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REVIEW

Cardiac resynchronisation therapy: current benefits and pitfalls

Annamaria Kosztin, Andras Mihaly Boros, Laszlo Geller, Bela Merkely

Heart and Vascular Centre, Semmelweis University, Budapest, Hungary

Abstract

Cardiac resynchronisation therapy (CRT) has been shown to reduce all-cause mortality, heart failure events, and symptoms while improving exercise capacity and quality of life. Nevertheless, despite a large number of multicentre randomised trials and clear evidence confirming the above, there is still a higher number of patients who fail to develop reverse remodelling. In order to select the optimal patient population, the current European Society of Cardiology guidelines recommend a simultaneous evaluation of QRS morphology and width. However, based on recent data, QRS width itself is a less accurate parameter in the prediction of the outcome, as compared to QRS morphology. Furthermore, the baseline left ventricular (LV) ejection fraction (LVEF), which is also an known criterion for selecting CRT candidates (partly applied due to cost-benefit reasons), can be misleading. Data showed that patients with LVEF > 35% might also benefit from this type of treatment. Thus, LVEF should be evaluated less rigorously when screening patients for resynchronisation therapy. While the subsequent beneficial response to CRT is multifactorial, procedure-related parameters, such as LV lead position, are also crucial. The first data released recently confirmed the previous empiric clinical experience indicating that the LV lead should be implanted into the lateral or posterior coronary sinus side branch. This location was associated with a better long-term clinical outcome in terms of death and heart failure events. Some issues related to CRT are awaiting further clarification, such as the choice of the type of the implanted device (pacemaker or defibrillator) or the decision about CRT device upgrade. This review discusses the current evidence regarding the above, focusing on the questions that should be handled with caution or require clarification.

Key words: cardiac resynchronisation therapy (CRT), current indications, predictors in CRT, upgrade, QRS morphology

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INTRODUCTION

In a selected patient population with symptomatic chronic systolic heart failure (HF), wide QRS, and reduced left ventricular (LV) ejection fraction (LVEF), cardiac resynchronisation therapy (CRT) is effective and can slow down or reverse further progression of the disease [1–3].

As a result of pacing along the latest activated area of the left ventricle, the intra- and interventricular dyssynchrony can be diminished, leading to a better activation pattern with narrower QRS and a more effective contraction with a higher stroke volume [4]. The acute beneficial haemodynamic and electromechanical effects lead to long-term clinical response resulting in reverse remodelling of the left ventricle in selected patients. In these cases, CRT has been shown to significantly reduce HF symptoms, improve survival, and prevent HF hospitalisation [1–3].

Despite clear evidence for CRT efficacy from a considerable amount of multicentre randomised trials in this field conducted in the last two decades, 20% to 40% of patients still do not respond to this therapy and fail to develop reverse remodelling [5].

There is conclusive evidence (class I level A) of the beneficial effect of CRT on HF symptoms, exercise capacity, LV function, and HF hospitalisation and mortality risk in symptomatic patients (New York Heart Association [NYHA] functional class II–IV) with sinus rhythm, typical left bundle branch block (LBBB) morphology, and wide QRS (> 150 ms) in the current guidelines, and level B evidence in patients with QRS width between 120 and 150 ms. In the presence of non-typical LBBB, the benefit is less pronounced, hence in patients with QRS width > 150 ms and non-LBBB morphology, CRT has a class IIa level B of recommendation, in patients with QRS

Address for correspondence:
Bela Merkely, MD, PhD, DSc, Semmelweis University, Heart and Vascular Centre, Varosmajor str. 68., Budapest, Hungary, tel: +361 458 6810, e-mail: merkely.study@gmail.com

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width 120–150 ms it has a class IIb level B of recommendation, while in patients with narrow QRS (< 130 ms) CRT is contraindicated (class III) [6, 7].

PATIENT SELECTION

QRS width vs. morphology

Despite the fact that QRS width and morphology are recognised as important prognostic factors of clinical outcome, their predictive strength and superiority to other prognosticators are still debated.

A poor response to CRT in patients with QRS < 150 ms has been confirmed in several trials and meta-analyses. The first recommendations specified in the European Society of Cardiology (ESC) guidelines were derived from the COMPANION [1] and CARE-HF [2] studies, which used QRS > 120 ms as a cut-off value for study inclusion. Later trials, which applied wider QRS as the inclusion criterion, such as MIRACLE [8], MADIT-CRT [3] (130 ms), and MUSTIC [9] (150 ms), revealed that the most pronounced benefit of CRT can be seen in patients with QRS > 150 ms.

The current guidelines recommend the evaluation of QRS morphology (typical LBBB vs. non-LBBB) as well as QRS width, which should be more than 130 ms, and preferably even wider than 150 ms, for optimal patient selection for CRT [6, 7]. In patients with narrow QRS (< 130 ms), CRT is contraindicated.

In the MADIT-CRT study it was demonstrated that the presence of LBBB is associated with a 53% reduction in the risk of death or HF events, while the presence of non-LBBB morphology is accompanied by no clinical benefit from CRT [3]. A recent meta-analysis has validated this landmark result, showing a 36% risk reduction in all-cause mortality in patients with LBBB, while no benefit was seen in patients with non-LBBB (defined as right bundle branch block [RBBB] or intraventricular conduction delay) [10]. In a subgroup analysis of the MADIT-CRT population, QRS morphology was the only predictor of the long-term clinical outcome (independently of QRS width > 135 ms), and patients with non-LBBB morphology and QRS width < 135 ms had the worst outcome [11].

A recent analysis revealed that non-LBBB patients with a prolonged PR-interval (> 230 ms) could also derive clinical benefit from the implantation of a CRT defibrillator (CRT-D) [12]. It was associated with a 73% reduction in the risk of HF/death and an 81% decrease in the risk of all-cause mortality, as compared with implantable cardioverter-defibrillator (ICD) therapy without CRT. In non-LBBB patients with normal PR-interval, CRT-D therapy was associated with a trend toward an increased risk of HF/death (hazard ratio [HR] = 1.45; 95% confidence interval [CI] 0.96–2.19; $p = 0.078$; $p < 0.001$) and a more than twofold higher mortality risk (HR = 2.14; 95% CI 1.12–4.09; $p = 0.022$; $p < 0.001$) [12]. These clinical outcomes were also irrespective of baseline QRS duration.

At the same time, an individual patient meta-analysis published by Cleland et al. [13] showed that QRS duration is the only parameter predicting the magnitude of CRT effect on outcomes. However, these results should be handled with caution and cannot obscure the fact that QRS width in LBBB morphology is over 150 ms, while in RBBB morphology it is usually shorter than 150 ms [14, 15].

Left ventricular ejection fraction

Left ventricular ejection fraction not only is a useful parameter in the selection of candidates for resynchronisation, but its improvement also correlates with survival and thus can be regarded as a surrogate clinical endpoint [16].

Early trials such as COMPANION [1] and CARE-HF [2] showed a clear benefit of resynchronisation in patients with severe HF symptoms and significantly reduced ejection fraction (LVEF ≤ 35%). In the REVERSE [17] trial the inclusion criterion for LVEF was extended (≤ 40%) and approximately one-third of the enrolled patients had LVEF between 30% and 40%. Interestingly, this patient population also showed a significant improvement in echocardiographic parameters and the reduction in composite clinical endpoint of HF events and all-cause mortality [17].

Furthermore, a unique subgroup analysis of the MADIT-CRT trial conducted by Kutyifa et al. [18], which focused on patients whose LVEF was far beyond the inclusion criteria (LVEF > 30%), demonstrated that patients with significantly decreased LVEF (≤ 25%) have the highest risk for subsequent HF events or all-cause mortality, and the echocardiographic response to CRT is more pronounced among patients with higher LVEF [18]. In view of the above results, more perceptive thinking about the evaluation of LVEF might be needed.

PROCEDURE-RELATED PARAMETERS: LV LEAD LOCATION

During the progression of chronic systolic HF, intraventricular dyssynchrony can be developed. Especially in LBBB, the activation shows a U-shaped pattern, where the line of a block generally parallels the septum [19]. Thus, the latest activated part is mostly the posterolateral/lateral region of the left ventricle [19, 20].

Although smaller studies [19, 20] have confirmed this phenomenon, large randomised trials so far failed to show conclusive results regarding the benefit of LV lead implantation into this lateral/posterolateral part.

Early findings from the REVERSE [17], RAFT [21], and MADIT-CRT [3] trials confirmed that avoiding the apical part is essential during implantation; however, no comprehensive data regarding the short-axis positions (anterior, lateral, or posterior) were included.

A recent subgroup analysis of the MADIT-CRT [22] was the first one to reveal the long-term benefit of LV lead implantation to the lateral or posterior side. The study showed that in HF patients with LBBB and an implanted CRT-D all lead locations (lateral, posterior, anterior, or apical) were similarly associated with a reduction in the risk of HF events compared

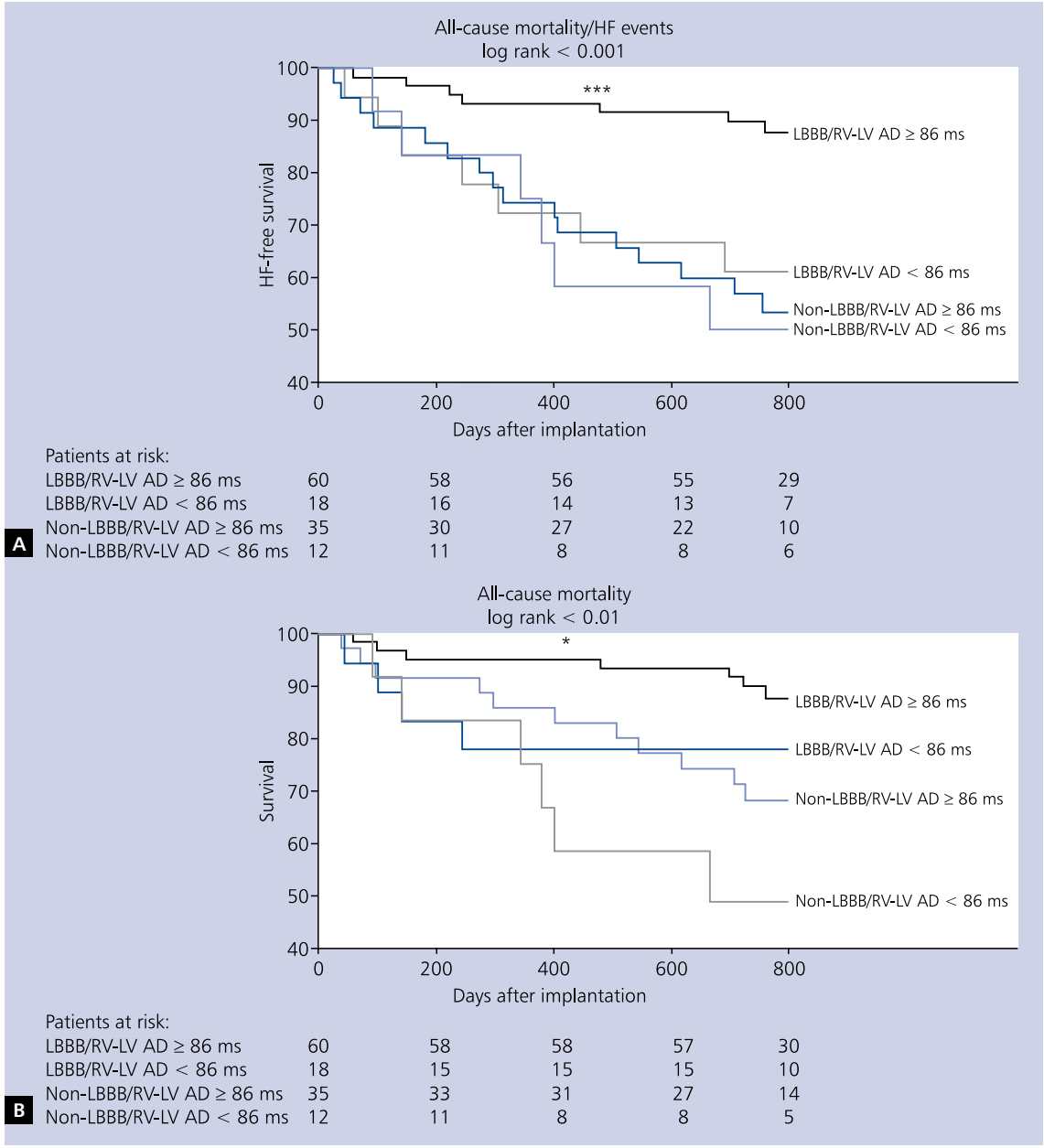

Figure 1. Reduced probability of heart failure (HF)/death (**A**) and all-cause death (**B**) in patients with a left bundle branch block (LBBB) and right to left ventricular activation delay (RV-LV AD) ≥ 86 ms vs. patients with non-LBBB receiving cardiac resynchronisation therapy (CRT); *p < 0.01; ***p < 0.001. Reprinted from: Kosztin A, et al. Longer right to left ventricular activation delay at cardiac resynchronization therapy implantation is associated with improved clinical outcome in left bundle branch block patients. EP Europace. 2016; 18(4): 550–559, by permission of Oxford University Press on behalf of the European Society of Cardiology

to ICD alone. However, the reduction in mortality derived from CRT-D was associated only with a lateral or posterior LV lead location.

Right to left ventricular activation delay (RV-LV AD) may also reflect the location of the LV lead, but it additionally presents the prolonged activation pattern derived from the slow conduction. In a few small studies the RV-LV AD or QRS to LV sensed (Q-LV) delay [23, 24] were able to predict the clinical and echocardiographic response to CRT. In a prospective study of our group, during a median follow-up of 2.2 years, 44 (35%) patients experienced HF events or death, and 36 (29%) patients died [25]. Patients with a longer activation delay (RV-LV AD ≥ 86 ms) had a lower rate of HF and death analysed cumulatively as compared to those with RV-LV AD < 86 ms. All-cause mortality occurred less frequently in the former group compared to the latter group. Importantly, patients with LBBB and RV-LV AD ≥ 86 ms at implantation had a lower cumulative probability of HF/death when compared

Table 1. Cardiac resynchronisation therapy (CRT) state of the art

Evaluation of QRS width and morphology	Patients with LBBB morphology should have QRS width > 130 ms. Non-LBBB patients with prolonged PR-interval (> 230 ms) might also benefit from CRT.
Assessment of LVEF	CRT is indicated in patients with LVEF < 35%. Patients with higher ejection fraction might also benefit from CRT, while significantly decreased LVEF (≤ 25%) is associated with higher risk of subsequent HF events or all-cause mortality.
Procedure-related parameters	Left ventricular lead should be implanted to a lateral or posterior vein, especially in patients with typical LBBB morphology. Measuring the right to left ventricular activation delay might also help to optimise the lead position.
Decision between CRT-P vs. CRT-D	Patients with ischaemic HF might benefit from CRT-D implantation, while in patients with non-ischaemic cardiomyopathy there is no additional reduction in mortality when adding an ICD.
CRT upgrade	Patients with a conventional pacemaker or an ICD and chronic high percentage of right ventricular pacing might be considered for CRT upgrade if symptomatic HF with reduced ejection fraction is present.

HF — heart failure; ICD — implantable cardioverter-defibrillator; LBBB — left bundle branch block; LVEF — left ventricular ejection fraction

with the remainder and patients with non-LBBB (Fig. 1A). This difference translated into a 77% reduction in the risk of HF or death (HR = 0.23; 95% CI 0.11–0.49; p < 0.001), after adjustment for relevant clinical covariates [25]. Similar findings were observed for all-cause mortality (Fig. 1B), which translated into a 65% risk reduction in the multivariate models (HR = 0.35; 95% CI 0.16–0.75; p = 0.007). Taken together, RV-LV AD could predict death or HF events in LBBB patients, while in patients with short delay or non-LBBB morphology, no significant clinical benefit was found [25].

THE DECISION BETWEEN CRT-P VS. CRT-D

To date, there have been no randomised clinical trials directly comparing the effect of CRT pacemaker (CRT-P) vs. CRT-D implantation. Current recommendations prefer CRT-D over CRT-P in patients with survival estimation > one year, ischaemic aetiology, and few comorbidities (particularly the lack of renal failure) [6, 7].

The only exception was the DANISH trial [26], which investigated non-ischaemic patients and partly randomised subjects to CRT-D vs. CRT-P. The subgroup analysis revealed that CRT-D had no mortality benefit over CRT-P in this patient population (HR = 0.91; 95% CI 0.64–1.29; p = 0.59).

Furthermore, results from our high-volume, single-centre study showed that in patients with ischaemic HF, CRT-D is associated with lower mortality as compared to CRT-P [27]. However, in patients with non-ischaemic cardiomyopathy, there is no reduction in all-cause mortality when adding an ICD. Moreover, patients with ischaemic and non-ischaemic cardiomyopathy experience similar echocardiographic improvement.

Partly in line with our results, a recent meta-analysis of Barra et al. [28], which included 18,874 patients from 44 studies and, demonstrated that CRT-D recipients were more often male, were younger, had less severe symptoms, less often experienced atrial fibrillation, were more often diagnosed with ischaemic heart disease, and more often received β-blocker therapy compared to CRT-P patients. The mortality rate was approximately twofold higher in CRT-P recipients, while sudden cardiac death was more prevalent in men, patients with ischaemic cardiomyopathy, and patients with severe HF symptoms (≥ NYHA class III).

Overall, the decision regarding CRT-P or CRT-D implantation should be made individually in each patient, on the basis of measuring the potential risk of sudden cardiac death and estimating the chance of reverse remodelling in light of the comorbidities.

CRT UPGRADE

Chronic right ventricular pacing correlates with and increases the risk of atrial fibrillation, HF events and all-cause mortality by causing ventricular dyssynchrony similar to LBBB [29, 30]. Despite the deleterious effects of right ventricular pacing, data regarding the benefit and indications for CRT upgrade in this scenario are scarce. The most recent European Heart Failure guidelines recommend CRT upgrade as class IIb (level B) in patients with progressive HF, while the American College of Cardiology guidelines focus on the percentage of pacing rather than the symptoms [7, 31]. In Europe, approximately a quarter of CRT implantations are upgrade procedures; however, candidates for CRT upgrade are selected at the discretion of the clinicians. The potential benefits and risks (e.g. higher complication rate) of this decision should be assessed individually [32].

To facilitate patient selection for CRT upgrade and clarify the indications, the first prospective, randomised, multicentre trial, the BUDAPEST CRT upgrade study, was initiated by our group [33]. This trial will gather evidence for CRT upgrade in symptomatic HF patients with reduced ejection fraction and a relatively high percentage (> 20%) of ventricular pacing by

randomising the participants to CRT-D or ICD therapy. The composite endpoint of echocardiographic response, all-cause mortality, and HF events during 12-month follow-up will be evaluated.

CONCLUSIONS

Despite the proven beneficial long-term clinical effect of CRT, there is still a significant number of patients who fail to develop reverse remodelling after the implantation, which also correlates with higher rates of mortality and HF hospitalisations. In order to decrease the rate of non-responders, optimal patient selection and assessment of implantation parameters are crucial (Table 1).

Current guidelines primarily recommend selecting patients with typical LBBB morphology and highlight the importance of QRS width in CRT candidate selection. Patients with non-typical LBBB might also be considered for CRT, regardless of QRS width, provided they have a prolonged PR-interval.

Baseline LVEF is an exact criterion for optimal patient selection indicated in the guidelines. Data showed that patients with higher ejection fraction might also benefit from CRT, therefore, a more perceptive thinking about the evaluation of LVEF might be needed when screening patients for resynchronisation therapy.

Apart from the optimal patient selection, procedure-related parameters, such as LV lead position, are also crucial in the clinical outcome. A recent subgroup analysis of the MADIT-CRT long-term follow-up data confirmed empirically that LV lead implantation to a lateral or posterior coronary sinus side branch is associated with better long-term clinical response and reduction in death and HF events.

Some issues related to CRT are still open and are awaiting further clarification, e.g. the decision between CRT-P vs. CRT-D implantation or CRT upgrade. The latter will be addressed in our investigator-initiated, prospective, randomised, multicentre trial: the BUDAPEST-CRT upgrade study.

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References

1. Bristow M, Saxon L, Boehmer J, et al. Cardiac-Resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004; 350(21): 2140–2150, doi: 10.1056/nejmoa032423.
2. Cleland JGF, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005; 352(15): 1539–1549, doi: 10.1056/NEJMoa050496, indexed in Pubmed: 15753115.
3. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009; 361(14): 1329–1338, doi: 10.1056/NEJMoa0906431, indexed in Pubmed: 19723701.
4. Leclercq C, Cazeau S, Le Breton H, et al. Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure. J Am Coll Cardiol. 1998; 32(7): 1825–1831, indexed in Pubmed: 9857858.
5. Ypenburg C, van Bommel RJ, Borleffs CJ, et al. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. J Am Coll Cardiol. 2009; 53(6): 483–490, doi: 10.1016/j.jacc.2008.10.032, indexed in Pubmed: 19195605.
6. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013; 34(29): 2281–2329, doi: 10.1093/eurheartj/eht150, indexed in Pubmed: 23801822.
7. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27): 2129–2200, doi: 10.1093/eurheartj/ehw128, indexed in Pubmed: 27206819.
8. St John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation. 2003; 107(15): 1985–1990, doi: 10.1161/01.CIR.0000065226.24159.E9, indexed in Pubmed: 12668512.
9. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001; 344(12): 873–880, doi: 10.1056/NEJM200103223441202, indexed in Pubmed: 11259720.
10. Khidir MJH, Delgado V, Ajmone Marsan N, et al. QRS duration versus morphology and survival after cardiac resynchronization therapy. ESC Heart Fail. 2017; 4(1): 23–30, doi: 10.1002/ehf2.12122, indexed in Pubmed: 28217309.
11. Biton Y, Kutyifa V, Cygankiewicz I, et al. Relation of QRS Duration to Clinical Benefit of Cardiac Resynchronization Therapy in Mild Heart Failure Patients Without Left Bundle Branch Block: The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy Substudy. Circ Heart Fail. 2016; 9(2): e002667, doi: 10.1161/CIRCHEARTFAILURE.115.002667, indexed in Pubmed: 26823498.
12. Kutyifa V, Stockburger M, Daubert JP, et al. PR interval identifies clinical response in patients with non-left bundle branch block: a Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy substudy. Circ Arrhythm Electrophysiol. 2014; 7(4): 645–651, doi: 10.1161/CIRCEP.113.001299, indexed in Pubmed: 24963007.
13. Cleland JG, Abraham WT, Linde C, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. Eur Heart J. 2013; 34(46): 3547–3556, doi: 10.1093/eurheartj/eht290, indexed in Pubmed: 23900696.
14. Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. J Am Coll Cardiol. 2005; 46(12): 2183–2192, doi: 10.1016/j.jacc.2005.01.071, indexed in Pubmed: 16360044.
15. Zareba W. Cardiac resynchronization therapy: forget QRS duration but do not forget QRS morphology. J Electrocardiol. 2013; 46(2): 145–146, doi: 10.1016/j.jelectrocard.2013.01.003, indexed in Pubmed: 23399052.
16. Anker SD, Schroeder S, Atar D, et al. Traditional and new composite endpoints in heart failure clinical trials: facilitating comprehensive efficacy assessments and improving trial efficiency. Eur J Heart Fail. 2016; 18(5): 482–489, doi: 10.1002/ejhf.516, indexed in Pubmed: 27071916.

17. Daubert C, Gold MR, Abraham WT, et al. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. J Am Coll Cardiol. 2009; 54(20): 1837–1846, doi: 10.1016/j.jacc.2009.08.011, indexed in Pubmed: 19800193.
18. Kutyifa V, Kloppe A, Zareba W, et al. The influence of left ventricular ejection fraction on the effectiveness of cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). J Am Coll Cardiol. 2013; 61(9): 936–944, doi: 10.1016/j.jacc.2012.11.051, indexed in Pubmed: 23449428.
19. Auricchio A, Fantoni C, Regoli F, et al. Characterization of left ventricular activation in patients with heart failure and left bundle-branch block. Circulation. 2004; 109(9): 1133–1139, doi: 10.1161/01.CIR.0000118502.91105.F6, indexed in Pubmed: 14993135.
20. Ghio S, Constantin C, Klersy C, et al. Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration. Eur Heart J. 2004; 25(7): 571–578, doi: 10.1016/j.ehj.2003.09.030, indexed in Pubmed: 15120054.
21. Tang ASL, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 2010; 363(25): 2385–2395, doi: 10.1056/NEJMoa1009540, indexed in Pubmed: 21073365.
22. Kutyifa V, Kosztin A, Klein H, et al. Left ventricular lead location impacts long-term clinical outcome in left bundle branch block patients. J Am Coll Cardiol. 2015; 65(10): A910, doi: 10.1016/s0735-1097(15)60910-x.
23. D'Onofrio A, Botto G, Mantica M, et al. The interventricular conduction time is associated with response to cardiac resynchronization therapy: interventricular electrical delay. Int J Cardiol. 2013; 168(5): 5067–5068, doi: 10.1016/j.ijcard.2013.07.201, indexed in Pubmed: 23953259.
24. D'Onofrio A, Botto G, Mantica M, et al. Incremental value of larger interventricular conduction time in improving cardiac resynchronization therapy outcome in patients with different QRS duration. J Cardiovasc Electrophysiol. 2014; 25(5): 500–506, doi: 10.1111/jce.12381, indexed in Pubmed: 24494797.
25. Kosztin A, Kutyifa V, Nagy VK, et al. Longer right to left ventricular activation delay at cardiac resynchronization therapy implantation is associated with improved clinical outcome in left bundle branch block patients. Europace. 2016; 18(4): 550–559, doi: 10.1093/europace/euv117, indexed in Pubmed: 26116830.
26. Køber L, Thune JJ, Nielsen JC, et al. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med. 2016; 375(13): 1221–1230, doi: 10.1056/NEJMoa1608029, indexed in Pubmed: 27571011.
27. Kutyifa V, Geller L, Bogyi P, et al. Effect of cardiac resynchronization therapy with implantable cardioverter defibrillator versus cardiac resynchronization therapy with pacemaker on mortality in heart failure patients: results of a high-volume, single-centre experience. Eur J Heart Fail. 2014; 16(12): 1323–1330, doi: 10.1002/ejhf.185, indexed in Pubmed: 25379962.
28. Barra S, Providência R, Duehmke R, et al. Cause-of-death analysis in patients with cardiac resynchronization therapy with or without a defibrillator: a systematic review and proportional meta-analysis. EP Europace. 2018; 20(3): 481–491, doi: 10.1093/europace/eux094.
29. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation. 2003; 107(23): 2932–2937, doi: 10.1161/01.CIR.0000072769.17295.B1, indexed in Pubmed: 12782566.
30. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-Chamber pacing or ventricular backup pacing in patients with an implantable defibrillator. JAMA. 2002; 288(24): 3115–3123, doi: 10.1001/jama.288.24.3115.
31. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013; 61(3): e6–75.
32. Linde CM, Normand C, Bogale N, et al. Upgrades from a previous device compared to de novo cardiac resynchronization therapy in the European Society of Cardiology CRT Survey II. Eur J Heart Fail. 2018 [Epub ahead of print], doi: 10.1002/ejhf.1235, indexed in Pubmed: 29806208.
33. Merkely B, Kosztin A, Roka A, et al. Rationale and design of the BUDAPEST-CRT Upgrade Study: a prospective, randomized, multicentre clinical trial. Europace. 2017; 19(9): 1549–1555, doi: 10.1093/europace/euw193, indexed in Pubmed: 28339581.

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