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# Cardiac resynchronization therapy (CRT) non-responders in the contemporary era: A State-of-the-Art review

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## Abstract

Since 2000s CRT became a revolutionary therapy for heart failure with reduced left ventricular ejection fraction (HFrEF) and wide QRS. However, about one third of CRT recipients do not show a favorable response.

This review of current literature aims to better define the concept of CRT response/non-response. The diagnosis of CRT non-responder should be viewed as a continuum, and it cannot rely solely on a single parameter. Moreover, several patients' baseline features might predict an unfavorable response. A strong collaboration between HF specialists and electrophysiologists is key to overcoming this challenge with multiple strategies.

In the contemporary era, new pacing modalities, such as His bundle pacing (HBP) and left bundle branch area pacing (LBBAP) represent a promising alternative to CRT. Observational studies demonstrated their potential; however, several limitations should be addressed. Large randomized controlled trials are needed to prove their efficacy in HFrEF with electromechanical dyssynchrony.



## Key words

Cardiac resynchronization therapy; heart failure; non-responders; conduction system pacing; left-bundle branch area pacing.


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## 1 INTRODUCTION

Heart failure (HF) is one of the leading causes of death and hospitalization worldwide(1) affecting 1-2% of adults in the general population with a prevalence that increases with aging(2). For many years, the prognosis of HF with reduced ejection fraction (HFrEF), i.e., left ventricular ejection fraction (LVEF) ≤35-40%, has been compared to that of many cancers with few therapeutic options(3), but in the last two decades several effective and innovative treatments have emerged.

The 2000s have been defined as the “device era”(4). Cardiac resynchronization therapy (CRT) became a revolutionary therapy for patients with impaired left ventricular (LV) function and wide QRS complex. Pivotal trials have demonstrated that CRT should be considered as an additional resource along with pharmacological therapy and not just as a sequential therapy after the pharmacological pillars(5-8).

Despite the strong evidence from randomized controlled trials (RCTs) endorsing the guidelines recommendations, there is considerable variability in the response to CRT due to various clinical, structural, and electrophysiological factors. About one-third of CRT recipients are considered non-responders(9). This complex diagnosis and its clinical implications closely depend on the definition of "CRT-response", which is still a topic of active debate.

This narrative review aims firstly to better define the concept of CRT-response (and non-response). Secondly, to identify those HF patients who are not likely to benefit from CRT and thirdly, to highlight the possible management strategies and future perspectives to overcome CRT non-response.

## 2 EPIDEMIOLOGY

The proportion of individuals showing no response to CRT varies among different studies, usually ranging between 25% and 33%(10). Nevertheless, this percentage is highly variable depending on the definition of CRT-response. Indeed, Fornwalt et al.(11) reported that the

percentage of patients defined as responders to CRT might range from 32% to 91%, when evaluating different clinical studies. Of note, echocardiographic parameters seem to be associated with hard clinical outcomes(9, 12); a lack of echocardiographic improvement have been associated with a poor long-term prognosis with mortality up to 50% at 4 years(13).

## 3. RESPONSE/NON-RESPONSE DEFINITION

An exact definition of CRT responder/non-responder is still a matter of debate and recently the concept has been object of some criticism(14). Indeed, no consensus exists on how or when to measure the response to CRT(11, 15). The response to CRT should not be considered as dichotomous event (yes/no), but rather as a continuum and a spectrum of outcomes following implantation. Indeed, the definition of non-response often relies on arbitrary remodeling cut-offs, such as LVESV reduction <15% from baseline, which do not always correspond to a lack of hard clinical outcomes improvement(14).

Moreover, considering the timing of remodeling, it has been demonstrated that CRT response might not always be evident within the first months following the implantation. Leclercq et al.(16) in a randomized controlled trial on 5850 patients, showed that about 30% of patients defined as non-responders at 6 months (because of <15% relative reduction in LVESV) were later reclassified as responders in the following 6 months, because of a significant remodeling. In addition, it has been demonstrated that, over a 10-year period, CRT was associated with improved prognosis, despite an increase in comorbidity burden(17), and that the earlier the CRT was implanted after a hospitalization for HF, the better was the long-term prognosis(18).
These findings stress the fact that giving an exact definition of CRT responder/non-responder might be very challenging because of the intrinsic dynamic nature of the response to resynchronization therapy over time.

On the other hand, a standardized definition may help to identify those patients who should benefit from additional interventions to improve outcome.
The parameters used to define a favorable/unfavorable response to CRT can be categorized into four groups as follows: 1) quality-of-life/functional status parameters (i.e., Minnesota score, NYHA functional class, cardiopulmonary exercise test (CPET) parameters, 6 minutes

walking test (6MWT) distance), 2) ECG criteria (i.e., QRS narrowing), 3) remodeling parameters (change in LVEF, LVESV and LVEDV), and 4) clinical outcome measures evaluated in RCTs or observational studies (i.e., hospitalizations and cardiovascular mortality)(19) (Figure 1).

### 3.1- Quality of life/functional status criteria

The quality of life (QoL) criteria come from specific questionnaires useful as predictors of echocardiographic and outcomes response to CRT(20, 21).

The Minnesota Living with Heart Failure questionnaire (MLHFQ) is the most used questionnaire in this setting. It contains 21 questions on patients' perceptions of the effects of heart failure and the total score ranges from 0 to 105, with higher scores reflecting a poorer quality of life(22).

In the Triple-Site Versus Standard Cardiac Resynchronization Therapy Trial (TRUST CRT) randomized trial(20) on 97 patients, the authors found that, after 6 months from implantation, QoL significantly improved in 81% of CRT recipients. A lack of QoL improvement was observed in 19% of the patients and was associated with a higher incidence of adverse events.

Other commonly used criteria to define CRT response are the NYHA functional class, the 6 minutes walking test (6MWT) distance improvement(23), and cardiopulmonary test (CPET) parameters such as minute ventilation/carbon dioxide production ($VE/VCO_2$ slope) and maximal oxygen consumption ($VO_2$ peak)(19).

### 3.2- ECG criteria

Narrowing of the QRS (defined as a reduction of QRS duration of at least 20 ms or >20% compared to baseline QRS)(24) has been associated with improved echocardiographic parameters and favorable clinical outcomes. Specifically, in a recent meta-analysis, Bazoukis et al.(25) found that narrowing of the QRS after CRT implantation was associated with a NYHA class reduction ≥ 1 and with a LVESV reduction ≥ 15%. Moreover, one retrospective multicenter study(26) demonstrated that the QRS area under the curve (independently of QRSd) can predict all-cause mortality, cardiac transplantation, and left ventricular assist device (LVAD) implantation.

### 3.3- Echocardiographic criteria:

The echocardiographic criteria focus on the improvement of mechanical dyssynchrony and ventricular remodeling parameters. The main remodeling parameters used as a marker of improved LV function are an increase in LVEF, a reduction in LVEDV/LVESV and an increase in stroke volume (SV) after CRT implantation.

Stellbrink et al.(27) reported that, after 6 months from CRT implantation, LV end-diastolic and end-systolic volumes were significantly reduced (LVEDV from 253 ± 83 to 227 ± 112 ml, p=0.017; LVESV from 202 ± 79 to 174 ± 101 ml, p=0.009). Similar results were found in a small study by Yu et al.(28). Among the predictors of improved outcomes after CRT, LV remodeling, in terms of reduction in LVESV, was one of the strongest(9, 29).

Finally, a reduction in functional mitral regurgitation (FMR) has been associated with a favorable response to CRT. Specifically, FMR improvement after CRT was associated with reduced all-cause mortality(30) and, in a post hoc analysis of the CARE-HF trial, more severe or persistent MR after CRT was associated with higher mortality(31).

### 3.4 - Outcome measures:

Clinical outcome criteria are primarily based on mortality and hospitalizations for heart failure. This definition of response is particularly crucial as the current recommendations for CRT in the HF guidelines(32) rely mainly on improved outcomes post-implantation (Table 1).

The COMPANION trial(6) demonstrated that CRT implantation reduced all-cause mortality or hospitalizations. In a follow-up period of more than two years, the CARE-HF trial(7) showed that in the CRT group there was a significant reduction of the primary endpoint (death or unplanned hospitalization for a cardiovascular event), compared to those treated with optimal medical therapy (OMT) alone.

The RAFT trial(33) evaluated the patients in terms of death from any cause and HF-related hospitalizations for over a median follow-up of 5 years. The authors found a greater benefit from CRT-D than ICD alone. In the RAFT long-term study(34), there were similar results in terms of death from any cause and time until death over a median follow-up of 14 years. Of note, the survival benefit was independent of the extent of QRSd reduction, the morphology of QRS at baseline, the worsening of heart failure, or the changes to pharmacologic treatment.

## 4 PREDICTORS OF CRT NON-RESPONSE

Studies on CRT recipients allowed partly to identify those patients who did not reach an adequate response to CRT and to find specific baseline characteristics which predict such an unfavorable response (Figure 1).

### 4.1 - Advanced HF

Advanced HF (NYHA functional class IV despite optimal medical therapy) has been associated with a blunted response to CRT. Particularly, inotrope-dependent patients (Interagency Registry for Mechanically Assisted Circulatory Support - INTERMACS class 3) seem to have a lower response rate(31). However, these patients were underrepresented in landmark RCTs, as they are often not considered for CRT implantation given their low survival probability(35).

### 4.2 - Ischemic cardiomyopathy

Ischemic etiology represents another group of HF patients associated with a reduced response to CRT. These patients typically show less remodeling and echocardiographic response after CRT implantation(36). Patients with coronary artery disease (CAD) have been associated to a lesser increase in LVEF and reduced improvement in NYHA functional class as compared to HF patients without CAD(37). However, rather than the ischemic etiology itself, the high burden of scar in ischemic heart disease seems to play a role in reducing the effect of CRT in these patients. In this context, cardiac magnetic resonance (CMR) has potential to identify non-responders(38-41).

### 4.3 - QRS duration (QRSd) <150 ms

Baseline QRSd might affect the response to resynchronization therapy. Median values for QRS were 160 msec in the COMPANION trial(6) and 160 msec (with an interquartile range of 152-180ms) in the CARE-HF trial(7). In the MADIT-CRT trial(8), 65% of patients had a QRSd ≥ 150 msec and in the REVERSE trial(42) QRSd was 153 ± 21 msec. A subsequent

meta-analysis of these trials confirmed that QRSd plays an important role in predicting CRT response and a QRS ≥150 msec is associated with a favorable response to CRT(43).

### 4.4- QRS morphology (wide QRS with non-LBBB morphology)

Patients with non-LBBB morphology of the QRS have less chance to respond to CRT, probably because of a less severe LV electrical and mechanical dyssynchrony(44, 45). Indeed, a sub-analysis of the MADIT-CRT trial demonstrated that LBBB patients benefit the most from CRT in terms of heart failure event-free survival(8, 33, 46). Furthermore, although the landmark clinical trials did not distinguish between LBBB and non-LBBB patients at the time of enrollment, a meta-analysis of 5 RCTs (CARE-HF, COMPANION, MADIT-CRT, RAFT and REVERSE) confirmed the lack of response to CRT, in terms of death or HF hospitalization, in non-LBBB patients(47).

### 4.5- Mechanical dyssynchrony on echocardiography (with narrow QRS)

Echocardiographic criteria of mechanical dyssynchrony (e.g., apical rocking and septal flash) can be present in the absence of LBBB and QRSd >150 msec. Whether patients with dyssynchrony on echo with narrow QRS might benefit from CRT has been for long a matter of debate. Three RCTs demonstrated that patients with narrow QRS (<120-130 msec) and echocardiographic criteria of mechanical dyssynchrony derive no benefit from CRT function ON, compared with the control group (CRT function OFF)(48-50). Moreover, the EchoCRT trial(50) found that in the CRT-D group, inappropriate shocks were more prevalent compared to the ICD-only group, possibly because of a proarrhythmic effect of CRT in heart failure patients with narrow QRS (e.g., in case of suboptimal placement of the left ventricular lead).

### 4.6- Atrial fibrillation

The clinical and survival benefit of CRT devices depends mainly on the percentage of biventricular (BiV) pacing, which should be close to 100% to obtain a significant reduction of hard outcomes, such as mortality(51, 52). The presence of AF may severely blunt the effect of CRT mainly by reducing the effective LV capture and synchronization. In landmark clinical trials on CRT, AF was an exclusion criterion, even though AF is the most prevalent

arrhythmia in HF patients, especially those in NYHA class III, who might benefit the most from CRT(53, 54). With this paucity of data, it is difficult to define its prognostic role. Few randomized studies included a consistent number of AF patients (55).

### 4.7 - Ventricular arrhythmias

Together with atrial tachyarrhythmias (AT) and AF, premature ventricular contractions (PVCs) are one of the main causes of suboptimal pacing and reduced BiV pacing in CRT recipients(56), leading to increased morbidity and mortality(57).

There is no specific cut-off at which PVCs burden might be significant, either in terms of CRT pacing loss or in terms of induced LV dysfunction. Niwano et al.(58) established a threshold of 20,000 PVCs within 24 h to identify the high-frequency group, while Kanei et al.(59) considered a cut-off of 10,000 PVCs/24h. Some studies characterized PVCs as frequent when they constituted more than 10% of the total daily beats. A PVC burden of at least 10% appeared to be the minimal threshold for having some consequences of LV function and CRT response, and the risk increases when the PVC burden exceeds 20%(60-62).

Also, episodes of ventricular tachycardia and ventricular fibrillation (VT/VF) have been associated with a worse prognosis. In 1308 CRT recipients, VT/VF occurrence over a 6-months period were independently associated with an increased risk of death and HF-related hospitalizations(63).

### 4.8 - Baseline right ventricular dysfunction

The assessment of the right ventricular (RV) function before CRT implantation might be crucial in predicting CRT response and clinical outcomes. Alpendurada et al.(64) found that, when evaluating RV with cardiac magnetic resonance (CMR), preserved RV ejection fraction (RVEF) (Odds Ratio (OR) 1.05, 95% CI 1.01-1.09, p=0.01) and RV myocardial scar burden (OR 0.90, 95% CI 0.83-0.96, p=0.004) were independent predictors of CRT response. Moreover, patients with RVEF <30% had a very poor response to CRT (18.2%). Among echocardiographic parameters, RV strain <-18% seems to have the highest sensitivity (79%) and specificity (84%) in predicting adverse outcomes(65).

### 4.9 - Advanced chronic kidney disease

Comorbidities can influence the response to CRT. Specifically, severe renal impairment (chronic kidney disease (CKD) stages 3-5) is often considered an obstacle to CRT response. Höke et al.(66) found that in patients with CKD stage 4 (defined by an estimated glomerular filtration rate (eGFR) of 15 - 29 ml/min per 1.73 m2), the response to CRT (a reduction of ≥15% in LVESV at 6-month follow-up) was obtained in only 30% of the patients, with a large proportion of non-responders. A favorable echocardiographic response was significantly associated with a reduction in a combined end point including appropriate defibrillator therapy, HF hospitalization, and all-cause mortality. More studies are needed to better define the role of CRT in patients with HF and advanced renal dysfunction.

## 5 MANAGEMENT STRATEGIES

The management of patients after CRT implantation is complex and always needs a multidisciplinary approach. Indeed, it requires communication and collaboration between electrophysiologists, HF specialists, and cardiac imaging expert cardiologists (67) (Figure 2).

The patient should be provided with remote monitoring device to detect those alerts related to early HF decompensation and potential CRT non-response(68-71).

After 1-3 months from implantation, the first approach to the patient should be a comprehensive assessment of the QoL and the onset of new signs or symptoms through an accurate medical history and physical examination. The functional evaluation of the patient should consider not only the NYHA class but also more reliable and objective parameters, such as the change in the distance walked in 6 minutes and in $VO_2$ peak. Through a standard 12 lead ECG the entity of QRS narrowing should be evaluated.
An echocardiographic evaluation is crucial in defining the response to CRT. After undergoing CRT, the aim should be a reduction in LVESV of more than 10% and an improvement in LVEF of more than 5%(12, 27, 72).
Those patients not achieving these targets might have a long-term unfavorable response after CRT implantation.

### 5.1 - Optimizing HF therapy

The significance of dose titration of beta-blockers (BB) and renin-angiotensin-aldosterone system blockers (RAASi) is particularly crucial for individuals at the highest risk and CRT non-response(73). However, observational data from real-world studies show that 45% of patients receiving submaximal doses of RAASi could withstand up-titration after CRT implantation. Additionally, up to 57% of patients on submaximal doses of beta-blockers could tolerate higher doses following CRT implantation, with a lower risk of HF hospitalization and mortality(74, 75). These data highlight the need to optimize the combined use of pharmacological therapy and device-based therapy. At the time of CRT landmark trials Sodium-Glucose Co-Transporter-2 (SGLT2) inhibitors and Sacubitril/Valsartan were not available for HF patients. It is unclear how current pharmacological therapy could influence the indication and the response to resynchronization therapy. More studies are needed to shed light on the potential synergic effect of current pharmacological HF therapy and device therapy together(76).

### 5.2 - Managing AF

Even if there are few data on AF and CRT from RCTs, AF should not be an obstacle to CRT implantation. Indeed, in these patients, the target should be to achieve a high percentage of BiV pacing (close to 100%). In patients with paroxysmal or persistent AF, pharmacological rate and rhythm control with amiodarone can be used, though with limited success(77). Pulmonary vein isolation is feasible in CRT patients and might improve BiV pacing percentage and LV echocardiographic remodeling parameters(78). In patients with permanent AF and a high ventricular rate, atrioventricular (AV) junction ablation should be considered(79, 80), to achieve >95-98% of BiV pacing. In the APAF-CRT trial(81) and in the APAF-CRT mortality trial(82), the investigators found that, in patients with CRT and permanent AF, AV junction ablation was superior to pharmacological rate-control therapy in terms of HF-related hospitalization and all-cause death.

### 5.3 - Improving device programming

Clinical improvement might not occur, even in the presence of adequate pharmacological therapy and a high percentage of BiV pacing (close to 100%). In these cases, it is essential to try to optimize device programming. Specifically, the main interventions are the

optimization of AV and VV delays. (83, 84). In clinical practice, AV and VV delays are set empirically to obtain the highest percentage of BiV pacing and the narrowest QRS. Moreover, most recent devices are provided with algorithms, such as the SyncAV or the AdaptivCRT, which can automatically set the AV and VV delays based on specific patient features to improve atrioventricular and interventricular synchrony, ameliorating hemodynamic and clinical parameters(85, 86).

## 6 FUTURE PERSPECTIVES

Considering the limitations and difficulties related to CRT implantation and the relatively high proportion of non-responders, the concept of cardiac physiologic pacing (CPP) has been recently introduced(87). Guidelines from the Heart Rhythm Society (HRS)(88) define CPP as any form of cardiac pacing aiming to restore ventricular synchrony. The definition includes CRT, but also conduction system pacing (CSP) with His bundle pacing (HBP) and left bundle branch area pacing (LBBAP).

HBP demonstrated a significant narrowing of QRS and improvement in LVEF(89). Although promising, only few small randomized controlled studies have been conducted (Table 2). Lustgarten et al.(90) randomized patients to either HBP or BiV pacing and found no significant differences between the two arms in terms of LVEF improvement, 6MWT distance, quality of life and NYHA class change. In the His-SYNC Pilot trial(91, 92), the authors compared a strategy of His-CRT compared to BiV-CRT in HF. HBP was associated with a greater reduction in QRSd and there was a trend, although non-statistically significant, toward higher echocardiographic response. No differences were found in hospitalizations or mortality. Considering these promising results, Vinther et al.(93) conducted the His-ALTERNATIVE trial, including only patients with LBBB with very stringent criteria, since previous studies have shown that the effectiveness of His pacing is less evident in cases of nonspecific intraventricular delay(94). In this small trial, HBP showed a similar effect in echocardiographic and clinical outcomes compared to CRT, but with reported higher pacing thresholds. Similar results were found in the ALTERNATIVE-AF trial(95), in which patients were randomized to either HBP or BiVP, following atrioventricular nodal ablation. Because of the known limitations of HBP, investigators focused on LBBAP, which shows increased sensing, lower capture thresholds, and similar durations of paced QRS.

Compared to BiV pacing, LBBAP demonstrated greater improvement of symptoms, improved LVEF, and a reduction in QRSd and left ventricular volumes (Table 2). In a multicenter observational study on patients with baseline LVEF ≤35% and LBBB, Li et al.(96) found a greater increase in LVEF and a greater reduction in QRSd with LBBAP compared to CRT. Moreover, LBBAP was tested as a viable option in those patients who failed BiV pacing because of coronary venous lead complications(97). Similar results have been found in other observational studies, confirming the promising effect of LBBAP, and showing a reduction in procedural complications and fluoroscopy time(98-104). The same conclusions were reached in a small randomized controlled study (LBBP-RESYNC), where the primary endpoint was the LVEF improvement(105).

Of note, LBBAP could be a possible solution also in HF patients with wide QRS and RBBB(106). Vijayaraman et al.(72, 107) showed that LBBAP is superior to BiV pacing, not only in terms of QRSd reduction and echocardiographic remodeling but also in terms of clinical outcomes, such as time to death or heart failure hospitalization. Finally, in the International Collaborative LBBAP Study (I-CLAS), a large multicenter observational study, it was recently shown that LBBAP, compared to CRT, not only reduced all-cause mortality and HF hospitalizations but also the incidence of sustained VT/VF and new-onset AF reducing the proarrhythmic effect of BiV pacing(108).

Given this evidence, the current guidelines from the HRS on CPP recommend HBP or LBBAP as a reasonable alternative to BiV pacing when the coronary sinus LV lead placement is suboptimal (class 2a, level of evidence C) and in patients with LVEF ≤35%, sinus rhythm, NYHA class II-IV and a non-LBBB pattern with QRSd ≥150 ms (class 2b, level of evidence C)(88).
Despite important limits of CSP, the paucity of data on the extraction of the leads(109), and the lack of data from high-quality large RCTs, LBBAP might become a promising therapeutic option in HFrEF patients with wide QRS(110).

Finally, artificial intelligence is growing as a new method to detect mechanical dyssynchrony. Koopsen et al.(111), from baseline features of 45 HF patients, created digital twins able to simulate the effect of pacing. After 6 months from CRT implantation, comparing the difference between measured and simulated strain and strain rate, as well as the difference between measured and simulated LVEDV/LVESV and LVEF, they found that the virtual

reduction of septal-to-lateral myocardial work difference in the digital twin was significantly associated with LVESV reduction at 6 months. The digital twin could be used to predict the response to CRT.

Moreover, also baseline ECG features, evaluated through a machine learning algorithm, could be predictive of the response following resynchronization therapy achieved with LBBAP(112). Such an approach, although not yet applicable in clinical practice, could help CRT patients' selection in the near future.

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## 7 CONCLUSIONS

The definition of CRT response/non-response is a multiparametric diagnosis and it should be considered as a continuum, rather than a dichotomous variable.

Clinical outcomes are the best way to assess the response to CRT, but, in the real-world setting, it is difficult to assess the single patient in terms of hard outcomes. Echocardiographic parameters are the best surrogate to predict a favorable/unfavorable response and LVESV reduction holds significant prognostic value.

Baseline features of the patients with HF should not be an obstacle to resynchronization therapy. Indeed, there are several strategies to overcome CRT non-response requiring a strong collaboration between HF specialists and electrophysiologists.

Finally, although more data from large RCTs are needed, new pacing modalities, specifically LBBAP, and artificial intelligence may change the approach to patients with HF, offering a promising alternative to manage electromechanical dyssynchrony in HFrEF and wide QRS.

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| Study | Design | n | Baseline NYHA class | Baseline QRS duration, ms | Baseline LVEF, % | Primary Endpoint | Main findings |
|---|---|---|---|---|---|---|---|
| MUSTIC-SR(55) | Single-blinded, crossover, CRT on/off | 58 | III | ≥ 150 | ≤ 35 | 6MWT distance (m) after 12 months | • + 20% compared to baseline (p=0.0001) |
| MIRACLE(113) | Double blinded, CRT on/off | 453 | III/IV | ≥ 130 | ≤ 35 | 6MWT distance (m), QOL (MLHFQ points), ↓ NYHA class after 6 months | • +39 vs +10 (p=0.005)<br>• -18.0 vs -9.0 (p=0.001)<br>• ↓ NYHA CRT on (p<0.001) |
| MIRACLE-ICD(5) | Double blinded, CRT on/off | 369 | III/IV | ≥ 130 | ≤ 35 | 6MWT distance (m), QOL (MLHFQ points), ↓ NYHA class after 6 months | • +55 vs +53 (p=0.36)<br>• -17.5 vs -11 (p=0.02)<br>• ↓ NYHA CRT on (p<0.007) |
| COMPANION(6) | Double blinded, CRT-D/OMT | 1520 | III/IV | ≥ 120 | ≤ 35 | All-cause mortality or hospitalization | • HR, 0.81; 95 % CI, 0.69 to 0.96; (p=0.015) |
| CARE-HF(7) | Double blinded, CRT-P/OMT | 813 | III/IV | ≥ 120 | ≤ 35 | All-cause mortality or unplanned CV hospitalization | • HR 0.63; 95 % CI, 0.51 to 0.77; (p<0.001) |
| REVERSE(42) | Single-blinded, CRT on/off | 610 | I/II | ≥ 120 | ≤ 40 | Clinical composite score | • CRT-ON vs -OFF 16% vs 21% worsened; (p=0.10) |
| MADIT-CRT(8) | Double blinded, CRT-D/ICD | 1820 | I/II | ≥ 130 | ≤ 30 | All-cause mortality or nonfatal HF event | • HR, 0.66; 95% CI, 0.52 to 0.84; (p=0.001) |
| RAFT(33) | Double-blinded, CRT-D/ICD | 1798 | II/III | ≥ 120 | ≤ 30 | All-cause mortality or HF hospitalization | • HR, 0.75; 95% CI, 0.64 to 0.87; p<0.001 |
| RAFT long-term(34) | Double-blinded, CRT-D/ICD | 1050 | II/III | ≥ 120 | ≤ 30 | All-cause mortality after a median of 14 years of follow-up | • 76.4% vs 71.2% (p=0.002) |

**Table 1.** Pivotal Randomized Clinical Trials (RCTs) on CRT. CRT = cardiac-resynchronization therapy; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter–defibrillator; MLWHFQ = Minnesota living with heart failure questionnaire; 6MWT = 6-minute walking test; NYHA = New York Heart Association; QOL = quality of life; OMT = optimal medical therapy.

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| Study | Aim | Design | n | Baseline NYHA class | Baseline QRS duration, ms /morphology | Baseline mean LVEF, % | Main findings |
|---|---|---|---|---|---|---|---|
| Arnold et al.(114) | HBP vs BiVP | Observational, prospective, acute crossover comparison | 17 | II/III | 178 ± 30 LBBB | 26 | **>** QRSd ↓**:** -18.6 ms (p=0.007)<br>**>** SBP ↑**:** +4.6 mmHg (p=0.04) |
| Lustgarten et al.(90) | HBP vs BiVP | Randomized controlled, crossover comparison | 16 | III | >130 LBBB | 30 | **≈** LVEF ↑**:** +6% vs. +5% (p=0.2)<br>**≈** NYHA class ↑**:** +1 vs. +1 (p=0.52)<br>**≈** 6MWTd ↑**:** +34 m vs. +28 m (p=0.69)<br>**≈** MLHFQ ↓**:** -23 pts vs. -16 pts (p=0.22) |
| Upadhyay et al.(91) | His-CRT vs BiV-CRT | Randomized controlled, single blinded | 41 | II/III/IV | >120 LBBB | 28 | **>** QRSd ↓**:** -50 ms vs. -3 ms (p<0.001)<br>**≈** LVEF ↑**:** +11.8% vs. +5.2% (p=0.11) |
| Vinther et al.(93) | His-CRT vs BiV-CRT | Randomized controlled, double blinded | 50 | II/III | >150 LBBB | ≤35 | **≈** LVEF ↑**:** +16% vs. +13% (p=0.27)<br>**≈** final QRSd: 131 ms vs. 134 ms (p=0.51)<br>**≈** final 6MWTd: 444 ± 133 m vs. 451 ± 105 m (p=0.91)<br>**>** pacing thresholds: 2.3 ± 1.4 V vs. 1.4 ± 0.5 V (p<0.01) |
| Li et al.(96) | LBBAP vs BiVP | Observational, prospective, multicenter | 27 | II/III | >150 LBBB | ≤35 | **>** QRSd ↓**:** -58 ms vs. -12.5 ms (p<0.001)<br>**>** LVEF ↑**:** +15.6% vs. 7% (p<0.001) |
| Vijayaraman et al.(97) | LBBAP in failed BiVP | Observational, prospective, multicenter | 200 | II/III | >150 LBBB | 29 | **>** QRSd ↓**:** 170 ms to 139 ms (p<0.001)<br>**>** LVEF ↑**:** 29% to 40% (p<0.001) |
| Liu et al.(98) | LBBAP vs BiVP | Observational, prospective, multicentre | 62 | II/III | >150 LBBB | ≤35 | **>** QRSd ↓**:** -64.1 vs. -32.5 ms (p<0.001) |

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| Wu et al.(100) | HBP/ LBBAP vs BiVP | Observational, prospective, single centre | 137 | II/III | >150 LBBB | ≤40 | **>** LVEF ↑**:** +23% (HBP) vs. +17% (BiVP) (p=0.008)<br>+24% (LBBAP) vs. +17% (BiVP) (p=0.015)<br>**≈** LVESV ↓**:** -71 ml (HBP) vs. -52 ml (BiVP) (p=0.139)<br>-67 ml (LBBAP) vs. -52 ml (BiVP) (p=0.045) |
| Wang et al.(101) | LBBAP vs BiVP | Observational, prospective, single centre | 40 | II/III/IV | >130 LBBB | ≤35 | **>** QRSd ↓**:** 60.80 vs. 33.00 ms (p=0.0009)<br>**≈** LVEF ↑**:** +18.86 % vs. +12.97% (p=0.11) |
| Diaz et al.(102) | LBBAP vs BiVP | Observational, prospective, multicentre | 371 | II/III | >150 LBBB | <35 | **>** HFH ↓**:** 22.6% vs 39.5%; HR 0.6 [95% CI: 0.4-0.9] (p=0.021)<br>**>** procedure time ↓**:** 95 min vs. 129 min (p<0.001)<br>**>** fluoroscopy times ↓**:** 12 min vs. 21.7 min (p<0.001) |
| Chen et al.(103) | LBBAP vs BiVP | Observational, prospective, multicentre | 100 | II/III | >150 LBBB | ≤35 | **>** LVEF ↑**:** +18.52% vs. +12.89 (p=0.020) |
| Vijayaraman et al.(104) | LBBAP vs BiVP | Observational, prospective, multicentre | 325 | II/III/IV | >120 LBBB (39%) non-LBBB (46%) | ≤50 | **>** QRSd ↓**:** 152 ms to 137 ms (p<0.01)<br>**>** LVEF ↑**:** 33% to 44% (p<0.001) |
| Wang et al.(105) | LBBP-CRT with BiVP-CRT | Randomized controlled, double blinded | 40 | II/III/IV | >150 LBBB | ≤40 | **>** LVEF ↑**:** +21% vs. +15% (p=0.039) |
| Vijayaraman et al.(107) | LBBAP vs BiVP | Observational, prospective, multicentre | 1778 | II/III | >150 LBBB | ≤35 | **>** Time to death and HFH ↓**:** 20.8% vs. 28%; HR 1.4 [95% CI: 1.2-1.8] (p<0.001)<br>**>** QRSd ↓**:** 128 vs 144 (p<0.001) |
| Herweg et al.(108) | LBBAP vs BiVP | Observational, prospective, multicentre | 1778 | II/III | >150 LBBB | ≤35 | **>** incidence of VT/VF ↓**:** 4.2% vs. 9.3%; HR 0.46 [95% CI: 0.3-0.7] (p<0.001)<br>**>** new-onset AF ↓ 2.8% vs. 6.6%; HR 0.34 [95% CI: 0.1-0.7] (p=0.008) |

**Table 2.** Studies comparing BiVP with HBP and LBBAP (cardiac physiologic pacing). AF = atrial fibrillation; BiVP = biventricular pacing; CRT = cardiac-resynchronization therapy; HBP = His-Bundle Pacing; HF = heart failure; HFH = heart failure hospitalization; HR = hazard ratio; LBBB = left bundle branch block; LBBAP = Left Bundle Branch Area Pacing; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; MLWHFQ = Minnesota living with heart failure questionnaire; 6MWT = 6-minute walking test; NYHA = New York Heart Association; SBP = systolic blood pressure; VT = ventricular tachycardia; VF = ventricular fibrillation.

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**Figure 1.** Predictors of an unfavorable response to CRT **(left)** and methods to assess the response to CRT during patient's follow-up **(right)**. CRT response is evaluated in a multiparametric way with quality of life, echo, ECG, and outcomes criteria. AF = Atrial fibrillation; CKD = chronic kidney disease; FMR = functional mitral regurgitation; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; MLHFQ = Minnesota Living with Heart Failure Questionnaire; 6MWT = 6-minute walking test; non-LBBB = non-left bundle branch block; PVCs = premature ventricular contractions; QRSd = QRS duration; RV = right ventricle.

**Figure 2.** Diagram showing the diagnostic and management strategies following CRT implantation and the importance of a collaboration between HF specialists and electrophysiologists. Abl. = ablation; AF = atrial fibrillation; BiV = biventricular; CPET = cardio-pulmonary exercise test; CRT = cardiac-resynchronization therapy; CV = cardiovascular; HF = heart failure; 6MWT = 6-minute walking test; NYHA = New York Heart Association; PVCs = premature ventricular complexes; PWD = pulsed wave doppler; VT = ventricular tachycardia.

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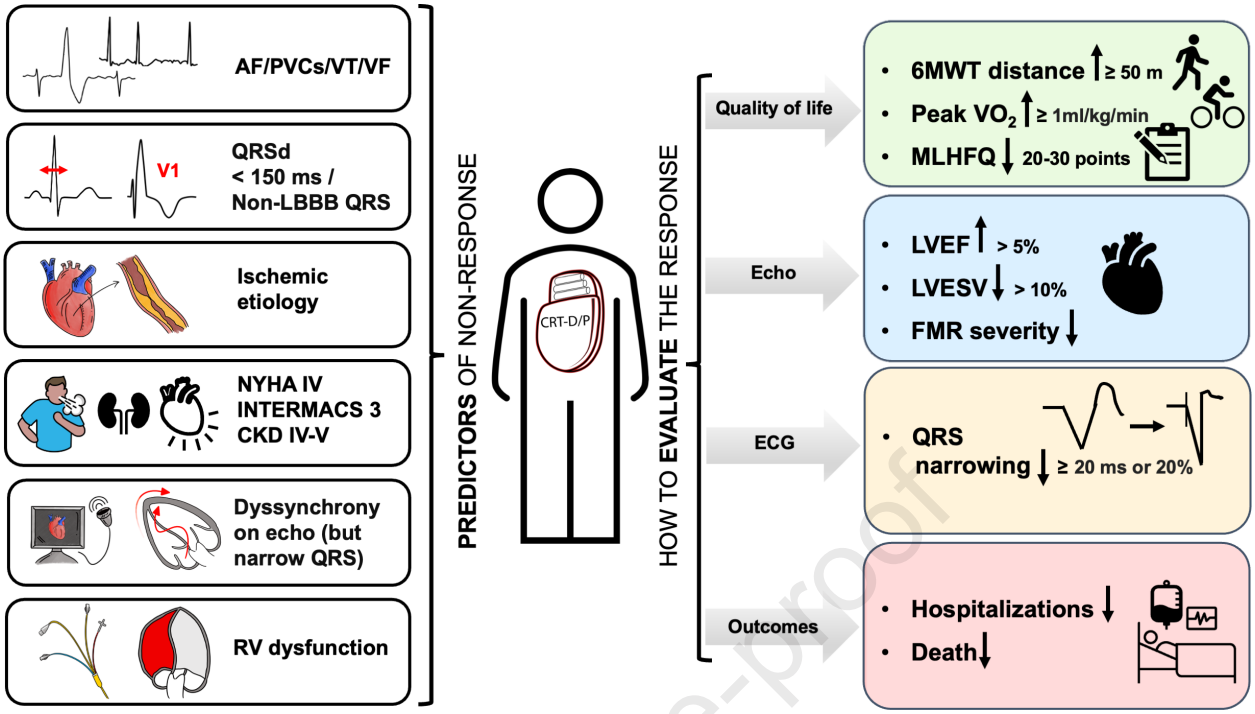


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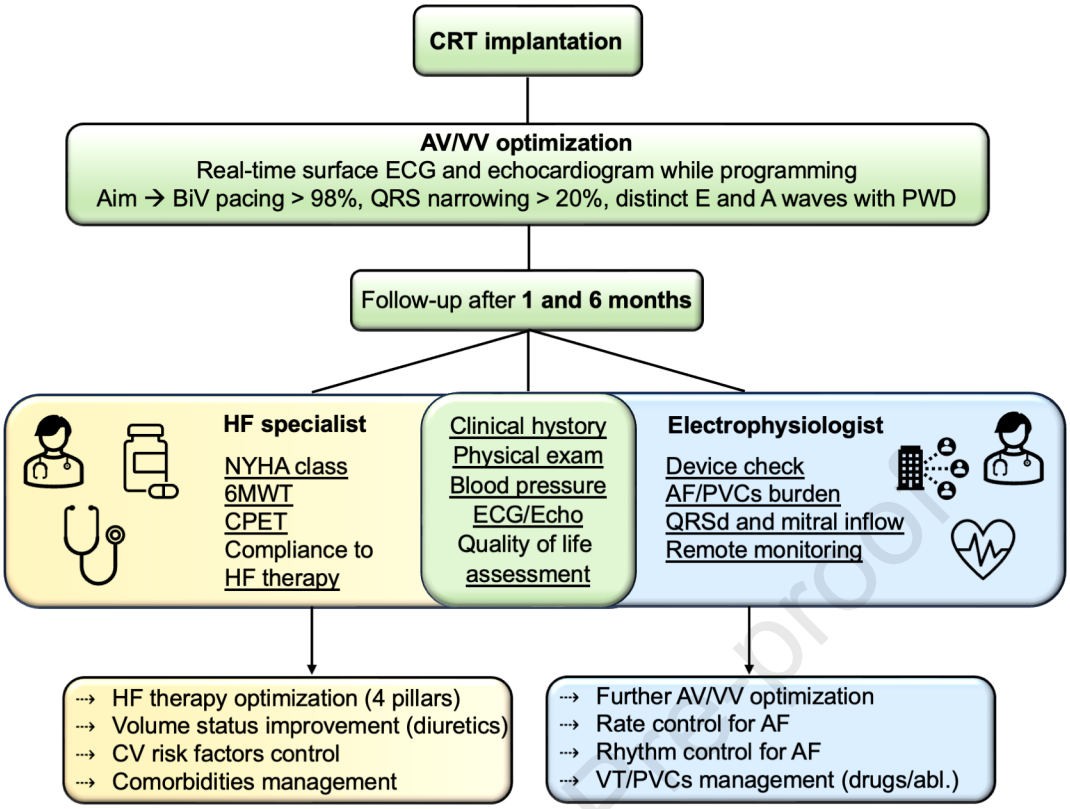


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