Cardiac resynchronization in heart failure: Recent advances and their practical implications

Cecilia Linde

Heart, Vascular and Neurology Theme, Karolinska University Hospital and the Karolinska Institutet, Stockholm, Sweden

Correspondence to:
Cecilia Linde, MD, PhD,
Heart, Vascular and Neurology Theme,
Karolinska University Hospital and the Karolinska Institutet,
Stockholm, Sweden,
phone: +46 (0)760 526494
e-mail: cecilia.linde@ki.se

DOI: 10.33963/KP.a2023.0020

Received:
January 3, 2023

Accepted:
January 3, 2023

Early publication date:
January 15, 2023

ABSTRACT

Cardiac resynchronisation (CRT) improves survival and reduces heart failure hospitalisations, in symptomatic patients with heart failure (HF) with reduced ejection fraction with wide QRS despite guidelines indicated medical therapy. In patients with mild HF symptoms (New York Heart Association [NYHA], class II) CRT delays or reverses disease progression. Still, CRT is largely underused. The results of CRT Survey II indicates wide adoption of class I indications in European Society of Cardiology guidelines but with important national differences. As an example more patients in Poland had ischemic HF etiology and in NYHA III than in the overall CRT cohort. Similar patterns were seen in other countries suggesting that some patients such as those in NYHA II and with non-ischemic aetiology may be especially underserved by CRT. But the Survey results also shows wide use in areas with week scientific evidence such in atrial fibrillation (AF) and when upgrading from ongoing implantable cardioverter defibrillator or right ventricular pacing to CRT. This practise may imply the belief of the physcian than CRT may but also highlights the need of randomised studies to elucidate CRT effects in such patients. Besides, gaps of evidence the review further discusses reasons for obstacles for CRT implementation and the challenges with the traditional responder definition which may deter the clinician from offering CRT therapy. Finally, the importance of sex and body size for electrical selection criteria for CRT are discussed. A person with small body size and/or female sex may may derive CRT benefit at shorter QRS durations than a bigger individual indicating the need to shift to personalized medicine.

Key words: cardiac resynchronization therapy, chronic heart failure, implementation, indications, atrial fibrillation, sex-differences

INTRODUCTION

Cardiac resynchronization therapy (CRT) first introduced in the late 1990s has been shown to improve survival, reduce heart failure hospitalizations, improve exercise tolerance, and quality of life in patients with heart failure (HF) with reduced ejection fraction (HFrEF) who remain symptomatic and with wide QRS despite guidelines indicating medical therapy (GMDT) in pivotal trials [1–7]. In later years there have been many breakthroughs in HF medication reflected in recent guidelines, with the SGLT2 inhibitors indicated in patients with HFrEF. In addition, the sequential approach to initiating HF drugs has been recommended to be replaced by initiation of all four guidelines-indicated drugs within the first month of treatment. Moreover, most of these drugs also reduce the risk of sudden cardiac death (SCD), which makes the decision to provide a primary preventive defibrillator in CRT (CRT-D) especially challenging.

Guidelines state that CRT is indicated in a subset of HFrEF patients when HF medication is insufficient [8]. CRT is indicated in patients with left bundle branch block (LBBB) and wide QRS, with a class I level of evidence A for QRS width ≥150 ms and with a class IIa for QRS width 130–149 ms [8]. For patients without LBBB, the recommendations are class IIa or IIb depending on QRS width. Importantly, CRT is contraindicated in QRS width <130 ms [9] because normal or near normal conduction and activation of the ventricles are always superior to those induced by pacing, including biventricular pacing.

CRT is effective in symptomatic HF patients, meaning New York Heart Association

(NYHA) class II–IV [1–7]. One of the main mechanisms of action is left ventricular (LV) reverse remodeling. This process starts immediately after CRT is turned on [10] and further evolves over 2 years [11]. In REVERSE, we could also demonstrate sustained LV reverse remodeling over 5 years [12] and linked it to low mortality and morbidity. This means that CRT both reverses remodeling and delays disease progression at least when given in early disease states. But do patients get access to this life-saving therapy?

CRT PRACTICE ACROSS ESC COUNTRIES: EHRA HFA CRT SURVEY I AND II

Registry studies have shown that up to two-thirds of eligible patients are not treated with CRT [13], and CRT care is often suboptimal, which reduces treatment effects. We know from the European Heart Rhythm Association (EhrA) white book that implementation of CRT is low with a median implantation rate of 86/milion [13, 14]. CRT Survey II therefore aimed at studying indications and practice of CRT across European Society of Cardiology (ESC) countries to identify obstacles to device implementation and to enhance therapy use [15]. It included 11 088 CRT recipients (*de novo* or upgrades) from 42 ESC member countries. Poland was the greatest contributor with 1241 patients. The most common reason for CRT in this Survey was moderate HF, with 58% of CRT implantations performed in patients in NYHA class III. In addition, 48% had an HF hospitalization within the last year as a marker of disease severity. Importantly, even in countries like Germany with the highest overall implantation rate in all ESC countries, the proportion of CRT in NYHA II was low, suggesting overall under-implementation of therapy and in particular in NYHA class II for which CRT might be of particular value in delaying disease progression.

CRT practice in CRT Survey II reflected the ESC guidelines. However, weaker recommendations were also used. For example, 26% of CRT therapy was given in atrial fibrillation (AF) patients, and upgrades from ongoing implantable cardioverter defibrillator (ICD) or right ventricular (RV) pacing constituted 28%, particularly in countries with a long tradition of CRT therapy.

In the Survey, more patients in Poland had ischemic HF etiology than in the overall CRT cohort, and there were more patients in NYHA class III and with more comorbidities [16].

CRT IN PATIENTS IN NEED OF RV PACING

It is well-known that patients paced in the RV ≥20% and with a normal intrinsic conduction risk developing LV dysfunction and, in time, heart failure as evidenced in the DAVID [17] and MOST trials [18], which is both avoidable and unacceptable. The BLOCK-HF study showed that CRT therapy in such patients is superior to RV pacing for reducing mortality and HF hospitalizations and improving LV function [19] and thus is preferable in patients in need of RV pacing. Reflecting this fact, 18% of CRT was given to patients in need of pacing in CRT Survey II [15]. The guidelines' recommendation was, however, published after Survey II was planned.

There is a reason to believe that this indication is not widely adopted although it has a class I level A recommendation in the current guidelines [8]. It may be because many patients have intermittent high-degree atrioventricular (AV) block and most DDD-pacemakers have algorithms adjusting AV delay to allow intrinsic conduction and thus minimize the level of RV pacing. But this approach will require careful monitoring and documentation since the extent of RV pacing, as well as LV function, may change over time. In the future, the risk of RV pacing-induced HF may decline due to the potential greater use of leadless pacing or His pacing when such techniques are available and feasible.

But currently and according to the 2021 ESC and EHRA pacing and CRT guidelines, His pacing should be considered when placement of a coronary sinus lead to achieve CRT is not possible [8]. The guidelines also stress that lead problems, such as stimulation threshold elevations in His bundle or lead dislodgement, may arise and state that an RV backup pacing lead should be implanted in pacemaker-dependent pacing [8].

CRT IN ATRIAL FIBRILLATION

Atrial fibrillation accompanies heart failure, and its prevalence increases in patients with more severe HF symptoms meaning that 10%–50% of those with HFrEF have AF. Yet the efficacy of CRT in AF patients has not been studied in CRT randomized controlled studies, and the results of small randomised studies (MUSTIC-AF) and observational studies are still conflicting. The MUSTIC-AF was a small crossover study of HF patients with permanent AF. Comparing RV to CRT pacing, the study showed improved exercise tolerance but only modest LV remodeling with CRT compared to RV pacing [20]. In the much larger RAFT trial, there were 229 HF patients with permanent AF randomized to CRT-ICD or ICD alone [7]. In a post hoc analysis, no benefit in the combined primary endpoint of all-cause mortality and HF hospitalizations was shown in AF patients, but the trial was not powered to show clear treatment effects in patients with AF. The results of a meta-analysis of retrospective studies suggest CRT benefits may be attenuated in patients with a history of AF [21]. Although AF has been an exclusion criterion in many CRT recipients, many study patients had a history of AF when randomized. In a post hoc analysis of the COMPANION trial, the benefits of CRT were compared between patients with sinus rhythm and those with a history of AF [22]. Again, there was no benefit of CRT in patients with a history of AF. One probable contributing factor to the inferiority or no benefit of CRT in AF patients is the lack of delivery of therapy since intrinsic conduction overrides biventricular stimulation, for example, during exercise. AV junction ablation is recommended to ascertain delivery of biventricular pacing in such patients [8, 23].

Despite a clear lack of evidence, CRT Survey II shows that as much as 1 in 4 of those who received CRT therapy were AF patients, which shows that many cardiologists are convinced that CRT is beneficial despite the lack of evidence. In conclusion, there is a clear need for a randomized study in AF patients.

UPGRADING

Patients who develop HF and LVEF <35% during treatment with an ICD or an RV-based pacemaker and who have RV pacing ≥20% of the time should be considered for upgrading to CRT (level of evidence IIa B) based on the current guidelines [8], but the scientific evidence for this recommendation is insufficient. From CRT Survey II, we know that upgrading is common across ESC countries with no apparent excess perioperative risk in conjunction with the implantation procedures compared to *de novo* CRT implantation despite older age in upgraded patients [24].

The Budapest CRT upgrade study [25] is a prospective randomized trial that is ongoing. It compares upgrades from RV pacing or ICD to CRT-D or CRT-P in patients who had low LVEF (150 ms) and ≥20% RV pacing without having intrinsic LBBB, RV dilatation (RV diameter >50 mm), severe valve impairment, or severe renal impairment (>200 µmol/l). The baseline characteristics have been published [26] and show that patients are in their early 70s and with multiple comorbidities. Results will be presented very soon and will show the outcomes of CRT upgrade with respect to all-cause mortality, HF events, and echocardiographic response. The results may contribute to a more precise definition and extension of the current guidelines for CRT upgrades. The study is unique and will hopefully elucidate the value of upgrading to CRT for better? outcomes.

CRT RESPONSE

Response to therapy traditionally has been categorized as improved, unchanged, or worsened. Indeed, in HF trials, Packer introduced a combined endpoint for HF trials, and this endpoint has been extensively used in CRT trials. It consists of a combination of mortality, HF hospitalization, NYHA class, and patients' global assessment, defining patients as improved, unchanged, or worsened [27].

In oncology, partial remission has long been recognized as an acceptable response to therapy. In contrast, cardiology has only accepted improvements as a response to CRT even though HF is a chronic disease just like many cancers (Figure 1). One of the major challenges is thus that as much as 30%–40% of patients are said not to "respond" to CRT, which encompasses both cases unchanged or worsened by CRT. Such a high non-response rate may well deter physicians from referring patients for CRT, and it may well contribute to under-implementation of CRT together with the high upfront cost of the device and the fear of complications. Requirements for individual response are absent in HF drug therapy, and thus many patients do not perceive a difference when additional guidelines indicated medications should be given in addition to the existing ones. CRT is always given on top of HF medication, but still a "response" — meaning improved disease state — is required for a physician to classify the outcome benefits.

In CRT studies, the response is defined by a 6- or 12-month reduction in LV end-systolic volume index and NYHA class or a combination of the two. But there are many reasons to believe this definition may be outdated. There is emerging evidence that an unchanged condition (often called stabilization or non-progression) is also positive for the patient. For example, it has long been known that CRT in patients with ischemic HF etiology improves outcomes despite the limited extent of reverse remodeling [10].

REVERSE was a multinational randomized controlled trials (RCT) comparing CRT to non-CRT in NYHA class II HF patients. In the trial design, left ventricular end-systolic volume index (LVEVSI) change was the secondary powered endpoint, and the primary endpoint was the composite Packer's endpoint. Packer's combined endpoint was only significant after 2 years of results [10] but reached only borderline significance after one year [7] reflecting mild disease state in randomized patients.

In a subsequent substudy based on patients assigned to CRT at randomization, we looked at the impact of these two endpoints, both evaluated within the first year, and compared 5-year mortality in patients judged as worsened to those judged as stabilized (unchanged) or improved. A similar probability of death in those stabilized or improved was found (Figure 2). In contrast, patients who worsened had significantly worse prognoses [28–29]. The conclusion is twofold. Firstly, the lack of early improvement in LVESVi or clinical improvement does not preclude subsequent outcome benefits. Secondly and importantly, patients who deteriorate during CRT need to be considered for advanced therapies [30].

WOMEN AND BODY SIZE

There is reason to believe that women are undertreated with CRT and women constituted 25% of CRT implantations in CRT Survey II [15]. Women more often have LBBB [31] than men and dilated cardiomyopathy, both linked to CRT benefits.

But women also have smaller QRS width than men and therefore may not fulfill guidelines Class I recommendations for CRT [8]. In addition, CRT studies are based on 25% females as study patients. Women are said to have been underrepresented in CRT trials, and not fulfilling the QRS width criteria may be one reason, but another is that women less often have HFrEF and more often have HF with preserved ejection fraction (HFpEF) [32].

Both differences in QRS widths but also in body size and height may distinguish women and men more likely to respond to CRT. In a pooled metanalysis based on 4076 patients in 2 RCTs, women [33] benefited from CRT-D more than men. In patients with LBBB and QRS of

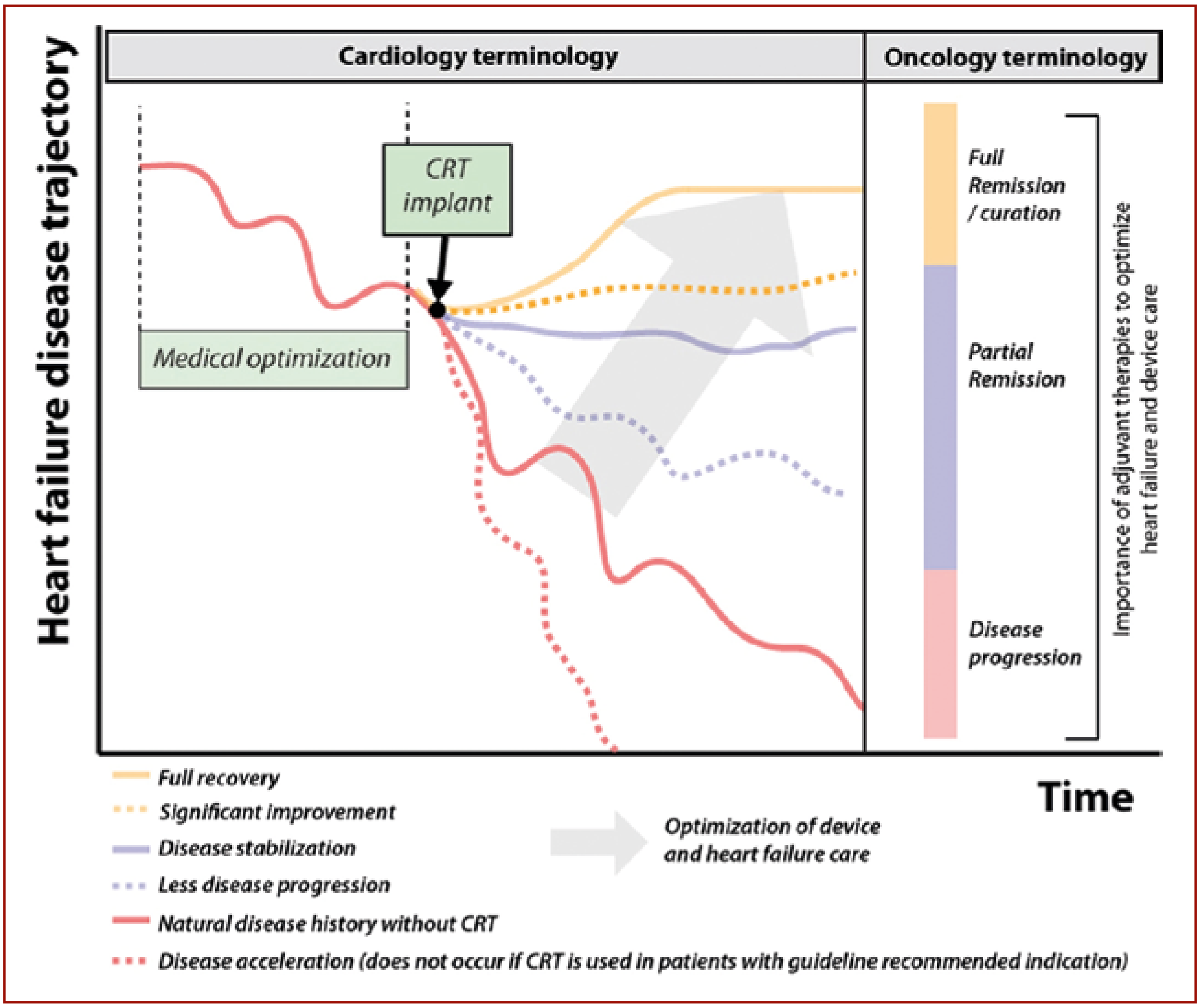

Figure 1. Role of cardiac resynchronization therapy (CRT) in disease modification of the heart failure trajectory

Reproduced with permission, from: Mullens W, et al. Optimized implementation of cardiac resynchronization therapy: a call for action or referral and optimization of care. Eur J Heart Fail. 2020; 22(12): 2349–2369, doi: 10.1002/ejhf.2046, indexed in Pubmed: 33136300

Abbreviations: CRT, cardiac resynchronisation therapy

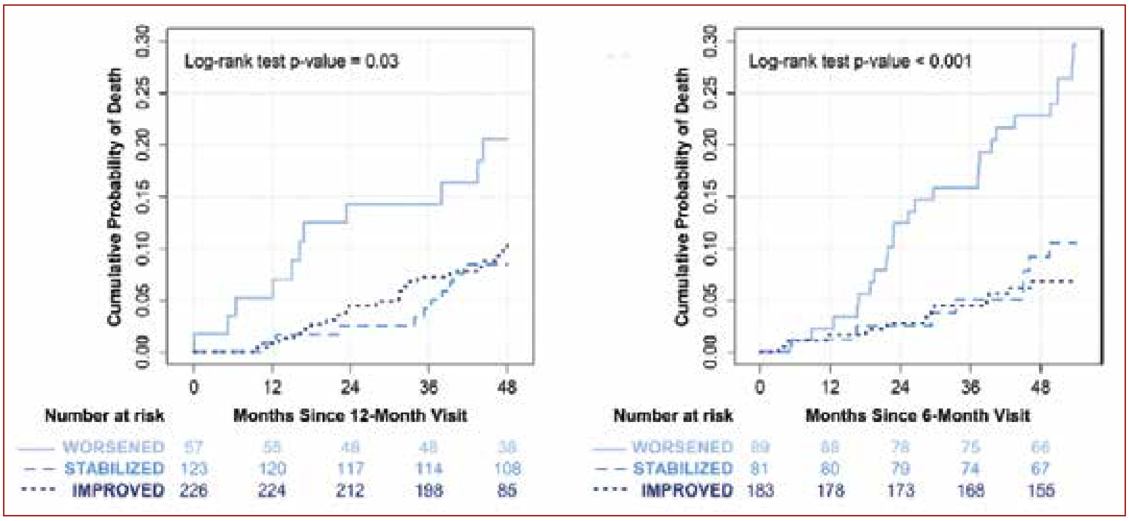

Figure 2. Long-term mortality in patients assigned to CRT ~~in~~ the REVERSE study according to one-year response: worsened, stabilized, or improved

Reproduced with permission, from: Gold MR, et al. Redefining the classiications of response to cardiac resynchronization therapy. JACC Clin Electrophysiol. 2021; 7(7): 871–880, doi: 10.1016/j.jacep.2020.11.010, indexed in Pubmed: 33640347

130–149 ms (for which current guidelines have class IIa recommendation [8]), only women benefited from CRT. Women had a 76% reduction in HF or death (absolute CRT-D to ICD difference, 23%; hazard ratio [HR], 0.24; 95% confidence interval [CI], 0.11–0.53; *P* <0.001) and a 76% reduction in death alone (absolute difference 9%; HR, 0.24; 95% CI, 0.06–0.89; *P* = 0.03). Both sexes with LBBB benefited at QRS of ≥150 ms. What could be the reason? Firstly, the relationship between QRS width and CRT benefit for outcomes has been clearly demonstrated in another individual case-based meta-analysis of 5 RCTs [34]. Secondly, when sex differences were analyzed in a subsequent publication, height was shown to be more important for response than sex per se with a greater CRT response in shorter persons. Thus, when height for men was divided into tertiles, the shorter men (median 167 cm) responded better to CRT and those with smaller QRS widths just like women [35]. Taller men only benefited at QRS widths >150 ms. A later case-based meta-analysis confirmed a greater CRT response with smaller height, body weight, and body surface area (BSA) (better effects for small/low or medium rather than tall) (Figure 3) [36].

Finally, there may be a reluctance to give women CRT since in CRT Survey II, they had a higher procedural complication rate related to vascular access as evidenced by pneumothorax (1.4%), coronary sinus dissection (2.1%), and pericardial tamponade (0.3%). The probable reason is the smaller dimensions of vessels in women compared to men [37]. In conclusion: we need to move into precision medicine taking not only sex but body size and ethnicity into account in clinical decision-making for CRT.

CHOICE OF CRT-D OR CRT-P IN PRIMARY PREVENTION OF SUDDEN CARDIAC DEATH

With the evolution of HF-modifying medication and CRT, the relative risk of sudden cardiac death has been reduced by more than 40% [38]. Not all sudden death is due to ventricular tachyarrhythmia and is thus preventable with ICD. Moreover, with each added guideline indicating HF medication, the risk of both total mortality and SCD decreased [39]. CRT per se also reduces the risk of sudden cardiac death [40]. Following the negative results of the DANISH trial [41] comparing ICD with or without CRT with no ICD, the challenges to deciding on CRT-P and CRT-D have increased. Preventive models to evaluate the risk of SCD against that of total mortality have been introduced, for example, with an updated version of the Seattle risk model which balances the risk of SCD vs. non-SCD to help in decision-making [42]. The 2021 ESC and EHRA guidelines on pacing and CRT also include such help and take the presence of myocardial scar tissue into account [8]. Ultimately, there is a need for a randomized study, and the RESET CRT study that randomizes patients to CRT-P to CRT-D is ongoing. However, a published prelude to the RESET CRT study reported no survival benefit in CRT-D patients over CRT-P patients after entropy balancing and age adjustment [43].

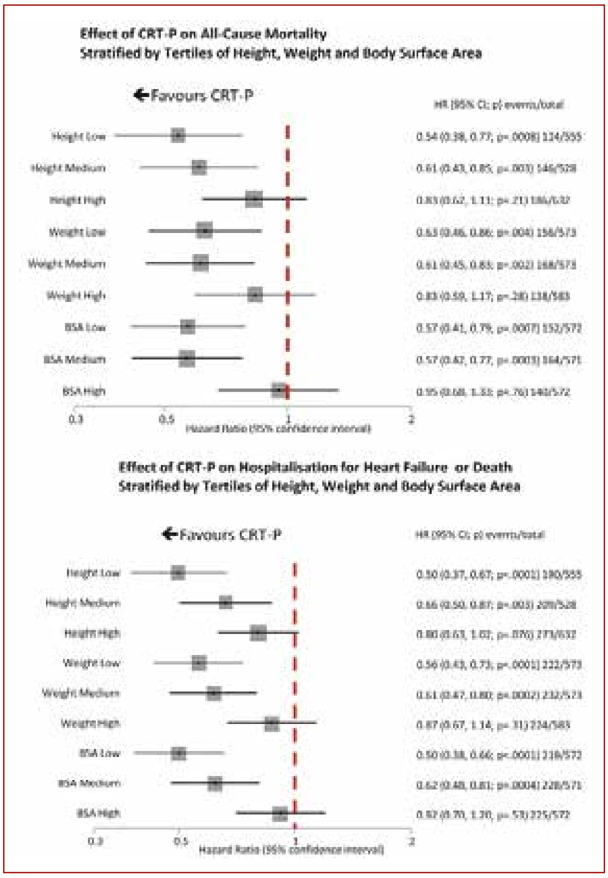

Figure 3. Effect of cardiac resynchronization therapy (CRT) on all-cause mortality and heart failure hospitalizations stratified by height, weight, and body surface area (BSA) tertiles

Reproduced with permission, from: Cleland JWG, et al. The effect of cardiac resynchronization without defibrillator on morbidity and mortality. Eur J Heart Fail. 2022; 24(6): 1080–1090, doi: 10.1002/ejhf.2524

Abbreviations: BSA, body surface area; CRT-P, cardiac resynchronization therapy pacemaker

Ongoing projects to build models to predict risk for SCD after acute myocardial infarction such as PROFID will determine the value of clinical prediction models in neural networks (profid-project.eu).

HF THERAPY IMPLEMENTATION

But the greatest challenge is to properly ensure that HF medications are given to HFrEF patients. Beta-blockers, angiotensin receptor-neprilysin inhibitor (ARNI) and MRA all reduce the risk of sudden cardiac death as does CRT through reverse remodeling [39, 40, 44]. SGLT2i also reduces the risk of sudden cardiac death [45]. Therefore, a swift introduction of these disease-modifying drugs is needed and thorough evaluation of clinical findings and echocardiography before deciding on device implantation [46].

This new more rapid approach will require good organization of HF care and deciding whether the patient is a potential candidate for CRT ± ICD. If the patient improves to an extent such that CRT or ICD are unnecessary, it is always easier to cancel plans for device therapy than the reverse. In short, HF care, including device therapy, heavily depends on multidisciplinary HF teams with a care plan for each patient with rapid revision according to the disease state of the individual. Results from the Swedish HF National registry show that therapy implementation including CRT is increased in such care, which, in turn, is linked to improved outcomes [47, 48].

In conclusion: after ascertaining optimal medical therapy and shared decision-making with the patient [8], as suggested in the ESC EHRA pacing and CRT guidelines, life expectancy, and comorbid factors are the best premises for decision-making we have at present.

Future implications

Except for the challenges in therapy implementation, new pacing techniques such as physiologic pacing will become increasingly important. However, the scientific evidence is not sufficient for guidelines [8] to make firm recommendations for His pacing unless when conventional LV lead placement is not possible. Both His pacing and left bundle pacing are currently studied in many ongoing RCTs. Conduction system pacing appears to prevent adverse effects of chronic RV pacing, and early data suggest potential benefits in CRT-indicated patients. Randomized clinical trials to evaluate the role of His bundle or left bundle area pacing as an alternative to RV pacing or in CRT-indicated patients are needed

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. 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.
2. Bristow MR, Saxon LA, 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, indexed in Pubmed: 15152059.
3. Abraham WT, Young JB, León AR, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. Circulation. 2004; 110(18): 2864–2868, doi: 10.1161/01.CIR.0000146336.92331.D1, indexed in Pubmed: 15505095.
4. 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.
5. Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol. 2008; 52(23): 1834–1843, doi: 10.1016/j.jacc.2008.08.027, indexed in Pubmed: 19038680.
6. 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.
7. 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.
8. Glikson M, Nielsen J, Kronborg M, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Europace. 2021; 24(1): 71–164, doi: 10.1093/europace/euab232, indexed in Pubmed: 34455427.
9. Bax JJ, Delgado V, Sogaard P, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med. 2013; 369(15): 1395–1405, doi: 10.1056/NEJMoa1306687, indexed in Pubmed: 23998714.
10. Sutton MJ, Ghio S, Plappert T, et al. Cardiac Resynchronization Induces Major Structural and Functional Reverse Remodeling in Patients With New York Heart Association Class I/II Heart Failure. Circulation . 2009; 120(19): 1858–1865, doi: doi.org/10.1161/CIRCULATIONAHA.108.818724.
11. Daubert JC, Gold MR, Abraham WTR, et al. Resynchronization Therapy Prevents Disease Progression in NYHA Class I and II Heart Failure Patients 24-month results from the European cohort of the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction trial. J Am Coll Cardiol. 2009; 54(20): 1837–1846, doi: https://doi.org/10.1016/j.jacc.2009.08.011.
12. Linde C, Gold MR, Abraham WT, et al. Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-year results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. Eur Heart J. 2013; 34(33): 2592–2599, doi: 10.1093/eurheartj/eht160, indexed in Pubmed: 23641006.
13. Raatikainen MJ, Arnar DO, Zeppenfeld K, et al. Statistics on the use of cardiac electronic devices and electrophysiological procedures in the European Society of Cardiology countries: 2014 report from the European Heart Rhythm Association. Europace. 2015; 17 Suppl 1: i1–75, doi: 10.1093/europace/euu300, indexed in Pubmed: 25616426.
14. Lund LH, Benson L, Ståhlberg M, et al. Age, prognostic impact of QRS prolongation and left bundle branch block, and utilization of cardiac resynchronization therapy: findings from 14,713 patients in the Swedish Heart Failure Registry. Eur J Heart Fail. 2014; 16(10): 1073–1081, doi: 10.1002/ejhf.162, indexed in Pubmed: 25201219.
15. Dickstein K, Normann C, Auricchio A, et al. Survey II: An ESC Survey of Cardiac Resynchronization Therapy in 11088 patients – Who is doing What to Whom and How? . Eur J Heart Fail. 2018; 20(6): 1039–1051, doi: 10.1002/ejhf.1142 , indexed in Pubmed: 29457358.
16. Tajstra M, Łasocha D, Gadula-Gacek E, et al. Cardiac resynchronization in Poland – comparable procedural routines? Insights from CRT Survey II. Adv Interv Cardiol . 2019; 15(4): 477–484, doi: 10.5114/aic.2019.90223.
17. Wilkoff BL, Kudenchuk PJ, Buxton AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA. 2002; 288(24): 3115–3123, doi: 10.1001/jama.288.24.3115, indexed in Pubmed: 12495391.
18. Sweeney M, Hellkamp A, Ellenbogen K, 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.
19. Curtis AB, Worley SJ, Adamson PB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med. 2013; 368(17): 1585–1593, doi: 10.1056/NEJMoa1210356, indexed in Pubmed: 23614585.
20. Leclercq C, Walker S, Linde C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J. 2002; 23(22): 1780–1787, doi: 10.1053/euhj.2002.3232, indexed in Pubmed: 12419298.
21. Wilton SB, Leung AA, Ghali WA, et al. Outcomes of cardiac resynchronization therapy in patients with versus those without atrial fibrillation: a systematic review and meta-analysis. Heart Rhythm. 2011; 8(7): 1088–1094, doi: 10.1016/j.hrthm.2011.02.014, indexed in Pubmed: 21338711.
22. Kalscheur MM, Saxon LA, Lee BK, et al. Outcomes of cardiac resynchronization therapy in patients with intermittent atrial fibrillation or atrial

flutter in the COMPANION trial. Heart Rhythm. 2017; 14(6): 858–865, doi: 10.1016/j.hrthm.2017.03.024, indexed in Pubmed: 28323173.

23. Gasparini M, Leclercq C, Lunati M, et al. Cardiac resynchronization therapy in patients with atrial fibrillation: the CERTIFY study (Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry). JACC Heart Fail. 2013; 1(6): 500–507, doi: 10.1016/j.jchf.2013.06.003, indexed in Pubmed: 24622002.
24. 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; 20(10): 1457–1468, doi: 10.1002/ejhf.1235, indexed in Pubmed: 29806208.
25. 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.
26. Merkely B, Gellér L, Zima E, et al. Baseline clinical characteristics of heart failure patients with reduced ejection fraction enrolled in the BUDAPEST-CRT Upgrade trial. Eur J Heart Fail. 2022; 24(9): 1652–1661, doi: 10.1002/ejhf.2609, indexed in Pubmed: 35791276.
27. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. J Card Fail. 2001; 7(2): 176–182, doi: 10.1054/jcaf.2001.25652, indexed in Pubmed: 11420770.
28. Gold MR, Rickard J, Daubert JC, et al. Redefining the Classifications of Response to Cardiac Resynchronization Therapy: Results From the REVERSE Study. JACC Clin Electrophysiol. 2021; 7(7): 871–880, doi: 10.1016/j.jacep.2020.11.010, indexed in Pubmed: 33640347.
29. Chung ES, Gold MR, Abraham WT, et al. The importance of early evaluation after cardiac resynchronization therapy to redefine response: Pooled individual patient analysis from 5 prospective studies. Heart Rhythm. 2022; 19(4): 595–603, doi: 10.1016/j.hrthm.2021.11.030, indexed in Pubmed: 34843964.
30. Mullens W, Auricchio A, Martens P, et al. Optimized implementation of cardiac resynchronization therapy: a call for action for referral and optimization of care: A joint position statement from the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology. Eur J Heart Fail. 2020; 22(12): 2349–2369, doi: 10.1002/ejhf.2046, indexed in Pubmed: 33136300.
31. Linde C, Ståhlberg M, Benson L, et al. Gender, underutilization of cardiac resynchronization therapy, and prognostic impact of QRS prolongation and left bundle branch block in heart failure. Europace. 2015; 17(3): 424–431, doi: 10.1093/europace/euu205, indexed in Pubmed: 25164429.
32. Lund LH, Jurga J, Edner M, et al. Prevalence, correlates, and prognostic significance of QRS prolongation in heart failure with reduced and preserved ejection fraction. Eur Heart J. 2013; 34(7): 529–539, doi: 10.1093/eurheartj/ehs305, indexed in Pubmed: 23041499.
33. Zusterzeel R, Selzman KA, Sanders WE, et al. Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. JAMA Intern Med. 2014; 174(8): 1340–1348, doi: 10.1001/jamainternmed.2014.2717, indexed in Pubmed: 25090172.
34. 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.
35. Linde C, Cleland JGF, Gold MR, et al. The interaction of sex, height, and QRS duration on the effects of cardiac resynchronization therapy on morbidity and mortality: an individual-patient data meta-analysis. Eur J Heart Fail. 2018; 20(4): 780–791, doi: 10.1002/ejhf.1133, indexed in Pubmed: 29314424.
36. Cleland JGF, Bristow MR, Freemantle N, et al. The effect of cardiac resynchronization without a defibrillator on morbidity and mortality: an individual patient data meta-analysis of COMPANION and CARE-HF. Eur J Heart Fail. 2022; 24(6): 1080–1090, doi: 10.1002/ejhf.2524, indexed in Pubmed: 35490339.
37. Auricchio A, Gasparini M, Linde C, et al. Sex-Related Procedural Aspects and Complications in CRT Survey II: A Multicenter European Experience in 11,088 Patients. JACC Clin Electrophysiol. 2019; 5(9): 1048–1058, doi: 10.1016/j.jacep.2019.06.003, indexed in Pubmed: 31537334.
38. Shen Li, Jhund PS, Petrie MC, et al. Declining risk of sudden death in heart failure. N Engl J Med. 2017; 377(1): 41–51, doi: 10.1056/NEJMoa1609758, indexed in Pubmed: 28679089.
39. Merchant FM, Levy WC, Kramer DB. Time to shock the system: moving beyond the current paradigm for primary prevention implantable cardioverter-defibrillator use. J Am Heart Assoc. 2020; 9(5): e015139, doi: 10.1161/JAHA.119.015139, indexed in Pubmed: 32089058.
40. Cleland JGF, Daubert JC, Erdmann E, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. Eur Heart J. 2006; 27(16): 1928–1932, doi: 10.1093/eurheartj/ehl099, indexed in Pubmed: 16782715.
41. Elming MB, Nielsen JC, Haarbo J, 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.
42. Levy WC, Hellkamp AS, Mark DB, et al. Improving the Use of Primary Prevention Implantable Cardioverter-Defibrillators Therapy With Validated Patient-Centric Risk Estimates. JACC Clin Electrophysiol. 2018; 4(8): 1089–1102, doi: 10.1016/j.jacep.2018.04.015, indexed in Pubmed: 30139491.
43. Hadwiger M, Dagres N, Haug J, et al. Survival of patients undergoing cardiac resynchronization therapy with or without defibrillator: the RESET-CRT project. Eur Heart J. 2022; 43(27): 2591–2599, doi: 10.1093/eurheartj/ehac053, indexed in Pubmed: 35366320.
44. Rohde LE, Chatterjee NA, Vaduganathan M, et al. Sacubitril/Valsartan and sudden cardiac death according to implantable cardioverter-defibrillator use and heart failure cause: a PARADIGM-HF analysis. JACC Heart Fail. 2020; 8(10): 844–855, doi: 10.1016/j.jchf.2020.06.015, indexed in Pubmed: 32919916.
45. Sfairopoulos D, Zhang N, Wang Y, et al. Association between sodium-glucose cotransporter-2 inhibitors and risk of sudden cardiac death or ventricular arrhythmias: a meta-analysis of randomized controlled trials. Europace. 2022; 24(1): 20–30, doi: 10.1093/europace/euab177, indexed in Pubmed: 34333592.
46. McDonagh T, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42(36): 3599–3726, doi: 10.1093/eurheartj/ehab368.
47. Lund LH, Braunschweig F, Benson L, et al. Association between demographic, organizational, clinical, and socio-economic characteristics and underutilization of cardiac resynchronization therapy: results from the Swedish Heart Failure Registry. Eur J Heart Fail. 2017; 19(10): 1270–1279, doi: 10.1002/ejhf.781, indexed in Pubmed: 28176416.
48. Schrage B, Lund LH, Melin M, et al. Cardiac resynchronization therapy with or without defibrillator in patients with heart failure. Europace. 2022; 24(1): 48–57, doi: 10.1093/europace/euab233, indexed in Pubmed: 34486653.