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Society Guidelines

Canadian Cardiovascular Society Guidelines on the Use of Cardiac Resynchronization Therapy: Implementation

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ABSTRACT

Recent studies have provided the impetus to update the recommendations for cardiac resynchronization therapy (CRT). This article provides guidance on the implementation of CRT and is intended to serve as a framework for the implementation of CRT within the Canadian health care system and beyond. These guidelines were 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 judgement 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.

RÉSUMÉ

Des études récentes ont incité à mettre à jour les recommandations sur la thérapie de resynchronisation cardiaque (TRC). Cet article fournit des lignes directrices sur la mise en application de la TRC et est destiné à servir de cadre à la mise en application de la TRC dans le système de soins de santé canadien et au-delà. Ces lignes directrices

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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

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developed through a critical evaluation of the existing literature, and expert consensus. The panel unanimously adopted each recommendation. The 9 recommendations relate to patient selection in the presence of comorbidities, delivery and optimization of CRT, and resources required to deliver this therapy. The strength of evidence was weighed, taking full consideration of any risk of bias, and 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.

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 9 recommandations concernent la sélection des patients en présence de comorbidités, l'offre et l'optimisation de la TRC, et les ressources requises pour offrir ce traitement. 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.

The 9 recommendations in this document are based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment method and expert consensus.[1] This document was developed to directly address the practical use of cardiac resynchronization therapy (CRT), beyond clinical trial inclusion/exclusion criteria, in a real-world population. The consensus panel consisted of experts in cardiac electrophysiology, heart failure (HF), cardiac surgery, cardiac imaging, general cardiology, internal medicine, knowledge translation, and health services. Competing interests of panel members are provided on the Canadian Cardiovascular Society (CCS) Web site (www.ccs.ca). These guidelines are intended for internists, nurse clinicians in heart function and device clinics, general cardiologists, HF experts, cardiac electrophysiologists, policy makers, and trainees. This document is meant to provide guidance for patient selection, platform selection, and appropriate preoperative, operative, and postoperative patient management to reduce risk, and optimize CRT delivery. The economics and accessibility of CRT are also addressed, including the timely application of this therapy.

Preimplant Assessment and Procedural Preparation

Patient selection

Functional assessment. New York Heart Association (NYHA) Functional Classification is the most commonly used measure of HF clinical severity and is one of the central criteria in deciding on the appropriateness of CRT. Categorizing patients into a NYHA class is a subjective process. Nevertheless, it is relatively straightforward to identify patients with NYHA class I (asymptomatic) or nonambulatory NYHA class IV (ie, severe HF requiring intravenous diuretics, inotropic therapy, or intra-aortic balloon pump support), for whom CRT is not currently recommended because of a lack of evidence.[2] Yet, it might be difficult to determine if symptoms are attributable to HF or comorbidities such as musculoskeletal, pulmonary, or other chronic diseases, aging, frailty, or physical deconditioning. Therefore, an objective assessment of functional capacity should be considered in patients with confirmed HF and multiple comorbidities, or if there is disparity between reported symptoms and the clinical assessment.[2] The 6-minute walk test and cardiopulmonary exercise test[3] were included in earlier CRT trials as objective measures of changes in functional capacity in response to treatment.[4–7] The use of more reproducible and reliable measures of functional capacity than NYHA class, such as the Specific Activity Scale, should also be considered.[8] Finally, it is important to emphasize that serial determinations of functional capacity provide benchmarks for disease severity, response to CRT, and progression of HF.[9]

Practical tip. Objective evaluation of the pre-CRT implantation functional capacity and symptoms is important, particularly in patients in whom there is disparity between the reported symptoms and the clinical assessment, or to distinguish the non-HF related causes of functional limitation.

Patient factors and comorbidities

As with most clinical trial populations, patients included in the major CRT trials differ from those in a general HF patient population.[10] As noted in part 1 of the 2013 CRT Guidelines, sex, the presence of atrial fibrillation (AF) and type of intraventricular conduction delay (left bundle branch block [LBBB] vs right bundle vs nonspecific) help to identify potential benefit from CRT.[11] Other factors affecting patients who would benefit most are discussed in this section. Table 1 presents the overall considerations before CRT implantation.

Age. In CRT trials, the mean age among patients ranged from 62 to 66 years.[12] The evidence to support the use of CRT in elderly patients, who otherwise qualify, is presently limited. However, a cohort study found similar outcomes with CRT in patients aged $\geq$ 80 years to those $<$ 80 and both groups had similar device-related complication rates.[13] Hence, elderly patients with comorbidities, but a good life expectancy ($>$ 1 year) who otherwise fulfil criteria, might derive functional improvements with CRT and should be considered for referral.

Table 1. Factors to consider before CRT implantation

Factors to consider	Recommended	For consideration
Patient selection	NYHA II, III, or ambulatory IV, HF, LVEF $\leq$ 35%, QRS $\geq$ 130 ms if LBBB; sinus rhythm, and the absence of severe CKD (creatinine $<$ 200 mmol/L or GFR $>$ 30 mL/min/m^2)	QRS $>$ 150 ms if non-LBBB; presence of AF; elderly age; evidence of frailty; chronic RV pacing with LVEF $\leq$ 45%
Imaging	Evaluation of LVEF: echocardiogram, nuclear imaging, cardiac magnetic resonance	Imaging for assistance in LV lead placement
Anticoagulation	Continue warfarin if high risk for thromboembolism	Novel oral anticoagulants will need to be considered on an individual basis (see text)
Renal insufficiency	Adequate hydration; hold or decrease diuretics	

AF, atrial fibrillation; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; HF, heart failure; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricular.

Renal function. Significant concomitant chronic kidney disease (CKD) might be present in up to a third of HF patients and is associated with a poor prognosis.[14] The large clinical trials of CRT excluded patients with CKD so there is limited evidence to guide clinical decision-making in this population.[15] The mortality benefit achieved with adding CRT to an implantable cardioverter defibrillator (ICD) appears attenuated in those with more advanced CKD (glomerular filtration rate [GFR], $<$ 30 mL/min/1.73 m^2).[16] Adelstein et al[16] analyzed 787 patients with a CRT plus an ICD (CRT-D) and correlated survival, changes in left ventricular (LV) ejection fraction (LVEF) and LV end-systolic diameter and GFR with a control group in whom LV lead implant was unsuccessful. Survival improved for each 10 mL/min/1.73m^2 in GFR with a hazard ratio of 1.21 (95% confidence interval [CI], 1.13-1.30; $P < 0.0001$). Those with a GFR $<$ 30 mL/min/1.73m^2 had no echocardiographic benefit. Those with moderate renal insufficiency (GFR, 30-59) had significantly better survival than control subjects (hazard ratio, 2.23; 95% CI, 1.34-1.70; $P = 0.002$), and improved renal and cardiac function. Other studies have also demonstrated improvements in renal function with CRT that have correlated with greater favourable LV remodelling and reduced mortality.[17] Considering the increased procedural risks of device implantation in patients with advanced CKD (see the section on Avoidance of Complications), the risk vs benefit of CRT and the selection of a CRT pacemaker (CRT-P) vs CRT-D need to be carefully considered.[18]

Etiology of LV dysfunction. The mortality benefit with CRT is similar in patients with an ischemic vs a nonischemic etiology and should not be a factor in the decision to prescribe CRT.[19,20] The degree of favourable LV remodelling is less with an ischemic vs nonischemic cause of LV dysfunction.[21] This might relate to the extent of the scar, a differential effect of CRT on diastolic function, or other factors.

Frailty. The concept of frailty is not always considered in the chronic care of patients with cardiac disease. Yet, considering our aging population it should be considered. Clarke et al. have demonstrated that overall mortality and nonsudden death (53% because of HF) was associated with an increase in the Charlson Comorbidity Index ($P < 0.0001$), with a Charlson Index $>$ 4 resulting in a 49% risk of nonsudden death in a competing risk model.[22] The most widely used definition of frailty includes subjective and objective measures of weight loss, weakness, a sense of exhaustion, slowed walking speed, and low physical activity.[23] Those displaying 1 or 2 of these characteristics are considered "pre-frail," and those with 3 or more are categorized as "frail." Quantification of frailty and comorbidity can be accomplished through use of validated instruments such as the Charlson Comorbidity Index and the Clinical Frailty Scale (see Supplemental Tables S1 and S2).[22,24,25] Familiarity with these scales might be helpful in determining the degree of frailty. Frail patients might be unable to withstand device implantation, which might reduce the overall benefit of CRT. However, many of the factors that contribute to frailty might be reversible with CRT, including weakness and low physical activity. Assessment by a clinician familiar with frailty (eg, a geriatrician) might be helpful when the likelihood of benefit from CRT is less certain.

RECOMMENDATION

1. We recommend that the prescription of CRT and the choice of platform (CRT-P vs CRT-D) should take into account clinical factors that would affect the overall goals of care (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places great value on the benefit of CRT in appropriately selected patients with HF, and minimization of risk.

Practical tip. Comorbid conditions and clinical factors (eg, age, renal function, frailty) should be considered together, and 1 alone should not preclude a patient from CRT implantation. Therapy should be individualized in accordance with the overall goals of care and patient preference.

De novo onset of pacemaker dependence

Evidence has emerged regarding new-onset atrioventricular (AV) block requiring ventricular pacing. The Biventricular vs Right Ventricular Pacing in Patients With Left Ventricular Dysfunction and AV Block (BLOCK HF) trial randomized 691 patients with LVEF $\leq$ 50%, high-degree AV block

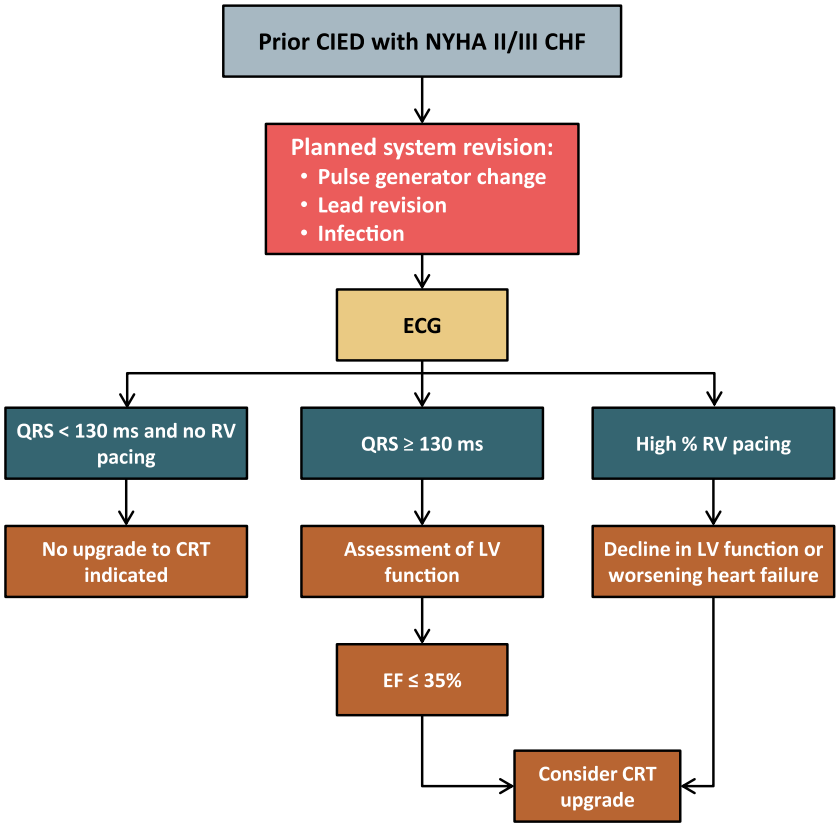

Figure 1. Evaluation of patients with a CIED and HF. CHF, congestive heart failure; CIED, cardiovascular implantable electronic device; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; EF, ejection fraction; LV, left ventricular; NYHA, New York Heart Association; RV, right ventricular.

requiring pacing, and NYHA class I/II/III limitation requiring a pacemaker or ICD to CRT vs right ventricular (RV) -only pacing.[26] The mean LVEF of participants was 40 ± 8.3% (pacemaker, 43% and ICD, 33%). A 26% relative risk reduction (95% CI, 10%-40%) in the primary end point of all cause mortality, urgent care visit for HF, or an increase in the LV end systolic volume index of ≥ 15% was found with CRT vs standard RV apical pacing.

RECOMMENDATION

2. We suggest that CRT might be considered for patients with new-onset high-degree AV block requiring chronic RV pacing, signs and/or symptoms of HF, and LVEF ≤ 45% (Conditional Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places value on the knowledge that CRT might provide more benefit than RV apical pacing, even though the strength of evidence is moderate and the available data result in a conditional rating.

Practical tip. Most patients in BLOCK HF had reduced LV systolic function (LVEF ≤ 45%) and symptomatic (NYHA class II/III) HF. Further, BLOCK HF enrolled patients with de novo implants and the same considerations might not apply in patients who are chronically RV-paced. (See Supplemental Tables S3 for further details.) There are limited randomized clinical trial (RCT) data with respect to CRT upgrade and potential benefits must be balanced with the significantly higher risk with CRT vs generator replacement alone.

Consideration for upgrade to CRT

Patients with HF who are undergoing a system revision of a previous cardiac implantable electronic device (CIED) should be evaluated for CRT indication considering the expanded indications for CRT (Fig. 1). Although there are no RCT data in this population, observational studies have reported improvements in functional class, favourable LV remodelling, fewer atrial and ventricular arrhythmias, and improved clinical outcomes after CRT upgrade.[27,28] The risk of intervention in a patient not requiring system revision for another reason (eg, generator change or lead revision) needs to be balanced by potential benefits of CRT.[29]

RECOMMENDATION

3. We recommend that all patients with HF who are planned to receive a CIED system revision should be considered for their eligibility for upgrade to CRT (Strong Recommendation, Low-Quality Evidence).

Values and preferences. Careful evaluation of the risks and benefits of upgrades in patients with existing CIED systems who are eligible for CRT should be considered.

Practical tip. Considering the expanding indications for CRT and the changes over time that might occur in a patient's condition, the need for CRT should be considered at the time of CIED change, because risk/benefit of adding an LV lead when a procedure is being performed might be favourable. For further details, refer to Figure 1.

Patients undergoing open heart surgery

There are data that support the utility of epicardial LV lead placement to facilitate CRT delivery.[30] However, there are a paucity of data with respect to indications and outcomes for prophylactic placement of an LV epicardial lead at the time of open heart surgery. A single retrospective study identified that 2.3% of patients undergoing cardiac surgery could benefit from CRT.[31] However, the precise characteristics of patients that would benefit from prophylactic LV lead placement are unknown. Patients likely to benefit from the cardiac surgical procedure and less likely to later require CRT include those with severe aortic stenosis or extensive coronary artery disease with demonstrated viability. In contrast, those with a pre-existing LBBB, HF, and previous sustained ventricular tachycardia or a cardiac arrest represent a group more likely to require CRT in the future. The ideal location for epicardial LV lead placement likely varies in a given patient. In general, placement of the LV epicardial lead in a posterobasal position between the ramus intermedius and the obtuse marginal arteries when that region is free of scar is generally preferred.[32] The incremental intraoperative risk is low and the ease of LV lead placement at the ideal location on the epicardium makes this an important consideration for those who fit the criteria. Transvenous implantation for LV leads is the usual method but is limited by venous anatomy, lead stability, pacing threshold, and potential for diaphragmatic capture. These considerations do not pose challenges in epicardial placement. Preoperative consultation between the cardiac surgeon and the cardiac electrophysiologist is important in identifying patients most likely to benefit from intraoperative LV lead placement and the appropriate location for the LV lead.

RECOMMENDATION

4. We suggest that placement of an LV lead at the time of open heart surgery, for the purpose of facilitating future CRT, might be considered in patients for whom CRT is recommended and the need for device therapy is unlikely to be changed by the surgical procedure (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places value on practical considerations and multidisciplinary discussion in the absence of substantial data.

Practical tip. Patients who have severe structural abnormalities that can be easily corrected with cardiac surgery are the least likely to benefit from LV lead placement. The risk and costs of placing hardware that might be unnecessary needs to be balanced with the feasibility and risk of placing/testing an LV lead at the time of surgery in an eligible patient. As discussed in part 1 of the 2013 Guidelines, an apical LV lead position should be avoided.[6]

Use of antithrombotic agents periprocedurally

There is now definitive evidence that CRT implantation can be performed safely without interruption of warfarin or vitamin K-dependent antagonist treatment in patients at high risk for thromboembolism. Examples of high-risk patients include those with mechanical mitral valve or nonvalvular AF and **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) score ≥ 3.[33] In the **Br**idge or Contin**u**e Coumad**i**n for Device **S**urg**e**ry Randomized **Control**led Trial (BRUISE CONTROL) trial, 668 patients with a high risk of thromboembolism undergoing a CIED procedure were randomized to bridging, per-operative use of low molecular weight heparin, vs continued warfarin. The primary outcome was the development of a clinically significant pocket hematoma. The trial was terminated early because continuation of warfarin resulted in an 81% relative risk reduction in the primary outcome (95% CI, 64%-90%; $P < 0.001$). A meta-analysis of 8 studies enrolling 2321 patients confirmed that uninterrupted warfarin therapy was associated with a significantly lower risk of postoperative bleeding than heparin-based bridging therapy (odds ratio, 0.30; 95% CI, 0.18-0.50; $P < 0.01$), shorter hospital admission (mean difference, 2.4 days), and no difference in thromboembolic events.[34] There are no safety data on an uninterrupted use of the new oral anticoagulation agents (Factor Xa and direct thrombin inhibitors) during CIED surgery. Temporary cessation of oral anticoagulation (OAC) before a procedure is typically preferred in patients with lower thromboembolic risk ($CHADS_2 \leq 2$).[35]

RECOMMENDATION

5. We recommend that in patients taking warfarin for whom perioperative anticoagulation is deemed necessary, continued warfarin is recommended over the use of heparin-based bridging (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places great value on safely preventing perioperative bleeding and the quality of the evidence.

Practical tip. Perioperative OAC is usually deemed necessary in patients at high risk of thromboembolism ($CHADS_2 \geq 3$ or $>$ 5% annual risk, refer to *Use of Antithrombotic Agents Periprocedurally* section for details). No data are presently available on the use of novel oral anticoagulants in this population; interruption of these agents should be of short duration in patients at high risk of thromboembolism, but renal function, procedural risk, and complexity of the procedure might need to be considered in these situations. The rapidity of onset and offset make these more facile to control periprocedurally. Discontinuation of OAC in patients at lower risk of thromboembolism should be considered to minimize the risk of bleeding.

Operative Issues

General principles

Patients undergoing CRT implantation typically have substantial LV dysfunction and symptomatic HF and are

Table 2. Complications with CRT implantation

Complication	Incidence	Suggested methods to prevent
Contrast-induced nephropathy	7%-43%	Prehydration; lower dose of diuretics; lower dose of contrast, dilution of contrast[46]
Pneumothorax	0.6%-1.0%	Extrathoracic puncture, echo-guided or contrast-guided venous puncture, axillary is preferred to subclavian; use of cephalic vein[47]
Pericardial effusion	1.5%	Use of soft-tip guides and access tools
Hematoma	3%-6%	Avoid low molecular weight heparin periprocedurally[33]
Phrenic nerve stimulation	Up to 13%	Conscious sedation; no paralytic agents; identify all available coronary vein branches; use of multipolar leads (additional electrodes)
Lead-related complications	3.5%-18.7%[29]	Appropriate training and adequate procedural volumes
Device infection	1.3%-2.6%	Appropriate antibiotic prophylaxis before skin incision[48]; chlorhexidine skin preparation[49]; limited shaving
In-hospital mortality	0.3%	Careful preoperative assessment; intraoperative monitoring; appropriate postoperative care

CRT, cardiac resynchronization therapy.

high-risk surgical candidates.[36] Hence, the procedure should be performed in an environment with careful hemodynamic monitoring and the capacity to provide appropriate hemodynamic support. Infection prevention is central to all CIED procedures. Preoperative antibiotics that provide adequate coverage against skin flora are the standard of care. They must be administered before skin incision to provide appropriate protection. Appropriate attention to sterile technique, minimal handling of the implanted components, and adequate air flow are also essential proven infection prevention control strategies.[37]

RECOMMENDATION

6. We recommend that CRT implantation be performed only in facilities that have strict infection prevention control standards (Strong Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation takes into account that infection prevention is a key aspect to CRT implantation and system revision.

Radiation safety

The amount of ionizing radiation to which CRT recipients and operators are exposed during a complex CRT procedures is significant (might exceed 60 minutes of fluoroscopy). Deterministic effects including cataracts and stochastic effects such as cancer are of primary concern. For every 60 minutes of fluoroscopy, the mean total lifetime risk of fatal malignancy is estimated to increase by 0.03%-0.065%.[38] If appropriate radiation shielding is not in place the operator is subject to scatter radiation. Scatter radiation is greatly increased when: (1) the distance between the image intensifier and the patient increases; (2) steep lateral or oblique positions are used; and (3) when body mass or other factors require increased fluoroscopic output (kv).[39] Major exposure-reduction techniques include: (1) exposure time reduction by using short bursts of "on-time"; (2) field limitation ("coning" and avoidance of magnification); and (3) lower frame rates (pulsed mode; 10-15 frames per second reduces the radiation dose by more than 50% vs nonpulsed modes), and shielding. Typical forms of shielding include the use of a protective (lead) apron, thyroid collar, and eyeglasses. These interventions are used by most electrophysiologists.[40] However, nonprotected areas (eg, cranium, arms, hands) receive large doses of radiation. Radiation shields above and below the operating table, protective cabins and suspended vests, and sterile radiation-absorbing drapes provide additional protection, but do not protect some areas (eg, hands).[41,42] Although desirable, the **A**s **L**ow **a**s **R**easonably **A**chievable (ALARA) principle has to be balanced with sufficient image quality to safely perform these complex procedures without unnecessary radiation exposure.[43] Further information on radiation issues is discussed in the CCS Position Statement on Radiation Exposure from Cardiac Imaging and Interventional Procedures.[44]

RECOMMENDATION

7. We recommend that appropriate fluoroscopic equipment, radiation shielding, and radiation reduction imaging methods be used to minimize radiation exposure to the operator, patient, and other staff (Strong Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation takes into account that fluoroscopic exposure poses risk to patients, staff, and operators, and must be minimized using all available means.

Avoidance of complications

CRT implantation is a surgical procedure and should only be performed by highly trained physicians. As with many surgical procedures, the outcome and complication rate is directly related to the implant volume performed by the operator and implanting centre.[45] Methods to prevent and avoid complications are listed in Table 2.[29,33,46–49]

Operative considerations related to CRT upgrade. Performing an upgrade to CRT in the setting of existing hardware can be challenging because of partial or total venous occlusion, resistance along the LV lead course from the existing leads, the presence of scar tissue, and other factors. Venoplasty or lead extraction in the setting of venous occlusion or abandoned hardware might be required to facilitate transvenous LV lead placement.[50,51] Ipsilateral contrast injection from a peripheral vein (contralateral device placement, lead extraction, venoplasty, tunneling, or direct surgical

Table 3. Experimental tools to optimize LV pacing site

Tool	Measurement
Imaging	Echocardiography, nuclear, CMR
Anatomic position	LV lead to latest activation site determined using imaging
	Greatest distance between LV and RV lead
Timing	Greatest delay from onset of QRS to local LV electrogram
Contractility	Acute increase in dP/dt_{max} or pulse pressure (systolic minus diastolic blood pressure)

CMR, cardiac magnetic resonance; LV, left ventricular; RV, right ventricular.

epicardial lead placement) and referral of patients to more experienced implantation centres might be helpful in procedural planning. These more complex procedures should be performed in high volume centres with low complication rates.[52] These considerations should be explored well in advance of a CRT upgrade procedure to best assess the most successful approach for a given patient.

Lead placement to optimize response. As recommended in part 1 of the CRT Guidelines, LV leads should be placed in a nonapical location.[11,53] Challenges in precisely defining the location of the lead on the LV, the extent of myocardial scarring, and the etiology of LV dysfunction might partially explain the poor relationship between the location of LV pacing and the likelihood of benefit from CRT.[54,55] Areas of scar might be identified using imaging techniques such as echocardiography, nuclear, and cardiac magnetic resonance (CMR).[56] It is known that the site of latest LV activation in patients with nonischemic LV dysfunction and LBBB typically is lateral or posterior, but this might be very different in patients with ischemic LV dysfunction. There appears to be a "sweet spot" for LV pacing[57] that is large in patients with nonischemic etiologies for LV dysfunction, but more restricted and variable in ischemic LV dysfunction or in patients with non-LBBB conduction patterns.[55] Three small RCTs (INCREMENTAL [**I**nvestigating **N**on-response to **C**ardiac **R**esynchronization: **E**valuation of **M**ethods to **E**liminate **N**on-response & **T**arget **A**ppropriate **L**ead Location], TARGET [Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy], STARTER [**S**peckle **T**racking **A**ssisted **R**esynchronization **T**herapy for **E**lectrode **R**egion]) have demonstrated[57–59] that LV lead placement in a viable late-contracting LV segment improves response to CRT. CMR might also provide a 3-D roadmap for LV lead positioning, although this has yet to be assessed in clinical trials.[60] CMR myocardial tagging provides accurate measurement of interventricular and intraventricular dyssynchrony with high reliability and specificity and appears to be a promising method for identifying an optimal site for LV pacing.[61] The presence of transmural posterolateral scar identified using late gadolinium enhancement or global LV necrosis are important predictors of the lack of benefit from CRT.[56,62]

The integration of imaging technologies might facilitate the planning and delivery of LV pacing. Preprocedural evaluation of mechanical dyssynchrony and intraprocedural integration with venous mapping appears promising,[63] but requires prospective validation (Table 2).

Practical tip. In patients with an ischemic etiology or non-LBBB patterns of QRS morphology, correlation of venous anatomy using CMR with mechanical dyssynchrony might be helpful in guiding LV lead placement and optimizing response to CRT.

Even though concordance between the position of the LV lead and the area of latest activation seem to predict a better response to CRT, at the time of implantation, the anatomy of the venous system remains the most important limitation. Other electrical parameters that have shown some benefit are shown in Table 3. A secondary analysis of the **Smart**Delay Determined **AV** Optimization: A Comparison of AV Optimization Methods Used in Cardiac Resynchronization Therapy (SMART-AV) study revealed that a Q-LV > 95 ms was associated with improved reverse remodelling.[64] The basic determinants of a successful LV lead implantation remain the same: pacing with an adequate threshold, avoiding capture of the nearby phrenic nerve, and long-term stability of the LV lead. Emerging technologies to assist in 3-D reconstruction of the venous anatomy and its electrical activation patterns are being investigated.

Endocardial pacing. Initial human studies evaluating endocardial LV pacing have shown either no differences or small improvements in LV contractility (dP/dt_{max}) with this approach vs standard epicardial pacing.[65] Although there might be a future role for endocardial pacing it has a limited role at present because of a lack of long-term data on its safety and efficacy.

Device Follow-up

Factors to consider in CRT follow-up

Follow-up of CRT devices, whether pacemaker or ICD, should be done in accordance with published guidelines.[66] CRT implantation is the first step in optimal delivery of CRT. There are many more factors to consider when the implant has been successful. These are shown in Figure 2. Collaboration between the heart rhythm service, HF specialists, and other caregivers is necessary to enhance the likelihood of benefit from CRT.

Optimization of medications

Before CRT delivery, optimal medical therapy might not have been possible because of hemodynamic limitations or bradycardia. However, after initiation of CRT, the clinical condition might improve, and attempts should be made to introduce medications previously not tolerated, or an increase of the dose of guideline-recommended medications should be undertaken.

Definition of response

Response to CRT can be defined in various ways (Table 4).[6,7,67–76] The correlation between these methods is poor[77] and the relationship of many of these outcomes to more objective clinical outcomes such as survival and HF hospitalization is unclear. Cardiac performance has been studied in several trials and an improvement in the 6-minute walk, peak VO_2, NYHA class, and quality of life (QOL) were commonly used.[67] Remodelling end points have been studied such as a decrease in the LV end-systolic volume (LVESV) or

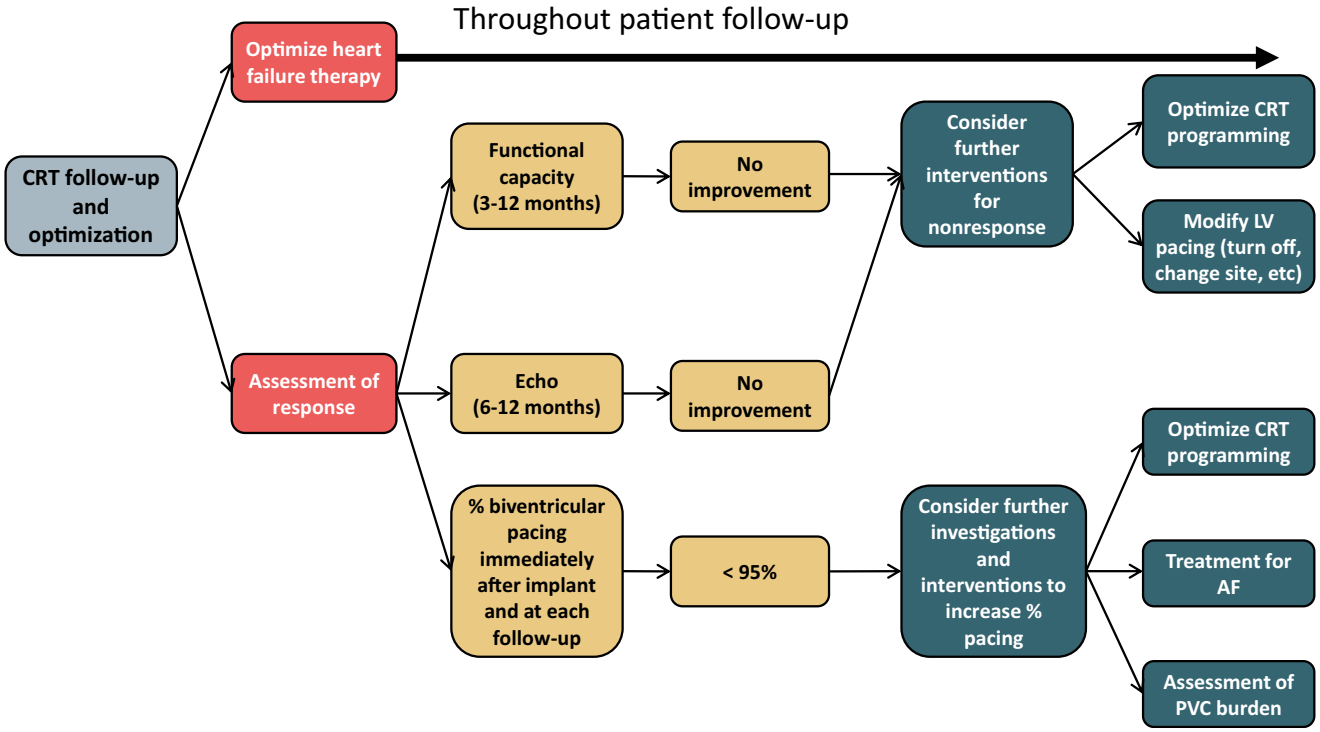

Figure 2. Follow-up and optimization of CRT delivery. AF, atrial fibrillation; CRT, cardiac resynchronization therapy; LV, left ventricular; PVC, premature ventricular contraction.

an improvement in LVEF. Such remodelling effects have also been associated with a reduction in mortality. A reduction of $\geq$ 30% in the LVESV was associated with a 2% reduction in total mortality compared with a 29% increase in mortality if the reduction in LVESV was between 0 and 14%.[78] Neurohormones such as N-terminal pro-type B natriuretic peptide can be used as a surrogate measure of improvement.[79] However, there is imperfect correlation between these variables and survival. Other parameters such as improved diastolic dysfunction, decreased mitral regurgitation, and prevention of LV dilatation are associated with clinical benefit from CRT, but are not routinely assessed.

Practical tip. Use of a "treatment effect" based on individual patient goals of improved QOL, symptom reduction, fewer hospitalizations, and improved survival should be used to define response to CRT. This should include validated composite end points (death, hospitalization, QOL) and is preferred over the more ambiguous "response rate" comprised of a myriad of variables that might not correspond with clinical outcomes or be relevant to CRT recipients.[77]

Evaluation of response during follow-up and approach to CRT nonresponse

Response to CRT depends on the delivery of biventricular or LV pacing. Patient-related factors including atrial arrhythmias, and in particular AF with a poorly controlled ventricular rate, will lead to a reduction in CRT delivery. In a large cohort study, patients with AF and $\leq$ 98.5% biventricular pacing had a higher mortality rate compared with patients in sinus rhythm, whereas those with a biventricular pacing rate $\geq$ 98.5% had survival rates equivalent to those in patients without AF.[80] However, it is not known if the lack of rate control itself is a marker of a poorer prognosis vs the lack of biventricular pacing (ie, confounding). If AF developed, or was present at the time of CRT delivery, the ventricular response rate in AF should be controlled and due consideration given to restoration and maintenance of sinus rhythm or nonpharmacological rate control if a high percentage of biventricular pacing cannot be achieved using medications. AV junctional ablation appears to be a useful approach to facilitate biventricular pacing in patients with AF and suboptimal rate control, but there is a lack of randomized trial data to support the routine use of this nonreversible intervention.[81] Planned and ongoing RCTs will better define the appropriate role of rate vs rhythm control, and the role of routine AV junctional ablation in these patients. In addition, a high burden of ventricular ectopy ($>$ 10,000 in 24 hours) has been linked with HF and a reduction in biventricular pacing. There are preliminary data that suggest enhanced CRT response after catheter ablation of premature ventricular beats, but additional data are needed.[82] Loss of LV pacing because of lack of capture or lead dislodgement will impair the delivery of CRT. A 12-lead electrocardiogram should be used to compare QRS morphology pre- and post-CT and a postoperative chest radiograph is useful to document LV lead placement and changes in position (ie, dislodgement). Although optimization of atrioventricular (AV) and interventricular (VV) timing was thought to be important in enhancing response to CRT, several large clinical trials have uniformly shown no benefit using mandatory optimization vs usual care.[83–87] These data suggest that factors other than AV and VV timing are important in explaining a lack of benefit with CRT.

Table 4. Large clinical studies (≥ 99 patients) assessing predictors of CRT response

Study	Definition of CRT response	Follow-up (months)	Predictors of CRT response
Lecoq et al.[68]	Alive, no HF readmission, > 1 NYHA class improvement (or > 10% increase in peak VO_2 and 6MW)	6	QRS shortening during CRT
Achilli et al.[69]	Improved clinical composite score and LVEF increase ≥ 5%	6	Smaller LVESD, longer interventricular mechanical delay
MIRACLE/ MIRACLE ICD[6,7]	Alive and > 1 NYHA class improvement	1, 3, and 6	None
Yeim et al.[70]	> 1 NYHA class improvement and no HF admission	6	Nonischemic etiology, wider baseline QRS width, QRS shortening during CRT
Mollema et al.[71]	≥ 1 NYHA class improvement or 10% decrease in LVESV	6	None
PROSPECT[72]	Improved clinical composite score and LVESV decrease ≥ 15%	6	None
Buck et al.[73]	LVESV decrease > 10%	6	Interlead distance > 127 mm, septal-lateral delay > 60 ms, nonischemic etiology, LV end-diastolic diameter < 67 mm, use of ACE inhibitor, absence of tricuspid regurgitation
Rickard et al.[74]	LVESV decrease ≥ 10%	> 2	Wider QRS
MADIT-CRT[75]	% decrease in LVEDV and response score	12	Female, nonischemic etiology, LBBB, QRS > 150 ms, previous HF hospitalization, LVEDV > 125 mL/m^2, left atrial volume < 40 mL/m^2
PROSPECT-ECG[57,76]	Improved clinical composite score, LVESV decrease ≥ 15%	6	LBBB morphology, LV paced QRS width and QRS shortening

ACE, angiotensin-converting enzyme; CRT, cardiac resynchronization therapy; HF, heart failure; LBBB, left bundle branch block; LV, left ventricular; LVEF, LV ejection fraction; LVEDV, LV end-diastolic volume; LVESD, LV end-systolic dimension; LVESV, LV end-systolic volume; MADIT-CRT, **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial - **C**ardiac **R**esynchronization **T**herapy; MIRACLE, **M**ulticenter **I**nSync **Ra**ndomized **Cl**inical **E**valuation; MIRACLE ICD, Mulitcenter Insync ICD Randomized Clinical Evaluation; 6MW, 6-minute walk; NYHA, New York Heart Association; PROSPECT, Predictors of Response to Cardiac Resynchronization Therapy; PROSPECT-ECG, Predictors of Response to Cardiac Resynchronization Therapy ECG.

Modified from Ellenbogen et al.[67] with permission from Elsevier.

Super-response to CRT

The definition of super-response to CRT is variable amongst studies.[67,88] This typically refers to a significant improvement in either functional capacity or LVEF to a significant degree after CRT. Some studies have used a definition of improvement in the LVEF to ≥ 50%, and others have used an absolute increase in LVEF, with or without improvement in functional capacity. Despite these differences in definition, there are predictors common to many of the studies that predict a super response in 10%-38% of CRT recipients including female sex,[72,75] presence of typical LBBB,[74,75] nonischemic LV dysfunction,[72] smaller left atrial volume, shorter duration of HF symptoms,[89] and a QRS duration of ≥ 150 ms.[72,75] Super response is also linked to reduced mortality and fewer HF hospitalizations.[19]

Optimal timing for assessment of response

There is no definitive evidence to guide the optimal timing for the assessment of benefit from CRT (Table 5). Large RCTs have reported CRT "response rates" at 3 (**Ca**rdiac

Table 5. Select trials assessing optimization of intracardiac timing

Study	Comparison	Results
RHYTHM II[83]	Echo-optimized VV timing vs nominal VV settings	No difference in QOL, NYHA or 6MW
DECREASE-HF[85]	Simultaneous VV pacing vs EGM optimized VV timing	No difference in LV volumes or EF
FREEDOM[86]	Clinically optimized AV and VV timing vs serial EGM optimized AV and VV timing	No difference in clinical outcomes or functional measures
CLEAR[84]	Echo optimized AV and VV timing vs automatic adjustment of AV delays via contractility sensor	Improved clinical response with the contractility sensor
SMART AV[87]	Echo optimized AV and VV timing vs EGM optimized AV and VV timing vs fixed AV (120 ms) and VV (0 ms)	No difference in LV volumes, EF, or functional measures

AV, atrioventricular; CLEAR, **Cl**inical **E**valuation on **A**dvanced **R**esynchronization; DECREASE-HF, **D**evice **E**valuation of **C**ONTAK **R**ENEWAL 2 and E**A**SYTRAK 2**: A**ssessment of **S**afety and Effectiveness in **H**eart **F**ailure; EF, ejection fraction; EGM, electrogram; FREEDOM, Frequent Optimization Study Using the QuickOpt Method; LV, left ventricular; 6MW, 6-minute walk; NYHA, New York Heart Association; QOL, quality of life; RHYTHM II, **R**esynchronization for **H**emody**n**amic **T**reatment for **H**eart Failure **M**anagement II; SMART-AV, **Smart**Delay Determined **AV** Optimization: A Comparison of AV Optimization Methods Used in Cardiac Resynchronization Therapy; VV, interventricular.

Modified from Exner et al.[57] with permission from Elsevier.

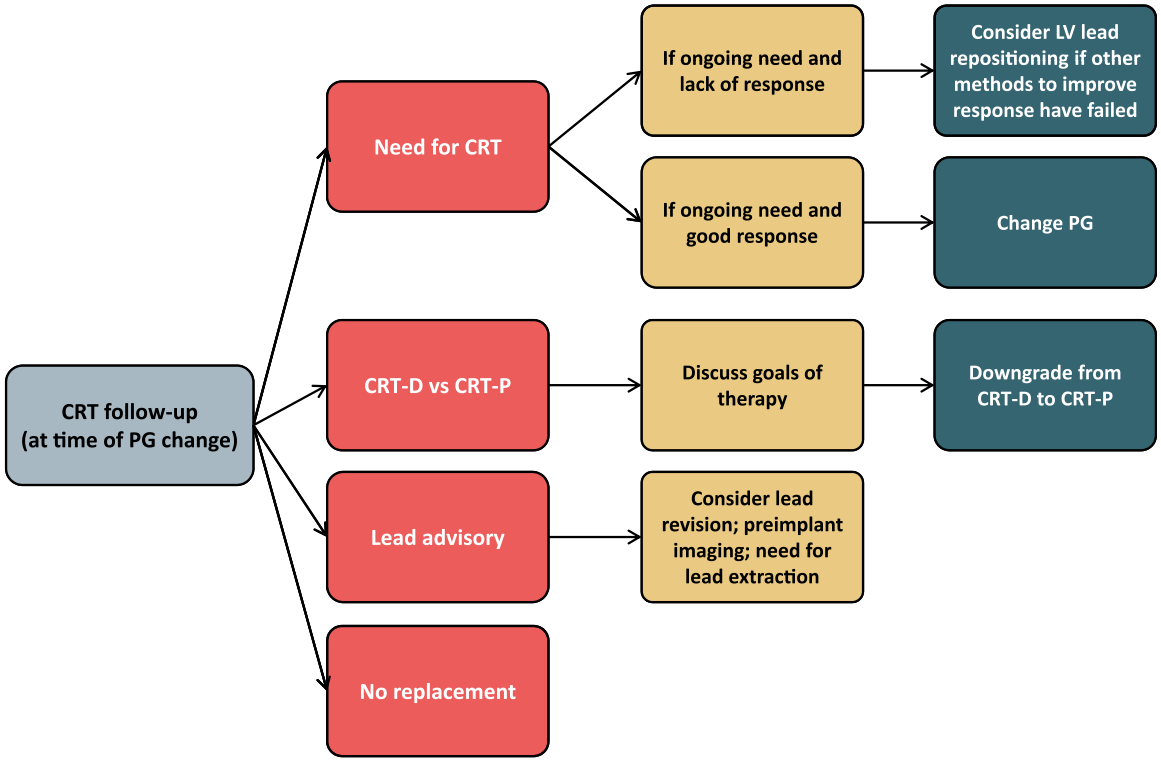

Figure 3. Evaluation process at the time of generator change. CRT, cardiac resynchronization therapy; CRT-D, CRT defibrillator; CRT-P, CRT pacemaker; LV, left ventricular; PG, pulse generator.

Resynchronization in **H**eart **F**ailure [CARE-HF]) and 6 months (**Re**synchronization Re**ve**rses **R**emodeling in **S**ystolic Left V**e**ntricular Dysfunction [REVERSE]) with further improvements in echocardiographic assessment at 1 year.[90–92] The earliest reported assessment of improvement in LVESV index and mitral regurgitation was at 3 months in the CARE-HF trial. This same study reported a statistically significant improvement in NYHA class and health-related QOL as early as 90 days after a successful CRT implant.

RECOMMENDATION

8. We recommend that alterations in clinical parameters after vs before CRT be assessed within 6 to 12 months after CRT implantation to guide ongoing HF management (Strong Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation is based on the importance of ensuring optimal medical therapy and deriving important benefit in improvement in reverse remodelling and QOL with CRT delivery.

Practical tip. See Figure 2. The process of LV remodelling is a dynamic process that begins at the time of CRT implantation, but requires ongoing reassessment throughout follow-up.

Remote monitoring

Remote monitoring (RM) of devices is integral to the care of patients with CRT and other CIED implants. A recent CCS/Canadian Heart Rhythm Society (CHRS) position statement provides further guidance on this topic.[93]

Practical tip. Alternating RM visits with direct device clinic follow-up visits in a 1:1 ratio is a suggested starting point. The proportion of RM-based follow-up assessments might increase or decrease as dictated by individual patient circumstances.

Referral for cardiac transplantation and mechanical circulatory support

Not all CRT recipients will derive benefit despite what appears to be optimal delivery of this therapy and aggressive medical management. Hence, progressive HF might ensue, requiring other interventions, such as ventricular assist devices or cardiac transplantation. The CCS HF Management Guideline update provides additional information on the role of ventricular assist devices and cardiac transplantation.[94]

Assessment of a patient at the time of pulse generator change

Issues requiring consideration at the time of a generator replacement in CRT recipients are summarized in Figure 3. A change in the clinical status of the patient might occur between the time of the original implant and the time of generator replacement. Clinical deterioration, alteration in cognitive function, other illnesses (eg, cancer), and QOL should also be considered in the decision-making process. A multidisciplinary approach (HF team, geriatrician, family) might be of value in the decision-making process. In some patients, downgrading from a CRT-D to a CRT-P device at

time of replacement is worth considering depending on the goals of care.

Device and lead advisories

With the increased use of ICD and CRT devices, there have been increases in the number of advisories or safety alerts.[95] The device follow-up clinic (and implanting centre) should have standard operating procedures for safety alerts and advisories. Although general recommendations are available on the CHRS Web site to help in the management, risks should be individualized. With increasing device complexity the likelihood of system-related problems increases. For example, the risk vs benefit of reusing a lead under advisory at time of generator replacement vs adding or extracting leads needs to be carefully considered and individualized.[96,97] However, lead revisions are best deferred to the time of a generator change to reduce the likelihood of complications including infection and bleeding.

Deactivation of ICD therapy

ICD deactivation is recommended when the goals of care, based on patient HF deterioration, other comorbidities or patient values, shift from one of prevention of death from ventricular arrhythmias to symptom-managed care. ICD therapy can be deactivated without affecting CRT delivery, when a decision for palliative care has been made. This option for choice needs to be addressed before the device implant and at subsequent visits when a worsening in clinical status is noted. A detailed discussion on this topic, can be found in the 2011 CCS HF management guidelines update.[94]

Health Economics and Accessibility of CRT

Regional issues

The expanded indication for CRT is yet to be effectively translated into practice. Data from the United States and Europe show utilization rates vary widely between regions, hospitals, and even patients based on nonclinical determinants such as sex, ethnicity, and race, with underuse and potentially inappropriate use suggested.[98] Considering the established mortality and QOL benefits of CRT on the one hand, and the high cost of the technology on the other, the accumulation and dissemination of such data should be a priority for providers and policy-makers across Canada to ensure appropriate and equitable use. Acquiring such data from the relatively few hospitals across the country capable of providing CRT should be relatively easy, and the development and linkage of device registries at such centres should be encouraged and supported by provincial authorities to ensure clinical and cost-effective use.

Wait times

There are no direct data regarding wait-times for CRT. Previous reports have advocated for an acceptable wait-list mortality of 0.5% from death and a HF hospitalization rate of $< 10\%$.[99,100] Using these benchmarks, the CCS Access to Care Working Group, in conjunction with the CHRS, have recommended that CRT be implanted within 6-8 weeks of referral. Invariably, access, and hence waits, for procedures can vary by physician, centre and, in Canada, by province. Such data, as with those relating to potential regional variation in CRT referral and implantation, should also be a matter of surveillance priority for patients, providers, and policy-makers. Adequate resources for the delivery of CRT are required to meet the expanding indications for CRT and the low utilization of this therapy in some regions.

RECOMMENDATION

9. We suggest that CRT implantation occur within 6-8 weeks from the decision to implant to avoid preventable adverse events, such as HF hospitalizations and death (Conditional Recommendation, Low-Quality Evidence).

Cost/benefit

Several analyses of the cost-effectiveness of CRT have now been published including from a Canadian perspective.[101–106] Most studies now suggest that, using a lifetime time horizon, CRT in comparison with optimal medical therapy appears consistently to meet the traditional USD$50,000/quality-adjusted life-year benchmark for health care interventions in the United States and elsewhere.[107] The most significant limitation of current cost-effectiveness analyses is that it has been analyzed from RCTs with limited follow-up, and these data might not be generalizable to population-based use because of differences in patient selection, use of CRT-D vs CRT-P, and appropriateness of use.

Summary and Future Directions

These guidelines provide direction on how to apply CRT in more complex patient cases, manage patients perioperatively, and optimize CRT delivery. Many of the areas are lacking in high-quality evidence. As more information becomes available, these recommendations 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.2013.09.009.