Université de Montréal

Revues systématiques et méta-analyses en chirurgie cardiaque : Défis et solutions

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Revues systématiques et méta-analyses en chirurgie cardiaque : Défis et solutions

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Résumé

Objectif: Explorer, adapter et développer de nouvelles méthodologies permettant de réaliser des revues systématiques et méta-analyses en chirurgie cardiaque.

Méthodes: Le *text mining* et la *citation chasing* ont été utilisés pour l'optimisation de l'efficience et de la sensibilité de la recherche. Nous avons participé à l'évaluation des nouveaux outils (Risk of Bias 2.0 et Risk of bias in non-randomized studies of interventions) pour l'évaluation de la qualité des études randomisées et non randomisées et qui ont été adoptés pour nos projets futurs. Une nouvelle méthodologie graphique a été développée pour la réalisation des méta-analyses de données de survie.

Résultats: Ces approches ont été utilisées pour répondre à diverses questions de recherche touchants différents aspects de la chirurgie cardiaque : 1) la rédaction des premières lignes directrices de *l'Enhanced Recovery After Cardiac Surgery*, 2) une revue systématique des résultats de la chirurgie valvulaire et aortique chez le transplanté cardiaque, démontrant les bons résultats de ces procédures dans une population à haut risque et l'émergence des techniques trans-cathéters dans la prise en charge de ces pathologies, 3) une méta-analyse portant sur les arythmies supra-ventriculaires chez les patients ayant eu une intervention de Fontan, concluant à un effet bénéfique de la technique du conduit extra-cardiaque et 4) une méta-analyse portant sur l'insuffisance aortique chez les patients porteurs d'assistance ventriculaire gauche, objectivant une incidence sous-estimée de cette situation clinique avec un impact significatif sur la survie de cette population de patients.

Conclusion: Cette thèse aborde certaines contraintes de la littérature en chirurgie cardiaque comme la sensibilité sous optimale de la recherche systématique et les méta-analyses de données de survie, et a proposé des solutions. D'autres contraintes telles que les comparaisons multiples subsistent. Des recherches futures axées sur de nouvelles approches comme le *network meta-analysis* ou l'approche bayésienne pourraient offrir des solutions.

Mots-clés :

Revue systématique, méta-analyse, méthodologie, données de survie, chirurgie cardiaque.

Abstract

Objective: To explore, adapt and develop new methodologies for performing systematic reviews and meta-analyses in cardiac surgery.

Methods: Text mining and citation chasing were used to optimize the efficiency and sensitivity of search process. We participated in the evaluation of new tools (Risk of Bias 2.0 and Risk of bias in non-randomized studies of interventions) for quality assessment of randomized and nonrandomized studies and we have adopted them for our future projects. A new graphic methodology has been developped for the performance of meta-analyses of time-to-event data.

Results: These approaches have been used to answer various research questions touching different aspects of cardiac surgery: 1) writing the first guidelines of enhanced recovery after cardiac surgery, 2) a systematic review of the results of valvular surgery and aortic in cardiac transplantation, demonstrating good results of these procedures in a high-risk population and the emergence of trans-catheter techniques in the management of these pathologies, 3) a meta-analysis of supra-ventricular arrhythmias in patients who had a Fontan intervention, finding a beneficial effects of the extracardiac conduct technique and 4) a meta-analysis of aortic insufficiency in patients with left ventricular assist device, showing an under-estimated incidence of this clinical entity with a significant impact on the survival of this population of patients.

Conclusion: This thesis addresses some of the short comings of the heart surgery literature such as the sensitivity of the systematic search and time-to-event data meta-anlysis and proposed novel solutions. Other issues such as the need to summarize a comprehensive and coherent set of comparisons remain. Future researchs focused on new approaches such as the network meta-analysis or the Bayesian approach can solve these issues.

Keywords:

Systématic review, meta-analysis, methodology, time-to-event data, cardiac surgery.

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Abréviations

AHRQ	*Agency for Healthcare Research and Quality*
ASV	Arythmies supra-ventriculaires
AVG	Assistance ventriculaire gauche
CRD	Centre for Reviews & Dissemination
EC	Extra-cardiaque
EFSA	*European Food Safety Authority*
ERAS	*Enhanced Recovery After Surgery*
HR	Hazard Ratio
IAo	Insuffisance aortique
LT	Tunnel latéral intra-cardiaque
Log HR	Logarithme hazard ratio
NOS	*Newcastle Ottawa Scale*
OR	Odds Ratio
PICO	*Population, Intervention, Comparator, Outcome*
PRISMA	*Preferred Reporting Items for Systematic review and Meta-analysis*
PRISMA-P	*Preferred Reporting Items for Systematic review and Meta-analysis Protocols*
RoB 2.0	*Risk of Bias*
ROBINS-I	*Risk of Bias In Non-randomized Studies of Interventions*
RSMT	*Restricted survival mean time*
RR	Risque relatif
TM	*Text Mining*

À la mémoire du Professeur Jean Lambert dont la disponibilité, l'enthousiasme exceptionnel et l'enseignement de qualité ont été et demeureront déterminants et hautement « significatifs » dans ma future carrière de chercheur

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Finalement, tout ce travail ne serait pas possible sans le support et la compréhension de ma conjointe le Dr Wissal Ben Jmaa et de mes deux enfants, Sayf et Nour.

Puisse ce travail être utile à tous les professionnels de la santé spécialement en chirurgie cardiaque et en cardiologie désireux de se lancer dans la rédaction de revues systématiques et de méta-analyses.

Introduction

Les revues systématiques et les méta-analyses deviennent des éléments clés aussi bien pour la rédaction de lignes directrices que pour la pratique d'une médecine basée sur des données probantes [1] et une recherche scientifique fondée sur des faits [2,3].

La réalisation de revue systématiques et de méta-analyses en chirurgie cardiaque se heurte à plusieurs défis incluant la prépondérance d'études non randomisées dans la littérature en chirurgie cardiaque, la taille limitée des séries spécialement en chirurgie cardiaque pédiatrique, des données non publiées et une littérature grise qui ne cessent de croitre.

De plus, les résultats des procédures chirurgicales sont mesurables dans le temps. Les données de survie constituent essentiellement l'issue principale des études chirurgicales. Il n'existe pas, à ce jour, de méthode largement adoptée pour la réalisation de méta-analyses de ce type de données.

Ces problématiques soulèvent quatre questions méthodologiques abordées par cette thèse :

1) Comment développer une stratégie de recherche permettant une récupération exhaustive des évidences pour la rédaction de lignes directrices ?

2) Comment gérer les sources supplémentaires de données ?

3) Comment évaluer la qualité des essais non randomisés ?

4) Comment faire une analyse quantitative des données de survie en tenant compte des différences de durée de suivi entre les études sélectionnées ?

Diverses approches développées pour répondre à ces questions ont été appliquées par la suite pour répondre à des questions cliniques touchants différents aspects de la chirurgie cardiaque.

Cette thèse inclut quatre études clés :

A) La première étude décrira une stratégie de recherche systématique exhaustive d'évidences nécessaires à l'écriture des premières lignes directrices de l'*Enhanced Recovery After Cardiac Surgery Society*.

B) La deuxième étude utilisera une approche systématisée pour la gestion de source de données supplémentaires nécessaires à l'écriture d'une revue systématique de la chirurgie valvulaire aortique après transplantation cardiaque.

C) Le troisième manuscrit sera une application d'une nouvelle approche d'analyse quantitative de données de survie portant sur la prévalence des arythmies supra-ventriculaires chez les patients ayant une intervention de Fontan selon la technique chirurgicale [4].

D) Le quatrième manuscrit portera sur la prévalence de l'insuffisance aortique chez les patients porteurs d'assistance ventriculaire gauche et son impact sur la survie.

Chapitre 1 Défis de revue systématique en chirurgie cardiaque

Dans ce premier chapitre, nous définirons les étapes clés pour effectuer une revue systématique. Nous traiterons par la suite, la stratégie de recherche, qui se veut exhaustive tout en restant la plus transparente possible. Nous finirons ce chapitre en traitant de deux défis importants que présente la littérature en chirurgie cardiaque à savoir la littérature grise et l'évaluation de la qualité des essais non randomisés.

1.1 Historique, définition et structure de revues systématiques

1.1.1 Historique

L'idée de chercher et résumer les données probantes pour guider la pratique médicale et appuyer les prises de décision n'est pas nouvelle. En 1904, dans une parution du *British Medical Journal*, Karl Pearson [5] faisait une synthèse des études pertinentes sur l'efficacité de la vaccination pour la fièvre typhoïde. Sa rationnelle était : « *Many of the groups … are far too small to allow for any definite opinion being formed at all, having regard to size of the probable error involved* ». Cependant, une approche plus systématique n'a été développée que lors des dernières décennies. Le concept d'une approche critique de la recherche et une synthèse critique des données probantes émerge dans les années 70 sous le terme méta-analyse. Le terme est lancé par Glass et ses collègues en 1977 [6]. Le milieu médical s'intéresse à ce nouveau concept dans la fin des années 70. Archie Cochrane [7] écrivait : « *it is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials* » préludant la naissance de la médecine basée sur des preuves à la fin du vingtième siècle.

1.1.2 Définition

La première vraie définition d'une revue systématique a été introduite par Last [8] en 2001 : « *the application of strategies that limit bias in the assembly, critical appraisal and synthesis of all relevant studies on a specific topic* ». *The Cochrane Collaboration* [9], *the Agency for Healthcare Research and Quality's Evidence-based Practice Center program* [10] et *the Preferred reporting items for systematic review and meta-analysis (PRISMA) Statement* [11] ont depuis adopté une définition commune et structurée des revues systématiques : « *A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in*

order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made [12,13] ».

Les éléments clés d'une revue systématique sont :

1) Un ensemble d'objectifs clairement énoncés avec des critères d'éligibilité prédéfinis des études à inclure.

2) Une méthodologie explicite, reproductible pour la conduite et la rédaction d'une revue systématique.

3) Une stratégie de recherche systématique exhaustive et transparente qui identifie les études qui répondent aux critères d'éligibilité prédéfinis.

4) Une évaluation de la validité des observations des études incluses, par exemple par l'évaluation du risque de biais.

5) Une présentation et une synthèse systématique des caractéristiques et des résultats des études incluses.

De nombreuses revues systématiques contiennent des méta-analyses. En combinant l'information provenant de toutes les études pertinentes, les méta-analyses peuvent fournir des estimations plus précises des effets des soins de santé que celles dérivées d'études individuelles.

1.1.3 Structure d'une revue systématique

Par leur rigueur méthodologique, les revues systématiques sont devenues l'étalon d'or dans la synthèse des données probantes de la pratique médicale, supportant la rédaction de lignes directrices et la prise de décisions cliniques. Les revues systématiques ont été utilisées dans le domaine des soins de santé pour traiter d'un éventail de questions liées à la santé, comme la prévalence et l'incidence des maladies, l'étiologie et leurs facteurs de risque, l'exactitude des tests de diagnostic et l'évaluation des interventions préventives ou thérapeutiques. Leur nombre ne cesse d'augmenter. En 2010, 11 nouvelles revues systématiques étaient publiées chaque jour dans le domaine médical comparées à deux par jour au début des années 2000 [14]. Il existe encore malheureusement une croyance erronée qu'une revue systématique est une revue narrative plus complète [15]. Le Tableau 1 décrit les principales différences méthodologiques entre une revue systématique et une revue narrative.

Tableau 1 : Différences méthodologiques entre une revue systématique et une revue narrative

	Revue systématique	**Revue narrative**
Question de recherche	Claire et précise	Non ciblée
Source et stratégie de recherche	Recherche approfondie de bases de données électroniques. Recherche manuelle de revues pertinentes. Examen des listes de références et contact avec les chercheurs. Stratégie de recherche explicite fournie, y compris les tentatives d'accès aux données non publiées. Description explicite des types d'études à inclure. Critères précisés pour limiter le biais de l'examinateur	Généralement non précisées Possibilité de biais de sélection.
Sélection des études	Description explicite des types d'études à inclure. Critères précisés pour limiter le biais de l'examinateur.	Généralement non précisées. Possibilité de biais de sélection.
Évaluation de risque de biais	Évaluation formelle et systématique de risque de biais des études incluses.	Pas d'évaluation de biais. Pas d'emphase mise sur la différence méthodologique des études incluses.
Synthèse de résultat	L'hétérogénéité des études est prise en compte dans l'analyse qualitative ou quantitative ainsi que les potentiels risques de biais.	Pas d'analyses qualitatives ou quantitatives effectuées de façon systématique.
Conclusions	Conclusions basées sur la totalité des évidences possibles en tenant compte de potentiels biais	Conclusions pas nécessairement basées sur des évidences

Il est clair que les revues systématiques ont besoin d'un protocole rigoureux qui accompagne le chercheur dans l'élaboration de sa revue. En 2010, l'*European Food Safety Authority (EFSA)* proposait aux chercheurs une série d'étapes structurées à suivre pour diminuer le risque de biais (Figure 1). Les efforts se sont multipliés par la suite pour bâtir un protocole structuré pour les revues systématiques. *The Preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P) statement* [16] définit un protocole de revues systématiques comme suit: « *In the context of systematic reviews and meta-analyses, a protocol is a document that presents an explicit plan for a systematic review. The protocol details the rationale and a priori methodological and analytical approach of the review* ». PRISMA-P a élaboré une liste de vérification [17] qui vise à guider l'élaboration de protocoles de revues systématiques et de méta-analyses évaluant l'efficacité thérapeutique. Elle est destinée à être utilisée principalement par les auteurs qui préparent des protocoles de revues systématiques pour la publication, l'utilisation publique ou autre. Cette liste est également destinée pour les pairs examinateurs afin de déterminer si un protocole contient des détails essentiels. PRISMA-P checklist contient 17 éléments (26 sous-éléments) qui devraient être décrits, au minimum, dans les protocoles de revues systématiques et méta-analyses (Annexe 1). Elle est divisée en trois principales sections :

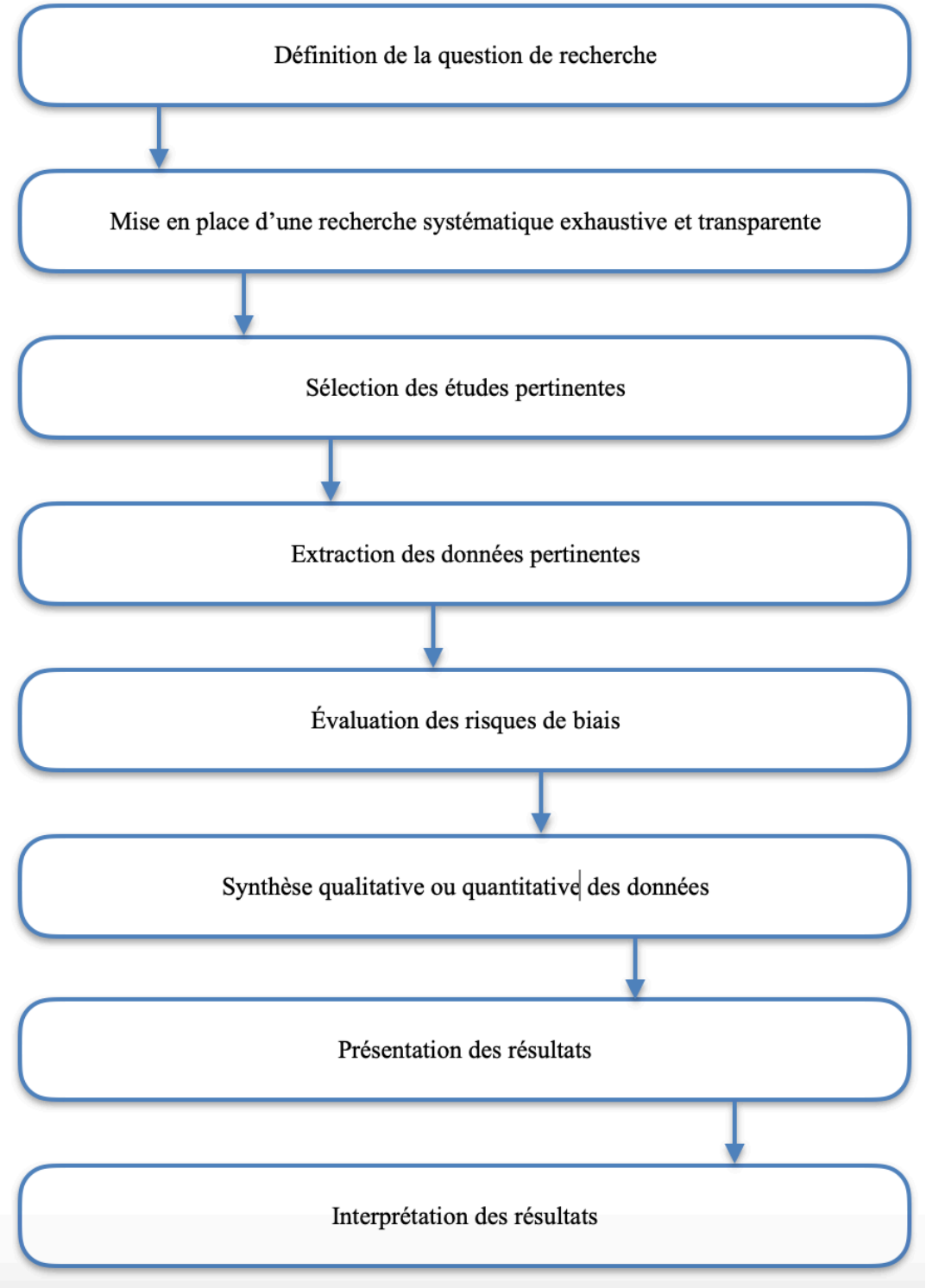
1) Information administrative.

2) Introduction.

3) Méthodologie.

La stratégie de recherche ainsi que l'évaluation de la qualité des études incluses dans une revue systématique prennent une place prépondérante aussi bien dans le protocole de l'EFSA que dans la *PRISMA-P checklist*. Le reste du chapitre sera dédié à ces deux étapes clés d'une revue systématique.

***Figure 1 : Différentes étapes proposées par l'European Food Safety Authority pour un protocole de* revues systématiques**



1.2 Stratégie de recherche

La revue de cinq guides de pratiques (GP) pour l'élaboration de revues systématiques [18-22] identifie huit étapes clés nécessaires à la réussite d'un processus de recherche systématique, le plus complet possible et rapporté de façon transparente. Ces huit étapes sont :

1. Qui doit faire la recherche de la littérature ?
2. Quels sont les objectifs de la recherche de la littérature ?
3. La préparation de la recherche
4. La stratégie de la recherche
5. La recherche des bases de données bibliographiques
6. La recherche de sources supplémentaires et de la littérature grise
7. Comment gérer les références ?
8. Comment rapporter le processus de recherche systématique ?

Dans ce qui suit, nous rapporterons pour chacune des étapes les directives des cinq GP. L'applicabilité de ces directives dépend directement de la qualité de la littérature et des ressources mises à la disposition des chercheurs.

1.2.1 Qui doit faire la recherche de la littérature ?

Les cinq GP [18-22] recommandent l'implication d'une bibliothécaire ou d'un coordinateur de recherche dans le processus. Si cette recommandation est largement adoptée dans la littérature, aucune obligation n'est par contre émise [23]. Plusieurs études méthodologiques [24-27] mettent l'emphase sur l'apport de la bibliothécaire dans la qualité des revues systématiques. Meert et al. [27] rapportent une augmentation de la sensibilité et de la précision de la recherche systématique en présence d'une bibliothécaire comme co-auteur. La connaissance de base de données ainsi que la sélection des ressources en général sont reconnues par deux GP [19,20] comme une compétence clé pertinente des spécialistes de l'information et des bibliothécaires.

1.2.2 Quels sont les objectifs de la recherche de la littérature ?

Les mots *exhaustivité, transparence et reproductibilité* reviennent avec insistance dans les cinq GP [18-22] pour définir les objectifs de la recherche. Ils s'accordent sur le but de ce processus qui est de minimiser les potentiels biais de sélection. Une recherche exhaustive et rapportée de façon transparente augmente la confiance du lecteur dans l'estimation de l'effet retrouvée et dans les conclusions tirées de la revue systématique et/ou de la méta-analyse. Ceci s'applique particulièrement aux revues systématiques d'efficacité et aux méta-analyses [28], mais peut ne pas être le cas pour la revue systématique narrative où un échantillonnage ciblé de la littérature peut être suffisant [29]. Si les objectifs de la recherche sont bien définis par les cinq GP [18-22], l'exhaustivité ne l'est malheureusement pas. Le Tableau 2 résume les recommandations de chaque GP pour obtenir une sensibilité de recherche adéquate.

Au-delà de ces GP, certains auteurs [30] ont tenté de définir empiriquement l'exhaustivité de la recherche escomptée :

1) Rechercher des bases de données électroniques combinant *the Cochrane CENTRAL* à au moins deux autres bases de données (généralement MEDLINE et EMBASE), ce qui donne une sensibilité de recherche avoisinant les 90 %.

2) Ne pas se limiter à la langue anglaise.

3) Associer au moins une autre source de recherche (Registre d'essais, contact avec les experts, abstract de conférence et thèses).

Par contre, l'exhaustivité ne rime toujours pas avec qualité d'une revue systématique [31]. Au contraire, l'inclusion d'études de moindre qualité ou de la littérature grise peut surestimer ou sous-estimer l'effet étudié [32]. Les autres défis que pose l'exhaustivité sont les contraintes du temps et de budget [30]. *Le Cochrane Handbook* [18] estime qu'une recherche systématique doit être faite dans les limites des ressources. Ces limitations doivent être cependant clairement rapportées, discutées et justifiées par les chercheurs [31].

Tableau 2 : Étapes proposées par les cinq guides de partiques [18-22] pour une recherche exhaustive.

Étapes	The Cochrane Handbook	The CRD Handbook	Campbell Handbook	Collaboration for environmental evidence	Systematic reviews in the social sciences: a practical guide
1	Bases de données bibliographiques	Bases de données électroniques	Bases de données spécifiques et générales	Bases de données en ligne	Bases de données
2	Recherche manuelle	Scanner les références des études pertinentes	Résumés de conférence	Recherche du site web d'organisations	Identifier les études en cours
3	Résumés de conférence	Recherche manuelle de journaux	Scanner les références des études pertinentes	Recherche web plus large	Identifier les études en cours
4	Autres revues	Registre d'essais cliniques	Recherche du web	Scanner les références des études pertinentes	Thèses
5	Recherche du web	Contact des experts	Études non publiées	Contact des experts	Abstract de conférences
6	Identifier les études en cours et non publiées	Recherche internet de sources pertinentes	Identifier les études en cours	Recherche par citation	Recherche par citation
7		Recherche par citation	Archives institutionnelles		Recherche du web
8			Recherche manuelle de journaux		Contact des experts
9					Registre d'essais cliniques

CRD : Centre for Reviews & Dissemination (politiques de santé), Campbell collaboration :politiques sociales et économiques, Collaboration for environmental evidence : politiques environnementales,

1.2.3 La préparation de la recherche.

Deux tâches clés conditionnent la bonne préparation d'un processus de recherche [19, 20, 22]. Premièrement, le chercheur doit s'assurer de l'absence d'une revue systématique préexistante ou en cours pour éviter la redondance. La CRD [19] recommande d'explorer au minimum *The Cochrane Database of Systematic Reviews* et le registre PROSPERO. Deuxièmement, le chercheur doit déterminer les mots-clés de son projet, ce qui permettra une recherche initiale *(scoping*) qui évaluera le volume du travail envisagé. Plusieurs moyens peuvent aider à l'accomplissement de cette étape; on cite entre autres le *text mining (TM)* qui sera traité dans le sous-chapitre 1.2.9. Ces approches méthodologiques, même si de plus en plus utilisées, restent à l'étape exploratoire et ne sont pas complètement approuvées [33,34].

1.2.4 La stratégie de la recherche.

The Population, Intervention, Comparator, Outcome (PICO) est la structure de choix proposée pour concevoir une stratégie de recherche systématique [18, 20, 22]. Les critères d'éligibilité des études doivent répondre aux concepts PICO (***P****opulation,* ***P****atient or* ***P****roblem/****I****ntervention/****C****omparaison of interventions/****O****utcomes*). Les cinq GP [18-22] fournissent aux chercheurs une méthodologie claire quant au choix des mots-clés, à l'approche booléenne (AND/OR) et à la combinaison des termes de recherche. Les limitations (langages, dates) sont mentionnées par tous les GP [18-22]. Toutes limitations doivent être discutées, leurs implications considérées pour éviter d'engendrer de potentiels biais. Certains auteurs [35] recommandent d'utiliser le PICOs (s pour study design) pour les revues systématiques d'efficacité. Plusieurs limites des structures PICO et PICOs ont été rapportées [36] à savoir :

1) L'incapacité de reconstruire la question originale.
2) L'incapacité d'encoder une relation entre les éléments de la structure.
3) L'incapacité de capturer des relations anatomiques.
4) L'absence de modèle temporel explicite.

La structure PICO est considérée plus adaptée pour les questions de thérapeutique, mais moins pour les questions d'étiologie, diagnostic et pronostic. D'autres structures sont recommandées pour établir une stratégie de recherche [37] telles que :

1) *BeHEMoTh (Behaviour of interest; Health context; Exclusions; Models or Theories).*

2) *SPICE (Setting, Perspective, Intervention, Comparison, Evaluation).*
3) *SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, Research type).*

1.2.5 La recherche des bases de données bibliographiques.

Les cinq GP [18-22] s'accordent à prioriser les bases de données comme source de recherche systématique. Par contre, aucun consensus n'est établi sur les bases de données à prioriser ni sur le nombre minimum de bases de données à inclure dans une recherche systématique. Seul le *Cochrane Handbook* [18] recommande de combiner la recherche de *CENTRAL* à au moins deux autres bases de données (MEDLINE et EMBASE). Les autres documents listent seulement les bases de données disponibles. Le nombre moyen de bases de données utilisées ne cesse d'augmenter, passant de 1 à 4 entre 1994 et 2014 [38]. Il est plus intéressant de se concentrer sur le type de base de données à chercher et ne pas se limiter à leur nombre. Le choix de base de données en fonction du sujet de recherche est primordial. En effet, certaines études rapportent un intérêt particulier à chercher prioritairement la *CINAHL* pour les revues systématiques qualitatives [39] et la rédaction de lignes directrices [40]. La priorité est habituellement donnée aux bases de données. Par contre, certaines études empiriques [41] ont démontré l'efficacité supérieure des approches basées sur des sources de données supplémentaires dont *Google Scholar* comparées à celles faisant appel aux bases de données conventionnelles dont PubMed et Embase.

1.2.6 La recherche de source supplémentaire et littérature grise.

Aucun consensus n'est atteint par les cinq GP quant à la priorisation des sources supplémentaires de données et de la littérature grise (Tableau 2). Trois GP [18, 19, 21] encouragent les chercheurs à aller chercher de l'information au-delà des seules bases de données, mais aucun GP ne stipule quand le faire dans le processus. L'approche de ce type de données sera détaillée dans le sous-chapitre 1.3.

1.2.7 Comment gérer les références ?

Les cinq GP [18-22] fournissent des directives claires pour la gestion des téléchargements et des doublons. Ils recommandent unanimement l'utilisation de logiciels *web-based* pour y parvenir.

Les logiciels de gestion des données sont de plus en plus courants. Des exemples de ces logiciels ainsi que leurs différentes fonctionnalités sont listés dans l'Annexe 2

1.2.8 Comment rapporter le processus de recherche systématique ?

Seul le *Cochrane Handbook* recommande spécifiquement l'utilisation de la *PRISMA Checklist* [11] pour rapporter la stratégie de recherche. Il y a consensus des cinq GP sur la nécessité de rapporter les bases de données cherchées, la stratégie de recherche et les filtres appliqués. La CRD [19] exige des chercheurs de justifier les limitations de langue qu'ils ont adoptées et les filtres qu'ils ont appliqués lors du processus de recherche. Malgré la recommandation de la Cochrane, l'adhésion au *PRISMA checklist* a peu augmenté entre 2009 et 2018. Dans une étude de Radar et al. [42], 86 % des chercheurs interrogés ne trouvaient pas le *PRISMA Checklist* très aidant et pratique dans leur processus de recherche. D'autres outils, comme l'*AMSTAR 2* [43] ou le *ROBIS* [44] lui y sont préférés pour leur simplicité.

Par contre, il n'existe pas de directives claires des cinq GP quant à la nécessité de l'évaluation par des pairs de la stratégie de cherche. Le *PRESS checklist* [45] est un essai prometteur pour écrire les lignes directrices de l'évaluation de la qualité de la stratégie de recherche par des pairs. Cet aspect du processus de la recherche systématique reste à développer dans le futur.

1.2.9 Les défis d'exhaustivité en chirurgie cardiaque et solutions.

1.2.9.1 Les défis.

La littérature en chirurgie cardiaque est caractérisée par une paucité d'essais randomisés et la prépondérance d'études non randomisées, d'études cas-contrôle et de cas cliniques. Ce type de littérature pose plusieurs problèmes méthodologiques :

1) La relation entre les sujets abordés et les mots-clés n'est pas toujours établie.

2) Les résumés de ces études ne répondent pas toujours au concept de PICO.

3) La tendance à publier les études positives plus volontiers que les études négatives comporte un sérieux risque de biais de publication.

Pour sursoir à ces problèmes, le chercheur qui entrevoit réaliser une revue systématique doit élargir son champ de synonymes pour assurer une recherche exhaustive générant un nombre ingérable d'études à sélectionner. Ceci est d'autant plus vrai lors de la rédaction des lignes

directrices, pour lesquelles une recherche systématique doit être réalisée pour chacun des sujets. Ceci engendre un deuxième défi pour le chercheur, à savoir les limites de temps et des ressources matérielles et humaines. Plusieurs approches ont été décrites pour augmenter l'efficacité de la recherche systématique dont entre autres le *text mining* et les stratégies d'échantillonnage randomisé de la littérature. Nous avons opté pour le *text mining* pour la réalisation de la recherche systématique du premier manuscrit. Les avantages et les limites de cette approche seront discutés dans le prochain sous chapitre.

1.2.9.2 *Le text mining*

Le *text mining (TM)* est défini comme *: « the process of discovering knowledge and structure from unstructured data* (i.e., text) » [46]. Un des logiciels les plus recommandés [11,18] est l'EPPI - Reviewer 4 (EPPI-Centre, London, United Kingdom).

Les outils du TM permettent un balayage complet de résultats de recherche préliminaire sur le sujet sélectionné afin de détecter les mots-clés ou la combinaison optimale de termes de recherche permettant d'optimiser l'efficience de la stratégie de recherche. Plusieurs études [34, 47, 48] ont montré que les mots-clés générés par le TM étaient plus représentatifs du sujet de recherche.

Les outils du TM opèrent par trois technologies différentes :

1) La fréquence d'un terme dans un texte donné : Elle se base sur le calcul automatique de l'occurrence et la co-occurrence d'un terme dans un texte.

2) La reconnaissance automatique d'un terme : Elle fait appel à des outils tels que *TerMine (NaCTeM, London, United Kingdom)*. TerMine est un algorithme de reconnaissance automatique des termes qui intègre les analyses linguistiques et statistiques pour déterminer la *C-Value* de chaque terme. La *C-Value* d'un terme dépend de la fréquence de son occurrence et de sa signification dans les textes étudiés. Les termes sont ensuite priorisés en fonction de leur *C-Value* [49]. Les termes avec une *C-Value* supérieure à 1 sont des potentiels mots-clés pour la recherche systématique.

3) Le regroupement (*clustering*) de termes : La technologie de regroupement de termes analyse la distribution d'un terme dans des textes courts comme les résumés et identifie par la suite un groupe de documents qui utilisent une combinaison de mots similaires [50].Ces trois

technologies sont appliquées dans un deuxième temps aux résultats de la recherche utilisant les mots-clés générés. Les références sont ainsi priorisées en fonction de l'occurrence des mots-clés. Le nombre de références à classer est ainsi nettement diminué réduisant la charge de travail et optimisant le temps alloué à la recherche.

Le TM facilite aussi le processus de sélection des études en dédiant une première équipe qui classera les références priorisées et passera rapidement à la deuxième phase de sélection (*full text screening*) et une seconde équipe qui classera les références moins pertinentes. Plusieurs études [51,52] ont rapporté une réduction de la charge de travail de 40 à 50 %.

Le TM peut augmenter le taux de *screening*. Une fois que le chercheur a sélectionné une référence pertinente type, et à l'aide d'outil de *visual data mining*, le TM aide le chercheur à prioriser dans son processus de sélection certaines références présentant des similitudes avec la référence type.

Le TM peut augmenter la fluidité du *screening*. En plaçant les références les plus pertinentes en premier, le chercheur acquiert une certaine maitrise des critères d'éligibilité très tôt dans son processus de sélection, ce qui augmente son efficience.

Certains auteurs [53,54] utilisent le TM pour se substituer à la recommandation d'un deuxième *reviewer* pour le premier niveau de sélection. Cette application du TM reste tout de même controversée dans la littérature [18].

Si l'apport du TM dans l'optimisation de la recherche est indéniable, certains aspects restent à explorer. Le TM est validé pour des bases de données bien structurées comme MEDLINE et EMBASE alors qu'il est moins pour d'autres comme Scopus [47]. De plus, le TM a été développé pour le domaine d'ingénierie ou précision et exactitude priment sur la sensibilité. Ceci ne rend pas le TM forcément transposable au domaine des revues systématiques où les priorités sont inversées.

Pour le premier manuscrit, nous avons procédé à une étude de validité avant d'adopter le TM comme pierre angulaire du processus de recherche pour la rédaction des lignes directrices. Un des sujets des lignes directrices a été choisi de façon aléatoire, dans ce cas « *Maintenance of chest tube patency* ». La stratégie de recherche basée sur le TM a été comparée à celle basée sur les mots-clés fournis par l'expert responsable du sujet. L'approche par TM a réduit de 38 % le nombre de références avec une sensibilité de la recherche comparable à celle obtenue par

l'approche conventionnelle. L'approche TM a été adoptée pour la réalisation des recherches systématiques de chacun des sujets en utilisant le logiciel l'EPPI - Reviewer 4 (EPPI-Centre, London, United Kingdom).

1.3 Gestion de sources supplémentaires de données et de la littérature grise

1.3.1 Les sources supplémentaires de données

Pour répondre à l'impératif d'exhaustivité, le recours à d'autres sources de données est de plus en plus recommandé [18, 19, 21], en faisant appel à diverses méthodes telles que : *la Citation chasing*, la recherche du web, le *Hand searching*, le contact des auteurs et les experts et la recherche dans des registres d'essais cliniques. Plusieurs études [55-57] ont démontré leur potentiel à identifier des données pertinentes manquées par la recherche de bases de données bibliographiques. Si l'apport de ces méthodes en termes d'exhaustivité est indéniable, il n'existe pas de structures formelles encadrant l'utilisation de ces méthodes dans le processus de recherche systématique. Nous détaillerons dans ce qui suit les deux principales méthodes à savoir la *Citation chasing* et la recherche du web. Le Tableau 3 résume les directives de 3 GP [18, 19, 21] ainsi que les avantages et désavantages de chaque méthode.

1.3.1.1 *La citation chasing*

Deux GP [18,19] fournissent un très bref aperçu de cette méthode de recherche et listent les principaux outils utilisés. Le *CRD Handbook* [19] définit cette méthode comme suit : « *identifying further studies, and clusters or networks of studies that cite (forward) or are cited by a primary study (backward) »*. Les principales ressources pour cette méthode de recherche [58] sont : *Web of Science*, *Scopus* et *Google Scholar*.

Les avantages de cette méthode sont :

1) L'indépendance vis-à-vis de mots-clés et de la qualité de l'indexation [55].

2) La recherche de citation peut découvrir des thèmes parallèles au sujet de recherche principale n'ayant pas été explorés dans la recherche de base de données [59].

3) La recherche est plus efficiente pour des sujets dont la terminologie n'est pas bien codifiée [60].

Linder et al [61] ont comparé une stratégie de recherche basée sur la recherche de citation dans les trois principales sources sus-citées à une approche conventionnelle par mots-clés dans PubMed. Les recherches dans *Web of Science*, *Scopus et Google Scholar* étaient plus sensibles que l'approche conventionnelle (45-54 % versus 16 %). Par contre, la précision de ces recherches était plus basse que celle de l'approche conventionnelle (40-75 % versus 90 %).

La *Citation chasing* a aussi des limites :

1) Elle dépend de l'exactitude et de l'exhaustivité du réseau de citations [62].

2) La sensibilité de la recherche peut être affectée par le délai entre la parution d'une citation et son inclusion dans le réseau [63].

3) L'approche n'est pas toujours reproductible, car les trois sources sont contrôlées par des algorithmes, sujets à des changements temporels [64].

4) Le manque de précision de cette approche génère une importante consommation des ressources. Hinde et al. [59] ont parcouru 4529 citations pour détecter 76 références. Levay et al. [63] rapporte que les recherches de citation de 46 études sur *Web of Science* et *Google Scholar* ont consommé 79 h de travail avec les conséquences budgétaires qui en découlent.

1.3.1.2 La recherche du web

Le *CRD Handbook* [19] définit cette méthode comme suit : « *identifying published or unpublished studies not indexed or included in bibliographic databases, or studies missed by database (or other) search methods, identifying and retrieving gray literature and identifying study protocols and ongoing studies* ». Il distingue deux différentes approches : 1) la recherche spécifique de site web de certaines organisations pertinentes au sujet de recherche et 2) la recherche web au sens large du terme en faisant appel à des moteurs de recherche. Les plus communément acceptés sont Google (www.google.com), Yahoo (yahoo.com) et les moteurs de *Metasearch* : DogPile (www. dogpile.com) et Metacrawler (www.metacrawler.com). Les recommandations *du Cohrane Handbook* [18] ne sont pas très structurées et exigent seulement de rapporter le nom du site et la date d'accès. Les deux autres GP [19,21] encadrent de façon plus rigoureuse la recherche web en exigeant du chercheur de rapporter le nom du site, l'adresse URL, la date d'accès et la stratégie de recherche. Certaines études rapportent un intérêt de la recherche web dans l'exhaustivité de recherche en repérant des études en cours, des études non

publiées et les essais complétés et en cours de publications. Eysenbach et al. [65] rapportent avoir retracé 14 études non publiées ou en cours dont 9 étaient pertinentes à sa revue systématique. Plusieurs limites à cette méthode sont à déplorer :

1) La quantité de références retracées peut être non gérable [66].

2) La qualité n'est pas toujours assurée, puisque la majorité des références retracées n'incluent pas de résumés [67].

3) La transparence du processus n'est pas toujours limpide malgré des tentatives de développer des *checklist*s spécifiques pour la recherche web [68].

Le *hand searching* peut se faire soit sur des journaux pertinents au sujet de recherche, ou sur des journaux non inclus dans les bases de données ou sur une liste de journaux fournis par les experts du sujet [18,19]. Le Cochrane Handbook [19] recommande de contacter les auteurs des études incluses dans la revue systématique à la recherche de données non publiées, et fournit une liste de registres d'essais cliniques à explorer (Tableau 3).

Tableau 3 : Approches pour la recherche de données supplémentaires

Méthode	Directive	Avantages	Désavantages	Consommation de ressources
Citation chasing	Identification de références dans les 3 sources principales	Indépendant de mots-clés ni de système d'indexation	Dépend de l'exactitude et l'exhaustivité du réseau de citation	80 h (moyenne)
Recherche du web	Explorer les sites web d'organisation ou l'utilisation de moteurs de recherche	Peut détecter des études non publiées, en cours ou récemment complétées	Un souci de transparence	20 h (moyenne)
Hand searching	Recherche manuelle de suppléments de journaux, d'éditoriaux ou abstract de congrès et conférence	Augmente la sensibilité de la recherche	Peut compromettre la précision d'une recherche	1 h par journal en moyenne
Contact auteur	Contacter les auteurs des études incluses ou les experts du sujet par email ou téléphone	Obtenir des données non publiées	Moins de succès pour les études plus ancienne Apport non garanti	Peut nécessiter jusqu'à trois tentatives de contact
Recherche de registres d'essais	Explorer la liste de registres	Peut détecter des études non publiées, en cours ou récemment complétées	Interfaces de recherche en retard par rapport aux grandes bases de données	

1.3.2 La littérature grise.

Le *Gray Literature Network Service* [69] définit la littérature grise comme suit : « *Gray Literature is a field in library and information science that deals with the production, distribution, and access to multiple document types produced on all levels of government, academics, business, and organization idea publication in electronic and print formats not controlled by commercial publishing i.e., where publishing is not the primary activity of the producing body* ». La recherche se fait dans des bases de données dédiées à la littérature grise, des moteurs de recherche dédiés, des catalogues de librairie et des dépôts et archives dans le web. La littérature grise offre un spectre de recherche plus large qui pourrait enrichir la littérature commentée par des pairs et renforcer les évidences tirées d'une revue systématique. Autre grand avantage de la littérature grise est qu'elle est plus riche en études négatives et neutres. L'inclusion de ces études diminue nettement le risque de biais encourus lors d'inclusion exclusive d'études positives qui sont plus prépondérantes dans la littérature conventionnelle [70-73]. La recherche de la littérature grise est par contre un processus long et couteux et il est difficile de savoir où exactement chercher par manque de grande base de données dédiée. Le format de documents retracés dans ce type de littérature est aussi long, ne se conformant pas au format de la littérature conventionnelle (abstract/introduction/méthodes/résultats/discussion). La qualité scientifique de ces documents est toujours questionnable. Les stratégies de recherches de ce type de littérature sont aussi complexes et peu reproductibles. Tous ces éléments précédemment cités font de telle sorte que les études recupérées après recherche de la littérature grise sont rarement incluses dans les revues systématiques.

1.3.3 Application à la chirurgie cardiaque

Le deuxième manuscrit a comme devis de faire une revue systématique des évidences sur la prise en charge chirurgicale ou par approche trans-cathéter de la pathologie valvulaire et aortique après transplantation cardiaque. Le nombre de références générées par la recherche conventionnelle était très faible. Nous avons procédé à une recherche de citation dans les 3 sources sus-citées en partant de deux revues narratives sur le sujet. Ceci a généré 40 % des références incluses dans la revue finale. Le processus de recherche avait une très bonne sensibilité avoisinant les 80 % dans *Web of Science* et *Scopus* et les 70 % pour *Google Scholar*.

La précision était de 55 % pour les trois sources. Ce manque de précision explique la surcharge de travail qui a été engendrée. Cette surcharge était estimée à 7 jours (2 jours de téléchargement pour *Web of Science* et *Google Scholar* chacun, un jour de téléchargement pour *Scopus* et 2 jours de processus de sélection).

Nous avons fait appel au *hand searching* pour les manuscrits 3 et 4. Quatre journaux spécialisés en chirurgie cardiaque à savoir *The Annals of Thoracic Surgery, The European Journal of Cardiothoracic Surgery, The Journal of Thoracic and Cardiovascular Surgery et Journal of the American College of Cardiology* ont été explorés manuellement à la recherche de publications pertinentes.

Tous les premiers auteurs et auteurs séniors de chaque étude incluse dans les manuscrits 3 et 4 ont été contactés par courriel. Le retour de contact a été en deçà des 20 % avec des données fournies pas toujours pertinentes.

Nous avons décidé de ne pas faire appel à la recherche du web et la littérature grise dans l'élaboration des 4 manuscrits inclus dans cette thèse. Ces deux approches n'étaient pas encore parfaitement structurées de point de vue méthodologique et le bénéfice escompté ne justifiait pas la consommation de ressources nécessaires.

1.4 Évaluation de risques de biais.

Le *Cochrane Handbook* [18] définit le biais comme suit : « *is a systematic error, or deviation from the truth, in results or inferences. Biases can operate in either direction: different biases can lead to underestimation or overestimation of the true intervention effect* ». Une étude doit répondre à la question de recherche de façon objective, en d'autres termes sans biais possibles, ceci définit la validité interne d'une étude. L'inclusion d'études dans une revue systématique ou une méta-analyse dont la validité interne est incertaine affecte aussi bien l'analyse, l'interprétation et les conclusions d'une revue systématique. Il est donc crucial pour garantir la validité d'une revue systématique d'évaluer de façon rigoureuse la qualité des études incluses. Trois sortes d'outils ont été développés à cette fin : les échelles numériques, les *checklists* et l'évaluation objective par domaine de biais. Les deux premières catégories ont été longtemps utilisées, mais elles incluaient à des degrés variables des items qui n'évaluaient pas forcément la validité tels que le calcul de puissance (évaluation la précision des résultats) ou l'évaluation

de critères d'inclusion et exclusion (évaluation de l'applicabilité) [74,75]. Dans un effort d'uniformisation, *l'Agency for Healthcare Research and Quality (AHRQ)* [76] a publié les critères spécifiques nécessaires à l'évaluation de risque de biais de chacun des cinq types d'études communément publiées (Annexe 3). La Cochrane [18] a migré depuis 2006 dans ces recommandations vers l'évaluation objective par domaine de biais. Les groupes *Cochrane Bias Methods Group* et *Cochrane Non-Randomised Studies Methods Group* ont été constitués, et de nouveaux outils basés sur les domaines de biais ont été développés en 2008 pour les études randomisées et en 2017 pour les études non randomisées.

1.4.1 Essais randomisés.

Avant l'avènement de l'outil Risk of Bias (RoB) de la Cochrane [18] en 2007, l'échelle Jadad [77] était l'outil le plus utilisé pour évaluer la validité des études randomisées. Développée initialement pour la recherche en douleur, cette échelle numérique couvrait trois champs de biais : 1) randomisation, 2) *blinding* et 3) *handling of withdrawals and drop-outs*. Plusieurs études [78,79] ont soulevé de grosses insuffisances de cette échelle, notamment l'absence d'évaluation de la dissimulation de l'attribution (*allocation concealment*). Avec l'avènement du *Cochrane Bias Methods Group*, une uniformisation de l'évaluation des risques de biais pour les études randomisées est ainsi devenue possible.

L'outil RoB a vu le jour en 2007 et a été mis à jour en 2017 sous l'appellation RoB 2.0 [80]. L'outil se base sur l'évaluation objective de cinq domaines de biais : 1) le processus de randomisation, 2) la déviation du protocole planifié, 3) les données manquantes, 4) la mesure de l'issue et 5) le rapport sélectif des résultats. Un gabarit de l'outil est listé dans l'Annexe 4. Au moins deux évaluateurs doivent répondre à différentes questions pour classifier le risque de biais pour chacun des domaines en faible, modéré (*some concerns*) et sérieux. Une décision concordante des deux évaluateurs classifira le risque de biais de chaque étude incluse dans une revue systématique ou méta-analyse. Nous avons été sondés, comme beaucoup d'autres *reviewers Cochrane* pour évaluer l'outil RoB2. Nous avons exploré cet outil lors de l'évaluation des études incluses dans le manuscrit #1. Un avantage indéniable de la nouvelle version est la transparence, l'information est facilement retraçable par le lecteur. Le gros inconvénient de cet outil est la difficulté de juger et de prendre une décision pour un domaine

particulier après les multitudes de questions. Un algorithme de jugement a été développé [80] et adapté pour la littérature que nous avons évaluée (Annexe 5). Cet algorithme n'est pas rigide et permet des modifications comme le suggèrent les concepteurs de l'outil [80]. L'autre inconvénient majeur de la nouvelle version est sa contrainte en termes de temps. Le temps alloué à l'évaluation de risques de biais d'une étude a ainsi littéralement doublé ou triplé avec cet outil.

1.4.2 Essais non randomisés.

Contrairement aux études randomisées pour lesquelles l'évaluation de leur qualité est devenue codifiée depuis l'avènement de l'outil RoB, les études non randomisées (dont l'inclusion dans une revue systématique ou une méta-analyse soulève encore le débat [18]) posent un sérieux problème d'évaluation de leur validité interne. Jusqu'à très récemment, la Cochrane listait certains outils pour évaluer le risque de biais des études non randomisées, mais n'en recommandait aucun. Plusieurs revues systématiques ont tenté de recommander certains outils par rapport à d'autres. Deux de ces revues systématiques [81, 82] ont recommandé 6 outils chacun et étaient concordantes sur l'utilisation de l'outil Black [83]. L'outil Black est par contre difficile à appliquer pour les études cas-contrôle, exigeant une certaine expertise en épidémiologie et donc long à compléter. Sanderson et al. [84], dans une revue systématique plus exhaustive et mieux conduite que les deux précédentes, a identifié 86 outils dont seulement 15 % étaient adaptés à l'évaluation de la qualité des études non randomisées. Ils n'en recommandaient aucun, mais conseillaient aux auteurs d'utiliser un outil qui avait les caractéristiques suivantes : 1) contient un petit nombre de composantes ou domaines, 2) le plus spécifique possible au *design* de l'étude et au sujet de recherche en question, 3) développé avec rigueur méthodologique et 4) plutôt une checklist qu'une échelle numérique.

Le *Newcastle Ottawa Scale (NOS)* [85] est actuellement l'outil le plus utilisé dans la littérature pour évaluer le risque de biais des études non randomisées. Développé selon un processus Delphi et introduit en 2000 au troisième symposium des revues systématiques à Oxford, il peut être utilisé comme liste de vérificationou comme échelle numérique. Il peut être appliqué aux études de cohorte (Annexe 6) et aux études cas-contrôle (Annexe 7) et touche trois domaines : la sélection, la comparabilité et selon le type de l'étude : l'issue (études de cohorte) ou l'exposition (études cas-contrôle). Basée sur un système de cotation par étoile pour chaque

rubrique (seule la comparabilité peut en avoir deux par rubrique), une étude peut recevoir jusqu'à neuf étoiles. Lors de l'utilisation de cet outil pour les fins de cette thèse et pour les projets de méta-analyses auxquels nous avons contribuées, nous avons constaté plusieurs limites de cet outil : 1) à notre connaissance, aucune étude de validité n'a été effectuée pour cet outil. En faisant une revue systématique d'études traitant de la validité du NOS, nous avons trouvé seulement un résumé d'une étude présentée lors d'un congrès en Espagne [86], mais aucune étude publiée. 2) Il n'est pas approprié de coter une étude avec *matching* et une sans *matching* de la même façon. 3) De plus, l'outil surestimait la qualité de l'étude et 4) il y avait une grande variabilité entre évaluateurs surtout pour l'exposition et la mesure de l'issue. Ces constatations sont partagées par plusieurs autres auteurs [87-89]. Pour ces raisons, lors de l'utilisation de cet outil pour les manuscrits #3 et #4, le seuil d'inclusion d'études est passé d'un NOS strictement supérieur à 5 tel que recommandé par les auteurs [85] à strictement supérieur à 6. Une étude récente [90] a évalué la fiabilité du NOS en mesurant la variabilité inter-évaluateur. La concordance était médiocre pour l'évaluation de l'exposition, la mesure de l'issu, la longueur du suivi et le score en globalité (indice de corrélation Kappa à 0,14. Pour une corrélation parfaite, l'indice doit être égal à 1). Quand le risque du biais est plutôt classé faible (NOS 7 à 9), modéré (NOS 4 à 6) ou élevé (NOS 0 à 3), la concordance s'améliorait légèrement.

Après l'avènement du *Cochrane Non-Randomised Studies Methods Group*, la Cochrane a lancé une réflexion sur le développement d'un nouvel outil d'évaluation pour des études non randomisées qui a abouti à la mise en place de l'outil Risk of bias in non-randomized studies of interventions (ROBINS-I) en 2017 [91] et son évaluation en 2018. Le ROBINS-I a été construit sur le gabarit du RoB 2.0. Il couvre sept domaines de biais. Deux au stade de pré-intervention (*confounding* et sélection des participants), un au stade de l'intervention (classification des interventions) et quatre au stade post-intervention (déviation du protocole planifié, données manquantes, mesure de l'issue et le rapport sélectif des résultats). Un gabarit de l'outil est listé dans l'Annexe 8. Au moins deux évaluateurs doivent répondre à différentes questions pour classifier le risque de biais pour chacun des domaines en faible, modéré, sérieux et critique. Une étude est classée : 1) à bas risque si tous les domaines sont à bas risque, 2) à risque modéré si un ou plusieurs domaines sont à bas risque ou à risque modéré, 3) à risque sérieux si un ou plusieurs domaines sont à sérieux risque et 4) à risque critique si un ou plusieurs domaines sont

à risque critique. Nous avons essayé l'outil ROBINS-I à titre d'évaluation pour les manuscrits #1 et #2. Tout comme l'outil RoB 2.0, cet outil offre une grande transparence. De plus et contrairement au RoB 2.0, le jugement de l'évaluateur est facilité par un tableau pour chaque domaine qui le guide dans la prise de décision. Le gros inconvénient reste la surcharge de travail qu'il engendre par rapport au NOS. Une à deux heures doivent être allouées à l'évaluation de la validité d'une étude par le ROBINS-I comparées aux dix à vingt minutes avec le NOS. Des études de validité du ROBINS-I sont en cours.

1.4.3 Comment tenir compte des bias dans l'analyse de données ?

Deux approches sont possibles pour gérer des études avec un risque sérieux de biais. L'approche puriste est d'exclure ces études de l'analyse qualitative ou quantitative des données. Ceci était notre approche dans les manuscrits #1, #3 et #4. Seules les études avec faible risque de biais qu'elles soient randomisées ou non, ont été incluses pour rédiger les lignes directrices. Seules les études qui avaient un NOS de 6 et plus (manuscrit #3) et 7 et plus (manuscrit #4) ont été incluses. L'augmentation du seuil d'éligibilité est due au fait que le NOS surestimait la qualité des études.

Cependant, le chercheur est fréquemment confronté à une rareté de publications, tel que dans la littérature en chirurgie cardiaque, spécialement lorsqu'elle touche des procédures rares. Ceci oblige par conséquent à inclure des études avec un risque de biais modéré et même parfois des risques sérieux. Ce risque de biais doit être obligatoirement intégré dans le processus d'analyse des données. Plusieurs solutions s'offrent aux chercheurs pour le faire : 1) l'approche narrative où le chercheur justifie sa décision, 2) l'étude de sensibilité ou de sous-groupes, les résultats sont alors présentés en incluant et excluant les études problématiques, 3) la modulation des poids des études en fonction de leur qualité ou 4) la méta-régression. Dans les manuscrits #3 et #4, et malgré l'exclusion des études avec un risque de biais modéré ou élevé, nous avons réalisé des méta-régressions pour nous assurer que l'hétérogénéité inter-études n'affectait pas les résultats des deux travaux.

Chapitre 2 Manuscrit #1

Avant-propos

Pour le premier manuscrit, nous avons eu le mandat de réaliser les recherches systématiques spécifiques de chacun des sujets des lignes directrices pour *l'Enhanced Recovery After Cardiac Surgery*, d'être impliqués dans les deux processus de sélections ainsi que le processus d'évaluation des études sélectionnées, de coordonner le consensus entre les différents experts et de rédiger la partie méthodologie. La charge de travail pour les stratégies de recherche était conséquente, ce qui a nécessité l'intégration de plusieurs approches pour augmenter la sensibilité de la recherche et son efficience, essentiellement l'approche *text mining*. Le manuscrit a permis l'évaluation des outils RoB 2.0 et ROBINS-I. Le manuscrit a été accepté pour publication à JAMA surg le 16 mars 2019.

Guidelines for Perioperative Care in Cardiac Surgery : Enhanced Recovery After Surgery (ERAS®) Society Recommendations.

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Key Points : Enhanced Recovery After Surgery (ERAS®) are evidence based protocols for perioperative care that can lead to improvements in clinical outcomes and cost savings. This review aims to present consensus recommendations for the optimal perioperative management of patients undergoing cardiac surgery. A systematic review of meta-analyses, randomized controlled trials, large non-randomized studies, and reviews was conducted for each protocol element. The quality of the evidence was graded by the authors and used to form consensus recommendations for each topic. Development of these recommendations was endorsed by the *Enhanced Recovery After Surgery Society®*.

Question : Which perioperative care approaches have the best evidence to support their incorporation into an ERAS® protocol for cardiac surgery ?

Findings : Using a Delphi survey process, we used the STS/AATS "Classification of Recommendations and Level of Evidence," as published by the ACC/AHA, to make a list of 22 graded preoperative, intraoperative and postoperative recommendations.

Meaning : Developing ERAS® guidelines using evidence based protocols can help standardize best practice and improve outcomes after cardiac surgery.

Tweet : @ERASCardiac
Enhanced Recovery After Surgery (ERAS®) Cardiac publishes evidence-based recommendations of perioperative care elements for patients after surgery.

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BACKGROUND :

Enhanced Recovery After Surgery (ERAS®) is a multimodal, transdisciplinary care improvement initiative to promote recovery of surgical patients throughout their entire perioperative journey.[1] These programs aim to reduce complications and promote earlier return to normal activities.[2,3] ERAS® protocols have been associated with a reduction in overall complications and length of stay of up to 50% when compared with conventional perioperative patient management in non-cardiac surgery populations.[4-6] Evidence-based ERAS® protocols have been published across multiple surgical specialties.[1] In early studies, the ERAS® approach showed promise in cardiac surgery (CS), however, evidence-based protocols have yet to emerge.[7]

To address the need for evidence-based ERAS® protocols, we formed a registered nonprofit organization (ERAS® Cardiac Society) to use an evidence-driven process to develop recommendations for pathways to optimize CS patient care through collaborative discovery, analysis, expert consensus, and best practices. The ERAS® Cardiac Society has a formal collaborative agreement with the ERAS® Society. This manuscript reports the first expert-consensus review of evidenced-based CS ERAS® practices.

METHODS :

We followed The Institute of Medicine (IOM) 2011 *Standards for Developing Trustworthy Clinical Practice Guidelines* using a standardized algorithm that included : experts, key questions, subject champions, systematic literature reviews, selection/appraisal of evidence quality, and development of clear consensus recommendations.[8] We minimized repetition of existing guidelines and consensus statements and focused on specific information in the framework of ERAS® protocols.

As sanctioned by the ERAS® Society, we began with a public organizational meeting in 2017 where broad topics of ERAS® in CS were discussed and solicited public comment regarding appropriate approaches and protocols. A multidisciplinary group of 16 cardiac surgeons, anesthesiologists, and intensivists were identified demonstrating expertise and experience with

ERAS®. The group agreed on 22 potential interventions, divided into preoperative, intraoperative, and postoperative phases of recovery.

After selecting topics and assigning group leaders, the literature search was conducted according to PRISMA guidelines (Table 1), and included studies, reviews, and evidence conducted on human subjects published in English from PubMed, EMBASE, Cochrane, Agency for Healthcare Research and Quality, and selected databases relevant to this consensus since 2000.[9] Medical Subject Heading terms were used, as were accompanying entry terms for the patient group, interventions, and outcomes. Two independent reviewers screened the abstracts considered for topics. Prospective randomized controlled trials, meta-analyses, and well-designed, non-randomized studies were given preference. When multiple publications had sample overlap, the most recent report was selected. Controversies were discussed and resolved via in-person meetings, conference calls, and discussions. A minimum of 75% agreement on class and level was required for consensus.[10] Consistent with the IOM guidelines, panel members with relevant conflicts of interest (COI) were identified and recused from voting on related recommendations. The structure of the recommendations was modeled after prior published ERAS® guidelines.[11] We used the STS/AATS 2017 updated "Classification of Recommendations and Level of Evidence," and ACC/AHA clinical practice guidelines to grade the consensus class (strength) of recommendation and level (quality) of evidence with associated color schemes.[10,12] (Table 2).

RESULTS :

The resulting consensus statements are summarized in Table 3. They are organized into preoperative, intraoperative and postoperative strategies :

I. Preoperative Strategies :

IIa	**C-LD**	**Preoperative measurement of hemoglobin A1c is recommended to assist with risk stratification.**

Optimal preoperative glycemic control, defined by a hemoglobin A1c (HbA1c) < 6.5%, has been associated with significant decreases in deep sternal wound infection, ischemic events, and other complications.[13,14] Evidence-based guidelines based on poor quality meta-analyses recommend preoperative screening all patients for diabetes and interventions to improve glycemic control to achieve A1C of <7%.[15] Despite this recommendation, ~25% of CS patients have A1C >7% and 10% have undiagnosed diabetes, indicating a failure to apply current evidence-based recommendations for preoperative diabetes management.[16] A recent retrospective review demonstrated that preadmission glycemic control, as assessed by HbA1c, is predictive of decreased long-term survival.[17] It is unclear whether preoperative interventions in CS patients will result in improved outcomes. Based on this moderate quality evidence, we recommend preoperative measurement of A1C to assist with risk stratification. (Class IIa, Level C-LD)

IIa	**C-LD**	**Preoperative measurement of albumin is recommended to assist with risk stratification.**

IIa	**C-LD**	**Preoperative correction of nutritional deficiency is recommended when feasible.**

Low preoperative serum albumin in CS patients is associated with an increased risk of morbidity and mortality postoperatively (independent of BMI).[18] Hypoalbuminemia is a prognosticator of preoperative risk, correlating with increased length of time on the ventilator, acute kidney injury, infection, length of stay and mortality.[19-21] Low-quality meta-analyses support measuring preoperative albumin to predict postoperative CS complications.[21] Based on the moderate quality of evidence, it can be useful to assess preoperative albumin before CS to assist with risk stratification. (Class IIa, Level C-LD)

For malnourished patients, oral nutritional supplementation has the greatest effect if started 7–10 days preoperatively and has been associated with a reduction in the prevalence of infectious complications in colorectal patients.[22] In CS patients with a serum albumin <3.0 g/dL,

supplementation with 7-10 days of intensive nutrition therapy may improve outcomes.[23-26] Currently, however, no adequately powered trials of nutritional therapy initiated early in high-risk CS patients are available.[27] In addition, this may not be feasible in urgent/emergent settings. Further studies are needed to determine when to delay surgery to correct nutritional deficits. Based on these data, we note that correction of nutritional deficiency is recommended when feasible. (Class IIa, Level C-LD)

IIb	**C-LD**	**A clear liquid diet may be continued up until 2-4 hours before general anesthesia.**

Most CS programs mandate that a patient be NPO after midnight for surgery the following day, or at the very least, they should fast for 6-8 hours from the intake of a solid meal before elective cardiac surgery.[28] Several RCTs have demonstrated, however, that non-alcoholic clear fluids can be safely given up to 2 hours before the induction of anesthesia, and a light meal up to 6 hours before elective procedures requiring general anesthesia.[28-30] Encouraging a clear liquid diet until 2-4 hours preoperatively is an important component of all ERAS® protocols outside of CS.[31] However, no large studies have been performed in CS populations. The supporting evidence is extrapolated from noncardiac surgical populations. A small study in CS patients demonstrated that an oral carbohydrate drink 2 hours preoperatively was safe, and no aspiration occurred.[32] Aspiration pneumonitis has not been reported, although this potential remains in CS patients with delayed gastric emptying due to diabetes mellitus, and transesophageal echocardiography may increase aspiration risk. Based on the data available in CS, a clear liquid diet may be continued up to 2-4 hours before general anesthesia (Class IIb, Level C-LD)

IIb	**C-LD**	**Preoperative carbohydrate loading may be considered before surgery.**

A carbohydrate drink (clear 12 ounce/24 gram complex carbohydrate beverage 2 hours preoperatively) reduces insulin resistance and tissue glycosylation, improves postoperative glucose control, and enhances return of gut function.[31] In a recent Cochrane review in CS

patients, carbohydrate loading reduced postoperative insulin resistance and hospital length of stay.[30] In a large randomized trial in CS patients, preoperative carbohydrate administration was found to be safe and improved cardiac function immediately following cardiopulmonary bypass.[29,30] However, it did not affect postoperative insulin resistance.[33,34] Given the current minimal supportive data in CS patients; carbohydrate loading is given a weak recommendation at this time. (Class IIb, Level C-LD)

IIa	**C-LD**	**Patient engagement tools, including online/application-based systems to promote education, compliance, and patient-reported outcomes are recommended.**

Patient education and counseling prior to surgery can be completed in person, through printed material, or through novel online/application-based approaches. These efforts include explanations of procedures and goals that may help reduce perioperative fear, fatigue and discomfort, and enhance recovery and early discharge. Data is emerging that software applications can engage patients, promote compliance, and capture patient-reported outcome measures.[35] They are designed to increase preventive care and engage patients in physical exercise. These platforms have the potential to increase patient knowledge, decrease anxiety, improve health outcomes, and reduce variation in care.[36,37] Pilot studies in CS have demonstrated the effectiveness of e-health platforms without any evidence of harm, thus it is recommended that these efforts be undertaken.[37] (Class IIa, Level C-LD)

IIa	**B-NR**	**Prehabilitation is recommended for patients undergoing elective surgery with multiple comorbidities or significant deconditioning.**

Prehabilitation (a.k.a. “prehab”) enables patients to withstand the stress of surgery by augmenting functional capacity.[38-40] Preoperative exercise decreases sympathetic over-reactivity, improves insulin sensitivity, and increases lean body mass to body fat ratio.[41-43] It also improves physical and psychological readiness for surgery, reduces postoperative

complications and length of stay, and improves the transition from the hospital to the community.[38,39] A cardiac prehab program should include education, nutritional optimization, exercise training, social support, and anxiety reduction, although current existing evidence is limited.[41-44] Three non-CS studies have successfully demonstrated the benefits of 3-4 weeks of prehab in the context of ERAS.[45-47] Prehab interventions prior to CS must be further examined in order to advance this area of research. The small number of studies, and the diversity of validation tools, limits the strength of the recommendation. In addition, this may not be feasible in urgent/emergent settings. (Class IIa, Level B-NR)

I	**C-LD**	**Smoking and hazardous alcohol consumption should be stopped 4 weeks before elective surgery.**

Screening for hazardous alcohol use and cigarette smoking should be performed preoperatively.[48] Tobacco smoking and hazardous alcohol consumption are risk factors for postoperative complications and present another opportunity for preoperative interventions. They are associated with respiratory, wound, bleeding, metabolic and infectious complications.[23,49-51] Smoking cessation and alcohol abstinence for one month are associated with improved postoperative outcomes after surgery.[51-53], Only a small number of studies are available, and further CS specific studies are needed. However, given the low risk of this intervention, patients should be questioned regarding smoking and hazardous alcohol consumption using validated screening tools and consumption should be stopped 4 weeks before elective surgery.[54] However, this may not be feasible in urgent/emergent settings. (Class I, Level C-LD)

II. Intraoperative Strategies :

I	**B-R**	**A care bundle of evidenced based best practices is recommended to reduce surgical site infections.**

To help reduce surgical site infections (SSIs), CS programs should include a care bundle that includes topical intranasal therapies, depilation protocols, appropriate timing and stewardship of perioperative prophylactic antibiotics combined with smoking cessation, adequate glycemic

control, and promotion of postoperative normothermia during recovery. Moderate quality meta-analysis have concluded care bundles of 3-5 evidence-based interventions can reduce SSIs.[55,56] This subject has been reviewed extensively with class of recommendation and level of evidence in an expert consensus review by Lazar and colleagues.[57]

Evidence supports topical intranasal therapies to eradicate staphylococcal colonization in CS patients.[57,58] From 18-30% of all surgical patients are S. aureus carriers, and they have 3 times the risk of S. aureus SSI and bacteremia.[59] It is recommended that topical therapy be applied universally.[60-62] Two studies validate the reduction of SSI in patients receiving mupirocin.[58,63] Level IA data exists suggesting that weight-based cephalosporins should be administered <60 minutes from the skin incision and continued for 48 hours after completion of CS. When the surgery is >4 hours, antibiotics require re-dosing.[64,65] Continuous versus intermittent dosing of cefazolin requires further data.[66] A meta-analysis of skin prep and depilation protocols indicates that clipping is preferred to shaving.[67] Clipping using electric clippers should occur close to the time of surgery.[68] A pre-operative shower with chlorhexidine has only been demonstrated to reduce bacterial counts in the wound and is not associated with significant efficacy.[57] Postoperative measures including sterile dressing removal within 48 hours and daily incision washing with chlorhexidine are potentially beneficial.[69,70]

In summary, we recommend the implementation of a care bundle to include topical intranasal therapies to eradicate staphylococcal colonization, weight-based cephalosporin infusion < 60 minutes from skin incision, with redosing for cases > 4 hours, skin prep and depilation protocols with dressing changes every 48 hours to reduce SSIs. (Class I, Level B-R) The bundle of recommendations to reduce SSI are summarized in Table 4 with the classification of recommendations and level of evidence referenced from Lazar and colleagues.[57]

III (Harm)	**B-R**	**Hyperthermia (>37.9 C) while rewarming on cardiopulmonary bypass is potentially harmful and should be avoided.**

Moderate quality prospective studies have demonstrated that when rewarming on cardiopulmonary bypass (CPB), hyperthermia (core temperature >37.9 C) is associated with cognitive deficits, infection and renal dysfunction.[71-73] Any postoperative hyperthermia within 24 hours following CABG has been associated with cognitive dysfunction at 4-6 weeks.[71]

Rewarming on CPB to normothermia should be combined with continuous surface warming.[74] Based on this evidence, we recommend avoiding hyperthermia while rewarming on cardiopulmonary bypass (Class III, Level B-R)

IIa	**B-R**	**Rigid sternal fixation can be useful to improve/accelerate sternal healing and reduce mediastinal wound complications.**

Most cardiac surgeons use wire cerclage for sternotomy closure because of the perceived low rate of sternal wound complications and low cost of wires. Wire cerclage brings the cut edges of bone back together by wrapping a wire/band around or through the two portions of bone, then tightening the wire/band to pull the two parts together. This achieves approximation and compression but does not eliminate side-by-side movement, and thus rigid fixation is not achieved with wire cerclage.[75]

In two randomized multicenter trials, sternotomy closure with rigid plate fixation resulted in significantly better sternal healing, fewer sternal complications, and no additional cost compared with wire cerclage at 6 months after surgery.[75,76] Patient-reported outcome measures demonstrated significantly less pain, better upper extremity function, and improved quality of life scores, with no difference in total 90-day cost.[76] Limitations of these studies include a sample size designed to test the primary end-point of improved sternal healing but not the secondary end-points related to pain and function as well as unblinded radiologists. Additional research demonstrated decreased mediastinitis, and painful sternal nonunion relief after median sternotomy, and superior bony healing when compared to wire cerclage.[77-79] Based on these studies, the consensus concluded that rigid sternal fixation has benefits in sternotomy patients and should be especially considered in high-risk individuals such as those with a high BMI, previous chest wall radiation, severe COPD, or steroid use. Rigid sternal fixation can be useful to improve/accelerate sternal healing and reduce mediastinal wound complications (Class IIa, Level B-R)

I	**A**	**Tranexamic acid or epsilon aminocaproic acid is recommended during on-pump cardiac surgical procedures.**

Bleeding is a common occurrence after CS and can adversely impact outcomes.[80,81] Publications on patient blood management are typically focused on reducing red blood cell transfusions through identification/treatment of preoperative anemia, delineation of safe transfusion thresholds, intraoperative blood scavenging, monitoring of the coagulation system, and data-driven algorithms for appropriate transfusion practices. This has been an area of focus in previously published large, comprehensive, multi-disciplinary, multi-society clinical practice guidelines.[82,83] The inclusion of all aspects of patient blood management are beyond the scope of our recommendations, though we encourage the incorporation of these existing guidelines within a local ERAS framework. This includes education, audit, and continuous practitioner feedback. Due to the near-universal accessibility, low-risk profile, cost-effectiveness, and ease of implementation, we did evaluate antifibrinolytic use with tranexamic acid or epsilon aminocaproic acid. In a large randomized controlled trial of patients undergoing coronary revascularization, total blood products transfused, and major hemorrhage or tamponade requiring reoperation were reduced using tranexamic acid.[84] Higher dosages, however, appear to be associated with seizures.[85,86] A maximum total dose of 100 mg/kg, is recommended.[87] Based on this evidence, tranexamic acid or epsilon aminocaproic acid is recommended during on-pump cardiac surgical procedures. (Class I, Level A)

III. Postoperative Strategies :

I	**B-R**	**Perioperative glycemic control is recommended.**

Interventions to improve glycemic control are known to improve outcomes. Multiple randomized trials, involving diverse patient cohorts, support intensive perioperative glucose control.[88-91] Preoperative carbohydrate loading has resulted in reduced glucose levels following abdominal surgery and CS.[92,93] Epidural analgesia during CS has been demonstrated to reduce the incidence of hyperglycemia.[94] Following CS, the morbidity of hyperglycemia is multifactorial and attributed to glucose toxicity, increased oxidative stress, prothrombotic effects, and inflammation.[14,15,89,91,95] Perioperative glycemic control is recommended based on

randomized data not specific to the CS population and quality observational studies.[96] (Class I, Level B-R)

IIa	**B-NR**	**An insulin infusion is recommended to treat hyperglycemia in all patients postoperatively.**

Treatment of hyperglycemia (glucose > 160-180 mg/dL or 8-10 mmol/L) with an insulin infusion for the CS patient may be associated with improved perioperative glycemic control. Postoperative hypoglycemia should be avoided, especially with a tight blood glucose target range (i.e., 80-110 mg/dl or 4-6 mmol/L).[95,97,98] Randomized trials support insulin infusion protocols to treat hyperglycemia perioperatively, however, more high-quality CS specific studies are needed. (Class IIa, Level B-NR)

I	**B-NR**	**A multimodal, opioid-sparing, pain management plan is recommended postoperatively.**

Until recently, parenteral opioids were the mainstay of postoperative pain management after CS. Opioids are associated with multiple side effects including sedation, respiratory depression, nausea, vomiting, and ileus.[99] There is growing evidence that multimodal opioid-sparing approaches can adequately address pain through the additive or synergistic effects of different types of analgesics permitting lower opioid doses in the CS population.[100]

Nonsteroidal anti-inflammatory drugs are associated with renal dysfunction after CS.[101] Selective COX-2 inhibition is associated with a significant risk of thromboembolic events after CS.[102] The safest non-opioid analgesic may be acetaminophen.[103] IV acetaminophen may be better absorbed until gut function has recovered postoperatively.[104] According to a medium quality meta-analysis, when added to opioids, acetaminophen produces superior analgesia, an opioid-sparing effect, and independent antiemetic actions.[105] Acetaminophen dosing is 1g every 6 hours. Combination acetaminophen preparations with opioids should be discontinued.

Tramadol has dual opioid/non-opioid effects but with a high delirium risk.[106] Tramadol produces a 25% decrease in morphine consumption, decreased pain scores, and improved

patient comfort postoperatively.[107] Pregabalin also decreases opioid consumption and is used in postoperative multimodal analgesia.[108] Pregabalin given one hour before surgery and for two postoperative days improves pain scores compared to placebo.[109] A 600 mg gabapentin dose, two hours before CS, lowers pain scores, opioid requirements, and postoperative nausea and vomiting.[110]

Dexmedetomidine, an intravenous alpha-2 agonist, reduces opioid requirements.[111] A medium quality meta-analysis of dexmedetomidine infusion reduced all-cause mortality at 30 days with a lower incidence of postoperative delirium and shorter intubation times.[112,113] Dexmedetomidine may reduce AKI after CS.[114] Ketamine has potential uses in CS due to its favorable hemodynamic profile, minimal respiratory depression, analgesic properties, and reduced delirium incidence, although, further studies are needed in this setting.[115]

Patients should receive preoperative counseling to establish appropriate expectations of perioperative analgesia targets. Pain assessments must be made in the intubated patient to ensure the lowest effective opioid dose. The critical care pain observation tool (CPOT), behavioral pain scale (BPS), and bispectral index (BIS) monitoring may have a role in this setting.[116-119] Although no single pathway exists for multimodal opioid-sparing pain management, there is sufficient evidence to recommend that CS programs use acetaminophen, Tramadol, dexmedetomidine, and pregabalin/Gabapentin based on formulary availability. (Class I, Level B-NR)

I	**B-NR**	**Postoperative systematic delirium screening is recommended at least once per nursing shift.**

Delirium is an acute confusional state characterized by fluctuating mental status, inattention, and either disorganized thinking or altered level of consciousness that occurs in ~50% of postoperative CS patients.[120-125] Delirium is associated with reduced in-hospital and long-term survival, freedom from hospital readmission, and cognitive and functional recovery.[126] Early delirium detection is essential to determine the underlying cause (i.e., pain, hypoxemia, low cardiac output, sepsis) and initiate appropriate treatment.[127] A systematic delirium screening tool such as the confusion assessment method for ICU (CAM-ICU) or ICU delirium screening

checklist (ICDSC) should be employed.[128,129] The perioperative team should consider routine delirium monitoring at least once per nursing shift.[121]

Due to the complexity of delirium pathogenesis, it is unlikely that a single intervention or pharmacologic agent will reduce the incidence of delirium following CS.[127] Non-pharmacologic strategies are a first-line components of management.[130,131] There is no evidence that prophylactic antipsychotics (e.g., haloperidol) reduces delirium.[132,133] Based on moderate quality, non-randomized studies in non-CS patients, delirium screening is recommended at least once per nursing shift to identify patients at risk and to facilitate implementation of prevention and treatment protocols. (Class I, Level B-NR)

I	**B-NR**	**Persistent hypothermia after CPB should be avoided in the early postoperative period.**

Postoperative hypothermia is the failure to return to/or maintain normothermia (>36°C) 2-5 hours after CS ICU admission.[134] Hypothermia is associated with increased bleeding, infection, prolonged hospital stay and death. Large registry observational studies suggest if hypothermia is of short duration, outcomes can be improved.[135,136] Based on this evidence, we recommend prevention of hypothermia using forced air warming blankets, raising the ambient room temperature, and warming of irrigation and IV fluids to avoid hypothermia in the early postoperative period.[71,137-139] (Class 1, Level B-NR)

I	**B-NR**	**Maintenance of chest tube patency is recommended to prevent retained blood.**

III	**A**	**Stripping or breaking the sterile field of chest tubes to remove clot is not recommended.**

Immediately following CS, most patients have some degree of bleeding.[81] If left un-evacuated, retained blood can cause tamponade or hemothorax. Thus a pericardial drain is always necessary following CS to evacuate shed mediastinal blood.[80] Drains used to evacuate shed

mediastinal blood are prone to clogging with clotted blood in up to 36% of patients.[140,141] When these tubes clog, shed mediastinal blood can pool around the heart or lungs, necessitating re-interventions for tamponade or hemothorax.[142-144] Retained shed mediastinal blood hemolyzes and promotes an oxidative inflammatory process that may further cause pleural and pericardial effusions and trigger postoperative atrial fibrillation.[143,145]

Chest tube manipulation strategies that are commonly employed in an attempt to maintain tube patency after CS are of questionable efficacy and potentially unsafe. One such example is chest tube stripping or milking, where the practitioner strips the tubes toward the drainage canister to break-up visible clot or create short periods of high negative pressure to remove clots. In meta-analyses of randomized trials, chest tube stripping has been shown to be ineffective and potentially harmful.[146,147] Another technique used to maintain patency is to break the sterile field to access the inside of chest tubes and use a smaller tube to suction the clot out. This technique may be dangerous as it can increase infection risk and potentially damage internal structures.[148]

To address the unmet need to prevent chest tube clogging, active chest tube clearance methods can be used to prevent occlusion without breaking the sterile field. This has been demonstrated to reduce the subsequent need for interventions to treat retained blood compared to conventional chest tube drainage, in 5 non-randomized CS clinical trials.[149-153] Active chest tube clearance has also been shown to reduce postoperative atrial fibrillation, suggesting that retained blood may be a trigger for this common problem.[145]

While there are no standard criteria for the timing of mediastinal drain removal, evidence suggests that they can be safely removed as soon as the drainage becomes macroscopically serous.[154] Based on these clinical trials, maintenance of chest tube patency without breaking the sterile field is recommended to prevent retained blood complications. (Class I, Level B-NR). Stripping or breaking the sterile field of chest tubes to remove clot is not recommended. (Class IIIA, Level B-R)

IIa	**C-LD**	**Chemical thromboprophylaxis is recommended following surgery.**

Vascular thrombotic events (VTE) include both deep venous thrombosis and pulmonary embolism and represent potentially preventable complications following CS. Patients remain hypercoagulable after CS, increasing VTE risk.[155,156] All patients benefit from mechanical thromboprophylaxis achieved with compression stockings and/or intermittent pneumatic compression during hospitalization or until mobilized to reduce the incidence of DVT after surgery even in the absence of pharmacological treatment.[157-159] Prophylactic anticoagulation for VTE should be considered on the first postoperative day and daily thereafter.[160] A recent medium quality meta-analysis suggested that chemical prophylaxis could reduce VTE risk without increasing bleeding or cardiac tamponade.[161] Based on this evidence, pharmacological prophylaxis should be employed as soon as satisfactory hemostasis has been achieved (most commonly postoperative day one through discharge) in addition to mechanical measures, such as intermittent pneumatic compression devices.[160-162] (Class IIa, Level C-LD)

IIa	**B-NR**	**Strategies to ensure extubation within 6 hours of surgery are recommended.**

Prolonged mechanical ventilation after CS is associated with longer hospitalization, higher morbidity, mortality and increased costs.[163] Prolonged intubation is associated with both ventilator-associated pneumonia and significant dysphagia.[164] Early extubation, within 6 hours of ICU arrival, can be achieved with time-directed extubation protocols and low-dose opioid anesthesia. This approach is safe (even in high-risk patients) and associated with decreased ICU time, length of stay, and costs.[165-172] A meta-analysis demonstrated that ICU times and LOS were reduced, however, no difference in morbidity and mortality occurred, likely due to disparate study design and under-powering.[173] Thus, studies have shown early extubation to be safe, but efficacy in reducing complications has not been conclusively demonstrated. Based on this evidence, we recommend strategies to ensure extubation within 6 hours of surgery. (Class IIa, Level B-NR)

IIa	**B-R**	**Early detection of kidney stress and interventions to avoid acute kidney injury are recommended following surgery.**

Acute kidney injury (AKI) complicates 22-36% of cardiac surgical procedures, doubling total hospital costs.[174-176] Strategies to reduce AKI involve predicting which patients are at risk and then implementing therapies to reduce the incidence. Urinary biomarkers (such as TIMP-2 X IGFBP7) can identify patients as early as 1 hour after CPB who are at increased risk of developing AKI.[177,178]

In a randomized controlled trial following CS, patients with positive urinary biomarkers who were assigned to an intervention algorithm had reductions in subsequent AKI.[179,180] The algorithm included avoiding nephrotoxic agents, discontinuing ACE inhibitors/angiotensin II antagonists for 48 hours, close monitoring of creatinine and urine output, avoiding hyperglycemia and radiocontrast agents, and close monitoring to optimize volume status and hemodynamic parameters. Similar results have been reported in a randomized controlled trial following surgery in a non-CS population.[181]

Although many risk-prediction scores for AKI after CS have been published, these scoring systems have good discrimination in assessing low-risk groups but relatively poor discrimination in moderate to high-risk patients.[182] This would suggest that all CS patients may benefit from detection of modifiable early kidney stress to prevent AKI. Based on these studies, biomarkers are recommended for early identification of patients at risk and to guide an intervention strategy to reduce AKI. (Class IIa, Level B-R)

I	**B-R**	**Goal directed therapy is recommended to reduce postoperative complications.**

Goal directed therapy (GDT) utilizes monitoring techniques to guide clinicians with administering fluids, vasopressors, and inotropes to avoid hypotension and low cardiac output.[183] While many clinicians do this informally, GDT uses a standardized algorithm for all patients to improve outcomes. Quantified goals include blood pressure, cardiac index, systemic venous oxygen saturation, and urine output. Additionally, oxygen consumption, oxygen debt, and lactate levels, may augment therapeutic tactics. GDT trials consistently demonstrate reduced

complication rates and LOS broadly in surgery, and specifically in CS.[184-188] Based on this evidence, we recommend GDT to reduce postoperative complications (Class I, Level B-R)

Other Important Ungraded ERAS Elements :

Preoperative anemia is common and associated with poor outcomes in non-CS patients.[189] Patients scheduled for CS may have multifactorial etiologies for anemia including acute or chronic blood loss, vitamin B12 or folate deficiency, and anemia of chronic disease.[190] If time permits, all causes of anemia should be investigated, but data supporting improved outcomes in the CS literature is weak. Intraoperative anesthetic and perfusion considerations are also important ERAS elements. Impaired renal oxygenation has been demonstrated during CPB and is ameliorated by an increase in CPB flow.[191] This may contribute to postoperative renal dysfunction and suggests that goal-directed perfusion strategies need to be considered. Other anesthetic considerations may include a comprehensive protective lung ventilation strategy. Multiple studies have established that providers should utilize a low tidal volume strategy for mechanical ventilation in CS.[192] Early postoperative enteral feeding and mobilization after surgery are other essential components of ERAS surgical protocols.[1] We recommend programs tailor these recommendations to achieve these goals working with staff with expertise in nutrition, early cardiac rehabilitation, and physical therapy.

Conclusion :

In CS, a "Fast Track" project to improve outcomes was first initiated by bundling perioperative treatments.[193] The ERAS® pathway was initiated in the 1990s by a group of academic surgeons to improve perioperative care for colorectal patients but is now practiced in most fields of surgery.[1,194] Although ERAS® is relatively new to CS, we anticipate that programs can benefit from these recommendations as they develop protocols to decrease unnecessary practice variation and improve quality, safety, and value for their patients. CS involves a large group of providers working in concert throughout all phases of care. Patient and caregiver education and system-wide engagement (facilitated by specialty champions and nurse coordinators) are necessary to implement these best practices. A successful implantation of ERAS® protocols is possible in CS, but a broad-based multidisciplinary approach is imperative for success.

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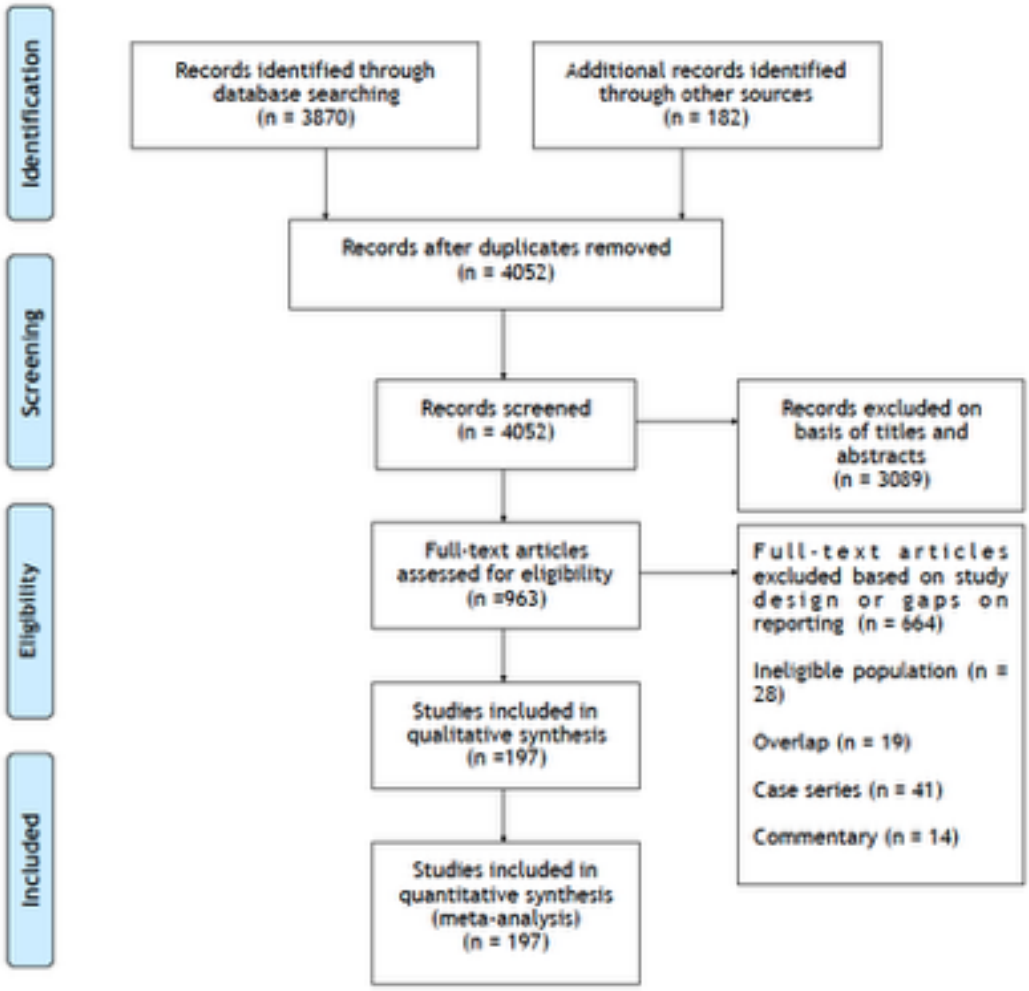
Table 1 : PRISMA Flow Chart



Class (Strength) of Recommendation
Class I (Strong) Benefit >>>Risk
Class IIa (Moderate) Benefit >> Risk
Class IIb (Weak) Benefit > Risk
Class III: No Benefit (Moderate) Benefit = Risk
Class III: Harm (Strong) Risk > Benefit

Level (Quality) of Evidence
Level A -High-quality Evidence from more than one RCT. -Meta-analysis of high quality RCTs -One or more RCTs corroborated by registry studies
Level B-R -Moderate -quality evidence from 1 or more RCT -Meta-analysis of moderate-quality RCTs
Level B-NR -Moderate -quality evidence from 1 or more well designed, well executed non randomized studies, observational studies
Level C-LD -Randomized or non-randomized observational or registry studies with limitations of design or execution
Level C-EO -Consensus of expert opinion based on clinical experience

Table 2 : Class of recommendation and levels of evidence (adapted from Bakaeen FG, Svensson LG, Mitchell JD, Keshavjee S, Patterson GA, Weisel RD. The American Association for Thoracic Surgery/Society of Thoracic Surgeons position statement on developing clinical practice documents. The Journal of Thoracic and Cardiovascular Surgery. 2017;153:999-1005).

COR	LOE	Recommendation
I	A	Tranexamic acid or epsilon aminocaproic acid is recommended during on-pump cardiac surgical procedures.
I	B-R	Perioperative glycemic control is recommended.
I	B-R	A care bundle of evidenced based best practices is recommended to reduce surgical site infections.
I	B-R	Goal directed therapy is recommended to reduce postoperative complications.
I	B-NR	A multimodal, opioid-sparing, pain management plan is recommended postoperatively.
I	B-NR	Persistent hypothermia after CPB should be avoided in the early postoperative period.
I	B-NR	Maintenance of chest tube patency is recommended to prevent retained blood.
I	B-NR	Postoperative systematic delirium screening is recommended at least once per nursing shift.
I	C-LD	Smoking and hazardous alcohol consumption should be stopped 4 weeks before elective surgery.
IIa	B-R	Early detection of kidney stress and interventions to avoid acute kidney injury are recommended following surgery.
IIa	B-R	Rigid sternal fixation can be useful to improve/accelerate sternal healing and reduce mediastinal wound complications.
IIa	B-NR	Prehabilitation is recommended for patients undergoing elective surgery with multiple comorbidities or significant deconditioning.
IIa	B-NR	An insulin infusion is recommended to treat hyperglycemia in all patients postoperatively.
IIa	B-NR	Strategies to ensure extubation within 6 hours of surgery are recommended.
IIa	C-LD	Patient engagement tools, including online/application-based systems to promote education, compliance, and patient-reported outcomes are recommended.
IIa	C-LD	Chemical thromboprophylaxis is recommended following surgery.

IIa	C-LD	Preoperative measurement of hemoglobin A1c is recommended to assist with risk stratification.
IIa	C-LD	Preoperative correction of nutritional deficiency is recommended when feasible.
IIb	C-LD	A clear liquid diet may be continued up until 2-4 hours before general anesthesia.
IIb	C-LD	Preoperative carbohydrate loading may be considered before surgery.
III (NoBenefit)	A	Stripping or breaking the sterile field of chest tubes to remove clot is not recommended.
III (Harm)	B-R	Hyperthermia (>37.9 C) while rewarming on cardiopulmonary bypass is potentially harmful and should be avoided.

Table 3 : Classification of Recommendation (COR) and Level of Evidence (LOE)

Recommendation	COR	LOE
Perform topical intranasal decolonization prior to surgery.	Class I	A
Administer intravenous cephalosporin prophylactic antibiotic 30-60 minutes prior to surgery.	Class I	A
Clipping immediately prior to surgery (as opposed to shaving).	Class I	C
Use a chlorhexidine-alcohol based solution for skin preparation before surgery.	Class IIb	C
Remove operative wound dressing after 48 hours.	Class IIa	C

Table 4 : Surgical Site Infection Bundle including Classification and Recommendation (COR) and Level of Evidence (LOE)

Chapter 3 Manuscrit #2

Avant-propos

L'intérêt pour la prise en charge chirurgicale des valvulopathies et aortopathies acquises du greffon cardiaque telles que les maladies mitro-tricuspides et les dissections de l'aorte, se justifie par un contexte social de paucité de donneurs rendant plus que primordiale la prolongation de la survie du greffon. Le devis de cette étude était donc de revoir de façon systématique toutes les données pertinentes publiées dans la littérature. Sur ces sujets, aucune revue systématique n'avait été faite et seule une revue narrative s'était intéressée à l'atteinte de la valve tricuspide suivant la transplantation cardiaque. Nous avons été surpris lors de l'exécution de la recherche préliminaire, scrutant les trois bases de données habituellement consultées, par le faible nombre d'études pertinentes disponibles. Ceci a motivé le recours à la *citation chasing* et le *hand searching* pour obtenir des sources supplémentaires de données. Non seulement ces approches ont quasiment doublé le nombre d'études incluses dans la revue systématique, mais ont également permis d'étendre le protocole de recherche aux techniques trans-cathéters. Ce manuscrit a été soumis au *journal of Heart and Lung Transplant (08 mars 2019).*

Valvular surgery in the transplanted heart : Montreal Heart Institute experience and Scoping Review.

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Word count : 6232

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Abstract

Introduction:

This systematic review was performed to evaluate the literature regarding optimal surgical management of valvular dysfunctions after cardiac transplantation either by open surgical conventional approach or with trans-catheter techniques.

Evidence acquisition:

Medline, EMBASE, and the Cochrane Central register were systematically searched for studies that reported surgical or trans-catheter management of valvular dysfunction in cardiac allografts. To improve the sensitivity of the literature search, we performed a citation chasing in Google Scholar, Scopus, and Web of Science. A retrospective review of cardiothoracic surgical interventions or trans-catheter procedures carried out in patients who had previously undergone heart transplantation at our institution was also performed.

Evidence synthesis:

A total of 440 patients underwent cardiac transplantation at Montreal Heart Institute since 1990. Among them, 5 (1.1%) patients were operated for valvular dysfunctions.

Fifty-one studies met the criteria for inclusion in the present analysis, yielding a total of 144 patients, addressing 5 different types of valvular dysfunctions. The tricuspid valve was the most affected with regurgitation secondary to biopsy-induced injury. Repair was feasible in most patients with durable results in the setting of the functional etiology of the valvular dysfunction. Biological prosthesis was the substitute of choice when replacement was required.

Conclusion: Reoperation for valve surgery, repair and replacement are feasible in this high-risk population achieving good results with emerging minimally invasive techniques and trans-catheter approaches.

Word count : 215

Introduction

Over the last four decades, improvement in immunosuppression has led to greater survival after cardiac transplantation, resulting in surviving recipients at risk of developing long-term complications including cancer, infection and coronary allograft vasculopathy (CAV). Acquired valvular dysfunction is not an infrequent finding but is generally medically managed. When it fails, conventional surgery is usually performed in patients with preserved cardiac allograft function in the absence of CAV. Reports of conventional surgery to correct a valvular dysfunction in cardiac transplantation recipients remain very limited both in terms of feasibility and postoperative outcomes in these high risk surgical patients [1, 2]. Therefore, the purpose of this systematic review was to evaluate the available literature regarding optimal choice of intervention for valvular dysfunction after cardiac transplantation whether with a surgical approach or with trans-catheter techniques and to summarize the experience of the Montreal Heart Institute.

Methods

Evidence Acquisition

Systematic review and meta-analysis were performed based on the Meta-analysis of Observational Studies in Epidemiology guidelines [3]. The manuscript was structured using the recommendations of the Systematic Reviews and Meta-Analyses (PRISMA) statement [4]. PubMed, EMBASE, and the Cochrane Central register of controlled trials were searched for studies published from January 1990 to November 2018 using the following Medical subject heading terms: “heart transplantation,” “valve replacement,” “heart valve prosthesis implantation,” and “trans-catheter aortic valve implantation/replacement.” To improve the sensitivity of the literature search, we performed citation chasing in Google Scholar, Scopus, and Web of Science. For the cited reference searches, we used a narrative review published in 2008 by Wong et al. [5]. Related journals and list of references of selected articles were also crosschecked for other relevant studies. We included all studies reporting on short or long terms results of surgical or trans-catheter management of valvular dysfunction in cardiac allografts. Case reports were included considering the scarcity of surgical series. Series reporting on mycotic aortic aneurysm, review articles, letters to the editor were excluded. The study selection

was performed by two independent reviewers (WBA and MC) through the following two levels of screening: the titles and abstracts of the searched studies were screened at the first level then the full texts were reviewed at the second level. In case of multiple publications with sample overlap, the most recent report was selected. Controversies were discussed and resolved via e-mail discussions. Quality assessment of the included studies was evaluated using the ROBINS-I tools.

During the same time interval, we performed a retrospective review of cardiothoracic surgical interventions or trans-catheter procedures carried out in patients who had previously undergone heart transplantation at our institution.

Results

Literature Search Results

The search results are summarized in a PRISMA diagram (Figure 1). One thousand and nine studies were identified. A first level screen was undertaken on articles' titles and abstracts. Fifty-seven articles remained for full-text review. From these, 6 were excluded: 3 review papers, 2 overlap and one case report reporting a mycotic aneurysm. The 51 studies [6–56] included a total study population of 144 recipients, and addressed 5 different valvular dysfunctions: 1) Tricuspid valve regurgitation, 2) Mitral and mitro-tricuspid valves disease, 3) Aortic valve disease, 4) Ascending aortic dissection and dilation and 5) Trans-catheter valve procedures (aortic, mitral and tricuspid). All studies had at least a moderate risk of bias.

Montreal Heart Institute Experience

Since 1990, a total of 440 patients underwent cardiac transplantation at Montreal Heart Institute. Among them, 5 (1.1%) patients were operated for valvular dysfunctions: Three isolated tricuspid regurgitation, one isolated mitral regurgitation and one mitral regurgitation with concomitant tricuspid regurgitation.

Tricuspid Valve

In the local experience, three patients underwent tricuspid valve replacement. Tricuspid damage following biopsies occurred in one patient and annular dilatation was the cause of tricuspid regurgitation in the 2 other patients. Results of tricuspid surgery were not optimal, two of our

patients died at mid-term follow-up (29 and 37 months) and one patient underwent retransplantation 2 years after tricuspid valve replacement for valvular cardiomyopathy.

Sixteen studies [6–21] reporting surgical management of the tricuspid valve dysfunction in cardiac allograft included 89 patients. Patients' baseline and operative characteristics and outcomes are summarized in Table 1. The time span between cardiac transplantation and tricuspid valve surgery averaged 91 ± 46 months (range from 19 to 144 months). All but five patients had a presumed biopsy-induced tricuspid regurgitation. Four studies [13,17,18,19] totaling 53 patients reported a bi-atrial technique at the time of transplantation.

Only one series [20] reported the use of minimally invasive access to the tricuspid valve. Twenty-five tricuspid valve repairs (25/89, 28%) were carried out with 3 early failures (respectively at 8, 14 days and 6 months postoperatively) and one 1 late failure (4 years postoperatively) reported. All others (64/89,72%) underwent tricuspid valve replacement with bioprosthetic valves, with two failures (4 and 10 months postoperatively) reported. One patient had antibody-mediated destruction of a mitral homograft and the other one had pulmonary allograft replacement with a bioprosthetic valve after 10 months for valvular stenosis.

Mitral and Mitro-Tricuspid Valve Disease

Fifteen studies [11,20-33] reported surgical management of mitral and mitro-tricuspid valve dysfunction in 20 patients following cardiac transplantation. Patients' baseline and operative characteristics and outcomes are summarized in Table 2. The time interval between cardiac transplantation and valve surgery averaged 81 ± 75 months (range from 5 to 252 months). The mechanisms for mitral regurgitation were degenerative and/or ischemic secondary to allograft vasculopathy. Of note, 2 patients presented a left side endomyocardial biopsy-induced mitral insufficiency. Mitral stenosis was described in only one patient and all others dysfunctions were valve regurgitation. About half of patients underwent mitral repairs. One repair failed 2 months postoperatively following ring dehiscence. Only one series [19] reported minimally invasive access to the atrioventricular valves.

Aortic Valve Disease

Seven studies [12, 21,28, 34–37] reported surgical management of aortic valve dysfunction in cardiac allograft including 9 patients. Patients' baseline and operative characteristics and

outcomes are summarized in Table 3. The time interval between cardiac transplantation and aortic valve surgery averaged 104 ± 61 months (range from 31 to 192 months). Indications for surgery were aortic stenosis in 6 patients and aortic regurgitation in the remaining 3 cases.

Aortic Pathology

A total of ten studies [15, 16, 38–45] reported surgical management of aortic disease in cardiac allograft in 13 patients. Patients' baseline and operative characteristics and outcomes are summarized in Table 4. Three patients developed early aortic dissection limited to the donor aorta in the first month postoperatively. One patient presented with an aneurysm of the ascending aorta presumably due to significant marfanoid changes in the donor's aorta.

Transcatheter Procedures

Twelve case reports [21, 46–56] reported trans-catheter management for valve dysfunction in cardiac allografts. Patients' baseline and operative characteristics and outcomes are summarized in Table 5. Seven patients underwent trans-catheter aortic valve replacement, all but two through a trans-femoral access. One patient had a trans-catheter aortic valve replacement (TAVR) at the age of 25 years [52]. In our center, one patient had 2 Mitra-clips implanted in 2013, but required mitral valve replacement the following day due to device migration.

Discussion

Valvular dysfunction following cardiac transplantation is not an infrequent finding and has been reported to develop in 18% of patients [57]. The optimal timing of surgical intervention in cases refractory to the medical management is controversial in order to avoid development of ventricular dysfunction or cardio-renal syndrome due to intractable fluid overload. Historically, these patients were considered for cardiac retransplantation. Two studies [58, 59] reported that repeat heart transplantation carries a much higher risk than primary transplantation, with 3- and 5-year survival of 55% and 33%, respectively. Recent efforts have been made to preserve the allograft and proceed with valve repair and/or replacement, because of the scarcity of donor hearts.

Tricuspid valve regurgitation is the most common valvular dysfunction encountered after cardiac transplantation with a reported incidence up to 84% [5], but only 34% are clinically

significant (i.e., moderate or severe) [60]. Tricuspid regurgitation (TR) following cardiac transplantation has both functional and organic etiologies. The predominant mechanism of the organic etiology is the biopsy-induced chordal tear resulting in a leaflet flail. The septal leaflet was the most affected one in the series of AlHarethi et al. [19] whereas Yanka et al. [13] reported more tear in the antero-posterior leaflet. The TR incidence after cardiac transplantation has been correlated with the number of endomyocardial biopsies performed. Mielniczuk et al. [61] reported that 47% of patients with new onset of TR had chordal tissue found in their biopsy specimens. In a series of 101 patients reported by Nguyen et al. [62], there was no case of significant TR in patients who had fewer than 18 endomyocardial biopsies during follow-up, while 60% of those with more than 31 biopsies developed severe TR. The use of the longer 45 cm sheet across the tricuspid valve is an approach that reduces the incidence of TR. The use of echocardiography rather than fluoroscopy to guide endomyocardial biopsy has also been suggested [63]. The windows for viewing the right ventricle are not always optimal and the chords and sub-valvular apparatus can be very difficult to visualize in order to avoid the bioptome.

Functional TR results from a geometric distortion of the tricuspid annulus secondary to a dilation or misalignment of the atrium, tricuspid valve and right ventricle. This misalignment may result from either tension caused by the atrial anastomosis or by size mismatch between the donor heart and the pericardial cavity. Koch et al. [64] believe that the bi-atrial technique, which results in a very large combined atrium, increases both atrial wall tension and tricuspid annular size. It may also lead to asynchronous atrial contractions causing further dilation over time. Moreover, Park et al. [65] reported a much lower prevalence of significant TR with the introduction of the bi-caval technique when compared to the bi-atrial (10.5% versus 36.4%). While the bi-caval technique avoids the issue of the atrial anastomosis, it may create tension on the venous anastomoses, especially the inferior vena cava, which can also be responsible for development of TR. Extension of this anastomosis using a recipient's venous flap reduces the occurrence and the severity of TR after cardiac transplantation [66]. Other mechanisms of functional TR include progressive annular dilation secondary to pulmonary hypertension or right ventricular dysfunction. Repeated episodes of rejection with subsequent tricuspid papillary muscle edema

and dysfunction with asymmetrical right ventricle contraction [67] that subsist after the resolution of rejection episodes may also cause TR.

Twenty-five patients underwent repair (28%) in the present review, with three early failures. Repair should be reserved for functional etiologies. Tricuspid valve replacement with biological prostheses is preferred since it enables access to the right ventricle for endomyocardial biopsy, while avoiding anti-coagulation and the subsequent high risk of thrombosis with mechanical TVR. Bishawi et al. [68] reported that significant TR is a common finding immediately after transplant and is associated with early morbidity and reduced survival. Some authors [69, 70] have advocated prophylactic tricuspid valve annuloplasty to reduce the incidence of early TR. Jeevanandam et al. [70] reported no significant TR at 1 year when a prophylactic tricuspid valve annuloplasty was performed compared to the 34% observed to historical controls. Thus, prophylactic tricuspid valve annuloplasty may confer long-term benefit to cardiac transplant recipients.

Mitral valve regurgitation is also a common finding in patients after heart transplantation. Cladellas et al. [71] reported a rate of moderate mitral regurgitation (MR) of 32% two years after cardiac transplantation. While edema of the valvular and subvalvular areas may explain early occurrence of MR, annular dilatation as consequence of allograft vasculopathy and/or ventricular dysfunction is the principal mechanism for late MR following cardiac transplantation. Contrary to the tricuspid valve, atrial distortion secondary to the bi-atrial technique is not correlated to the incidence of MR [72]. Mitral repair confers durable results with only one early failure reported (2 months postoperatively). Repair or replacement may be carried out through a left atrial or trans-septal approach especially if concomitant tricuspid repair is required. Minimally invasive surgery has been described as a safe and durable procedure with favorable technique-related mortality, in-hospital morbidity, and long-term cardiac-specific outcomes [19].

A few cases of aortic valve disease following cardiac transplantation have been reported in the literature [73]. In some instances, aortic regurgitation can be caused by an aortic aneurysm, or valvular endocarditis. Aortic valve replacement after cardiac transplantation is feasible, safe and carries a low-operative risk [74]. Aortic dissection occurs in 1 to 2% of cardiac allograft [75], with a bimodal presentation: In the early postoperative period, aortic dissection is mainly

explained by the weakness of the aortic tissue and/or mismatch between the donor and recipient aorta, generating a difference in wall tension at the suture line. Late dissection, on the other hand, is associated with hypertension, diabetes mellitus, connective tissue disorder and accelerated atherosclerosis as well as tissue weakness caused by immunosuppressive agents, especially steroids.

Despite the favorable results of redo valve surgery after cardiac transplantation, it remains technically challenging, requires more blood product transfusions and potentially subsequent further sensitization. Redo allograft valve surgery is associated with increased morbidity and mortality compared to the primary cardiac interventions [76]. TAVR appears as a promising and effective therapeutic option for aortic valve disease in high-risk or inoperable heart transplant recipients. Percutaneous approaches of the mitral valve using the Mitra-Clip device in the presence of a favorable anatomy have been used with immediate success in patients at high risk for conventional surgery. Some authors [53, 54] reported technical issues due to the particular atrial and atrioventricular anatomy of these patients after transplantation. Longer follow-up and larger clinical experience will better define the role of percutaneous approaches in heart transplant patients.

Limitation of Study

This review included several case reports and a group of limited series from numerous transplantation centers around the world. Although regrouping these experiences raises serious concerns of a publication bias, it remains the largest summary of surgical treatment of valve disease among heart transplant recipients.

Conclusion

Cardiac valve disease, especially tricuspid regurgitation is common in patients following heart transplantation and may require surgical intervention. The mechanisms causing valvular dysfunctions are various with endomyocardial biopsy induced chordal damage resulting in a leaflet flail of the tricuspid valve being the most prominent. Surgical repair and replacement are feasible in these high-risk patients. Minimally invasive surgical approaches and trans-catheter techniques are evolving and could facilitate future management of valvular dysfunction following cardiac transplantation.

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Table 1: Tricuspid valve. Baseline, operative characteristics and outcomes.

Author	N	Cause of CMP	Valve dysf	N Biopsy	Time Months	Procedures	Access	Failure repair	Re-TVR	Outcome
Votapka 1994 [6]	1	Ischemic	TR prolapse	n/a	55	1TVR Bio	Sterno	n/a	0	Alive at 2 months
Crumbley 1994 [7]	2	Post-partum Ischemic	TR prolapse	n/a	28	2 Repairs	Sterno	0	n/a	Alive at 34 months
Weston 1996 [8]	1	Ischemic	TR prolapse	n/a	19	1 TVR Bio	Sterno	n/a	0	Alive at 4 months
Hoffmeier 1996 [9]	1	Idiopathic	TR prolapse	n/a	49	1 TVR Bio	Sterno	n/a	0	Alive at time of report
Whalers 1996 [10]	12	Dilated idiopathic	TR prolapse	n/a	72	4 repairs 8 TVR bio	Sterno	0	0	2 died < 1 year 8 alive at 21 months
Koyanagi 1999 [11]	2	n/a	TR prolapse	n/a	n/a	2 TVR Mec	Sterno	n/a	0	Alive at time of report
Ichikawa 2000 [12]	1	Idiopathic	TR prolapse	n/a	65	1 TVR Bio	Sterno	n/a	0	Unknown
Yankah 2000 [13]	19	Dilated Ischemic	TR prolapse	12	105	7 repairs 8 TVR Bio 4 Xenografts	Sterno	1	0	5 died < 1 year 10 alive at 29 months
Chan 2001 [14]	6	n/a	TR prolapse	n/a	n/a	TVR Bio	Sterno	n/a	0	Alive at 13 months
Reddy 2002 [15]	1	n/a	TR prolapse	n/a	n/a	1 Repair	Sterno	0	n/a	Unknown
Rothenburger 2005 [16]	3	Dilated Ischemic	TR prolapse	n/a	90	1 repair 2 TVR	Sterno	0	0	Unknown
Raghavan 2006 [17]	9	n/a	TR prolapse	n/a	144	9 TVR Bio	Sterno	n/a	0	1 died at 2 months 8 alive at 6 months
Filsoufi 2006 [18]	8	Idiopathic Ischemic	4 TR prolapse 4 TR dilation	18	21	6 repairs 1 TVR bio 1 P- allograft	Sterno	3	1	2 died < 1 year 6 alive at 55 months
AlHarethi 2006 [19]	17	n/a	16 TR prolapse 1 TR dilation	33	n/a	2 repairs 14 TVR Bio 1 M-homograft	Sterno	0	1	Alive at 33 months
VanderMerwe 2017 [20]	3	n/a	TR prolapse	n/a	n/a	3 TVR Bio	Port-access	n/a	0	Alive at time of report
Goekler 2017 [21]	3	N/a	3 TR dilation	n/a		2 repairs 1 TVR Bio	Sterno	0	0	1 died at 58 months 2 alive at 43 months
MHI experience	3	Post-partum/ ischemic	1 TR prolapse 2 TR dilation	19	204	3 TVR Bio	Sterno	n/a	0	2 died at 60 months 1 reTx at 24 months

TR : tricuspid, TVR : tricuspid valve replacement, Bio : biological, sterno : sternotomy, CMP : cardiomyopathy, dysf : dysfonction, reTx : retransplantation, , n/a : not available.

Table 2 : Mitral and Mitro-Tricuspid valves. Baseline, operative characteristics and outcomes.

Author	N	Cause of CMP	Valve dysfonction	Rejection	Time Months	Procedures	Access	Failure repair	Re-MVR	Outcome
Mitral										
Copeland 1991 [22]	1	Ischemic	MR	1	72	MVR Bio	Sterno	n/a	0	Alive at 8 months
Cavero 1996 [23]	1	Idiopathic	MR prolapse	n/a	52	MVR Mec	Sterno	n/a	0	Alive at 24 months
Myers 1996 [24]	1	Ischemic	MR prolapse	n/a	26	MVR Mec	Sterno	n/a	0	Unknown
Koyanagi 1999 [11]	1	n/a	MR	n/a	n/a	MVR Bio	Sterno	n/a	0	Alive at time of report
Ladowski 2000 [25]	1	Idiopathic	MR degenerative	1	47	Repair	R. Thor	0	n/a	Alive at 3 months
Aleksic 2005 [26]	1	Dilated	MR	1	8	MVR Mec	Sterno	n/a	0	Alive at 72 months
Mohammadi 2007 [27]	1	Ischemic	MR degenerative	0	144	MVR Bio	Sterno	0	0	Alive at 6 months
Musci 2007 [28]	1	n/a	MR	n/a	n/a	MVR Mec	Sterno	n/a	0	Alive at time of report
Bouna 2012 [29]	1	Dilated	MR	0	23	Repair	Sterno	1	n/a	Alive at 43 months
Goekler 2017 [21]	2	n/a	1 MR 1 MS	n/a	68	1 Repair 1 MVR Mec	Sterno	0	0	Alive at 32 months
MHI experience	1	Restrictive	MR	0	1	MVR Bio	Sterno	n/a	0	Alive at time of report
Mitro-Tricuspid										
Goldstein 1997 [30]	1	Idiopathic	MR/ TR	n/a	5	MVR Bio TR repair	Sterno	0	0	Alive at 12months
Wijburg 1998 [31]	1	n/a	MR/ TR	n/a	72	MVR Bio TV repair	Sterno	0	0	Died at 2 months
Mohammadi 2007 [27]	1	Ischemic	MR/TR	0	136	MVR Bio TV repair	Sterno	0	0	Alive at 6 months
Yoshikawa 2009 [32]	1	Dilated	MR/ TR	n/a	84	MV Repair TV repair	Sterno	0	n/a	Alive at 48 months
Fernandez 2010 [33]	1	Post-partum	MR/ TR	n/a	252	MV Repair TV repair	Sterno	n/a	0	Alive at 6 months
VanderMerwe 2017 [20]	4	n/a	MR/ TR	n/a	n/a	4 MV Repairs TV repair	Port-access	0	n/a	Alive at time of report
MHI experience	1	Dilated	MR/ TR	1	228	MVR Bio TV repair	Sterno	n/a	0	Alive at time of report

MR : mitral regurgitation, MS : mitral stenosis, TR : tricuspid regurgitation, MV : mitral valve, TV : tricuspid valve, Bio : Biological, Mec : Mechanical, sterno: sternotomy, R Thor: right thoracotomy, CMP: cardiomyopathy, n/a : not available

Table 3 : Aortic valve. Baseline, operative characteristics and outcomes.

Author	N	Cause of cardiomyopathy	Valve dysfunction	Time Months	Procedures	Access	Re-AVR	Outcome
Goenen 1991 [34]	1	Ischemic	AI	31	AVR Mec	Sternonotomy	0	Alive at 2 months
Fiane 1993 [35]	1	Idiopathic	AI	48	AVR Mec	Sternonotomy	0	Alive at 5 months
Ichikawa 2000 [12]	1	Post-partum	AI	81	AVR Mec	Sternonotomy	0	Alive at 3 months
Joyce 2009 [36]	1	Idiopathic	AS- BAV	132	AVR Bio	Sternonotomy	0	Alive at time of report
Musci 2007 [28]	3	n/a	AS	n/a	AVR Mec	Sternonotomy	0	Alive at time of report
Vistarini 2010 [37]	1	n/a	AS	192	AVR Bio	Mini-Sternotomy	0	Alive at time of report
Goekler 2017 [21]	1	n/a	AS	139	AVR Bio	Sternonotomy	0	Died at 7 months

AI : aortic insufficiency, AS : aortic stenosis, BAV : bicuspid aortic valve, AVR : aortic valve replacement, Bio : Biological, Mec : Mechanical, n/a : not available

Table 4 : Aortic disease. Baseline, operative characteristics and outcomes

Author	N	Cause of cardiomyopathy	Valve dysfunction	Time Months	Procedure	Access	Outcome
Pak 1995 [38]	1	n/a	Dissection type A	n/a	Bentall	Sternotomy	Alive at time of report
Teebeken 1999 [39]	1	Ischemic	Dissection type A	1	Valve sparing	Sternotomy	Alive at time of report
Reddy 2002 [15]	2	n/a	Dissection type A	n/a	AA replacement	Sternotomy	Unknown
Korkut 2003 [40]	1	n/a	Dissection type A	84	Bentall	Sternotomy	Alive at time of report
Schellemans 2004 [41]	1	n/a	Dissection type A	n/a	Bentall	Sternotomy	Alive at time of report
Cafarelli 2005 [42]	1	Ischemic	Dissection type A	108	Bentall	Sternotomy	Alive at time of report
Rothenburger 2005 [16]	3	Ischemic Dilated	2 Dissection type A 1 Dissection type B	58	2 AA replacement 1 stent graft	Sternotomy	1 died day 1 2 Alive at time of report
Lopez 2009 [43]	1	Ischemic	Dissection type A	1	Bentall	Sternotomy	Alive at time of report
Saritas 2009 [44]	1	Dilated	Dissection type A	5	Bentall	Sternotomy	Alive at 7 months
Elhenawy 2012 [45]	1	n/a	AA aneurysm	204	Valve sparing	Sternotomy	Alive at 19 months

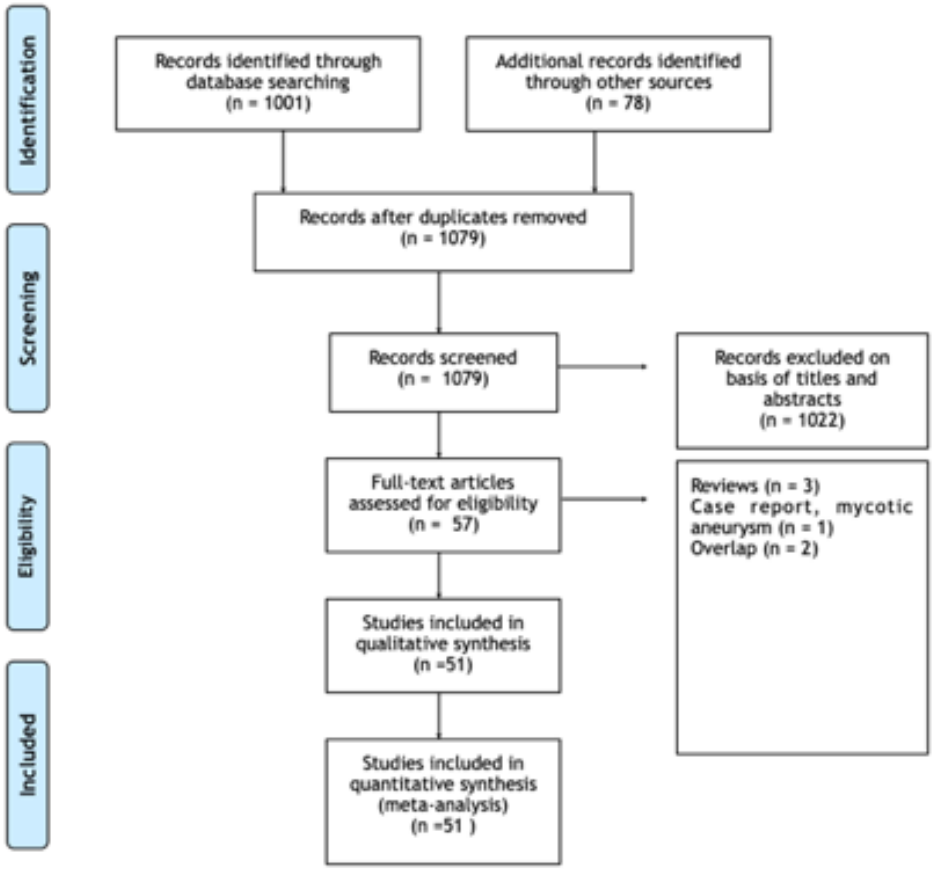
AA : ascendant aorta, n/a : not available

Table 5 : Trans-catheter procedures. Baseline, operative characteristics and outcomes

Author	N	Cause of cardiomyopathy	Valve dysfunction	Time Months	Valve	Access	Outcome
Aortic							
Bruschi 2010 [46]	1	Dilated	AS	108	CoreValve	TF	Alive at 4 months
Chandola 2012 [47]	1	Dilated	AI (Impella)	4	CoreValve	TF	Alive at 6 months
Zanuttini 2013 [48]	1	n/a	AI	168	CoreValve	TF	Alive at time of report
De Praetere 2013 [49]	1	Ischemic	AS	204	Sapien	TA	Alive at time of report
Gopalamurugan 2014 [50]	1	n/a	AI	204	CoreValve	TF	Alive at time of report
Kyranis 2016 [51]	1	Ischemic	AS	144	Lotus	TF	Alive at time of report
Ahmad 2016 [52]	1	Congenital	AS	120	Sapien S3	TF	Alive at time of report
Julien 2017 [53]	1	Dilated	AS BAV	156	Sapien S3	TF	Alive at time of report
Goekler 2017 [21]	1	n/a	AS	279	Sapien S3	TA	Alive at 30 months
Mitral							
Ioro 2015 [54]	1	Ischemic	MR	3	Mitra-clip	TF	Alive at time of report
Ferraro 2016 [55]	1	n/a	MR	n/a	Mitra-clip	TF	Alive at 3 months
MHI experience	1	Dilated	MR	227	Mitra-clip	TF	Failure, MVR BIO Alive at time of report
Tricuspid							
Hafiz 2017 [56]	1	n/a	TV Prothesis stenosis	180	Sapien	VIV	Alive at time of report

A I : aortic insufficiency, AS : aortic stenosis, BAV : bicuspid aortic valve, MR : mitral regurgitation, TV: tricuspid valve, TF: trans-femoral, TA : trans-apical, VIV : valve in valve, n/a : not available

Figure 1 : PRISMA Flow Diagram



Chapitre 4 Méta-analyse de données de survie : Nouvelle méthodologie Gr-RMST

Les effets et les complications d'une technique chirurgicale sont mesurables dans le temps. Les données de survie (*time-to-event data*) prennent par conséquent une place prépondérante dans la littérature chirurgicale cardiaque. Le Cochrane Handbook [18] les définit comme suit *: « time-to-event data consist of pairs of observations for each individual: 1) a length of time during which no event was observed, and 2) an indicator of whether the end of that time period corresponds to an event or just the end of observation. They are known generically as survival data in statistics, since death is often the event of interest, particularly in cancer and heart disease ».*

Toute revue systématique ou méta-analyse de séries de chirurgie cardiaque doit composer avec ce type de données. Historiquement, des mesures statistiques comme le odds ratio (OR) ou le risque relatif (RR), disponibles sur RevManager (The Nordic Cochrane Center, Copenhagen Denmark) ont été longtemps utilisées pour faire des méta-analyses de données de survie. Altman et al. [92] ont étudié les approches utilisées dans des méta-analyses de données de survie dans le domaine de cancer. Sur les 43 méta-analyses incluses dans ces deux études, 27 ont utilisé l'OR ou le RR pour rapporter leurs résultats. Ces deux mesures statistiques sont développées pour des évènements dichotomiques et ne prennent pas en compte le temps de réalisation de l'évènement. L'utilisation de ces deux mesures statistiques en méta-analyses cumulerait le nombre de décès rapportés sans prendre en compte les différences de longueurs de suivi entre les études. Ceci induit généralement une surestimation de l'effet. D'autres approches [93] ont été développées pour utiliser les OR et RR en méta-analyses de données de survie. L'OR ou le RR sont calculés à des points-tempsprécis comme 1 an, 5 ans ou 10 ans. Cette approche, même si elle tend à supprimer le facteur temps, propre à toute donnée de survie, soulève des limites et de sérieux biais de sélection rendant difficile l'interprétation des résultats. Généralement, l'auteur d'une étude rapporte la valeur minimale et maximale. En plus, le chercheur qui conduit la méta-analyse choisit ces points-temps de façon subjective, généralement imposés par les données rapportées par les études incluses dans la méta-analyse.

Si la Cochrane ne recommande pas une approche particulière pour les méta-analyses de données de service, elle stipule par contre : « *It is not appropriate to analyze time-to-event data using methods for continuous outcomes as the relevant times are only known for the subset of participants who have had the event. Censored participants must be excluded, which almost*

certainly will introduce bias ». Plusieurs approches ont été développées par la suite pour la réalisation de méta-analyse de données de survie. Ces approches peuvent être classées en trois catégories : 1) approche par agrégat, 2) approche par données individuelles des patients et 3) approche graphiques. Nous détaillerons ces principales approches et leurs limites méthodologiques avant de détailler la nouvelle approche que nous avons développée pour la réalisation des méta-analyses de données de survie.

4.1 Approche par agrégat

Cette approche consiste à méta-analyser des agrégats extraits des études ou calculables moyennant certaines suppositions statistiques à partir des données rapportées [94]. L'agrégat le plus utilisé est le hasard ratio (HR) ou plus précisément le logarithme du HR (log HR). L'approche se fait en deux étapes, calcul du log HR pour chaque étude et puis méta-analyse des résultats de log HR par variance inversée pondérée (*inverse-variance weighted*) ou *DerSimonian-Laird random effects* [95] quand une forte hétérogénéité est suspectée. Deux méthodes différentes sont rapportées dans littérature : la méthode Peto et la méthode LogRank test.

4.1.1 La méthode Peto

La méthode Peto [96] se base sur le calcul du log HR et sa variance à partir du nombre d'évènements observés versus celui d'évènements estimés, le HR et la variance du HR. Ces données ne sont généralement rapportées qu'en partie dans les études. Parmar et al. [97] ont rapporté une série d'équations mathématiques pour calculer le log HR et sa variance à partir des données rapportées dans chaque étude. Ces équations sont détaillées en fonction des données rapportées, de façon complète ou non, mais restent complexes et difficiles à appliquer. Tierney et al. [98] ont simplifié ces équations les rendant plus accessibles et familières aux chercheurs et ne nécessitent pas forcément une expertise particulière en statistique.

4.1.2 La méthode Log-Rank

Le Log-Rank test est largement utilisé dans les analyses de données de survie [99]. Il intègre une série d'intervalles de temps, définis chacun par la réalisation d'un évènement. Il permet de prendre en considération les points de censures, ce qui n'est pas le cas pour la méthode de Peto.

Cette méthode repose aussi sur le nombre d'évènements observés versus estimés, le HR et la variance du HR, mais leur intégration statistique par le modèle Log-Rank est plus robuste.

4.1.3 Limites

Ces approches sont restées jusqu'à récemment les méthodes choix pour faire les méta-analyses de données de survie. Une revue systématique de méta-analyses de données de survie [100] réalisée en 2005 a objectivé que plus que la moitié des méta-analyses de données de survies publiées depuis 1991 ont fait appel à ces approches pour présenter leurs résultats. La large adoption de ces approches est expliquée par la facilité d'exécution et la faible utilisation de ressources et d'expertise statistique. La grande limite de l'approche reste les suppositions statistiques sur lesquelles elles se basent. Ces approches font appel à des suppositions hyper-géométriques qui ont tendance à induire de gros biais dans les résultats si l'effet étudié est large [101]. En plus, ces approches ne permettent pas l'ajustement pour des covariables pouvant interagir avec l'effet étudié. Avec le développement de la modélisation basée sur des logiciels statistiques, cette approche est de moins en moins utilisée comme le démontre une revue systématique de Riley et al. [102]. Le nombre de méta-analyses de données de survies utilisant une approche par données individuelles est passé de 2 à 3 par année dans les années 90 à une moyenne de 50 méta-analyses après 2005.

4.2 Approche par données individuelles

La modélisation statistique permet d'extraire à partir des données rapportées par les études (HR, nombre d'évènements, p value) les données individuelles de chaque patient et de les combiner par la suite dans une méta-analyse. Plusieurs études [103,104] recommandent cette approche plutôt que l'utilisation d'agrégats pour réaliser des méta-analyses de données de survie. Les avantages de cette approche [105] sont : 1) l'approche standardisée, 2) l'extraction des données individuelles qui peut aider à l'évaluation de la qualité de chaque étude, 3) l'inclusion de séries avec un long suivi, 4) les suppositions statistiques peuvent être vérifiées et 5) l'ajustement des résultats pour certains confondants. Cette approche peut se faire aussi en une seule étape modélisant toutes les études en même temps. Ceci permet une meilleure évaluation de l'hétérogénéité et d'éviter les méta-régressions et les biais qui leur sont inhérents [106].

4.2.1 Modèles proportionnels de Cox

Cette approche se base sur les modèles robustes de régression de Cox pour déterminer le log HR de chaque étude à partir des données rapportées. Elle fait appel à des logiciels de modélisation comme le logiciel R (R Core Team, Auckland, New Zealand) pour développer des algorithmes qui intègrent des millions de modèles de Cox afin d'ajuster au mieux l'équation de régression de l'étude. Différents modèles ont été développés : le modèle à effet fixe, le modèle stratifié, le modèle à effet aléatoire et les modèles marginaux. Une étude [107] a comparé ces différents modèles et a validé leur applicabilité aux méta-analyses de données de survie aussi bien dans une approche à une étape que dans une approche à deux étapes. Par contre, Anderson et al. [108] suggèrent l'utilisation du modèle à effet aléatoire dès que le nombre d'études dépasse cinq pour mieux corriger l'hétérogénéité inter-études et diminuer l'erreur de type I (rejeter une hypothèse nulle alors qu'elle est vraie).

4.2.2 Régression de Poisson

La régression de Poisson est essentiellement utilisée dans la modélisation des tableaux de contingence et peut être appliquée aux données de survie via une transformation exponentielle [109]. Ceci repose sur l'intégration de la fonction de survie par des modèles linéaires appliqués à une série d'intervalles de temps [110]. La largeur d'intervalle la plus communément utilisée est un an [111]. Cette approche a pour avantage de déterminer le taux de hasard ce qui permet de calculer la différence de risque et le *number needed to treat (nombre de patients à traiter pour prévenir un nouvel évènement adverse)*, données pertinentes en clinique [112].

4.2.3 Limites

La validation des deux approches repose sur deux suppositions statistiques, qui ne sont pas toujours valables pour la réalité de la littérature médicale.

Les modèles de Cox assument que le hasard est proportionnel tout au long du suivi. Ceci n'est pas toujours vrai dans le domaine de la recherche médicale, car il est fréquent que les courbes de survie convergent ou même se croisent [113 114]. La présomption d'un hasard constant le long du suivi est inappropriée en recherche médicale [115]. Le hasard dérivé par cette approche

devient biaisé dans ces conditions et dépend de la longueur du suivi [116] et le log rank test perd ainsi toute sa puissance statistique [117].

En fractionnant la courbe de survie en plusieurs intervalles de temps, la régression de Poisson assume que la fonction de survie tend vers un modèle linéaire dans chacun de ces intervalles. Ceci est réaliste seulement si les intervalles sont définis par la survenue d'un évènement, ce qui rend l'intégration de ce nombre infini de fonctions linéaires quasi impossible même en ayant recours à des logiciels aussi puissants tels que R (R Core Team, Auckland, New Zealand) [118]. En assumant la linéarité, la régression de Poisson sous-estime aussi la variance de la fonction de survie et sous-estime donc par conséquent l'hétérogénéité induisant de gros biais dans les résultats surtout si la majorité des évènements se produisent à un *time-point* donné [119].

Les deux approches partagent aussi une autre limite qui est la nécessité d'utiliser des logiciels dédiés et le recours à une expertise poussée en statistique ce qui limite leur utilisation.

4.3 Méthodes graphiques

Devant la complexité des approches sus-citées, les limites des suppositions statistiques sur lesquelles elles se basent et les avantages de méta-analyses portant sur des données individuelles de patients plutôt que sur les agrégats, il est apparu un intérêt particulier lors de la dernière décade pour développer des approches d'extraction de données individuelles par méthodes graphiques.

4.3.1 Méthodes

Ouwens et al. [120] et Jansen et al. [121] sont les premiers à avoir utilisé graphiquement les courbes de survie en faisant appel à des logiciels de digitalisation. Leur approche était d'extraire des données de survie en certains *time-points* pour faire une approximation de la fonction de survie. Cependant, ceci ne tient pas compte du nombre de patients à risque ni du nombre de censures rendant cette approche rapidement désuète [122].

Guyot et al [122] ont développé un algorithme en langage R (R Core Team, Auckland, New Zealand) pour pouvoir imputer le nombre de patients à risque et les censures à partir du nombre d'évènements rapportés ainsi que les patients à risque au début et à la fin de l'étude. Une fois le nombre de patients à risque et les censures calculés, les évènements sont extraits par un logiciel

de digitalisation à partir des graphiques publiés dans les diverses études. Ces données sont compilées par l'algorithme qui permet la construction de nouvelles courbes qui sont vérifiées et comparées visuellement aux courbes originales. Cette approche a été validée sur six différentes courbes avec une erreur moyenne de la fonction de survie de 0,103 % et de la survie médiane de 1,1 %.

4.3.2 Limites

Deux limites sérieuses sont à déplorer pour cette approche prometteuse. Premièrement, l'imputation du nombre de patients à risque et des censures n'est pas toujours valide. En procédant à plusieurs simulations pour adopter cette approche, nous avons constaté qu'en absence du nombre total d'évènements ou du nombre des patients à risque à un *time-point* autre que 0, l'algorithme produit une imputation de censures de très mauvaise qualité et a tendance à surestimer l'effet. Ces constatations sont d'ailleurs partagées par d'autres auteurs [123]. Deuxièmement, la vérification des courbes reconstruites se fait de façon visuelle sans aucun critère objectif, ceci peut entacher la validité de cette approche.

4.4 Méthodologie développée

4.4.1 La méthode

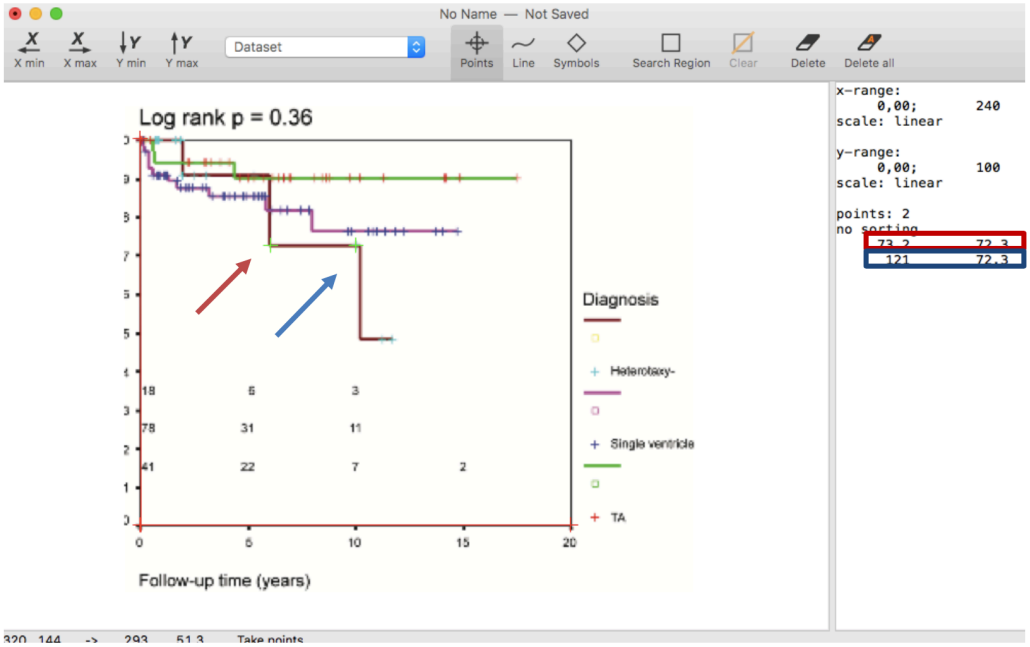
On a pris en considération les limites de l'approche de Guyot el al. [122] et on s'est fixé comme but de développer une nouvelle approche graphique ne se basant sur aucune supposition ou imputation statistiques et qui serait vérifiable de façon objective.

Plusieurs étapes de réflexion ont été nécessaires à la mise en place de cette approche :

1) Le choix d'utiliser une approche graphique était motivé par la performance de ces approches à extraire les données individuelles de patients permettant de réaliser des méta-analyses plus robustes.
2) Par la nécessité de sursoir à toute imputation statistique, il a été décidé d'extraire aussi bien les évènements que les censures à partir des courbes de survie. Par conséquent, seules les études qui rapportent les patients à risque et les censures ont été sélectionnées.
3) Les logiciels jusque là utilisés pour la digitalisation des courbes de survie n'étaient pas performants pour extraire les censures. Nous avons fait appel au logiciel Digitizelt

(Digitizelt ®, Braunschweig, Germany) pour extraire ce type d'information. Ce logiciel peut séparer la courbe en plusieurs parties, les agrandir et permet d'extraire les évènements et les censures avec une grande précision (Figure 2). Lorsque l'extraction des censures est incomplète, le reste des censures est affecté à la borne supérieure de l'intervalle.

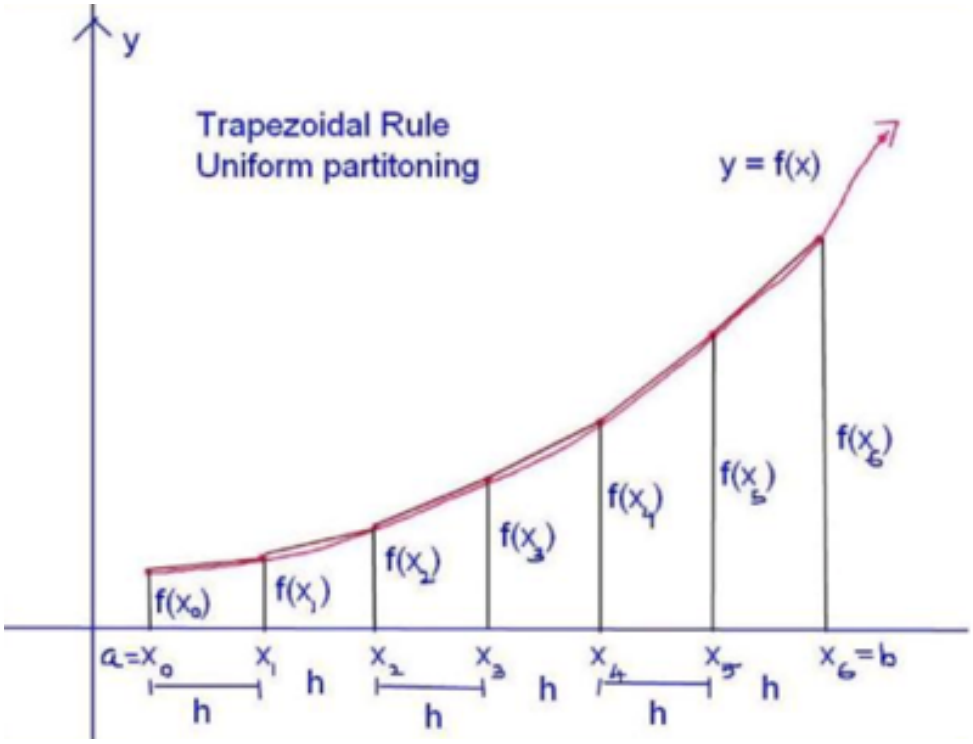
Figure 2 : Extraction d'un évènement (flèche rouge) et d'un point de censure (flèche bleue) par Digitizelt®.



À droite de la figure, le time-point et la valeur de la fonction de survie correspondante pour chaque type d'évènements (encadré rouge pour l'évènement, bleu pour la censure.

4) Une fois tous les évènements et les censures extraits, un tableau de survie usuel est constitué et la courbe de survie est construite sans aucune imputation statistique ou algorithme d'inférence.
5) Nous avons réfléchi à une méthode objective pour comparer la courbe reconstruite à la courbe originale en faisant appel à la notion du *restricted mean survival time (RMST)*. Le RMST se définit comme l'aire sous la courbe de survie. L'aire sous la courbe est calculée selon la loi des trapèzes (Figure 3). Ainsi, aussi bien la courbe de survie originale que reconstruite sont partagées en trapèzes dont le nombre dépend du nombre de valeurs de la fonction de survie rapportées dans l'étude. Seules les études rapportant au moins deux valeurs de survie sont incluses. Le nombre de trapèzes et la durée de l'intervalle temps qu'ils couvrent sont les mêmes pour les deux études. Le calcul est fait à l'aide de logiciels statistiques qui offrent cette fonctionnalité comme SAS (SAS Institute, Cary, NC, United States).

Figure 3 : Méthode des trapèzes pour le calcul de l'aire sous la courbe.



6) Un ratio de RMST est calculé et doit être supérieur à 0.98 pour que la courbe soit valide.
7) Une fois la courbe validée, les données extraites (évènements et censures) sont combinées aux données des autres courbes pour constituer un tableau de survie de la méta-analyse.
8) Une fois le tableau de survie de la méta-analyse constitué, les courbes de survie de toute la cohorte incluse dans la méta-analyse peuvent être construites, et les tests non paramétriques de données de survie tels que les log-rank test ou la régression de Cox peuvent être appliqués.

4.4.2 Étude de validité et simulation

Une fois la nouvelle méthodologie développée et baptisée Gr-RSMT, une étude de validité a été conduite. Dans un premier temps, on a procédé à une validation de l'exactitude de l'extraction de données de survie et de censure par le logiciel Digitizelt et dans un deuxième temps, on a évalué le procédé de vérification graphique faisant appel au ratio de RSMT.

Pour cette fin, nous avons collaboré avec Dr Johana Takkenberg, chirurgienne cardiaque et statisticienne néerlandaise. Dr Takkenberg s'est beaucoup intéressé à l'intervention de Ross qui consiste à 1) une substitution de la valve aortique par une autogreffe pulmonaire et 2) la reconstruction de la voie d'éjection du ventricule droit par une homogreffe. Elle avait auparavant publié l'expérience de son équipe en termes d'intervention de Ross en population pédiatrique en 2005 [124] rapportant des courbes de survie et de survie sans ré-opération et aussi publié en 2009 une méta-analyse sur le sujet [125] utilisant une approche par régression de Poisson.

Nous avons donc appliqué l'approche Gr-RSMT aux courbes publiées par Dr Takkenberg et al. en 2005, ce qui a permis d'extraire les évènements et censures et de construire les tableaux de survie pour les deux issues rapportées. Ces tableaux ont été envoyés au Dr Takkenberg qui les a comparés aux données brutes de survie et de ré-opérations à l'aide d'un test d'ANOVA pour calculer l'erreur moyenne de la fonction de survie pour les deux issues. L'erreur moyenne était de -0,103 % (95 % CI : -0,260 ; 0,055) pour la survie et de -0,051 % (95 % CI : -0,186 ; 0,083) pour la ré-opération. Ceci se lit de la façon suivante : pour une survie de 50 %, la survie

déterminée à partir des données extraites est de 49,897 % (95 % CI : 49,740 ; 50,055) éliminant tout risque significatif d'erreur systématique.

Dans un second temps, les courbes Kaplan Meier de survie et de ré-opérations ont été reconstruites à partir des données extraites (Figures 4 et 5). Le RSMT a été calculé pour chaque courbe utilisant la méthode de trapèzes. Le ratio de RSMT était de 0,998 pour les courbes de survie et de 0,999 pour les courbes de réopérations. Les chiffres obtenus montrent une similitude parfaite avec les chiffres d'erreur moyenne de fonction de survie.

Figure 4 : Comparaison des courbes de survie : courbe originale versus courbe reconstruite.

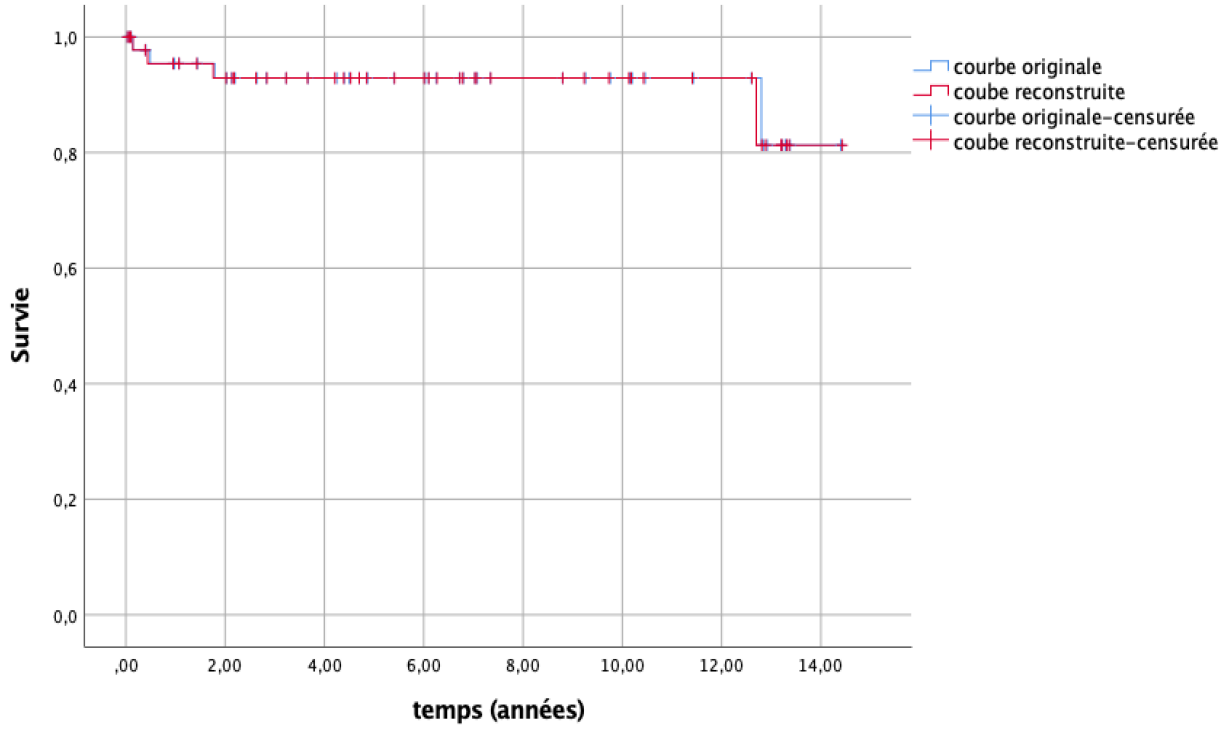
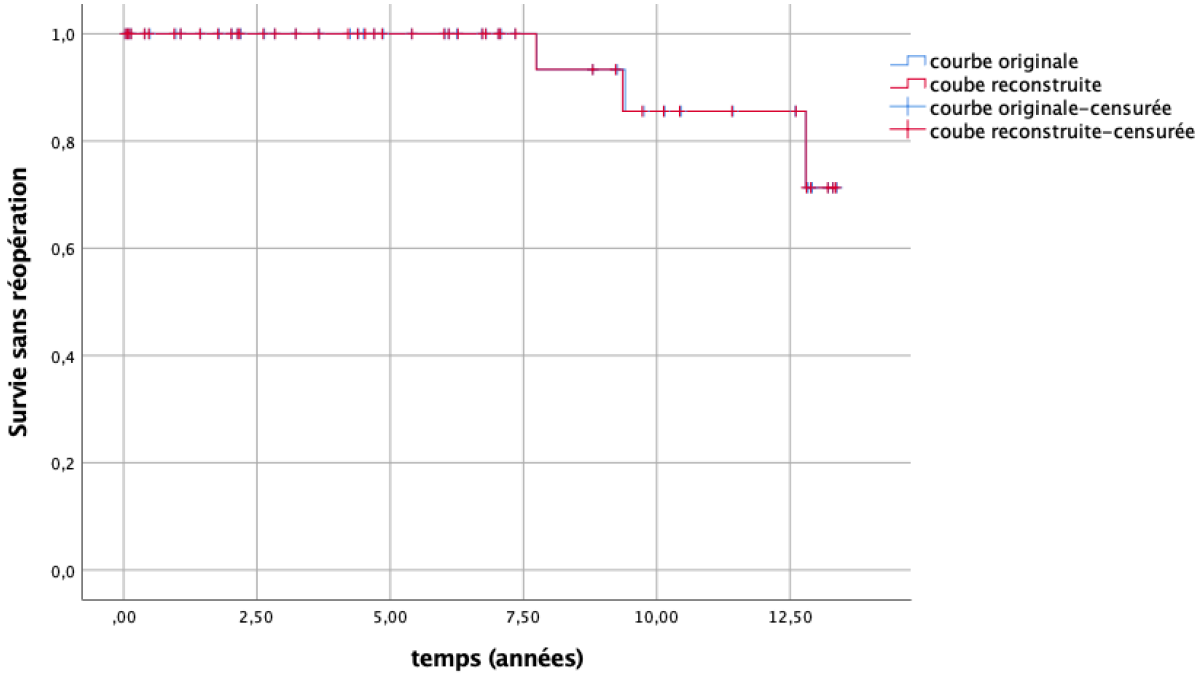


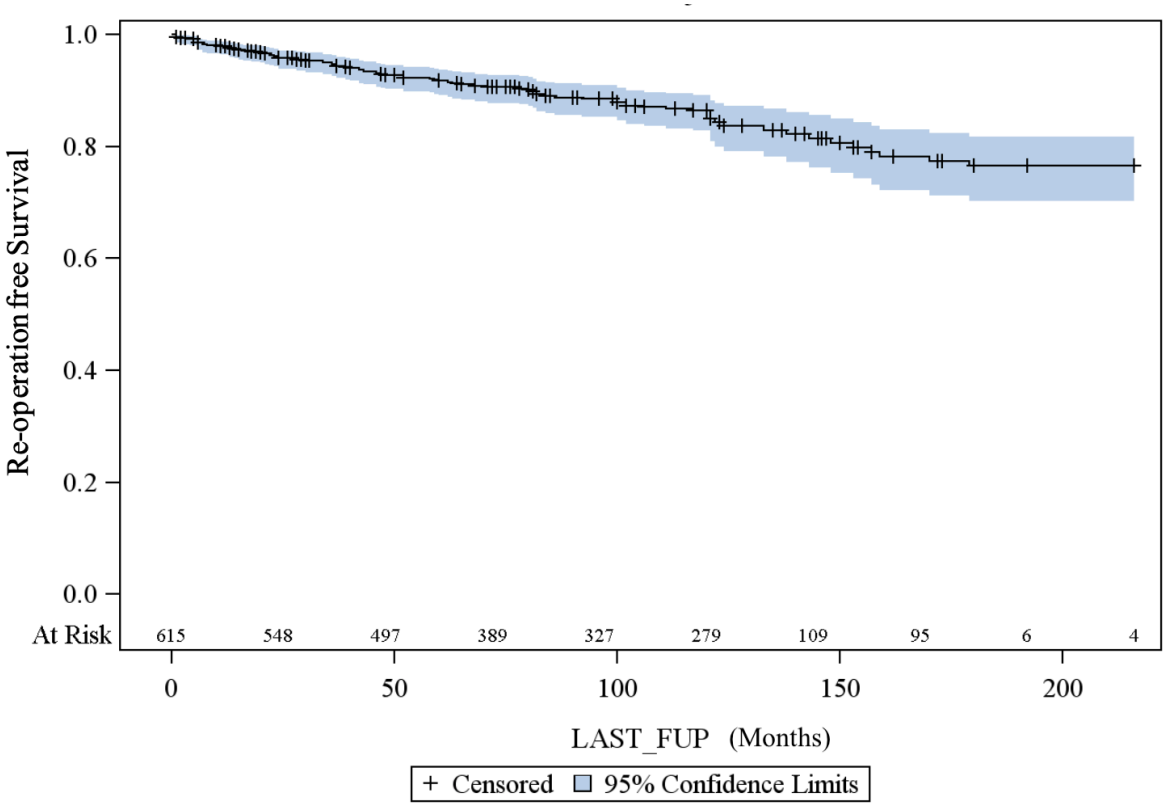
Figure 5 : Comparaison des courbes de survie sans réopérations : courbe originale versus courbe reconstruite.



Une fois la méthodologie Gr-RSMT validée, nous avons procédé à une simulation de la même méta-analyse réalisée par Dr Takkenberg en 2009 en appliquant l'approche Gr-RSMT et en comparant les résultats obtenus par les deux approches.

Pour les résultats de ré-opérations pour l'autogreffe ou pour la voie d'éjection du ventricule droit, les résultats étaient concordants aux différents *time-points*. Par exemple, pour la voie d'éjection du ventricule droit, la survie sans ré-intervention obtenue par la nouvelle approche (Figure 6) était de 97 % (95 % CI : 95 ; 99 %), 92 % (95 % CI : 90 ; 94 %), 86 % (95 % CI : 82 ; 90 %) et 77 % (95 % CI : 71 ; 83 %) à 1, 5, 10 et 15 ans respectivement. Le modèle linéaire utilisé pour la méta-analyse donnait un taux de réintervention pour la voie d'éjection du ventricule droit de 1.6 % par année (95 % CI : 0,84 ; 3,05).

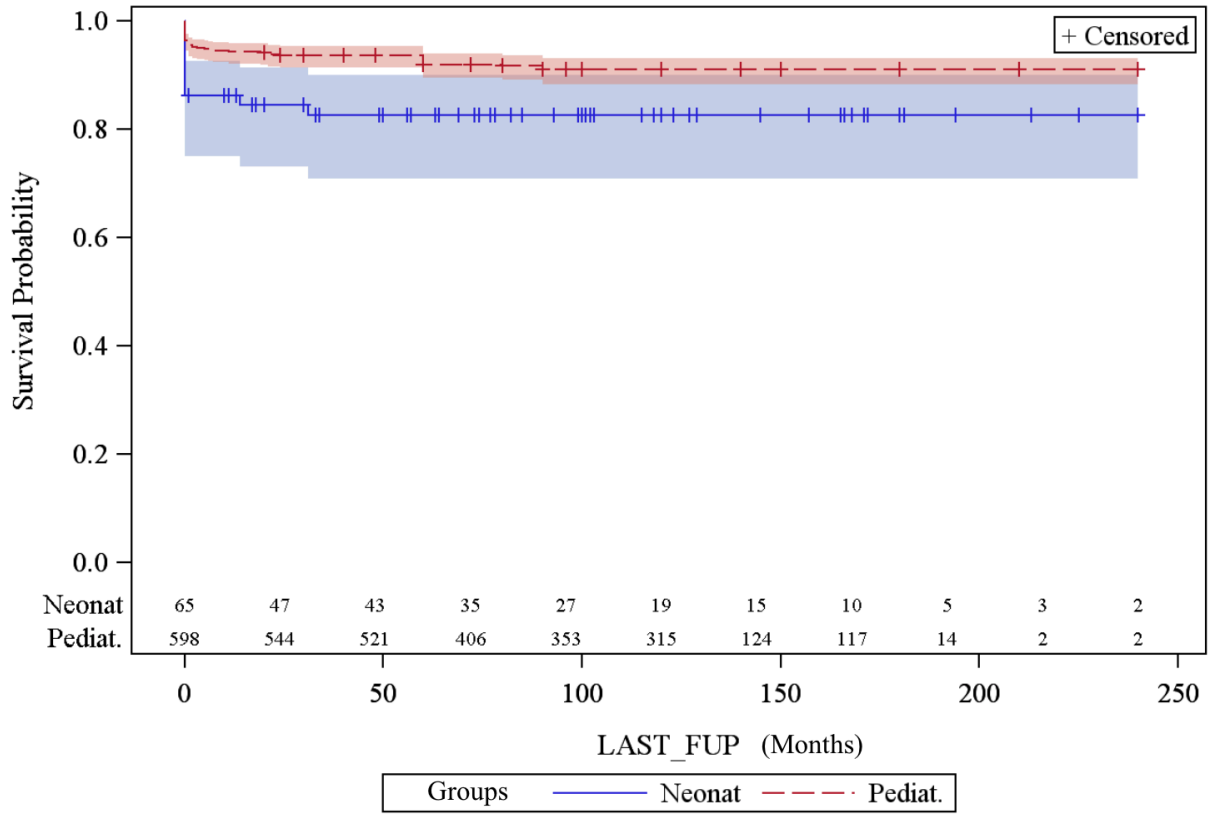
Figure 6 : Survie sans ré-opération de la voie d'éjection du ventricule droit après intervention de Ross en population pédiatrique.



Concernant la survie, les deux approches étaient concordantes à long terme mais complètement discordantes pour le court terme. Ceci est d'autant plus marqué pour la survie des patients opérés à l'âge néonatal. La survie pour ce sous-groupe obtenue par la nouvelle approche (Figure 7) était de 86 % (95 % CI : 82 ; 90 %) et de 82 % (95 % CI : 74 ; 90 %) respectivement à 1 et 15 ans. Le modèle linéaire utilisé pour la méta-analyse donnait un taux de décès de 1.06 % par année (95 % CI : 0,88 ; 3,13).

Ces résultats confirment les limites du modèle linéaire utilisé par Dr Takkenberg à estimer la fonction de survie tel que décrit auparavant. Le modèle s'applique bien aux courbes de survie qui sont globalement linéaires (la courbe de ré-opération de la voie d'éjection du ventricule droit). Par contre, ce modèle assimile mal les courbes de survie quand un nombre important d'évènements se produit à un *time-point* particulier (la courbe de survie du sous-groupe néonatal où la majorité des décès ayant été observés lors de la première année)

Figure 7 : Survie stratifiée en fonction du groupe d'âge après intervention de Ross en population pédiatrique.



4.4.3 Limites

Cette approche, bien que prometteuse, robuste et fiable a néanmoins certaines limites : 1) elle dépend de la qualité des courbes publiées, 2) les courbes doivent rapporter le nombre de patients à risque à intervalle régulier ainsi que les censures et de plus les auteurs doivent rapporter au moins deux valeurs de fonction de survie nécessaires à la vérification graphique. Ceci peut limiter l'inclusion de certaines études et 3) la validation d'une courbe peut prendre jusqu'à deux heures dans des mains entrainées ce qui augmente la charge de travail de l'équipe de recherche.

Chapitre 5 Manuscrit #3

Avant-propos

L'intervention de Fontan fut introduite en 1962 pour la prise en charge des cardiopathies congénitales uni-ventriculaires [126]. Plusieurs modifications techniques ont été apportées à l'intervention originale, telles que le tunnel latéral intracardiaque (LT) et le conduit extracardiaque (CE). Les arythmies supra-ventriculaires (ASV) constituent une des complications les plus fréquentes à long terme. Une revue narrative a été réalisée en 2012 par l'équipe de cardiopathies congénitales adultes de l'Institut de Cardiologie de Montréal [127] et devait répondre à la question suivante : laquelle des deux techniques est moins pourvoyeuse d'arythmies supra-ventriculaires ? Sans méthodologie pour combiner les résultats à long terme, la conclusion de cette revue était que le tunnel intracardiaque ne semble pas donner plus d'arythmies supra-ventriculaires. La réponse à cette question deumeurait donc incomplète. Nous avons donc décidé en collaboration avec les auteurs de cette revue d'appliquer la méthodologie Gr-RSMT pour réaliser une méta-analyse de données de survie afin de répondre à la question de façon adéquate basée sur des courbes de survie et sur le test de log-rank. Cette étude a été présentée au 54^{e} congrès de la *Society of Thoracic Surgeons en 2018*, session congénitale. L'étude a été publiée [4] dans le *Ann Thorac Surg, 2019 Mar ;107(3) : 837-843.*

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Extracardiac Versus Lateral Tunnel Fontan : A Meta-Analysis of Long-term Results with special focus on Arrhythmias

Running Head : EC vs LT Fontan

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ABSTRACT

Objective : There is growing awareness of the long-term impact of a Fontan circulation on the associated morbidity and mortality. Comparative data on the incidence of supraventricular arrhythmia and sinus node dysfunction following extra cardiac (EC) and lateral tunnel (LT) Fontans are controversial. We performed a meta-analysis pooling all available long-term results comparing the EC and LT Fontan with a special focus on arrhythmia.

Methods : We performed a systematic search of PubMed, EMBASE, and Cochrane Library for articles reporting long-term results of Fontan comparing the EC and the LT Fontan.

Results : 12 studies were selected with 3330 patients (1729 EC, 1601 LT). Freedom from tachyarrhythmia was significantly higher in the EC group (92% versus 83% at 15 years; p <0.0001) while there was no difference in term of bradyarrhythmias (p= 0.7). The survival was 93% and 89% at 20 years respectively in the EC and LT groups (p=0.007). The risk of thromboembolic events was 2.87% patients-years in the EC group vs 0.9% in the LT group (OR= 2.15 [0.95; 4.85]; p=0.07).

Conclusion : The EC Fontan confers long-term survival advantage over the LT without a higher rate of reoperations. The EC Fontan preserves the sinus node function and reduces significantly the incidence of long-term postoperative arrhythmia.

Word count: 204

INTRODUCTION

Since the first Fontan operation described in the early 1970s [1], multiple modifications and adaptations of the Fontan procedure have been introduced in order to improve surgical outcomes. These modifications include the lateral tunnel (LT) described in 1983 [2] and lastly the extra-cardiac conduit (EC) in 1988 [3]. Through these improvements have reduced perioperative mortality and morbidity, there is a concern about the long-term consequences of the different Fontan procedures in regard to the long-term outcomes, especially arrhythmia. Indeed, atrial tachyarrhythmias are the leading source of morbidity in these patients' population [4]. These complications can lead to a reduction in the ventricular systolic function, an increase in the atrioventricular valve regurgitation and the development of atrial thrombosis. Therefore, arrhythmias are poorly tolerated in this patient population due to the limited cardiac reserve and a chronic low cardiac output [5].

The relative merit of the LT and the EC approaches on the incidence of supraventricular arrhythmia and sinus node dysfunction is still controversial and based on small single-center and retrospective studies. The aim of this meta-analysis was to pool all available long-term results data comparing the EC and LT Fontans with a special focus on arrhythmia.

METHODS

Study Design and Eligibility Criteria

This systematic review and meta-analysis was performed based on the Meta-analysis of Observational Studies in Epidemiology guidelines [6]. The manuscript was structured using the recommendations of the Systematic Reviews and Meta-Analyses (PRISMA) statement [7]. We included all studies comparing long-term results following a LT and an EC Fontan procedures. Only studies with a completeness of follow-up> 90% and a NewCastle-Ottawa Scale Score (NOS) > 5 were included. The NewCastle-Ottawa Scale Score was developed to assess the quality of non-randomized studies included in meta-analysis regarding different categories, namely the study design, content and ease of use. A 'star system' has been developed in which a study is judged on three aspects : the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or

cohort studies respectively [8]. Non-comparative series, case reports, small case series (<30 patients), review articles, letters to the editor and articles written in languages other than English or French were excluded.

Search Strategy

A PubMed and EMBASE search was conducted with the following keywords : « extra cardiac Fontan », « lateral tunnel Fontan », « long-term results », and « arrhythmia » limited to publications between 2000 and 2016 conducted in humans. The entire Cochrane library was screened for "Fontan" and "arrhythmia". To avoid losing major related publications, a second search was made on the 4 major cardiothoracic surgery journals : *The Annals of Thoracic Surgery, The European Journal of Cardiothoracic Surgery, The Journal of Thoracic and Cardiovascular Surgery* and *Journal of the American College of Cardiology*. Related journals and references list of selected articles were also cross-checked for other relevant studies.

Study Records

Two reviewers (WBA, IB) screened the titles and abstracts of all the identified studies. In case of multiple publications with sample overlap, the most recent report was included. Three independent reviewers (NP, IB and WBA) assessed whether inclusion and exclusion were performed correctly and evaluate the degree of bias of each paper. In case of disagreement, a consensus was negotiated. The first and the corresponding author of all included studies were contacted to retrieve additional unpublished data.

Meta-Analysis Outcomes

The primary outcome was the freedom from tachyarrhythmia. The accepted definition of atrial tachyarrhythmias was a documented atrial flutter, an atrial fibrillation or a junctional ectopic tachycardia. Secondary endpoints were freedom from bradyarrhythmia, long-term survival, freedom from reoperation and freedom from thromboembolic events.

Data Analysis

Data extraction from each available Kaplan-Meier (KM) curve was performed using the methodology described by Guyot and colleagues [9]. Briefly, each KM curve was digitized using a digitalization software (Digitizelt, Germany). The individual patient data was derived

from the KM curve using the software. In the same manner, extraction of censored information was performed where censoring marks were present on the KM graph. Derived KM curves were graphically checked with the original ones using a ratio of restricted mean survival time (RMST) of each curve. RMST is defined as the area under the KM curve calculated based on the trapeze rule. A ratio superior to 0.98 was mandatory. Once validated, the KM data from different studies were stored together in the study database. Statistical methods for time-to-event data were employed to analyze outcomes at follow-up, including the KM estimator with the log-rank test for comparisons. When time-to-event data were unavailable (thromboembolic events), events were calculated ([number of events/number of patient- years] 100) for each individual study and pooled on a logarithmic scale with the use of the inverse variance method in a fixed-effects model. Baseline data were extracted and analyzed with RevMan 5 (RevMan 5.3, Cochrane Collaboration, Oxford, UK). Statistics included odds ratio (OR) and weighted mean difference (MD) with the respective 95% confidence interval (CI). Heterogeneity was examined using Cochran's Q test as well as the I^2 statistic. Because of patients and treatment procedure heterogeneity in the included studies, random effects models were used to calculate OR and their 95% CI when I^2 statistic was superior to 25%. Quality of observational study was assessed by Newcastle-Ottawa Scale and funnel plots were used to study publication bias. Statistical significance was set at a *p* value of 0.05 or less. Meta-regression analysis was used to investigate the effects of covariates, especially variations in patient characteristics.

RESULTS

Literature Search Results

Two hundred and thirty studies were identified. A first level screen was undertaken on articles' titles and abstracts. Twenty-six articles remained for full text review. From these, 7 were excluded due to the inconsistencies in study design, 4 with no extractable KM curves, 2 for cohorts overlap, 1 for insufficient follow-up and 1 case report. The meta-analysis flowchart is summarized in **Figure 1**. Twelve retrospective studies with 3330 patients were included [10-21]. All studies had a Newcastle-Ottawa Scale score> 6 **(Table 1)**. The publication was assessed with funnel plots. The funnel plots showed symmetrical distributions.

Freedom from Atrial Tacharrhythmias

Two thousand six hundred and nine patients (4 studies [10,13,20,21]) were included in this analysis. The freedom from atrial tachyarrhythmia was 96% (95–97%) and 92% (91–93%) in the EC group versus 93% (92–95%) and 83% (81–85%) in the LT group ($p < 0.0001$) at 10 and 15 years respectively (**Figure 2A**).

Freedom From Bradyarrhythmias or Pace Maker implantation

One thousand two hundred and eight patients (2 studies [10,16]) were included in this analysis. The freedom from bradyarrhythmias was 85% (81–89%) in the EC group versus 86% (83–89%) in the LT group ($p=0.7$) at 10 years (**Figure 2B**).

Survival

One thousand four hundred and ninety-two patients (7 studies [11-15,19,20]) were included in this analysis. The overall survival was 96% (95–98%) and 93% (87–99%) in the EC group versus 94% (92–96%) and 89% (83–95%) in the LT group ($p < 0.007$) at 10 and 20 years respectively (**Figure 3A**).

Freedom from Reoperations

Two hundred and eighty patients (2 studies [11,21]) were included in this analysis. The freedom from reoperation was 83% (75–91%) in the EC group versus 74% (59–89%) in the LT group ($p=0.7$) at 10 years (**Figure 3B**).

Thromboembolic events

There was a trend toward a higher rate of thromboembolic events in the EC group (2.87% patients-years in the EC group vs 0.9% patients-years in the LT group, odds ratio = 2.15 [0.95;4.85], $p=0.07$).

Metaregression

Six confounding factors reported as confounding factors on the occurrence of long-term tachyarrhythmia and death (age, gender, right ventricle morphology, heterotaxy, tricuspid atresia, and pre-operative mean pulmonary artery pressure [mPAP]) were extracted. These data

were pooled and compared between the two groups (EC and LT). Patients in the EC group were significantly older. In addition, heterotaxy was significantly more frequent in the EC group (**Table 2**). The inter-study heterogeneity of the patient age (p=0.68), male gender (p=0.86), right ventricle morphology (p = 0.86), tricuspid atresia (p=0.86) or mPAP (p=0.65) had not effect / Similarly, the meta-regression did not find any significant effect of patient age (p=0.68), male gender (p=0.86), right ventricle morphology (p=0.86), heterotaxy (p=0.68), tricuspid atresia (p=0.86) or mPAP (p=0.65) on long-term survival.

COMMENT

Although the early and mid-term results of the Fontan procedure have improved since the total cavopulmonary connection era, the late attrition observed after the Fontan circulation remains a major concern. Patients are prone to develop late complications such as tachyarrhythmia, reoperations, ventricular dysfunction and progressive exercise intolerance. In this meta-analysis, the incidence of atrial arrhythmias following Fontan procedure increases during follow-up, with 13% of patients experiencing atrial tachycardia at 15 years. In addition, the EC Fontan, which results in less sinus node dysfunction, reduces significantly the incidence of long-term postoperative arrhythmias when compared to the LT and was associated with a higher long-term survival with a similar rate of re-operations. Recently, Backer et al. [23] and Khairy et al. [24] published two reviews on the long-term results of the Fontan circulation. The two studies tried to pool death events and the incidence of arrhythmias without accounting for the difference in duration of follow-up between the included studies. Though the risk of arrhythmia development is cumulative over time, pooling these data with a time-to-event methodology is more accurate and robust to evaluate these outcomes.

In our study, the incidence of arrhythmia increases during the follow-up. Resistant to antiarrhythmic agents, late tachyarrhythmia following Fontan procedure is known to significantly contribute to the mortality and morbidity observed in these patients. Indeed, Alphonso et al. [25] reported that early and late postoperative arrhythmia were significantly associated with a limited prognosis. In the present study, the LT Fontan was associated with a higher tachyarrhythmia incidence. The EC Fontan avoid exposing the right atrium to the

elevated systemic pressure, necessitates fewer atrial incisions and suture lines and stays far from the sinus node which all together was hypothesized to result in a lower rate of tachyarrhythmia in the long-term. A preclinical study involving 17 dogs had established that the LT Fontan baffle sutureline alone created a sufficient anatomic substrate for atrial flutter [26]. In contrast, Khairy et al. reported that the relationship between suture lines and arrhythmia is nonlinear and more complex. Indeed, suture lines that connect areas of electrically unexcitable scar may protect against potential reentrant circuits. They imputed the difference in terms of tachyarrhythmia reported by some studies [16, 21] to unequal follow-up duration, heterogeneous populations, variable definitions, discrepancy in outcomes assessment, and differences in surgical techniques. Similarly, Balaji et al. [10] in one of the largest published Fontan series did not report any difference in terms of tachyarrhythmia and suggested that the perceived lower incidence of arrhythmias after the EC is more likely due to the shorter length of this group. Therefore, the high statistical power and the longer follow-up of the EC group are two major strengths of the present meta-analysis. In addition, typical risk factors of long-term tachyarrhythmia occurrence reported in classic Fontan cohorts, such as age at Fontan, heterotaxy, right ventricle morphology, tricuspid atresia and pulmonary artery pressure were studied in the meta-regression and exert no effect upon the observed difference.

In the present study, long-term survival was higher in the EC group. In contrast, anatomic features such as ventricular morphology and function [5], heterotaxy syndromes [27] and pulmonary artery pressure [5] have been associated with the long-term risk of death. These risk factors were included in a meta-regression and none of them exerted an effect upon the observed long-term survival difference. While this finding could be explained by the lowest risk of tachyarrythmias observed with the EC Fontan, this result could also be attributed to the temporal improvement of the Fontan circulation management in the last decades. Indeed, the overall long-term survival is excellent and exceeds 90% at 20 years.

The extra cardiac conduit procedure has potential disadvantages relating to the use of a conduit, including lack of growth potential and conduit stenosis due to intimal peel formation [28]. In our analysis, there was no difference between the 2 techniques in term of freedom from reoperations. Fukuoka et al. [29] reported a series of 32 patients who underwent an extra cardiac total cavopulmonary artery connection. They showed an appropriate growth of the pulmonary

artery and the inferior vena cava. In our meta-analysis, patients in the EC Fontan group were significantly older. Indeed, an adult-sized conduit can be used when the patient weight exceeds 15 to 20 kg, which may accommodate the patient's future growth. In a magnetic resonance imaging flow study on EC Fontans, Itatani et al. [30] concluded that 16- and 18 mm conduits proved to be optimal for adult patients.

Thromboembolic events are an important cause of morbidity [31] and mortality [5] after the Fontan operation. Despite EC Fontan avoid intracardiac prosthetic material, in our study, there was an obvious trend toward a higher rate of thromboembolic events in the EC group without reaching a statistical significance which may carry a high risk of multiple pulmonary emboli and, if a fenestration is placed, systemic emboli. In a systematic review that included 1075 patients with an extra cardiac Fontan from 20 studies, 5.2% of patients had a thromboembolic event over a mean follow-up that ranged from 2 to 144 months [31]. We believe that all patients undergoing a Fontan procedure, whatever the surgical technique, require long-term anticoagulant therapy. Studies discussing optimal anticoagulation therapy for Fontan patient yield to discouraging results with similar rates of thromboembolic events in patients with antiplatelet versus anticoagulant agents [31].

Limitations of Study

The main limitation of the study is the lack of randomized trials. There are no available randomized studies addressing the subject of interest, pooling observational studies in meta-analysis is the only choice to have enough power to attain statistical significance. Studies present some variation in patient selection, support used and surgical technique. To agrees the heterogeneity, we have adopted a random effects model when I^2 was superior to 25% and conducted a meta-regression to solve inter-study heterogeneity. The second limitation of study is the lack of uniformity to define significant atrial arrhythmia. The third limitation of this study is the potential era bias as Lateral tunnel repair was introduced in clinical practice much earlier than EC. Indeed, differences in terms of improvement in the intensive care and electrophysiologic management may explain part of the differences observed.

CONCLUSION :

The incidence of arrhythmia following the Fontan procedure increases with time since surgery. The extra-cardiac Fontan, even though more challenging for the electrophysiologist, preserves sinus node function and reduces significantly the incidence of long-term postoperative arrhythmia as compared with the LT Fontan. The long-term survival of the Fontan population is excellent and contemporary techniques are associated with even better survival. The EC confers long-term survival advantage over the LT without higher rate of re-operations. A trend to a higher risk of embolic events was observed in the extra-cardiac conduit patients.

Acknowledgments and disclosures

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Table 1 : studies characteristics

Author	Year	N Pts	NOS	Age (years)		RV (%)		Heterotaxy (%)		TA (%)		MPAP (mmHg)	
				LT	EC	LT	EC	LT	EC	LT	EC	LT	EC
Kumar [15]	2003	70	7	2,7	3,9	60	48	5	18	16	24	9	9
Nürnberg [16]	2004	74	7	5,8	3,8	NR	NR	NR	NR	17	38	12	13
Schreiber [18]	2004	125	6	6,3	6,2	NR	NR	NR	NR	NR	NR	NR	NR
Fiore [14]	2007	162	7	3,6	5,6	49	43	3,5	18	19	22	11	12
Stephenson [20]	2010	342	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Robbers-Visser [21]	2010	209	7	NR	NR	47	41	NR	NR	16	36	11	11
Chungsomprasong [11]	2011	103	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sinha [19]	2013	54	7	1,8	2,7	NR	NR	3	43	NR	NR	14	13
Balagi [10]	2014	1271	7	NR	NR	49	40	NR	NR	NR	NR	NR	NR
De Vadder [12]	2014	55	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
D'udekemp [13]	2014	803	7	NR	NR	31	36	6	8	25	20	13	11
Qinton [17]	2015	14	6	NR	NR	NR	NR	NR	NR	NR	N	NR	NR

N Pts: number of patients, NOS: Newcastle Ottawa Scale, RV: right ventricle, TA: tricuspid atresia, MPAP: mean pulmonary artery pressure NR: not reported

Table 2 : Baseline data

Variables	N	Statistical Method	Effect Estimate	P value	Heterogeneity
Age (years)	1661	RE	MD : 1.08 [0.59, 1.57]	<0.001	32%
Male gender	2641	FE	OR : 1.12 [0.95, 1.31]	0.18	16%
Right ventricule morphology	1483	RE	OR : 0.82 [0.60, 1.13]	0.23	60%
Heterotaxy	1119	RE	OR : 4.28 [1.16, 15.82]	0.03	76%
Tricuspid atresia	1286	RE	OR : 1.12 [0.86, 1.47]	0.41	75%
Mean pulmonary artery pressure (mmHg)	1370	RE	MD : -0.31 [-1.25, 0.63]	0.52	89%

MD : Mean difference, OR : odds ratio, FE: Fixed effect, RE: Random effect.

Figure 1 : Flow Chart of study

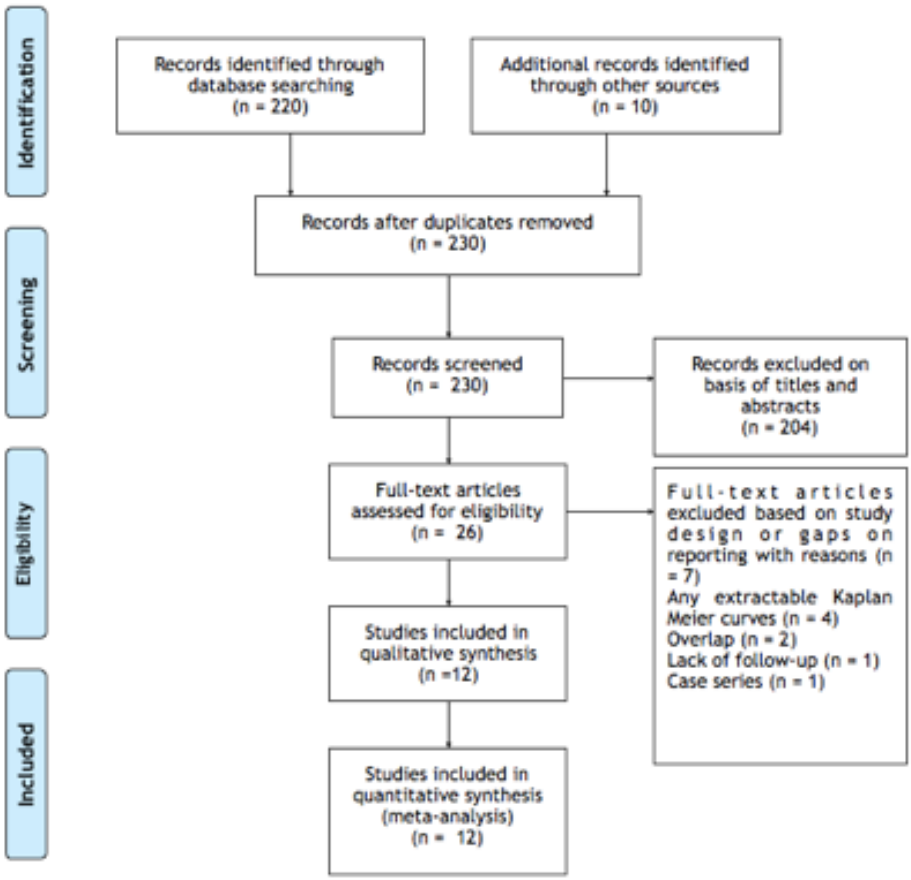


Figure 2 : 2A : Freedom from tachyarrhythmia, 2B : Freedom from bradyarrhythmia or Pacemaker implantation, time in months

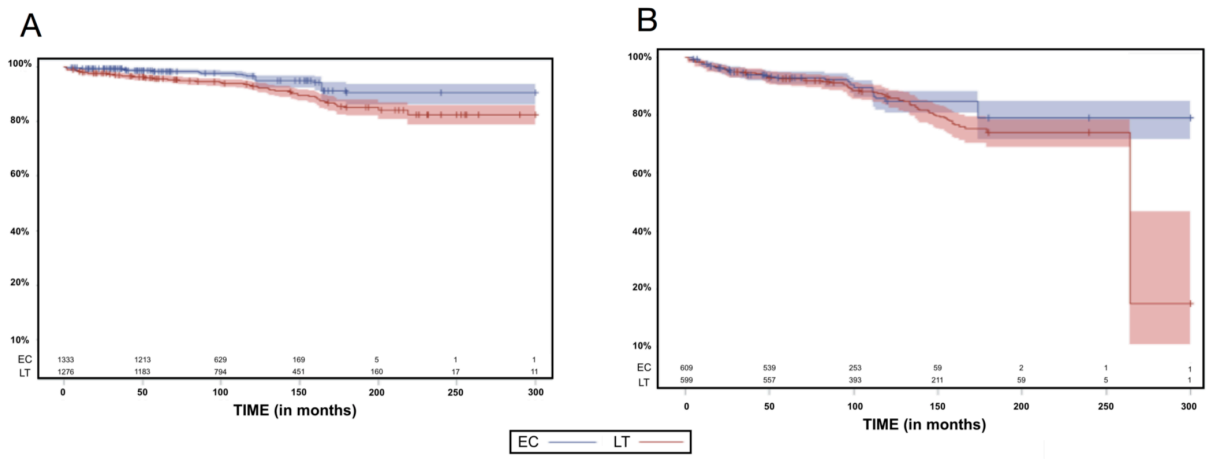
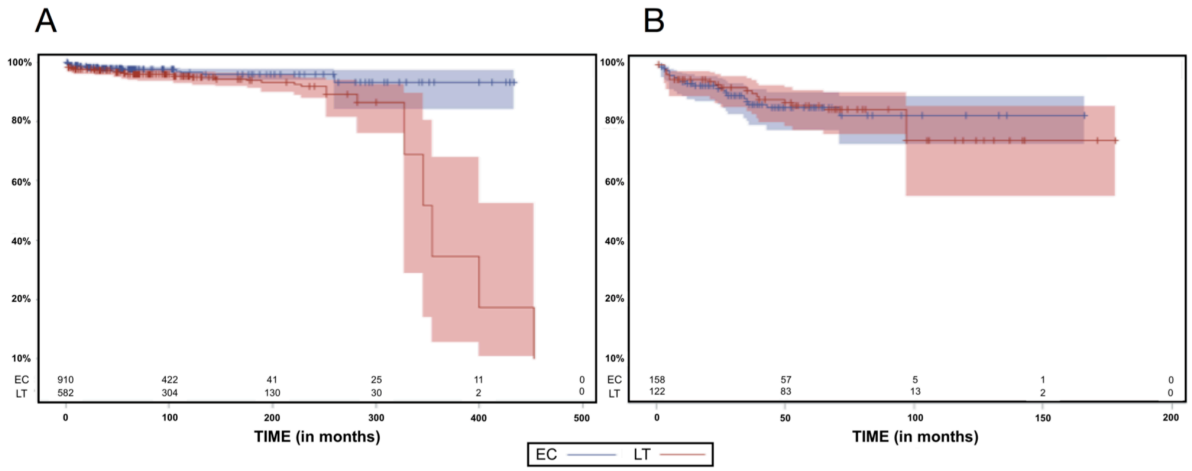


Figure 3 : 3A : Survival, 3B : Freedom from reoperations, time in months



Chapter 6 Manuscrit #4

Avant-propos

La rareté de donneurs des greffons cardiaques combinée aux avancés techniques des assistances ventriculaires gauches (AVG) ont mené à une augmentation du nombre d'implantations avec un allongement de la durée d'utilisation. La communauté scientifique s'accorde sur le fait que l'insuffisance aortique (IAo) est une complication quasi inévitable des AVG, mais l'incidence de l'IAo chez les patients porteurs d'AVG n'est pas connue ainsi que son impact sur la survie. Nous avons décidé de réaliser une méta-analyse des données publiées sur ce sujet dans la littérature en utilisant la méthodologie Gr-RSMT pour répondre à ces deux questions : 1) l'incidence de l'IAo chez les patients porteurs d'AVG et 2) son impact sur la survie. Cette étude est en cours de révision à *Ann Thorac Surg (Soumission le 29 novembre 2018, 1 ère révision le 05 mars 2019).*

Prevalence and impact of de novo aortic insufficiency during support with a left ventricular assist device : A systematic review and meta-analysis

Running Head : AI in LVAD

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Abstract

Background: Progressive aortic insufficiency (AI) may occur in left ventricular assist device (LVAD) patients as the duration of support increases.

Objective: The aim of this meta-analysis was to report the incidence of AI in patients on LVAD support, identify factors associated with its occurrence and determine its impact on survival.

Methods: A systematic search of PubMed, EMBASE, and Cochrane Central register for articles reporting on freedom from de novo aortic AI and/or its impact on survival among LVAD recipients.

Results: 12 studies were selected with 1176 patients. The freedom from significant AI (at least moderate) at 1 and 3 years was 67%, 95% confidence interval (CI): [63–71%] and 35%, 95% CI: [29–41%], respectively. Freedom from significant AI was significantly higher when the aortic valve continues to open and close (log-rank $p < 0.001$) and with pulsatile flow ($p < 0.0001$). Survival at 3 years was 56%, 95% CI: [44–68%] and 65%, 95% CI: [57–73%] respectively with or without significant AI (log-rank $p=0.26$). In the subgroup of patients receiving continuous flow device, survival was significantly higher in the absence of significant AI (76 %, 95 % CI : [66–86%] versus 58%, 95% CI: [46–70%] at 3 years of follow-up, $p=0.01$).

Conclusion: A significant number of patients develop de novo AI during LVAD support. Longer support duration, continuous-flow pumps, and a closed aortic valve were associated with AI. Significant AI decreases survival in patients supported with continuous-flow pumps. Further research to prevent AI through blood pressure management, pump management, or new pump technology is required.

Word count: 250

Progressive aortic insufficiency (AI) occurs in left ventricular assist device (LVAD) supported patients, especially as the duration of support increases [1]. This is caused by commissural fusion and deterioration of leaflet tissue, both phenomena promoted by failure of the aortic valve (AV) to open during support [2]. This LVAD-related complication induces a recycling of the regurgitant volume back into the inflow cannula, decreases effective LVAD output and leads to end-organ malperfusion [3]. Limited donor availability and better left ventricular assist device (LVAD) technology has led to both increased numbers of LVAD implantation and longer duration of support [4,5]. As number and duration of LVADs increase, there is a growing concern and awareness of the long-term consequences of AI and its associated morbidity and mortality especially in destination therapy (DT) patients where bailout strategies are unavailable. Far less is known about the incidence of AI in the LVAD population and comparative data on survival are controversial. Because the only available contemporary data on this topic is limited to small single-center series compromised by small numbers and referral bias, we performed a meta-analysis of studies reporting the occurrence of de novo AI in patients on LVAD support, with the aim of analyzing patient and pump factors related to this LVAD complication and determine its impact on survival.

Methods

Study Design and Eligibility Criteria

The systematic review and meta-analysis were done based on the Meta-analysis of Observational Studies in Epidemiology guidelines [6]. The manuscript was structured using the recommendations of Systematic Reviews and Meta-Analyses (PRISMA) statement [7]. We included all studies reporting on freedom from de novo aortic AI and/or its impact on survival among LVAD recipients. LVAD support can be either pulsatile or continuous flow. All patients must have a trace AI or less at the time of LVAD implantation. To be included, all studies were required a completeness of the follow-up> 90% and a NewCastle-Ottawa Scale Score > 6 [8]. The following exclusion criteria were used to select the final articles for the meta-analysis: 1) prior or concomitant aortic valve surgery at the time of LVAD implantation, 2) case reports, 3) small case series (fewer than 10 patients), 4) review articles, 5) letters to the editor and 6) articles written in languages other than English or French.

Search Strategy

On January 1st, 2017, a PubMed, EMBASE search was conducted with as keywords : “aortic valve insufficiency,” “aortic regurgitation,” “left ventricular assist device,” “mechanical circulatory support” and “cardiac replacement therapy” limited to publications from 2000 until 2017 in humans. The entire Cochrane Central register was screened for “aortic valve insufficiency” and “left ventricular assist device.” In addition, to avoid missing major related publications, a second search was conducted of four major cardiothoracic surgery journals in the electronic format ; *The Annals of Thoracic Surgery, The European Journal of Cardiothoracic Surgery, The Journal of Thoracic and Cardiovascular Surgery and Journal of the American College of Cardiology*. Related journals and list of references of selected articles were also crosschecked for other possible relevant studies.

Study Records

Two reviewers (WBA, IB) screened the titles and abstracts of identified studies. In cases of multiple publications with sample overlap, the most recent report was selected. Three independent reviewers (MC, IB and WBA) assessed whether inclusion and exclusion were performed correctly and evaluated the degree of bias of each paper. In case of disagreement, a consensus was negotiated. First and corresponding authors of studies (N=8) were contacted when a publication could not be obtained or when the required information could not be retrieved from the publication.

Meta-Analysis Outcomes

The main outcome of interest was freedom from significant AI. The accepted definition of significant AI was defined as being more than mild based on a semiquantitative analysis at transthoracic echocardiograms. Secondary endpoints were freedom from AI stratified by AV status and type of LVAD flow as well as survival for the whole cohort and for the subgroup of continuous flow LVADs (Cf-LVAD).

Data Analysis

Data extraction from each available Kaplan-Meier (KM) curve was performed using the methodology described by Guyot and colleagues [9]. Briefly, each KM curve was digitized using a digitalization software (Digitizelt ®, Braunschweig, Germany). The individual patient data was derived from the KM curve using the software. In the same manner, extraction of censored information was performed where censoring marks were present on the KM graph. Derived KM curves were graphically checked with the original ones using a ratio of restricted mean survival time (RMST) of each curve. RMST is defined as the area under the KM curve calculated based on the trapeze rule. A ratio superior to 0.98 was mandatory. Once validated, the KM data from different studies were stored together in the study database. Statistical methods for time-to-event data were employed to analyze outcomes at the follow-up, including the KM estimator with the log-rank test for comparisons. Baseline data were extracted and analyzed with RevMan 5 (RevMan 5.3, Cochrane Collaboration, Oxford, UK). Statistics included odds ratio (OR) and weighted mean difference (MD) with the respective 95% confidence interval (CI). Heterogeneity was examined using Cochran's Q test as well as the I^2 statistic. Because heterogeneity of patients and treatment procedures in the included studies, random effects models were used to calculate OR and their 95% CI when I^2 statistic was superior to 25%. Quality of observational study was assessed by Newcastle-Ottawa Scale and funnel plots were used to study publication bias. Statistical significance was set at a *P* value of 0.05 or less. Meta-regression analysis was used to investigate the effects of covariates, especially variations in patient characteristics.

Results

Literature Search Results

Four hundred and fifty studies were identified. The article titles and abstracts were initially screened for suitability, after which only 35 articles remained for full-text review. From these articles, nine articles were excluded due to the inconsistencies in study design or reporting, four for any extractable KM curves, four for concomitant aortic valve intervention, two for overlap, two for lack of follow-up, two due to case series design and 1 meta-analysis. **Figure 1** represents

the flowchart outlining study selection and inclusion into the meta-analysis. Eleven retrospective studies [10-20] that fulfilled the criteria were included (**Table 1**). This comprised a total of 1176 patients. All studies had a Newcastle-Ottawa Scale score > 6. Publication bias was assessed with funnel plots. These funnel plots showed almost symmetrical distributions and did not raise any major concerns about potential publication bias. However, the possibility of such bias still exists and should be taken into account when considering the results.

Freedom From Significant AI

Five hundred and eighty-five patients were included in this analysis. The freedom from significative AI at 1 and 3 years of follow-up was 67% (95 % CI : [63–71 %]) and 35% (95 % CI : [29–41 %]), respectively (**Figure 2A**). Stratifying by the country of series, freedom from AI was significantly higher in non-US series with a log-rank p <0.0001 (**Figure 2B**).

Duration of Left Ventricular Support

Freedom from AI decreased significantly from 83% (95 % CI : [79 - 87 %]) at 6 months of follow-up to 35% (95 % CI : [29–41 %]) at 3 years of follow-up. This finding was uniformly corroborated by data from all included trials.

Aortic Valve Status

Two hundred and thirty-three patients were included in this analysis. Freedom from significant AI was significantly higher when the aortic valve continues to open and close with a log-rank p <0.0001 (**Figure 3A**). This finding was uniformly corroborated by data from all included trials.

Type of LVAD Flow

Three hundred and forty-five patients were included in this analysis. Patients with continuous-flow pumps were more likely to develop AI compared to the patients with pulsatile pumps (log-rank p <0.0001, **Figure 3B**). Only Pak and colleagues [11] did not observe this finding. In this study, the 2 KM curves intersect at the beginning of the follow-up. After 6 months, the difference becomes significant.

Survival

Three hundred and eighty-three patients were included in this analysis. Overall survival was similar in both groups. Survival at 3 years was 56% (95 % CI : [44–68 %]) and 65% (95 % CI : [57–73 %]) with or without significant AI (log-rank p=0.26, **Figure 4A**) respectively. The same analysis was conducted in the subgroup of Cf-LVAD recipients (124 patients). Survival was significantly higher in the absence of significant AI (76% [66–86%] versus 58% [46–70%] at 3 years, p=0.01, **Figure 4B**). None of the individual studies included in this analysis corroborated this finding but pooling of the data empowers the meta-analysis to attain statistical significance.

Meta-regression

Baseline data of five confounding factors (age, gender, body surface area, and sinuses of the Valsalva diameter) reported by literature as covariates of the occurrence of de novo AI were extracted, pooled and compared between the two groups (AI+ and AI-). Patients developing AI were significantly older than those who did not develop AI. Body surface area and aortic root dimensions were significantly different between the two groups (**Table2**). The inter-study heterogeneity of patient age (p = 0.68), male gender (p = 0.86) and body surface area (p = 0.65) had no effect on the observed difference in terms of survival between the two groups (**Figure 5**).

Discussion

As 2-year survival of Cf-LVAD therapy reaches 70%, the number of LVAD supported patients who develop progressive AI will increase [21]. This meta-analysis pooling eleven single-center institutional studies (1176 patients) demonstrates that AI is a serious underestimated clinical entity with significant AI increasing with longer duration of the support, reaching up to 65% at 3 years. Older patients were more prone to develop significant AI. Permanently closed AV and Cf-LVAD were predictive factors of development of progressive AI. Significant AI impacted survival in Cf-LVAD recipients but not in the whole cohort of study. This presumes that AI is not only more frequent but have also more severe hemodynamic impacts with continuous flow devices.

Deo et al. [22] and more recently Gasparovic et al. [23] published two reviews on the incidence of AI in LVAD recipients and its impact on survival. The two studies pooled the incidence of

AI in each study without accounting for differences in duration of the follow-up between the studies included, which limits the robustness of their findings. As the risk of AI development is cumulative over time, we consider that freedom from AI is a more accurate answer to our search question and only a robust statistical methodology that permit pooling time-to-event data can meta-analyze these data. Contrary to Gasparovic et al. [23], we included both continuous and pulsatile flow devices in our analysis, allowing stratification of results by devices flow type and exploring the potential role of integrating pulsatility algorithms or intermittent low speed phases to avoid AI after LVAD therapy.

In the present study, AI developed more frequently in older patients, which can be explained by age-related aortic valve structural deficiency and degeneration [24] hastened by the exposure to positive pressure especially in a continuous flow setting. Despite the fact that aging correlated to the AI occurrence, age per se exerts no effect upon the observed survival difference as demonstrated by the meta-regression.

Permanent aortic valve closure and continuous flow support were predictive factors of AI occurrence in this review. AV opening is determined by the pressure differential across the valve. Left ventricular unloading concomitant to positive aortic pressure secondary to the outflow cannula blood flow generates negative transvalvular pressure and causes the AV to remain closed. Mudd et al. [2] retrospectively reviewed pathologic samples from 9 patients enrolled in the HeartMate II Bridge to Transplantation Trial with a mean duration of support of 367 days: all but 1 explant had evidence of commissural fusion of the native aortic valve leaflets. Martina et al. [25] in another study of explanted hearts reported that 58% of the aortic valves showed fusion of single or multiple commissures. The commissural fusion may be explained by several theories such as thrombus formation on the ventricular aspect of the aortic valve [26,27] and shear stress induced by the retrograde flow hitting the aortic root side of the aortic valve [28]. This later hemodynamic alteration in the ascending aorta is conditioned by position and angle of the outflow graft and native aorta [28, 29].

In this study, freedom from AI was significantly higher with the use of Pf-LVAD. Considering the current strategies in the management of end-stage heart failure, it is important to understand why continuous flow support is a predictive factor of the occurrence of AI. Indeed with

continuous flow, AI is present throughout the entire cardiac cycle causing a greater regurgitant volume [30]. As AI is not limited to diastole, it is clear that the magnitude of AI in this situation is largely underestimated and developing specific parameters to assess the severity of AI with the use of Cf-LVAD are mandatory [31]. Speed modulation using artificial pulsatility could theoretically reduce AI occurrence but needs to be validated clinically [32]. Moreover, the use of Pf-LVAD was mostly reported by series from outside the United States. This partly explains the finding of this study that freedom from AI was higher in these series.

In this analysis, no difference was observed in terms of survival for the whole cohort with or without AI. One possible explanation for this finding is that bridge to transplant (BTT) LVAD recipients will be transplanted in presence of significant AI. BTT indications were predominant in series using pulsatile flow devices. On the other hand, survival was significantly higher in the absence of AI with the use of continuous flow. This can be explained by the fact that continuous AI leads to elevated wedge pressures with resultant exercise intolerance and gradual end-organ dysfunction which promote the development of mitral regurgitation and/or secondary pulmonary hypertension with subsequent right ventricle dysfunction.

No universally accepted AI management algorithms after LVAD implantation are available. Jorde et al. [16] proposed repair of the aortic valve with a Park stitch at the time of implantation for patients with AI greater than mild, in case of DT indication and if heart transplantation is not expected within 12 months. When AI is diagnosed after LVAD implantation: 1) For asymptomatic patients, speed optimization of device rpm to maintain an intermittent AV opening is mandatory. This can be achieved by decreasing the pump speed in increments of 200 to 400 rpm below the pump speed associated with complete aortic valve closure to identify the highest pump speed associated with at least intermittent aortic valve opening [16, 33]. 2) For symptomatic patients, diuretics and lowering arterial pressure by systemic oral vasodilators are first-line treatment. If these measures fail, increase of LVAD speed in increments between 400 and 1,000 rpm, from 8,000 to 12,000 rpm are recommended [16]. This speed optimization leads to better left ventricle decompression, decreasing wedge pressure and minimizes congestion [30]. This can be followed by a surgical approach to repair or replace the valve. The surgical approach consists of either bioprosthetic valve replacement, patch closure, valve repair [34] or

transcatheter procedures for patients in whom the risk of reoperation is prohibitive or in case of DT indication [35, 36].*Limitations of Study*

The main limitation of the study is the lack of randomized trials. As there are no available randomized studies addressing AI after LVAD implantation, pooling observational studies in meta-analysis was the only choice to have sufficient statistical power to analyze the data and lead to hypothesis generation. Studies present variations in patient selection, support used and surgical technique. To manage the heterogeneity, we have adopted a random effects model when I^2 was superior to 25% and conducted a meta-regression to solve inter-study heterogeneity. The second limitation of study is the lack of uniformity in type of definition of significant AI. All studies adopted a semi-quantitative assessment of AI with probable underestimation of the grade of AI. The third limitation of study was the lack of data concerning the cf-LVAD types.

Conclusion

De novo AI is a significant complication of LVAD therapy. A significant number of patients develop de novo AI during LVAD support. Longer support duration, continuous-flow pumps, and a permanently closed aortic valve were associated with AI. AI impacts survival in continuous flow recipients. Further research to prevent AI through blood pressure management, pump management, or new pump technology is required. A greater consensus for management of AI in LVAD patient is also necessary.

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Table 1 : Studies characteristics

Author	Year	Study Period	Country	No Pts	Device type	Significant AI definition
Pak [10]	2010	2004-2009	United States	130	Cf/ Pf	More than Mild
Hatano [11]	2011	2002-2010	Japan	37	Cf/ Pf	More than Mild
Toda [12]	2011	1999-2009	Japan	47	Cf/ Pf	More than Mild
Soleimani [13]	2012	2008-2010	United States	63	Cf	More than Mild
Aggrawal [14]	2013	2005-2011	United States	79	Cf	Mild or more
Rajagopal [15]	2013	2004-2011	United States	184	Cf/ Pf	More than Mild
Jorde [16]	2014	2004-2013	United States	174	Cf	More than Mild
Hiraoka [17]	2015	2005-2012	United States Japan	82	Cf	More than Mild
Imamura [18]	2015	2006-2013	Japan	52	Cf	Mild or more
Patil [19]	2015	2006-2012	United Kingdom	90	Cf	Mild or more
Da Rocha [20]	2016	2009-2013	Germany	102	Cf	Mild or more

Pts : Patients, AI : aortic insufficiency, Cf : continuous Flow, Pf : Pulsatile flow

Table 2 : Baseline data

Variables	N	Statistical Method	Effect Estimate	P value	Heterogeneity
Age (years)	503	MD/ RE	7.08 [4.64, 9.52]	<0,001	27 %
Male Gender	688	OR/ FE	0.50 [0.33, 0.77]	0,002	16 %
Body surface area (m^2)	347	MD/ RE	-0.09 [-0.16, -0.03]	0,006	42 %
Sinus Valsalva diameter (cm)	333	MD/ RE	0.13 [0.01, 0.26]	0,004	51 %

MD: Mean difference, FE: Fixed effect, RE: Random effect

Figure 1 : Flow Chart of study

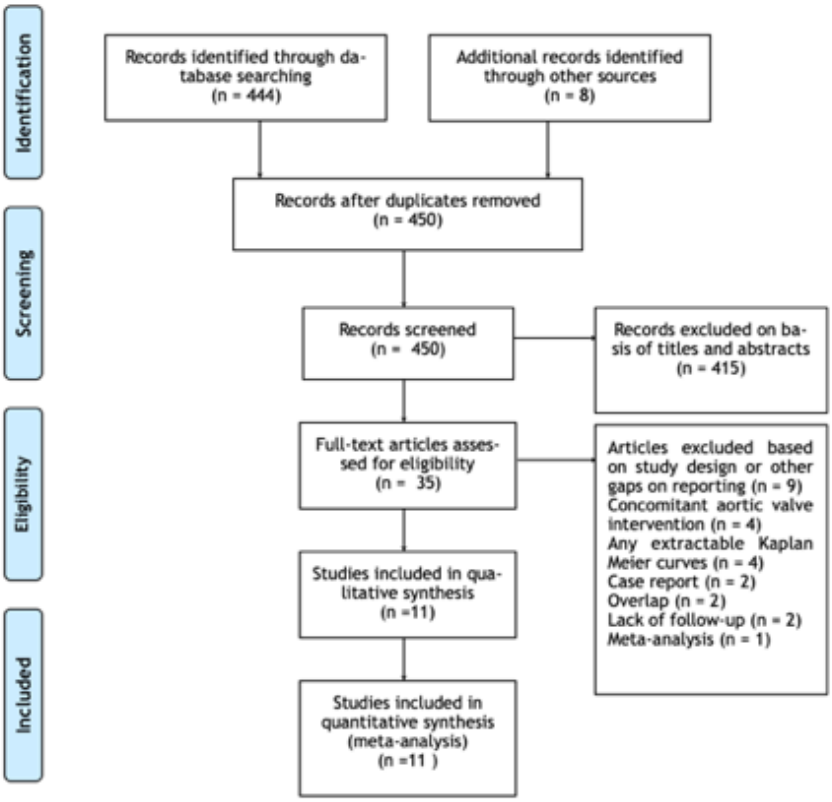


Figure 2 : 2A : Freedom from AI, 2B : Freedom from AI stratified by country of study (time in months).

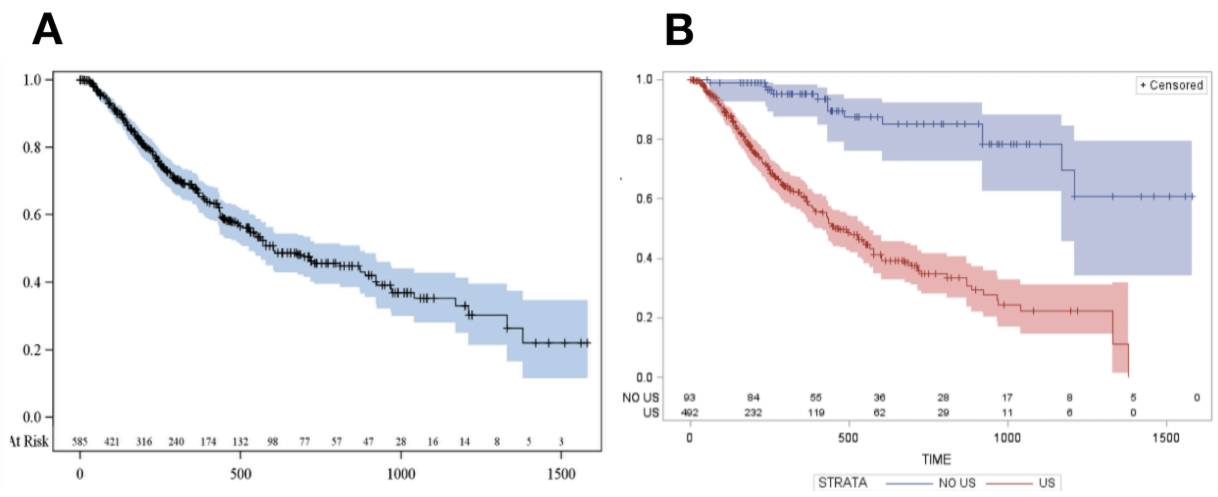


Figure 3 : 3A : Freedom from AI according by AV opening status, 3B : Freedom from AI stratified by LVAD flow type (time in months).

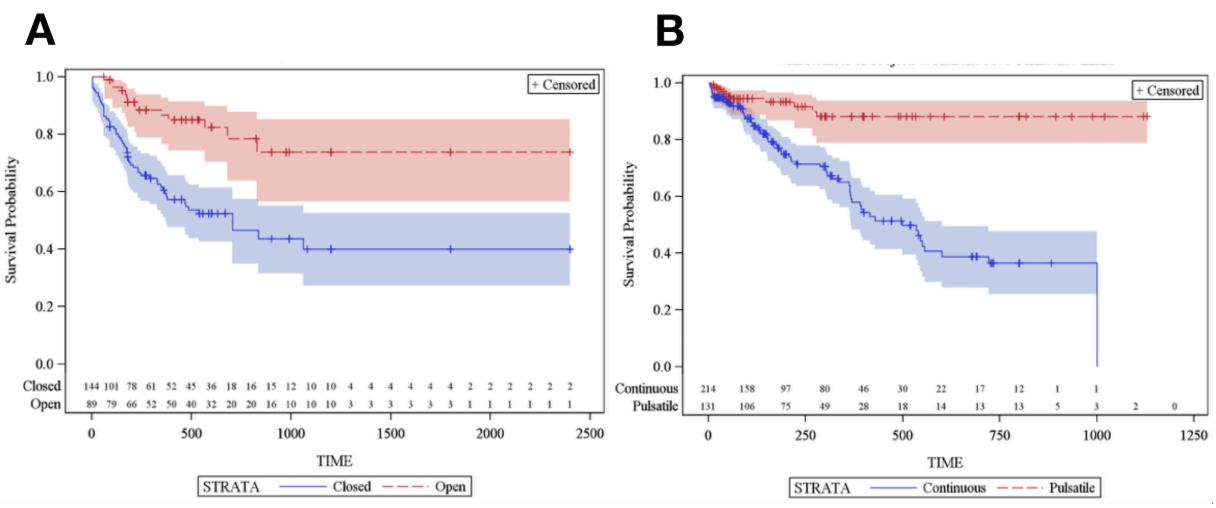


Figure 4 : 4A : Survival, whole cohort 4B : Survival, continuous flow cohort (time in months).

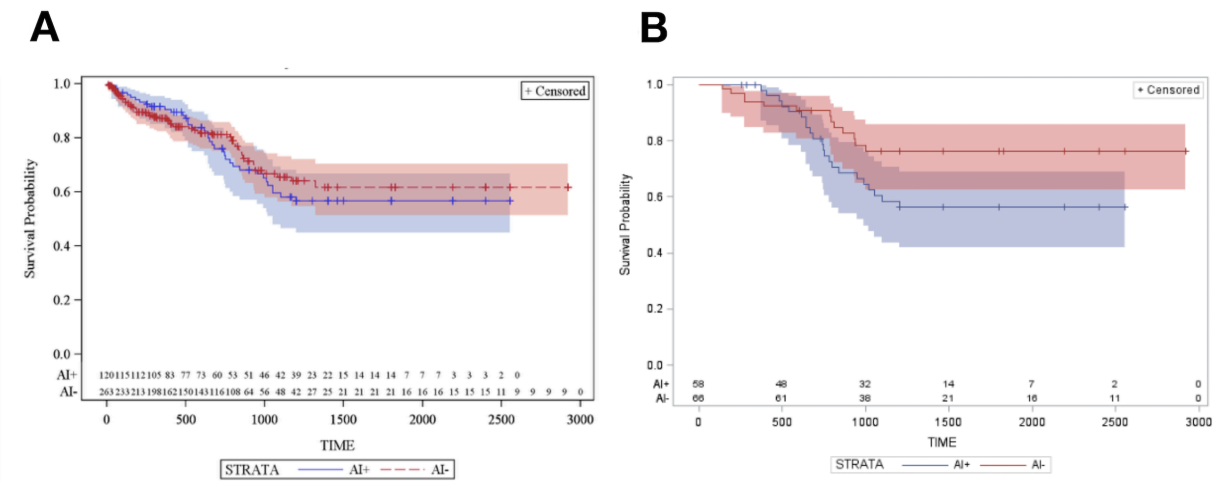
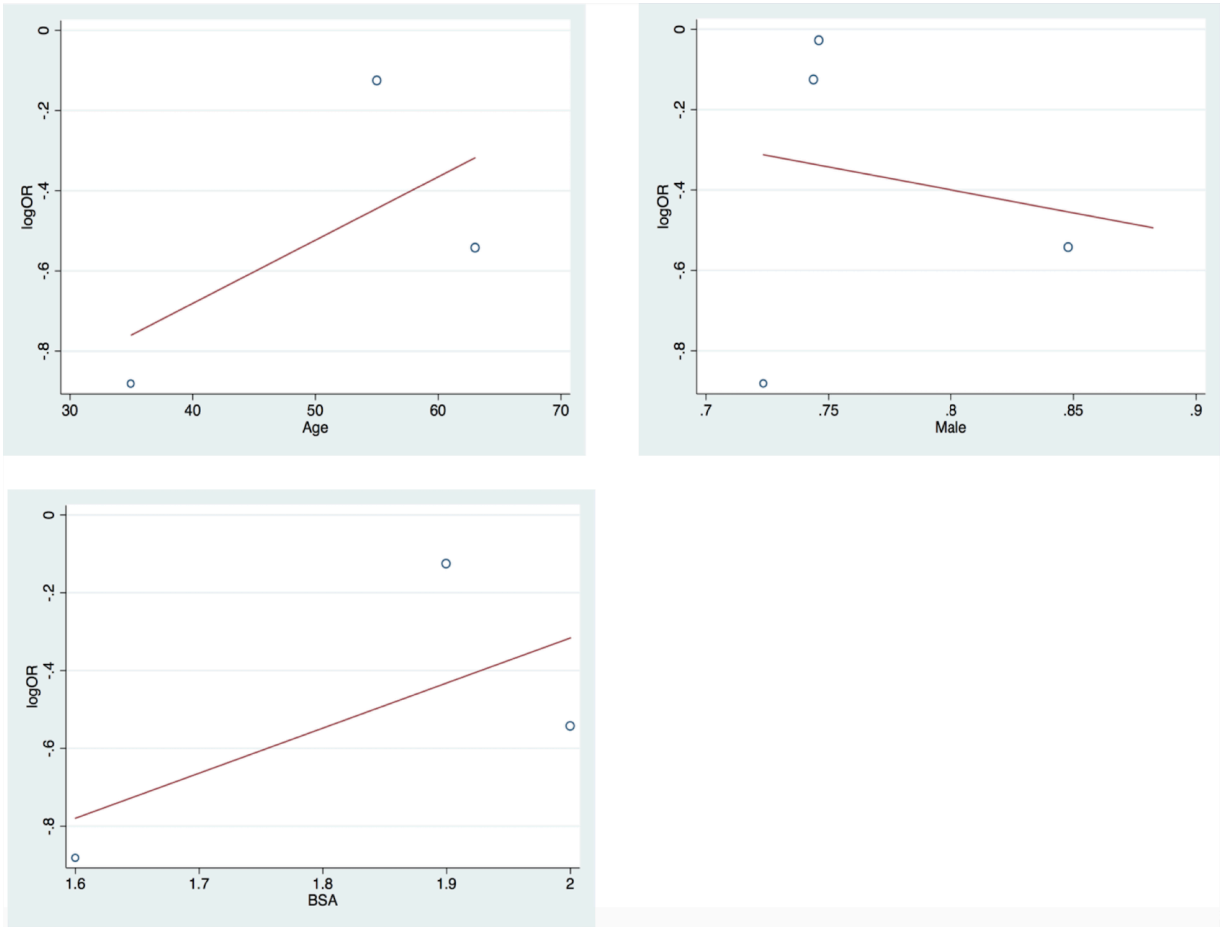


Figure 5 : Meta-regression



Chapitre 7 Discussion

7.1 Originalité et sommaire de la thèse

L'inspiration de départ de cette thèse était le cours de revue systématique et méta-analyse au département de biostatistique de l'Université de Montréal. Fraichement débarqué des bancs de l'université, nous nous sommes donné comme objectif de réaliser une première méta-analyse portant sur la plastie tricuspide prophylactique concomitante à une chirurgie mitrale. Rapidement, nous nous sommes rendu compte que les connaissances acquises durant le cours ne pouvaient pas forcément s'appliquer à la littérature en chirurgie cardiaque. Un retour à l'école était alors plus que nécessaire et des *workshops* de la Cochrane Collaboration se sont succédés pour approfondir mes connaissances en revues systématiques et méta-analyses. La surprise était grande en s'apercevant que les défis posés par la littérature en chirurgie cardiaque demeuraient les mêmes malgré cette série de formations. Les essais randomisés étaient rares, la littérature peu étoffée sur certains sujets et l'évaluation de la qualité des études non randomisées était toujours problématique et controversée. Une grande difficulté existait de méta-analyser les données de survie avec des approches aussi biaisées l'une que l'autre. Un ensemble de questions sans réponses dans le petit livre de poche que la Cochrane offrait à la fin du processus de formation persistait. Pour les fins de cette thèse, il a donc fallu :

1) Chercher d'autres approches pour optimiser le processus de recherche en se formant sur des logiciels poussés comme EPPI-Reviewer (EPPI-Centre, London, United Kingdom) permettant le *text miming* et la *citation chasing*.

2) Participer au processus de validation de nouveaux outils d'évaluation d'études randomisées et non randomisées de la Cochrane Collaboration

3) Développer la méthodologie Gr-RSMT pour méta-analyser les données de survie avec la collaboration des statisticiens de l'unité de recherche clinique appliquée du CHU Sainte-Justine. Une approche que l'on voulait valide, robuste et adaptée aux besoins du clinicien.

Cette démarche a été utilisée pour répondre à diverses questions de recherche touchant différents aspects de la chirurgie cardiaque :

1) La rédaction des premières lignes directrices de *l'Enhanced Recovery After Cardiac Surgery*.

2) Les résultats de la chirurgie valvulaire et aortique chez le transplanté cardiaque.

3) L'incidence des arythmies supra-ventriculaires chez les patients ayant eu une intervention de Fontan.

4) L'incidence de l'insuffisance aortique chez les patients porteurs d'assistance ventriculaire gauche et son impact sur leur survie.

Le manuscrit #1 (Guidelines for Perioperative Care in Cardiac Surgery: Enhanced Recovery After Surgery (ERAS®) Society Recommendations.) contient les premières lignes directrices de *l'Enhanced Recovery After Surgery Society (ERAS)* en chirurgie cardiaque. L'ERAS est une initiative multimodale et transdisciplinaire dont le but est d'optimiser la récupération du patient après sa chirurgie [128]. Ce type de programme a été déjà utilisé dans d'autres spécialités chirurgicales avec un franc succès réduisant le nombre de complications, la durée de séjour d'hospitalisation et le temps de retour au travail [129]. Un groupe de seize chirurgiens cardiaques, d'anesthésistes et d'intensivistes ont sélectionné 22 champs d'interventions couvrant les périodes pré, per et post-opératoires pour lesquels des lignes directrices ont été développées pour optimiser la récupération du patient après chirurgie cardiaque. Un des défis de cette étude était de mener une recherche systématique pour chacun des 22 sujets avec une contrainte de temps et de ressources. L'utilisation d'approche alternative pour la recherche de littérature, particulièrement le *text mining*, a permis d'augmenter la sensibilité, la précision et l'efficience de la recherche systématique. L'autre enjeu était l'évaluation de la qualité des études sélectionnées pour la rédaction des lignes directrices. À notre connaissance, il s'agit de la première fois où les outils RoB 2.0 et ROBINS ont été utilisés pour la rédaction de lignes directrices. En organisant le consensus entre les différents intervenants, cette étude a permis de démontrer à travers les recommandations de ses auteurs que l'implantation d'un programme d'ERAS en chirurgie cardiaque est possible. Ces recommandations permettraient d'uniformiser la pratique et d'améliorer la qualité et la sécurité des soins prodigués aux patients. L'implantation de ce type de programme doit se faire par une approche multidisciplinaire pour en assurer le succès.

Le manuscrit #2 (Valvular surgery in the transplanted heart: Montreal Heart Institute experience and Systematic Review) s'est intéressé à la chirurgie valvulaire et aortique chez le greffé cardiaque. La rareté de donneurs et les résultats mitigés de la re-transplantation cardiaque [130] expliquent l'intérêt porté à ce sujet. Cette étude est la première revue systématique faite

sur le sujet. La difficulté principale rencontrée lors de la recherche systématique de la littérature était la rareté des études portant sur le sujet. Le recours à la *citation chasing* a non seulement augmenté la sensibilité de la recherche mais a également permis d'élargir le devis de recherche aux procédures trans-cathéter qui sont des techniques émergentes et prometteuses dans la prise en charge d'atteintes valvulaires chez des patients à haut-risque chirurgical telles que les greffés cardiaques [131]. L'autre défi non négligeable était de composer avec des études dont la majorité avait un risque de biais modéré. Vu la rareté des études, nous avons opté pour une approche narrative pour justifier leur inclusion. Le manuscrit a permis de constater que : 1) la pathologie valvulaire n'était pas si rare touchant un greffé cardiaque sur cinq, 2) la valve tricuspide était la valve la plus atteinte, essentiellement une conséquence des biopsies myocardiques, 3) la chirurgie dans ce contexte de patients fragiles se fait avec de très bons résultats, faisant de plus en plus appel aux techniques mini-invasives et 4) les techniques trans-cathéters prennent de plus en plus de place dans la prise en charge thérapeutique des atteintes valvulaires et aortiques chez le greffé cardiaque.

Le manuscrit #3 (Extracardiac Versus Lateral Tunnel Fontan: A Meta-Analysis of Long-term Results with special focus on Arrhythmias) a porté sur la survenue des arythmies supra-ventriculaires chez les patients ayant eu une intervention de Fontan. Plusieurs modifications ont été apportées à la technique décrite initialement par Baudet et Fontan [126]. Ces principales modifications décrites sont le tunnel latéral intracardiaque [132] et le conduit extracardiaque [133]. Il a été démontré [134] que le Fontan LT avait un potentiel de croissance diminuant le taux de réintervention et un avantage en termes de complications thromboemboliques alors que le Fontan EC offrait une meilleure hémodynamique des flux et avait un avantage en termes de préservation myocardique en sursoyant à un clampage aortique. En confectionnant un tube extracardiaque, on réduit nettement le nombre de sutures intra-auriculaires, un des substratums d'arythmies supra-ventriculaires. Cet avantage théorique est très débattu dans la littérature [126, 135]. Nous avons appliqué la méthodologie Gr-RSMT pour extraire les données des courbes de survie publiées dans la littérature. La méta-analyse réalisée incluait 3300 patients. Le Fontan EC diminue significativement les ASV à long terme et confère une meilleure survie. Les deux techniques par contre sont comparables en termes de réintervention et de bradyarythmies. L'hétérogénéité inter-étude en termes d'âge, de sexe, d'hétérotaxie, de morphologie du

ventricule droit, d'atrésie tricuspide et de pression pulmonaire moyenne préopératoire a été explorée par une méta-régression et n'affectait pas les effets observés.

Le manuscrit #4 (Prevalence and impact of de Novo aortic insufficiency during support on a left ventricular assist device: A systematic review and meta-analysis) s'est intéressé à l'insuffisance aortique chez les patients porteurs d'assistance ventriculaire gauche, son incidence et son impact sur la survie de ces patients. Le nombre d'AVG implantées augmente de 2500 par année selon *l'Interagency Registry for Mechanically Assisted Circulatory Support* [136]. Si l'IAo est listée par ce registre comme une complication possible à long terme de l'AVG, ce registre ne rapporte ni son incidence ni les facteurs de risque de sa survenue. La littérature sur ce sujet se limite à des petites séries institutionnelles et ramène des résultats très controversés en termes d'impact de l'IAo sur la survie de ce groupe de patients. Le risque de survenue d'IAo étant cumulatif au cours du temps, seule une approche combinant des données de survie est capable de méta-analyser les données publiées de la littérature. La méta-analyse réalisée incluait 1176 patients. En utilisant la méthodologie Gr-RSMT, une courbe de survie sans IAo a été reconstruite et a permis d'objectiver l'absence d'IAo significative chez seulement 35 % des patients à 3 ans de suivi. Ainsi, cette entité clinique a longtemps été sous-estimée chez ce sous-groupe de patient. L'incidence d'IAo est significativement plus élevée lorsqu'on ne réussit pas à maintenir la valve aortique ouverte ou lorsqu'on utilise une AVG avec un flux continu. En reconstituant les courbes de survie, l'IAo significative n'affectait pas la survie de la cohorte entière, mais diminuent significativement celle du sous-groupe de patients recevant une AVG à flux continu. Cette observation est d'autant plus importante que les AVG à flux continu représentent actuellement la majorité de l'activité en assistance ventriculaire gauche. L'hétérogénéité inter-étude en termes d'âge, de sexe, de surface corporelle et de diamètre de sinus de Valsalva a été explorée par une méta-régression et n'affectait pas les effets observés. Ce manuscrit a été aussi l'occasion de mener une recherche systématique pour essayer de mettre sur pied un algorithme décisionnel aidant le clinicien dans la prise en charge de l'IAo après AVG.

7.2 Perspectives futures de méta-analyses en chirurgie cardiaque

Cette thèse représente un continuum d'acquisition de compétences en revues systématiques et méta-analyses pour les transposer sur la réalité de la littérature en chirurgie cardiaque. Ce processus continue actuellement en explorant deux nouvelles avenues en méta-analyses à savoir les *network meta-analyses* et l'approche bayésienne.

Traditionnellement, une méta-analyse compare deux interventions ou traitements en même temps. La nécessité de combiner et méta-analyser plusieurs comparaisons dans la même revue a abouti au développement du concept de *network meta-analysis* ou *mixed treatment comparisons meta-analysis* [137-139]. Le nombre de ce type de méta-analyse ne cesse d'augmenter [140]. L'intérêt grandissant pour ce type de méta-analyse s'explique par la multitude de possibilités de comparaison d'interventions qu'offre cette approche. Les *network meta-analyses* permettent de réaliser à la fois des comparaisons directes et indirectes. Si par exemple, des comparaisons des traitements A et B et B et C sont rapportées dans la littérature, la *network meta-analysis* de ces évidences permettent des comparaisons indirectes entre traitements A et C. Les résultats sont exprimés sous forme de hiérarchisation des interventions en fonction de leur probabilité de classement. PRISMA [141] définit les probabilités de classement de la façon suivante : « *The term treatment ranking probabilities refers to the probabilities estimated for each treatment in a network of achieving a particular placement in an ordering of treatment effects from best to worst. Robust reporting of rankings also includes specifying median ranks with uncertainty intervals, cumulative probability curves, and the surface under the cumulative ranking curve ».* La méthodologie est différente des méta-analyses classiques, l'hétérogénéité laisse place à la consistance des études et la géométrie du réseau remplace l'évaluation de la qualité des études. La checklist PRISMA [16] a été modifiée en 2016 pour s'adapter à ce type de méta-analyse [141]. Cinq items ont été rajoutés et 11 autres ont été modulés pour la *network meta-analysis*. Nous collaborons actuellement avec les unités de cardiopathies congénitales adultes de Cincinnati et de la Mayo clinic pour la réalisation d'une *network meta-analysis* comparant trois techniques chirurgicales pour la tétralogie de Fallot en termes d'arythmie à long terme. Plusieurs études comparaient l'approche trans-atriale au patch trans-annulaire ou l'approche trans-atriale à la mise en place de tube valvé. La structure des

network meta-analysses a permis une comparaison indirecte du patch trans-annulaire au tube valvé et a permis une hiérarchisation des trois techniques.

L'approche bayésienne est très populaire en essais cliniques, mais ne connait pas le même succès en revues systématiques et méta-analyses [142]. La Cochrane [18] définit cette approche comme : « *In a Bayesian analysis, initial uncertainty is expressed through a* ***prior distribution*** *about the quantities of interest. In the context of a meta-analysis, the prior distribution will describe uncertainty regarding the particular effect measure being analyzed, such as the odds ratio or the mean difference. This may be an expression of subjective belief about the size of the effect, or it may be from sources of evidence not included in the meta-analysis, such as information from non-randomized studies ».* Nous collaborons actuellement à l'élaboration d'une méta-analyse portant sur l'effet du remplacement valvulaire pulmonaire sur le volume du ventricule droit qui servira à la rédaction de nouvelles lignes directrices canadiennes de cardiopathies congénitales adultes. L'utilisation de cette approche a permis de résoudre plusieurs lacunes de la littérature sur ce sujet à savoir les données manquantes, spécialement la variance et l'ajustement des résultats en fonction de la qualité limitée des études. Elle a été aussi utilisée pour estimer la probabilité d'observer l'effet obtenu par la méta-analyse.

Conclusion

Les revues systématiques et les méta-analyses prennent une place de plus en plus prépondérante dans la rédaction des lignes directrices pour une médecine basée sur des données probantes. Ceci est d'autant plus vrai pour la chirurgie cardiaque, où les essais randomisés sont rares avec des séries institutionnelles de petite envergure, surtout si elles touchent des sujets hyper-spécialisés. L'approche offerte par les guides de pratique n'est pas toujours applicable à la littérature en chirurgie cardiaque. Il est devenu donc plus que nécessaire d'explorer d'autres avenues pour la réalisation de ce type de recherche en chirurgie cardiaque.

Cette thèse est le fruit d'un long cheminement pour l'acquisition d'une certaine expertise en revue systématique et méta-analyse. Ce processus m'a permis d'être aux aguets de nouvelles technologies, permettant aussi l'optimisation du processus de recherche. L'utilisation de ces technologies a été primordiale pour la réalisation de la recherche systématique nécessaire à la rédaction des premières lignes directrices de *l'Enhanced Recovery After Surgery Society* en chirurgie cardiaque. Ce cheminement m'a permis aussi de devenir un *reviewer Cochrane* me donnant accès à des collaborations internationales comme dans le cas de la validation des outils d'évaluation de la qualité des études. La collaboration avec les statisticiens a été des plus intéressante. Elle a été l'occasion de mettre au point la méthodologie Gr-RSMT pour réaliser les méta-analyses de données de survie, méthodologie qui se voulait robuste, valide, mais surtout facilement applicable par le chercheur clinicien. L'utilisation de cette méthodologie dans des méta-analyses de données de survie a permis de répondre à des questions de recherche jusque là sans réponses et surtout de changer certaines convictions de quelques-uns de mes collègues comme dans le cas de l'étude portant sur les procédures de Fontan.

Cette thèse se veut aussi être un tremplin vers des projets futurs. Des collaborations avec la Société Internationale des Cardiopathies Congénitales et la Société Canadienne de Cardiologie sont en cours faisant appel à de nouvelles approches comme l'approche bayésienne et la *network meta-analysis*.

Enfin, j'ose espérer que ces travaux soient source d'inspiration pour d'autres collègues désireux de s'impliquer dans la rédaction de thèse de sciences, de revues systématiques et de méta-analyses. Ceci serait l'aboutissement final de cette démarche de Ph.D.

Annexes

Annexe 1 PRISMA-P Checklist. Adapté de Shamseer L et al [17]

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

Annexe 2 Systematic review software

	covidence	DistillerSR	EPPI REVIEWER
Searching	×	×	PubMed only
Upload from Endnote	✓	✓	✓
Duplicates removal	✓	✓	✓
Double screening	✓	✓	✓
Generate PRISMA Flow Chart	✓	✓	✓
Quality appraisal	✓	✓	✓
Auto-populate tables	✓	×	×
Meta-analysis	Export to RevMan	✓	✓
Cost (4 months)	US$160	US$1500	£220
Access once subscription finished	Currently N/A	Read only 1 year	Read only 2 months

×: Non, ✓: oui

Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia.

DistillerSR, Evidence Partners, Ottawa, Canada

l'EPPI – Reviewer, EPPI-Centre, London, United Kingdom

Annexe 3 Critères spécifiques de l'évaluation de chaque type d'étude selon l'Agency for Healthcare Research and Quality

Risk of bias	Criterion	RCTs	Cohort	Case-control	Case series	Cross-sectional
Selection bias	Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	X				
	Was the allocation of treatment adequately concealed (e.g., pharmacy- controlled randomization or use of sequentially numbered sealed envelopes)?	X				
	Were participants analyzed within the groups they were originally assigned to?	X				
	Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?		X			X
	Were cases and controls selected appropriately (e.g., appropriate diagnostic criteria or definitions, equal application of exclusion criteria to case and controls, sampling not influenced by exposure status)			X		
	Did the strategy for recruiting participants into the study differ across study groups?		X			
	Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?	X	X	X	X	X
Performance bias	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	X	X	X	X	X
	Did the study maintain fidelity to the intervention protocol?	X	X	X	X	X
Attrition bias	If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?	X	X	X	X	X

Annexe 3 (continued) Critères spécifiques de l'évaluation de chaque type d'étude selon l'Agency for Healthcare Research and Quality

Risk of bias	Criterion	RCTs	Cohort	Case-control	Case series	Cross-sectional
Detection bias	In prospective studies, was the length of follow-up different between the groups, or in case- control studies, was the time period between the intervention/exposure and outcome the same for cases and controls?	X	X	X		
	Were the outcome assessors blinded to the intervention or exposure status of participants?	X	X	X	X	X
	Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?	X	X	X	X	X
	Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?	X	X	X	X	X
	Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?		X	X	X	X
Reporting bias	Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?	X	X	X	X	X

Annexe 4 Outil RoB 2.0

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0)

TEMPLATE FOR COMPLETION

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Version of 9 October 2018

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Study details

Reference

Study design

☐ Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

Specify which outcome is being assessed for risk of bias

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Is the review team's aim for this result ?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

☐ Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Description	Response options
1.1 Was the allocation sequence random?		Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Domain 2: Risk of bias due to deviations from the intended interventions

Signalling questions	Description	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA / Y / PY / PN / N / NI
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?		NA / Y / PY / PN / N / NI
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?		NA / Y / PY / PN / N / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y / PY / PN / N / NI

2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement Optional: What is the predicted direction of bias due to deviations from intended interventions?		Low / High / Some concerns Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Domain 3: Missing outcome data

Signalling questions	Description	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?		NA / Y / PY / PN / N / NI
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Description	Response options
4.1 Was the method of measuring the outcome inappropriate?		Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?		Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?		Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Description	Response options
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis ?		Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI
5.3 ... multiple analyses of the data?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

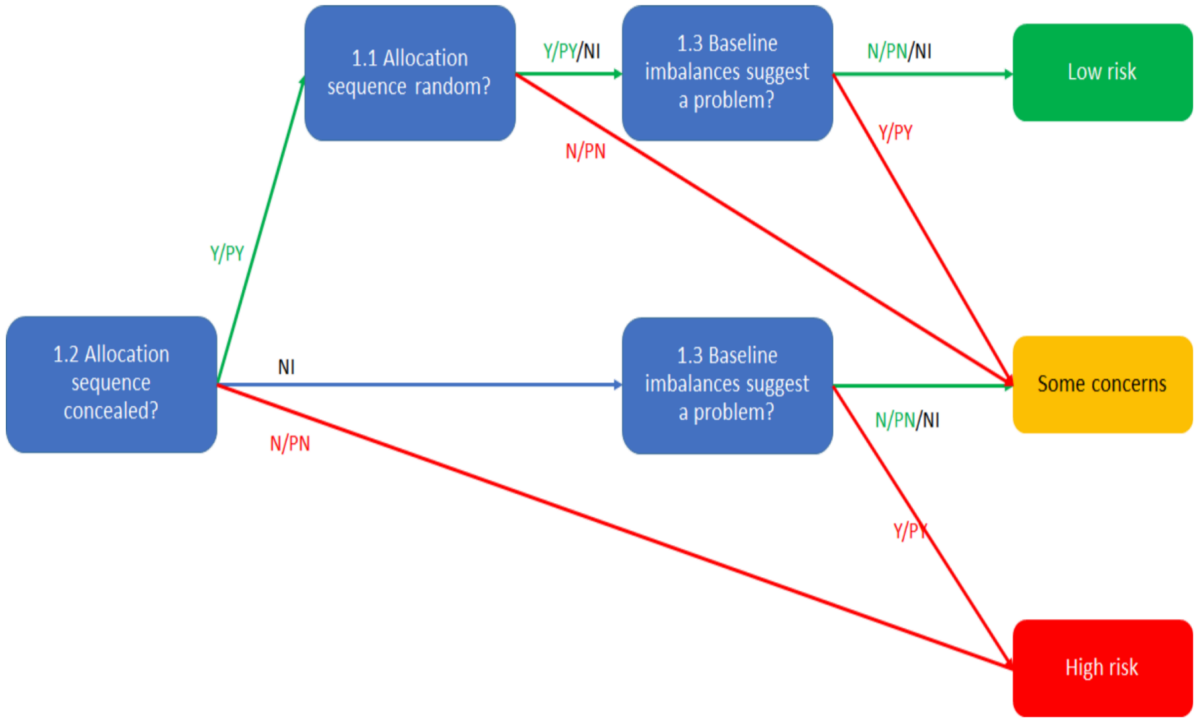
Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Overall risk of bias

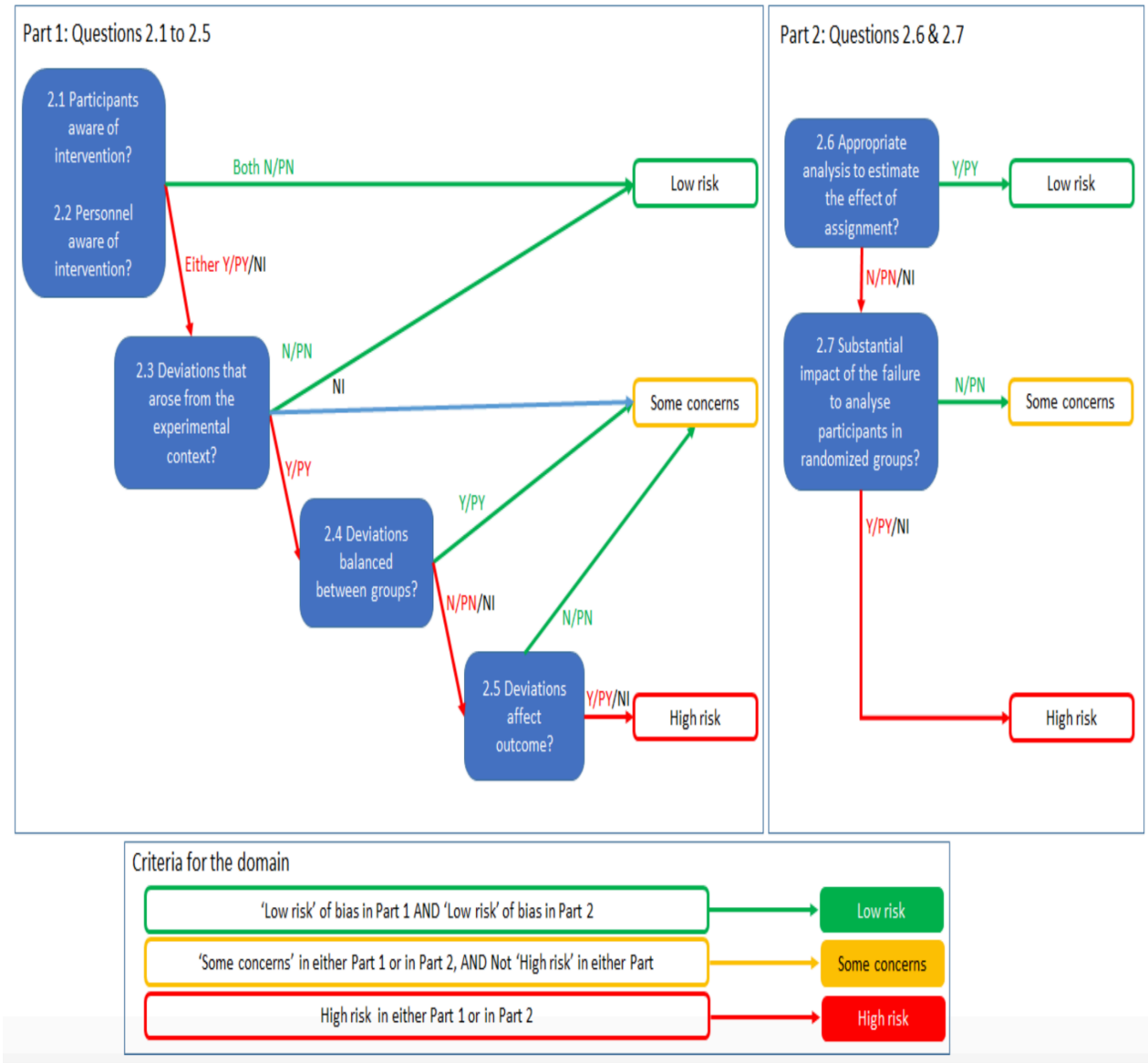
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Annexe 5 Algorithme de jugement de l'outil RoB 2.0

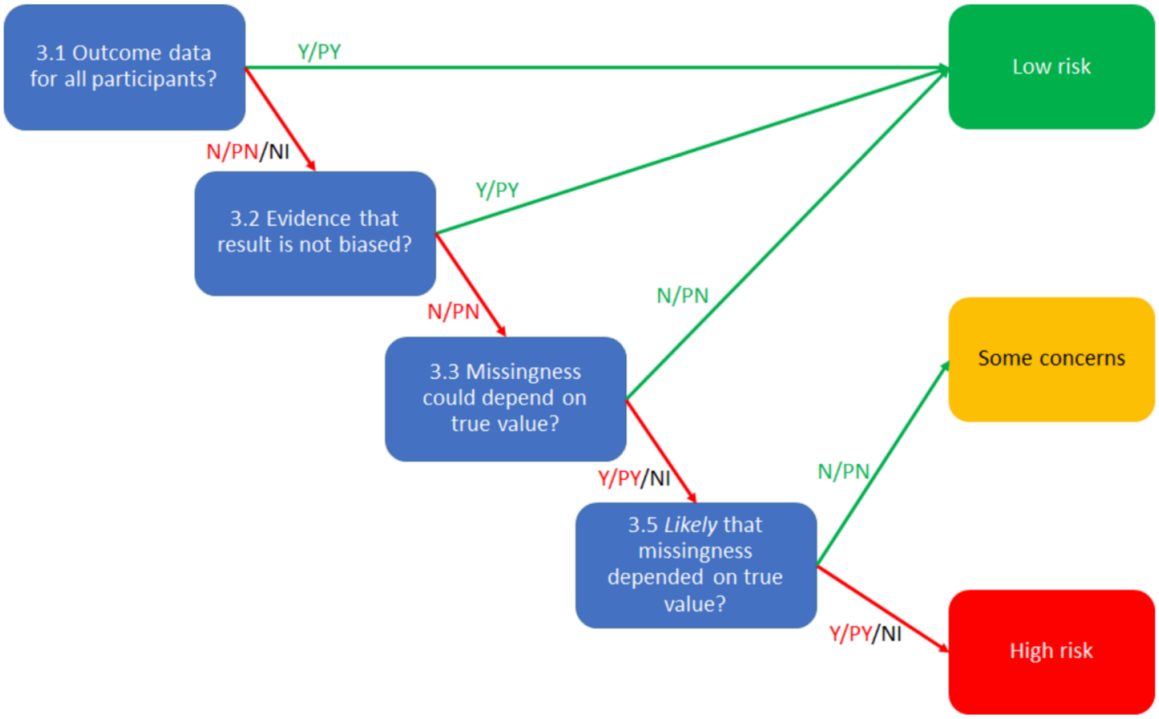
Domain 1 : Randomization process



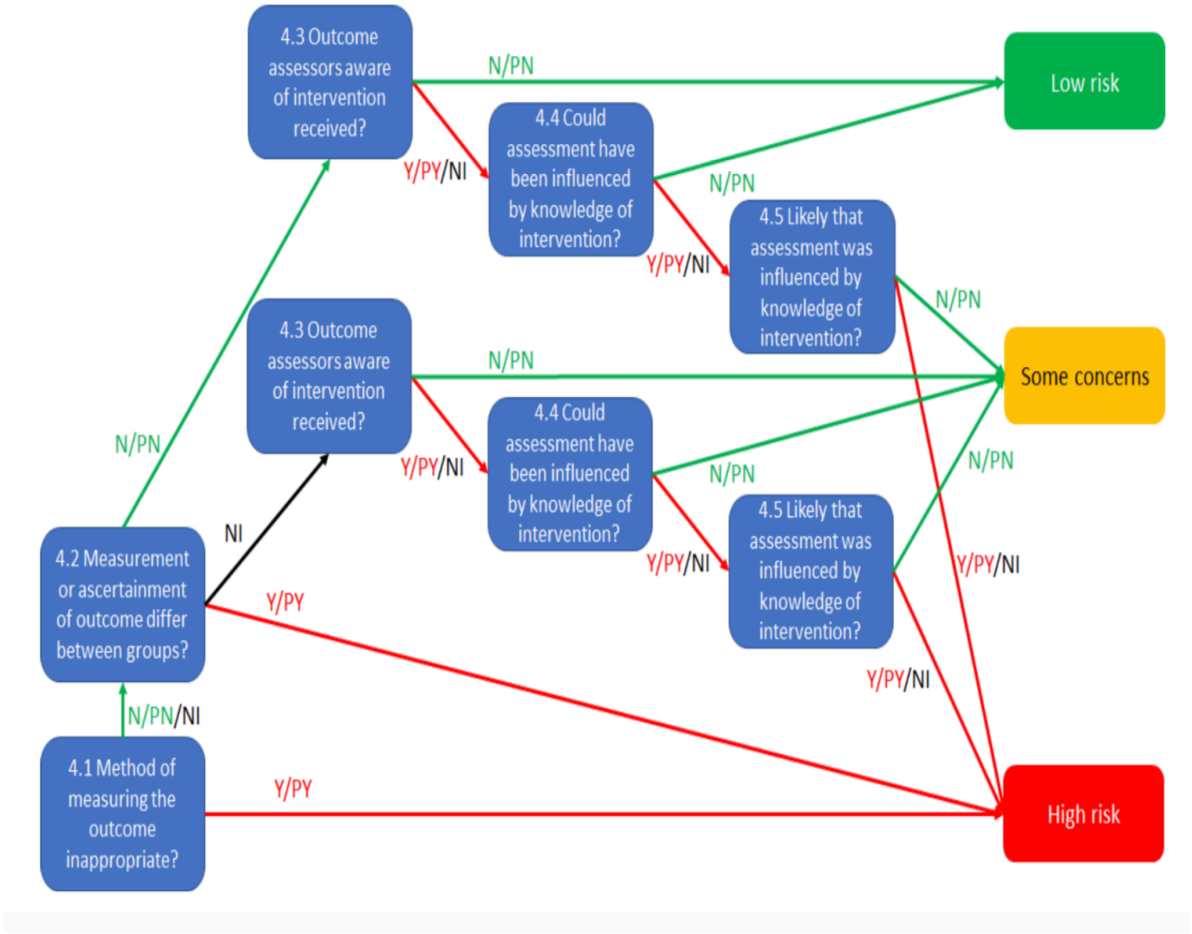
Domain 2 : Deviations from the intended intervention



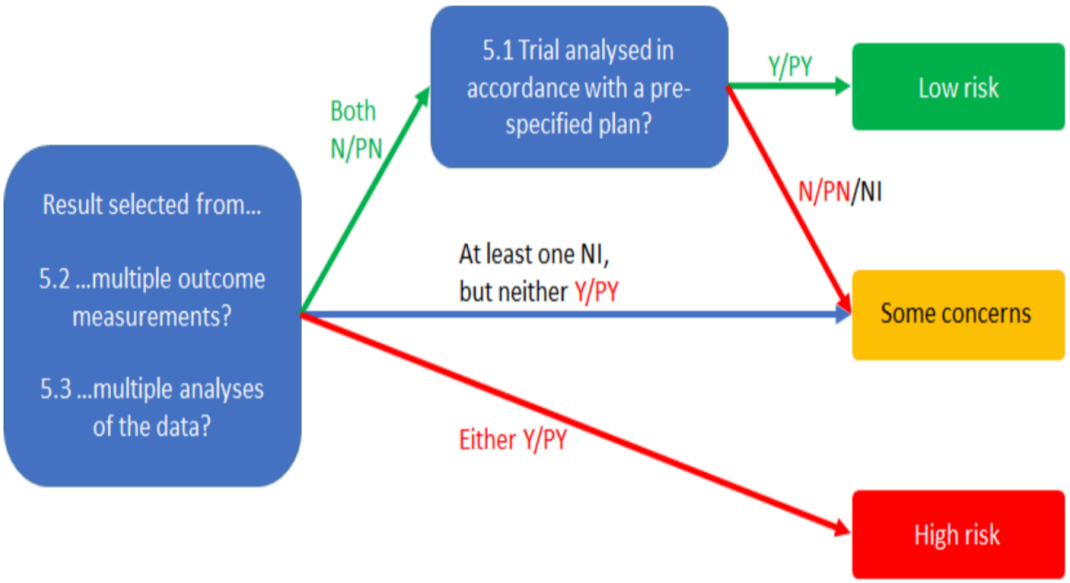
Domain 3 : Missing outcome



Domain 4 : Measurement of the outcome



Domain 5 : Selective reporting



Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Annexe 6 Newcastle Ottawa Scale. For Cohort Study

Group: **Paper:**

Assessment of quality of a cohort study – Newcastle Ottawa Scale	
Selection (tick one box in each section)	
1. Representativeness of the intervention cohort	
a) truly representative of the average, elderly, community-dwelling resident ★	□
b) somewhat representative of the average, elderly, community-dwelling resident ★	□ □
c) selected group of patients, e.g. only certain socio-economic groups/areas	□
d) no description of the derivation of the cohort	
2. Selection of the non intervention cohort	□
a) drawn from the same community as the intervention cohort ★	□
b) drawn from a different source	□
c) no description of the derivation of the non intervention cohort	
3. Ascertainment of intervention	□
a) secure record (eg health care record) ★	□
b) structured interview ★	□
c) written self report	□
d) other / no description	
4. Demonstration that outcome of interest was not present at start of study	□
a) yes ★	□
b) no	
Comparability (tick one or both boxes, as appropriate)	
1. Comparability of cohorts on the basis of the design or analysis	□
a) study controls for age, sex, marital status ★	□
b) study controls for any additional factors (e.g. socio-economic status, education) ★	
Outcome (tick one box in each section)	
1. Assessment of outcome	□
a) independent blind assessment ★	□
b) record linkage ★	□
c) self report	□
d) other / no description	

2.	Was follow up long enough for outcomes to occur	□
	a) yes, if median duration of follow-up >= 6 month ★	□
	b) no, if median duration of follow-up < 6 months	
3.	Adequacy of follow up of cohorts	□
	a) complete follow up: all subjects accounted for ★	□
	b) subjects lost to follow up unlikely to introduce bias: number lost <= 20%, ★ or description of those lost suggesting no different from those followed	□
	c) follow up rate < 80% (select an adequate %) and no description of those lost	□
	d) no statement	

NB Underlined text 'customised' for the intervention being reviewed

NOS – CODING MANUAL FOR COHORT STUDIES

SELECTION

9. Representativeness of the Exposed Cohort (NB exposure = intervention)

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the study sample from some general population. For example, subjects derived from groups likely to contain exposed people are likely to be representative of exposed individuals, while they are not representative of all people the community.

Allocation of stars as per rating sheet

II. Selection of the Non-Exposed Cohort

Allocation of stars as per rating sheet

IV. Ascertainment of Exposure

Allocation of stars as per rating sheet

4) Demonstration That Outcome of Interest Was Not Present at Start of Study

In the case of mortality studies, outcome of interest is still the presence of a disease/ incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

COMPARABILITY

1) Comparability of Cohorts on the Basis of the Design or Analysis

Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

A maximum of 2 stars can be allotted in this category.

OUTCOME

2) Assessment of Outcome

For some outcomes, reference to the medical record is sufficient to satisfy the requirement for confirmation. This may not be adequate for other outcomes where reference to specific tests or measures would be required.

a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (health records, etc.)
b) Record linkage (e.g. identified through ICD codes on database records)
c) Self-report (i.e. no reference to original health records or documented source to confirm the outcome)

d) No description.

3) Was Follow-Up Long Enough for Outcomes to Occur

An acceptable length of time should be decided before quality assessment begins.

4) Adequacy of Follow Up of Cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

Allocation of stars as per rating sheet

Annexe 7 Newcastle Ottawa Scale. For Case Control Study

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✵
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✵
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✵
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✵
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✵
   b) study controls for any additional factor ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✵
   b) structured interview where blind to case/control status ✵
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✵
   b) no

3) Non-Response rate
   a) same rate for both groups ✵
   b) non respondents described
   c) rate different and no designation

The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

Version 19 September 2016

ROBINS-I tool (Stage I): At protocol stage

Section 1.01 Specify the review question

Participants	
Experimental intervention	
Comparator	
Outcomes	

Section 1.02 List the confounding domains relevant to all or most studies

Section 1.03 List co-interventions that could be different between intervention groups and that could impact on outcomes

ROBINS-I tool (Stage II): For each study

Section 1.04 Specify a target randomized trial specific to the study

Design	Individually randomized / Cluster randomized / Matched (e.g. cross-over)
Participants	
Experimental intervention	
Comparator	

Section 1.05 Is your aim for this study…?

☐ to assess the effect of *assignment to* intervention
☐ to assess the effect of *starting and adhering to* intervention

Section 1.06 Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Section 1.07 Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Section 1.08 Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

(i) "Important" confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the domain, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

(i) Confounding domains listed in the review protocol				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?
			Yes / No / No information	Favour experimental / Favour comparator / No information

(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important				
Confounding domain	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding domain measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator?
			Yes / No / No information	Favour experimental / Favour comparator / No information

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that "no statistically significant association" is not the same as "not predictive".

Section 1.09 Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

(i) "Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

(i) Co-interventions listed in the review protocol		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

Section 1.10 Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Signalling questions	Description	Response options
Bias due to confounding		
1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered		Y / PY / PN / N
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.		NA / Y / PY / PN / N / NI
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)		NA / Y / PY / PN / N / NI

Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Questions relating to baseline confounding only		
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?		NA / Y / PY / PN / N / NI
1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA / Y / PY / PN / N / NI
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?		NA / Y / PY / PN / N / NI
Questions relating to baseline and time-varying confounding		
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?		NA / Y / PY / PN / N / NI
1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA / Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to confounding?		Favours experimental / Favours comparator / Unpredictable

Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Bias in selection of participants into the study		
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4		Y / PY / PN / N / NI
2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?		NA / Y / PY / PN / N / NI
2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA / Y / PY / PN / N / NI
2.4. Do start of follow-up and start of intervention coincide for most participants?		Y / PY / PN / N / NI
2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?		NA / Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to selection of participants into the study?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Bias in classification of interventions		
3.1 Were intervention groups clearly defined?		Y / PY / PN / N / NI
3.2 Was the information used to define intervention groups recorded at the start of the intervention?		Y / PY / PN / N / NI
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?		Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to classification of interventions?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Bias due to deviations from intended interventions		
If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?		Y / PY / PN / N / NI
4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?		NA / Y / PY / PN / N / NI
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
4.3. Were important co-interventions balanced across intervention groups?		Y / PY / PN / N / NI
4.4. Was the intervention implemented successfully for most participants?		Y / PY / PN / N / NI
4.5. Did study participants adhere to the assigned intervention regimen?		Y / PY / PN / N / NI
4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to deviations from the intended interventions?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?		Y / PY / PN / N / NI
5.2 Were participants excluded due to missing data on intervention status?		Y / PY / PN / N / NI
5.3 Were participants excluded due to missing data on other variables needed for the analysis?		Y / PY / PN / N / NI
5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?		NA / Y / PY / PN / N / NI
5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?		NA / Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to missing data?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Bias in measurement of outcomes		
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?		Y / PY / PN / N / NI
6.2 Were outcome assessors aware of the intervention received by study participants?		Y / PY / PN / N / NI
6.3 Were the methods of outcome assessment comparable across intervention groups?		Y / PY / PN / N / NI
6.4 Were any systematic errors in measurement of the outcome related to intervention received?		Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to measurement of outcomes?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome *measurements* within the outcome domain?		Y / PY / PN / N / NI
7.2 ... multiple *analyses* of the intervention-outcome relationship?		Y / PY / PN / N / NI
7.3 ... different *subgroups*?		Y / PY / PN / N / NI
Risk of bias judgement		Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Y/PY = 'Yes' or 'Probably yes'; N/PN = 'No' or 'Probably no'; NI = 'No information'

Overall bias		
Risk of bias judgement		Low / Moderate / Serious / Critical /
Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bibliographie

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