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Review

Cardiol Res. 2020;11(1):1-8

Indications of Cardiac Resynchronization in Non-Left Bundle Branch Block: Clinical Review of Available Evidence

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Abstract

Cardiac resynchronization therapy (CRT) benefits have been firmly established in patients with heart failure and reduced left ventricular ejection fraction (HFrEF), who remain in New York Heart Association (NYHA) functional classes II and III, despite optimal medical therapy, and have a wide QRS complex. An important and consistent finding in published systematic reviews and in subgroup analyses is that the benefits of CRT are maximum for patients with a broader QRS durations, typically described as QRS duration > 150 ms, and for patients with a typical left bundle branch block (LBBB) QRS morphology. It remains uncertain whether patients with non-LBBB QRS complex morphology clearly benefit from CRT or only modestly respond.

Keywords: Non-LBBB; RBBB; Typical LBBB; HFrEF: Cardiac resynchronization therapy; QRS duration

Introduction

Cardiac resynchronization therapy (CRT) benefits have been firmly established in patients with heart failure and reduced left ventricular ejection fraction (HFrEF), who remain in New York Heart Association (NYHA) functional classes II and III despite optimal medical therapy, and have a wide QRS complex [1]. An important and consistent finding in published systematic reviews and in subgroup analyses is that the benefits of CRTs are maximum for patients with a broader QRS durations, typically described as QRS duration > 150 ms, and for patients with a typical left bundle branch block (LBBB) QRS morphology [2]. It remains uncertain whether patients with non-LBBB QRS complex morphology clearly benefit from CRT or only modestly respond [3-6].

In this article, we reviewed the major trials that enriched the most recent international guidelines for CRT implantation focusing on the available data about the outcome of using CRT in non-LBBB cohort. Furthermore, we conferred the current guidelines, including the comprehensive update of the Canadian Cardiovascular Society (CCS) guidelines for the management of heart failure (HF) 2017 [2], the European Society of Cardiology (ESC) Heart Failure Association guidelines for the diagnosis and treatment of acute and chronic HF 2016 [7], the National Institute of Health and Care Excellence (NICE) guidelines for ICD (implantable cardioverter defibrillator) and CRT for arrhythmia and heart failure 2014 [8], the American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure 2013 [9], the ESC European Heart Rhythm Association guidelines on cardiac pacing and cardiac resynchronisation therapy 2013 [10], and the update to National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand guidelines for the prevention, detection and management of chronic HF in Australia 2011 [11].

The Non-LBBB Wide QRS Complex Electrocardiogram (ECG) Criteria

Non-LBBB wide QRS complex patterns include the following four groups are represented in Figure 1 as follow: 1) Atypical LBBB represent "QRS duration greater than or equal to 120 ms in adults, broad notched or slurred R wave in leads I, aVL, V5, and V6, and an occasional RS pattern in V5 and V6 attributed to displaced transition of QRS complex, absent q waves in leads I, V5, and V6, and R peak time greater than 60 ms in leads V5 and V6" with atypical feature such as Q wave in I and aVL, larger R wave in V1 and V2, or V6 QRS complex morphology which is different from those in I and aVL (Fig. 1a). 2) Complete (typical) right bundle branch block (RBBB) is described as QRS duration ≥ 120 ms in adults, rsr′, rsR′, or rSR′ in leads V1 or V2, R or r deflection is usually wider than the initial R wave patients, S wave of greater duration than R wave or greater than 40 ms in leads I and V6 in adults, and normal R peak time in leads V5 and V6 but > 50 ms in lead V (Fig. 1b). 3) Interventricular conduction delay (IVCD) which characterized by wide QRS morphology that does not resem-

Manuscript submitted November 19, 2019, accepted December 16, 2019

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doi: https://doi.org/10.14740/cr989

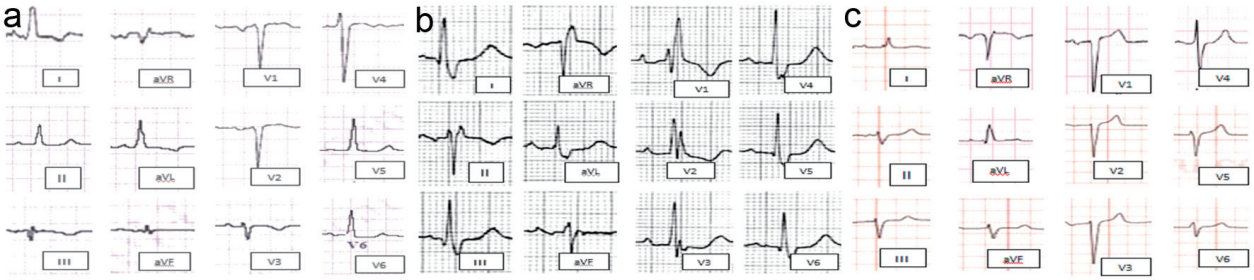

Figure 1. Different ECG morphological pattern of non-LBBB wide QRS complex. (a) Atypical LBBB. (b) Typical RBBB. (c) Non-specific interventricular conduction block. ECG: electrocardiogram; LBBB: left bundle branch block; RBBB: right bundle branch block.

ble either typical LBBB or RBBB. The definition may also be applied to a pattern with RBBB criteria in the precordial leads and LBBB criteria in the limb leads, and vice versa (Fig. 1c). 4) Atypical RBBB may represent underlying delay in left ventricular (LV) activation as well. RBBB masks the underlying co-existent LBBB in broader QRS indicating advanced grade of dyssynchrony (Fig. 2) [12].

The ECG morphological patterns of atypical LBBB, typical RBBB and IVCD ECGs are illustrated in Figure 1. The atypical RBBB ECG is illustrated in Figure 2.

Indications of CRT in Non-LBBB QRS Morphology in the Landmark Clinical Trials

Over last decade, 13 major studies, involving the outcomes of CRT use in patients with HFrEF, were conducted between 2002 and 2018 (Table 1, [13-25]). Remarkably, from 2002 to 2010, the ECG selection criteria were based solely on prolonged QRS duration without differentiation between types of bunch branch block morphology [13-23]. On the other hand, the ENHANCE CRT pilot study (2018) was conducted solely in such "non-LBBB" patients to investigate the advantage of using an electrophysiologic measure of left ventricular (LV) delay to guide lead placement when implanting the CRT's biventricular lead system [25].

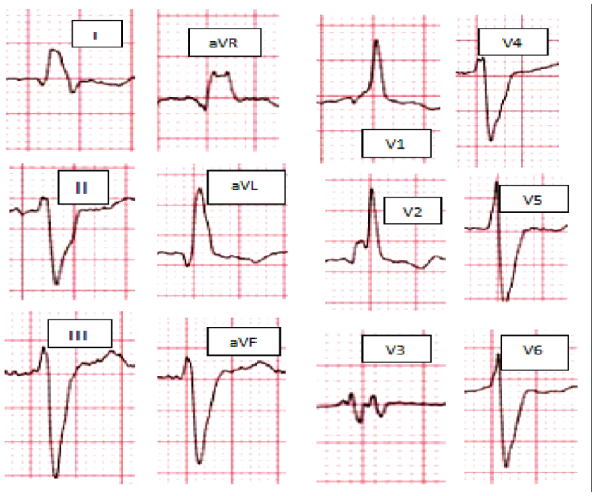

Figure 2. Atypical RBBB: broad, slurred, and notched R wave on leads I and aVL, together with a leftward axis deviation. RBBB: right bundle branch block.

Until 2015, the major trials lacked the evidence that non-LBBB patients as a group would benefit from CRT implantation. The MIRACLE ICD trial stated that the benefit of CRT was positive regardless of QRS morphology although they admit they may have been underpowered in this regard [16].

Investigators of the COMPANION trial did a subgroup univariate analysis on factors associated with hospitalization risk for all patients in RBBB and/or IVCD and compared to LBBB, which produced clear evidence that the benefit of CRT was mainly observed in patients with LBBB (hazard ratio (HR) of 1.26). Similarly, IVCD was compared to RBBB or LBBB yielding a similar outcome (HR of 1.24) [22]. However, RAFT trial had comparable outcomes (HR = 1) [23].

The MADIT-CRT trial stated that the benefits from CRT among the trial's patients without LBBB were not the same as LBBB patients, and in fact it suggested CRT might increase their mortality [20]. However, recently in 2018, the ENHANCE CRT study, the first head-to-head comparison of additional LV lead placement guided by electrical delay versus the standard of care, concluded that CRT is an effective therapy in patients with non-LBBB with no apparent distinction seen in responses by subgroups, including RBBB vs. IVCD, QRS interval, sex, HF cause, or left ventricular ejection fraction (LVEF). In addition, there were no significant differences between the two interventional arms in quality of life or LVEF [25]. The earlier trials finding of possible harm in non-LBBB are less relevant to this study as the included patients were in softer indications (i.e. NYHA class I to II in MADIT-CRT versus III to IV in ENHANCE CRT).

Guidelines and Recommendations for CRT in Non-LBBB QRS Morphology

ACC/AHA/HRS, ESC, and CCS guidelines agree that if a patient has a QRS duration > 150 ms and is in NYHA functional class III or ambulatory IV, then a CRT "better to be considered" (class IIa). When QRC duration is < 150 ms, there is considerable inconsistency in the guidelines. Both ACC/AHA/HRS and ESC guidelines favor the CRT (class IIb), however the CCS guidelines do not provide a formal recommendation

Table 1. Summary of the CRT Landmark Clinical Trials

Study	Aim	Patients and randomization	QRS complex pattern	Results
Path CHF, Auricchio et al, 2002 [13]	Compare the short- and long-term clinical effects of atrial synchronous, pre-excitation of univentricular or biventricular therapy with cardiac CRT.	N = 42; randomized to biventricular CRT (24)/ univentricular CRT (17); followed for 9 months	QRS ≥ 120 ms; LBBB, 39 (93%)/ RBBB, 3 (7%)	CRT produces a long-term improvement in the clinical symptoms of patients with HF who have significant IVCD.
MIRACLE, Abraham et al, 2002 [14]	Evaluate the clinical benefit of CRT in symptomatic heart failure with IVCD.	N = 453; randomized to CRT group (228)/ control (225); followed for 6 months	QRS ≥ 130ms	Significant clinical improvement in moderate to severe heart failure with IVCD.
CONTAK CD, Higgins et al, 2003 [15]	Assess the safety and effectiveness of cardiac CRT when combined with an ICD.	N = 490; randomized to CRT (245)/control (245); followed for 6 months	QRS ≥ 120 ms; CRT group: LBBB 50%/ NSIVCD 32%/RBBB 18%; non-CRT group: LBBB 54%/NSIVCD 34%/RBBB 12%	CRT implant has improved the functional status in all patients that were indicated for ICD and have HFrEF and IVCD.
MIRACLE ICD, Young et al, 2003 [16]	Examine the efficacy and safety of combined CRT and ICD therapy in patients with NYHA class III or IV CHF despite appropriate medical management.	N = 369; randomized to CRT on (187)/ CRT off (182); followed for 6 months	QRS ≥ 130 ms; CRT group: LBBB 87%/ RBBB 13%; control group: LBBB 86%/ RBBB 14%	CRT improved quality of life, functional status, and exercise capacity in patients with moderate to severe HF, a wide QRS interval, and life-threatening arrhythmias. CRT effect on QOL score and NYHA functional class was not influenced by morphology of the BBB (R vs. L)
MIRACLE ICD II, Abraham et al, 2004 [17]	Assess the efficacy and safety of combined CRT and ICD therapy in patients with NYHA class II CHF despite appropriate medical management.	N = 186; randomized to CRT on (86)/control (101); followed for 6 months	QRS ≥ 130 ms; CRT group: LBBB 88%/ RBBB 12%; non-CRT group: LBBB 79%/RBBB 21%	Significant improvement in cardiac structure and function over 6 months. CRT did not alter exercise capacity.
CARE HF, Cleland et al, 2005 [18]	Evaluation of CRT on morbidity and mortality in patients with NYHA class III or IV.	N = 813; randomized to CRT group (409)/ control (404); followed for 18 months	QRS ≥ 120 ms	CRT improves symptoms, the QOL and reduces complications and improves mortality. The broader the QRS in general the overall better results.
REVERSE, Linde et al, 2008 [19]	Assess the effects of CRT use in patients with NYHA functional class I and II.	N = 610; randomized to CRT group (419)/ control (191); followed for 12 months	QRS ≥ 120 ms	CRT in combination with optimal medical therapy (+/-defibrillator), reduces the risk for HF hospitalization and improves ventricular structure and function in NYHA I and II.
MADIT CRT, Breithardt et al, 2009 [20]	Determine whether CRT with biventricular pacing would reduce the risk of death or HF events in patients with NYHA I or II, reduced EF of ≤ 30% and QRS duration ≥ 130 ms.	N = 1,820; randomized to CRT (CRT and ICD on) group (1,089)/control (CRT off and ICD on) (731); followed for up of 2.4 years	QRS ≥ 130 ms; CRT group: LBBB (761)/RBBB (136); control: LBBB (520)/RBBB (92)	CRT combined with ICD decreased the risk of HF events in relatively asymptomatic patients with a low ejection fraction and wide QRS complex.

Table 1. Summary of the CRT Landmark Clinical Trials - *(continued)*

Study	Aim	Patients and randomization	QRS complex pattern	Results
REVERSE, Daubert et al, 2009 [21]	Evaluate the long-term effects of CRT in the European cohort of patients enrolled in the REVERSE trial.	N = 262, randomized to CRT group (ICD activated, CRT on) (180)/control (ICD activated, CRT off) (82); followed for 24 months	QRS ≥ 120 ms	Clinical functional outcomes improved and LV end systolic volume decreased by a greater mean in CRT on than CRT off. First HF hospitalization or death was significantly delayed by CRT (HR: 0.38; P = 0.003).
COMPANION, Anand et al, 2009 [22]	Assess the use of CRT as a treatment of CHF on mortality and hospitalization.	N = 1,520; randomized in 1:2:2 ratios for optimal medical management (308)/ CRT-p (617)/CRT-d (595); followed for 15 months	QRS ≥ 120 ms	CRT pacing with or without ICD capability was associated with a significant 1-year relative risk reduction of about 20% for all-cause death or hospitalization.
RAFT, Tang et al, 2010 [23]	Evaluate whether CRT benefits patients with LV systolic dysfunction and a wide QRS.	N = 1,798; randomized to CRT group (ICD activated, CRT on) (894)/control (ICD activated, CRT off) (904); followed up for 40 months	QRS ≥ 120 ms; CRT group: LBBB72.9%/ NIVCD 11.9%/ RBBB 7.6%; control group: LBBB71.1%/ NIVCD11.2%/ RBBB 7.4%	The combined use of CRT with ICD has reduced the mortality and hospitalization for HF patients.
BLOCK HF, Curtis et al, 2016 [24]	Assess biventricular pacing against primary end points of reduce mortality, morbidity, and adverse left ventricular remodeling in patients with high grade AV block; and NYHA class I, II, or III; and a LVEF of 50% or less.	N = 691; randomized to Biventricular pacing (349)/ RV pacing (342); followed for 24 months	QRS ≥ 120 ms; biventricular pacing: 1st AV block (68)/2nd AV block (119)/3rd AV block 162/LBBB (123)/ RBBB (73); RV pacing: 1st AV block (66)/2nd AV block (108)/3rd AV block (167)/LBBB (102)/RBBB (74)	Biventricular pacing was superior to conventional right ventricular pacing alone in patients with AV block and left ventricular systolic dysfunction with NYHA class I, II, or III HF.
ENHANCE CRT, Singh et al, 2018 [25]	Evaluate the effect of a non-traditional LV lead implant strategy on the clinical composite score in a non-LBBB patient population.	N = 248; randomized to QLV implant strategy (161)/standard of care (81); followed up for 12 months	QRS ≥ 120 ms; QLV study arm: IVCD (55)/ RBBB (86)/RBBB and LAFB (15)/RBBB and LPFB (2)/others (3); standard of care study arm: IVCD (33)/ RBBB (36)/RBBB and LAFB (9)/RBBB and LPFB (1)/others (2)	CRT is an effective therapy in patients with non-LBBB. No apparent variation was documented in responses by subgroups analysis (i.e. RBBB vs. IVCD, QRS interval, sex, HF cause, or LVEF).

The table summarized all landmark trials influencing CRT guidelines since 2002. Most of these trials do not have any subgroup analysis of patients with non-LBBB. The trials consist of patients of varying classes of NYHA, using different endpoints such as rehospitalization or mortality, the cohort however is primarily LBBB or non-specified QRS prolongation. CHF: congestive heart failure; CRT: cardiac resynchronization therapy; NYHA: New York Heart Association; ICD: implantable cardioverter defibrillator; IVCD: intraventricular conduction delay; NSIVCD: nonspecific interventricular conduction delay; LVEF: left ventricular ejection fraction; LBBB: left bundle branch block; RBBB: right bundle branch block; QOL: quality of life; HFrEF: heart failure with reduced ejection fraction; LBFB: left posterior fascicular block; LAFB: left anterior fascicular block; LV: left ventricular; RV: right left ventricular; AV: atrioventricular.

for this patient group; instead, they simply state that there is no clear evidence of benefit with CRT among patients with QRS duration < 150 ms because of non-LBBB conduction.

NICE guidelines recommend CRT device insertion in patients with non-LBBB QRS morphology, who have QRS duration ≥ 150 ms and in NYHA functional classes II, III, and IV. CRT pacemaker without ICD insertion is indicated in patients with non-LBBB QRS morphology who have a QRS between 120 and 149 ms and in NYHA functional class IV. NICE guidelines also provide a clear guidance on whether to implant a cardiac resynchronization therapy with pacemaker (CRT-P) or a cardiac resynchronization therapy defibrillator (CRT-D).

Table 2. Summary of the CRT Landmark Clinical Trials

Guideline	Recommendation
American College of Cardiology Foundation/ American Heart Association 2013, ESC European Heart Rhythm Association 2013	CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class III/ambulatory class IV symptoms on GDM. Class IIa, level of evidence A.
	CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with QRS duration 120 to 149 ms, and NYHA class III/ambulatory class IV on GDM. Class IIb, level of evidence B.
National Institute of Health and Care Excellence (NICE) guidelines for ICD and CRT for arrhythmia and HF 2014	CRT device insertion is indicated in patients with non-LBBB QRS morphology, who have QRS duration ≥ 150 ms and in NYHA functional classes II, III, and IV.
	CRT pacemaker without ICD insertion is indicated in patients with non-LBBB QRS morphology who have a QRS between 120 and 149 ms and in NYHA functional class IV.
ESC Heart Failure Association guidelines for the diagnosis and treatment of acute and chronic HF 2016	CRT should be considered for symptomatic patients with HF in sinus rhythm with QRS duration ≥ 150 ms and non-LBBB QRS morphology and with LVEF ≤ 35% despite OMT in order to improve symptoms and reduce morbidity and mortality. Class IIa, level of evidence B.
	CRT may be considered for symptomatic patients with HF in sinus rhythm with QRS duration of 130 to 149 ms and non-LBBB QRS morphology and with LVEF ≤ 35% despite OMT in order to improve symptoms and reduce morbidity and mortality. Class IIb, level of evidence B.
Comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure 2017	CRT may be considered for patients in sinus rhythm with NYHA class II, III, or ambulatory class IV HF despite optimal medical therapy, LVEF ≤ 35% and QRS duration ≥ 150 ms with non-LBBB (weak recommendation; low-quality evidence).
	There is no clear evidence of benefit with CRT among patients with QRS durations < 150 ms because of non-LBBB conduction.

The table showed the summary of different international guidelines on indications of CRT in patients with non-LBBB wide QRS complex pattern. ESC: European Society of Cardiology; GDM: guideline-directed medical therapy; OMT: optical medical therapy; HF: heart failure; CRT: cardiac re-synchronization therapy; NYHA: New York Heart Association; ICD: implantable cardioverter defibrillator; LBBB: left bundle branch block; RBBB: right bundle branch block.

In addition, NICE does not provide classes of recommendation or levels of evidence.

Finally, the guidelines published by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand in 2011, do not distinguish between LBBB and non-LBBB in their recommendations for CRT in patients in sinus rhythm. In Table 2, we summarize the different international guidelines of indications of CRT in patients with non-LBBB wide QRS complex.

Evidence for CRT Efficacy in RBBB (Typical vs. Atypical RBBB Responders)

Since the introduction of CRT in the treatment of patients with HF, an increasing number of patients with RBBB QRS morphology or long-drawn-out IVCD have been treated. The reason for that is QRS duration ≥ 120 ms had been considered initially as the only ECG selection criterion for CRT [26, 27]. Angelo et al recently reviewed the past observational studies that assessed the effect of CRT on some surrogate end points of mortality/morbidity and mortality directly. The results of two large US registries including patients with LBBB, IVCD, and RBBB were also included in the review. Neither the observational studies nor the meta-analysis demonstrated any significant benefit in CRT implant in patients with non-LBBB QRS complex pattern including typical RBBB. Moreover, the evidence of excess in mortality in RBBB CRT-treated patients than in LBBB CRT-treated patients is observed in both registries. The straightforward application of CRT in patients with typical RBBB was accordingly discouraged [28].

Although RBBB typically reflect delayed right ventricular (RV) activation, some patients with HF and RBBB pattern on ECG have concomitant superimposed delay in LV activation as well. RBBB commonly masks the underlying co-existent LBBB in broader QRS, the theory that was confirmed by electroanatomic mapping data, which demonstrated that not only RV activation is abnormally delayed but also LV activation delayed [29]. Rosenbaum et al [30] described atypical RBBB pattern as broad, slurred, sometimes bifid R wave on leads I and aVL, together with a leftward axis deviation frequently noted in LBBB QRS morphology patients (Fig. 2).

A recent review of several studies, that considered CRT in the subset of atypical RBBB, stated that acute response to CRT is clinically relevant and has positive values. Additional studies should be valued also as to whether a subset of patients with RBBB may benefit from CRT [28]. Subsequently, a study evaluated 66 patients with RBBB (31 with typical RBBB and 35 with atypical RBBB) treated with CRT and followed up for almost 2 years. The target end points of reduction in LV end-

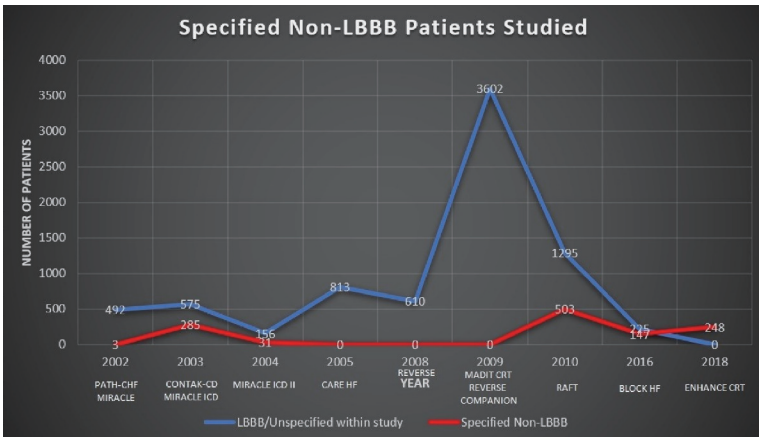

Figure 3. Line-graph representing the volume of patients studied over time, both LBBB/unspecified (blue) and specified non-LBBB (red). Only since 2016 can we see the gap beginning to narrow.

systolic volume index (ESVI)≥15% or reduction in the NYHA class≥1 or Packer score variation (NYHA response with no HF-related hospitalization events or death) were considered. This showed 71.4% ESVI responders in atypical RBBB group in comparison with only 19.4% in typical RBBB group (P=0.001). Furthermore, 74.3% of patients in atypical RBBB group were NYHA responders compared with 32.3% in typical RBBB group (P=0.002). Similarly, in the atypical and typical RBBB groups, respectively 71.4% and 29.0% of patients exhibited a 2-year Packer score of 0 (P=0.002) [31].

We have represented the comparative number of patients studied with specified non-LBBB versus LBBB and unspecified groups in a line graph as shown in Figure 3. This graph clearly demonstrates the much greater numbers of subjects in the LBBB or unspecified IVCD arms of each study. We can see that only from 2016 onwards does the discrepancy of patients' numbers between the two begin to narrow and increase data for non-LBBB patients.

Conclusions and Recommendations

Non-LBBB (including atypical RBBB) in symptomatic HF patients may benefit from CRT implants. While the ESC task forces guidelines were directed towards symptomatic HF with EF < 35% patients with broad QRS > 150 ms in non-LBBB patients, yet QRS 130 - 149 may respond with modest expectations of a good response. The American guidelines have the same considerations. However, it is clear that the Canadian guidelines still weakly support non-LBBB/CRT implants if QRS > 150 ms, and in fact, it discourages CRT implants in QRS duration less than 150 ms in non-LBBB patients. Finally, NICE recommendation of non-LBBB with QRS 120 - 149 ms is only indicated in disabling HF (NYHA IV).

Non-LBBB CRT implants remain an area of debate. The previous support to CRT in those patients was on the basis of atypical features of RBBB and great IVCD. It remains a valid clinical decision to consider CRT implant in symptomatic patients (despite of optimized medical therapy) in non-LBBB with QRS duration ≥ 150 ms. Multidisciplinary approaches (e.g. cardiac electrophysiologists, HF cardiologists, physiologist and specialists liaison HF nurses) and new techniques of multipoint pacing are promising in such difficult group of patients with debated indication and expected poor responders. The data are not encouraging in regards to typical RBBB with QRS duration less than 150 ms.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Author Contributions

Maged Henin contributed to study design, manuscript writing and references check. Hany Ragy involved in manuscript review and re editing; James Mannion contributed to creating the tables of the major trials and edited the summary for each and language check. Santhosh David contributed to manuscript review and re-editing. Beshoy Refila contributed to study design, editing the manuscript and review. Usama Boles, the main supervisor, involved in study design, review, editing, and pre-submission check.

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