ORIGINAL ARTICLE

True left bundle branch block and long-term mortality in cardiac resynchronisation therapy patients

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Abstract

Background: Left bundle branch block (LBBB) is an important qualification criterion and determinant of prognosis in cardiac resynchronisation therapy (CRT) patients.

Aim: Our goal was to investigate the long-term mortality and morbidity in a sizable cohort of patients with CRT with regard to the new strict LBBB definition proposed by Perrin.

Methods: We performed a longitudinal cohort study that included consecutive CRT patients. Primary endpoint (all-cause death) and secondary endpoint (all-cause death and hospitalisation for heart failure) were analysed. All preimplantation electrocardiograms were categorised as LBBB or non-LBBB according to the new definitions/criteria analysed.

Results: The survival analysis comprised 552 patients with CRT. The Perrin criteria, CRT guidelines class I indication criteria, and Strauss criteria were fulfilled in 38.9%, 79.4%, and 62.3% of all LBBB patients, respectively. During the nine-year study period, 232 patients died and the combined endpoint was met by 292 patients. The Perrin "true LBBB" definition criteria were inferior to the Strauss "complete" LBBB definition criteria in predicting survival as reflected by Kaplan-Meier survival curves (C-statistics). Multivariate Cox regression models showed that both LBBB definitions predicted mortality, however, the Perrin definition had a higher hazard ratio (HR 0.67) compared to the Strauss definition (HR 0.51).

Conclusions: It seems that the Perrin "true LBBB" criteria are not well-suited for the selection of CRT candidates. Perhaps they do not reflect the presence of a true/complete LBBB or exclude too many patients who, despite some residual conduction in the left bundle branch, responded well to CRT.

Key words: cardiac resynchronisation therapy, complete block, criteria, left bundle branch block, mortality

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INTRODUCTION

Cardiac resynchronisation therapy (CRT) improves heart failure (HF)-related symptoms and long-term outcome in chronic HF patients, mainly by correcting the delayed contraction of the lateral segments of the left ventricle induced by left bundle branch block (LBBB). Several clinical echocardiographic and electrocardiographic parameters predict the long-term outcome in CRT [1–6]. The prognostic importance of LBBB in patients scheduled for CRT has been especially well-studied in the past [7, 8]. However, conflicting results have made clinical recommendations uncertain. In some studies, patients with an LBBB morphology had better outcomes than patients with a non-LBBB morphology [8–10]. In other studies, no clinical difference or even a worse clinical prognosis was seen in patients with LBBB [11, 12]. However, in CRT studies, several substantially different electrocardiographic criteria for LBBB have been used. We and others have shown the importance of LBBB definition/criteria in predicting long-term mortality and
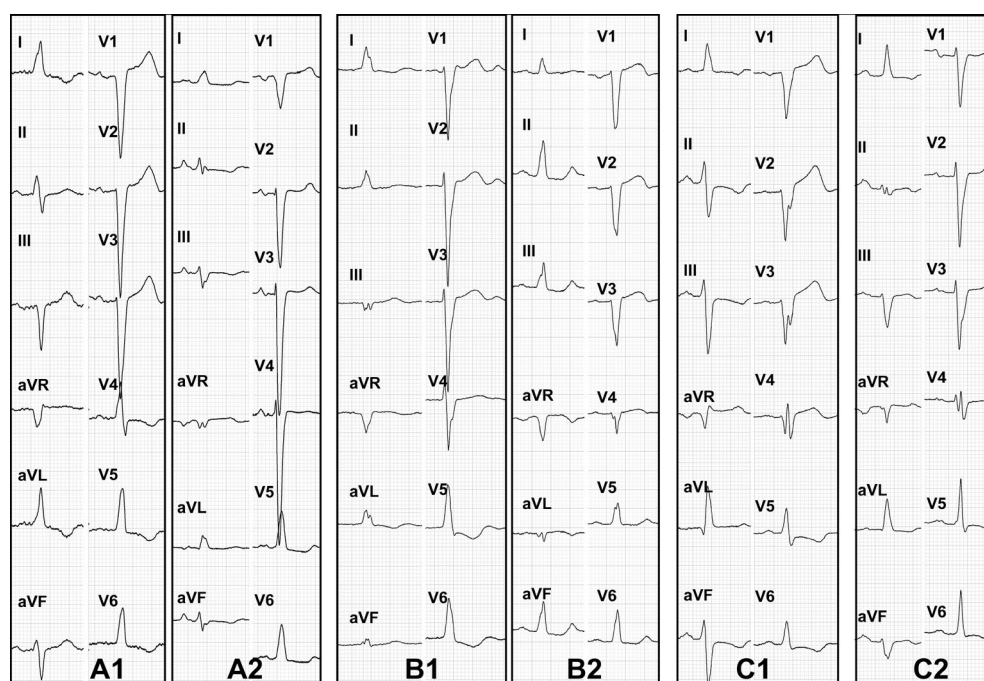
Figure 1. Examples of 12-lead electrocardiograms (ESCs) that fulfil different left bundle branch block (LBBB) criteria. **A1, A2.** Two examples of LBBB according to Padanilam/Perrin but not according to Strauss (only a single QRS with slur/notch) and not fulfilling the European Society of Cardiology (ESC) guidelines class I indications for cardiac resynchronisation therapy (CRT) (QRS < 150 ms); **B1.** LBBB according to Strauss definition and fulfilling the ESC CRT guidelines class I criteria but a non-LBBB morphology according to Perrin (r in $V_1 \geq 1$ mm); **B2.** LBBB according to Strauss definition but neither fulfilling the ESC CRT guidelines class I criteria (QRS < 150 ms) nor the LBBB criteria according to Perrin (r in V_1 and q in aVL ≥ 1 mm and no R/qR in aVL); **C1, C2.** ECGs indicating LBBB according to the ESC CRT guidelines class I/level A indications for CRT but categorised as non-LBBB according to both Perrin (q in aVL ≥ 1 mm in C1 and r in $V_1 \geq 1$ mm in C2) and Strauss LBBB definitions (lack of two QRS complexes in I, aVL, V_1–V_2, V_5–V_6 with a notch/slur)

morbidity in CRT patients, which might explain the divergent results of the clinical studies regarding the impact of LBBB on CRT outcome and help to formulate an optimal LBBB definition for CRT candidate selection [13, 14].

Recently, two new definitions were proposed with the intention to identify "complete" or "true" LBBB — theoretically, an optimal substrate for cardiac resynchronisation. Strauss et al. [15, 16], on the basis of pathophysiological data, proposed that the "complete LBBB" definition should include a 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, V_1, V_2, V_5, or V_6. Padanilam et al. [17] analysed the QRS morphology of patients with electrophysiologically-confirmed total LBBB without any residual conduction and concluded that an R wave ≥ 1 mm in V_1 points to an incomplete LBBB. On the basis of that study, Perrin et al. [18] proposed a new "true LBBB" definition that included the obligatory lack of hypothetical markers of residual left to right conduction, i.e. no R wave ≥ 1 mm in V_1 and no Q wave ≥ 1 mm in aVL. Examples of QRS morphologies that fit these two new LBBB definitions are presented in Figure 1. The Strauss definition was clinically validated by two large studies (Jastrzębski et al. [13] and Caputo et al. [14]) which showed better long-term

survival of CRT patients when the "complete LBBB" definition was fulfilled. Other studies which assessed "soft" endpoints, such as better echocardiographic or clinical response [19, 20], also supported the Strauss definition as being more suitable for LBBB diagnosis in CRT candidates. In contrast, the "true LBBB" definition by Perrin et al. [18] was validated only by the PREDICT study sub-analysis, which was limited to the assessment of short-term echocardiographic response. Neither long-term mortality/morbidity analysis nor "head-to-head" comparison with the other new stricter LBBB definition is available for the Padanilam/Perrin criteria.

Our aim was to assess, in a sizable cohort of CRT patients, the "true LBBB" definition as proposed by Perrin, with regard to the long-term mortality and morbidity, and run a comparison to the Strauss LBBB definition and to the QRS morphology compliant with the current class I CRT indications according to the recognised guidelines.

METHODS
Study group and outcome endpoints

Patients who received CRT at our institution in the period from mid-2006 to the end of 2014 were included in this retrospective analysis. Relevant clinical data and pertinent procedural

Table 1. Criteria included in the two new definitions of left bundle branch block (LBBB) and the European Society of Cardiology (ECS) class I indications for cardiac resynchronisation therapy (CRT)

	Perrin: "True LBBB"	Strauss: "Complete LBBB"	ESC CRT guidelines Class I
QRS ≥ 120 ms	+		
QRS ≥ 130 ms (female)			
QRS ≥ 140 ms (male)		+	
QRS ≥ 150 ms			+
R peak > 60 ms in V_5/V_6	+		+
rS or QS in V_1/V_2 (with R peak time < 60 ms)	+	+	+
Monophasic R in I	+		
Monophasic R or qR in aVL	+		
Notched or slurred R in ≥ 1 lead: I, aVL, V_5, V_6*	+		
Mid-QRS notch or slur in ≥ 2 leads: I, aVL, V_1, V_2, V_5, V_6		+	
No Q wave in I, V_5, V_6	+		
No Q wave ≥ 1 mm in aVL and no R wave ≥ 1 mm in V_1	+		

*The notch/slur does not have to be "mid-QRS"

data were obtained from patient medical records. Endpoint data (deaths and hospitalisations) were obtained during outpatient follow-up visits (most of our patients routinely visit our clinic for diagnostic check-ups) or telephone interviews with patients or their family members. If the patients could not be contacted (directly or indirectly), the national PESEL registry was used to check the dead or alive status. Two endpoints were analysed: primary — all-cause mortality/heart transplantation and secondary — HF hospitalisation or death from any cause.

Electrocardiographic data

Continuous 12-lead preimplantation electrocardiograms (ECGs) were recorded on an electrophysiological system (BARD LabSystems Pro, Boston Scientific, Boston, MA, USA) in all patients undergoing CRT device implantation. Both QRS duration and R wave peak delay in V_6 were measured using a global method. R wave peak delay was measured from the earliest onset of QRS in all 12 leads on a standard ECG to the R wave peak in V_6, as recommended by the American Heart Association (AHA) and the World Health Organisation (WHO) [21, 22]. ECG tracings were analysed by two physicians blinded to the outcome of the study according to three different criteria sets: the Strauss LBBB definition, the Perrin definition, and the European Society of Cardiology (ESC) guidelines class I/level of evidence A indications for CRT [23]. The Strauss LBBB definition was based on the original publication with a later modification which removed the requirement that the leads with notch/slur be "contiguous." The Perrin definition, as provided in the original publication, was based on the AHA LBBB definition with the added extra Padanilam/Perrin criteria. The ECS guidelines do not specify any LBBB definition; therefore, the guideline criteria in this study were based on the conventional LBBB definition based on V_1 and V_6 morphology with an added requirement of QRS duration > 150 ms. The three sets of criteria/definitions are summarised in Table 1.

Any disparity in classifying patients as having LBBB or non-LBBB morphology were solved by reaching consensus between the two researchers or through consulting a third investigator when necessary. Measurements were taken using precise interval measurements and morphology assessment on the electrophysiological system with high signal augmentation and a sweep speed of 100 mm/s.

A non-specific intraventricular conduction delay (NIVCD) was diagnosed when the QRS was ≥ 120 ms and the criteria for diagnosis of LBBB or right bundle branch block were not met.

Statistical analysis

Continuous variables are presented as mean and standard deviation while categorical variables are presented as number and percentage. Kaplan-Meier curves were generated to trace the survival of each study endpoint. The discriminative power of a single LBBB definition was obtained using Harrell's C-statistic. C-statistic values were compared in order to determine which LBBB definition was better at predicting survival. Cox proportional hazards (CPH) models were then used to determine the impact of LBBB on survival after adjusting for potential confounders. Variables that were deemed to have clinical relevance were preselected and entered into the multivariate CPH models. Results of these models are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). The proportionality assumption required for the CPH method was met. All statistical analyses were performed using

Table 2. Baseline clinical and procedure-related data in patients with and without left bundle branch block (LBBB) according to the different LBBB criteria and the European Society of Cardiology (ESC) guidelines QRS morphology criteria for cardiac resynchronisation therapy (CRT) class I indications

	All (n = 552)	Perrin		Strauss		ESC CRT guidelines	
		LBBB (n = 136)	Non-LBBB (n = 416)	LBBB (n = 226)	Non-LBBB (n = 326)	LBBB (n = 278)	Non-LBBB (n = 274)
Age [years]	67.8 ± 10.4	67.8 ± 11.1	67.8 ± 10.2	65.5 ± 11.1*	69.4 ± 9.7	66.6 ± 10.7*	69.0 ± 10.0
Male sex	451 (81.7)	102 (75.0)	349 (83.9)*	170 (75.2)*	281 (86.2)	216 (77.7)*	235 (85.8)
DCM	203 (36.8)	61 (44.9)	142 (34.1)*	102 (45.1)*	101 (31.0)	114 (41.0)*	89 (32.5)
NYHA II	47 (8.5)	15 (11.0)	32 (7.7)	21 (9.3)	26 (8.0)	25 (9.0)	22 (8.0)
NYHA III	434 (78.6)	109 (80.1)	325 (78.1)	181 (80.1)	253 (77.6)	218 (78.4)	216 (78.8)
NYHA IV	71 (12.9)	12 (8.8)	59 (14.2)	24 (10.6)	47 (14.4)	35 (12.6)	36 (13.1)
LVEF [%]	24.5 ± 7.6	24.4 ± 6.6	24.6 ± 7.9	23.4 ± 5.9*	25.3 ± 8.5	23.5 ± 7.3*	25.5 ± 7.8
LVEDD [mm]	69.4 ± 9.4	68.5 ± 9.4	69.8 ± 9.4	70.7 ± 9.4*	68.6 ± 9.3	70.9 ± 9.8*	68.0 ± 8.7
Permanent AF	156 (28.3)	29 (21.3)	127 (30.6)*	37 (16.4)*	119 (36.6)	53 (19.1)*	103 (37.7)
QRS duration	172.7 ± 33.1	176.8 ± 24.0	171.3 ± 35.5*	180.5 ± 24.2*	167.3 ± 37.2	180.3 ± 21.4*	164.9 ± 40.4
Diabetes mellitus	243 (44.0)	62 (45.6)	181 (43.5)	97 (42.9)	146 (44.8)	117 (42.1)	126 (46.0)
Creatinine [µmol/L]	107.7 ± 44.3	101.0 ± 39.7	109.9 ± 45.5*	103.4 ± 48.0	110.7 ± 41.2	104.6 ± 45.3	110.9 ± 43.0
ACEI/ARB	479 (86.6)	115 (84.6)	363 (87.3)	192 (85.0)	286 (87.7)	235 (84.5)	243 (88.7)
β-blocker	524 (92.6)	131 (96.3)	393 (94.5)	216 (95.6)	308 (94.5)	261 (93.9)	263 (96.0)
Aldosterone antagonist	362 (65.6)	93 (68.4)	269 (64.7)	162 (71.2)*	201 (61.7)	196 (70.5)	166 (60.6)
LV lead apical	61 (11.1)	16 (11.9)	45 (10.8)	28 (12.4)	33 (10.2)	32 (11.6)	29 (10.6)
LV lead lateral	468 (96.1)	112 (96.6)	356 (96.0)	193 (97.5)	275 (95.2)	235 (96.7)	233 (95.5)
CRT-P	247 (44.7)	78 (57.4)	169 (40.6)*	102 (45.1)	145 (44.5)	125 (45.0)	122 (44.5)
LV pacing threshold [mV]	1.2 ± 0.9	1.2 ± 1.0	1.2 ± 0.9	1.1 ± 0.9*	1.3 ± 0.9	1.1 ± 0.9	1.3 ± 0.9

Data are presented as number (percentage) or mean ± standard deviation.
*$p < 0.05$
ACEI/ARB — angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AF — atrial fibrillation; CRT-P — cardiac resynchronisation therapy pacemaker; DCM — dilated cardiomyopathy, encompassing all non-ischaemic aetiologies; LV — left ventricular; LVEDD — left ventricular end-diastolic dimension; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association functional class

the R 3.2 software (the R Foundation for Statistical Computing, Vienna, Austria) with p-values < 0.05 considered statistically significant.

RESULTS

Population and implant results

The inclusion criteria were met by 590 patients who underwent CRT device implantation during the previously specified study period. Of these, 38 patients were excluded: 15 due to an unsuccessful left ventricular (LV) lead implantation (a success rate of 97.5%), eight due to incomplete medical records, five due to a late LV lead repositioning/loss of CRT, seven due to a necessary upgrade to triple-site pacing (two LV leads), and three due to the usage of a non-standard resynchronisation approach (i.e. direct His bundle pacing, dual-site right ventricular pacing). As a result, 552 patients were left in the dataset. Baseline clinical characteristics, the presence or absence of LBBB, and the outcomes of CRT device implantation are presented in Table 2.

ECG categorisation according to LBBB definitions

According to the conventional definition of LBBB (rS/QS morphology in V_1 and R peak in $V_6 \geq 60$ ms, QRS ≥ 120 ms), 350 (63.4%) patients had LBBB, 52 (9.4%) had NIVCD, 31 (5.6%) had right bundle branch block, 98 (17.7%) had paced QRS, and 21 (3.8%) had a narrow QRS. The Perrin and Strauss definitions and the CRT ESC guideline criteria were fulfilled in 136 (24.6%), 218 (39.5%), and 278 (50.4%) of all patients, respectively, and in 38.9%, 62.3%, and 79.4% of patients with LBBB according to the conventional definition.

During the nine-year investigatory period, 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 one to seven were 89.7%, 80.7%, 70.6%, 63.6%, 57.2%, 52.7%, and 46.9%, respectively. During this same period, 128 patients were hospitalised for an exacerbation of HF symptoms and 68 of these patients eventually died. Consequently, 292 patients met the combined secondary endpoint of all-cause mortality or hospitalisation for HF (232 patients who died and 60 patients who had HF exacerbations but survived).

Kaplan-Meier curves for the two study endpoints with regard to the Perrin definition, CRT guidelines, and Strauss criteria are presented in Figure 2. C-statistics for the Perrin definition, CRT guidelines criteria, and Strauss criteria for all-cause mortality were 0.547 (p = 0.004), 0.542 (p = 0.036), and 0.581 (p < 0.001), respectively, and for the secondary combined endpoint of all-cause mortality and HF hospitalisation they were 0.557 (p < 0.001), 0.553 (p = 0.003), and 0.581 (p < 0.001), respectively. The comparison of C-statistics showed that the Padanilam/Perrin definition was inferior to the Strauss definition for predicting all-cause mortality (p = 0.039) but not for predicting the secondary combined endpoint of all-cause mortality and HF hospitalisation (p = 0.101); no differences in C-statistics between Perrin and ESC CRT guidelines class I criteria were present for the primary (p = 0.745) or secondary endpoint (p = 0.985).

Multivariate Cox HRs for the three LBBB definitions/criteria, including other pertinent clinical variables, are presented in Tables 3 and 4. The presence of LBBB according to the Perrin definition was associated with all-cause mortality and the combined end-point of all-cause mortality and hospitalisation for HF. Prognostic value of the Perrin definition was similar to the prognostic value of the ECS CRT guidelines criteria and lower than the prognostic importance of the Strauss definition.

DISCUSSION

To our best knowledge, this is the largest cohort study with the longest follow-up to date that examines the new "true LBBB" definition proposed by Perrin et al. [18]. The major finding of the current study is that the Perrin definition seems less useful for the prediction of outcome in CRT patients. Firstly, the Perrin definition was much more exclusive because it was fulfilled by only 38.9% of all LBBB patients, whereas the Strauss definition and ESC CRT guidelines class I QRS morphology criteria were met by 62.3% and 79.4% of patients, respectively. This is an unfavourable characteristic for the potential use for CRT patient selection. Based on the known non-responder rate of approximately 30%, it can be speculated that an optimal LBBB definition should not exclude more than 30% of patients with LBBB morphology. Secondly, the absolute difference in all-cause mortality at six years between patients with and without LBBB according to this definition was 11%, which was much less than the 20% difference seen when the Strauss definition was applied. This was also reflected by the significant difference in C-statistics between these two LBBB definitions. Results for the combined endpoint of all-cause mortality and HF hospitalisations were very similar.

A possible explanation for the observed findings is that the R wave ≥ 1 mm in V_1 is, after all, not a marker for left-to-right ventricular septum activation that indicates residual conduction over the left bundle branch. Wellens [24] suggests that larger R waves in V_1 might result from unopposed activation of the free wall of the right ventricle, which produces an activation vector directed at lead V_1. Such a situation takes place in patients with LBBB and after a large anteroseptal myocardial infarction that causes the absence or diminished right-to-left activation of the interventricular septum.

Another possible explanation is that the presence of residual LBBB conduction is not important from the perspective of mechanistic paradigm behind CRT. Probably, when the Strauss LBBB features are present in the ECG, the delay in the left bundle conduction must be significant enough and residual conduction might not play any important role in alleviating the delay of the activation of the lateral LV wall. Moreover, an R wave ≥ 1 mm in V_1 and/or Q ≥ 1 mm in aVL
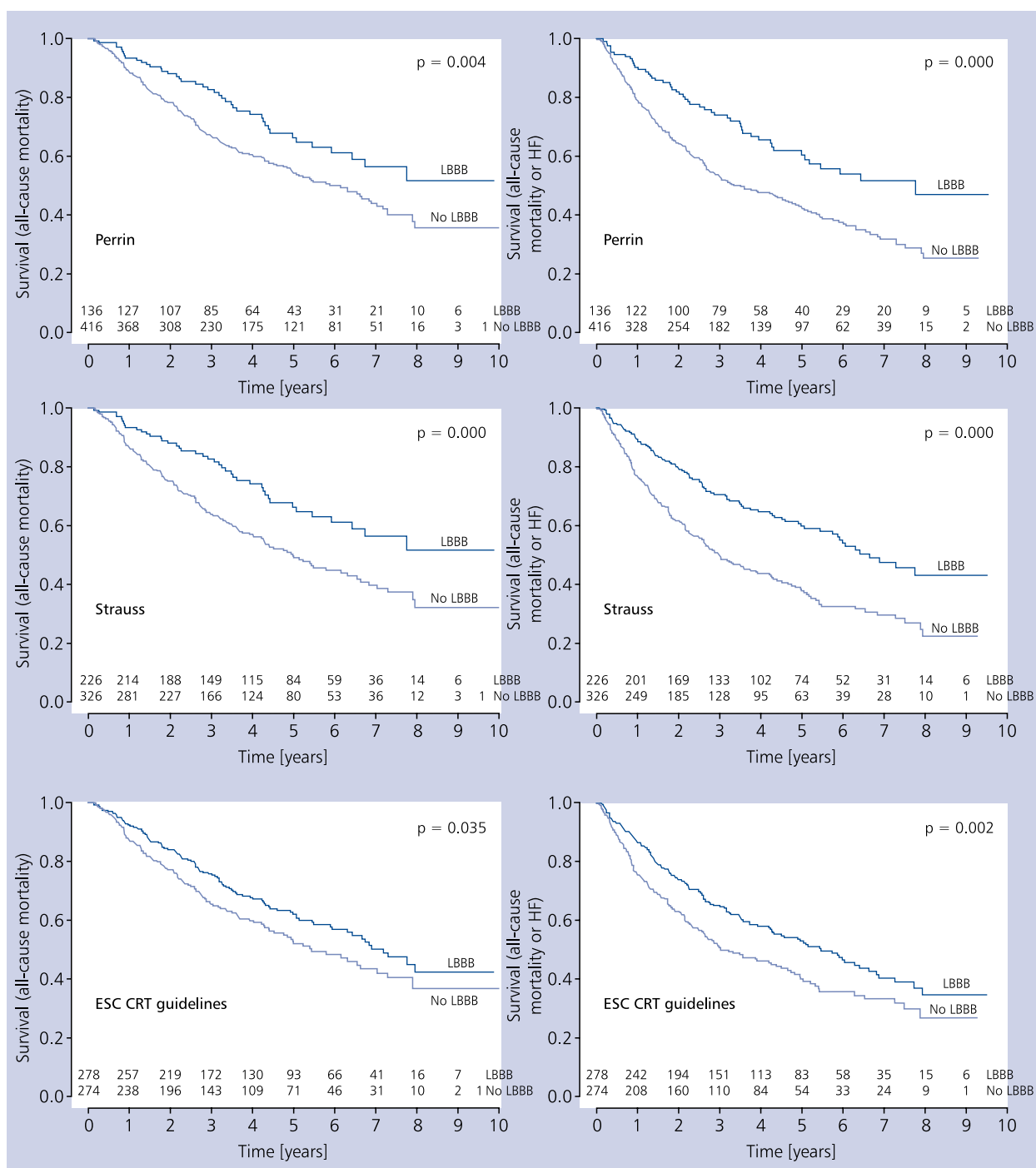
Figure 2. Kaplan-Meier survival curves for two endpoints: all-cause mortality and the combination of all-cause mortality and hospitalisation for heart failure (HF) with regard to the two different definitions of left bundle branch block (LBBB; Perrin and Strauss) and the European Society of Cardiology (ESC) guidelines class I (level of evidence A) for cardiac resynchronisation therapy

might be related to the residual conduction in the left septal fascicle only (no conduction in the left anterior and posterior fascicles of the left bundle branch). Such a situation probably results in the asynchronous activation of the LV, similar to the activation seen in complete LBBB (when LV is also activated from the interventricular septum via breakthrough points from the right ventricular depolarisation). Therefore, despite some residual left bundle conduction, the asynchrony might be large enough to warrant CRT and relate to a better prognosis post CRT. If this is the case, then the exclusion of

Table 3. Multivariate Cox regression models for all-cause mortality in patients with and without left bundle branch block (LBBB) according to the Perrin and Strauss definitions and the European Society of Cardiology (ESC) guidelines QRS morphology criteria for cardiac resynchronisation therapy (CRT) class I indications with regard to potential confounding variables

	HR (95% CI)		
	Perrin	**Strauss**	**ESC CRT guidelines**
LBBB	0.67* (0.48–0.95)	0.51** (0.38–0.69)	0.73* (0.56–0.96)
Age 60–70 years	1.02 (0.70–1.50)	0.88 (0.59–1.29)	0.99 (0.68–1.45)
Age > 70 years	1.36 (0.94–1.97)	1.20 (0.82–1.74)	1.31 (0.90–1.90)
Male sex	1.05 (0.72–1.53)	1.04 (0.71–1.52)	1.05 (0.72–1.54)
Ischaemic aetiology	1.34* (0.99–1.82)	1.31 (0.96–1.77)	1.35 (1.00–1.83)
NYHA III	1.82 (0.89–3.72)	1.90 (0.93–3.90)	1.88 (0.92–3.84)
NYHA IV	4.30** (2.00–9.21)	4.63** (2.16–9.92)	4.54** (2.12–9.72)
Permanent AF	0.83 (0.61–1.12)	0.73 * (0.54–1.00)	0.78 (0.57–1.07)
LVEF 20%–30%	0.75 (0.56–1.01)	0.75 (0.55–1.01)	0.76 (0.56–1.02)
LVEF > 30%	0.61* (0.40–0.95)	0.56* (0.36–0.87)	0.58* (0.38–0.90)
LVEDD 60–70 mm	0.76 (0.51–1.12)	0.75 (0.50–1.10)	0.75 (0.51–1.10)
LVEDD > 70 mm	0.82 (0.55–1.23)	0.84 (0.56–1.24)	0.83 (0.56–1.23)
Diabetes mellitus	1.24 (0.95–1.62)	1.27 (0.97–1.66)	1.22 (0.93–1.59)
Creatinine 80–100 μmol/L	1.10 (0.73–1.64)	1.07 (0.72–1.61)	1.10 (0.73–1.65)
Creatinine 101–120 μmol/L	1.07 (0.72–1.60)	0.99 (0.64–1.52)	1.06 (0.69–1.63)
Creatinine > 120 μmol/L	1.30 (0.87–1.96)	1.25 (0.83–1.88)	1.32 (0.88–1.98)

*p < 0.05; **p < 0.01; CI — confidence interval; HR — hazard ratio; other abbreviations — see Table 2

Table 4. Multivariate Cox regression models for the combined endpoint of all-cause mortality and heart failure hospitalisations in patients with and without left bundle branch block (LBBB) according to the Perrin and Strauss definitions and the European Society of Cardiology (ESC) guidelines QRS morphology criteria for cardiac resynchronisation therapy (CRT) class I indications with regard to potential confounding variables

	HR (95% CI)		
	Perrin	**Strauss**	**ESC CRT guidelines**
LBBB	0.58** (0.43–0.79)	0.50** (0.38–0.66)	0.68* (0.53–0.88)
Age 60–70 years	0.98 (0.71–1.37)	0.83 (0.59–1.17)	0.95 (0.68–1.33)
Age > 70 years	1.07 (0.77–1.48)	0.92 (0.66–1.28)	1.02 (0.74–1.41)
Male sex	0.94 (0.68–1.30)	0.93 (0.67–1.29)	0.95 (0.68–1.31)
Ischaemic aetiology	1.15 (0.88–1.49)	1.12 (0.86–1.46)	1.16 (0.89–1.51)
NYHA III	1.52 (0.86–2.68)	1.62 (0.92–2.85)	1.58 (0.90–2.79)
NYHA IV	2.90** (1.56–5.40)	3.18** (1.71–5.91)	3.11** (1.67–5.79)
Permanent AF	1.03 (0.79–1.34)	0.92 (0.70–1.21)	0.97 (0.74–1.27)
LVEF 20%–30%	0.79 (0.61–1.04)	0.80 (0.62–1.05)	0.81 (0.62–1.05)
LVEF > 30%	0.68 (0.47–1.00)	0.64* (0.44–0.94)	0.65* (0.45–0.96)
LVEDD 60–70 mm	0.81 (0.58–1.15)	0.81 (0.57–1.15)	0.81 (0.57–1.14)
LVEDD > 70 mm	0.86 (0.60–1.22)	0.88 (0.61–1.25)	0.87 (0.61–1.24)
Diabetes mellitus	1.34* (1.06–1.70)	1.35* (1.07–1.71)	1.32* (1.04–1.67)
Creatinine 80–100 μmol/L	1.04 (0.73–1.48)	1.05 (0.74–1.49)	1.07 (0.75–1.52)
Creatinine 100–120 μmol/L	1.05 (0.72–1.53)	0.99 (0.68–1.44)	1.05 (0.72–1.54)
Creatinine > 120 μmol/L	1.34 (0.94–1.93)	1.32 (0.92–1.90)	1.37 (0.95–1.97)

*p < 0.05; **p < 0.01; abbreviations — see Tables 2 and 3

patients with an R wave ≥ 1 mm in V_1, despite other features pointing to a true LBBB (notches, QRS duration), results in the inclusion of good CRT responders into the non-LBBB group and hence the small difference in mortality between LBBB and non-LBBB subgroups — as was observed in the current study.

We have previously assessed the prognostic value of the Strauss definition and compared it with three other LBBB definitions [13]. That study showed the superiority of the Strauss definition over the conventional, Marriott and WHO/AHA definitions of LBBB [13]. However, in that study we did not assess the new Perrin definition and we failed to compare these definitions with the QRS morphology fulfilling the highest level of indications for CRT according to the recognised guidelines. Some studies suggest that QRS duration is more important than QRS morphology (i.e. LBBB vs. non-LBBB) [11]. The CRT guidelines on QRS morphology criteria for class I//level of evidence A potentially combine the "best of both worlds" — both LBBB morphology criteria and QRS duration criteria. However, such QRS morphology criteria were never compared against new, stricter LBBB definitions. These issues were addressed in the current study: the completion of the ESC CRT guideline QRS criteria was found to be inferior to fulfilment of the refined LBBB morphology criteria alone (Strauss definition). This suggests that the QRS duration is less important than the diagnosis of a complete LBBB. Similarly, compliance with the Perrin "true LBBB" criteria did not surpass the completion of the "complete LBBB" definition by Strauss. The only other study that assessed the "true LBBB" definition was the analysis performed on the patients included in the PREDICT study by Perrin et al. [18]. In that analysis, only a three-month echocardiographic response was assessed; therefore, it is not directly comparable with the current study, which, for the first time, assessed the prognostic value of these criteria with regard to the "hard endpoint" of mortality and morbidity, had a much longer follow-up, and was based on a much larger cohort (552 vs. 40 patients). However, the percentage of LBBB/NIVCD patients in whom "true LBBB" criteria were fulfilled was similar in both studies: 30% in the study by Perrin et al. [18] vs. 34% in the current study. This points to a similar ECG assessment methodology, the exclusive nature of these criteria, and the comparability of the studied groups.

The strengths of our study include the large sample size of the analysed patients, the availability of complete medical data and ECG recordings for almost all participants, and the long follow-up period. The sizable number of patients meeting the primary endpoint, with lack of cases whose status could not be determined, ensures the reliability of mortality data. The limitations are typical for any type of retrospective, longitudinal, single-centre cohort study. There is a possibility of the presence of unmeasured confounding variables not accounted for during this investigation. The single-centre design could lead to the possibility of the introduction of treatment bias, which could have influenced the outcome of the CRT. The patient cohort evaluated in the present study were comparable to cohorts in other large studies assessing the outcomes of CRT, increasing the reliability of the presented results. Devices were implanted using standard approaches by several experienced electrophysiologists and the mortality rates were within the expected range for patients predominantly in New York Heart Association class III.

In conclusion, it seems that the "true LBBB" criteria proposed by Perrin et al. [18] are not well-suited for the selection of CRT candidates, due to the fact they do not reflect the presence of a true LBBB. The results of this study add further evidence to the fact that the new LBBB definition proposed by Strauss is superior to other QRS morphological criteria in identifying good CRT responders. This is possibly related to better identification of patients with complete LBBB or a significant delay of the left ventricular free wall that is correctable with biventricular pacing.

Conflict of interest: *none declared*

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WHAT IS NEW?

For the first time, an evaluation of the strict left bundle branch block (LBBB) criteria recently proposed by Perrin et al. was performed in a sizable cohort of patients with cardiac resynchronisation therapy (CRT). To our best knowledge, this is the first study assessing the Perrin LBBB definition with regard to the long-term mortality and morbidity and the only "head-to-head" comparison of this definition with the other increasingly recognised strict LBBB criteria proposed by Strauss. The study also offers the first comparison of the prognostic impact of QRS morphology that combines both bundle branch criteria and extra QRS duration requirements as proposed by the European Society of Cardiology CRT guideline indications (class I, level of evidence A), versus both Perrin and Strauss strict LBBB definitions. The major practical application of these novel findings is that the Perrin LBBB definition is not advantageous when compared to the Strauss LBBB definition; our data do not support the notion that it should be preferred for CRT candidate selection. The other practical conclusion is that the presence of a substantial R wave in V_1 probably should not be considered as a clue that LBBB is not complete.