Centre universitaire
de santé McGill

McGill University
Health Centre

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

The CardioMEMS™ pulmonary artery pressure monitor for preventing heart failure-related hospitalisations in patients with previously diagnosed heart failure

Le système de surveillance de la pression artérielle pulmonaire CardioMEMS™ pour lutter contre les hospitalisations liées à l'insuffisance cardiaque chez les patients ayant déjà eu un diagnostic de la maladie

Report number: 91

DATE: 30 August 2022

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

by

Thiphavone Oudanonh, MSc and Nisha Almeida, PhD

Approved by the Policy Committee of the TAU on 30 August, 2022

Mission Statement

The MUHC Health Technology Assessment Unit (TAU) advises hospital administrators and clinical teams in difficult resource allocation decisions regarding novel and existing medical equipment, drugs and procedures used by our healthcare professionals. Using an approach based on independent, critical evaluations of the available scientific evidence and a transparent decision-making process, health interventions are prioritized on a continuous basis ensuring the best care for life with the best use of resources.

TAU Policy Committee

Nisha Almeida, Manager, Health Technology Assessment Unit
James Brophy (Chair), Professor of Medicine & Epidemiology
Julio Flavio Fiore Jr, Assistant Professor, Department of Surgery
Rona Fleming, Patient Partner
Chantal Guévremont, Pharmacist and Coordinator, Programme de gestion thérapeutique des medicaments (PGTM)
André Guigui, Financial Advisor, Financing and Budget
Claudine Lamarre, Associate Director- Adult sites, MUHC Professional Services
Jesse Papenburg, Pediatric Infectious Disease Specialist and Medical Microbiologist
William Parker, Clinical Chief, Department of Medical Physics
Kit Racette, Patient Partner

Declaration of Conflicts of Interest

Members of TAU's research staff and policy committee declare no conflicts of interest.

Suggested Citation

Oudanonh T. and Almeida N. The CardioMEMS™ pulmonary artery pressure monitor for preventing heart failure-related hospitalisations in patients with previously diagnosed heart failure; 2022 August 30. Report no. 91. 60 pages

Report available from https://muhc.ca/tau

ACKNOWLEDGEMENTS

REPORT REQUESTOR

This report was requested by Nadia Giannetti, Associate Physician-in-Chief, Department of Medicine, in September 2021. The new report will be presented to her on completion.

TYPES OF RECOMMENDATIONS ISSUED BY THE TAU COMMITTEE

Type of recommendation	Explanation
Approved	• Evidence for relevant decision criteria, including efficacy, safety, and cost, as well as context-specific factors such as feasibility, is sufficiently strong to justify a recommendation that the technology be accepted, used and funded through the institutional operating budget
Approved for evaluation	• There is a *probability* that relevant decision criteria, including efficacy, safety, and cost, as well as context-specific factors such as feasibility, are favorable but the evidence is not yet sufficiently strong to support a recommendation for permanent approval. • The evidence is sufficiently strong to recommend a *temporary* approval for the purposes of evaluation, funded through the institutional operating budget.
Not approved	• There is insufficient evidence for the relevant decision criteria, including efficacy, safety, and cost; • The costs of any use of the technology (e.g. for research purposes) should not normally be covered by the institutional budget.

DISCLAIMER

The Technology Assessment Unit ("TAU") of the McGill University Health Centre ("MUHC") was created in order to prepare accurate and trustworthy evidence to inform decision-making and when necessary to make policy recommendations based on this evidence. The objective of the TAU is to advise the hospitals in difficult resource allocation decisions, using an approach based on sound, scientific technology assessments and a transparent, fair decision-making process. Consistent with its role within a university health centre, it publishes its research when appropriate, and contributes to the training of personnel in the field of health technology assessment.

The information contained in this report may include, but is not limited to, existing public literature, studies, materials, and other information and documentation available to the MUHC at the time it was prepared, and it was guided by expert input and advice throughout its preparation. The information in this report should not be used as a substitute for professional medical advice, assessment and evaluation. While MUHC has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up to-date, MUHC does not make any guarantee to that effect. MUHC is not responsible for any liability whatsoever, errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

We encourage our readers to seek and consult with qualified health care professionals for answers to their personal medical questions. Usage of any links or websites in the report does not imply recommendations or endorsements of products or services.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

CI	Confidence interval
HTA	Health technology assessment
INESSS	Institut National d'Excellence en Santé et en Service Sociaux
MUHC	McGill University Health Centre
RCT	Randomized controlled trial
TAU	MUHC Technology Assessment Unit
NRS	Non-randomized study
HF	Heart failure
PAP	Pulmonary Arterial Pressure
NYHA	New York Heart Association
LVEF	Left Ventricular Ejection Fraction
HFpEF	Heart failure with preserved Ejection Fraction
HFrEF	Heart failure with reduced Ejection Fraction
FDA	Food and Drug Administration
CMS	Centers for Medicare and Medicaid Services
BMI	Body Mass Index
NT-proBNP	N-terminal pro b-type natriuretic peptide

ABSTRACT

- Higher pulmonary artery pressure (PAP) is associated with higher risk of heart failure hospitalisation. Monitoring PAP with CardioMEMS sensor to adjust treatment before clinical congestion, defined as an accumulation of fluid in the intravascular compartment and interstitial space, might reduce heart failure hospitalisation.

- The objective of this report was to assess the evidence on the effectiveness of the CardioMEMS HF system to reduce heart failure hospitalisation compared to standard care for heart failure management in patients with NYHA class III and recent heart failure hospitalisation.

- We identified 2 randomized controlled trials (RCT) and 10 non-randomized studies (NRS) that examined the effect of CardioMEMS on heart failure hospitalisations. Five of the 10 NRS were retrospective subgroup analyses based on 2 studies.

- The 2 RCTs reported conflicting results. The CHAMPION trial (n=550), published in 2011, found that CardioMEMS reduced the risk of heart failure hospitalisation in patients with NYHA class III compared to standard care management [Hazard ratio (HR) =0.63, 95% confidence interval (CI): 0.52-0.77], while the GUIDE-HF trial (n=1000), published in 2021, reported no significant association in patients with NYHA class II-IV (HR=0.83, 95%CI: 0.69-1.01). The quality of the evidence was low for the CHAMPION trial due to contamination from unblinded outcome assessors, and moderate for the GUIDE-HF trial.

- All 10 non-randomized studies found a lower risk of heart failure hospitalisation in the group monitored with CardioMEMS sensor compared to the group with standard care management in patients with NYHA class III. However, the quality of the evidence was low for all 10 NRS, due to lack of adjustment for confounding and uncontrolled before-after study designs.

- The CardioMEMS device currently costs Canadian $17,500. Assuming a hospitalisation avoidance rate of 28% (95% CI: 5% - 45%), based on a meta-analysis of the two RCT results, the additional cost of using CardioMEMS in one NYHA class III patient would be $14,734. The additional cost of monitoring 49 NYHA class III patients per year would be $564,473.

RÉSUMÉ

- Une pression artérielle pulmonaire (PAP) élevée est associée à un risque accru d'hospitalisation pour insuffisance cardiaque. La surveillance de la PAP avec le système CardioMEMS pour ajuster le traitement avant la congestion clinique, soit une accumulation de liquide dans le compartiment intravasculaire et l'espace intracellulaire, pourrait réduire les hospitalisations pour insuffisance cardiaque.

- Ce rapport vise à évaluer les preuves de l'efficacité du système CardioMEMS HF dans la réduction des hospitalisations pour insuffisance cardiaque par rapport aux soins standard pour la prise en charge de la maladie chez les patients de classe III selon la NYHA qui ont récemment été hospitalisés pour insuffisance cardiaque.

- Nous avons ciblé 2 essais contrôlés randomisés (ECR) et 10 essais non randomisées (ENR) qui ont examiné l'effet du CardioMEMS sur les hospitalisations pour insuffisance cardiaque. Cinq des 10 ENR étaient des analyses rétrospectives de sous-groupes fondées sur 2 études.

- Les 2 ECR ont donné des résultats contradictoires. L'essai CHAMPION (n=550), publié en 2011, a montré que le CardioMEMS réduisait le risque d'hospitalisation pour insuffisance cardiaque chez les patients de classe III selon la NYHA par rapport aux soins standard (rapport de risque [RR]=0,63; intervalle de confiance [IC] de 95 % : 0,52-0,77), tandis que l'essai GUIDE-HF (n=1000), publié en 2021, n'a indiqué aucune association notable chez les patients de classes II-IV selon la NYHA (RR=0,83; IC de 95 % : 0,69-1,01). Les preuves de l'essai CHAMPION étaient de faible qualité en raison de la contamination par des évaluateurs qui connaissaient les résultats, et de qualité modérée pour l'essai GUIDE-HF.

- Les 10 essais non randomisés ont révélé un risque plus faible d'hospitalisation pour insuffisance cardiaque dans le groupe utilisant le système CardioMEMS par rapport au groupe recevant des soins standard chez les patients de classe III selon la NYHA. Toutefois, toutes les preuves étaient de faible qualité en raison du manque d'ajustement pour les facteurs de confusion et le modèle d'études non contrôlées avant-après.

- Le dispositif CardioMEMS coûte actuellement 17 500 $ CA. Si on considère un taux d'évitement des hospitalisations de 28 % (IC de 95 % : 5-45 %), d'après une méta-analyse des résultats des 2 ECR, le coût supplémentaire associé à l'utilisation du système CardioMEMS chez un patient de classe III selon la NYHA

s'élèverait à 14 734 $. Pour la surveillance de 49 patients de cette même classe, le coût supplémentaire serait de 564 473 $ par année.

EXECUTIVE SUMMARY

BACKGROUND

Heart failure hospitalisation is a major burden on the healthcare system. Abnormally elevated pulmonary artery pressure (PAP) occurs days or weeks before clinical congestion, defined as an accumulation of fluid in the intravascular compartment and interstitial space, which gives an opportunity to intervene before heart failure. The aim of the CardioMEMS HF system is to monitor PAP and use it to adjust treatment in heart failure management.

OBJECTIVES

The objective of this report was to assess the evidence on the effectiveness of the CardioMEMS HF system to reduce heart failure hospitalisation compared to standard care for heart failure management in patients with NYHA class III and recent heart failure hospitalisation. A secondary objective was to evaluate the budget impact of using the device in NYHA III class patients at our hospital.

METHODS

We reviewed evidence from relevant randomized clinical trials and non-randomized studies on the association between CardioMEMS and heart failure hospitalisation by searching PubMed, Cochrane Library and the health technology assessment (HTA) database. We also identified one clinical practice guideline pertaining to this subject.

RESULTS

We identified 2 randomized controlled trials (RCT) and 10 non-randomized studies (NRS) for our review.

- The CHAMPION trial (2011) is an RCT that reported a lower risk of heart failure hospitalisation (HR=0.63, 95% CI: 0.52-0.77, n=550) in the group monitored with CardioMEMS than the group managed with standard care in patients with NYHA class III after an average follow-up of 15 months. However, the quality of the evidence was low mainly due to unauthorized medical recommendations from unblinded outcome assessors working for the sponsor to local investigators for 180 of the 270 patients in the treatment group.

- Moderate-quality evidence from a single-blinded (investigators not blinded) RCT, the GUIDE-HF trial (2021), suggests that there was no statistically significant association (HR=0.83, 95%CI: 0.69-1.01, n=1000) between heart failure management through CardioMEMS and heart failure hospitalisation in patients with NYHA class II-IV (65% NYHA class III) one year after implantation.

- In a follow-up uncontrolled before-and-after study, 170 of the 280 patients in the control group from the CHAMPION trial had their PAP data made available to the investigators. Those 170 patients were monitored by CardioMEMS and were compared with the 280 patients in the original control group. After an average 13 months of follow-up, patients monitored by CardioMEMS had a lower risk of heart failure hospitalisation (HR=0.52, 95% CI: 0.40-0.69). However, the quality of the evidence was poor since no adjustment was done for confounding factors.

- The CHAMPION Post-Approval study was an uncontrolled before-and-after study assessing the effect of CardioMEMS in patients with NYHA class III. The risk of heart failure hospitalisation was lower 1 year after implantation than 1 year before implantation (HR=0.43, 95% CI: 0.39-0.47, n=1200). However, the lack of an external comparison group to control for temporal trends makes it difficult to attribute the reduction in heart failure hospitalisation to only CardioMEMS.

- Five retrospective subgroup analyses of data from the CHAMPION trial and Post-Approval study showed similar reduction in heart failure hospitalisation in the group monitored with CardioMEMS, regardless of BMI, sex or ejection fraction. However, these studies have the same limitations as their main study due to the deviation from protocol.

- Two observational studies, one in USA and one in Europe, used an uncontrolled before-and-after design to examine the effect of CardioMEMS. One year after implantation, the risk of heart failure hospitalisation was reduced for both the American (HR=0.66, 95% CI: 0.57-0.76, n=480) and European (HR=0.38, 95% CI: 0.31-0.48, n=234) studies. However, the causal relation was weak due to the study design i.e. lack of a control group.

- A retrospective matched cohort study using Medicare database reported that monitoring by CardioMEMS reduced the risk of heart failure hospitalisation (HR=0.76, 95% CI: 0.65-0.89, n=1087) 1 year after implantation. However, information on medication changes after implantation and PAP data were not available.

- All 12 studies were sponsored by the manufacturer of the CardioMEMS system. Moreover, the sponsor participated substantially in the studies, including data collection, data analysis and interpretation.

- No major safety issues were reported 6 months after implantation of the sensor device and all implanted sensor devices were operational.

- In 2016, the guideline of the European Society of Cardiology gave the CardioMEMS HF system a class IIb recommendation, i.e. "usefulness/efficacy is less well-established by evidence/opinion" and the intervention "may be considered in symptomatic patients with HF with previous HF hospitalization in order to reduce the risk of recurrent HF hospitalization."

COSTS

We estimated the budget impact of using CardioMEMS for monitoring NYHA class III patients at our hospital. Assuming a hospitalisation avoidance rate of 28% (95% CI: 5% - 45%), based on a meta-analysis of the two RCT results, and a device cost of $17,500, the additional cost of using CardioMEMS in one NYHA class III patient would be $14,734. The additional cost of monitoring 49 NYHA class III patients per year would be $564,473.

CONCLUSIONS

- The best available evidence, derived from two randomized controlled trials published in 2011 and 2021 (CHAMPION and GUIDE-HF, respectively), provided conflicting results:

  o Moderate-quality evidence from the GUIDE-HF trial indicates that there is no conclusive evidence that the CardioMEMS HF system could be effective in reducing heart failure hospitalisation in adult patients with NYHA class II-IV and with recent hospitalisations for heart failure.

  o On the other hand, low-quality evidence from the CHAMPION trial suggests that CardioMEMS[TM] might decrease heart failure hospitalisation in the subset of adults with NYHA class III.

- Although data from the non-randomized studies also concluded that CardioMEMS[TM] reduced heart failure hospitalisation in adults with NYHA class III,

the quality of the evidence was poor due to the presence of confounding bias and weak study design.

- CardioMEMS^{TM} sensor implantation appears to be safe, with the majority of patients with the PAP sensor reporting no complications 6 months after implantation of the sensor device.

- The current cost of the CardioMEMS^{TM} device remains relatively high at $17,500, and the resultant cost savings ($2,766 per patient) from an estimated hospitalisation avoidance rate of 28% would not offset these device costs. The additional cost of monitoring 49 NYHA class III patients at the MUHC would be $564,473.

- The decision to adopt this technology at the MUHC needs to consider:

  o the equivocal results from the randomized trials and their low to moderate quality evidence

  o that even a large impact on hospitalisation avoidance will not offset the relatively high device costs for this patient population.

RECOMMENDATIONS

- The TAU Policy Committee, made up of stakeholders from across the McGill University Health Centre, reviewed the evidence and issued the following recommendation: Not Approved
- This recommendation was reached based on the following:
  o Evidence for the effectiveness of CardioMEMS in reducing hospitalizations is weak, and it is difficult to ascertain whether reductions in hospitalizations can be attributed to the use of CardioMEMS.
  o Device costs are high and are not justifiable given the uncertainty in clinical benefit and patient compliance.
- This recommendation may be reviewed in 3 years, if new data from the literature and/or the local context become available.

SOMMAIRE

CONTEXTE

L'hospitalisation pour insuffisance cardiaque représente une charge importante pour le système de santé. Une pression artérielle pulmonaire (PAP) anormalement élevée survient quelques jours ou semaines avant la congestion clinique, soit une accumulation de liquide dans le compartiment intravasculaire et l'espace intracellulaire; il y a donc une occasion d'intervenir avant que l'insuffisance cardiaque ne survienne. Le système CardioMEMS HF vise à surveiller la PAP et permet d'ajuster le traitement dans la prise en charge de la maladie.

OBJECTIFS

Ce rapport vise à évaluer les preuves de l'efficacité du système CardioMEMS HF dans la réduction des hospitalisations pour insuffisance cardiaque par rapport aux soins standard pour la prise en charge de la maladie chez les patients de classe III selon la NYHA qui ont récemment été hospitalisés pour insuffisance cardiaque. Un objectif secondaire consiste à évaluer l'incidence financière de l'utilisation du dispositif chez les patients de classe III selon la NYHA à notre hôpital.

MÉTHODES

Nous avons examiné les données probantes d'essais cliniques randomisés et d'essais non randomisés pertinents sur le rapport entre le système CardioMEMS et les taux d'hospitalisation pour insuffisance cardiaque. Pour ce faire, nous avons effectué des recherches dans PubMed, la Cochrane Library et la base de données d'évaluation des technologies de la santé. Nous avons également trouvé un guide de pratique clinique portant sur ce sujet.

RÉSULTATS

Pour notre examen, nous avons ciblé 2 essais contrôlés randomisés (ECR) et 10 essais non randomisés (ENR).

- L'ECR CHAMPION (2011) a indiqué un risque plus faible d'hospitalisation pour insuffisance cardiaque (RR=0,63; IC de 95 % : 0,52-0,77; n=550) dans le groupe utilisant le système CardioMEMS par rapport au groupe recevant des soins standard chez les patients de classe III selon la NYHA après un suivi de 15 mois en moyenne. Cependant, les preuves étaient de faible qualité, principalement parce

que des évaluateurs qui connaissaient les résultats et qui travaillaient pour le commanditaire ont fait des recommandations médicales non autorisées aux investigateurs locaux pour 180 des 270 patients du groupe de traitement.

- Les preuves de qualité modérée de l'essai GUIDE-HF (2021), un ECR en simple aveugle (les investigateurs étaient au courant), suggèrent qu'il n'y a pas de rapport statistiquement notable (RR=0,83; IC de 95 % : 0,69-1,01; n=1000) entre la prise en charge de l'insuffisance cardiaque avec le système CardioMEMS et le taux d'hospitalisation pour insuffisance cardiaque chez les patients de classes II-IV selon la NYHA (65 % pour la classe III selon la NYHA) un an après l'implantation des capteurs.

- Dans le cadre d'une étude de suivi avant-après sans groupe témoin, les investigateurs ont pu avoir accès aux données de PAP de 170 des 280 patients du groupe témoin de l'essai CHAMPION. La PAP de ces 170 patients était surveillée au moyen du système CardioMEMS et les données ont été comparées à celles des 280 patients du groupe initial de l'essai clinique. Après un suivi de 13 mois en moyenne, les patients avec le système CardioMEMS présentaient un risque plus faible d'hospitalisation pour insuffisance cardiaque (RR=0,52; IC de 95 % : 0,40-0,69). Cependant, les preuves étaient de faible qualité puisqu'aucun ajustement n'avait été fait pour les facteurs de confusion.

- L'étude de post-approbation CHAMPION suivait le modèle avant-après sans groupe témoin et évaluait l'effet du système CardioMEMS chez des patients de classe III selon la NYHA. Le risque d'hospitalisation pour insuffisance cardiaque était plus faible un an après l'implantation des capteurs par rapport à un an avant l'implantation (RR=0,43; IC de 95 % : 0,39-0,47; n=1200). Cependant, en raison de l'absence d'un groupe externe de comparaison pour le contrôle des tendances relatives au temps, il est difficile d'attribuer la réduction des hospitalisations pour insuffisance cardiaque au seul fait du système CardioMEMS.

- Cinq analyses rétrospectives de sous-groupes des données de l'essai et de l'étude post-approbation CHAMPION ont montré une réduction similaire des hospitalisations pour insuffisance cardiaque dans le groupe avec le système CardioMEMS, indépendamment de l'IMC, du sexe ou de la fraction d'éjection. Toutefois, ces études présentent les mêmes limites que la principale en raison du détournement du protocole.

- Deux études d'observation, l'une aux États-Unis et l'autre en Europe, ont utilisé un modèle avant-après sans groupe témoin pour examiner l'effet du système

CardioMEMS. Un an après l'implantation des capteurs, le risque d'hospitalisation pour insuffisance cardiaque avait diminué tant pour l'étude américaine (RR=0,66; IC de 95% : 0,57-0,76; n=480) que pour l'européenne (RR=0,38; IC de 95 % : 0,31-0,48; n=234). Toutefois, le modèle d'étude (absence de groupe témoin) a affaibli la relation de cause à effet.

- Une étude de cohorte rétrospective et appariée qui utilisait la base de données Medicare a indiqué que la surveillance de la PAP au moyen du système CardioMEMS réduisait le risque d'hospitalisation pour insuffisance cardiaque (RR=0,76; IC de 95 % : 0,65-0,89; n=1087) un an après l'implantation des capteurs. Cependant, les informations sur les changements de médication après l'implantation et les données de PAP n'étaient pas disponibles.

- Le fabricant du système CardioMEMS a commandité les 12 études. En outre, il a participé de manière notable aux études, y compris à la collecte, à l'analyse et à l'interprétation des données.

- Aucun problème grave de sécurité n'a été signalé 6 mois après l'implantation des capteurs et tous les dispositifs implantés étaient fonctionnels.

- En 2016, la ligne directrice de la Société européenne de cardiologie a donné au système CardioMEMS HF une recommandation de classe IIb, c'est-à-dire que « l'utilité/efficacité est moins bien établie par la preuve/opinion » et que l'intervention « peut être envisagée chez les patients symptomatiques atteints d'insuffisance cardiaque qui ont déjà été hospitalisés, afin de réduire le risque d'hospitalisation récurrente pour insuffisance cardiaque » [traduction libre].

Coûts

Nous avons évalué l'impact financier de l'utilisation du système CardioMEMS pour la surveillance de la PAP chez les patients de classe III selon la NYHA dans notre hôpital. Si on considère un taux d'évitement des hospitalisations de 28 % (IC de 95 % : 5-45 %), d'après une méta-analyse des résultats des 2 ECR, ainsi que le prix du système CardioMEMS (17 500 $), le coût supplémentaire associé à l'utilisation de ce dispositif chez un patient de classe III selon la NYHA s'élèverait à 14 734 $. Pour la surveillance de 49 patients de cette même classe, le coût supplémentaire serait de 564 473 $ par année.

CONCLUSIONS

- Les meilleures données disponibles, qui sont issues de 2 essais contrôlés randomisés publiés en 2011 (CHAMPION) et en 2021 (GUIDE-HF), ont fourni des résultats contradictoires :

  - d'une part, les données de qualité modérée de l'essai GUIDE-HF indiquent qu'il n'y a pas de preuve concluante à l'effet que le système CardioMEMS HF pourrait être efficace pour réduire les taux d'hospitalisation pour insuffisance cardiaque chez les patients adultes de classes II-IV selon la NYHA et ayant été hospitalisés récemment pour insuffisance cardiaque;

  - d'autre part, des données de faible qualité issues de l'essai CHAMPION suggèrent que le système CardioMEMS pourrait réduire le taux d'hospitalisation pour insuffisance cardiaque dans le sous-groupe d'adultes de classe III selon la NYHA.

- Bien que les données des essais non randomisés aient également conclu que le système CardioMEMS réduisait les taux d'hospitalisation pour insuffisance cardiaque chez les adultes de classe III selon la NYHA, les preuves étaient de faible qualité en raison de biais de confusion et de la faiblesse du modèle d'étude.

- Les capteurs CardioMEMS semblent sûrs puisque la majorité des patients dont on surveillait la PAP avec ce système n'ont signalé aucune complication 6 mois après l'implantation.

- Le prix actuel du système CardioMEMS est relativement élevé, soit 17 500 $, et les économies qui résulteraient de l'utilisation du dispositif (2 766 $ par patient) et d'un taux d'évitement des hospitalisations d'environ 28 % ne compenseraient pas le coût. Pour la surveillance de 49 patients de cette même classe au CUSM, le coût supplémentaire serait de 564 473 $.

- La décision d'adopter cette technologie au CUSM doit tenir compte des éléments suivants :

  - les résultats équivoques des essais randomisés et leurs preuves de qualité faible à modérée;

o l'impact notable du système sur l'évitement des hospitalisations ne compensera pas les coûts relativement élevés de ce dispositif pour les patients considérés.

RECOMMANDATION

- Le comité consultatif de l'Unité d'évaluation des technologies de la santé, composé de parties prenantes de tout le Centre universitaire de santé McGill, a examiné les données probantes et formulé la recommandation suivante : **non approuvé**.
- Le comité est parvenu à cette recommandation sur la base des éléments suivants :
  - o les preuves de l'efficacité de CardioMEMS dans la diminution des taux d'hospitalisation sont faibles, et il est difficile d'attribuer la réduction des hospitalisations pour insuffisance cardiaque à la seule utilisation du système CardioMEMS;
  - o les coûts liés au système sont élevés et ne sont pas justifiables compte tenu de l'incertitude quant au bénéfice clinique et à l'observance thérapeutique.
- Cette recommandation pourra être revue dans 3 ans s'il y a de nouvelles données dans la littérature ou le contexte local.

The CardioMEMS^{TM} pulmonary artery pressure monitor for preventing heart failure-related hospitalizations in patients with previously diagnosed heart failure

1.   BACKGROUND

Heart failure occurs when the heart is unable to properly pump blood through the body. Almost 700,000 Canadians aged ≥40 years had a history of heart failure in 2012-2013,[1] resulting in a considerable burden not only for patients and their caregivers, but for the healthcare system as well. Although the rate of heart failure-related hospitalisation has declined between 2007 and 2016, it remains the third cause of admission in Canadian hospitals in 2018-2019 and the second cause in American hospitals in 2005-2018.[2] The total cost of Canadian hospital admission was estimated to be 722$ millions in 2030.[3]

Elevated pulmonary artery pressure (PAP) occurs days or weeks before clinical congestion, defined as an accumulation of fluid in the intravascular compartment and interstitial space, thus providing an opportunity for medical intervention before heart failure. The CardioMEMS^{TM} HF system consists of a PAP sensor and an electronic unit. The sensor does not require a battery and is permanently implanted through catheterization. The daily uploaded PAP is used by treating physicians to remotely monitor and guide heart failure management before clinical deterioration.

Given the high cost of the CardioMEMS^{TM} HF system, TAU was requested by the department of finance and Dr. Nadia Giannetti, Medical Director of the Heart Failure and Heart Transplant program at the MUHC, to conduct an evaluation of the effectiveness of CardioMEMS^{TM} in reducing heart failure hospitalisation.

2.   POLICY AND EVALUATION QUESTIONS

2.1 Policy Question

- Should the CardioMEMS^{TM} HF system be used for guiding heart failure management in NYHA class III heart failure patients with previous heart failure hospitalisation?

2.2   Evaluation questions (Objective of this report)

- What is the evidence on the effectiveness of CardioMEMS™ HF system to reduce heart failure-related hospitalisations in adult patients with previous heart failure compared to standard care for heart failure management?

- What is the budget impact of using the device in NYHA III class patients at our hospital?

3.   METHODS

3.1   Literature search and quality assessment

We conducted a literature search through PubMed, Cochrane Library and the Health Technology Assessment (HTA) database of the Centre for Reviews and Dissemination. The literature search was conducted on 24 November 2021 and details on the search strategy are shown in Appendix Table A. An update was performed on 26 April 2022, but no new relevant articles were found.

The intervention was heart failure management guided by PAP data uploaded through the CardioMEMS™ HF system, while the comparative group was standard care for heart failure management. The outcome of interest was heart failure-related hospitalisation.

The risk of bias assessment for RCTs and observational studies were performed according to version 2.0 of the Cochrane tool for assessing risk of bias in RCT and the ROBIN-I tool, respectively.[4,5] Subsequently, the quality of evidence was graded as low, moderate or high. It was based primarily on the risk of bias assessment of the studies. The quality was graded as low if the risk of bias was reported as high or serious/critical. For low (moderate) risk of bias, the quality was graded as high (moderate), but it could be downgraded by other components that could affect the quality of the evidence. The Robvis visualisation tool, a web application, was used to generate traffic-light tables for the risk of bias assessment.

4.   LITERATURE REVIEW

A total of 12 relevant studies were identified and included in the report, comprising of 2 randomized controlled trials (RCTs) and 11 non-randomized studies (NRS). The 2 RCTs

are the CHAMPION trial and the GUIDED-HF trial. Eight of the 11 NRS are related to the CHAMPION trial, either as a follow-up study or a subgroup analysis study. The remaining NRS used either the Medicare database or was a single-arm observational study. Details on the selection process are shown in Figure 1.

The study characteristics are shown in Table 1 and Table 2, while the main findings and quality of evidence assessment are summarized in Table 3 and Table 4. Summaries of the risk of bias assessment are presented in Figure 2 and Figure 3, while detailed summaries are given in Appendices Table B and Table C.

4.1   CHAMPION trial

- The CHAMPION trial, conducted by Abraham et al, enrolled adults with NYHA class III heart failure symptoms who were hospitalised at least once for heart failure within 1 year of the beginning of the study.[6] After undergoing surgery for the implantation of the CardioMEMS™ sensor, 550 participants from 64 centres in the USA were randomized to either the treatment group (n=270) or the control group (n=280). Patients were kept in their allocated group until the end of the follow-up in August 2010 (Randomized Access period). Participants in both groups were told to upload their PAP data daily. Management of heart failure was guided by PAP data as well as standard care for patients in the treatment group, while it was based only on standard care for patients in the control group. After an average 15 months of follow-up, the risk of heart failure hospitalisation was lower (Hazard Ratio [HR]=0.63, 95% CI: 0.52-0.77, n=550) in the treatment group compared to control group. However, the statistical model did not account for censorship from death, a competing risk. Moreover, unblinded nurses working for the sponsor made therapy recommendations to the local investigators for 2/3 of patients in the treatment group, which were not allowed by the protocol. Overall, the quality of the evidence was low.

- Retrospective subgroup analyses of data from the CHAMPION trial were published in 3 studies.[7–9] The heart failure hospitalisation rate was reported to be lower in the treatment group compared to control group for patients with preserved ejection fraction (LVEF ≥40%) (Rate Ratio [RR] =0.54, 95% CI: 0.38-0.70, n=119) or with reduced ejection fraction (LVEF <40%) (RR=0.76, 95% CI: 0.61-0.91, n=430) after ≤6 months of follow-up. However, the statistical model was adjusted only for the group and duration of trial. Unadjusted risk of heart failure hospitalisation, after an average 18 months of follow-up, remained lower (hazard ratio [HR]=0.72, 95% CI: 0.59-0.88, n=456) in the treatment group with reduced

ejection fraction (defined as LVEF ≤40%). Moreover, the risk of heart failure hospitalisation was also lower (HR=0.70, 95% CI: 0.51-0.96, n=190) in the treatment group among patients with cardiac resynchronization therapy (CRT) implants after an average 18 months of follow-up. Though the statistical model was adjusted for covariates with p< 0.15 based on the backward elimination method, no other details were provided. Overall, the quality of the evidence was low for the 3 studies as they have the same limitations as the main study.

- In a follow-up study, 347 of 550 patients that completed the Randomized Access period in August 2010 transitioned to the Open Access period ending in April 2012.[10] During the latter period, PAP data monitored via CardioMEMS[TM] of patients in the control group became available for heart failure management to the investigators. In this before-after retrospective analysis of control participants, patients during the Open Access (n=170) had a reduced risk of heart failure hospitalisation compared to the patients during Randomized Access (n=280) (HR=0.52, 95% CI: 0.40-0.69) after an average follow-up of 13 months. However, the statistical model did not account for censorship from death, a competing risk. Not accounting for competing events overestimates the incidence of the outcome of interest. Moreover, the authors used a before-and-after design adjusting only for frailty status. Overall, the quality of the evidence was low.

4.2   CHAMPION Post-Approval study

- The approval of the monitoring system by the Food and Drug Administration (FDA) was contingent to a Post-Approval study to confirm the efficacy of CardioMEMS[TM] in clinical practice.[11] A total of 1200 adults with NYHA class III heart failure symptoms and hospitalised at least once for heart failure within 1 year of the beginning of the study were enrolled between September 2014 and October 2017. Participants were implanted with the CardioMEMS[TM] sensor and told to upload their PAP data daily. The 1-year follow-up was completed by 875 patients. The authors reported that the risk of heart failure hospitalisation was lower at 1-year post-implantation than 1-year pre-implantation (HR=0.43, 95% CI: 0.39-0.47, n=1200). However, the authors used a before-and-after design without adjusting for confounding factors, such as new treatment available only or mostly during the post-implantation period. Moreover, the management of heart failure before the implantation was not standardized, but it was done according to local usual care. Overall, the quality of the evidence was low.

- Retrospective subgroup analyses of data from the Post-Approval study were published in 2 studies.[12,13] Although unadjusted risk of heart failure hospitalisation was lower at 1-year post-implantation than 1-year pre-implantation for men (HR=0.46, 95% CI: 0.40-0.52, n=748) and women (HR=0.39, 95% CI: 0.33-0.46, n=452), it was not different between men and women ($P_{interaction}$= 0.16). Heart failure management guided by PAP data also reduced the risk of heart failure hospitalisation at 1-year post-implantation in obese (HR=0.37, 95% CI: 0.30-0.45, n=357) and non-obese (HR=0.45, 95% CI: 0.40-0.51, n=841) patients, but once again, obesity did not modify the association between PAP-guided management and risk of hospitalization ($P_{interaction}$= 0.07). Similar risk of heart failure hospitalisation at 1-year post-implantation was also observed between obese and non-obese patients among those with LVEF <40% ($P_{interaction}$= 0.28) or with LVEF ≥40% ($P_{interaction}$= 0.20). No adjustment for confounding factors was done. Overall, the quality of the evidence was low for both studies as they have the same limitations as the main study.

4.3 GUIDE-HF trial

- The GUIDED-HF trial, conducted by Lindenfeld et al, expanded the eligibility criteria of the CHAMPION trial to include patients with NYHA class II to IV heart failure symptoms.[14] 65% of included patients were NYHA class III. Eligible patients either had been hospitalised at least once for heart failure within 1 year of the study consent or had elevated natriuretic peptides within 30 days before study consent. Between March 2018 and December 2019, enrolled patients were implanted with a CardioMEMS[TM] sensor and then randomized to either the treatment or control group. Participants in both groups were told to upload their PAP data daily. Management of heart failure was guided by PAP data as well as standard care for patients in the treatment group, while it was based only on standard care for patients in the control group. The primary endpoint was a composite measure of death, heart failure hospitalisations and urgent heart failure visits. One year after sensor implantation, the risk of heart failure hospitalisation (secondary endpoint) was not statistically different in the treatment group compared to the control group (HR=0.83, 95%CI: 0.69-1.01; event rate per patient-year (n): 0.410 (185) vs. 0.497 (225), respectively); all other endpoints including the primary endpoint were also not significantly different between the treatment and control group. Since the Covid-19 pandemic started during the follow-up period and the pre-specified Covid-19 effect was statistically significant ($P_{interaction}$=0.11) at a significance level of p=0.15, the

authors performed separate analyses for the pre-Covid-19 period (up to March 13, 2020). For the pre-Covid period, the authors reported a lower risk of heart failure hospitalisation for the treatment group (HR=0.72, 95%CI: 0.57-0.92; event rate per patient-year (n): 0.380 (124) vs. 0.525 (176), respectively); however, other endpoints were not statistically significant [HR and 95%CI for death: 1.24 (0.73-2.11); urgent heart failure visits: 1.02 (0.57-1.82); composite primary endpoint: 0.81 (0.66-1.00)]. The statistical model did not account for censorship from death, a competing risk. Moreover, not all personnel were blinded. Overall, the quality of the evidence was moderate.

4.4   Other observational studies

- Desai et al used the Centers for Medicare and Medicaid Services (CMS) data to evaluate the effectiveness of CardioMEMS[TM] in clinical practice by comparing outcomes before and after implantation among patients that made an insurance claim for the PAP sensor.[15] Eligible patients need to have at least 6 months of data before and after implantation. A total of 1114 patients implanted with the PAP sensor between June 2014 and December 2015 were included in the study. Retrospective analysis shows that heart failure hospitalisation was lower at 6-month post-implantation (HR=0.55, 95% CI: 0.49-0.61, n=1114) and at 1-year post-implantation (HR=0.66, 95% CI: 0.57-0.76, n=480). However, the statistical model did not account for censorship from death, a competing risk. Moreover, the authors used a before-and-after design without adjusting for potential confounding factors, such as new treatment available only or mostly during the post-implantation period. Overall, the quality of the evidence was low.

- Abraham et al evaluate the effectiveness of CardioMEMS[TM] in clinical practice by using also CMS database.[16] Insurance claims identified 1185 patients implanted with the PAP sensor between 1-June 2014 and 31-December 2016. They were matched 1-to-1 to 1087 patients without PAP sensor that have been hospitalised at least once for heart failure between 1-July 2013 and 31-March 2016. They were further matched for demographic characteristics and comorbidities. The authors found that patients with PAP sensor have reduced heart failure hospitalisation at 1-year post-implantation (HR=0.76, 95% CI: 0.65-0.89, n=1087) compared to patients without the sensor. Although matching made patients in both groups similar, potential confounders such as co-treatments or NYHA classification were not considered. Additionally, the statistical model did not

account for censorship from death, a competing risk. Overall, the quality of the evidence was low.

- The MEMS-HF, conducted by Angermann et al, was a non-randomized European study comparing the efficacy of CardioMEMS[TM] before and after its implantation in patients with NYHA class III.[17] The authors reported a lower heart failure hospitalisation at 1-year post-implantation (HR=0.38, 95% CI: 0.31-0.48, n=234). However, the statistical model did not account for censorship from death, a competing risk. Moreover, the authors used a before-and-after design without adjusting for potential confounding factors, such as new treatment available only or mostly during the post-implantation period. Overall, the quality of the evidence was low.

4.5   Main limitations

The quality of the evidence in the literature is affected by several limitations. Some of them were general concerns, while others were related to the study design. The main limitations are listed below.

- The main statistical model used was the Andersen-Gill model. It censored patients who died before the end of the follow-up, but dead is a competing event for heart failure hospitalisation.

- Subgroup analyses were done post-hoc and thus are considered as exploratory analyses.

- The sponsor of all the studies was the manufacturer of CardioMEMS[TM] and its participation was substantial. The sponsor was often involved in the design of the study, data collection, data analysis and interpretation. For some studies, data analysis was done only by the sponsor. Moreover, several authors were consultants or employee of the sponsor.

Randomized controlled trials (RCT)

- The personnel, including attending physicians and nurses, were unblinded for the CHAMPION trial and mostly unblinded for the GUIDE-HF trial. The main difference was that the nurse in charge of the PAP data was not blinded in the CHAMPION trial but was blinded in the GUIDE-HF trial.

- In the CHAMPION trial, the unblinded nurse working for the sponsor and having access to the patient PAP data made therapy recommendations to the local investigators for 180 of the 270 patients in the treatment group. This type of communication was not allowed by the protocol.

- The protocol for the CHAMPION trial was published toward the end of the study. The protocol manuscript was first sent to the Journal in April 2010, but the last patient was randomized in October 2009 and patient follow-up for the Randomized Access period was completed in August 2010. No protocol was published for the GUIDE-HF trial.

Non-randomized studies (NRS)

- One major limitation is the absence or insufficient control for confounding factors in the non-randomized studies

- The medication Sacubitril/Valsartan is a treatment for heart failure approved by the FDA on 7-July 2015 and in Europe on 24-November 2015. In the studies that used an uncontrolled before-and-after design, the patients during the pre-implantation period could not have access to the new treatment since their follow-up period was often before the approval date.

- In the CHAMPION Post-Approval study, patients were scheduled for 3 follow-up visits (at 1, 6 and 12 months) during the post-implantation period but not during the pre-implantation period. Thus, the uncontrolled before-and-after design makes it difficult to separate the effect of CardioMEMS[TM] from the effect of closer patient follow-up.

- Administrative claim database lacks information such as medication changes post-implantation and PAP data, making it difficult to link the reduction of heart failure to CardioMEMS[TM].

4.6 Safety

In the CHAMPION trial, the authors reported that 98.6% of patients (95% CI: 97.3% - 99.4%, n=575) were free of device-related or system-related complications at ≤6-month follow-up.[6] Moreover, implanted PAP sensors were functional for all patients at ≤6-month follow-up.

4.7 Guidelines

In 2016, the European Society of Cardiology guideline gave CardioMEMS[TM] a class IIb recommendation, i.e. the device may be considered for monitoring symptomatic patients with previous heart failure hospitalisation to decrease recurrent hospitalisation due to heart failure.[18] For class IIb, the evidence on the treatment efficacy is defined as "not well established". The recommendation was based on the CHAMPION trial and its follow-up non-randomized study[6,10], which were both appraised as low-quality of evidence in our report.

5.   COST AND BUDGET IMPACT ANALYSES

The 2020 financial analysis done by the department of finance at the MUHC estimated that the average encounter cost of an NYHA class III patient is $24,386, but that only $9,878 of these costs constitute variable costs that could contribute towards potential savings. We performed a meta-analysis with a random effects model on the 2 RCTs (CHAMPION and GUIDE-HF trials) to obtain the hospitalisation avoidance rate due to CardioMEMS[TM] (Figure 4). The avoidance rate is estimated to be 28% (95% CI: 5% - 45%) and thus the potential savings would be 2,766$ i.e. 28% of $9,878 (494$ - 4,445$) per patient. Given that each CardioMEMS[TM] HF system costs 17,500$, the *additional* cost of managing an NYHA class III patient with CardioMEMS[TM] would be $14,734 ($13,055-$17,006) (Table 5). Annually, the cost for CardioMEMS[TM] devices would be 700,000$ for 49 patients, which include 9 free devices for the first year. Consequently, the total cost would be $1,759,388 per year for CardioMEMS[TM] vs. $1,194,914 per year for current practice, for an additional cost of $564,474 per year.

6.   DISCUSSION

Only 2 RCTs, CHAMPION and GUIDE-HF trials, evaluated the effectiveness of the CardioMEMS[TM] HF system on reducing heart failure hospitalisation in adult patients recently hospitalised for heart failure compared to standard care management. Results from the CHAMPION trial shows that heart failure management guided by PAP data from CardioMEMS[TM] reduced the risk of heart failure hospitalisation in patients with NYHA class III compared to standard care. However, the evidence was of poor quality,

with a particularly serious contravention of the protocol because of the impact of unblinded outcomes assessors. Conversely, moderate-quality evidence from the GUIDE-HF trial indicates that the risk of heart failure hospitalisation was not statistically different between PAP-guided management and standard care management in patients with NYHA class II-IV. Further analysis suggests that Covid-19 status (pre-Covid-19 and during Covid-19) is an effect modifier. An analysis restricted to data before Covid-19 shows that CardioMEMS[TM] decreases heart failure hospitalisation in patients with NYHA class II-IV. Given that the level of significance was set higher at p=0.15 instead of the usual p=0.05, this result should be considered as a hypothesis-generating result; further studies are needed to determine whether the null effect seen in the overall analysis was due to the impact of the pandemic. Authors from the other 10 studies reported lower risk of heart failure hospitalisation for CardioMEMS[TM] in patients with NYHA class III, regardless of sex, BMI or ejection fraction. However, the quality of the evidence was low since they were non-randomized studies with no or not enough adjustment for confounding factors. Moreover, these studies often used the before-and-after design, which is not the most appropriate design to demonstrate a causal association.

Initially, the FDA did not approve the CardioMEMS[TM] HF monitoring system following the FDA advisory panel meeting for the premarket approval application on 8-December 2011. Most of the advisory panelists did not think (7 to 3 votes) that data from the Randomized Access of the CHAMPION trial provided clear evidence on CardioMEMS[TM] effectiveness and did not believe (6 to 4 votes) that the benefits of CardioMEMS[TM] outweigh the risk of use. A major concern was the potential bias due to the medical therapy recommendations made by unblinded nurses working for the sponsor for 180 of the 270 patients in the treatment group, which were not allowed by the protocol. Following additional analyses and data from the Open Access of the CHAMPION trial, a second FDA advisory panel meeting was held on 9-October 2013. Again, most of the advisory panelists did not think (7 to 4 votes) there was reasonable assurance that CardioMEMS[TM] was effective, citing presence of confounding biases. However, most of the panelists believed (6 to 4 votes, 1 abstain) that the benefits of CardioMEMS[TM] outweigh the risk of use. The FDA did not agree with the vote of the advisory panel regarding the lack of reasonable assurance on CardioMEMS[TM] effectiveness. Consequently, CardioMEMS[TM] was approved by the FDA on 28-May 2014 for remotely monitoring patients with NYHA class III who were hospitalised for heart failure at least once in the past year.[19] Based on data from the GUIDE-HF trial, in February 21, 2022 the FDA expanded CardioMEMS[TM] indication to include patients with NYHA class II who either were hospitalised for heart failure in the past year or had elevated natriuretic peptides.
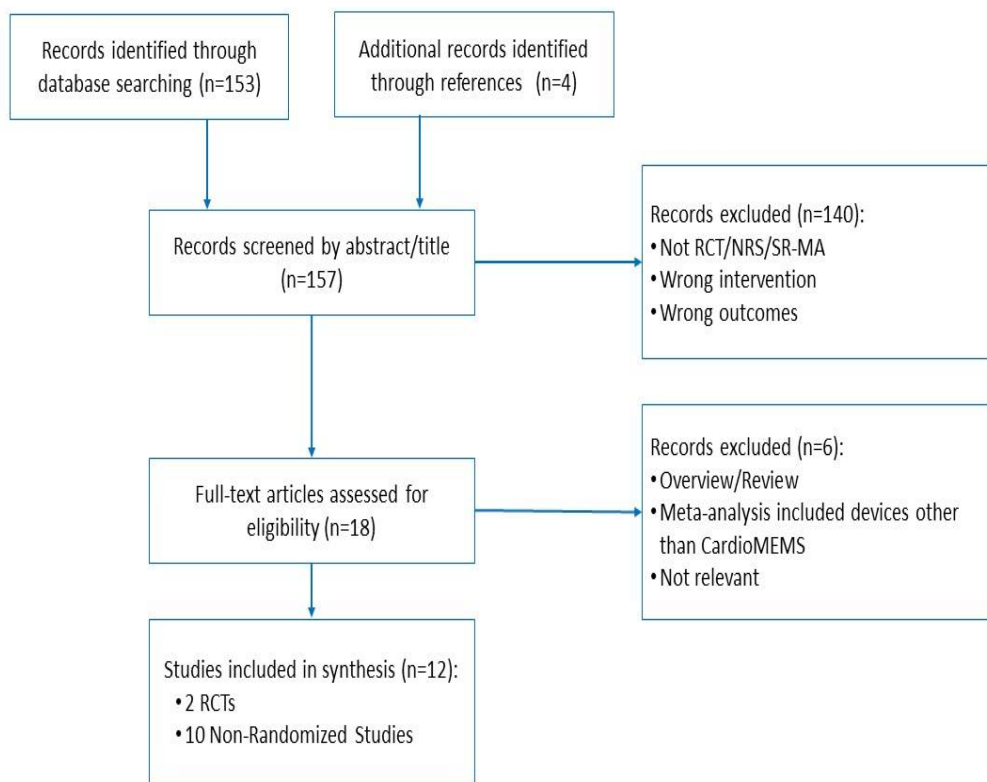
7. CONCLUSIONS

- The best available evidence, derived from two randomized controlled trials published in 2011 and 2021 (CHAMPION and GUIDE-HF, respectively), provided conflicting results:

  - Moderate-quality evidence from the GUIDE-HF trial indicates that there is no conclusive evidence that the CardioMEMS^{TM} HF system could be effective in reducing heart failure hospitalisation in adult patients with NYHA class II-IV and with recent hospitalisations for heart failure.

  - On the other hand, low-quality evidence from the CHAMPION trial suggests that CardioMEMS^{TM} might decrease heart failure hospitalisation in the subset of adults with NYHA class III.

- Although data from the non-randomized studies also concluded that CardioMEMS^{TM} reduced heart failure hospitalisation in adults with NYHA class III, the quality of the evidence was poor due to the presence of confounding bias and weak study design.

- CardioMEMS^{TM} sensor implantation appears to be safe, with the majority of patients with the PAP sensor reporting no complications 6 months after implantation of the sensor device.

- The current cost of the CardioMEMS^{TM} device remains relatively high at $17,500, and the resultant cost savings ($2766 per patient) from an estimated hospitalisation avoidance rate of 28% would not offset these device costs. The additional cost of monitoring 49 NYHA class III patients at the MUHC would be $564,473.

- The decision to adopt this technology at the MUHC needs to consider:

  - the equivocal results from the randomized trials and their low to moderate quality evidence

  - that even a large impact on hospitalisation avoidance will not offset the relatively high device costs for this patient population.

8.   RECOMMENDATIONS

- The TAU Policy Committee, made up of stakeholders from across the McGill University Health Centre, reviewed the evidence and issued the following recommendation: Not Approved
- This recommendation was reached based on the following:
  - o Evidence for the effectiveness of CardioMEMS in reducing hospitalizations is weak, and it is difficult to ascertain whether reductions in hospitalizations can be attributed to the use of CardioMEMS.
  - o Device costs are high and are not justifiable given the uncertainty in clinical benefit and patient compliance.
- This recommendation may be reviewed in 3 years, if new data from the literature and/or the local context become available.

FIGURES


```
┌─────────────────────────┐   ┌─────────────────────────┐
│ Records identified      │   │ Additional records      │
│ through database        │   │ identified through      │
│ searching (n=153)       │   │ references  (n=4)       │
└─────────────────────────┘   └─────────────────────────┘
```

Records screened by abstract/title (n=157)

Records excluded (n=140):
• Not RCT/NRS/SR-MA
• Wrong intervention
• Wrong outcomes

Full-text articles assessed for eligibility (n=18)

Records excluded (n=6):
• Overview/Review
• Meta-analysis included devices other than CardioMEMS
• Not relevant

Studies included in synthesis (n=12):
• 2 RCTs
• 10 Non-Randomized Studies

RCT, randomized controlled trial; NRS, non-randomized studies; SR-MA, systematic reviews and meta-analyses

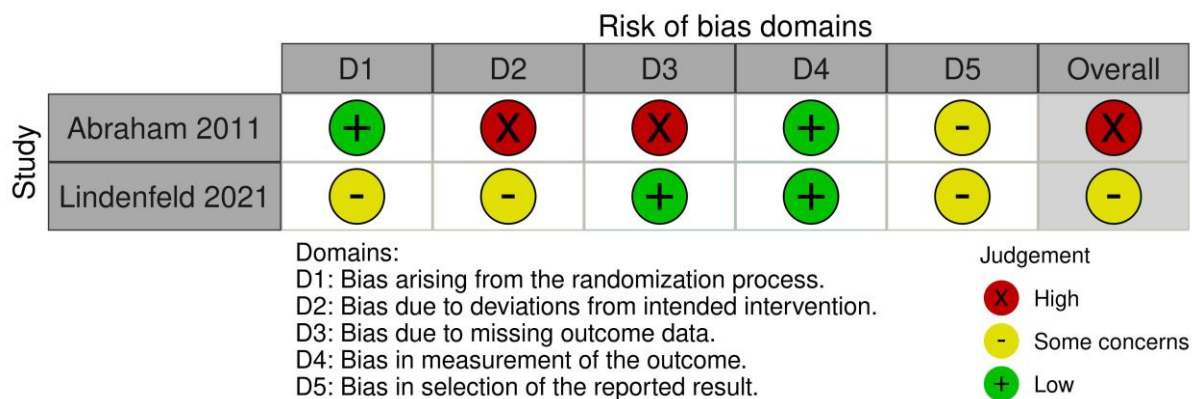**Figure 1. Flowchart of selection process of the studies**

Figure 2. Risk of bias summary of randomized clinical trials

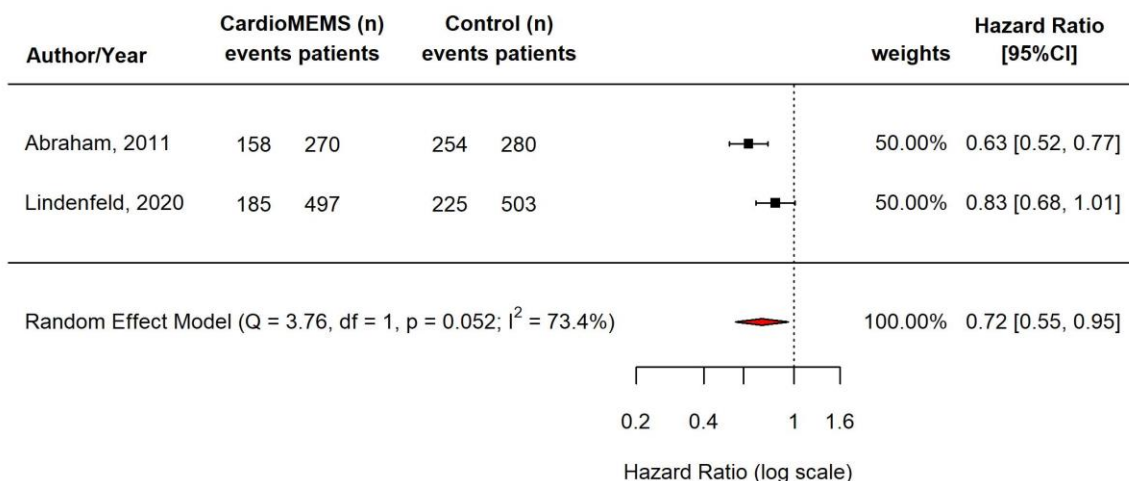**Figure 3. Risk of bias summary of non-randomized trials**

Figure 4. Estimation of heart failure hospitalisation avoidance rate for cost-effectiveness analysis

TABLES

Table 1. Characteristics of included randomized clinical trials

Author/Year	Study Design	Population	Intervention	Control
Abraham[6] 2011	Multicentre RCTs (CHAMPION trial)	Between Sept-6 2007 and Oct-7 2009, 550 ≥18 years patients at 64 centres in USA were randomized: • had NYHA functional class III heart failure symptoms for ≥3 months, regardless of left ventricular ejection fraction • had ≥1 heart failure hospitalisation within 1 year of the study • received best guideline-directed drug and device treatments Randomized patients CardioMEMS[TM]: n=270 Control: n=280	• Standard care heart failure management • Heart failure management was also guided by the daily uploaded pulmonary artery pressure data from CardioMEMS[TM] implanted before randomization • Data was collected prospectively • Number of patients with completed follow-up at 6-month was 244/270	• Standard care heart failure management • Heart failure management was based only on patients' clinical signs and symptoms • Patients also had CardioMEMS[TM] implanted before randomization and uploaded pulmonary artery pressure daily, but investigators did not have access to their data during trial • Data was collected prospectively • Number of patients with completed follow-up at 6-month was 254/280
Lindenfeld[14] 2021	Multicentre RCTs (GUIDED-HF trial)	Between March-15-2018 and Dec-20 2019, 1000 patients at 118 centres in USA or Canada were randomized: • had NYHA functional class II-IV heart failure symptoms, regardless of ejection fraction • either had a heart failure hospitalisation within 1 year of the study or elevated natriuretic peptides (or NT proBNP) within 30 days before consent Randomized patients CardioMEMS[TM]: n=497 Control: n=503	• Heart failure management according to guideline-recommended medical therapy • Heart failure management was also guided by the daily uploaded pulmonary artery pressure data from CardioMEMS[TM] implanted before randomization • Data was collected prospectively	• Heart failure management according to guideline-recommended medical therapy • Heart failure management was based only on patients' clinical signs and symptoms • Patients also had CardioMEMS[TM] implanted before randomization and uploaded pulmonary artery pressure daily, but investigators did not have access to their data • Data was collected prospectively

NYHA, New York Heart Association functional; NT proBNP, N-terminal pro b-type natriuretic peptide

Table 2. Characteristics of included non-randomized studies

Author/Year	Study Design	Population	Intervention	Comparator
Adamson[7] **2014**	Non-randomized study (Sub-analysis of CHAMPION trial)	549 participants from the CHAMPION trial: • ≥18 years patients at 64 centres • with NYHA functional class III heart failure symptoms for ≥3 months • had ≥1 heart failure hospitalisation within 1 year of the study • received best guideline-directed drug and device treatments Patients with HFrEF (LVEF < 40%) CardioMEMS[TM]: n=208 Control: n=222 Patients with HFpEF (LVEF ≥ 40%) CardioMEMS[TM]: n=62 Control: n=57	• Standard care heart failure management • Heart failure management was also guided by the daily uploaded pulmonary artery pressure data from CardioMEMS[TM] implanted before randomization • Data was collected prospectively	• Standard care heart failure management • Heart failure management was based only on patients' clinical signs and symptoms • Patients also had CardioMEMS[TM] implanted before randomization and uploaded pulmonary artery pressure daily, but investigators did not have access to their pulmonary artery pressure data • Data was collected prospectively
Givertz[8] **2017**	Non-randomized study (Sub-analysis of CHAMPION trial)	456 participants with HFrEF (LVEF ≤40%) from the CHAMPION trial: • ≥18 years patients at 64 centres • with NYHA functional class III heart failure symptoms for ≥3 months • had ≥1 heart failure hospitalisation within 1 year of the study • received best guideline-directed drug and device treatments Patients with HFrEF (LVEF ≤40%) CardioMEMS[TM]: n=222 Control: n=234	• Standard care heart failure management • Heart failure management was also guided by the daily uploaded pulmonary artery pressure data from CardioMEMS[TM] implanted before randomization • Data was collected prospectively	• Standard care heart failure management • Heart failure management was based only on patients' clinical signs and symptoms • Patients also had CardioMEMS[TM] implanted before randomization and uploaded pulmonary artery pressure daily, but investigators did not have access to their pulmonary artery pressure data • Data was collected prospectively
Varma[9] **2021**	Non-randomized	190 participants with cardiac resynchronization	• Standard care heart failure management	• Standard care heart failure management

Author/Year	Study Design	Population	Intervention	Comparator
	study (*Sub-analysis of CHAMPION trial*)	therapy (CRT) from the CHAMPION trial: • with NYHA functional class III heart failure symptoms for ≥3 months • had ≥1 heart failure hospitalisation within 1 year of the study • received best guideline-directed drug and device treatments Patients with CRT CardioMEMS™: n=91 Control: n=99	• Heart failure management was also guided by the daily uploaded pulmonary artery pressure data from CardioMEMS™ implanted before randomization • Data was collected prospectively	• Heart failure management was based only on patients' clinical signs and symptoms • Patients also had CardioMEMS™ implanted before randomization and uploaded pulmonary artery pressure daily, but investigators did not have access to their data • Data was collected prospectively
Abraham[10] **2016**	Before-After study (*CHAMPION open access period*)	280 participants enrolled in the control group from the CHAMPION trial: • ≥18 years patients at 64 centres • with NYHA functional class III heart failure symptoms for ≥3 months • had ≥1 heart failure hospitalisation within 1 year of the study • received best guideline-directed drug and device treatments Patients Intervention: n=280 (*Randomized Access*) Comparator: n=170 (*Open Access*)	• During open access period: August 2010 to April 2012 (*Open Access*) • Pulmonary artery pressure data became available to investigators to guide heart failure management • No recommendation on medical therapy was made from the sponsor, unlike the CHAMPION trial • Data was collected prospectively	• Before open access period: September 2007 to August 2010 (*Randomized Access*) • Standard care heart failure management • Heart failure management was based only on patients' clinical signs and symptoms • Patients also had CardioMEMS™ implanted before randomization and uploaded pulmonary artery pressure daily, but investigators did not have access to their pulmonary artery pressure data • Data was collected prospectively

Author/Year	Study Design	Population	Intervention	Comparator
Shavelle[11] **2020**	Before-After study (*CHAMPION Post-Approval Study*)	Between 1-Sept 2014 and 11-Oct 2017, 1200 ≥18 years patients were implanted with CardioMEMS™ in 104 centres in USA: • with chronic NYHA functional class III heart failure symptoms • had ≥1 heart failure hospitalisation within 1 year of the study	• Post-implantation: 1 year after patients were implanted with CardioMEMS™ HF system sensor • Standardized management strategies were based on daily uploaded pulmonary artery pressure data • Data was collected prospectively	• Pre-implantation: 1 year before patients were implanted with CardioMEMS™ HF system sensor • Management strategies were based on local standard care • Data was collected retrospectively
DeFilippis[12] **2021**	Before-After study (*subgroup analysis of CHAMPION Post-Approval Study*)	1200 participants from the CHAMPION Post-Approval study: • ≥18 years patients at 104 centres • with chronic NYHA functional class III heart failure symptoms • had ≥1 heart failure hospitalisation within 1 year of the study Patients Men: n=748 Women: n=452	• Post-implantation: 1 year after patients were implanted with CardioMEMS™ HF system sensor • Standardized management strategies were based on daily uploaded pulmonary artery pressure data • Data was collected prospectively	• Pre-implantation: 1 year before patients were implanted with CardioMEMS™ HF system sensor • Management strategies were based on local standard care • Data was collected retrospectively
Brinkley[13] **2021**	Before-After study (*subgroup analysis of CHAMPION Post-Approval Study*)	1200 participants from the CHAMPION Post-Approval study: • ≥18 years patients at 104 centres • with chronic NYHA functional class III heart failure symptoms • had ≥1 heart failure hospitalisation within 1 year of the study Patients EF<40%/BMI< 35kg/m^2: n=489 EF<40%/BMI≥ 35kg/m^2: n=148 EF≥40%/BMI< 35kg/m^2: n=352 EF≥40%/BMI≥ 35kg/m^2: n=209	• Post-implantation: 1 year after patients were implanted with CardioMEMS™ HF system sensor • Standardized management strategies were based on daily uploaded pulmonary artery pressure data • Data was collected prospectively	• Pre-implantation: 1 year before patients were implanted with CardioMEMS™ HF system sensor • Management strategies were based on local standard care • Data was collected retrospectively

Author/Year	Study Design	Population	Intervention	Comparator
Desai[15] **2017**	Before-After study (*Medicare data*)	1114 patients identified in Medicare database in USA with billing codes (38.26, 02HF30Z, 02HR30Z, C9741 or C2624): • had CardioMEMS™ implanted between 1-June 2014 and 31-December 2015 • with NYHA functional class III heart failure symptoms • had to be continuously enrolled in Medicare or HMO insurance (CMS) for ≥6 months before and after implantation • had ≥6 months of follow-up before and after implantation	• Post-implantation: 6 to 12 months after patients were implanted with a Pulmonary Artery Pressure sensor • Heart failure management was guided by the uploaded pulmonary artery pressure data • Data was collected retrospectively from Medicare claims database	• Pre-implantation: 6 to 12 months before patients were implanted with a Pulmonary Artery Pressure sensor • Unclear heart failure management strategies • Data was collected retrospectively from Medicare claims database
Abraham[16] **2019**	Matched cohort study (*Medicare data*)	Intervention group 1185 patients identified in Medicare database in USA with billing codes (38.26, 02HF30Z, 02HR30Z, C9741 or C2624): • had CardioMEMS™ implanted between 1-June 2014 and 31-Dec 2016 • with NYHA functional class III heart failure symptoms • had to be continuously enrolled in Medicare (CMS) for ≥12 months before and after implantation • had ≥12 months of follow-up before and after implantation Comparator group 1087 patients identified in Medicare database in USA through matching: • did not get CardioMEMS™ sensor • had ≥1 heart failure hospitalisation between 1-July 2013 and 31-March 2016 • unspecified NYHA class	• Patients were implanted with CardioMEMS™ HF system sensor • Heart failure management was guided by the uploaded pulmonary artery pressure data • Data was collected retrospectively from Medicare claims database	• Patients without CardioMEMS™ sensor implanted • Unspecified heart failure management strategies • Data was collected retrospectively from Medicare claims database

Author/Year	Study Design	Population	Intervention	Comparator
Angermann[17] **2020**	Before-After study (*MEMS-HF*)	Between 13-May 2016 and 29-March 2018, 234 ≥18 years patients were implanted with CardioMEMS™ in 31 centres in Germany, Netherlands and Ireland: • with NYHA functional class III heart failure symptoms for at ≥1 months • had ≥1 heart failure hospitalisation within 1 year of the study	• Post-implantation: 1 year after patients were implanted with CardioMEMS™ HF system sensor • Standardized heart failure management strategies were based on daily uploaded pulmonary artery pressure data • Data was collected prospectively	• Pre-implantation: 1 year before patients were implanted with CardioMEMS™ HF system sensor • Heart failure management strategies were based on local standard care • Data was collected retrospectively

NYHA, New York Heart Association functional; HF, heart failure; EF, ejection fraction; BMI, body mass index; CRT, cardiac resynchronization therapy; HFpEF, heart failure preserved ejection fraction; HFrEF, heart failure reduced ejection fraction; LVEF, left ventricular ejection fraction

Table 3. Result summary of randomized clinical trials

Author/Year	Analytical methods	Results (CardioMEMS vs Control)	Quality of Evidence	
			Score	Comments
Abraham[6] 2011	• Negative binomial regression for the primary endpoint • Anderson-Gill model for prespecified supplementary endpoint	HF hospitalisation at ≤6 months of follow-up (n=550) • RR=0.72, 95% CI: 0.60-0.85 (Negative Binomial) • Rate of events: 0.32 vs 0.44 per patient-year HF hospitalisation for entire follow-up period (mean=15 months) (n=550) • HR=0.63, 95% CI: 0.52-0.77 (Andersen-Gill) • Nb of events: 158 vs 254 Proportion of patients hospitalised for HF at 6-month (n=550) *(secondary outcome)* • 55 vs 80, p=0.029	Low	• High risk of bias • Serious protocol violations from unblinded outcome assessors • Women and non-white patients were under-represented • Sponsored by the manufacturer of CardioMEMS™ system
Lindenfeld[14] 2021	Overall or Pre-Covid-19 analysis • Andersen-Gill model with robust sandwich variance estimate Covid-19 effect analysis • Andersen-Gill model with robust sandwich variance estimate • Interaction term between a time-varying covariate and treatment was added to the model	HF hospitalisation at 1-year post-implant (n=1000) • HR=0.83, 95%CI: 0.69- 1.01 • Rate of events: 0.410 vs 0.497 per patient-year HF hospitalisation at 1-year post-implant (n=1000) *(pre-COVID-19)* • HR=0.72, 95%CI: 0.57-0.92 • Rate of events: 0.380 vs 0.525 per patient-year	Moderate	• Moderate risk of bias • HF hospitalisation was a component of the primary endpoint; thus, study could have been underpowered for this outcome • Analyses for the pre-Covid-19 are exploratory analyses since the authors used a significance level of p=0.15 to determine the Covid-19 effect • Sponsored by the manufacturer of CardioMEMS™ system

HF, heart failure; RR, rate ratio; HR, hazard ratio; CI, confidence intervals

Table 4. Result summary of non-randomized studies

Author/Year	Analytical methods	Results (CardioMEMS[TM] vs Comparator)	Quality of Evidence	
			Score	Comments
Adamson[7] 2014	• Negative binomial regression model • Adjusted for duration in trial and group • Pre-specified subgroup analysis	HF hospitalisation in patients with HFpEF (LVEF ≥ 40%) at ≤6 months of follow-up (n=119) • RR=0.54, 95% CI: 0.38-0.70 • Rate of events: 0.18 vs 0.33 per patient-year HF hospitalisation in patients with HFrEF (LVEF < 40%) at ≤6 months of follow-up (n=430) • RR=0.76, 95% CI: 0.61-0.91 • Rate of events: 0.36 vs 0.47 per patient-year	Low	• Critical risk of bias • Women and non-white patients were under-represented • Post-hoc analysis • Sponsored by the manufacturer of the CardioMEMS[TM] system • No statistical test done for the comparison between patients with LVEF ≥40% and LVEF <40%
Givertz[8] 2017	• Andersen-Gill model with robust sandwich variance estimate • No adjustment for confounding factors	HF hospitalisation in patients with HFrEF after an average 18 months of follow-up (n=456) • HR=0.72, 95% CI: 0.59-0.88 • Rate of events: 0.49 vs 0.69 per patient-year	Low	• Critical risk of bias • Women and non-white patients were under-represented • Post-hoc analysis • Sponsored by the manufacturer of the CardioMEMS[TM] system
Varma[9] 2021	• Andersen-Gill model with robust sandwich variance estimate • Adjusted for randomization variable and covariates with p<0.15 (backward elimination)	HF hospitalisation in patients with CRT implants after an average 18 months of follow-up (n=190) • HR=0.70, 95% CI: 0.51-0.96 • Rate of events: 0.46 vs 0.68 per patient-year	Low	• Critical risk of bias • Women and non-white patients were under-represented • Post-hoc analysis • Sponsored by the manufacturer of the CardioMEMS[TM] system
Abraham[10] 2016	• Andersen-Gill model with robust sandwich variance estimate • Adjusted for frailty variable • Not pre-specified analysis	HF hospitalisation open vs close access period in control group • HR=0.52, 95% CI: 0.40-0.69 • Rate of events: 0.36 vs 0.68 per patient-year	Low	• Serious risk of bias • Weak causal relation due to the before-and-after study design • Sponsored by the manufacturer of the CardioMEMS system
Shavelle[11]	• Andersen-Gill model with robust	HF hospitalisation at 1-year post vs 1-year pre-implant	Low	• Serious risk of bias

Author/Year	Analytical methods	Results (CardioMEMS™ vs Comparator)	Quality of Evidence	
			Score	Comments
2020	sandwich variance • No adjustment for confounding factors	<u>(n=1200)</u> • HR=0.43, 95% CI: 0.39-0.47 • Rate of events: 0.54 vs 1.25 patient-year <u>HF hospitalisation at 1-year post vs 1-year pre-implant among patients who survived 1-year (n=938)</u> • HR=0.35, 95% CI: 0.31-0.39 • Rate of events: NR		• Weak causal relation due to the before-and-after study design • When analysis was restricted to patients that survived at 1-year (n=938), it excluded patients with poorer health • Sponsored by the manufacturer of the CardioMEMS™ system
DeFilippis[12] **2021**	• Andersen-Gill model with robust sandwich variance estimate • No adjustment for confounding factors for main analyses • <u>Interaction with Sex:</u> Regression model was adjusted for age, sex, race, ejection fraction, systolic blood pressure, serum creatinine, BMI, coronary artery disease, diabetes, ICD/CRT or CRT-defibrillator	<u>HF hospitalisation at 1-year post vs 1-year pre-implant between **men and women** ($P_{interaction}$= 0.16 not adjusted, $P_{interaction}$= 0.13 adjusted)</u> • HR=0.46, 95% CI: 0.40-0.52 (*Men, n=748*) • HR=0.39, 95% CI: 0.33-0.46 (*Women, n=452*)	Low	• Serious risk of bias • Weak causal relation due to the before-and-after study design • Sponsored by the manufacturer of the CardioMEMS™ system

Author/Year	Analytical methods	Results (CardioMEMS™ vs Comparator)	Quality of Evidence	
			Score	Comments
Brinkley[13] **2021**	• Andersen-Gill model with robust sandwich variance estimate • No adjustment for confounding factors	HF hospitalisation at 1-year post vs 1-year pre-implant between ***<35kg/m^2 vs ≥35kg/m^2*** (P$_{interaction}$= 0.07) • HR=0.45, 95% CI: 0.40-0.51 (*BMI < 35kg/m^2, n=841*) • HR=0.37, 95% CI: 0.30-0.45 (*BMI ≥ 35kg/m^2, n=357*) HF hospitalisation at 1-year post vs 1-year pre-implant between ***<35kg/m^2 vs ≥35kg/m^2*** **in EF < 40%** (P$_{interaction}$= 0.28) • HR=0.48, 95% CI: 0.41-0.55 (*BMI < 35kg/m^2, n=331*) • HR=0.40, 95% CI: 0.31-0.53 (*BMI ≥ 35kg/m^2, n=107*) HF hospitalisation at 1-year post vs 1-year pre-implant between ***<35kg/m^2 vs ≥35kg/m^2*** **in EF ≥ 40%** (P$_{interaction}$= 0.20) • HR=0.42, 95% CI: 0.35-0.52 (*BMI < 35kg/m^2, n=238*) • HR=0.34, 95% CI: 0.25-0.45 (*BMI ≥ 35kg/m^2, n=160*)	Low	• Serious risk of bias • Weak causal relation due to the before-and-after study design • Sponsored by the manufacturer of the CardioMEMS™ system

Desai[15] **2017**	• Andersen-Gill model for main analysis with robust variance estimate
	 • For sensitivity analyses:
	   ○ GEE Negative binomial model
	   ○ GEE Poisson model
	   ○ Andersen-Gill model restricted to patients who did not die during follow-up
	 • No adjustment for confounding factors
		HF hospitalisation at 6-month post vs 6-month pre-implant (n=1114)
		 • HR=0.55, 95% CI: 0.49-0.61 (*Andersen-Gill*)
		 • HR=0.64, 95% CI: 0.57-0.73 (*GEE Negative Binomial*)
		 • HR=0.60, 95% CI: 0.53-0.68 (*GEE Poisson*)
		 • Rate of events: 0.37 vs 0.92 per patient-6 months
		
		 HF hospitalisation in patients still alive 6-month post vs 6-month pre-implant (n=975)
		 • HR=0.36, 95% CI: 0.31-0.42 (*Andersen-Gill*)
		 • Rate of events: NR
		
		 HF hospitalisation at 1-year post vs pre-implant (n=480)
		 • HR=0.66, 95% CI: 0.57-0.76
		 • Rate of events: NR
			Low	• Serious risk of bias
				 • When analysis was restricted to patients that survived at 6-month (n=958), patients with higher risk of complications were excluded
				 • Weak causal relation due to the before-and-after without concurrent control study design
				 • Sponsored by the manufacturer of the CardioMEMS™ system

Author/Year	Analytical methods	Results (CardioMEMS™ vs Comparator)	Quality of Evidence	
			Score	Comments
Abraham[16] **2019**	• Andersen-Gill model with robust variance estimate • Matched by a stepwise iterative algorithm on demographic characteristics (*sex, race, history of ICD/CRT implant, end-stage renal disease status, age within 5 years*) • Further matched on propensity score for comorbidities (*arrhythmia, diabetes, hypertension, renal disease, pulmonary disease*) • Additional matching on same number of HF and non-HF hospitalisation	HF hospitalisation at 1-year post vs 1-year pre-implant (n=1087 matched 1-to-1) • HR=0.76, 95% CI: 0.65-0.89 • Rate of events: 0.65 vs 0.88 per patient-year	Low	• Serious risk of bias • Sponsored by the manufacturer of the CardioMEMS™ system
Angermann[17] **2020**	• Andersen-Gill model • Unspecified method for variance estimation • No adjustment for confounding factors • Secondary outcome	HF hospitalisation at 1-year post vs 1-year pre-implant (n=234) • HR=0.38, 95% CI: 0.31-0.48 • Rate of events: 0.60 vs 1.55 per patient-year	Low	• Serious risk of bias • Weak causal relation due to the before-and-after without concurrent control study design • Sponsored by the manufacturer of the CardioMEMS™ system

HF, heart failure; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; HFpEF, heart failure preserved ejection fraction; HFrEF, heart failure reduced ejection fraction; LVEF, left ventricular ejection fraction; HR, hazard ratio; RR, rate ratio; CI, confidence intervals; NR, not reported; GEE, generalized estimating equation

Table 5. Budget impact of CardioMEMS^TM

	Without CardioMEMS^TM	With CardioMEMS^TM	
		Per patient	Per year (49 patients/year)
Device cost			
1. Cost of CardioMEMS^TM device	-	17,500$	700,000$ [1]
Average encounter cost for NYHA class III patient			
2. Fixed costs	14,508$	14,508$	710892$
3. Variable costs (Potential saving) [2]	9,878$	9,878$	484,022$
Hospital avoidance rate [3]	N/A	28% (95% CI: 5% - 45%)	
4. Avoided cost (avoidance rate x variable costs)	N/A	2,766$ (494$ - 4,445$)	135,526$ (24,201$ - 217,810$)
Net cost (1+2+3-4)	**24,386$**	**39,120$ (22,933$ - 26,884$)**	**1,759,388$ (1,677,104 $ - 1,870,713$)**
Additional cost of CardioMEMS^TM	N/A	14,734$ (13,055$ - 17,006$)	564,474$ (482,190$ - 675,798$)

[1] Discounted device price for volume (technology credits $4,025 for 40 devices): $14,286/device
[2] Variable cost obtained from the financial analysis 2020
[3] Avoidance rate obtained from the meta-analysis of 2 RCTs (see Figure 4)

REFERENCES

1. Canada PHA of. Report from the Canadian Chronic Disease Surveillance System: Heart Disease in Canada, 2018 [Internet]. 2018 [cited 2022 May 20]. Available from: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/report-heart-disease-Canada-2018.html

2. Salah HM, Minhas AMK, Khan MS, Pandey A, Michos ED, Mentz RJ, et al. Causes of hospitalization in the USA between 2005 and 2018. Eur Heart J Open [Internet]. 2021 Aug 19 [cited 2022 May 20];1(1). Available from: https://academic.oup.com/ehjopen/article/1/1/oeab001/6294753

3. Tran DT, Ohinmaa A, Thanh NX, Howlett JG, Ezekowitz JA, McAlister FA, et al. The current and future financial burden of hospital admissions for heart failure in Canada: a cost analysis. Can Med Assoc Open Access J. 2016 Jul 21;4(3):E365–70.

4. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898.

5. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016 Oct 12;355:i4919.

6. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet Lond Engl. 2011 Feb 19;377(9766):658–66.

7. Adamson PB, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail. 2014 Nov;7(6):935–44.

8. Givertz MM, Stevenson LW, Costanzo MR, Bourge RC, Bauman JG, Ginn G, et al. Pulmonary Artery Pressure-Guided Management of Patients With Heart Failure and Reduced Ejection Fraction. J Am Coll Cardiol. 2017 Oct 10;70(15):1875–86.

9. Varma N, Bourge RC, Stevenson LW, Costanzo MR, Shavelle D, Adamson PB, et al. Remote Hemodynamic-Guided Therapy of Patients With Recurrent Heart Failure Following Cardiac Resynchronization Therapy. J Am Heart Assoc. 2021 Feb;10(5):e017619.

10. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB, et al. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. Lancet Lond Engl. 2016 Jan 30;387(10017):453–61.

11. Shavelle DM, Desai AS, Abraham WT, Bourge RC, Raval N, Rathman LD, et al. Lower Rates of Heart Failure and All-Cause Hospitalizations During Pulmonary Artery Pressure-Guided Therapy for Ambulatory Heart Failure: One-Year Outcomes From the CardioMEMS Post-Approval Study. Circ Heart Fail. 2020 Aug;13(8):e006863.

12. DeFilippis EM, Henderson J, Axsom KM, Costanzo MR, Adamson PB, Miller AB, et al. Remote Hemodynamic Monitoring Equally Reduces Heart Failure Hospitalizations in Women and Men in Clinical Practice: A Sex-Specific Analysis of the CardioMEMS Post-Approval Study. Circ Heart Fail. 2021 Jun;14(6):e007892.

13. Brinkley DM, Guglin ME, Bennett MK, Redfield MM, Abraham WT, Brett ME, et al. Pulmonary Artery Pressure Monitoring Effectively Guides Management to Reduce Heart Failure Hospitalizations in Obesity. JACC Heart Fail. 2021 Nov;9(11):784–94.

14. Lindenfeld J, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmanshof D, et al. Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. Lancet Lond Engl. 2021 Sep 11;398(10304):991–1001.

15. Desai AS, Bhimaraj A, Bharmi R, Jermyn R, Bhatt K, Shavelle D, et al. Ambulatory Hemodynamic Monitoring Reduces Heart Failure Hospitalizations in "Real-World" Clinical Practice. J Am Coll Cardiol. 2017 May 16;69(19):2357–65.

16. Abraham J, Bharmi R, Jonsson O, Oliveira GH, Artis A, Valika A, et al. Association of Ambulatory Hemodynamic Monitoring of Heart Failure With Clinical Outcomes in a Concurrent Matched Cohort Analysis. JAMA Cardiol. 2019 Jun 1;4(6):556–63.

17. Angermann CE, Assmus B, Anker SD, Asselbergs FW, Brachmann J, Brett ME, et al. Pulmonary artery pressure-guided therapy in ambulatory patients with symptomatic heart failure: the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF). Eur J Heart Fail. 2020 Oct;22(10):1891–901.

18. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129–200.

19. Loh JP, Barbash IM, Waksman R. Overview of the 2011 Food and Drug Administration Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting on the CardioMEMS Champion Heart Failure Monitoring System. J Am Coll Cardiol. 2013 Apr 16;61(15):1571–6.

APPENDICES

APPENDIX A: SEARCH STRATEGY

Table A. Keywords for literature search in PubMed

#	Keyword	Nb of articles
	Intervention	
1	"CardioMEMS"[All Fields]	153

APPENDIX B: RANDOMIZED CLINICAL TRIALS

Table B. Details on the risk of bias assessment of RCTs

Outcomes	Randomisation process	Deviations from intended intervention	Missing outcome data	Measurement of the outcome	Selection of reported results	Comments	Overall Risk of bias
Abraham[6] 2011							
Heart failure hospitalisation	L	H	H	L	M	− Personnel members were not blinded − Investigators were not blinded but did not have access to PAP of patients in the control group during trial. However, they managed clinical symptoms for both groups − Patients was censored at the time of death, but death is a competing event − The sponsor participated in the study design. Data monitoring, collection and management were done by the sponsor − The sponsor was responsible for the data collection and analysis, and participated in the interpretation of results (Abraham et al 2016) − According to the FDA summary, nurses working for the sponsor made therapeutic recommendations for 180/270 patients in the treatment group − Several authors worked/consulted for the sponsor, including the lead and corresponding author − Protocol was published after the randomisation period	High
Lindenfeld[14] 2021							
Heart failure hospitalisation	M	M	L	L	M	− No information on concealment method − Some of the personnel were not blinded − Investigators were not blinded, but they did not have access to PAP of patients in the control group. However, they managed clinical symptoms for both groups − More patients in the control group (n=44) dropout of the study than in the treatment group (n=25), though the reasons were similar − Though data up to their dropout was included in the analysis, it is unclear if these patients	Moderate

Outcomes	Randomisation process	Deviations from intended intervention	Missing outcome data	Measurement of the outcome	Selection of reported results	Comments	Overall Risk of bias
						withdrew earlier or later in the study, and if it differs between the 2 groups − Patients was censored at the time of death, but death is a competing event − The sponsor participated in the study design, data collection, data analysis, data interpretation and report writing − Several authors worked/consulted for the sponsor, including the lead and corresponding author	

APPENDIX C: NON-RANDOMIZED STUDIES

Table C. Details on the risk of bias assessment of non-randomized studies

Outcomes	Confounding	Selection of participants	Intervention classification	Deviations from intended intervention	Missing data	Measurement of outcome	Selection of the reported result	Comments	Overall Risk of bias
Adamson[7] 2014									
Heart failure hospitalisation	S	L	L	C	M	M	L	− Adjustment only for duration trial and group − No comparison between treatment and control groups for missing data − failure hospitalisation within the past 12 months − Analysis did not account for patients that were loss-to-follow-up − The sponsor participated in the study design. Data monitoring, collection and analysis were done by the sponsor. − Several authors worked/consulted for the sponsor, including the first author	Critical
Givertz[8] 2017									
Heart failure hospitalisation	S	L	L	C	M	M	L	− No adjustment for confounding factors − No comparison between treatment and control groups for missing data − Patients were censored at the time of death, but death is a competing event − The sponsor participated in the study design. Data monitoring, collection and management were done by the sponsor. − Several authors worked/consulted for the sponsor	Critical

Outcomes	Confounding	Selection of participants	Intervention classification	Deviations from intended intervention	Missing data	Measurement of outcome	Selection of the reported result	Comments	Overall Risk of bias
Varma[9] 2021									
Heart failure hospitalisation	M	L	L	C	M	M	L	− Unclear which covariates were included in the model − No comparison between treatment and control groups for missing data − Patients were censored at the time of death, but death is a competing event − The sponsor participated in the study design. Data monitoring, collection and management were done by the sponsor. − Several authors worked/consulted for the sponsor	Critical
Abraham[10] 2016									
Heart failure hospitalisation	S	S	L	L	M	M	M	− No adjustment for confounding factors − Selected patients were healthy enough to be transferred to the Open Access study − Patients in the pre-implant period were required to have ≥1 HF hospitalisation within the past 12 months when the outcome is HF hospitalisation − HF hospitalisation was not defined − Patients were censored at the time of death, but death is a competing event − Data analysis was done by the sponsor − Several authors worked/consulted for the sponsor, including the leading author	Serious

Outcomes	Confounding	Selection of participants	Intervention classification	Deviations from intended intervention	Missing data	Measurement of outcome	Selection of the reported result	Comments	Overall Risk of bias
Shavelle[11] 2020									
Heart failure hospitalisation	S	S	L	S	M	L	L	− No adjustment for confounding factors, including heart failure medication not available during pre-implantation period − Selected patients were healthy enough to participate in the study − Patients in the pre-implant period were required to have ≥1 HF hospitalisation within the past 12 months when the outcome is HF hospitalisation − Data was collected retrospectively for the comparative group − Patients were censored at the time of death, but death is a competing event − The sponsor participated in the design and conduct of the study (data collection, data management, data analysis and data interpretation, review of the manuscript) − Several authors worked/consulted for the sponsor	Serious
DeFilippis[12] 2021									
Heart failure hospitalisation	S	S	L	S	M	L	L	− No adjustment for confounding factors, including heart failure medication not available during pre-implantation period − Selected patients were healthy enough to participate in the study − Patients in the pre-implant period were required to have ≥1 HF hospitalisation within the past 12 months when the outcome is HF hospitalisation − Data was collected retrospectively for the comparative group − Patients were censored at the time of death, but death is a competing event − N=357 patients did not have hemodynamic data at 12-month due to death (n=185), no available measurement (n=93), investigator withdrawal (n=24), subject withdrawal (n=21), noncompliance (n=21), loss-to-follow up (n=7) and others (n=6) − The sponsor participated in the design and conduct of the study (data collection, data management, data analysis and data interpretation, review of the manuscript) − Several authors worked/consulted for the sponsor	Serious

Outcomes	Confounding	Selection of participants	Intervention classification	Deviations from intended intervention	Missing data	Measurement of outcome	Selection of the reported result	Comments	Overall Risk of bias
Brinkley[13] 2021									
Heart failure hospitalisation	S	S	L	S	M	L	M	− No adjustment for confounding factors, including heart failure medication not available during pre-implantation period − Patients in the pre-implant period were required to have ≥1 HF hospitalisation within the past 12 months when the outcome is HF hospitalisation − Data was collected retrospectively for the comparative group − Patients were censored at the time of death, but death is a competing event − N=357 patients did not have hemodynamic data at 12-month due to death (n=185), no available measurement (n=93), investigator withdrawal (n=24), subject withdrawal (n=21), noncompliance (n=21), loss-to-follow up (n=7) and others (n=6) − Data analysis was provided by the sponsor − Several authors worked/consulted for the sponsor	Serious
Desai[15] 2017									
Heart failure hospitalisation	S	S	L	S	M	M	L	− No adjustment for confounding factors, including heart failure medication not available during pre-implantation period − Patients in the pre-implant were required to have ≥1 HF hospitalisation when the outcome is HF hospitalisation − Selected patients were required to be continuously enrolled in Medicare or HMO insurance to be included in the study − Patients were censored at the time of death, but death is a competing event − Data was collected retrospectively from Medicare database and does not include paid claims from Health maintenance organisations − Heart failure hospitalisation was defined by methods from Centers for Medicare and Medicaid Services (CMS) instead of being adjudicated − The sponsor was involved in the conception of the analytical plan − Data analysis was done by the sponsor. Results were independently reviewed by an	Serious

Outcomes	Confounding	Selection of participants	Intervention classification	Deviations from intended intervention	Missing data	Measurement of outcome	Selection of the reported result	Comments	Overall Risk of bias
								external healthcare economic consultant but unclear if it was only for cost analysis − Several authors worked/consulted for the sponsor, including the leading author	
Abraham[16] 2019									
Heart failure hospitalisation	M	M	L	S	M	M	L	− Potential confounding factors were not matched, such as medications/co-treatments or NYHA class − Data was collected retrospectively from Medicare database and does not include paid claims from Health maintenance organisations − No information on medication changes post-implant or PAP data − Heart failure hospitalisation was defined by methods from Centers for Medicare and Medicaid Services (CMS) − Patients were censored at the time of death, but death is a competing event − The sponsor participated in the study design and in conducting the study (management, collection, analysis and interpretation of data) − Several authors received grants from the sponsor, including the leading author	Serious

Outcomes	Confounding	Selection of participants	Intervention classification	Deviations from intended intervention	Missing data	Measurement of outcome	Selection of the reported result	Comments	Overall Risk of bias
Angermann[17] 2020									
Heart failure hospitalisation	S	S	L	S	M	S	M	− No adjustment for confounding factors, including heart failure medication not available during pre-implantation period − Patients in the pre-implant period were required to have ≥1 HF hospitalisation within the past 12 months when the outcome is heart failure hospitalisation − HF hospitalisation was not defined − Data was collected retrospectively for the pre-implant period − Patients were censored at the time of death, but death is a competing event − Several authors worked/consulted for the sponsor, including the leading author − Protocol was published toward the end of enrollment	Serious

L: low, M: moderate, S: serious, C: critical, NI: no information