



# CRT Optimization: What Is New? What Is Necessary?

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## Abstract

Cardiac resynchronization therapy (CRT) has proven to improve quality of life, reduce heart failure hospitalization, and prolong life in selected heart failure patients with reduced ejection fraction, on optimal medical therapy and with electrical dyssynchrony. To ensure maximal benefit for CRT patients, optimization of care should be implemented. This begins with appropriate referring as well as selecting patients, knowing that the presence of left bundle branch block and  $QRS \geq 150$  ms is associated with the greatest reverse remodeling. The LV lead, preferably quadripolar, is best targeted in a postero-lateral position. After implantation, optimal device programming should aim for maximal biventricular pacing and in selected cases further electrical delay optimization might be of use. Even as important, is the implementation of thorough multidisciplinary heart failure care with medication uptitration, remote monitoring, rehabilitation, and patient education. The role of newer pacing strategies as endocardial or His-bundle pacing remains the subject of ongoing investigation.

## Introduction

Since its first introduction 25 years ago, cardiac resynchronization therapy (CRT) has become a fundamental part of heart failure (HF) therapy, supported by a

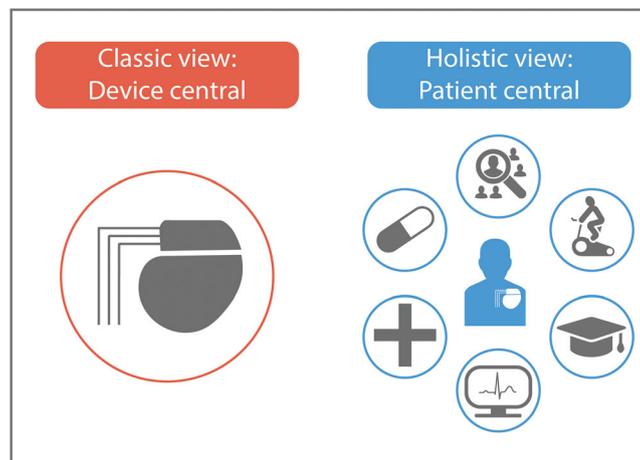
large body of evidence. Current American and European guidelines recognize CRT as a class I life-saving therapy in HF with reduced ejection fraction (HFrEF) patients

**Table 1. Optimization recommendations**

Pre-implant	Patient selection	Thorough screening for patients with guideline indication Timely referral No exclusion based on comorbidities
Peri-implant	Lead positioning	Posterolateral or lateral branch of coronary sinus vein Target zone of latest activation (QLV)
	Lead choice	Quadripolar
Post-implant	Device	Maximize biventricular pacing (goal ~ 100%) AV optimization in selected cases Treat arrhythmias
	Heart failure therapy	Uptitration of neurohormonal blockers Patient education Rehabilitation Remote monitoring Treat comorbidities

with a left bundle branch block (LBBB) and QRS  $\geq$  150 ms in sinus rhythm [1, 2]. In addition, most guidelines also suggest the use of CRT in patients with a less wide QRS (130–149 ms), a non-LBBB morphology, atrial fibrillation, or patients with moderate left ventricular (LV) dysfunction needing ventricular pacing. In approximately one third of CRT implants, a so-called non-response is reported, meaning that certain goals of improvement are not reached within the desired time frame [3]. Depending on the study, these goals can be either clinical improvement (measured as New York

Heart Association class, quality of life questionnaires, 6-min walk test, and/or cardiopulmonary exercise test), reverse remodeling (as a decrease of 15% in LV end-systolic or end-diastolic volume or an increase in ejection fraction), or a reduction in events (HF hospitalizations and/or death). In addition to the large heterogeneity in defining non-response, the concept of non-progression has been the focus of more attention lately. Indeed, the natural history of HF is progressive of nature [4] and even stabilization should be regarded as treatment success in selected cases. For example, in 40



**Fig. 1.** Different views on optimization. Left panel represents classic view on optimization, focusing on device programming. Right panel represents a holistic approach towards CRT optimization. The patient with his device is central. Pictograms represent patient selection (top), rehabilitation (following clockwise), patient education, remote monitoring, treating comorbidities, and heart failure medication uptitration.

advanced HF patients with clinical deterioration after CRT implant, biventricular pacing (BiV) continued to provide hemodynamic benefits compared to a non-paced rhythm [5]. Also, the relevance of measuring the response to CRT therapy can be questioned, as it is not performed for other HF therapies such as ACE inhibitors

or beta-blockers. Historically, CRT optimization has focused on the optimization of different pacing intervals to maximize hemodynamics. However, given the widespread underutilization of CRT and failing post-implant HF care, we propose that CRT optimization requires a more holistic approach (Table 1 and Fig. 1).

## Pre-implantation

### Patient selection

A key issue and probably one of the most important aspects in optimization is patient referral. Historically, the number of HF patients eligible for CRT has been estimated at around 10% [1, 6]. More recent registries suggest that up to 27% of HFrEF patients have a class I-IIa indication according to current guidelines [7•, 8]. However, in reality, only a minority of these patients eventually receives a CRT device. In the ESC Heart Failure Long Term Registry, containing follow-up data from 7401 European HF patients between 2011 and 2013, CRT was indicated in around one fifth of cases, yet 40% of indicated patients were not implanted because of physician uncertainties or patient refusal [8]. The underutilization was even more pronounced in the Swedish HF registry where only 6.8% of HFrEF patients had a CRT, while 26.8% had a class I-IIa recommendation [9]. In the USA, underutilization has also been reported in the Get With The Guidelines Registry, where only 30% of eligible patients received a CRT [10]. The same holds true for large randomized controlled HF trials. For example, in the PARADIGM (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, only 7% had a CRT [11]. Several reasons for underutilization can be given, including physician inertia, misinterpretation of benefit of CRT, perceived risks, need for referral to another center, cost issues, and patient reluctance [12]. If CRT optimization is interpreted on a population level, a better implementation of guidelines and not withholding patients from a lifesaving therapy should be a more important aspect of optimization. As such, the number one reason for a non-response is not getting the device. Education can facilitate better CRT adoption in clinical practice [13].

Contemporary CRT registries indicate that patients have a higher comorbidity burden and are significantly older than the landmark trial patients. For instance, in the ESC CRT-survey II [14], the median age was 70 years with 32% of total patients being  $\geq 75$  years. USA data are comparable with 23% of patients older than 80 years and an increasing comorbidity burden over the past 10 years [15•]. This might suggest that often CRT is postponed until later disease stages [9], despite data indicating that early implantation yields a higher benefit [16]. However, the presence of comorbidities does not affect the benefit from CRT [17••].

As CRT is aimed at treating dyssynchrony and given the varying rate of reverse remodeling in guideline indicated patients, some have advocated to add echocardiographic dyssynchrony parameters to the current ECG

criteria to have a better patient selection. However, in the multicenter PROSPECT (Predictors of Response to CRT) trial, this hypothesis was refuted as no single parameter was neither sensitive nor specific enough to predict a significant decrease in LV end-systolic volume (LVESV) [18]. In addition, in HFrEF patients with normal conduction, but with echocardiographic signs of dyssynchrony, CRT increased mortality [19]. Thus, echocardiographic signs of dyssynchrony cannot be used to rule out or rule in CRT. Imaging prior to implantation should be reserved to the confirmation of HFrEF and can play a role in assessing the mechanism of dyssynchrony and the presence of structural heart disease or scar [20].

## Peri-implantation

### Implantation strategy

#### Anatomy guided

During a standard CRT implantation, the LV lead is preferably positioned in a suitable posterolateral or lateral branch of the coronary sinus vein, as these zones are latest activated in patients with a typical LBBB [1] thus allowing maximal resynchronization. This is further supported by post hoc analyses of landmark CRT randomized control trials [21–23] showing a reduction in HF hospitalization and mortality with a posterolateral or lateral LV lead position. Apical positions should be avoided because of an increased mortality [23•]. In general, it is recommended to keep the distance between RV and LV lead as far as possible [24, 25].

#### Electrical delay guided

Because the activation pattern in LBBB and other forms of conduction delay are not always homogeneous in the HF population, the latest activated zone might not always be congruent with the posterolateral lead position [26]. As such, an alternative approach might be to target the latest electrically activated zone. During the procedure, the delay between the onset of the QRS complex on the surface ECG and the first activation at the tip of the LV lead can be measured and is called the QLV time. Longer QLV-times are associated with improved reverse remodeling and quality of life [27], as well as reduced HF hospitalization and death [28, 29]. However, the longest QLV is located in the posterolateral region in the large majority of cases, indicating that this is indeed the sweet spot. Moreover, since the introduction of quadripolar leads, more pacing options are easily available for the operator, even in case of few anatomical options, improving QLV feasibility. The current approach of many operators is to introduce a quadripolar lead in a suitable posterolateral vein, sequentially test the different poles and eventually select the pole with the longest QLV and the lowest pacing threshold without phrenic nerve stimulation. Two ongoing trials investigate whether a QLV targeted approach is beneficial compared to standard LV lead implantation (DANISH-CRT NCT03280862, ENHANCE CRT NCT01983293 [30]).

## Imaging guided

Some investigators have advocated to primarily select the latest mechanically activated zone rather than the latest electrically activated zone for lead implantation. In the TARGET (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy) study [31], 220 patients were randomized to either targeted LV lead implantation, guided by 2D speckle tracking echocardiography identifying the latest zone of mechanical activation or routine non-guided LV placement in a lateral or posterolateral vein. After 6 months, there was a higher proportion of patients meeting the LVESV reduction threshold of  $\geq 15\%$  in the echocardiographic guided group compared to controls. Also, a higher clinical response and a reduction in combined all-cause mortality and HF-related hospitalization were noted. These results were confirmed by the STARTER (Speckle Tracking Assisted Resynchronization Therapy for Electrode Region) trial [32], where a similar approach in 187 patients led to a significant reduction in the combined end point of HF hospitalization or death in the echocardiography-guided group. However, despite these positive results, pre-implantation imaging to identify the target implantation site has not been widely adopted in routine clinical practice. Several reasons can be given. First, adequate echocardiographic imaging and especially speckle tracking is often not feasible because of poor acoustic windows, occurs off-line, and is time-consuming. Second, in the majority of guided cases, the LV lead is positioned in a lateral or posterolateral branch, which is also the main target of non-guided procedures. Third, technical issues including unsuitable anatomy, unstable lead position, high-pacing thresholds, and phrenic nerve stimulation might hamper the implantation success in targeted regions. Fourth, pacing from the latest mechanical activation also induces a different activation pattern. Moreover, in post hoc analyses it seems that avoiding scar zones is the main driver of outcome benefits rather than implantation in the zone of the latest mechanical activation [33, 34].

Other implantation strategies with the intention to avoid scar to improve CRT response have also been described. One single-center study suggested that implantation in non-scar regions guided by cardiac magnetic resonance reduces HF hospitalization or death [35]. However, these results need confirmation in larger randomized studies. Further, different forms of multimodality imaging to guide implantation have been introduced [36]. Although promising results have been published, these forms of imaging are laborious, time-consuming, and not applicable in routine clinical practice to date.

## Lead and pacing configuration

### Quadripolar leads

Quadripolar leads have a tip electrode and three ring electrodes, offering more programmable pacing vectors compared to classic bipolar leads. Given the often encountered implantation difficulties such as unfavorable anatomy, phrenic nerve stimulation, instable lead position, or high-pacing threshold, these quadripolar leads are currently the most used. In the MORE-CRT (More Options Available With a Quadripolar LV Lead Provide In-Clinic Solutions to CRT Challenges) trial [37••], the lead-related event rate was compared in 1074

patients randomized to either bipolar or quadripolar lead implantation. Quadripolar leads were associated with more than 50% reduction in intra-operative events, driven by a reduction in implant failure rate as well as less phrenic nerve stimulation, lower pacing thresholds, and less lead instability. Quadripolar leads have also been associated with reduced mortality, deactivation, and replacement need compared to bipolar leads [38]. If available, quadripolar leads are thus currently the first choice.

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### Multipoint pacing

Pacing from multiple sites simultaneously along a multipolar lead, or so called multipoint pacing (MPP), is a new option since the introduction of quadripolar leads. MPP can initiate larger activation wavefronts, possibly enhancing resynchronization and CRT response. Several studies have shown an improved acute hemodynamic response of MPP compared to conventional BiV [39, 40], and a large prospective Italian registry suggests a greater improvement in clinical composite score and LV ejection fraction [41]. However, the only randomized trial has failed to show benefit of MPP over conventional BiV in converting non-response to response, defined as a > 15% reduction in LVESV [42•]. Though other trials are ongoing, routine use of MPP cannot be advised, especially in the light of the higher battery use associated with MPP versus classic BiV.

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### Multisite pacing

Multisite pacing (MSP) is an alternative to MPP and was already introduced before the availability of multipolar leads. Using two bipolar LV leads in addition to the conventional RV apical and right atrial lead, different LV sites can be stimulated simultaneously. Small studies have suggested that MSP can increase CRT response [43, 44] and possibly reduce ventricular arrhythmias and mortality [45]. In contrast, in the only randomized study, there was no benefit of MSP over BiV in terms of clinical or echocardiographic improvement, but MSP was associated with a higher peri-procedural complication rate [46]. Since quadripolar leads are a lot easier to implant, have a shorter procedural and fluoroscopy time, require less hardware, and are implanted according to the same principle of maximizing the activation wavefront, future developments will probably mainly focus on MPP.

## Post-implantation

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### Device optimization

#### AV and VV optimization

CRT is a treatment of dyssynchrony in HF, which is composed of intra-ventricular, interventricular (VV), and atrioventricular (AV) dyssynchrony. After device implantation, programming should be aimed at maximizing the resynchronization of these different components. Various techniques for AV and VV optimization, using echocardiography, electrocardiography, or invasive hemodynamical evaluation, have been described [47–

49]. Despite evidence of hemodynamic improvement with AV optimization [50], the routine implementation of this strategy did not yield the expected benefit in trials. In the SMART-AV (The SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy) [51] and FREEDOM (Frequent Optimization Study Using the QuickOpt Method) trial [52] echocardiographic optimization of the AV interval and an automated device algorithm were not better than an “out-of-the-box” setting of 100–120 ms in terms of reverse remodeling and clinical composite score, respectively. The role of VV optimization is even less clear, as evidence is limited to small trials with conflicting results [53–55]. In addition, observational data indicate that AV and VV optimization are not performed in the majority of CRT implants, due to its time-consuming nature [56]. Current guidelines thus do not recommend routine AV and VV optimization and suggest to reserve this strategy for initial non-responders [1, 2].

As the optimal AV and VV interval at rest can change over time and during exercise, newer automated device algorithms that address this dynamic issue have recently been developed. The AdaptivCRT algorithm (Medtronic, Inc., Mounds View, Minnesota) provides automatic adjustments to AV and VV intervals and selects between BiV or LV only pacing according to the measured intrinsic AV conduction and heart rate. This algorithm was non-inferior to echocardiographic optimization in a recent study in patients with normal AV conduction and LBBB and resulted in a 44% reduction of RV pacing [57]. Whether AdaptivCRT can reduce mortality and HF hospitalization is the subject of an ongoing prospective trial [58]. Another new automated algorithm uses the SonR sensor (LivaNova, Paris, France), which is a micro-accelerometer embedded in the tip of the right atrial lead. The sensor measures cardiac muscle vibrations, correlated with  $dp/dt$  and thus reflecting contractility. The device uses these measurements to optimize AV and VV intervals on a weekly basis, at rest, and during exercise. In the RESPOND CRT (SonRtip lead and automatic AV-VV optimization) trial, the use of this algorithm was non-inferior to echocardiographic optimization in the rate of clinical response after 12 months [59]. Of note, after a mean follow-up of 548 days, there was a 35% risk reduction in HF hospitalization.

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### Biventricular pacing optimization

A key issue and probably the most important step towards effective CRT programming is maximizing the amount of BiV to as close to 100% as possible [1]. Several studies have consistently shown that BiV > 92% [60] or > 98% [61] is associated with decreased mortality and HF hospitalization. Therefore, at every follow-up, the device counter should be checked and effective BiV should be electrocardiographically confirmed. In case of low BiV, special attention should be given to inadequate AV delay programming, loss of BiV during exercise, or the presence of arrhythmias, as these are the most common causes [62]. However, ineffective sensing or pacing, also leading to loss of BiV, might not influence the counters and should be kept in mind as well. In case of atrial fibrillation, AV junctional ablation should strongly be considered,

especially if other rate or rhythm control strategies fail to improve the percentage of BiV [1, 2].

## Heart failure care optimization

### Heart failure therapy uptitration

As CRT only treats a piece of HF pathophysiology (i.e., dyssynchrony), after implantation, the focus should not only be on the device, but also on HF therapy optimization. Data from the IMPROVE-HF (Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting) registry indicate that prior to CRT implant, most HF patients are treated with sub-optimal doses of neurohormonal blockers [63]. CRT can often reduce several reasons why further uptitration of neurohormonal blockers was not possible before CRT implant, such as bradycardia, AV conduction disorders, or low blood pressures. Uptitration of neurohormonal blockade was indeed feasible in more than half of CRT patients and was associated with a reduction in mortality and HF hospitalization in a retrospective analysis of 650 patients [64]. In addition, loop diuretic downtitration could often be performed, especially in patients with non-ischemic cardiomyopathy and improved LVEF, and was also associated with improved outcomes [65]. Despite being on maximal tolerated doses prior to CRT implantation, hemodynamic improvements after CRT might reduce the needs for diuretics and facilitate medication uptitration. Other retrospective studies have also shown the association between higher doses of neurohormonal blockade and survival free of HF hospitalization after CRT [66–68]. The implementation of a post-implant HF protocol incorporating primary care physicians might overcome the shortcomings of current practice as this approach, combining medication uptitration, device optimization, arrhythmia management, and HF education in a multidisciplinary setting led to improved reverse remodeling and fewer adverse events in a single center study [69].

### Rehabilitation

Exercise training reduces HF hospitalization and mortality [70] and is a class I indication according to current European HF guidelines [71]. Several studies evaluated the value of exercise training after CRT implantation. Exercise training not only improves symptoms, exercise capacity, and quality of life [72–74], but might also improve outcomes [75]. In contrast, a subanalysis of the randomized HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial could not show any benefit in a large (non-CRT) HF patient population on HF hospitalization or death, possibly due to insufficient power [74]. Nevertheless, exercise training itself after CRT is feasible, safe, and might improve patient outcome.

### Remote monitoring

With remote monitoring, close monitoring of the outpatient's amount of BiV, presence of arrhythmias, impending pulmonary fluid accumulation, and device integrity is possible. Whether early intervention triggered by remote monitoring information of contemporary devices might lead to improved outcomes was

tested in different trials. The IN-TIME (Influence of Home Monitoring on Mortality and Morbidity in Heart Failure Patients with Impaired Left Ventricular Function) trial [76] randomized 716 NYHA class II–III patients undergoing ICD or CRT-D implantation to either remote monitoring with daily data transmission or routine follow-up. After 1 year, remote monitoring reduced the composite clinical score as well as all-cause mortality. The recent MORE-CARE trial with 865 randomized CRT-D patients could not reproduce these results but showed a significant reduction in healthcare resource utilization [77]. In addition, home telemonitoring may be considered for patients with HF in order to reduce the risk of recurrent cardiovascular and HF hospitalizations and cardiovascular death [78]. Awaiting results of new trials, remote monitoring is a valuable tool in HF care and attempts should be made to maximally adopt it in CRT patients.

## Comorbidity treatment

HF patients in general suffer from an increasing number of comorbidities [79, 80]. Treatment should thus not only focus on HF, but also on patient's comorbidities as they might impair prognosis [81, 82]. Of these comorbidities, iron deficiency is of specific interest. The importance of iron deficiency and its treatment in HFrEF to improve symptoms and exercise capacity is now well established [71]. Interestingly, iron deficiency was present in up to 56% of CRT patients and was also associated with a reduced clinical response as well as less reverse remodeling in a retrospective cohort [83]. As iron is a co-factor in energy proteins and involved in reverse remodeling [84], its deficiency might hamper CRT response. An ongoing randomized trial is investigating the effect of IV iron on reverse remodeling and rate-dependent cardiac contractility in iron-deficient CRT patients (NCT03380520).

## Alternative pacing strategies

Because of the sometimes encountered technical issues during implantation such as unsuitable anatomy, venous occlusion, high-pacing thresholds, or phrenic nerve stimulation and the fact that the latest activated LV site does not always coincide with the epicardial lateral or posterolateral position, new approaches for LV lead placement are under investigation [85]. These include endocardial pacing and His-bundle pacing.

## Endocardial pacing

Endocardial pacing has several potential advantages such as access to all regions of the LV, a faster propagation of the activation wavefront than during epicardial stimulation, a more physiologic endocardial to epicardial LV activation, and avoidance of technical issues specific to the transvenous approach [86]. Analyses of the acute hemodynamic response to different epicardial and endocardial pacing sites in 35 patients with non-ischemic cardiomyopathy suggested that there is a high inter-individual variability in optimal pacing site and that endocardial pacing may improve diastolic function [87]. A small study compared multisite, multipolar, and endocardial pacing and found that the best overall hemodynamic response was achieved with endocardial pacing [88]. A

multicenter safety study in 138 patients with non-response or failed implant showed that implantation, using an atrial trans-septal approach, was successful in 89% of cases with a clinical or echocardiographic response after 6 months in more than half [89•]. However, complications rates were high, especially transient ischemic attacks and strokes that occurred in 6.8% and 3.8% of patients, respectively, despite oral anticoagulation.

Following the recent developments of leadless pacing, a leadless LV pacing electrode (WiSe-CRT, EBR Systems, Sunnyvale, CA, USA) has been introduced. The SELECT-LV (Safety and Performance of Electrodes implanted in the Left Ventricle) feasibility study evaluated the safety and performance of the WiSe-CRT system in 35 patients with failed transvenous LV lead implantation [90]. The procedure was successful in all but one patient with a clinical response of 85% after 6 months. Currently, the SOLVE-CRT (Stimulation of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders and Previously Untreatable Patients) study (NCT02922036) is ongoing, investigating the safety and efficacy of this system in 350 non-responders and failed transvenous implant patients. In summary, the potential role of endocardial pacing in CRT remains unclear to date.

### His-bundle pacing

His-bundle pacing is an emerging form of more physiological pacing, possibly also applicable in CRT eligible patients. As fibers from the LBB and RBB are already separated in the AV node [91], a LBBB might be overcome with His-bundle pacing in case of a proximal block. Moreover, His-bundle pacing does not require anticoagulation or transseptal puncture in contrast to endocardial pacing. In 23 patients with LBBB, His-bundle pacing resulted in an increased resynchronization and greater hemodynamic response than BiV [92]. Very recently, the His-SYNC (His Corrective Pacing or Biventricular Pacing for Cardiac Resynchronization in Heart Failure) study [93••] randomized 41 patients with CRT indication to either His-bundle pacing or conventional CRT. In the intention-to-treat analysis, there was no difference in terms of reverse remodeling with low event rates and no lead issues. Because of high cross-over rate, a subsequent per-protocol analysis was performed. However, besides a superior electrical resynchronization with His-bundle pacing, there was only a non-significant trend towards improved reverse remodeling, possibly explained by insufficient statistical power [94]. Of note, 48% of patients assigned to His-bundle pacing had cross-over, half of whom were due to a not correctable intraventricular conduction delay. This illustrates the importance of patient selection in future trials. For now, His-bundle pacing is promising, but more data are needed before it can be widely adopted in CRT eligible patients.

## Conclusion

CRT improves survival and reduces HF hospitalization in HFrEF patients with electrical dyssynchrony. A holistic approach to CRT optimization as a multifaceted process with better referral and optimal patient selection, implantation targeting the latest activated zone, optimal device programming, and rigorous follow-up with multidisciplinary HF care might further improve patient benefit from CRT.

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## Compliance with Ethical Standards

### Conflict of Interest

The authors declare that they have no conflicts of interest.

### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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First small randomized controlled trial comparing His-bundle pacing to conventional CRT in first implants. In the intention to treat analysis, there was no difference in terms of reverse remodelling or heart failure

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