Cardiac Resynchronization Therapy
Who is and who is not a Candidate? Who Decides?
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Introduction
It is estimated that nearly 500,000 Canadians are currently living with heart failure, a disease process associated with considerable morbidity and mortality. Despite significant evidence for effective medical therapies, heart failure remains one of the leading causes of hospitalization in Canada and patients with the disease experience an annual mortality of up to 10%.1

Approximately one in three patients with systolic heart failure have some degree of intraventricular conduction delay, manifest as increased QRS duration on electrocardiogram (ECG), the most common of which is left bundle branch block (LBBB). This conduction delay, or electrical dyssynchrony, can lead to mechanical uncoupling and inefficiency, which, in turn, can lead to exacerbation of systolic dysfunction, altered myocardial metabolism, functional mitral regurgitation, negative remodeling and worsening clinical outcomes. Cardiac resynchronization therapy (CRT), also known as biventricular pacing, involves coordinating contraction between the left (LV) and right ventricles (RV) through programmed pacing of both ventricles. CRT is an established non-pharmacological therapy for patients with systolic heart failure due to a low ejection fraction, who have a QRS >130 ms and who are symptomatic despite optimal medical therapy. In carefully selected patients, CRT has been shown to promote positive LV remodeling, increase functional capacity, improve quality of life, reduce heart failure hospitalizations and reduce mortality.2 CRT systems can include defibrillator capabilities (CRT-D) or act as a stand-alone pacemaker (CRT-P).

The insertion of a CRT system consumes significant resource (costs), requires a commitment to regular clinical follow-up, and the acceptance of permanent implantation of a large medical device. Clinicians are tasked with identifying patients who would be expected to benefit from CRT and making the decision whether to proceed with CRT implantation. Therefore a careful consideration of the risks and benefits of this technology is required by both the healthcare providers and the patient.

Herein we hope to offer guidance on identifying ideal candidates for CRT and to remind health care providers that the patients’ goals must be taken into consideration when counseling a patient for treatment with CRT.
The potential for benefit from CRT was established early in small trials demonstrating technical feasibility and clinical benefits including improved ventricular function, exercise tolerance and quality of life, as well as a reduction in hospitalizations. 3-6

Beginning in 2004, a series of larger trials brought CRT into mainstream heart failure care, gradually expanding evidence for its benefit across a spectrum of symptomatic ambulatory heart failure. The COMPANION trial reported on 1520 patients with NYHA Class III-IV heart failure, a QRS interval > 120 msec, and an LVEF < 35% who were randomly assigned in a 1:2:2 ratio to receive optimal pharmacologic therapy alone or in combination with a CRT-P or CRT-D. After a mean follow-up of 15.7 months, the risk of the primary composite end point (time to death from any cause or hospitalization for any cause) was reduced by both CRT-P (HR, 0.81; P=0.014) and CRT-D (HR, 0.80; P=0.01), as compared to optimal medical therapy alone. This trial was the first to show benefit in hard clinical endpoints. Both the CRT-P and CRT-D showed a progressive lowering of hazard ratios with increasing QRS interval, suggesting that patients with the longest QRS intervals may derive the most benefit.7

The CARE-HF trial evaluated 813 patients with NYHA Class III-IV symptoms, sinus rhythm, a QRS of > 120 ms and an LVEF of < 35% and randomly assigned them to either medical therapy alone or with CRT-P for a mean follow-up of 29.4 months. The primary end points of death from any cause or an unplanned hospitalization for a major cardiovascular event were significantly lower in the CRT-P group (HR 0.63; P<0.001) showing the benefit of CRT-P even without defibrillation. Like COMPANION, it showed greater benefit in patients with longer QRS duration.8

The MADIT-CRT study was the first to include less symptomatic patients, assigning 1820 patients with NYHA class I-II symptoms (85% were NYHA II), an LVEF of 30% compared to optimal medical therapy alone. This trial was the first to show benefit in hard clinical endpoints. Both the CRT-P and CRT-D showed a progressive lowering of hazard ratios with increasing QRS interval, suggesting that patients with the longest QRS intervals may derive the most benefit.7
or less, and a QRS duration of 130 ms or more in a 3:2 ratio to receive CRT-D or an implantable cardioverter defibrillator (ICD). During an average follow-up of 2.4 years, the primary end point of death from any cause or a nonfatal heart-failure event was decreased in the CRT-D group (HR 0.66; \( P = 0.001 \)). The pre-specified subgroup of patients with NYHA I symptoms did not show benefit.9

Most recently, the RAFT trial randomly assigned 1798 patients with NYHA class II-III heart failure symptoms, LVEF < 30%, and a QRS duration > 120 ms or a paced QRS duration of > 200 ms to receive either an ICD alone or a CRT-D over a mean follow-up of 40 months. The primary outcome of death from any cause or hospitalization for heart failure occurred less frequently in the CRT-D group (HR 0.75; \( P<0.001 \)). This benefit was maintained across both the NYHA II and III subgroups.10 Sub-studies of the RAFT trial showed that patients with permanent atrial fibrillation or flutter and patients without left bundle branch block (LBBB) appear to derive minimal benefit from CRT.11,12

There are several groups of patients that are underrepresented in the trials. These include patients in permanent atrial fibrillation, patients with right bundle branch block (RBBB), very elderly patients and patients who are dependent on right ventricular pacing. There are trials underway to address this limitation.13 There is emerging evidence that patients with a bradycardic indication for right ventricular pacing who have mild to moderate left ventricular systolic dysfunction (EF 35-50%) may benefit from biventricular pacing. However, trial results are not consistent so which patients will benefit is not yet well established.14,15

Current Canadian Cardiovascular Society Guidelines make a strong recommendation with high-quality evidence that CRT be offered to patients who are NYHA class II-IV (ambulatory), on optimal medical therapy, have an LVEF < 35% and are in sinus rhythm with LBBB and a QRS duration > 130 ms.16 Ideal candidates, possible candidates, and patients for whom CRT is not recommended are summarized in Table 1.

### Implantation of CRT: Who decides?

Patients with significant systolic heart failure who have reached the stage of consideration for CRT have invariably lived through an extensive illness experience. The process of diagnosis, patient education and medication titration can take several months. Over this time course, it is also important to establish the patients’ goals of care. A cardiac implantable electronic device such as a CRT is inherently different from most other established therapies in both its invasiveness, commitment to regular follow-up care, and permanency. The anticipated benefits from a CRT system, with or without an ICD, must be weighed against the risks of the procedure, the long-term limitations in activities (e.g. employment restrictions) and the psychological impact.

The decision to implant a CRT system can be complex and requires important collaboration between well-informed health care providers and well-informed patients. An interdisciplinary team approach can assist in the care of such patients and may include specialist and primary care physicians, nurse specialists as well as social workers and spiritual care, where appropriate.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ideal CRT Candidates</th>
<th>Possible CRT Candidates</th>
<th>CRT Not Recommended</th>
</tr>
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<tbody>
<tr>
<td>NYHA HF Class</td>
<td>II-III</td>
<td></td>
<td>Asymptomatic</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Non-ambulatory IV</td>
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<tr>
<td>Medical Therapy</td>
<td>GDMT</td>
<td>Revascularized (where indicated)</td>
<td>Not taking GDMT</td>
</tr>
<tr>
<td>Rhythm and QRS duration</td>
<td>Sinus rhythm LBBB &gt; 150 ms</td>
<td>Controlled AF LBBB &gt; 130 ms RBBB/IVCD &gt; 150 ms PM dependent</td>
<td>QRS &lt; 130 ms</td>
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<tr>
<td>LVEF</td>
<td>&lt; 30%</td>
<td>&lt; 35%</td>
<td></td>
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<tr>
<td>Life Expectancy</td>
<td></td>
<td></td>
<td>&lt; 1 year</td>
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</tbody>
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CRT - Cardiac Resynchronization therapy, PM - Pacemaker, LVEF - left ventricular ejection fraction, AF - atrial fibrillation, NYHA - New York Heart Association, GDMT - Guideline-directed medical therapy, LBBB - left bundle branch block, RBBB - right bundle branch block, IVCD - intraventricular conduction delay.
Conclusions
The evidence presented supports improved symptoms and survival for subgroups of patients with systolic heart failure who receive a CRT device. Patients should be carefully selected by health care providers after considering the benefits and risks based on the clinical circumstances. Careful discussion must occur to ensure that CRT with or without ICD is consistent with patients’ goals of care. Patients who would be expected to derive clinical benefit from CRT are taking guideline-directed medical therapy, have (i) NYHA II-II symptoms, (ii) LVEF <30% (iii) sinus rhythm with LBBB and (iv) a QRS duration of > 150 ms.

References