

REVIEW TOPIC OF THE WEEK

# 20 Years of Cardiac Resynchronization Therapy



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## ABSTRACT

Cardiac resynchronization therapy (CRT) is an accepted treatment for patients with heart failure (HF), impaired left ventricular (LV) function, and a wide QRS complex. It has been revolutionary for patients with advanced HF whose only previous option was cardiac transplantation, and it is now a realistic option for patients with mild HF. The development of CRT also has united the previously disparate cardiological subspecialties of electrophysiology and HF. This review, written on the occasion of the 20th anniversary of the first clinical use of CRT for HF, takes a historical perspective on CRT's evolution from "bench to bedside." We also comment on the task faced by electrophysiologists and HF specialists as they make this life-saving therapy available to an increasing number of eligible patients. (J Am Coll Cardiol 2014;64:1047-58) © 2014 by the American College of Cardiology Foundation.

Cardiac resynchronization therapy (CRT) is an accepted treatment for patients with heart failure (HF), impaired left ventricular (LV) function, and a wide QRS complex. This therapy has been no less than revolutionary for patients with advanced HF whose only previous option was cardiac transplantation. Now, CRT is also a realistic option for patients with mild HF.

The recognition in 1925 that conduction disturbances lead to LV dysfunction (1) can be traced to experiments that provided the paradigm for CRT. Pacemaker technology, designed to correct interventricular (VV) and intraventricular conduction disturbances, was eventually tested in randomized, controlled CRT trials, driven by engineers, clinicians, and the industry. In addition to transforming patient care, CRT has united the fields of electrophysiology and HF, once far-removed cardiological subspecialties.

This year marks the 20th anniversary of the first clinical use of CRT for HF (2,3). In this historical review, we review the evolution of CRT, from "bench to bedside." We also comment on the task faced by

electrophysiologists and HF specialists as they make this life-saving therapy available to an increasing number of eligible patients.

## THE PRE-CRT ERA: BUILDING THE PARADIGM

In 1925, Wiggers (1) showed that surface stimulation of the canine myocardium reduced the maximal LV pressure derivative (LV  $dp/dt_{max}$ ) and lengthened isometric contraction. He proposed that this effect and the degree of "asynchrony" depend on how much myocardium is activated before excitation of the Purkinje system.

When regional wall function became quantifiable with radionuclide ventriculography in the 1980s, Grines et al. (4) described how a left bundle branch block (LBBB) reduced the diastolic filling time and the septal contribution to LV ejection. By the 1990s, a link emerged between electrical dyssynchrony and LV function, in which conducting tissue disturbances give way to conduction through the slower conducting myocardium (Figure 1), wasted work, and a reduction

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## ABBREVIATIONS AND ACRONYMS

**AF** = atrial fibrillation

**AV** = atrioventricular

**CMR** = cardiac magnetic resonance

**CRT-D** = cardiac resynchronization therapy-defibrillation

**CRT-P** = cardiac resynchronization therapy-pacing

**HF** = heart failure

**ICER** = incremental cost-effectiveness ratio

**ICD** = implantable cardioverter-defibrillator

**LBBB** = left bundle branch block

**LV** = left ventricular

**LVEF** = left ventricular ejection fraction

**NYHA** = New York Heart Association

**OPT** = optimal pharmacological therapy

**RV** = right ventricular

**Vo<sub>2</sub>** = oxygen uptake

**VV** = interventricular

in cardiac output (5). In this construct, inappropriate atrioventricular (AV) delays lead to delayed systole and reduced diastolic filling. Consequently, LV diastolic pressures exceed atrial pressure and diastolic mitral regurgitation. A decrease in LV preload then reduces contraction via the Starling mechanism. Systolic mitral regurgitation also occurs as a result of mitral valve ring dilation, LV remodeling, and papillary muscle dyssynchrony. Other, more recently described effects of CRT are shown in [Figure 2](#).

## EARLY CRT STUDIES: PROOF OF CONCEPT

By the 1990s, it was apparent that LV pacing was more hemodynamically favorable than right ventricular (RV) pacing, but there was little interest in abandoning the traditional pacing site. Befeler et al. (6) first described temporary, simultaneous biventricular pacing to assess arrhythmias. In 1983, de Teresa et al. (7) first reported sequential AV pacing of the left ventricle in patients with AV block and LBBB, and without HF. Key findings were that simultaneous septal and LV free wall contraction was hemodynamically superior to dyssynchronous contraction and that the best hemodynamic effect arose from fusion

between intrinsic LBBB conduction and the LV pacing stimulus.

In 1987, Mower devised and was granted a patent for the concept of “biventricular pacing,” explicitly aimed at HF treatment. Mower conceived biventricular pacing as a method of pacing both ventricles after a predetermined AV interval. Two electrodes would be connected in series, 1 in the right ventricle and another around the LV free wall. Bakker’s group (8) subsequently used a dual-chamber pacemaker with a Y adapter to treat 12 patients with HF. This case series (8), which began in 1993, showed that biventricular pacing improved functional capacity and LV function. Cazeau et al. (3) subsequently described a 4-chamber pacing system that reduced pulmonary capillary wedge pressure and increased cardiac output. This group (9) later described a wholly transvenous CRT implantation that, coupled with the innovative over-the-wire technique of Auricchio et al. (10), began a new era for CRT.

In 1995, Leclercq et al. (11) showed that, compared with AAI pacing, CRT-pacing (CRT-P) led to an increase in cardiac index and a reduction in pulmonary capillary wedge pressure. Auricchio et al. (12) subsequently

demonstrated that patient-specific AV delay variations led to changes in LV  $dP/dt_{max}$  and aortic pulse pressure. The recognition of patient-specific variations in response to CRT (13) is key to the current AV optimization debate and to the influence of QRS duration and morphology on the response to CRT.

## THE CORE TRIALS

In 2001, the safety and efficacy of CRT were first addressed by both the MUSTIC (Multisite Stimulation in Cardiomyopathies) (14) and PATH-HF (Pacing Therapies in Congestive Heart Failure) studies (15). In the MUSTIC study, 67 patients with HF were randomized to 3 months of off or on CRT. Compared with CRT-off, CRT-on improved walking distance, quality of life, and peak oxygen uptake ( $Vo_2$ ). In the PATH-HF study (15), improvements in walking distance and peak  $Vo_2$  were observed after 12 months of biventricular pacing. It was the first study to show LV reverse remodeling after CRT. In the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study (16), the first double-blind CRT trial, 453 patients with HF were randomized to CRT-P or to no pacing. At 6 months, CRT-P improved walking distance, quality of life, exercise capacity, left ventricular ejection fraction (LVEF) and peak  $Vo_2$ , paralleling LV reverse remodeling.

By the 2000s, secondary prevention trials began to show a benefit of implantable cardioverter-defibrillator (ICD) therapy in patients with impaired LV function. Eight landmark primary prevention trials demonstrated that ICDs improved survival (17). The case for the use of ICDs in primary prevention was evident.

The addition of CRT to ICD (CRT-defibrillation [CRT-D]) was first explored by the MIRACLE-ICD (Multicenter InSync ICD Randomized Clinical Evaluation) study (18), in which patients with HF receiving optimal pharmacological therapy (OPT) underwent CRT-D and were randomized to CRT on or off. After 6 months, CRT-D led to improved quality of life and NYHA functional class, but not walking distance. Essentially, CRT-D led to clinical improvements without safety concerns.

The COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) trial (19) was the first trial to compare CRT-P and CRT-D with OPT. Compared with OPT, CRT-P and CRT-D led to a 20% reduction in death or hospitalization from any cause. Total mortality was least with CRT-D, and no benefit emerged for CRT-P. The incremental benefit of adding ICD to CRT was apparent. However, in a substudy of the COMPANION study, neither CRT-P

nor CRT-D reduced all-cause mortality in NYHA functional class IV patients (20).

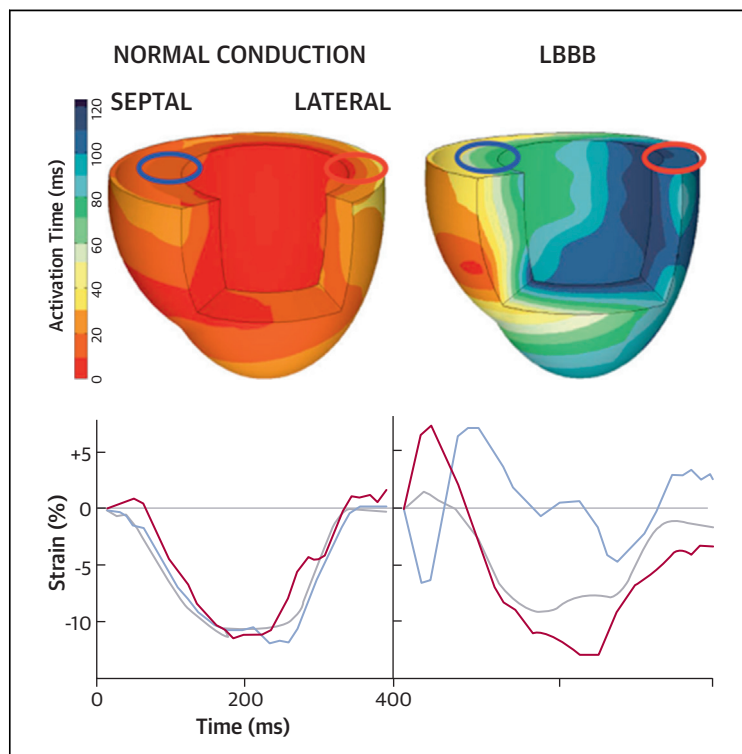
The CARE-HF (Cardiac Resynchronization-Heart Failure) study (21), which randomized patients to OPT with or without CRT-P, showed that CRT-P reduced death from any cause or unplanned hospitalizations for major cardiovascular events, as well as total mortality after 29 months. In addition, CRT-P improved quality of life and LVEF, induced LV reverse remodeling, and reduced mitral regurgitation.

The COMPANION trial (19) and the CARE-HF study (21) established CRT as a treatment for HF (NYHA functional class III or IV), impaired LV function, and a wide QRS complex. Although the characteristics of device-treated patients were similar, the control group was ICD plus OPT in the COMPANION trial and OPT only in the CARE-HF study. This may account for the apparently lower efficacy of CRT-P in the COMPANION trial. Although some would argue on the basis of the COMPANION trial that the treatment effect of CRT-D is superior to that of CRT-P, others propose that a definitive comparison is still required because CRT-D and CRT-P were not compared.

## CRT IN MILD HF

The efficacy of CRT-D in mild HF was suggested by the CONTAK CD study, which demonstrated LV reverse remodeling across NYHA functional classes II to IV (22). In the MIRACLE ICD II study (23), which included patients in NYHA functional class II, CRT-D induced LV reverse remodeling compared with ICD. Subsequently, in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) (24), which randomized 1,820 patients in NYHA functional class I and II to CRT-D or ICD, CRT-D reduced total mortality or HF events by 34%. This endpoint was mainly driven by reductions in HF events, with no difference in total mortality.

In the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) study (25), 610 patients in NYHA functional class I/II with primary prevention ICD indications were randomized to CRT-on or CRT-off. Compared with CRT-off, CRT-on did not reduce composite HF endpoints, nor did it improve quality of life or walking distance, but it improved LVEF and reduced HF hospitalizations. A similar study, the RAFT (Resynchronization/Defibrillation for Ambulatory Heart Failure Trial) (26), compared CRT-D with ICD in NYHA functional class II or III patients. The primary endpoint of total mortality or HF hospitalization occurred in 33.2% in the CRT-D group and in 40.3% in the ICD group (hazard ratio: 0.75; 95% confidence interval: 0.64 to 0.87).



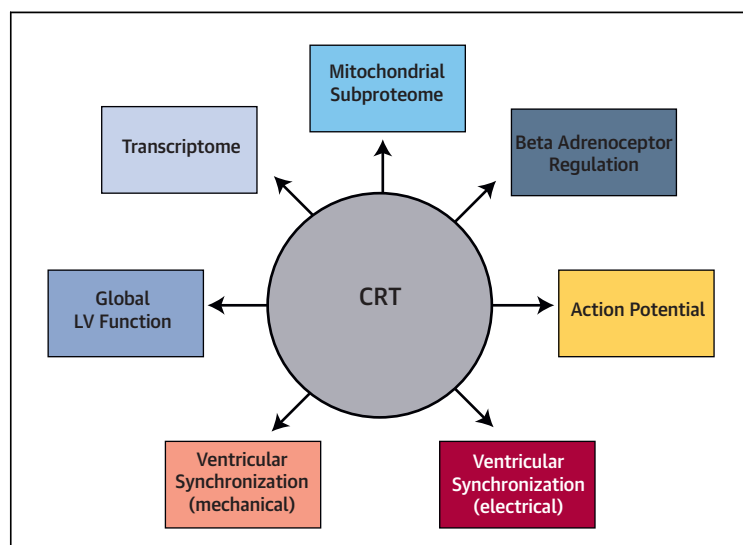
**FIGURE 1** Mechanical Effects of LBBB

Three-dimensional representation of ventricular activation (**top**) and strain (**bottom**) during normal activation and left bundle branch block (LBBB) in a canine heart showing how early septal activation (**blue circles**) leads to early shortening (**blue tracing**) and late lateral wall activation (**red circle**) leads to stretching in early systole followed by shortening during the ejection phase. **Gray tracings** denote mean left ventricular strain. Adapted with permission from Prinzen et al. (86) and derived from De Boeck et al. (87) and Mills et al. (88).

The failure of the MADIT-CRT and the REVERSE study to demonstrate an independent effect on mortality reflects the low background mortality (2% to 3%) in NYHA functional classes I and II. However, in both trials, CRT led to LV reverse remodeling and a 41% to 53% reduction in HF events. Additionally, the 5-year follow-up of the REVERSE study showed a remarkably low mortality (annualized 2.9%) in patients randomized to CRT-on (27). Together with the RAFT (26), these findings provide compelling evidence for CRT in early stages of HF.

## CRT AND RIGHT VENTRICULAR PACING

It has long been shown that HF is common during RV pacing. In the DAVID (Dual Chamber and VVI Implantable Defibrillator) trial (28) and the MOST (MMode Selection Trial) (29), RV pacing was associated with increased HF hospitalizations, lending support for using CRT in patients with LV dysfunction and conventional indications for pacing (30). In



**FIGURE 2 Effects of CRT**

Cardiac resynchronization therapy (CRT) has an impact on the following. 1) Transcriptome in dyssynchronous heart failure (DHF): there is increased regional heterogeneity in gene expression within the left ventricle that is reduced with CRT (47). 2) Mitochondrial subproteome: CRT also leads to mitochondrial protein changes such as increased pyruvate carboxylation and branched-chain amino acid oxidation, increasing the pool of Krebs cycle intermediates and fuel oxidative phosphorylation (89). 3) CRT also improves rest and beta-adrenergic-stimulated myocyte function and calcium handling, up-regulating beta-1 receptors and adenylate cyclase activity and suppressing G<sub>i</sub>-coupled signaling (90). 4) Action potential: the action potential duration in DHF is more prolonged in the lateral than in the anterior wall, and this effect is reduced by CRT, particularly in the lateral wall (91). 5) Ventricular synchronization: CRT induces a pattern of activation different from a left bundle branch block, with the right ventricular activation proceeding from apex to base. The base of the right ventricle and of the interventricular septum is activated later than in a left bundle branch block, whereas the left ventricular (LV) free wall is activated early (92). 6) Ventricular synchronization (mechanical): DHF involves disparities in the timing of shortening and reciprocal shortening/stretch in the anterior and lateral LV walls, which are corrected by CRT (90). 7) Atrioventricular (AV) synchronization: when the left ventricle is pre-excited with pacing, the start of pressure development in the left ventricle occurs earlier. Shortening of an inappropriately long AV delay by CRT increases pulse pressure and LV  $dP/dt_{max}$ . An optimal pulse pressure occurs when peak left atrial systole coincides with the start of LV contraction (13). 8) The final common pathway of these actions is to alter the LV pressure-volume relationship. A leftward shift in pressure-volume loops reflects reverse remodeling (93).

BLOCK-HF (Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block) (31), 691 patients with HF and conventional indications for pacing were randomized to CRT or RV pacing. After 37 months, CRT was associated with a 26% reduction in the primary composite endpoint of total mortality, urgent HF care, or an increase in LV end-systolic volume. Despite its limitations, this study supports CRT over conventional RV pacing in patients with LV dysfunction. More definitive evidence is expected from the BIOPACE (Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization) study (32).

## CRT IN ATRIAL FIBRILLATION

In atrial fibrillation (AF), CRT can only correct VV and intraventricular dyssynchrony. CRT delivery is also hampered by high intrinsic ventricular rates and irregularity, leading to reduced capture, fusion, and pseudofusion. Whether CRT is effective in the context of AF is an important issue, as it occurs in up to 25% of patients with HF in New York Heart Association (NYHA) functional classes II and III and in up to 50% of patients in NYHA functional class IV (33).

Some studies have shown that CRT in AF improves symptoms (34,35), whereas others have suggested that it is only effective after AV junction ablation. In the largest observational study to date, Gasparini et al. (36) explored the outcome of CRT, in combination with either ablation or rate-slowing drugs, in patients with permanent AF. Over a median follow-up of 37 months, patients receiving AF + ablation had risks of total and cardiac mortality comparable to those of patients in sinus rhythm, whereas AF patients treated with drugs had worse outcomes. Randomized data on the effects of CRT in patients with AF are lacking.

## CRT AND A NARROW QRS COMPLEX

The finding of mechanical dyssynchrony in patients with a QRS duration <120 ms (37) provided a rationale for extending CRT to this patient population. Several single-center studies showed a symptomatic benefit from CRT (38-40). However, the 2 most recent multicenter, randomized, controlled studies, LESSER-EARTH (Evaluation of Resynchronization Therapy for Heart Failure) trial (41) and EchoCRT (Echocardiography Guided Cardiac Resynchronization Therapy) (42), failed to show a mortality benefit from adding CRT to ICD in this patient group. In LESSER-EARTH, CRT did not improve clinical outcomes or induce LV reverse remodeling. Indeed, there was a suggestion of potential harm. In Echo-CRT (42), patients with a QRS duration ≤130 ms, LVEF ≤35%, and mechanical dyssynchrony underwent CRT-D implantation and were then randomized to CRT-on or -off. The trial was stopped prematurely for futility after finding increased mortality with CRT-D.

## DEVICE OPTIMIZATION

The basis for device optimization is the discovery that LV function varies according to AV delays (12). Traditionally, echocardiography is used to identify the AV delay yielding optimal LV filling. However, because this technique requires exhaustive, iterative sampling, busy departments have (not surprisingly) abandoned AV and VV optimization. In practice, the

operator finds the highest response for each programming iteration. Although pragmatic and practical, this is methodologically unsound. We should also consider that, although regarded as a gold standard, echocardiographic optimization has not been shown to improve outcomes, but appears as effective as nominal device settings (43). Other proposed surrogates of response, such as changes in LV dP/dt after CRT do not predict outcome (44).

Automatic, device-based AV and VV optimization has obvious practical advantages. The FREEDOM (Frequent Optimization Study Using the QuickOpt Method) (45) compared device-based AV/VV optimization using the QuickOpt algorithm with echocardiographic optimization. In this study, QuickOpt was inferior to echocardiography. In the Smart-AV (Comparison of AV Optimization Methods Used in Cardiac Resynchronization Therapy) study (43), AV optimization by the Smart-AV algorithm did not lead to LV reverse remodeling compared with nominal settings. Adaptive CRT is based on an algorithm that provides automatic selection between synchronized LV or bi-ventricular pacing, as well as AV and VV optimization. Although the Adaptive CRT (Adaptive Cardiac Resynchronization Therapy) study showed that the algorithm was comparable to echocardiographic optimization (46), it is unclear whether this benefit is attributable to AV/VV optimization or to the pacing mode.

## NONRESPONDERS

The concept of CRT nonresponders emerged from the demonstration that 33% of patients did not exhibit a hemodynamic response (11). We may ask, however, why we need to measure individual response. After all, we do not do so in the case of medical therapy or after operations. For example, the success of a coronary artery bypass operation is not defined in terms of long-term outcome. In fact, in most medical interventions, the approach is to treat a population so as to achieve an average treatment effect, even though some patients do not respond. This may be due to inescapable genetic factors (47). In this context, we should consider that drugs with proven prognostic benefits do not necessarily improve symptoms. Using the definition of response as an improvement by  $\geq 1$  NYHA functional classes in HF, the nonresponder rate is 53.3% for enalapril (48), 79% for bisoprolol (49), and 59% for spironolactone (50).

One difficulty in assessing a prognostic response is the lack of an adequate surrogate. In this respect, LV reverse remodeling is a potential candidate because it predicts cardiovascular mortality with a sensitivity of

87% and a specificity of 69% (51). Although this may seem statistically acceptable, some patients could be wrongly classified as prognostic nonresponders. Importantly, LV reverse remodeling does not predict a symptomatic response (51).

Other proposed surrogates are more troublesome. Peak  $\dot{V}O_2$  only weakly predicts mortality in HF, and the cutoff for predicting survival has not been defined (52). Moreover, it correlates poorly with symptoms and not at all with quality of life (53). In contrast, natriuretic peptides predict the outcome of CRT, but intraindividual variations are high, even in healthy individuals. Such “noise” limits their use in clinical management.

Reduced response to CRT is seen with increasing scar burden (54), posterolateral (55) and mid-wall (56) scar location, and extreme mechanical dyssynchrony (57). Comorbidities such as severe RV dysfunction, pulmonary hypertension, end-stage renal failure, and valvular disease also appear to diminish response. Importantly, because none of these factors have been assessed in relation to OPT control patients, we cannot ascertain whether they completely negate the effects of CRT. We should also consider that preventing deterioration also amounts to a response, but this has never been quantified. On the other hand, female sex (58,59) and a nonischemic HF etiology (56) are associated with better CRT outcomes.

## THE ROLE OF IMAGING

**DYSSYNCHRONY IMAGING.** The finding that mechanical resynchronization paralleled a benefit from CRT formed the basis for dyssynchrony assessment in patient selection. Many echocardiographic measures of mechanical dyssynchrony once held promise as predictors of response to CRT in single-center studies. Their utility was then tested by the PROSPECT (Predictors of Response to CRT) trial (60). Even after validation by blinded core laboratories, no echocardiographic measure of dyssynchrony could reliably predict the response to CRT. Negative evidence also comes from the recent EchoCRT study, which failed to show a benefit from CRT-D in patients with QRS duration  $\leq 130$  ms and dyssynchrony assessed echocardiographically (42). Accordingly, all clinical guidelines have abandoned echocardiographic measures of dyssynchrony.

Mechanical dyssynchrony also can be measured using cardiac magnetic resonance (CMR). Myocardial “tagging” is the most powerful technique for the study of myocardial motion in humans, but it is laborious, time-consuming, and not clinically applicable. Although CMR-derived measures of mechanical



dyssynchrony appear to predict the outcome of CRT (57), they have not been externally validated.

There remains something fundamentally elusive about using mechanical dyssynchrony in predicting the response to CRT. In this respect, mechanical dyssynchrony is not only due to conduction disturbances, but also to other myocardial wall properties, such as perfusion, viability, and passive motion due to tethering by neighboring myocardial segments within an extraordinarily complex architecture of myocardial fibers. As a methodological limitation, mechanical dyssynchrony measures generally reflect the temporal dispersion of cardiac events, but not their magnitude or hemodynamic effects.

**IMAGING TO GUIDE LV PACING.** Although dyssynchrony imaging may not have a role in patient selection, it may be useful in LV lead deployment. As discussed in the following, the TARGET (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy) study (61) and STARTER (Speckle Tracking Assisted Resynchronization Therapy for Electrode Region) trial (62) suggested that targeting late-activated segments using echocardiography may improve outcomes. Imaging of the coronary veins by computed tomography may also be useful in guiding implantation. On the other hand, CMR can be used to guide LV leads away from scars (63). A role for electroanatomic and ECG body surface mapping is also emerging. Image fusion could allow real-time, multimodality targeting of LV pacing sites. Computational modeling (64) could predict the effects of different pacing sites in individual patients.

**SCAR BURDEN.** CMR (65,66) and nuclear imaging (54) studies have shown that scar burden is higher in nonresponders than in responders (65,66). So far, however, the critical cutoff for scar burden has not been identified or validated.

## HEMODYNAMICS AND RESPONSE

Conceptually, an acute hemodynamic response should predict the outcome of CRT. In a recent study, the change in LV  $dp/dt_{max}$  at the time of CRT implantation predicted LV reverse remodeling (67). The absolute change was small and, arguably, difficult to use in clinical practice. Other studies have shown that it is not the change in LV  $dp/dt_{max}$  with CRT, but the absolute pre-implantation value that predicts outcome (44). This, however, has not been externally validated.

## QRS COMPLEX AND RESPONSE

With respect to the lower cutoff of QRS duration, a meta-analysis of individual patient data from major

CRT trials confirms a survival benefit at a QRS duration  $>140$  ms, with less clear benefit between 120 and 140 ms (68). In a post-hoc analysis of the REVERSE study (69), clinical response correlated positively with QRS duration beyond 120 ms (Central Illustration). The arbitrary cutoff of a QRS duration  $\geq 120$  ms chosen by landmark trials (19,21,26,70) is cunningly close.

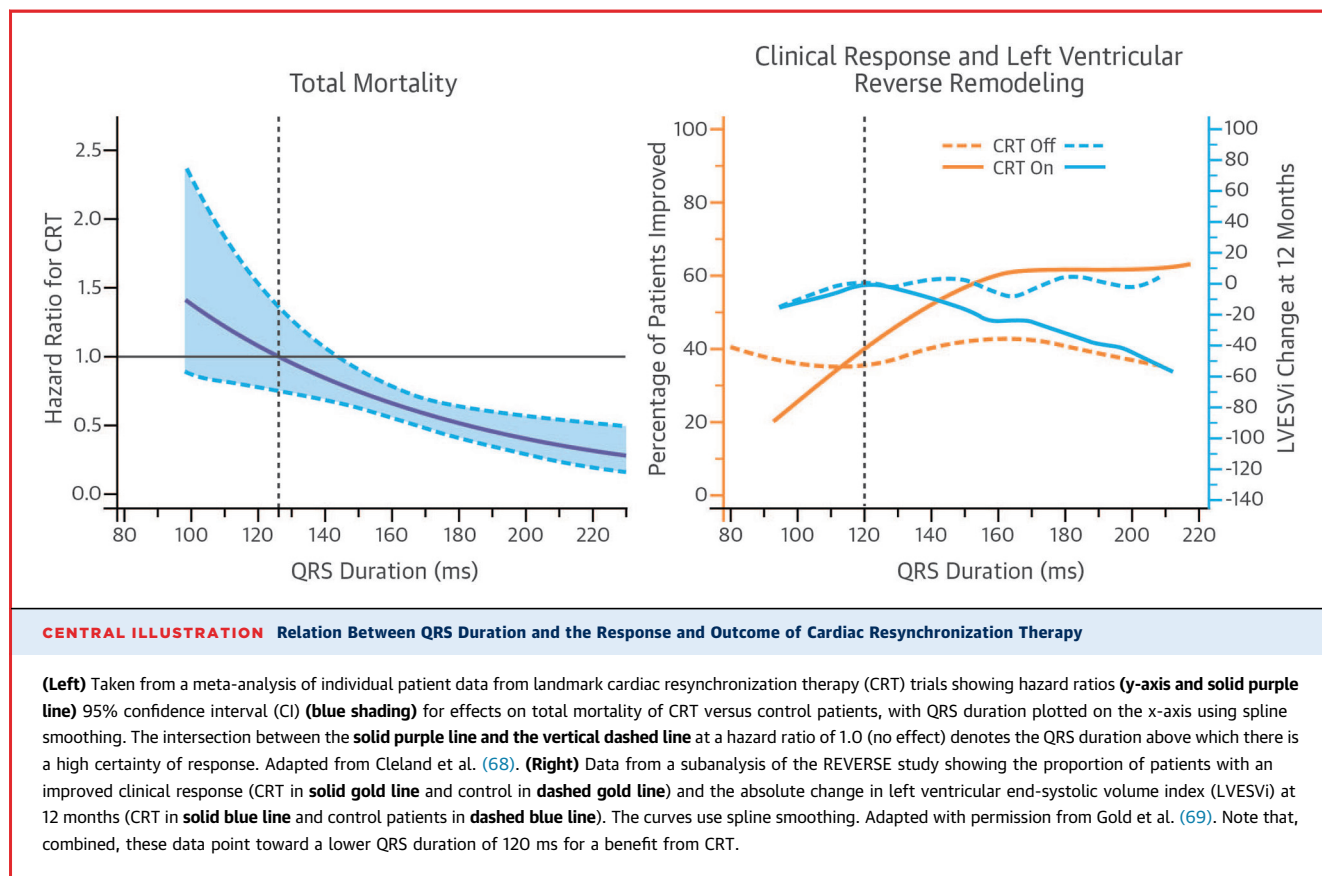
Post-hoc analyses of both the REVERSE (69) and MADIT-CRT (71) studies suggested a reduced benefit in patients with non-LBBB QRS morphology. However, a meta-analysis of individual patient data from CRT trials has shown that LBBB morphology is not an independent predictor of outcome (68). Notwithstanding, current guidelines adopt LBBB as the primary substrate for CRT.

## TARGETING THE LV PACING SITE

The wholly transvenous technique for CRT implantation remains virtually unchanged since it was first described in 1994 (9). Most implanters are satisfied with a good angiographic result, that is, a posterolateral position with acceptable pacing parameters and no diaphragmatic stimulation. In some studies, however, the position of the LV lead over the LV free wall, avoiding anterior or inferior positions, does not influence outcome of CRT (72), whereas in others, an apical position appears less favorable (73).

Even when the LV lead is deployed in a “good” fluoroscopic position, the response is variable. This is, perhaps, not surprising because fluoroscopy is opaque to properties of the myocardium that govern the LV pacing response. A concept has evolved according to which targeting segments of latest LV “activation” improves response. The STARTER trial (62) showed that deploying LV leads in late-activated segments reduced the risk of death or HF hospitalization. However, exact concordance between late-activated segments and LV lead position was achieved in only 30% of patients. Furthermore, segments with likely scar were regarded as missing data. Therefore, we cannot ascertain whether these results were influenced by avoiding scar or by targeting late-activated segments.

Viability in the paced LV segment could also influence the CRT outcome. In this regard, pacing scar is associated with a worse response (66,74) than pacing viable myocardium. Increasing scar transmural (66) and scar density (54) also portend a worse response. Use of CMR to avoid scar appears to improve the response to CRT (63), but this strategy has not been externally validated.



**MULTISITE LV PACING.** Advantages of multipolar LV leads include avoidance of diaphragmatic stimulation and availability of multiple pacing vectors, which, speculatively, could permit targeting toward viable and/or late-activated myocardium at implantation and thereafter. Studies on multiple LV leads (75) loosely support this concept, but further studies are needed to determine whether a multipolar approach improves CRT outcomes. Notwithstanding, multipolar LV leads are a “game changer” and, purely because of implanters’ preference, are likely to render conventional leads obsolete.

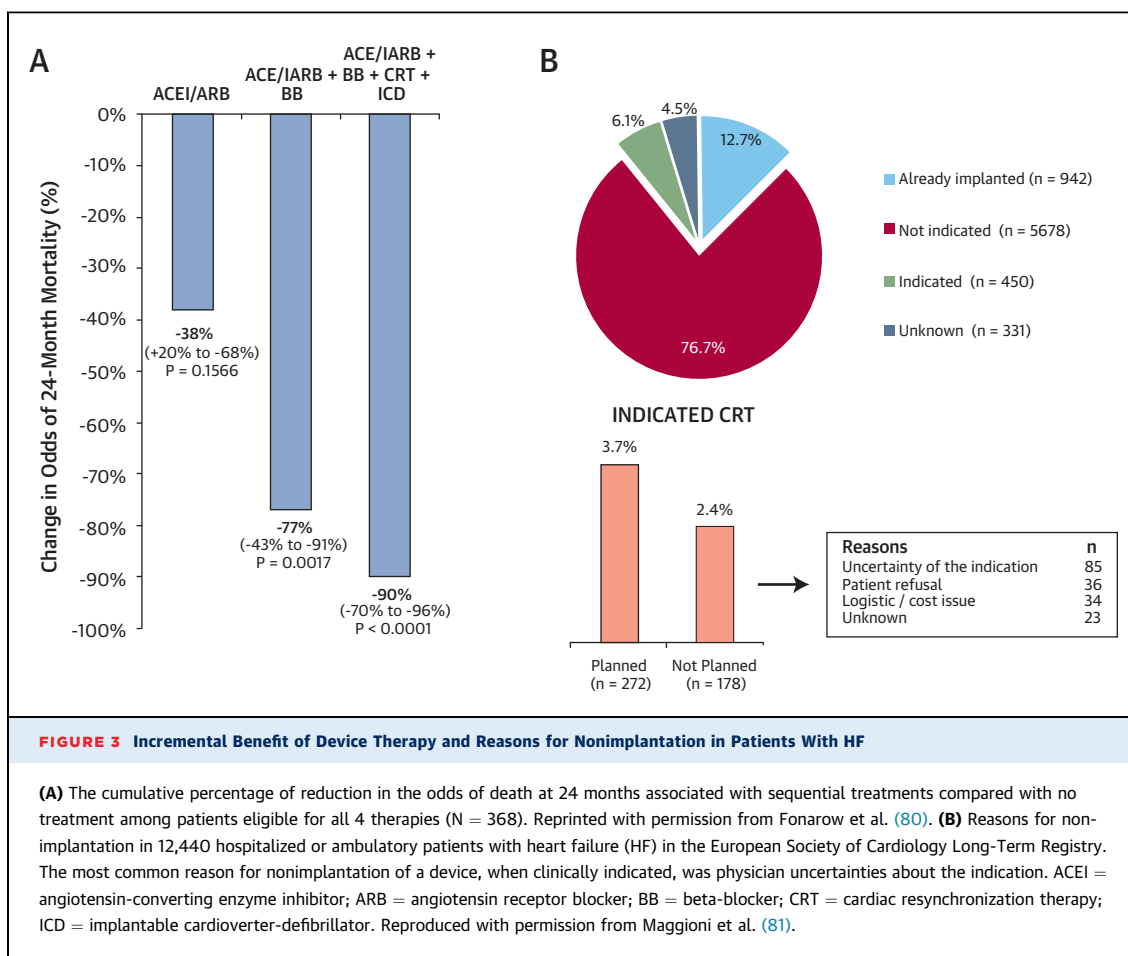
**ELECTROANATOMIC MAPPING.** Electroanatomic mapping has shown that in an LBBB, LV activation is typically U shaped, with a line of functional block that assumes a basolateral or mid-anterior position, depending on QRS duration (76). Importantly, CRT modifies functional blocks, which are associated with mechanical dyssynchrony. Whether electroanatomic mapping has a place in assessing nonresponders to CRT requires further study. Further research on surface electrocardiographic mapping (77) is also required.

**ENDOCARDIAL LV PACING.** In animal models, endocardial LV pacing produces more rapid depolarization and probably more effective resynchronization than epicardial pacing. In humans, LV endocardial pacing improves resynchronization and systolic function, but a clinical benefit has not been shown (78). Transeptal/transmitral and transapical endocardial LV pacing remains experimental. The WiSE-CRT (Wireless Stimulation Endocardially for CRT) study (79) recently demonstrated the feasibility of endocardial stimulation for CRT with a leadless ultrasound-based technology.

#### DELIVERY OF CRT IN THE REAL WORLD

In a nested case-control study in the IMPROVE HF study (IMPROVE HF: Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting) (80), device therapy added an incremental survival benefit to OPT in advanced HF (Figure 3A). Additionally, recent evidence shows that CRT can retard disease progression in mild HF (24,26), yet CRT uptake is low (Figure 3B) (81).

HF has devastating effects on survival and quality of life. In the CARE-HF study, the annual mortality



rate in the non-CRT group was 12.6% (21), which is worse than for regional colonic carcinoma and other cancers. For a condition comparable to cancer in survival terms, we are far from matching the field of oncology in offering this therapy to all eligible patients with advanced, let alone early, disease. In this context, however, we should consider that CRT involves complications (82).

An obstacle in therapy delivery is the disconnection between HF and electrophysiology fields. We need a multidisciplinary approach and a shift from electrophysiology to HF (or vice versa). As in oncology, we need to systematically “capture” patients from our specialty and other specialties, including general practice. Computerized alerts on QRS duration and LV function, throughout secondary and primary care, are likely to bear fruit.

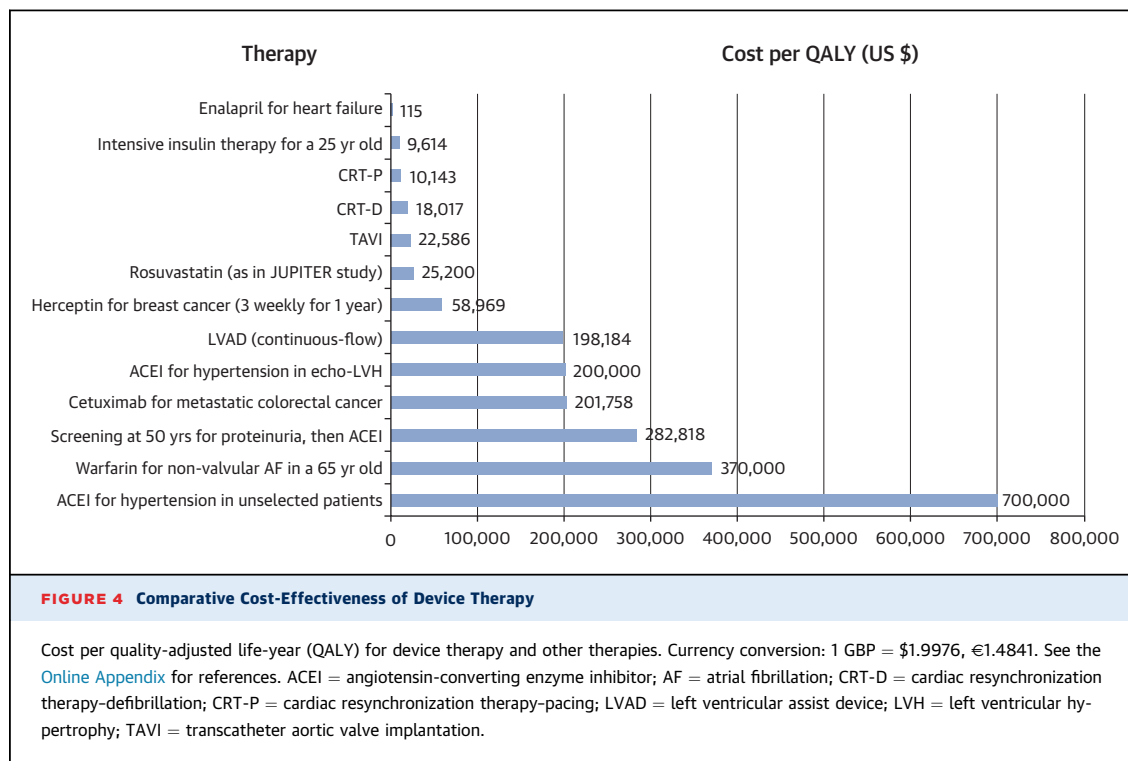
## HEALTH ECONOMICS

The cost of interventions has to match the “willingness to pay.” The incremental cost-effectiveness

ratio (ICER), or the additional cost of a quality-adjusted life-year saved, is a widely accepted measure of the cost of medical interventions. Acceptable ICERs are <\$50,000 (€35,920) in the United States and <\$55,677 (€40,000) in Europe.

The wealth of economic data available in the field of device therapy reflects the commitment of the specialty to health economics. A simulation model using a lifetime horizon, on the basis of advanced HF patient data from the CARE-HF and COMPANION studies, yielded an ICER \$10,143 (€7,538) for CRT-P and \$24,243 (€18,017) for CRT-D compared with OPT (83). For mild HF, a MADIT-CRT analysis (84) yielded an ICER for CRT-D of \$58,330 compared with ICD implantation. A longer time horizon and a pre-implantation LBBB reduced the ICER to \$7,320. Similar figures have emerged from the REVERSE study (85). Over a 10-year time horizon, CRT-on was associated with an ICER of €14,278 per quality-adjusted life-year. Together, these studies demonstrate that CRT-P and CRT-D are as cost-effective as many other medical interventions (Figure 4) (86-93).





## CONCLUSIONS

The invention of CRT can be traced to the demonstration from almost a century ago of a link between conduction disturbances and impaired LV function. A small community of clinical electrophysiologists, engineers, and industry initially developed this technology. Throughout the past 20 years, a proof-of-concept culminated in robust clinical trials. As it currently stands, CRT is a clinically and cost-effective treatment for patients with both advanced and mild HF and a wide (intrinsic or paced) QRS complex. Speculatively, biventricular pacing may someday replace RV pacing.

Although implantation and subsequent optimization could be refined, present-day CRT has been as revolutionary as drug therapy for selected patients with HF. Our attention should be directed toward increasing its delivery. To “get with the guidelines,” we need to increase awareness outside the field of electrophysiology. Most importantly, we will need a team effort from electrophysiologists and HF specialists.

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**KEY WORDS** artificial, atrial fibrillation, cardiac resynchronization therapy, defibrillators, implantable, electrophysiology, heart failure, pacemaker, ventricular remodeling

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**APPENDIX** For supplemental material for Figure 4, please see the online version of this article.