

# Cardiac Resynchronization Therapy—Emerging Therapeutic Approaches

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## Abstract

Cardiac resynchronization therapy (CRT) is an important therapeutic tool in the management of patients with heart failure and electrical dyssynchrony. In appropriately selected patients, landmark randomized controlled trials have demonstrated morbidity and mortality benefit beyond standard goal-directed medical therapy. Current guidelines emphasize the greatest clinical efficacy of CRT in patients with symptomatic heart failure, left bundle branch block, and wide QRS duration (> 150 ms). Other relevant considerations include the presence of atrial fibrillation, the presence of AV block, the etiology of cardiomyopathy, the presence of masked left-sided conduction delay, and the impact of comorbidities that might predict poor clinical response. At the time of CRT implantation, key considerations include targeting of the left ventricular (LV) lead to sites of greatest electrical and/or mechanical delay, the use of quadripolar versus bipolar LV pacing leads, evaluation of multiple pacing vectors to maximize electrical resynchronization, and in select instances pre-procedure imaging of the coronary venous anatomy to help guide decision-making at the time implant. Post-implant care includes the selective use of atrio-ventricular and inter-ventricular optimization algorithms, mitigation of right ventricular pacing, recognition, and treatment of suboptimal biventricular pacing, as well as management by a multi-disciplinary team of cardiovascular specialists. Emerging therapeutic strategies for patients eligible for CRT include the use of endocardial LV pacing, novel LV pacing options including multi-point pacing, His bundle pacing, and the integration of remote monitoring platforms that may identify patients at risk for clinical worsening.

## Introduction

Cardiac resynchronization therapy (CRT) is a key therapeutic strategy for patients with symptomatic heart failure, depressed left ventricular function, and electrical dyssynchrony [1, 2]. Biventricular pacing therapy in appropriately selected patients is associated with favorable remodeling of the left ventricle, improvements in the efficiency of ventricular contraction, and ultimately improvements in clinical outcomes including quality of life, risk of heart failure hospitalization, and survival [3–7]. The evaluation and care of the patient undergoing CRT involves the coordinated cooperation of specialists in electrophysiology, advanced heart failure, and cardiovascular imaging [8].

### Landmark trials in cardiac resynchronization therapy

#### Advanced heart failure

There are now numerous landmark trials establishing the efficacy of CRT therapy in patients with heart failure (Table 1). For patients with advanced heart failure (NYHA III/IV), the first double-blind randomized controlled comparison of CRT was the MIRACLE (Multicenter Insync Randomized Clinical Evaluation) trial in which 453 patients with advanced HF (NYHA III/IV), LVEF  $\leq 35\%$ , and QRS  $\geq 130$  ms were randomized to CRT or goal-directed medical therapy (GDMT) [3]. CRT was associated with left ventricular reverse remodeling (improved LVEF, decreased LV diastolic dimension), improved functional capacity, and a 40% decrease in the composite primary endpoint of heart failure hospitalization or death. Similar findings were reported in the CARE-HF (Cardiac Resynchronization on Morbidity and Mortality in Heart Failure) trial [5] which randomized patients with symptomatic heart failure (NYHA III/IV), LVEF  $\leq 35\%$ , and QRS  $> 120$  ms to CRT pacing (CRT-P) or GDMT. CRT-P was associated with improvements improved functional capacity, LV reverse remodeling, and decreased HF hospitalization. In long-term follow-up, CRT-P was associated with a 36% reduction in all-cause mortality when compared to GDMT, which established a mortality benefit from CRT pacing in the absence of a defibrillator [9]. The COM-

PANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) trial compared a strategy of GDMT to that of CRT-P and CRT with ICD (CRT-D) in patients with LVEF  $\leq 35\%$ , NYHA III/IV, and QRS  $> 120$  ms [4]. Both CRT strategies (CRT-P, CRT-D) reduced the risk of death or HF hospitalization compared to GDMT and both CRT strategies reduced the hazard for all-cause mortality (24% for CRT-P, 36% for CRT-D), although the reduction in mortality for CRT-P was only of borderline significance. To date, there remains no direct and appropriately powered randomized comparison of CRT-D versus CRT-P.

#### Mild heart failure

The efficacy of CRT therapy in patients with mildly symptomatic HF was demonstrated in the REVERSE-HF, MADIT-CRT, and RAFT trials. In REVERSE (Resynchronization Reverse Remodeling in Systolic Left Ventricular Dysfunction), patients with an LVEF  $< 40\%$ , QRS  $\geq 120$  ms, and mild HF (NYHA I/II) were randomized to CRT or GDMT [10]. CRT was associated with LV reverse remodeling as well as a 50% reduction in HF hospitalizations at 1 year follow-up. In the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial, 1820 patients with mild HF (NYHA I with ischemic etiology or NYHA II), QRS  $> 130$  ms, and LVEF  $< 30\%$  were randomized to CRT-D or ICD therapy alone [6]. CRT therapy was associated with a 34% reduction in the primary endpoint of death or symptomatic HF, driven primarily by a reduction in HF events. Finally, in the RAFT (Resynchronization/Defibrillation for Ambulatory Heart Failure Trial) study [7], CRT-D versus ICD therapy was compared in patients with mild HF (NYHA II/III), LVEF  $\leq 30\%$ , and QRS  $> 120$  ms. CRT therapy was associated with a 25% reduction in the primary endpoint of death or HF hospitalization with significant reductions in both mortality (25% risk reduction) and HF hospitalization (30%). Of trials of CRT in patients with mild HF, RAFT was the only one to demonstrate a significant mortality benefit, which likely reflects the

**Table 1. Landmark trials in cardiac resynchronization therapy**

Trial (year of publication)	Patient population (trial N)	Comparison	Endpoints (median follow-up)	Findings
<b>Advanced heart failure</b>				
MIRACLE (2002)	NYHA III/IV, LVEF $\leq$ 35%, QRS $\geq$ 130 ms, 6MWD $<$ 450 m (N = 453)	CRT-P vs. GDMT	Primary: NYHA class, QOL score, 6MWD (6 months) Secondary: LVEF	$\uparrow$ 6MWD (+39 vs. +10 m), $\uparrow$ QOL score, $\downarrow$ NYHA class (68 vs. 38%), $\uparrow$ LVEF (5 vs. 0%)
CARE-HF (2005)	NYHA III/IV, LVEF $\leq$ 35%, LVEDD $\geq$ 30, QRS $\geq$ 120 ms (N = 813)	CRT-P vs. GDMT	Primary: death or CV hospitalization (29 months) Secondary: LV measures, QOL	$\downarrow$ all-cause mortality (20 vs. 30), $\downarrow$ IVMD, $\downarrow$ LVESVi, $\uparrow$ QOL
COMPANION (2004)	NYHA III/IV, QRS $\geq$ 120 ms (N = 1520)	CRT-D/CRT-P vs. GDMT	Primary: death/hospitalization any cause (12–16 months) Secondary: all-cause mortality	$\downarrow$ primary endpoint for CRT vs. GDMT (34% $\downarrow$ CRT-P, 40% $\downarrow$ CRT-D). $\downarrow$ all-cause mortality (24% CRT-P [ $p = 0.06$ ], 36% CRT-D [ $p = 0.003$ ]) vs. GDMT
<b>Mild heart failure</b>				
MADIT-CRT (2009)	NYHA I/II, LVEF $\leq$ 30%, QRS $\geq$ 130 ms (N = 1820)	CRT-D vs. ICD	Primary: death or non-fatal HF event (2.4 years) Secondary: LV measures, death	$\downarrow$ death/HF with CRT-D (17 vs. 25%) driven by 41% $\downarrow$ HF events. No in mortality, $\uparrow$ LVEF (+11 vs. +3%)
REVERSE (2008)	NYHA I/II, LVEF $\leq$ 40%, QRS $\geq$ 120 ms (N = 610)	CRT-On vs. CRT-Off	Primary: HF clinical composite score (12 months) Secondary: LV measures, HFH	Fewer pts. worsened with CRT-ON vs. OFF (16 vs. 21%), $\downarrow$ LVESV, $\uparrow$ LVEF, 53% $\downarrow$ HF hospitalization
RAFT (2010)	NYHA II/III, LVEF $\leq$ 30%, QRS $\geq$ 120 ms (or paced $>$ 200 ms) (N = 1798)	CRT-D vs. ICD	Primary: death or HF hospitalization (40 months) Secondary: components of primary	$\downarrow$ death/HFH with CRT (33 vs. 40%), $\downarrow$ mortality (29 vs. 35%), $\uparrow$ device-related adverse events
<b>Chronic right ventricular pacing</b>				
BLOCK-HF (2013)	NYHA I–III, LVEF $\leq$ 50%, indication for pacing with A-V block (N = 691)	CRT vs. RV pacing	Primary: death, HF event, $\uparrow$ LVESVi (37 months) Secondary: components of primary	$\downarrow$ composite outcome w/ CRT (46 vs. 56%), no death, 30% $\downarrow$ HFH
<b>Narrow QRS and mechanical dyssynchrony</b>				
RethinQ (2007)	NYHA III, LVEF $\leq$ 35%, QRS $<$ 130 ms (N = 172)	CRT-D vs. ICD	Primary: peak oxygen consumption (6 months)	No in peak oxygen consumption or HF events.

**Table 1.** (Continued)

Trial (year of publication)	Patient population (trial N)	Comparison	Endpoints (median follow-up)	Findings
ECHO-CRT (2013)	NYHA III/IV, LVEF $\leq 35\%$ , QRS $< 130$ ms, echo-evidence dyssynchrony	CRT-On vs. CRT-Off	Secondary: HF events Primary: death or HF hospitalization (19 months)	Study stopped for futility with significant $\uparrow$ all-cause mortality

*NYHA* New York Heart Association Class, *LVEF* left ventricular ejection fraction, *6MWD* 6-min walk distance, *QOL* quality of life, *m* meter, *IVMD* interventricular mechanical delay, *LVESVi* left ventricular end-systolic volume index, *CRT-P* cardiac resynchronization therapy pacing, *GDMT* goal-directed medical therapy, *ICD* implantable cardioverter-defibrillator, *HF* heart failure, *HFH* heart failure hospitalization, *A-V* atrioventricular

baseline mortality risk in the study (placebo group mortality of 21% in patients with NYHA II/III HF) versus trials that included NYHA I patients (MADIT-CRT, REVERSE) in which the mortality was significantly lower (placebo group mortality 2–7%) and follow-up time was shorter.

#### Chronic RV pacing

Right ventricular (RV) pacing is associated with asynchronous activation of the left ventricle and several previous studies have shown an association between RV pacing burden and an increased risk of heart failure hospitalization, atrial fibrillation, and left ventricular dysfunction [11–13]. In this context, current North American guidelines recommend biventricular pacing therapy in patients with LVEF  $\leq 35\%$  who are undergoing new or replacement device with anticipated requirement for significant ( $> 40\%$ ) ventricular pacing [2]. The BLOCK-HF (Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block) study examined the impact of CRT versus RV pacing alone in patients with an indication for pacing, LVEF  $\leq 50\%$ , and HF (NYHA I-III) [14]. CRT was associated with a 26% reduction in the primary endpoint of death or HF hospitalization, which was driven by a reduction in HF events. In contrast, the BIOPACE (Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization) study did not demonstrate a morbidity or mortality benefit of CRT versus RV pacing in patients with a preserved left ventricular ejection fraction [15].

#### Narrow QRS and mechanical dyssynchrony

In addition to patients with electrical dyssynchrony, investigators observed that some patients with a narrow QRS demonstrated mechanical LV dyssynchrony and initial studies suggested that patients with mechanical dyssynchrony and normal QRS duration demonstrated clinical improvement with CRT [16, 17]. These studies prompted the larger scale evaluation of CRT in this population including the RethinQ, LESSER-EARTH, and ECHO-CRT trials, all of which showed no benefit and in the case of LESSER-EARTH and ECHO-CRT, possible harm [18–20]. The RethinQ (Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS) study compared CRT-D to ICD therapy in patients with NYHA III HF, LVEF  $\leq 35\%$ , and QRS  $< 130$  ms with mechanical dyssynchrony as assessed by tissue Doppler imaging (TDI) [18]. There was no improvement in peak oxygen consumption or LV remodeling parameters at 6 months. The LESSER-EARTH (Evaluation of Resynchronization Therapy for Heart Failure) study compared a CRT-On versus CRT-Off strategy in patients with symptomatic HF, LVEF  $\leq 35\%$ , and narrow QRS ( $< 120$  ms) [20]. The study was terminated early for futility with evidence of a trend to increased HF hospitalization in the CRT-On arm. Finally, the ECHO-CRT (Echocardiography Guided Cardiac Resynchronization Therapy) study assessed the impact of CRT in patients with advanced HF (NYHA III/IV), LVEF  $\leq 35\%$  and QRS  $< 130$  ms with mechanical dyssynchrony (tissue Doppler imaging or speckle-tracking radial strain delay) [19]. Similar to LESSER-EARTH, the study was terminated early in the context

of a significant increase in mortality associated with CRT therapy (11 vs. 6.4%) at 20 month follow-up. Presently, we believe the available literature to date does not favor the use of CRT in patients with narrow QRS with or without mechanical dyssynchrony, in the absence of AV block necessitating ventricular pacing.

### Defining response to CRT

To date, there remains no standardized definition of response to CRT. Historically, studies have used measures of left ventricular reverse remodeling (improvements in LVEF, decrease in LV volumes), improvement in functional capacity (6 min walk distance, peak oxygen consumption, quality of life scores), or reduction in clinical endpoints (worsening HF or mortality) [21]. In a seminal study examining the agreement amongst these response criteria, Fornwalt and colleagues applied 17 echocardiographic and clinical criteria for CRT response to a prospective registry of patients undergoing CRT [22]. Agreement amongst echocardiographic response criteria was poor, agreement amongst clinical response criteria was moderate, and agreement between echocardiographic and clinical criteria was generally no better than chance alone. Recent studies have shown that short-term LV reverse remodeling, and particularly 'super-response' (LVEF improvement > 10–15%, reduction in LV volume > 20–30%), is associated with improvements in long-term survival [23, 24]. In general, we believe that CRT response should be defined as a composite of short and intermediate-term (3–12 month) echocardiographic reverse remodeling as well as longer-term (years) clinical outcomes including survival and heart failure events.

### Patient selection for CRT

In landmark trials of CRT efficacy, the presence of electrical dyssynchrony, defined by a wide QRS duration (> 120–130 ms), is a unifying feature of identifying patients who benefit from CRT. The salutary effects of CRT are related to reversal of this electrical dyssynchrony through effective fusion of electrical wavefronts generated by RV and LV pacing. In patients with a left bundle branch block (LBBB), the site of latest LV activation is generally in the basal posterior/postero-lateral segment of the LV [25], and targeting this region for LV pacing has been the standard approach during CRT implantation. By comparison, patients with a right bundle branch block (RBBB) or non-specific intraventricular conduction delay (IVCD) are not expected to have the same activation pattern and may therefore not be expected to

derive the same benefit from CRT. Meta-analysis of previous randomized studies has found that the clinical benefits of CRT are generally restricted to patients with LBBB and not those with IVCD or RBBB [26]. Post hoc analysis of the MADIT-CRT study, which evaluated CRT therapy in patients with mild HF, identified an increased risk of HF hospitalization and death with randomization to CRT therapy in patients with a non-LBBB and relatively narrow QRS ( $\leq 134$  ms) [27•]. By comparison, the same post hoc analysis found that CRT was associated with improved clinical outcomes in patients with non-LBBB, prolonged QRS duration (> 134 ms) and prolonged PR interval (PR > 230 ms). The benefit in this subgroup may have been related to improvements in atrio-ventricular synchrony. We would note that some patients with RBBB or IVCD, including those with very wide QRS duration (> 180 ms) may demonstrate prolonged LV activation times (i.e., masked left bundle branch delay) [28, 29] and in some instances, these patients may still derive benefit from CRT [30]. Overall, these data underlie the current North American guidelines for CRT therapy which identify a class I recommendation only in patients with symptomatic HF, LVEF  $\leq 35\%$ , LBBB, and QRS  $\geq 150$  ms [2].

Other considerations for patient selection beyond QRS morphology include the presence of atrial fibrillation, etiology of cardiomyopathy, and comorbidities. In patients with atrial fibrillation, there is often suboptimal effective biventricular pacing related to high and/or irregular ventricular rates causing fusion, pseudo-fusion, or lack of pacing. Previous meta-analyses of randomized trials have found decreased CRT benefit in patients with AF [31, 32] including an analysis of the RAFT study which found that CRT did reduce HF hospitalization but did not impact mortality in this population [33]. In patients with atrial fibrillation and suboptimal biventricular pacing, the adjunctive role of atrioventricular junction ablation is an important option to consider and has been associated with improved clinical outcomes [34].

Previous studies have also suggested that patients with non-ischemic cardiomyopathy are more likely to demonstrate LV reverse remodeling following CRT compared to patients with non-ischemic cardiomyopathy [35]. LV reverse remodeling after CRT is associated with a decreased risk of ventricular arrhythmias [36•] and patients with non-ischemic cardiomyopathy are at generally lower risk of ventricular arrhythmias compared to ischemic cardiomyopathy [37]. In this context,

investigators have inquired as to whether ICD therapy might be foregone at the time of CRT implant for patients with non-ischemic cardiomyopathy and no previous history of ventricular arrhythmias. Recent observational work has suggested no difference in survival for non-ischemic patients undergoing CRT-P versus CRT-D [38]. The potential role of a CRT-P only strategy in patients with non-ischemic cardiomyopathy warrants prospective evaluation.

Finally, several medical comorbidities have been shown to be associated with decreased CRT efficacy including the presence of chronic renal insufficiency [39, 40], pre-capillary pulmonary hypertension [41], and non-revascularizable coronary artery disease [42, 43]. A recent sub-analysis of the MADIT-CRT study confirmed a relationship between increasing comorbidity burden and attenuated LV reverse remodeling, although the burden of comorbidity did not seem to impact the overall clinical benefits of CRT [44•].

## Treatment

### Pharmacologic

- Patients being considered for CRT should be treated with guideline-recommended goal-directed medical therapy for heart failure and left ventricular dysfunction [45] including treatment with  $\beta$ -blockers as well as renin-angiotensin-aldosterone system antagonists such as angiotensin-converting enzyme (ACE) inhibitors and mineralocorticoid receptor antagonists (MRA).

### Interventional procedures

#### Intra-procedural strategies

- The standard approach to implantation of the left ventricular lead during CRT is to target the lateral or posterolateral branch of the coronary sinus veins. As detailed above, this strategy reflects the expected pattern of electrical dyssynchrony in patients with a LBBB. Previous studies have shown that placement of the LV lead can be constrained by absence of available venous branches, and the response to CRT can often be variable even in this traditional anatomic location [46]. This heterogeneous response may reflect variations in electrical dyssynchrony related to the underlying myocardial substrate, the distribution of ventricular scar, as well as RV pacing-induced changes in LV activation. Post hoc analysis of the MADIT-CRT study showed that placement of the LV lead in an apical position was associated with an increased risk of worse clinical outcome [47], and we believe that in general, pacing from an apical LV lead position should be avoided (noting that the critical aspect is the location of the LV electrode selected for pacing, rather than the tip of the LV lead).
- Other strategies for LV lead targeting include positioning of the LV lead at the site of latest electrical or mechanical activation [48, 49] or employing lead positions which maximize hemodynamic improvement [50]. During implantation of the LV lead, electrical delay can be standardly assessed by assessing the delay between the surface QRS and the initial sensed LV lead electrogram (Q-LV) [51]. Lead placement at sites of increasing QLV is

associated with greater rates of LV reverse remodeling and improvement in patient symptoms [51, 49]. The ongoing ENHANCE-CRT study (NCT01983293) is evaluating the efficacy of a QLV-based strategy in patients with non-LBBB undergoing CRT [52].

- Other considerations at the time of LV lead implantation include avoiding LV lead targeting at areas of LV scar as this has been associated with poor response to CRT [42]. The routine role of pre-procedure LV imaging to guide LV lead implantation (e.g., to evaluate underlying LV scar) remains unknown.
- Given limitations of coronary venous anatomy, contemporary LV leads now commonly employ multi-polar (quadripolar) LV lead pacing capabilities, employing a distal tip electrode and three ring electrodes. These quadripolar leads can be programmed to yield numerous possible pacing vectors and as such could theoretically overcome some of the limitations of lead stability and anatomy associated with standard bipolar LV leads. The selection of optimal pacing vector is often guided by the greatest narrowing of the QRS complex or maximizing the electrical delay at the LV pacing electrode. The recent MORE-CRT trial (NCT01510652) was a randomized comparison of standard bipolar CRT and quadripolar CRT in 1078 patients. Quadripolar pacing was associated with reduced LV lead-related events including lead instability, phrenic nerve stimulation, elevated pacing threshold, or dislodgement.
- In addition to increased flexibility of pacing vectors, quadripolar LV leads additionally offer the ability for multi-site or multi-point pacing (MPP), when placed with MPP-compatible generators. The ability to pace from multiple sites yields a larger wavefront that may improve resynchronization over standard biventricular pacing [53]. Recent studies have reported improvement in acute hemodynamic response and short-term LV reverse remodeling with an MPP strategy compared to standard biventricular pacing [54, 55]. Ongoing studies including the MultiPoint Pacing in CRT trial (NCT01786993) [56] and the MORE-CRT MPP study, NCT02006069) [57], are examining the role of MPP in patients undergoing CRT, including its use at the time of implant as well as in patients who demonstrate non-response to standard biventricular pacing.

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## Optimization algorithms and strategies

- Previous studies in patients with atrio-ventricular pacemakers demonstrated that optimization of the atrio-ventricular delay can improve cardiac hemodynamics [58, 59]. In patients undergoing CRT, options for such atrio-ventricular optimization include echocardiographic-based optimization (i.e., using mitral inflow patterns) [60] or use of intrinsic device algorithms which integrate native A-V conduction [51, 61, 62]. Randomized studies of routine A-V optimization have not shown significant benefit [51, 61, 62], whereas such optimization may be of clinical use in patients demonstrating non-response [8]. Similarly, optimization of inter-ventricular timing has also been shown to improve hemodynamic response in patients undergoing CRT [63, 64]. While routine V-V optimization using either echocardiographic or intrinsic device algorithms has not

shown benefit when applied routinely [59, 63, 62], such optimization may be most helpful in patients with heterogeneous LV activation patterns (e.g., LV scar from prior myocardial infarction). At least one previous study identified a clinical benefit to V-V optimization in CRT patients with ischemic as opposed to non-ischemic etiologies to cardiomyopathy [65].

- An emerging investigational optimization algorithm has been the use of contractility sensors embedded in the right atrial lead to guide optimization of A-V and V-V timing (e.g., the SonR system). In the RESPOND-CRT (SonR tip lead and automatic AV-VV optimization algorithm in the paradigm RF SonR) study, 998 patients were randomized to a contractility-based optimization algorithm versus standard echocardiographic optimization of A-V and V-V timing. At 12 month follow-up, there was a marginal but significantly higher rate of clinical response in the SonR arm compared to the echocardiographic optimization arm (75 vs. 70%).
- As most patients undergoing CRT have normal right ventricular synchrony, recent device algorithms have attempted to facilitate intrinsic RV activation by timing LV-pacing to the sensed RV electrogram. The AdaptCRT algorithm (Medtronic Inc., Fridley, MN) is one such algorithm which has been shown to decrease RV pacing by nearly 44% [66] and was associated with improved clinical outcomes when compared to standard echocardiography-optimized biventricular pacing [67]. The ongoing AdaptResponse study (NCT02205359) will be a randomized comparison of the AdaptivCRT algorithm versus conventional CRT and evaluate clinical endpoints including all-cause mortality and HF events [68].

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## Post-implant care and remote monitoring

- Contemporary implantable devices, including CRT implants, offer the ability to remotely measure a range of patient and device parameters including information regarding biventricular pacing percentage, patient activity, trans-thoracic impedance, and atrial or ventricular arrhythmias. In the recent MORE-CARE study, patients undergoing CRT were randomized to remote monitoring versus standard in-office evaluation [69]. Over a median follow-up of 2 years, remote monitoring was associated with significant decreased use of healthcare resources but no difference in clinical outcomes including all-cause mortality or cardiovascular hospitalization.
- Previous studies have suggested that a higher biventricular pacing percentage is associated with improved clinical outcomes, with at least one real-world study suggesting that biventricular pacing percentage > 98% was associated with improved survival [70]. Reasons for suboptimal biventricular pacing include the presence of atrial tachyarrhythmias (most commonly atrial fibrillation), inappropriately programmed sensed, and paced atrio-ventricular intervals, and premature ventricular contractions [71]. Appropriate recognition of these common mechanisms of suboptimal biventricular pacing is a key component to post-implant care.
- Multidisciplinary care for the CRT patient is a critical component to improving clinical outcomes. Such care offers the opportunity to integrate expertise from electrophysiology, advanced heart failure, and cardiac



imaging. In our experience, this multidisciplinary approach was associated with improved clinical outcome when compared to standard clinical follow-up [72].

## Surgery

- In patients for whom left ventricular lead placement via an endovascular approach cannot be achieved, LV leads can be implanted via a surgical epicardial approach [73]. A recent small randomized controlled trial of standard trans-venous versus epicardial LV lead placement for patients undergoing CRT [74] showed no clinical or LV reverse remodeling benefit to an upfront epicardial LV lead implant strategy. We believe that such an approach should be generally restricted to patients who have either failed an endocardial LV lead implant attempt or patients who qualify for CRT and are undergoing cardiothoracic surgery for another indication.

## Emerging therapies

### Endocardial LV pacing

- Given the potential challenges of trans-venous LV lead implantation including limitations of coronary sinus anatomy, high LV pacing threshold and/or phrenic nerve capture, there has been considerable interest in the role of an endocardial LV lead strategy in patients eligible for CRT [75, 46]. Pacing the LV endocardium reflects a more rapid and physiological activation of the left ventricle as compared to standard epicardial LV pacing, and previous studies have identified greater acute hemodynamic improvements with endocardial versus conventional LV pacing [76]. The ALSYNC (Alternate Site Cardiac Resynchronization) study demonstrated both safety and efficacy of LV endocardial pacing patients who either demonstrated CRT non-response or in for whom LV lead placement was not technically possible [77]. LV endocardial pacing in this study was associated with clinical and echocardiographic improvement in two-thirds of patients. It should be noted that anticoagulation was required in this study given permanent LV endocardial leads, and that thromboembolic events were detected in some patients in this study despite anticoagulation.
- The WiSE-CRT (EBR Systems, Sunnyvale, CA) system employs a pacing system using a small leadless ultrasound-based electrode placed into the LV endocardial surface [75]. In the recent SELECT-LV (Safety and Performance of Electrodes implanted in the Left Ventricle) study, 35 patients who had failed conventional CRT underwent successful implant in 97% of cases [78••]. At 6 months, approximately two-thirds of patients demonstrated LV reverse remodeling (improved LVEF  $\geq 5\%$ ) and 85% of patients demonstrated an improvement in clinical composite score. The soon to enroll SOLVE-CRT (Stimulation of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders and

Previously Untreatable Patients) study (NCT02922036) will be the first randomized comparison of an endocardial LV pacing strategy in CRT non-responders or those in whom a standard trans-venous LV lead implantation was not feasible.

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## His bundle pacing

- His bundle pacing (HBP) represents a theoretically ideal site for ventricular pacing as it retains activation of the intrinsic electrical conduction system [79]. Several limited case series have suggested that HBP may lead to resynchronization in CRT-eligible patients with LBBB [80••]. For example, in a recent series of 21 patients eligible for CRT, HBP was successfully implanted in 16 with evidence of electrical resynchronization (i.e., narrowing of QRS duration) in 76% and LV reverse remodeling overall (improved LVEF and decreased LV dimensions), although not all studies of HBP have demonstrated this high a rate of QRS narrowing in LBBB patients. The ongoing His-SYNC (His Bundle Pacing versus Coronary Sinus Pacing for Cardiac Resynchronization Therapy, NCT02700425) will be the first randomized comparison of HBP versus standard coronary sinus LV lead implantation in CRT-eligible patients. HBP is a clear alternative to traditional CRT in patients with a narrow QRS but AV block in which a narrow QRS can be maintained with HBP.

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## Integrated multisensor algorithms

- The recent MultiSENSE (Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients) study examined the clinical impact of a multi-modal sensor strategy combining heart sounds, respiration, thoracic impedance, heart rate, and activity [81•]. Over a 1 year follow-up, the multi-sensor algorithm (HeartLogic) was able to identify a HF event with a lead time of 34 days. The routine use of such multi-modal sensor strategies to identify 'at-risk' CRT patients remains a point of future investigation.

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## Conclusion

In appropriately selected patients with heart failure and electrical dyssynchrony, CRT improves survival beyond standard goal-directed medical therapy. Important considerations in patient selection include the pattern and magnitude of electrical dyssynchrony, etiology of cardiomyopathy, as well as the presence of atrial arrhythmias and other medical comorbidities which may attenuate clinical response to CRT. Intra-procedural strategies that may optimize the delivery of CRT include targeting of the LV lead to sites of maximal electrical delay as well as the use of multi-site LV pacing. Post-implant considerations include the targeted use of atrio-ventricular and interventricular optimization, avoidance of right ventricular pacing, recognition and treatment of suboptimal biventricular pacing, and management by a multi-disciplinary cardiovascular care team. Emerging therapeutic strategies for patients who are

candidates for CRT include the use of endocardial LV pacing, His bundle pacing, multi-point pacing strategies, and the integration of multi-modal remote monitoring into clinical care.

## Compliance with Ethical Standards

### Conflict of Interest

Neal A. Chatterjee declares no potential conflicts of interest.

E. Kevin Heist reports personal fees from Boston Scientific, grants and personal fees from Biotronik, grants and personal fees from St. Jude Medical, personal fees from Medtronic, grants from LivaNova, outside the submitted work. In addition, Dr. Heist has a patent Patented LV lead pacing design issued.

### 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.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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