Centre universitaire de santé McGill

McGill University Health Centre

Technology Assessment Unit of the McGill University Health Centre (MUHC)

Cardiac Resynchronization Therapy in Heart Failure

Report number: 77

DATE: February 22, 2016

Report available from http://www.mcgill.ca/tau

Report prepared for the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC)

by

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Approved by the Committee of the TAU on 29 January, 2016

Suggested citation

Suarthana E.,* Almeida N.,* Dendukuri N. Cardiac Resynchronization Therapy in Heart Failure. Montreal (Canada): Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC); 2016 February 22. Report no. 77. 82 p.

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ACKNOWLEDGEMENTS

The expert assistance of the following individuals is gratefully acknowledged:

- Mona Black, Supervisor, Electrophysiology/Pacemaker Lab at the Montreal General Hospital and the Cath Lab at the Glen, Division of Cardiology, MUHC
- Nathalie Comtois, Nurse Manager, Division of Cardiology, MUHC
- Anique Ducharme, Cardiologist, Montreal Heart Institute
- Vidal Essebag, Electrophysiologist, MUHC
- Nadia Giannetti, Chief, Division of Cardiology, MUHC
- Melissa Hakim, Department of Finance, MUHC
- Paul Khairy, Electrophysiologist, Montreal Heart Institute
- Peggy Verhoef, Assistant Nurse Manager, the Electrophysiology/Pacemaker Lab at the Montreal General Hospital, Division of Cardiology, MUHC

This report was supported by a grant obtained through the PSI-ETMI competition organized by L'Institut Nationale d'Excellence en Santé et en Services Sociaux (INESSS).

REPORT REQUESTOR

This report was requested by Ann Lynch, Associate Director General, Clinical Operations, Adult Missions, McGill University Health Centre.

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ABSTRACT

- Since the first review of cardiac resynchronisation therapy (CRT) by the Technology Assessment Unit (TAU) in 2004, there has been an expansion of indications for its use and a steady increase in the number of devices implanted at the McGill University Health Centre (MUHC). In 2014/2015, the MUHC spent $490,653 on 45 CRT pacemaker (CRT-P) implants ($11,073 per initial implant and $10,649 per re-implantation). In the same period, $3,688,974 was spent on 162 CRT with defibrillator (CRT-D) implants ($23,007 per initial implant and $22,583 per re-implantation), of which $3,278,070 was covered under a fund for defibrillator devices from the Quebec government. With the change in the financial model at the MUHC in 2015, CRT-D costs will be covered by the global Cardiology budget rather than by a special fund for defibrillators.

- Randomized trials have shown that CRT is beneficial in selected heart failure patients. However, as many as one-third of patients who receive the device do not respond and would have been subject to the risks of CRT implantation for no additional benefit. Therefore, the TAU was requested, and to identify subgroups of heart failure patients in whom CRT will result in the greatest benefit in order to optimize use of this high-cost procedure.

- We found that there is sufficient evidence to support use of CRT for patients in sinus rhythm with systolic heart failure with severely prolonged QRS interval (>150 msec); left bundle branch block (LBBB) morphology, and left ventricular ejection fraction (LVEF) <30%.

- Patients with severe symptoms (i.e. New York Heart Association (NYHA) Functional Class III), experienced significant clinical improvement from the addition of CRT-P to optimal pharmacologic therapy (OPT) alone. Among mildly symptomatic patients (NYHA class II), CRT-D significantly reduced mortality compared to the implantable cardioverter defibrillator (ICD) alone.

- The benefit of CRT is less certain in patients with any of the following characteristics: NYHA Class IV, moderate QRS interval (120-150 msec), non-LBBB morphology, and LVEF >30%, because none of the trials included sufficient patients with these characteristics to draw concrete conclusions. Given the limited evidence in these subgroups, patient selection is crucial to determine the response to CRT.

- We found that though many clinical guidelines, including the Canadian Cardiovascular Society (CCS) recognize that the evidence of CRT benefit is limited in certain sub-groups, they none the less recommend considering CRT for such patients. Unlike clinical practice guidelines, our report does not provide guidance on the treatment of individual patients, which is left to the discretion of the treating physician. Rather, the focus of our report has been to distinguish between those situations where there is good evidence to support the use of CRT and where there is not.

- Given the increasing use, high costs and residual uncertainty regarding the benefit of CRT in certain patients, there is an urgent need for a registry to assess local practice patterns and outcomes and further contribute to the overall evidence base. In light of the impending provincial evaluation of CRT, unavailability of local clinical data to support current practices may further hamper funding for this technology, which has proven beneficial effects in a sub-group of heart failure patients.

RÉSUMÉ

- Depuis la première revue de la thérapie de resynchronisation cardiaque (TRC) par le Technology Assessment Unit (TAU) en 2004, implantés au Centre Universitaire de Santé McGill (CUSM). En 2014/2015, le CUSM a dépensé 490 653$ pour l'implantation de 45 stimulateurs cardiaques TRC (TRC-P) (11 073$ pour la première implantation et 10 649$ par réimplantation). Pour la même période, 3 688 974$ étaient dépensés pour l'implantation de 162 stimulateurs TRC avec défibrillateur (TRC-D) (23 007$ pour la première implantation et 22 583$ par réimplantation), dont 3 278 070$ étaient couverts par un fonds du gouvernement du Québec pour les stimulateurs/défibrillateurs. Suite aux changements apportés au modèle financier du CUSM en 2015, les coûts de la TRC-D seront couverts par le budget global de la cardiologie plutôt que par un fonds spécial pour les stimulateurs/défibrillateurs.

- Des études randomisées ont montré que la TRC est bénéfique chez certains patients ciblés, souffrant d'insuffisance cardiaque. Cependant, pas moins d'un tiers des patients ayant reçu ce stimulateur n'ont montré aucune réponse et auraient été exposés aux risques d'une implantation pour la TRC, sans aucun bénéfice additionnel. Par conséquent, le TAU fut interpelé pour identifier les sous-groupes de patients souffrant d'insuffisance cardiaque chez qui la TRC procurera les plus grands bénéfices de façon à optimiser l'utilisation de cette procédure dispendieuse.

- Nous avons constaté qu'il y a assez de preuves supportant l'utilisation de la TRC chez les patients en rythme sinusal avec une insuffisance cardiaque systolique, un intervalle QRS sévèrement allongé (>150 msec), une morphologie de bloc de branche gauche et une fraction d'éjection ventriculaire gauche (FEVG) <30%.

- Les patients avec de sévères symptômes (i.e. classe fonctionnelle III, New York Heart Association (NYHA)) ont montré une amélioration clinique significative suite à l'ajout de la TRC-P à la thérapie pharmacologique optimale, seule. Chez les patients modérément symptomatiques (classe II NYHA), la TRC-D a réduit la mortalité de façon significative comparativement au défibrillateur cardioverteur implantable (DCI), seul.

- Le bénéfice de la TRC est moins évident chez les patients présentant les caractéristiques suivantes: classe IV NYHA, un intervalle QRS modéré (120-150 msec), aucune morphologie d'un bloc de branche gauche et une FEVG >30% parce qu'aucune étude ne comprenait assez de patients avec ces caractéristiques pour en tirer des

conclusions précises. Étant données le peu de preuves de ces sous-groupes, la sélection des patients est critique pour déterminer la réponse à la TRC.

- Nous avons constaté que malgré le fait que plusieurs lignes directrices cliniques, incluant la Canadian Cardiovascular Society (CCS), reconnaissent que les preuves des bénéfices de la TRC sont limitées à certains sous-groupes, elles recommandent néanmoins de considérer la TRC pour de tels patients. Contrairement aux lignes directrices cliniques, notre rapport ne propose pas de conseils quant au traitement d'un patient donné, ce qui est laissé à la discrétion du médecin traitant. Le centre d'intérêt de notre rapport visait plutôt à identifier les situations où il y a assez de preuves pour supporter l'utilisation de la TRC et les situations où les preuves sont inexistantes.
- Étant donné l'utilisation croissante, les coûts élevés et l'incertitude toujours présente concernant les bénéfices de la TRC chez certains patients, un besoin urgent s'impose en regard d'un registre permettant l'évaluation des modes de pratique locaux et des résultats, et contribuer de plus à l'ensemble des données probantes. À la lumière de l'évaluation provinciale imminente de la TRC, la non disponibilité de données cliniques locales pour supporter les pratiques courantes peut entraver davantage le support financier de cette technologie qui démontre des bénéfices tangibles dans un sous-groupes de patients souffrant d'insuffisance cardiaque.

LIST OF ABBREVIATIONS

ACCF/AHA	American College of Cardiology Foundation/American Heart Association
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
BVP	Biventricular pacemaker
CCS	Canadian Cardiovascular Society
CRT	Cardiac resynchronization therapy
CRT-P	CRT pacemaker
CRT-D	CRT with defibrillator
ESC	European Society of Cardiology
HF	Heart Failure
HR	Hazard ratio
HTA	Health Technology Assessment
ICD	Implantable cardioverter defibrillator
INAHTA	International Network of Agencies for Health Technology Assessment
INESSS	L'Institut national d'excellence en santé et en services sociaux
IPD MA	Individual patient data meta-analysis
LBBB	Left bundle branch block
LVEF	Left ventricle ejection fraction
LVESv	Left ventricle end systolic volume
MLWHFQ	Minnesota Living with Heart Failure Questionnaire
MUHC	McGill University Health Centre
NICE	National Institutes for Health and Clinical Excellence
NYHA	New York Heart Association
OPT	Optimal pharmacologic therapy
QALY	Quality adjusted life-year
QOL	Quality of life
RCT	Randomized controlled trial
RR	Risk ratio
TAU	MUHC Technology Assessment Unit
6-MWT	6-minute walk test

EXECUTIVE SUMMARY

BACKGROUND

Since the first review of cardiac resynchronisation therapy (CRT) by the Technology Assessment Unit (TAU) in 2004, there has been an expansion of the indications for its use and a steady increase in the number of devices implanted in the McGill University Health Centre (MUHC). Although landmark trials show that cardiac resynchronisation therapy (CRT) is beneficial in heart failure patients, it has also been reported that as many as one-third of the patients who received the device did not respond and would have been subjected to the additional costs and risks of the procedure for no further benefit.

OBJECTIVES

In the following report we review literature on CRT efficacy, safety and cost-effectiveness to identify subgroups of heart failure patients in whom CRT will result in the greatest benefit in order to support optimal use of this high-cost procedure. We also report the trends in use of CRT over the last 5 years and the budget impact at the MUHC. A separate report has been prepared on CRT in heart block patients.

METHODS

We carried out a search for relevant randomized controlled trials (RCT); observational studies, health technology assessment (HTA) reports, systematic reviews and meta-analyses on efficacy, cost-effectiveness, and safety; and clinical guidelines for CRT in heart failure patients. We repeated some meta-analyses using a Bayesian hierarchical model to appropriately consider between-study heterogeneity and provide accurate pooled estimates.

RESULTS FOR EFFICACY AND SAFETY OF CRT

We identified 20 RCTs examining the efficacy of CRT use in heart failure patients, who were all sinus rhythm patients with reduced ejection fraction (i.e. systolic heart failure).

- Five RCTs were carried out in patients with QRS duration <130 msec.
    - One RCT of 60 patients concluded that CRT pacemaker (CRT-P) was superior to optimal pharmacologic therapy (OPT) in terms of a composite outcome (6

months free of heart failure hospitalisations; improvement in patients' symptoms or exercise capacity).

- Four RCTs evaluated efficacy of CRT with defibrillator (CRT-D) versus implantable cardioverter defibrillator (ICD). One of these (n=56) concluded that CRT-D was superior to ICD in terms of a composite outcome (improvement in patients' symptoms; or no heart failure hospitalisations or deaths). Other RCTs, including the largest (ECHO-CRT, n=809) found that CRT-D was not beneficial and could even be harmful. ECHO-CRT was interrupted for futility as there were 11.1% deaths in the CRT-D group compared to 6.4% in the ICD group (hazard ratio (HR) 1.8, 95% confidence interval (CI) 1.1 to 2.9). The risk of the primary outcome (composite of death from any cause or hospitalization for heart failure) was 28.7% in the CRT-D group vs. 25.2% in the ICD group (HR 1.2, 95% CI 0.9 to 1.6).

- Fifteen RCTs studied patients with prolonged QRS duration (>120 msec).
  - Efficacy of CRT-P compared to OPT was evaluated in five RCTs of severely symptomatic patients (NYHA Functional Class III and IV-ambulatory). CRT-P was associated with a clinical and statistically significant improvement in functional class (≥1 NYHA class), exercise capacity (~40 m increase in distance walked in 6 minutes), and ventricular function (5% increase in LVEF). One large RCT (CARE-HF) with long follow-up demonstrated significant reduction in all-cause mortality.
  - Efficacy of CRT-D compared to ICD was evaluated in 10 RCTs of mildly symptomatic (NYHA class II) patients. Only RAFT, a large RCT (n=1,798) with long duration, demonstrated a significant reduction in all-cause mortality. MADIT, the largest RCT, also demonstrated a reduction in mortality, though not statistically significant, whereas the small trials showed conflicting results.
  - It is important to note that there are discrepancies between entry criteria and the characteristics of the enrolled patients in these trials: (1) the mean QRS interval values were much wider than the entry criteria (>150 msec vs. >120 msec), (2) mean LVEF values (20.7% to 26.7%) were much lower than trial entry criteria (<30% to <40%), (3) NYHA Class IV-ambulatory patients made up less than 5% of the total participants.

In terms of safety, the most commonly reported adverse events following CRT are implantation failure (7.6% to 9%) and lead dislodgement (3.8% to 10%). Risk of device-related death is low in general (range: 0.04-0.5% in CRT-D patients and 0.2-0.8% in CRT-P patients). Large RCTs and observational studies reported significantly higher incidents of device-related complications in the CRT-D group compared to ICD group: infections 1.7-1.9% vs. 1.0-1.3%, and hematoma requiring interventions 2.5% vs. 1.8%, respectively.

PREDICTORS OF CRT RESPONSE IDENTIFIED BY META-ANALYSES

The main predictor of a favourable response to CRT, defined as reduction in all-cause mortality or a composite of death and heart-failure hospitalization, was severely prolonged QRS duration (>140 or 150 msec), according to two meta-analyses that pooled studies of any CRT intervention (CRT-D or CRT-P) versus control (ICD or OPT). One of the meta-analyses used an individual patient data analysis (IPD MA), while the other used aggregated data. Both also found that LBBB morphology was an important predictor of good CRT response, but results were inconclusive in non-LBBB patients perhaps due to the small numbers of patients included in the trials.

HTAS AND CLINICAL GUIDELINES FOR CRT USE

We compared three clinical guidelines for CRT use from the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA), the European Society of Cardiology (ESC), and the Canadian Cardiovascular Society (CCS), and two health technology assessment reports by the National Institute for Care and Excellence (NICE UK) and the Agency for Healthcare Research & Quality (AHRQ, USA).

- None recommend CRT in NYHA class I, except NICE, which recommends CRT-D when QRS interval ≥150 msec, regardless of morphology, and ACCF/AHA which recommended that CRT-D may be considered in patients with QRS interval ≥150 msec, LBBB and LVEF ≤ 30%.
- All recommend CRT-D in patients with NYHA class II, with LVEF ≤ 35%, LBBB and QRS interval ≥120 msec (>130 msec in the Canadian guidelines).
- All recommend CRT-P in patients with NYHA class III and IV-ambulatory, LVEF ≤ 35%, LBBB and QRS interval ≥120 msec (>130 msec in the Canadian guidelines).

EXPERIENCE AT THE MUHC

Usage data for the 2010-2015 fiscal years at the MUHC shows that dual chamber standard pacemakers remain the most implanted device. Nevertheless, the use of CRT at the MUHC has been increasing over time. Compared to 2010-11, total CRT-P implants have increased from 7 to 45, and CRT-D implants have increased from 91 to 162 in 2014-15. There has been a steady increase in the number of replacements/upgrades versus de-novo implants, with replacements/upgrades accounting for 40% of total CRT-P implants, and 55% of all CRT-D implants in 2014-15.

COSTS

In the fiscal year 2014/2015, the MUHC spent $490,653 on 45 CRT-P implants ($11,073 per initial implant and $10,649 per re-implantation). In the same period, $3,688,974 was spent on 162 CRT-D implants ($23,007 per initial implant and $22,583 per re-implantation), of which $3,278,070 was covered under a fund for defibrillator devices from the Quebec government. Since May 2015, CRT-D device costs have fallen substantially from $14,800 to $6,210, on average, but the special government fund for defibrillators has been dissolved. Funding for these devices is now included within the global Cardiology budget.

CONCLUSIONS

- There is sufficient evidence to support the use of CRT for patients with NYHA Class II/III, severely prolonged QRS interval (>150 msec); LBBB morphology, and LVEF <30%.
- The effect of CRT is less certain in patients with NYHA Class IV-ambulatory, moderate QRS interval (120-150 msec), non-LBBB morphology, and LVEF >30%. Though some guidelines and HTAs have recommended CRT use in these subgroups, their recommendations appear to be based on the entry criteria and not the actual characteristics of patients enrolled in the RCTs. (It should be noted that unlike clinical guideline documents our report does not provide guidance on how individual patients should be treated. Rather our focus has been to distinguish between those situations where there is good evidence to support the use of CRT and where there is not. The decision to treat an individual patient is left to the discretion of the treating physician.)

- QRS duration >150 msec is the strongest predictor of CRT response. QRS morphology i.e. the presence of LBBB may also be a potential indicator of good response to CRT.
- The use and budget impact of CRT-P and CRT-D at the MUHC has been increasing over the years. Since 2015 the MUHC has adopted a new funding model under which the cost of these devices is now covered within the global Cardiology budget.
- At the MUHC, there is currently no systematic documentation of patient selection criteria or evaluation of patient outcomes following CRT.

RECOMMENDATIONS

- The use of CRT is recommended for the treatment of heart failure patients only after careful consideration of clinical criteria known to influence the outcomes (i.e. severely prolonged QRS interval and LBBB morphology).
- Given the paucity of evidence in the literature and lack of consensus in published guidelines regarding other criteria (including NYHA Class IV-ambulatory, moderate QRS interval (120-150 msec), non-LBBB morphology, and LVEF >30%), it is necessary to systematically document patient selection criteria for CRT and to evaluate whether patient outcomes improve following CRT. Furthermore, as clinical decision-making requires taking into consideration multiple factors such as patient preference, referring doctor preference, and comorbidities, among other variables, it is necessary that these reasons also be systematically documented.
- The increasing use, high costs and residual uncertainty of the benefits of CRT in certain patients underscore the need for the development of a database to systematically document patient selection criteria and outcomes. The availability of local data is important for hospital decision-making and patient welfare. Furthermore, in light of reduced government funding and an impending provincial evaluation of CRT, unavailability of local data may further hamper funding of a technology with proven benefits in a significant proportion of heart failure patients. Therefore, it is recommended that continued use of CRT at the MUHC be made **conditional** on a systematic recording of patient data. The TAU recommends the systematic collection of a few key variables (**Appendix E**), either in the patient chart or electronically, to evaluate patient selection and outcomes.

- These recommendations should be reviewed in 6 months to assess progress or barriers to progress in implementing a data documentation system.

SOMMAIRE

CONTEXTE

Depuis la première revue de la thérapie de resynchronisation cardiaque (TRC) par le Technology Assessment Unit (TAU) en 2004, il y a eu un accroissement des indications pour son utilisation ainsi qu'une augmentation constante du nombre de stimulateurs implantés au Centre Universitaire de Santé McGill (CUSM). Bien que les essais de référence montrent que la thérapie de resynchronisation cardiaque bénéficie aux patients souffrant d'insuffisance cardiaque, il a été aussi mentionné que pas moins d'un tiers des patients ayant reçu ce stimulateur n'ont montré aucune réponse et auraient été exposés aux coûts supplémentaires et aux risques additionnels de la procédure sans aucun bénéfice additionnel.

OBJECTIFS

Dans ce rapport, nous revoyons la littérature concernant l'efficacité de la TRC, son innocuité et son coût-efficacité pour identifier les sous-groupes de patients souffrant d'insuffisance cardiaque chez qui la TRC procurera les plus grands bénéfices de façon à supporter l'utilisation optimale de cette procédure dispendieuse. Nous soulignons aussi les tendances de l'utilisation de la TRC au cours des 5 dernières années ainsi que son impact budgétaire au Centre Universitaire de Santé McGill (CUSM). Un rapport distinct a été élaboré sur l'utilisation de la TRC chez les patients présentant un bloc cardiaque.

MÉTHODOLOGIE

Nous avons effectué une recherche pertinente concernant les études randomisées (RR), les études par observation, les rapports d'évaluation des technologies (HTA), les revues systématiques et les méta-analyses sur l'efficacité, le coût-efficacité et l'innocuité ainsi que lignes directrices cliniques sur la TRC chez les patients avec insuffisance cardiaque. Nous avons refait quelques méta-analyses en utilisant un modèle hiérarchique bayésien pour dûment prendre en considération l'hétérogénéité entre les études et pour obtenir des estimés sommatifs précis.

RÉSULTATS

Nous avons identifié 20 études randomisées portant sur l'efficacité de la TRC chez les patients avec insuffisance cardiaque ayant tous un rythme sinusal et une fraction d'éjection réduite (i.e. insuffisance cardiaque systolique).

- Cinq études randomisées furent menées chez des patients avec un intervalle QRS<130 msec.
    - Une étude randomisée de 60 patients conclua que la TRC avec pacemaker (TRC-P) était supérieure à la thérapie pharmacologique optimal (TPO) en termes de résultats combinés (6 mois sans hospitalisation pour insuffisance cardiaque; amélioration des symptômes patients ou de la capacité à l'exercice).
    - Quatre études randomisées évaluèrent l'efficacité de la TRC avec défibrillateur (TRC-D) versus le défibrillateur cardioverteur implantable (DCI). Une de ces études (n=56) conclua que la TRC-D était supérieure à l'approche DCI en termes de résultats combinés (amélioration des symptômes patients, ou aucune hospitalisation pour insuffisance cardiaque ou décès). D'autres études randomisées, incluant la plus importante (ECHO-CRT, n=809), ont montré que la TRC-D n'apportait aucun bénéfice et pouvait même être préjudiciable. L'étude ECHO-CRT fut interrompue pour incapacité à atteindre les objectifs car il y avait 11.1% de décès dans le groupe TRC-D comparé à 6.4% dans le groupe DCI (risque relatif (RR) de 1.8, intervalle de confiance à 95% (IC) 1.1 à 2.9). Le risque associé au résultat principal (décès résultant de n'importe quelle cause ou hospitalisation pour défaillance cardiaque) était de 28.7% pour le groupe TRC-D versus 25.2% pour le groupe DCI (RR 1.2, 95% IC 0.9 à 1.6).
- Quinze études randomisées ont étudié les patients avec un intervalle QRS allongé (>120 msec)
    - L'efficacité de la TRC-P comparée à la TPO fut évaluée dans 5 études randomisées chez des patients sévèrement symptomatiques (classe fonctionnelle III et IV - ambulatoire, NYHA). La TRC-P était associée à une amélioration clinique statistiquement significative au niveau de la classe fonctionnelle (≥1 classe NYHA), de la capacité à l'exercice (augmentation

d'une distance de marche de ~ 40 m en six minutes) et de la fonction ventriculaire (augmentation de 5% de la fraction d'éjection ventriculaire gauche (FEVG)). Une étude randomisée importante (CARE-HF) incluant un suivi à long terme, démontra une diminution significative de la mortalité, toutes causes confondues.

- L'efficacité de la TRC-D comparée au DCI fut évaluée dans 10 études randomisées chez les patients modérément symptomatiques (classe II NYHA). Seule la vaste étude randomisée RAFT (n=1 798) avec un suivi à long terme démontra une diminution significative de la mortalité, toutes causes confondues. De même, la plus vaste étude randomisée, soit l'étude MADIT, démontra aussi une réduction de la mortalité, mais non statistiquement significative, bien que de petites études montrèrent des résultats conflictuels.

- Il est important de souligner la présence de divergences entre les critères de sélection et les caractéristiques des patients retenus dans ces études: (1) les valeurs moyennes des intervalles QRS étaient beaucoup plus grandes que les critères de sélection (>150 msec vs >120 msec), (2) les valeurs moyennes de la FEVG (20.7% à 26.7%) étaient beaucoup plus faibles que les critères de sélection (<30% à <40%), (3) les patients ambulatoires (classe IV NYHA) représentaient moins de 5% du nombre total de participants.

Concernant l'innocuité, les événements indésirables les plus communs rapportés suite à la TRC sont l'échec de l'implantation (7.6% à 9%) et le déplacement de l'électrode (3.8% à 10%). De façon générale, le risque de décès lié au stimulateur est faible (plage: 0.04-0.5% pour les patients dans le groupe TRC-D et 0.2-0.8% pour les patients dans le groupe TRC-P). Les vastes études randomisées et les études par observation rapportèrent un nombre d'incidents significativement plus élevé en regard des complications liées aux stimulateurs dans le groupe TRC-D, comparativement au groupe DCI: infections 1.7-1.9% vs 1.0-1.3% et hématomes nécessitant une intervention 2.5% vs 1.8%, respectivement.

INDICATEURS DE LA REPONSE A LA TRC IDENTIFIES PAR LES META-ANALYSES

L'indicateur principal d'une réponse positive à la TRC, défini comme étant la réduction de la mortalité, toutes causes confondues, ou le regroupement des décès et des

hospitalisations pour défaillance cardiaque, était un intervalle QRS allongé de façon importante (>140 ou 150 msec) selon deux méta-analyses regroupant des études de toute intervention de TRC (TRC-D ou TRC-P) versus des interventions de contrôle (DCI ou TPO). Une de ces méta-analyses utilisa une analyse individuelle des données patients (DPI MA) tandis que l'autre analyse utilisa des données agrégées. Ces deux études montrèrent que la morphologie du bloc de branche gauche était un indicateur important d'une bonne réponse à la TRC, mais les résultats n'étaient pas concluants chez les patients sans bloc de branche gauche, peut-être dû au faible nombre de patients dans ces études.

LES RAPPORTS D'EVALUATION DES TECHNOLOGIES (HTA) ET LES LIGNES DIRECTRICES POUR L'UTILISATION DE LA TRC

Nous avons comparé trois ensembles de lignes directrices cliniques pour l'utilisation de la TRC, soit celles de l'American Heart Association (ACCF/AHA), de l'European Society of Cardiology (ESC) et de la Canadian Cardiovascular Society (CCS), ainsi que deux rapports d'évaluation des technologies par le National Institute for Care and Excellence (NICE UK) et par l'Agency for Healthcare Research & Quality (AHRQ, USA).

- Aucune ligne directrice ne recommande l'utilisation de la TRC chez les patients de la classe I NYHA, excepté NICE qui recommande la TRC-D lorsque l'intervalle QRS est ≥ 150 msec, quelle que soit la morphologie, et l'ACCF/AHA qui recommande que la TRC-D puisse être considérée chez les patients avec un intervalle QRS ≥ 150 msec, un bloc de branche gauche ainsi qu'une FEVG ≤ 30%.
- Toutes les lignes directrices recommandent la TRC-D chez les patients de classe II NYHA avec une FRVG ≤ 35%, un bloc de branche gauche ainsi qu'un intervalle QRS ≥ 120 msec (>130 msec selon les lignes directrices canadiennes).
- Toutes les lignes directrices recommandent la TRC-P chez les patients de classe III et IV ambulatoires NYHA avec une FEVG ≤ 35%, un bloc de branche gauche et un intervalle QRS ≥ 120 msec (>130 msec selon les lignes directrices canadiennes).

EXPÉRIENCE AU CUSM

Les données d'utilisation au CUSM pour les années financières 2010 à 2015 nous montrent que les stimulateurs cardiaques classiques à double chambre demeurent les plus implantés. Néanmoins, l'utilisation de la TRC au CUSM a augmenté au cours des années. Comparées aux données des années 2010/2011, les implantations totales de stimulateurs

TRC-P ont augmentées de 7 à 45 et celles de stimulateurs TRC-D, de 91 à 162, en 2014-2015. Il y a eu une augmentation régulière du nombre de remplacements/rehaussements versus les implantations *de novo*; en 2014-2015 les remplacements/rehaussements représentaient 40% des implantations totales de stimulateurs TRC-P et 55% des implantations de TRC-D.

COÛTS

Pour l'année financière 2014/2015, le CUSM a dépensé 490 653$ pour 45 implantations de stimulateurs TRC-P (11 073$ pour une première implantation et 10 649$ par réimplantation). Pour la même période, 3 688 974$ ont été dépensés pour l'implantation de 162 stimulateurs TRC-D (23 007$ pour une première implantation et 22 583$ par réimplantation), où un montant de 3 278 070$ était couvert par un fonds du gouvernement québécois dédié à l'implantation de stimulateurs-défibrillateurs. Depuis le mois de mai 2015, le coût des stimulateurs TRC-D a baissé substantiellement de 14 800$ à 6 210$, en moyenne, mais le fonds spécial du gouvernement pour les stimulateurs-défibrillateurs a été dissous. Le support financier pour ces appareils est maintenant inclus dans le budget global de la cardiologie.

CONCLUSIONS

- Il existe assez de preuves pour supporter l'utilisation de la TRC pour les patients de classe II/III NYHA avec un intervalle QRS fortement allongé (>150 msec), une morphologie de bloc de branche gauche et une FEVG <30%.
- Les effets de la TRC sont moins évidents chez les patients ambulatoires de classe IV NYHA avec un intervalle QRS modéré (120-150 msec), sans morphologie de bloc de branche gauche et avec une FEVG >30%. Néanmoins, certaines lignes directrices et rapports d'évaluation des technologies ont recommandé l'utilisation de la TRC chez les patients de ce sous-groupe, leurs recommandations semblant être basées sur les critères de sélection et non sur les caractéristiques des patients admis dans les études randomisées. (Il est à noté que contrairement aux document de lignes directrices cliniques, notre rapport ne propose pas de conseils quant au traitement d'un patient donné. Le centre d'intérêt de notre rapport visait plutôt à identifier les situations où il y a assez de preuves pour supporter l'utilisation de la TRC et les situations où les preuves sont inexistantes. La décision de traiter un patient donné est laissée à la discrétion du médecin traitant.)

- Un intervalle QRS >150 msec est le plus solide indicateur de la réponse à la TRC. La morphologie du QRS, i.e. la présence d'un bloc de branche gauche, peut aussi être un indicateur potentiel d'une bonne réponse à la TRC.

- L'utilisation et l'impact budgétaire des stimulateurs TRC-P et TRC-D au CUSM ont augmenté au cours des années. Depuis 2015, le CUSM a adopté un nouveau modèle financier où le coût de ces stimulateurs est maintenant couvert pas le budget global de la cardiologie.

- Actuellement au CUSM, il n'y a pas de documentation systématique des critères de sélection des patients ni d'évaluations des résultats patients suite à la TRC.

RECOMMANDATIONS

- L'utilisation de la TRC est recommandée pour le traitement des patients souffrant d'insuffisance cardiaque seulement après un examen prudent des critères cliniques reconnus pour influencer les résultats (i.e. un intervalle QRS fortement allongé et une morphologie de bloc de branche gauche).

- Étant donné la rareté des preuves dans la littérature et l'absence de consensus dans les lignes directrices en regard d'autres critères [incluant la classe IV ambulatoire NYHA, l'intervalle QRS modéré (120-150 msec), la morphologie de l'absence de bloc de branche gauche et une FEVG >30%], il est nécessaire de documenter systématiquement les critères de sélection des patients pour la TRC et d'évaluer si les résultats patients montrent une amélioration suite à la TRC. De plus, puisque la prise de décision clinique exige de prendre en considération de multiples facteurs, entre autres, la préférence des patients, la préférence du médecin référant et les comorbidités, il est nécessaire que ces données soient aussi systématiquement documentées.

- L'augmentation de l'utilisation, les coûts élevés et l'incertitude toujours présente quant aux bénéfices de la TRC chez certains patients, soulignent le besoin du développement d'une base de données pour documenter systématiquement les critères de sélection des patients ainsi que les résultats. La disponibilité de données locales est importante pour la prise de décision hospitalière et pour le bien-être des patients. De plus, à la lumière de la réduction du support financier du gouvernement

et d'une évaluation provinciale imminente de la TRC, la non disponibilité de données locales peut entraver davantage le support financier de cette technologie qui démontre des bénéfices tangibles chez une portion significative des patients avec insuffisance cardiaque. Par conséquent, il est recommandé que la poursuite de l'utilisation de la TRC au CUSM soit **conditionnelle** à l'enregistrement systématique des données patients. Le TAU recommande la collecte systématique de quelques variables clés (voir **Annexe E**), que ce soit dans le dossier patient ou de façon électronique, pour évaluer la sélection des patients et les résultats.

- Ces recommandations devraient être revues dans 6 mois pour évaluer les progrès ou les obstacles aux progrès, dans l'implantation d'un système de documentation des données.

CARDIAC RESYNCHRONIZATION THERAPY IN HEART FAILURE

1. BACKGROUND

Cardiac resynchronization therapy (CRT), also known as biventricular pacing, was developed to improve coordination of ventricular contraction in patients with severely symptomatic heart failure despite best medical management. CRT uses a biventricular pacemaker (BVP) to pace the right and left ventricles simultaneously, and is thus used to treat ventricular dyssynchrony, a difference in timing between right and left ventricular contractions. CRT, when implanted alone, is referred to as CRT-P (for pacing). For selected patients at risk of malignant ventricular arrhythmias, CRT can be combined with an implantable cardioverter defibrillator (ICD), and is then referred to as CRT-D (for defibrillator). Landmark trials[2,3] show that cardiac resynchronisation therapy (CRT) is beneficial to selected heart failure patients as it can prolong life and improve patients' quality of life. [See Appendix F for an explanation of technical details related to CRT and heart failure.]

Since the first review of CRT by the Technology Assessment Unit (TAU) in 2004,[4] there has been an expansion of the indications for its use and a steady increase in the number of devices implanted in the McGill University Health Centre (MUHC). In the 2014/2015 fiscal year, the MUHC spent almost $0.5 million on CRT-P implants for 45 patients. In the same period, $3.7 million was spent on CRT-D implants for 162 patients, most of which was covered under a special fund for defibrillator devices from the Quebec government.

However, it is also known that as many as one-third of the patients who received the device did not respond in some cohorts and would have borne the risks of the surgical procedure for no apparent benefit from the CRT component of the therapy.[5] Response to CRT may differ by clinical characteristics such as severity of heart failure symptoms (assessed with the NYHA classification system); QRS duration (an indicator of ventricular dyssynchrony); or QRS morphology (such as the presence of left bundle branch block (LBBB), a conduction disorder causing the left ventricle to contract after the right ventricle). Therefore, the TAU was requested to identify potential subgroups of heart failure patients in whom CRT will result in the greatest benefit in order to optimize this high-cost procedure. A separate report has been prepared for CRT evaluation in heart block patients.[6] In the interim, the government of Quebec has identified cardiac

defibrillators (which are sometimes used together with CRT) as a key health technology whose appropriate usage should be studied by a field evaluation.[7]

2. OBJECTIVES

The objectives of this assessment are:

- To review evidence on the efficacy and safety of CRT compared to alternative therapies;
- To identify subgroups of heart failure patients in whom CRT will result in the greatest benefit;
- To report the trends in use of CRT over the last 5 years and the budget impact at the MUHC.

3. METHODS

3.1 Literature search and quality assessment

We carried out a search for relevant randomized controlled trials (RCT); observational studies, health technology assessment (HTA) reports, systematic reviews and meta-analyses on efficacy, cost-effectiveness, and safety; and clinical guidelines for CRT in heart failure patients. The search was limited to the databases maintained by York University (http://www.york.ac.uk/inst/crd/), Cochrane Library, and PubMed. In addition to published studies, we searched for randomized controlled trials in progress from ClinicalTrials.gov. We also carried out a search for HTA reports on the website of the Agency for Healthcare Research and Quality (AHRQ) (http://www.ahrq.gov/research/findings/ta/index.html).

Descriptions of the parameters (i.e. population, intervention, comparator), search keywords, and databases searched are summarized in **Appendix B**. The last search was conducted on June 4, 2015. The literature search and review were carried out independently by two authors (ES and NA). There were no disagreements between authors.

The quality of the trials in terms of risk of bias was assessed on the basis of random sequence generation, allocation concealment, blinding of participants /personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and potential conflict of interest (e.g. sources of funding) (**Appendix C**).

Published meta-analyses of efficacy of CRTs have generally used the methods proposed by DerSimonian-Laird, which are shown to under-estimate between-study heterogeneity and provide an overly precise pooled estimate.[8] Therefore, we repeated these meta-analyses using a Bayesian hierarchical model instead.[9]

4. LITERATURE REVIEW

We found 20 original RCTs of CRT devices for patients with heart failure associated with left ventricular systolic dysfunction (LVSD) and cardiac dyssynchrony who are also at increased risk of sudden cardiac death (SCD) as a result of ventricular arrhythmias despite optimal pharmacologic therapy (OPT) (**Appendix Figure B-1**).

We summarized the efficacy of CRT from these trials according to QRS duration, because response to CRT may differ by QRS interval. Five RCTs were carried out in patients with QRS duration< 130 msec (summarized in **Section 4.1.1**) and fifteen RCTs were carried out in patients with prolonged QRS duration (summarized in **Section 4.1.2**). In the last five years, there have been no new RCTs.

We identified eleven observational studies: only two evaluated the efficacy of CRT (summarized in **Appendix D**) while the others evaluated the potential clinical predictors of CRT response.

We reviewed the findings from the HTA reports of the National Institute for Care and Excellence (NICE, UK)[10] and the Agency for Healthcare Research & Quality (AHRQ, USA).

We also summarized three clinical guidelines for CRT use in heart failure that were published by three major cardiology associations in North America and Europe: The American College of Cardiology Foundation and the American Heart Association (ACCF/AHA),[11] the European Society of Cardiology (ESC),[12] and the Canadian Cardiovascular Society (CCS).[13]

Most guidelines and HTAs considered evidence from the same pool of RCTs. Below, we summarize the results from the RCTs, and compare recommendations across guidelines and HTAs within subgroups defined by clinical characteristics that are potential predictors of successful outcomes of CRT (such as NYHA class, QRS morphology and QRS interval width).

4.1 Efficacy

4.1.1 The efficacy of CRT in patients with QRS <130 msec

The QRS interval represents the time taken for ventricular depolarization, which signals the ventricles to contract. Normal values range from 80-120 msec; a prolonged QRS duration (≥120 msec) on an electrocardiogram is considered to be a marker of interventricular dyssynchrony i.e. a difference in timing of contractions between the right and left ventricles.

The five RCTs that assessed CRT use in patients with QRS duration < 130 msec are summarized below.

A. CRT-Pacemaker vs. optimal pharmacologic therapy (OPT) [The RESPOND trial]

The RESPOND clinical trial[14] (n=60 patients with NYHA class III or IV, LVEF ≤35%, and QRS <120 msec) found that 83% of patients randomized to CRT-P vs. 23% in the OPT group [p<0.0001] showed improvement in a composite measure of soft outcomes [survival for 6-months free of heart failure hospitalisations plus improvement in patients' symptoms (≥1 class improvement in NYHA functional classification) or exercise capacity (>25% increase in distance walked in 6-minutes)]. However, although the number of all-cause deaths in the OPT group was twice that in the CRT-P group (10 vs. 5, respectively), this difference was not statistically significant. This RCT is at risk of performance and detection biases as personnel and outcome assessors were not blinded.

B. CRT-Defibrillator vs. ICD [Echo-CRT, NARROW-CRT, RethinQ, LESSER-EARTH trials]

- The Echo-CRT study,[15] the largest double-blind trial (n=809, NYHA class III and IV HF patients with mechanical dyssynchrony, mean LVEF of 27%, and QRS duration <130 msec) was interrupted for futility. After a mean of 19.4 months follow up, there were 11.1% deaths in the CRT-D group and 6.4% in the ICD group (HR 1.8, 95% CI 1.1 to 2.9).

The composite of death from any cause or first hospitalization for worsening heart failure was found in 28.7% in the CRT-D group and 25.2% in the ICD group (HR 1.2, 95% CI 0.9 to 1.6).

- The NARROW-CRT study[16] (n=56 patients with NYHA class II or III HF, intraventricular dyssynchrony on echography, average LVEF of 29%, and QRS duration <120 msec) found that at 12-month follow up, more patients in the CRT-D arm had an improvement in their clinical composite score (free of HF hospitalization, display improvement in NYHA class and patient global assessment) compared with the ICD arm (41% vs. 16%, p=0.004, respectively).

- The RETHINQ study[17] (n=172 patients with NYHA Class III symptoms, mechanical dyssynchrony on echography, average LVEF of 26%, and QRS duration <130 msec) found that patients in the CRT-D group did not differ significantly from the ICD group in the proportion of patients with the primary outcome (i.e., increase in peak oxygen consumption): 46% and 41%, respectively. There was no significant difference in heart-failure related death or hospitalization.

- The LESSER-EARTH study[18] (n=85 patients from all NYHA classes, with LVEF < 35%, and QRS duration <120 msec) found that neither exercise capacity, symptoms, quality of life, nor remodelling improved with active CRT-D compared to ICD. Moreover, at 12 month follow-up, QRS duration significantly increased in the active CRT-D arm compared to controls (an average increase of 40.2 msec vs. 3.4 msec, respectively) suggesting that CRT could provoke dyssynchrony in sinus rhythm patients with narrow QRS duration. All-cause mortality was similar in both arms.

Assessments of bias show that the overall risk of bias was low for most trials, except NARROW-CRT where there was no blinding of personnel and outcome assessors (**Appendix Table C-1**). All except NARROW-CRT received funding from the device manufacturers.[14-18]

4.1.2 The efficacy of CRT in patients with prolonged QRS (>130msec)

A. CRT-pacemaker vs. optimal pharmacologic therapy (OPT)

Five RCTs compared the combination of OPT and CRT-P versus OPT alone: CARE-HF[2], COMPANION[19], MIRACLE[20], MUSTIC[21], and VECTOR[22], and results are summarized in Table 1.

Study and patient characteristics

- Across all five RCTs, the average age at inclusion was 66 years and the proportion of males was 70% (**Appendix Table A-1**). Only severely symptomatic patients (i.e. NYHA Class III and IV-ambulatory) were included, with 89.7% of participants belonging to Class III, and 35-60% had ischemic heart diseases. The average QRS interval was reported in four of the RCTs with the lowest average value being 158 msec. The mean or median LVEF was reported in three RCTs and ranged from 20-25%. QRS morphology was only reported in COMPANION trial where 69.3% of the patients had LBBB and 11.0% had RBBB.

- Other than the CARE-HF, studies provided no information on random sequence generation and allocation concealment, and thus, may be at risk for selection bias (**Appendix Table C-2**). Participants and/or personnel were not blinded in all trials, except MIRACLE, and thus there is a high risk of perception bias (i.e. systematic difference in care provided to the two arms). The outcome assessment was not blinded, except in COMPANION and MIRACLE, and thus there is a high risk of detection bias for subjective outcomes such as QoL and NYHA class. All trials received funding from the device manufacturers.[10,23]

Summary of the efficacy

- The CARE-HF study is the only RCT that demonstrated significant reduction in all-cause mortality. Meta-analyses of all five RCTs by Wells[24] and four of them by NICE[10] (all except VECTOR) using a random-effects model found that CRT-P in combination with OPT significantly reduced all-cause mortality compared to OPT alone (**Table 1** and **Table 2**).

- Meta-analyses by NICE[10] reported that CRT-P reduced hospitalization related to heart failure by 40% (HR 0.58, 95% 0.35 to 0.96) (Table 1). Improvement ≥1 NYHA class was 1.7 times (95% CI 1.5 to 1.9) higher in the CRT-P group. A pooled mean improvement on the 6-MWT in the CRT-P group was 38 m (95% CI 22 to 55 m).[10]

- Effect on LVEF was only reported in MIRACLE: at 6 month follow-up median LVEF increased with CRT-P (+4.6, 95% CI 3.2 to 6.4), but reduced with OPT alone (-0.2, 95% CI - 1.0 to 1.5). The difference was statistically significant ($p<0.001$).[20]

- Both meta-analyses by NICE and Wells et al. reported no between-study heterogeneity, though CARE-HF, the large trial with the longest duration of follow-up clearly dominated both meta-analyses. Sensitivity analysis by Wells showed that without CARE-HF trial, the reduction in mortality in the CRT-P group was not significant compared with OPT.[24] Therefore, we repeated the meta-analyses by Wells with a Bayesian approach. We found that CRT-P in combination with OPT did reduce all-cause mortality, but the reduction was not statistically significant (HR 0.72, 95% CI 0.46 to 1.83) as the between-study heterogeneity was now estimated to be non-zero (**Table 2**).

- Subgroup analyses of CRT on mortality from the CARE-HF trial found no conclusive evidence of an interaction between the effect of CRT-P and NYHA class, QRS duration, LVEF or sex; CRT-P was beneficial within all subgroups, though the risk ratio was reported to be lower in patients with QRS duration >160 msec and NYHA class IV (**Table 1**).[2]

B. The efficacy of CRT-defibrillator vs. optimal pharmacologic therapy (OPT)

There was only one RCT (COMPANION[19]) that compared the combination of CRT-D and OPT (n=617) to OPT alone (n=318) with a follow-up duration ranging from 14.8 to 16.5 months.

Study characteristics

The mean age at inclusion was 67.3 years and 67.7% were males. Only severely symptomatic patients (NYHA Class III and IV-ambulatory) were included, with 85% of the patients in Class III and 15% in Class IV. The average QRS interval was 160 msec while the average LVEF was 20.7%. There were 69.3% patients who had LBBB, 11.0% had RBBB, and 57.7% had ischemic heart diseases.

Summary of the efficacy

- All-cause mortality (HR 0.64, 95% CI 0.48 to 0.86), total cardiac deaths (HR 0.68, 95% CI 0.50 to 0.93), sudden cardiac deaths (HR 0.44, 95% CI 0.23 to 0.86) and heart failure hospitalisations (HR 0.77, 95% CI 0.63 to 0.93) were reduced with CRT-D and OPT

compared with OPT alone. The proportion of people with an improvement of one or more NYHA class (57% vs. 38%, p<0.001), improvements in exercise capacity (change in 6-MWT 46 m vs. 1 m, p<0.001), and QoL (Minnesota Living with Heart Failure Questionnaire or MLWHFQ score -26 vs -12, p<0.001) at 6 months were statistically significantly greater with CRT-D.

- Subgroup analysis showed that patients with age >65 years, male sex, ischemic heart disease, very severe symptoms (class IV-ambulatory), LVEF <20% and very severely prolonged QRS interval (>168 msec) may be more likely to benefit from CRT-D versus OPT in terms of all-cause mortality or HF hospitalisation, though the only statistically significant difference was in those with ischemic heart disease.

C. The efficacy of CRT-Defibrillator vs. ICD

We summarize the results from seven major trials (MADIT-CRT[25,26], REVERSE[27,28], MIRACLE ICD I[29],MIRACLE ICD II [30], RAFT[3], CONTAK-CD[31], Rhythm ICD[22]) and three smaller trials (Piccirillo[32], Pinter[33], and Diab[34]) that compared CRT-D versus ICD in **Table 3**.

Study characteristics

- Across ten trials, the average age ranged from 59 to 67 years and the proportion of males was 79% (**Appendix Table A-2)**. All NYHA Class patients were included with the following proportions: 6.6% Class I, 67.6% Class II, 23.6% Class III, and 2.2% Class IV-ambulatory. The average QRS interval was >150 msec except in the study by Diab et al (the mean QRS was 134-142 msec). The average LVEF ranged from 21.5% to 26.7%. Only five trials reported QRS morphology and 69% had LBBB.

- Other than the MIRACLE ICD and RAFT trials, studies provided no information on random sequence generation, and may be at risk for selection bias (**Appendix Table C-3**). There was no blinding of personnel in the MADIT, whereas CONTAK, Piccirillo, and Rhythm trials did not provide information on blinding of the participants and personnel. It was unclear whether outcome assessors were blinded in MIRACLE, CONTAK, and Rhythm trials. The overall risk of bias was low in REVERSE, MIRACLE, and RAFT trials. All trials except Piccirillo received funding from the device manufacturers.[10,23]

Summary of the efficacy

- Meta-analyses by Wells[24] (only included the major RCTs) and NICE[10] (included all, except trial by Diab) using the random-effects model reported that CRT-D significantly reduced all-cause mortality compared to ICD (**Table 3**). When stratified by symptom severity, both meta-analyses found significant reduction in mortality in Class I/II patients, but not in the Class III/IV-ambulatory patients. However, again both Wells and the NICE meta-analyses reported no between-study heterogeneity, while RAFT, with the longest duration of follow-up, clearly dominated both meta-analyses. Therefore, we repeated meta-analyses by Wells with a Bayesian approach. We found that the effect of CRT-D in reducing all-cause mortality as compared to ICD was no longer statistically significant (pooled RR 0.82, 95% CI 0.63 to 1.07) as the between-study heterogeneity was now estimated to be non-zero (**Table 2**). The pooled RR was unaffected by NYHA class.

- Meta-analyses by NICE[10] showed statistically significant improvement in clinical parameters (**Table 3**), but none was clinically significant (i.e. mean improvement of 0.2 in NYHA class, 2% in LVEF, and 15 metres of distance walked in 6 minutes). When stratified by severity of symptoms, it appeared that Class I/II patients benefited more in terms of change in LVEF, while Class III patients benefited more in terms of soft outcomes (changes in QoL and 6-MWT).[10]

4.2 Predictors of CRT response

Several individual trials attempted to identify clinical predictors of response to CRT, and these data were pooled in two meta-analyses that compared any CRT intervention (either CRT-D or CRT-P) to control (either ICD or OPT). A third publication used a network meta-analysis approach allowing for indirect comparisons between CRT-D, CRT-P, ICD and OPT.

4.2.1 QRS duration as a predictor of CRT response

Prolonged QRS interval on an electrocardiogram is an indicator of ventricular dyssynchrony, and its association with CRT response was assessed in all meta-analyses.

A. Individual patient meta-analysis (IPD MA)

Cleland and colleagues analyzed individual patient data (IPD) from CARE-HF, MIRACLE, MIRACLE ICD, REVERSE and RAFT.[35]

- Of 3782 patients in sinus rhythm, median (inter-quartile range) age was 66 (58–73) years, QRS duration was 160 (146–176) msec, and LVEF was 24% (20–28%). Most patients (78%) were men; 48.5% were in NYHA Class II, 47.8% in class III, and 3.8% in class IV; 58% had ischemic heart disease; 78% had LBBB and 8.9% had RBBB.
- The outcomes studied were all cause mortality (n=662) and a composite of first hospitalization for HF or death (n=1082). Overall, compared to the control group, CRT significantly reduced all-cause mortality (HR 0.66, 95% CI 0.57–0.77), and the composite outcome (HR 0.65, 95% CI 0.58–0.74).
- The authors found that the strongest predictor of CRT response (death or composite of first HF hospitalization and death) was QRS duration [p-value for interaction with CRT: <0.001), with the greatest benefit in the strata with QRS durations above 140 msec. For QRS<130 msec, estimates were suggestive of a harmful effect of CRT, but these results are inconclusive due to the wide confidence intervals.
- In univariate analyses, CRT was generally beneficial across all ages and for both sexes. CRT was also beneficial in patients with NYHA Class II/III, LBBB morphology and LVEF ≤30%, though results were inconclusive for patients with NYHA Class IV, non-LBBB morphology, and LVEF >30% (**Table 4**).
- Nevertheless, none of these potential predictors (age, sex, NYHA class, LVEF, LBBB, ischemic etiology of heart failure) were found to have a significant interaction with CRT effect in multivariate analyses.

B. Meta-analysis using aggregated data

Sipahi and colleagues conducted a meta-analysis examining the association between QRS duration and CRT response using aggregated data from five RCTs: the COMPANION, CARE-HF, REVERSE, MADIT-CRT, and RAFT (n=5,813). Using a fixed effects meta-analysis model, they found that CRT significantly reduced the risk of composite clinical outcomes in patients with severely prolonged QRS (>150 msec)

[pooled RR: 0.60; 95% CI: 0.53, 0.67], but not in patients with moderately prolonged QRS (120-149 msec) [RR:0.95; 95% CI: 0.82, 1.10].[36] We repeated the meta-analyses with a Bayesian approach and found similar results (**Table 2**).

4.2.2 QRS morphology as a predictor of CRT response

Abnormal QRS morphology often indicates a disturbance in the electrical conduction system of the heart, and can be distinguished into LBBB, right bundle branch block (RBBB), and non-specific intraventricular conduction delays (IVCD). LBBB occurs when the electrical impulse is blocked at the level of the left bundle branch, resulting in delayed contraction of the left ventricle vis a vis the right ventricle.

Sipahi et al. conducted a second meta-analysis assessing the association between QRS morphology and CRT response using aggregated data from four RCTs: COMPANION, CARE-HF, MADIT-CRT, and RAFT. Using a random effects model due to high between-study heterogeneity, they found that CRT significantly reduced the risk of composite clinical events in patients with LBBB [pooled RR: 0.64; 95% CI: 0.52, 0.77]. They did not find a similar effect among patients with non-LBBB morphology [RR: 0.97; 95% CI: 0.82, 1.15].[37]The Bayesian analysis yielded similar results (**Table 2**).Therefore, LBBB appears to be an important predictor of CRT response. Although most trials included very small numbers of patients with non-LBBB morphology, hampering our ability to draw definitive conclusions for this group, MADIT, the largest trial (n=1818), did find a statistically significant difference in the effect of CRT-D vs. ICD between the LBBB and non-LBBB groups for all -cause mortality and HF events.

4.2.3 Individual patient data network meta-analysis

The largest meta-analysis to date has been carried out as part of the manufacturers' submission to National Institute of Clinical Excellence (NICE). Biotronik, Boston Scientific, Medtronic, Sorin Group and St Jude Medical prepared an individual-patient data network meta-analysis (IPD NMA) based on 13 of 22 trials (COMPANION, CONTAK-CD, MADIT, MADIT II, MADIT-CRT, CARE-HF, MIRACLE, MIRACLE-ICD, RAFT, REVERSE, SCD-HeFT, DEFINITE and RethinQ trials), which included 12,638 patients (accounting for ~95% patients of the 22 trials).[38]

All numerical results from this work pertaining to sample size and efficacy within sub-groups have been redacted as they were considered "commercial in-confidence information". Some general conclusions reported include:

- Covariates that appear to affect CRT efficacy include QRS interval width, LBBB, gender and age.
- CRT-D offers an advantage over CRT-P in all sub-groups considered.
- In men without LBBB, CRT-P offers minimal benefit in those < 60 years of age and those with QRS <150msec. The benefit in women is more pronounced.
- In men with LBBB, CRT-P offers only a modest benefit when the QRS ≥120 to <150msec and far greater benefit if the QRS ≥150msec.

The lack of numerical data to support these conclusions makes it impossible to judge their clinical or statistical significance.

Several concerns with this IPD NMA should be noted:

- An independent review commissioned by NICE found that the modeling methods used were not described in sufficient detail to judge their appropriateness.[38]
- We noted that a preference was given to fixed effects over random effects meta-analysis models based on a negligible improvement in model selection criteria. Given the variability in populations and interventions across the trials included, a fixed effects meta-analysis is likely to provide artificially precise confidence intervals.
- Another concern is the lack of consideration for transitivity or comparability in the different study populations.[39] The network model used allowed for the comparison of CRT-P and CRT-D even though only one study (COMPANION) compared these two interventions directly. Generally, CRT-D studies were more likely to include males, patients with NYHA class II symptoms and with ischemic disease, compared to CRT-P studies, suggesting the two technologies were not studied in similar population.

4.3 Safety

Adverse events from implantable devices are mostly related to implantation of the device, including implant failure, lead dislodgement, and infection.[19,20,40] In addition, patients with defibrillator devices (ICD and CRT-D) who experience defibrillator shocks may have adverse psychological symptoms (notably anxiety).[10] Device-related death is low in general.

4.3.1 CRT-Pacemakers

MIRACLE[20] reported a 7.6% implant failure rate. The most common complication during implantation was coronary sinus dissection (2.4-4.0%). LV lead dislodgement was the most frequent complication after implantation (3.8-5.9%).[20] In the COMPANION trial, implant failure occurred in 13% subjects in the CRT-P arm. Other adverse events, including infection and lead dislodgement, occurred in 10% of cases.[19] COMPANION[19] and CARE-HF[2] reported 0.8% and 0.2% device-related death, respectively.

4.3.2 CRT-Defibrillator vs. ICD

Adabag et al.[40] did a meta-analysis on the adverse event of CRT-D and ICD in patients with NYHA class I or II. Overall, 562 (12.7%) of 4,144 patients from RAFT, MADIT-CRT, REVERSE and MIRACLE ICD II had an adverse event. The most frequent adverse events were lead dislodgement followed by implant failure, pocket hematoma and infection (**Table 5**). In general, adverse events occurred more frequently in patients with CRT-D than with ICD.

4.4 Cost-effectiveness

Following a literature search on PubMed on January 26, 2015, we found 34 relevant published cost-effectiveness analyses of CRT. However, only one study analyzed resource utilization and related costs associated with heart failure for patients who receive ICD versus those who receive CRT-D in Canada.[41] Researchers of the RAFT study are developing economic models for Canadian resource utilization and costing[42], but their results are not yet published.

We chose not to report the cost-effectiveness analysis of NICE as it relied on the individual patient data network meta-analysis (IPD NMA) described under **Section 4.2.3**, whose methods and results could not be adequately reviewed.

4.5 HTAs and Clinical guidelines

We compared guidelines for CRT use by five different organizations: the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA),[11] the European Society of Cardiology (ESC),[12] the Canadian Cardiovascular Society (CCS),[13] the National Institute for Care and Excellence (NICE UK),[10] and the Agency for Healthcare Research & Quality (AHRQ, USA). The ACCF/AHA and the ESC presented their guidelines in classes of recommendation (CoR) and the related level of evidence (LoE) by subgroups of NYHA class, QRS morphology, and QRS interval (**Table 6**). Overall, they all agreed upon the following:

- None recommend CRT in NYHA class I, regardless of QRS interval and morphology, except NICE, which recommends CRT-D when QRS interval ≥150 msec, regardless of morphology, and ACCF/AHA which suggests considering CRT-D when QRS interval ≥150 msec, with LBBB and LVEF ≤ 30%.
- All recommend CRT-D in patients with NYHA class II, with LVEF ≤ 35%, LBBB and QRS interval ≥120 msec (>130 msec in the Canadian guidelines).
- All recommend CRT-P in patients with NYHA class III and IV-ambulatory, LVEF ≤ 35%, LBBB and QRS interval ≥120 msec (>130 msec in the Canadian guidelines).

In all cases to be considered for CRT therapy, the Canadian guidelines recommend that potential patients be free of severe chronic kidney disease (creatinine < 200 mmol/L or glomerular filtration rate > 30 mL/min/m^2), due to the limited evidence in this subgroup.[43]

The CARE-HF and COMPANION studies were the principal studies that led to the change in guidelines recommending that CRT-P be used in addition to OPT in treating heart failure patients. Based on the ACC/AHA guideline in 2001, patients with NYHA class III and ambulatory-IV were only treated by OPT.[44] In 2005 the ACC/AHA guideline was updated and CRT-P was recommended for these patients.[45]

5. CRT AT THE MUHC

5.1 Current treatment policy

In 2004, the Technology Assessment Unit (TAU) evaluated the use of CRT at the McGill University Health Centre (MUHC)[4]. Based on evidence available at that time, the TAU did not recommend routine use of CRT-D at the MUHC due to the lack of impact on mortality, the marginal impact on quality of life, the lack of long term results, and the considerable opportunity costs. Nevertheless, the TAU did recognize exceptional cases that could benefit from this technology. It was recommended that a decision to initiate CRT-D therapy in these exceptional cases should only be made after formal approval by a committee of the Division of Cardiology.

To date, the device has been used at the MUHC only in heart failure patients who are not responding to medical treatment. A breakdown of the number of implantations by type of devices during the 2010-2015 fiscal years at the MUHC shows that the use of CRT at the MUHC has been increasing over the years (**Table 7)**. Compared to 2010/2011, initial CRT-P implantation increased from 6 to 27 while initial CRT-D implantation increased from 49 to 72 in 2014/2015. There has been a steady increase in the number of re-implant/upgrades versus de-novo implants, with re-implant/upgrades accounting for 40% of all CRT-P implants, and 55% of total CRT-D implants in 2014-15.

Dr. Vidal Essebag of the MUHC confirmed that patient selection currently follows the Canadian guidelines i.e. CRTs have been implanted in heart failure patients with NYHA Class II/III/IV-ambulatory, LVEF <=35%, with QRS > 130 msec and LBBB morphology (strongest recommendation) or QRS >=150 msec not because of LBBB (weaker recommendation – patients accepted for this indication according to careful evaluation of all clinical factors).

5.2 Cost and budget impact estimates

In this section we present some figures on ICDs and pacemakers, though they are not the focus of this report. These figures only serve to put CRT use and cost in context.

Based on the MUHC experience, the device cost of a CRT-P with three leads is $8,470 compared to $3,768 for a dual-chamber pacemaker. Until recently, the device cost of a CRT-D with three leads was $20,235 compared to $16,020 for a dual-chamber ICD.

Starting May 2015, CRT-D and ICD costs were substantially reduced as a result of the collective buying power of hospitals across the province. CRT-D costs fell to an average of $11,645, while a dual-chamber ICD costs $8,033 on average. The procedure costs, which include the cost of nursing and supplies in the operating room, stay in the cardiac care unit, and peri-operation procedures, vary from $2,179 to $2,772 for initial implantation (**Table 8**). Thus, until April 2015, the total cost of implanting an initial CRT-P device in a patient at the MUHC was approximately $11,073, versus $23,007 for an initial CRT-D implant. From May 2015, the CRT-D cost is $14,417 per initial implant.

Overall, for the 2014-15 fiscal year, $3,278,070 (3.3M) was spent on CRT-D devices (not including procedure costs) (**Figure 2**). However, the Quebec government had set up a special fund to cover defibrillator device (ICD and CRT-D) costs, and for the 2014-15 fiscal year, 95% of these costs ($6.5M of the $6.9M spent on CRT-D and ICD) was borne by the Quebec government. With the dissolution of the Agence de la santé et de services sociaux de Montréal in 2015 and the changes in the financial model at the MUHC, this special fund has been eliminated. Funding for defibrillators will now be covered by the global Cardiology budget. The projected impact on the MUHC budget for implanting a similar number of defibrillator devices as in 2014-15 (162 CRT-D and 236 ICD) is $3.6M ($1.9M for CRT-D and $1.7M for ICD) (**Table 9**).

The cost of CRT-P devices remains unchanged, and for the fiscal year 2014-15, $490,653 (almost 0.5M) was spent on CRT-P (includes devices and procedure costs for initial implants, replacements, and upgrades) at the MUHC (**Figure 1**).

Implantable cardiac devices are a lifelong treatment commitment for patients, requiring generator replacements every 5 to 7 years on average. At the MUHC, replacement/upgrades accounted for 40% of the total spending on CRT-P implants ($191K of $490K), and 55% of total spending on CRT-D devices (2.0M of $3.7M) in 2014-15 (**Figure 3**).

6. DISCUSSION

6.1 Is CRT effective?

- Large RCTs with long durations of follow-up (i.e., CARE-HF that evaluated CRT-P vs. OPT, and RAFT that evaluated CRT-D vs. ICD) found that CRT significantly reduced the clinical

composite of first hospitalization for heart failure or death. Results from smaller RCTs with shorter follow-up were less optimistic.

- Some meta-analyses looking at the efficacy of CRT by type of device were driven by the large RCTs and did not properly taking into account the heterogeneity between studies. On repeating those meta-analyses using a Bayesian method, we found that CRT-P and CRT-D reduced the risk of the composite outcome (pooled RR <1), but the reduction was not statistically significant.

- Nevertheless, adding CRT-P to optimal pharmacological treatment appears to be beneficial in severely symptomatic patients (NYHA class III and IV-ambulatory) with significant improvement in symptom severity (≥1 NYHA class), 6-MWT (~40 m increase in distance walked), and ventricular function (5% increase in LVEF). On the other hand, compared to ICD, CRT-D appears to significantly prolong survival (reduction in mortality) and improved ventricular function in mildly symptomatic (NYHA class II) patients. This group had good functional status to begin with, and thus improvement in symptom severity and 6-MWT over the course of treatment was rather marginal.

6.2 What are the predictors of CRT efficacy?

- The two meta-analyses that pooled studies of any CRT intervention (CRT-D or CRT-P) versus control (ICD or OPT) found that the strongest predictor of CRT response (death or a composite measure including death and other clinical outcomes) was severely prolonged QRS duration (>140 or 150 msec).

- Both meta-analyses also found that LBBB morphology was an important predictor of good CRT response, but results were inconclusive in non-LBBB patients due to the small numbers of patients included in the trials.

6.3 Is CRT safe?

The most common adverse events from implantable devices are implantation failure (7.6%-13% for CRT-P and 3.2%-9% for CRT-D) and lead dislodgement (3.8%-10% for CRT-P and 7.3%-8% for CRT-D). At the MUHC, implant success rate in a series of 171 consecutive patients was 98.8%, and lead dislodgement occurred in 3% of these patients (Dr. Vidal Essebag, personal communication, 24 November, 2015).

Device-related death is low in general (0.2%-0.8% for CRT-P and 0.04%-0.5% for CRT-D). Large RCTs and observational studies reported significantly higher incidents of device-related complications in CRT-D group compared to ICD group: infections 1.7-1.9% vs. 1.0-1.3%, and hematoma requiring interventions 2.5% vs. 1.8%, respectively.

6.4 Discrepancies between guidelines and evidence

The effect of CRT is less certain in patients with NYHA Class IV-ambulatory, moderate QRS interval (120-140 msec), non-LBBB morphology, and LVEF >30%. CRT can even be harmful in patients with QRS duration <120 msec. Nevertheless, some guidelines and HTAs do recommend CRT use for these subgroups. It seems that they based their recommendation on the entry criteria and not the actual characteristics of patients enrolled in the RCTs.

6.5 Is CRT cost-effective?

Cost-effectiveness results specific to Canada have yet to be published. While it may be possible to determine cost-effectiveness in those sub-groups of patients where a clear benefit of CRT has been demonstrated, the lack of conclusive efficacy data in other sub-groups precludes the study of cost-effectiveness in these patients.

6.6 CRT impact on the MUHC budget

CRT is a relatively high cost technology. In the fiscal year 2014-15, the MUHC spent almost $0.4M on CRT-P devices and leads, and $3.3M on CRT-D devices and leads (**Figure 2**). However, the latter was covered under a special fund set up by the Quebec government for defibrillator devices, which no longer exists. Hence, although the cost of CRT-D devices has fallen considerably since May 2015 from $14,800 to $6,210 on average (**Table 8**), the removal of government support will result in a net increase in spending of $1.9M for CRT-D devices, a substantial impact on the MUHC budget. Although three times more CRT-D than CRT-P devices were implanted in 2014-15 (162 vs. 45), the number of CRT-P devices implanted has increased since 2010 (**Figure 2**).

The increase in CRT use over the past five years, and the uncertainty in government funding of CRT-D imply that these devices will continue to have a significant impact on the MUHC budget. Therefore, systematic documentation of which patients receive these devices in lieu of standard pacemakers/defibrillators is necessary to understand the projected budget impact of CRT.

7. CONCLUSIONS

- There is sufficient evidence to support the use of CRT for patients with NYHA Class II/III, severely prolonged QRS interval (>150 msec); LBBB morphology, and LVEF <30%.
- The effect of CRT is less certain in patients with NYHA Class IV-ambulatory, moderate QRS interval (120-150 msec), non-LBBB morphology, and LVEF >30%. Though, some guidelines and HTAs have recommended CRT use in these subgroups, their recommendations appear to be based on the entry criteria and not the actual characteristics of patients enrolled in the RCTs. (It should be noted that unlike clinical guideline documents our report does not provide guidance on how individual patients should be treated. Rather our focus has been to distinguish between those situations where there is good evidence to support the use of CRT and where there is not. The decision to treat an individual patient is left to the discretion of the treating physician.)
- QRS duration >150 msec is the strongest predictor of CRT response. QRS morphology i.e. the presence of LBBB may also be a potential indicator of good response to CRT.
- The use and budget impact of CRT-P and CRT-D at the MUHC has been increasing over the years. Since 2015 the MUHC has adopted a new funding model under which the cost of these devices is now covered within the global Cardiology budget.
- At the MUHC, there is currently no systematic documentation of patient selection criteria or evaluation of patient outcomes following CRT.

8. RECOMMENDATIONS

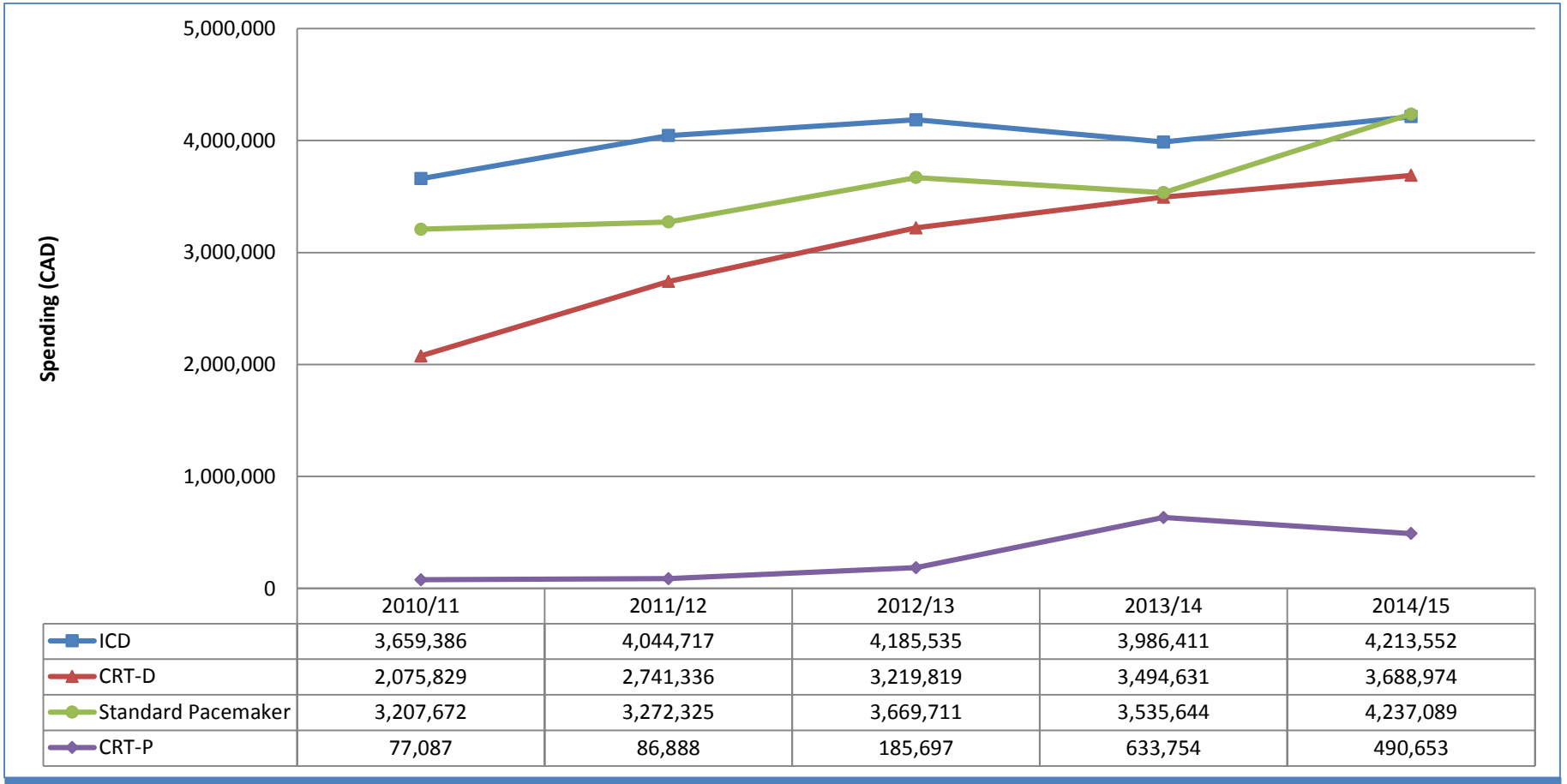
- The use of CRT is recommended for the treatment of heart failure patients only after careful consideration of clinical criteria known to influence the outcomes (i.e. severely prolonged QRS interval and LBBB morphology).
- Given the paucity of evidence in the literature regarding other criteria (including NYHA Class IV-ambulatory, moderate QRS interval (120-150 msec), non-LBBB morphology, and LVEF >30%), it is necessary to systematically document patient selection criteria for CRT and to evaluate whether patient outcomes improve following CRT. Furthermore, as clinical decision-making requires taking into

consideration multiple factors such as patient preference, referring doctor preference, and comorbidities, among other variables, it is necessary that these reasons also be systematically documented.

- The increasing use, high costs and residual uncertainty of the benefits of CRT in certain patients underscore the need for the development of a database to systematically document patient selection criteria and outcomes. The availability of local data is important for hospital decision-making and patient welfare. Furthermore, in light of reduced government funding and an impending provincial evaluation of CRT, unavailability of local data may further hamper funding of a technology with proven benefits in a significant proportion of heart failure patients. Therefore, it is recommended that continued use of CRT at the MUHC be made **conditional** on a systematic recording of patient data. The TAU recommends the systematic collection of a few key variables (Appendix E), either in the patient chart or electronically, to evaluate patient selection and outcomes.

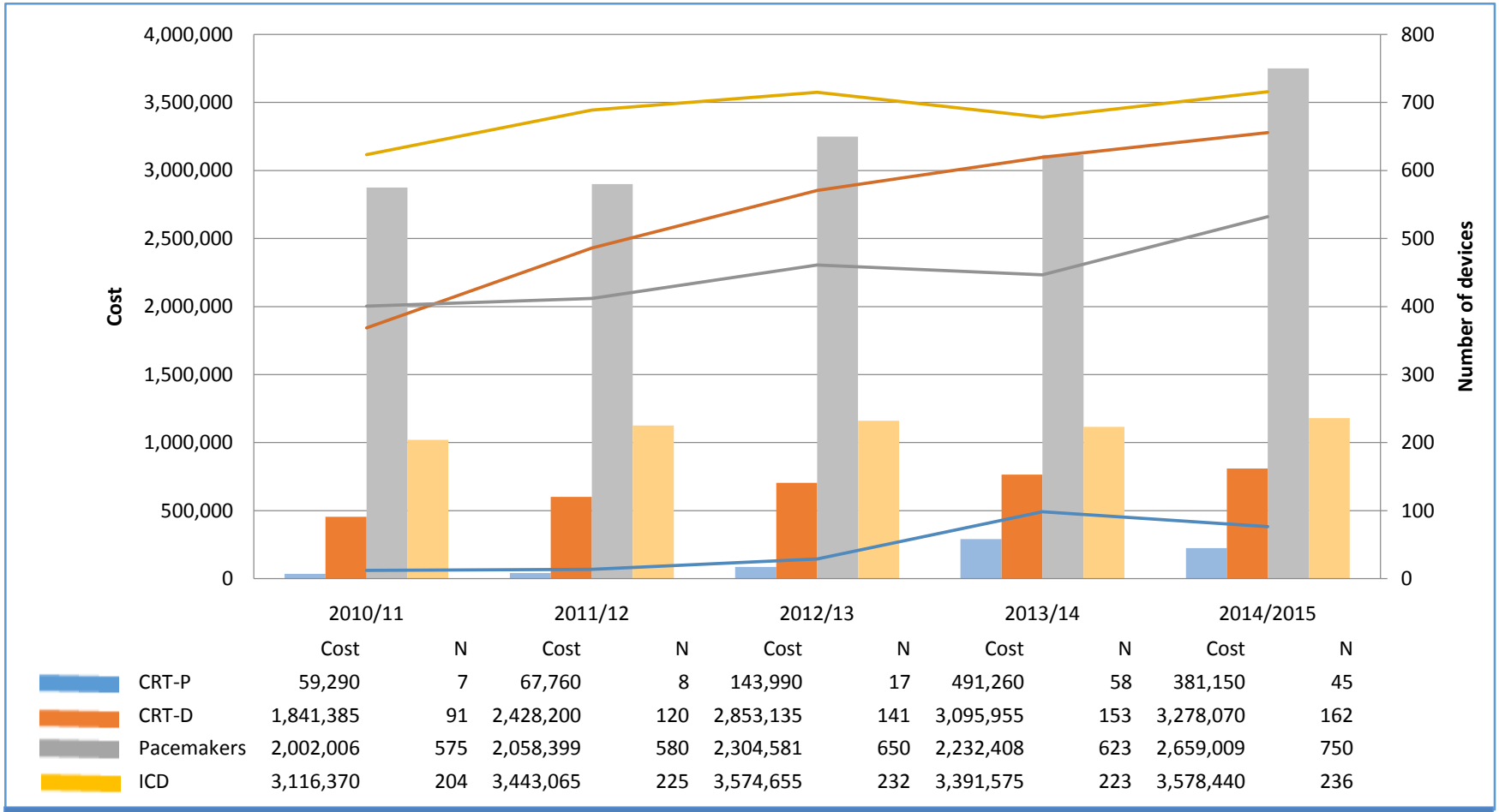
- These recommendations should be reviewed in 6 months to assess progress or barriers to progress in implementing a data documentation system.

FIGURES



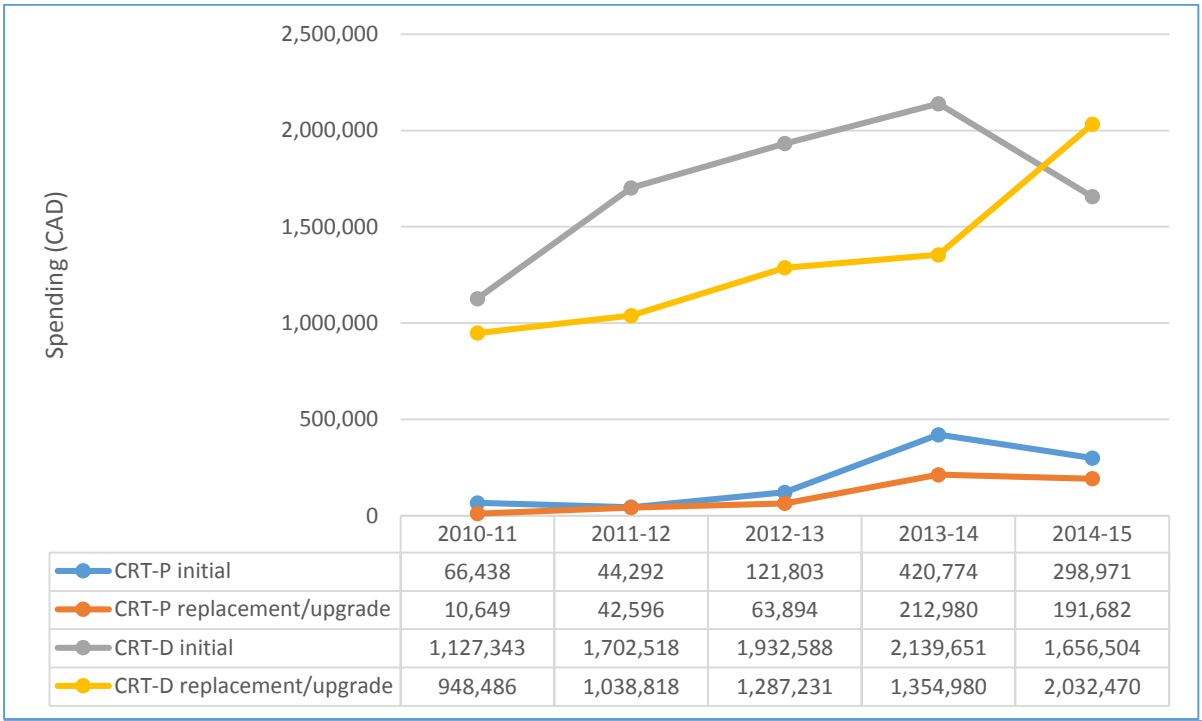
	2010/11	2011/12	2012/13	2013/14	2014/15
ICD	3,659,386	4,044,717	4,185,535	3,986,411	4,213,552
CRT-D	2,075,829	2,741,336	3,219,819	3,494,631	3,688,974
Standard Pacemaker	3,207,672	3,272,325	3,669,711	3,535,644	4,237,089
CRT-P	77,087	86,888	185,697	633,754	490,653

Figure 1: Spending (in CAD) on implanted devices during the 2010-2015 fiscal year at the MUHC (includes devices, leads and procedure costs for initial implants, replacements, and upgrades).



	2010/11		2011/12		2012/13		2013/14		2014/2015	
	Cost	N	Cost	N	Cost	N	Cost	N	Cost	N
CRT-P	59,290	7	67,760	8	143,990	17	491,260	58	381,150	45
CRT-D	1,841,385	91	2,428,200	120	2,853,135	141	3,095,955	153	3,278,070	162
Pacemakers	2,002,006	575	2,058,399	580	2,304,581	650	2,232,408	623	2,659,009	750
ICD	3,116,370	204	3,443,065	225	3,574,655	232	3,391,575	223	3,578,440	236

Figure 2: Number and cost (device and leads) of cardiac implantable devices at the MUHC, 2010-15



	2010-11	2011-12	2012-13	2013-14	2014-15
CRT-P initial	66,438	44,292	121,803	420,774	298,971
CRT-P replacement/upgrade	10,649	42,596	63,894	212,980	191,682
CRT-D initial	1,127,343	1,702,518	1,932,588	2,139,651	1,656,504
CRT-D replacement/upgrade	948,486	1,038,818	1,287,231	1,354,980	2,032,470

Figure 3: Spending on CRT initial implants and upgrades for the 2010-2015 fiscal year at the MUHC (includes devices, leads and procedure costs).

Data were provided by Mona Black, Division of Cardiology, MUHC.

TABLES

Table 1: Summary table of the efficacy of CRT-P versus OPT by outcome in patients with QRS > 120 msec [all trials only included patients with NYHA class III or IV]

Outcome	Study or subgroup	CRT-P		OPT		Estimate
All-cause mortality		N	Events	N	Events	**Hazard Ratio**
	CARE-HF	409	101	404	154	0.65 (0.53, 0.80)
	NYHA class III		349/763**			0.64 (0.52,0.80)
	NYHA class IV		34/50**			0.50 (0.25,1.01)
	QRS <160ms		152/290**			0.74 (0.54,1.02)
	QRS≥ 160 ms		222/505**			0.60 (0.46,0.79)
	Male		290/597**			0.62 (0.49,0.79)
	Female		93/215**			0.64 (0.42,0.97)
	LVEF <24.7%		205/372**			0.65 (0.49,0.86)
	LVEF≥24.7%		152/373**			0.62 (0.44,0.85)
	COMPANION	617	131	308	77	0.85 (0.66, 1.09)
	MIRACLE	228	12	225	16	0.74 (0.36, 1.53)
	MUSTIC	58	3	58	0	7.00 (0.37, 132.56)
Total		**1312**		**995**		**0.75 (0.58,0.96)***
Heart failure deaths		N	Events	N	Events	**Hazard Ratio**
	CARE-HF	409	38	404	64	0.59 (0.40, 0.86)
	COMPANION	617	53	308	34	0.78 (0.52, 1.17)
		1026		**712**		**0.67 (0.51, 0.88]***
Heart failure hospitalizations		N	Events	N	Events	**Hazard ratio**
	CARE-HF	409	72	404	133	0.53 (0.42, 0.69)
	COMPANION	617	179	308	112	0.80 (0.66,0.97)
	MIRACLE	228	18	225	34	0.52 (0.30, 0.90)
	MUSTIC	29	3	29	9	0.33 (0.10,1.11)
		1283		**966**		**0.61 (0.44, 0.83)***
Δ in ≥1NYHA class		N	Events	N	Events	**Risk ratio**
	CARE-HF	409	255	404	151	1.67 (1.44,1.93)
	COMPANION	489	298	199	76	1.60 (1.32, 1.93)
	MIRACLE	211	143	196	74	1.80 (1.47, 2.20)
		1109		**799**		**1.68 (1.52, 1.86)***
Δ 6 min walk distance		N	Mean	N	Mean	**Mean difference**
	COMPANION	373	40ǂ	142	1ǂ	39.00 (20.86, 57.14)
	MIRACLE	214	39ǂ	198	10ǂ	29.00 (10.34, 47.66)
	MUSTIC	46	399.2†	46	134.4†	73.50 (25.00, 122.00)
		633		**386**		**38.14 (21.74, 54.54)***
Δ in QoL (MLHFQ)		N	Mean	N	Mean	**Mean difference**
	COMPANION	460	-25ǂ	207	-12ǂ	-13.00 (-16.93, -9.07)
	MIRACLE	213	-18ǂ	193	-9ǂ	-9.00 (-15.07, -2.93)
	CARE-HF	409	27.2†	404	25.6†	-7.90 (-11.29, -4.51)
	MUSTIC	45	29.6†	45	22.8†	-13.60 (-22.72, -4.48)
		1127		**849**		**-10.33 (-13.31, -7.36)***

* Estimates from the meta-analysis by NICE[10]; ** No. of events/no. of participants; ǂ Mean change from baseline;† Final mean value

Table 2: Revised meta-analysis of the effect of CRT on all-cause mortality in subgroups

Meta-analysis comparison (outcome)	Original trials included in the analysis	Original authors	Original meta-analysis	Revised Bayesian random-effects analysis	
			95% confidence interval	95% credible interval for pooled RR	95% credible interval for predicted RR
CRT vs OPT (mortality)	MUSTIC MIRACLE COMPANION CARE-HF VECTOR	Wells	0.73 (0.62, 0.85)	0.72 (0.46, 1.83)	0.72 (0.27, 2.78)
CRT-D vs ICD (mortality)	CONTAK-CD MIRACLE ICD MIRACLE ICD II RHTHYM ICD REVERSE MADIT-CRT RAFT	Wells	0.78 (0.70, 0.87)	0.82 (0.63, 1.07)	0.82 (0.46, 1.42)
CRT-D vs ICD in NYHA 1 & 2 (mortality)	MIRACLE ICD II REVERSE MADIT-CRT RAFT	Wells	0.80 (0.67, 0.96)	0.82 (0.50, 1.38)	0.82 (0.29, 2.51)
CRT-D vs ICD in NYHA 3 & 4 (mortality)	CONTAK-CD MIRACLE ICD RHYTHM ICD RAFT	Wells	0.86 (0.69, 1.07)	0.82 (0.45, 1.53)	0.82 (0.24, 2.91)
CRT-P or CRT-D vs comparator in QRS > 150 msec (clinical composite events)	COMPANION CARE-HF REVERSE MADIT-CRT RAFT	Sipahi	0.60 (0.53, 0.67)	0.56 (0.44, 0.73)	0.56 (0.31, 1.05)
CRT-P or CRT-D vs comparator in QRS 120-149 msec (clinical composite events)	COMPANION CARE-HF REVERSE MADIT-CRT RAFT	Sipahi	0.95 (0.82, 1.10)	0.95 (0.77, 1.18)	0.95 (0.62, 1.47)
CRT-P or CRT-D vs comparator in LBBB (clinical composite events)	COMPANION CARE-HF MADIT-CRT RAFT	Sipahi	0.64 (0.52, 0.77)	0.64 (0.40, 0.99)	0.64 (0.23, 1.69)
CRT-P or CRT-D vs comparator in non-LBBB (clinical composite events)	COMPANION CARE-HF MADIT-CRT RAFT	Sipahi	0.97 (0.82, 1.15)	0.99 (0.86, 1.12)	0.99 (0.82, 1.16)

Table 3: Summary table of the efficacy of CRT-D versus ICD by outcome in patients with QRS > 120 msec

Outcome	Study	Subgroup	CRT-D		ICD		Estimate (95% CI)
All-cause mortality			N	Events	N	Events	**Hazard Ratio**
	MADIT, MIRACLE, RAFT	NYHA class II	2068	262	1736	291	0.82 (0.71, 0.96)
	CONTAK, RHYTHM, MIRACLE, RethinQ	NYHA class III	638	40	591	36	0.95 (0.60,1.50)
	Piccirillo	NYHA class IV	16	0	15	0	Could not be estimated
		Overall	**2722**	**302**	**2342**	**327**	**0.84 (0.73,0.96)***
	RAFT	LBBB	594	105	581	145	0.66 (0.52,0.85)
	RAFT	Non-LBBB	143	29	165	47	0.71 (0.44,1.12)
	MADIT	QRS<150ms		147/645**			1.06 (0.74,1.52)†
	MADIT	QRS≥150 ms		225/1175**			0.48 (0.37,0.64)†
	MADIT	Male		294/1367**			0.76 (0.59,0.97)†
	MADIT	Female		78/453**			0.37 (0.22,0.61)†
Total cardiac deaths			N	Events	N	Events	**Hazard Ratio**
	MIRACLE, RAFT	NYHA class II	979	132	1005	164	0.82 (0.66, 1.01)
	Pinter, CONTAK, RHYTHM, RethinQ	NYHA class III	451	13	409	13	0.89 (0.40, 1.96)
	Piccirillo	NYHA class IV	16	0	15	0	Could not be estimated
		Overall	**1446**	**145**	**1429**	**177**	**0.82 (0.67, 1.00]***
Heart failure hospitalizations			N	Events	N	Events	**Hazard Ratio**
	RAFT	NYHA class II	894	174	904	236	0.75 (0.63, 0.89)
	CONTAK	NYHA class III	245	32	245	39	0.82 (0.53,1.26)
	Piccirillo	NYHA class IV	16	0	15	2	0.19 (0.01, 3.63)
		Overall	**1155**	**206**	**1164**	**277**	**0.75 (0.64, 0.88)***
Δ NYHA class score from baseline			N	Mean	N	Mean	**Mean difference**
	MIRACLE	NYHA class II	82	-0.18	98	0.01	-0.19 (-0.37, -0.01)
	MIRACLE, RHYTHM	NYHA class III	248	-0.48	205	-0.28	-0.20 (-0.43, 0.03)
		Overall	**330**		**303**		**-0.19 (-0.34, -0.05)***
Δ LVEF			N	Mean	N	Mean	**Mean difference**
	MADIT, MIRACLE	NYHA class II	814		705		5.05 (0.23, 9.87)
	Pinter, CONTAK, RHYTHM, MIRACLE, RethinQ	NYHA class III	541		502		0.79 (-0.58, 2.16)
	Piccirillo	NYHA class IV	16	28	15	22	6.00 (1.50, 10.50)
		Overall	**1371**		**1222**		**2.15 (0.45, 3.86)**
Δ 6 min walk distance			N	Mean	N	Mean	**Mean difference**
	MIRACLE	NYHA class II	78	38	93	33	5.00 (-26.33,36.33)
	Pinter, CONTAK, RHYTHM, MIRACLE, RethinQ	NYHA class III	570		531		16.04 (3.56, 28.51)
		Overall	**648**		**624**		**14.53 (2.94, 26.11)***
Δ Quality of life score (MLHFQ) from baseline‡			N	Mean	N	Mean	**Mean difference**
	MIRACLE	NYHA class II	81	-13.3	96	-10.7	-2.60 (-9.58, 4.38)
	Pinter, CONTAK, RHYTHM, MIRACLE, RethinQ	NYHA class III	591		541		-7.83 (-11.53, -4.12)
		Overall	**648**		**624**		**-6.90 (-10.41, -3.40)***

* Estimates from the meta-analysis by NICE[10]; ** No. of events/no. of participants
† Risk of death or heart failure event; ‡ Higher scores correspond to worse quality of life

Table 4: Univariate analysis evaluating the effect of CRT on all-cause mortality in subgroups*

Parameter	Subgroup	Deaths/total subjects	HR (95% CI)
Age, years	< 58	100/980	0.6 (0.4, 0.8)
	58-66	150/967	0.7 (0.5, 1.0)
	66-72.5	181/964	0.6 (0.5, 0.9)
	>72.5	231/961	0.7 (0.5, 0.9)
Sex	Male	534/3004	0.7 (0.6, 0.8)
	Female	128/868	0.6 (0.4, 0.8)
NYHA Class	II	229/1877	0.6 (0.5, 0.8)
	III	386/1849	0.7 (0.6, 0.8)
	IV	47/146	0.6 (0.3, 1.1)
LVEF, %	<15	97/365	0.6 (0.4, 0.9)
	16-20	143/784	0.6 (0.4, 0.8)
	21-30	352/2162	0.8 (0.6, 0.9)
	31-35	32/318	0.5 (0.3, 1.1)
	>35	17/174	0.8 (0.3, 2.0)
QRS morphology	LBBB	528/3036	0.7 (0.6, 0.8)
	RBBB	65/346	0.7 (0.4, 1.2)
	Neither	54/467	0.8 (0.5, 1.4)
Ischemic	Yes	458/2232	0.7 (0.6, 0.8)
	No	204/1640	0.6 (0.4, 0.7)

*Adapted from the forest plot of the univariate frailty analysis in the original paper by Cleland et al.[35]

Table 5: Adverse events reported in RCTs of CRT-D versus ICD in patients with mild heart failure

	Total* n =4,414	CRT-D+OPT† n =1,983	ICD+OPT† n =1,635
LV lead dislodgement	182 (7.3%)	101 (5.1%)	NA
Implant failure	170 (3.9%)	130 (6.6%)	1 (<0.1%)
Pocket hematoma‡	84 (1.9%)	50 (2.5%)	29 (1.8%)
Pocket infection‡	54 (1.2%)	33 (1.7%)	21 (1.3%)
Pneumothorax	48 (1.1%)	30 (1.5%)	14 (0.8%)
Coronary sinus dissection	22 (0.5%)	16 (0.8%)	0 (0%)
In-hospital death	2 (0.04%)	1 (0.05%)	1 (0.06%)
Total	562 (12.7%)	361 (18.2%)	66 (4%)

* Pooled from the MADIT-CRT, RAFT, REVERSE, and MIRACLE ICD II trials.
† Pooled from the MADIT-CRT and RAFT trials, which did not implant left ventricle (LV) leads in the control group.
‡ Hematoma or infection that required intervention.

Table 6: Summary of the HTAs and clinical guidelines for the use of CRT in heart failure

Clinical Characteristics			HTA		Guidelines		
NYHA class	QRS morphology	QRS duration	AHRQ 2014	NICE 2014	ACCF/AHA 2013	Canadian Guidelines 2013	ESC 2012
I	LBBB	120-129 msec	Consider CRT-D			No CRT	
		130-149 msec	Consider CRT-D			No CRT	
		≥ 150 msec	Consider CRT-D	Recommend CRT-D	May consider CRT-D[a]*	No CRT	
	Non-LBBB	120-129 msec			No CRT-D‡	No CRT	
		130-149 msec			No CRT-D‡	No CRT	
		≥ 150 msec		Recommend CRT-D		No CRT	
II	LBBB	120-129 msec	Consider CRT-D	Recommend CRT-D	Consider CRT-D*	No CRT	
		130-149 msec	Consider CRT-D	Recommend CRT-D	Consider CRT-D*	Recommend CRT	Recommend CRT-D
		≥ 150 msec	Consider CRT-D	Recommend CRT-D	Recommend CRT-D*	Recommend CRT	Recommend CRT-D
	Non-LBBB	120-129 msec			No CRT-D†	No CRT	
		130-149 msec			No CRT-D†	Unclear	
		≥ 150 msec		Recommend CRT-D	May consider CRT-D[b]*	Consider CRT	Consider CRT-D
III	LBBB	120-129 msec	Consider CRT-P	Recommend CRT-D/P‡	Consider CRT-P*	No CRT	Recommend CRT-D/P‡
		130-149 msec	Consider CRT-P	Recommend CRT-D/P‡	Consider CRT-P*	Recommend CRT	Recommend CRT-D/P‡
		≥ 150 msec	Consider CRT-P	Recommend CRT-D/P‡	Recommend CRT-P*	Recommend CRT	Recommend CRT-D/P‡
	Non-LBBB	120-129 msec			May consider CRT-D[b]†	No CRT	
		130-149 msec			May consider CRT-D[b]†	Unclear	
		≥ 150 msec		Recommend CRT-D/P‡	Consider CRT-P*	Consider CRT	Consider CRT-D/P‡
IV-ambulatory	LBBB	120-129 msec	Consider CRT-P	Recommend CRT-P	Consider CRT-P*	No CRT	Recommend CRT-D/P‡
		130-149 msec	Consider CRT-P	Recommend CRT-P	Consider CRT-P*	Recommend CRT	Recommend CRT-D/P‡
		≥ 150 msec	Consider CRT-P	Recommend CRT-P	Recommend CRT-P*	Recommend CRT	Recommend CRT-D/P‡
	Non-LBBB	120-129 msec		Recommend CRT-P	May consider CRT-D[b]‡	No CRT	
		130-149 msec		Recommend CRT-P	May consider CRT-D[b]‡	Unclear	
		≥ 150 msec		Recommend CRT-P	Consider CRT-P*	Consider CRT	Consider CRT-D/P§

Clinical Characteristics			HTA		Guidelines		
NYHA class	QRS morphology	QRS duration	AHRQ 2014	NICE 2014	ACCF/AHA 2013	Canadian Guidelines 2013	ESC 2012
AF					Consider CRT-P* for AF with LVEF ≤ 35%	No CRT due to insufficient data	NYHA class III and ambulatory IV , LVEF ≤ 35%, QRS ≥ 120, LBBB

AHRQ: Agency for Healthcare Research and Quality, USA ; NICE: National Institutes for Health and Clinical Excellence, UK; ACCF/AHA: American College of Cardiology Foundation/American Heart Association; ESC: European Society of Cardiology

[a] For patients who have LVEF ≤30%, [b] For patients who have LVEF ≤35%

* Checked the references for the type of CRT

[†] CRT-D in RAFT and MADIT, but Rickard et al didn't specify the device

[‡] Most studies only evaluated CRT-P vs. OPT, except COMPANION, which also compared CRT-D vs. OPT

Colour guide for class of recommendation

I	Recommended because benefit >>> risk
IIa	Considered because benefit >> risk
IIb	May be considered because benefit ≥ risk
III	Do not recommend
	Unclear
Blank	No recommendation

Table 7: Number of initial implantations/re-implantations or upgrades of pacemakers and defibrillators during the 2010-2015 fiscal year at the MUHC

Type of device	Number of devices (Initial/re-implant or upgrade)				
	2010-2011	2011-2012	2012-2013	2013-2014	2014-2015
Pacemakers					
CRT-P	6/1	4/4	11/6	38/20	27/18
Standard simple-chamber pacemaker	170/36	124/35	146/35	122/22	172/37
Standard dual-chamber pacemaker	302/67	348/73	394/75	384/95	458/83
Defibrillators					
CRT-D	49/42	74/46	84/57	93/60	72/90
Simple-chamber ICD	66/12	70/13	55/18	77/16	89/15
Double-chamber ICD	85/41	103/39	101/58	91/39	102/30

Data were provided by Nathalie Comtois and Mona Black, Division of Cardiology, MUHC

Table 8: Device and procedure costs by type of implantable devices at MUHC

Cost type	Pacemaker		Defibrillator			
			Until April 2015		From May 2015	
Device costs	**Standard**	**CRT-P**	**ICD**	**CRT-D**	**ICD**	**CRT-D**
Device		4,495		14,800		6,210
Single chamber	2,479		12,225		4,502	
Dual chamber	2,788		13,025		5,038	
Leads	490 each	3,975[a]	1,850-2,995	5,435[a]	1,850-2,995	5,435 [a]
A. Total	**2,969-3,768**	**8,470**	**14,075-16,020**	**20,235**	**6,352-8,033**	**11,645**
Procedure-cost						
Initial implantation						
Use of operating room (unit cost x hour)	847 x 1= 847	847 x 1.5 = 1,271	847 x 1.75 = 1,440	847 x 1.75 = 1,440	847 x 1.75 = 1,440	847 x 1.75 = 1,440
Over-night stay in the cardiac care unit (unit cost x patient day)	1,009 x 1 =1,009	1,009 x 1 =1,009	1,009 x 1 =1,009	1,009 x 1 =1,009	1,009 x 1 =1,009	1,009 x 1 =1,009
Perioperation procedures (unit cost x patient)	323 x 1 =323	323 x 1 =323	323 x 1 =323	323 x 1 =323	323 x 1 =323	323 x 1 =323
B. Total	**2,179**	**2,603**	**2,772**	**2,772**	**2,772**	**2,772**
Battery change/ re-implantation with repositioning of lead						
Use of operating room (unit cost x hour)	847 x 0.5 = 424	847 x 1= 847	847 x 1.25 = 1,016	847 x 1.25 = 1,016	847 x 1.25 = 1,016	847 x 1.25 = 1,016
Over-night stay in the cardiac care unit (unit cost x patient day)	1,009 x 1 =1,009	1,009 x 1 =1,009	1,009 x 1 =1,009	1,009 x 1 =1,009	1,009 x 1 =1,009	1,009 x 1 =1,009
Perioperation procedures (unit cost x patient)	323 x 1 =323	323 x 1 =323	323 x 1 =323	323 x 1 =323	323 x 1 =323	323 x 1 =323
C. Total	**1,756**	**2,179**	**2,348**	**2,348**	**2,348**	**2,348**
Total cost (CAD)						
Initial implantation	**5,947[b]**	**11,073**	**18,792[b]**	**23,007**	**10,805[b]**	**14,417**
Battery change/ re-implantation	**5,524[b]**	**10,649**	**18,368[b]**	**22,583**	**10,381[b]**	**13,993**

[a] Cost of three leads; [b] Cost for dual-chamber devices.

Data were provided by Mona Black and Peggy Verhoef, Division of Cardiology, MUHC

Table 9: Projected impact on the MUHC budget for the 2015-16 fiscal year due to spending on implantable cardiac devices

2014-2015						2015-2016 (Projected estimates)					
Device type	N	Generator cost	Leads cost	Total cost	Budget impact	Device type	N	Generator cost	Leads cost	Total cost	Budget impact
PACEMAKERS						**PACEMAKERS**					
Single	209	2,479	490	620,521		Single	209	785	490	266,475	
Dual	541	2,788	980	2,038,488		Dual	541	1015	980	1,079,295	
CRT-P	45	4,495	3975	381,150		CRT-P	45	4495	3975	381,150	
Total	**795**			**3,040,159**	**3,040,159**	**Total**	**795**			**1,726,920**	**1,726,920**
DEFIBRILLATORS						**DEFIBRILLATORS**					
Single	104	12,225	1850	1,463,800		Single	104	4502.25	1850	660634	
Dual	132	13,025	2995	2,114,640		Dual	132	5037.975	2995	1060353	
CRT-D	162	14,800	5435	3,278,070		CRT-D	162	6210.05	5435	1886498	
Total	**398**			**6,856,510**	**379,003***	**Total**	**398**			**3607485**	**3,607,485**
Total spending					**3,419,162**						**5,334,405**

* 95% of the cost of defibrillator devices was covered by a special Quebec government fund, and thus the budget impact to the MUHC was $379,003 of the total $6,856,510 spent on defibrillator devices. Since 2015, there is no longer dedicated government funding of defibrillator devices, and the budget for these devices is calculated based on 2013-14 volumes and included within the global Cardiology budget.

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APPENDICES

Appendix A: CHARACTERISTICS OF STUDIES INCLUDED IN REPORT

Table A-1: Study characteristics of trials comparing CRT-P versus OPT in patients with QRS > 120 msec

Parameter	CARE-HF Cleland 2005[2]		COMPANION Bristow 2004[19]		MIRACLE Abraham 2002[20]		MUSTIC Cazeau 2001[21]		VECTOR FDA 2005[22]	
Study design	RCT		RCT		RCT		Randomised cross-over		RCT	
Follow-up (mos)	Median 29.4 (18.0, 44.7)		14.8-16.5 months		6 months		3 months		19.9 months	
Key inclusion criteria										
LVEF %	≤ 35		≤ 35		≤ 35		≤ 35		≤ 35	
LVEDD	≥ 30 mm		≥ 60mm		≥ 55 mm		> 60 mm		> 54 mm	
QRS interval	≥ 120 msec		≥ 120 msec		≥ 130 msec		> 150 msec		≥ 140 msec	
Others	HF for ≥ 6 weeks, no atrial arrhythmia		Sinus rhythm		HF for > 1 month, a 6-MWD of ≤ 450m		Severe HF due to idiopathic or ischemic LVSD; sinus rhythm,		HF for ≥ 6 months	
Participant characteristics	CRT-P + OPT	OPT	CRT-P + OPT	OPT	CRT-P on + OPT	CRT-P off + OPT	CRT-P on + OPT	CRT-P off + OPT	CRT-P on + OPT	CRT-P off + OPT
n	409	404	617	308	228	225	29	29	59	47
Age, yrs, mean (SD)	67	66	67	68	63.9 (10.7)	64.7 (11.2)	64 (11)	64 (8)	NR	NR
Male, %	74	73	67	69	68	68	66	83	NR	NR
NYHA Class										
III, n (%)	384 (94)	376 (93)	537 (87)	253 (82)	205 (90)	205 (91)	29 (100)	29 (100)	NR	NR
IV, n (%)	25 (6)	28 (7)	80 (13)	55 (18)	23 (10)	20 (9)	0	0	NR	NR
LVEF (%)*	25	25	20	22	21.8 (6.3)	21.6 (6.2)			NR	NR
QRS interval (msec)**	160 (152, 180)	160 (152, 180)	160	158	167 (21)	165 (20)	172 (22)	175 (19)	NR	NR
LBBB/RBBB, %	NR	NR	69/12	70/9	NR	NR	NR	NR	NR	NR
Ischemic etiology, %	40	36	54	59	50	58	NR	NR	NR	NR

*median or mean (SD); **median (range) or mean (SD)

Table A-2: Study characteristics of trials comparing CRT-D versus ICD in patients with QRS > 120 msec

Parameter	MADIT-CRT[25]		REVERSE[27]		MIRACLE ICD II[30]		RAFT[3]		CONTAK-CD[31]		MIRACLE ICD I[29]	
Study design	RCT		RCT		RCT		RCT		Crossover/ Parallel RCT		RCT	
Follow-up	Average 5.6 years		12 months		6 months		Mean (SD) 40 (20) months		max 6 months		6 months	
Key inclusion criteria												
LVEF	≤ 30%		≤ 40%		< 35%		≤ 30%		≤ 35%		≤ 35%	
QRS interval	≥ 130 msec		≥ 120 msec		≥ 130 msec		≥ 120 msec or >200 paced		≥ 120 msec		≥ 130 msec	
Other	Sinus rhythm		LVEDD ≥ 55 mm		LVEDD ≥ 55 mm		Sinus rhythm/ permanent AF				LVEDD ≥ 55mm	
Participants' characteristics	CRT-D	ICD	CRT-D ON	CRT-D OFF	CRT-D ON	CRT-D OFF	CRT-D	ICD	CRT-D ON	CRT-D OFF	CRT-D ON	CRT-D OFF
N	1089	731	419	191	85	101	894	904	397	359	187	182
Age, mean	65 (11)	64(11)	63 (11)	62 (12)	63.0 (12.8)	63.1 (12.1)	66.1 (9.3)	66.2(9.4)	66 (11)	66 (11)	66.6 (11.3)	67.6 (9.2)
Sex male, %	74.7	75.6	78	80	88.2	90.1	84.8	81.0	85	83	75.9	77.5
NYHA Class												
I, n (%)	152 (14)	113 (15)	75 (18)	32 (17)	0	0	0	0	152 (38)	113 (31)	0	0
II, n (%)	937 (86)	618 (85)	344 (82)	159 (83)	85 (100)	101 (100)	708 (79)	730 (81)	78 (20)	81 (23)	0	0
III, n (%)	0	0	0	0	0	0	186 (21)	174 (19)	147 (37)	140 (39)	165 (88)	163 (90)
IV, n (%)	0	0	0	0	0	0	0	0	20 (5)	25 (7)	22 (12)	19 (10)
LVEF (%), mean (SD)	24 (5)	24 (5)	26.8 (7.0)	26.4 (7.1)	24.4(6.6)	24.6 (6.7)	22.6 (5.4)	22.6(5.1)	21 (7)	22 (7)	24.2 (6.5)	23.9 (6.0)
QRS interval (msec), mean (SD)	64% ≥150 msec	65% ≥150 msec	153 (21)	154 (24)	166 (25)	165 (23)	157 (23.6)	158.3 (24.0)	160 (27)	156 (26)	165 (22)	162 (22)
LBBB/RBBB, %	70/13	71/13	77/10		83/17		73/8	71/10	54/14	55/12	NR/13	NR/13
Ischemic etiology, %	55	55	56	51	55.3	58.4	68.7	64.9	67	71	64.0	75.8

Table A-2 (continued): Study characteristics of trials comparing CRT-D versus ICD in patients with QRS > 120 msec

	Piccirillo[32]		Pinter [46]		Diab[34]		Rhythm ICD[22]	
Study design	RCT		RCT		RCT	RCT		
Length of follow-up	1 year		6 months		6 months		Mean 12 (3) months	
Key inclusion criteria	Key inclusion criteria							
LVEF	≤ 35%		≤ 35%		≤ 35%		≤ 35%	
QRS interval	≥ 120 msec		≥ 120 msec		≥ 120 msec		≥ 150 msec	
Other	Sinus rhythm		Sinus rhythm		LVEDD ≥ 55mm			
Participants' characteristics	CRT-D	ICD	CRT-D ON	CRT-D OFF	CRT-D	ICD	CRT-D ON	CRT-D OFF
n	16	15	36	36	24	22	119	59
Age, mean	65 (4)	65 (8)	66.1 (8.8)	66.1 (9.3)	67 (7)	63 (13)	NR	NR
Sex male, %	81	80	77.8	80.6	88	90	NR	NR
NYHA Class								
I, n (%)	0	0	NR	NR	0	0	1 (1)	2 (3)
II, n (%)	0	0	NR	NR	0	0	6 5)	4 (7)
III, n (%)	5 (31)	5 (33)	NR	NR	21 (88)	17 (77)	104 (87)	50 (85)
IV, n (%)	11 (69)	10 (67)	NR	NR	3 (12)	5 (23)	8 (7)	3 (5)
LVEF (%), mean (SD)	23 (4)	22 (8)	21.2 (7.9)	24.0 (8.3)	25 (5)	27 (6)	25.6 (8.3)	23.3 (6.4)
QRS interval (msec), mean (SD)	160 (4)	159 (8)	NR	NR	134 (15)	142 (20)	169 (16)	167 (15)
LBBB/RBBB, %	NR	NR	NR	NR	NR	NR	NR	NR
Ischemic etiology, %	100	100	77.8	80.6	88	73	NR	NR

Appendix B: SEARCH STRATEGY AND FLOW CHART

Table B-1: Description of the parameters and databases searched

	CRT in Heart Failure
Population	Patients with heart failure with LVSD and cardiac dyssynchrony and at increased risk of SCD as a result of ventricular arrhythmias despite OPT
Intervention	ICD, CRT-D, or CRT-P
Comparator	OPT alone, CRT-D vs. ICD
Search keywords	((biventricular pacing[Title/Abstract] OR cardiac resynchroni* therapy[Title/Abstract] OR biventricular pacemaker*[Title/Abstract]) AND "heart failure"
Database searched	
• **Published studies and guidelines**	York University, Cochrane Library, PubMed
• **Ongoing studies**	ClinicalTrials.gov
• **HTAs**	National Institute for Health Research (UK), Agency for Healthcare Research and Quality (USA)

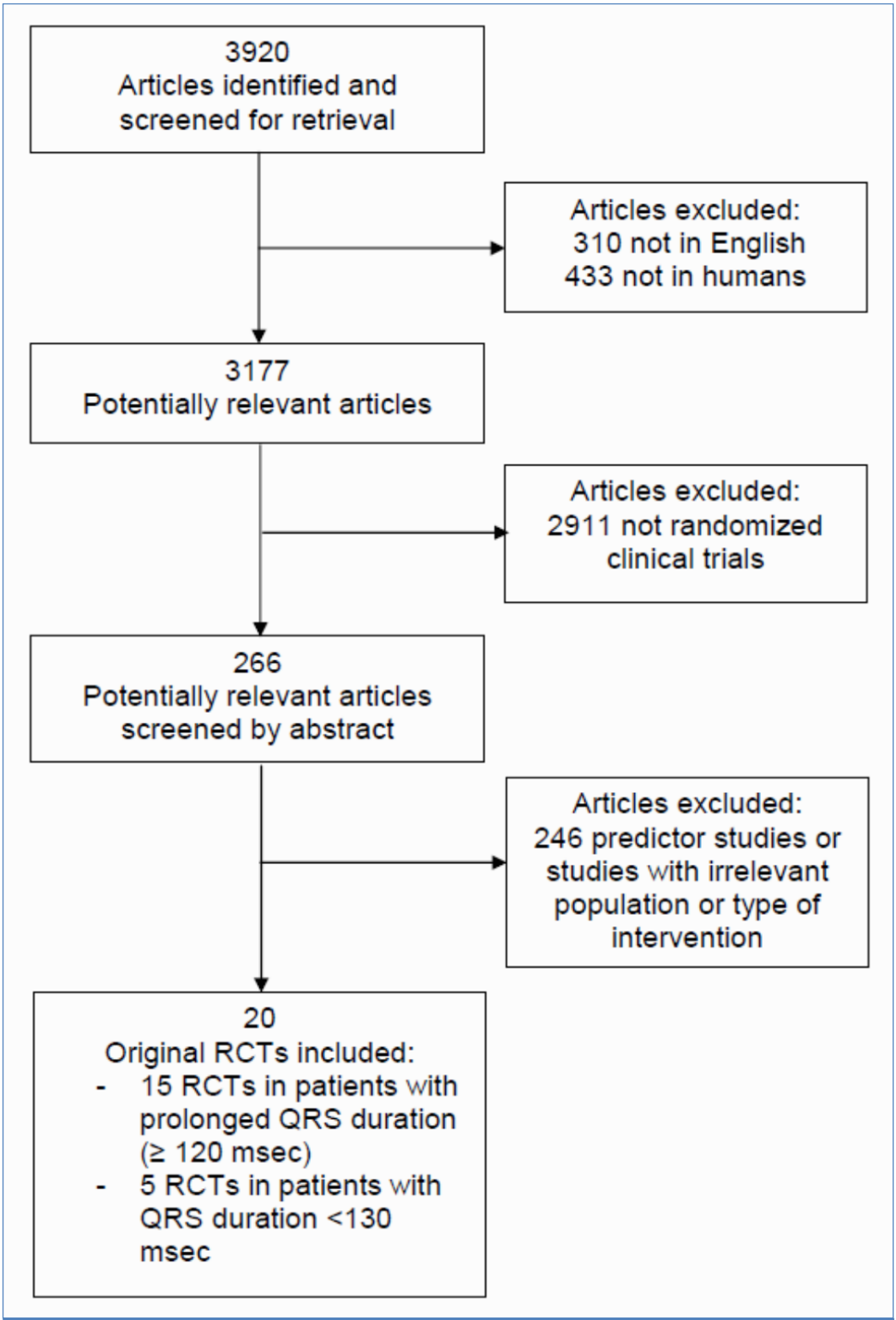

Figure B-1: Flowchart of the RCT search on CRT in heart failure

Appendix C: ASSESSMENT OF BIASES

Table C-1: Risk of bias in CRT trials in patients with QRS <130 msec

Judgement *	Echo-CRT study[15]	NARROW-CRT study[16]	RETHINQ study[17]	LESSER-EARTH study[18]	RESPOND study[14]
Selection bias					
Random sequence generation	+	+	+	+	+
Allocation concealment	+	+	?	+	+
Performance bias					
Blinding of participants and personnel	+	+	+	+	-
Detection bias					
Blinding of outcome assessment	+	-	+	+	-
Attrition bias					
Incomplete outcome data addressed	+	+	+	+	+
Funding source	Industrial: Biotronik	Independent	Industrial: St Jude	Industrial: St Jude	Heart of England NHS Trust

+ Low risk of bias; - High risk of bias; ? Unclear (not reported) risk of bias

Table C-2: Risk of bias in the trials comparing CRT-P versus OPT in patients with QRS > 120 msec

Judgement *	CARE-HF[2]	COMPANION[19]	MIRACLE[20]	MUSTIC[21]	VECTOR[22]
Selection bias					
Random sequence generation	+	?	+	+	?
Allocation concealment	+	?	+	?	?
Performance bias					
Blinding of participants and personnel	-	-	+	+	+
Detection bias					
Blinding of outcome assessment	+	+	+	-	?
Attrition bias					
Incomplete outcome data addressed	+	+	+	+	+
Funding source	Industrial: Medtronic	Industrial: Guidant	Industrial: Medtronic	Industrial: ELA Recherche, Medtronic	Industrial: St Jude Medical

+ Low risk of bias; - High risk of bias; ? Unclear (not reported) risk of bias

Table C-3: Risk of bias in the trials comparing CRT-D versus ICD in patients with QRS > 120 msec

Judgement *	MADIT-CRT[25]	REVERSE[27]	MIRACLE ICD II[30]	RAFT[3]	CONTAK-CD[31]	MIRACLE ICD I[29]	Piccirillo[32]	Pinter [46]	Diab[34]	Rhythm ICD[22]
Selection bias										
Random sequence generation	?	+	+	+	?	+	?	+	?	?
Allocation concealment	?	?	+	+	?	+	?	?	?	?
Performance bias										
Blinding of participants and personnel	?	+	+	+	?	+	?	+	+	?
Detection bias										
Blinding of outcome assessment	+	+	?	+	?	?	+	+	+	?
Attrition bias										
Incomplete outcome data addressed	+	+	+	+	+	+	+	+	+	+
Funding source	Industrial: Boston Specific	Industrial: Medtronic	Industrial: Medtronic	Industrial: Medtronic	Industrial: Guidant	Industrial: Medtronic	Independent	Industrial: Guidant	???	Industrial: St Jude Medical

+ Low risk of bias; - High risk of bias; ? Unclear (not reported) risk of bias

Appendix D: OBSERVATIONAL STUDIES

The efficacy of CRT-Pacemaker vs. CRT-Defibrillator

Looi and colleagues conducted a single centre retrospective cohort study with a mean follow up of 29 months in 500 subjects directly comparing CRT-P to CRT-D.[47] The objective was to determine whether patients who qualify for a CRT-P and separately for an ICD receive any additional benefit from a CRT-D. At inclusion, the mean age was 69 years, QRS interval 160 msec, and LVEF 25%. There were 77% male patients, 92.2% patients who had NYHA Class III or IV-ambulatory, 7.8% had NYHA Class II, and 52.8% had ischemic heart diseases. At 1 year, the all-cause mortality in the CRT-D group was half that in the CRT-P group (HR 0.54, 95% CI 0.27 to 1.07), however the effect attenuated in the 2nd year (HR 0.71, 95% CI 0.43 to 1.17). Multivariate analysis showed that device type was not a significant predictor. Younger age, female sex, hypertension and use of beta blocker were significant predictors of improved survival. Therefore, though the hazard ratio suggests that severely symptomatic patients qualifying for ICD and CRT-P do benefit from CRT-D, the evidence is not conclusive.

They also found that CRT-D was associated with higher risks of device-related complications (HR 1.90, 95% CI 1.07 to 3.37) compared to ICD.

The efficacy of CRT-Defibrillator vs. ICD

Masoudi and colleagues conducted a large (n=7,090) retrospective cohort in a registry of patients who received either ICD or CRT-D and showed that the CRT-D group had lower risks of death (HR 0.82, 95% CI 0.73 to 0.93) and heart-failure readmissions (HR 0.78, 95% CI 0.69 to 0.88).[48] These benefits were pronounced particularly among patients with LBBB and QRS duration ≥150 msec, but not seen in those with non-LBBB and QRS duration 120-149 msec. Nevertheless, compared to ICD, CRT-D was associated with higher risks of device-related complications (HR 1.90, 95% CI 1.07 to 3.37).

Appendix E: LIST OF VARIABLES TO BE DOCUMENTED FOR CRT PATIENTS

Table E-1: Patient selection criteria and outcomes to be documented for CRT patients treated at the MUHC

Date:					**Hospital name:**
Patient ID:					
PATIENT CHARACTERISTICS					**COMMENTS**
Age (years)					
Sex	☐ Male				
	☐ Female				
NYHA class	☐ I				
	☐ II				
	☐ III				
	☐ IV	☐ ambulatory	☐ non-ambulatory		
Stress test or 6-min walk test performed?	☐ Yes	No. of METS completed:_____			
		Distance walked in 6 mins:_____			
	☐ No	Reasons:			
LBBB	☐ Yes				
	☐ No	☐ RBBB	☐ IVCD	☐ Other:	
AV block	☐ Yes				
	☐ No				
Ischemic etiology of heart failure	☐ Yes				
	☐ No				
QRS duration (msec)					
LVEF (%)					
Referring physician preference for specific device?	☐ Yes	Type of device:			
	☐ No	Name of referring institution:			
Patient preference for specific device?	☐ Yes	Type of device:			
	☐ No				
DEVICE CHARACTERISTICS					
Type of device	☐ CRT-P				
	☐ CRT-D	☐ Brava Quad	☐ Quadra Assura	☐ Viva Quad	
	☐ Pacemaker	☐ Single	☐ Dual	☐+ MRI	
	☐ ICD	☐ Single	☐ Dual	☐ +MRI	

Type of implant	☐ de novo		
	☐ re-implant	Date of previous implant:	
	☐ upgrade	Previous device:	
		Date of previous implant:	

Date:				**Hospital:**
Patient ID:				
OUTCOMES				**COMMENTS**
Adverse events associated with implantation procedure	☐ Implant failure			
	☐ Lead dislodgement			
	☐ Pocket hematoma			
	☐ Pneumothorax			
	☐ Other			
Heart failure hospitalizations since implant	☐ Yes	Number of hospitalizations:		
		Date of last hospitalization:		
	☐ No			
Mortality	☐ Alive			
	☐ Dead	☐ Cardiac death	☐ Non-cardiac death	
Quality of life measures	☐ MLWHF	Score:	Change since last visit:	
	☐ SF 36	Score:	Change since last visit:	
	☐ Patient self-report			

Appendix F: GLOSSARY OF TERMS

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT), also known as biventricular pacing, was developed to improve coordination of ventricular contraction in patients with severely symptomatic heart failure despite best medical management. CRT uses a biventricular pacemaker (BVP) to pace the right and left ventricles simultaneously, and is thus used to treat ventricular dyssynchrony, a difference in timing between right and left ventricular contractions. Ventricular dyssynchrony leads to physiological changes in the structure of the heart, a dilatation of the left ventricle referred to as "remodelling". CRT reverses remodelling of the left ventricle by decreasing the left ventricle end systolic volume (LVESv) and increasing left ventricular ejection fraction (LVEF). Moreover, optimizing atrioventricular synchrony can also lead to decreased mitral regurgitation and increased diastolic filling time.

CRT, when implanted alone, is referred to as CRT-P (for pacing). For selected patients at risk of malignant ventricular arrhythmias, CRT can be combined with an implantable cardioverter defibrillator (ICD), and is then referred to as CRT-D (for defibrillator).

The CRT device has two or three leads (wires) (**Figure F-1**). Typically, the leads are implanted through a transvenous approach. A local anesthetic is administered and an incision is made in the chest where the leads and pacemaker are inserted. The leads are inserted through the incision and into a vein, then guided to the heart with the aid of fluoroscopy. The lead tip attaches to the heart muscle, while the other end of the lead (attached to the pulse generator) is placed in a pocket created under the skin in the upper chest. When this approach is used, the hospital recovery time is generally 24 hours.[1]

The crude rate of adult patients receiving CRT pacemakers (CRT-P) in Canada (except Quebec province) was 0.6 per 100,000 population in 2010/2011. The rate climbed to 1.0 per 100,000 population in 2013/2014. The number of patients who received CRT with defibrillator (CRT-D) or implant cardiac defibrillator (ICD) remained stable at 17-18 per 100,000 population rate.[49]

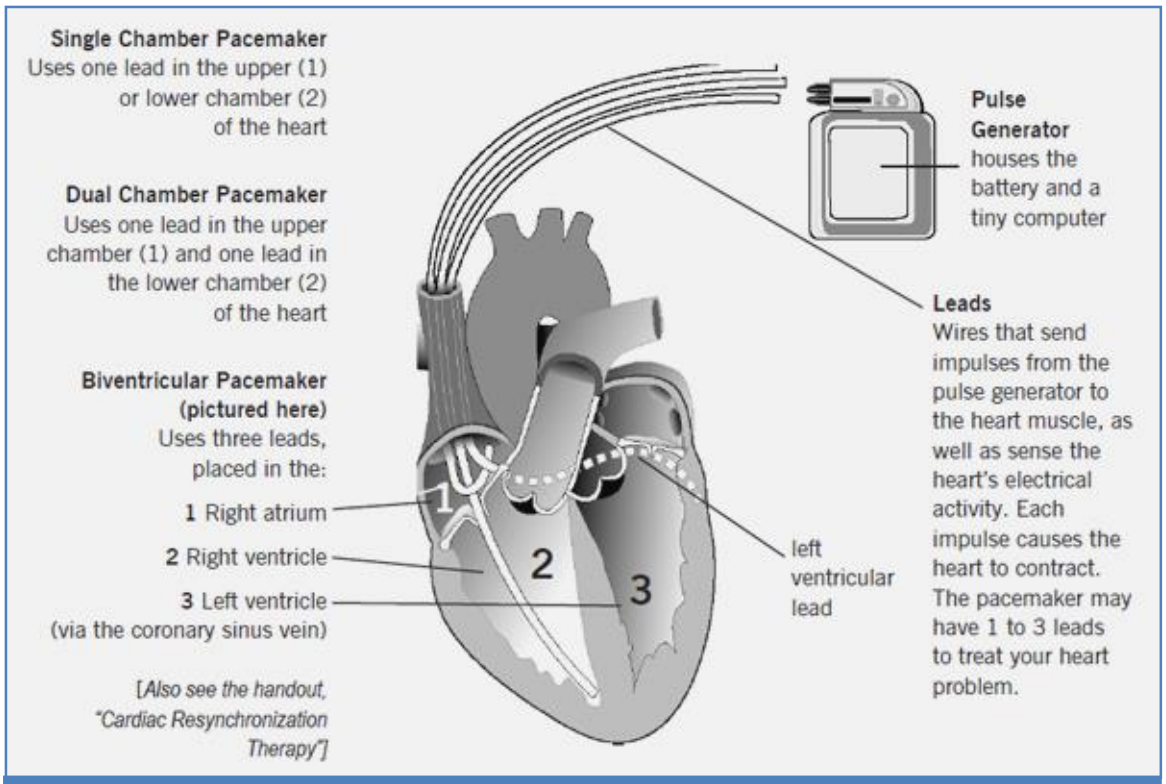

Figure F-1: Illustration of different types of pacemakers (from the Cleveland Clinic Webpage [1])

Dyssynchrony

A lack of synchrony in activation of the cardiac chambers, which can be a result of diverse myocardial pathologies including heart disease, and conduction disorders such as left bundle branch block.[50] Dyssynchrony results in impaired LV systolic function, increased end-systolic volume, and delayed relaxation. Three types of dyssynchrony can occur:

- *Atrioventricular* (AV) dyssynchrony is a difference in timing between atrial and ventricular contractions wherein atrial systole is completed long before ventricular systolic contraction, resulting in suboptimal diastolic filling of the left ventricle. Parameters measuring AV dyssynchrony such as left ventricular pre-ejection interval are used to assess LV function.
- *Interventricular* dyssynchrony occurs when there is a difference in timing between right ventricular (RV) and left ventricular (LV) contractions. Left bundle branch block causes interventricular dyssynchrony because left ventricular contraction occurs after right ventricular contraction. Interventricular dyssynchrony is often assessed as the interventricular mechanical delay, the time difference between RV and LV ejection.[50]

- *Intraventricular* dyssynchrony or LV dyssynchrony, refers to abnormalities in timing of regional LV activation, resulting in disordered contraction of the LV segments.[51] Left bundle branch block (LBBB) causes intraventricular dyssynchrony wherein the interventricular septum is activated early and the posterior and lateral LV walls are activated late.[50]

Prolonged QRS duration (≥120 msec) on an electrocardiogram is considered to be a marker of ventricular dyssynchrony (i.e. electrical dyssynchrony). However, dyssynchrony may also be present in some heart failure patients with narrow QRS, and hence measures of *mechanical dyssynchrony* using echocardiographic Doppler tools have been developed, to assess changes in the dynamic behaviour of the tissues.[51]

Heart failure prevalence

In Quebec, the estimated prevalence of heart failure (HF) in 2008/2009 was approximately 140,000 cases, which represents more than 3.3% of the population aged 40 years and older.[52,53] The incidence rate was 5.4 per 1,000, which means there are more than 22,000 new cases yearly.[52,53]

Left ventricular ejection fraction (LVEF)

LVEF measures the ability of the left ventricle to pump out blood with each contraction. We can distinguish two types of heart failure based on LVEF – heart failure with preserved ejection fraction (HFpEF) or diastolic heart failure, and heart failure with reduced ejection fraction (HFREF) or systolic heart failure. LVEF ranging from 55-70% is considered normal, while a value ≤40% indicates moderately and <30% severely impaired left ventricular systolic function.[54]

Left ventricle end diastolic volume (LVEDv)

The volume of blood in the left ventricle at the end of a diastole when the ventricle fills with blood, or just before systole, when the ventricle contracts. Normal values range from 65-240ml.[55]

Left ventricle end systolic volume (LVESv)

The volume of blood in the left ventricle at the end of a contraction (systole) and just before diastole, when the ventricle fills with blood. Normal values range from 16-143ml.[55]

NYHA class

The clinical severity of HF cases is commonly classified according to New York Heart Association (NYHA) Functional Classification (**Table F-1**).[56] Although this classification

has been used for patient selection in studies as well as for making recommendations for CRT use in clinical guidelines, there is no consistent method of assessing NYHA class. Raphael and colleagues demonstrated how difficult it is to reach agreement even among cardiologists, especially to differentiate class II from III.[57] Moreover, it has also been shown that there can be a substantial discrepancy in NYHA class assignment between patients and physicians.[58] Only two-third of patients assigned to NYHA class III or IV agreed with this assessment. About one-fifth of the patients felt that a milder class (NYHA I or II) was a more appropriate description of their functional status. Nevertheless, there is a strong association between NYHA class and outcomes in heart failure patients. A retrospective cohort study in almost 1,000 heart failure patients with preserved ejection fraction reported 15%, 21%, 36%, and 58% all-cause mortality in NYHA class I, II, III, IV, respectively, after a median follow-up of 38 months (ranged from 0.3 to 58 months).[59]

Table F-1: New York Heart Association (NYHA) Functional Classifications*

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Unable to carry on any physical activity without discomfort, or symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Quality of life (QoL) score-Minnesota Living with Heart Failure score

Comprehensive assessment of the effect of heart failure and treatment for HF on the patient's quality of life, with scores ranging from 0-5 on 21 facets of life (including clinical, physical, emotional, and psychological dimensions), with higher scores indicating worse quality of life.[60]

QRS duration

The duration of the Q, R, and S waves on an electrocardiogram, corresponding to depolarization of the right and left ventricles of the heart, which signals the ventricles to contract. Normal values range from 80-120ms; a prolonged QRS duration (≥120

msec) on an electrocardiogram is considered to be a marker of ventricular dyssynchrony.

QRS morphology

Electrical stimuli are conducted from the AV node to the ventricles via the His-Purkinje system. The bundle of His splits into right and left bundle branches at the level of the interventricular septum, conducting stimuli to the right and left ventricles respectively.

- Left bundle branch block (LBBB): Results when conduction to the left bundle branch is impaired, causing the left ventricle to contract later than the right ventricle.
- Right bundle branch block (RBBB): Results when conduction to the right bundle branch is impaired, causing the right ventricle to contract later than the left ventricle.

Six minute walk test (6MWT)

ii) To test exercise tolerance in patients with chronic respiratory disease and heart failure. Normal range is 400-700m in healthy adults.[61]