Centre universitaire de santé McGill

McGill University Health Centre

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

What is the added clinical value of pre-operative brain natriuretic peptide (BNP/NT-proBNP) in predicting post-operative cardiac complications in patients undergoing non-cardiac surgery across the MUHC RUIS?

Report number: 83

DATE: April 1st, 2020

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

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

by

Nisha Almeida and Nandini Dendukuri

Approved by the Committee of the TAU on April 1st, 2020

TAU Committee

Andre Bonnici, James Brophy, Nandini Dendukuri, Rona Fleming, Todd Lee, Nancy Mayo, Emily McDonald, Maurice McGregor, Carlos Noriega, Kit Racette, Alyson Turner

Suggested citation

Almeida N. and Dendukuri N. What is the added clinical value of pre-operative brain natriuretic peptide (BNP/NT-proBNP) in predicting post-operative cardiac complications in patients undergoing non-cardiac surgery across the MUHC RUIS? Montreal (Canada): Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC); 2019 April 1. Report no. 83. 65 pages

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

ACKNOWLEDGEMENTS

The expert assistance of the following individuals is gratefully acknowledged:

- Gabriele Baldini, Anesthesiologist and Medical Director, Montreal General Hospital Preoperative Centre of the McGill University Health Centre (MUHC)
- Amal Bessissow, Medical Director of the Preoperative Clinic at the Montreal General Hospital
- David Blank, MUHC Site Chief, Division of Biochemistry, Department of Clinical Laboratory Medicine - MUHC
- Andre Dascal, Chief, Department of Clinical Laboratory Medicine – MUHC and Medical Director - OPTILAB Montreal-MUHC Cluster
- Julie St-Cyr, Chief, Division of Biochemistry, Department of Clinical Laboratory Medicine - MUHC

REPORT REQUESTOR

This report was requested by David Blank on May 9th, 2019. The completed report will be presented to Dr. Andre Dascal, Director of OPTILAB Montreal-MUHC Cluster.

TYPES OF RECOMMENDATIONS ISSUED BY THE TAU COMMITTEE

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

DISCLAIMER

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

- There is no consensus on pre-operative clinical risk stratification methods to assess post-operative cardiovascular complications. The various methods include clinical risk indices, non-invasive cardiac testing, and the use of cardiac biomarkers.
- Cardiac biomarkers are an attractive option because they are non-invasive, rapidly available, and inexpensive. Yet, their utility in patients undergoing non-cardiac surgery is unclear.
- The objective of this report was to evaluate the evidence on the added clinical value of pre-operative BNP/NT-proBNP testing in predicting post-operative cardiac complications in patients undergoing major non-cardiac surgery, in light of the 2016 Canadian Cardiovascular Society guidelines recommending routine natriuretic peptide (NP) testing in this population.
- We first evaluated the evidence included in the Canadian guidelines, and then performed a literature review of studies published since June 2012, the date of the literature search of the most recent meta-analysis included in the Canadian guidelines.
- The Canadian guidelines included three meta-analyses, including an individual-patient data meta-analysis by Rodseth et al. in 2014, which was instrumental in influencing their recommendations. We further identified two more meta-analyses and 30 observational studies.
- The majority of studies found an association between elevated pre-operative NP levels and cardiac complications, particularly death and non-fatal myocardial infarction. However, the individual studies were often small and did not control for important risk factors. The meta-analyses were limited by the high between-study heterogeneity arising from including various surgical populations, different outcome definitions, and wide range of NP cutoffs.
- The European and American guidelines also considered the Rodseth meta-analysis but concluded that the evidence was not sufficient to warrant a recommendation of pre-operative NP testing in all non-cardiac surgery patients.
- Importantly, there is no evidence that targeting pre-operative NP levels will reduce post-operative complications. Furthermore, there are no data on the impact on service and cost of routine pre- and post-operative biomarker testing.

RÉSUMÉ

- Il n'existe aucun consensus sur les méthodes de stratification des risques cliniques préopératoires pour évaluer les complications cardiovasculaires postopératoires. Les diverses méthodes incluent les indices de risques clinique, les évaluations cardiaques non invasives et l'utilisation des biomarqueurs cardiaques.

- Les biomarqueurs cardiaques représentent une option intéressante car ils sont non-invasifs, disponibles rapidement et peu coûteux. Par contre, leur utilité n'est pas évidente chez les patients subissant une chirurgie autre que cardiaque.

- L'objectif de ce rapport était d'évaluer les preuves sur la valeur clinique ajoutée des tests préopératoires BNP/NT-proBNP pour prédire les complications cardiaques postopératoires chez les patients subissant une chirurgie majeure autre que cardiaque, à la lumière des lignes directrices de 2016 de la Canadian Cardiovascular Society recommandant une évaluation de routine des peptides natriurétiques (NP) chez cette population.

- Premièrement, nous avons évalué les preuves des lignes directrices du guide Canadian guidelines, puis réalisé une revue de la littérature des études publiées depuis le mois de juin 2012, date correspondant à la recherche des plus récentes méta-analyses incluses dans le Canadian guidelines.

- Le Canadian guidelines comprenait trois méta-analyses, incluant une méta-analyse de Rodseth et al. (2014) portant sur des patients donnés, ce qui contribua à influencer leurs recommandations. De plus, nous avons identifié deux autres méta-analyses et 30 études d'observation.

- La majorité de ces études identifièrent une relation entre les niveaux NP préopératoires élevés et les complications cardiaques, incluant en particulier le décès et l'infarctus du myocarde non mortel. Cependant, les études sur des patients donnés étaient souvent de petite taille et ne tenaient pas compte des facteurs de risque importants. Les méta-analyses étaient limitées par une forte hétérogénéité entre les études résultant de l'inclusion de populations chirurgicales variées, de différentes définitions pour les résultats et d'une large gamme de seuils NP.

- Les lignes directrices des guides européens et américains ont aussi considéré la méta-analyse de Rodseth mais ont conclu que les preuves n'étaient pas suffisantes

pour justifier la recommandation de tests NP préopératoires chez tous les patients subissant une chirurgie autre que cardiaque.

- Il est important de noter qu'il n'y a aucune preuve que le ciblage des niveaux NP préopératoires réduira les complications postopératoires. De plus, il n'y a aucune donnée de l'impact des tests de routine des biomarqueurs préopératoires et postopératoires sur les services et les coûts.

LIST OF ABBREVIATIONS

AUC	Area under the receiver operator curve
BNP	B-type or brain natriuretic peptide
CCTA	Computed tomographic angiography
CI	Confidence interval
hs-cTnT	High-sensitivity cardiac troponin T
HR	Hazard ratio
HTA	Health technology assessment
INESSS	Institut National d'Excellence en Santé et en Service Sociaux
IPD	Individual-patient data
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MUHC	McGill University Health Centre
NICE	National Institutes for Health and Clinical Excellence
NP	Natriuretic peptide
NRI	Net reclassification improvement index
NSQIP MICA	National Surgical Quality Improvement Program risk index for Myocardial Infarction and Cardiac Arrest
NT-proBNP	Amino-terminal fragment proBNP
OR	Odds ratio
RCRI	Revised cardiac risk index
RCT	Randomized controlled trial
ROC	Receiver operator characteristics curve
TAU	MUHC Technology Assessment Unit

EXECUTIVE SUMMARY

Background

The use of cardiac biomarkers, such as natriuretic peptides (NP), to evaluate perioperative risk and predict post-operative complications is attractive given their ease of availability, non-invasiveness and low cost. However, their utility in adult patients undergoing major non-cardiac surgery is unclear.

Objectives

The objective of this report is to evaluate the evidence on the added clinical value of pre-operative BNP/NT-proBNP testing in predicting post-operative cardiac complications in patients undergoing major non-cardiac surgery, within the context of the 2017 Canadian Cardiovascular Society guidelines recommendation for routine NP testing in this population.

Methods

We first evaluated the three meta-analyses included in the Canadian guidelines. We then reviewed the literature to identify any new studies published since June 2012, the last search date of the most recent meta-analysis included in the Canadian guidelines. We included randomized controlled trials (RCT), cohort studies or systematic reviews and meta-analyses of BNP/NT-proBNP for predicting post-operative cardiac complications following major non-cardiac surgery. We also identified clinical guidelines pertaining to the use of perioperative NP in non-cardiac surgery patients.

Results: Literature review

In addition to the three meta-analyses included in the Canadian guidelines, we identified two further meta-analyses and 30 observational studies published since June 2012. There are no randomized controlled trials (RCTS) that have evaluated the added clinical value of pre-operative BNP/NT-proBNP testing in predicting post-operative cardiac complications.

- The majority of the studies found an association between elevated pre-operative NP and post-operative cardiac complications, particularly death and non-fatal myocardial infarction. The individual patient data meta-analysis by Rodseth et al. in 2014 reported an odds ratio of 1.90 (95%CI: 1.44, 2.40) for death and nonfatal MI at 30 days with a pre-operative BNP above 92 pg/ml or NT-proBNP above 300 ng/ml, after adjusting for RCRI≥3, urgent vs non-urgent surgery, vascular vs other

surgeries, and age. This study was instrumental in influencing the final recommendation in the Canadian guidelines.

- However, all studies had serious limitations. Individual studies had low event rates, did not adjust for major risk factors, and had assessed NP levels at differing time points. The meta-analyses were limited by large between-study heterogeneity due to the inclusion of varied surgical populations, wide NP cut off ranges, and different outcome definitions. They were also not able to adjust for important confounders.

- While studies that assessed predictive power using the c-statistic (or area under the curve (AUC)) or the net reclassification improvement index (NRI) found that the addition of NP generally improved the ability of the revised cardiac risk index (RCRI) to predict cardiac complications, neither of these metrics provided information on the clinical significance of such improvements.

- The Rodseth study found that their NP cutoffs had high negative predictive value (95%) i.e. the probability of not having the outcome given low NP levels. Hence, there may be some clinical utility of NP to rule out low risk patients.

- To date, there is no evidence on the clinical utility and cost of intervening on elevated NP levels in all patients undergoing non-cardiac surgery. For example, Rodseth et al. found that 22% of patients with NP values above the cutoff had post-operative MI or died, which means that 78% of those with high NP values would receive unnecessary monitoring with ECG.

- The European and American guidelines, both published in 2014, also considered the Rodseth meta-analysis but concluded that the evidence was not sufficient to recommend use of pre-operative NP testing in all non-cardiac surgery patients.

Experience at the MUHC

- On July 23rd 2018, the Clinical Practice Review Committee of the MUHC issued a directive on pre-operative diagnostic tests for all adult patients undergoing elective surgery requiring at least one overnight stay. Following the 2017 Canadian guidelines, it recommended pre-operative BNP testing for adult patients undergoing inpatient surgery who are ≥65 years or between 45 and 65 years with significant cardiovascular disease or an RCRI score ≥1. A BNP value ≥92 ng/ml was considered abnormal.

- Pending a review of pre-operative BNP testing by TAU, routine testing of pre-operative BNP for non-cardiac surgery has been permitted at the MUHC since June

2019. Pre-operative BNP samples are sent to St-Mary's hospital once a day; the McGill optilab cluster plans to standardize to NT-proBNP in the future, pending verification of the assay.

- From January 1st to September 30th, 2019, 1546 pre-operative BNP tests were ordered for both cardiac and non-cardiac surgeries across all MUHC sites.

Costs

The cost of a BNP test across the province of Quebec for 2019-2020, published by the provincial health ministry, is CAD 18.00, while that of NT-proBNP is CAD 19.50. It is estimated that approximately 60-65 patients receive BNP/NT-proBNP testing per month at each of the RVH and MGH clinics. Assuming an approximate cost of $20 per test, the annual budget impact would be $28,800 to $31,200. These costs could increase if BNP/NT-proBNP testing is expanded to out-patient surgeries as well, and if BNP/NT-proBNP thresholds to classify high risk patients are lowered.

CONCLUSIONS

- Studies suggest that elevated levels of pre-operative BNP/NT-proBNP is associated with cardiac complications, most notably cardiac death and nonfatal myocardial infarction, in patients undergoing major non-cardiac surgery.
- A 2014 individual-patient data meta-analysis established that a pre-operative BNP cutoff of 92 ng/l or an NTpro-BNP cutoff of 312 ng/l was associated with the composite end-point of death and myocardial infarction at 30 days and ≥180 days post-surgery, after accounting for age, severe RCRI score, and type and urgency of surgery. These findings were instrumental in changing the 2017 Canadian guidelines.
- However, the quality of the evidence from the studies included in this review is weak. The meta-analyses had high heterogeneity stemming from the inclusion of studies with different populations, wide ranges of NP cutoffs, and variation in outcome definitions. The individual studies often had very few events, and most did not adjust for important confounders. Additionally, there is no consensus on NP cutoff, and those established by Rodseth et al. have not been validated in different settings.

- Metrics such as the AUC and NRI indicate that natriuretic peptide (NP) levels add to the ability of the revised cardiac risk index (RCRI) to predict cardiac complications. However, they do not allow us to interpret the clinical relevance or utility of adding NP to clinical practice in this population. Furthermore, there are several markers, such as cardiac troponin, that are also strongly predictive of post-operative cardiac complications, and the added value of BNP relative to such markers has not been established.

- There is some evidence that NP cutoffs have good negative predictive value, indicating NP may have some utility in ruling out low-risk patients for further testing. However, the positive predictive value is low, indicating that large numbers of patients will be subjected to unnecessary daily testing. To date, there have been no evaluations on the clinical impact and cost of such interventions.

RECOMMENDATIONS

- Given that the BNP/NT-proBNP blood test is already available to physicians at the MUHC, but also given that there is no evidence of its clinical impact in patients undergoing major elective inpatient non-cardiac surgery, we recommend an **Approval for Evaluation**, conditional on the following:

    - Adherence to a protocol that is more stringent than the current Canadian guidelines in that the assessment of the patient's risk of post-operative cardiac outcomes is based not only on age but also on the Revised Cardiac Risk Index (RCRI) and clinical judgment as follows:
        - Age ≥45 years

      AND
        - (Significant cardiovascular disease OR RCRI ≥1 OR Clinical judgement)

    - Development of a research protocol to systematically document the following for all patients receiving the BNP/NT-proBNP test:
        - Patient characteristics including age, sex, RCRI and co-morbidities;
        - Pre- and post-operative troponin testing;
        - post-operative follow-up including number of cardiology consults, length of stay, and cardiac complications.

- The protocol will be developed jointly by the clinical experts and TAU to create a standardized process to record and analyse locally collected data. The TAU Policy Committee will be apprised regularly of the progress.

- This recommendation will be reassessed in 1 year after evaluation of local data and/or evidence in the scientific literature on clinical impact.

SOMMAIRE

Contexte

L'utilisation de biomarqueurs cardiaques, tel les peptides natriurétiques (NP), est attrayante pour évaluer les risques peropératoires et prédire les complications postopératoires étant donné leur disponibilité, leur caractère non invasif et leur faible coût. Par contre, leur utilité chez les patients adultes subissant une chirurgie majeure autre que cardiaque n'est pas évidente.

Objectifs

L'objectif de ce rapport est d'évaluer les preuves de la valeur clinique ajoutée des tests préopératoires BNP/NT-proBNP pour prédire les complications cardiaques postopératoires chez les patients subissant une chirurgie majeure autre que cardiaque, dans le contexte des lignes directrices de 2017 du *Canadian Cardiovascular Society* recommandant l'évaluation de routine des peptides natriurétiques chez cette population.

Méthodologie

Nous avons premièrement évalué les trois méta-analyses comprises dans le *Canadian guidelines*. Par la suite, nous avons fait une revue de la littérature pour identifier toutes nouvelles études publiées depuis le mois de juin 2012, date correspondant à la recherche des plus récentes méta-analyses incluses dans le *Canadian guidelines*. Nous avons inclus les études randomisées (RCT), les études de cohortes ou les revues systématiques et les méta-analyses du BNP/NT-proBNP prédisant les complications cardiaques postopératoires suite à une chirurgie majeure autre que cardiaque. Nous avons aussi identifié les lignes directrices cliniques concernant l'utilisation du NP peropératoire chez les patients subissant une chirurgie autre que cardiaque.

Résultats : Revue de la littérature

En plus des trois méta-analyses comprises dans le *Canadian guidelines*, nous avons identifié deux autres méta-analyses et 30 études d'observation publiées depuis le mois de juin 2012. Aucune étude randomisée (RCT) n'a évalué la valeur clinique ajoutée des tests préopératoires du BNP/NT-proBNP prédisant les complications cardiaques postopératoires.

- La plupart de ces études ont trouvé une association entre les NP préopératoires élevés et les complications cardiaques postopératoires, en particulier le décès et l'infarctus du myocarde non mortel. La méta-analyse de Rodseth et al. (2014) avec des patients donnés mentionna un rapport de cotes de 1.90 (95%CI: 1.44, 2.40) pour le décès et l'infarctus du myocarde non mortel après 30 jours avec un BNP préopératoire supérieur à 92 pg/ml ou un NT-proBNP supérieur à 300 ng/ml après un ajustement pour le RCRI ≥3, une chirurgie urgente vs non urgente, des chirurgies vasculaires vs d'autres chirurgies et l'âge. Cette étude contribua à influencer la recommandation finale dans le Canadian guidelines.

- Cependant, toutes les études avaient de sérieuses restrictions. Les études sur des patients donnés avaient un faible taux d'événements, n'avaient pas d'ajustements pour les principaux facteurs de risque et avaient des niveaux NP prédéfinis pour différents moments dans le temps. Les méta-analyses étaient limitées par une forte hétérogénéité entre les études résultant de l'inclusion de populations chirurgicales variées, d'une large gamme de seuils NP et de différentes définitions pour les résultats. Ils n'étaient pas non plus en mesure de s'adapter aux facteurs de confusion importants.

- Tandis que les études qui avaient évalué le pouvoir prédictif de l'utilisation de la statistique C (ou la surface sous la courbe) (AVC) ou de l'index d'amélioration du reclassement net (NRI) et avaient trouvé que l'ajout du NP améliorait généralement la capacité de l'index de risques cardiaques révisé (RCRI) pour prédire les complications cardiaques, aucune de ces mesures n'avait fourni d'information sur la signification clinique de tels améliorations.

- L'étude de Rodseth a révélé que leurs seuils NP avaient une valeur prédictive fortement négative (95%) i.e. la probabilité de ne pas avoir le résultat escompté étant donné les faibles niveaux NP. En fait, il pourrait y avoir une certaine utilité clinique du NP pour exclure les patients à faible risque.

- À ce jour, il n'y a pas de preuve de l'utilité clinique ainsi que des coûts résultant des interventions associées à des niveaux NP élevés chez tous les patients subissant une chirurgie autre que cardiaque. Par exemple, Rodseth et al. trouvèrent que 22% des patients avec des valeurs NP au-dessus du seuil avaient un infarctus du myocarde postopératoire ou décédaient, ce qui signifie que 78% des patients avec une valeur NP élevée bénéficieraient d'une surveillance ECG inutile.

- Les lignes directrices européennes et américaines, toutes deux publiées en 2014, avaient aussi tenu compte de la méta-analyse de Rodseth mais avaient conclu que les preuves n'étaient pas suffisantes pour recommander l'utilisation des tests NP préopératoires chez tous les patients subissant une chirurgie autre que cardiaque.

Expérience au CUSM

- Le 23 juillet 2018, le comité d'examen des pratiques cliniques du Centre Universitaire de Santé McGill (Clinical Practice Review Committee) émit une directive concernant les tests diagnostiques préopératoires pour tous les patients adultes subissant une chirurgie élective impliquant au moins une nuitée. Suivant les lignes directrices de 2017 du Canadian guidelines, ce comité recommanda les tests préopératoires du BNP pour les patients adultes hospitalisés subissant une chirurgie, âgés de 65 ans ou plus, ou âgés entre 45 et 65 ans, avec une maladie cardiovasculaire importante ou avec une valeur RCRI ≥1. Une valeur BNP ≥92 ng/ml était considérée anormale.

- En attente d'une revue des tests préopératoires du BNP par le Technology Assessment Unit (TAU), les tests préopératoires de routine du BNP pour les chirurgies autre que cardiaques sont permis au Centre Universitaire de Santé McGill depuis le mois de juin 2019. Les échantillons BNP préopératoires sont envoyés à l'Hôpital St-Mary's une fois par jour; le McGill optimal cluster prévoit une normalisation du NT-proBNP dans le futur, en attente de la vérification de l'essai.

- Du 1er janvier au 30 septembre 2019, 1546 tests BNP préopératoires ont été commandés pour les chirurgies cardiaques et autre que cardiaques, par tous les sites du Centre Universitaire de Santé McGill.

Coûts

Pour les années 2019-2020, le coût d'un test BNP dans la province de Québec est de 18,00 $ publié par le Ministère de la Santé, et de 19,50 $ pour le test NT-proBNP. On estime qu'environ 60-65 patients ont un test BNP/NT-proBNP par mois, à la fois aux cliniques de l'Hôpital Général de Montréal et de l'Hôpital Royal-Victoria. Si l'on évalue à environ 20 $ le coût d'un test, l'impact budgétaire annuel varierait entre 28 800 $ et 31 200 $. Ces coûts pourraient augmenter si le test BNP/NT-proBNP était aussi appliqué aux chirurgies ambulatoires et si le seuil du test BNP/NT-pro était abaissé pour le classement des patients à risque élevé.

CONCLUSIONS

- Les études nous suggèrent que les niveaux élevés des tests BNP/Nt-proBNP préopératoires sont associés à des complications cardiaques, notamment le décès et l'infarctus du myocarde non mortel, chez les patients subissant une chirurgie majeure autre que cardiaque.

- En 2014, une méta-analyse impliquant des patients donnés a établi qu'un seuil BNP de 92 ng/l ou un seuil NTpro-BNP de 312 ng/l étaient associés, à critères d'évaluation combinés, au décès et à l'infarctus du myocarde à 30 jours et ≥ 180 jours après chirurgie, tout en tenant compte de l'âge, d'un score RCRI élevé, du type et de l'urgence de la chirurgie. Ces résultats contribuèrent à modifier les lignes directrices du Canadian guidelines en 2017.

- Cependant, la qualité des preuves des études comprises dans cette revue est faible. La méta-analyse montrait une grande hétérogénéité résultant de l'inclusion d'études avec des populations différentes, d'une large gamme de seuils NP et d'une variation dans la définition des résultats. Les études avec des patients donnés avaient peu d'événements et la plupart n'avaient pas d'ajustements pour les facteurs de confusion importants.

- Par ailleurs, il n'y a pas de consensus sur le seuil NP, et ceux établis par Rodseth et al. n'ont pas été validés dans des contextes différents.

- Des paramètres tels que l'AUC et le NRI montrent que les niveaux de peptide natriurétique (NP) ajoutent à la capacité de l'index révisé de risques cardiaques (RCRI) de prédire les complications cardiaques. Cependant, ils ne nous permettent pas d'interpréter la pertinence clinique ou l'utilité d'ajouter le paramètre NP à la pratique clinique chez cette population. De plus, il existe plusieurs marqueurs, telle la troponine cardiaque, qui peuvent aussi nettement prédire les complications cardiaques postopératoires, tout en sachant que la valeur ajoutée du BNP à ces marqueurs n'a pas été établie.

- Il existe des preuves selon lesquelles les seuils de NP ont une valeur de prédiction négative intéressante, indiquant que le NP peut avoir quelque utilité en éliminant les patients avec de faibles risques et pouvant être sujets à plus de tests. Cependant, une faible valeur de prédiction positive peut indiquer qu'un grand nombre de patients seront soumis à des tests quotidiens inutiles. À ce jour, il n'y a aucune évaluation de l'impact clinique et des coûts résultant de telles interventions.

RECOMMANDATIONS

- Étant donné que le test sanguin BNP/NT-proBNP est déjà disponible pour les médecins au CUSM mais aussi en tenant compte qu'il n'y a aucune preuve de son impact clinique chez les patients subissant une chirurgie majeure autre que cardiaque mais élective, nous recommandons une Approbation pour évaluation, selon les conditions suivantes:
    - Une adhésion à un protocole plus rigoureux que celui du guide Canadian guidelines actuel où l'évaluation des risques du patient concernant les résultats cardiaques postopératoires n'est pas basée uniquement sur l'âge mais aussi sur l'index du risque cardiaque révisé (RCRI) et sur le jugement clinique comme suit:
        - Âge ≥45 ans

        ET
        - Une maladie cardiovasculaire importante OU un RCRI≥1 OU un jugement clinique.
    - L'élaboration d'un protocole de recherche pour documenter de façon systématique les paramètres suivants, pour tous les patients recevant le test BNP/NT-proBNP:
        - Les données du patient incluant l'âge, le sex, le RCRI et les facteurs de comorbidité;
        - Les tests préopératoires et postopératoires de troponine;
        - Le suivi postopératoire incluant le nombre de consultations en cardiologie, la durée du séjour et les complications cardiaques.
- Le protocole sera développé conjointement avec les experts cliniciens et le TAU (Technology Assessment Unit), pour créer un processus standardisé permettant d'enregistrer et d'analyser localement les données colligées. Le TAU Policy Committee sera régulièrement informé des progrès.
- Cette recommandation sera réévaluée dans un an après l'évaluation des données recueillies et/ou de preuves de la littérature scientifique en regard de l'impact clinique.

WHAT IS THE ADDED CLINICAL VALUE OF PRE-OPERATIVE BRAIN NATRIURETIC PEPTIDE [BNP] AND N-TERMINAL FRAGMENT OF PROBNP [NT-PROBNP] IN PREDICTING POST-OPERATIVE CARDIAC COMPLICATIONS FOLLOWING NON-CARDIAC SURGERY?

1. BACKGROUND

Risk of post-operative cardiac complications depends on the type of surgery and patient risk factors. 30-day mortality in patients undergoing major non-cardiac surgery with at least one cardiac risk factor is estimated to be 0.5 to 2 %.[1,2] However, there is no consensus on pre-operative clinical risk stratification methods to assess post-operative cardiovascular complications. Methods for estimating peri-operative cardiac risk complications fall into three broad categories: clinical risk indices; non-invasive cardiac testing; and the use of cardiac biomarkers:[3]

1.1 Risk indices:

Generic and Bayesian clinical risk indices have been developed to assess peri-operative risk of cardiac events in patients undergoing non-cardiac surgery. Generic indices (Lee, Goldman, Larsen and Gilbert) include a number of predictors (e.g. cardiac history, diabetes, type of surgery) to calculate a score indicative of post-operative risk.[4-7] The model developed by Lee et al., also known as the Revised Cardiac Risk Index (RCRI) is one of the more commonly used indices, and has been recommended by the most recent Canadian guidelines.[8] The RCRI includes six risk factors (high risk surgery; ischemic heart disease; prior congestive heart failure; stroke or transient ischemic attack; use of insulin; creatinine >2mg/dl) worth one point each, with scores ≥3 indicating a 9.1% risk of a major cardiac complication (myocardial infarction, pulmonary edema, ventricular fibrillation or primary cardiac arrest, and complete heart block). However, it is not generalizable to patients undergoing emergency surgery. Recently, the National Surgical Quality Improvement Program risk index for Myocardial Infarction and Cardiac Arrest (NSQIP MICA) was shown to be a better predictor of risk in comparison with the RCRI;[9] however, this index also has some methodological issues.[3]

Bayesian risk indices (Kumar and Detsky) estimate an individual's risk of peri-operative cardiac complications (the post-test probability) by multiplying the hospital average rate of cardiac events (the pre-test probability) with a patient's individual risk score (converted into a likelihood ratio using the sensitivity and specify of each risk category) derived from a risk index incorporating a variety of predictors.[10,11] While these models compared well with the RCRI index in terms of predictive ability, the indices used to derive individual risk scores have not been validated in different settings.[12]

The main concern with clinical cardiac risk indices is that they fail to capture underlying risk in patients with asymptomatic disease, and in non-ambulatory patients in whom cardiac disease symptoms may be missed due to immobility.[12,13] Hence, researchers have sought to evaluate the added value of other methods, including non-invasive cardiac testing, and biomarkers.

1.2 Non-invasive testing:

Several non-invasive diagnostics tests for peri-operative risk stratification exist, including ambulatory electrocardiography, exercise electrocardiography, radionuclide ventriculography, myocardial perfusion scintigraphy, dobutamine stress echocardiography, and dipyridamole stress echocardiography. Several of these have been evaluated in meta-analyses to assess their ability to predict per-operative cardiac complications.[14,15] Recent evidence indicates there is no added value of these tests in cardiac risk stratification.[3]

For example, an international, multi-centre, prospective study (n=955) evaluating the ability of coronary computed tomographic angiography (CCTA) to predict cardiac complications found that, while CCTA was able to correctly reclassify 22% of patients with the outcome versus the RCRI alone, it also incorrectly classified 11% of patients without the event.[16]

1.3 Cardiac biomarkers:

Cardiac natriuretic peptides (NPs) are a family of hormones secreted by cardiac muscle cells in response to stretching of the atrial or ventricular wall. These hormones play an important role in maintaining sodium and blood volume homeostasis, and have thus come under intense scrutiny as markers of cardiac dysfunction.[17]

B-type or brain natriuretic peptides (BNP), and its biologically inert form, amino-terminal fragment (NT-proBNP), are released from the myocardium as a result of myocardial stress, chiefly due to filling pressure and volume overload states.[18] Plasma NT-proBNp levels are higher than that of BNP because the latter has a shorter half-life. Studies have demonstrated that elevated NP concentrations can predict cardiovascular complications in healthy adults, and pre-operative BNP levels have been used to screen cardiac surgery patients for post-operative cardiac complications.

However, the utility of NPs in predicting post-operative cardiac complications in non-cardiac surgery patients is unclear.

2. CONTEXT

In 2016 the Canadian Cardiovascular Society released guidelines on perioperative cardiac risk assessment and management for patients undergoing non-cardiac surgery, in which they recommended BNP/NT-proBNP testing for all patients undergoing elective surgery who are ≥65 years and with an RCRI score ≥1, or who are aged 45-64 years with significant cardiovascular disease (Strong recommendation, moderate quality of evidence).[8]

Due to the expected increased burden on laboratory testing with this new recommendation, the TAU was commissioned to review the added value of BNP/NT-proBNP in predicting post-operative cardiac complications in patients undergoing non-cardiac surgery.

3. OBJECTIVES

The objective of this report is to:

- evaluate the evidence on the added clinical value of pre-operative BNP/NT-proBNP testing in predicting post-operative cardiac complications in patients undergoing major non-cardiac surgery

4. METHODS

4.1 Literature search and quality assessment

We first reviewed the three meta-analyses included in the 2017 Canadian guidelines. We then conducted a literature search to identify studies of pre-operative BNP/NT-proBNP for predicting cardiac complications in non-cardiac surgery patients published since June 2012, the date of the literature search of the most recent meta-analysis included in the Canadian guidelines.

We searched Pubmed, the Cochrane library and the health technology assessment (HTA) database of the Centre for Reviews and Dissemination, using the following search strategy: ((((surgery) OR operative) AND noncardiac)) AND ((natriuretic peptide) AND ("2014"[Date - Publication] : "3000"[Date - Publication])). The most recent search was conducted on 12 June 2019. Figure 1 shows our selection process.

Our literature search was limited to randomized controlled trials (RCT), cohort studies or systematic reviews and meta-analyses of BNP/NT-proBNP for predicting post-operative cardiac complications following major non-cardiac surgery. Thus, uncontrolled studies, case reports, and studies or reviews evaluating other risk stratification techniques were excluded. We also identified relevant HTAs and clinical guidelines assessing the use of BNP for risk stratification of non-cardiac surgery patients.

4.2 MUHC experience

We describe the current policy for cardiac risk stratification of patients undergoing major non-cardiac surgery at the MUHC.

5. LITERATURE REVIEW

5.1 Use of plasma BNP in non-surgical patients to predict cardiovascular outcomes

In 2004, **Wang et al.** published a prospective analysis of 3,346 participants without heart failure in the Framingham Offspring Cohort.[19] The authors evaluated the association between baseline BNP levels and various cardiovascular outcomes (death from any cause, a first major cardiovascular event, heart failure, atrial fibrillation, stroke or transient ischemic attack, and coronary heart disease) over a mean follow-up period of 5.2 years.

In multivariable survival analysis adjusting for age, sex, the presence or absence of hypertension and diabetes, the ratio of total to high-density lipoprotein cholesterol, body-mass index, serum creatinine level, and smoking status, the authors report a hazard ratio (HR) for every 1 SD increase in log BNP of 1.27 (1.06, 1.52) for all-cause death, 1.28 (1.03, 1.59) for first cardiovascular event, and 1.77 (1.31, 2.41) for heart failure. Similar results were found for NT-proBNP. However, neither NP was associated with coronary heart disease events. Values above the 80th percentile were associated with increased risk for all outcomes; these thresholds were 20.0 ng/l for men and 23.3 ng/l for women, which were far lower than contemporary thresholds used for the diagnosis of heart failure (80 to 100 ng/l).

To evaluate whether NP levels are associated with increased risk of cardiac outcomes because of their effect on left ventricular function, the authors adjusted their analyses for increased left ventricular mass, left atrial diameter, or left ventricular systolic dysfunction. Accounting for these echocardiographic variables attenuated the association between BNP and death, and first major cardiovascular event, but not the association with heart failure or atrial fibrillation.

The results of this study indicated an association between increased plasma NP levels and risk of future cardiovascular outcomes, in a clinically asymptomatic population, after accounting for cardiac risk factors including hypertension and diabetes. However, other biomarkers, such as C-reactive protein were not included. Furthermore, the Framingham Cohort study is racially homogeneous, and results may not be generalizable to a more racially diverse population.

5.2 Utility of pre-operative BNP/NT-proBNP in non-cardiac surgery patients to predict cardiovascular outcomes

Canadian guidelines published in 2017 recommended: “measuring NT-proBNP or BNP before non-cardiac surgery to enhance peri-operative cardiac risk estimation in patients who are 65 years of age or older, are 45-64 years of age with significant cardiovascular disease, or have an RCRI score >1 (Strong Recommendation; Moderate-Quality Evidence).”[8] The guidelines included evidence from 3 meta-analyses, including 2 individual-patient data meta-analyses.[20-22] Our review includes three further meta-analyses, in addition to the 3 included in the Canadian guidelines.[23-25] The studies included in these six meta-analyses are shown in Table 1. Notably, the different meta-analyses did not always include the same studies in their evaluation.

5.2.1 Methods used in the included studies to determine predictive power

Area under the receiver operator curve (AUC):

The area under the receiver operator curve (AUC), also known as the c-statistic, is often used to compare improvements in baseline models after the addition of a new marker or predictor. The AUC calculates the area under the receiver operator characteristics (ROC) curve, which is a plot of the true positive rate (sensitivity) versus the false positive rate (1-specificity) for each value of the measure. The AUC or c-statistic is a measure of how well a new test or risk factor discriminates between cases and non-cases, and is indicative of the probability that the novel marker is higher in cases than in non-cases.[26] Thus, an AUC of 0.70 for a risk model containing only BNP indicates that the probability that BNP is higher in cases of cardiac complications than in non-cases is 70%. An AUC of 0.50 indicates that the novel marker is no better than chance in differentiating between cases and non-cases.

Net Reclassification Improvement (NRI):

- Category-based NRI:

  Due to limitations of the AUC (further discussed in Section 5.4), particularly with interpreting the clinical relevance of small changes in AUC, a new measure, the net reclassification improvement, was introduced in 2008 with the goal of determining the clinical meaningfulness of a new predictor. The NRI quantifies the net improvement in the predictive ability of the new model containing the novel predictor versus the baseline model in terms of correct reclassification of events and non-events.[27] Individuals are cross-tabulated according to categories of their predicted risks from the baseline and new models, and an overall reclassification score is calculated as the sum of two components: the net percentage of patients with the event who are correctly reclassified upwards; and the net percentage of patients without the event who are correctly reclassified downwards. The NRI can range from -2 to +2, with positive values indicating overall improvement over the baseline model. However, as the overall NRI score (a unitless statistic) is derived from two underlying components, and thus identical scores can be achieved from different individual components, it is more clinically meaningful to interpret the underlying components.[28] High positive values for the event NRI component indicate that the new predictor is better at identifying patients with the event, and hence may be helpful to clinicians to target treatments and prevent events. On the other hand, large positive values for the non-event NRI component indicate the

marker is better than the baseline model at differentiating non-events; hence, the new marker will have limited value in decreasing the burden of disease, but would be helpful in reducing overtreatment.

- Category-free NRI:

  Pencina et al. also proposed a category-free NRI for situations where categories do not naturally exist.[28] In this case, predicted probabilities are calculated on a continuous scale for events and non-events; thus the overall NRI is a measure of the net percentage of persons correctly assigned a higher or lower predicted risk. However, this makes the clinical interpretation different from the category-based NRI, because patients whose predicted risk increases from 1% to 2% may not require different treatment. Pencina et al. contend that the continuous NRI is most useful in determining the added value of a marker in settings where the distributions of other risk factors are not representative of the population.[28]

According to its creators, the NRI is useful as a first-step in assessing new markers or prediction models. Decision analytic measures, such as a weighted NRI, would be needed in the next step to evaluate the clinical utility of these novel markers.[28]

Net Absolute Reclassification Improvement (NARI):

In 2017, Alba et al. introduced the NARI, because they assert that the additive NRI, described above, does not account for the prevalence of events and non-events in the population.[29] They calculate the NARI as the absolute change in reclassification in events and non-events, divided by the total population. They contend that, as the NARI is calculated as a percentage, it is easier to interpret. However, the NARI has been widely criticized as being misleading, because it assigns equal weights to events and non-events, thus equally valuing improvements in sensitivity and specificity.[30,31] This is uncommon in clinical practice, because very few clinical risk prediction models have a threshold of 50%. In cardiology, such risk thresholds are closer to 5%, thus giving far greater weight to reducing false negatives than false positives.[31]

5.2.2 Meta-analyses included in the Canadian Guidelines

The Canadian Guidelines included 3 meta-analyses: Ryding 2009, Rodseth 2011 and 2014.[8,20-22] Results are summarized in Table 2.

Aggregate data meta-analyses

- In 2009, **Ryding et al.** published a meta-analysis of 15 studies (n=4,856) that evaluated the association between pre-operative BNP (8 studies) or NT-proBNP (7 studies) and post-operative cardiovascular complications following non-cardiac surgery.[22] 13 studies (>90% of participants) included only elective surgery populations. Outcomes included major adverse cardiovascular events (MACE) defined as cardiac death or non-fatal myocardial infarction (MI) in the short-term (within 43 days of surgery) and the long-term (≥6 months). BNP and NT-proBNP were dichotomized according to varying cut-offs in the different studies based on receiver operator characteristics (ROC) curves (BNP cut-off range: 35 to 255 ng/l; NT-proBNP range: 201 to 791 ng/l). Participants above the cut-off ranged from 18% to 55% in the various studies.

  The authors used unadjusted effect estimates in a random-effects model, and reported an increased risk of cardiac death or non-fatal MI in participants with either elevated pre-operative BNP or NT-proBNP levels [short term OR: 19.77 (95% CI: 13.18, 29.56); I^2= 30%; Long-term OR (from 2 studies of NT proBNP): 17.70 (95% CI: 3.11, 100.8); I^2= 74%]. Short-term risk of all-cause mortality was 9.28 (95% CI: 3.51, 24.56), and short-term risk of cardiac death was 23.88 (95% CI: 9.43, 60.43).

- Another meta-analysis was published in 2009 by **Karthikeyan et al**. that included 9 studies (n=3281).[23] 8 of these studies were also included in the meta-analysis by **Ryding et al.,** and hence the **Karthikeyan** meta-analysis was not reviewed by the Canadian guidelines. The population of mostly elective surgery patients was similar to the earlier meta-analysis. In this analysis, the authors evaluated the association of BNP or NT-proBNP with a variety of perioperative cardiovascular complications (death, cardiac death, cardiovascular death, myocardial infarction (MI), acute coronary syndrome, unstable angina, coronary artery revascularization, cardiac arrest, cardiac arrhythmia resulting in hemodynamic compromise or requiring an intervention, congestive heart failure, or rehospitalization due to a cardiac cause) within 30 days of surgery.

Unlike the previous analysis, the authors of this study used *adjusted* odds ratios in a random-effects model. They reported that the proportion of participants with a NP value above the cut-off across studies was 24.8% (20.1, 30.4; I^2=89%). They also concluded that individual studies had too few events in the groups with NP levels below the thresholds to include important confounding variables in their final models. Hence, those models were over-fitted, resulting in unreliable risk estimates. After pooling 7 studies, the authors reported an OR for post-operative cardiovascular complications of 19.3 (95% CI: 8.5, 43.7). However, they also reported high heterogeneity between studies (I^2=58%) which couldn't be explained by type of NP biomarker, type of surgery, blinding of data collectors and outcome adjudicators, and number of known predictors adjusted for in the analysis.

Individual-patient data (IPD) meta-analyses

- More recently, two IPD meta-analyses have been published by the same author.[20,21] In 2011, **Rodseth et al**. performed an IPD meta-analysis of 6 studies that used BNP to predict composite endpoint of cardiac death and MI within 30 days of vascular surgery.[21] They aimed to identify an optimal cutoff for BNP to predict cardiovascular event after vascular surgery, and to determine whether the addition of BNP or NT-proBNP improved current risk stratification methods.

  The authors identified 10 studies, but were able to include patient-level data from only 6 [5 studies of BNP (n=632) and 1 study of N-terminal pro=BNP (n=218)]. The unadjusted OR for MACE, defined as cardiovascular death and nonfatal MI, at 30 days post-surgery was 7.36 (95% CI: 2.23, 24.31) with significant heterogeneity (I^2=70%). After merging the studies, the authors used received operating characteristics (ROC) statistics to identify the optimal cut-off, which was 116 ng/l for BNP and 277.5 ng/l for NT-proBNP. The ORs associated with NP higher than this threshold were 4.3 (95% CI: 1.7, 11.3) for cardiac death; 7.5 (95% CI: 4.1, 13.6) for non-fatal MI; and 3.1 (95% CI: 1.4, 6.7) for all-cause mortality within 30 days.

  In 2016, a re-analysis of this study was published using the minimum p-value method, which identified very similar cutoffs for the BNP and NT-proBNP (115.57 ng/l for BNP and 241.70 ng/l for NT-proBNP), thus arriving at similar estimates for risk of outcomes.[32]

  Rodseth et al. used the net reclassification improvement (NRI) statistic to determine whether NP can improve risk classification of patients over RCRI.[21] The authors report that this reclassification process resulted in a net improvement of

58%. However, this statistic was both incorrectly analysed and interpreted. The NRI, according to its creators, cannot be expressed as a percentage, but as a unitless measure (0.58 rather than 58%), because of different denominators in its summed component measures.[28] Hence, it is more useful to interpret the individual components rather than the overall measure, but these were not provided by Rodseth et al. Furthermore, the NRI is meant to be calculated using *predicted* risks of the outcome derived from models with and without the novel predictor.[28] In this analysis, the authors simply reclassified *observed* events of MACE according to RCRI score categories by moving patients whose NP levels fell below the optimal cutoff down one risk category, and those with NP levels above the optimal threshold up a risk category. Hence, their use and interpretation of the NRI statistic to indicate better predictive power of NP is not meaningful.

- In 2014, **Rodseth et al.** published another IPD meta-analysis, this time to evaluate whether the addition of a post-operative BNP test to pre-operative BNP test improves prediction of a composite of death and myocardial infarction at 30 days and ≥180 days post-surgery.[20] They included individual patient data (n=2179) from 18 studies; 8 studies of BNP (n=619) and 10 of NTproBNP (n=1560). The studies included a variety of surgeries (30% vascular surgeries). This meta-analysis proved instrumental in shaping the 2017 Canadian guidelines.

  The optimal NP threshold was determined by identifying the cutoff associated with the lowest p-value for the outcome of death and nonfatal MI at 30 days. This was determined to be 92 ng/l for BNP, and 300 ng/l for NT-proBNP. Of the 235 (10.8%) patients who had the outcome, 166 (70%) had pre-operative BNP or NT-proBNP above the cutoff. An elevated pre-operative NP level was associated with an OR for death and nonfatal MI of 3.40 (95% CI: 2.57, 4.47). An RCRI ≥3 score and type of surgery (urgent vs elective) were also independent predictors of the outcome at 30 days. Pre-operative NP levels above the cutoff were also associated with death and nonfatal MI at 180 days (OR: 2.6; 95% CI: 2.0, 3.43). A final merged model containing pre-operative and post-operative NP dichotomized at the optimal cutoff, RCRI≥3, urgent vs non-urgent surgery, vascular vs other surgeries, and age found that the OR of death and nonfatal MI for pre-operative NP above 92 ng/l was 1.90 (95%CI: 1.44, 2.40) at 30 days and 1.90 (95%CI: 1.38, 2.58) at 180 days, while the OR for post-operative NP was 3.70 (95%CI: 2.18, 6.24) at 30 days and 2.20 (95%CI: 1.85, 2.65) at 180 days after surgery.

  In this analysis, the authors calculated the net reclassification improvement (NRI) of adding pre-operative NP to a baseline model containing age, RCRI score ≥3, type

of surgery (vascular vs. nonvascular), and urgency of surgery (urgent/emergent vs. elective). Risk of outcome was categorised into 5 levels. The analysis found that adding pre-operative BNP to the baseline model resulted in the correct reclassification of 16% of patients with the event and 15% of patients without the event, for an overall NRI of 0.31. While these numbers indicate that adding pre-operative BNP to baseline risk factors improves the predictive power for death and nonfatal MI, the relatively modest improvements in reclassification make a meaningful interpretation of its clinical utility difficult. The NRI indicates that an additional 16% of patients with the outcome would be considered high risk while a further 15% without the event would be reclassified as low risk; however, it remains unclear whether intervening on NP levels would improve outcomes.

5.2.3 Other meta-analyses not included in the Canadian Guidelines, and studies published since 2012

Meta-analyses

- In 2014, **Young et al**. published a meta-analysis including 24 studies evaluating the role of pre-operative BNP/NT-proBNP in predicting cardiac outcomes after surgery (cardiac or non-cardiac).[25] BNP values from the included studies ranged from 30 to 385 ng/l, and NT-proBNP ranged from 201 to 2017 ng/l. The diagnostic odds ratio of either biomarker in predicting MACE in 10 studies of non-cardiac surgery was 15.0 (95%CI: 8.84-25.5; I^2=35%), with an AUC of 0.84 (0.80, 0.87).

- A recent meta-analysis published in 2019 by **Zhang et al**. evaluated the association of 5 cardiac biomarkers (BNP, NT-proBNP, cardiac troponin (cTn), high sensitive C reactive protein (hs-CRP and CRP) with post-operative major adverse cardiovascular events (MACE).[24] MACE was defined as heart failure, acute coronary syndrome, atrial fibrillation, paroxysmal supraventricular tachycardia, ventricular tachycardia, angina pectoris, acute myocardial infarction, thromboembolic events, deep vein thrombosis, acute renal failure, transient ischemic attack, cardiac death, all-cause mortality, major arrhythmia, unstable angina, stroke, cardiac revascularization procedure. 11 of the 26 included studies evaluated BNP/NT-proBNP.

  Pooled estimates from a fixed-effects model of the 4 BNP studies found an increased risk of MACE for elevated BNP levels, defined according to the individual study cut-offs (range of BNP cut-offs: 39 to 822 ng/l) [OR: 4.57 (3.37, 6.20); I^2: 0%]. The pooled OR for NT-proBNP from 7 studies was 3.48 (2.71, 4.46); I^2: 49%. The

authors also reported a significant risk of MACE for cardiac troponin and CRP. Given the wide range of NP cutoffs in the individual studies and high between-study heterogeneity, the authors should have used a random-effects model to meta-analyse data. Furthermore, these analyses were not adjusted for important CVD risk factors including age, sex, cardiac history, diabetes, and renal function.

Recent observational studies

Since the most recent meta-analysis by Rodseth in 2014, which included studies published until June 2012, we identified 30 observational studies that evaluated the association of BNP/NT-proBNP with cardiac complications following non-cardiac surgery. The characteristics and results of these studies are shown in Table 3. All except two were single-centre studies; the majority were prospective, and evaluated diverse populations including lung, esophageal, and hip surgeries in patients with varying risk factors. Sample sizes ranged from 27 to 10,402, and outcomes evaluated included MACE, short and long-term mortality, and atrial fibrillation. We highlight the two higher quality studies.

- A multi-national, multi-centre, prospective study (Measurement of Exercise Tolerance before Surgery [METS]) was conducted by **Wijeysundera et al.** in 2018 to evaluate the ability of subjective assessment of patients' functional capacity versus alternative measures such as cardiopulmonary exercise testing [CPET], scores on the Duke Activity Status Index [DASI] questionnaire, and pre-operative NT pro-BNP concentrations to predict death or myocardial infarction following elective non-cardiac surgery.[33] The study included 1401 patients recruited from 25 hospitals in Canada, the UK, Australia and New Zealand, who were ≥40 years with at least one cardiac risk factor. 28 (2%) of participants had the primary outcome of death or MI. Secondary outcome was death within one year, and other outcomes of interest included death or myocardial injury within 30 days after surgery, and moderate or severe complications during the index admission. In a baseline model containing RCRI score, log transformed NT-proBNP was not associated with 30-day MI or death (OR: 1.88; 95% CI: 0.89, 3.96). The AUC was 0.65 versus 0.59 for the baseline model with only RCRI. The event NRI for NT-proBNP and RCRI versus the baseline model was 11% while the non-event NRI was 14%, for an overall NRI score of 0.25. Duke Activity Status Index was the only measure associated with 30-day MI or death (OR: 0.91; 95% CI: 0.83, 0.99) with an event NRI of 7% and a non-event NRI of 21%. For secondary outcomes, NT-proBNP was associated with 30-day death and myocardial injury (defined as postoperative troponin concentrations exceeding both the 99th percentile of the normal reference population, and the threshold at which the assay coefficient of variation was 10%) (OR: 1.78; 95% CI:

1.21, 1.62; no. of events=176), and death at 1 year (OR: 2.91; 95% CI: 1.54, 5.49; no. of events=38). The authors conclude that more objective measures, such as DASI and NT-proBNP, should replace subjective measures of pre-operative cardiac risk assessment. However, given serious limitations, such as the very low event rate, and low participation rate (27%) that can induce selection bias, the authors state that further research is needed to determine optimal thresholds and identify alternative pre-operative biomarkers that could be used in conjunction with NT-proBNP to address this biomarker's limitations in the presence of obesity, chronic renal kidney, or heart failure with preserved ejection fraction.

- In 2019, **Duceppe et al.** conducted a retrospective sub-analysis (n=10,402) of patients enrolled in the VISION (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation) study, a multicentre, prospective cohort of inpatient non-cardiac surgery patients.[34] The aim of the sub-study was to evaluate the added value of pre-operative NT-proBNP over RCRI in predicting a composite outcome of vascular death and myocardial injury after non-cardiac surgery (MINS). Vascular death was defined as any death with a vascular cause and included death following an MI, cardiac arrest, stroke, cardiac revascularization procedure, pulmonary embolus, hemorrhage, or due to an unknown cause. MINS was defined as postoperative troponin T ≥ 0.03 ng/mL, high-sensitivity TnT (hsTnT) ≥20 ng/L with a change ≥5 ng/L, or hsTnT ≥ 65 ng/L in a patients without evidence of a non-ischemic etiology of troponin elevation in the 30 days post-surgery. There were 1269 (12%) unique outcome events, and the authors reported a dose-response relationship between increasing NT-proBNP thresholds and the composite outcome. In comparison to an NT-proBNP level of <100 ng/l, the hazard ratios (HR) of the outcome, adjusted for RCRI score, for NT-proBNP levels of 100 to <200 ng/l; 200-1500 pg/ml; and ≥1500 ng/l were 2.27 (1.90–2.70), 3.63 (3.13–4.21), and 5.82 (4.81–7.05), respectively. However, there were many limitations to this study: the authors failed to adjust for any risk factors including age and gender, which differed by outcome in their study; they do not provide information on the 8,518 patients who were excluded from the study (risk of selection bias if they differed significantly from the included patients in NT-proBNP levels and risk of outcome); they also do not report information on censored observations making interpretation of their survival analysis difficult. Additionally, their use of cardiac troponin thresholds and delta to define MINS are arbitrary.[35] Finally, their use of the net absolute reclassification index (NARI) has been criticized as being misleading and inaccurate.[30,31]

5.2.4 Head to head comparisons/Utility of BNP/NT-proBNP vs other measures

Improvement to RCRI with the addition of NP alone

Five studies, including two IPD meta-analyses, evaluated the additional ability of NP markers over RCRI to predict adverse cardiac outcomes following non-cardiac surgery. Three used the NRI statistic, one used the NARI, and one used AUC.[20,21,33,36]

- In the first meta-analysis by Rodseth et al. in 2011, the authors calculated the improvement in risk classification with the use of pre-operative NP over the RCRI. However, the authors incorrectly calculated the NRI, using observed event rates instead of predicted probabilities, and hence their reported NRI of 58% is not interpretable.[21]

- In their second IPD meta-analysis in 2014, Rodseth et al. calculated the net reclassification improvement (NRI) of adding pre-operative NP to a baseline model containing age, RCRI score ≥3, type of surgery (vascular vs. nonvascular), and urgency of surgery (urgent/emergent vs. elective). As described in Section 5.2.2, the authors report an overall NRI of 0.31. In other words, the addition of pre-operative NP to the RCRI score allows for the identification of an additional 16% of patients at risk of the event, and a lowering of risk in another 15% of patients without the event who would have otherwise received treatment. While these numbers indicate that adding pre-operative BNP to baseline risk factors improves the ability to predict death and nonfatal MI, the relatively modest improvements in reclassification do not allow for a meaningful interpretation of its clinical utility. There are no studies that have evaluated whether intervening on NP levels will have a concrete impact on outcomes.[20]

- In a multicentre prospective analysis of 1401 patients, **Wijeysundera et al**. report that log transformed NT-proBNP was not associated with 30-day MI or death (OR: 1.88; 95% CI: 0.89, 3.96) in a baseline model containing only RCRI. The AUC was 0.65 versus 0.59 for the baseline model. The event NRI for NT-proBNP versus the baseline model was 11% while the non-event NRI was 14%, for an overall NRI score of 0.25.[33]

- **Binh et al**. in 2019 conducted a prospective analysis of 366 moderate to high risk patients undergoing non-cardiac surgery and evaluated the discriminative ability of NT-proBNP versus RCRI in predicting myocardial infarction, pulmonary edema, severe cardiac arrhythmias, and cardiac death occurring within 30 days post-surgery. 48 (13%) of patients had the primary outcome. In univariable analysis,

NT-proBNP as a continuous measure, RCRI, presence of ischemic heart disease, and history of congestive heart failure were all independently associated with the outcome. The AUC for RCRI alone was 0.661 (0.583, 0.738), and the addition of RCRI to NT-proBNP risk models did not significantly improve the AUC [NT-proBNP alone: 0.875 (0.819, 0.932) vs NT-proBNP + RCRI: 0.882 (0.827, 0.937)].[36]

- Most recently, **Duceppe et al.** conducted a sub-study of a large, multicentre prospective analysis (n=10,402) to evaluate the added value of pre-operative NT-proBNP over RCRI in predicting a composite outcome of vascular death and myocardial injury after non-cardiac surgery.[34] They calculate the NARI, a controversial new statistic to discriminate between 2 models. They report the individual components of the NRI as 21.4% net reclassification among events, and 26.4% net reclassification among non-events, for a total of 0.47. They calculate the NARI, or net absolute improvement in risk classification, as 258 per 1000 patients. They also report the optimism corrected c-statistic to predict the primary outcome increased to 0.73 (CI, 0.72 to 0.74) with NT-proBNP vs 0.65 (CI, 0.64 to 0.67) with RCRI alone.

<u>Improvement to risk indices with addition of NP and other measures</u>

- **Kopec et al**. in 2018 evaluated the utility of pre-operative high-sensitivity cardiac troponin T (hs-cTnT) and NT-proBNP in predicting MI within 3 days of non-cardiac surgery in 572 patients with established coronary artery disease or known risk factors for CAD.[37] This was an ancillary study of participants enrolled in the Vitamins in Nitrous Oxide (VINO) randomized controlled trial conducted in St-Louis, Missouri. Association of the biomarkers and RCRI with MI were assessed in separate models, adjusting for age, sex, eGFR, and history of CAD. Predictive power of each measure was assessed using area under the ROC curve (AUC). Net reclassification improvement was used to assess the ability of the biomarkers to improve on the RCRI in predicting MI. 30 patients (5.2%) developed MI, suggesting the study was underpowered to detect significant differences. After adjusting for age, sex, eGFR and pre-existing coronary artery disease, neither elevated NT-proBNP (>300 ng/L) nor hs-CTnT >14ng/L were associated with acute MI (OR for NT-proBNP:1.55; 95% CI: 0.66, 3.36) and (OR for hs-cTnT: 2.26; 95% CI; 0.93, 5.83). Addition of hs-cTnT to a model containing only RCRI and NT-proBNP rendered the latter two measures' association with MI non-significant [OR of hs-cTnT: 3.15 (95% CI: 1.26, 7.86); NT-proBNP: 1.43 (95% CI: 0.61, 3.35); RCRI: 1.31 (95% CI: 0.84, 2.02)]. AUC of RCRI alone was 0.59 (0.49, 0.69); RCRI + hs-cTnT >14ng/L was 0.69 (0.61, 0.78); RCRI + NT-proBNP was 0.65 (0.55, 0.75); and for all 3 was 0.71 (0.63,

0.79). Furthermore, the continuous NRI of RCRI was not further improved by the addition of NT-proBNP to hs-cTnT (0.66 for RCRI + hs-cTnT vs. 0.66 for RCRI + hs-cTnT + Nt-proBNP).

5.3 Risk of bias in the included studies and interpretation of results

5.3.1 Limitations of the meta-analyses

- There was high heterogeneity between the studies resulting from the evaluation of different biomarkers (BNP vs NT-proBNP), different assays used to measure the biomarkers, the different cut-offs to dichotomize the biomarkers, varying outcome definitions, and different surgical populations. High between-study heterogeneity makes interpretation of summary measures less straight-forward.

- There were very few events in the groups with NP below the cut-off (a few studies had 0 events for short-term MACE). This resulted in very wide confidence intervals, i.e. high uncertainty in the effect estimates.

- The analyses by **Ryding et al., Young et al., and Zhang et al**. used only unadjusted measures. As there are large differences in BNP according to age, sex, cardiac history, diabetes, and renal function among other CVD risk factors, it is unclear whether the association between BNP and cardiovascular outcomes would be attenuated after accounting for these and other risk factors.

- In the individual patient data analyses, not all the contacted investigators provided individual-patient data, which could lead to selection bias affecting the pooled effect estimate.

- The aggregate data meta-analyses used the study-specific cutoffs, which varied widely and contributed to the inter-study variability. However, the IPD analyses by Rodseth calculated a single optimal threshold from the pooled data using ROC curve statistics or the minimum p-value method, which was a strength of their analyses. A recent meta-analysis that included the same studies as Rodseth et al.[21] showed that using individual study-specific cut-offs can overestimate the prognostic utility of NT-proBNP for post-operative MACE by inflating the odds ratio.[38] Using study-specific cut-offs resulted in a pooled OR for 30-day MACE associated with elevated NT-proBNP of 6.45 (95% CI: 3.98, 10.46; I^2=45%). This analysis calculated an optimal NT-proBNP threshold of 367.15 ng/l using ROC curve statistics, and using this threshold for the entire pooled population yielded an OR for MACE of 4.38 (95% CI: 3.31, 5.81); while using this cutoff for each individual

study and meta-analysing the results produced an OR of 3.43 (95% CI: 2.08, 5.64; I^2=39%).

5.3.2 Limitations of the individual observational studies

- A large number of studies did not adjust for potential confounding variables. Those that did conduct multi-variable analyses did not select these variables *a priori,* but instead used backward stepwise logistic regression, which eliminates variables above a pre-specified significance threshold. Not including an *a priori* set of risk factors provides an incomplete picture of the effect of BNP on post-operative cardiac complications.

- All studies determined NP cutoffs in a *post-hoc* manner to maximize the predictive power of the biomarker in that specific population. Hence, these study-specific thresholds varied widely.

- Most but not all studies assessed myocardial infarction or injury using cardiac troponin assays. There is variability in the different assays used, contributing to between-study heterogeneity. There is no consensus on how the 99th percentile upper reference limit should be defined.[39] Furthermore, these assays are sensitive to age and gender, producing higher values in older populations and lower values in women.[35,40]

- Most studies did not measure pre-operative cardiac troponin. The Fourth Universal Definition of Myocardial Infarction recommends that in order to properly interpret the cause of elevated post-operative troponin values, a baseline pre-operative value is necessary to exclude chronic causes (e.g. renal failure) versus acute increases.[35]

- Many of the studies evaluating the predictive power of BNP/NT-proBNP relied solely on the area under the receiver operator curve (AUC), also known as the c-statistic, to compare improvements in the baseline models after addition of the new marker. However, the AUC has certain limitations, most commonly with interpretation of the clinical relevance of its results, and its ability to distinguish between the predictive importance of several risk factors in the same model.[26] The AUC is also a function of sensitivity and specificity of the new test, which can be dependent on various characteristics of the underlying population and not generalizable to other populations. Finally, positive predictive value i.e. the probability of outcome given a positive test, may be of more clinical significance than the sensitivity and specificity of a test, particularly for prognostic models.

- In 2008, a new statistic, the Net Reclassification Index (NRI) was introduced to measure the improvement in prediction performance gained by adding a new predictor to a baseline set of variables.[27] However, this measure has been used and interpreted incorrectly, as in the Rodseth et al 2011 study above, and as demonstrated in a recent review.[28] The NRI also is limited by the choice of arbitrary categories. Selection of categories are often not based on the literature, and may be manipulated to yield higher NRIs. Additionally, the NRI has been shown to result in misleading information on predictive power.[41]

- A newer statistic, derived from the NRI, called the NARI was recently introduced in 2017.[29] It has been criticized for weighting true negatives (specificity) as equally valuable as true positives (sensitivity), which implies a 50% risk threshold that is rarely applicable to the clinical context, particularly in cardiology, where risk thresholds are closer to 5%. In other words, such a clinical context usually values sensitivity more than specificity; reliance on the NARI would thus result in a misleading interpretation of predictive power.

5.4 Guidelines or HTAs on perioperative risk assessment of non-cardiac surgery patients

5.4.1 Canadian Guidelines

- The 2017 Canadian Cardiovascular Society guidelines on perioperative risk assessment, discussed above, recommend the use of pre-operative BNP/NT-proBNP testing in conjunction with the RCRI over other forms of pre-operative risk assessment including resting echocardiography, coronary computed tomographic angiography (CCTA), exercise stress testing, and pharmacological stress echocardiography.[8]

- The recommended algorithm is for all patients age ≥45 years or 18-44 years with known significant cardiovascular disease undergoing elective non-cardiac surgery requiring overnight hospital admission to:

    - first be screened with the RCRI;

    - to have BNP/NT-proBNP ordered for those with RCRI ≥1, or age ≥65 years, or 45-65 years with significant cardiovascular disease;

  - to have electrocardiogram in the postanesthesia care unit and daily troponin monitoring for 48 to 72 hours post-surgery if BNP ≥92 ng/l or NT-proBNP ≥300 ng/l.

- The recommendation in support of BNP/NT-pro-BNP was a strong recommendation based on moderate quality evidence, most significantly, the individual-patient data meta-analysis by Rodseth et al. in 2014.

- Of the 13-member expert panel who issued the recommendation, 4 recused themselves due to intellectual conflicts of interest. No members had financial conflicts of interest, and no external or industry support was received for the guideline development.

5.4.2 American Guidelines

- The 2014 American College of Cardiology/American Heart Association guidelines took into consideration the 2014 Rodseth meta-analysis and concluded that biomarker measurement, especially NP, may be useful for the assessment of post-operative heart failure in high risk patients. However, they found that most of the studies had serious limitations, and that there was no evidence that targeting these biomarkers would reduce post-operative complications.[42]

5.4.3 European Guidelines:

- The 2014 European Society of Cardiology (ESC)/ European Society of Anaesthesiology (ESA) guidelines also included the 2014 Rodseth meta-analysis, and concluded that routine preoperative determination of serum biomarkers (brain natriuretic peptide [BNP], NT-proBNP, cardiac troponins) for risk stratification is not recommended in patients undergoing non-cardiac surgery (Class III, level C), but BNP/NT-proBNP may be considered for obtaining prognostic information in high-risk patients (Class IIb).[43]

6. INTERVENTION AT THE MUHC

6.1 Current treatment policy

- On July 23rd 2018, the Clinical Practice Review Committee of the MUHC issued a directive on pre-operative diagnostic tests for all adult patients undergoing elective surgery requiring at least one overnight stay. Following the 2017 Canadian guidelines, it recommended pre-operative BNP testing for adult patients undergoing inpatient surgery who are ≥65 years or between 45 and 65 years with significant cardiovascular disease or an RCRI score ≥1. A BNP value ≥92 ng/l was considered abnormal, and patients with abnormal values are monitored with an ECG post-surgery, and daily troponin monitoring 48-72 hours post-surgery. Currently, NT-proBNP is not measured at the MUHC.

- The 2017 Canadian guidelines recommended an electrocardiogram (ECG) and daily post-operative troponin measurements in patients with NP values above the cutoff, but the impact on clinical outcomes or on cost of such measures have not been evaluated.

6.2 MUHC experience with intervention

- Pending a review of pre-operative BNP testing by TAU, routine testing of pre-operative BNP for non-cardiac surgery has been permitted since June 2019. Currently, all pre-operative BNP samples are sent to St-Mary's hospital once a day for analysis. The McGill Optilab cluster plans to standardize to NT-proBNP in the future, pending verification of the assay.

- Figure 2 shows the volume of pre-operative BNP tests ordered at the 4 MUHC sites for both cardiac and non-cardiac surgeries from January 1st to September 30th, 2019, which shows that:

    - A total of 1546 pre-operative BNP tests were ordered in this period: 151 at Lachine, 291 at the Montreal Neurological Hospital (MNH), 573 at the Montreal General Hospital (MGH), and 531 at the Royal Victoria Hospital (RVH).

    - The average pre-operative BNP values at Lachine, the MNH, the MGH, and the RVH were 68 ng/l, 65 ng/l, 94 ng/l, and 115 ng/l, respectively.

- The proportion of values at or above the BNP threshold of 92 ng/l established by the Canadian guidelines is 20% at Lachine, 16% at the MNH, 28% at the MGH, and 33% at the RVH.

- A retrospective chart review is being conducted by an anesthesiology resident to track compliance with the new measures, and record outcomes associated with BNP levels.

- A prospective analysis is also planned to measure the impact of pre-operative BNP testing on outcomes and cost.

6.3 Cost and budget impact estimates

The cost of a BNP test across the province of Quebec for 2019-2020, published by the provincial health ministry, is CAD 18.00, while that of NT-proBNP is CAD 19.50.[44]

It is estimated that currently, approximately 60-65 patients receive BNP/NT-proBNP testing per month at the RVH and MGH clinics each. Assuming an approximate cost of $20 per test, the annual budget impact would be $28,800 to $31,200. These costs could increase if BNP/NT-proBNP testing is expanded to out-patient surgeries as well, and if thresholds to classify high risk patients are lowered.

7. DISCUSSION

7.1 Summary of the evidence

The majority of studies summarized above suggest that elevated pre-operative natriuretic peptide levels predict post-operative cardiac complications in patients undergoing non-cardiac surgery. However, given the methodological limitations of these studies, and the lack of evidence on the clinical impact of intervening on elevated NP levels, the clinical utility of measuring pre-operative BNP/NT-proBNP in this population is less clear. To date, there have been no RCTs to evaluate the added value of pre-operative natriuretic peptides for cardiac risk assessment.

The large individual patient data meta-analysis by Rodseth et al. in 2014 was instrumental in changing the 2016 Canadian guidelines. However, as discussed above, this study as well as the others included in the meta-analyses and in this review had several limitations including a wide range of NP cutoffs used in the individual studies, heterogeneous surgical

populations, different outcome definitions, low event rates and lack of adequate control for confounders. The IPD meta-analysis by Rodseth et al. only adjusted for RCRI≥3, age, urgency of surgery, and vascular vs. non-vascular surgery. Factors known to affect both NP levels and cardiac outcomes include sex, ethnicity, renal function, diabetes, obesity, and pulmonary hypertension. The cutoffs of 92 ng/l for BNP and 300 ng/l for NT-proBNP established in the Rodseth meta-analysis have not been validated in other settings. Furthermore, the clinical utility and cost of intervening on elevated NP levels is unclear. For example, Rodseth et al. found that 22% of patients with NP values above the cutoff had post-operative MI or died, which means that 78% of those with high NP values would receive unnecessary monitoring with ECG and daily troponin testing.

The lack of head to head comparisons is a serious limitation, as it is hard to ascertain the added value of BNP/NT-proBNP in predicting cardiac complications without accounting for other important predictors. Most studies compared BNP/NT-pro-BNP with the RCRI score using AUC or the newer metric, net reclassification improvement (NRI). While these metrics showed that NP generally improved the ability of RCRI to predict cardiac complications, they do not provide enough information on the clinical utility of NP. Further analytic measures, such as a weighted NRI, would be needed to evaluate clinical utility.[28] Finally, while the RCRI is currently used as the standard measure of cardiac risk assessment, its utility in non-cardiac surgery patients is unclear.[45] It does not include important variables such as age or gender, or give an accurate assessment of a patient's current functional status, and hence measuring newer tests against the RCRI may be uninformative.

Furthermore, there are several other cardiac biomarkers that are associated with post-operative cardiac complications including C-reactive protein and cardiac troponin. The recent study by Kopec et al. found that the addition of high-sensitivity cardiac troponin T to models containing RCRI and NT-proBNP greatly attenuated the latter two measures' association with post-operative MI. It is unclear why natriuretic peptides have been given greater attention in the literature than other cardiac biomarkers in risk prediction.

Importantly, even if BNP may predict post-operative cardiac complications, there are currently no studies showing that knowledge of this information will lead to interventions that will improve outcomes. The current evidence points to a correlation between elevated NP levels and post-operative cardiac complications; the natural progression of research would be to then evaluate whether intervening on these higher risk patients would prevent adverse events. Without this knowledge, it is premature to mandate routine use of a test that may in fact have no benefit on outcomes.

Given these limitations, there is a fair degree of uncertainty regarding the strength of the association between BNP/NT-proBNP and post-operative cardiac complications, and its clinical utility.

7.2 Utility of BNP/NT-proBNP as a clinical risk predictor

7.2.1 Advantages of using BNP/NT-proBNP

The advantages of using BNP/NT-proBNP over other pre-operative risk stratification tools are that it is non-invasive, rapidly available, more objective than clinical risk assessment tools and less expensive than echocardiographic tests.

7.2.2 Threshold determination

An important issue with incorporating BNP/NT-proBNP into pre-operative risk stratification for non-cardiac surgery patients is the lack of consensus on an appropriate threshold. All the observational studies determined their thresholds *post-hoc*, which are specific to their populations. The wide range of cutoffs also indicate that BNP/NT-proBNP thresholds are likely to differ in patients with cardiac risk factors and by type of surgery. There may be a need to develop different thresholds based on these factors, to discriminate between high and low risk populations.

7.2.3 Added prognostic value vs other tools

One possibility of using BNP for risk stratification is to incorporate its use along with RCRI and calculate individual post-test probabilities. Some studies have shown that BNP has high negative predictive value, and hence could be used to rule out low risk individuals.[46] In effect, in the 2014 meta-analysis by Rodseth et al., the negative predictive value i.e. the proportion of patients with NP below the cutoff who did not have the outcome of death or non-fatal MI was 95% (1347/1416), while the positive predictive value was only 22% (166/763).

7.2.4 Lack of evidence on clinical impact of using pre-operative NP

To date, there have been no studies showing that intervening on pre-operative NP reduces rates of cardiac complications.

8. CONCLUSIONS

- Studies suggest that elevated levels of pre-operative BNP/NT-proBNP is associated with cardiac complications, most notably cardiac death and nonfatal myocardial infarction, in patients undergoing major non-cardiac surgery.
- A 2014 individual-patient data meta-analysis established that a pre-operative BNP cutoff of 92 ng/l or an NTpro-BNP cutoff of 312 ng/l was associated with the composite end-point of death and myocardial infarction at 30 days and ≥180 days post-surgery, after accounting for age, severe RCRI score, and type and urgency of surgery. These findings were instrumental in changing the 2016 Canadian guidelines.
- However, the quality of the evidence from the studies included in this review is weak. The meta-analyses had high heterogeneity stemming from the inclusion of studies with different populations, wide ranges of NP cutoffs, and variation in outcome definitions. The individual studies often had very few events, and most did not adjust for important confounders. Additionally, there is no consensus on NP cutoff, and those established by Rodseth et al. have not been validated in different settings.
- Metrics such as the AUC and NRI indicate that natriuretic peptide (NP) levels add to the ability of the revised cardiac risk index (RCRI) to predict cardiac complications. However, they do not allow us to interpret the clinical relevance or utility of adding NP to clinical practice in this population. Furthermore, there are several markers, such as cardiac troponin, that are also strongly predictive of post-operative cardiac complications, and the added value of BNP relative to such markers has not been established.
- There is some evidence that NP cutoffs have good negative predictive value, indicating NP may have some utility in ruling out low-risk patients for further testing. However, the positive predictive value is low, indicating that large numbers of patients will be subjected to unnecessary daily testing. To date, there have been no evaluations on the clinical impact and cost of such interventions.

9. RECOMMENDATIONS

- Given that the BNP/NT-proBNP blood test is already available to physicians at the MUHC, but also given that there is no evidence of its clinical impact in patients undergoing major elective inpatient non-cardiac surgery, we recommend an **Approval for Evaluation**, conditional on the following:
    - Adherence to a protocol that is more stringent than the current Canadian guidelines in that the assessment of the patient's risk of post-operative cardiac outcomes is based not only on age but also on the Revised Cardiac Risk Index (RCRI) and clinical judgment as follows:
        - Age ≥45 years

      AND
        - (Significant cardiovascular disease OR RCRI ≥1 OR Clinical judgement)
    - Development of a research protocol to systematically document the following for all patients receiving the BNP/NT-proBNP test:
        - Patient characteristics including age, sex, RCRI and co-morbidities;
        - Pre- and post-operative troponin testing;
        - Post-operative follow-up including number of cardiology consults, length of stay, and cardiac complications.
- The protocol will be developed jointly by the clinical experts and TAU to create a standardized process to record and analyse locally collected data. The TAU Policy Committee will be apprised regularly of the progress.
- This recommendation will be reassessed in 1 year after evaluation of local data and/or evidence in the scientific literature on clinical impact.

FIGURES

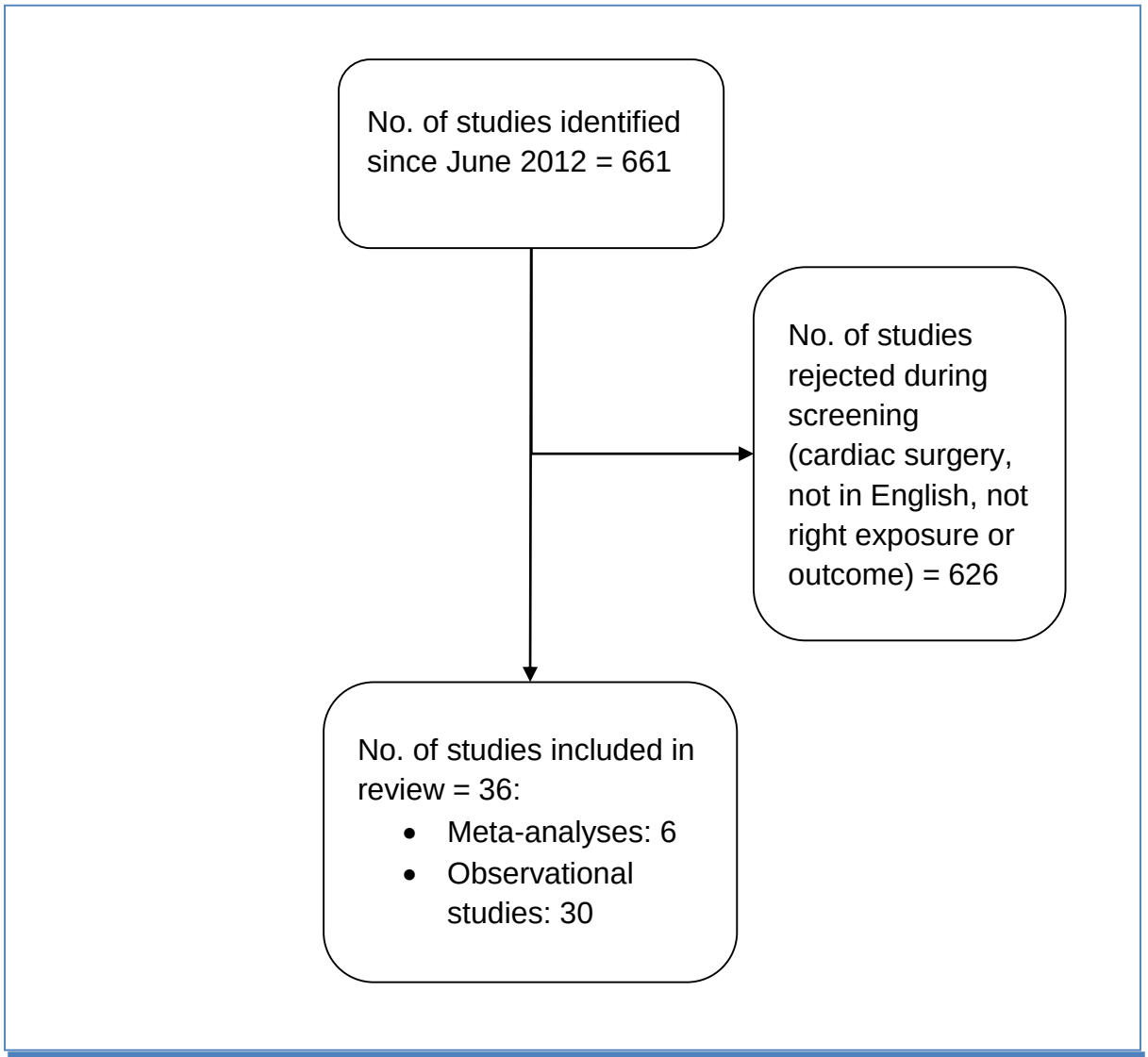

Figure 1: Flowchart of the literature search

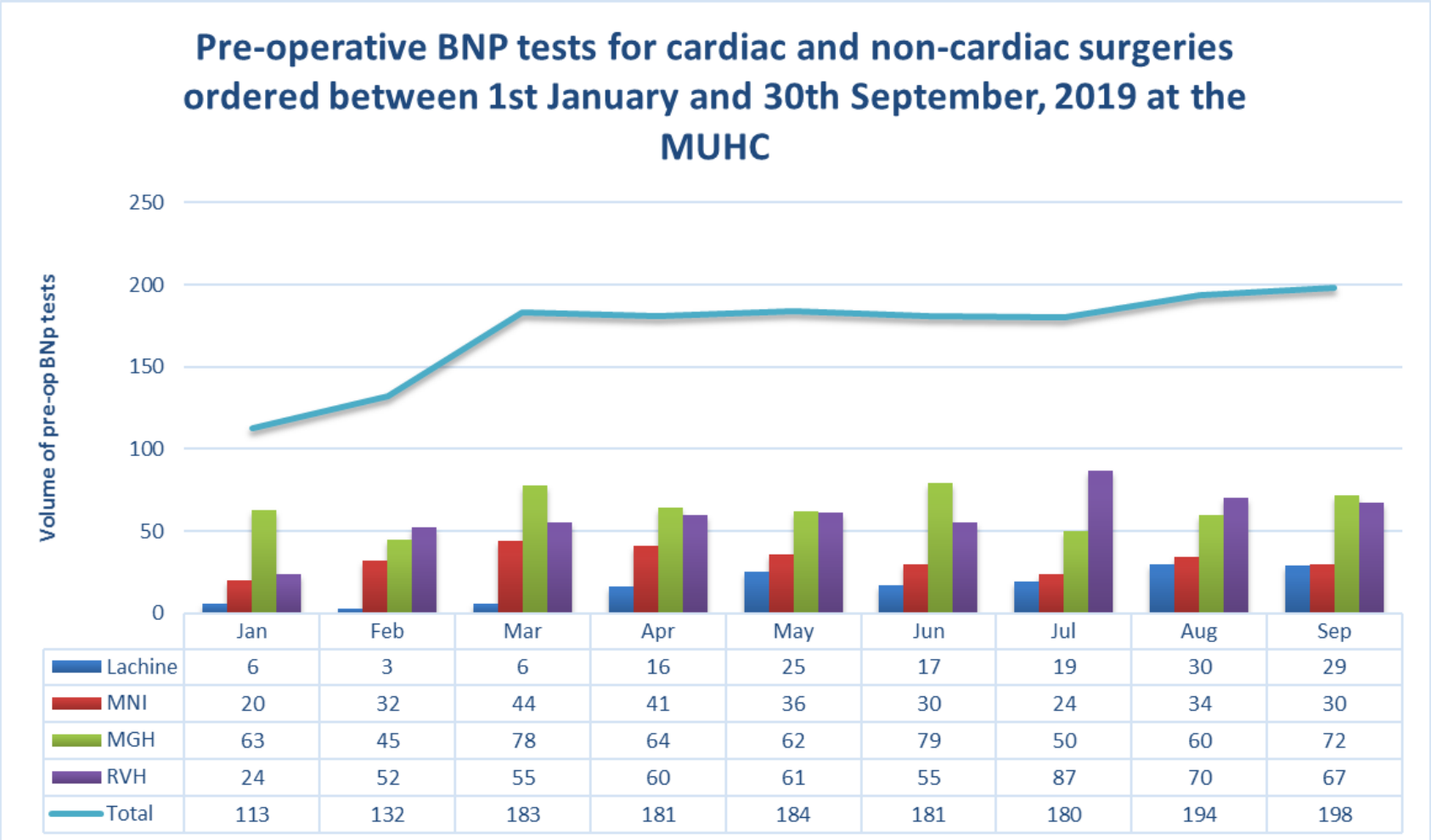

Figure 2: Pre-operative BNP tests for cardiac and non-cardiac surgeries ordered between 1st January and 30th September, 2019 at the MUHC

TABLES

Table 1. Studies included in the 6 meta-analyses

Individual study	Biomarker	Meta-analyses					
		Ryding 2009	Karthikeyan 2009	Rodseth 2011	Rodseth 2013	Rodseth 2014	Zhang 2019
Berry 2006	BNP	x					
Bolliger 2009	BNP			x			
Biccard 2011	BNP			x			
Cagini 2011	BNP				x	x	x
Cahill 2009	BNP				x		
Cuthbertson 2006	BNP	x	x				
Cuthbertson 2007	BNP	x	x	x			
Dernellis 2006	BNP	x	x				
Gibson 2007	BNP	x	x	x	x		
Hoksch 2007	BNP				x	x	
Leibowitz 2008	BNP	x		x			
Long 2016	BNP						x
Mercantini 2012	BNP				x	x	
Park 2012	BNP				x	x	
Radovic 2011	BNP				x	x	
Rodseth 2012	BNP				x	x	
Stone 2014	BNP						x
Suttie 2011	BNP				x	x	
Vetrugno 2012	BNP						x
Cardinale 2007	NT-proBNP		x		x	x	
Cho 2006	NT-proBNP	x					
Chong 2010, 2012	NT-proBNP				x	x	

Individual study	Biomarker	Meta-analyses					
Cnotiwy 2011	NT-proBNP				x	x	
Feringa 2006	NT-proBNP	x	x				x
Goei 2008	NT-proBNP	x					
Kim 2016	NT-proBNP						x
Kopec 2017	NT-proBNP						x
Larati Buse 2012	NT-proBNP				x	x	
Mahla 2007	NT-proBNP	x	x	x	x	x	
Manikandan 2005	NT-proBNP				x	x	
Oscarsson 2009	NT-proBNP						x
Rajagopalan 2011	NT-proBNP				x	x	x
Riemersma 2008	NT-proBNP	x					
Schutt 2009	NT-proBNP				x	x	
Waliszek 2011	NT-proBNP				x	x	
Yeh 2006	NT-proBNP		x				
Yun 2008	NT-proBNP	x	x				

Table 2: Characteristics and results of the meta-analyses evaluating the association between natriuretic peptides and post-operative complications

Author	Study type and sample	Population	Exposure	Outcome	BNP cutoff	Results				
						All-cause mortality	Cardiac death	Nonfatal MI	Composite death + nonfatal MI	Other composite outcomes
Ryding 2009	15 studies (n=4856)	Elective, emergent (2 studies) non-cardiac surgery	Pre-op BNP or NT-proBNP	MACE, al-cause mortality, cardiac mortality ≤43 days and ≥ 6 mos post-op	Used study-specific cutoffs	• Short term (5 studies): 9.28 (3.51, 24.56); • Long-term (4 studies): 4.72 (2.99, 7.46; I^2=0)	• Short-tem (6 studies): 23.88 (9.43, 60.43; I2=0);		• Within 43 days (10 studies): 19.77 (13.18, 29.56; I2= 30%); • Long-term (2 studies of NT proBNP):17.70 (3.11, 100.8; I2= 74%)	
Karthikeyan 2009	9 studies (n=3281)	Non-cardiac surgery; mostly elective surgery studies (1 emergent)	Pre-op BNP or NT-proBNP	Composite of cardiac death & non-fatal MI; atrial fibrillation	Used study-specific cutoffs				OR (7 pooled studies): 19.3 (8.5, 43.7; I^2:58%)	
Rodseth 2011	IPD of 5 BNP studies (n=632) and 1 N-terminal pro=BNP study (n=218)	Pts undergoing non-cardiac vascular surgery	Pre-operative NP concentrations	MACE (composite of cardiac death and nonfatal MI) and 30-day all-cause mortality	116 ng/l	OR: 3.1 (1.4, 6.7)	OR: 4.3 (1.7, 11.3)	OR: 7.5 (4.1, 13.6)	OR: 7.9 (4.7, 13.3)	
Rodseth 2014	IPD meta-anlaysis	Non-cardiac	Post-op NP + pre-op NP	Composite of death and MI at	BNP: 92 ng/l				• 30 days OR: 3.40 (2.57, 4.47);	

	including 18 studies (n=2179): 8 BNP (n=619) & 10 NT-pro BNP(n=1560); prospective cohort studies	surgeries, elective or urgent		30 and ≥180 days	NT-proBNP: 300 ng/l				• 180 days OR: 2.6 (2.0, 3.43)	
Young 2014	Meta-analysis of 24 NP studies	Cardiac or non-cardiac surgeries	Post-op NP + pre-op NP	A variety of post-operative cardiac complications	Used study-specific cutoffs					• Pooled OR (24 studies):14.3 (9.87, 20.7); • aOR (21 studies): 7.37 (4.41, 12.3); • Cardiac studies: 13.9 (8.43, 22.8); • Non-cardiac studies: 15.0 (8.84 ,25.5)
Zhang 2019	Meta-analysis of 4 BNP studies (n=1759) and 7 NT-proBNP studies (n=1804)	Non-cardiac surgery patients	BNP/NT-proBNP	heart failure, acute coronary syndrome, atrial fibrillation, paroxysmal supraventricular tachycardia, ventricular tachycardia, angina pectoris, acute	Used study-specific cutoffs					• BNP: 4.57 (3.37, 6.20) • NT-proBNP: 3.48 (2.71, 4.46) • Either biomarker: 3.92 (3.23, 4.75)

				myocardial infarction, thromboembolic events, deep vein thrombosis, acute renal failure, transient ischemic attack, cardiac death, all-cause mortality, major arrhythmia, unstable angina, stroke, cardiac revascularization procedure						

Table 3. Studies identified since June 2012

Author	Study design & sample size	Study Population	Exposure	Outcome	Cutoff	Number of events	Results
Vertrugno 2013	Prospective; n=45	Pts undergoing repair of an infrarenal abdominal aortic aneurysm	Pre-and post-operative BNP	In-hospital cardiac events			Statistically significant difference in BNP between cases and non-cases
Amar 2012	Prospective; N=415	Patients >60y undergoing lung or esophageal surgery	Pre-operative BNP	Postoperative atrial fibrillation	Median: 30 ng/l	65 (16%)	OR: 4.52 (95% CI, 2.19-9.32) adjusted for age, gender, hypertension, coronary artery disease, preoperative use of β-blockers, and pneumonectomy
Park 2012	Prospective; N=97	elderly hypertensive patients after total knee or hip replacement	Post-operative BNP	Length of stay	217.5 ng/l	LoS>30 days=31 (32%)	No sig difference in BNP levels for LoS> vs < 30 days
Pili-Floury 2012	Prospective; N=75	hip-fractured patients aged ≥65 years	Pre-operative BNP	Pre-operative major echocardiographic abnormality	285 ng/l	24 (32%)	HR: 23.8 (3.7, 142.9)
Yang 2012	Prospective; N=365	non-cardiac vascular surgery	Pre-operative NT-proBNP	composite of acute myocardial infarction, congestive heart failure including acute pulmonary edema, and primary cardiac death within 5 days after surgery	302 ng/l	49 (13.4%)	No difference in AUC between NT-proBNP and RCRI; OR of NT-proBNP>302: 4.5 (2.3, 8.7)
Farzi 2013	Prospective; N=297	emergency non-cardiac procedures	Pre-and post-operative NT-proBNP	composite of non-fatal myocardial infarction (MI), acute heart failure, or death between index	Pre-op: 725 ng/l; Post-op:1600 ng/l	34 (11.4%) for in-hospital MACE	unadjOR for in-hospital MACE: 6.9 (3.5, 13.4); NS in adjusted analysis

Author	Study design & sample size	Study Population	Exposure	Outcome	Cutoff	Number of events	Results
				surgery and 3 yr follow-up; MACE	Preop for in-hospital MACE: 1740 ng/l		
Borges 2013	Prospective; N=145	intermediate and high risk cardiovascular patients undergoing noncardiac surgery.	Pre-and post-operative NT-proBNP	MACE: composite of vascular death, nonfatal myocardial infarction and nonfatal cardiac arrest after index surgery.	Pre-op: 917 ng/l Post-op: 2962 ng/l	17 (11%)	In multivariate analyses, preoperative NT-proBNP level > 917 pg/mL (OR 4.2; 95% CI: 1.38-12.62
James 2014	N=73	major elective non-cardiac surgery	Pre-op BNP, and cardiopulmonary exercise testing (CPET)	28-day MACE defined as myocardial infarction, cardiogenic pulmonary oedema, cardiac arrest, or complete heart block	Unclear	9 (12.3%)	BNP associated with MACE in unadjusted analysis. AUC of BNP for MACE: 0.75 (0.59–092). The predictive value of CPET derived variables was greater than that of scoring systems and plasma biomarkers, using AUC
Vetrugno 2014	227	elective prosthesis orthopedic surgery	Pre- and post-operative BNP	(MACE: atrial fibrillation, flutter, acute heart failure or non-fatal/fatal myocardial infarction)	Pre-op: 39 ng/l Post-op: 69 ng/l	14 (6%)	OR for MACE of pre-op BNP>39: 9.007 (95% CI: 1.051 – 77.191); not clear what other variables included in model; NRI of RCRI improved with addition of BNP
Katasanos 2015	Prospective; n=242	Elderly patients undergoing orthopedic surgery	Pre-operative BNP	In-hospital MACE and 1-yr morality	149 ng/l	MACE: 20 (8.3%); 1-yr mortality: 41 (21.1%)	HR for 1-yr mortality: 1.002, 95% CI: 1.000-1.003
Nojiri 2015	Restrospective study; n=675	curative surgery for lung cancer	Pre-operative BNP	Cardiovascular complications were defined as angina	Mildly elevated: 30 - 100 ng/l	Cardiovascular complications: 98 (15%)	All complications: OR for 1-unit BNP: 1.03 (1.02–1.04); BNP had best AUC (0.68) vs FEV, Beta-blockers, video-assisted thoracoscopic surgery

Author	Study design & sample size	Study Population	Exposure	Outcome	Cutoff	Number of events	Results
				pectoris, myocardial infarction, congestive heart failure, arrhythmias (atrial fibrillation, paroxysmal supraventricular tachycardia, ventricular tachycardia), and thromboembolic events	Severely elevated: >100 ng/l		
Ma 2015	Prospective; 2519	emergent non-cardiac surgery	NT-proBNP and cardiac troponin	30-day MACE (cardiac death, non-fatal myocardial infarction (MI), or cardiac arrest)	917 ng/l (not clear how this was determined)	251 (10.0%)	OR for MACE of NT-proBNP>917: 4.81 (95% CI: 3.45, 6.72); OR for MACE of cTNI)>0.07: 8.74 (95% CI 5.88–12.99) adjusting for age, sex, co-morbidities and pre-op meds
Toussaint 2016	Prospective; n=207	Liver transplant patients	Pre-operative BNP	ICU and 180-day Mortality	155 (ROC)	ICU mortality: 6%; 180-day mortality: 8%	HR for ICU mortality: 1.04 [1.02-1.05]; HR for 180-day mortality: 1.04 [1.01-1.06], adjusting for model of end stage liver disease
Nording 2016	Prospective;	Hip surgery patients	Pre-operative NT-proBNP	Short (30-day) and long (1000 day) term mortality	Intermediate: 806-2370 ng/l; High; >2370 ng/l	30-day mortality: 17 (9%) 100-day mortality: 48%	HR for 30-day mortality of Intermediate/high versus low NT-proBNP levels: 7.8 (95% CI 1.03 to 59.14) model including age, renal impairment, TnT elevation, NT-proBNP levels, ASA and Lee scores. HR for 1000-day mortality of Intermediate/high NT-proBNP levels: 2.27 (95% CI 1.30 to 3.96) adjusting for TnT elevation, age,

Author	Study design & sample size	Study Population	Exposure	Outcome	Cutoff	Number of events	Results
							renal impairment, the presence of dementia, atrial fibrillation and coronary artery disease, preoperative ASA and Lee's scores
Kim 2016	N=506	patients >70y with normal left ventricular function undergoing major non-cardiac surgery	Pre-operative NT-proBNP	major adverse cardiac and cerebrovascular events (MACCE)	425.3 ng/l	40 (7.9%)	OR for NT-proBNP>425.3: 6.381
Long 2016	N=1120	Pts undergoing primary total knee arthroplasty (TKA).	Preoperative BNP, postoperative BNP or the difference between them	Cardiac events	825.5 ng/l		Difference between the 2 measures best predicted cardiac evetns
Brecher 2017	Retrospective; n=191	Pts undergoing major lung or esophageal resection	preoperative transthoracic echocardiogram and serum BNP	postoperative atrial fibrillation (POAF)		41 (21%)	when evaluated together with greater preoperative left atrial diastolic volume index and transmitral flow deceleration time, BNP not sig assoc with POAF
Chokengarmwong 2017	N=387	general surgical and trauma patients admitted to the ICU	Pre-operative NT-proBNP	AF	600 ng/l		OR: 4.3; 95% CI, 1.3-14.2
Katsanos 2017	Prospective; n=152	Elderly Patients Undergoing Hip Fracture Surgery	Pre-and post-operative BNP	Major cardiac events in hospital; 1-year mortality	Pre-op: 190 ng/l; Post-op: 190 ng/l	In-hospital MACE: 9 (6%); 1-yr mortality: 37 (24%)	BNP not a significant predictor of 1-yr mortality
Ushirozako 2017	Prospective; n=328	Elderly Patients Undergoing Hip Fracture Surgery	Pre-operative NT-proBNP	Cardiac complications (congestive heart failure, major arrhythmia, acute	600 ng/l	24 (7%)	OR for NT-proBNP>600: 12.902 (95% CI: 4.39–37.93) after controlling for

Author	Study design & sample size	Study Population	Exposure	Outcome	Cutoff	Number of events	Results
				myocardial infarction, or cardiac death)			age, gender, body weight, and creatinine clearance
Kanakaraj 2017	Prospective; n=70	Patients undergoing infra-inguinal bypass surgery	Pre-operative NT-proBNP; cardiopulmonary exercise testing (CPET)	1-yr mortality; MACE	320 ng/l	1 yr mortality; 4(6%) MACE: (6) 8.5%	OR of 1-yr mortality ofr NT-proBNP>320: 18 (95% CI 2.5-140)
Golubovic 2018	Prospective; n=122	major vascular surgical patients	RCRI, V-POSSUM, NT-proBNP, hs-CRP, hs-TnI	myocardial infarction, arrhythmias, pulmonary edema, acute decompensated heart failure, and cardiac arrest within 90 days		13 (11%)	Models containing NT-proBNP+ RCRI+hs TnI+V-POSSSUM had the best AUC
Kopec 2018	Prospective; n=572	patients with known CAD or multiple risk factors for CAD who scheduled for major non-cardiac surgery	preoperative hs-cTnT and NT-proBNP	postoperative MI within the first three days after surgery	300 ng/l (based on literature)	30 (5.2%)	OR for cTnT: 3.15, (1.26, 7.26), OR NT-proBNP >300 ng/L): 1.43 (0.61, 3.35) in models also containing RCRI
Wijeysundera 2018	Prospective multicentre; n=1401	Pts ≥40 years scheduled for elective major non-cardiac with ≥1 risk factors for cardiac complications	Cardiopulmonary exercise testing [CPET], scores on the Duke Activity Status Index [DASI] questionnaire, and serum N-terminal pro-B-type natriuretic peptide [NT pro-BNP	death or myocardial infarction within 30 days	Continuous	28 (2%)	OR of log transformed NT-proBNP for 30-day MI or death: 1.78 (1.21, 2.62) after adjusting for age, sex, and RCRI score

Author	Study design & sample size	Study Population	Exposure	Outcome	Cutoff	Number of events	Results
Binh 2019	Prospective; n=366	non-cardiac surgical patients with moderate or high risk	NT-proBNP vs RCRI	MACE (myocardial infarction, pulmonary edema, severe cardiac arrhythmias, and cardiac death occurring within 30 days)			AUC of NT-proBNP + RCRI not significantly different from AUC of NT-proBNP alone
Pu 2019	Retrospective; n=207	Pts undergoing non-cardiac thoracic surgery	Pre-operative BNP	Postoperative atrial fibrillation	59 ng/l	46 (22%)	male gender, open thoracotomy, and BNP at the level of 59 pg/mL associated with POAF
Amar 2019	Retrospective; n=635	Patients in sinus rhythm before anatomic lung (n = 540) or esophageal (n = 95) resection.	Pre-operative BNP	Postoperative atrial fibrillation	57.5 vs 12.5 ng/l	124 (20%)	BNP level (75th vs 25th percentile, 57.5 vs 12.5 pg/mL; OR, 2.08; 95% CI, 1.26-3.43;
Young 2019	N=27	patients undergoing lung resection	Pre- and post-operative BNP	functional deterioration was assessed using 6-min walk test		17 (63%)	AUC of BNP 0.82
Tang 2019	Retrospective; n=335	radical surgery of esophageal cancer.	Pre-operative BNP and 12 other risk factors	AF	100 ng/l	48 (14%)	OR: 41.515; CI: 9.380-183.732; along with age, sex, history of cardiac stents or angina pectoris, open surgery, intraoperative blood transfusion, adhesion between lymph nodes and pericardium
Duceppe 2019	Prospective cohort; multicentre (16 centres, 9 countries) n=10,402	patients aged 45 years or older having inpatient non-cardiac surgery (a sub-study of the VISION study)	Pre-operative NT-proBNP	Composite of vascular death and myocardial injury after non-cardiac surgery (MINS) within 30 days after surgery	<100 ng/l (reference)	1269 (12%)	Adj HR vs <100 ng/l: 100-<200 ng/l: 2.27 (95% CI, 1.90 to 2.70) 200-<1500 ng/l: 3.63 (CI, 3.13 to 4.21) ≥1500 ng/l: 5.82 (CI, 4.81 to 7.05)

REFERENCES

1. Semel ME, Lipsitz SR, Funk LM, Bader AM, Weiser TG, Gawande AA. Rates and patterns of death after surgery in the United States, 1996 and 2006. *Surgery.* 2012;151(2):171-182.

2. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study I, Devereaux PJ, Chan MTV, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA.* 2012;307(21):2295-2304.

3. Devereaux PJ, Sessler DI. Cardiac Complications in Patients Undergoing Major Noncardiac Surgery. *New England Journal of Medicine.* 2015;373(23):2258-2269.

4. Gilbert K, Larocque BJ, Patrick LT. Prospective evaluation of cardiac risk indices for patients undergoing noncardiac surgery. *Annals of internal medicine.* 2000;133(5):356-359.

5. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *The New England journal of medicine.* 1977;297(16):845-850.

6. Larsen SF, Olesen KH, Jacobsen E, et al. Prediction of cardiac risk in non-cardiac surgery. *European Heart Journal.* 1987;8(2):179-185.

7. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and Prospective Validation of a Simple Index for Prediction of Cardiac Risk of Major Noncardiac Surgery. *Circulation.* 1999;100(10):1043-1049.

8. Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. *Canadian Journal of Cardiology.* 2017;33(1):17-32.

9. Gupta PK, Gupta H, Sundaram A, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. *Circulation.* 2011;124(4):381-387.

10. Kumar R, McKinney WP, Raj G, et al. Adverse cardiac events after surgery: assessing risk in a veteran population. *Journal of general internal medicine.* 2001;16(8):507-518.

11. Detsky AS, Abrams HB, McLaughlin JR, et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. *Journal of general internal medicine.* 1986;1(4):211-219.

12. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the

problem, the pathophysiology of the events and methods to estimate and communicate risk. *Canadian Medical Association Journal.* 2005;173(6):627-634.

13. Biccard B. Proposed research plan for the derivation of a new Cardiac Risk Index. *Anesthesia and analgesia.* 2015;120(3):543-553.

14. Kertai MD, Boersma E, Bax JJ, et al. A meta-analysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery. *Heart.* 2003;89(11):1327-1334.

15. Beattie WS, Abdelnaem E, Wijeysundera DN, Buckley DN. A meta-analytic comparison of preoperative stress echocardiography and nuclear scintigraphy imaging. *Anesthesia and analgesia.* 2006;102(1):8-16.

16. Sheth T, Chan M, Butler C, et al. Prognostic capabilities of coronary computed tomographic angiography before non-cardiac surgery: prospective cohort study. *BMJ (Clinical research ed.).* 2015;350:h1907.

17. Bonow RO. New Insights Into the Cardiac Natriuretic Peptides. *Circulation.* 1996;93(11):1946-1950.

18. Kim H-N, Januzzi JL. Natriuretic Peptide Testing in Heart Failure. *Circulation.* 2011;123(18):2015-2019.

19. Wang TJ, Larson MG, Levy D, et al. Plasma Natriuretic Peptide Levels and the Risk of Cardiovascular Events and Death. *New England Journal of Medicine.* 2004;350(7):655-663.

20. Rodseth RN, Biccard BM, Le Manach Y, et al. The Prognostic Value of Pre-Operative and Post-Operative B-Type Natriuretic Peptides in Patients Undergoing Noncardiac Surgery. *B-Type Natriuretic Peptide and N-Terminal Fragment of Pro-B-Type Natriuretic Peptide: A Systematic Review and Individual Patient Data Meta-Analysis.* 2014;63(2):170-180.

21. Rodseth RN, Lurati Buse GA, Bolliger D, et al. The Predictive Ability of Pre-Operative B-Type Natriuretic Peptide in Vascular Patients for Major Adverse Cardiac Events. *An Individual Patient Data Meta-Analysis.* 2011;58(5):522-529.

22. Ryding Alisdair DS, M.R.C.P., Ph.D., Kumar S, M.B.B.S., Worthington Angela M, M.B.B.S., Burgess D, F.R.A.C.P., Ph.D. Prognostic Value of Brain Natriuretic Peptide in Noncardiac Surgery: A Meta-analysis. *Anesthesiology: The Journal of the American Society of Anesthesiologists.* 2009;111(2):311-319.

23. Karthikeyan G, Moncur RA, Levine O, et al. Is a Pre-Operative Brain Natriuretic Peptide or N-Terminal Pro–B-Type Natriuretic Peptide Measurement an Independent Predictor of Adverse Cardiovascular Outcomes Within 30 Days of Noncardiac Surgery?

A Systematic Review and Meta-Analysis of Observational Studies. 2009;54(17):1599-1606.

24. Zhang LJ, Li N, Li Y, Zeng XT, Liu MY. Cardiac Biomarkers Predicting MACE in Patients Undergoing Noncardiac Surgery: A Meta-Analysis. *Frontiers in physiology.* 2018;9:1923.

25. Young YR, Sheu BF, Li WC, et al. Predictive value of plasma brain natriuretic peptide for postoperative cardiac complications--a systemic review and meta-analysis. *Journal of critical care.* 2014;29(4):696 e691-610.

26. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation.* 2007;115(7):928-935.

27. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Statistics in medicine.* 2008;27(2):157-172; discussion 207-112.

28. Leening MJ, Vedder MM, Witteman JC, Pencina MJ, Steyerberg EW. Net reclassification improvement: computation, interpretation, and controversies: a literature review and clinician's guide. *Annals of internal medicine.* 2014;160(2):122-131.

29. Alba AC, Agoritsas T, Walsh M, et al. Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. *JAMA.* 2017;318(14):1377-1384.

30. Steyerberg EW, Van Calster B, Vickers AJ. The net absolute reclassification index (NARI) should be quickly forgotten. . *BMJ (Clinical research ed.).* 2016;350:h1907.

31. Leening MJ, Pencina MJ. Absolute vs Additive Net Reclassification Index. *JAMA.* 2018;319(6):616.

32. Vanniyasingam T, Rodseth RN, Lurati Buse GA, et al. Predicting the occurrence of major adverse cardiac events within 30 days of a vascular surgery: an empirical comparison of the minimum p value method and ROC curve approach using individual patient data meta-analysis. *SpringerPlus.* 2016;5:304.

33. Wijeysundera DN, Pearse RM, Shulman MA, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. *Lancet (London, England).* 2018;391(10140):2631-2640.

34. Duceppe E, Patel A, Chan MTV, et al. Preoperative N-Terminal Pro-B-Type Natriuretic Peptide and Cardiovascular Events After Noncardiac Surgery: A Cohort Study. *Annals of internal medicine.* 2019.

35. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *Journal of the American College of Cardiology.* 2018;72(18):2231-2264.

36. Binh TQ, Trang DV, Vuong NL, et al. NT-proBNP incorporated in prediction rule of major peri-operative adverse cardiac event in non-cardiac surgery. *The Surgeon.* 2019;17(3):127-132.

37. Kopec M, Duma A, Helwani MA, et al. Improving Prediction of Postoperative Myocardial Infarction With High-Sensitivity Cardiac Troponin T and NT-proBNP. *Anesthesia and analgesia.* 2017;124(2):398-405.

38. Potgieter D, Simmers D, Ryan L, et al. N-terminal pro-B-type Natriuretic Peptides' Prognostic Utility Is Overestimated in Meta-analyses Using Study-specific Optimal Diagnostic Thresholds. *Anesthesiology.* 2015;123(2):264-271.

39. Collinson PO, Heung YM, Gaze D, et al. Influence of population selection on the 99th percentile reference value for cardiac troponin assays. *Clinical chemistry.* 2012;58(1):219-225.

40. Shah AS, Griffiths M, Lee KK, et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ (Clinical research ed.).* 2015;350:g7873.

41. Pepe MS, Fan J, Feng Z, Gerds T, Hilden J. The Net Reclassification Index (NRI): a Misleading Measure of Prediction Improvement Even with Independent Test Data Sets. *Statistics in biosciences.* 2015;7(2):282-295.

42. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* 2014;64(22):e77-e137.

43. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2014;35(35):2383-2431.

44. Ministère de la Santé et des Services sociaux. *Répertoire québécois et système de mesure des procédures de biologie médicale 2019-2020: Les annexes.* 2019. http://publications.msss.gouv.qc.ca/msss/fichiers/2017/17-922-05W.pdf. Accessed August, 2019.

45. Ford MK, Beattie WS, Wijeysundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. *Annals of internal medicine.* 2010;152(1):26-35.

46. Vetrugno L, Orso D, Matellon C, Giaccalone M, Bove T, Bignami E. The Possible Use of Preoperative Natriuretic Peptides for Discriminating Low Versus Moderate-High Surgical Risk Patient. *Seminars in Cardiothoracic and Vascular Anesthesia.* 2018;22(4):395-402.