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STATE OF THE ART REVIEW

The evolving state of cardiac resynchronization therapy and conduction system pacing: 25 years of research at EP Europace journal

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Abstract

Cardiac resynchronization therapy (CRT) was proposed in the 1990s as a new therapy for patients with heart failure and wide QRS with depressed left ventricular ejection fraction despite optimal medical treatment. This review is aimed first to describe the rationale and the physiologic effects of CRT. The journey of the landmark randomized trials leading to the adoption of CRT in the guidelines since 2005 is also reported showing the high level of evidence for CRT. Different alternative pacing modalities of CRT to conventional left ventricular pacing through the coronary sinus have been proposed to increase the response rate to CRT such as multisite pacing and endocardial pacing. A new emerging alternative technique to conventional biventricular pacing, conduction system pacing (CSP), is a promising therapy. The different modalities of CSP are described (Hirs pacing and left bundle branch area pacing). This new technique has to be evaluated in clinical randomized trials before implementation in the guidelines with a high level of evidence.

Keywords Cardiac resynchronization therapy • Cardiac conduction system pacing • Clinical trials

What's new?

- Review article for EHRA 25th anniversary
- Review of clinical trials on cardiac resynchronization therapy
- Review of clinical trials on conduction system pacing
- Future directions

The inauguration of *Europace* coincides with the beginning of a new era in cardiac pacing, the treatment of heart failure (HF) with cardiac implantable electronic devices. Following the description of biventricular pacing in left bundle branch block (LBBB) by Mower and Cazeau about the haemodynamic benefit of multisite pacing, more than 781 original articles have since appeared on this subject in *Europace*, emphasizing its significant contribution to this field.

Although the detrimental effect of ventricular pacing on cardiac function has been recognized for a century, the lack of treatment alternatives stymied this field. In a similar manner, cardiac conduction disturbance such as LBBB was regarded a consequence rather than a cause of HF. The appreciation of the adverse effect of both right ventricular (RV) pacing and ventricular conduction disturbance, in particular LBBB, on cardiac mechanics started after the publication of two landmark trials, MOST and DAVID. A subanalysis of the MOST trial showed that a higher percentage RV pacing was associated with a larger prevalence of atrial fibrillation and hospitalization for HF.[1] The DAVID trial investigated the potential benefit of ventricular pacing to create a higher heart rate in patients with HF. Instead, the greater percentage of RV pacing was detrimental.[2] Mechanistic studies on the causes of adverse effects involved pre-clinical studies by the Kass and Prinzen groups. Both RV pacing and LBBB resulted in poorer haemodynamic function that is most likely explained by loss of mechanical co-ordination. Early-activated regions do not contribute much to systolic function whereas late-activated—pre-stretched—regions have a stronger contraction and cause a mid-systolic 'rebound' stretch of the earlier activated regions, thus resulting in 'wasted

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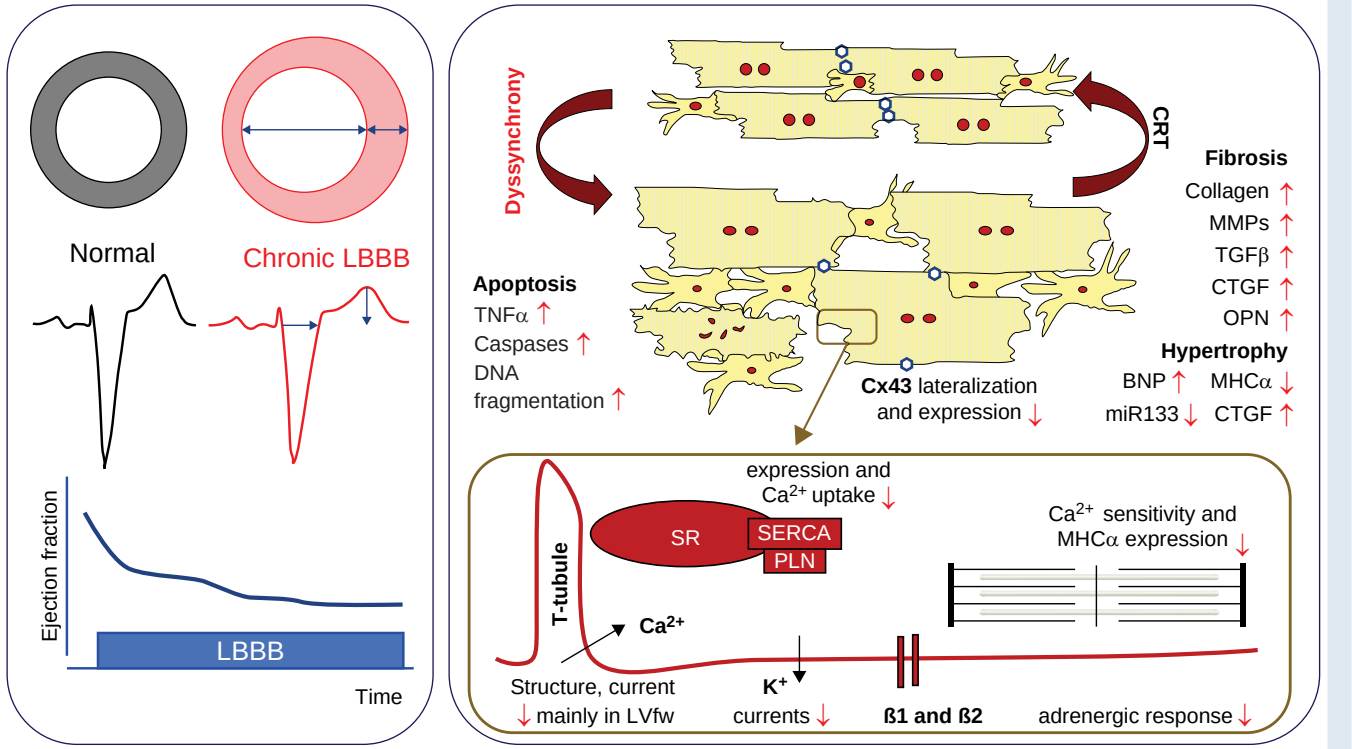

Figure 1 Processes contributing to the structural, electrical, and contractile remodelling in the dyssynchronous heart as seen on functional measurements (left) and on a cellular and molecular level (right). Red colour indicates the situation during dyssynchrony. Dyssynchrony causes asymmetric and eccentric hypertrophy, and (in the failing heart) fibrosis as well as apoptosis. Some of the molecular factors are mentioned. Similarly, some of the processes involved in altered excitation–contraction coupling are displayed in the inset, illustrating a part of the plasmalemma, T-tubule, and sarcoplasmatic reticulum (SR). BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; CTGF, connective tissue growth factor; Cx43, connexin43; LBBB, left bundle branch block; LVfw, LV free wall; MHCa, myosin heavy chain a; MMP, matrix metalloproteases; OPN, osteopontin; PLN, phospholamban; SR, sarcoplasmic reticulum; SERCA, SR Ca2fl ATP-ase; TGFβ, transforming growth factor beta; TNFα, tumour necrosis factor alpha. From Nguyen *et al.* [5].

myocardial work'.[3] Longer-lasting abnormal electrical and mechanical activation initiate and aggravate adverse ventricular remodelling, affecting the genome, transcriptome, proteome, metabolome, cell organelles, and entire organ function.[4] Whilst the initiation of ventricular remodelling is difficult to demonstrate in patients, reverse remodelling is well known and represents an important part of the response to cardiac resynchronization therapy (CRT). This has resulted in the recognition of a new clinical entity: 'dyssynchrony induced cardiomyopathy', (*Figure 1*).

From the beginning of CRT, proper atrioventricular and interventricular timing as well as the selection of the proper LV site play a crucial role. A properly timed atrioventricular interval not only increases the active contribution of left atrial systole to LV filling but also improves resynchronization by fusion of LV or biventricular (BiV) pacing-generated activation wavefronts pacing with intrinsic conduction. Although a relatively simple pathlength model, i.e. the time delay between upslope of LV and RV pressure curves (interVA), was useful to predict optimal resynchronization, the wide range of optimal interVA intervals between patients indicated the need for individual optimization of CRT. Furthermore, the haemodynamic benefit of properly timed LV pacing was at least as large as that of biventricular pacing. Nearly 20 years after these findings, the prospectively designed Adapt-CRT trial showed that LV pacing at a well-tuned AV delay is clinically superior to biventricular pacing.[5]

The technological evolution of the over-the-wire coronary sinus pacing lead from a bipolar lead to a quadripolar lead not only resulted in reduced probability of phrenic nerve stimulation and lower risk of lead dislodgement but also opened several new research areas, like the potential existence of an LV target area, the avoidance of myocardial scar, and the added value of pacing multiple LV sites. Invasive and non-invasive mapping studies including body surface electrocardiogram (ECG) have consistently shown that, in a typical LBBB and right bundle branch block (RBBB) QRS morphology, there is a large electrically delayed area of the LV or RV lateral wall, respectively. Therefore, pacing at a late region (especially in LBBB) increases contractility, stroke volume, and stroke work as well as efficiency.

A clinically useful approach is therefore to locate the latest-activated region by measuring local Q-LV timing. However, more sophisticated non-invasive mapping methods, based upon the combination of two cardiac imaging methods, e.g. 12-lead ECG and computed tomography or cardiac magnetic resonance, now allow the display of three-dimensional biventricular activation, possibly leading to a more personalized delivery of the pacing lead.[6]

Quadripolar leads enable pacing from multiple electrodes simultaneously. In contrast to acute haemodynamic promising results when multiple electrodes are paced achieving higher LV contractility, clinical trial results did not confirm the expected beneficial effect on heart failure hospitalization and mortality.[7] Several studies used measures of mechanical rather than electrical dyssynchrony. However, the relation between electrical and mechanical activation is variable and particularly weak in hearts with scar. Importantly, the effects of scar appear independent of the distance between scar and latest-activated region, implying that scar also affects electromechanical coupling remote from the scar.[8] Therefore, LV lead positioning should not be guided solely by measurements of mechanical dyssynchrony.

The continued search of a more physiological pacing approach resulted in novel strategies like pacing the LV endocardium and the infrahisian conduction system. In pre-clinical LBBB models, LV endocardial pacing increased LV contractility and systolic function by engaging rapid conducting layers. The practical implementation of endocardial CRT is however technically and clinically challenging.[9] Significantly more promising is conduction system pacing (CSP), and particularly LBB (area) pacing. Multiple acute haemodynamic studies showed a consistent superiority of this pacing modality compared to RV pacing, and a haemodynamic performance at least as good as biventricular pacing (BVP).

Computer models have contributed to better insight in mechanisms and better diagnosis of dyssynchronous heart failure.[10] A benefit of computer models is that they can estimate the consequences of the multiple interactions between electrical and mechanical properties of the heart and between regional behaviour and global pump function, beyond the capabilities of the human brain.[11]

The primary issue in CRT is the spread of the depolarization wavefront across the ventricles. A technique that is already in use for clinical research is ECG imaging. It is built on the relation between potentials at the heart surface and on the torso, dictated by the laws of electromagnetism. Inverting this relation enables the reconstruction of epicardial potentials from the electrocardiograms recorded at the body surface. ECG imaging showed that any late-activated LV region, regardless of whether the QRS morphology was classified as Intraventricular conduction delay (defect) (IVCD) or LBBB, predicts CRT benefit. Recent studies show that the distance between LV pacing site and latest electrical activation is a strong independent predictor for CRT response and that ECG imaging can delineate the electrical synchronization provided by multipoint pacing and dynamic AV delay programming targeting fusion with intrinsic conduction.

Whilst ECG imaging uses resolution of the inverse problem, another approach is to estimate activation maps using 12-lead ECG, thoracic anatomy, and an Eikonal diffusion model.[12] The latter assumes that ventricular depolarization is a binary state. The advantage of this approach compared with classical ECG imaging is that in the Eikonal model, myocardial properties are used, and full 3D activation maps are obtained. In a subsequent study, investigators used a patient-specific Eikonal model of cardiac activation with spatially varying action potential duration (APD) and repolarization rate to fit to ECGs measured in patients at various time intervals after the start of CRT. These computer simulations indicated that the increase in area of the T-wave during CRT-off with longer lasting CRT can be explained by changes in APD that are opposite to the change in CRT-induced activation time. These APD changes were associated with a reduction in LV dispersion in repolarization during chronic CRT.

Mechanical models have been used to assess the influence of (ab)normal activation on cardiac pump function. These models were able to reproduce the typical regional strain patterns by simply delaying the onset of contraction between the two walls.[13] An important finding from these simulations was that the time-to-peak shortening, often used in clinical studies, correlated poorly with the time differences of onset of activation. The model simulations demonstrated that increasing degrees of imposed dyssynchrony create two peaks in septal strain, the timing of which hardly change, whilst their amplitude did. Consequently, when defining peak shortening as the peak with the largest amplitude, the time-to-peak shortening interval may change considerably with only a very small changes in actual activation time. This finding may explain why studies investigating the use of markers of mechanical dyssynchrony as indicator of CRT response were negative. In a next step, the computer model was used to develop a CRT marker. The best marker [systolic stretch index, the sum of early systolic (pre)stretch of the lateral wall and mid-systolic ('rebound') stretch] was retrospectively evaluated using data from a clinical trial showing that systolic stretch index (SSI) was powerful in predicting the CRT response, even in patients not having a class I indication. Notably, a later study showed that a large SSI is

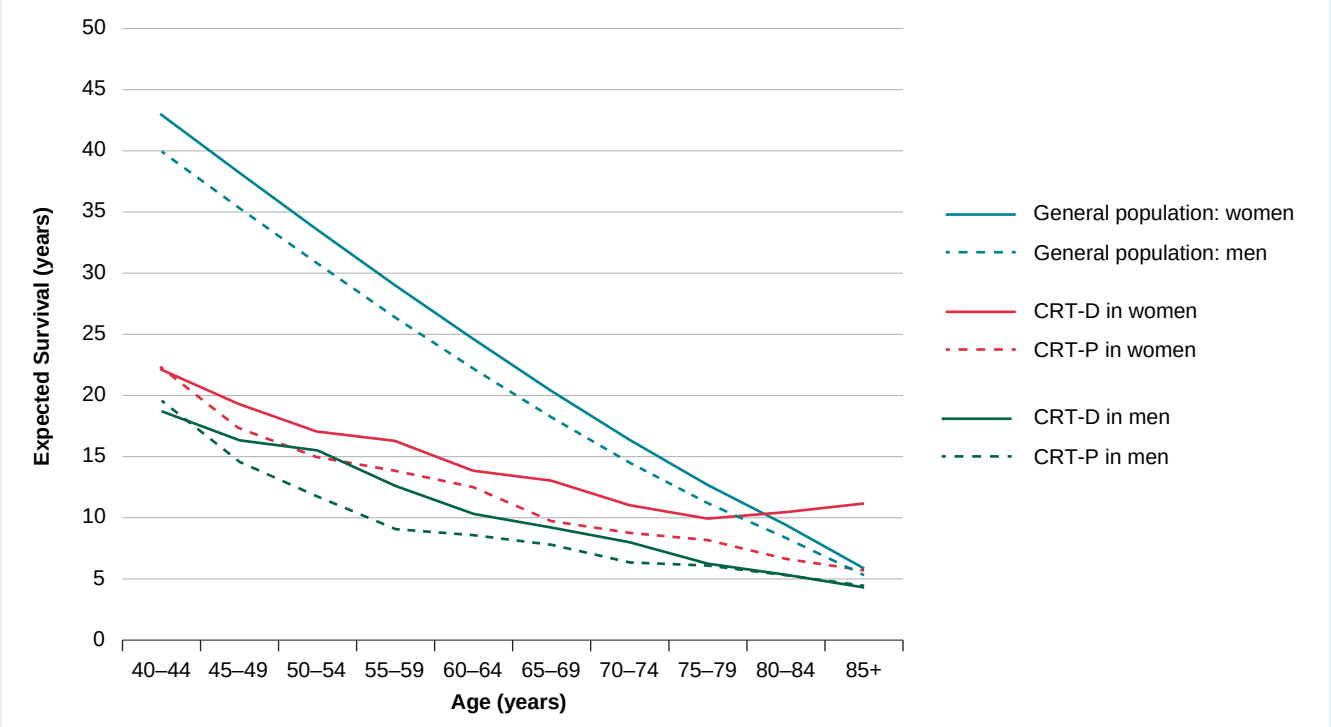

Figure 2 Expected survival (in years) after CRT-P or CRT-D undertaken in the period 2015–2017 according to sex. Expected survival in the general population is shown in blue. Adapted from Leyva *et al.*[36]

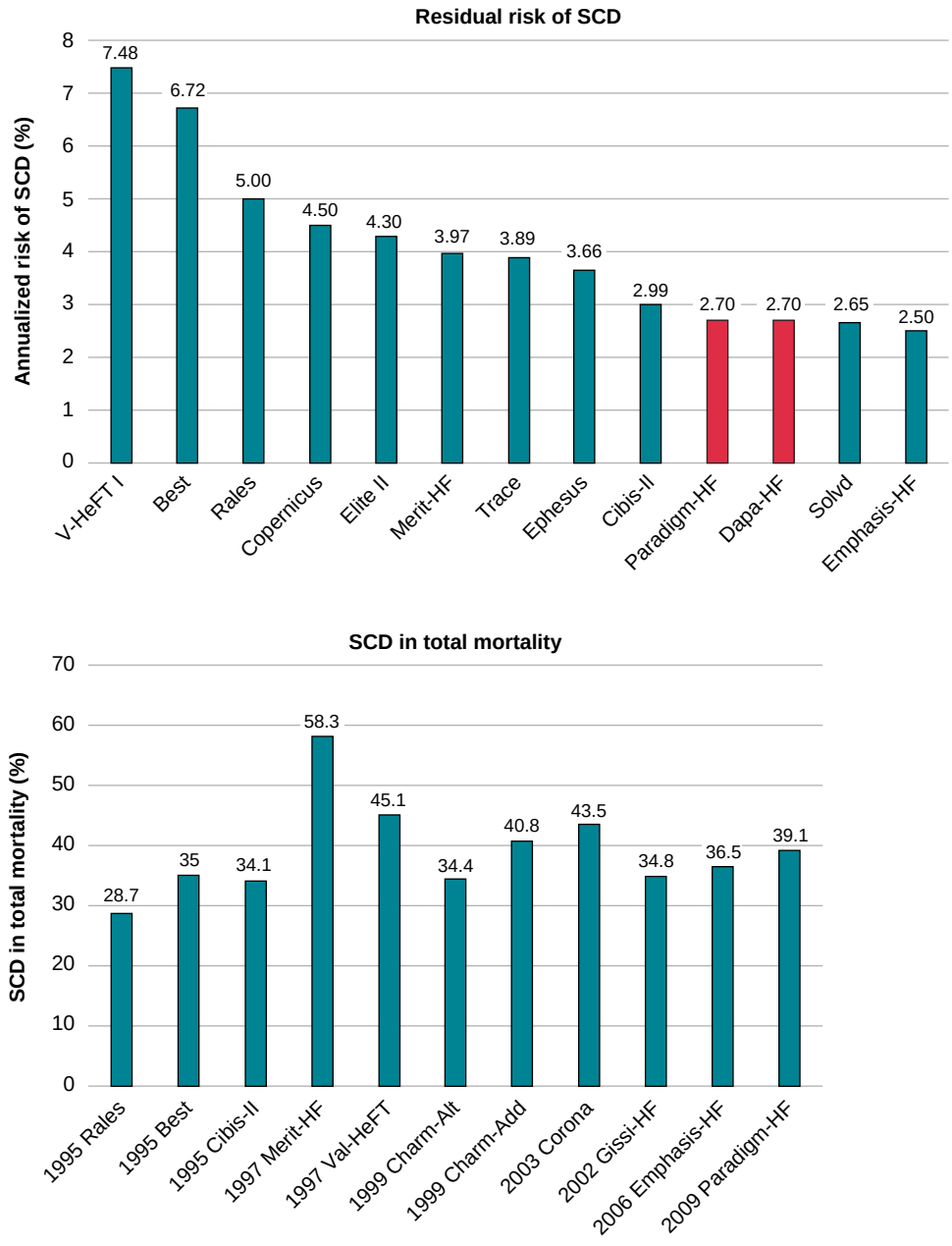

Figure 3 Sudden cardiac death (SCD) in heart failure (HF) trials. The left-sided graph shows the residual risk of SCD in the intervention arm of HF trials, expressed as annualized risk (%). The most recent trials, namely PARADIGM-HF and DAPA-HF, are shown in red. Patients with an ICD have not been excluded. The right-sided graph shows the proportion of SCDs as a proportion of total mortality in HF trial, excluding patients receiving an ICD. Reproduced with permission from Leyva F, Israel CW, Singh J. Declining Risk of Sudden Cardiac Death in Heart Failure: Fact or Myth? *Circulation* 2023; 147: 759–767. *Left-sided graph*: CIBIS-II, Cardiac Insufficiency Bisoprolol Study II; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HF, heart failure; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; RALES, Randomized Aldactone Evaluation Study; SCD, sudden cardiac death; SOLVD, Study of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation; and Val-HeFT, Valsartan Heart Failure Trial. *Right-sided graph*: CIBIS-II, Cardiac Insufficiency Bisoprolol Study II; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF, heart failure; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; RALES, Randomized Aldactone Evaluation Study; SCD, sudden cardiac death; Val-HeFT, Valsartan Heart Failure Trial.

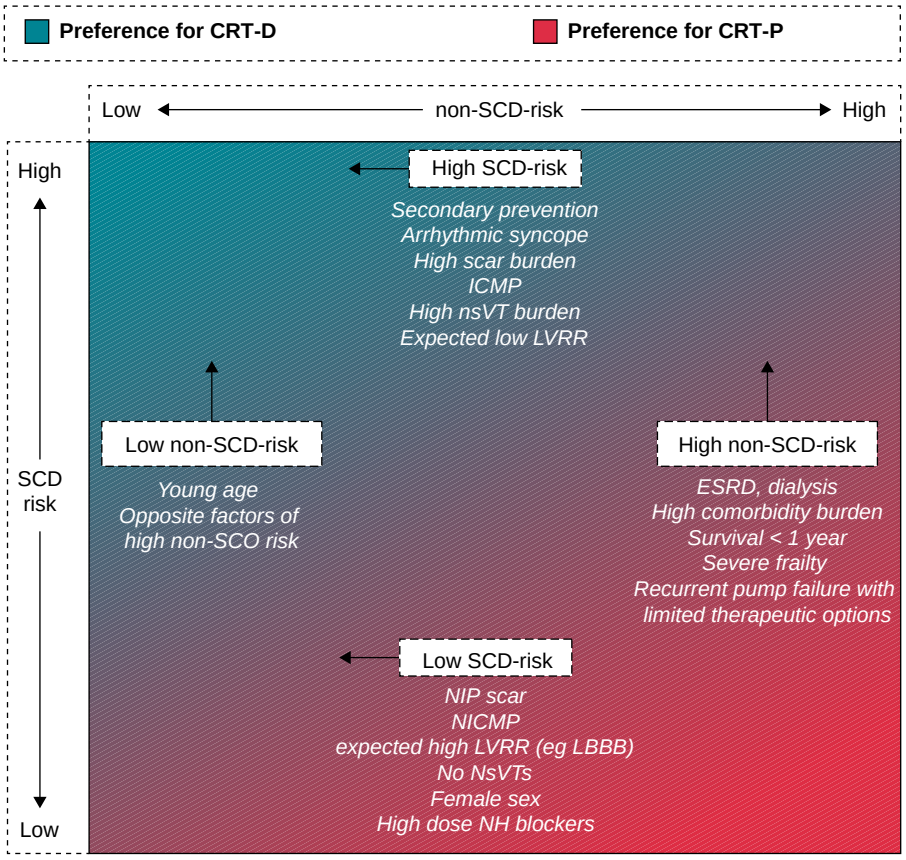

Figure 4 Choice between CRT-D and CRT-P according to the 2021 joint position statement from the European Heart Failure Association, European Heart Rhythm Association, and European Association of Cardiovascular Imaging of the European Society of Cardiology.[37]

only predictive of CRT outcome in case there is already a clear electrical dyssynchrony (QRSarea).[14] In another approach, patient-specific models were developed in eight CRT candidates using computed tomography/magnetic resonance imaging and single-photon-emission computed tomography (scar) imaging in combination with electrical activation based on endocardial LV mapping and a mono-domain model. The model-generated total LV activation time as well as the septum-lateral wall activation time difference significantly correlated to the observed reduction in left ventricular end-systolic volume (LVESV).

Mechanical models were also used to investigate the best location of the pacing electrodes. A finite element model showed that in non-infarcted hearts, the best location of the LV lead is the mid-lateral wall, even if it is not the latest-activated region. Explanation for this paradoxical finding is that the combination of mid-lateral wall and RV apical lead positions provides the most synchronous activation. Another study showed that, in hearts with a scar, the optimal LV lead position is a compromise between a position distant from the scar and from the septum, thus achieving the most effective electromechanical resynchronization of the remaining viable myocardium. Mechanical modelling may also play a role in determining the best position of the pacing lead in the increasingly popular LBB area pacing. Meiburg *et al.* coupled a high resolution Eikonal activation model of ventricular activation to the lumped mechanical and haemodynamic model CircAdapt model. Their simulation results predict that a lead position at ~80% of the septum creates the best compromise between interventricular and intra-LV dyssynchrony and the best biventricular pump function.[15]

The ultimate goal of computer modelling is to generate a 'digital twin' of the patient. The inductive and deductive reasoning built in the digital twin will provide better mechanistic understanding of the disease and better diagnosis and treatment prediction. The results so far indicate that Digital Twins can be of significant value in the field of pacing and CRT.[16] The challenges in develop such patient-specific models are that they are at simple as possible (requiring not too high computational power), require patient information that is readily available and easy to acquire and yet provide a significant added value on top of the available clinical data.

Current status of cardiac resynchronization therapy

Proof of concept

The first studies to provide proof of concept for CRT were Multisite Stimulation in Cardiomyopathies-Sinus Rhythm (MUSTIC-SR), in which 67 patients with HF were randomized to 3 months of 'CRT-off' or 'CRT-on'.[17] Compared with 'CRT-off', 'CRT-on' improved walking distance, quality of life (QoL), and peak oxygen uptake (VO_2). In the subsequent Pacing Therapies for Congestive Heart Failure (PATH-CHF),[18] CRT improved walking distance and peak VO_2, and reversed LV remodelling after 12 months. Similar findings emerged from Multicentre InSync Randomized Clinical Evaluation (MIRACLE),[19] the first double-blind CRT trial, in which 453 patients with HF were randomized to CRT-on or CRT-off. At 6 months, CRT-pacing (CRT-P) improved walking distance, QoL, exercise capacity, left ventricular ejection

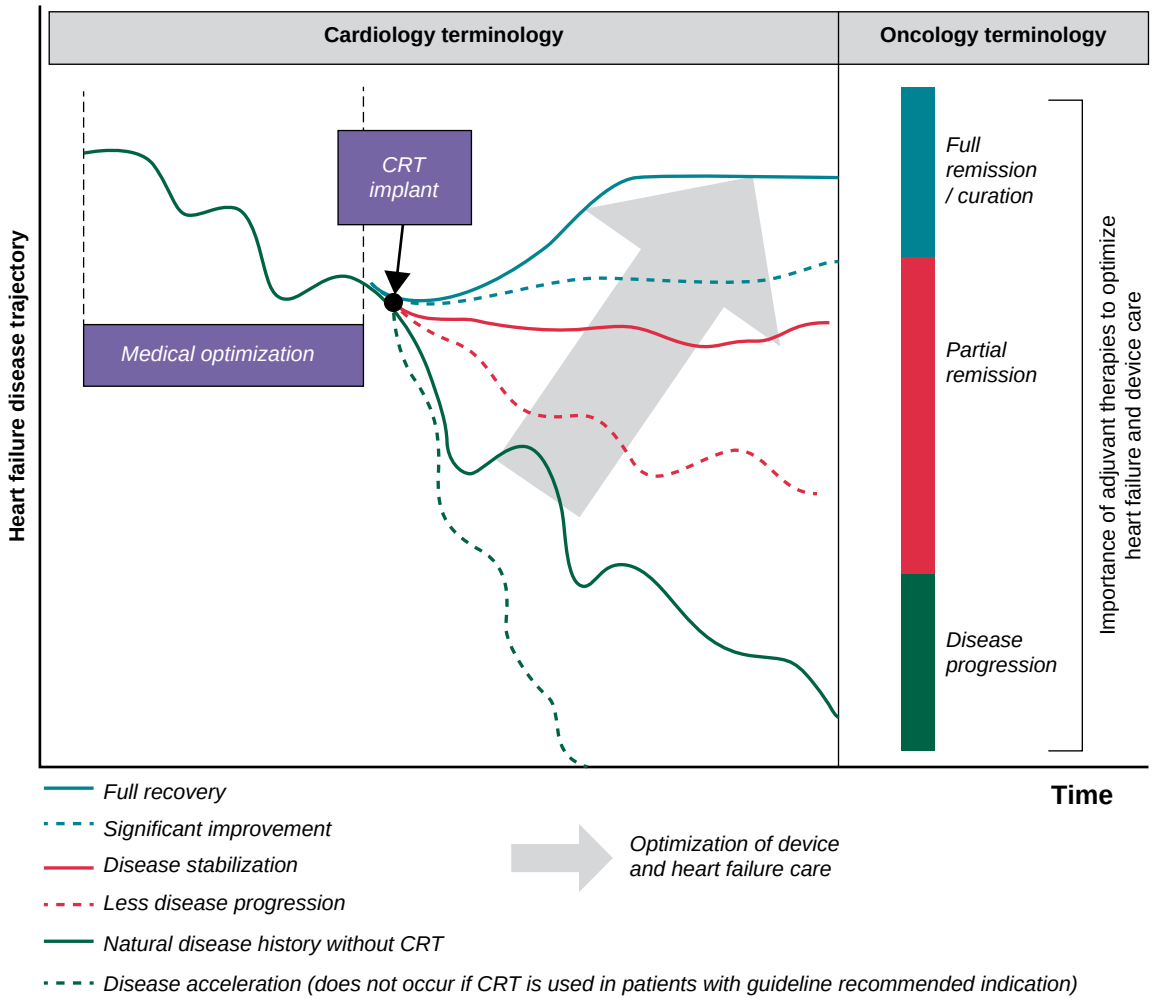

Figure 5 Model of heart failure progression according to the 2021 joint position statement from the European Heart Failure Association, European Heart Rhythm Association, and European Association of Cardiovascular Imaging of the European Society of Cardiology.[37]

fraction (LVEF), and peak VO_2, and reduced HF hospitalizations. As in PATH-HF, CRT was also shown to reverse LV remodelling. In addition, it showed that CRT reduced functional mitral regurgitation.

The landmark clinical trials

By the early 2000s, the HF community recognized that arrhythmic, sudden cardiac death (SCD) accounted for a large proportion of deaths in patients with HF. In parallel, primary prevention implantable cardioverter-defibrillators (ICDs) had been shown to improve survival in HF. In this melting pot of promising device therapies for HF, some conceived that the ideal device for HF and a wide QRS complex was a CRT pacemaker (CRT-P) whilst others favoured CRT-defibrillation (CRT-D). The effects of adding of CRT to an ICD were tested in the 2003 MIRACLE-ICD trial,[20] in which patients with HF undergoing CRT-D implantation were randomized to CRT-on or CRT-off. It showed that CRT-D led to an improvement in QoL and New York Heart Association (NYHA) class, but not walking distance.

Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION)[21] emerged amidst debates as to which device might be best for patients with HF. In a three-arm randomized, controlled study, it compared CRT-P and CRT-D with optimum pharmacological therapy (OPT). Compared with OPT, both CRT-P and CRT-D reduced total mortality or any cause hospitalizations. The risk of total mortality or hospitalization for HF was reduced by both CRT-P (by 34%) and CRT-D (by 40%). The CRT-D reduced total mortality by 36% ($P = 0.003$) whilst a non-significant trend emerged for CRT-P ($P = 0.059$). The immediate interpretation of these findings was that CRT-D was indeed superior to CRT-P. Cardiac Resynchronization-Heart Failure (CARE-HF),[22] which was undertaken in at the same time as COMPANION, showed that compared to OPT, CRT-P reduced total mortality or unplanned hospitalizations for major cardiovascular events, as well as total mortality alone after 29 months. In addition, CRT-P improved QoL and LVEF, induced LV reverse remodelling, and reduced mitral regurgitation. By 2005, both COMPANION and CARE-HF had shown that CRT was an effective treatment for selected patients with moderate to severe HF (NYHA class III or IV). In the extended follow-up in CARE-HF, CRT-P was also associated with a reduction in SCD in association with progressive LV reverse remodelling.

A benefit of CRT in mild HF had been suggested by randomized controlled trial of the CONTAK-CD device (CONTAK-CD)[23] and MIRACLE-ICD II,[24] in which CRT was shown to reverse LV remodelling across NYHA classes II to IV. In REsynchronization reVErses

Table 1 Landmark trials in CRT

Year	Study	Number	Design	Inclusion criteria	Comparison	Effect of CRT	Ref
2001	MUSTIC-SR	67	Single-blind, cross-over RCT	NYHA III, LVEF < 35%, QRS ≥ 150 ms, LVEDD > 60 mm, 6MWD < 450 m	CRT vs. VVI (no pacing indications)	CRT improved QoL, walking distance, peak VO_2; reduced hospitalizations	14
2002	MUSTIC-AF	43	Single-blind, cross-over RCT	NYHA III, LVEF < 35%, RV-paced QRS ≥ 200 ms, LVEDD > 60 mm, 6MWD < 450 m	VVIR vs. BiV	CRT improved 6MWD, peak VO_2, QoL, and NYHA class; reduced hospitalizations (but no difference on intention-to-treat analysis)	64
	PATH-CHF	42	Single-blind, cross-over RCT	NYHA II–IV, LVEF < 35%, PR ≥ 150 ms, QRS > 120 ms	RV vs. LV vs. BiV	CRT improved NYHA class, QoL, and walking distance	65
	MIRACLE	453	Double-blind RCT	NYHA III–IV, LVEF < 35%, QRS ≥ 130 ms, LVEDD > 55 mm	CRT-on vs. CRT-off	CRT improved NYHA class, QoL, walking distance, LVEF, peak VO_2, mitral regurgitation; reduced hospitalizations	16
2003	MIRACLE-ICD I	369	Double-blind RCT	NYHA III–IV, LVEF < 35%, QRS ≥ 130 ms, LVEDD > 55 mm	CRT-D vs. ICD	CRT improved NYHA class, QoL, and walking distance, and reduced hospitalization	19
	CONTAK-CD	490	Double-blind, cross-over RCT	NYHA II–IV, LVEF < 35%, QRS ≥ 120 ms, ICD indications	CRT-on vs. CRT-off	CRT improved peak VO_2 and walking distance, not NYHA or QoL; reduced LV volumes and improved LVEF; no effect on HF progression	23
	COMPANION	1520	Unblinded RCT (1:2:2)	NYHA III–IV, LVEF < 35%, QRS > 120 ms	OMT vs. CRT-P or CRT-D	CRT-D and CRT-P reduced composite of all-cause mortality and hospitalization	20
2004	MIRACLE-ICD II	186	Double-blind RCT	NYHA II, LVEF < 35%, QRS ≥ 130 ms, ICD indications	CRT-on vs. CRT-off	CRT reduced LV volumes and LVEF and improved CCS; no effect on QoL, walking distance, or peak VO_2	66
2005	CARE-HF	813	Unblinded RCT	NYHA III–IV, LVEF < 35%, QRS > 120 ms	CRT-P vs. OPT	CRT reduced total mortality and HF hospitalizations	21
2006	HOBIPACE	30	Double-blind, cross-over RCT	Pacing indications, LVEF < 40%, LVEDD > 60 mm	CRT-P vs. RV pacing	CRT reduced LV volumes and improved QoL, LVEF, peak VO_2	67
2007	ReThinQ	172	Double-blind RCT	NYHA III, LVEF < 35%, QRS < 130 ms, echo dyssynchrony	CRT-on vs. CRT-off in CRT-D recipients	CRT improved NYHA class, but not walking distance, LVEF, or QoL	30
2008	PROSPECT	498	Prospective, observational	NYHA II–IV, LVEF < 35%, QRS > 130 ms, OMT	Echo dyssynchrony measures as predictor of CCS and LVRR	Echo dyssynchrony measures did not predict outcome after CRT	68
	REVERSE	610	Double-blind RCT (2:1)	NYHA I–II, LVEF < 40%, QRS > 120 ms	CRT-on vs. CRT-off (ICD on)	CRT reduced HF hospitalization and improved LVEF and NYHA class; no effect on mortality	25
2009	MADIT-CRT	1820	Single-blind RCT	NYHA I–II, LVEF < 30%, QRS > 130 ms	CRT-D vs. ICD	CRT-D reduced HF events; no effect on mortality	27
2010	RAFT	1798	Double-blind RCT	NYHA II–III, LVEF < 30%, QRS > 120 ms	CRT-D vs. ICD	CRT reduced total mortality and HF hospitalization	28

Continued

Table 1 *Continued*

Year	Study	Number	Design	Inclusion criteria	Comparison	Effect of CRT	Ref
2011	BLOCK-HF	691	Single-blind RCT	NYHA I–III, AV block, LVEF < 50%	CRT vs. RV pacing	CRT reduced composite of total mortality, HF event, or 15% increase in LVESVi	69
2013	Echo-CRT	809	Double-blind RCT	NYHA III–IV, LVEF < 35%, QRS < 130 ms, echo dyssynchrony	CRT-on vs. CRT-off	No effect on composite of total mortality or HF hospitalization; higher total mortality with CRT-on	32
	LESSER-EARTH	85	Double-blind RCT	NYHA III–IV, LVEF ≤ 35%, QRS < 120 ms	CRT-D vs. ICD	Stopped prematurely after recruiting 85 patients: CRT reduced walking distance and increased QRS duration; trend towards increased HF hospitalizations	31

Study acronyms: BLOCK-HF, Biventricular vs. Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block; CARE-HF, Cardiac Resynchronization-Heart Failure; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CONTAK-CD, randomized controlled trial of the CONTAK-CD device; HOBIPACE, HomborgBiventricular Pacing Evaluation; LESSER-EARTH, Evaluation of Resynchronization Therapy for Heart Failure; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy; MIRACLE-ICD, Multicentre InSync Randomized Clinical Evaluation; MUSTIC, Multisite Stimulation in Cardiomyopathies; PATH-CHF, Pacing Therapies for Congestive Heart Failure; PROSPECT, Predictors of Response to CRT; RAFT, Resynchronization–Defibrillation for Ambulatory Heart Failure trial; REVERSE, REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction trial; ReThinQ, Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS.
AV, atrioventricular; BiV, biventricular; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy-defibrillation; CRT-P, cardiac resynchronization therapy-pacing; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESVi, left ventricular end-systolic volume index; NYHA, New York Heart Association; OPT, optimum pharmacological therapy; QoL, quality of life; QRSd, QRS duration; RCT, randomized, controlled trial; RV, right ventricular; 6MWD, 6 minute walking distance; OMT, optimal medical therapy; CCS, clinical composite score; LVRR, left ventricular reverse remodeling.

Remodeling in Systolic left vEntricular dysfunction (REVERSE),[25,26] in which 610 patients in NYHA class I/II with primary prevention ICD indications were randomized to 'CRT-on' or 'CRT-off', CRT improved LVEF and reduced HF hospitalizations. The early studies in mild HF culminated in the largest CRT trial, Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT).[27] In this trial, 1820 patients in NYHA I–II, a LVEF < 30%, and a QRS > 130 ms were randomized to CRT-D or ICD. It showed that CRT-D reduced total mortality or HF events. Further supporting evidence for a benefit of CRT in mild HF was provided by Resynchronization–Defibrillation for Ambulatory Heart Failure trial (RAFT),[28] which compared CRT-D to ICD in patients in NYHA class II or III. This showed that compared to ICD, CRT-D reduced the primary endpoint of total mortality or HF hospitalization. These trials are summarized in *Table 1*.

QRS duration

The finding of mechanical dyssynchrony in patients with a QRS < 120 ms, assessed echocardiographically, provided a rationale for extending CRT to this patient population. In Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (ReThinQ), which included HF patients with a LVEF < 35%, a QRS < 130 ms, and echocardiographic evidence of dyssynchrony, CRT improved NYHA class, but not walking distance, LVEF, or QoL.[29] Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) study was stopped prematurely after finding that CRT reduced walking distance, increased QRS duration, and increased HF hospitalizations.[30] The definitive study, Echo-CRT,[31] showed excess mortality from adding CRT to ICD in patients with a QRS < 130 ms. This very important study clearly showed that CRT should not be used in patients with normal ventricular conduction, a view that was reflected in clinical guidelines. Crucially, it also confirmed that echocardiographic measures of dyssynchrony are not useful in selecting patients for CRT. The interplay between QRS duration, QRS morphology, and outcomes beyond a QRS > 120 ms is complex.

Cardiac resynchronization therapy-defibrillation vs. cardiac resynchronization therapy-pacing

Were it not for the cost of a CRT-D, which is typically three- to four-fold that of a CRT-P, debates of CRT-D vs. CRT-P would have been less heated. Proponents of CRT-P argued that CRT-P alone reduces the risk of SCD,[32] whilst proponents of CRT-D argued that the residual risk of SCD after CRT requires a defibrillator. In a European registry of 1705 consecutive patients, CRT-D was superior to CRT-P over a follow-up of 2 years,[33] but the excess mortality in CRT-P recipients was due to causes other than SCD. In contrast, a nationwide study of 50 084 implantations undertaken in England between 2009 and 2017 showed that total mortality after CRT-D was lower than after CRT-P over a median follow-up of 2.7 years (*Figure 2*). In the absence of RCTs specifically designed to compare CRT-D and CRT-P, clinical guidelines[34] show that large variations in the use of CRT-D and CRT-P exist. In this regard, CRT-P amounts to 15% of all CRT implants in the US and up to 48% in the UK.[35] In this context, we should consider that the risk of SCD is governed by the underlying type of cardiomyopathy and the timing of implantation.[36]

In choosing between CRT-D and CRT-P, we should also be aware on the residual risk of SCD in HF, even after treatment with sacubritril/valsartan and sodium glucose co-transporter 2 inhibitors is still high, at 2.7% per year. Moreover, the proportion of SCD vs. pump failure in HF may be increasing (*Figure 3*). Factors to consider when choosing between CRT-D and CRT-P are shown in *Figure 4*.

Response to cardiac resynchronization therapy

The concept of 'non-responders' is almost unique to the field of CRT. We know, however, that the response to any treatment is rarely 100%. In the field of medical therapy for HF, for example, the 'responder' rate compared to placebo in randomized, controlled trials, adopting a reduction by ≥1 NYHA classes as the definition of response, was 24.9% for enalapril, 6% for bisoprolol, and 8% for spironolactone.

Table 2 Seminal outcome studies on conduction system pacing based cardiac resynchronization therapy

Study	CRT modality	Design and follow-up	Outcomes
Deshmukh *et al. Circulation*, 2000	HBP-CRT	Observational; FU of 23 months.	Successful implantation in 12/18 patients with narrow QRS, AF, and heart failure. Improvement in LVEF (20% to 31%) and LVEDD 59–52 mm.
Barba-Pichardo *et al. Europace*, 2013	HBP-CRT	Observational; FU of 21 months.	Successful implantation in 9/13 patients with failed BiV-CRT in whom also acute correction of LBBB with HBP was demonstrated. Echocardiographic and functional improvement were observed but LBBB correction threshold was high (3.7 V).
Lustgarten *et al. Heart Rhythm*, 2015	HBP-CRT vs. BiV-CRT	Cross-over; FU of 12 months.	Successful implantation in 21/29 CRT candidates albeit only 12 patients completed cross-over analysis. No difference in echocardiographic response and functional class between groups.
Huang *et al.*[50] *Can J Card*, 2017	LBBAP-CRT	Single case report; FU of 12 months.	First report of LBBAP-CRT for heart failure treatment in a failed BiV-CRT case. LVEF increased to 62% from a baseline 32%, the LVEDD decreased from 76 to 42 mm.
Sharma *et al. Heart Rhythm*, 2018	HBP-CRT	Observational, retrospective, multicentre; FU of 14 months.	Largest HBP-CRT study to date, reporting very high success rate (95/106) in mixed population of primary HBP-CRT or after failed BiV-CRT, albeit only 34% had LBBB. QRS narrowing from 157 to 117 ms, echocardiographic (LVEF 30% to 43%), and functional class improvement were observed.
Huang *et al. Heart*, 2019	HBP-CRT	Observational, single centre; FU of 37 months.	Patients with typical LBBB and CRT indications, temporary LBBB correction in 72/74 whilst successful implantation in 56/74. LVEF increased from baseline 32.4% to 55.9%, and functional class significantly improved. Long-term LBBB correction threshold was 2.29 V at 0.5 ms.
Vijayaraman *et al.*[48] *Circ AE*, 2019	HOT-CRT	Observational, retrospective, multicentre; FU of 14 months.	Successful implantation in 25/27 patients with incomplete LBBB/IVCD correction by HBP-CRT alone. Significant echocardiographic response and functional class improvement were observed. QRS narrowing to 120 ms was significant both from baseline (162 ms) and from HBP-CRT (151 ms).
Upadhyay *et al.*[47] *Heart Rhythm*, 2019	HBP-CRT vs. BiV-CRT	His-Sync. Randomized, multicentre trial; FU of 12 months.	LBBB patients with CRT indications were recruited. Low rate of successful implantation in HBP-CRT arm (11/21, 52%) despite high LBBB corrective output allowed (up to 5 V at 1 ms); cross-over 46% from HBP to BVP and 26% from BVP to HBP. HBP-CRT was not superior to BiV-CRT with regard to LVEF improvement (9.1% vs. 5.23% or rate of echocardiographic response (76% vs. 53%).
Morina-Vazquez *et al. Europace*, 2020	HBP-CRT	Observational, prospective, single centre; FU of 1 month.	Successful implantation with correction of LBBB in 36/48 patients with LBBB and CRT indications. Echocardiographic improvement observed in all patients, LV EF increased from 30% to 51% and septum to posterior wall delay decreased from 138 to 41 ms.
Li *et al. ESC Heart Fail*, 2020	LBBAP-CRT vs. BiV-CRT	Prospective, multicentre, observational, matched BiV-CRT patients; FU of 6 months.	LBBAP-CRT as a primary strategy or for failed BiV-CRT, implantation successful in 30/37; only LBBB patients included. LVEF improved from 28.8% to 44.3%. LBBAP-CRT was superior to BiV-CRT: echocardiographic response: 88.9% vs. 66.7% and clinical response: 96.3% vs. 75.9%.
Vinther *et al. JACC EP*, 2021	HBP-CRT vs. BiV-CRT	His-Alternative. Randomized single-centre trial; FU of 6 months.	HBP-CRT was successful in 19/26 patients with LBBB and CRT indications; cross-over 28% from HBP to BVP and 4% from BVP to HBP. On-treatment analysis showed better echocardiographic response in patients who actually received HBP-CRT: LVEF (48% vs. 42% and LVESV (65 mL vs. 83 mL).
Vijayaraman *et al. JACC EP*, 2021	LBBAP-CRT	Observational, prospective, multicentre; FU of X month.	Implantation successful in 277/325 CRT candidates. LBBB present in 39% and found as the strongest predictor of echocardiographic response (odds ratio 3.96). LVEF improved from 33% to 44%. Clinical and echocardiographic responses were observed in 72% and 73% of patients, respectively.
Jastrzębski *et al. Heart Rhythm*, 2021	LOT-CRT	Prospective, observational, multicentre; FU of 7.8 months.	Successful LOT-CRT implantation in 91/112 CRT candidates with suboptimal response to LBBAP-CRT or BiV-CRT alone. LOT-CRT resulted in significantly greater narrowing of QRS complex from 182 ms at baseline to 144 ms than did BiV-CRT (170 ms); and LBBAP (162). LVEF improved From 27% to 37% and functional class improvement was noted in 76% of patients (2.9 vs. 1.9).

Continued

Table 2 *Continued*

Study	CRT modality	Design and follow-up	Outcomes
Jastrzebski *et al.*[51] *Eur Heart Jour*, 2022	LBBAP-CRT	MELOS: prospective multicentre registry of LBBP including LBBAP-CRT; FU of 10.1 months.	The study comprised 2533 patients; LBBAP-CRT was successful in 82.2% (572/696). Independent predictors of LBBAP lead implantation failure were related to CRT indications including: heart failure, broad baseline QRS, and left ventricular end-diastolic diameter. LVEF and LVEDD showed a favourable change after LBBAP-CRT: 31.5 ± 8.3% vs. 39.4 ± 11.2%, and 60 ± 8.2 mm vs. 57.4 ± 8.4 mm, respectively.
Vijayaraman *et al. Heart Rhythm O*^{2}, 2022	LBBAP-CRT	Observational, retrospective, multicentre; FU of 13 months.	Largest LBBA-CRT study with non-LBBB patients. Successful implantation in 107/121 RBBB patients. LVEF improved from 35% to 43%. Clinical and echocardiographic response was observed in 60% and 61% of patients, respectively. Female sex and reduction in QRS duration with LBBAP were predictive of echocardiographic response and super-response.
Chen *et al. Europace*, 2022	LBBAP-CRT vs. BiV-CRT	Prospective, multicentre, observational; FU of 12 months.	Implantation successful in 49/50 CRT candidates with LBBB. Higher LVEF increase: 18.5% vs. 12.9% and higher super-response rate (61.2% vs. 39.2%) was observed in LBBAP-CRT as compared to BiV-CRT.
Wang *et al. J Am Coll Cardiol.*, 2022	LBBAP-CRT vs. BiV-CRT	Prospective, randomized trial; FU of 6 months.	Successful LBBAP-CRT implantation in 22/24 CRT candidates with LBBB. Higher LVEF improvement after LBBAP-CRT: 49.4 ± 13.2% vs. 46.5 ± 9.4% and comparable functional class and QRS duration. Cross-over 10% from LBBP to BVP and 20% from BVP to LBBP.
Pujol-Lopez *et al.*[52] *JACC EP*, 2022	LBBAP-CRT vs. BiV-CRT	LEVEL-AT trial. Prospective, randomized trial; FU of 6 months.	Successful LBBAP-CRT implantation in 27/35 CRT candidates (LBBB present in 21). Both groups showed a similar change in left ventricular end-systolic volume and similar rates of mortality or heart failure hospitalizations.
Vijayaraman *et al. JACC*, 2023	LBBAP-CRT vs. BiV-CRT	Observational, retrospective, multicentre, case–control.	Largest LBBAP-CRT study to date. A total of 1778 patients were analysed comparing 981 BiV-CRT vs. 797 LBBAP-CRT. The primary composite endpoint of time to death or heart failure hospitalization was significantly reduced to 98 with LBBAP compared to BVP 20.8% vs. 28%; hazard ratio 1.495. After LBBAP-CRT, LVEF improved from 27% to 41%.

AF, atrial fibrillation; BiV-CRT, biventricular pacing-cardiac resynchronization therapy; BVP, biventricular pacing; CRT, cardiac resynchronization therapy; FU, follow-up; HBP, His bundle pacing; HBP-CRT, His bundle pacing-cardiac resynchronization therapy; HOT-CRT, His-Optimized CRT; LBBAP, left bundle branch area pacing; LBBAP-CRT, left bundle branch area cardiac resynchronization therapy; LBBB, left bundle branch block; LBBP, left bundle branch pacing; LOT-CRT, left bundle branch pacing optimized CRT; LVEDD, left ventricle end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume.

Thus, non-responder rates were 53.3% for enalapril, 79% for bisoprolol, and 59% for spironolactone. We should also consider that patients who are symptomatic after optimal pharmacologic therapy (OT), particularly those in NYHA class II or IV, are essentially non-responders to OPT. In this context, there is increasing recognition that 'response', be it using symptoms or LV reverse remodelling, may be too simplistic. Gold *et al.*[38] have used the term 'disease stabilization'. In a recent joint position statement, Heart Failure Association, EHRA, and European Association of Cardiovascular Imaging have proposed that we adopt three categories in describing response to CRT: full remission or cure; partial remission; and disease progression (*Figure 5*).[37]

Multisite cardiac resynchronization therapy

Rather than targeting LV lead positions using physiological measures, such as imaging or Q-LV, some authors proposed that simultaneous LV stimulation from two coronary sinus veins may improve response to CRT.[39] In the TRIPle Resynchronization in Paced Heart Failure Patients (TRIP-HF), 34 patients with slow permanent atrial fibrillation underwent CRT using 1 RV lead and 2 LV leads (3-V) or 1 RV lead and 1 LV lead (2-V).[40] After 3 months of biventricular stimulation, the patients were randomly assigned to stimulation for 3 months with either 1 RV and 2 LV leads (3-V) or to conventional stimulation with 1 RV lead and 1 LV lead (2-V), then crossed over for another 3 months to the alternate configuration. In analysis of available data from 26 patients, CRT using 2 trans-CS leads did not achieve a better synchronization nor improvements in QoL or walking distance, despite improving in LVEF and reversing LV remodelling. The subsequent Triple-Site versus Standard Cardiac Resynchronization Therapy Randomized Trial (TRUST CRT) also compared CRT using a single trans-CS lead with CRT using 2 trans-CS leads in 100 patients with HF and a LVEF ≤ 35%. After a median follow-up of 7.1 years, there was no survival benefit from Tri-V CRT. Standard care vs. TRIVEntricular pacing in Heart Failure (STRIVE-HF), in which 99 patients were randomized to 3-V or 2-V CRT, no group differences emerged in total mortality, LV reverse remodelling, or clinical composite scores after 6 months.[41] These findings together with those showing a higher complication rate, longer procedure times, and lack of dedicated pulse generators have led to abandonment of 3-V CRT.

Endocardial cardiac resynchronization therapy

In the context of trans-CS CRT, the haemodynamic response and long-term outcomes vary, even when LV leads are deployed in an 'ideal'

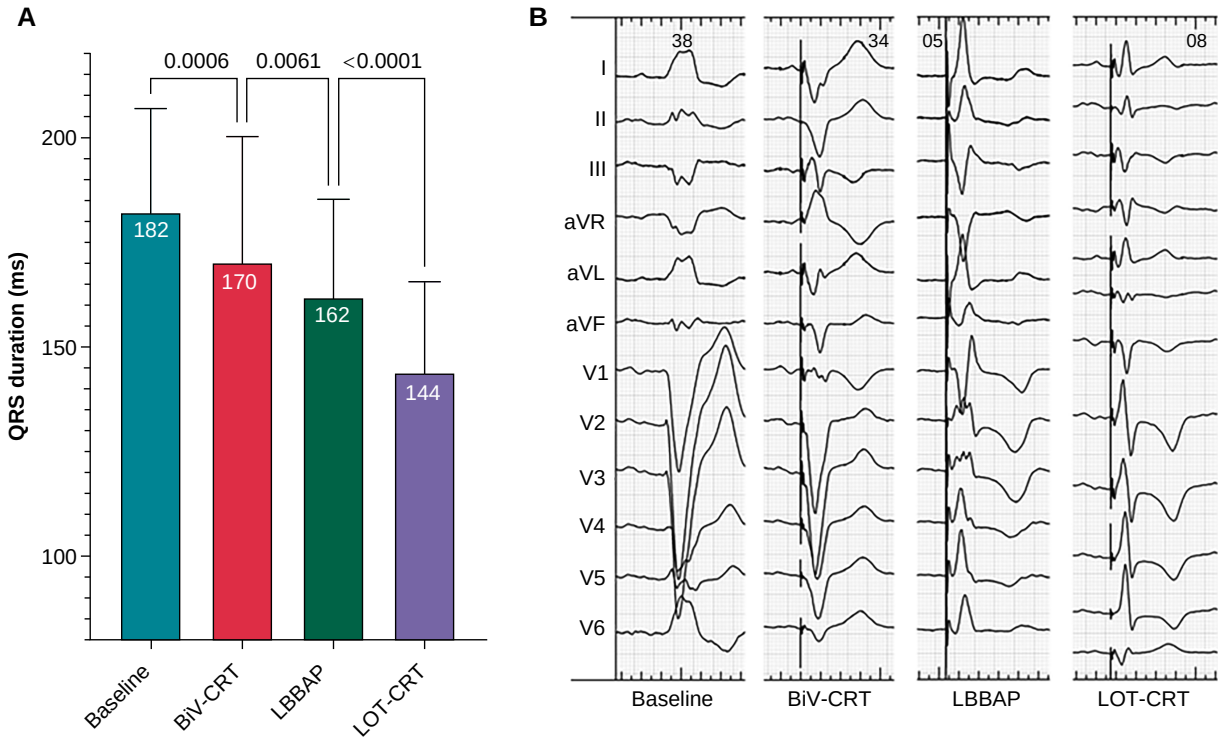

Figure 6 Incremental QRS narrowing with hybrid cardiac resynchronization modality: Left bundle branch-OpTimized cardiac resynchronization therapy (LOT-CRT). Reproduced with permission from Jastrzębski *et al.*[64]

positions. As conduction velocity in the endocardium is much faster than in the epicardium, some have proposed that endocardial pacing may be superior to coronary sinus pacing in CRT. Endocardial LV implantation techniques involve LV lead deployment using ventricular trans-septal or atrial trans-septal[42] approaches. Whereas animal experiments have shown a superior haemodynamic response to endocardial vs. epicardial LV pacing,[43] this has not been consistently reproduced in humans. In the ALternate Site Cardiac ResYNChronization (ALSYNC) study of atrial trans-septal LV endocardial CRT, complications, mainly cerebrovascular events, were alarming.[44] The WiSE CRT system, which consists of an ultrasound transmitter, was implanted on the anterior chest wall and connected to a generator and a wireless endocardial electrode.[45] A recent international registry from 14 European centres of 90 patients has proved that system implantation is feasible, although there are safety concerns.[46] In clinical trials, the overall clinical response rate has been over 80%, and included non-responders to 'conventional' CRT. An important limitation of the system in its current form is its reliance on another device capable of delivering RV pacing, however, early clinical trials have suggested a response rate over 80%, and these trials include patients who have failed CRT with epicardial coronary sinus leads.

Rational for conduction system pacing-cardiac resynchronization therapy

The paradigm of medicine is to heal what is broken and to restore physiology as close to the original state as possible. It is now evident that LBBB, a major cause of cardiac dyssynchronopathy, can be elegantly and completely 'repaired' with His bundle pacing (HBP) or left bundle branch area pacing (LBBAP). The advantages of conduction system pacing as well as the known shortcomings of BiV-CRT have attracted clinicians to the physiological pacing (as conduction system pacing is commonly labelled) and have led to is its adoption without evidence from large RCTs in pioneering centres.

Traditionally, CRT refers to the combination of left ventricular (LV) and RV pacing, i.e. BVP, that is synchronized with atrial activation. The BVP aims to restore the dyssynchronous ventricular electrical activation due to ventricular conduction delay or RV pacing. Nonetheless, BVP is a non-physiological pacing modality that restores ventricular synchronization through the fusion of two wavefronts from LV epicardial pacing and RV endocardial pacing. Consequently, BVP produces only modest ventricular resynchronization with a relatively small reduction in QRS duration.

Moreover, to achieve optimal effect of BVP, a personalized pacing electrode positioning strategy might be required. Given that the rationale of BVP aims is to resynchronize the LV, many studies showed that CRT response is best when the LV lead is positioned in the latest-activated region. However, anatomical limitations such as absence of suitable coronary veins and unavoidable phrenic nerve stimulation can influence CRT response. Also, LV scarring might hinder an optimal CRT response as pacing inside or close to the scar might lead to inadequate resynchronization. Also, the natural electrical activation sequence of the ventricles has multiple breakthrough points and fast endocardial conduction. Therefore, BVP could never match the physiological ventricular activation pattern, as the pacing induced activation wavefronts bypass the rapid ventricular conduction system.

His bundle pacing-cardiac resynchronization therapy

In the 1970s, pacing in the bundle of His was demonstrated to normalize the QRS complex in a subgroup of patients with LBBB.

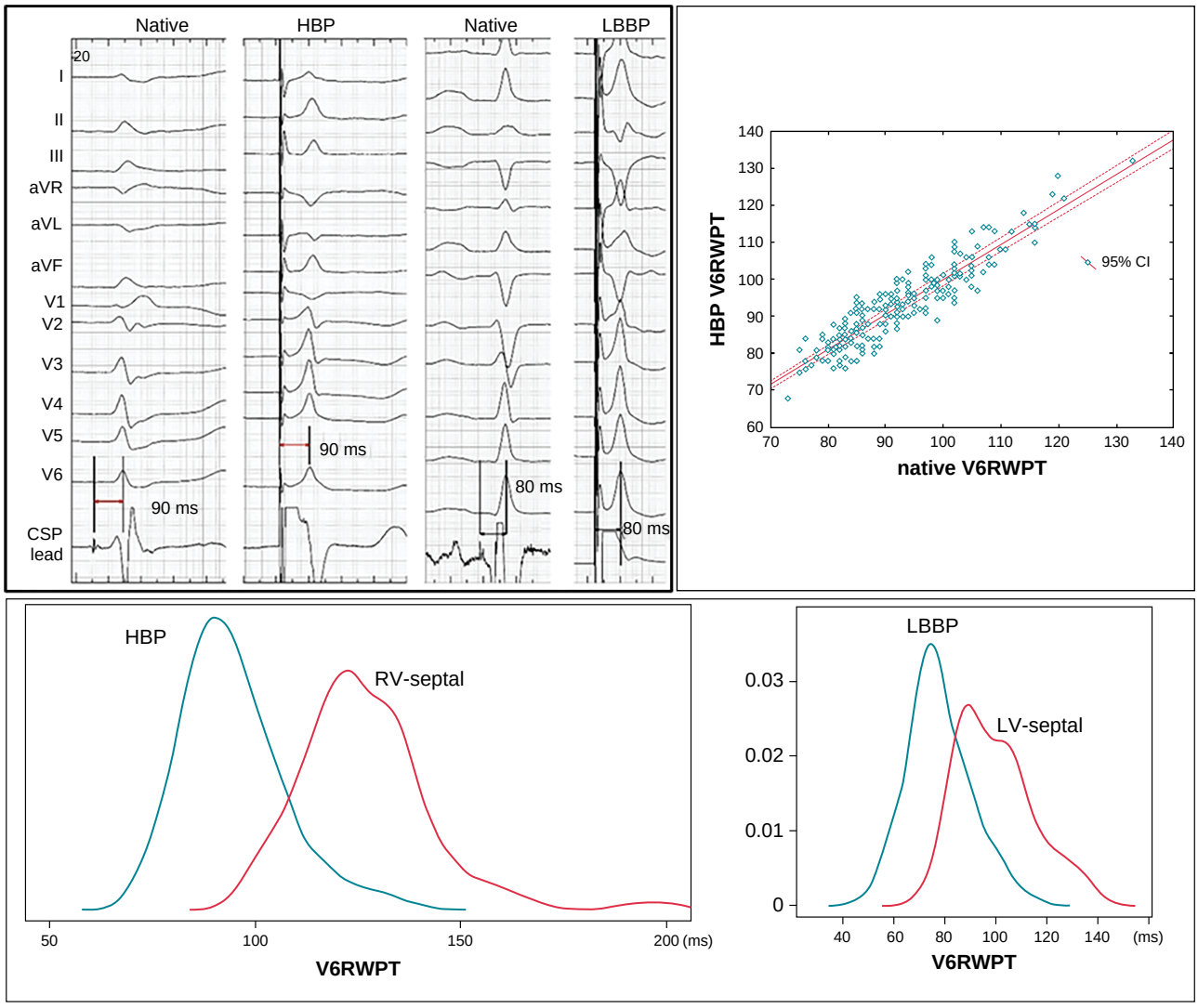

Figure 7 Conduction system pacing based cardiac resynchronization therapy (CSP-CRT) can be guided by the paced QRS metrics. Native peak time and paced V6 R-wave peak time (V6RWPT) are the same due to the physiological activation pathway of the lateral wall of the left ventricle during conduction system pacing. Lower panel shows distribution of V6RWPT values during His bundle pacing (HBP) and left bundle branch pacing (LBBP). Note that despite activation of the conduction system, V6RWPT is non-physiological in some patients indicating that the electrical synchrony is not restored to normal. Modified with permission from Jastrzebski *et al.*[62,63]

Conceptually, HBP can lead to ventricular resynchronization in the presence of a proximal conduction block and if HBP recruits activation in both bundle branch restoring a normal physiological activation. Evidence for the presence of proximal conduction delay in LBBB was obtained by detailed intracardiac mapping of the LV septum in patients with LBBB.[47] Complete conduction block was corrigible in 64% of the patients by pacing distally to the site of the block. Conversely, in the remaining 36% of the cases, they reported absence of conduction block and intact Purkinje activation. In this latter situation, HBP leads to incomplete QRS correction due to more distal conduction disturbances. In these patients, therapy could be optimized by sequential HBP followed by an additional coronary sinus lead in [His-Optimized CRT (HOT-CRT)] to maximize electrical resynchronization.[48] The HBP seems to have the potential to be the most physiological pacing modality that preserves or restores electrical and mechanical synchrony by simultaneously activating both ventricles.

The HBP-CRT seems especially well-suited for two subsets of CRT candidates: patients with narrow QRS at baseline, including ablate and pace strategy, and proximal intrahisian LBBB.[49]

Data on HBP-CRT outcomes are very promising but based on just a couple of small studies, most of them summarized in *Table 2*. Briefly, it seems that the acute success rate of HBP-CRT is ~50–70%, evidently lower than success rate of BiV-CRT. This is reflected by the high cross-over rate in randomized studies.[53,54] Success rate reported by the observational studies is higher—probably due to the pre-selection of cases and underreporting of failures. With HBP-CRT, QRS narrowing is much higher, and echocardiographic response is at least comparable to BiV-CRT.[55] Some of the limitations of this method are inherent—resulting from the pathophysiology of dyssynchrony (conduction system lesion/problem distal to the HB) whilst some are related to the potentially solvable technical aspects (inability to obtain HB capture with an acceptable output with the currently available tools). To address the

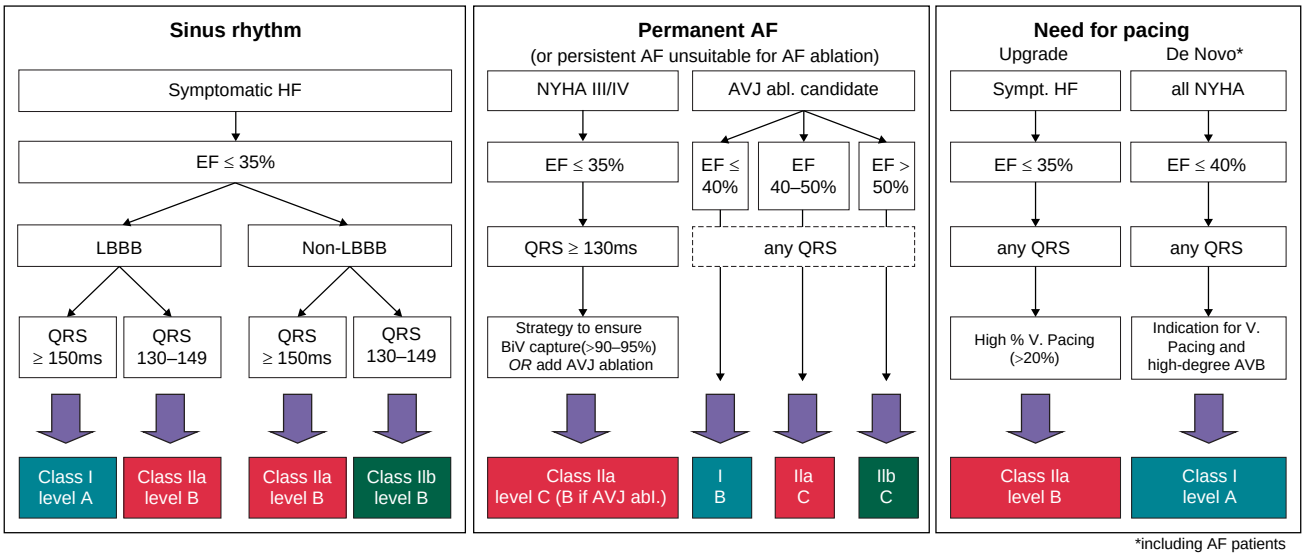

Figure 8 Summary of indications for CRT according to the 2021 ESC guidelines. AF, atrial fibrillation; AVB, atrioventricular block; AVJ, atrioventricular junction; BiV, biventricular; EF, ejection fraction; HF, heart failure; LBBB, left bundle branch block. Adapted with permission from Mr J. Mascheroni.

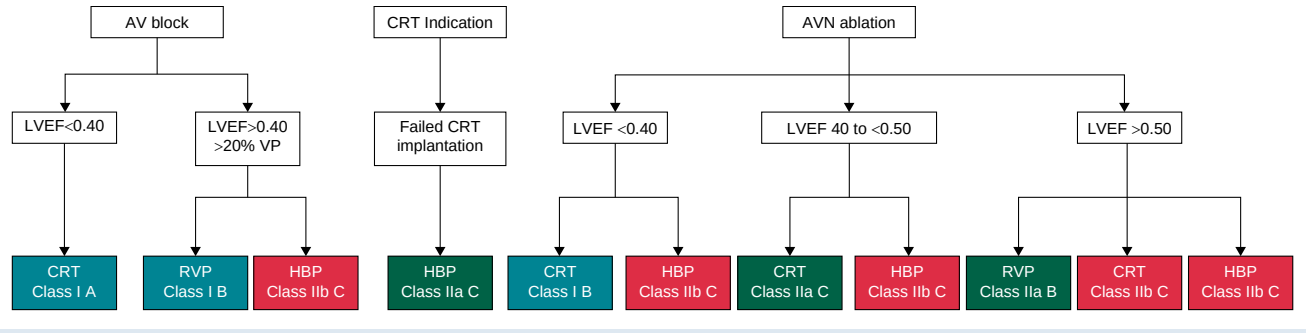

Figure 9 Summary of indications for CRT according to the 2021 ESC guidelines. AF, atrial fibrillation; AVB, atrioventricular block; AVJ, atrioventricular junction; BiV, biventricular; EF, ejection fraction; HF, heart failure; LBBB, left bundle branch block. Adapted with permission from Mr J. Mascheroni.

incomplete correction of conduction disturbance with HBP-CRT alone, a hybrid pacing approach that combines HBP and coronary venous pacing is explored. This CRT modality, known as His-Optimized CRT (HOT-CRT) results in incremental QRS narrowing over both BiV-CRT and HBP-CRT.

However, improvement of tools for easier positioning of the lead in the His bundle as well as methods for identifying patients that benefit from HBP might extend the scope of HBP-CRT.

Left bundle branch area pacing-cardiac resynchronization therapy

More recently, the procedural challenges associated with HBP opened the way for LBBAP.[51] The feasibility and beneficial haemodynamic effects of LV septal pacing by transvenous approach through the interventricular septum were first described by Mafi-Rad *et al.*[56] Subsequently, based on this trans-septal approach, Huang *et al.*[50] pioneered LBBAP in a patient in whom HBP failed to correct LBBB at the highest pacing output. The LBBAP seems to be more suited to restore conduction in left bundle branch than HBP as the pacing site is nearly always distal to the lesion in LBBB. Direct capturing the left bundle branch, manifesting electrocardiographically as an incomplete RBBB with a relatively narrow QRS duration, preserves or restores mainly the physiological activation of the LV[56] without the challenges as low sensing values or high thresholds as reported in HBP.[57]

The presence of baseline LBBB is a strong predictor of LBBAP-CRT outcome, indicating that the mechanism of clinical benefit is the same as with BiV-CRT (correction of LBBB induced dyssynchrony). Data on clinical outcomes of LBBAP-CRT are more robust than for HBP-CRT, based on several mid-sized to large, multicentre observation studies and several smaller studies including two randomized trials.[52,58–61] Most of these studies are summarized in *Table* 2. Briefly, echocardiographic, electrocardiographic, and clinical response, including functional class,

mortality, and heart failure hospitalization, seem superior to BiV-CRT. Large RCTs are needed however to provide definite answer. Acute success rate of LBBAP-CRT is 80–95%, slightly lower than for BiV-CRT and lower than LBBAP success rate for bradyarrhythmia indications as shown by the MELOS study. This results from anatomical challenges in patients with HF (dilated atria and ventricles and rotation of the heart), fibrous septum and left septal conduction system. The LBBAP-CRT cannot correct widespread or very distal conduction disturbance typical for non-specific intraventricular conduction delay that is more often present in heart failure patients either alone or on the top of LBBB. For such patients, hybrid pacing known as Left bundle branch-OpTimized CRT (LOT-CRT) can be used to maximize response (*Figure 6*).

Electrocardiographic response of conduction system pacing-cardiac resynchronization therapy

For CSP-CRT assessment of electrocardiographic outcome plays a bigger role than for BiV-CRT. Perhaps the most practical biomarker of electrical and mechanical synchrony is QRS narrowing that can be used for BiV-CRT optimization and even as a procedural goal and to maximize clinical benefit. For CSP-CRT, not only narrowing but QRS metrics normalization can be the goal as V6 R-wave peak time (V6RWPT) during CSP corresponds to physiological values of V6RWPT during native conduction—*Figure 7*.[62,63] Upper limit of normal V6RWPT values for native QRS is 50–60 ms, and this plus conduction system potential to QRS interval defines the normal values for paced QRS during CSP-CRT (i.e. 100–110 ms for HBP and 80–90 ms for LBBAP-CRT). Potentially, paced V6RWPT can be used to precisely 'gauge' the degree of restoration of synchrony and provide a criterion for adding coronary venous lead for hybrid pacing [His-OpTimized/Left bundle branch-OpTimized CRT (HOT/LOT-CRT)] when V6RWPT remains non-physiological.[64]

Complications of conduction system pacing-cardiac resynchronization therapy

Complication rate of CSP-CRT seems similar to BiV-CRT although complication profile is different—especially for LBBAP-CRT that is based on the trans-septal LV septal pacing technique with the potential for septal damage (haematoma, fistula, acute coronary event, etc.). Moreover, septal perforation, especially late (seen in ~0.05% cases) but also acute partial perforation might be related to the risk of systemic embolism. Long-term performance of deep septal leads is a remaining concern that must be addressed before wide adoption of this method.

Current practice of conduction system pacing-cardiac resynchronization therapy

Despite limited clinical evidence, both HBP and LBBAP seem already to play an important role in routine clinical practice as revealed by two recent European surveys.[65,66] Both surveys indicated that CSP is predominantly used for patient with a bradycardia pacemaker indication and that LBBP is preferred by most operators over HBP. For patients with HF and LBBB most operators still reserve conduction system pacing for biventricular implant failures, although there are a considerable number of operators who already use LBBP as first-line therapy for their CRT implantation.

Guidelines

CRT has established itself in pacing guidelines over the last two decades. A summary of the current indications for CRT according to the 2021 ESC pacing guidelines is shown in *Figure 8*.[34]

His bundle pacing was first included in European guidelines in the 2019 ESC guidelines on management of supra-ventricular tachycardia, where it was defined (along with CRT) as a class I, level of evidence C indication for a 'pace and ablate' strategy for treating patients with tachycardiomyopathy if the tachycardia cannot be controlled by ablation or drugs, and a IIa, level of evidence C in patients with left ventricular dysfunction due to refractory recurrent multifocal atrial tachycardia.[67] The 2021 ESC pacing guidelines[34] expanded the indications of HBP to patients with atrioventricular block (AVB) and as rescue therapy for patients with failed CRT implantation (see *Figure 2*), without any first-line indication for HBP in lieu of CRT. The guidelines did not formulate any recommendations for LBBAP, due to paucity of data at that time (*Figure 9*).

As indicated by the supplementary tables in the appendix of the 2021 ESC pacing guidelines,[34] at the time of its writing, there were only four randomized controlled trials on HBP, which included a total of 99 patients with successful HBP implantation, and none on LBBAP or on HOT/LOT-CRT. This explains why these guidelines had indications for CSP, which may be currently considered to be very conservative. The indications would no doubt be different if the guidelines were to be re-written today, as studies on CSP have moved fast since then. In a recent EHRA survey,[3] 85% of the respondents believed that CSP would predominate over RV pacing for bradycardia indications and 72% over biventricular pacing for CRT indications. In a recent European survey conducted on CSP implanters, the best indications were considered to be atrioventricular block in patients with a narrow QRS, failed CRT implantation, and pace and ablate.

Due to the uncertainty of long-term safety of HBP, the 2021 ESC pacing guidelines recommend use of a backup ventricular lead with a class IIa, level of evidence C recommendation in selected situations [e.g. pacemaker-dependency, high-grade AVB, infranodal block, high pacing threshold, and planned atrioventricular junction (AVJ) ablation], or for sensing in case of issues with detection (e.g. risk of ventricular undersensing or oversensing of atrial/His potentials). Backup leads are, however, most often not considered necessary with LBBAP.

Indications for CSP will no doubt evolve in the coming years with the growing evidence for its safety and efficacy. Economic factors are also likely to play a role, as CSP may reduce the need for more expensive CRT devices. The expansion of CSP not only depends upon evidence from studies conducted in selected centres but also in ensuring that CSP is properly performed in more widespread clinical practice. The 2023 EHRA clinical consensus statement on CSP implantation[68] forms a framework for performing the procedure safely and effectively. Lack of education and training are considered to be the greatest hurdle for adoption of CSP. Educational programmes, which may include simulator-based training, as well as evolution in leads and tools dedicated to CSP implantation, will no doubt facilitate adoption of CSP in the future.

Future directions

One of the hot topics in CRT today is the emergence of CSP as shown by the recent large number of publications during the last decade and its adoption in clinical practice.[66] For CSP, the technique most frequently used is the LBB area pacing, which is considered easier and with better chronic electrical parameters. However, we must recognize that the level of evidence for LBBAP is still low with small controlled randomized trials or observational studies. Before being implemented in the guidelines with a high level of recommendation, there is a definitive need of more randomized controlled clinical trials. Some trials are ongoing or will start soon in conventional indications for CRT such as the His-Sync II or Left versus Left trials comparing LBBAP and biventricular pacing. Interestingly, other RCTs are designed to evaluate LBBAP in patients with a low response rate to biventricular pacing such as patients

with RBBB but also the combination of CSP and LV pacing through the coronary sinus, or so called HOT-CRT.

For biventricular pacing, the recent data from the Adapt trial have shown that the rate of responders in selected patients with LBBB and normal AV interval with a rate of clinical response including improved or stable patients is over 90% and so higher than expected. This might be an explanation of the non-significant difference in the adaptive CRT algorithm providing LV pacing only.[69] However, identification of patients in whom a high percentage of LV pacing only might be interesting to increase the rate of response as demonstrated with a significant benefit with adaptive CRT algorithm in the Adapt response trial. Recent data of the planned interim analysis of the SOLVE-CRT trial presented during the Heart Rhythm Society 2023 congress did show the efficacy based of echocardiographic parameters and safety of endocardial pacing using the WISE system®. These interesting results have to be confirmed with the completion of the study to access the potential of endocardial pacing.

Finally, identification of responders before CRT implantation with a personalized approach is a very interesting challenge. Some promising results using artificial intelligence or digital twin models have to be confirmed by clinical trials and evaluation of outcomes from large databases.[70]

Conflict of interest: Kenneth A. Ellenbogen: Consultant and honoraria from Medtronic, Boston Scientific, Abbott and Biotronik, C. Leclercq: Lecture and honoraria from Abbott Medtronic, Boston Scientific, Biotronik, F. Leyva; No relevant conflicts, C. Linde: honoraria from Medtronic, Impulse Dynamic, A Auricchio: Consultant and honoraria to Boston Scientific, Cairdac, Corvia, MicroportCRM, Medtronic, XSpline; K Vernooy: Boston Scientific, Medtronic, Phillips, Biosense Webster, Abbott, F Prinzen; No relevant conflicts other than research support, M Jastrzebski: Consultant and speaker honoraria form Medtronic, Abbott and Biotronik; M Gold: Consultant: Boston Scientific and Medtronic; Haran Burri: Consultant and honoraria; Abbott, Biotronik, Boston Scientific, Medtronic and Microport.

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