Response to Coceani: Cardiac Resynchronization Therapy Has Earned Its Class I Recommendation and Continues to Thrive Under Scrutiny

Kenneth Dickstein, MD, PhD

Eva is a cheerful 76-year-old Norwegian woman with 5 grandchildren who had an anterior myocardial infarction 8 years ago and subsequently underwent coronary artery bypass grafting for triple-vessel disease. Over the last several years, she developed heart failure as the result of ischemic cardiomyopathy and became increasingly symptomatic. Until 1 year ago, she was reasonably active but has become short of breath on mild exertion, with New York Heart Association (NYHA) Class III symptoms. She does not have angina. We had an unusually cold winter this year, and she was unable to walk in the snow and was once hospitalized for an episode of decompensation with dyspnea at rest.

There is consistency across the European and American guidelines1–5 in providing the Class I recommendation level of evidence A for cardiac resynchronization therapy (CRT) for patients with heart failure, New York Heart Association class functional Class III-IV symptoms, left ventricular dysfunction, and a wide QRS complex. I was surprised to read that Dr Coceani is not convinced that CRT deserves this strong recommendation for patients with these conventional criteria.5 Well-founded skepticism is to be admired. However, in this case it is undeserved. The evidence is irrefutable. In CARE-HF, which found a 40% relative risk reduction in the primary end point of all-cause death or cardiovascular hospitalization and a 52% reduction in heart failure hospitalizations, the number needed to treat to prevent a primary end point was 9.5 In cardiovascular medicine, it is unusual to demonstrate such powerful intervention strategies.

It is beyond the scope of this brief editorial to review in detail the convincing evidence from the 12 carefully controlled, randomized clinical trials (RCTs). The results demonstrate substantial efficacy in both mortality and morbidity end points and improvements in symptoms and functional capacity. These results are strengthened by favorable changes in strong surrogate measurements, providing mechanistic support such as left ventricular remodeling and biomarker profiles.

There is considerable enthusiasm concerning the role of CRT in our treatment strategy in heart failure. It is not only the consistent and convincing results from the RCTs that have generated this enthusiasm. The concept is intuitively attractive. Health care professionals as well as patients can readily grasp the importance of synchronous left ventricular contraction and physiological interplay between the 2 ventricles. Electric dyssynchrony resulting in mechanical dyssynchrony is a readily understood mechanism. Most of us working with patients in this field have seen some super-responders. Impressive anecdotal experience sends a strong message and encourages clinicians to explore further this treatment strategy.

Eva’s ECG showed atrial fibrillation with a rate of 70 to 100 bpm and a left bundle-branch pattern with a QRS width of 140 ms. Her ejection fraction was approximately 25%, perhaps exaggerated by a moderate mitral insufficiency with an estimated systolic pulmonary artery pressure of 50 mm Hg. The left ventricle was dilated (65 mm), with areas of diffuse hypokinesis without obvious mechanical dyssynchrony. Coronary angiography demonstrated open, well-functioning grafts. She was treated with enalapril, bumetanide, spironolactone, bisoprolol, and digoxin. Her renal function was compromised with an eGFR of 30 and an N-BNP of 5500 pg/mL.

As Dr Coceani points out, RCTs have important limitations, and this issue was recently well reviewed in the journal.7 Of course, we have much to learn to better identify the population most likely to benefit from CRT and to better predict the likelihood of a poor response. However, it would be unfair to deny patients who are similar to the cohorts included in these trials the potential benefits that have been demonstrated. The guideline task forces are obligated to vigorously review the clinical trial data and make recommendations based on consensus expert opinion and evaluate the strength of the supportive evidence. It is imperative that treatment be tailored to the individual patient and that we evaluate the patient’s clinical status and expected prognosis before making any therapeutic decision and do not confuse “outcome with treatment and response to treatment.”8

True, there are gaps in the evidence, and important unanswered clinical questions remain concerning indications, contraindications, and technique. The most pressing are listed...
in the Table. Clinicians are continually exploring new territory, and currently active research programs are addressing these issues and expanding the role for CRT in the treatment of patients with heart failure. In a recent, real-life, clinical survey of practice in 13 European countries, it was reported that 22% of patients receiving CRT were in NYHA Class I or II, 23% had atrial fibrillation, and 19% had a QRS width of 130 ms; all off-label indications.9

Efficacious interventions, whether nonpharmacologic, pharmacological, or device therapies, are continually being reevaluated to refine our ability to target the most appropriate population and improve our use of these interventions; we are still debating how to optimally use diuretics in heart failure.

Pros and cons were discussed at our lively daily heart conference. There was concern that Eva was elderly with atrial fibrillation and mitral insufficiency. She had only a moderately widened QRS width and did not have obvious dyssynchrony on echocardiography. How much of her mitral valve dysfunction might be due to reversible papillary muscle dyssynchrony? A contrast MRI to detect viable myocardium would have been helpful, but her renal dysfunction made that risky. The indication for an implantable cardioverter-defibrillator seemed clear, but were we sure that her prognosis was good enough to defend the implantation? In which case, the device would obviously have to be a CRT-D. Was AV nodal ablation due to the atrial fibrillation necessary to slow ventricular rate, make the patient pacing-dependent, and ensure optimal benefit from the device? Dr Cociani is concerned about earlier reports suggesting high rates of nonresponders.10 Reports that conflict with the trial data and the more recent reports confirming high response rates in appropriately selected patients must be examined carefully. Unfortunately, there is no agreement among investigators concerning the criteria evaluated to determine response. A recent review of 26 of the most cited publications on predicting response to CRT demonstrated that response was defined using 17 different criteria.11 Although an elusive goal, the heart failure community should strive to develop a standard composite end point.12 In the meantime, clinicians should confirm that the patient was selected according to guideline criteria, excluding other important comorbidities that may decrease the likelihood of success. Was the device implanted by an operator experienced in placing the left ventricular lead in an optimal position, and was adequate time invested in follow-up, including optimizing the device program and adjusting medical therapy?

At the conference, we agreed that there is insufficient trial evidence to guide us adequately in our decisions in a patient such as Eva. She was not the typical patient included in the RCTs. We did not want to expose her to any unjustified risk and use considerable resources without the likelihood of real clinical benefit. In this case, however, we decided that the potential improvement would justify risking a poor response. She received her CRT-D 3 weeks ago. The procedure was uncomplicated, and she is convinced that her symptoms have improved. Currently, her device program and medical treatment are being fine-tuned at the outpatient department. The acid test is that she does not regret receiving the device. She looks forward to taking a long walk in the countryside once the snow melts and the volcanic ash from our neighbors in Iceland blows away.

Disclosures
Dr Dickstein received honoraria from Medtronic, Boston Scientific, and Biotronik.

References
6. Cleland JG, Calvert MJ, Verboven Y, Freemantle N. Effects of cardiac resynchronization therapy on long-term quality of life: an analysis from

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Table. Essential Yet Unresolved Issues in CRT

<table>
<thead>
<tr>
<th>Patient Selection</th>
<th>Implantation Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic biological age?</td>
<td>Role of imaging techniques to detect mechanical</td>
</tr>
<tr>
<td>Major comorbidities?</td>
<td>dyssynchrony/viable myocardium?</td>
</tr>
<tr>
<td>QRS width between 120 and 150 ms?</td>
<td>CRT-P or CRT-D?</td>
</tr>
<tr>
<td>Atrial fibrillation?</td>
<td>Importance of operator experience/lead placement?</td>
</tr>
<tr>
<td>Right bundle-branch pattern?</td>
<td>Skills in optimal AV, VV programming?</td>
</tr>
<tr>
<td>Ejection fraction &gt;35%?</td>
<td>Indications for AV nodal ablation in AF?</td>
</tr>
<tr>
<td>Echocardiographic evidence of left ventricular dilation/dyssynchrony?</td>
<td>Adequate follow-up provided?</td>
</tr>
<tr>
<td>Mitral insufficiency?</td>
<td>Safety and quality of life issues?</td>
</tr>
<tr>
<td>Heart failure, ICD indication with QRS &lt;120 ms?</td>
<td>Health resource use and cost/benefit ratio?</td>
</tr>
<tr>
<td>Heart failure, right ventricular pacing indication with QRS &lt;120 ms?</td>
<td>Which factors in selection/lead placement/ Follow-up</td>
</tr>
<tr>
<td>New York Heart Association Class I/II symptoms?</td>
<td>predict a poor response?</td>
</tr>
</tbody>
</table>


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