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Society Guidelines

Canadian Cardiovascular Society Guidelines on the Use of Cardiac Resynchronization Therapy: Evidence and Patient Selection

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ABSTRACT

Recent landmark trials provided the impetus to update the recommendations for cardiac resynchronization therapy (CRT). This article provides guidance on the prescription of CRT within the confines of published data. A future article will explore the implementation of these guidelines. These guidelines are intended to serve as a framework for the prescription of CRT within the Canadian health care system and beyond. They were developed through a critical evaluation of the existing literature, and expert consensus. The panel unanimously adopted each recommendation. The 8 recommendations relate to

RÉSUMÉ

Des essais novateurs récents ont stimulé la mise à jour des recommandations sur le traitement de resynchronisation cardiaque (TRC). Cet article fournit des lignes directrices sur la prescription de TRC dans les limites des données publiées. Un futur article explorera la mise en œuvre de ces lignes directrices. Ces lignes directrices sont destinées à servir de cadre à la prescription de TRC dans le système de soins de santé canadien et au-delà. Elles ont été développées par une évaluation critique de la littérature existante et le consensus des experts. Le panel a adopté unanimement chacune des recommandations. Les 8

Introduction

Rationale for cardiac resynchronization therapy

Heart failure affects more than 485,000 Canadians and results in significant morbidity and mortality.[1] Despite advances in medical therapy, patients with heart failure remain at high risk for death and hospitalization.[1] Dyssynchronous ventricular contraction affects 1 in 4 patients with systolic heart failure.[2] Cardiac resynchronization therapy (CRT) is designed to synchronize the mechanical activity of the ventricles, and the timing of the atria and ventricles among those in sinus rhythm. QRS duration, along with functional class and left ventricular ejection fraction (LVEF), are used to select candidates for CRT. Among selected patients, CRT has been shown to improve left ventricular (LV) function

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This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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ensuring the adequacy of medical therapy before the initiation of CRT, the use of symptom severity to select candidates for CRT, differing recommendations based on the presence or absence of sinus rhythm, the presence of left bundle branch block vs other conduction patterns, and QRS duration. The use of CRT in the setting of chronic right ventricular pacing, left ventricular lead placement, and the routine assessment of dyssynchrony to guide the prescription of CRT are also included. The strength of evidence was weighed, taking full consideration of any risks of bias, as well as any imprecision, inconsistency, and indirectness of the available data. The strength of each recommendation and the quality of evidence were adjudicated. Trade-offs between desirable and undesirable consequences of alternative management strategies were considered, as were values, preferences, and resource availability. These guidelines were externally reviewed by experts, modified based on those reviews, and will be updated as new knowledge is acquired.

recommandations visent à assurer l'adéquation du traitement médical avant le début du TRC, l'utilisation de la gravité des symptômes pour sélectionner les candidats au TRC, les diverses recommandations basées sur la présence ou l'absence de rythme sinusal, la présence de bloc de branche gauche par rapport à d'autres modèles de conduction et la durée du complexe QRS. L'utilisation du TRC dans le cadre de stimulation ventriculaire droite chronique, la pose de sonde ventriculaire gauche et l'évaluation systématique de la dyssynchronie pour orienter la prescription de TRC sont aussi incluses. La force des preuves a été pondérée, en tenant pleinement compte de tout risque de partialité, ainsi que de toute imprécision, toute incohérence et toute divergence des données disponibles. La force de chacune des recommandations et la qualité des preuves ont été soupesées. Les compromis entre les conséquences désirables et indésirables des autres stratégies de prise en charge ont été considérés, comme l'on été les valeurs, les préférences et la disponibilité des ressources. Ces lignes directrices ont été examinées à l'externe par des experts, modifiées selon ces revues, et seront mises à jour dès l'acquisition de nouvelles connaissances.

(reverse remodelling), reduce mitral regurgitation, enhance cardiac output, and reduce heart failure symptoms without increasing myocardial energy consumption.[3,4] Improved cardiac mechanical synchrony is thought to be central to the benefit of CRT.[5,6] Improved survival and reduced morbidity have been demonstrated among selected patients with systolic heart failure enrolled in large randomized trials of CRT.[7]

Updated guidelines

The completion of several landmark trials provided the impetus to update the Canadian CRT recommendations.[8,9] This document provides guidance on the prescription of CRT within the confines of published data. A subsequent publication will further explore the implementation of these guidelines. These guidelines are intended to serve as a framework for the prescription of CRT within the Canadian healthcare system and beyond. The intended audience for these documents includes specialist and generalist physicians and surgeons, allied professionals, and administrators involved in the care of patients with heart failure. These guidelines were developed through a critical evaluation of the existing literature, expert consensus, and use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[10] The strength of evidence was weighed, taking full consideration of any risks of bias, including publication bias, and any imprecision, inconsistency, and indirectness of the available data. The strength of each recommendation was categorized as "Strong" or "Weak (conditional)," and the quality of this evidence as "High," "Moderate," "Low," or "Very Low." The trade-off between desirable and undesirable consequences of alternative management strategies was considered, as were values, preferences, and resource availability. Valid systematic methods were used when possible, based on published evidence similar to previous guidelines.[11] These guidelines were externally reviewed by experts and modified, based on those reviews. The literature supporting each recommendation is discussed in the following sections. The committee's 8 recommendations are contained within the following sections and are summarized in Supplemental Table S1. The panel unanimously adopted each recommendation.

Clinical Selection Criteria

Clinical trials evaluating a new intervention for patients with heart failure typically require that it be assessed on a background of appropriate pharmacologic therapy. Thus, CRT is adjunct to, not a replacement of medical therapy. The prescription of CRT should typically only be considered in the setting of adequate background medical therapy for heart failure.[12] All of the landmark trials of CRT required that patients receive adequate medical therapy before enrollment. Further, because New York Heart Association (NYHA) functional class, QRS duration, and LVEF are each central in deciding on the appropriateness of CRT, these data need to be based on objective assessment methods.

Appropriate medical therapy

Heart failure medications should be optimized to enhance the probability that CRT will be successful. For patients with NYHA II-IV functional class, this should include guideline-specified doses of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, and mineralocorticoid receptor antagonists for patients with class III-IV symptoms and those with NYHA II symptoms and high-risk features.[12] A summary of medication use in selected trials is presented in Table 1.

RECOMMENDATION

1. It is recommended that adequate medical therapy be implemented before the initiation of CRT, that each patient's suitability for CRT be thoroughly assessed, and the details of that assessment be recorded in their medical record (Strong Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places greater value on the landmark CRT trials; all of which required patients to receive optimal medical therapy at the time of enrollment.

Practical tip. Reasons for nonuse of recommended heart failure medications or the prescription of lower than the recom-

Table 1. Baseline medication use in the major CRT trials (shown as percentages)

Study (year)	ACEi/ARB			β-Blocker			MRA			Diuretic		
	Med	**CRT**	**CRT-D**	**Med**	**CRT**	**CRT-D**	**Med**	**CRT**	**CRT-D**	**Med**	**CRT**	**CRT-D**
COMPANION (2004)[13]	89	89	90	6 6		6 8		5 3	5 5			9 7
	Med		**CRT**	**Med**		**CRT**	**Med**		**CRT**	**Med**		**CRT**
CARE-HF (2005)[14]	95		95	74		70	59		54	44		43
	ICD		**CRT-D**	**ICD**		**CRT-D**	**ICD**		**CRT-D**	**ICD**		**CRT-D**
MADIT-CRT (2009)[15]	97		98	93		93	31		32	73		76
	ICD		**CRT-D**	**ICD**		**CRT-D**	**ICD**		**CRT-D**	**ICD**		**CRT-D**
RAFT (2010)[16]	97		96	89		90	42		42	84		85

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CARE-HF, **Ca**rdiac **Re**synchronization in **H**eart **F**ailure; COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT, cardiac resynchronization therapy; CRT-D, CRT plus implantable cardioverter-defibrillator; ICD, implantable cardioverter-defibrillator; MADIT-CRT, **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial - **C**ardiac **R**esynchronization **T**herapy; Med, medical therapy alone; MRA, mineralocorticoid receptor antagonist; RAFT, **R**esynchronization/Defibrillation for **A**mbulatory Heart **F**ailure **T**rial.

mended doses of these medications should be recorded. Each patient's functional capacity should be assessed. Although measures of functional status other than the NYHA system have been proposed, the landmark trials solely used this as an inclusion criterion.[7] Thus, at a minimum, assessment of functional class should include the patient's NYHA class. Six-minute hall walk distance, disease-specific health-related quality of life, and cardiopulmonary testing should also be considered. In addition, the QRS duration should be measured from a standard 12-lead electrocardiograph and the LVEF quantified using a validated assessment method. The results of these assessments should be recorded in the patient's medical record.

Efficacy of CRT

Assessing benefit

Though CRT is efficacious on average, not all patients clearly benefit from this intervention. One challenge in assessing benefit from CRT is the lack of a common definition of response to CRT. Clinical response scores, LV remodelling, functional class, and clinical outcomes have all been used. Yet, there is poor correlation between these measures.[17] Further, lack of response to CRT by a given patient might relate to an absence of mechanical dyssynchrony, a failure to achieve adequate resynchronization, disease which has advanced too far, changes in a patient's underlying condition, other factors, or a combination of these elements.[18]

Randomized trial data

Wells and colleagues performed a detailed systematic review and meta-analysis of CRT.[7] This included 7539 patients enrolled in 12 trials, 4244 of whom were randomized to a CRT pacemaker (CRT-P) or CRT defibrillator (CRT-D) in addition to medical therapy, and 3295 patients assigned to medical therapy alone or in addition to an implantable cardioverter-defibrillator (ICD). These studies are summarized in Table 2. The length of follow up in these trials ranged from 3 to 40 months.[7] Most (63%-89%) patients were male, their mean age ranged from 62 to 66 years, and a sizable percentage (38%-70%) had ischemic cardiomyopathy. The mean LVEF ranged from 21%-25%. Nearly all studies required patients to be in sinus rhythm and limited enrollment to patients with QRS durations ≥ 130 ms. Mean QRS durations of enrolled subjects were similar, ranging from 153-176 ms. Of the studies that reported conduction patterns, most patients had left bundle branch block (LBBB). Right bundle branch block (RBBB) was present in only 10%-16% of subjects (see *Patient Selection* section). Patients with severe pulmonary, renal, or liver disease, or an estimated survival less than 6-12 months were uniformly excluded. Thus, some patients are too ill, too frail, or have extensive comorbidities that preclude consideration of CRT. An in-depth discussion of these issues will be dealt with in a future publication related to implementation of these guidelines.

Very few patients who were asymptomatic at the time of enrollment (ie, NYHA class I) or with chronic, nonambulatory NYHA class IV symptoms (ie, end-stage heart failure requiring intravenous diuretic therapy, inotropic therapy, or intraaortic balloon-pump support) were included in the randomized CRT trials. Most studies also excluded patients with previous pacing therapy or permanent atrial fibrillation (AF). These latter 2 subgroups are discussed in the *Patient Selection* section. The primary end points of the CRT trials encompassed safety, functional status, 6-minute hall walk distance, health-related quality of life, peak oxygen consumption (VO_2), along with hospitalizations and death.[7]

Sources of bias

Biases were taken into account in assessing the quality of the evidence, in that studies with less bias were considered to represent a higher quality of evidence. Studies were examined using the Cochrane risk of bias tool.[27] Most studies were double blind, with the exception of **Ca**rdiac **Re**synchronization in **H**eart **F**ailure (CARE-HF),[14] **Co**mparison of **M**edical Therapy, **P**acing **an**d Defibrilla**tion** in Chronic Heart Failure (COMPANION),[13] Lozano et al.,[19] and **Mu**ltisite **Sti**mulation in **C**ardiomyopathies **S**inus **R**hythm (MUSTIC-SR).[20] The 3 former studies, although not blinded, had end point evaluation performed by a blinded committee, and MUSTIC-SR was single-blinded. An important source of bias that is unique to CRT trials is that 8 trials randomized patients after the device was successfully implanted,[19-26] thereby introducing a

Table 2. Characteristics of the major CRT trials

Study (year)	Intervention/control Design Intervention (n)/control (n)	QRS duration (msec); LVEF (%) at inclusion	Mean follow-up (mo)	NYHA I-II (%) III-IV (%)	Primary end point
Lozano (2000)[19]	CRT-D/ICD Crossover 109/113	>120; ≤35	3	35 65	Mortality
MUSTIC-SR (2001)[20]	CRT-P/Med Crossover 29/29	>150; <35	6	100 0	Walk distance
MIRACLE (2002)[21]	CRT-P/Med Parallel 228/225	≥130; ≤35	6	0 100	NYHA, QOL, walk distance
MIRACLE ICD (2003)[22]	CRT-D/ICD Parallel 187/182	≥130; ≤35	6	0 100	QOL, NYHA, walk distance
MIRACLE ICD II (2004)[23]	CRT-D/ICD Parallel 85/101	≥130; ≤35	6	100 0	Peak VO_2
COMPANION (2004)[13]	CRT-D/CRT-P/ICD Parallel 617/595/308	≥120; ≤35	14.8-16.5	0 100	Mortality or all-cause hospitalization
CARE-HF (2005)[14]	CRT-P/Med Parallel 409/404	≥120 (120-149, dyssynchrony); ≤35	29.4	0 100	Mortality or cardiovascular hospitalization
REVERSE (2008)[24]	CRT-D/ICD Parallel 419/191	≥130; ≤40	12	100 0	Heart failure clinical composite
RHYTHM-ICD[25]	CRT-D/ICD Parallel 119/59	≥150; ≤35	12.1	8 92	LV lead/system complications; VF detection; peak VO_2
VECTOR[26]	CRT-P/Med Parallel 59/47	≥140; ≤35	19.9	29 71	Safety, rate of successful LV lead implant
MADIT-CRT (2009)[15]	CRT-D/ICD Parallel 1089/731	≥130; ≤30	28.8	100 0	Death or nonfatal heart failure event
RAFT (2010)[16]	CRT-D/ICD Parallel 894/904	≥120 or paced ≥200; ≤30	40	80 20	Death or heart failure hospitalization

CARE-HF, **Ca**rdiac **Re**synchronization in **H**eart **F**ailure; COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT, cardiac resynchronization therapy; CRT-D, CRT plus implantable cardioverter-defibrillator; CRT-P, CRT pacemaker; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEF, LV ejection fraction; MADIT-CRT, **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial - **C**ardiac **R**esynchronization **T**herapy; Med, medical therapy alone; MIRACLE, **M**ulticenter InSync **I**CD **Ra**ndomized **Cl**inical **E**valuation; MUSTIC-SR, **Mu**ltisite **Sti**mulation in **C**ardiomyopathies **S**inus **R**hythm; NYHA, New York Heart Association; QOL, health-related quality of life; RAFT, **R**esynchronization/Defibrillation for **A**mbulatory Heart **F**ailure **T**rial; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction; RHYTHM-ICD, Resynchronization for Hemodynamic Treatment for Heart Failure Management - **ICD**; VO_2, peak oxygen consumption; VECTOR, Ventricular Resynchronization Therapy Randomized Trial; VF, ventricular fibrillation.

systematic bias. Follow-up in several studies was less than 12 months,[7] limiting conclusions with respect to the effect of CRT on mortality. This is of particular importance, as the 2 studies that demonstrated a mortality benefit with CRT, CARE-HF and ICD **R**esynchronization/Defibrillation for **A**mbulatory Heart **F**ailure **T**rial (RAFT) noted a separation of survival curves beyond 1 year of follow-up. Finally, RAFT[16] and MUSTIC-SR[20] were primarily funded by peer-reviewed granting agencies; the others were funded by industry.

CRT pacemaker

Data on the efficacy of CRT-P is available from 5 studies.[13,14,20,21,25] These trials were limited to symptomatic patients; those with NYHA class II, NYHA class III, or ambulatory NYHA class IV symptoms. Wells et al. noted a 27% significant relative risk reduction (RRR) in all-cause mortality when the studies were combined ($P < 0.0001$; RR, 0.73; 95% confidence interval [CI], 0.62-0.85) (Figure 1).[7] CARE-HF and COMPANION provide the bulk of evidence in this group. These 2 larger studies, along with 3 smaller studies, uniformly found a significant reduction in heart failure hospitalizations, along with improvements in hall walk distance and health-related quality of life with CRT-P. Collectively, these studies provide high quality evidence for CRT-P in addition to medical therapy for patients with symptomatic heart failure, QRS durations ≥ 130 ms, and LVEF values ≤ 35%.

CRT defibrillator

The addition of CRT to ICD was evaluated in 7 studies.[15,16,19,22,23,25,28] These trials included a spectrum of heart failure severity, ranging from NYHA class I to IV. Wells et al. found a significant RR of 17% in mortality ($P = 0.01$; RRR, 0.83; 95% CI, 0.72-0.96) when these data were combined (Figure 2).[7] Three trials considered less symptomatic patients, with NYHA class I/II limitation,[15,23,28] and 3 evaluated patients with more advanced symptoms, NYHA class III/

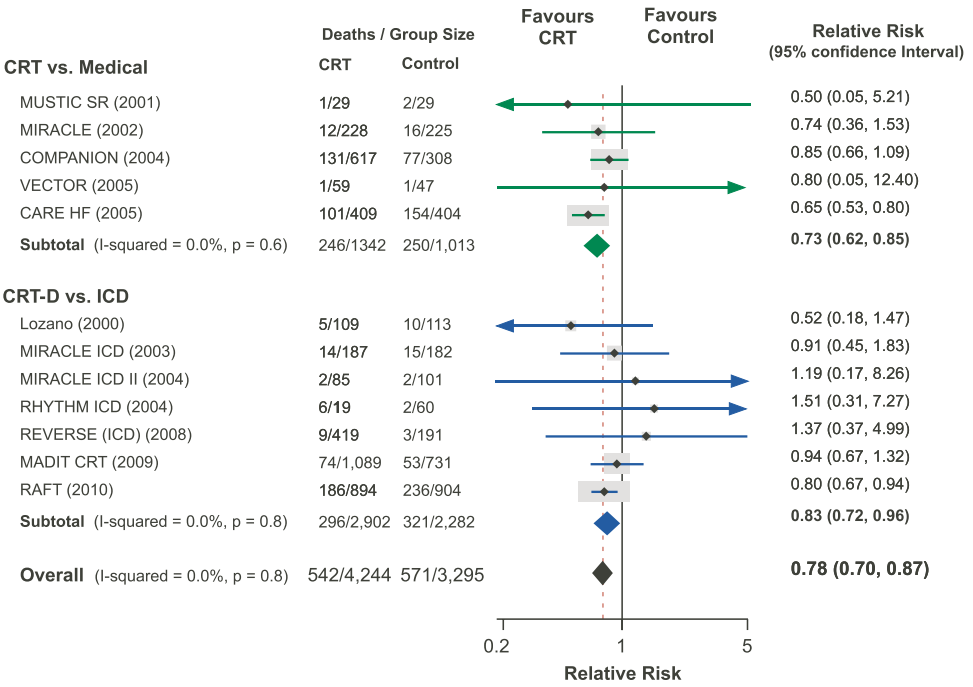

Figure 1. Random effects model for overall mortality in patients treated with cardiac resynchronization therapy (CRT) plus medical therapy or CRT plus an implantable cardioverter-defibrillator (ICD) vs their comparators. Random effects meta-analysis of overall mortality among patients with mildly symptomatic (New York Heart Association I-II) and advanced (III-IV) heart failure treated with CRT added to medical therapy or with CRT added to ICD. Values less than 1.0 indicate decreased risk of mortality with CRT. CARE-HF, Cardiac Resynchronization in Heart Failure; COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial - Cardiac Resynchronization Therapy; MIRACLE, Multicenter InSync ICD Randomized Clinical Evaluation; MUSTIC-SR, Multisite Stimulation in Cardiomyopathies Sinus Rhythm; RAFT, Resynchronization/Defibrillation for Ambulatory Heart Failure Trial; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction; RHYTHM, Resynchronization for Hemodynamic Treatment for Heart Failure Management; VECTOR, Ventricular Resynchronization Therapy Randomized Trial. Adapted from Wells et al.[7]

IV.[19,22,25] RAFT spanned these groups.[16] In the 4 studies that evaluated the addition of CRT to ICD in patients with NYHA class I/II symptoms a 20% reduction in the risk of death was found ($P = 0.02$; RRR, 0.80; 95% CI, 0.67-0.96).[15,16,23,28]

Of the 2 most recent CRT trials, **Re**synchronization Re**v**erses **R**emodeling in **S**ystolic Left V**e**ntricular Dysfunction (REVERSE) was the smallest. It demonstrated improvements in the clinical composite response (19% vs 34%; $P = 0.01$) and LV remodelling.[4] The 2 larger recent studies, **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial - **C**ardiac **R**esynchronization **T**herapy (MADIT-CRT) and RAFT, were powered to evaluate clinical outcomes. They provide the most conclusive evidence for CRT in a less symptomatic population. Both demonstrated significant reductions in their primary end points. The primary outcome in MADIT-CRT was worsening heart failure, defined as nonfatal heart failure events that were responsive to outpatient intravenous diuretic therapy or heart failure medication adjustment during hospital stay.[15] Patients assigned to CRT-D had a significantly lower (13.9%) risk of this outcome vs those randomized to an ICD alone (22.8%; $P < 0.001$). MADIT-CRT was stopped early, with an average follow-up of 29 months. The primary outcome in RAFT was all-cause death or hospitalization for heart failure. All-cause death was a secondary outcome.[16] The average follow-up in RAFT was 40 months. A lower risk of death or hospitalization for heart failure was observed in the group assigned to CRT-D (33%) vs an ICD alone (40%; $P = 0.0002$). The risk of death from any cause was also lower with CRT-D (34%) vs an ICD alone (45%) in RAFT ($P = 0.003$).

No heart failure symptoms

Adabag and colleagues performed a systematic review and meta-analysis of CRT in patients with asymptomatic and mildly symptomatic heart failure.[29] Among patients who were free of symptoms at the time of enrollment (ie, NYHA class I) a nonsignificant 15% reduction in the risk of death and a 43% reduction (95% CI, 3%-66%) in the risk of death or hospitalization for heart failure was identified.[29] Considering the present lack of clear evidence, there is not sufficient evidence to recommend CRT for patients without heart failure symptoms (NYHA class I).

Minimally symptomatic heart failure

In patients with mild symptoms, NYHA class II, Adabag et al. found a 22% reduction (95% CI, 4%-35%) in the risk of death and a 33% reduction (95% CI, 21%-43%) in the risk of hospitalization for heart failure.[29] In absolute terms, 28 patients with NYHA class II limitation would need to be treated with CRT to prevent 1 death and 2 admissions for heart failure during a period of 28 months.

Symptomatic heart failure

Four studies assessed the efficacy of CRT-D vs ICD on mortality in highly symptomatic patients (NYHA class III or

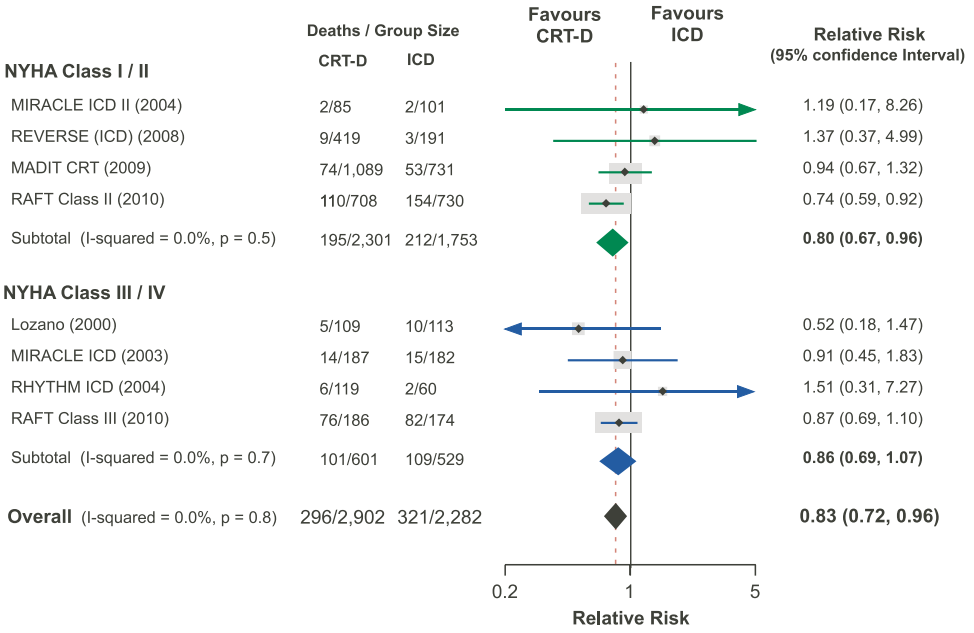

Figure 2. Random-effects model for overall mortality in those treated with CRT-D vs an ICD alone, stratified by NYHA class. Random-effects meta-analysis of overall mortality with mildly symptomatic (NYHA I-II) and advanced (III-IV) heart failure treated with CRT-D vs an ICD. Values less than 1.0 indicate decreased risk of mortality with CRT. CRT, cardiac resynchronization therapy; CRT-D, CRT plus implantable cardioverter-defibrillator; ICD, implantable cardioverter-defibrillator; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial - Cardiac Resynchronization Therapy; MIRACLE, Multicenter InSync ICD Randomized Clinical Evaluation; NYHA, New York Heart Association; RAFT, Resynchronization/Defibrillation for Ambulatory Heart Failure Trial; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction; RHYTHM, Resynchronization for Hemodynamic Treatment for Heart Failure Management. Adapted from Wells et al.[7]

ambulatory NYHA class IV).[16,19,22,25] In this group, Wells et al. demonstrated a nonsignificant reduction of 14% in the risk of death ($P = 0.17$).[7] This result, in conjunction with the evidence of benefit with CRT-P provides support for the use of CRT in this population. Considering these marginal results with CRT-D, its use in this group needs to be viewed in terms of the likelihood of benefit vs risk. There is not sufficient evidence to recommend CRT-D for patients with chronic, nonambulatory NYHA class IV symptoms considering the lack of data.

Risk vs benefit

Cardiac rhythm devices carry risk at the time of their implantation and over the long-term. The population evaluated for CRT therapy and the complexity of a CRT implant both need to be considered. This is particularly relevant when considering the potential added complexity of upgrading a patient with an existing cardiac rhythm device to CRT.

Adabag et al. summarized the risks associated with mostly de novo CRT implants and identified a 30-day adverse event rate of over 18% with CRT vs 4% with an ICD alone.[29] Most of these excess adverse events were related to LV lead dislodgment (5.1%) and implant failure (6.6%). In addition, the risks of repeated intervention might be significant in CRT recipients. For example, a large registry reported that complications related to pulse generator replacements, with or without lead revision, were significantly higher with CRT vs non-CRT procedures.[30] Though the noted advantages of CRT vs its comparators accounts for these risks in the near term, there is a lack of data on long-term outcomes. Hence, the application of CRT requires a thoughtful weighing of risks vs benefits in an individual patient.

Clinical risk scores have been promoted as a means of identifying patients less likely to benefit from arrhythmia device therapy, notably the very elderly, patients with very advanced symptoms of heart failure, and those with chronic renal failure.[31-36] However, none of these risk scores have been independently validated and there are no randomized data to guide clinical decision-making. Further, patients with advanced heart failure symptoms who undergo CRT might have a significant improvement in their heart failure symptoms and this might alter their long-term prognosis and perspective related to preventing sudden death.

RECOMMENDATION

2. CRT is recommended for patients in sinus rhythm with NYHA class II, NYHA class III, or ambulatory NYHA class IV heart failure symptoms, a LVEF $\leq$ 35%, and QRS duration $\geq$ 130 ms because of LBBB (Strong Recommendation, High-Quality Evidence).

Values and preferences. This recommendation places great value on the inclusion criteria of the landmark CRT trials, the characteristics of the patients enrolled in these trials, and the derived benefit of CRT in patient groups identified in subsequent analyses of these landmark trials.

Practical tip. There is insufficient evidence to recommend CRT in patients with NYHA class I limitation or for

nonambulatory class IV NYHA symptoms because these patients were largely not included in the major CRT studies. For this same reason, there is insufficient data to recommend CRT in patients with QRS durations < 130 ms. Patients with LBBB and QRS duration ≥ 150 ms appear more likely to benefit from CRT than patients with non-LBBB conduction and/or less QRS prolongation (see the *Patient Selection* section).

Delivery of CRT

CRT-P vs CRT-D

Significant geographic variation in CRT-P vs CRT-D prescription exists, with CRT-D accounting for > 70% of CRT systems.[37] This is likely because of the fact that most patients who qualify for CRT meet the criteria for a primary prevention ICD.[12] Only sparse data on the relative benefit of the 2 CRT platforms exist.[38] COMPANION evaluated the efficacy of CRT-P and CRT-D.[13] The primary end point was all-cause death or hospitalization. The secondary end point was mortality. CRT-P and CRT-D similarly reduced the primary end point (CRT-P hazard ratio [HR], 0.81; $P = 0.014$; and CRT-D HR, 0.80; $P = 0.01$) and the risk of death or hospitalization for heart failure (CRT-P HR, 0.66; $P < 0.002$; and CRT-D HR, 0.60; $P < 0.001$). In contrast, CRT-D reduced the risk of death significantly (HR, 0.64; $P = 0.003$), and only a trend toward a reduction was observed with CRT-P (HR, 0.76; $P = 0.059$). CARE-HF included only CRT-P.[14] After a mean follow-up of 29.4 months, the primary end point (all-cause death or hospitalization for heart failure) was significantly reduced with CRT-P (HR, 0.73; $P < 0.001$), as was the secondary outcome of all-cause death (HR, 0.74; $P < 0.002$). These reductions are comparable with those observed in COMPANION. However, 7% of the patients randomized to CRT-P in CARE-HF died suddenly. It is unclear whether some of these deaths would have been prevented by CRT-D. MADIT-CRT and RAFT only included patients treated with an ICD.

Cost effectiveness should also be considered. CRT-P is generally considered to be more cost effective than CRT-D. Based on present exchange rates, 1 analysis found that the incremental cost effectiveness ratio for CRT-P was CAD$13,900 (11,200 €) per quality-adjusted life year (QALY) vs CAD$38,400 (30,900 €) per QALY for CRT-D.[39] In another analysis the incremental cost effectiveness for CRT-D over CRT-P was CAD$59,500 (47,900 €) per QALY.[40,41]

A factual and comprehensive discussion with the patient as to the choice of CRT-P vs CRT-D is necessary.[18] This should take into consideration the patient's estimated life expectancy, comorbidities, expectations, beliefs regarding quality vs quantity of life, and the differential risks of CRT-D vs CRT-P over the long-term. CRT-P has been shown to improve survival, reduce morbidity, and enhance quality of life in patients with symptomatic heart failure. In fact, much of the data on the effect of CRT in these patients is based on CRT-P, rather than CRT-D.

RECOMMENDATION

3. A CRT-P is recommended for patients who are suitable for resynchronization therapy, but not for an ICD (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places a greater value on quality of life and improvement of heart failure symptoms, rather than prevention of sudden death.

Practical tip. CRT-P has been shown to reduce morbidity and mortality in patients with NYHA class III and ambulatory class IV heart failure symptoms. Therapy should be individualized in accordance with the overall goals of care.

Lead placement

Most studies have delivered CRT via biventricular pacing.[13-16,21] There are no reliable published data regarding the optimal right ventricular (RV) lead position.[42-48] Rather, its position is based on other considerations such as lead performance (pacing, sensing, and defibrillation), potential interaction with existing leads, and future removal.

There is significant variability in what defines an optimal LV lead position.[46,49] Various methods have been proposed to identify the optimal site for LV pacing, but no approach has been proven most effective.[50-55] Analysis of LV lead position in MADIT-CRT found no difference in clinical outcome based on lead position, apart from poorer outcomes in patients with LV leads placed in an apical region. Thus, pacing the LV from a nonapical LV epicardial region should be considered.[48,56] It is recognized that coronary venous anatomy, pacing thresholds, and phrenic nerve stimulation might limit LV lead placement in a specific region and that correlation between various imaging methods and standard radiography is imperfect.[57,58] One smaller randomized study found that LV pacing at a site of late mechanical activation resulted in greater LV remodelling vs placing an LV lead at a standard position.[59] Though targeted LV lead placement, where feasible, might be of benefit, additional data are required to support this notion.

RECOMMENDATION

4. In patients treated with CRT, pacing from a nonapical LV epicardial region might be considered (Weak Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places great value on the quality of the evidence.

Patient Selection

Sex

Data from multicentre studies evaluating the effects of sex on CRT benefit have been contradictory. COMPANION and CARE-HF found similar benefit in women and men,[14,60] and REVERSE, RAFT, and MADIT-CRT suggested greater ben-

efit in women than in men.[4,15,16] In most studies female patients were more likely to have nonischemic cardiomyopathy and LBBB, which might explain these differences. However, additional explanations have been proposed, including that QRS duration is, on average, 10 ms shorter in women vs men. Thus, for a given QRS duration, women might have more conduction disturbance and greater cardiac dyssynchrony vs men.[61]

QRS duration

Sipahi et al. performed a systematic review and meta-analysis of data from 5 randomized trials, totaling 5813 patients.[62] Patients were dichotomized to those with moderately vs severely prolonged QRS durations. This analysis was hampered by a lack of standardization between studies. For example, the QRS duration used to subdivide the patients in RAFT was 150 ms,[16] while it was 160 ms in CARE-HF.[14] Nonetheless, consistency across the trials was identified, with a 40% reduction in clinical events with CRT among those with more prolonged QRS durations ($P < 0.001$). A consistent, differential response across NYHA classes was also observed. Because patient level data were not used, the interaction between QRS morphology and duration could not be assessed. These data indicate that patients with LBBB and a QRS duration $\geq$ 150 ms appear more likely to benefit from CRT.

AF

Approximately 15% of patients with heart failure who receive an ICD have a history of AF.[63] These patients have reduced survival and more advanced symptoms of heart failure as compared with patients without AF.[64-66] Further, approximately 25% of patients who undergo CRT have a history of AF.[37] Yet, fewer than 5% of the patients enrolled in the aforementioned randomized trials of CRT had permanent AF.[7] In fact, only 2 of the trials included patients with chronic AF.[16,67] Thus, the efficacy of CRT in patients with permanent AF is less certain.

It is unclear if patients without regular, organized atrial activity derive the same benefit from CRT, as atrioventricular (AV) timing appears important for the response to CRT.[68,69] Moreover, even moderately rapid ventricular rates during AF might lead to a significant reduction in biventricular pacing, further reducing the potential benefit of CRT.[70] Observational studies suggest that the benefits of CRT are reduced among patients with a history of AF vs those without such a history.[71] Moreover, the benefits of CRT appear greatest in patients with $\geq$95% biventricular pacing.[72] AV junctional ablation might be necessary to achieve this. Importantly, though device counters are often used to estimate the percent of biventricular pacing, these data might be unreliable in patients with permanent AF.[73]

RAFT, the largest randomized evaluation of CRT in patients with permanent AF, failed to show a significant improvement in clinical outcomes, quality of life, or hall walk distance with CRT-D vs an ICD alone in these patients.[74] However, only one-third of patients with AF assigned to CRT-D in RAFT received $\geq$ 95% ventricular pacing and only 1 patient underwent an AV junctional ablation. A pooled analysis of 3 observational studies found a 60% reduction in the rate of nonresponse to CRT in CRT-treated patients who did vs did not undergo of AV junctional ablation.[71] Moreover, an observational study of CRT-treated patients with permanent AF reported lower annual mortality rate among CRT-treated patients with permanent AF who did (4.3%) vs did not (15.2%) undergo AV junctional ablation ($P < 0.001$).[72]

At present, randomized trial evidence supporting the use of CRT in patients with permanent AF is not conclusive. Additional trials are needed to determine the efficacy of CRT among these patients and how best to deliver CRT in this population. Until such data are available, CRT might be considered for patients in permanent AF who are otherwise suitable for this therapy. If CRT is undertaken in these patients it is important to ensure that a very high percentage of biventricular pacing is achieved.

RECOMMENDATION

5. CRT may be considered for patients in permanent AF who are otherwise suitable for this therapy (Weak Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places great value on the inclusion criteria of the landmark trials, the characteristics of the patients enrolled, the derived benefit of CRT in patients with permanent AF, and the quality of the evidence.

Practical tip. The amount of biventricular pacing needs to be evaluated. Arrhythmia device counters alone might not accurately reflect the true percent of biventricular pacing. It is important to ensure a very high percentage of biventricular pacing. AV junctional ablation might be necessary to achieve sufficient biventricular pacing.

Electrocardiographic morphology

A sizable proportion of patients being treated with CRT have RBBB, a nonspecific intraventricular conduction delay, or only a moderate prolongation in QRS duration (ie, QRS width $<$ 140 ms).[75,76] A better understanding of how QRS features can be used to better predict who is likely vs unlikely to benefit from CRT is necessary. This would best be achieved via a patient level meta-analysis of the major clinical trials. Until such data are available, summary data from trials can be used to guide clinical decision-making.

LBBB

Multiple studies have consistently found that a LBBB pattern is a strong predictor of benefit from CRT.[62,77-80] Overall, patients with a classic LBBB are much more likely to have favourable LV remodelling and are approximately twice as likely to derive clinical benefit from CRT vs those with other conduction patterns. Thus, these guidelines include separate recommendations for patients with LBBB vs other forms of conduction impairment.

RBBB

There are pathophysiologic reasons why CRT efficacy might differ among patients with heart failure and RBBB vs LBBB.[81,82] Nery et al. performed a systematic review and

meta-analysis of the data from 5 randomized trials in which outcomes among patients with vs without RBBB were reported.[78] They found no significant improvement in objective variables such as peak VO_2, LVEF, hall walk distance, or norepinephrine levels among patients with RBBB who received CRT. In fact, the presence of RBBB was an independent predictor of adverse outcomes in CARE-HF, with 2-fold higher risk of death or cardiovascular hospitalization.[83] Further, Bilchick et al. assessed the relationship between conduction pattern and outcomes in 14,946 Medicare registry patients who received CRT-D and were followed a median of 40 months.[75] In that analysis the presence of RBBB was independently associated with an increased risk of death despite being treated with CRT. Finally, though patients with non-LBBB conduction appear less likely to benefit from CRT, wider baseline QRS durations appear to be important determinants of favourable LV reverse ventricular remodelling and improved clinical outcomes among patients with non-LBBB conduction who receive CRT.[84] Thus, the present guidelines provide differing recommendation among patients with LBBB vs RBBB conduction patterns.

Nonspecific intraventricular conduction delay

There are few data on patients with nonspecific intraventricular conduction delay undergoing CRT. In the aforementioned analysis by Bilchick and colleagues[75] the 20% of CRT recipients categorized as having nonspecific intraventricular conduction delay had outcomes intermediate to patients with LBBB and RBBB.

RECOMMENDATION

6. CRT may be considered for patients in sinus rhythm with NYHA class II, NYHA class III, or ambulatory NYHA class IV heart failure, a LVEF $\leq$ 35%, and QRS duration $\geq$ 150 msec not because of LBBB conduction (Weak Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places great value on the inclusion criteria of the landmark trials, the characteristics of the patients enrolled, and the quality of this evidence. This recommendation also places greater weight on QRS duration as a determinant of CRT response.

Practical tip. There is no clear evidence of benefit with CRT among patients with QRS durations $<$ 150 ms because of non-LBBB conduction.

Chronically paced or high likelihood of RV pacing

There is uncertainty in predicting which patients with an indication for permanent cardiac pacing will require a high percentage of chronic RV pacing long-term.[85,86] Further, it is uncertain whether pacing-induced dyssynchrony is equivalent to an intrinsic LBBB.[87] Of the randomized CRT trials discussed, only RAFT included patients who had been previously chronically RV-paced.[16] All of the randomized trials excluded patients who had previously received an ICD. Yet, in clinical practice some pacemaker or ICD patients develop symptomatic LV systolic dysfunction. In fact, nearly 30% of present CRT implants in Europe involve upgrading of an existing pacemaker or ICD to a CRT system.[37]

Observational studies have reported improvements in functional class, favourable LV remodelling, fewer atrial and ventricular arrhythmias, and improved clinical outcomes after CRT upgrade.[88-91] Yet, as discussed, these procedures carry the potential for significant risk.[29,30] Moreover, it is unclear if patients with LBBB vs non-LBBB conduction before chronic RV pacing derive similar benefit with CRT upgrade.[92-95] Thus, based on the likelihood of benefit vs risk, CRT might be considered for patients who are chronically RV-paced or are likely to be chronically paced, have signs and/or symptoms of heart failure, and a LVEF $\leq$ 35%.

At present there is no clinical evidence to support the use of CRT in patients with preserved LV function and without heart failure. However, chronic RV pacing is known to increase the risk of heart failure among ICD recipients[96] and there are data to indicate that biventricular pacing is less detrimental than RV pacing among patients requiring chronic ventricular pacing.[97,98] Hence, patients undergoing AV junctional ablation with moderate LV dysfunction might benefit from CRT. Strategies to minimize RV pacing should be implemented before CRT upgrade. The Biventricular versus Right Ventricular Pacing in Patients with Left Ventricular Dysfunction and Atrioventricular Block (BLOCK HF) study randomized 691 patients with LV dysfunction and heart block requiring a pacemaker or ICD to CRT vs RV pacing.[99] These results have been recently presented, but are not yet published.[100] The reported average LVEF of these patients was 40%, 84% had NYHA class II or III limitation, and average follow-up was 37 months. A 25% (95% CI, 0.60-0.90) RRR in the primary outcome, a composite of death, need for intravenous heart failure therapy, or a 15% or larger reduction in LV end systolic volume index, was found with CRT vs RV pacing.[100] A 30% (95% CI, 0.52-0.93) RRR in the secondary outcome of hospitalization for heart failure was also found, but no significant alteration in mortality was identified (HR, 0.83; 95% CI, 0.61-1.14).

RECOMMENDATION

7. CRT may be considered for patients with chronic RV pacing or who are likely to be chronically paced, have signs and/or symptoms of heart failure, and a LVEF value $\leq$ 35% (Weak Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places great value on the inclusion criteria of the landmark trials and the characteristics of the patients enrolled.

Practical tip. Attempts to minimize RV pacing, when implemented, should be undertaken before consideration of CRT upgrade. There is less evidence for the utility of CRT in patients who do not have a pre-existing LBBB and are chronically RV-paced. The risks of CRT upgrade need to be considered and balanced with the potential benefits of CRT upgrade. Patients undergoing AV junctional ablation with moderate LV dysfunction might benefit from CRT, as may those who have

an indication for chronic pacing and characteristics similar to patients randomized in BLOCK HF. It is often difficult to predict reliably which patients will be chronically RV paced at the time of initiation of pacemaker therapy.

Role of imaging

Nearly half of the patients with LV systolic dysfunction and QRS durations > 120 ms lack evidence of mechanical dyssynchrony,[101] and a similar proportion with QRS durations < 120 ms have evidence of mechanical dyssynchrony.[102] Thus, identifying and quantifying the degree of mechanical dyssynchrony in a given patient to target those most likely to derive benefit from CRT and tailor CRT to enhance clinical benefit are important, unresolved needs.

Echocardiography (echo) is the most widely available technique for imaging of cardiac dyssynchrony. This includes visual identification of dyssynchrony,[103] assessment of mechanical timing,[104] and detailed tissue Doppler imaging assessment.[105] The capacity of echo and tissue Doppler imaging to identify patients with vs without dyssynchrony was assessed in a prospective observation study of 429 patients.[106] When assessed in a blinded manner, none of the 12 echo parameters evaluated reliably predicted clinical response or favourable LV remodelling. Thus, the routine assessment of dyssynchrony with the standard echo techniques is not recommended to guide prescription of CRT.

A variety of other imaging techniques have been advocated to identify patients more likely to respond to CRT. Speckle tracking[107] and 3-D echo techniques[108] have been developed, but their utility is uncertain. Cardiac magnetic resonance has excellent spatial and temporal resolution, and can be used to assess myocardial scar burden and/or location[109-111] and dyssynchrony.[112-114] Yet, most CRT systems are not magnetic resonance-compatible. Radionuclide imaging is widely available, but has poorer spatial resolution and entails radiation. Nonetheless, it can be used to estimate scar burden[115] and regional systolic function.[116] Computed tomography has excellent spatial resolution and has been shown to be useful in guiding for LV lead placement.[117] While these and other imaging techniques hold promise, larger studies are needed to better understand their respective roles in CRT recipients.

RECOMMENDATION

8. Routine assessment of dyssynchrony with present echo techniques is not recommended to guide the prescription of CRT (Strong Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation takes into account the quality of the evidence and the results of larger, multicentre studies.

Practical tip. Issues of reproducibility and inter- and intrarater assessment identified in the larger studies limit the routine role of echo to guide the prescription of CRT. Ongoing imaging research (eg, scar, viability) is presently under investigation.

Summary

These updated guidelines are intended to provide guidance on the prescription of CRT in Canada. A future article will provide direction on the implementation of these guidelines. As additional studies are completed these guidelines will be updated accordingly.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2012.10.006.