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CARDIAC RESYNCHRONIZATION

Evaluating Electrocardiography-Based Identification of Cardiac Resynchronization Therapy Responders Beyond Current Left Bundle Branch Block Definitions

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ABSTRACT

OBJECTIVES This study aimed to evaluate the association of 4 left bundle branch block (LBBB) definitions and their individual ECG characteristics with clinical outcome. Furthermore, it aimed to combine relevant outcome-associated electrocardiographic (ECG) characteristics into a novel outcome-based definition.

BACKGROUND LBBB morphology is associated with positive response to cardiac resynchronization therapy. However, there are multiple LBBB definitions. Associations with outcomes may differ between definitions and depend on varying contributions of the individual ECG characteristics that these LBBB definitions are composed of.

METHODS A retrospective multicenter study was conducted in 1,492 cardiac resynchronization therapy patients. Patients were classified as LBBB or non-LBBB according to definitions provided by the European Society of Cardiology, American Heart Association, MADIT-CRT (Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy) trial, and according to Strauss et al., the primary endpoint was left ventricular assist device implantation, cardiac transplantation, and all-cause mortality.

RESULTS LBBB classification differed significantly between the 4 definitions (kappa coefficients ranging from 0.09 to 0.92). The American Heart Association definition correlated the least (0.09 to 0.12) with the other definitions. Only 13.8% of patients were classified as LBBB by all definitions. During a follow-up period of 3.4 ± 2.4 years, 472 (32%) patients experienced the primary endpoint. For each LBBB definition survival analysis showed a significant association of LBBB with outcome, with relative risk reduction ranging from 39% to 43%. Each LBBB definition included characteristics that were not associated with outcome. Combining outcome-associated ECG characteristics into a novel prediction model did not significantly improve diagnostic performance (relative risk reduction 43%).

CONCLUSIONS The classification of LBBB is highly dependent on the LBBB definition used. However, each LBBB definition provides a comparable difference in risk of adverse clinical events between LBBB and non-LBBB patients. Combining individual outcome-associated ECG-characteristics into a novel prediction model does not improve association with outcome. (J Am Coll Cardiol EP 2020;6:193–203) © 2020 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACCF = American College of Cardiology Foundation

AHA = American Heart Association

AUC = area under the curve

CI = confidence interval

CRT = cardiac resynchronization therapy

ECG = electrocardiography/electrocardiogram

ESC = European Society of Cardiology

HRS = Heart Rhythm Society

LBBB = left bundle branch block

Since the first observation of left bundle branch block (LBBB) in humans by Carter (1) in 1914, the perception of LBBB has changed. LBBB was first perceived as an (innocent) electrocardiographic phenomenon, but more recently it was found to be associated with worse prognosis in both general heart disease and heart failure (2). In addition, after the clinical implementation of cardiac resynchronization therapy (CRT), it evolved into a sign of suitability for this therapy, because the presence of LBBB on 12-lead electrocardiography (ECG) is considered to reflect electrical dyssynchrony that is amenable to CRT (3-5).

Over time, several different definitions of LBBB have been proposed in large clinical CRT trials (6,7) and CRT guidelines (8,9). It is unclear to what extent these different LBBB definitions lead to differences in LBBB classification, and whether these different classifications lead to a difference in association with outcome in CRT patients.

The present study was undertaken to evaluate different LBBB definitions and their association with clinical outcome. Furthermore, we evaluated the contribution of the various individual ECG criteria that compose the various definitions and their association with outcome. Using associated ECG criteria, we designed a novel outcome-based definition and evaluated whether this might improve clinical outcome prediction in CRT patients.

SEE PAGE 204

METHODS

PATIENT POPULATION. The Maastricht-Utrecht-Groningen cohort consists of 1,492 consecutive patients, with baseline 12-lead ECG available, who received a CRT device in 3 university hospitals in the Netherlands from January 2001 up to January 2015. For the present study, we considered patients with a de novo CRT device implantation, following standard guideline indications (8). Baseline data were retrieved from local hospital patient information systems. Patient characteristics like heart failure cause and classification, comorbidities, and medication were retrieved from patient history and referral letters. Heart failure cause was deemed ischemic when there was clear evidence of myocardial infarction or coronary artery bypass graft in the medical history. Device data were retrieved from specific device databases. Left ventricular lead location was judged from the fluoroscopic images or chest x-ray. At the time of this study, the Dutch Central Committee on Human-related Research allowed 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.

ELECTROCARDIOGRAPHY. Recorded baseline 12-lead ECGs were stored digitally in the MUSE Cardiology Information system (GE Medical System, Milwaukee, Wisconsin) and were evaluated for QRS duration and baseline ECG parameters using automated ECG readings. Four trained, independent observers judged the ECGs for the presence of LBBB morphology according to 4 different definitions derived from major guidelines and large clinical trials: the European Society of Cardiology (ESC) guideline definition (8), the American Heart Association (AHA)/American College of Cardiology Foundation (ACCF)/Heart Rhythm Society (HRS) guideline definition (9,10), the MADIT-CRT (Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy) trial definition (3), the REVERSE (REsynchronization reVErses Remodeling in Systolic Left vEntricular dysfunction) trial definition (6,7), and the definition proposed by Strauss et al. (11). An example ECG is shown in **Figure 1**. Additional examples are provided in Online Figure 1.

CLINICAL STUDY ENDPOINT. The primary endpoint was a combination of left ventricular assist device implantation, cardiac transplantation, and all-cause mortality. Information was obtained from hospital records, which are linked to municipal registries. Outcome data were collected until end of follow-up (December 2015).

STATISTICAL ANALYSIS. Statistical analysis was performed using SPSS statistics software version 25

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and Biotronik. Dr. Vernooy has received research grant support from Medtronic and Abbott. Dr. Vernooy has received research grant support from Medtronic and Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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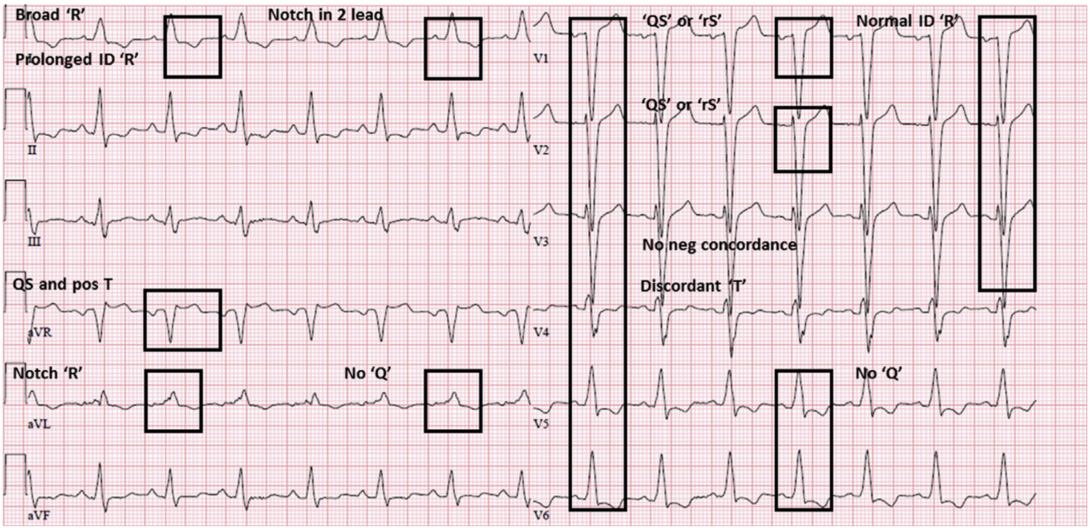
FIGURE 1 **Example Electrocardiogram With Classification of LBBB According to Multiple Definitions**



Example electrocardiogram meeting criteria for European Society of Cardiology (8) and MADIT-CRT (Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy) trial (3) left bundle branch block (LBBB) definitions. However, the absence of notching or slurring in 2 consecutive leads ($V_{5/6}$, I/aVL, or $V_{1/2}$) preclude it from qualifying as LBBB according to the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society (9,10) and Strauss et al. (11) definitions.

(IBM Corporation, Armonk, New York). Continuous and discrete variables are presented as mean ± SD and count and proportion, respectively. Dichotomous variables were compared using the chi-square test. Continuous variables were compared using the Student's *t*-test.

The degree of association between stratification by LBBB definitions was assessed using Cohen's kappa coefficient for correlation. Diagnostic performance (sensitivity, specificity, and positive and negative predictive value) of the different LBBB definitions for identifying patients without the clinical endpoint was evaluated using unadjusted receiver-operating characteristic curve analysis. The area under the curve (AUC) for tested variables was compared statistically using the DeLong method (12). Kaplan-Meier survival analyses were used when appropriate to evaluate the association between LBBB according to different definitions and clinical outcome. The log-rank test was used to determine probability values. Cox regression analysis was used to assess univariable and multivariable adjusted effects of LBBB according to different definitions on the association with the clinical study endpoint. Multivariable models were adjusted only for ECG characteristics in these analyses. A 2-sided p value <0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. A total of 1,492 patients were included in the current analysis. Baseline characteristics of the total cohort are displayed in **Table 1**. This represents a typical CRT cohort, with a mean age of 67 ± 11 years and predominantly male (71%) population. An ischemic cause of heart failure was present in 49% of patients; most patients were in New York Heart Association functional Class II to III (93%). QRS duration was 160 ± 21 ms and 15% of patients had atrial fibrillation. The subgroup of patients, qualified as LBBB by the AHA/ACCF/HRS definition (9,10), consisted of slightly but significantly more women, and in that group, LVEF was higher and left ventricular end-diastolic volume and left ventricular end-systolic volume were lower (**Table 1**).

Data on the primary endpoint of left ventricular assist device implantation, cardiac transplantation and all-cause mortality was available in 1,491 patients. One patient was lost to follow-up due to emigration.

PRESENCE OF LBBB ACCORDING TO DIFFERENT LBBB DEFINITIONS. **Figure 2** depicts the distribution of LBBB and non-LBBB QRS morphology at baseline according to the different LBBB definitions. The AHA/

TABLE 1 Baseline Characteristics of the Total Population and Different LBBB Populations

Patients, %*	Total (n = 100)	ESC (8) (n = 78)	AHA (9) (n = 14)	MADIT-CRT Trial (3) (n = 75)	Strauss et al. (11) (n = 69)
Demographics and history					
Age, yrs*	67 ± 11	67 ± 11	66 ± 10	67 ± 11	67 ± 11
Female*	29	32	34	32	34
BMI, kg/m^2	27 ± 5	27 ± 5	28 ± 5	27 ± 5	27 ± 5
Atrial fibrillation	15	13	9	13	12
Ischemic CMP	50	45	38	45	45
Diabetes mellitus	25	25	23	25	23
Hypertension	41	43	44	43	43
Echocardiographic characteristics					
LVEF, %*	25 ± 9	25 ± 9	26 ± 8	25 ± 9	24 ± 9
LVEDV, ml*	218 ± 88	217 ± 90	205 ± 82	217 ± 90	220 ± 90
LVESV, ml*	167 ± 77	167 ± 79	156 ± 71	167 ± 80	170 ± 81
NYHA functional class					
I	2	2	3	2	2
II	39	41	48	41	41
III	54	52	45	52	52
IV	5	5	4	5	5
Laboratory					
NT-proBNP, pmol/l	2,866 ± 5,017	2,868 ± 5,098	1,856 ± 2,796	2,892 ± 5,188	2,920 ± 5,283
Creatinine clearance, ml/min	71 ± 32	71 ± 33	76 ± 35	71 ± 32	71 ± 33
Medication					
Beta-blocker*	82	85	83	85	83
ACE inhibitor/ARB	90	91	90	91	91
MRA	45	44	41	44	45
Device characteristics					
CRT-D	93	93	93	93	93
ECG characteristics					
QRS duration, ms†	160 ± 21	161 ± 20	166 ± 18	163 ± 19	166 ± 18

Values are mean ± SD or %, unless otherwise indicated. *$p < 0.05$ for significance. †QRS duration was not tested for significant differences, as this is included as a criterion in LBBB definitions.

ACCF = American College of Cardiology Foundation; ACE = angiotensin-converting enzyme; AHA = American Heart Association; ARB = angiotensin receptor blocker; BMI = body mass index; CMP = cardiomyopathy; CRT-D = cardiac resynchronization therapy with defibrillator; ESC = European Society of Cardiology; HRS = Heart Rhythm Society; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; MADIT-CRT = Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

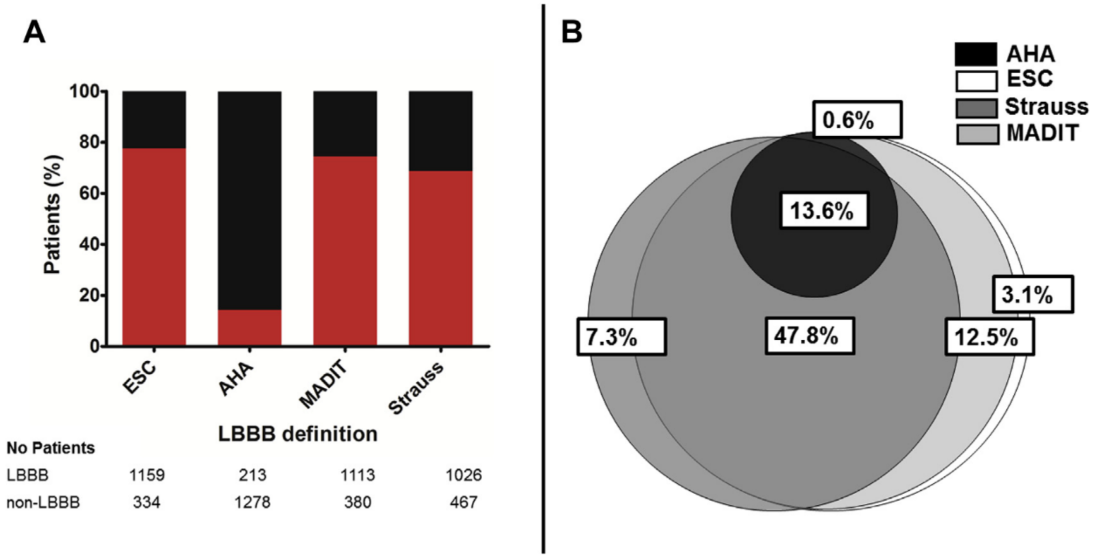
ACCF/HRS LBBB definition was the most stringent, classifying only 14% of patients as having LBBB. The other definitions, such as the ESC (8), MADIT-CRT trial (3), and Strauss et al. (11), provided rather similar proportions of LBBB-positive patients (78%, 75%, and 69%, respectively).

Only 13.6% of patients were classified as having LBBB according to all 4 definitions. The correlation of LBBB classification between the different definitions varied significantly, with kappa coefficients ranging from 0.09 between the ESC (8) and AHA/ACCF/HRS (9,10) definitions to 0.92 between the ESC (8) and MADIT-CRT trial definitions (Table 2).

FREQUENCY OF MORPHOLOGICAL CHARACTERISTICS OF DIFFERENT LBBB DEFINITIONS. Table 3 shows the frequency of individual ECG characteristics of all LBBB definitions used in this study. Although almost all ECG characteristics were highly prevalent in this CRT population (79.3% to 95.6% of patients), a broad R-wave (57.5%) and the absence of a Q-wave in the lateral leads were significantly less prevalent (63.4%). As these characteristics both belong to the AHA/ACCF/HRS LBBB definition (9), these may explain the low number of LBBB-positive patients according to this definition.

PERFORMANCE OF DIFFERENT LBBB DEFINITIONS. In a mean follow-up of 3.4 ± 2.4 years, 472 (31.7%) patients experienced the primary endpoint. Primary event rates for patients with and without LBBB morphology according to each of the definitions are shown in Figure 3. Event rates in the LBBB groups ranged from 22.9% (AHA/ACCF/HRS) to 33.3% (MADIT-CRT trial), and in non-LBBB groups from 33.3% (AHA/ACCF/HRS) to 44.1% (ESC).

FIGURE 2 **Distribution of LBBB and Non-LBBB QRS Morphology and Overlap According to Different LBBB Definitions**



No Patients				
LBBB	1159	213	1113	1026
non-LBBB	334	1278	380	467

(A) Percentage of patients classified as LBBB QRS morphology according to different LBBB definitions (European Society of Cardiology [ESC] [8], American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society [AHA] [9], MADIT-CRT trial [MADIT] [3], and Strauss et al. [11]). **Gray** represents the proportion of patients classified as non-LBBB in each definition. **(B)** Venn diagram displaying proportions of patients classified as LBBB according to different (combinations of) LBBB definitions; 15.1% of patients were not classified as LBBB by any definition.

Kaplan-Meier estimates of survival free from the primary endpoint showed significant associations with LBBB morphology for each definition ($p < 0.001$ for all) (**Figure 3**). Relative risk reduction in LBBB patients compared with non-LBBB patients according to the 4 different definitions ranged from 39% (AHA/ACCF/HRS [9] and Strauss et al. [11]) to 43% (ESC).

Diagnostic properties of the LBBB definitions are presented in **Table 4**. LBBB according to the AHA/ACCF/HRS definition had the highest specificity for predicting survival free from the primary endpoint (0.87) with a corresponding positive predictive value of 0.77. The ESC LBBB definition had the highest sensitivity (0.82) with a corresponding negative predictive values of 0.44 (**Table 4**). The AUC of the various LBBB definitions was similar for all LBBB definitions (0.53; 95% confidence interval [CI]: 0.50 to 0.56), except for the ESC definition, which showed a significantly higher AUC (0.57; 95% CI: 0.54 to 0.59; $p = 0.004$).

PERFORMANCE OF MORPHOLOGICAL CHARACTERISTICS. Three of the 11 individual ECG characteristics that made up the 4 definitions were independently associated with primary endpoint occurrence; QS or rS pattern in lead V_1; notching or slurring in lead V_5, V_6, I, or aVL and absence of a Q-wave in leads V_5, V_6, I, and aVL (**Table 3**). Strength of the associations ranged from 0.10 to 0.79.

PERFORMANCE OF OUTCOME-BASED LBBB CHARACTERISTICS. The aforementioned individual ECG characteristics that were independently associated with occurrence of the primary endpoint were combined into a novel outcome-based model. In the entire cohort, 21.7% of patients fulfilled the criteria of this model.

Of patients fulfilling model criteria, 21.9% experienced the endpoint during follow-up, compared with 33.9% in the patient group not fitting this model ($p < 0.001$). Kaplan-Meier estimates of survival free of events showed significant associations with the

TABLE 2 **Correlation of Classification as LBBB and Non-LBBB Between Different Definitions**

	ESC (8)	AHA/ACCF/HRS (9)	MADIT-CRT Trial (3)	Strauss et al. (11)
ESC	–			
AHA/ACCF/HRS	0.09	–		
MADIT-CRT trial	0.92	0.11	–	
Strauss et al.	0.41	0.12	0.50	–

Cohen's kappa between one and another LBBB definition for each possible pair of LBBB definitions. Abbreviations as in **Table 1**.

TABLE 3 **Association and Diagnostic Accuracy of Each of the LBBB Definitions for LVAD Implantation, Cardiac Transplantation, and All-Cause Mortality**

LBBB Definition	Sensitivity	Specificity	PPV	NPV	HR (95% CI)
ESC	0.82	0.31	0.72	0.44	0.57 (0.47–0.69)
AHA/ACCF/HRS	0.21	0.87	0.77	0.33	0.61 (0.46–0.79)
MADIT-CRT trial	0.79	0.34	0.72	0.42	0.59 (0.49–0.72)
Strauss	0.73	0.40	0.72	0.40	0.61 (0.51–0.73)

Values are in %. Univariable Cox regression was used to calculate hazard ratio (HR) and 95% confidence interval (CI).

LVAD = left ventricular assist device; NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Table 1.

presence of this outcome-based model ($p < 0.001$) (**Figure 4**). The unadjusted hazard ratio for event-free survival was 0.63 (95% CI: 0.50 to 0.78). Diagnostic properties showed sensitivity and specificity of 24.7% and 84.8%, respectively, with corresponding negative predictive value and positive predictive value of 33.9% and 78.1%, respectively. Diagnostic performance was not different from the aforementioned LBBB definitions (AUC: 0.55; 95% CI: 0.50 to 0.56).

DISCUSSION

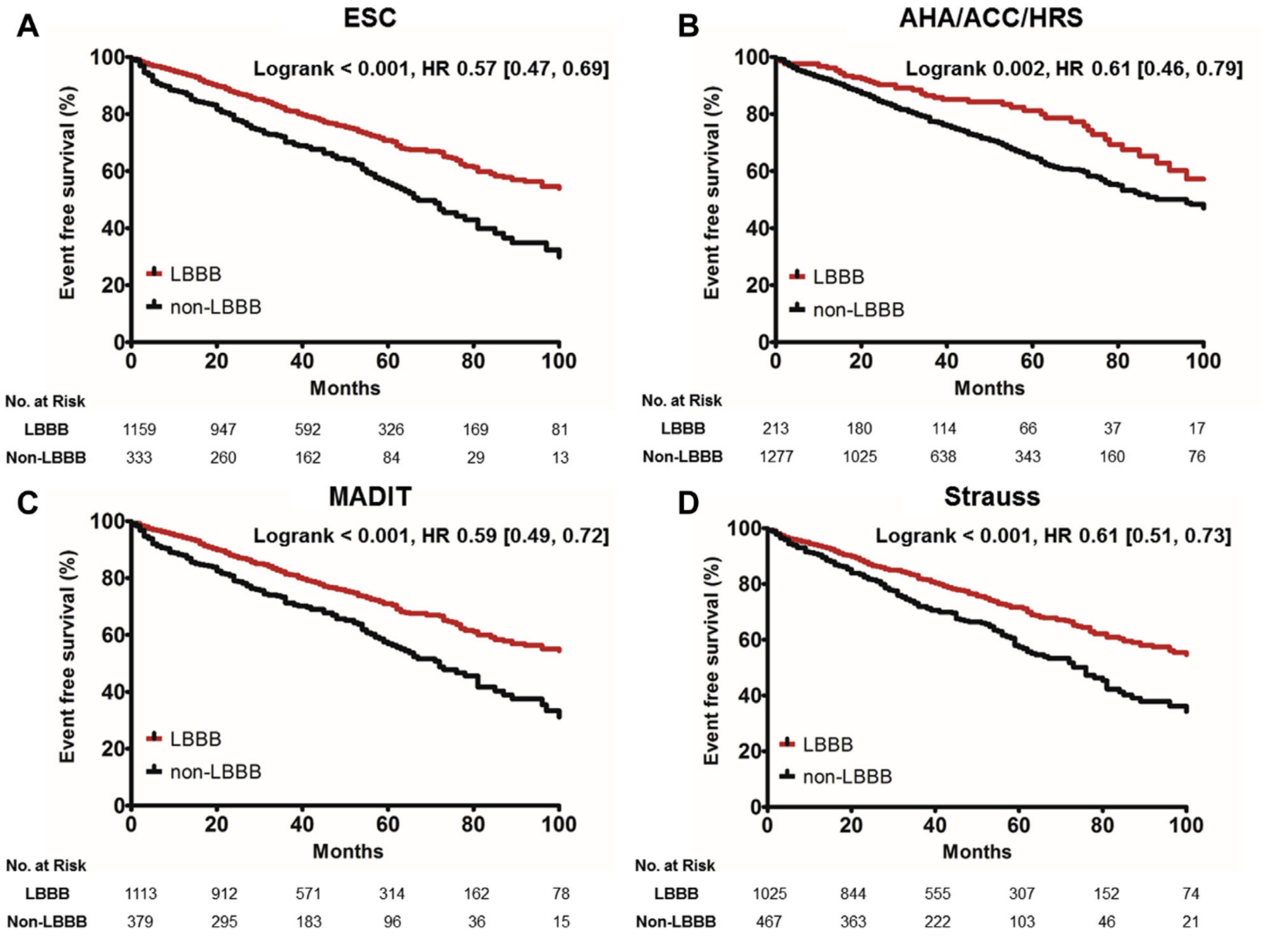
In this real-world CRT cohort, we show that there are pronounced differences in qualification of LBBB morphology and related diagnostic properties among 4 frequently used LBBB definitions. In this cohort, only 13.6% of ECGs fit all criteria of the 4 LBBB definitions. The presence of LBBB is significantly associated with survival free of the primary endpoint, without significant differences in hazard ratios between the definitions (**Central Illustration**). Interestingly, only 3 of the 11 characteristics included in any of the 4 LBBB definitions showed a significant association with clinical outcome. However, combining these 3 characteristics into an outcome-based model does not improve diagnostic characteristics beyond that of current LBBB definitions.

DIFFERENCES IN LBBB CLASSIFICATION. Despite the fact that currently LBBB is regarded as an important electrophysiological substrate for CRT response, only few previous studies have addressed the issue of the different LBBB definitions. A first finding of the present study is the large range of proportions of patients with LBBB according to the different definitions (between 18% and 78%). This may explain the large differences in the proportion of LBBB patients in landmark trials, ranging from 67% to 94% (13). One recent study, also assessing differences in LBBB definitions, showed equally large differences ranging from 29% to 61% of patients being classified as LBBB between multiple definitions (including definitions beyond the ones included in the present study). The difference in classification between various LBBB definitions seems to relate to the extensiveness of the definitions, as the AHA/ACCF/HRS (9) and Strauss et al. (11) definitions (being the most extensive and complicated) classify the lowest proportion of patients as LBBB. Definitions agree on the presence of LBBB in only 13.6% of patients. This low agreement is confirmed by the fact that correlation between definitions that result in similar prevalence of LBBB (MADIT-CRT trial 75% and Strauss et al. 69%) is only moderate (kappa coefficient = 0.50). Obviously, an LBBB definition, similar to the AHA/ACCF/HRS definition, with low prevalence is more selective as compared with definitions with higher prevalence. These differences should be recognized because they may influence decision making.

ASSOCIATION OF LBBB DEFINITIONS TO EVENT FREE SURVIVAL. Despite the difference in prevalence of LBBB according to the various definitions, the difference in clinical outcome (event-free survival) between LBBB and non-LBBB subgroups is consistently present. Although crude prevalence and definition of endpoints differ from earlier studies showing differences in outcome between LBBB and non-LBBB patients, we describe a similar difference in endpoint occurrence (33% to 44% in non-LBBB patients vs. 23% to 33% in LBBB patients). Gold et al. (4) conducted a post hoc study in the REVERSE population in which they found a 10% event rate (worsening composite clinical score, including death) in LBBB patients versus 26% event rate in non-LBBB patients in the CRT-ON group within 2 years of follow-up. In the MADIT-CRT trial, post hoc study event rates for the combined endpoint of heart failure events or mortality were 23% to 33% in non-LBBB patients and 16% for LBBB patients, as well as mortality alone (12% to 15% for non-LBBB patients vs. 7% for LBBB patients) over a 3-year follow-up period (3). The present cohort shows higher overall event rates than in the aforementioned randomized trials. This is a known phenomenon in real-life cohorts compared with randomized clinical trials. Furthermore, follow-up was slightly longer in the current analysis than in the aforementioned trials. The endpoint used in this analysis also differs from that used in MADIT-CRT and REVERSE trials, as it does not include heart failure hospitalizations or other heart failure events.

CONTRIBUTION OF INDIVIDUAL MORPHOLOGICAL CHARACTERISTICS TO ASSOCIATION WITH OUTCOME. This study is the first to evaluate individual ECG characteristics (from existing LBBB definitions) and

FIGURE 3 **Kaplan-Meier Estimates of the Time to Primary Endpoint (Combination of Left Ventricular Assist Device Implantation, Cardiac Transplantation, or All-Cause Mortality) for the ESC, AHA/ACC/HRS, MADIT-CRT Trial, and Strauss et al. (11) LBBB Definitions**



Estimates for the **(A)** ESC (8), **(B)**, American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society (AHA/ACC/HRS) (9), **(C)** MADIT-CRT trial (3), and **(D)** Strauss et al. (11) definitions. The **black line** represents patients classified as non-LBBB QRS morphology and the **red line** represents LBBB QRS morphology according to the respective definition. HR = hazard ratio; other abbreviations as in **Figure 1**.

their association with outcome in CRT patients. Theoretically, individual morphological characteristics are all related to the change in sequence and durations of electrical activation of the myocardium typically seen in LBBB (14), and therefore possibly related to clinical outcome.

QRS duration reflects the slowed activation of the myocardium without using the specialized conduction system but lacking any specific information on the direction of activation. This has been considered the main drawback of QRS duration as a diagnostic measure in patient selection for CRT (3,4,13,15,16). The current analysis confirms a lack of association of QRS duration with outcome, as none of the QRS duration-related criteria remained significantly associated with outcome in a model including characteristics from all LBBB definitions.

A hallmark feature of the more recent Strauss et al. (11) and AHA/ACCF/HRS (9) LBBB definitions is notching or slurring of the QRS complex. This aspect is thought to reflect endocardial breakthrough at the left side of the interventricular septum (first notch), after which left ventricular activation reaches the epicardial side of the left ventricular posterolateral wall (second notch), typical to LBBB activation (11). Occurrence of this ECG characteristic varies significantly among AHA/HRS/ACCF (9) and Strauss et al. (11) definitions (29% vs.

TABLE 4 **Frequencies and Univariable and Multivariable Association of ECG Characteristic per LBBB Definition and Overall With Event-Free Survival**

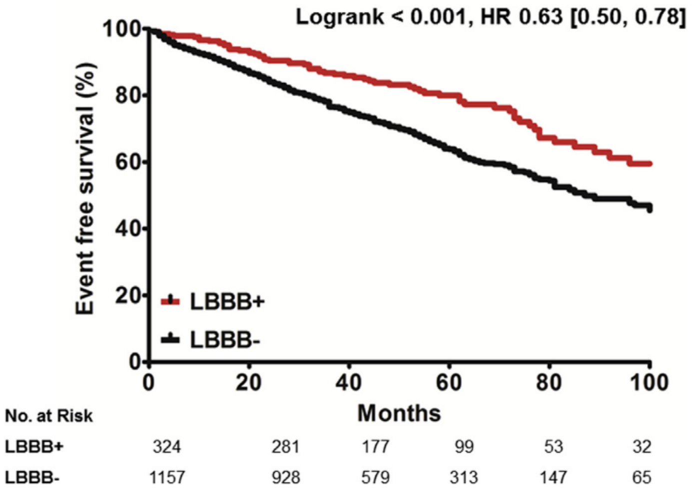
ECG Criterion	Frequency	HR (95% CI) Univariable	HR (95% CI) Multivariable Within Definition	HR (95% CI) Multivariable Overall
ESC				
QS or rS pattern in lead V_1	92.9 (1,388)	0.56 (0.41–0.76)	0.63 (0.46–0.84)	0.10 (0.01–0.75)
Broad R-wave lead V_5, V_6, I or aVL	95.6 (1,427)	0.90 (0.55–1.49)	0.97 (0.64–1.47)	–
No Q-wave in lead V_5 and V_6	83.9 (1,254)	0.66 (0.51–0.85)	0.70 (0.56–0.89)	–
AHA/ACCF/HRS				
Notch in lead V_5, V_6, I, or aVL	29.2 (436)	0.69 (0.55–0.88)	0.73 (0.58–0.93)	0.79 (0.63–0.99)
No Q-wave in lead V_5, V_6, I, and aVL	63.4 (947)	0.54 (0.44–0.66)	0.55 (0.45–0.66)	0.56 (0.45–0.69)
R peak >60 ms in lead V_5 and V_6	57.5 (858)	0.91 (0.74–1.12)	1.04 (0.85–1.26)	–
No negative concordance	82.6 (1,234)	0.99 (0.78–1.26)	0.96 (0.78–1.19)	–
MADIT-CRT trial (3)				
QRS duration ≥130 ms	93.5 (1,408)	1.10 (0.71–1.71)	1.01 (0.70–1.47)	–
QS or rS pattern in lead V_1	92.9 (1,388)	0.56 (0.41–0.76)	0.63 (0.46–0.85)	–
Broad R-wave lead V_5, V_6, I or aVL	95.6 (1,427)	0.90 (0.55–1.49)	0.96 (0.63–1.48)	–
No Q-wave in lead V_5 and V_6	83.9 (1,254)	0.66 (0.51–0.85)	0.70 (0.55–0.89)	–
Strauss et al. (11)				
♀QRS duration ≥ 130 ms, ♂QRS duration ≥140 ms	86.3 (1,300)	0.75 (0.56–0.99)	0.79 (0.62–1.02)	–
QS or rS pattern in leads V_1 and V_2	91.0 (1,359)	0.67 (0.50–0.92)	0.73 (0.55–0.97)	–
Notch in 2 consecutive leads V_1, V_2, V_5, V_6, I, and aVL	79.3 (1,184)	0.74 (0.58–0.95)	0.78 (0.62–0.98)	–

Values are % (n), unless otherwise indicated. Univariable and multivariable Cox regression was used to calculate HR and 95% CI. Multivariable regression within the LBBB definitions was conducted including all electrocardiography (ECG) characteristics composing the definition. Multivariable regression overall was conducted with univariably significantly associated ECG characteristics, not significantly interacting with each other.

Abbreviation as in Tables 1 and 3.

79%), as the AHA/ACCF/HRS (9) definition demands the presence of notching in all leads with a leftward orientation, whereas the Strauss et al. (11) definition requires only 2 consecutive leads with notching or slurring. The AHA/ACCF/HRS notching or slurring criterion remained significantly associated with the endpoint in a multivariable model of ECG characteristics (hazard ratio: 0.79).

FIGURE 4 **Kaplan-Meier Estimates of the Time to Primary Endpoint (Combination of Left Ventricular Assist Device Implantation, Cardiac Transplantation, or All-Cause Mortality) for Outcome-Based LBBB Characteristics**

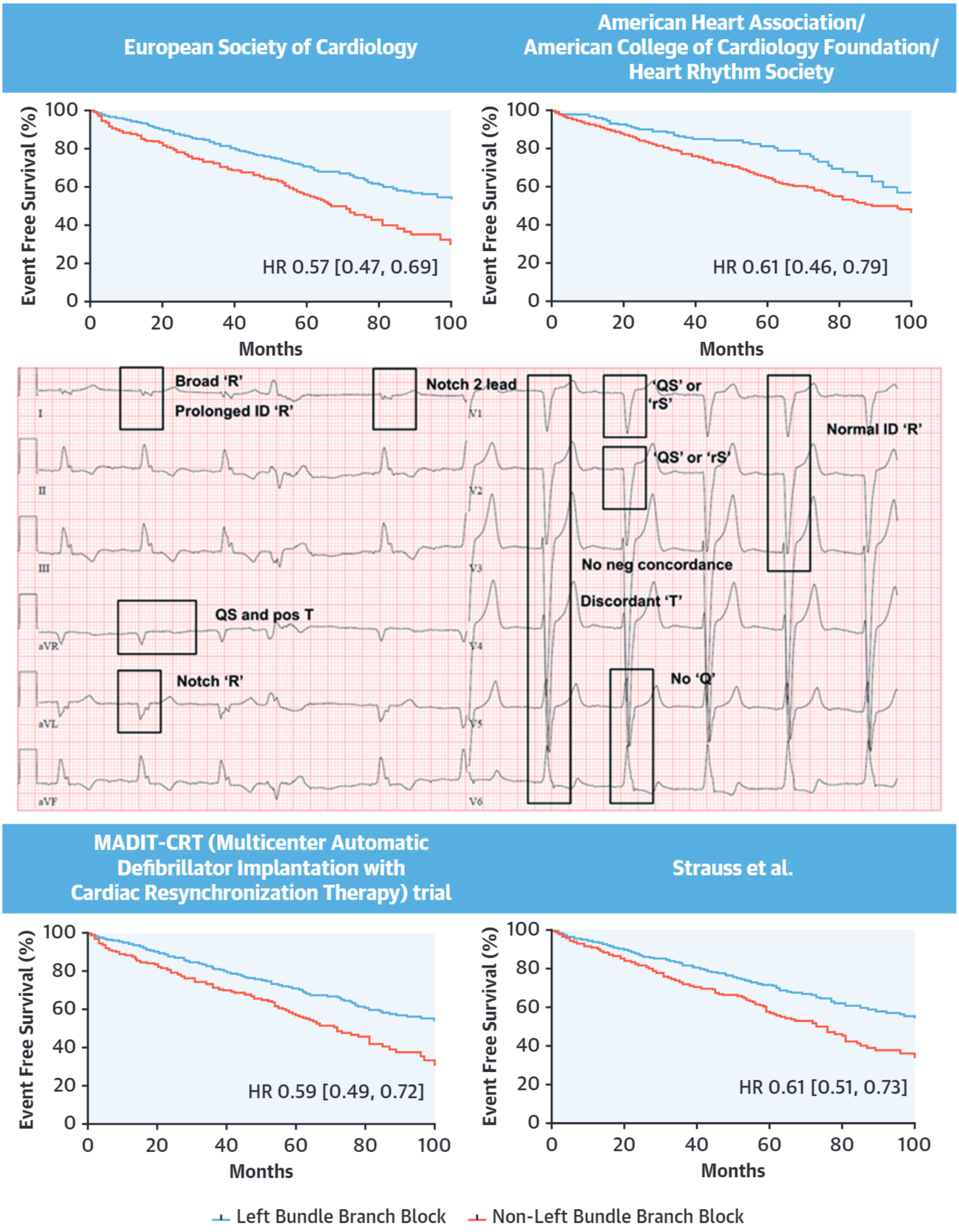


The **black line** represents patients classified as fulfilling electrocardiographic characteristics and the **red line** as patients not fulfilling electrocardiographic characteristics. Abbreviations as in Figures 1 and 3.

The presence of a QS or rS pattern in the first precordial leads (V_1 or V_1 and V_2) in LBBB definitions are explained by absence of normal initial septal left to right activation facilitated by the posterior fascicle of the left bundle branch (absence of R-wave in V_1) and subsequent slow right to left ventricular activation (broad S). A QS or rS pattern in V_1 appears to be a significant contributor to both individual LBBB definitions, as well as overall ECG characteristics association with outcome.

Furthermore, the initial activation of the intraventricular septum normally results in an initial Q-wave in leads V_5, V_6, I, and aVL, as activation travels from left to right. All but the Strauss et al. LBBB definition dictate that the initial Q-wave in the lateral leads should be absent. However, Strauss et al. (11) argue that this is not the case in the presence of septal myocardial infarction, as initial unopposed right ventricular activation will give an initial Q-wave as well. However, in the current analyses, we see that the absence of an initial Q-wave is independently associated with event-free survival in CRT patients. This contradiction to the sound argument of Strauss et al. (11) could be the result of the known lower probability of response in ischemic

CENTRAL ILLUSTRATION Left Bundle Branch Block Is Associated With Outcome Despite the Definition Used



van Stipdonk, A.M.W. et al. J Am Coll Cardiol EP. 2020;6(2):193–203.

ESC (8), American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society (9), MADIT-CRT (Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy) trial (3), and Strauss et al. (11) left bundle branch block definitions are, despite using significantly different electrocardiographic criteria, all significantly associated to the combined clinical outcome of all-cause mortality, cardiac transplantation, and left ventricular assist device implantation.

cardiomyopathy patients, which would explain the presence of Q waves in LBBB activation.

ASSOCIATION OF OUTCOME-BASED CHARACTERISTICS TO EVENT-FREE SURVIVAL. This is the first study to recombine individual ECG characteristics from different LBBB definitions, associated with clinical endpoint occurrence, into an outcome-based model. Unfortunately, the model failed to improve differentiation between clinical responders and nonresponders to CRT. This suggests that ECG parameters, recommended for classification of LBBB by current guidelines and experts, are simply not sensitive enough to truly identify patients able to respond and not specific enough to identify those that are not. Potential reasons for this mismatch are that the definition LBBB is originally not meant to predict CRT response and that late left ventricular activation, presumably linked to CRT response, also occurs in some non-LBBB patients (5,17). Accordingly, small studies using more extensive mapping indicate that the use of such techniques can improve response prediction in CRT (18,19). However, both ECG and mapping techniques lack the potential to clearly identify structural abnormalities such as scar, factors that also influence the response to CRT even in the presence of a good electrical substrate.

STUDY LIMITATIONS. Inherent to the real-world observational study design, there was no control group of patients not receiving CRT. Therefore, we cannot ascribe the association of LBBB with outcome to the effect of CRT based on the current study. However, previous analyses of landmark CRT trials including untreated patients, have shown that the association of LBBB with outcome, is indeed a treatment effect. The significant association with outcome in CRT as shown in this study can therefore be translated to a significant association with effectiveness of CRT. As this study aims to study the size of effect of the therapy, we feel that this does not impair the conclusion of the current study.

CONCLUSIONS

Currently used LBBB definitions differ significantly in the patient populations that are classified as LBBB. Regardless of the definition used, the outcome is significantly better in LBBB patients than in non-LBBB patients. Only 3 individual ECG criteria used in LBBB definitions were associated with clinical outcome, suggesting that LBBB definitions may be simplified. Combining these 3 criteria to a novel model performed as well as the more complicated LBBB definitions.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CRT remains an important part of current heart failure therapy. Current patient selection is largely based on QRS morphology criteria, which are diverse and complex. The results in this study reassure that no matter which LBBB definition is used, it is associated with better outcome in CRT. However, as different LBBB definitions classify different patients as LBBB, this will lead to heterogeneity in global CRT practice. Combining individual ECG characteristics from different LBBB definitions did not improve association with outcome.

TRANSLATIONAL OUTLOOK: As currently used LBBB definitions, nor an outcome-based approach to redefining these definitions seems to suffice in correctly differentiate responders from non-responders to CRT, we need to find another method not only identifying the same electrical substrate of LBBB, but also presenting it in a way that it can be easily and objectively interpreted.

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KEY WORDS cardiac resynchronization therapy, left bundle branch block, survival

APPENDIX For a supplemental figure, please see the online version of this paper.