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Comparison of four LBBB definitions for predicting mortality in patients receiving cardiac resynchronization therapy

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Abstract

Background: Left bundle branch block (LBBB) is considered an important prognostic parameter in cardiac resynchronization therapy (CRT). We aimed to evaluate, in a sizeable cohort of patients with CRT, long-term mortality, and morbidity according to four different electrocardiographic definitions of LBBB.

Methods: This longitudinal cohort study included consecutive patients who underwent CRT device implantation in our institution in years 2006–2014. Two endpoints were assessed: (a) death from any cause or urgent heart transplantation, and (b) death from any cause or heart failure admission. All preimplantation ECGs were analyzed by three physicians blinded to outcome and categorized as LBBB or non-LBBB according to four definitions.

Results: A total of 552 CRT patients entered survival analysis. According to the conventional definition, 350 (63.4%) patients had LBBB, and the Marriott, WHO/AHA, and Strauss definitions identified LBBB in 254 (46.0%), 218 (39.5%) and 226 (40.9%) patients, respectively. During the 9 years of observation, 232 patients died, the combined endpoint was met by 292 patients. The Strauss LBBB definition was significantly better to the other definitions in predicting survival (Kaplan–Meier analysis with comparison of C-statistics). Multivariate Cox regression model showed that LBBB was the major determinant of all-cause mortality with the Strauss definition having the lowest hazard ratio (0.51) of the four studied definitions.

Conclusions: Criteria included in various definitions of LBBB result in a diagnosis of LBBB in divergent groups of patients. Differences in LBBB definitions have clinical consequences, as patients without ‘complete/true’ LBBB probably get no mortality benefit from CRT.

KEYWORDS

cardiac resynchronization therapy, complete block, criteria, Left bundle branch block, mortality

1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) aims to improve symptoms and survival of heart failure patients by correcting delayed contraction of the lateral segments of the left ventricle induced by left bundle branch block (LBBB). The pathophysiological paradigm behind CRT is

supported by data showing that LBBB is a very important preprocedural electrocardiographic parameter determining CRT outcome. A meta-analysis of four large trials showed that CRT had no clinical benefits in patients with non-LBBB QRS morphology (Sipahi et al., 2012). However, several substantially different electrocardiographic criteria for LBBB have been used (Bertaglia et al., 2017; Hsing et al., 2011;

Surawicz, Childers, Deal, & Gettes, 2009; Wagner, 2008; Willems et al., 1985; Zareba et al., 2011). Recently, on the basis of pathophysiological considerations, endocardial mapping and computer simulations, a new definition of LBBB including longer QRS duration (≥ 130 ms in women and ≥ 140 ms in men) and the presence of at least two mid-QRS notches/slurs in leads I, aVL, V1, V2, V5, and V6 was proposed (Strauss, Selvester, & Wagner, 2011). Few studies to date have assessed the impact of different LBBB definitions on outcomes of CRT, and those studies were limited in that they compared only two LBBB definitions, assessed differences in short-term echocardiographic response, and/or included relatively small groups of patients (Bertaglia et al., 2017; Mascioli et al., 2012; Tian et al., 2013). The present study was designed to evaluate outcomes of CRT, as determined by “hard endpoints” of mortality and morbidity, in a sizeable cohort of patients and to compare outcomes according to four definitions of LBBB.

2 | METHODS

2.1 | Study population

This retrospective longitudinal cohort study included all patients who underwent CRT device implantation in our institution from February 2006 to December 2014, with outcomes for all included patients determined in June 2016. Study was approved by institutional review board (Bioethics Committee). All procedures were performed in standard fashion, with appropriate attention to put LV lead in lateral nonapical position. Baseline clinical characteristics and procedure-related data were obtained from medical records. Baseline data included preimplantation left ventricular (LV) ejection fraction (EF) and LV end-diastolic dimension (LVEDD); presence of permanent atrial fibrillation (AF) and diabetes mellitus; New York Heart Association (NYHA) functional class; use of cardiovascular drugs; serum concentration of creatinine; and etiology of heart failure etiology. Heart failure etiology was

categorized as ischemic, defined as a history of myocardial infarction or significant stenotic lesions on coronary angiography, or nonischemic. Procedure-related data included procedure success, type of device used (pacemaker or defibrillator), LV pacing threshold, and LV lead position. LV lead position was categorized as apical or nonapical and lateral or paraseptal, based on stored fluoroscopy images of right and left anterior oblique views, respectively (Jastrzebski, Wilinski, Fijorek, Sondej, & Czarnecka, 2013). Outcomes, including deaths and hospitalizations, were obtained from our outpatient department, as most patients who underwent CRT were followed up regularly, and from analysis of all available medical documentation (mainly hospital discharge notes), telephone contact with patients and their families. In the absence of any contact with a patient or family, death/life status was determined from the national PESEL registry. Hospitalizations were classified as due to worsening of heart failure, or for other reasons. Primary endpoint was defined as all-cause mortality or urgent heart transplantation and secondary as all-cause mortality or hospitalization for heart failure.

2.2 | Electrocardiographic data

Continuous 12-lead electrocardiograms (ECGs) were recorded and archived in all patients undergoing CRT device implantation. These high-quality ECGs were recorded prior to the implantation procedure on an electrophysiological system (BARD Labsystems, Boston Scientific, Boston, MA, USA), and printed at a paper speed of 25 mm/s with standard augmentation (1 mV/10 mm). QRS duration was assessed according to the global QRS method, and R wave peak delay in V6 was measured using a global method, i.e., from the earliest onset of the QRS of 12 simultaneously recorded standard ECG leads to the R wave peak in V6, as recommended by the American Heart Association (AHA) and the World Health Organization (WHO) (Surawicz et al., 2009; Willems et al., 1985). Each ECG was analyzed

	Conventional	Marriott	WHO/AHA	Strauss
QRS ≥ 120 ms	+	+	+	
QRS ≥ 130 ms (F); QRS ≥ 140 ms (M)				+
QRS ≥ 150 ms				
R peak >60 ms in V5/V6	+	+	+	
rS or QS in V1/V2 (with R peak time <60 ms)	+	+	+	+
Monophasic R in I		+	+	
Monophasic R or qR in aVL			+	
Monophasic R in V6		^a		
Notched or slurred R in ≥ 1 lead: I, aVL, V5, V6			^b	
Mid-QRS notch or slur in ≥ 2 leads: I, aVL, V1, V2, V5, V6				+
No q wave in I, V5, V6		+	+	

TABLE 1 Criteria included in the definitions of left bundle branch block (LBBB)

Notes. ^aA tiny s wave (<1 mm) in V6 was disregarded, with this type of QRS considered monophasic.

^bAccording to this definition, the notch/slur does not have to be “mid-QRS”.

by two physicians blinded to outcome, according to four different definitions of LBBB. Disagreements in LBBB/non-LBBB categorization were solved either by consensus or by ECG analysis by the third observer, supported, if necessary, by precise measurements on the electrophysiological system with high augmentation and high paper speed. Nonspecific intraventricular conduction delay was diagnosed

when QRS was ≥ 120 ms, but a diagnosis of LBBB or right bundle branch block could not be reached.

Four definitions of LBBB were evaluated in this study: conventional, Marriott, WHO/AHA, and Strauss. The criteria constellations used in these four definitions are summarized in Table 1, and examples of QRS morphologies that fit these definitions are shown in Figure 1.

FIGURE 1 Examples of QRS morphologies that fulfill different LBBB criteria. Panel a: LBBB according to all four definitions (note a slur after the R wave peak in lead I and a plateau type slur in aVL). Panel b: LBBB according to the conventional definition. Panel c: LBBB according to the Strauss definition. Panel d: LBBB according to the conventional and Strauss definitions. QRS Morphologies in panels b, c, and d do not fulfill the Marriott and WHO/AHA definitions, due to a q wave in V6/I and/or a lack of monophasic R in I/aVL. Panel e: LBBB according to all but the Marriott definition, as shown by the lack of monophasic R in V6 due to a small s wave. Panel f: LBBB according to all but the WHO/AHA definition, due to a lack of monophasic R in aVL. Panel g: LBBB according to all but the Strauss definition, due to a lack of two notches/slurs. Panel h: LBBB according to the conventional and Marriott definitions, but not the other three definitions, due to a lack of notch/slur and QRS < 150 ms. Panel i: non-LBBB according to all four definitions, as shown by the absences of slur/notch and monophasic R in V6 and intrinsicoid deflection in V6 < 60 ms, indicating a nonspecific intraventricular conduction delay. Other studies, however, have reported that this pattern is indicative of LBBB, as there is a typical rS morphology in V1 with a QRS duration of 140 ms (Cleland et al., 2013; Perrotta et al., 2016)

2.3 | Statistical methods

Continuous variables are presented as mean and standard deviation, and categorical variables as numbers and percentages. Survival to each study endpoint was assessed using the Kaplan–Meier method. The discriminative power of a single LBBB definition was measured using Harrell's C-statistic. C-statistics value were compared in order to determine which LBBB definition was significantly better in predicting survival. The effect of LBBB on survival, after adjustment for potential confounders, was analyzed using multivariate Cox proportional hazards (CPH) models. All variables believed to be clinically important were prespecified and entered into multivariate CPH models, with results presented as hazard ratios (HRs) and 95% confidence intervals (CIs). There were no significant violations of the proportionality assumption that underlies the CPH method. All statistical analyses were performed using R 3.2 software, with p -values <0.05 considered statistically significant.

3 | RESULTS

3.1 | Population and implant results

We identified 590 patients who underwent CRT device implantation procedures during the prespecified study period. Of these, 15 were excluded due to unsuccessful LV lead implantation (success rate of 97.5%); eight were excluded due to incomplete medical records; five were excluded due to late LV lead repositioning/loss of CRT; seven were excluded due to upgrade to triple site pacing (two LV leads); and three were excluded due to implementation of a non-standard resynchronization type (direct His bundle pacing, dual site RV pacing). Thus, 552 patients were further analyzed. Baseline clinical characteristics of these patients, as well as those with and without LBBB, are presented in Table 2, as are the results of CRT device implantation.

3.2 | ECG categorization according to LBBB definitions

According to the conventional definition of LBBB, 350 (63.4%) patients had LBBB, 52 (9.4%) had NIVCD, 31 (5.6%) had RBBB, 98 (17.7%) had paced QRS, and 21 (3.8%) had narrow QRS. The Marriott, WHO/AHA, and Strauss definitions identified LBBB in 254 (46.0%), 218 (39.5%), and 226 (40.9%) patients, respectively.

3.3 | Primary and secondary endpoints

During the 9 years of observation, 232 patients met the primary endpoint of death from any cause ($n = 228$) or urgent heart transplantation ($n = 4$). The survival rates at the end of years 1–7 were 89.7%, 80.7%, 70.6%, 63.6%, 57.2%, 52.7%, and 46.9%, respectively. During the same time period, 128 patients were hospitalized for unplanned heart failure-related reasons and 239 were hospitalized for other. Of the 128 patients hospitalized for unplanned heart

failure-related reasons, 68 patients eventually died. Thus, 292 patients met the combined endpoint of all-cause mortality or hospitalization for heart failure.

Kaplan–Meier curves for the two study end-points with regard to the four LBBB definitions are presented in Figures 1 and 2. C-statistics for the Strauss, AHA/WHO, Marriott, and conventional definitions were 0.581 ($p < 0.001$), 0.562 ($p = 0.001$), 0.541 ($p = 0.009$), and 0.521 ($p = 0.197$), respectively. The comparison of C-statistics showed that the C-statistic for all-cause mortality for the Strauss definition was significantly higher ($p < 0.05$) than for all other definitions with the exception of the AHA/WHO definition.

Multivariate Cox HRs for the four LBBB definitions, including other pertinent clinical variables, are presented in Tables 3 and 4. Despite inclusion of other prognostically significant variables (NYHA class, LV EF, permanent AF), the presence of LBBB was the major determinant of all-cause mortality and of the combined end-point of mortality and hospitalization for heart failure. Of the four LBBB definitions, the Strauss definition had the lowest HR (0.51).

4 | DISCUSSION

The principal findings of this study are: 1) differences in LBBB definitions are clinically significant for CRT recipients, as reflected by the differences in long-term mortality and morbidity rates, and 2) the Strauss definition of LBBB was better than other definitions, especially conventional definitions, in separating CRT recipients with good and poor long-term outcomes.

4.1 | Population studied and their mortality and morbidity rates

The patient cohort evaluated in the present study was comparable to cohorts in other large studies assessing the benefits of CRT (Bilchick, Kamath, DiMarco, & Stukenborg, 2010; Marijon et al., 2015). The short-term results of CRT device implantation, including success rate, LV lead position, and acute LV threshold, were good, and the long-term outcomes were within expected ranges. Although the death rate among our patients was higher than in patients with mild heart failure who participated in some controlled trials (e.g., MADIT-CRT), it was almost identical to the death rate observed in trials with sicker patients (e.g., COMPANION) and other large, “real life” patient cohorts, including those in the MEDICARE database and in a French registry (CeRtiTuDe) (Bilchick et al., 2010; Marijon et al., 2015). Moreover, we found that the usual determinants of long term prognosis (LV EF, permanent AF, NYHA class, heart failure etiology) were important in our patient cohort.

4.2 | LBBB definitions used in this study

Four definitions of LBBB were evaluated in this study (Table 1). The first was the conventional method, which includes universally

TABLE 2 Baseline clinical and procedure-related data in patients with and without left bundle branch block (LBBB) according to the four definitions of LBBB

	Conventional		Marriott		WHO/AHA		Strauss		
	All (n = 552)	LBBB (n = 350)	Non-LBBB (n = 202)	LBBB (n = 254)	Non-LBBB (n = 298)	LBBB (n = 218)	Non-LBBB (n = 334)	LBBB (n = 278)	Non-LBBB (n = 274)
Age (years)	67.8 ± 10.4	66.4 ± 10.6*	70.2 ± 9.6	66.9 ± 10.8*	68.6 ± 10.1	66.8 ± 11.1	68.5 ± 9.9	66.6 ± 10.7*	69.0 ± 10.0
Male sex	451 (81.7%)	275 (78.6%)*	176 (87.1%)	193 (76.0%)*	258 (86.6%)	168 (77.1%)*	283 (84.7%)	216 (77.7%)*	235 (85.8%)
DCM	203 (36.8%)	143 (40.9%)*	60 (29.7%)	110 (43.3%)*	93 (31.2%)	96 (44.0%)*	107 (32.0%)	114 (41.0%)*	89 (32.5%)
NYHA II	47 (8.5%)	31 (8.9%)	16 (7.9%)	27 (10.6%)	20 (6.7%)	23 (10.6%)	24 (7.2%)	25 (9.0%)	22 (8.0%)
NYHA III	434 (78.6%)	277 (79.1%)	157 (77.7%)	201 (79.1%)	233 (78.2%)	172 (78.9%)	262 (78.4%)	218 (78.4%)	216 (78.8%)
NYHA IV	71 (12.9%)	42 (12.0%)	29 (14.4%)	26 (10.2%)	45 (15.1%)	23 (10.6%)	48 (14.4%)	35 (12.6%)	36 (13.1%)
LVEF [%]	24.5 ± 7.6	23.5 ± 7.1*	26.3 ± 8.1	23.9 ± 7.6	25.0 ± 7.6	23.4 ± 6.3*	25.3 ± 8.3	23.5 ± 7.3*	25.5 ± 7.8
LVEDD [mm]	69.4 ± 9.4	70.8 ± 9.6*	67.1 ± 8.5	70.0 ± 9.8	68.9 ± 9.0	70.2 ± 9.9	69.0 ± 9.0	70.9 ± 9.8*	68.0 ± 8.7
Permanent AF	156 (28.3%)	77 (22.0%)*	79 (39.3%)	50 (19.7%)*	106 (35.7%)	39 (17.9%)*	117 (35.1%)	53 (19.1%)*	103 (37.7%)
QRS duration	172.7 ± 33.1	171.8 ± 26.5	174.2 ± 42.3	172.4 ± 25.8	172.9 ± 38.3	178.0 ± 24.1*	169.2 ± 37.5	180.3 ± 21.4*	164.9 ± 40.4
DM	243 (44.0%)	147 (42.0%)	96 (47.5%)	111 (43.7%)	132 (44.3%)	97 (44.5%)	146 (43.7%)	117 (42.1%)	126 (46.0%)
Creatinine [μmol/L]	107.7 ± 44.3	106.1 ± 45.4	110.4 ± 42.2	105.4 ± 47.1	109.6 ± 41.6	104.3 ± 48.4	110.0 ± 41.2	104.6 ± 45.3	110.9 ± 43.0
ACEI/ARB	479 (86.6%)	297 (84.9%)	181 (89.6%)	217 (85.4%)	261 (87.6%)	188 (86.2%)	290 (86.8%)	235 (84.5%)	243 (88.7%)
b-blocker	524 (92.6%)	332 (94.9%)	192 (95.0%)	246 (96.9%)	278 (93.3%)	212 (97.2%)	312 (93.4%)	261 (93.9%)	263 (96.0%)
Aldosterone ant.	362 (65.6%)	237 (67.7%)	125 (61.9%)	175 (68.9%)	187 (62.8%)	152 (69.3%)	211 (63.2%)	196 (70.5%)	166 (60.6%)
LV lead apical	61 (11.1%)	39 (11.2%)	22 (10.9%)	28 (11.1%)	33 (11.1%)	23 (10.6%)	38 (11.4%)	32 (11.6%)	29 (10.6%)
LV lead lateral	468 (96.1%)	295 (96.1%)	173 (96.1%)	219 (96.5%)	249 (95.8%)	187 (96.9%)	281 (95.6%)	235 (96.7%)	233 (95.5%)
CRT-P	247 (44.7%)	145 (41.4%)	102 (50.5%)	106 (41.7%)	141 (47.3%)	106 (48.6%)	141 (42.2%)	125 (45.0%)	122 (44.5%)
LV threshold [mV]	1.2 ± 0.9	1.1 ± 0.9*	1.3 ± 0.9	1.1 ± 0.9	1.2 ± 0.9	1.1 ± 0.9	1.2 ± 0.9	1.1 ± 0.9	1.3 ± 0.9

Notes. DCM: dilated cardiomyopathy, encompassing all nonischemic etiologies; NYHA: New York Heart Association functional class; LVEF: left ventricle ejection fraction; LVEDD: left ventricle end-diastolic dimension; AF: atrial fibrillation; DM: diabetes mellitus; ACEI/ARB: angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker; Aldosterone ant.: aldosterone antagonists; CRT-P: CRT device without defibrillation capacity; LV threshold: left ventricular pacing threshold.

* $p < 0.05$.

FIGURE 2 Kaplan-Meier survival curves for all-cause mortality in patients with and without left bundle branch block (LBBB) according to the four definitions of LBBB. The percentages in each panel indicate the difference in absolute 5-year mortality rates

accepted criteria such as minimal QRS duration of 120 ms and minimal morphological requirements in leads V1 and V6. Although this very sensitive definition likely includes all patients with LBBB, it also includes patients with other nonspecific disturbances in conduction due, for example, to ventricular enlargement/hypertrophy, thus reducing its specificity. Several studies have used this definition, sometimes with modifications, such as $QRS \geq 130$ ms and only assessing V1 morphology (Hsing et al., 2011; Mascioli et al., 2012).

The second definition of LBBB is the Marriott definition, a more strict conventional definition that is given with some variations in many popular ECG textbooks (Wagner, 2008). This definition is widely used and likely plays an important role in "real life" patient qualifications for CRT worldwide. Some studies have used this or a similar definition (Kronborg, Nielsen, & Mortensen, 2010). Because it includes additional morphological criteria, it is more specific, excluding some patients with nonspecific intraventricular conduction delay. However, it is less sensitive, likely

excluding some patients with complete/true LBBB, including patients with postinfarction q waves or with s waves in leads V5-V6 due to heart rotation.

The third definition of LBBB used in this study was formulated by the WHO and modified slightly by the AHA (Surawicz et al., 2009; Willems et al., 1985). This definition is more specific than Marriott's criteria, as it requires "broad notched or slurred R waves in leads I, aVL, V5, and V6". This might be interpreted as meaning that four slurred/notched leads are necessary to diagnose LBBB. However, interpretations present in the literature include the need for one notch/slur (Bertaglia et al., 2017), the need for three notched/slurred leads (Strauss, 2012), and a nonobligatory notch/slur (Perrotta et al., 2016; Zareba et al., 2011). In the current study, the presence of at least one lead with a notch/slur was deemed sufficient to fulfill the WHO/AHA definition criteria.

The fourth definition of LBBB is the recently proposed Strauss "complete/true" LBBB definition (Strauss et al., 2011). In contrast to the above definitions, which were formulated for the diagnosis

TABLE 3 Multivariate Cox regression models for all-cause mortality in patients with and without left bundle branch block (LBBB) according to the four definitions of LBBB and potential confounding variables

	ConventionalHR (CI)	MarriottHR (CI)	WHO/AHAHR (CI)	StraussHR (CI)
LBBB	0.88 (0.66; 1.17)	0.75* (0.57; 0.99)	0.58** (0.43; 0.77)	0.51** (0.38; 0.69)
Age 60–70 years	1.01 (0.69; 1.48)	1.01 (0.69; 1.47)	1.01 (0.69; 1.48)	0.88 (0.59; 1.29)
Age > 70 years	1.33 (0.92; 1.92)	1.34 (0.93; 1.94)	1.36 (0.94; 1.97)	1.20 (0.82; 1.74)
Male gender	1.06 (0.73; 1.54)	1.03 (0.71; 1.50)	1.04 (0.72; 1.52)	1.04 (0.71; 1.52)
Ischemic etiology	1.37* (1.01; 1.86)	1.33 (0.98; 1.81)	1.30 (0.96; 1.76)	1.31 (0.96; 1.77)
NYHA III	1.87 (0.91; 3.81)	1.82 (0.89; 3.73)	1.80 (0.88; 3.68)	1.90 (0.93; 3.90)
NYHA IV	4.45** (2.08; 9.54)	4.23** (1.97; 9.08)	4.37** (2.04; 9.36)	4.63** (2.16; 9.92)
AF permanent	0.82 (0.60; 1.12)	0.80 (0.59; 1.09)	0.77 (0.56; 1.05)	0.73* (0.54; 1.00)
EF 20%–30%	0.76 (0.56; 1.02)	0.76 (0.56; 1.02)	0.73* (0.54; 0.98)	0.75 (0.55; 1.01)
EF > 30%	0.60* (0.39; 0.93)	0.58* (0.38; 0.91)	0.56* (0.36; 0.87)	0.56* (0.36; 0.87)
LVEDD 60–70 mm	0.75 (0.51; 1.11)	0.74 (0.50; 1.09)	0.72 (0.49; 1.07)	0.75 (0.50; 1.10)
LVEDD > 70 mm	0.82 (0.55; 1.23)	0.81 (0.54; 1.20)	0.82 (0.55; 1.22)	0.84 (0.56; 1.24)
Diabetes mellitus	1.22 (0.93; 1.59)	1.22 (0.93; 1.59)	1.25 (0.95; 1.63)	1.27 (0.97; 1.66)
Creatinine 80–100 µmol/L	1.10 (0.73; 1.64)	1.13 (0.75; 1.69)	1.09 (0.73; 1.63)	1.07 (0.72; 1.61)
Creatinine 100–120 µmol/L	1.07 (0.70; 1.65)	1.09 (0.71; 1.67)	1.06 (0.69; 1.63)	0.99 (0.64; 1.52)
Creatinine > 120 µmol/L	1.34 (0.89; 2.01)	1.35 (0.90; 2.04)	1.29 (0.86; 1.95)	1.25 (0.83; 1.88)

Notes. HR: hazard ratio; CI: confidence interval.

* $p < 0.05$; ** $p < 0.01$.

TABLE 4 Multivariate Cox regression models for the combined end-point of all-cause mortality and heart failure hospitalizations in patients with and without left bundle branch block (LBBB) according to the four definitions of LBBB and potential confounding variables

	ConventionalHR (CI)	MarriottHR (CI)	WHO/AHAHR (CI)	StraussHR (CI)
LBBB	0.88 (0.68; 1.13)	0.82 (0.64; 1.04)	0.56 (0.43; 0.72)	0.50 (0.38; 0.66)
Age 60–70 years	0.99 (0.71; 1.37)	0.99 (0.71; 1.38)	0.98 (0.70; 1.36)	0.83 (0.59; 1.17)
Age > 70 years	1.05 (0.76; 1.45)	1.06 (0.77; 1.47)	1.06 (0.77; 1.47)	0.92 (0.66; 1.28)
Male sex	0.96 (0.69; 1.33)	0.94 (0.68; 1.31)	0.93 (0.67; 1.29)	0.93 (0.67; 1.29)
Ischemic etiology	1.19 (0.91; 1.55)	1.17 (0.89; 1.52)	1.10 (0.84; 1.44)	1.12 (0.86; 1.46)
NYHA III	1.57 (0.89; 2.76)	1.54 (0.87; 2.71)	1.51 (0.86; 2.67)	1.62 (0.92; 2.85)
NYHA IV	3.04 (1.64; 5.67)	2.93 (1.57; 5.46)	3.00 (1.61; 5.57)	3.18 (1.71; 5.91)
AF permanent	1.03 (0.79; 1.35)	1.01 (0.77; 1.33)	0.96 (0.73; 1.25)	0.92 (0.70; 1.21)
LVEF 20%–30%	0.81 (0.62; 1.06)	0.81 (0.62; 1.05)	0.78 (0.59; 1.01)	0.80 (0.62; 1.05)
LVEF > 30%	0.68 (0.46; 1.01)	0.68* (0.46; 0.99)	0.63* (0.43; 0.92)	0.64* (0.44; 0.94)
LVEDD 60–70 mm	0.81 (0.58; 1.15)	0.81 (0.57; 1.14)	0.78 (0.55; 1.11)	0.81 (0.57; 1.15)
LVEDD > 70 mm	0.86 (0.60; 1.23)	0.84 (0.59; 1.20)	0.84 (0.59; 1.20)	0.88 (0.61; 1.25)
Diabetes mellitus	1.32* (1.04; 1.67)	1.33* (1.05; 1.68)	1.35* (1.07; 1.71)	1.35* (1.07; 1.71)
Creatinine 80–100 µmol/L	1.06 (0.75; 1.51)	1.08 (0.76; 1.53)	1.07 (0.75; 1.52)	1.05 (0.74; 1.49)
Creatinine 100–120 µmol/L	1.06 (0.73; 1.55)	1.07 (0.73; 1.56)	1.06 (0.72; 1.54)	0.99 (0.68; 1.44)
Creatinine > 120 µmol/L	1.38 (0.96; 1.97)	1.39 (0.97; 2.00)	1.36 (0.95; 1.96)	1.32 (0.92; 1.90)

Notes. HR: hazard ratio; CI: confidence interval; LVEF: left ventricle ejection fraction; AF: atrial fibrillation; NYHA: New York Heart Association functional class; LVEDD: left ventricular end-diastolic dimension.

* $p < 0.05$; ** $p < 0.01$.

of uncomplicated LBBB, the Strauss definition expressly allows the presence of q waves in leads I, aVL, and V5–V6. This definition is therefore potentially more sensitive, especially in patients undergoing CRT, as all of these patients have LBBB complicated by some

myocardial disease. Moreover, this definition requires a longer QRS duration and precisely specifies the number of required leads with a notch/slur. Furthermore, the definition of notch is more precise, in that a mid-QRS notch is required.

FIGURE 3 Kaplan-Meier survival curves for the combination of all-cause mortality and hospitalization for heart failure (CHF) in patients with and without left bundle branch block (LBBB) according to the four definitions of LBBB. The percentages in each panel indicate the difference in absolute 5-year mortality rates

4.3 | LBBB-type morphologies and outcome

Earlier guidelines for cardiac pacing or CRT implantation did not include the requirement that candidates for CRT should have LBBB. Although these guidelines have been updated, the definition of LBBB has not been specified. Similarly, many studies analyzing the impact of LBBB on outcomes of CRT have not specified the criteria for LBBB or the method for measuring QRS duration (Bilchick et al., 2010; Cleland et al., 2013). Several of these studies used customized/private definitions (Hsing et al., 2011; Kronborg et al., 2010), or did not strictly adhere to a cited definition (Perrotta et al., 2016; Zareba et al., 2011). The results of the current study strongly indicate that the precise LBBB definition and ECG assessment method must be specified in studies assessing the prognostic value of LBBB morphology. The prognostic differences among LBBB definitions identified in the current study may explain the conflicting results of

studies assessing the prognostic value of LBBB morphology in CRT recipients (Cleland et al., 2013; Jastrzebski et al., 2013; Kronborg et al., 2010; Zareba et al., 2011).

The current study suggests that the conventional liberal definition of LBBB is likely insufficient to identify patients with significantly delayed activation of the lateral wall of the LV due to full LBBB since the survival rate of such LBBB patients did not differ from that of non-LBBB patients. In contrast, the other three definitions evaluated in this study did separate, although to significantly different degrees, patients with good and poor prognosis. Importantly, these definitions did not differ markedly among themselves with regard to being more or less strict, as all four identified similar numbers of patients with LBBB, albeit somewhat different patients. The superiority of the Strauss definition indicates that classic additional LBBB criteria, including lack of septal q or monophasic R waves in left ventricular leads, are less important than the requirement for a mid-QRS notch/slur.

The absolute 5-year mortality rates of patients with and without LBBB according to the Strauss definition differed by 20%, a greater difference than between patients with and without LBBB according to the other four definitions. Furthermore, absolute mortality rates were 10%–15% lower in LBBB patients according to the Strauss definition than in LBBB patients according to the conventional and Marriott criteria. Similar results were seen in the only other study that compared mortality in patients with LBBB according to the Strauss and conventional definitions, a retrospective study involving 111 patients (Mascioli et al., 2012). Moreover, patients with Strauss-defined LBBB had a better echocardiographic response to CRT than patients with conventionally defined LBBB (Tian et al., 2013), although not those with WHO/AHA defined LBBB (Bertaglia et al., 2017). The latter finding was similar to our results showing the smallest difference in long-term mortality between these two definitions, a finding that may be due to both definitions requiring a QRS notch. Although the requirement for a notch/slur was present already in the WHO/AHA definition, in our experience most clinicians are unaware of this requirement or regard it as optional (Perrotta et al., 2016; Zareba et al., 2011). This may be due to the relative imprecision in wording regarding the number of notches necessary to fulfill the WHO/AHA definition and/or to a lack of clinical studies showing the superiority of a notch/slur-based definition over the conventional definition. This drawback may be overcome by using the Strauss criteria, which focus on the mid-QRS notch/slur and provide a more precise definition of LBBB. Our results support the clinical validity of these recently developed criteria and the importance of a QRS notch/slur in defining LBBB.

5 | LIMITATIONS

This study had several limitations, including its retrospective design, its inclusion of patients at a single center, and the unavailability of complete data for all patients. However, complete clinical data and high-quality periprocedural ECG data were available for 98.6% of screened patients and the primary end-point of all-cause mortality could be determined error-free for 100% of participants, as in a prospective study. Collection of data at a single center may result in treatment bias, which could influence the treatment outcomes. However, our cohort was representative of patients who underwent CRT implantation, devices were implanted using standard approaches by experienced electrophysiologists, and the mortality rate was within the expected range.

The problem of nonresponse in CRT is multifactorial, and patient selection by ECG certainly cannot provide all answers. Optimal LBBB definition in patient selection should only be seen as one piece of the puzzle.

6 | CONCLUSIONS

Criteria included in various definitions of LBBB result in a diagnosis of LBBB in divergent groups of patients. Differences in LBBB

definitions have clinical consequences, as patients without complete LBBB get small or no mortality benefit from CRT implantation. Our finding suggest that the Strauss definition of LBBB better identifies patients with complete/true LBBB, i.e., patients with greater LV dyssynchrony and who therefore benefit more from resynchronization therapy. Perhaps CRT guidelines should recommend, a precise LBBB definition, capable of identifying patients who are likely to benefit from this type of interventional therapy.

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