# 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

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**POSITION PAPER**

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## 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

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Cardiac resynchronization therapy (CRT) is one of the most effective therapies for heart failure with reduced ejection fraction and leads to improved quality of life, reductions in heart failure hospitalization rates and all-cause mortality. Nevertheless, up to two-thirds of eligible patients are not referred for CRT. Furthermore, post-implantation follow-up is often fragmented and suboptimal, hampering the potential maximal treatment effect. This joint position statement from three European Society of Cardiology Associations, Heart Failure Association (HFA), European Heart Rhythm Association (EHRA) and European Association of Cardiovascular Imaging (EACVI),

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focuses on optimized implementation of CRT. We offer theoretical and practical strategies to achieve more comprehensive CRT referral and post-procedural care by focusing on four actionable domains: (i) overcoming CRT underutilization, (ii) better understanding of pre-implant characteristics, (iii) abandoning the term 'non-response' and replacing this by the concept of disease modification, and (iv) implementing a dedicated post-implant CRT care pathway.

**Keywords** Cardiac resynchronization therapy • Response • Heart failure • Implementation • Utilization • Care pathways • Disease modification • Disease management • Outcome

# Introduction

Cardiac resynchronization therapy (CRT) is one of the most effective therapies for heart failure with reduced ejection fraction (HFrEF) resulting in improved quality of life, beneficial reverse remodelling and reductions in heart failure hospitalization rates and all-cause mortality.[1–7] Despite its well established clinical benefits and cost-effectiveness, it remains a widely underutilized treatment option; recent European data suggest only one in three eligible patients actually receives a CRT device.[8] In contrast, the topic of 'non-response' to CRT ('failure to improve') has received disproportionally large research attention, with rates of non-response reported in 30% of implanted patients.[9] A binary definition of 'response' classified by arbitrary magnitudes of improvements in a variety of variables of questionable clinical significance underestimates the true benefits of CRT reported in the randomized clinical trials. This is in contrast with the message from all randomized controlled CRT trials in HFrEF patients with a QRS >130 ms, which consistently show a spectrum of stabilization or improvement of disease progression to even recovery of the disease.[10,11] Moreover, in addition to this 'failure to refer', optimization of both the device and the care of the patient following implant is hampered by a lack of integration of cardiological and non-specialist care, leading to suboptimal and variable post-implant management.[12,13] As a result, many heart failure patients are not exposed to the full potential benefit of CRT. This position paper aims to improve the implementation of CRT and follow-up of patients with CRT, by addressing the following topics: (i) underutilization of CRT, (ii) redefining response as disease modification of heart failure, (iii) better understanding of pre-implant patient characteristics, and (iv) integration and optimization of post-implant CRT care.

# Action plan for referral and optimization of cardiac resynchronization therapy-related care

## Action I: Overcome the underutilization of cardiac resynchronization therapy

### Eligibility vs. actual implantation

Observational data indicate that 35% to 40% of patients with HFrEF have a prolonged QRS width (classically defined as QRS >120 ms) and 20–30% of HFrEF patients have left bundle branch block (LBBB).[14,15] Since a considerable proportion of HFrEF patients do not tolerate or improve after other heart failure therapies have been introduced, ultimately 5–10% of all heart failure patients remain eligible for CRT. As such, estimates using eligibility criteria as stated in professional practice guidelines (QRS >130 ms) suggest that up to 400 patients per million inhabitants of European countries might be candidates for CRT implantation annually.[16,17] Between 2005 and 2013, European and US guideline indications have expanded to also include patients with less severe symptoms [New York Heart Association ((NYHA) class II], and in 2016 the guidelines tightened the proportion of patients eligible to CRT by prolonging the QRS duration and altering the morphology criteria.[18] Data from the European Heart Rhythm Association (EHRA) White Book indicate that within the European Union between 2010 and 2013 the average implantation rate varied between 106–123 per million inhabitants,[8] and more recent data from device registries reported a rate of 56 CRT pacemaker (CRT-P) and 119 CRT defibrillator (CRT-D) implants per million inhabitants in 2018 in Europe, with a slight increase of mainly CRT-P over recent years (*Figure 1*). Although significant geographical differences are clearly present, these data suggest that up to two thirds of those eligible for CRT on current guidelines are not implanted. Registry data provide some insights into factors associated with the non-referral of CRT, indicating that older age (>75 years), lack of CRT implant centres, shorter duration of heart failure, absence of a heart failure nurse and non-cardiology follow-up are factors that are independently associated with non-delivery of CRT.[19] One key issue is that many patients with heart failure including those eligible for CRT are managed in primary or non-specialist care where there is possibly less familiarity with the indications and benefits of CRT.[17] This lack of awareness is also illustrated in the recent European Society of Cardiology (ESC) CRT Survey II, which highlighted that most of those implanted had been identified within the cardiology department. Only a minority had been referred from other departments, including primary care.[20] Moreover, despite the well-established benefit of CRT in women, CRT remains underused in female patients. This gender gap has remained unchanged in Europe over the past 10 years with female CRT patients representing only 27% and 24% of all implants in the ESC CRT Survey I and II, respectively.

### Guidelines vs. registries

Professional practice guidelines have formulated recommendations for CRT in HFrEF patients based upon morbidity and mortality

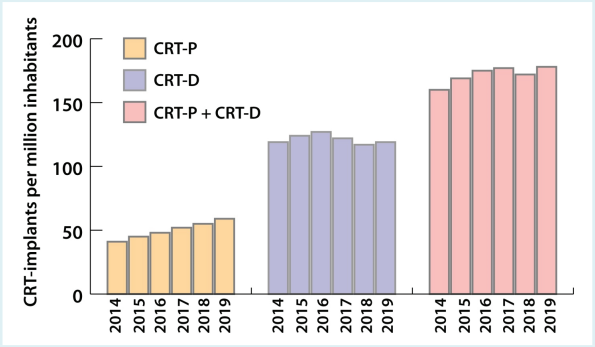


**Figure 1** Cardiac resynchronization therapy pacemaker (CRT-P) and cardiac resynchronization therapy defibrillator (CRT-D) implants in Europe between 2014 and 2019. Source: https://www.medtecheurope.org/.

reductions.[12,21–24] Guidelines offer a strong level of recommendation for patients in sinus rhythm, a wide QRS duration or LBBB. Data from the EuroCRT Survey II indicates that 67% of implanted patients had a class I indication, with 26% having a class IIa indication, 5% a class IIb indication and 2% a class III indication. It would appear that while CRT is globally underused, in clinical practice CRT is frequently offered to patients in whom the level of evidence is either less robust than a class I indication or non-existent.[25]

### Health economic considerations

Implantable devices such as CRT are often approached with scrutiny by health care regulating agencies and payers, due to their significant up-front cost and the fact that they are implanted in a patient population (if left untreated) with a relatively limited life expectancy. The cost of any intervention needs to balance the willingness to pay, which is typically reflected in the incremental cost-effectiveness ratio (ICER). This is expressed as the amount of money which has to be spent to gain a quality-adjusted life-year (QALY). A Markov model with Monte-Carlo simulation from the CARE-HF and COMPANION trials indicates an ICER of €7538 for CRT-P and €18 017 for CRT-D, which is below the generally accepted thresholds for cost-effectiveness (€30 000–40 000 or gross domestic product (GDP) per capita) in high income countries.[26] In the REVERSE trial focusing on NYHA class II patients, CRT was linked to 0.94 life years or 0.80 QALYs at an additional cost of €11 455, yielding an ICER of €14 278 per QALY gained.[27] Despite the additional up-front cost of a CRT-D device in comparison to a CRT-P device, it is still within the accepted cost-effectiveness boundaries for the USA and Europe.[27,28] Data from the EHRA White Book indicate lower utilization of CRT in European countries with a lower GDP per capita,[8] suggesting that supportive guidelines aiding appropriate selection between CRT-P vs. CRT-D in lower GDP countries might help to increase CRT implant rates in these areas.

### Strategies to overcome the underutilization of cardiac resynchronization therapy

Since one of the barriers to implantation is referral, improved strategies to identify potential eligible CRT candidates by cardiologists and non-cardiologists are urgently needed.[20] Importantly, electrocardiogram surveillance in heart failure patients is warranted as abnormalities (which often change over time) not only provide information on aetiology, but they also help to identify appropriate therapy. Furthermore, thorough and repeated education within primary and secondary care (including cardiologists less familiar with devices) about CRT, and openly addressing deeply-rooted myths that contribute to non-referral may improve CRT implementation (*Table 1*). Finally, deeper engagement with patient associations or support groups could improve the dissemination of information about therapeutic options. Screening through automated alerts in electronic health records based on information from QRS duration, left ventricular (LV) function and heart failure status might trigger more actionable referrals. Given the expansion of electronic health records, screening for patients eligible for optimization of heart failure therapy including CRT might be effective as it has been for other treatments for heart failure.[18,29]

## Action II: Replace ‘response to cardiac resynchronization therapy’ by ‘disease modification by cardiac resynchronization therapy’

Due to the up-front cost, life-long presence of the device, and potential device- and procedure-related complications, decisions for device-based interventions are often delayed until all other non-device-based therapies have ‘failed’.[30] This situation is exacerbated by the unique and widespread concept of ‘non-response’ where, based upon arbitrary cut-offs of remodelling (most often LV end-systolic volume reduction of >15%) or symptomatic ‘improvement’, it has been suggested that one in three patients do not ‘respond’ to CRT. As a result of these factors, CRT has been approached with an unprecedented scrutiny despite its firmly established benefits on morbidity and mortality in patients with heart failure and a wide QRS (>130 ms).[31,32] This situation is especially worrisome since no consensus exists on how or when to measure response to CRT and what magnitude of change constitutes response.[33] Adding to the confusion is a long list of potential ‘predictors of response’ of which many are based upon results of observational studies, which, due to a lack of control data, cannot conclusively determine the relation between the predictor and the clinical outcome benefit (risk reduction) from CRT.

### Response parameters, agreement and timing

Numerous variables including functional, event-based, imaging or composite outcomes have been used to describe response to CRT.[12] The importance of certain metrics might also differ according to the stakeholders, such as patients, their carers, doctors, payers, or industry. The placebo effect of an implant on functional outcomes is also often underestimated as noted after implantation

**Table 1** Myths and strategies for better implementation

| Common myths of CRT | Explanation |
|---|---|
| **Myths related to the pre-implant phase of CRT** | |
| 30% of patients do not respond to CRT | CRT response has been classified by arbitrary definitions: its effect in any one individual should be seen as continuous disease modification and whilst they may not feel 'better', they are highly likely to be 'better than without the device'. |
| Patients with an ischaemic aetiology of heart failure benefit less from CRT | On average, patients with an ischaemic aetiology of heart failure manifest less reverse remodelling but have an equal relative risk reduction after CRT for heart failure admission and death as the non-ischaemic group. |
| If the QRS is narrow, patients will never have an indication for CRT | In patients with HFrEF, remodelling of the left ventricle is accompanied by electrical remodelling such that QRS duration lengthens. Follow-up ECG is necessary. Consideration should be given to those with poor LVEF and a pacing indication that will lead to high proportion of RV pacing. |
| CRT is an expensive therapy | CRT is a cost-effective heart failure therapy. |
| Consideration of CRT should only occur after repeated (failed) attempts to achieve guideline-recommended doses of RAASi and beta-blockers | Only a minority of patients included in CRT trials were on optimal doses of RAASi and beta-blockers, and the effects of these drugs on LVEF improvement are far less pronounced in LBBB than in narrow QRS. CRT can help achieve guideline-recommended doses. |
| Patients with multiple comorbidities derive no benefit of CRT | Patients with comorbidities derive significant benefit from CRT, especially when the comorbidities are addressed. The need for CRT-D should be dealt with openly in this population. |
| All patients should receive CRT-D | The benefit of the ICD is determined by the risk of sudden cardiac death over the risk of non-sudden cardiac death. Those at highest risk of heart failure death derive no benefit from an ICD. |
| Physicians know when to refer patients for CRT | Most patients are only referred within cardiology. The non-cardiology medical and allied health community and patients need education to improve referral. |
| Echocardiography should be used as a technique to select patients that will not respond to CRT | Echocardiography is poor at determining 'need' or 'response' to CRT. Patients should not be denied CRT based upon echocardiography. |
| Access to CRT is not an issue as CRT implantation can be done by everyone who can implant a DDD pacemaker | CRT implant does have a higher risk, and does require more training than conventional DDD pacemakers. Efforts should be made to increase access. |
| **Myths related to the post-implant phase of CRT** | |
| Optimization of CRT is only needed in non-responders | Ideally, all CRT patients should receive regular review of their heart failure therapy, which should include a review of medical treatment (including drug doses) and device programming. Not only is heart failure a progressive disease, such that adjustments can be of benefit, but recent and future developments in medical therapy should be applied to this group as rapidly as possible. |
| Patients on CRT are on optimal medical therapy | Only a minority are on optimal dosages of GDMT at the moment of implant, more than 60% can be further up-titrated after CRT |
| Out of the box device programming suffices in most CRT patients | All CRT patients should receive regular (at least annual) device checks and might need optimization of device settings (brady/tachy) by physicians specifically trained in cardiac device programming and troubleshooting. |
| Remote monitoring is not useful | Comprehensive remote monitoring including device/lead integrity, % of biventricular pacing and arrhythmias in CRT patients has been demonstrated to improve clinical outcome in at least one randomized trial with tightly controlled review and action systems in place. Regular device checks (at least once per year) remain important in patients undergoing remote monitoring. |

CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; ECG, electrocardiogram; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RAASi, renin–angiotensin–aldosterone system inhibitor; RV, right ventricular.

during the run-in phase before LV only pacing was switched on in the GREATER-EARTH study.[34] Moreover, the agreement between outcomes is remarkably poor. It is well recognized that resting LV function is poorly related to exercise capacity or symptoms,[35] so it is not surprising that LV reverse remodelling poorly relates to the degree of functional improvement in many studies.[36–38] Indeed, the size and shape of the ventricle is irrelevant for patients complaining of exercise intolerance. Yet, LV reverse remodelling remains a commonly used endpoint, largely based upon the close relationship between changes in LV structure and outcomes.[39] However, these data have been over interpreted to imply that patients without significant LV reverse remodelling (e.g. LV end-systolic volume reduction >15%), derive no benefit from CRT whereas up to 30% of patients lacking remodelling benefits *will* experience an improvement in symptoms. Importantly, even patients who fail to demonstrate reverse remodelling and require a heart failure admission, still derive haemodynamic benefit from their device, as they often deteriorate when biventricular pacing is temporarily stopped.[40] Finally, the REVERSE trial showed a continuous reduction of both LV systolic and diastolic volumes for at least up to 2 years after CRT, which questions the appropriateness of any point-in-time assessment of therapy efficacy.[41]

### Baseline variables suggested to predict outcome following cardiac resynchronization therapy

In addition to the difficulty of timing, magnitude, congruity and outcome in assessing 'response', there is a plethora of pre-implantation features that are associated with certain response parameters and often wrongly drive decisions on implantation. Commonly quoted features predicting less LV reverse remodelling in observational studies include male sex, ischaemic aetiology, high LV volumes, low glomerular filtration rate, and absence of mechanical dyssynchrony.[42–46] In contrast, post-hoc analyses of the major CRT trials powered for mortality and morbidity (CARE-HF, RAFT, COMPANION and MADIT-CRT) revealed no heterogeneity between these aforementioned baseline characteristics and benefits on mortality or heart failure admission. Therefore, these subgroups gain similar relative risk reduction with CRT despite lesser degrees of LV reverse remodelling, and should not be used to de-select patients from receiving CRT.[3,4,6,47] More importantly, these patients often have a high risk for heart failure admission and mortality (baseline event rate) and might actually therefore have a higher absolute risk reduction after CRT. None of the studies have shown an adverse effect of CRT in patients with a QRS width >130 ms, especially in the LBBB population.[48,49] Finally, in the recent ADVANCE-CRT registry, patients labelled as responders, were less likely to have their therapy optimized following CRT implant,[13] suggesting that there are risks from suboptimal care delivery if someone is actually labelled a responder.

### Removing the term 'response'

Apart from rare isolated situations, heart failure is incurable. CRT is therefore not a curative therapy but rather should be seen as a treatment to ameliorate the contribution of electromechanical dyssynchrony to the heart failure syndrome in the hope that this will ultimately reduce heart failure-related morbidity and mortality. A slowing of a progressive disease is a positive outcome (*Figure 2*). Despite frequently quoted parallels between heart failure and cancer, the important concepts of 'remission' and 'non-progression' seem not to have permeated to cardiology. Therefore, this position statement calls to stop the current binary approach of CRT response, but rather we suggest that CRT should be classified as a treatment for 'disease modification'. One step towards such an approach is the Packer hierarchical scoring system which takes into account (lack of) mortality, (lack of) hospital admission for heart failure and stable functional status (without additional diuretic therapy), where lack of deterioration and therefore 'stability' is seen as a positive outcome (online supplementary *Figure S1*).[50] Furthermore, it needs to be underscored that if CRT is being implanted in HFrEF patients with a QRS width >130 ms (especially in the presence of LBBB), there is no proven patient population that experiences a negative response to CRT.[10]

## Action III: Better clinical interpretation of pre-implant characteristics

### Patient selection

European and American guidelines give a class I recommendation for CRT in symptomatic HFrEF patients in sinus rhythm with wide QRS (online supplementary *Table S1*).[23,24,51] The EchoCRT and RethinQ trials showed that the benefit of CRT does not extend to patients with a narrow QRS, even in the presence of some echocardiographic characteristics indicative of LV mechanical dyssynchrony.[48,49] The 2016 Heart Failure Association (HFA) guidelines reflect these data and do not recommend CRT in patients with a narrow QRS, defined as QRS <130 ms (class of recommendation III, level of evidence A).[48,49] The observation that QRS duration is dependent on body/heart size has resulted in ongoing research to determine if QRS duration should be individualized.[52–54]

Guidelines recommend the presence of LV ejection fraction (LVEF) <35%, as this was a major inclusion criterion in most CRT trials.[23,24,51] However, there is reason to believe that CRT may be effective in the higher range of reduced LVEF from both the MADIT-CRT and REVERSE trial.[55] For example, a core lab assessment of baseline LVEF from the MADIT-CRT trial indicated that 38% of patients actually had a LVEF above the entry criteria cut-off, with LVEFs up to 45%.[56] These patients had similar benefit in terms of death and heart failure hospitalization, and might also have a greater degree of reverse remodelling. This, together with the standard error of the measurement of LVEF by echocardiography, should be taken into account when determining eligibility based upon LVEF.

It is well acknowledged that visible pre-implant mechanical dyssynchrony (apical rocking, septal flash) is associated with an acute haemodynamic improvement following CRT.[57,58] However, using mechanical dyssynchrony for the selection of CRT does not select patients more likely to gain benefit.[48,49,59] As such, the absence of pre-implant mechanical dyssynchrony should not defer the implantation of a CRT device in patients with a guideline indication. Other imaging techniques or echocardiographic parameters

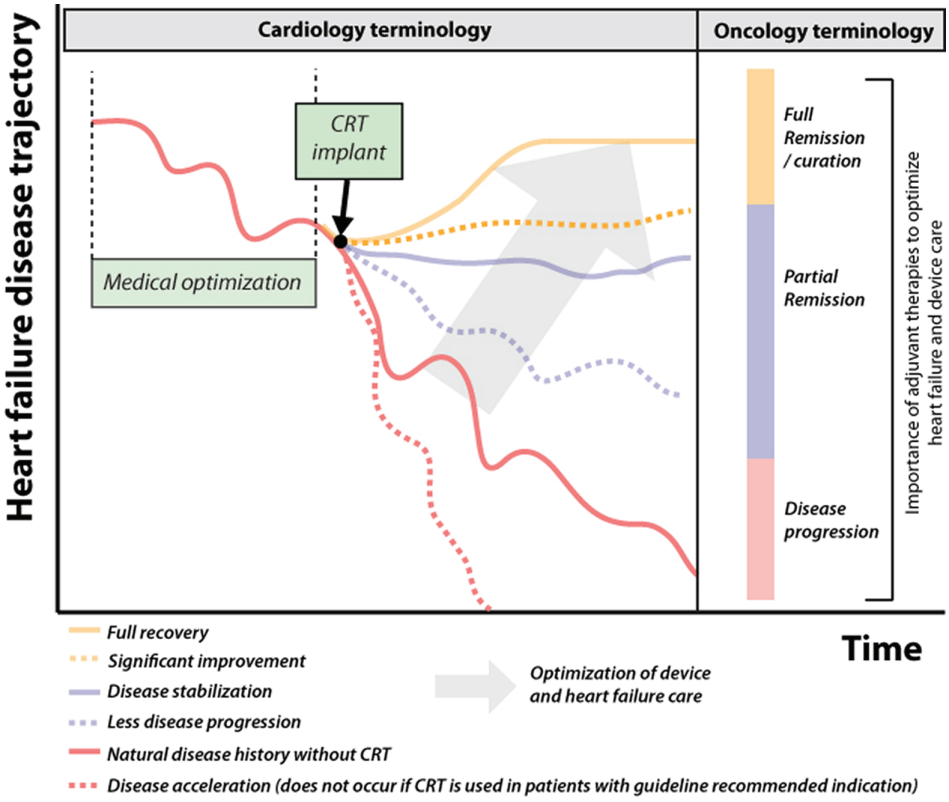


**Figure 2** Role of cardiac resynchronization therapy (CRT) in disease modification of the heart failure disease trajectory. The grey arrow indicates the role of auxiliary heart failure optimization following CRT implant.

have not been used to guide treatment in the randomized controlled trials, and should therefore not be used for the *de-selection* of patients otherwise eligible. That is not to say, however, that pre-implant imaging is not required. For instance, pre-implant magnetic resonance imaging is useful in the assessment of the risk for sudden cardiac death (SCD) (e.g. mid-wall fibrosis), and might therefore be helpful in determining the choice between CRT-P vs. CRT-D.[60,61] Additionally, echocardiography remains an indispensable tool to detect disease progression following CRT, and the mechanism(s) related to ongoing disease following implant, which might be amenable for auxiliary therapies (e.g. residual functional mitral regurgitation amenable for mitral edge-to-edge repair).[62,63]

Guidelines state a IIa indication for CRT in patients with atrial fibrillation (AF), despite the fact that only 262 patients with AF were randomized in the original CRT trials, which indicates that there is virtually no randomized trial data on CRT in AF patients. The RAFT trial randomized patients to an ICD vs. CRT-D stratified by the presence of permanent AF. In AF patients, there was only a trend towards fewer heart failure hospitalization in CRT-treated patients, and the primary outcome of death or heart failure hospitalization between those assigned to ICD vs. CRT-D was similar.[64] Despite this limited trial evidence, up to 26% of patients enrolled into the EuroCRT Survey II had AF.[20] Furthermore guidelines state that a pre-requisite for CRT to work in AF is a strategy to ensure biventricular capture is in place.[23,24,51] Observational data indicate that AF with rapid conduction is the leading reason for loss of biventricular pacing.[65,66] Furthermore, observational studies relate a low percentage of biventricular pacing to poor outcome. Although this is often interpreted that a strategy that ensures 100% of biventricular pacing results in better prognosis, it needs to pointed out that the phenotype of patients that suffer from low percentages of biventricular pacing might be sicker. This could partially explain the observed relation between biventricular pacing percentages and outcome. Indeed to date, no randomized trial study has proven that a higher number of biventricular pacing is better than a lower percentage of biventricular pacing.

Device-based features have been designed to attain higher percentages of biventricular pacing through fusion pacing [right ventricular (RV) sense will result in LV pacing], but should not be an alternative to optimal medical therapy, pulmonary vein isolation or atrio-ventricular (AV) junction ablation to ensure effective CRT in AF. Gasparini *et al.*[67] demonstrated in a small prospective study that CRT patients in permanent AF, only had improvement in LV function and functional capacity if AV junction ablation was performed. Furthermore, AV junction ablation has been associated with a reduced incidence of inappropriate ICD interventions.[68] The use of AV junction ablation in clinical practice is variable, but should be considered if pharmacologic therapies fail to result in

adequate percentage (target of >90–95%) of biventricular pacing. The current position paper recognizes the scarce data of CRT in AF. Nevertheless, despite the lack of large randomized clinical trials, guidelines as well as this position statement still recommend the use of CRT in permanent AF patients with similar indications as for patients in sinus rhythm, provided that AV junction ablation (or pulmonary vein isolation if indicated) is added in those with incomplete (<90–95%) biventricular pacing.[66,69,70] In addition, other causes for incomplete biventricular pacing such as premature ventricular beats might need to be treated as well. RAFT-PermAF (NCT01994252), which investigates whether CRT reduces heart size in CRT patients with permanent AF, is currently ongoing.

Next to selected patients in sinus rhythm and AF, guidelines recommend CRT in HFrEF patients with a classic pacing indication who are expected to receive a high burden of RV pacing (IA recommendation) or patients with a classic pacemaker or ICD who develop heart failure (IIa recommendation for upgrade).[23,24,51] In the EuroCRT II Survey, 23% of the entire CRT population were upgrades.[20] The American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines underscore that a high burden (e.g. >40%) of RV pacing is a prerequisite for benefit of an upgrade.[21] Few data are available from clinical trials. CRT was superior to conventional RV pacing in patients in sinus rhythm with AV block and LV systolic dysfunction in the BLOCK-HF trial.[71] Additionally, reduced clinical manifestations of heart failure were noted with CRT pacing compared to RV pacing in heart failure patients with symptomatic permanent AF who underwent AV junction ablation in the APAF trial.[72] Given the incremental risk of device upgrade or risk of pacemaker dependency after AV junction ablation, the benefits and risks should be assessed individually given the rather low level of evidence. The ongoing BUDAPEST-CRT trial (NCT02270840) will determine the effects of upgrade from an ICD to a CRT-D in symptomatic HFrEF patients with RV pacing (>20%).[73]

### Guideline-directed medical therapy

The evidence for CRT lies with HFrEF patients with residual symptoms and a persistently reduced LVEF despite optimal background treatment with neurohormonal blockers. However, only a minority of patients implanted with CRT are on maximal guideline-recommended doses of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (30%) and beta-blockers (20%) before CRT.[74] Although this might be the result of inertia in care, patients might not be able to tolerate higher doses due bradycardia and hypotension. While patients with HFrEF and narrow QRS often exhibit significant reverse remodelling to medical therapy, patients with HFrEF and LBBB seem to reverse remodel less following initiation of neurohormonal blockers.[75] For example, in one study, patients with LBBB experienced an improvement in LVEF of 2% whereas those with a narrow QRS had an increase of 8% after 6 months of medical therapy, which might be the result of differential expression of contractile genes in those with electromechanical dyssynchrony.[75,76] Therefore, this position statement from HFA, EHRA and European Association of Cardiovascular Imaging (EACVI) encourages clinicians not to postpone CRT implant too long, particularly in patients with LBBB and a QRS duration >150 ms.

### Role of comorbidities

Comorbidities are frequent in heart failure and affect the delivery and effect of heart failure therapy, functional status, and clinical outcomes.[77–80] Due to this competing risk patients with comorbidities derive less benefit from an ICD (see next section). However, an elegant analysis from the MADIT-CRT trial demonstrated that this was not the case for CRT, where the relative reduction in morbidity and mortality was consistent.[81] Hence, patients with comorbidities should not be denied CRT, although appropriate assessment of potential benefit of the combination of CRT with ICD therapy is particularly important in this population.[82]

Certain comorbidities are of particular interest in CRT candidates as they might influence the success of the implantation procedure, choice between CRT-P vs. CRT-D, symptomatic improvement, and reverse remodelling response after implant.[12] Although a history of valve replacement might make LV lead placement more challenging, it is not associated with less benefit from CRT.[83,84] Furthermore, while renal disease was an exclusion criteria in the major CRT trials and early observational data suggested less reverse remodelling in patients with chronic kidney disease stage IV and V,[1,3–6,47] more recent data indicate that patients with chronic kidney disease derive similar mortality benefit from lesser reverse remodelling.[31,45] Iron deficiency, which is common in CRT recipients (around 55%), might be associated with less functional improvement and less reverse remodelling following CRT,[85] possibly due to the role of iron as an essential co-factor for protein synthesis and normal cell functioning.[86]

In conclusion, CRT selection and optimization must occur in the context of other heart failure interventions and other comorbidities. With a growing heart failure treatment armamentarium, this is becoming increasingly challenging for the cardiologist, highlighting the need for early referral to a heart failure management team.[18,29]

### Cardiac resynchronization therapy pacemaker vs. cardiac resynchronization therapy defibrillator: individualizing choice

In order to derive maximal benefit from an ICD, patients need to have a high risk of dying from SCD mediated by ventricular arrhythmias, and a low risk of dying from other causes (non-SCD-mediated death).[87–89] This balance should be taken into account prior to device implantation (*Figure 3*). For example, large areas of scar and an ischaemic aetiology of heart failure or a high burden of non-sustained ventricular tachyarrhythmias (NSVTs) on Holter monitoring are associated with a higher risk of SCD.[60,90–94] Monitored SCD in patients with a CRT-P device is often pre-dated by an increasing burden of NSVTs, suggesting a role for remote monitoring to detect patients who might benefit from upgrade to a CRT-D.[95] On the other hand, women have a lower risk of SCD,[96] and data from the DANISH trial illustrate that a strategy for routine primary prevention ICD for patients with a non-ischaemic aetiology does not improve overall long-term survival.[97] This is in

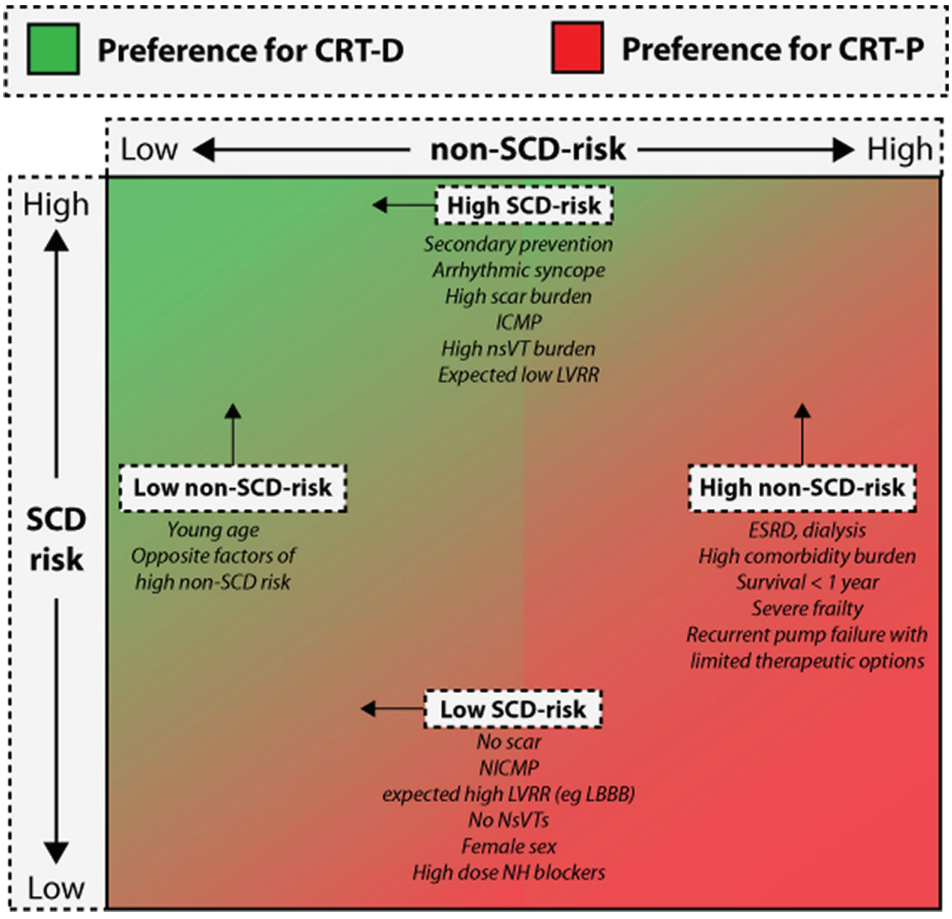


**Figure 3** Conceptual framework for individualizing of prescription of cardiac resynchronization therapy pacemaker (CRT-P) vs. cardiac resynchronization therapy defibrillator (CRT-D). Framework for individualizing CRT-P vs. CRT-D to help patients who have not opted to avoid an implantable cardioverter-defibrillator. Red indicates preference for CRT-P and green indicates preference for CRT-D. Balancing of choice is made by evaluating risk for sudden cardiac death (SCD) (yellow factors, with dark yellow indicating high SCD risk and light yellow indicating SCD risk) and the risk for non-SCD depicted in blue (dark blue indicates high risk for non-SCD and light blue indicates low risk for non-SCD). ESRD, end-stage renal disease; ICMP, ischaemic cardiomyopathy; LBBB, left bundle branch block; LVRR, left ventricular reverse remodelling; NH, neurohormonal; NICMP, non-ischaemic cardiomyopathy; nsVT, non-sustained ventricular tachycardia

line with other studies indicating that the risk for SCD is intrinsically lower in patients with a non-ischaemic aetiology of heart failure.[98] Notably, there was an age-by-therapy interaction in DANISH suggesting that younger patients (possibly those younger than 70 years) have a greater chance of benefiting from ICD implantation than older patients probably because of lower competing risk from comorbidities and the higher duration of exposure to the risk of SCD, which is reflected in the lower rate of SCD and all-cause mortality.[99–101] Finally, accurate estimation of the risk of life-threatening ventricular tachyarrhythmias by risk calculators in patients with underlying genetic mutations (i.e. LMNA mutations) helps to select candidates for ICD implantation.[102] CRT-D comes at higher cost and carries the risk of inappropriate therapy[103] and all post-hoc analyses including a Bayesian network analysis suggest equivalence between the two approaches but the randomized controlled trials also point at a favourable effect of CRT alone on the risk of sudden death. For example, the CARE-HF and REVERSE trials indicate that resynchronization therapy, and its potential to increase beta-blocking agents, diminishes ventricular tachycardia/fibrillation (VT/VF), especially in patients with extensive LV reverse remodelling,[104] possibly due to diminished electrical dispersion, early after depolarization and other cellular substrates for VT/VF.[105–107] Therefore, although factors associated with greater reverse remodelling following CRT, such as LBBB morphology, long QRS duration, female sex and non-ischaemic aetiology should not be used to select candidates for CRT, they could be considered in the decision to offer CRT-P over CRT-D (*Figure 3*). Advanced cardiac imaging technologies including assessment of conduction channels by cardiac resonance imaging and possibly radiomics may further help in individualizing risk of VT/VF in the future. Additional clinical factors favouring the use of CRT-P could include advanced age, more severe symptoms (NYHA class III/IV), and life-shortening

comorbidity (e.g. severe lung disease or Stage IV chronic kidney disease). Nevertheless, the difficult and currently unanswered paradox remains that whilst CRT reduces the need for ICD, it improves survival and reduces the rate of death due to heart failure, thereby exposing patients to an increased duration of life in which SCD can occur.

As such, individualized decision making based on patient characteristics, national/local resources, and patient preference for either CRT-P or CRT-D remains important given the lack of head-to-head trials. Supportive guidelines aiding appropriate selection between CRT-P vs. CRT-D in countries with lower GDP might help to increase CRT implant rates in these areas. The RESET-CRT (NCT03494933) trial will further provide information regarding this topic.

## Action IV: Organize a dedicated post-implant optimized cardiac resynchronization therpay care pathway

Follow-up of CRT patients is often divided over several cardiology subspecialties and large differences exist between hospitals and health care systems.[108] Although a comprehensive post-CRT implant follow-up programme has not been tested in randomized controlled trials, there are several easily-modifiable factors applicable directly following implant, before discharge, at early and longer follow-up that could improve short and longer-term outcomes following implantation (*Figure 4* and *Table 2*).[109,110] Furthermore, although such a comprehensive dedicated CRT follow-up programme is endorsed by several cardiac societies (EHRA, HRS, Heart Failure Society of America, American Society of Echocardiography, AHA, EACVI and HFA), and results in improvement of workflow of a typical multi-morbid complex patient population, an ongoing barrier is the need for focused training of medical and allied health care professionals in the holistic care of patients with heart failure and device-based interventions.[111] Such training has been endorsed by the European HFA and forms part of the certification by the EHRA.[112,113] Interestingly, just as referral for CRT is inadequate, referral for further interventions in patients who already have CRT is also inadequate, underscoring the importance of broad knowledge of the CRT team/CRT expert. For example, it has been shown that the need for heart transplantation and LV assist device was grossly underestimated among patients followed in CRT/ICD clinics.[18,29] The remainder of this section discusses major topics in the optimization of care following CRT implant.

### Improvement of heart failure management

Higher doses of both beta-blockers and renin–angiotensin system blockers are associated with lower event rates,[114,115] and the benefits of dose titration is especially important in patients at highest risk.[116] Although CRT is often considered only after implementation of optimal medical heart failure therapy, it needs to be emphasized that in clinical practice only a minority of patients are able to tolerate maximal doses of neurohormonal blockers before CRT implant.[74] On the other hand, the acute and chronic haemodynamic effects of CRT might significantly change tolerability and acceptance of medical therapy. For example, in the CARE-HF and COMPANION trials, CRT was associated with a 6–7 mmHg increase in systolic blood pressure.[3,4] Furthermore, CRT protects patients against slowing of AV conduction, bradycardia and sinoatrial nodal pauses allowing safe up-titration of beta-blockers. Two randomized controlled trials have tested higher vs. lower doses of neurohormonal blockers in heart failure, indicating a lower event rate with higher doses.[114,115] Attaining guideline-directed doses of evidence-based neurohormonal blockers is a cornerstone of the treatment of heart failure including patients with CRT devices which is insufficiently emphasized in current guidelines. Real-world data indicate that 45% of patients on submaximal dose of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers are able to tolerate up-titration following CRT implant, and up to 57% of patients on submaximal dose of beta-blockers are able to tolerate higher doses after CRT implant.[117] Although biased by the observational nature, up-titration was associated with a lower risk for heart failure hospitalization and mortality.[117,118] Furthermore, although between 73–97% of patients were taking loop diuretics at the time of implant in the major CRT trials,[1,3,4,6,47] loop diuretic down-titration is often feasible following CRT implant, with possible benefits on long-term renal function.[119]

Although initiation of sacubitril/valsartan improved outcome in the PARADIGM-HF trial, remarkably few were treated with CRT.[120] Sacubitril/valsartan use in CRT and ICD patients results in incremental reverse remodelling, and a significant reduction in the burden of VT/VF, appropriate ICD therapies, and premature ventricular complexes (PVCs), which can have additional benefits on CRT delivery.[121–123]

Although often underappreciated by patients and primary care physicians, physical exercise following CRT or ICD implant has proven to be safe in the HF-ACTION trial.[124] Furthermore, observational and randomized data suggested that cardiac rehabilitation following CRT implant is associated with a larger degree of functional improvement, LV reverse remodelling and reduction in heart failure hospitalization and mortality.[125–128]

### Optimal device programming

Individual programming of devices following implant and at each follow-up should be the aim. At each clinic visit an electrocardiogram and device analysis may help with assessment of patient status (*Table 3*). The key target of programming has been to deliver 100% of biventricular capture in order to achieve the optimal outcomes.[12,23] Although no randomized controlled trials exist comparing a lower vs. a higher degree of biventricular pacing, observational data link a low degree of biventricular pacing to poorer outcome. Although this might be to some extent a reflection of a different patient population, guidelines emphasize to try to attain a maximal percentage of biventricular pacing (class IIa recommendation).[23] There are a range of other programmable options including pacing mode, pacing rate, upper tracking rate, rate-adaptive pacing, capture output, AV and interventricular (VV) intervals and tachy-programming which should be reviewed at each clinic visit.

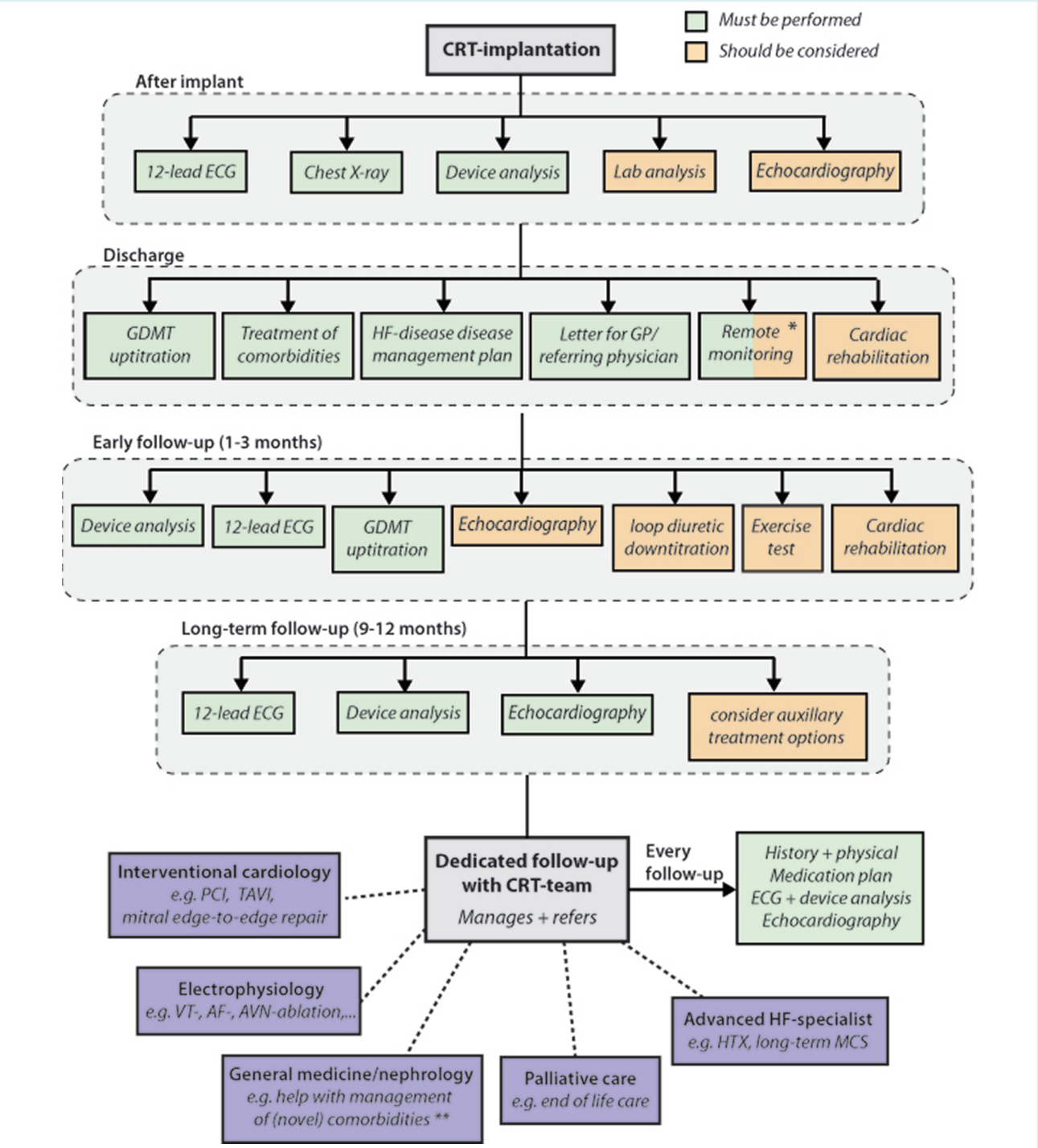


**Figure 4** Structured post-implant cardiac resynchronization therapy (CRT) care. Flowchart of essential elements of post-CRT care. AF, atrial fibrillation; AVN, atrio-ventricular node; ECG, electrocardiogram; GDMT, guideline-directed medical therapy; GP, general practitioner; HF, heart failure; HTX, heart transplant; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation; VT, ventricular tachycardia. *The evidence for remote monitoring for device-related technical issues is stronger as for remote monitoring of HF parameters to detect worsening of HF, hence the different colours. **Comorbidities often change during follow-up and also novel comorbidities need to be persistently addressed. The type of exercise test can be according to local expertise, but the aim is to see if there is persistent biventricular pacing during exercise or presence of chronotropic incompetence. The extent of application of this flowchart depends on the physical status (e.g. ability to perform an exercise test), but also the eligibility towards more advanced therapies such as a left ventricular assist device or HTX.

**Table 2 Role and utility of interventions in cardiac resynchronization therapy follow-up**

| Intervention | Potential relevance |
|---|---|
| 12-lead ECG | • Ensure and determine BiV-paced complex (QRS width, degree of QRS reduction, capture, morphology and LV latency), ECG after implant is the template for future troubleshooting<br>• Consider performing at least once ECG with BiV off and LV and RV only pacing (large QRS difference between LV and RV only pacing might indicate need for VV optimization)<br>• Positive R-wave V1? If not, rule out LV lead displacement and loss of LV capture, and if other causes are negative if lead was placed in middle or anterior cardiac vein<br>• Always repeat ECG following significant device changes |
| Chest X-ray (PA and lateral) | • Detect complication or comorbid condition such a pneumothorax, COPD, pleural effusion<br>• Determine position of LV lead after implant, and use as template for future troubleshooting |
| Laboratory assessment | • Determine creatinine and potassium in patients with CKD as they received i.v. contrast, and neurohormonal blocker up-titration will follow<br>• Consider determining Hb, ferritin and TSAT and treating iron deficiency accordingly |
| Device analysis, consists of:<br>(1) Diagnostics<br>(2) Measurements<br>(3) Programming | • Essential testing; battery status, lead impedance, sensing, pacing thresholds<br>• Analyse device counters; BiV pacing should be 100% (dedicated counters differ from company, quid percentage true BiV pacing, e.g. LV pace on ventricular sensed complexed), V-sensing should be 0%, assess PVC burden (might be reason for low % BiV pacing). High PVC burden can also indicate atrial undersensing or ventricular oversensing<br>• Optimize brady and tachy-programming (see text)<br>• Consider optimizing AV and VV interval<br>• Assess presence of phrenic nerve stimulation at maximal LV output<br>• Assess atrial pacing vs. atrial sensing %, aim to lower basic pacing rate to reduce unnecessary and deleterious atrial pacing.<br>• Assess rate histograms; sufficient heart rate increase? Consider programming R-mode<br>• Determine AT/AF burden; high AT/AF burden could be reason for low % BiV pacing. Determine appropriateness of mode switches (might be due to atrial oversensing, with DDI/VDI pacing as a result and potentially pacemaker syndrome)<br>• Evaluate presence of VT/VF episode triggers (appropriate vs. non-appropriate)<br>• Assess NSVT burden; high burden might be reason for low % of BiV pacing, but could also reflect atrial undersensing or ventricular oversensing |
| Transthoracic echocardiography | • Detect potential new pericardial effusions<br>• Consider evaluating the mitral inflow pattern, consider AV optimization in selected cases<br>• Consider assessing the effects of CRT pacing: acute vs. chronic |
| Exercise test | • Ensure persistent BiV pacing at high heart rate (solution: rate adaptive AV optimization)<br>• Presence of chronotropic incompetence, best assessed once beta-blocker up-titration is performed (need for R modus) |
| Holter evaluation | • Detection of QRS-fused beats if suspicion of intrinsic conduction fused beats (not detected by device counters)<br>• Determine morphology of PVCs if frequent PVCs lead to low % of BiV pacing<br>• Detect arrhythmias not detected by device, detect device malfunction |

Diagnostic procedures should be individualized to the patients' need and physical status and not be considered 'routine' (e.g. repeat treadmill tests in older adults, or those with frailty or comorbidity, may not be helpful or useful).
AF, atrial fibrillation; AT, atrial tachycardia; AV, atrio-ventricular; BiV, biventricular; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; Hb, haemoglobin; i.v., intravenous; LV, left ventricular; NSVT, non-sustained ventricular tachycardia; PA, posterior–anterior; PVC, premature ventricular complex; RV, right ventricular; TSAT, transferrin saturation; VV, interventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.

The pacing mode depends on the underlying atrial rhythm. In patients in sinus rhythm, a DDD pacing mode is preferred but the base rate should allow sensing of intrinsic sinus rhythm as much as possible to avoid unnecessary atrial pacing. Landmark CRT trials often used a lower rate of 35–40/min with hysteresis off.[129,130] Atrial support pacing (base rate of 70/min in DDDR mode) did not show benefit in the PEGASUS-CRT trial,[131] possibly because right atrial pacing is associated with left atrial dyssynchrony and progressive left atrial remodelling, which also are independent predictors for the development of AF.[132–134] Therefore, lower rates are generally programmed low (40–50/min) in patients in sinus rhythm, although in patients in whom AF leads to mode switch, attention should be given to program a high enough base rate when this occurs (DDIR or VDIR mode). In patients in permanent AF, an inhibited mode is preferred, which can be DDIR or VVIR depending on the presence of an atrial lead. The DDDR mode

**Table 3 Template for cardiac resynchronization therapy device analysis**

**Diagnostics**

1. Battery longevity
2. %ASVP/%APVP/%BiV vs. LV only/% BiV vs. RV sense response/% effective
3. Heart failure log: HR variability, activity, lung impedance, sleep …
4. Arrhythmias (AF, ectopy, VT, V-sense response … )
5. Impedance trends

**Measurements**

1. Impedance
2. Sensitivity
3. Thresholds

**Programming**

1. Lower/upper frequency (+ mode switch)
2. R-response (accelerometer/CLS/minute ventilation)
3. BiV vs. RV vs. LV only
4. AV/VV times (manual: fixed vs. dynamic/device-based)
5. Output leads
6. Sensitivity
7. BiV sense response
8. Tachy-settings

AF, atrial fibrillation; APVP, atrial pace ventricular pace; ASVP, atrial sense ventricular pace; AV, atrio-ventricular; BiV, biventricular; CLS, closed loop stimulation; HR, heart rate; LV, left ventricular; RV, right ventricular; VT, ventricular tachycardia; VV, interventricular.

should be reserved for patients with paroxysmal AF.[12,23] In patients with AF who receive adequate rate control, a slightly higher base rate of 60 bpm together with rate-adaptive pacing might improve the proportion of biventricular capture.[12,23] However, in those with sinus rhythm, rate-adaptive pacing should be programmed off until the presence of significant iatrogenic or intrinsic chronotropic incompetence affecting exercise intolerance is proven, bearing in mind that simple age-related rate-adaptive pacing does not improve exercise capacity and may be disadvantageous in some.[116,135,136]

Whether rate-adaptive pacing is activated or not, the upper tracking rate should be programmed sufficiently high (e.g. 80% of maximal age-predicted heart rate), to ensure persistent biventricular pacing during periods of faster intrinsic sinus rhythm (e.g. exercise). Device diagnostics can be used to check this, although an exercise test is also useful.

Left ventricular output should be programmed with sufficient margin to ensure biventricular capture. Modern devices are equipped with auto-capture features that might improve battery longevity in some,[137] although nocturnal threshold testing can be unpleasant if there is diaphragmatic capture at higher outputs. Quadripolar LV leads and their multiple vectors offer the opportunity of avoiding phrenic nerve stimulation, and output optimization to extend battery longevity,[138] whereas the use of multiple vectors simultaneously (multi-point pacing) has not shown clinical benefit whilst reducing battery life.[139]

The most commonly assessed programming options include the AV and VV intervals. Poor attention to detail around especially AV delays is a contributor to reduced efficacy of CRT.[109] However, routine echocardiographic AV interval optimization is not superior in comparison to empiric programming of a 100–120 ms sensed AV interval.[140] Most new devices from different vendors have automated algorithms that individualize AV/VV intervals, creating fusion between spontaneous conduction and LV stimulation to avoid RV pacing, or optimizing AV/VV intervals using a haemodynamic sensor.[141,142] None of these algorithms have proven to be superior to echocardiographic optimization, although a superiority study with LV fusion pacing is ongoing.[143] In the light of the neutral clinical results of a routine approach of optimizing AV and VV intervals, one can consider this for specific patients (e.g. long interatrial delay). Nevertheless post-implant echocardiography with assessment of the mitral inflow pattern allows for a quick evaluation of the appropriateness of the AV interval programming. Indeed, if the A-wave is truncated or there is a lot of wasted mechanical time (fusion of E and A wave with A-wave ending before beginning of electrical systole), this should prompt the attention that the AV interval is not programmed correctly.

The programming of therapies for tachycardia should be individualized based on the indication for the ICD (primary vs. secondary prevention) and has been reviewed in more detail recently.[144] Adequate brady- and tachy-programming requires specialist device knowledge and expertise which aims at preventing morbidity, rather than to react to it (e.g. preventing ICD interventions, ensuring high biventricular-pacing, etc.). Therefore, these patients should be followed at specialized centres having multidisciplinary collaboration (i.e. heart failure and arrhythmology) and by physicians having undergone extensive device training and certification.

## Inclusion in remote monitoring

In remote monitoring of CRT devices, a distinction should be made between device-related remote monitoring and monitoring of heart failure status through measurement of physiological variables. Patients with CRT have heart failure, and are therefore at an increased risk of clinical events such as ventricular or supraventricular arrhythmias which can interrupt CRT or worsen heart failure status.[145] Additionally, technical problems related to battery and leads can have an impact on patient status and prognosis, and might warrant detection and appropriate action as early as possible. These variables can be monitored by the device and remotely transmitted to the treating team.[146] Early detection of clinical or technical issues improved clinical outcomes in the IN-TIME trial,[147] although several larger trials failed to show benefit of remote monitoring.[148–151] Large registries have shown benefits of remote monitoring in CRT patients especially when devices are capable of collecting multiple key physiological parameters such as heart rate, respiration frequency, heart sounds and physical activity, in addition to technical checks on the device.[23,152] This approach requires an organizational change including funding of virtual visits and training of personnel who should react appropriately to transmitted information.[153] With the recent EU General Data Protection Regulation, hospitals and physicians must be aware of certain rules

that need to be complied with and agreements with manufacturers that need to be in place to implement remote monitoring. Finally, patients preference should be taken into account, as observational data indicates that around 20–35% of patients prefer in-clinic visits instead of remote monitoring.[154]

### Managing arrhythmias in cardiac resynchronization therapy

Arrhythmias are common in heart failure patients, and often have an impact on morbidity, mortality and functioning of the CRT device. Atrial tachyarrhythmias and frequent PVCs are responsible for 50% and 10%, respectively, of the cases of a low percentage of biventricular pacing, thereby further compromising LV systolic dysfunction and contributing to decompensation.[66,155]

Whether suppression of atrial tachyarrhythmia, mainly AF, in the presence of HFrEF is of benefit and which strategy might be appropriate is unknown.[156,157] Despite concerns around long-term safety and overall neutral clinical outcomes,[153,158] guidelines recommend amiodarone (IA recommendation) if a rhythm control strategy is chosen. AF ablation has gained a lot of interest (IIA recommendation),[24,157] due to possible improvements in LVEF, functional capacity and quality of life in comparison to rate control in heart failure patients.[159–163] For example, long-term follow-up of the highly-selected CASTLE-AF patients suggests that AF ablation is associated with a lower risk of heart failure admission and all-cause mortality.[160] Importantly, the benefit was demonstrated not by elimination of AF but rather by reducing overall AF burden.[160] In patients with HFrEF and AF who have a CRT device, AF ablation could be considered for those with a high likelihood of attaining sinus rhythm and thus subsequently 100% of biventricular pacing. AV nodal ablation should be considered as a treatment strategy for patients who fail to achieve sufficient biventricular pacing despite AV blocking medical therapy or efforts to maintain sinus rhythm (e.g. amiodarone or AF ablation in selected patients).

Frequent PVCs can also result in a low percentage of biventricular pacing and further worsen LV systolic function.[66] If despite heart failure therapy optimization, PVCs continue to cause low proportions of biventricular pacing, amiodarone or PVC ablation can be considered.[157] A study in which patients with poor improvement after CRT and more than >10 000 PVCs per 24 h were subjected to PVC ablation showed improvements in symptoms and incremental reverse remodelling.[164]

Ventricular arrhythmias are a key concern in HFrEF patients especially in those with reduced LVEF and ischaemic heart disease.[82] The prevalence of ventricular arrhythmias is associated with the disease severity of HFrEF.[165–167] The event rates for mortality and heart failure admission are markedly higher following appropriate ICD therapy, but not after inappropriate therapy,[168,169] which indicates that a ventricular arrhythmic event in HFrEF is a marker of disease progression. Hence, heart failure therapy optimization is mandatory not only to treat, but also to prevent ventricular arrhythmias in HFrEF.[170] Additionally, triggers such as volume overload, ion disturbances, loss of biventricular pacing and others should be actively assessed and treated. Furthermore, guidelines recommend consideration of amiodarone and VT ablation in CRT-D patients after a first sustained episode.[170] Any arrhythmic event should also prompt a review of the device programming.[144]

### Disease progression and remission

As indicated in *Figure 2*, CRT can stabilize the disease trajectory but some patients have persistent symptoms and will eventually deteriorate. Some of these patients might be indicated for advanced heart failure therapies. Therefore, the CRT specialist team should not only be experienced in the management of technical aspects of the CRT devices, and medical therapy for heart failure, but should also be competent to detect and understand the mechanisms underlying disease progression (*Figure 4*). Imaging plays an essential role[171] in identifying persistence of secondary mitral regurgitation, and progressive atrial, LV and RV remodelling, all of which indicate progression of the heart failure syndrome, and warrant consideration of appropriate interventions,[172–174] including additional device therapies such as mitral edge-to-edge repair,[175,176] or newer medical therapies.[120,177] Cardiopulmonary exercise test with determination of peak oxygen consumption and other variables might[29,178] provide information on prognosis and appropriate timing of more advanced interventions in selected patients.[179,180] The CRT specialist team should be able to determine if palliative care is more suitable than onward referral for more invasive therapies.[181]

Cardiac resynchronization therapy teams are also the best at determining whether and when the possibility for ICD interventions should be withdrawn. For example, at time of battery depletion and box change, patient and physician perspective might warrant consideration of withdrawal of ICD therapy by replacement of a CRT-D device with a CRT-P device.[182–184] Unfortunately, this is increasingly difficult in the absence of a DF-4 to IS-1 connector necessitating an additional RV pace-sense lead implantation. Additional liability issues might occur if patients, following downgrading from CRT-D to CRT-P, die suddenly or subsequently show a deterioration in cardiac function, and therefore this should be comprehensively discussed with the expert team and with the patient and/or his family and in the light of therapeutic aims and relevant comorbidity, such as dementia or malignancy.

A very small subgroup of CRT patients demonstrate overwhelming benefit from CRT that every aspect of their heart failure disease seems to dissipate (normalization of echocardiogram and N-terminal pro B-type natriuretic peptide, and resolution of symptoms). These patients can be considered to be in 'full remission'. A small prospective randomized pilot trial suggested that closely supervised neurohumoral blocker withdrawal ('CRT only strategy') is feasible and safe in patients with myocardial recovery after CRT.[185] These results differ from TRED-HF in that those in TRED-HF did not have LBBB with improved LV function following CRT.[186] In contrast, data from MUSTIC and MADIT-CRT indicated that turning off biventricular pacing ('medical strategy only') led to a re-occurrence of the heart failure syndrome.[7]

### Patient engagement and education

Cardiac resynchronization therapy recipients are often older adults with multiple comorbidities. Adequate information on the purpose

**Table 4 Element of patient-centred cardiac resynchronization therapy education**

| Pre-implantation | Early post-implantation | Living with CRT |
|---|---|---|
| • Discuss the position in the heart failure trajectory<br>• Include patient and caregiver in decision making<br>• Provide information and understanding of the device indication (ask-tell-ask)<br>• Provide information on the procedure<br>• Discuss expectations<br>• Provide information of consequences (long and short term)<br>• Include family caregivers<br>• Discussion of potential complications (lead displacement, shocks, infection) with the patients and caregivers | • Discuss questions related to discomfort, pain, placement<br>• Discuss effect and expectations<br>• Discuss the role of CRT in heart failure treatment and consequence for treatment (lifestyle and medication changes)<br>• Discuss how to adjust medications after implant<br>• Inform on when to contact a health care provider<br>• Include family caregivers | • Provide tailored follow-up<br>• Discuss the role of CRT in the heart failure trajectory<br>• Discuss consequences for survival, treatment, lifestyle, exercise<br>• Be open for coping issues (feeling dependent on technology, anxiety for failure)<br>• Inform the patients about relevant issues: insurance, travel<br>• If relevant, discuss deactivation of the ICD<br>• Include family caregivers<br>• End of life care |

CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.

of CRT, the implant procedure including risk and post-implant care is essential for them and their family. A recent survey indicated that almost half of patients felt insufficiently informed about technical aspects or had worries about aspects of their implantable devices.[187] A considerable number of heart failure patients suffer from depressive symptoms, which are associated with worse outcomes.[188] Psychosocial concerns and worries should be addressed in a multidisciplinary approach. Furthermore, end of life decisions such as ICD withdrawal are rarely discussed.[187] Information through health care providers (e.g. CRT specialist, heart failure nurse) and paper and web-based education (e.g. www.heartfailurematters.org) might improve patients' understanding and engagement. *Table 4* summarizes important patient-centred aspects regarding the education of patients and families with regard to use of CRT.

## Future perspectives

Alternative resynchronization strategies have been developed that might also effectively treat the electromechanical dyssynchrony in HFrEF patients. Such strategies include His bundle and LBBB area pacing, endocardial LV lead pacing, wireless LV stimulation, or even deep interventricular septal LV pacing.[189–191] In patients with a classical CRT indication, pacing strategies such as His bundle pacing are often propagated as an alternative because of the equipoise induced by the 30% non-response rate to CRT.[192] However, it is clear from this manuscript that this concept of non-response to CRT is intrinsically flawed. Although acute haemodynamic and short-term reverse remodelling studies with these novel pacing strategies illustrate a similar haemodynamic, functional and remodelling improvement as CRT,[190,193–198] they will have to show at least equal benefit in terms of morbidity and mortality endpoints in HFrEF and be as safe in order to be implemented in clinical practice as an alternative to CRT.[197] Additionally, His bundle is also being tested in HFrEF for other indications such as PR prolongation.[199] Whether CRT might be of benefit in patients with heart failure with preserved ejection fraction is also under investigation.[200]

## Conclusion

Cardiac resynchronization therapy is an underutilized lifesaving therapy, strongly recommended in guidelines for a common subgroup of HFrEF patients. This HFA, EHRA and EACVI endorsed document offers theoretical and practical strategies to achieve more comprehensive CRT referral and post-procedural care by focusing on several actionable domains.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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