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Comparison of the relation of the ESC 2021 and ESC 2013 definitions of left bundle branch block with clinical and echocardiographic outcome in cardiac resynchronization therapy

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Abstract

Introduction: We aimed to investigate the impact of the 2021 European Society of Cardiology (ESC) guideline changes in left bundle branch block (LBBB) definition on cardiac resynchronization therapy (CRT) patient selection and outcomes.

Methods: The MUG (Maastricht, Utrecht, Groningen) registry, consisting of consecutive patients implanted with a CRT device between 2001 and 2015 was studied. For this study, patients with baseline sinus rhythm and QRS duration ≥ 130ms were eligible. Patients were classified according to ESC 2013 and 2021 guideline LBBB definitions and QRS duration. Endpoints were heart transplantation, LVAD implantation or mortality (HTx/LVAD/mortality) and echocardiographic response (LVESV reduction ≥15%).

Results: The analyses included 1.202, typical CRT patients. The ESC 2021 definition resulted in considerably less LBBB diagnoses compared to the 2013 definition (31.6% vs. 80.9%, respectively). Applying the 2013 definition resulted in significant separation of the Kaplan–Meier curves of HTx/LVAD/mortality ($p < .0001$). A significantly higher echocardiographic response rate was found in the LBBB compared to the non-LBBB group using the 2013 definition. These differences in HTx/LVAD/mortality and echocardiographic response were not found when applying the 2021 definition.

Conclusion: The ESC 2021 LBBB definition leads to a considerably lower percentage of patients with baseline LBBB then the ESC 2013 definition. This does not lead to better differentiation of CRT responders, nor does this lead to a stronger association with clinical outcomes after CRT. In fact, stratification according to the 2021 definition is not associated with a difference in clinical or echocardiographic outcome, implying that the guideline changes may negatively influence CRT implantation practice with a weakened recommendation in patients that will benefit from CRT.

KEYWORDS

cardiac resynchronization therapy, guidelines, heart failure, left bundle branch block, patient selection

1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) has proven to be one of the most effective therapies in heart failure with reduced ejection fraction in the last decades.[1,2] Results of the landmark randomized trials that led to the widespread adaptation of CRT in heart failure used a QRS duration of >120 ms as the only electrocardiographic inclusion criterion.[3–5] Sub analyses and a meta-analysis of these trials subsequently suggested that patients with a left bundle branch block (LBBB) derive greater benefit than patients with nonspecific intraventricular conduction delay and right bundle branch block.[6,7] The ESC 2013 guidelines on cardiac pacing and CRT adopted these findings, resulting in a class I recommendation for CRT in heart failure patients with an LBBB and a QRS duration ≥ 120ms.[8] The definition of LBBB remains, however, a matter of dispute. Several criteria have been proposed and used to define LBBB over the years.[8–10] In the recently published 2021 ESC guidelines on cardiac pacing and CRT, changes have been made to the LBBB definition by adding the prerequisite of notching or slurring in two adjacent leads.[11] In addition, the weight of recommendation of CRT for patients with LBBB with a QRS duration below 150 ms changed from a level I to a IIa recommendation.[8,11]

These features are based on a report from Strauss et al.[10] based on the observation that the notching or slurring represents true "LBBB" conduction due to the delay in the interventricular septum.

The aim of the present study was to evaluate the effects of the changed LBBB definition in the ESC 2021 guidelines compared with the previous LBBB definition used in the 2013 guidelines for the effect on patient selection, clinical outcome after CRT, and echocardiographic (reverse) remodeling. For this purpose, we studied a large cohort of CRT treated patients with baseline electrocardiograms (ECGs) and clinical and echocardiographic outcome available.

2 | METHODS

2.1 | Study population

In the present study, the MUG (Maastricht, Utrecht, Groningen) CRT registry was used.[12] This CRT registry consists of consecutive patients implanted with a CRT device in three university hospitals in the Netherlands. Patients were included from 2001 to 2015 (Maastricht University Medical Centre, January 2010 to December 2015; University Medical Centre Utrecht, January 2005 to 2015; University Medical Centre Groningen, January 2001 to December 2015). No inclusion criteria regarding left ventricular ejection fraction, New York Heart Association (NYHA) class or QRS duration were set initially. Patient selection, device implantation, lead positioning, device and patient follow-up were applied according to then prevailing guidelines, local protocols and physicians' preferences. Patients were included if a baseline 12-lead ECG was available and if CRT was continued until end of follow-up. The database includes extensive baseline (clinical, electrocardiographic, echocardiographic), and clinical outcome (all-cause mortality, cardiac transplantation and left ventricular assist device implantation) data, derived from hospital electronic patient databases, connected to municipal registries for mortality data in 1.492 patients. For the purpose of this study, we included patients with baseline sinus rhythm, QRS duration ≥130 ms and without right ventricular pacing on their baseline ECG. The Dutch Central Committee on Human-related Research (CCMO) allows for 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.

2.2 | Electrocardiography

The 12-lead ECGs recorded before CRT implantation were digitally stored in the MUSE Cardiology Information system (GE Medical System) and were evaluated for QRS duration using automated ECG readings. Four trained, independent observers judged the baseline ECG on the individual morphological criteria included in the LBBB definitions used in the ESC 2013 and ESC 2021 guidelines on cardiac pacing and CRT (Table 1). Interobserver agreement was good for the different LBBB definitions (p range .81–.88) in a random subset of 100 patients in the same cohort with the same observers.[13]

2.3 | Study endpoints

The primary endpoint in this study was heart transplantation (HTx), left ventricular assist device (LVAD) implantation or mortality.

TABLE 1 2013 and 2021 ESC Guideline LBBB definitions and recommendation levels for CRT implantation.[8,11]

ESC 2013	ESC 2021
LBBB criteria	*LBBB criteria*
• QRS duration ≥120 ms • QS or rS in lead V_1 • Broad (frequently notched or slurred) R waves in leads I, aVL, V_5 or V_6 • Absent Q waves in leads V_5 or V_6	• QRS duration ≥120 ms • Notches or slurring in the middle third of QRS in at least 2 of the following leads: V_1, V_2, V_5, V_6, I and aVL—with a prolongation at the delayed peak in R in V_5–V_6, to longer than 60 ms • Generally, ST segment is slightly opposed to the QRS polarity, particularly when it is at least 140 ms and is rapidly followed by an asymmetrical T wave, also of opposed polarity • Horizontal plane: QS or rS in V1 with small "r" with ST slightly elevated and positive asymmetrical T wave and unique R wave in V6 with negative asymmetric T wave. When QRS is less than 140 ms, the T wave in V6 may be positive • Frontal plane: exclusive R wave in I and aVL often with a negative asymmetrical T wave, slight ST depression, and usually QS in aVR with positive T wave • Variable QRS axis
Guideline recommendations ESC 2013 (SR)	*Guideline recommendations ESC 2021 (SR)*
Class I LBBB QRS ≥ 150 ms	Class I LBBB QRS ≥ 150 ms
Class I LBBB QRS 120–149 ms	Class IIa LBBB QRS 130–149 ms
Class IIa non-LBBB QRS ≥ 150 ms	Class IIa non-LBBB QRS ≥ 150 ms
Class IIb non-LBBB QRS 120–149 ms	Class IIb non-LBBB QRS 130–149 ms

Abbreviations: ESC, European Society of Cardiology; LBBB, Left Bundle Branch Block; SR, sinus rhythm.

Data on survival were recorded until the end of follow-up (December 2015).

Secondary endpoint was echocardiographic remodeling, defined as left ventricular end-systolic volume (LVESV) reduction at 6 months follow-up. Echocardiographic response to CRT was defined as LVESV reduction ≥15%.

2.4 | Statistical analysis

Statistical analyses were performed using IBM SPSS statistics software version 26 (SPSS Inc). Continuous variables are presented as mean ± SD. All continuous variables were verified as normally distributed using the Kolmogorov–Smirnov and Shapiro–Wilk test. Discrete variables are presented as count and proportion (%). When comparing two groups with continuous variables, student's *t*-test was used. When comparing more than two groups with continuous variables, a one-way analysis of variance and post-hoc Tukey's multiple comparison test was used.

Survival analyses for the different LBBB definitions and recommendation levels were performed using Kaplan–Meier survival analysis and compared using the Log-rank test. Discrete variables were compared using the χ^2 test, subgroup analyses were performed with a post-hoc Bonferroni correction for multiple comparisons. Odd's ratio (OR) and 95% confidence interval (CI) were calculated with the Baptista pike method when comparing two groups. When comparing more than two groups, logistic regression analyses was performed. A p-value < .05 was considered statistically significant.

3 | RESULTS

The current analyses included 1.202 patients implanted with a CRT device. The cohort represents a typical, predominantly male (69%), CRT patient cohort with an age of 66 ± 11 years at implantation of the CRT device. Heart failure etiology was ischemic in 49% of patients, with a mean baseline left ventricular ejection fraction (LVEF) of 25%. Baseline NYHA functional class was II-III in over 93% of patients. (Table 2).

4 | DISTRIBUTION OF QRS MORPHOLOGY AND DURATION

Classification according to the 2013 LBBB definition (Table 1) resulted in 974 (81%) patients classified as having an LBBB. When adding QRS duration ≥150 ms or QRS duration 130–149 ms, 734 (61%) of patients are classified as having a wide (QRS ≥ 150 ms) LBBB pattern and 240 (20%) as having a narrow (QRS 130–149 ms) LBBB pattern. Furthermore, 156 (13%) patients were classified as wide (QRS > 150ms) non-LBBB pattern and 72 (6%) as narrow (QRS 130–149 ms) non-LBBB. (Figure 1A) According to the ESC 2013 guidelines (Table 1), 974 (81%) patients would receive a class I recommendation (both wide LBBB and narrow LBBB), 156 (13%) a class IIa recommendation and 72 (6%) a class IIb recommendation. (Figure 1B).

Classification according to the 2021 LBBB definition (Table 1) resulted in 300 (25%) patients as having a wide LBBB pattern, 72 (6%) having a narrow LBBB pattern, 589 (49%) as wide non-LBBB pattern, and 240 (20%) as narrow non-LBBB pattern. (Figure 1A) When implementing the ESC 2021 guidelines (Table 1) significantly less patients would receive a class I recommendation due to the changed LBBB definition. In our cohort a total of 594 (49%) patients that were classified as LBBB according to ESC 2013 were classified as non-LBBB according to ESC 2021 guidelines, including a lower level of recommendation for CRT. (Figure 1B).

TABLE 2 Baseline characteristics.

Baseline Characteristics (*N* = 1.202)	
Male gender, %	69
Age, years	66 (±10.8)
BMI, kg/m^2	27 (±5.1)
DM, %	25
HT, %	42
Ischemic etiology %	49
LVEF, %	25 (±8.9)
NYHA, %	
I	2
II	40
III	53
IV	5
Laboratory	
Kreat Clearence, mL/min	72 (±32.6)
NTproBNP, pg/mL	2728 (±5024)
Medication	
Betablocker, %	82
ACEi/ARB, %	90
MRA, %	44

Note: Values are mean ± SD or % unless otherwise indicated.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DM, diabetes mellitus; HT, hypertension; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N terminal brain natriuretic peptide; NYHA, New York Heart Association classification.

5 | CLINICAL OUTCOME

Overall, 351 (29.2%) patients experienced the primary clinical endpoint of HTx, LVAD implantation or mortality during a follow-up of 46.7 ± 29.5 months. Distributions of HTx, LVAD implantation or mortality when classifying according to both LBBB definitions combined with QRS duration and subsequent level of recommendation are shown in Table 3. The survival differences when classifying according to the 2013 LBBB definition and subsequent level of recommendation are significant for both wide LBBB versus wide non-LBBB (75% vs. 55%, $p < .0001$) and both class I versus class IIa and class I versus class IIb (74% vs. 55%, $p < .0001$ and 74% vs. 60%, $p = .03$, respectively). (Table 3). Whereas there is no significant survival difference between subgroups classified according to the 2021 LBBB definition and level of recommendation.

Kaplan–Meier estimates of HTx/LVAD free survival showed significant separation of the curves when the 2013 LBBB definition combined with QRS duration was used. (Figure 2A). Analyses of the different subgroups showed significant differences between a wide LBBB and narrow LBBB, and the wide LBBB and both non-LBBB subgroups. (Figure 2A). Subgroup analysis on ESC 2013 level of recommendation showed similar results with significant differences in HTx/LVAD free survival between class I and both class IIa and class IIb level of recommendation. (Figure 2B).

On the other hand, when the 2021 LBBB definition and subsequent levels of recommendation were applied, the Kaplan Meier estimates of HTx/LVAD free survival showed no significant separation of the curves ($p = .138$ and $p = .070$, respectively). (Figure 2C,D) Subgroup analysis no longer showed a significant

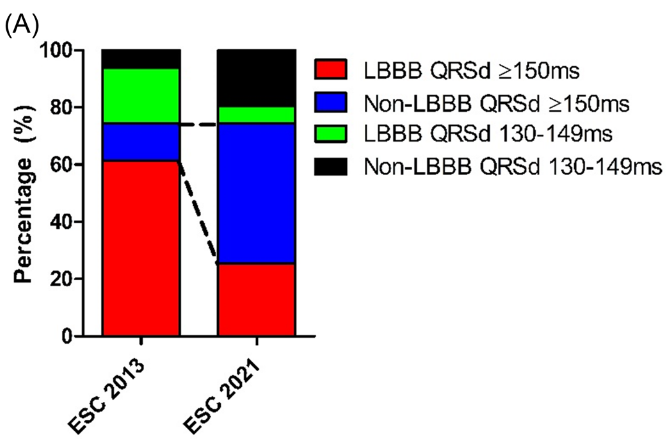

FIGURE 1 Distribution of QRS morphology (A) and recommendation level (B) according to ESC 2013 and ESC 2021 guidelines on cardiac pacing and cardiac resynchronization therapy. ESC, European Society of Cardiology.

TABLE 3 Distribution of HTx/LVAD free survival when stratifying according to ESC 2013 and ESC 2021 definitions on LBBB combined with QRS duration and subsequent level of recommendation.

HTx/LVAD free survival when stratifying according to ESC 2013 and ESC 2021 definition on LBBB and QRS duration and level of recommendation.					
	ESC 2013 (%)	ESC 2021 (%)		ESC 2013 (%)	ESC 2021 (%)
LBBB QRS duration ≥ 150 ms	75	71	Class I	74	71
LBBB QRS duration 130–149 ms	71	69	Class IIa	55	72
Non-LBBB QRS duration ≥ 150 ms	55	72	Class Iib	60	69
Non-LBBB QRS duration 130–149 ms	60	69			

Abbreviations: ESC, European Society of Cardiology; LBBB, left bundle branch block.

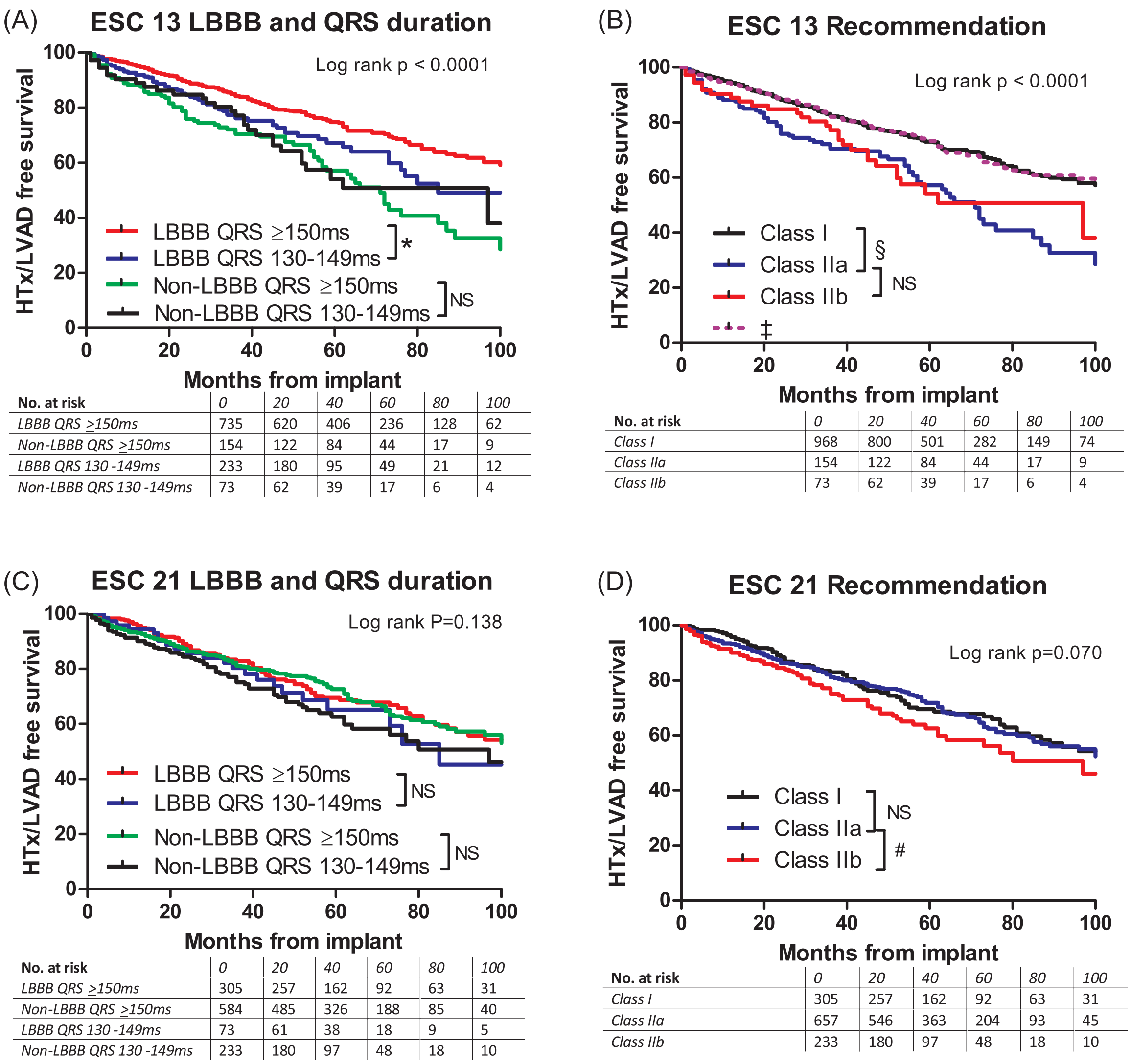

FIGURE 2 HTx/LVAD free survival for LBBB stratification combined with QRS duration (A, C) and level of recommendation (B, D) for ESC 2013 and ESC 2021 guidelines on cardiac pacing and cardiac resynchronization therapy. ‡ Patients downgraded from class I level of recommendation due to changed LBBB definition in ESC 2021 guidelines* $p < .001$, HR 0.49 (0.37, 0.65), § $p < .001$, HR 0.54 (0.41, 0.70), # $p = .039$, HR 0.75 (0.57, 0.98). ESC, European Society of Cardiology; LBBB, left bundle branch block.

HTx/LVAD or mortality difference between a wide LBBB and wide non-LBBB. Importantly, no significant HTx/LVAD or mortality difference is found between a class I and class IIa level of recommendation. (Figure 2C,D) Furthermore, Figure 2B shows that patients receiving a lower level of recommendation due to the changed LBBB definition show a similar survival curve as their original level of recommendation according to ESC 2013 guidelines.

6 | ECHOCARDIOGRAPHIC RESPONSE

A subgroup of 757 (63%) patients in the cohort had baseline and follow-up echocardiographic data available for analysis of echocardiographic response to CRT. LVESV reduction after CRT was 20.6 ± 31.3%. Overall, 448 patients (59.2%) showed echocardiographic response to CRT.

LVESV reductions in subgroups classified according to the ESC 2013 and ESC 2021 LBBB definition, combined with QRS duration and subsequent levels of recommendation are shown in Table 4 and Figure 3.

Classification according to the 2013 LBBB definition and QRS duration resulted in significant differences in LVESV reduction ($p < .0001$), which is also found for level of recommendation ($p < .0001$). (Figure 3A,B). Post-hoc analyses showed a significant difference in LVESV reduction in favor of both wide LBBB over wide non-LBBB and narrow LBBB over narrow non-LBBB. (Figure 3A). Post-hoc analyses on level of recommendation showed a significant difference in LVESV reduction in favor of class I when compared with class IIa and class IIb subgroups. (Figure 3B).

Classification according to the ESC 2021 LBBB definition, combined with QRS duration and subsequent levels of recommendation showed an over-all significant difference in mean LVESV reduction ($p = .0012$ and $p = .0005$, respectively, Figures 3C,D). However, no significant difference in LVESV reduction is found between wide LBBB and wide non-LBBB subgroups, nor between narrow LBBB and narrow non-LBBB. (Figure 3C). Also, post-hoc analyses on level of recommendation according to ESC 2021 guidelines did not show a significant difference between class I and class IIa subgroups (Figure 3D).

The 2013 LBBB definition generated a stronger association (OR 3.1 [2.1–4.6]) with echocardiographic response than the 2021 LBBB definition (OR 1.5 [1.1–2.0]). In addition, according to ESC 13 guidelines a wide LBBB QRS morphology was associated with response significantly better than wide non-LBBB (OR 2.8; 95% CI 1.8–4.5), than narrow LBBB (OR 1.7 95% CI 1.2–2.5), and than narrow non-LBBB (OR 5.7; 95% CI 2.7–12.0).

In contrast, in the ESC 2021 definition, a wide LBBB did not show a better association with response than a wide non-LBBB (OR 1.4; 95% CI 0.995–2.0). It was only associated whit a significantly higher chance of response, when compared to the narrow non-LBBB subgroup.

Examining the level of recommendations, in ESC 2013 a class I level of recommendation was strongly associated with echocardiographic response compared to class IIa (OR 2.5; 95% CI 1.6–4.0) and class IIb (OR 5.1; 95% CI 2.4–10.6) levels of recommendation. For the ESC 2021 guidelines, a class I level of recommendation was less convincingly associated with better echocardiographic response than a class IIa (OR 1.46; 95% CI 1.0–2.1) and IIb (OR 2.6; 95% CI 1.7–4.1) levels of recommendation.

7 | DISCUSSION

This study shows that the changed LBBB definition that has been introduced in the ESC 2021 guidelines on cardiac pacing and CRT has a potential impact on patient selection for CRT. First, according to the new 2021 guidelines, a considerably lower number of patients have a class I recommendation for CRT. A large part of patients that had a class I recommendation for CRT according to the ESC 2013 guidelines will have a class IIa or IIb recommendation for CRT according to the ESC 2021 guidelines. Second, the transition to more restrictive recommendations, appears to lead to a significantly worse differentiation with respect to clinical and echocardiographic outcomes.

Sub analyses of the landmark trials in CRT have shown the importance of adding LBBB as a criterion in assessing patients' eligibility for CRT.[6,7,14] However, different definitions of LBBB have been used in literature throughout the years.[6–8,10,14,15] Sub analyses of MADIT-CRT,[7] REVERSE,[6] and RAFT[14] proved the added benefit of LBBB as a selection criterion with a similar definition as used in the ESC 2013 guidelines.[8] However, none of the aforementioned sub analyses, which paved the way for LBBB as an eligibility criterion for CRT, used the strict definition as used in the ESC 2021 guidelines.[11]

There may have been several reasons for adjusting the LBBB definition to stricter criteria. Generally, using stricter criteria, will lead to fewer patients being offered the treatment, possibly preventing unnecessary implantations and associated complications and health care costs. As shown in the current analyses, the changes will indeed lead to a lower level of recommendation for CRT in almost 50% of

TABLE 4 Mean percentual LVESV reduction when classifying according to ESC 2013 and ESC 2021 definition in LBBB combined with QRS duration and level of recommendation.

Mean relative LVESV reduction when stratifying according to ESC 2013 and ESC 2021 definition on LBBB and QRS duration and level of recommendation.					
	ESC 2013	ESC 2021		ESC 2013	ESC 2021
LBBB QRS duration ≥ 150 ms	25.4 ± 30.5	24.2 ± 33.2	Class I	23.5 ± 30.7	24.2 ± 33.2
LBBB QRS duration 130–149 ms	16.5 ± 30.2	17 ± 30.7	Class IIa	8.4 ± 30.1	21.7 ± 30.1
Non-LBBB QRS duration ≥ 150 ms	8.4 ± 30.1	22.2 ± 30	Class IIb	0.3 ± 29.8	11.1 ± 30.7
Non-LBBB QRS duration 130–149 ms	0.3 ± 29.8	11.1 ± 30.7			

Note: LVESV reduction in % ±SD.

Abbreviations: ESC, European Society of Cardiology; LBBB, left bundle branch block.

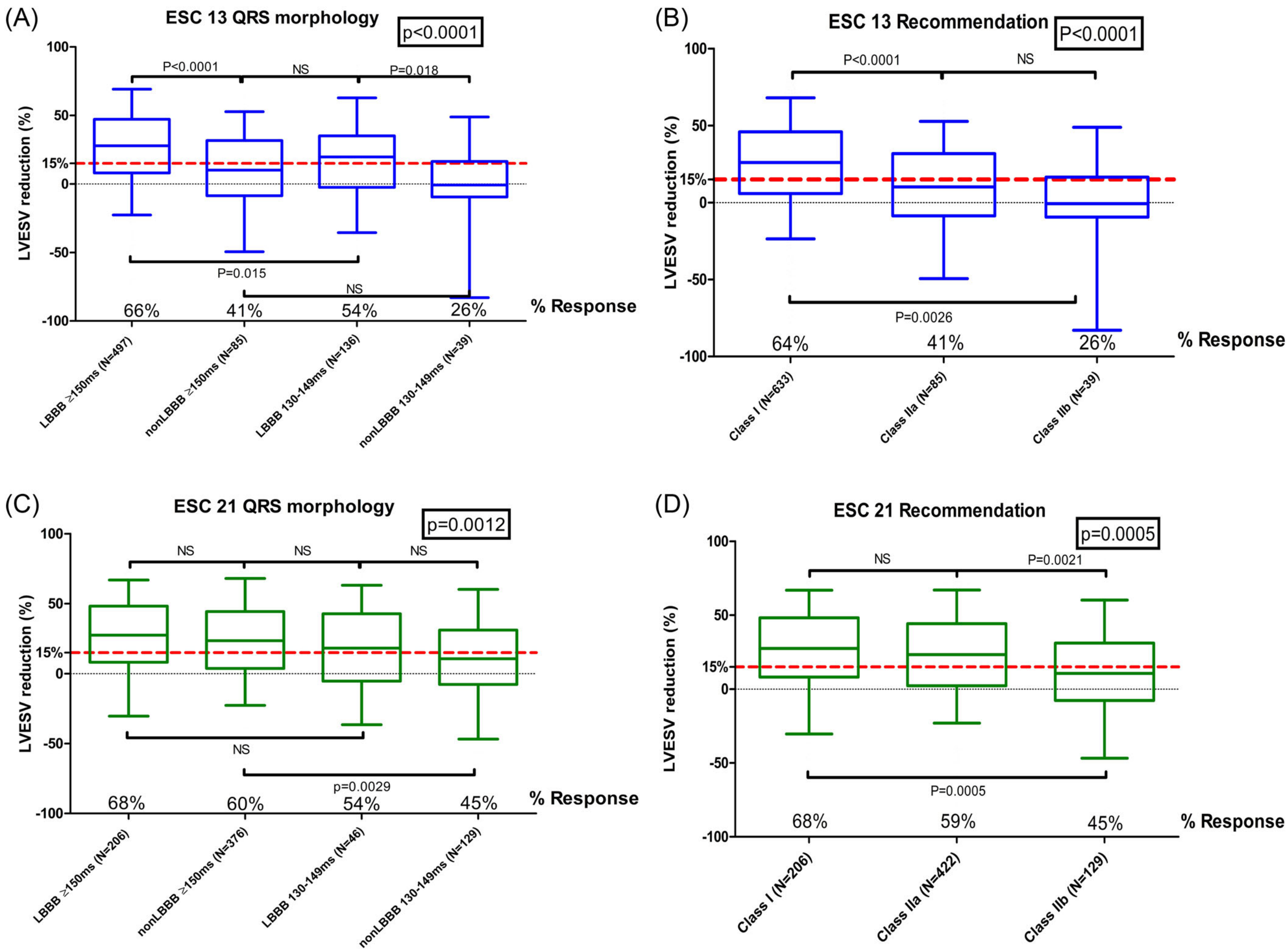

FIGURE 3 Response stratified according to ESC 2013 and ESC 2021 LBBB criteria combined with QRS duration (A, C) and level of recommendation (B, D). ESC, European Society of Cardiology; LBBB, left bundle branch block.

patients receiving a class I recommendation in the ESC 2013 guidelines. However, the current general opinion prevails that CRT is insufficiently applied to those that could benefit. In fact, although a class I ("is recommended") and class IIa ("should be considered") level of recommendation should generally lead to the implantation of a CRT device, up to two thirds of those considered eligible for CRT are currently not being treated with CRT.[16]

Still the restrictive patient selection recommended by the 2021 ESC guidelines could lead to superior differentiation between those patients that could benefit and those that do not, which would justify the use of the new LBBB definition. In the current analysis however, clinical and echocardiographic outcomes did not significantly differ within the LBBB and non-LBBB and subsequent level of recommendation subgroups, when using the ESC 2021 definition. This differentiation between subgroups with better and worse outcome when treated with CRT, was present when using the ESC 2013 LBBB definition, with significantly better outcomes in patients with a class I recommendation than those with class IIa and IIb recommendations.

Van Stipdonk et al.[12] showed that the "simpler" ESC 2013 definition, compared to the more complicated AHA/ACC/HRS LBBB definition, led to the largest difference in relative risk reduction between LBBB and non-LBBB subgroups. Our observations on clinical outcomes are in accordance with a study from Caputo et al.[17] This study is showing that the "simpler" definition as used in ESC 2013 provides the best association with the clinical endpoint of heart failure hospitalization and mortality, compared to more complicated definitions like the one used in the AHA/ACC/HRS guideline which resembles the definition used in the ESC 2021 guidelines.

Baseline differences could explain a worse clinical outcome in non-LBBB subgroups, compared to the LBBB subgroups. This might confound the differences in clinical outcome found in the current analysis. However, we also found significantly better differentiation of the odds of echocardiographic response in the 2013 subgroups compared to the 2021 subgroups. This strengthens the association with clinical outcomes. The findings all together, suggest that the 2021 ESC guideline changes could lead to patients with a good chance of positive remodeling and associated improvement in clinical outcomes being denied CRT, instead of the possible prevention of CRT device implantation in patients that do not have a chance of improvement to therapy.

Another possible reason for the changes made in LBBB definition is better identification of super-responders. Echocardiographic (super)response (defined as LVESV reduction >20%–30% or an absolute LVEF improvement >20% or final LVEF ≥ 50%) has previously been reported to be strongly associated with the presence of baseline LBBB as defined by Strauss et al.[10,18,19] In a direct comparison, García-Seara et al.[19] showed that patients with LBBB according to the Strauss criteria was associated with better echocardiographic response (greater improvement in LVESV reduction and LVEF increase) as compared to conventional LBBB definitions as used in ESC 2013. Whereas they found a stronger association of the Strauss LBBB definition with echocardiographic response, they did not find a similar association with clinical outcomes, including mortality.[19] These findings could not be confirmed in the current analyses, with comparable mean LVESV reduction in ESC 2013 and ESC 2021 LBBB subgroups. One of the possible reasons for the seemingly contradictory results regarding super-response presented in the current analysis, is that abovementioned studies focused on the strength of the association in the LBBB subgroup of patients, whereas this study focusses on the strength of the differentiation between the association in one subgroup with the others. Apart from the fact that we could not confirm the abovementioned association with echocardiographic response, we argue that super-response should be the aim of CRT. Recent evidence indicates that patients who exhibit no clear positive echocardiographic remodeling or "response" to CRT, can still derive clear clinical benefit from this therapy.[20] Importantly, as HF is essentially a progressive disease with significant morbidity and loss of quality of life, the slowing of progression of disease should be the clinical aim of therapy.[21] A joint position paper by the HFA/EHRA/EACVI[16] suggests to abandon the term of response and replace it by the concept of disease modification, where lack of deterioration and therefore "stability" is seen as a positive outcome after CRT.[16] Therefore, designating a significantly smaller group of patients as having a class I indication will potentially lead to the denial of an effective therapy to slow the progression of clinical disease in a large group of patients. Especially in light of the suggestion that, already, two thirds of those eligible for CRT according to current guidelines (ESC 2013) are not being treated with CRT.[16]

Although the true impact of the changes in the LBBB definition in the ESC 2021 guidelines in daily practice remains uncertain, any change in a guideline document should be supported by substantial evidence of its positive impact on patient care. We believe that the current analyses indicate that such support for the adjustments made to the LBBB definition does not exist and may even have the opposing effect than what the guidelines aim for.

8 | LIMITATIONS

This study has all the limitations of a retrospective, noncontrolled observational cohort, hampering any sturdy conclusions on the attribution of CRT on clinical outcomes (lacking untreated controls). However, as echocardiographic response uses a baseline and follow-up measurement, the addition of these data in part compensate the lack of a nontreated control group. The effects found in the analyses presented, are largely explained by the change in LBBB definition, however the levels of recommendation between ESC 2013 and 2021 also changed regarding QRS duration, where LBBB with a QRS duration between 130 and 150ms in 2013 still had a class I recommendation, in 2021 this is downgraded to a class IIa recommendation (Table 2). This will have influenced the changes seen with respect to the level of recommendation analyses. Because we have observed the same significant differences when analyzing the LBBB (combined with QRS duration) subgroups before translating it to the recommendations, we assume that the different definition in LBBB contributes significantly to the differences found with respect to the levels of recommendation.

9 | CONCLUSION

The changes made to the LBBB definition in the "ESC 2021 guidelines on cardiac pacing and CRT" made them stricter with the potential to have a significant impact on patient selection for CRT, as a significant proportion of patients will receive a lower level of recommendation for therapy. These changes however cannot be justified by a better differentiation between patients deriving benefit from therapy. In fact, the current analysis shows that these changes may lead to a significant proportion of patients that derive clinical and echocardiographic benefit from CRT, to have a lower level of recommendation.

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