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Association of left bundle branch block definitions with response to cardiac resynchronisation therapy in patients with congestive heart failure

Aim	To compare diagnostic significance of different criteria for complete left bundle branch block (cLBBB) in prediction of reverse left ventricular (LV) remodeling associated with cardiac resynchronization therapy (CRT).
Material and methods	This study included 93 patients (men, 81.7%; mean age at the time of implantation, 56.6±9.3 years). Achievement of a maximum decrease in LV end-systolic volume (ESV) was recorded during the entire follow-up period for evaluation of LV reversibility by CRT. Based on the dynamics of LV ESV, patients were divided into two groups, non-responders (n=27) and responders (n=66). cLBBB was determined by 9 criteria (ESC 2006 and 2013, AHA 2009, Strauss, and MIRACLE, CARE-HF, MADIT-CRT, REVERSE, and RAFT used in large multicenter studies).
Results	Incidence of cLBBB was significantly higher in the group of responders as demonstrated by the AHA (p=0.001), ESC 2013 (p=0.014), Strauss (p=0.002), MADIT-CRT (p=0.014), REVERSE (p=0.013), and RAFT (p<0.001) criteria. The highest specificity was shown for the AHA and RAFT (92.6%) criteria, and the highest sensitivity and overall accuracy were shown for the Strauss (80.3% and 72.04%, respectively) criterium. The criteria proposed in actual clinical guidelines (AHA and ESC 2013) demonstrated a strong consistency in detecting cLBBB (κ=0.818, 95% CI, 0.7–0.936; p<0.001). However, the Strauss and ESC 2006/AHA/ESC 2013 showed the least consistency in identifying cLBBB. For the criteria described in large multicenter studies, consistency in detecting cLBBB was minimal in most cases. However, criteria with moderate or strong consistency were used in the studies, which results have substantiated the use of cLBBB as a selection criterium (MADIT-CRT, REVERSE, and RAFT).
Conclusion	The reversibility of LV remodeling associated with CRT was different in patients with cLBBB determined by different criteria. All actual cLBBB criteria (AHA, ESC 2013, and Strauss) were significantly more frequently observed in the responder group. Nevertheless, these criteria differed in their sensitivity and specificity. A number of large multicenter studies have used criteria with minimal consistency in detecting cLBBB, which should be taken into account in interpreting results of these studies.

Keywords Heart failure; cardiac resynchronization therapy; left bundle branch block

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Introduction

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with chronic heart failure (CHF) with reduced left ventricular ejection fraction (LVEF) and ventricular conduction disorders. It is intended to resynchronize ventricular electrical activity, thus restore myocardial contractility and improve the functional class (FC) of HF. The rate of hospital admissions for CHF decompensation decreases, and the survival of patients increases [1]. However, 9 to 68% of patients (depending on the response criteria: hemodynamic, clinical, or combined) do not benefit from the treatment [2]. Different response criteria have a low correlation with each other. Less pronounced improvement of symptoms and lesser reverse remodeling of LV in CRT are not always associated with a lesser improvement of prognosis in CRT [2, 3].

Careful selection of patients for CRT is one of the main ways to increase the efficacy of resynchronization [4]. In the large multi-center trials, a complete left bundle branch block (cLBBB) was recognized as a key selection criterion for CRT [5–8]. However, two meta-analyses of the results of those trials did not show a significant relationship of QRS morphology with the reduced risk

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of all-cause mortality, hospitalization for CHF, and death, which is why the use of this selection criterion is often questioned [9, 10]. The lack of a consistent approach in determining the QRS morphology may be an explanation for these contradictions [11].

There are many criteria for the definition of cLBBB that include various electrocardiographic signs. However, the cLBBB criteria differ in the current clinical practice guidelines of the American Heart Association (AHA) and the European Society of Cardiology (ESC), and in the large multi-center trials assessing the QRS morphology [5–7, 12–15]. The significance of differences between the cLBBB criteria is unknown. Thus, it is of immediate interest to compare the efficacy of CRT in patients with cLBBB defined by the known criteria.

Objective

Compare the diagnostic significance of various cLBBB criteria in the prediction of reverse LV remodeling in CRT.

Material and methods

A total of 93 patients included in the Register of Cardiac Resynchronization Therapy Procedures were examined (81.7% of male patients, mean age at the time of implantation 56.6±9.3 years old) [16]. The primary inclusion criteria are QRS duration ≥120 ms, no continuous pacing, New York Heart Association (NYHA) FC II–IV CHF, LVEF ≤35%. The mean follow-up period from the implantation to the completion of the study or patient death was 39 [16; 61] months. Patients were examined at baseline before the implantation of a pacemaker, in 1 and 3 months, and every 6 months during the entire follow-up period. The achievement of the maximum decrease in LV end-systolic volume (ESV) during the entire follow-up period was included in the estimation of the reversibility of LV remodeling in CRT. Depending on the dynamics of LVESV, patients were divided into two groups: non-responders (a decrease in LVESV <15% of baseline, n=27) and responders (a decrease in LVESV≥15%, n=66) [17]. Mortality was considered from the day of the visit when first response criteria were detected to the day of death or the last day of the study in the responder group and from the day of the first visit (to estimate the response) to the day of death or the last day of the study in the non-responder group. All patients received the best possible drug therapy under the current guidelines [8]. Clinical characteristics of patients are provided in Table 1. 12-Lead electrocardiogram was performed at the rate of 50 mm/s in a Poly-Spectrum-8/E system (signal bandwidth: 0.05–250 Hz; line filter: 50/60 Hz; 1 mm/mV; Neurosoft, Russia) and a CORINA Cardiosoft system (signal bandwidth: 0.08–150 Hz; line filter: 50/60 Hz; 1 mm/mV; General Electric, USA). The QRS duration was measured only automatically.

Table 1. Patients' clinical characteristics

Parameter	Responders (n=66)	Non-responders (n=27)	p
Age (years)	57.5 [53; 62]	55 [49; 60]	0.18
Sex (male), n (%)	54 (81.8)	22 (81.5)	0.97
Smoking status, n (%)	14 (21.2)	10 (37)	0.11
Follow-up period (months)*	36.5 [12.75; 70.25]	22 [13; 37]	00.03
Mortality, n (%)	13 (19.7)	11 (40.7)	0.035
Mortality per 100 person-years	5.57	19.5	–
CAD, n (%)	41 (62.1)	20 (74.1)	0.27
FC III-IV, n (%)	27 (40.9)	17 (63)	0.053
Hypertension, n (%)	51 (77.3)	20 (74.1)	0.74
AF, n (%)	18 (27.3)	5 (18.5)	0.34
DM, n (%)	8 (12.1)	6 (22.2)	0.22
MI, n (%)	24 (36.4)	16 (59.3)	0.043
QRS (ms)	168.5 [149.5; 187.75]	148 [138; 164]	0.006
LVEF, %	32 [27; 34]	30.5 [27.75; 34]	0.64
6MWD (m)	344 [290; 405]	290 [232; 348]	0.033
CRT-D, n (%)	45 (68.2)	23 (85.2)	0.093

* In the responder group, the follow-up period was calculated from the day of the visit when first response criteria were detected to the last day of the study or the day of death; in the non-responder group, from the day of the first visit the last day of the study or to the day of death. The follow-up period from the time of implantation to the last day of the study or the day of death was 45.5 [23.25; 75.75] months in the responder group and 21 [13; 38] months in the non-responder group. CAD, coronary artery disease; FC, NYHA functional class; AF, atrial fibrillation; DM, diabetes mellitus; MI, myocardial infarction; LVEF, left ventricular ejection fraction; 6MWD, 6-minute walk distance; CRT-D, cardiac resynchronization therapy with defibrillation.

Table 2. Electrocardiographic signs included in the cLBBB criteria

Criteria	Signs								
	ESC 2006	AHA 2009	Strauss 2011	ESC 2013	MIRACLE	CARE-HF	MADIT-CRT	REVERSE	RAFT
QRS duration (ms) ≥	120	120	F – 130, M – 140	120	130	120	130	120	120
QS or rS in V_1	+	-	+	+	-	+	+	+	–
Monophasic QS in V_1	-	-	-	-	+	-	-	-	–
Positive T-wave in V_1	+	-	-	-	-	-	-	-	–
Normal ID R in V_1–V_3	-	+	-	-	-	-	-	-	+
ID R in V5 ≥ 60 ms	-	+	-	-	-	-	-	-	+
ID R in V6 ≥ 60 ms	+	+	-	-	-	-	-	-	+
ID R in I ≥ 60 ms	+	-	-	-	-	-	-	-	–
Monophasic R-wave in V_6	-	-	-	-	+	-	-	-	–
Notched / smoothed R-wave in I, aVL, and V_5 V_6	-	+	-	-	-	-	-	+	+
Notching/slurring in the middle of QRS at least in two leads: V_1–V_2, V_5–V_6, I, and aVL	-	-	+	-	-	-	-	-	–
Wide R-wave (with frequent notching and slurring) in I, aVL, and V_5–V_6	-	-	-	+	-	-	+	-	–
Notched / smoothed R-wave in I and V_6	-	-	-	-	-	+	-	-	–
No q-wave in V_5 V_6	-	+	-	+	-	+	+	+	+
No q-wave in lead I	-	+	-	-	-	+	-	-	+
QS with positive T-wave in aVR	+	-	-	-	-	-	-	-	–
rS in aVF	-	-	-	-	-	+	-	-	–
Discordant T-wave	+	+	-	-	-	+	-	-	–

cLBBB, complete left bundle branch block; ID, intrinsicoid deflection, f, female, m, male. We analyzed the electrocardiographic signs (if any) mentioned in the articles to arrange cLBBB criteria used in large multi-center trials.

cLBBB was defined by 9 criteria (suggested by ESC 2006 and 2013 [7, 18], AHA 2009 [12], developed by Strauss et al. [19] and used in large multi-center trials or relevant sub-analyzes: MIRACLE, CARE-HF, MADIT-CRT, REVERSE, RAFT [5, 6, 13–15]). Each criterion included 3 to 8 electrocardiographic signs (Table 2), which were independently identified by two experts. If their opinions differed, an electrocardiographic sign was evaluated by a third master-level expert. Each sign was evaluated individually, and cLBBB was diagnosed only if all signs included in a certain criterion were present. According to Almer et al. and Clark et al., notching was defined as a sudden change in the direction of an ascending or descending wave at an angle of ≥90° and slurring as a sudden change in the direction at an angle from 0 to 90° [20, 21].

The statistical analysis was performed using the IBM SPSS Statistics 25 software suite. The normality of the distribution was tested using the Kolmogorov-Smirnov/Lilliefors test and the Shapiro-Wilk test. The quantitative data are expressed as M±SD (where M is the arithmetic mean and SD is the standard deviation) for the normal distribution and Me [25;75] (the median and the interquartile range between 25th and 75th percentiles) for the non-normal distribution.

The Student's t-test was used for the analysis of normally distributed qualitative variables, and the non-parametric Mann–Whitney test was used for the non-normal distribution. The analysis of categorical data was carried out using Pearson's chi-squared test. Cohen's kappa coefficient (κ) was calculated to assess the consistency of the cLBBB criteria. The κ coefficient <0.2 corresponded to the absence of consistency; κ=0.21–0.39 to the minimal consistency; κ=0.40–0.59 – weak consistency; κ=0.6–0.79 – moderate consistency; κ=0.8–0.9 – strong consistency; and κ>0.9 – almost ideal consistency [22]. The differences between the parameters studied were significant at $p<0.05$.

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Results

The percentage of responders and non-responders with cLBBB defined by various criteria is shown in Table 3.

In the responder group, cLBBB was statistically more common as defined by the criteria suggested in the AHA 2009 and ESC 2013 current clinical practice guidelines, and the criteria developed by Strauss et al. Only 29 patients were diagnosed with cLBBB by the AHA, ESC 2013, and Strauss criteria at the same time, which 42% of patients with cLBBB defined by either of these criteria. Statistically significant differences between groups were also found by the MADIT-CRT, REVERSE, and RAFT criteria.

Despite the high specificity of the AHA and RAFT criteria (92,6%) and high predictive value of the favorable outcome (93.6% and 93.9%, respectively), these criteria allowed to define cLBBB in less than half of respondents (Table 3, 4). On the other hand, among all criteria, the Strauss criterion has the highest sensitivity (80.3%) and the predictive value of the adverse outcome (51.9%), but it allowed us to identify cLBBB in almost half of the non-responders (Table 4). The criterion used in the REVERSE study showed the most well-balanced but relatively low rates of sensitivity and specificity. It should be noted that all criteria had a relatively high predictive value of the favorable outcome and low predictive value of the adverse outcome. The criterion developed by Strauss et al. demonstrated the highest total accuracy.

The κ coefficient analysis of the criteria suggested in the clinical practice guidelines and by trial teams established a minimal consistency between the Strauss and ESC 2006/AHA/ESC 2013 criteria for the definition of cLBBB (Table 5). At the same time, the criteria suggested in the current clinical practice guidelines (AHA and ESC 2013) were highly consistent in the definition of cLBBB.

Table 3. Percentage of patients with cLBBB

	All patients (n=93)	Responders (n=66)	Non-responders (n=27)	p
ESC 2006, n (%)	38 (40.9)	30 (45.5)	8 (29.6)	0.16
AHA 2009, n (%)	31 (33.3)	29 (43.9)	2 (7.4)	0.001
Strauss 2011, n (%)	66 (71)	53 (80.3)	13 (48.1)	0.002
ESC 2013, n (%)	39 (41.9)	33 (50)	6 (22.2)	0.014
MIRACLE, n (%)	19 (20.4)	16 (24.2)	3 (11.1)	0.154
CARE-HF, n (%)	27 (29)	22 (33.3)	5 (18.5)	0.153
MADIT-CRT, n (%)	39 (41.9)	33 (50)	6 (22.2)	0.014
REVERSE, n (%)	53 (57)	43 (65.2)	10 (37)	0.013
RAFT, n (%)	33 (35.5)	31 (47)	2 (7.4)	<0.001

The consistency of the cLBBB definition criteria described in large multi-center trials was minimal in most cases (Table 6). However, trials that justified the inclusion of cLBBB as a selection criterion (MADIT-CRT, REVERSE, RAFT) used criteria with moderate or high consistency.

Discussion

After the publication of subanalyses of multi-center trials MADIT-CRT and REVERSE, cLBBB was recognized as an essential selection criterion for CRT, which found its way into the Russian and foreign clinical guidelines [5–7]. The diagnostic significance of cLBBB was later confirmed in other large multi-center trials [15]. However, the beneficial effect of CRT was also observed in multi-center trials in patients with a wide QRS complex without cLBBB. Many researchers question the use of cLBBB as a selection criterion for CRT [13, 15, 23]. Cleland et al. conducted an individual meta-analysis of five randomized trials (CARE-HF, MIRACLE, MIRACLE ICD, REVERSE, and RAFT). They showed

Table 4. Diagnostic significance of various cLBBB criteria in respect of reverse LV remodeling in CRT

	Sensitivity	Specificity	Predictive value of the positive result	Predictive value of the negative result	Accuracy
ESC 2006, %	45.5 [38.3–51.3]	70.4 [52.8–84.6]	78.9 [66.4–89]	34.5 [25.9–41.5]	52.7 [42.5–60.9]
AHA, %	43.94 [37.5–46.4]	92.59 [76.8–98.7]	93.55 [79.8–98.9]	40.32 [33.5–43]	58.06 [48.9–61.6]
Strauss, %	80.3 [73.5–86.5]	51.85 [35.2–67]	80.3 [73.5–86.5]	51.85 [35.2–67]	72.04 [62.4–80.8]
ESC 2013, %	50 [42.9–55.1]	77.78 [60.3–90.1]	84.62 [72.5–93.2]	38.89 [30.2–45.1]	58.06 [47.9–65.2]
MIRACLE, %	24.2 [18–27.6]	88.9 [73.6–97]	84.2 [62.5–95.7]	32.4 [26.9–35.4]	43 [34.2–47.7]
CARE-HF, %	33.3 [26.5–37.9]	81.5 [64.8–92.6]	81.5 [64.8–92.6]	33.3 [26.5–37.9]	47.3 [37.6–53.8]
MADIT-CRT, %	50 [42.9–55.1]	77.78 [60.3–90.1]	84.62 [72.5–93.2]	38.89 [30.2–45.1]	58.06 [47.9–65.2]
REVERSE, %	65.15 [57.9–71.4]	62.96 [45.3–78.3]	81.13 [72.1–88.9]	42.5 [30.6–52.8]	64.52 [54.3–73.4]
RAFT, %	46.97 [40.5–49.5]	92.59 [76.8–98.7]	93.94 [81–98.9]	41.67 [34.6–44.4]	60.22 [51–63.8]

Table 5. Consistency of cLBBB criteria suggested in the clinical guidelines and by trial teams

Trial	κ value	p
ESC 2006 - AHA	0.519 [0.34–0.69]	< 0.001
ESC 2006 - Strauss	0.241 [0.08–0.398]	0.005
ESC 2006 - ESC 2013	0.535 [0.36–0.709]	< 0.001
AHA - Strauss	0.264 [0.128–0.399]	0.001
AHA - ESC 2013	0.818 [0.7–0.936]	< 0.001
Strauss - ESC 2013	0.335 [0.18–0.49]	< 0.001

κ, Cohen's kappa.

Table 6. Consistency of cLBBB criteria used in large multi-center trials

Trial	κ value	p
MIRACLE - CARE-HF	0.199 [0–0.41]	0.048
MIRACLE - MADIT-CRT	0.334 [0.156–0.51]	< 0.001
MIRACLE - REVERSE	0.245 [0.108–0.38]	0.001
MIRACLE - RAFT	0.377 [0.18–0.57]	< 0.001
CARE-HF - MADIT-CRT	0.354 [0.166–0.54]	< 0.001
CARE-HF - REVERSE	0.309 [0.15–0.468]	< 0.001
CARE-HF - RAFT	0.412 [0.218–0.606]	< 0.001
MADIT-CRT - REVERSE	0.664 [0.52–0.807]	< 0.001
MADIT-CRT - RAFT	0.865 [0.76–0.969]	< 0.001
REVERSE - RAFT	0.587 [0.44–0.734]	< 0.001

κ, Cohen's kappa.

that the duration of a QRS complex, but not its morphology, was statistically significantly associated with a decrease in the risk of mortality of all causes of hospitalization for CHF and death [9].

The use of heterogeneous cLBBB definition criteria is one of the possible explanations of controversial results of the trials [11]. In 2014, van Deursen et al. were the first to compare the ESC, AHA, Strauss, MADIT-CRT, and REVERSE criteria at the same time [24]. Patients with cLBBB defined by the Strauss criteria showed the most significant decrease in LVESV 6 months after the implantation.

In our study, the rates of all relevant criteria of cLBBB (AHA, ESC 2013, and Strauss) were significantly higher in the responder group. The criteria suggested in the current clinical practice guidelines (AHA and ESC 2013) demonstrated high consistency in the definition of cLBBB (κ=0.818, 95% confidence interval (CI) 0.7–0.936, p<0.001). However, minimal consistency was established between Strauss and ESC 2006/AHA/ESC 2013 in the definition of cLBBB.

In the multi-center trial, van Stipdonk et al. identified differences in the definition of cLBBB when the AHA, ESC, Strauss, and MADIT-CRT criteria were used [25]. For example, cLBBB was identified by all four criteria only in 13.8% of the patients, and sensitivity, specificity, and consistency of the definition of cLBBB varied significantly (κ=0.09–0.92). However, the presence of cLBBB defined by either of those criteria contributed a comparable significant decrease in the rate of events included the composite primary endpoint (all-cause death, heart transplantation, implantation of an LV assist device), despite the identified differences. In the Caputo et al. trial, the estimated rates of hospitalization for CHF and survival were statistically significantly higher in patients with cLBBB defined by all relevant criteria: ESC 2013 (odds ratio (OR) 0.55, 95% CI: 0.36–0.82, p=0.003), Strauss (OR 0.55, 95% CI: 0.38–0.82, p=0.002), AHA (OR 0.60, 95% CI: 0.37–0.97, p=0.03) [26]. However, the differences in the composite endpoint (death and hospitalization for CHF) were significant only in patients with cLBBB defined by ESC 2009, ESC 2013, and Strauss. According to the multivariate analysis, only the ESC 2009 and 2013 criteria were statistically significantly associated with the response to CRT (odds ratio (OR) 8.8, 95% CI: 1.3–56.5, p<0.01 and OR 8.7, 95% CI: 1.4–56.4; p<0.01, respectively).

In our study, the sensitivity and specificity of the cLBBB criteria analyzed varied despite the comparable association with the prediction of reverse remodeling in CRT. The Strauss criteria demonstrated the highest sensitivity (80.3%), and AHA (94.7%) showed the highest specificity. However, cLBBB met the AHA criteria in less than half of the responders. The findings of the multi-center trial by van Stipdonk et al., in which the sensitivity and specificity of the AHA criteria were 21 and 87%, respectively, were similar [25]. We assume that the highest specificity corresponds to a more accurate identification of electrical dyssynchrony when this criterion is used. However, the possibility of reverse remodeling of LV in CRT in particular patients is due to other reasons: the presence of mechanical dyssynchrony, the severity and localization of fibrosis, the relationship with localization of ventricular electrodes, and the condition of the right ventricle [27, 28]. It may explain the low sensitivity of the AHA criterion, which is apparently intended to detect electrical dyssynchrony alone.

It should also be noted that despite the high sensitivity of the Strauss criterion, almost half of non-responders had cLBBB, which shows relatively low specificity. However, this criterion demonstrated the highest total accuracy in predicting a decrease in LVESV in CRT. When developing this criterion, the authors emphasized a wider QRS complex and the presence of notching/slurring in

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the middle of QRS in at least two leads of: V_1 V_2, V_5 V_6, I, and aVL [19]. It was shown that cLBBB defined by Strauss is associated with higher survival rates and better echocardiographic response to CRT compared to other cLBBB criteria [29–31]. The Strauss criterion in computer-modeled LV hypertrophy/dilation and incomplete LBBB had higher specificity (100% vs. 48%) compared to the traditional cLBBB criterion (QRS width >120 ms and the presence of QS or RS in V_1 according to the authors) [32].

In our work, the cLBBB criteria used in the trials that justified the revision of guidelines for the use of CRT and the inclusion of cLBBB as the relevant selection criteria (MADIT-CRT, REVERSE, and RAFT) demonstrated statistically significant intergroup differences and moderate to high consistency in the definition of cLBBB. It should be noted that, in the MADIT-CRT criterion, we used electrocardiographic signs described by Zareba et al. in the main analysis [5]. However, the authors performed an additional post-hoc analysis, which included patients with an LBBB-like morphology as well as patients with cLBBB: (1) predominantly negative QRS morphology in the V_1 V_3/V_4 leads and (2) the presence of Q-waves in V_5/V_6 or ID R interval in V_5–V_6 <60 ms. In our study, 33.3% of patients had such morphology, which was negatively correlated with reverse LV remodeling in CRT (Kramer $\varphi = -0.251$, p=0.015). When patients with cLBBB and patients with the LBBB-like morphology were brought together, the prediction of reverse LV remodeling in CRT lacked statistical significance (p=0.864). However, in the MADIT-CRT study, the group of patients with a combined QRS morphology demonstrated a lower risk of the composite endpoint (death or hospitalization for CHF). Thus reverse remodeling could not be used to analyze all effects of CRT [5].

We analyzed four of the five trials (MIRACLE, CARE-HF, REVERSE, RAFT) included in the individual meta-analysis by Cleland et al. Only two of the four cLBBB criteria were statistically significantly associated with reverse LV remodeling in CRT. Fifty-nine patients had cLBBB according to at least one of those criteria, and only 13.6% of the cLBBB cases were identified by all four criteria at the same time. The consistency between the criteria defining cLBBB was minimal in most cases (Table 6). Cleland et al. used such different criteria in a single analysis, which may explain that the QRS duration, but not its morphology, was the only significant electrocardiographic predictor of better prognosis in CRT. Nonetheless, we established the high sensitivity and general accuracy of the approach proposed suggested by Cleland et al. (QRS≥140 ms) for the prediction of reverse LV remodeling in CRT (81.8 and 66.6%, respectively), but the specificity was 29.6%.

Conclusion

Thus, the reversibility of LV remodeling in CRT differs in patients with cLBBB defined by different criteria. The rates of all relevant criteria of cLBBB (AHA, ESC 2013, and Strauss) were significantly higher in the responder group. However, these criteria differ by sensitivity and specificity. Several large multi-center trials used criteria that are minimally consistent in the definition of cLBBB, which should be taken into account when interpreting the results of those trials.

Limitations

This study has several limitations.

Firstly, the analysis was conducted in a relatively small sample.

Secondly, only reverse LV remodeling rather than all effects of CRT was assessed. At the same time, one of the most common but not the only hemodynamic criterion (a decrease in LVESV ≥15%) was chosen to define the response to CRT. And less reverse remodeling of LV in CRT is not always associated with a smaller improvement of prognosis in CRT [2, 3].

Thirdly, we analyzed the electrocardiographic signs (if any) mentioned in the articles to arrange cLBBB criteria used in large multi-center trials. However, the criteria of cLBBB are not always explicitly described in large multi-center trials. For example, it was noted in the RAFT study subanalysis that the AHA 2009 criterion was used, but when describing the electrocardiographic sings included in the criterion, the authors missed two sings: QS or RS in V_1 and discordant T-wave. The MADIT-CRT and REVERSE subanalyses used the cLBBB criteria based on the World Health Organization 1985 and AHA 2009 criteria. However, the authors also cut these criteria and excluded several electrocardiographic signs (Table 2). These changes can be associated with both the abbreviation of the article and the actual exclusion of signs from the criteria.

Fourthly, there was no information on whether the expert opinions matched or differed during the analysis of the electrocardiogram. It should be noted that each electrocardiographic sign included in a certain criterion was analyzed independently, and cLBBB was only defined if all signs were present. Thus, experts assessed only the electrocardiographic signs, rather than the cLBBB criteria. When their opinions differed, a third expert was involved to reduce the risk of errors described in the literature [33].

No conflict of interest is reported.

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