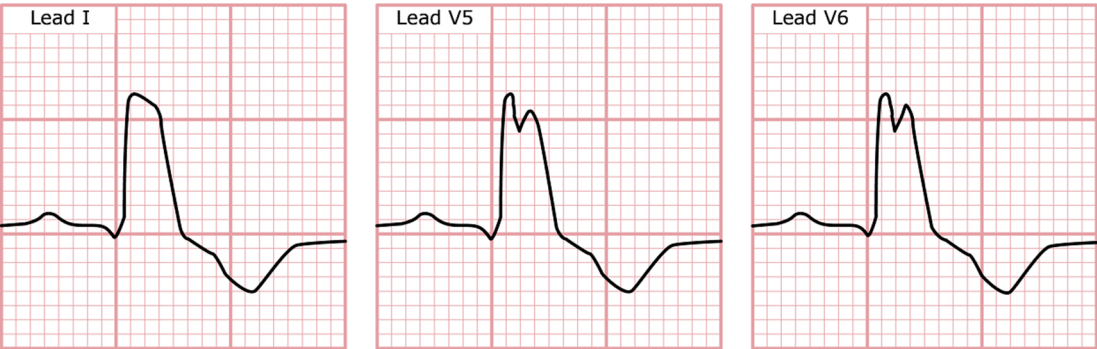


Figure 1

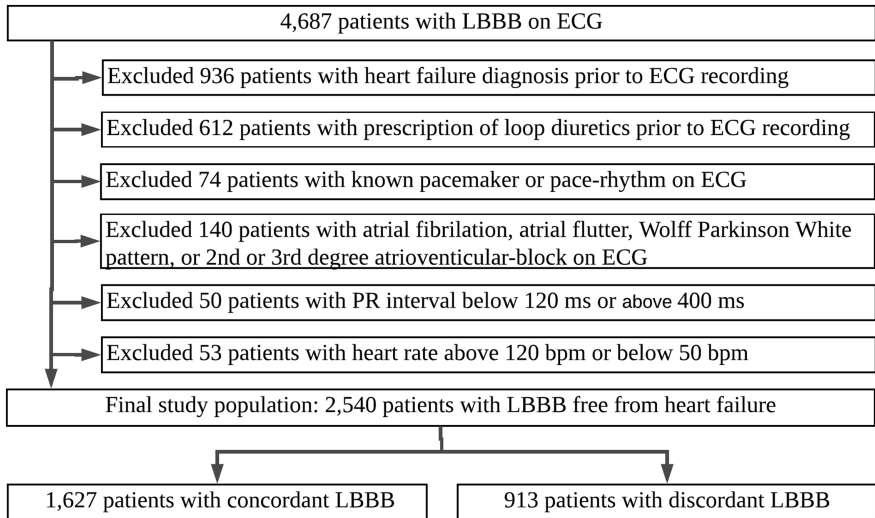


Figure 2

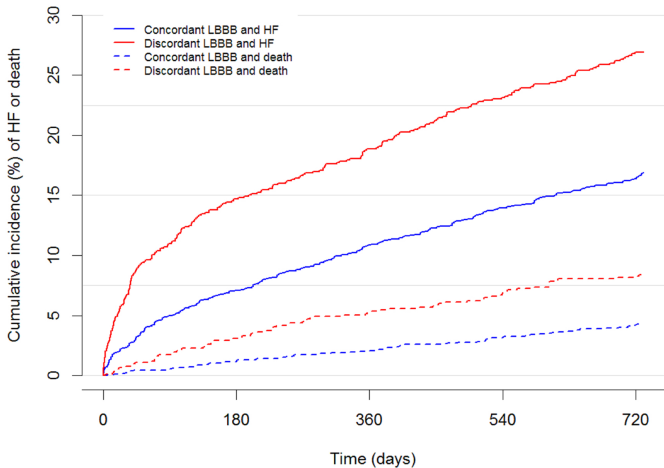


Figure 3

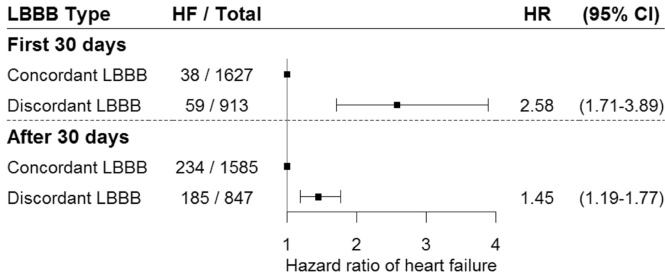


Figure 4

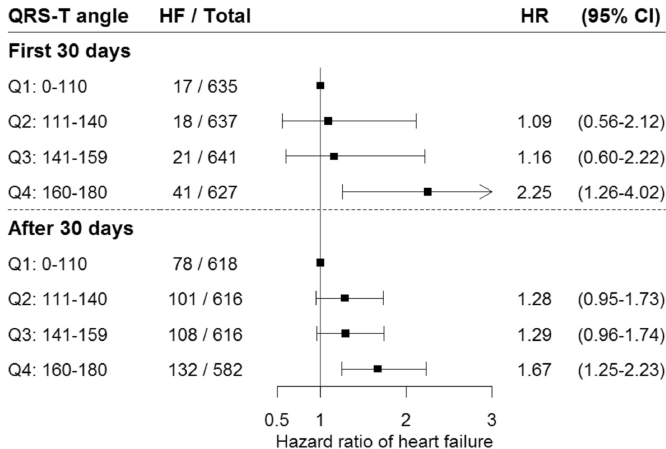


Figure 5

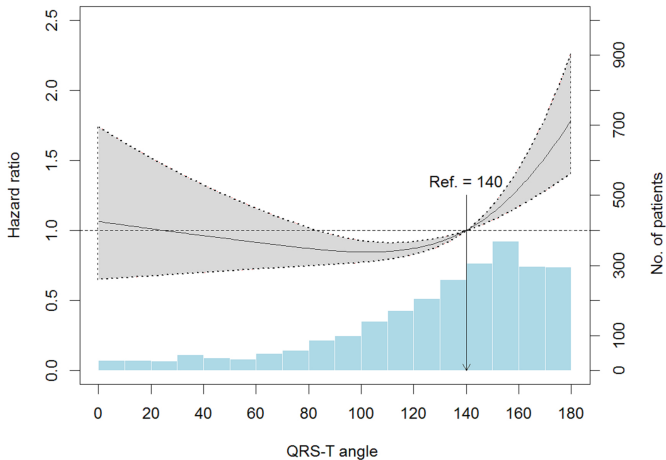


Figure 6

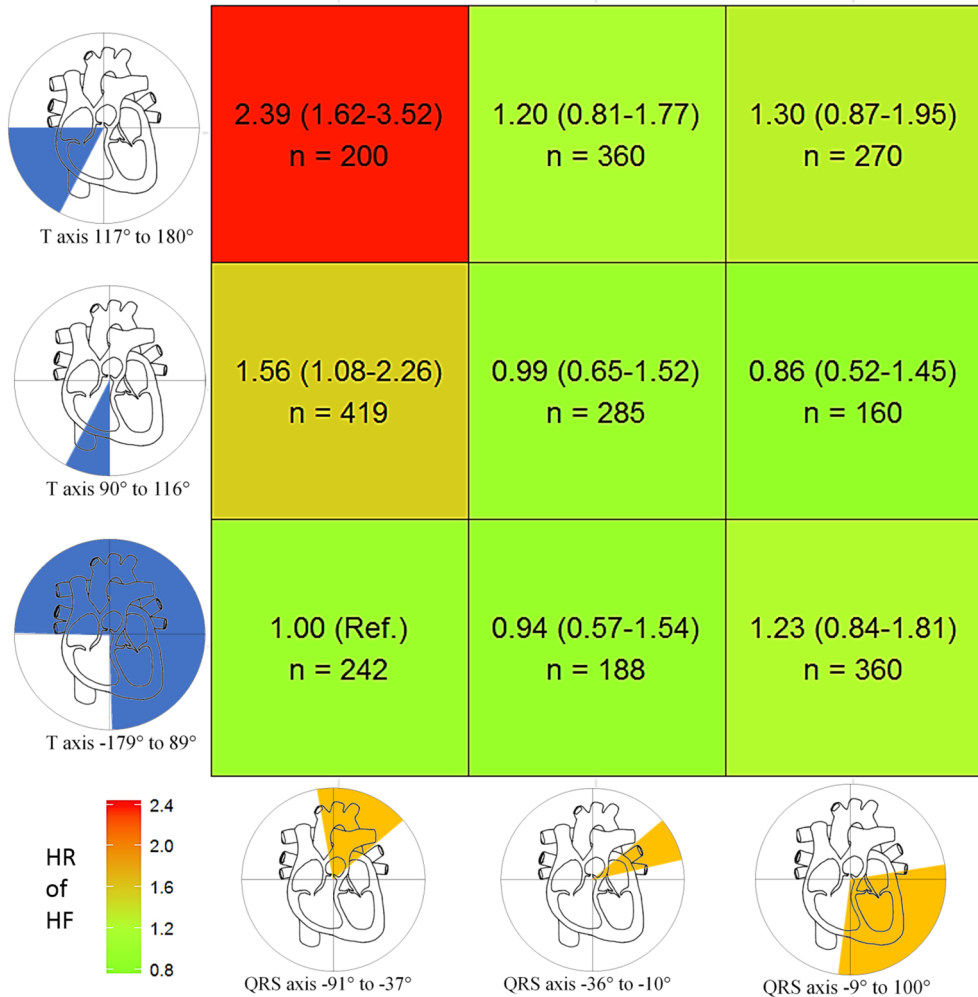


Figure 7