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

Use of Biventricular Pacing in Atrioventricular Heart Block

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

by

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REPORT REQUESTOR

This report was requested by Ann Lynch, the Associate Director General for clinical operations in the Adult Missions at McGill University Health Centre (MUHC) in February 2014.

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ABSTRACT

- Right ventricular pacing (RVP) may induce left ventricular (LV) dysfunction and ventricular dyssynchrony contributing to heart failure (HF) over time. Therefore, there has been an interest in comparing biventricular pacing (BVP) [also known as cardiac resynchronization therapy (CRT)], an accepted therapy for moderate to severe HF, to RVP either for *de novo* pacing or upgrades in AV block patients.

- We reviewed studies of *de novo* implantations in AV block patients, stratifying them according to mean LV ejection fraction (LVEF):

    - Four RCTs that included patients with normal mean LVEF at baseline showed no evidence of benefit of BVP over RVP with respect to LV function parameters, patient-reported outcomes, exercise capacity, hospitalization rates due to HF or mortality during follow-up.

    - Three RCTs included patients with low mean LVEF at baseline, most of whom had characteristics known to be associated with BVP efficacy, such as wide QRS and left bundle branch block (LBBB). Overall compared to RVP, BVP was reported to statistically improve LV function parameters, though clinical benefits are unclear. An improvement in quality of life was reported by BVP patients, though no difference was reported in exercise capacity and no consistent benefit in mortality.

- We reviewed three small studies evaluating an upgrade from RVP to BVP in HF patients (initially AV block patients). These studies suggest BVP may be associated with an improvement in LV function parameters, exercise capacity and quality of life. One study reported a reduction in HF hospitalizations and mortality.

- In conclusion, this current systematic review has demonstrated that:

    - BVP as an initial mode of pacing in AV block patients with normal LVEF does not offer any clinical advantage over RVP and is therefore not recommended.

    - In AV block patients with low LVEF or with characteristics known to be associated with BVP efficacy such as wide QRS duration or LBBB, BVP may improve some heart failure parameters though the clinical significance of this remains unclear. Furthermore, the available evidence is inadequate to identify characteristics of AV block patients most likely to benefit from BVP. Therefore, BVP is not recommended routinely for *de novo* pacing or for an upgrade from RVP in this population.

- The Canadian Cardiovascular Society (CCS) consider that the evidence in favour of *de novo* BVP implantation in AV Block patients is "moderate". They none the less recommend considering BVP for such patients conditional on the presence of HF symptoms and low LVEF. 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.
- Any usage of BVP in AV block patients with heart failure should be documented with a view to generate data that can aid appropriate patient selection.

RÉSUMÉ

- La stimulation ventriculaire droite (SVD) peut induire une dysfonction ventriculaire gauche (DVG) et un asynchronisme ventriculaire contribuant à une insuffisance cardiaque (IC) avec le temps. Ainsi, un intérêt s'est développé pour comparer la stimulation biventriculaire (SBV) (aussi connue sous l'appellation thérapie de resynchronisation cardiaque (TRC)), une thérapie acceptée lors d'insuffisances cardiaques modérées à sévères à la SVD, que ce soit *de novo* ou lors de rehaussements chez les patients avec un bloc auriculo-ventriculaire (AV).

- Nous avons revu les études d'implantations *de novo* chez les patients avec un bloc AV, les répartissant selon la valeur moyenne de la fraction d'éjection ventriculaire gauche (FEVG):

    - Quatre études randomisées incluant des patients ayant des valeurs moyennes initiales normales de FEVG, ne montrèrent aucun signe de bénéfices de la SBV par rapport à la SVD en regard des paramètres de la fonction ventriculaire gauche, des résultats déclarés par les patients, de la capacité à l'exercice et des taux d'hospitalisation pour insuffisance cardiaque ou à la mortalité durant le suivi.
    - Trois études randomisées incluaient des patients avec des valeurs moyennes initiales faibles de FEVG, la plupart d'entre eux ayant des caractéristiques associées avec l'efficacité de la SBV tel qu'un QRS élargi et un bloc de branche gauche (BBG). Comparée de façon globale à la SVD, la SBV fut citée pour statistiquement améliorer les paramètres de la fonction ventriculaire gauche, malgré que les bénéfices cliniques ne soient pas évidents. Une amélioration de la qualité de vie fut mentionnée par les patients du groupe SBV, bien qu'aucune différence ne fut rapportée au niveau de la capacité à l'exercice ainsi qu'aucun bénéfice cohérent en regard de la mortalité.

- Nous avons revu trois courtes études évaluant le rehaussement de la SVD à la SBV chez les patients avec insuffisance cardiaque (initialement des patients avec un bloc AV). Ces études suggèrent que la SBV peut être reliée à une amélioration des paramètres de la fonction ventriculaire gauche, de la capacité à l'exercice et de la qualité de vie. Une étude mentionna une diminution des hospitalisations pour insuffisance cardiaque ainsi qu'une diminution de la mortalité.

- En conclusion, la revue systématique actuelle a démontré que:

  - La SBV comme mode de stimulation initial chez les patients avec un bloc AV et une FEVG normale n'offre aucun avantage clinique par rapport à la SVD et n'est donc pas recommandée.
  - Chez les patients avec un bloc AV et une FEVG réduite ou avec des caractéristiques associées avec l'efficacité de la SBV tel un QRS allongé ou un bloc de branche gauche, la SBV peut améliorer quelques paramètres relatifs à l'insuffisance cardiaque bien que la signification clinique de ces faits demeure incertaine. De plus, les preuves existantes sont insuffisantes pour identifier les caractéristiques des patients avec un bloc AV les plus susceptibles de bénéficier de la SBV. Par conséquent, la SBV n'est pas recommandée de façon routinière pour la stimulation *de novo* ou pour un rehaussement de la SVD chez cette population.

- La Canadian Cardiovascular Society (CCS) considère que les preuves en faveur de l'implantation *de novo* de la SBV chez les patients avec un bloc AV sont modérées. Néanmoins, elle recommande de considérer la SBV pour de tels patients conditionnellement à la présence de symptômes d'insuffisance cardiaque et d'une faible FEVG. 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.
- Toute utilisation de la SBV chez les patients avec un bloc AV et une insuffisance cardiaque devrait être documentée dans le but de cumuler des données supportant une sélection pertinente des patients.

LIST OF ABBREVIATIONS

AE	Adverse event
AF	Atrial fibrillation
AHRQ	US Agency for Healthcare Research and Quality
AV	Atrioventricular
BVP	Biventricular pacing
CRT	Cardiac resynchronization therapy
ECG	Electrocardiogram
EMBASE	Excerpta Medica Database
DDD-R	Dual chamber (atrium and ventricle) pacing system , R for right ventricle
HB	Heart block
HF	Heart Failure
HR	Hazard ratio
HTA	Health technology assessment
ICD	Implantable cardioverter defibrillator
INESSS	L'Institut national d'excellence en santé et en services sociaux
LBBB	Left bundle branch block
LV	Left ventricle
LVEDv	Left ventricle end diastolic volume
LVEF	Left ventricle ejection fraction
LVESv	Left ventricle end systolic volume
LVIDD	LV internal diameter in systole
LVIDS	LV internal diameter in diastole
MLWHFQ	Minnesota Living with Heart Failure Questionnaire
MUHC	McGill University Health Centre
NICE	National Institutes for Health and Clinical Excellence
NIHR	UK National institute for health research
NYHA	New York Heart Association
Pro-BNP	Pro-Brain type natriuretic peptide
QoL	Quality of life
RBBB	Right bundle branch block
RCT	Randomized controlled trial
RVP	Right ventricular pacing
SD	Standard deviation
TAU	MUHC Technology Assessment Unit
6-MWT	6-minute walk test

EXECUTIVE SUMMARY

Background

Heart block or atrioventricular (AV) block is a conduction disorder. It can range from asymptomatic first degree heart block to severe third degree block associated with a high risk of sudden cardiac arrest and death. Third degree block is an indication for right ventricular pacing (RVP).

RVP may induce left ventricular (LV) dysfunction and ventricular dyssynchrony which may contribute to heart failure (HF) over time. Therefore, there has been an interest in comparing biventricular pacing (BVP) (also known as cardiac resynchronization therapy (CRT)), an accepted therapy for moderate/severe HF, to RVP as a primary pacing choice for AV block patients.

Objectives

The objective of this report is to systematically review the evidence for the use of BVP, as either a *de novo* implant or as an upgrade, in the management of AV block with normal left ventricular systolic function at the MUHC.

Methods

We conducted a review of the literature for BVP use, either as a *de novo* implant or upgrade in AV block patients, focussing on randomized controlled trials, controlled observational studies, and recent systematic reviews. We stratified studies of *de novo* implantation into two groups based on mean LVEF at baseline.

Results: Literature review

RVP versus BVP as *de novo* pacing: We identified seven RCTs comparing RVP to BVP as the initial mode of pacing and one review published in 2014. Four RCTs, with normal mean LVEF (≥55%) at baseline, found no significant difference between the two groups with respect to LV function parameters, patient-reported outcomes, exercise capacity, hospitalization rates due to HF or mortality rates during follow-up.

The remaining three RCTs, with low mean LVEF (<55%) at baseline, included a number of patients with HF, a condition known to respond to BVP in some patients, particularly those with prolonged QRS and left bundle branch block. Two studies showed a statistically significant superiority of BVP over RVP in improving LV function parameters; though the

clinical significance of this is unclear as the mean LVEF value remained low after follow-up. Two studies reported that BVP proved superior to RVP in terms of patient-reported quality of life and one study reported a decrease in hospitalizations due to HF. One study that measured exercise capacity found no improvement due to BVP. Two studies found no significant impact on mortality; the one study that did was in patients with Chagas' disease.

Upgrade from RVP to BVP: We identified 2 small RCTs and one small observational study addressing the issue of upgrading patients on RVP to BVP. The upgrade studies were conducted in HF patients who had AV block at the time of initial RVP. These patients were also more likely to have characteristics known to respond to BVP, such as wide QRS and left bundle branch block. These studies reported an improvement in LV function parameters, patient-reported outcomes and exercise capacity.One study reported a reduction in HF hospitalizations and mortality.

BVP use for heart block at the MUHC

To date, BVP has not been used for *de novo* pacing in AV block patients without heart failure at the MUHC.

Cost and budget impact

The current cost of a BVP device with three leads is $8,470 compared to $3,758 for a dual-chamber standard pacemaker (RVP). The total cost for implanting a new BVP device is $11,073 compared to $5,937 for a new dual-chamber standard pacemaker. Thus, the incremental cost to the MUHC of a new BVP implant compared to RVP would be $5,116 per patient.

CONCLUSIONS

- The available evidence regarding the use of BVP in AV block patients is weak in terms of the number of studies identified, the relatively small sample sizes, and the lack of meaningful clinical outcome data and short duration of follow-up within each study. Based on the GRADE guidelines the quality of the evidence was rated as Low to Very Low on all outcomes.
- In patients with normal LVEF, the use of BVP as an initial mode of pacing in AV block patients remains unsupported as the evidence shows no significant difference in clinical endpoints compared to RVP.

- In patients with low LVEF undergoing *de novo* pacing and in those with HF undergoing an upgrade from RVP, there is fairly consistent evidence of modest improvement of ventricular function (increased LVEF, reduced end systolic volume), and modest symptomatic improvement (NYHA score, walk test and QoL). It should be noted that these studies included a substantial number of patients with characteristics that are indications for BVP in heart failure at baseline, and therefore do not provide evidence regarding the independent risk of AV block in contributing to heart failure.

- The 2013 guidelines for use of BVP published by the Canadian Cardiovascular Society (CCS) also reached a similar conclusion to our report in terms of the quality of evidence. Based on the BLOCK-HF trial alone, the CCS noted that the quality of evidence was "moderate". None the less, they issued a "Conditional Recommendation" that BVP "might be considered for patients with new-onset high-degree AV block requiring chronic RV pacing, signs and/or symptoms of HF, and LVEF≤ 45%". The CCS guideline points out that the BLOCK-HF trial enrolled only those with de novo implants and its results may not apply to those who are already chronically paced. Further it notes that most patients in the BLOCK-HF trial had symptomatic HF. This is similar to our own observation above regarding RCTs of de novo BVP implantation in AV Block patients with low LVEF.

- 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 BVP and where there is not.

RECOMMENDATIONS

- In AV block patients with normal LVEF, the use of BVP as an initial mode of pacing in AV block patients is not recommended.

- In AV block patients with low LVEF, there is insufficient evidence to justify the routine use of BVP either for *de novo* implantation or for an upgrade from RVP.

- Given the paucity of evidence available so far, any usage of BVP in AV block patients with heart failure should be **conditional** on documentation of patient selection criteria and patient outcomes (see Report 77 for details).

SOMMAIRE

Contexte

Le bloc cardiaque ou le bloc auriculo-ventriculaire (AV) est un trouble de conduction. Il peut varier d'un bloc cardiaque asymptomatique du premier degré à un bloc sévère du troisième degré, associé à un risque élevé d'arrêt cardiaque subit et de décès. Le bloc du troisième degré est une indication pour une stimulation ventriculaire droite (SVD).

La SVD peut induire une dysfonction ventriculaire gauche et un asynchronisme ventriculaire pouvant entraîner une insuffisance cardiaque avec le temps. Pour cette raison, il y a eu un intérêt pour comparer la stimulation biventriculaire (SBV) (aussi connue sous l'appellation thérapie de resynchronisation cardiaque (TRC)), une thérapie acceptée pour traiter les insuffisances cardiaques modérées à sévères, à la SVD comme premier choix de stimulation pour traiter les patients avec un bloc AV.

Objectifs

L'objectif de ce rapport est de revoir systématiquement les preuves pour l'utilisation de la SBV, que ce soit comme implantation *de novo* ou comme rehaussement dans le management du bloc AV avec fonction ventriculaire gauche normal, au Centre Universitaire de Santé McGill (CUSM).

Méthodologie

Nous avons réalisé une revue de la littérature portant sur l'utilisation de la SBV, que ce soit comme implantation *de novo* ou comme rehaussement chez les patients avec un bloc AV, en concentrant sur les études randomisées, les études par observation et les revues systématiques récentes. Nous avons réparti les études d'implantations *de novo* en deux groupes basés sur la FEVG moyenne initiale.

Résultats : Revue de la littérature

SVD versus SBV comme stimulation *de novo*: Nous avons identifié sept études randomisées comparant la SVD à la SBV comme mode initial de stimulation et une revue publiée en 2014. Quatre études randomisées avec une FEVG moyenne initiale normale (≥55%), n'ont trouvé aucune différence significative entre les deux groupes concernant les paramètres de la fonction ventriculaire gauche, les résultats déclarés par les patients, la capacité à l'exercice et les taux d'hospitalisation dus à l'insuffisance cardiaque ou les taux de décès durant le suivi.

Les trois dernières études randomisées avec une FEVG moyenne initiale réduite (<55%), comprenaient un certain nombre de patients souffrant d'insuffisance cardiaque, une condition reconnue pour favoriser une réponse à la SBV chez certains patients, et tout particulièrement ceux avec un QRS allongé et un bloc de branche gauche. Deux études montrèrent une supériorité statistiquement significative de la SBV par rapport à la SVD suite à l'amélioration des paramètres de la fonction ventriculaire gauche, même si la signification clinique de ce fait est incertaine car la valeur moyenne de la FEVG demeure faible après le suivi. Deux études montrèrent que la SBV était supérieure à la SVD en termes de la qualité de vie rapportée par les patients, et une étude rapporta une diminution des hospitalisations due à l'insuffisance cardiaque. Une étude qui mesurait la capacité à l'exercice ne trouva aucune amélioration due à la SBV. Deux études ne trouvèrent aucun impact significatif quant à la mortalité; l'étude qui trouva ce fait concernait les patients avec la maladie de Chagas.

Rehaussement de la SVD à la SBV: Nous avons identifié deux petites études randomisées ainsi qu'une petite étude observationnelle abordant la question du rehaussement de la SVD à la SBV chez les patients. Les études de rehaussement furent menées chez les patients avec insuffisance cardiaque qui ont un bloc AV au moment de l'implantation initiale de la SVD. Ces patients étaient plus susceptibles de présenter les caractéristiques reconnues pour répondre à la SBV tel un QRS allongé et un bloc de branche gauche. Ces études montrèrent une amélioration des paramètres de la fonction ventriculaire gauche, des résultats déclarés par les patients et de la capacité à l'exercice. Une étude montra une diminution des hospitalisations due à l'insuffisance cardiaque ainsi qu'une diminution de la mortalité.

L'utilisation au CUSM de la SBV lors de blocs cardiaques

À ce jour, la SBV n'a pas été utilisée au CUSM comme stimulation *de novo* chez les patients avec un bloc AV, sans insuffisance cardiaque.

Coût et impact budgétaire

Le coût actuel d'un stimulateur biventriculaire à trois électrodes est de 8 470$ comparé à 3 758$ pour un stimulateur ventriculaire droit classique à double chambre. Le coût total pour l'implantation d'un nouveau stimulateur biventriculaire est de 11 073$, comparativement à 5 937$ pour un nouveau stimulateur classique à double chambre. Ainsi, le coût additionnel pour le CUSM pour l'implantation d'un stimulateur

biventriculaire comparée à l'implantation d'un stimulateur classique à double chambre serait de 5 116$ par patient.

CONCLUSIONS

- Les preuves disponibles concernant l'utilisation de la SBV chez les patients avec un bloc AV sont faibles en termes du nombre d'études identifiées, de la taille relativement réduite des échantillons, de l'absence de résultats cliniques significatifs et de la courte période de suivi de chaque étude.

- Chez les patients avec une FEVG normal, l'utilisation de la SBV comme mode initial de stimulation chez les patients avec un bloc AV n'est pas supportée car les preuves ne montrent pas de différence significative au niveau des résultats cliniques finaux, comparée à la SVD.

- Chez les patients avec une faible FEVG, soumis à une stimulation cardiaque *de novo,* et chez ceux avec une insuffisance cardiaque subissant un rehaussement par rapport à la SVD, il existe des preuves assez cohérentes d'améliorations modérées au niveau de la fonction ventriculaire (augmentation de la FEVG, volume systolique réduit à la fin de l'éjection) et une amélioration modérée des symptômes (score NYHA, évaluation de la marche et qualité de vie). Il est noté que ces études incluaient un nombre substantiel de patients présentant initialement des caractéristiques qui sont une indication pour une SBV lors d'insuffisances cardiaques, , et par conséquent, n'apportent pas de preuves concernant le seul risque d'un bloc AV contribuant à l'insuffisance cardiaque.

- En 2013, les lignes directrices de la Canadian Cardiovascular Society (CCS) émettaient aussi à une conclusion similaire à celle de notre rapport en termes de qualité de la preuve. En se basant sur l'étude BLOCK-HF, seulement, la CCS notait que la qualité de la preuve était modérée. Néanmoins, ils ont émis une "recommandation conditionnelle" selon laquelle la SBV "peut être considérée chez les patients montrant une nouvelle apparition d'un bloc AV de haut degré exigeant une stimulation chronique ventriculaire droite, avec des indices et/ou des symptômes d'insuffisance cardiaque et une FEVG $\leq$ 45%". Les lignes directrices de la CCS soulignaient que l'étude BLOCK-HF incluait uniquement les patients avec des implantations *de novo* et que les résultats pourraient ne pas s'appliquer aux patients déjà stimulés de façon chronique. De plus, elles notaient que la plupart des patients dans l'étude BLOCK-HF montraient des symptômes d'insuffisance cardiaque. Ces remarques sont similaires à nos propres observations concernant les études randomisées sur les implantations *de novo* chez les patients avec bloc AV et une faible FEVG.

- Il est à noté que contrairement aux documents des lignes directrices, 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.

RECOMMANDATIONS

- Chez les patients avec un bloc AV et une FEVG normal, l'utilisation de la SBV comme mode initial de stimulation chez les patients avec un bloc AV n'est pas recommandée.
- Chez les patients avec un bloc AV et une faible FEVG, les preuves sont insuffisantes pour justifier l'utilisation de routine de la SBV, que ce soit pour une implantation *de novo* ou un rehaussement par rapport à la SVD.
- Étant donné la rareté des preuves à ce jour, tout utilisation de la SBV chez les patients avec un bloc AV et une insuffisance cardiaque devrait être conditionnelle à la documentation des critères de sélection des patients et des résultats patients (voir le Rapport 77 pour plus de détails).

USE OF BIVENTRICULAR PACING IN ATRIOVENTRICULAR HEART BLOCK

1. BACKGROUND

1.1 Heart Block

Heart block or atrioventricular (AV) block is a conduction disorder where the electrical impulse from the heart's upper chambers (atria) to the lower chambers (ventricles) is impaired or blocked. There are three degrees of AV heart block (**Appendix C**). Patients with a third-degree heart block (the most severe) are at risk of sudden cardiac arrest and death. This type of heart block is an indication for cardiac pacing.[4]

1.2 Right ventricular pacing and Bi-ventricular pacing

Right ventricular pacing (RVP) has been an effective treatment in the management of patients with different indications including sick sinus syndrome[5] and AV conduction disorders (**Appendix C**). However, some studies have suggested that RVP can cause left ventricular dysfunction, the most common cause of heart failure, by inducing ventricular dyssynchrony.[6] Furthermore, this detrimental effect of RVP on left ventricular function may be aggravated in patients with pre-existing left ventricular dysfunction.[7] Biventricular pacing (BVP) [also known as cardiac resynchronization therapy (CRT)] has been found to reduce ventricular dyssynchrony in certain heart failure patients and it has been hypothesized that BVP may better preserve left ventricular function in patients with third degree atrioventricular heart block. There has thus been a growing interest in comparing biventricular pacing (BVP) to RVP as a primary pacing choice for AV block patients.

However, the evidence for the routine use of BVP in heart block patients remains inconsistent,[8,6,9,10] and this health technology assessment report was undertaken to review the current state of the evidence for the use of BVP versus RVP in heart block patients, differentiating between those with and without pre-existing left ventricular dysfunction.

Ms. Ann Lynch, the Associate Director General for clinical operations in the Adult Missions at McGill University Health Centre (MUHC) requested this health technology assessment report for BVP use in AV heart block patients. Although BVP is being used at the McGill University Health Centre (MUHC) for the management of heart failure, it has not been used in the management of AV block without heart failure to date.

2. OBJECTIVES

The objectives of this report are to

- Review the evidence in terms of efficacy and safety for the use of BVP, as either a *de novo* implant or as an upgrade, for the management of AV heart block;
- Estimate the budget impact of using BVP for the treatment of heart block at the MUHC.

Evaluation of the use of BVP for the management of patients with heart failure is reported separately.[11]

3. METHODS

3.1 Literature search and quality assessment

We carried out a search for relevant randomized controlled trials (RCTs), observational studies, systematic reviews and meta-analyses reporting on efficacy, safety and cost-effectiveness for BVP in heart block patients. We also made a search for relevant clinical guidelines. The search for randomized controlled trials and observational studies was limited to the databases maintained by the Cochrane Library and PubMed. We also searched for randomized controlled trials in progress from ClinicalTrials.gov. We carried out a search for health technology assessment (HTA) reports in the databases maintained by York University (http://www.york.ac.uk/inst/crd/), by the National Institute for Health Research (NIHR) (http://www.hta.ac.uk/), and the US Agency for Healthcare Research and Quality (AHRQ) (http://www.ahrq.gov/research/findings/ta/index.html).

We used the following search keywords to identify studies evaluating the initial implantation of BVP/CRT in AV block patients versus RV pacing:

(Biventricular pacing [Title/Abstract] OR cardiac resynchronization therapy [Title/Abstract] OR biventricular pacemaker [Title/Abstract]) AND (heart block[Title/Abstract] OR AV block[Title/Abstract] OR atrioventricular block[Title/Abstract] OR AV-block[Title/Abstract] OR bradycardia[Title/Abstract]).

A flowchart summarizing the search for studies of BVP as the initial pacing mode is presented in **Figure 1.**

We used the following search keywords to identify studies on the upgrade from RVP to CRT versus the *de novo* implantation of CRT:

(biventricular pacing[Title/Abstract] OR biventricular pacemaker [Title/Abstract] OR cardiac resynchronization therapy[Title/Abstract] OR BiV stimulation[Title/Abstract])) AND (upgrade[Title/Abstract] OR upgrading [Title/Abstract]).

We had to drop the search terms related to "AV block" to identify relevant upgrade studies, as study keywords sometimes mentioned heart failure rather than AV Block. A flowchart summarizing the search for studies of an upgrade from RVP to BVP is given in **Figure 2.**

The excluded RCTs and observational studies from the two searches are listed in a web page appendix**.**

The search was conducted by two of the authors (ES and LS). The last search was conducted on July 26, 2015. We retained only studies published in English and in adult subjects.

The quality of the RCTs 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, and incomplete outcome data using the Cochrane Collaboration's tool for assessing risk of bias.[12] Each entry for these categories assesses the risk of bias as 'low', 'high', or 'unclear'. We also evaluated if there is potential conflict of interest attributable to sources of funding. The risk of bias in the observational studies was assessed using the Newcastle-Ottawa scale.[13] The risks of bias ratings were carried out by two co-authors (LS and NA).

We used GRADE guidelines to assess the quality of the evidence by evaluating the following criteria: 'Risk of bias', 'Inconsistency', 'Imprecision', 'Indirectness' and 'Publication bias'.[14] The results were summarized in **Appendix D.**

We chose not to do any meta-analyses as few studies (typically a maximum of two) reported comparable outcomes.

3.2 Cost analysis

Average cost for the procedures and equipment for BVP and RVP implantation at the MUHC were obtained from Nathalie Comtois, Mona Black and Peggy Verhoef from the Division of Cardiology at the MUHC. The cost analysis includes the costs of the operating room, stay in the cardiac care unit, and the peri-operative procedures.

4. LITERATURE REVIEW

Our systematic review will focus on 2 types of studies:

- Studies comparing RVP to BVP as initial pacing: seven RCTs[8-10,15-19] (summarized in **Section 4.1**)
- Studies comparing the upgrade from RVP to BVP: two RCTs[20,21] and one observational study[22] (summarized in **Section 4.2**)

We also evaluated two clinical guidelines for BVP use in adult patients with AV block.[23,24] We found no health technology assessment reports on the use of BVP in AV block patients.

4.1 RVP versus BVP as initial pacing

As RVP is thought to adversely affect LV function and induce ventricular dyssynchrony, the primary outcomes of most trials included in our review were measures of LV function (LVEF, LVESv, LVEDv) and ventricular dyssynchrony (QRS width, IVMD, LV dyssynchrony index). The definitions and normal values of these parameters are summarized in **Appendix Table C-1**. Secondary outcomes included quality of life score and 6 minute walk test. A minority of studies reported on outcomes such as mortality or hospitalization.

We chose to stratify the included studies by the mean baseline left ventricular ejection fraction (LVEF), based on the hypothesis that pre-existing left ventricular dysfunction may aggravate the effect of RVP on left ventricular function. LVEF is a measure of the percentage of blood pumped out of the left ventricle of the heart with each contraction, with values <40% indicative of left ventricular dysfunction.[25] It has been reported that baseline LVEF was associated with the occurrence of left ventricular (LV) dyssynchrony during RVP treatment; for example, Pastore et al, found that LV dyssynchrony occurred in 45% of patients with normal LVEF (>55%), in 93% with moderately reduced LVEF (35-55%), and in all patients with severely reduced LVEF (<35%).[7]

4.1.1 RCTs of heart block patients with normal LVEF at baseline

We identified four RCTs of patients with mean normal LVEF at baseline (≥55%): Albertsen et al,[15,16] Yu et al (PACE),[17,26] PREVENT-HF,[18] and BIOPACE.[9,10] Study results are summarized in **Table 1,** patient characteristics are summarized in **Appendix Table A-1**, and risk of bias in individual studies in **Appendix Table B-1**. **Table 1** reports the results for all trials except BIOPACE,[10] an unpublished study. Below we provide some salient points from each of these four studies.

- The study by **Albertsen et al.**[15,16] was a single blind RCT conducted in patients with high degree AV block randomized to RVP or BVP (n=50, mean age 76 years, mean LVEF 60%, majority were in NYHA Class I/II, predominately male with hypertensive or ischemic aetiology, QRS was much narrower in RVP than in BVP group, 117 vs. 143 msec). After a follow-up of 3 years, there was no significant statistical difference between the two groups in LVEF (53% in RVP vs. 58% in BVP, p=0.19). There was also no difference in LV dyssynchrony, LV remodelling or measurements of clinical heart failure (N-terminal pro-brain natriuretic peptide, 6 minute walking test, and NYHA class) between the two groups.

- The **PACE study,**[17,26] a double blind, randomized multicentre study (n=177, mean age 47-49 years, mean LVEF 62%, QRS duration 107 msec, mean LV dyssynchrony 12-14 msec), found after a 24 month follow-up that mean LVEF remained normal in both groups, although it was significantly lower in the RVP group compared to the BVP group (53.8% vs. 62.9%, p<0.001) (**Table 1**). LVESv was also significantly lower in the RVP group. Subgroup analyses (by pacing indication, age, sex, QRS duration, and comorbidity) of the differences in LVEF or LVESv did not reveal any predictor of these primary endpoints. Hospitalization for heart failure was similar in the two groups and there were 4 deaths in the RVP group and 3 in the BVP group. The two groups did not show any difference in distance on the 6-minute walk test, or on the QoL score.

- The **PREVENT-HF study**[18] was a randomized, double-blinded trial conducted in AV block patients (n=108, mean age 71 years, mean LVEF 56%, 72% male, majority in NYHA classI/II). At 12 months of follow-up, both groups (RVP and BVP) showed no significant difference in LVEDv, the primary outcome (**Table 1**). There was also no difference in mean LVESv, LVEF or in a composite endpoint (cardiac mortality or hospitalization due to cardiovascular causes) (HR 0.78, 95% CI 0.27 to 2.23).

- **BIOPACE**[9,10] was a randomized, controlled, single blind trial (n=1810, mean age 74 years, 68% male, 17% left-bundle branch block (LBBB), mean LVEF 55%, mean QRS duration 118 msec). After an average of 5.6 years of follow up, the preliminary results reported an inconclusive hazard ratio tending to favour BVP over RVP in reducing the primary end point (i.e. composite of death or first hospitalization due to heart failure). Sub-analysis by LVEF lower or higher than 50% produced similar results. The secondary outcomes (cardiovascular death, LVEF, QoL, exercise capacity) have not yet been reported. To date, the final results have not been published in peer reviewed articles, preventing us from retrieving more information on the randomization process, loss to

follow-up and subgroup analyses as not all enrolled patients had AV block as pacing indication (only 22% had 3rd degree AV block).

Summary of efficacy results from RCTs of heart block patients with normal LVEF at baseline

The abovementioned RCTs show that in patients with normal baseline LVEF, the short-term follow-up (max 3 years) reveals that the two modes of pacing show no clinically significant difference on LV function variables (LVEF, LVESv, LVEDv), ventricular synchrony, patient-reported outcomes (QoL score), and exercise capacity (6MWT). Moreover, outcomes such as mortality rate/hospitalization for HF were also similarly affected by RVP and BVP on long term follow-up (5.6 years).

4.1.2 RCTs of heart block patients with low LVEF at baseline

We identified three RCTs of patients with low mean LVEF at baseline (<55%): HOBIPACE,[8] COMBAT,[27] and BLOCK-HF.[19] Study outcomes are summarized in **Table 2**, while study characteristics and risk of bias in individual studies are summarized in **Appendix Table A-2** and **Table B-1**, respectively.

- **HOBIPACE** [8] is a randomized cross-over trial conducted in AV block patients with LV dysfunction (n= 30, mean age 70 years, 77% male, 63% with LBBB, and 57% with ischemic etiology, mean LVEF 26%, mean QRS 174 msec, mean NYHA class III). Among these 30 patients, 6 had an ICD implanted in addition to the pacemaker due to atrial fibrillation. After 3 months of follow-up, LVEF had increased in the BVP group versus RVP group, but both values were within the severely impaired range (28.5 ± 11.2% in RVP vs. 34.8 ± 8.9% in BVP, p<0.05). The same comment applies to QoL and exercise capacity [**Table 2**]. The mean QRS interval was wide in both groups although it was more pronounced in the RVP group (193 msec) than in the BVP group (151 msec, p<0.001). Mean interventricular mechanical dyssynchrony (IVMD) was higher in the RVP group (47 msec) than in the BVP group (8 msec; p<0.001).

- **COMBAT**[27] is a double blind, randomized, multicentre trial of AV block patients, most of whom had Chagas disease, who were crossed over between RVP and BVP (n=60, mean age 57-59 years, mean LVEF 29%, mean QRS duration 154 msec, 67% males, 83% in NYHA class III/IV). We extracted data from the first phase of 3-months only, i.e. prior to the cross-over. After a mean follow-up of 3 months, LVEF had increased in the BVP group versus RVP group, but both values were within the severely impaired range (21.9

% in RVP vs. 30.4% in BVP, p=0.018). LVESv was higher in the RVP group than in the BVP group (224 ml vs. 160 ± 49 ml, p=0.08), and again both values are greater than the normal cut-off. The mean NYHA class was significantly worse in the RVP than in the BVP group (2.5 ± 0.6 vs. 1.8 ± 0.6, p=0.006), and the QoL score was significantly lower in RVP than in BVP group (19.8 ± 8.1 vs. 35.2 ±18, p=0.008). No significant differences were observed in LVEDv, 6MWT or the VO_2max between the two groups. The authors found a higher mortality rate in the RVP group than in the BVP group (45% vs. 6.5%), although hospitalizations for HF were similar (14% vs. 10%), hence it is unclear how many of the deaths were cardiac-related. In addition, the cross-over nature of the study makes it difficult to isolate the effect of each pacing phase on the final outcomes, given that the mortality rate was only reported for the end of the study. Finally, these results may not be generalizable to patients without Chagas disease.

- **BLOCK-HF** [19] is a randomized controlled, double-blind trial conducted among patients who had an indication for ventricular pacing with AV block, (n= 484; mean age 73 years; mean LVEF 40%; 75% male). The mean LVEF was thus higher than in the other two studies of patients with low mean LVEF. Correspondingly, patients appeared to have less severe cardiac dysfunction characteristics- QRS interval of 124 msec; predominantly in NYHA Class II; 33% had LBBB; and 45% had ischemic etiology. After a mean of 37 months of follow-up, BVP was superior to RVP in reducing the composite of death from any cause, an urgent care visit for heart failure that required intravenous therapy, or ≥15% increase in the LVESv (HR 0.73, 95% CI 0.58, 0.91) [**Table 2**]. However, there was no difference in the percentage of urgent care visits for HF in both groups (15.8 %, 38/241 in RVP vs. 16.4%, 40/243 in BVP). In addition, there was no significant difference between the two procedures in reducing mortality alone (HR 0.83, 95% CI 0.59, 1.17).

Summary of efficacy results from RCTs of heart block patients with reduced LVEF at baseline

In this set of studies, the RCTs were conducted in patients with pre-existing LV dysfunction and heart failure-like symptoms. In this population of patients, BVP resulted in a statistically significant improvement compared to RVP in LV function parameters (LVEF, LVESv, LVEDv), though the clinical significance of these improvements is unclear as the mean values fall outside the normal range even at follow up. Improvements were also reported exercise capacity (6MWT) and in patient-reported outcomes (QoL score), in the short-term follow-up. The BLOCK-HF study found no difference between RVP and BVP in mortality rate or urgent care visits for HF during a median follow-up of 3 years.

4.2 Upgrade from RVP to BVP

Our systematic review included 2 RCTs and one observational study evaluating an upgrade from RVP to BVP in HF patients. We summarized the results in **Table 3**. Study characteristics and risk of bias are presented in **Appendix Table A-3**, and **Appendix Table B-1** and **Table B-2**, respectively.

- **Höijer et al.**[20] conducted a randomized cross-over trial in patients with RVP upgraded to BVP (n=10), median age 68 years, 80% male, majority in NYHA class III, median QRS duration 235 msec, 60% had AV block as initial pacing indication and 40% had sinus node disease, bradycardia and atrial fibrillation as pacing indication). All patients had LVEF <25%. After 6 months of follow-up, the results showed a significantly greater improvement in 6MWT in patients receiving BVP (240 m in RVP vs. 400 m in BVP, p<0.05) [**Table 3**]. The levels of brain natriuretic peptide (pro-BNP) were statistically significantly reduced in the BVP group (median value of 5064 ng/L in RVP vs. 3030 ng/L in BVP, p<0.05) though the clinical significance of this difference is unclear as both values correspond to severe HF.[28] The LV diameter parameters remained similar in both groups. The LVEF percentage and the QRS duration after follow up were not reported.

- **Leclercq et al.**[21] conducted an upgrade randomized cross-over trial in RVP patients (n=44, mean age 73 years, 90% were males, mean LVEF 26%, all in NYHA class III, mean QRS duration of 206 msec, all in AV block). After 3 months of follow-up, BVP was superior to RVP in shortening QRS duration (200 ± 20 msec in RVP vs. 153.5 ± 25.5 ms in BVP, p<0.05), reducing interventricular dyssynchrony (40 ± 36 msec in RVP vs. 0.8 ± 34 msec in BVP, p<0.05), improving QoL scoring (28 ± 23 in RVP vs. 50 ± 20 in BVP, p<0.05) and improving 6MWT (324 ± 149 m in RVP vs. 386 ± 99 m in BVP, p<0.05) [**Table 3**]. There were no significant differences reported in mean LVEF (29.5 ± 11% in RVP vs. 29 ± 11% in BVP, p=0.1).The all-cause mortality rate (21% in RVP vs. 8% in BVP) and hospitalization rate due to HF (47% in RVP vs. 4% in BVP, p=0.01) were higher in the RVP than in the BVP group.

- **Sideris et al.**[22] conducted a prospective cohort study to monitor the evolution of RVP patients after upgrade to BVP (n=37, mean age 71 years, mean QRS duration 157 msec, mean LVEF 26%, predominately in NYHA class III). The indications for RV pacing were complete heart block (HB), atrial fibrillation (AF) and/or symptomatic bradycardia. Among these patients, 29 were RV paced, and 8 had RVP/ICD at the time of upgrade. After 6 months of upgrading to BVP, there was improvement in mean QRS duration

(129 vs. 157 ms, p<0.001), mean LVEF (31 vs. 26%, p<0.001), mean NYHA class (2.5 vs. 3.3, p<0.001) and 6MWT (321 vs. 246 m, p<0.001).

Summary of efficacy results from the upgrade studies

The studies evaluating an upgrade from RVP to BVP were conducted in patients paced with RVP (mostly having AV block as initial indication) and with heart failure symptoms. The upgrade to BVP showed improvement in LVEF, ventricular synchrony, patient-reported outcome (QoL score) and exercise capacity (6MWT), during short-term follow-up. When reported, mortality/hospitalization due to HF were higher in RVP than in the BVP group.

4.3 Safety

In general, the infrequent complications of pacing reported in the above studies occur with approximately equal frequency in RVP and BVP (Table 4). However, four reports (14, 15, 16, and 19) record phrenic nerve stimulation in association with BVP compared to only one such event with RVP. Given these very limited data, and the lack of evidence in the literature directly comparing RVP to BVP, the relative safety of RVP over BVP remains inconclusive.

4.4 Risk of bias in individual studies

4.4.1 Threats to internal validity

Selection and confounding bias

Improper randomization and allocation concealment may subvert randomization and introduce bias. All trials except HOBIPACE[8] reported random sequence generation (**Table B-1**). However, none of the trials reported allocation concealment. In addition, the small sample size of several studies may prevent complete randomization and also induce bias.

Performance and detection bias (Information bias)

Lack of blinding among patients, care providers and outcome assessors can lead to systematic differences in patient-reported outcomes and care provided, and differential misclassification of outcomes. In the trials of HOBIPACE,[8] BIOPACE,[9] Höijer et al,[20] and Leclercq et al,[21] the research personnel were not blinded and thus there is a risk of both performance bias (difference in care provided) and detection bias (differential measurement of outcomes) which may distort the true risk association.

Attrition bias

Loss to follow-up that is associated with both exposure and outcome can result in a biased risk estimate. Most trials provided inconclusive results owing in part to the relatively small sample size. Only BIOPACE[9] and BLOCK-HF[19] had substantial sample sizes of 1800 and 700 patients respectively. However, in the BLOCK-HF trial there was a significant potential for attrition bias because 140 patients in the BVP arm and 224 patients in the RVP arm either withdrew, died or crossed-over. Although an intention to treat analysis was applied, 83 patients in the BVP group and 71 patients in the RVP group were censored for the analysis of the primary end point due to missing LVESv.[19]

Conflict of interest

Four of the seven RCTs (besides HOBIPACE[8], Höijer et al.[20] and Leclercq et al.[21]) received funding from the device manufacturers (Medtronic) raising concerns for the impact of conflict of interest on the reporting and interpretation of results.

4.4.2 Threats to external validity

The COMBAT[27] trial was the only trial to report a significant difference in mortality between the RVP and BVP groups. However, the majority of participants had Chagas disease, and the overall mortality rate of 25% after a mean follow-up of only 17 months suggests that these results may not be generalizable to populations where Chagas disease is uncommon.

4.5 Summary of clinical practice guidelines

In 2007, the European Society of Cardiology in collaboration with the European Heart Rhythm Association concluded in their guidelines that in patients with AV block and narrow QRS interval, biventricular stimulation is superior to right ventricular apical pacing in terms of contractile function and LV filling.[23] However, they do not mention the clinical significance of this observation. As our review has shown, improvement in LV function parameters does not necessarily translate into clinically meaningful improvements.

In 2013, referring to findings from the BLOCK-HF trial, the Canadian Cardiovascular Society suggested that BVP might be considered for patients with new-onset high-degree AV block requiring chronic RVP, signs and/or symptoms of heart failure, and LVEF ≤45%.[24] This is more in keeping with our own observations in this systematic review.

5. BVP FOR HEART BLOCK AT THE MUHC

The standard of care at the MUHC for atrioventricular block is right ventricular pacing (RVP). To date, BVP has never been used for *de novo* pacing or as an upgrade in AV block patients without heart failure symptoms at the MUHC according to Dr Vidal Essebag.

6. INCREMENTAL COST OF BVP VS RVP

The current cost of a BVP device with three leads at the MUHC is $8,470, compared to $3,768 for a dual-chamber standard pacemaker (**Table 5**). The total cost for implanting a new BVP is $11,073 compared to $5,947 for a new dual-chamber standard pacemaker, after accounting for procedure costs such as use of operating room, over-night stay in the cardiac care unit, and preoperative cost. Thus, the incremental cost to the MUHC of use of a new BVP device compared to RVP would be $5,116 per patient.

Table 6 provides the total number of RVP implanted (either first implantation or upgrade) between 2010 and 2015 at the MUHC. It should be noted that only a minority of these corresponds to AV block patients.

7. DISCUSSION

Our systematic search highlighted that there are two distinct groups of studies that have attempted to evaluate BVP for *de novo* pacing in AV block patients – those which recruited patients with a normal LVEF at baseline vs. those that recruited patients with low LVEF at baseline. The conclusions in these two groups are quite different. Studies of patients with normal LVEF consistently found that *de novo* implantation of BVP does not appear to offer any significant benefit over RVP. On the other hand, studies of patients with low LVEF often included a substantial number of patients with characteristics that are indications for BVP in heart failure [e.g. wide QRS, LBBB, Chagas's disease (in the COMBAT study) and ischemia]. It is therefore perhaps not surprising that these studies generally found a benefit of BVP over RVP as it has been demonstrated that BVP is beneficial to certain severe HF patients.[11,29]

Two RCTs that evaluated upgrading RVP patients to BVP also tended to include patients with low LVEF and concluded that BVP was more beneficial than RVP. In these latter studies, patients at baseline had characteristics that are predictors of CRT response,[11] and therefore it could be expected that they might benefit from upgrading to CRT. In fact, these patients had AV-block at the time of initial RV pacing but developed LV dysfunction

over time. This chronic RVP-induced cardiomyopathy does not occur in all RV-paced AV block patients; it rather depends on many factors such as the dose of pacing or asynchrony induced by RVP (pacing rate >40%),[30] the duration of pacing and the presence of certain clinical indicators at the baseline such as an impaired ventricular function, symptomatic HF or myocardial infarction.[31] Moreover, long-term follow-up of AV block patients paced with RVP, showed no significant effect of right ventricular apical pacing on the LV structural changes, which could affect the LV function.[32]

Though the evidence accrued so far is largely based on smaller RCTs, there was one large trial of 1800 patients (BIOPACE) with the longest follow-up duration of 5.6 years. This trial, which was among patients with a low mean LVEF, concluded that there was no difference in health outcomes between RVP and BVP groups, but detailed results of this trial are yet to be published in peer-reviewed literature.

Another limitation of the evidence is the crossover model used in some studies. A significant disadvantage of this type of design is the carryover effect, defined as the effect of the pacing from the previous time period on the response at the current time period. Therefore, for example, an HF hospitalization occurring during RVP phase could potentially be attributed to the previous BVP phase or change from BVP to RVP.

Following the GRADE approach, the overall quality of the evidence for the impact of BVP on critical outcomes was rated as either “Low” or “Very Low” (**Appendix D**).

8. CONCLUSIONS

- The available evidence regarding the use of BVP in AV block patients is weak in terms of the number of studies identified, the relatively small sample sizes, and the lack of meaningful clinical outcome data and short duration of follow-up within each study. Based on the GRADE guidelines the quality of the evidence was rated as Low to Very Low on all outcomes.

- In patients with normal LVEF, the use of BVP as an initial mode of pacing in AV block patients remains unsupported as the evidence shows no significant difference in clinical endpoints compared to RVP.

- In patients with low LVEF undergoing *de novo* pacing and in those with HF undergoing an upgrade from RVP, there is fairly consistent evidence of modest improvement of ventricular function (increased LVEF, reduced end systolic volume), and modest symptomatic improvement (NYHA score, walk test and QoL). It should be noted that

these studies included a substantial number of patients with characteristics that are indications for BVP in heart failure at baseline, and therefore do not provide evidence regarding the independent risk of AV block in contributing to heart failure.

- The 2013 guidelines for use of BVP published by the Canadian Cardiovascular Society (CCS) also reached a similar conclusion to our report in terms of the quality of evidence. Based on the BLOCK-HF trial alone, the CCS noted that the quality of evidence was "moderate". None the less, they issued a "Conditional Recommendation" that BVP "might be considered for patients with new-onset high-degree AV block requiring chronic RV pacing, signs and/or symptoms of HF, and LVEF≤ 45%". The CCS guideline points out that the BLOCK-HF trial enrolled only those with de novo implants and its results may not apply to those who are already chronically paced. Further it notes that most patients in the BLOCK-HF trial had symptomatic HF. This is similar to our own observation above regarding RCTs of de novo BVP implantation in AV Block patients with low LVEF.

- 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 BVP and where there is not.

9. RECOMMENDATIONS

- In AV block patients with normal LVEF, the use of BVP as an initial mode of pacing in AV block patients is not recommended.

- In AV block patients with low LVEF, there is insufficient evidence to justify the routine use of BVP either for *de novo* implantation or for an upgrade from RVP.

- Given the paucity of evidence available so far, any usage of BVP in AV block patients with heart failure should be **conditional** on documentation of patient selection criteria and patient outcomes (see Report 77 for details).

TABLES

Table 1. Outcome of the trials comparing right versus bi-ventricular initial pacing in AV block patients with normal baseline LVEF

	Albertsen et al. [15,16]		Yu et al. [17,26]		PREVENT-HF[18]	
	RVP	**BVP**	**RVP**	**BVP**	**RVP**	**BVP**
Sample size	24	24	88	89	87	86
Mortality (n) (%)	5 (21%)*	5 (21%)*	4 (4.5%)	3 (3%)	1 (1%)	NR
Hospitalization due to HF(n) (%)	NR	NR	10 (11%)	8 (9%)	8 (9%)	3 (3%)
Ventricular dyssynchrony						
QRS duration msec (mean, SD)	155 (28)[a]	137 (23)	NR	NR	NR	NR
LV dyssynchrony index (msec) (mean, SD)	32(17)[a]	23(17)[a]	NR	NR	NR	NR
LV function						
LVEF (%)	Median 57(Quartiles 52-61)[a]	Median 60 (Quartiles 55-63)	Mean 53 (SD 10)[b]	Mean 63(SD 8.8) [b]	Mean 56.2 (SD 14.5)	Mean 60.1 (SD 9.6)
LVESv ml (mean, SD)	NR	NR	38.3(20.3)[b]	25.3(10.2)[b]	44.7 (25.3)	42.2 (23.6)
LVEDv ml (mean, SD)	NR	NR	NR	NR	104.4 (36.4)	99.4 (30.2)
Exercise capacity						
6-MWT (m) (mean, SD)	488 (91)[a]	509(66)[a]	363(117)	361(105)	NR	NR
Peak oxygen consumption (ml/min/kg) (mean, SD)	NR	NR	NR	NR	NR	NR
Quality of life MLHF score (mean, SD)	NR	NR	No significant difference in SF-36 score between the 2 groups		NR	NR

[a] p<0.05 difference between baseline and follow-up values within a treatment group, [b] p<0.05 difference between treatment groups.* Deaths reported on the second follow-up at 3 years. NR: Not reported.

Table 2. Outcome of the trials comparing right versus bi-ventricular initial pacing in AV block patients with low baseline LVEF

	HOBIPACE[8]		COMBAT[27] ‡		BLOCK-HF [19]§	
	RVP	**BVP**	**RVP**	**BVP**	**RVP**	**BVP**
Sample size	30 (crossover)		31	29	241	243
Mortality n (%)	1 (3%)	1 (3%)	13 (45%)[b]	2 (6.5%)[b]	64 (26%)	52 (21%) HR 0.83 (0.59-1.17)
Hospitalization due to HF n (%)	NR	NR	4 (14%)	3 (10%)	63 (26%)	49 (20%) HR 0.68 (0.49-0.94)
Ventricular dyssynchrony						
QRS duration msec (mean, SD)	193 (25)[b]	151 (21)[a, b]	NR	NR	NR	NR
Interventricular mechanical delay (IVMD) (msec) (mean, SD)	47 (26)[b]	8 (24)[a, b]	NR	NR	NR	NR
LV function						
LVEF (%)(mean, SD)	28.5 (11.2)[b]	34.8 (8.9)[a, b]	21.9 (7.9)	30.4 (7.2)	NR	NR
LVESv ml (mean, SD)	160.2 (73.4)[b]	133.1 (66.5)[a, b]	224 (51)	160 (59)	NR	NR
LVEDv ml (mean, SD)	215.6 (76.2) [b]	196.3 (77.3)[a, b]	272 (51)	237 (90)	NR	NR
Exercise capacity						
6-MWT (m) (mean, SD)	NR	NR	430 (124)	428 (131)	NR	NR
Peak oxygen consumption (ml/min/kg) (mean, SD)	12.5 (2.9)[b]	14 (3)[b]	16.3 (8.2)	19.6 (4.5)	NR	NR
Quality of life MLHFscore(mean, SD)Ŧ	31.2 (20.7)[b]	25.3 (18.1)[b]	19.79 (8.15)[b]	35.24 (18.1)[b]	NR	NR

[a]p<0.05 difference between baseline and follow-up values within a treatment group, [b] p<0.05 difference between treatment groups. ‡: the values reported are those measured at the initial evaluation phase of the COMBAT crossover trial. §: the values reported are those measured only for pacemaker group (n=484).Ŧ The COMBAT authors had interchanged the direction of MLHF QoL scores (the higher is the better).

Table 3. Outcomes of studies of upgrade from right to bi-ventricular pacing in HF/AV Block patients

	Höijer et al[33]		Leclercq et al [34]		Sideris et al [22]
	RVP	**BVP**	**RVP**	**BVP**	
Sample size	10 (crossover design)		19	25	37
Mortality n (%)	NR	NR	4 (21%)	2 (8%)	NR
Hospitalization due to HF n (%)	NR	NR	9 (47%)[b]	1 (4%)[b]	Rate per 6 months: 0.7 (0.8)[a]
Ventricular dyssynchrony					
QRS duration msec (mean, SD)	NR	NR	200(20)[b]	153.5 (25.5)[b]	129.3 (9.5)[a]
Interventricular mechanical delay (IVMD) (msec)	NR	NR	40 (36)[b]	0.8 (34)[b]	NR
LV function					
LVEF (%)(mean, SD)	NR	NR	29.5 (11)	29 (11)	31.4 (6.7)[a]
LVESv ml (mean, SD)	NR	NR	NR	NR	111.9 (41.1)[a]
LVEDv ml (mean, SD)	NR	NR	NR	NR	
Exercise capacity					
6-MWT (m)	240[b]	400[a, b]	324[b]	386[b]	321 (101)[a]
Peak oxygen consumption (ml/min/kg) (mean, SD)	NR	NR	13 (3)	14 (3)	NR
Quality of life score (mean, SD) ₸	126[b]	221[a,b]	28 (23)[b] (MLHF score)	50(20)[b] (MLHF score)	NR

[a] p<0.05 difference between baseline and follow-up values within a treatment group, [b] p<0.05 difference between treatment groups. ₸Leclercq et al. had interchanged the direction of MLHF QoL scores (the higher is the better).

Table 4. Adverse events as cited in the RCTs.

	Albertsen et al[16,15]		Yu et al[17]		PREVENT-HF[18]		BIOPACE[10]		HOBIPACE[8]		COMBAT[27]		BLOCK-HF[19]		Leclercq et al.[21]	
Sample size	48		177		108		1810		30		60		484		44	
Implant failure	NR		16 out of initial total 193 (8%)		NR		131(7.4%, all BVP)		NR		4 out of initial total 68 (≈6%)		51 out of initial total 918 (5.5%)		12 out of initial total 56 (≈18%)	
	RVP (24)	**BVP (24)**	**RVP (88)**	**BVP (89)**	**RVP (58)**	**BVP (50)**	**RVP (908)**	**BVP (902)**	**RVP**	**BVP**	**RVP (31)**	**BVP (29)**	**RVP (241)**	**BVP (243)**	**RVP (19)**	**BVP (25)**
Pneumothorax	NR	NR	NR	NR	1 (2%)	1 (2%)	NR	NR	NR		NR	NR	NR	NR	NR	NR
Infection	NR	NR	NR	NR	NR	NR	10 (1.1%)	19 (2.1%)	NR		NR	1 (3.5%)	37 (5%)		3 (≈7%)	
Lead displacement	1 (4%)	4 (16%)	NR	NR	NR	NR	NR	NR	3(9%)		NR	2(7%)	25(≈4%)		NR	4 (16%)
Phrenic nerve stimulation	NR	3 (6%)	NR	7 (3%)	1 (2%)	3 (6%)	NR	NR	NR		NR	NR	NR		NR	1 (4%)
Other cardiac complications	NR	NR	3(3%) (ACS)	2 (2%) Stroke	1 (2%)	3 (6%)	NR	NR	NR		2 (6.5%) (AF)	2 (7%) (ICD)	9 (1.3%) (AF)		NR	

AF: Atrial fibrillation, BVP: Biventricular pacing, CI: Confidence interval, HF: heart failure, NR: Not reported, RVP: Right ventricular pacing.

Table 5: Cost of standard and biventricular pacemakers at the MUHC

Cost type	Pacemaker	
Device costs	**Standard**	**CRT-P**
Device		4,495
Single chamber	2,479	
Dual chamber	2,788	
Leads	490 each	3,975[a]
A. Total	**2,969-3,768**	**8,470**
Procedure-cost		
Initial implantation		
Use of operating room (unit cost x hour)	847 x 1= 847	847 x 1.5 = 1,271
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
Perioperation procedures (unit cost x patient)	323 x 1 =323	323 x 1 =323
B. Total	**2,179**	**2,603**
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
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
Perioperation procedures (unit cost x patient)	323 x 1 =323	323 x 1 =323
C. Total	**1,756**	**2,179**
Total cost (CAD)		
Initial implantation (A+B)	**5,947[a]**	**11,073**
Battery change/ re-implantation (A+C)	**5,524[a]**	**10,649**

[a]Cost for dual-chamber devices

Data provided by Mona Black, Nathalie Comtois, and Peggy Verhoef fromthe Electrophysiology/Pacemaker Lab at the Montreal General Hospital and the Cath Lab at the Glen, Division of Cardiology, MUHC

Table 6. Number of initial implants and replacements/upgrades of devices during the 2010-2015 fiscal years at the MUHC.

Type of device	Number of devices				
	2010-2011	**2011-2012**	**2012-2013**	**2013-2014**	**2014-2015**
Initial/re-implant or upgrade	**n**	**n**	**n**	**n**	**n**
Pacemakers					
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

Data provided by Mona Black, Nathalie Comtois, and Peggy Verhoef from the Electrophysiology/Pacemaker Lab at the Montreal General Hospital and the Cath Lab at the Glen, Division of Cardiology, MUHC

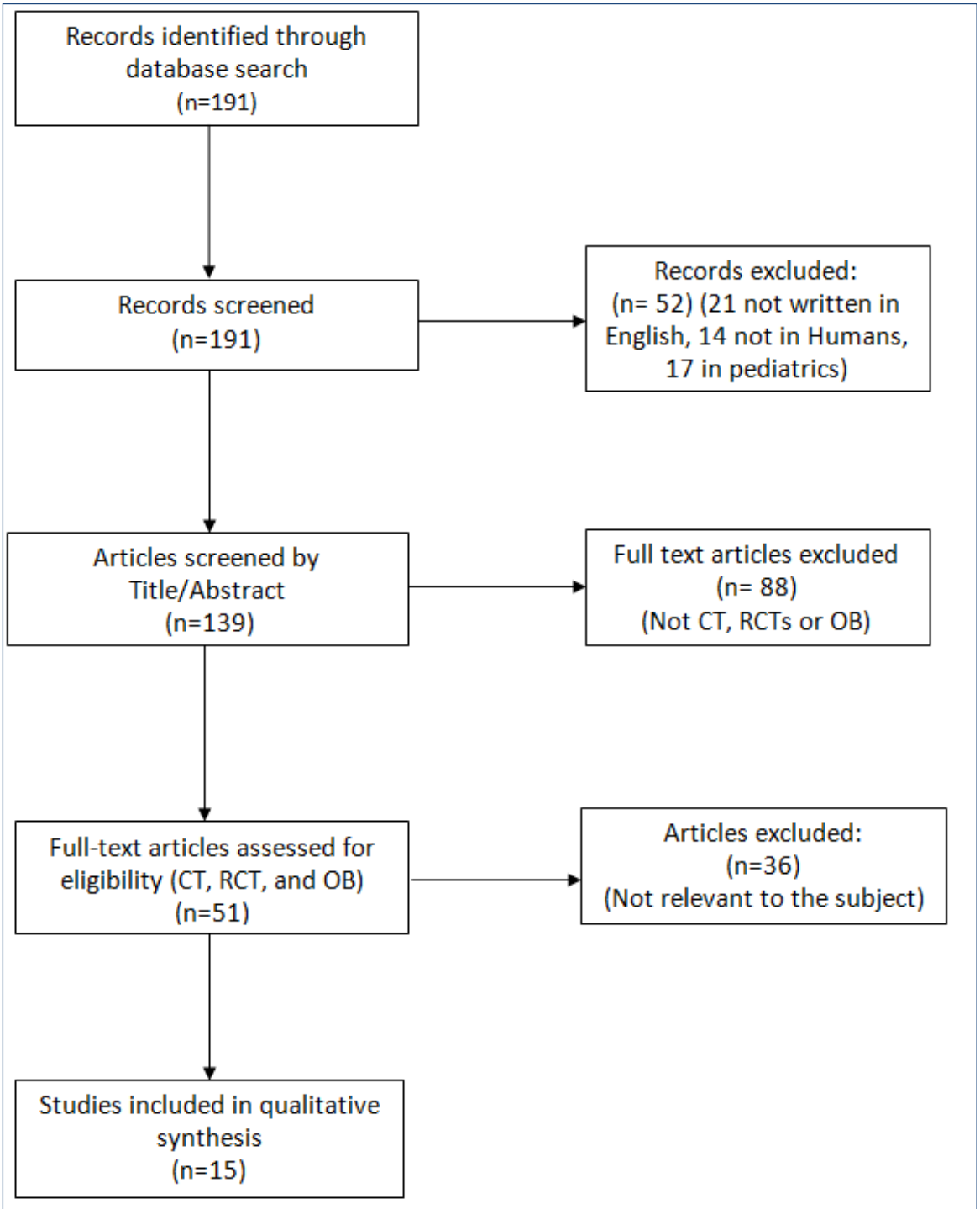

Figure 1. The flowchart of the literature search for the initial pacing mode.

CT: clinical trial, OB: observational studies, RCT: randomized clinical trial. The flow chart was adapted from the PRISMA diagram model[3]

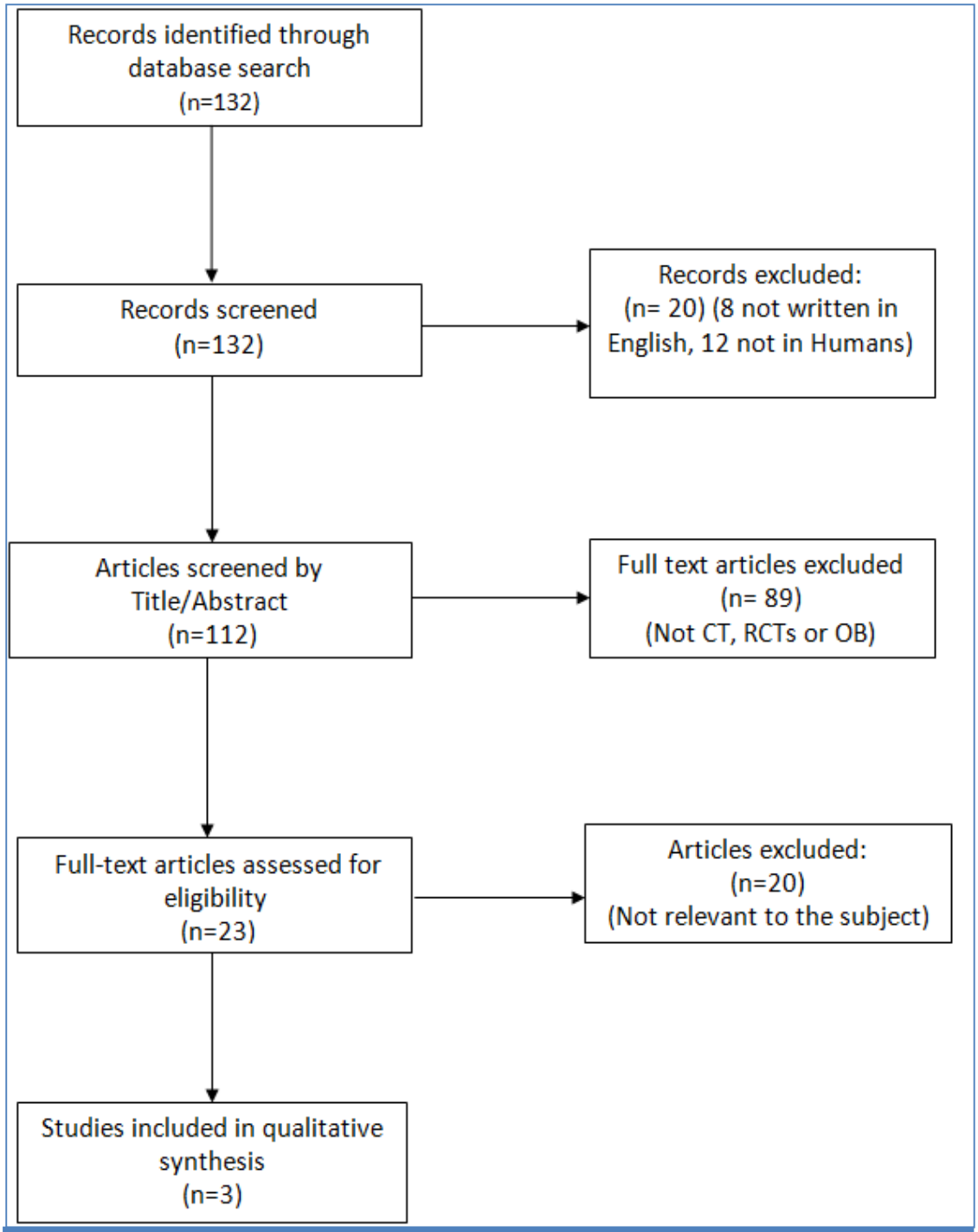

Figure 2. The flowchart of the search for upgrade to BVP studies.

CT: clinical trial, OBS: observational studies, RCT: randomized clinical trial. The flow chart was adapted from the PRISMA diagram model[3]

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APPENDICES

APPENDIX A : CHARACTERISTICS OF STUDIES INCLUDED IN REPORT

Table A-1: Study characteristics of trials comparing right versus bi-ventricular initial pacing in AV Block patients with normal baseline LVEF

	Albertsen et al.[15,16]		Yu et al. [17]		PREVENT-HF[18]		BIOPACE[9,10]	
Study design	RCT		RCT		Randomized, controlled, double-blind trial.		Controlled, randomized, single blind, parallel group trial	
Target population **Concise**	Patients with permanent or paroxysmal high grade AV block. Patients with grade 1 AV block, sick-sinus syndrome or atrial fibrillation were excluded		Patients with indication for pacing (sinus dysfunction or bradycardia due to advanced AV block)		Patients with Class I and/or Class IIa implantation criteria for acquired AV block patients who need ventricular pacing of at least 80%		Patients with Class I indications for permanent ventricular pacing in acquired AV block	
Intervention	BV pacing		CRT		BV pacing with/without ICD		BV pacing	
Comparator	RV pacing (DDD-R)		RVP (DDD-R)		RV pacing with/without ICD		RV pacing	
Country	Denmark		Hong Kong		Europe		Europe (98% patients), Tunisia, Australia, Canada	
Length of follow-up	3 years		12 months		12 months		Average 5.6 years	
Inclusion Criteria			Normal LVEF (>45%)		NYHA Class I-II		No restriction in NYHA classes, LV size, LVEF, QRS, etiology, etc	
Participants' Characteristics	**BVP**	**RVP**	**BVP**	**BVP**	**BVP**	**RVP**	**BVP**	**RVP**
N	25	25	50	50	87	86	902	908
Age (years), Mean (SD) or Median (min, max)	76 (71, 81)	76 (67, 81)	72 (9)	72 (9)	69 (11)	68 (11)	74 (9)	73 (9)
Sex male, %	68	68	68	68	53	56	69	67
NYHA Class								

Participants' Characteristics	**BVP**	**RVP**	**BVP**	**BVP**	**BVP**	**RVP**	**BVP**	**RVP**
I, n (%)	12 (48)	12 (48)	24 (48)	24 (48)	NR	NR	NR	NR
II, n (%)	9 (36)	12 (48)	26 (52)	26 (52)	NR	NR	NR	NR
III, n (%)	3 (12)	1 (4)	0	0	NR	NR	NR	NR
IV, n (%)	1 (4)	0 (0)	0	0	NR	NR	NR	NR
(History of) AF, %			10	10			25	25
LVEF (%), Mean (SD) or Median (min, max)	59 (47, 62)	60 (57, 61)	58 (12)	58 (12)	62 (7)	62 (7)	55(12)	56(12)
QRS interval (msec)*	143 (38)	117 (33)	121 (32)	121 (32)	107 (27)	107 (30)	118 (31)	119 (30)
LBBB/RBBB, %	12/NR	4/NR	NR	NR	NR	NR	17/NR	18/NR
Ischemic etiology, %	96*	92*	NR	NR	NR	NR	NR	NR

* Hypertensive or ischemic heart disease.

Table A-2: Study characteristics of trials comparing right versus bi-ventricular initial pacing in AV Block patients with low baseline LVEF

	HOBIPACE[8]	COMBAT[27]		BLOCK-HF [19]	
Study design	Randomized crossover trial	Randomized double blind crossover trial		Randomized, double-blind, controlled trial	
Target population	Patients with symptomatic bradycardia and impaired AV condition who need permanent ventricular pacing support	Non-paced patients with symptomatic HF and AV block		Patients who a high percentage of ventricular pacing because of atrioventricular block	
Concise Intervention	3 mths BVP	3 mths BVP		BV pacing with/without ICD	
Comparator	3 mths RVP	3 mths RVP		RV pacing with/without ICD	
Country	Germany	Brazil		US, Canada	
Length of follow-up	3 months	17 months ±10.5		37 months	
Inclusion Criteria	LVED diameter ≥60 mm and an LVEF≤40%	NYHA class II-IV, LVEF < 40%, AV block class I indication for DDD/DDDR pacing		NYHA class I, II, III; LVEF ≤50%	
Participants' Characteristics		**Group A (RVP)**	**Group B (BVP)**	**BVP**	**RVP**
N	30	31	29	349	342
Age (years), Mean (SD)	70 (8)	57.4 (15)	59.3 (13.3)	74 (10)	73 (10)
Sex male, %	77	67.7	62.7	77	73
NYHA Class	Mean class III (SD 0.6)				
I, n (%)		0	0	46 (13)	63 (18)
II, n (%)		5 (16.1)	5 (17.3)	208 (60)	184 (54)
III, n (%)		16 (51.6)	15 (51.7)	94 (27)	95 (28)
IV, n (%)		10 (32.3)	9 (31)	0	0
(History of) AF, %	37			52	54
LVEF (%), median or mean (SD)	26 (8)	29.2 (7.4)	30.1 (9.2)	40 (8)	40 (8)
QRS interval (msec)*	174 (42)	154 (13.1)	148 (16.4)	125 (32)	123 (31)
LBBB/RBBB, %	63/NR	NR	NR	35/21	30/22
Ischemic etiology, %	57	22.6%	10.3%	46	44

Mths: Months.

Table A-3: Characteristics of studies of upgrade from right to bi-ventricular pacing in HF/AV Block patients

Study characteristics	Höijer et al [33]	Leclercq et al [34]	Sideris et al [22]
Study design	Randomized crossover trial	Randomized crossover trial	Prospective cohort
Target population concise	Patients receiving a standard RV DDD pacing for high degree AV block , SND, AF and/or bradycardia	Patients receiving a standard RV pacing for conventional indication, patients with pre-existent LV pacing were excluded	Patients receiving a standard RV pacing (complete HB, AF, symptomatic bradycardia)
Intervention	Six months of Upgrade to BV pacing	Six months of Upgrade to BV pacing	6 months of upgrade to BV pacing
Comparator	RV pacing	RV pacing	RV pacing(VVIR-DDDR)
Country	Sweden	France	Greece
Length of follow-up	6 months	6 months	6 months
Inclusion criteria	NYHA functional class III/IV	NYHA functional class III/IV, LVEF< 35%	NYHA functional class III/IV
	No LBBB in pre-pacing ECG	Optimal tolerated treatment for HF	LVEF< 35%
		Ventricular dyssynchrony ≥40 ms	QRS> 120 ms
Participants' Characteristics			
N	10	44	37
Age (years), Mean (SD) or Median (min, max)	68 (55-79)	73 (8)	71.4 (7.7)
Sex male, %	80	90	70
NYHA Class, Mean (SD)		3 (0.4)	
I, n (%)	0		0
II, n (%)	0		0
III, n (%)	8 (80)		28 (76)
IV, n (%)	2 (20)		9 (24)
(History of) AF, %	40	45	NR
LVEF (%), Mean (SD) or Median (min, max)	All had LVEF <25%	25 (9)	26.3 (5.4)
QRS interval (msec), Mean (SD) or Median (min, max)	235 (200-260)	206 (26)	157.3 (17.8)
LBBB/RBBB, %	NR	NR	NR
Ischemic etiology, %	NR	52	62

APPENDIX B : RISK OF BIAS

Table B-1: Risk of bias in the trials comparing right versus bi-ventricular pacing in AV block patients.

	Studies of initial pacing							Upgrade studies	
Judgement [a]	Albertsen et al.[15,16]	Yu et al. [17]	PREVENT-HF[18]	BIOPACE[9,10]*	HOBIPACE[8]	COMBAT [27]	BLOCK-HF [19]	Höijer et al. [33]	Leclercq et al.[34]
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	Medtronic	Medtronic	Medtronic	St Jude Medical	Independent	Medtronic	Medtronic	Independent	Independent

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

Table B-2: Risk of bias in the observational study of upgrade from right to bi-ventricular pacing in HF/AV block patients

Judgement [a]	Sideris et al [22]
Selection bias	
Representativeness of the exposed group	b★
Selection of the non-exposed group	N/A
Ascertainment of exposure	a★
Demonstration that outcome of interest was present at the start of study	N/A
Comparability	
Comparability of cohorts on the basis of the design or analysis	N/A
Outcome	
Assessment if outcome	b★
Was follow-up long enough for outcomes to occur	a★
Adequacy of follow-up of cohorts	b★
Funding source	Independent

a The judgement was made according to the New-Castle-Ottawa quality assessment scale for observational studies [13]. The bias categories range from a to d, a being the lowest and d being the highest risk of bias. A star means a low risk of bias for the correspondent item.

APPENDIX C : GLOSSARY OF TERMS

Table C-1: List of cardiac parameters cited in the report with their correspondent normal values

Variable	Value in healthy population	Interpretation
QRS duration	60-120 msec	Combination of three of the graphical deflections seen on a typical electrocardiogram (Figure C-1).[2]
Left Ventricular Ejection fraction (LVEF)	50-70% (Lower limit of normal is 40%)	Measure of the percentage of blood being pumped out of the left ventricle of the heart with each contraction.Values <40% are risk factors of HF.[25]
Left ventricle end systolic volume(LVESv)	Mean value 50 ml (16-143 ml)	Volume of blood remaining in the left ventricle at the end of each ventricular contraction, or systole.[35]
Left ventricle end diastolic volume (LVEDv)	Mean value 120 ml (62-240 ml)	Volume of blood present in the ventricle during the diastolic phase, or between 2 consecutive contractions.[35]
Interventricular Mechanical dyssynchrony (IVMD)	<20 msec cut-off value of 40 msec.	The time difference between RV to LV ejection.[36]
Left ventricular dyssynchrony	<50 msec, cut-off value of 65 msec.	The difference in timing of LV segments activation.[36]
New York Heart Association functional classification (NYHA class)	I to IV with I being the best and IV the worst	Classification of patients with cardiac disease based on clinical severity and physical functionality. [37]
Quality of life score-Minnesota Living with Heart Failure score (QoL)	Score from 0-5, on 21 facets of life (clinical, physical, emotional, psychological...)	Comprehensive assessment of the effect of heart failure and treatment for HF on the patient's quality of life.[38]
Short-Form General Health Survey (SF-36)	Higher scores on a scale of 0-100 indicate better health status	Self-reported survey consisting of 36 items of patient health.[39]
Peak oxygen consumption (VO_2 max)	35–40 ml/min/kg in men 27–31 ml/min/kg in women	Maximum rate of oxygen consumption as measured during incremental exercise.[40]
Six minute walk test (6MWT)	400m to 700m in healthy adults	To test exercise tolerance in patients with chronic respiratory disease and heart failure.[41]
N-terminal pro b-type Natriuretic Peptide (NT-proBNP)	Normal: <300ng/ml; Abnormal: Age < 50 years, >450 pg/mL Age 50-75 years, >900 pg/mL Age >75 years >1800	NT-proBNP are substances released when the heart is stretched and overworked, and is used to detect signs of heart failure.

Biventricular Pacing

Biventricular pacing (BVP) also known as cardiac resynchronization therapy (CRT) was developed to improve coordination of ventricular contraction in patients with severely symptomatic heart failure despite best medical management. The biventricular pacemaker (BVP) pace the right and left ventricles simultaneously, and is thus used to treat ventricular dyssynchrony, which is believed to lead to physiological changes in the structure of the heart, a dilatation of the left ventricle referred to as "remodeling". CRT reverses remodeling of the left ventricle by decreasing the left ventricle end systolic volume (LVESv) and increasing left ventricular ejection fraction (LVEF).

BVP can be used alone (also referred to as cardiac resynchronization therapy pacemaker or CRT-P), or for selected patients at risk of malignant ventricular arrhythmias, BVP can be combined with an implantable cardioverter defibrillator (ICD), and is then referred to as CRT-D. BVP device has 2 or 3 leads (wires) (**Figure C-1**).

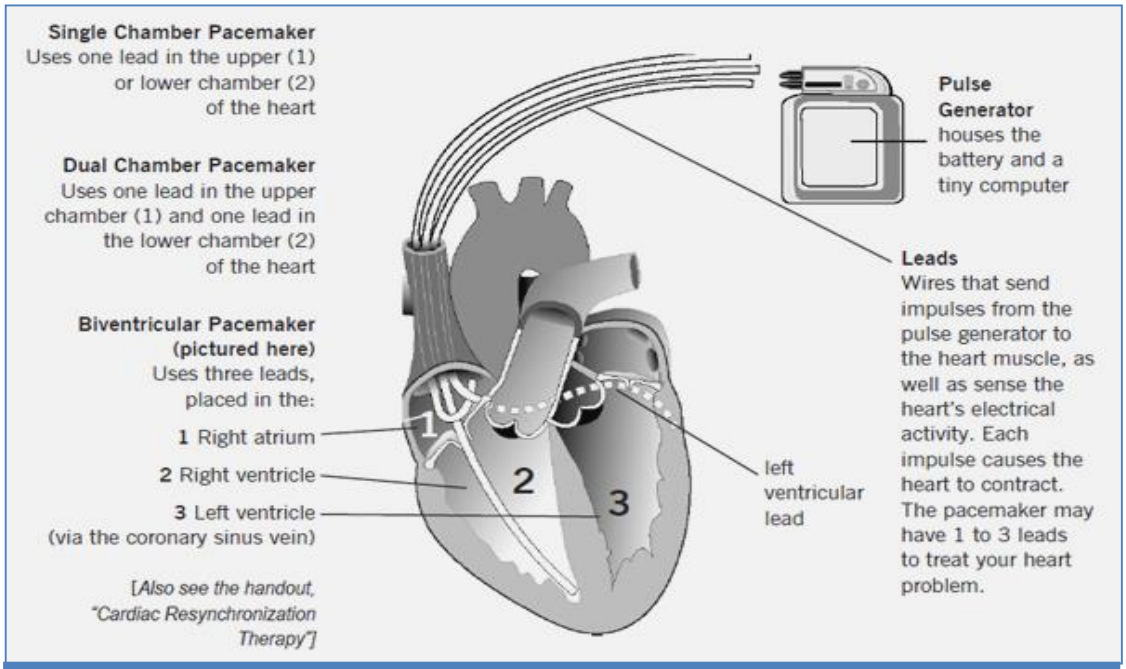

Figure C-1: Illustration of different types of pacemakers

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.[42] Dyssynchrony results in impaired LV systolic function, increased end-systolic volume, and delayed relaxation. Three types of dyssynchrony can occur:

- Atrioventricular (AV) dyssynchrony occurs when there is a difference in timing between atrial and ventricular contractions, which can produce shortened ventricular filling time as well as superimposition of atrial contraction on early passive filling, both of which reduce LV filling.[43] 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.[42]
- Intraventricular dyssynchrony, or LV dyssynchrony, refers to abnormalities in timing of regional LV activation, resulting in disordered contraction of the LV segments.[44] 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.

Prolonged QRS duration (≥120 msec) on an electrocardiogram is considered to be a marker of interventricular 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.[44]

Heart Block

There are three degrees of A-V heart block:

- First-degree heart block

In this type of heart block, every atrial stimulus is conducted to the ventricles, but the stimulus is slowed down. The electrocardiogram (ECG) shows prolonged PR interval to >200 msec (**Figure C-2**).[4,23]

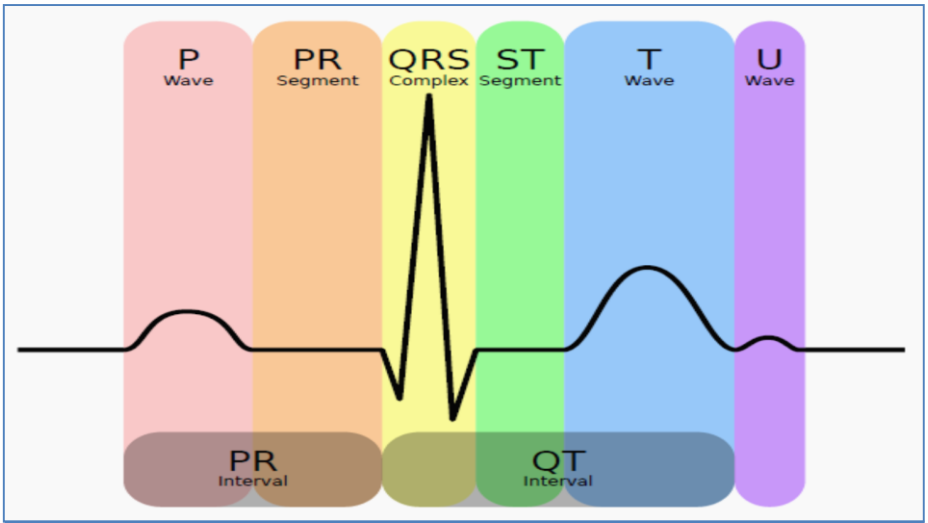

Figure C-2: Schematic diagram of normal sinus rhythm for a human heart as seen on the electrocardiogram (ECG).

A typical ECG tracing is a repeating cycle of three electrical entities: a P wave (marks the electrical depolarisation of the atria), a QRS complex (the R wave marks the depolarisation of the left ventricle), and a T wave (marks ventricular repolarisation).[2]

- Second-degree heart block

This type of heart block is characterized by the fact that one or more atrial stimuli are not conducted to the ventricles.[23] On the ECG, the pattern of QRS waves doesn't follow each P wave as it normally would. Second degree heart block can be classified as:

- Mobitz Type 1: Commonly referred to as Wenckebach's block. The ECG shows a progressively increasing PR interval until an atrial stimulus fails to be conducted to the ventricles (the QRS waves don't follow the next P wave). Patients may not experience noticeable symptoms. This type may not require treatment but can be a forerunner for Type 2 and needs to be monitored by a physician.
- Mobitz Type 2: Some of the atrial stimuli don't reach the ventricles. However, the pattern is less regular than it is in Mobitz type I. Some stimuli are conducted between the atria and ventricles normally, while others are blocked. On the ECG, the QRS wave follows the P wave at a normal speed. Sometimes, though, the QRS wave is missing (when a signal is blocked). Patients may experience chest pain, faintness (syncope), and palpitations, breathing difficulties, such as shortness of

breath with exertion, rapid breathing, nausea, and fatigue. Often times having a pacemaker inserted is necessary to maintain the heart rates.[4]

- Third-degree heart block

In this type of heart block, none of the electrical signals reach the ventricles. This type also is called complete heart block or complete atrioventricular (AV) block. On an electrocardiogram, the normal pattern is disrupted. The P waves occur at a faster rate, and it isn't coordinated with the QRS waves. Complete heart block can result in sudden cardiac arrest and death. This type of heart block often requires emergency treatment. A temporary pacemaker might be used until the patient get a long-term pacemaker.[4]

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.[45]

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.[46]

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.[46]

Left ventricular dysfunction

Left ventricular dysfunction is a precursor of heart failure, and is characterized by reduced myocardial contractility and ventricular remodelling. Measures of LV function include LVEF, LVEDv, LVESv, and measures of dyssynchrony.

Left ventricular dyssynchrony (Intraventricular dyssynchrony)

LV dyssynchrony occurs when the normal ventricular activation sequence is disrupted, resulting in disordered contraction of the LV segments.[44] Mechanical left ventricular dyssynchrony is measured using the pulsed wave Tissue Doppler (PW TD) and deriving the following data:

- Time interval between the onset of ECG derived QRS and the Sm peak (systolic myocardial velocity) (=time to Sm peak)
- Time interval between the onset of QRS and the onset of Sm (= time to Sm onset), which correspond to LVPEP (left ventricular pre-ejection period)

Values less than 50 msec are considered normal, with an upper normal limit of 65 msec.

Left ventricular dyssynchrony index

A measure of intraventricular dyssynchrony, assessed as the standard deviation of the time to minimal systolic volume among the 16 left ventricular segments. This index, also known as Yu index, is normal when less than 30 msec and with cut-off value of 33 msec. [36]

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).[47]

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.

Sick Sinus Syndrome

Sick sinus syndrome (SSS) is a relatively uncommon heart rhythm disorder. SSS is not a specific disease, but rather a group of signs or symptoms that indicate the sinus node, the heart's natural pacemaker, is not functioning properly. A person with SSS may have a heart rhythm that is too slow (bradycardia), too fast (tachycardia), or one that alternates between the fast and slow (bradycardia-tachycardia).[5]

APPENDIX D : GRADE RATINGS

Outcome	Quality assessment								
	Patient population	Study design (No. of studies)	Risk of bias	Inconsistency	Patient population	Study design (No. of studies)	Risk of bias	Overall quality	Comments
Non critical outcomes (Primary outcome)									
LV function	Normal baseline LVEF	RCT (3)	Moderate	No serious concerns	No serious concerns	Serious concerns	Serious concerns	Low ⨁⨁	**Risk of bias**: Small studies with less apparent bias, short follow-up **Imprecision:** Small sample size **Publication bias**: Funding by industry influenced the conclusions of the studies, which did not reflect the evidence presented
	Low baseline LVEF	RCT (2)	High	No serious concerns	No serious concerns	Serious concerns	Serious concerns	Very low ⨁	**Risk of bias**: selection, performance and attrition bias **Imprecision:** Small sample size **Publication bias**: Funding by industry influenced the conclusions of the studies, which did not reflect the evidence presented

Quality assessment									
Outcome	Patient population	Study design (No. of studies)	Risk of bias	Inconsistency	Patient population	Study design (No. of studies)	Risk of bias	Overall quality	Comments
Critical outcomes (Secondary outcome)									
Mortality	Normal baseline LVEF	RCT (3)	Moderate	No serious concerns	No serious concerns	No serious concerns	Serious concerns	Low ⨁⨁	**Risk of bias**: Small studies with less apparent bias, short follow-up **Imprecision:** Small sample size except for one study that cannot be judged. **Publication bias**: Funding by industry influenced the conclusions of the studies, which did not reflect the evidence presented
	Low baseline LVEF	RCT (3)	High	Serious concerns	Serious concerns	Serious concerns	Serious concerns	Very low ⨁	**Risk of bias**: selection, performance and attrition bias **Indirectness:** different populations (Patients with Chaga's disease in COMBAT study)

Outcome	Quality assessment								
	Patient population	Study design (No. of studies)	Risk of bias	Inconsistency	Patient population	Study design (No. of studies)	Risk of bias	Overall quality	Comments
Critical outcomes (contd.)									
	Normal baseline LVEF	RCT (2)	Moderate	No serious concerns	No serious concerns	Serious concerns	Serious concerns	Low ⨁⨁	**Risk of bias**: Small studies with less apparent bias, short follow-up **Imprecision:** Small sample size **Publication bias**: Funding by industry influenced the conclusions of the studies, which did not reflect the evidence presented
6MWT	Low baseline LVEF	RCT (1)	High	No serious concerns	Serious concerns	Serious concerns	Serious concerns	Very low ⨁	**Risk of bias**: selection, performance and attrition bias **Indirectness:** different populations (Patients with Chaga's disease in COMBAT study) **Imprecision**: Small sample size **Publication bias**: Funding by industry influenced the conclusions of the studies, which did not reflect the evidence presented

Outcome	Quality assessment								
	Patient population	Study design (No. of studies)	Risk of bias	Inconsistency	Patient population	Study design (No. of studies)	Risk of bias	Overall quality	Comments
QoL	Normal baseline LVEF	RCT (1)	Moderate	No serious concerns	No serious concerns	Serious concerns	Serious concerns	Low ⨁⨁	**Risk of bias**: Small studies with less apparent bias, short follow-up **Imprecision**: Small sample size **Publication bias**: Funding by industry influenced the conclusions of the studies, which did not reflect the evidence presented
	Low baseline LVEF	RCT (2)	High	No serious concerns	Serious concerns	No serious concerns	Serious concerns	Very low ⨁	**Risk of bias**: selection, performance and attrition bias **Indirectness**: different instruments used to measure QoL scores **Imprecision**: Small sample size **Publication bias:** Funding by industry influenced the conclusions of the studies, which did not reflect the evidence presented