Maximizing Outcomes in Patients Receiving Cardiac Resynchronization Therapy

Featured Articles

Maximizing Outcomes in Cardiac Resynchronization Therapy: Lessons Learned

Pre-Implant Considerations for Reducing Complications and Risk for CRT Patients: Patient Selection

Selecting the Optimal Pacing Location Without Compromise

The Role of Electrical Timing in CRT Therapy: Maximizing Response

Management of Heart Failure Patients with Cardiac Resynchronization Therapy in Follow-Up
EnduraLife™ – Powered CRT-Ds Are Outlasting the Competition

Only EnduraLife Battery Technology is supported by 9 clinical studies, over 8 years of real-world data... and a recommendation from NICE. Clinical trials with over 11,300 patients all showed that Enduralife-powered CRT-Ds are lasting longer than comparable devices from both Medtronic and St. Jude Medical.1-10

EnduraLife™ Battery Technology: 9 Clinical Studies

1. Haarbo J, Hjortshoj S, Johansen J, Jorgensen O, Nielsen J, Petersen H. Device Longevity in Cardiac Resynchronization Therapy Implantable Cardioverter Defibrillators Differs Between Manufacturers: Data from the Danish ICD Registry. Presented at HRS 2014. http://on-demand.hrsdes.com/common/presentation-detail.aspx/15/35/1241/9000. Boston Scientific = 136 patients, Medtronic = 607 patients, St. Jude Medical = 1,067 patients, Boston Scientific = 309 patients. Time to exchange of the device because of battery depletion or device failure recorded in the Danish ICD Registry was the endpoint. The four-year survival rate for devices in the Danish Registry study was 91.1% for Medtronic and 69.7% for Boston Scientific. P<0.01. J. Williams, R. Stevenson.


3. Contemporary cardiac resynchronization Implantable Cardioverter Defibrillator Pulse Generator Battery Longevity: A Multicenter Study. PAGE 2016 ed 10.1111/pac.12831 first published online 11-MAR-2016. The five major institutions performing the study include, at Vanderbilt University, Henry Ford Hospital, University of Michigan, Thomas Jefferson University, Cooper Health System, North Ohio Heart Center. Boston Scientific = 322 patients, Medtronic = 794 patients, St. Jude Medical = 186 patients. Five-year survival rate calculated using device replacements for battery depletion as indicated by ERI. C. Ellis CR, Dickerman DI, Orton JM, Hassan S, Good EG, Obik T, Andreoli JA, Poon KL, Greenopon AJ. Ampere Hour as a Predictor of Cardiac Resynchronization Defibrillator Pulse Generator Battery Longevity: A Multicenter Study. PACE 2016 doi: 10.1111/pace.12831 first published online 11-MAR-2016. The five major institutions performing the study include, at Vanderbilt University, Henry Ford Hospital, University of Michigan, Thomas Jefferson University, Cooper Health System, North Ohio Heart Center. Boston Scientific = 322 patients, Medtronic = 794 patients, St. Jude Medical = 186 patients. Five-year survival rate calculated using device replacements for battery depletion as indicated by ERI.

4. Landolina M, Curto A, Moroni G, Zed A, Ammenheid E, D’Onofrio A, Bajab, 309 patients. Time to exchange of the device because of battery depletion or device failure recorded in the Danish ICD Registry was the endpoint. The four-year survival rate for devices in the Danish Registry study was 91.1% for Medtronic and 69.7% for Boston Scientific. P<0.01. J. Williams, R. Stevenson.


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Kevin P. Jackson, MD, FHRS
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Maximizing Outcomes in Cardiac Resynchronization Therapy: Lessons Learned

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More than 20 years ago, clinicians recognized that left bundle branch block (LBBB), either native or induced by right ventricular apical pacing, had deleterious consequences in patients with left ventricular dysfunction. This spurred the investigation of cardiac resynchronization therapy (CRT) as a treatment modality in these patients. Much has been learned since the first case report of the patient with a dilated cardiomyopathy, LBBB, and congestive heart failure who successfully underwent four-chamber pacing, which resulted in significant improvements in his hemodynamics and symptoms.¹

The aim of this article is to review the history of CRT trials, define the goals of therapy, discuss the implications of CRT response on patient outcomes, and summarize the current guidelines for therapy.

CLINICAL TRIALS

Proof of principle, single-blinded studies. Following the initial case report of CRT, investigators started to design clinical trials to formally investigate the efficacy of this therapy. During this early juncture, two distinct approaches were undertaken with respect to the left ventricular (LV) lead. One group used epicardial LV leads implanted surgically, whereas the other group used epicardial leads that were implanted transvenously into a tributary of the coronary sinus.²,³ The specifics of the trial design of the landmark CRT trials (of patients with a wide QRS duration) and the characteristics of the enrolled patients are summarized in Tables 1 and 2, respectively.

The PATH-CHF trial was designed in 1995; however, due to the complicated trial design, there was a lengthy enrollment period such that the results were not published until 2002.⁴ In this study, all patients were implanted with 2 separate dual-chamber pacemakers. One pacemaker was connected to endocardial leads placed in the right atrium and right ventricle; the other pacemaker was connected to a separate lead in the right atrium and to a lead implanted surgically onto the epicardium of the left ventricle. Biventricular pacing was achieved by programming one pacemaker to a DDD mode and the other pacemaker to a VVT mode. The patients were blinded to their pacing treatment. Following device implantation, patients were randomized to receive either univentricular or biventricular pacing for weeks. Pacing was then turned off in both arms for 4 weeks, following which patients received 4 weeks of pacing in the other arm. The primary endpoints were oxygen uptake at peak exercise, oxygen uptake at the anaerobic threshold, and the 6-minute walk distance. In this study, CRT improved exercise capacity, NYHA class, and quality of life after one month of treatment. Importantly, these benefits were lost when pacing was stopped after a month, and could be restored with resumption of pacing. The MUSTIC trial utilized transvenously delivered coronary sinus leads to pace the left ventricle.⁵ Patients were randomly assigned to 12 weeks of either inactive or active biventricular pacing; then they crossed over to the alternative arm and were followed for another 12 weeks. The primary endpoint was the distance walked in 6 minutes. In contrast to inactive pacing, active biventricular pacing was associated with a 23% greater distance walked.

Double-blinded studies. The initial, small, single-blinded crossover studies paved the way for the first large, double-blinded CRT trial. In the MIRACLE study, 453 patients underwent implantation of a CRT-pacemaker.⁶ Following device implantation, patients were programmed to either

The aim of this article is to review the history of CRT trials, define the goals of therapy, discuss the implications of CRT response on patient outcomes, and summarize the current guidelines for therapy.
| Table 1: Summary of cardiac resynchronization therapy clinical trials. |
|-----------------------------|-------------|-------------------------------|-----------------|-----------------|-----------------|
| Name                        | Year        | Patients, n                  | Inclusion Criteria                        | LV Lead         | Unique Design    | Endpoints                                                                 |
|                             |             |                               |                                              |                 |                 | Results                                                                 |
| Single-blinded, crossover studies of CRT-pacemaker                          |             |                               |                                              |                 |                 |                                                                                   |
| MUSTIC                      | 2001        | 67                            | NYHA III; LVEF ≤35%; LVEDD >60 mm; sinus rhythm; QRS ≥150 ms | Transvenous CS LV lead | Use of dedicated CRT-pacemaker generator | Distance walked in 6 minutes | CRT associated with improved exercise tolerance and quality of life in HF patients with intraventricular conduction delay |
| PATH-CHF                    | 2002        | 42                            | NYHA III/IV; sinus ≥55 bpm; PR ≥150 ms; QRS ≥120 ms | Unipolar epicardial (surgical) | 2 separate dual-chamber pacemakers implanted | Exercise capacity measures | CRT associated with long-term improvement in the clinical symptoms of HF patients |
| Double-blinded, non-crossover study of CRT-pacemaker                        |             |                               |                                              |                 |                 |                                                                                   |
| MIRACLE                     | 2002        | 453                           | NYHA III/IV; LVEF ≤35%; LVEDD >55 mm; sinus rhythm; QRS ≥130 ms 6-min HWD ≤450 meters | Transvenous CS LV lead | Use of dedicated CRT-pacemaker generator | NYHA class, quality of life, and distance walked in 6 minutes | CRT associated with improvements in NYHA class, distance walked in 6 minutes, and quality of life. CRT also resulted in decreased need for IV medications to treat HF and was associated with fewer hospitalizations |
| Double-blinded, non-crossover study of CRT-defibrillator                    |             |                               |                                              |                 |                 |                                                                                   |
| MIRACLE ICD                 | 2003        | 369                           | History of VT/VF; NYHA III/IV; LVEF ≤35%; LVEDD >55 mm; sinus rhythm; QRS ≥130 ms 6-min HWD ≤450 meters | Transvenous CS LV lead | All patients implanted with a CRT-defibrillator; LV pacing turned off in ½ the cohort | NYHA class, quality of life, and distance walked in 6 minutes | CRT associated with improvements in NYHA class, distance walked in 6 minutes, and quality of life |
| CONTAK CD                   | 2003        | 490                           | History of VT/VF; NYHA II/III/IV; LVEF ≤35%; sinus rhythm; QRS ≥120 ms | Unipolar epicardial (surgical) or transvenous CS LV lead | All patients implanted with a CRT-defibrillator; LV pacing turned off in ½ the cohort | Progression of HF, defined as a composite of all-cause mortality, hospitalization for worsening HF, and VT/VF requiring ICD therapy | A non-significant 15% reduction in HF progression observed with CRT |
| Mortality trials            |             |                               |                                              |                 |                 |                                                                                   |
| COMPANION                   | 2004        | 1520                          | NYHA III/IV; LVEF ≤35%; sinus rhythm; PR ≥150 ms; QRS ≥120 ms; Prior HF hospitalization in past 12 months | Transvenous CS LV lead | 1:2:2 randomization to GDMT, GDMT + CRT-P, GDMT + CRT-D | Composite of death from any cause or hospitalization for any cause | CRT-P and CRT-D associated with 20% reduction in the primary endpoint |
| CARE-HF                     | 2005        | 813                           | NYHA III/IV; LVEF ≤35%; sinus rhythm; QRS ≥150 ms; select pts with QRS 120-149 ms; LVE2D ≥30 mm (indexed to height) | Transvenous CS LV lead | 1:1 randomization to GDMT or GDMT + CRT-P | Composite of death from any cause or hospitalization for any cause | CRT-P associated with a 37% reduction in the primary endpoint as well as 38% reduction in total mortality |
### Table 1: Summary of cardiac resynchronization therapy clinical trials.  
*continued from page 5*

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Patients, n</th>
<th>Inclusion Criteria</th>
<th>LV Lead</th>
<th>Unique Design</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Market expansion trials, class I and II heart failure patients</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>REVERSE</td>
<td>2008</td>
<td>610</td>
<td>NYHA I-II;</td>
<td>Transvenous CS LV lead</td>
<td>All patients received either a CRT-P or CRT-D. CRT-on vs CRT-off in 2:1 manner and maintained for 12 months (24 months in Europe)</td>
<td>HF clinical composite response</td>
<td>CRT associated with greater LV reverse remodeling and lower likelihood of HF hospitalization</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>LVEF ≤40%; sinus rhythm; QRS ≥120 ms; LVEDD ≥55 mm</td>
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<tr>
<td>MADIT-CRT</td>
<td>2009</td>
<td>1820</td>
<td>NYHA I-II;</td>
<td>Transvenous CS LV lead</td>
<td>3.2 randomization of CRT-D vs ICD only</td>
<td>Death from any cause or nonfatal heart failure events</td>
<td>CRT associated with 34% reduction in primary endpoint, driven mostly by 41% reduction in HF events</td>
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<tr>
<td></td>
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<td></td>
<td>LVEF ≤30%; sinus rhythm; QRS ≥130 ms</td>
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<tr>
<td>RAFT</td>
<td>2010</td>
<td>1798</td>
<td>NYHA II or III;</td>
<td>Transvenous CS LV lead</td>
<td>1.1 randomization of CRT-D vs ICD only</td>
<td>Death from any cause or nonfatal heart failure events</td>
<td>CRT associated with 25% reduction in primary endpoint</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LVEF ≤30%; QRS ≥120 ms</td>
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<tr>
<td><strong>Market expansion trials, “narrow” QRS duration patients</strong></td>
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<tr>
<td>RETHINQ</td>
<td>2007</td>
<td>172</td>
<td>NYHA III;</td>
<td>Transvenous CS LV lead</td>
<td>Septal posterior wall delay ≥130 ms (M-mode); septal to lateral wall delay ≥65 ms (Doppler)</td>
<td>Proportion of patients who had an increase of at least 1.0 ml per kg of body weight per minute in peak oxygen consumption during cardiopulmonary exercise testing at 6 months after baseline</td>
<td>No benefit to CRT</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>LVEF ≤35%; sinus rhythm; QRS &lt;130 ms; mechanical dyssynchrony</td>
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<tr>
<td>ESTEEM-CRT</td>
<td>2011</td>
<td>68</td>
<td>NYHA III;</td>
<td>Transvenous CS LV lead</td>
<td>Standard deviation of time to peak systolic veloc- ity (Ts) of 12 segments (Ts-SD) &gt;28.7 ms</td>
<td>Hemodynamics assessed acutely at time of CRT implant; echocardiographic indices evaluated during 6-month follow-up</td>
<td>No improvement in structural outcomes with CRT; echocardiographic indices difficult to collect, discordant, and failed to predict clinical outcomes</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>LVEF ≤35%; sinus rhythm; QRS &lt;120 ms; mechanical dyssynchrony</td>
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</tr>
<tr>
<td>Echo-CRT</td>
<td>2013</td>
<td>809</td>
<td>NYHA III-IV;</td>
<td>Transvenous CS LV lead</td>
<td>Septal to lateral wall delay ≥80 ms (Doppler); antero-septal to posterior wall delay ≥130 ms (radial strain)</td>
<td>Death from any cause or first heart failure hospitalization events</td>
<td>20% worse outcome with CRT (non-significant); 91% increase in mortality with CRT (significant)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LVEF ≤35%; sinus rhythm; QRS &lt;130 ms; LVEDD ≥55 mm; mechanical dyssynchrony</td>
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<tr>
<td>NARROW-CRT</td>
<td>2013</td>
<td>120</td>
<td>NYHA II-III;</td>
<td>Transvenous CS LV lead</td>
<td>Septal to lateral wall delay ≥60 ms (Doppler); ICD vs CRT-D</td>
<td>HF clinical composite response</td>
<td>More improvement in CRT arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LVEF ≤35%; sinus rhythm; QRS &lt;120 ms; Ischemic etiology; mechanical dyssynchrony</td>
<td></td>
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</tr>
</tbody>
</table>

**CRT** = cardiac resynchronization therapy; CRT-P = CRT-pacemaker; CRT-D = CRT-defibrillator; CS = coronary sinus; GDMT = guideline-directed medical therapy; HF = heart failure; HWD = hall walk distance; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RV = right ventricular; VT/VF = ventricular tachycardia / fibrillation.
**Table 2: Comparison of patients with a QRS duration >120 msec enrolled in cardiac resynchronization therapy clinical trials.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients, n</th>
<th>Age</th>
<th>Male, %</th>
<th>EF, %</th>
<th>LVEDD, mm</th>
<th>PR, ms</th>
<th>QRS, ms</th>
<th>LBBB, %</th>
<th>HF Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC</td>
<td>67</td>
<td>63 ± 10</td>
<td>75</td>
<td>23 ± 7</td>
<td>73 ± 10</td>
<td>215 ± 43</td>
<td>176 ± 19</td>
<td>87</td>
<td>NA</td>
</tr>
<tr>
<td>PATH-CHF</td>
<td>42</td>
<td>60 ± 7</td>
<td>50</td>
<td>21 ± 7</td>
<td>73 ± 11</td>
<td>196 ± 33</td>
<td>175 ± 32</td>
<td>93</td>
<td>Non-ischemic, 71%</td>
</tr>
<tr>
<td>MIRACLE</td>
<td>543</td>
<td>64 ± 11</td>
<td>68</td>
<td>22 ± 6</td>
<td>70 ± 10</td>
<td>---</td>
<td>166 ± 20</td>
<td>---</td>
<td>Non-ischemic, ~50%</td>
</tr>
<tr>
<td>MIRACLE ICD</td>
<td>369</td>
<td>67 ± 10</td>
<td>77</td>
<td>24 ± 6</td>
<td>76 ± 10</td>
<td>---</td>
<td>164 ± 22</td>
<td>---</td>
<td>Non-ischemic, 31%</td>
</tr>
<tr>
<td>CONTAK CD</td>
<td>490</td>
<td>66 ± 11</td>
<td>84</td>
<td>21 ± 7</td>
<td>---</td>
<td>---</td>
<td>158 ± 26</td>
<td>---</td>
<td>Non-ischemic, ~30%</td>
</tr>
<tr>
<td>COMPANION</td>
<td>1520</td>
<td>67</td>
<td>68</td>
<td>21</td>
<td>68</td>
<td>---</td>
<td>159</td>
<td>70</td>
<td>Non-ischemic, ~50%</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>813</td>
<td>67</td>
<td>73</td>
<td>25</td>
<td>---</td>
<td>---</td>
<td>160</td>
<td>---</td>
<td>Non-ischemic, ~50%</td>
</tr>
<tr>
<td>REVERSE</td>
<td>610</td>
<td>62 ± 11</td>
<td>79</td>
<td>27 ± 7</td>
<td>70 ± 9</td>
<td>---</td>
<td>154 ± 22</td>
<td>---</td>
<td>Non-ischemic, ~50%</td>
</tr>
<tr>
<td>MADIT-CRT</td>
<td>1820</td>
<td>65 ± 11</td>
<td>75</td>
<td>24 ± 5</td>
<td>---</td>
<td>---</td>
<td>159 (65% of pts had QRS ≥150 ms)</td>
<td>70</td>
<td>Non-ischemic, 45%</td>
</tr>
<tr>
<td>RAFT</td>
<td>1798</td>
<td>66 ± 9</td>
<td>82</td>
<td>23 ± 5</td>
<td>---</td>
<td>---</td>
<td>158 ± 23</td>
<td>72</td>
<td>Non-ischemic, ~33%</td>
</tr>
</tbody>
</table>

**Table 3: Evolution in recommendations for cardiac resynchronization therapy device implantation.**

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>2008</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Not addressed</td>
<td>Sinus rhythm, LVEF ≤35%, QRS duration ≥120 ms, and NYHA class III, or ambulatory class IV symptoms on GDMT</td>
<td>Sinus rhythm, LVEF ≤35%, LBBB with a QRS duration ≥150 ms, and NYHA class II, III, or ambulatory class IV symptoms on GDMT</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Not addressed</td>
<td>Atrial fibrillation, LVEF ≤35%, QRS duration ≥120 ms, and NYHA class III, or ambulatory class IV symptoms on GDMT</td>
<td>Sinus rhythm, LVEF ≤35%, LBBB with a QRS duration ≥120-149 ms, and NYHA class II, III, or ambulatory class IV symptoms on GDMT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LVEF ≤35%, NYHA class III or ambulatory class IV symptoms on GDMT, who have frequent dependence on ventricular pacing</td>
<td>Sinus rhythm, LVEF ≤35%, non-LBBB with a QRS duration ≥150 ms, and NYHA class III, or ambulatory class IV symptoms on GDMT</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Not addressed</td>
<td>LVEF ≤35%, NYHA class I or II symptoms on GDMT, who have frequent dependence on ventricular pacing</td>
<td>Atrial fibrillation, LVEF ≤35%, on GDMT, if (a) patient requires ventricular pacing or otherwise meets CRT criteria, and (b) AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LVEF ≤35%, on GDMT, and undergoing new or replacement device placement with anticipated requirement for significant (&gt;40%) ventricular pacing</td>
</tr>
<tr>
<td>Class III</td>
<td>Not addressed</td>
<td>Asymptomatic patients with reduced LVEF in the absence of other indications for pacing</td>
<td>Sinus rhythm, LVEF ≤30%, ischemic etiology, LBBB with a QRS duration ≥150 ms, and NYHA class I symptoms on GDMT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Functional status and life expectancy are limited predominantly by chronic non-cardiac conditions</td>
<td>Sinus rhythm, LVEF ≤35%, non-LBBB with a QRS duration ≥150 ms, and NYHA class II symptoms on GDMT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comorbidities limit survival with good functional capacity to &lt;1 year</td>
<td>Sinus rhythm, LVEF ≤35%, non-LBBB with a QRS duration ≥150 ms, and NYHA class II symptoms on GDMT</td>
</tr>
</tbody>
</table>

^GDMT = guideline-directed medical therapy; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association
inactive or active biventricular pacing, and followed for 6 months. Neither the patients nor the treating heart failure physicians were aware of the treatment assignment. The primary endpoints of the study were NYHA class, quality of life, and distance walked in 6 minutes. Within a month of randomization, active pacing was associated with a significant improvement in each of the 3 primary endpoints; these results were maintained through the 6 months of follow-up. The MIRACLE ICD trial evaluated a similar population that also had an indication for an ICD. All patients underwent implantation of a CRT-defibrillator, and then were randomized to have the left ventricular lead programmed either on or off.7 The primary endpoints were identical to MIRACLE, as were the results. In addition, no proarrhythmia was observed with left ventricular pacing in this cohort. The CONTAK CD trial used a similar design. However, this study included patients with NYHA class II heart failure symptoms. The primary endpoint was a composite of all-cause mortality, hospitalization for worsening heart failure, and defibrillator therapy to treat ventricular tachycardia or fibrillation. There was a non–significant 15% reduction in heart failure progression in patients receiving CRT; of note, patients with class III and IV heart failure experienced significant benefits in peak oxygen consumption, distance walked in 6 minutes, NYHA class, and quality of life.8

Mortality studies. COMPANION and CARE-HF were two large randomized studies that sought to assess the impact of CRT on mortality.9,10 In COMPANION, patients with heart failure, left ventricular dysfunction, and a wide QRS were randomized in a 1:2:2 fashion to receive guideline-directed medical therapy (GDMT) only vs GDMT and insertion of a CRT-pacemaker vs GDMT and insertion of a CRT-defibrillator. In contrast, CARE-HF studied a similar population but randomized patients in a 1:1 manner to either GDMT only or GDMT and insertion of a CRT-pacemaker. The primary endpoint for both trials was a composite of all-cause mortality and need for repeat hospitalization for heart failure management. Both studies showed significant improvement in the primary endpoint with the addition of CRT. These studies paved the way for CRT to be included in the 2008 guidelines on device implantation (Table 3).11 Subsequent studies demonstrated that the benefit also extended to patients with less advanced heart failure symptoms.12-14

GOALS OF CARDIAC RESYNCHRONIZATION THERAPY

Dyssynchronous electrical activation of the heart, as reflected by a wide QRS duration, causes major contraction abnormalities. Local contraction patterns become out of

Figure 1: Schematic representation of events after the onset of dyssynchronous electrical activation. (Reprinted with permission from Vernooy K et al.)

8 Supplement to EP Lab Digest • April 2017
Figure 2: Impact of left ventricular (LV) remodeling on outcomes following cardiac resynchronization therapy (CRT). (A) Extent of LV reverse remodeling after 6 months of CRT. (B) Clinical and echocardiographic improvement after 6 months of CRT. (C) Long-term outcome after CRT according to the extent in LV reverse remodeling. LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; QOL = quality of life. (Reprinted from Ypenburg C et al,16 with permission from Elsevier.)
phase, which causes local strain abnormalities and inefficiency in cardiac function. Ultimately, adverse molecular and cellular remodeling ensue, leading to deleterious clinical outcomes in patients (Figure 1). The main goal of CRT is to alleviate these adverse changes.

DEFINING RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY

A variety of methods have been proposed as requisites to define the presence of CRT response (Table 4). However, in intermediate and long-term follow-up, the presence of echocardiographic defined improvements in left ventricular volume and/or ejection fraction appears to translate into significant clinical benefits. Ypenburg and colleagues followed 302 patients who underwent CRT implantation for a standard indication; an echocardiogram was obtained 6 months post-CRT and compared to the pre-implant echocardiogram. Based on the LV end-systolic volume (LVESV), patients were divided into 4 groups (Figure 2A). Those with the greatest decline in LVESV had the greatest improvement in distance walked in 6 minutes, quality of life, LV ejection fraction, and reduction in LV end-diastolic volume (Figure 2B). Over nearly 2 years of follow-up, these patients were also least likely to have a heart failure hospitalization, require a heart transplant, or die (Figure 2C). Pickard and colleagues reported similar findings over 5 years of follow-up. They followed 880 consecutive patients for 5 years. The best long-term outcomes were observed in patients who were “super-responders” to CRT (defined as a change in ejection fraction of >20%).

Table 4: Proposed criteria to define “non-response” to cardiac resynchronization therapy.

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“Soft” clinical</strong></td>
<td>- Stable medical therapy</td>
</tr>
<tr>
<td></td>
<td>- Heart failure hospitalizations</td>
</tr>
<tr>
<td><strong>“Hard” clinical</strong></td>
<td>- Heart transplantation</td>
</tr>
<tr>
<td></td>
<td>- Death</td>
</tr>
<tr>
<td><strong>Subjective capacity</strong></td>
<td>- Improvement in NYHA class</td>
</tr>
<tr>
<td></td>
<td>- Improvement in quality of life</td>
</tr>
<tr>
<td><strong>Objective capacity</strong></td>
<td>- Increase in distance walked in 6 minutes</td>
</tr>
<tr>
<td></td>
<td>- Increase in peak oxygen consumption</td>
</tr>
<tr>
<td><strong>Left ventricular remodeling</strong></td>
<td>- Decrease in left ventricular end-systolic volume</td>
</tr>
<tr>
<td></td>
<td>- Increase in left ventricular ejection fraction</td>
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DEFINING RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY

IDENTIFYING THE BEST CANDIDATES: ELECTRICAL VS MECHANICAL DYSSYNCHRONY

Early studies of CRT focused on QRS width as a criteria for inclusion. However, it soon became apparent that QRS width as well as QRS morphology were associated with patient outcome following CRT. As an example, in COMPANION, it was demonstrated that the benefit of CRT increased as the QRS width became wider and that the benefit of CRT was driven primarily by patients who had underlying left bundle branch block. This was confirmed in trials of patients with less advanced heart failure as well as numerous real-world datasets. What has been less clear is what to do about patients with a QRS duration <130 msec. It was suggested that echocardiographic indices of mechanical dyssynchrony could be used to select appropriate patients for CRT with a “narrow” QRS duration. However, four clinical studies have now shown that this approach is not effective and that most patients with a narrow QRS derive either no benefit or experience harm when exposed to CRT, even when echocardiographic evidence of mechanical dyssynchrony can be demonstrated (Table 1).

Additional articles in this compendium will discuss the additional impact of lead placement, device programming, and remote monitoring for follow-up to maximize the outcomes of patients receiving cardiac resynchronization therapy.

CURRENT STATE OF CARDIAC RESYNCHRONIZATION THERAPY

Since the first case report in 1994, there has been a tremendous increase in our understanding of patients who are most likely to benefit from CRT. This is reflected in the evolution of the clinical guidelines over time (Table 3). The most recent recommendations reflect our appreciation of the importance of QRS duration and morphology, the recognition that patients with less advanced forms of heart failure derive significant benefit, and the deleterious impact of long-term obligate right ventricular pacing. Additional articles in this compendium will discuss the additional impact of lead placement, device programming, and remote monitoring for follow-up to maximize the outcomes of patients receiving CRT.
References


Pre-Implant Considerations for Reducing Complications and Risk for CRT Patients: Patient Selection

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While cardiac resynchronization therapy (CRT) has been one of the most important advances over the last 20 years in the treatment of patients with heart failure and a reduced ejection fraction, selecting patients most apt to benefit from CRT remains an important goal. Guideline documents put forth by a collaboration of American cardiology societies (the American Heart Association, American College of Cardiology, and the Heart Rhythm Society), the European Society of Cardiology, the Canadian Cardiovascular Society, and the National Institute for Health and Care Excellence (NICE) have sought to create standards for appropriate utilization of CRT.1-6 Such guidelines have used various methodologies to grade evidence and have relied on expert opinion when necessary. Of the various guideline committees listed, only the NICE document employed an economic component to its recommendations.6 The Institute of Medicine in the United States has stipulated that guideline documents be based on systematic review of the medical literature. As such, the various guidelines have typically employed systematic reviews of the evidence, with differing degrees of rigor in evaluating strength of evidence. The strongest recommendations arise from scenarios in which randomized trial data exists. When randomized data is unavailable, non-randomized studies and expert opinion are relied upon. An issue that has arisen in clinical practice is when patients do not fall neatly into one of the guideline categories, creating considerable grey areas where physicians are stuck making difficult clinical choices. This problem is not unique to CRT. In response to this, a collaborative document endorsed by multiple American medical societies was produced in 2013 that outlined appropriate use for CRT in a myriad of clinical scenarios, many of which are not specifically addressed in current guidelines.7 While neither the guidelines nor this document can capture every clinical situation that arises, medical societies have come a long way in providing physicians with guidance for a large number of commonly encountered clinical scenarios. Another issue yet to be resolved is the disconnect that remains between guidelines and reimbursement decisions.8 In some situations, CRT may in fact be the best choice and supported by appropriate use criteria and/or guidelines, but it is not covered by payers. Such situations have put physicians in difficult situations.8

While the guidelines on CRT produced by the various societies do not completely match up, especially in terms of strength of evidence determinations, multiple common threads are found throughout that basically mirror the findings from the many well-conducted randomized clinical trials on CRT. When selecting a patient’s candidacy for CRT, a patient should be on optimal medical therapy for heart failure for at least three months’ duration and have a left ventricular ejection fraction (LVEF) of ≤35% despite such therapy. In addition, an assessment of NYHA class, bundle branch block morphology, QRS duration, presence of atrial fibrillation (AF), and the need for right ventricular pacing is necessary to determine the strength of the indication. For patients with severe heart failure (NYHA class III-IV), the various guidelines are in agreement that CRT is strongly indicated in patients with sinus rhythm, a left bundle branch block (LBBB), and a QRS duration >150 ms. The recommendations across the guidelines become a bit less congruent in terms of non-LBBB morphologies (right bundle branch block [RBBB] and non-specific intraventricular conduction delay) and when the QRS duration is <150 ms. In patients with severe heart failure, a non-LBBB, and a QRSd <150 ms, there is controversy as to CRT appropriateness. In similar patients with NYHA class I and II heart failure, there is general agreement that CRT is not appropriate. In addition, the presence of atrial fibrillation reduces the strength of indication given the well-known reduction of efficacy that AF can have on CRT efficacy.

While both QRS duration and morphology appear in selection criteria across the guidelines, considerable controversy exists as to the relative importance of each. Data from large single-center cohorts suggest bundle branch block morphology has important prognostic information over and above QRSd.9 More recently, an individual meta-analysis...
from the randomized controlled trials of CRT suggested that QRSd, and not bundle branch block morphology, was the most important predictor of outcome. While many studies have shown that patients with an LBBB benefit to a greater extent than those with a non-LBBB, such patients with an LBBB commonly also have wider QRS durations, making the relative importance of each somewhat more difficult to tease out. It is generally felt that QRSd is of particular importance in patients with a non-LBBB. Those arguing in favor of CRT for patients with a non-LBBB commonly cite physiologic studies showing that at wide QRS durations (termed RBBB masking LBBB), such patients may in fact have left ventricular activation delay that could be mitigated by CRT. Those arguing against CRT in non-LBBB patients commonly point to subgroup analyses from trials such as MADIT-CRT and COMPANION, which showed not just a paucity of benefit in such patients, but potentially a trend towards harm.

Multiple randomized trials have now shown no benefit in patients with a narrow QRS without a need for right ventricular pacing. More recently, the EchoCRT trial showed a strong trend towards harm with CRT in this population. While there may be a small subset of patients with a narrow QRS who still have dyssynchrony and could benefit from CRT, the number of such patients is small, and current tools lack to identify such patients.

The introduction of quadripolar leads has marked a major advance in providing optimal cardiac resynchronization.

Patients with systolic dysfunction with bradycardia who are expected to pace at least 40% of the time are good candidates for CRT. Right ventricular paced patients have response rates similar to those with intrinsic LBBB. In the BLOCK–HF trial, CRT was found to be superior to right ventricular pacing in terms of prevention of a combined endpoint of death, heart failure events, or adverse ventricular remodeling in 691 patients with an LVEF ≤50%.

In addition to cardiac factors affecting eligibility as discussed, it has increasingly been recognized that non-cardiac comorbidities play a major role in dictating outcomes following CRT. The ACC/AHA/HRS guidelines for device implantation mandate at least 1 year life expectancy. Comorbid conditions such as chronic kidney disease, chronic obstructive pulmonary disease, and diabetes have all been shown to reduce survival and increase heart failure hospitalizations. Ultimately, physicians must make judgement calls as to the appropriateness of CRT in given situations, especially in borderline candidates with multiple comorbidities.

TOOLS AVAILABLE AND DEVICE SELECTION

In the early 2000s, when CRT came into widespread use, relatively few lead choices and implantation tools were available, making LV lead implantation time-consuming and difficult. Over the last 15 years, significant advances in left ventricular pacing leads and delivery tools/techniques have been developed that have increased the procedural success rate and, at the same time, cut down procedural times. Still, failure to place pacing leads via the coronary sinus (CS) still occurs in roughly 7.5-10% of cases. In addition, lead position in multiple studies has been shown to play a significant role in CRT outcomes. Delivery systems have evolved to help implanters access even the most tortuous of vessels, with the goal of successful implantation of leads in the chosen target vein. Typically, the technique for placing a left ventricular pacing lead via the CS involves accessing the vein with a guidewire or EP catheter via an outer sheath. Despite access to the CS with an outer sheath, often a guidewire alone lacks the stability needed to advance leads. The advent of telescoping sheaths has been a major advance in the delivery of left ventricular pacing leads. Such sheaths facilitate wire delivery into tortuous vessels and provide extra support for the delivery leads. The use of telescoping sheaths has been shown to result in fewer procedural failures, improved lead location, and shorter procedural times.

While telescoping sheaths have been a big technical advance, some cases prove more challenging despite the use of such sheaths. Snare techniques have been developed in cases where a vessel can be wired but due to vessel tortuosity, there is not enough support, even with telescoping sheaths in place to allow for lead advancement. A number of other obstacles have more recently have been overcome with various techniques. Stenosis in the subclavian vein is a commonly encountered problem in patients undergoing upgrade to CRT. Subclavian venoplasty has been shown to be safe and effective in many such scenarios.

The introduction of quadripolar leads has marked a major advance in providing optimal cardiac resynchronization. Quadripolar leads allow for multiple pacing vectors, which can provide numerous opportunities to obtain acceptable capture thresholds at the same time avoiding significant diaphragmatic stimulation. In addition, such leads may enable lead stability by lodging the lead apically, at the same time allowing for mid to basal pacing from the proximal poles. In a meta-analysis of 8 studies comparing quadripolar and traditional bipolar leads, quadripolar leads were associated with a decreased risk of left ventricular lead deactivation, revision, or replacement.
IMPORTANT CLINICAL CONSIDERATIONS

While CRT has benefited many patients since its inception, several complications have been noted. Generally, systematic review of the literature has deemed the risks of CRT implant to be low. A recent large-scale NIH-funded systematic review of the CRT literature identified several potential harms of CRT implant. In general, complications are slightly higher with implantation of CRT-D devices compared with ICDs alone. Pneumothorax, pocket hematoma, and device infection are all uncommon complications of CRT-D implant, but are slightly more common when compared to an ICD alone. For CRT-D devices, the incidence of pneumothorax is 1.3-2.8%, pocket hematoma 0.9-3.3%, and infection 1.3-2.8%, respectively. Infection amongst CRT-D devices is especially problematic. In a retrospective cohort study from the Mayo Clinic, the presence of >2 transvenous leads was identified as an independent predictor of increased infection risk. In addition, extraction of biventricular systems, which by their nature incorporate multiple leads, are often more complicated and carry greater risk than single-lead systems. While coronary sinus pacing leads commonly are able to be extracted with manual traction alone, up to 25% in some series require more advanced extraction tools. Studies have shown that while device infections carry a high morbidity and mortality burden, patients with biventricular systems who develop a device infection and who are able to be fully extracted and successfully re-implanted have excellent outcomes.

Cardiac perforation/tamponade has been noted in multiple trials of CRT-D, but appears to be a rare event that does not seem to be more frequent than in the ICD population. Lead dislodgement has traditionally been amongst the most common adverse events seen in the CRT-D population. However, the advent of telescoping sheaths and the wide variety of available coronary sinus leads seem to be reducing this complication. There is no apparent difference in the incidence of inappropriate ICD shocks in patients receiving a CRT-D device compared to an ICD alone. Procedural deaths in patients undergoing a CRT-D device are extremely uncommon. Less is known about complications associated with CRT-P devices. Based on limited non-randomized data, the incidence of infection may be slightly higher in patients undergoing CRT-D vs CRT-P implant; otherwise, the rates of most other complications would be expected to be similar.

Phrenic nerve stimulation has traditionally been a nuisance during CRT implant, and may prevent the use of an otherwise suitable vein. With traditional bipolar leads, the target vein would often need to be abandoned due to either phrenic nerve stimulation in all vectors, or phrenic nerve stimulation in one vector and high thresholds in the others. The advent of quadripolar leads with multiple spacing patterns has decreased the incidence of this problem. In the EffaceQ study, which followed 299 patients undergoing new CRT implant with quadripolar leads, approximately 6 vectors were noted to have acceptable thresholds without phrenic nerve stimulation. In addition, more patients achieved a viable left ventricular pacing configuration with quadripolar leads compared to what would have been achieved in traditional leads (the distal two poles alone).

Modern LV pacing leads have been documented to have excellent stability and performance over time. In a cohort of 193 patients with biventricular systems followed over time, 7 lead dislocations and 15 individual lead impedances rising >1000 ohms were documented over long-term follow-up.

DEVICE LONGEVITY

Battery life is an important consideration in selecting a biventricular device. Oftentimes, CS pacing lead thresholds may be elevated despite placement in a desirable location. In such situations, a large device battery can mean the difference between an acceptable and unacceptable result. In addition, candidates for biventricular devices are commonly a more comorbid population than in other device categories. Limiting device changeouts, which in turn limits device infection, is an important consideration. The economic impact of device longevity has been well studied. In an economic analysis from Sweden, CRT-D devices with extended longevity were shown to reduce device replacements and the associated device replacement costs and complications, provide cost savings, and perhaps result in increased quality of life for CRT patients.

Multiple studies have sought to compare longevity of CRT-D devices amongst the various major manufacturers. In a multicenter cohort study of Italian patients undergoing device changeout, the median service life for CRT-D devices was 4.9 years. Of the five manufacturers studied, Boston Scientific CRT-D devices had the longest time to device replacement. In a separate analysis from the University of Pittsburgh, the authors compared device longevity at their center with manufacturer-published data. Based on this single-center cohort of 621 patients, the authors found their industry-published product performance reports overestimated actual device longevity. As with the Italian cohort, the Pittsburgh cohort also found significant variations in longevity of CRT-D devices amongst manufacturers.

WHEN TO IMPLANT A CRT-D VS CRT-P DEVICE?

The decision to place a biventricular device with or without an ICD in patients without a history of ventricular arrhythmias remains an area of controversy. There are arguments to be made for and against each. In the United States, roughly 90% of implanted biventricular devices are CRT-Ds. Such
is not the case in certain parts of Europe, especially France, Sweden, and Belgium, where CRT-P devices account for 35–45%. While both the COMPANION and REVERSE trials had both CRT-D and CRT-P patients, neither were designed to compare the two.

The arguments to be made for CRT-Ds are several fold. First, CRT-D devices offer greater protection from sudden cardiac death. In the CARE-HF trial, which compared CRT-Ps to optimal medical therapy, there was a statistically significant improvement in sudden cardiac death (SCD) in favor of CRT-Ps over medical therapy. However, this effect was not noted until almost two years into the trial. Over the course of the trial, there were 32 sudden deaths (7.8%) in the CRT-P arm, which presumably would have been mitigated by CRT-D. In the COMPANION trial, CRT-D but not CRT-P reduced sudden cardiac death compared to optimal medical therapy. In the REVERSE trial, CRT-D use was an independent predictor of survival in multivariate analysis. This finding needs to be taken with caution, given the REVERSE trial did not randomize patients to CRT-D vs CRT-P, raising the specter of bias. Secondly, albeit infrequently, CRT may be proarrhythmic. Both the MADIT-CRT and REVERSE trials demonstrated that in patients who experience reverse ventricular remodeling with CRT, the risk of sudden cardiac death decreases. Unfortunately, predicting the presence and extent of reverse ventricular remodeling in an individual patient is notoriously difficult. The MADIT-CRT trial also showed that patients who did not experience reverse ventricular remodeling with CRT had more ventricular arrhythmic events compared to patients with an ICD alone. Patients who fail to remodel from CRT may be subjected to another procedure, which could have been prevented from CRT-D implant in the first place.

While the arguments for CRT-D implant are compelling, several arguments can be made for CRT-P. In the COMPANION trial, the only trial with separate CRT-D and CRT-P arms, post-hoc analysis showed no significant benefit of CRT-D over CRT-P (HR 0.92; P=0.33), although the trial was not powered sufficiently for this comparison. When CRT-D was compared with CRT-P in the REVERSE trial (345 CRT-D vs only 74 with CRT-P), changes in the clinical composite score, LVESVi, 6-minute hall walk, and quality of life indices were similar between the two device types. Of note, CRT device type in this trial was selected based on national guidelines rather than randomization. In terms of clinical experience outside randomized trials, comparisons between CRT-P and CRT-D have been limited by inherent selection bias. In most such studies, CRT-P inpatients have tended to be older and have more comorbid conditions.

Overall, the decision to implant a CRT-D vs CRT-P device must be individualized to the patient. Oftentimes, CRT-P may be a very reasonable option, especially in elderly patients who may prefer quality rather than quantity of life (recognizing that CRT-P still provides mortality benefit above optimal medical therapy). A thorough discussion with the patient of the pros and cons of each strategy is advised.

**COST-EFFECTIVENESS OF CRT THERAPY**

After the publication of the first major randomized trials of CRT, cost-effectiveness analyses soon followed. The first analyses looked at the cost-effectiveness of cardiac resynchronization pacemakers compared to optimal medical therapy. In an analysis of data from 9 clinical trials, Markov model estimates showed the cost of CRT-P to be $107,800 per quality-adjusted life-year saved compared to medical therapy alone. This was found to be in the general range of other commonly used interventions. This analysis was sensitive to changes in the relative risk for death or hospitalization and the probability of death during lead failure or battery replacement. Based on data from the COMPANION trial, Feldman et al looked at the cost-effectiveness of the CRT-D and CRT-P. The authors found the incremental cost-effectiveness ratio compared to optimal medical therapy for the CRT-P and CRT-D were $19,600 and $43,000, respectively. Both values are below accepted benchmarks. More recently, cost analyses were conducted on CRT trials of patients with mild heart failure. Woo et al found the CRT-D to be cost effective compared to an ICD alone in patients with minimally symptomatic heart failure aged 65 or older with an LVEF ≤30% and a QRSd ≥120 ms, with an incremental cost-effectiveness ratio of $61,700 per quality-adjusted life-year gained. Of note, similar to what was found in patients with more advanced heart failure, cost-effectiveness for CRT devices depends on the degree of mortality reduction. When the degree of mortality reduction is significantly reduced, the cost-effectiveness of CRT-D devices is more questionable. Such a finding lends support to the ongoing efforts of the electrophysiology and heart failure communities to identify which patients are most opt to benefit from CRT. In addition, in the analysis by Woo et al, older age, a more expensive CRT-D device, and a shorter battery life were factors associated with less cost-effectiveness.

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Selecting the Optimal Pacing Location Without Compromise

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Cardiac resynchronization therapy (CRT) has been established as an important treatment for heart failure patients of New York Heart Association (NYHA) functional class II, III, and ambulatory IV, reduced left ventricular (LV) function, and a wide QRS complex. CRT has been shown to improve CHF symptoms, LV function, hospitalization rates, and survival. Transvenous CRT has evolved considerably since its earliest description in 1998.1 CRT devices are increasing in use, constituting up to 41% of the implanted pacing systems.2 Compared to a standard transvenous pacemaker or defibrillator implant, CRT involves accessing and placing a lead in the epicardial branch of the coronary sinus (CS). Considerations for selecting the optimal CS branch location include: obtaining adequate pacing thresholds, avoiding phrenic nerve stimulation (PNS), reducing lead dislodgment, obtaining hemodynamic improvement, and avoiding an increase in mortality4 by pacing at a non-apical site. More recently, innovations in quadripolar LV lead design have advanced the capabilities of the CRT implanters to improve the likelihood of basal midventricular pacing while maintaining long-term stability, pacing flexibility, and performance.

Selecting the optimal LV lead position for transvenous CRT at the time of implant poses unique challenges. For any given patient, the nature of their left ventricular dysfunction can vary in etiology and severity. LV dysfunction may be ischemic or non-ischemic, with damaged myocardium occurring globally or regionally. In the setting of a wide QRS, the extent of electromechanical dyssynchrony and uncoupling may depend on the location and quantity of LV scar tissue. Ideally, the LV lead is placed in the region of the most electrical/mechanical activation delay in order to improve LV ejection fraction and chamber remodeling.3 However, there may be anatomic mismatches as the transvenous LV lead may be constrained by the availability of appropriate CS branches. The LV lead is typically placed in an anterolateral, midlateral, or posterolateral branch. An analysis of randomized trials suggest that apical pacing sites (with the least electromechanical delay) should be avoided, in favor of more midventricular or basal sites.4-6 An analysis of the MADIT-CRT study found that the apical lead location was associated with a significantly increased risk for heart failure/death when compared with leads located in the basal midventricular region (hazard ratio=1.72; 95% confidence interval, 1.09 to 2.71; P=0.019).4 In addition, a study from 2012 found that improvement in NYHA class was significantly greater in patients who underwent LV lead implantation in anterolateral and posterolateral sites with a tendency for greater improvement in LVEF in these regions compared to anterior wall.7

During the lead implantation, the region of latest electric activation may be assessed in the EP lab using the QLV interval (Figure 1), defined as the interval measured from onset of the QRS on the surface ECG to the first positive or negative peak of the LV electrogram.8-9 Pacing from the site of longest LV electric delay was associated with acute hemodynamic improvement as measured by improvements in LV dP/dtmax. The acute hemodynamic response resulted

![Figure 1: The QLV interval, defined as the interval measured from onset of the QRS on the surface ECG to the first positive or negative peak of the LV electrogram. Stimulation at sites with a QLV \(\geq 95\) ms has been shown to be associated with significant improvement in LV reverse remodeling.](image-url)
in a 1.7% increase in %LV dP/dt for every 10-millisecond prolongation of QLV. Stimulation at sites with a QLV $\geq$ 95 ms has been shown to be associated with significant improvement in LV reverse remodeling and quality of life. Another technique at the time of implantation is to perform ECG-guided CRT optimization in order to achieve a biventricular paced complex with the greatest negativity in lead I and positivity in V1 without extending the QRS width. This can be performed by altering both the lead position and the LV offsets (0 to -60 ms). Real-time imaging modalities such as echocardiography could be helpful during the implant procedure to assess a response; however, they can be time-consuming, difficult to reliably reproduce, and technically challenging due to the sterile field.

One of the major limitations of unipolar and bipolar LV leads is the inability to maintain good long-term stability in a non-apical location. In order to reduce the risk of dislodgment, the LV lead tip must be advanced into a distal CS branch. Therefore, the ability to pace in a non-apical location becomes restricted by the presence of side branches which terminate in the basal midventricular region. The diameter of the more proximal basal midventricular vessels is typically wider than the apical terminus. Quadrupolar leads with varying designs have been developed to address the limitations of unipolar and bipolar LV leads. The use of pre-shaped curves have been present in unipolar and bipolar leads in order to reduce dislodgment. The shapes and locations of the pre-shaped curves have been adapted in quadrupolar leads to improve the long-term stability of the lead and maximize the electrode(s) performance (Figure 2). Attain Performa leads (Medtronic) have a pre-shaped S-curve, canted and straight model. The second and third electrodes have a short 1.3 mm spacing which can reduce the possibility of PNS at that site, but limits the number of pacing zones and bipolar programming options. The Quartet lead (Abbott) platform has a pre-shaped S-curve with electrode spacing of 40, 47, and 60 mm. The pre-shaped S-curve has a single-plane design, and a regular and small radius. The ACUITY X4 platform of leads (Boston Scientific) have 3 configurations: a long-spiral (40 mm spiral to tip), a short-spiral (25 mm spiral to tip), and a straight lead (14 mm spacing). In the spiral leads, the proximal electrodes are incorporated into a three-dimensional helix. This configuration is engineered to increase the probability that at least one or more of the electrodes will have contact with the LV myocardium in a larger basal midventricular vessel (Figure 3). However, this lead design limits the number of pacing zones to two. An important advantage of quadrupolar lead design is that the LV
lead tip can be advanced and stabilized in the distal terminus of the branch and pacing can be performed from the proximal electrodes. This multi-zone LV pacing capability may be useful for post-procedural hemodynamic optimization or altering a pacing vector in the setting of PNS or change in capture thresholds, thus avoiding intraoperative repositioning. It is important to note that a balloon occlusion CS venogram is critical for assessing the appropriate lead configuration for the unique anatomy of each patient. A ‘puff’ at the proximal CS will not sufficiently delineate the distal CS branch anatomy (Figure 4), reducing the likelihood of placing the proximal electrodes in a basal midventricular site relative to the final tip position.

The lead design for the proximal electrodes in a quadripolar lead may dictate whether the poles make suitable contact with the basal midventricular myocardium and ultimately, whether they can be used for pacing. For instance, Sperzel et al found that the pacing thresholds were highest for the proximal electrodes (M3, P4) for Abbott’s Quartet leads (M3-RV coil: 2.5 ± 2.4V, P4-RV coil: 3.5 ± 2.7V, M3-P4: 3.1 v ± 2.6V) and lowest for the distal (D1-RV coil: 1.4 ± 1.3V, M2-RV coil: 1.5 ± 1.2V). In the Abbott Quartet 1458Q LV Lead IDE trial, 10.6% of the discharge implants were programmed with basal midventricular electrodes. Similarly, Crossley et al found that with the Attain Performa (Medtronic), the most basal pacing site had higher thresholds compared to proximal (LV4-RV coil: 2.4 ± 1.7V, LV1-RV coil: 1.2 ± 1.2V). In contrast, the NAVIGATE X4 study revealed that the ACUITY X4 LV lead platform had similar performance from both the proximal and distal electrodes. In paired analysis, the proximal electrodes had lower thresholds than tip electrodes for Spiral (Long) (0.9V vs 1.3V) and Spiral (Short) (0.9V vs 1.3V) leads, but not for Straight (1.2V vs 1.0V). Most patients were programmed to use the proximal (basal midventricular) electrodes in final configuration. Proximal poles were programmed in 78% of the Spiral (Long), 76% of the Spiral (Short), and in 65% of the Straight leads. The median (IQR) thresholds in programmed configuration were: Spiral L and Spiral S = 1.0V (0.8V, 1.4V); Straight = 1.2V (0.9V, 1.8V). Pacing thresholds were ≤2.5V in 96% of Spiral L and Spiral S leads, and in 90% of Straight leads. The presence of the proximal electrodes on the 3D spiral may allow for a higher likelihood of obtaining myocardial contact in larger diameter, proximal vessels than a single-plane pre-shaped curve or a straight quadripolar lead. A straight

**Figure 5:** Proximal electrode pacing performance and programmed percentage in the Abbott Quartet (M3, P4 electrodes), Medtronic Attain Performa (LV4, LV3), and Boston Scientific ACUITY X4 (Spiral-proximal E4, E3, E2, Straight M4, M3).

**Table 1:**

<table>
<thead>
<tr>
<th>Lead Design</th>
<th>Pacing Threshold (0.5 ms)</th>
<th>% Programmed at Discharge</th>
</tr>
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<tbody>
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<td>SJM-Quartet</td>
<td>M3-P4</td>
<td>M3-RV Coil</td>
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<tr>
<td></td>
<td>3.1 v ± 2.6V</td>
<td>2.5 v ± 2.4V</td>
</tr>
<tr>
<td></td>
<td>0.6%</td>
<td>3.5%</td>
</tr>
<tr>
<td>MDT Attain Performa</td>
<td>LV4-RV Coil</td>
<td>LV4-LV3 coil</td>
</tr>
<tr>
<td></td>
<td>2.4 v ± 1.7V</td>
<td>2.8 v ± 1.6V</td>
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<td>6.7%</td>
<td>1.2%</td>
</tr>
<tr>
<td>BSC-ACUITY X4</td>
<td>Spiral (Long) Proximal vs Distal</td>
<td>Spiral (Short) Proximal vs Distal</td>
</tr>
<tr>
<td></td>
<td>0.9V vs 1.3V</td>
<td>0.9V vs 1.3V</td>
</tr>
<tr>
<td></td>
<td>78%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Future clinical studies will help to further clarify the optimal programming modalities and pacing configurations to enhance CRT response rates and in turn, reduce the impact of heart failure for patients.
Figure 6: ACUITY X4 Straight used in (A) short, tortuous CS branch in which the lead spiral would likely extend into the main body of the CS, (B) CS branch with a constant diameter proximal to distal, allowing good contact in all 4 poles.

Figure 7: ACUITY X4 Short Spiral (25 mm) used in (A) shorter, tortuous CS branch with larger basal vessel caliber (B) shorter CS branch with tortuosity and increased diameter proximally.

Figure 8: ACUITY X4 Short Spiral (25 mm) used in (A) shorter, tortuous CS branch, (B) shorter CS branch with tortuosity and increased diameter proximally.

Figure 9: ACUITY X4 Long Spiral (40 mm) used in (A) longer, proximal tortuous CS branch, (B) long, wide diameter CS branch. In large diameter branches, stability may be poor. Note: the lead tip is wedged distally, providing stability. Pacing could then be performed from one or more of the three midventricular poles.
quadripolar LV lead may be best utilized in a CS branch that has significant proximal tortuosity or has relative uniformity in diameter along its course. (Figures 6–10)

A major limitation of LV lead placement is the lack of stability and fixation in the epicardial CS vessels. LV leads are at risk for retraction (micro-dislodgment) and complete dislodgment. LV lead dislodgment often requires intraoperative repositioning, leading to increased hospital stays. Prior studies of unipolar and bipolar LV leads reveal that the risk of lead dislodgment using unipolar or bipolar leads is in the 5–12.5% range18–20, and possibly higher when considering the possibility of micro-dislodgment resulting in elevated thresholds necessitating repositioning.18 Overall, quadripolar LV lead dislodgment is lower when compared to bipolar leads. A multicenter registry study found a dislodgment rate in quadripolar leads of 1.7% compared to bipolar leads 4.6% (P=0.03).22 Dislodgment rates for the Quartet (Abbott) and Attain (Medtronic) range from 0.4–4.3%,13,23–25 LV lead dislodgment for the ACUITY X4 leads (Boston Scientific) occurred in 1% in the NAVIGATE X4 trial.13

The presence of PNS can occur in 15–37% of CRT implantations.10–11 Frequently, PNS occurs during the initial procedure during lead testing. Generally, testing is performed at maximal output to assess for diaphragmatic stimulation. A PNS threshold can be obtained for a given lead location. The difference between the PNS threshold and the LV myocardial pacing threshold constitutes a pacing “safety margin”. Despite a “safety margin”, PNS may develop later in the patient’s clinical course. PNS may occur in approximately 10% of patients who had no PNS at the time of implant.30 PNS may develop as a result physical exertion, positional changes, cardiac movement during sleep or as a result cardiac remodeling within the thoracic cavity. Not surprisingly, PNS is more common in apical locations (17.8%) when compared to midventricular (12.7%) or basal (7.1%) locations. Lateral sites have a four-fold increase in incidence compared to anterior sites.10 PNS may result in termination of CRT and the necessity for re-intervention in 1.6–2.1%.10 The Abbott and Medtronic quadripolar leads have similar PNS rates of 7.2–13.5%, but reprogramming results in much lower re-intervention rates (0.0%–0.4%).12,23

The ACUITY X4 (Boston Scientific) performed similarly, with PNS detected more commonly at maximum output with the tip electrode with extended bipolar pacing. PNS at maximum output existed in 6% of patients when pacing in true bipolar configuration and proximal electrodes. Presence of PNS during intraoperative testing was significantly higher when pacing was true bipolar with the tip electrode in Spiral L (27%), Spiral S (23%), and Straight (18%). During follow-up in the NAVIGATE X4 trial, clinical PNS occurred in 8% (58/744) of patients, and occurred more often when the tip electrode was the programmed cathode (15%) than in patients where the proximal electrodes were the cathode (5%). PNS was successfully mitigated by reprogramming in 95% of cases. The need for intraoperative revision was necessary in just 0.5% of patients (4/744).13

Despite significant engineering improvements in quadripolar lead design and deliverability, additional studies are necessary to further define the optimal management and efficacy of patients undergoing CRT using these leads.

- The Boston Scientific SMART (Strategic Management to Optimize response to CRT) Registry will be used to compare and analyze differing clinical optimization strategies in approximately 2000 patients. Heart failure events, all-cause mortality, NYHA class, and quality of life (QOL) scores will be assessed in selected subgroups. In some CRT patients, an AV search algorithm may improve LV hemodynamics compared to fixed AV delays.26
- The upcoming SMART-CRT trial will try to resolve whether SmartDelay™ (an AV delay algorithm which also takes LV lead position into account) may result in a greater reduction in LV end-systolic volume in patients with CRT and the ACUITY X4 leads. Despite the improvements in CHF symptoms for many, CRT has a non-responder rate of approximately one-third.27
- There are many factors which contribute to a lack of a response; however, single-site LV pacing may not be sufficient in some patients to restore resynchronization. In particular, patients with significant heterogeneity in their LV scar zones have complex activation wavefronts and may benefit from multi-site LV pacing.28 The SMART-MSP
(Multi-Site Pacing) trial will evaluate the safety and efficacy of LV MSP in non-responders to conventional CRT. At 6 months, approximately 110 non-responders are expected out of an enrollment of 568 patients. The non-responders will then have LV MSP activated and be evaluated for an improvement in CHF symptoms.

**SUMMARY**

The optimal placement of the LV lead in CRT poses many challenges, including obtaining adequate pacing thresholds, avoiding PNS, reducing the chances of lead dislodgment, and obtaining hemodynamic improvement and a reduced mortality by pacing at a non-apical LV site. With previous unipolar and bipolar LV leads, compromises were necessary in final lead placement largely due to the anatomic constraints of tip stability, adequate pacing performance, and PNS. The development of a quadripolar LV lead platform has attempted to address these compromises with improved lead stability, electrical performance, and decreased PNS. The presence of proximal electrodes on a 3D-epicardial may have an advantage when attempting to pace from a basal midventricular site, particularly if there are no midventricular side branches. As techniques for the periprocedural assessment of cardiac resynchronization evolve, such as the use of ECHO speckle-strain imaging or 3D electroanatomic mapping within the CS, the CRT implanter will have more opportunities to help deliver the quadripolar lead to the ideal location. Future clinical studies will help to further clarify the optimal programming modalities and pacing configurations to enhance CRT response rates and in turn, reduce the impact of heart failure for patients.

**References**

The Role of Electrical Timing in CRT Therapy: Maximizing Response

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Cardiac resynchronization therapy (CRT) exerts its physiological impact via synchronizing ventricular contraction, which in turn results in an improved pumping efficiency, optimized left ventricular filling, and a reduction in the extent of the mitral regurgitation. CRT can substantially alter the natural course of a failing ventricle through favorable ventricular remodeling, which occurs over time with a reduction in left ventricular volumes and improvement in ejection fraction. Several prospective randomized studies have demonstrated the long-term clinical benefits such as enhanced quality of life (QOL), improved functional capacity, and a reduction in heart failure (HF) hospitalization and all-cause mortality. Despite these overt CRT-related benefits, approximately one-fourth of the patients treated with CRT do not derive any noticeable benefit. On account of the high prevalence of heart failure, marked morbidity and mortality related to this disease, and the consequent price label to society both from HF as a disease and from CRT as a therapy, the need to ensure an adequate clinical response in most patients receiving CRT is increasingly important. There are several determinants of successful delivery and response to device therapy, which include selecting the appropriate patient, patient-specific appropriate left ventricular lead placement, and optimal post-implant device care and follow-up.

AV AND VV INTERVALS: INFLUENCING THE VENTRICULAR ELECTRICAL ACTIVATION SEQUENCE

The electrical activation sequence of the heart is one of the key determinants of coordinated cardiac contraction and relaxation, and overall cardiac function. Abnormalities in electrical activation leading to dyssynchronous cardiac contraction can lessen the mechano-energetic efficiency of the heart, causing progressive adverse left ventricular remodeling and heart failure. CRT is based on the premise that pacing-induced changes in the pattern of electrical activation of both ventricles can improve intraventricular and interventricular synchrony, and ultimately, the hemodynamic efficiency of the failing heart. Although there is significant interpatient variability, ventricular activation during simultaneous biventricular pacing allows for the generation of two ventricular activation wavefronts that are initiated at the LV and RV pacing sites and move in opposite directions towards each other. Notably, the resulting activation pattern can be impacted by several variables:

- AV and VV pacing timings;
- Location and extent of scar;
- Local infiltrative pathologies and preceding conduction defect;
- RV and LV lead positions;
- Local myocardial health and responsiveness.

AV Interval

Of note, the AV interval impacts the pattern of activation during both LV pacing and biventricular pacing. Atrio-biventricular pacing delivered with very long AV intervals in a myopathic heart with a LBBB will result in depolarization initiated from the atria that descends via the atrioventricular node (AVN) and right bundle branch propagating from the right to the left ventricle. With intermediate AV delays, there are different degrees of fusion between the depolarization wavefronts coming down the right bundle branch (intrinsic conduction) with that from the RV and LV leads. At short AV delays, ventricular depolarization may be singularly representative of the activation wavefronts generated from the LV and RV leads.
pacing locations. Although the length of the AV interval can determine the electrical activation sequence and ensure cardiac synchrony and hemodynamic performance, the exact value of this AV delay is variable and patient specific.

**VV TIMINGS**

The interventricular (VV) timing is another important variable that can influence cardiac synchrony. CRT devices have the option of programming the VV pacing interval, allowing LV-RV simultaneous or sequential pacing with different degrees of LV or RV pre-excitation. These adjustments, together with AV interval modifications, can produce a throng of patterns of ventricular depolarization. Although in a substantial proportion of patients, simultaneous RV-LV pacing produces good hemodynamic results, pre-exciting the LV before RV pacing in patients with ischemic cardiomyopathy and LV scar can optimize synchrony and increase LV systolic function.8

As alluded to before, another factor that impacts electromechanical activation and optimal VV timing is the location of the right and left ventricular lead position. The ideal lead locations are those that offer the greatest reduction in total activation time by producing two activation wavefronts that start from the furthest locations, relative to each other. Given that in a conventional LBBB, the last region to be activated during sinus rhythm is the basal posterolateral wall, placing the pacing lead in the vicinity of this area should supposedly result in maximal electrical synchrony.9

Targeting the lead position via transvenous lead placement is often challenging because of the constraints imposed by the coronary venous anatomy. Investigators have demonstrated using non-contact endocardial mapping that electrical activation in patients with heart failure and ventricular conduction delays depends on LV lead placement. They identified areas of slow conduction within the LV, present mainly in patients with ischemic cardiomyopathy probably related to myocardial hibernation or fibrosis.10 Depolarization generated by an LV lead located in a slow conduction zone was late in leaving the area. Specifically, in such situations to achieve simultaneous activation of the LV with biventricular pacing, the LV had to be paced 30-40 ms before the RV to allow the pacing wavefront to leave the region of the slow conduction zone. Of note, the impact of the RV pacing site on the activation sequence or fusion of the depolarization wavefront is underestimated.11 Prior work has demonstrated that by changing the RV pacing site, the electrical distance from the LV lead can be varied and the dyssynchrony patterns of the LV can also be altered. Adjusting the AV and VV interval, as alluded to above, enables a variable extent of the activation wavefront originating from each of the pacing leads and intrinsic conduction.

**PHYSIOLOGY OF ECHO-GUIDED OPTIMIZATION**

**AV Optimization**

AV optimization is geared towards enhancing active and passive filling of the left ventricle, with the intent of improving stroke volume and cardiac output. Of note, beyond LV filling, the AV interval duration also helps achieve electrical resynchronization of the ventricle, via its direct impact on regulating the extent of fusion of the LV and RV wavefront. AV optimization has a direct impact on LV diastolic and systolic function. Echocardiography-guided...
approaches for this, which have been in vogue for a while, are logistically challenging.\textsuperscript{12}

The most common echo method used is the iterative method. This was a strategy used in the CARE-HF and SMART-AV trials.\textsuperscript{5, 13} This is a fairly straightforward qualitative strategy, where the mitral inflow pattern is evaluated with progressive changes in the AV interval (Figure 1A). The intent is to obtain maximal E and A wave separation with minimal to no truncation of the A wave. There are issues with reproducibility that have brought the validity of this approach into question. In some centers, the aortic pulsed-wave Doppler velocity time integral (VTI) is used as a strategy for AV optimization (Figure 1B). This is on account of the fact that the VTI is a surrogate for LV stroke volume. For this technique, the VTI is measured over a range of AV intervals.\textsuperscript{14}

**VV Optimization**

VV optimization at our center is done using the VTI strategy. The VTI is measured over a range of LV-RV offset timings. Notably, the reproducibility for this measure is challenging, and our protocol insists on making sure the measurements are made in the same phase of respiration, with an average of 3 consecutive measurements. Only changes in VTI greater than 15\% are considered clinically meaningful enough (above the intra-observer variability) to make changes to the programming of the device.

Even though several prior reports have demonstrated the value of echo-guided optimization in reducing the number of non-responders to CRT, clinicians desist from optimizing the AV and VV timings in their patients because of the aforementioned inter- and intra-observer variability, concerning noise-to-signal ratio, paucity of skilled staff, limited resources, and logistical challenges. The difficulty of this method is further augmented by the fact that the heart is continually remodeling post CRT, making it necessary for repeated reassessment and reprogramming.

**KEY STUDIES AND THE ROLE IN CRT**

There are several non-echocardiographic strategies of optimization.\textsuperscript{3, 14} These are summarized in Table 1. The device-based automated methods will be discussed at greater length.

The optimal AV interval is fundamental to enhancing response to CRT, and a suboptimal AV interval may result in a decline in cardiac output by up to 20\%. Even though tailoring the delivery of CRT with AV and VV optimization is considered best practice, this has not been implemented as a part of routine clinical care. Earlier reports from worldwide surveys have suggested that the vast majority of physicians do not optimize the programming at implant, and under 10\% of clinicians bother to systematically optimize the AV and VV delays during routine follow-up.\textsuperscript{15} Also, defining response to CRT is complex, and there remains a high degree of variance between responder rates when one examines functional endpoints versus that of anatomical remodeling.

The above-mentioned alternative strategies inclusive of impedance cardiography, acoustic parameters, and the surface EKG have not been successfully validated and are burdensome to perform and repeat on a continual basis. This, in turn, has created the need for a simpler, automated approach to individualize the optimization of AV and VV intervals within patients. Algorithms derived using intracardiac electrograms and measures of electrical activity within the heart and between the right and left ventricular pacing leads have been tested prospectively in 3 separate studies, via large RCTs.
The SMART-AV trial was a study designed to compare a device-based algorithm with echo-guided optimization and a fixed nominal AV delay in a randomized pattern. The SmartDelay (Boston Scientific) optimization is designed to recommend optimal sensed and paced AV delays to maximize LV contractile function (LV dP/dt max) based on each individual’s intrinsic conduction characteristics. The algorithm uses a combination of three inputs, namely: (1) intrinsic AV intervals; (2) QRS duration (via RV-LV timing); and (3) LV lead location.\(^5\)

This was a multicenter, randomized trial of atrioven-tricular (AV) optimization/programming methods among patients with advanced HF undergoing CRT deﬁbrillator implantation. The major inclusion criteria for the study were New York Heart Association (NYHA) class III or IV despite optimal medical therapy, an LV ejection fraction (LVEF) of <35%, and a QRS duration of >120 milliseconds. Patients were required to be in sinus rhythm, and those who were in complete heart block were excluded. CRT implantation was performed using standard techniques, with no requirements regarding lead positions. The primary endpoint in this study was LV end-systolic volume, and a fixed nominal AV delay in a randomized pattern. The algorithm did not show any positive impact on clinical outcome when examining the pre-specified endpoints for superiority.\(^6\) This algorithm has shown some propensity to reduce the incidence of AF and repeated HF hospitalizations, but a point of contention is that it works well only in patients with a normal intrinsic AV conduction (i.e., PR <200 msec).\(^18\) This is being studied in a larger prospective study.

To give AV and VV optimization an opportunity to effectively contribute to enhancing response, it will need to be coupled with favorable lead locations.

secondarily considered NYHA class, quality of life score, and 6-minute walk test at 6-month follow-up. The study concluded that neither the device-based algorithm (SmartDelay) nor echo-guided optimization was superior to a fixed AV delay of 120 ms.

It does appear that this study was underpowered and the definition of a responder may have been too stringent. However, this well-conducted study led to many substudies that have significantly impacted our understanding of the importance of LV and RV lead implantation, as well as the interdependence of the performance of the SmartDelay algorithm and lead placement.\(^16\)

The FREEDOM trial randomized 1647 patients receiving CRT. The primary endpoints for this study included the HF clinical composite score at 3, 6, and 12 months.\(^17\) This study examined the benefit of frequent optimization of AV and VV delays using a device-based algorithm compared to standard of care (i.e., with or without echocardiography-guided optimization). The primary endpoint of enhanced clinical response and secondary endpoints of all NYHA class, QOL, 6-minute walk distance, LVEF, all-cause mortality, cardiovascular and HF mortality, and hospitalization were also evaluated. The AV and VV intervals were optimized frequently in the algorithm arm compared to the control arm. Details of the optimization strategy in the control arm have not been elaborated on in detail. This too was a non-inferiority result, with no evident differences between the two arms of the study. The results of this study have not been published.

The Adaptive CRT (aCRT) trial recently studied an algorithm enabling RV-synchronized left ventricular and biventricular pacing in the setting of intact intrinsic AV conduction.\(^6\) This algorithm enables repeated adjustment of the AV and VV intervals on the basis of periodic automatic evaluation of the degree of intrinsic conduction. This report showed non-inferiority of the algorithm when compared with echo-guided optimization at 6 months of follow-up. The algorithm did not show any positive impact on clinical outcome when examining the pre-specified endpoints for superiority.\(^3\) This algorithm has shown some propensity to reduce the incidence of AF and repeated HF hospitalizations, but a point of contention is that it works well only in patients with a normal intrinsic AV conduction (i.e., PR <200 msec).\(^18\) This is being studied in a larger prospective study.

Notably, modifying the electrical activation of the heart may not always translate into improved cardiac performance. In fact, a direct measure of cardiac function such as cardiac output or contractility may serve as the better guide for automatic adjustment of the AV and VV intervals. Unlike any of the above optimization strategies, the signal recorded by the SonR sensor (LivaNova) reflects global ventricular contractility. Previous work has suggested that the signal recorded on the atrial lead is stable and reproducible during atrial fibrillation and exercise, and sensitive to pacing conditions. Optimal programming to improve cardiac contractility was first tested prospectively in the Clinical Evaluation on Advanced Resynchronization (CLEAR) pilot study.\(^19\) This study used a hemodynamic sensor on the right ventricular lead in CRT-pacemaker patients, and showed an increased rate of responders compared to standard of care. This study was significantly limited by bias due to its single-blind design, with the positive impact of the sensor arm being mainly driven by the unblinded assessment of NYHA class. The RESPOND-CRT study built upon this pilot data with a much larger and improved trial design.\(^20\) The majority of the patients were NYHA class III, with an even distribution of ischemic and non-ischemic cardiomyopathy. This study used a hierarchical strategy incorporating functional as well as hard endpoints inclusive of HF and all-cause mortality in defining responders. This
study also showed that the automated sensor-driven strategy to optimize the AV and VV timings was non-inferior to an echo-guided approach. 21

Heart failure hospitalization was a pre-specified endpoint and was examined separately. The SonR arm was also observed to have a reduced HF hospitalization rate. Importantly, the sensor strategy also appeared to do better in sicker patients, especially in those with a past history of atrial fibrillation, renal dysfunction, and a lower ejection fraction. This finding reaffirms that frequently optimizing and adjusting for exercise periods may result in a benefit for sicker patients, especially during the augmented stress of exercise and over the course of remodeling. Of note, there were no differences in reverse remodeling between the sensor- and echo-guided arms. 21

PACING LOCATION AND OPTIMAL TIMING

Analyses of large pivotal CRT studies have demonstrated that a purely anatomic approach to lead positioning is of limited value to reduce non-responder rates. In the era of precision medicine, individualized targeting of leads seems to make sense to maximize response.

The LV and RV lead location throughout the delivery of biventricular pacing is fundamental. Defining an optimal lead position is still unclear, and the choice between an optimal anatomical position targeting either the segment with maximal mechanical dyssynchrony or a region with maximal electrical delay, is still up for debate. There is evidence to suggest that maximal electrical separation between the right and left ventricular leads, and positioning the LV lead as far out into the electrical activation sequence may have a beneficial impact on clinical outcomes. 22-24 Also, the RV-LV interval is strongly associated with remodeling responses and HF hospitalization with CRT. 29 Thus, it seems reasonable to measure this parameter at the time of LV lead implantation and repositioning when short intervals are observed. There is a paucity of data comparing different measures of electrical and mechanical delay, but the RV-LV time has the potential benefit of simplicity, not requiring echocardiography or surface electrocardiographic measurements. Moreover, it can be measured automatically through the devices, which could serve as another objective parameter while measuring and enhancing response after CRT device implant, especially for a quadrupolar LV lead. In addition to identifying a site with long RV-LV at the implant, RV-LV may further be maximized by choosing the electrode on a quadrupolar lead with the longest RV-LV delay. This can be facilitated by the device features such as LV VectorGuide (Boston Scientific). LV VectorGuide automatically measures RV-LV delay for up to 17 vectors associated with a quadrupolar lead along with the assessment of impedance, presence of phrenic nerve stimulation, and LV threshold. Modulating the AV delay over and above, achieving longer RV-LV at the LV stimulation site, has a significant impact on the depolarization wavefront, and consequently on the extent of RV and LV pre-excitation and ventricular contractility. 16 Also noteworthy is that changes in the AV delay can influence the location and size of the line of conduction block. Work from Gold et al has also suggested that optimizing the AV delay via the SmartDelay algorithm has superior impact on ventricular remodeling when performed in patients with a longer QLV (Figure 2). 16

Modern CRT devices also offer a range of monitoring parameters that are relevant for the longitudinal care of patients with heart failure. Data pertinent to patient activity, heart rate, atrial and ventricular ectopic burden, autonomic parameters, and fluid balance via transthoracic impedance are obtainable through present-day CRT devices, and may help identify those at risk of non-response, and perhaps recognize worsening heart failure status early in its course, thus preventing HF hospitalizations. 25, 26 Biventricular pacing percentage has been identified as an important determinant of clinical outcome following CRT. A study from the LATITUDE investigators of nearly 37,000 patients suggested biventricular pacing percentages >98% were connected with improved survival relative to reduced pacing percentages. 27 Notably, device data including burden of atrial or ventricular ectopy or tachyarrhythmias may make possible targeted intervention to advance CRT pacing percentage and clinical outcome.

Caring for the CRT patient requires the multidisciplinary care of subspecialists from electrophysiology, heart failure, and cardiac imaging. This integrated care offers a coordinated rendering of expertise to risk stratify patients likely to be non-responders, optimize device programming, as well as provide adept care of pathology known to impact outcome in CRT (e.g., management of right ventricular dysfunction, pulmonary hypertension). In addition, this integrated infrastructure may facilitate the optimization of medical therapy, adherence, and patient education. Recent reports have suggested that this multidisciplinary approach may have a positive impact on clinical outcome in this subset of patients with implanted CRT devices. 28

CONCLUSION

The incremental contribution of AV and VV optimization will always be difficult to measure due to the influence of multitude of covariates. If there is an unwilling substrate (high scar burden) or poorly positioned LV and RV leads, then despite spending hours on optimizing the device, the chances of converting the patient to a responder is remote. To give AV and VV optimization an opportunity to effectively contribute to enhancing response, it will need...
to be coupled with favorable lead locations. For widespread adoption, this needs to be an automated strategy, with limited involvement of the caring clinical practitioner. Larger randomized studies powered to show clinical effectiveness and superiority to standard of care will be necessary for this to become a widely adopted tool. Clinical studies like the SMART-CRT study, which consider lead position and device optimization strategy interactions, will help address some of these questions. Continued innovation will eventually lead to the “holy grail” of automated, closed-loop sensor-driven systems with integrated self-learning algorithms that improve cardiovascular outcome and mortality.

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Management of Heart Failure Patients with Cardiac Resynchronization Therapy in Follow-Up

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Heart failure (HF) affects more than five million Americans and accounts for more than one million hospitalizations annually. Cardiac resynchronization therapy (CRT-P/D) improves symptoms, prevents hospitalization, and improves survival in patients with left bundle branch block and symptomatic heart failure. Unfortunately, patients remain at risk for heart failure hospitalization following implantation. Appropriate management following CRT implantation is essential in order to optimize outcomes and avoid hospitalization.

Heart failure and the impact of hospitalization

Heart failure hospitalization remains a significant problem in the U.S. healthcare system and across the world. While heart failure mortality has declined over time, heart failure hospitalization has been more resistant to change. Despite advances in heart failure therapies over the past decade, the absolute number of hospitalizations each year in the U.S. has not improved, as evidenced by 1,008,000 discharges in 2000 and 1,023,000 discharges in 2010. Hospitalization is a troublesome and costly problem, as hospitalizations account for 80% of the direct costs for heart failure ($21 billion in 2012). Payors and healthcare systems are motivated to prevent and reduce hospitalizations for many reasons. This is even more important now that CMS penalizes hospitals with high heart failure readmission rates with 1% lower reimbursement.

While CRT reduces the risk of hospitalization for heart failure, hospitalization remains a problem in the CRT population. Not surprisingly, hospitalization is particularly problematic in CRT non-responders — approximately 25 to 30% of all CRT recipients. The rate of heart failure hospitalization is approximately twice as high in non-responders versus responders (0.96 vs 0.43 per patient year), and overall Medicare costs are 50% higher in non-responders (Figure 1). Remote monitoring and hospitalization

Remote monitoring plays an important role in patients with CRT and may also have an important role in reducing heart failure hospitalization and readmissions. Like all device patients, patients with CRT should be monitored remotely as an adjunct to in-clinic follow-up (Class I, Level of Evidence [LOA] A). Remote monitoring offers several advantages in the care of CRT patients, including but not limited to early detection of lead or device failure, arrhythmias, and findings relevant to heart failure management. For example, remote monitoring has been shown to reduce inappropriate shocks and improve survival.

Surprisingly, the available data regarding the impact of remote monitoring on hospitalization have been mixed. For example, the TRUST trial demonstrated reduced healthcare utilization (scheduled and unscheduled office and hospital visits) with remote monitoring in ICD patients (2.1 visits per patient-year compared with 3.8; P<0.001). On the other hand, several other randomized trials have not shown reduced hospitalization with remote monitoring when compared to routine clinical care.
The recently completed MORE-CARE study also failed to demonstrate reduced cardiovascular hospitalization in CRT-D patients managed with remote monitoring, although cardiovascular healthcare utilization was 38% lower in the remote monitoring versus the standard care arm. It is important to note that the failure to detect a difference in MORE-CARE may have been due to low power as a result of premature study termination. When examining the totality of the data, a meta-analysis of 21 randomized trials (total of 5715 patients) demonstrated that remote monitoring reduces heart failure hospitalization (rate ratio 0.77, 95% CI 0.65-0.91).

A recent assessment of nationwide U.S. data suggests that remote monitoring is associated with significant reductions in healthcare utilization and hospitalization, including heart failure hospitalization. In fact, remote monitoring may reduce hospitalization costs by 30% in patients with implanted devices. For every 100,000 patient years of follow-up, remote monitoring is associated with 9810 fewer hospitalizations, and $370,270,000 lower hospital payments. The benefits appear to be even greater in heart failure patients with CRT-D devices, where remote monitoring is associated with a 36% lower rate of repeat heart failure hospitalization (Figure 2).

Device-based data (remote monitored or not) can predict clinical decompensation and/or hospitalization for heart failure. For example, declining intrathoracic impedance can precede the presence of decompensated heart failure symptoms by as many as 15 ± 11 days. In a cohort of 326 CRT-D recipients, decreased intrathoracic impedance and high night heart rate independently predicted hospitalization for HF. When device-recorded impedance crossed threshold, there was a 35% increased risk of HF hospitalizations over the next four months (OR 1.352; 95% CI 1.126-1.623).

The PARTNERS-HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients with Heart Failure) sought to determine whether a device-based algorithm could predict acute heart failure decompensation in CRT-D patients. The algorithm utilized changes in intrathoracic impedance, an AF burden of six hours or more in a day, ventricular rate >90 during AF, biventricular pacing <90%, high night-time heart rate (NHR), low heart rate variability, and low patient activity level. CRT-D patients who were deemed high risk (two or more of the above conditions) by the algorithm had dramatically increased risk of heart failure hospitalization over the next 30 days (HR 5.5; 95% CI 3.4-8.8).

A pooled analysis including data from the PARTNERS-HF, OFISSER, FAST, and CONNECT trials similarly found that a weighted score based on intrathoracic impedance, AF diagnostics, and NHR was able to risk stratify patients as low, moderate, or high risk. Patients identified as high risk were 23 times more likely to be readmitted for HF within 30 days when compared to those identified as low risk. More recently, the MultiSENSE (Multi-sensor Algorithm Predicts HF Events in Patients With Implanted Devices) study demonstrated that an algorithm based upon thoracic impedance, respiration, heart rate, activity, and a device-detected S3 had a sensitivity of 70% for detection of HF decompensation in patients with CRT-D devices. Risk-stratification systems could be helpful in identifying patients who require intervention in order to prevent...
Table 1: EHRA/HRS CRT post-discharge follow-up and management recommendations.28 (Table adapted from Heart Rhythm. 2012;9(9):1524-1576.)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Status</th>
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<tr>
<td>1. Close cooperation between the heart failure and electrophysiology follow-up physicians.</td>
<td>Recommended</td>
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<tr>
<td>2. Minimum in-clinic follow-up interval of 6 months.</td>
<td>Recommended</td>
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<tr>
<td>3. Remote monitoring (in addition to in-clinic follow-up).</td>
<td>Recommended</td>
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<tr>
<td>4. Catheter ablation of the atrioventricular node in patients with atrial fibrillation and native conduction may be useful if CRT is not being delivered consistently.</td>
<td>May be useful</td>
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<td>5. Patients should be instructed to initiate a remote transmission if new symptoms arise.</td>
<td>Recommended</td>
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<td>6. Follow-up visits should include a patient history, physical examination, device interrogation and testing, and a systematic analysis of device data.</td>
<td>Recommended</td>
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<tr>
<td>7. Optimization, including up-titration of heart failure drug therapies (if appropriate) is recommended to maximize response to CRT.</td>
<td>Recommended</td>
</tr>
<tr>
<td>8. Evaluation of left ventricular function to assess heart failure progression is recommended during follow-up.</td>
<td>Recommended</td>
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<tr>
<td>9. Assessment of patient response to CRT, including symptom, functional response, and echocardiographic measures.</td>
<td>Recommended</td>
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<td>10. Echocardiographic-directed or empiric AV or VV optimization or LV lead repositioning may be considered in selected patients.</td>
<td>May be useful</td>
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<tr>
<td>11. Device interrogation should assess for atrial andventricular arrhythmias, quality of CRT delivery (including percentage biventricular pacing) and rate response.</td>
<td>Recommended</td>
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</table>

hospitalization. Such systems could be particularly helpful if automated, generating an admission risk score at each interrogation, whether remote or in-person.

GUIDELINES FOR CRT-D FOLLOW-UP

Patients who undergo CRT-D implantation should have an in-person evaluation within 12 weeks of implant. Furthermore, the European Heart Rhythm Association and Heart Rhythm Society have established consensus recommendations for the follow-up and management of CRT-D patients. These recommendations are detailed in Table 1. In general, a clinic evaluation with a functional assessment (NYHA or 6-minute walk) and echocardiogram at 3 or 6 months after implant is an opportune way to assess CRT response, although echocardiographic evidence of continued reverse remodeling may be seen out to 2 years beyond CRT implant. Fortunately, some patients with improvement in their functional status experience a survival benefit even without a positive echocardiographic response (improved LVEF).27

Central to the evaluation of CRT in follow-up is an assessment of the quality of CRT delivery. This begins with confirming adequate biventricular capture with an adequate safety threshold and without evidence of diaphragmatic stimulation or anodal capture (Figure 3). A quick but careful review of the paced 12-lead electrocardiogram can be very useful. A dominant R-wave in lead V1 and q/Q wave in lead I are highly suggestive of left ventricular capture.29 A negative paced QRS complex in V1 or absence of a q/Q wave in lead I should be thoroughly investigated, as they likely represent failure of left ventricular capture. The lateral precordial leads (V4-V6) are also helpful. Negative deflections in the lateral precordial leads suggest an apical pacing location and may indicate a need to reprogram to an alternative pacing vector (more basal electrode pair) or a need to reposition the LV lead. A careful review of a PA

Figure 3: Follow-up evaluation of biventricular pacing to ensure optimal outcomes.

Given the importance of optimal CRT delivery, particularly in patients who are non-responders, it is important to consider all therapeutic options for improving biventricular pacing percentage.
and lateral view chest x-ray is an important component of any non-responder assessment.

Once biventricular capture has been confirmed, attention should turn to evaluating the percentage of biventricular pacing and its optimization. As emphasized in the 2012 EHRA/HRS expert consensus statement, biventricular pacing percentage should be as close to 100% as possible. The best outcomes, including mortality reduction, are achieved when biventricular pacing is 98% or greater. Unfortunately, as many as 41% of patients do not achieve optimal biventricular pacing (<98%). When biventricular pacing is less than optimal, the factors contributing to reduced biventricular pacing should be identified and treated (Table 2). Important causes of reduced biventricular pacing include frequent ventricular ectopy, atrial fibrillation with short RR intervals, repetitive non-reentrant VA synchrony, and accelerated atrioventricular conduction. Due to suboptimal hemodynamic response, ventricular sense triggered biventricular pacing should not be included in the biventricular pacing percentage.

Given the importance of optimal CRT delivery, particularly in patients who are non-responders, it is important to consider all therapeutic options for improving biventricular pacing percentage. For patients with frequent monomorphic PVCs refractory to medical therapy, consideration should be given to catheter ablation. Similarly, in patients with paroxysmal or persistent AF who continue to have rapid conduction and reduced biventricular pacing despite maximal tolerated medical therapy and increasing the lower rate limit, AF ablation should be considered. In patients with permanent AF, atrioventricular node ablation should be considered. It is also important to note that the device-based count of biventricular pacing may be an overestimate of the true biventricular pacing percentage due to QRS fusion and pseudofusion. In cases of concern, a Holter may be helpful to assess the true biventricular pacing percentage. A protocol-based review of biventricular pacing in remote transmissions can significantly improve biventricular pacing (90 ± 6 to 94 ± 4%; P<0.001).

If patients have confirmed biventricular capture with an optimal biventricular pacing percentage, yet do not appear to have responded to CRT, then other potential causes of non-response should be considered. CRT optimization with echocardiography should be considered (see section below). Lead position and pacing vector should be reviewed to ensure it is neither apical nor anterior. If so, an alternative vector should be chosen (i.e., more basal), or if necessary, a lead revision procedure should be considered if there is an alternative target vessel. Targeting the longest QLV (the interval from the onset of the surface ECG QRS complex to onset of the LV electrogram) should be strongly considered when non-responders are brought back to the lab for lead revision. Multisite pacing may also prove beneficial in patients who fail to respond to conventional CRT; however, there are no randomized data demonstrating improved outcomes with multisite pacing compared to conventional CRT with a quadripolar lead.

It is also important to verify, particularly in patients referred for non-response, that there was an appropriate indication for CRT at the time of implant. For example, if a patient has an underlying narrow QRS, then disabling biventricular pacing may be the most important intervention for the patient.

**PROGRAMMING IN FOLLOW-UP: AV AND VV OPTIMIZATION**

The goal of CRT optimization is to maximize cardiac

<table>
<thead>
<tr>
<th>Cause of Reduced Biventricular Pacing</th>
<th>Potential Interventions</th>
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<tbody>
<tr>
<td>Intrinsic atrioventricular conduction/undesired QRS fusion</td>
<td>• Reduce paced and sensed AV delays</td>
</tr>
<tr>
<td>Loss of biventricular pacing with exercise/activity (sinus rhythm above tracking rate)</td>
<td>• Increase beta-blocker therapy • Increase maximal tracking rate</td>
</tr>
<tr>
<td>Atrial fibrillation with rapid ventricular conduction</td>
<td>• Increase AVN blocker therapy • Increase LRL • Catheter ablation of AF (when appropriate) • AV node ablation</td>
</tr>
<tr>
<td>Frequent premature ventricular contractions</td>
<td>• Increase beta-blocker • Increase LRL • Antiarrhythmic drug therapy • Catheter ablation of PVC</td>
</tr>
<tr>
<td>Repetitive non-reentrant ventriculoatrial synchrony (RNRVAS)</td>
<td>• Reduce LRL • Shorten AV delays</td>
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</table>

Despite the notable effectiveness of CRT, heart failure progression and hospitalization remain significant clinical problems in patients treated with CRT. There are several interventions that should be enacted to ensure the best outcomes possible for each patient.
hemodynamic performance. One of the challenges of CRT optimization is that there is no consensus on the best or optimal method. Furthermore, randomized trials have failed to show significant improvement in outcomes with both AV or VV optimization. As a result, the EHRA/HRS consensus statement regarding CRT follow-up does not recommend optimization in all patients, but suggests that it may be useful in select patients. In clinical practice, AV and VV intervals are often adjusted (55% and 26%, respectively), but these changes are highly variable.

Imperfect atrioventricular timing can impair ventricular filling time, decrease preload, and can consequently lead to decreased cardiac output. The goal of AV optimization is to determine and program an AV delay that maximizes ventricular filling before the onset of systole. While sensed AV delays less than 120 msec are generally associated with improved outcomes, if the AV interval is too short, the A wave can be truncated or absent. If the AV interval is too long, E-A wave fusion and diastolic mitral regurgitation can occur. While outside the scope of this review, several echocardiographic and electrophysiologic methods can be used to optimize the AV interval. The SMART-AV (SmartDelay determined AV Optimization) randomized trial compared a fixed AV delay set at 120 msec, versus echocardiographic AV optimization via mitral inflow technique (iterative method) and AV optimization with an electrogram-based method (SmartDelay). Neither echocardiographic nor SmartDelay AV optimization was superior to a fixed AV delay. Thus, at present, AV optimization is largely reserved for nonresponders.

Biventricular pacing is designed to eliminate interventricular dyssynchrony. VV optimization seeks to maximize stroke volume, contractility, or global LV performance. Accordingly, dp/dt max, left ventricular outflow tract VTI, and peak global longitudinal strain are echocardiographic parameters frequently used to optimize the VV interval in nonresponders. VV optimization is further complicated as the optimal VV delay is frequently different at rest versus exercise. Outcomes data suggest that most patients do appear to benefit from left ventricular pre-excitation (LV ~40 msec). However, most patients in clinical practice are programmed with no LV offset (simultaneous RV and LV pacing). Again, as with AV optimization, the role of VV optimization appears to be most compelling in non-responders.

SUMMARY

Despite the notable effectiveness of CRT, heart failure progression and hospitalization remain significant clinical problems in patients treated with CRT. There are several interventions that should be enacted to ensure the best outcomes possible for each patient. Initiation of remote monitoring with close follow-up and routine assessment of device-based risk factors for heart failure decompensation may help reduce hospitalization and healthcare utilization while improving quality of life and patient satisfaction. Follow-up management should also emphasize continued titration of medical therapy, optimization of biventricular pacing vector, maintenance of biventricular pacing percentage as close to 100% as possible, and AV and VV optimization in nonresponders for successful follow-up and management of CRT. A systematic (and iterative) approach will help ensure success throughout each center and in every patient.

References


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