Queen's UNIVERSITY

DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Thursday April 28, 2016
1800 HOURS

LOCATION:
Aqua Terra
1 Johnson Street

PRESENTING ARTICLES:
Dr. Rick Zamora & Dr. Curtis Nickel

Sponsored by: Abbvie – Ms. Penny Reid

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?

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REPORTS OF ORIGINAL INVESTIGATIONS

The Revised Cardiac Risk Index in the new millennium: a single-centre prospective cohort re-evaluation of the original variables in 9,519 consecutive elective surgical patients

L'indice de risque cardiaque modifié dans le nouveau millénaire: une réévaluation prospective et unicentrique de cohorte des variables originales chez 9519 patients consécutifs devant subir une chirurgie non urgente

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Abstract

Purpose *Cardiac complications following non-cardiac surgery are major causes of morbidity and mortality. The Revised Cardiac Risk Index (RCRI) has become a standard for predicting post-surgical cardiac complications. This study re-examined the original six risk factors to confirm their validity in a large modern prospective database.*

Methods *Using the definitions in the original risk index, this study included 9,519 patients aged ≥ 50 undergoing elective non-cardiac surgery with an expected length of stay ≥ two days at two major tertiary-care teaching hospitals. The validity of the original predictors was tested in this population using binomial logistic regression modelling, area under the receiver operator curve (ROC) analysis, and the net reclassification index.*

Results *Rates of major cardiac complications with 0, 1, 2, ≥ 3 of the predictors were 0.5%, 2.6%, 7.2%, and 14.4%, respectively, in our patient cohort compared with 0.4%, 1.1%, 4.6%, and 9.7%, respectively, in the original cohort. Similar to the original report, binary logistic regression analysis showed that both preoperative treatment with insulin (odds ratio [OR] 1.4; 95% confidence interval [CI] 0.7 to 2.6) and preoperative creatinine > 176.8 mmol·L^{-1} (OR 1.7; 95% CI 0.8 to 3.6) did not improve the predictive ability of the index. Analysis of the remaining four factors resulted in an area under the curve (AUC) identical to that seen for the reconstructed six-factor RCRI (AUC = 0.79). We found that a*

Author contributions *Christopher Davis* organized and performed the analysis, wrote the first draft of the manuscript, and was responsible for major revisions to both the analysis and manuscript. *Gordon Tait* was responsible for creation of the database and the data integrity. He performed and or supervised quality checks on the data and helped perform the data analysis. *Gordon Tait, Jo Carroll,* and *Duminda N. Wijeysundera* made key revisions to the manuscript. *Jo Carroll* assisted in the creation of the database and quality control of the data. *Duminda N. Wijeysundera* and *W. Scott Beattie* were responsible in part for the concept of the study. *Duminda N. Wijeysundera* revised key aspects of the data analysis. *W. Scott Beattie* was responsible in part for supervision of the project. He obtained funding for the project, helped write all drafts of the manuscript, and made revisions to the data analysis. Dr. Beattie was Mr. Davis's summer elective supervisor. All authors have seen the data analysis and the revised manuscript and vouch for the authenticity of all aspects of this manuscript.

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glomerular filtration rate (GFR) < 30 mL·min^{-1} was a better predictor of major cardiac complications (OR 2.2; 95% CI 1.2 to 4.3) than creatinine > 176.8 mmol·L^{-1}. The receiver operating characteristic analysis of this resultant 5-Factor model resulted in an AUC of 0.79, with 0, 1, 2, ≥ 3 of the predictors representing 0.5%, 2.9%, 7.4%, and 17.0% risk, respectively, among our patient cohort.

Conclusion *Compared with the RCRI, a simplified 5-Factor model using a high-risk type of surgery, a history of ischemic heart disease, congestive heart failure, cerebrovascular disease, and a preoperative GFR < 30 mL·min^{-1} results in superior prediction of major cardiac complications following elective non-cardiac surgery.*

Résumé

Objectif *Les complications cardiaques suite à une chirurgie non cardiaque constituent d'importantes causes de morbidité et de mortalité. L'indice de risque cardiaque modifié (IRCM) est devenu un étalon or pour prédire les complications cardiaques après une chirurgie. Cette étude a réévalué les six facteurs de risque originaux afin de confirmer leur validité dans une importante base de données prospective et moderne.*

Méthode *À l'aide des définitions de l'indice de risque d'origine, cette étude a inclus 9519 patients âgés ≥ 50 ans subissant une chirurgie non cardiaque non urgente, dont la durée de séjour prévue était de deux jours ou plus dans deux importants hôpitaux universitaires de soins tertiaires. La validité des prédicteurs originaux a été testée dans cette population à l'aide d'un modèle de régression logistique binomiale, d'une analyse de la surface sous la courbe ROC, et de l'indice NRI (net reclassification index).*

Résultats *Les taux de complications cardiaques majeures avec 0, 1, 2, ≥ 3 des prédicteurs étaient de 0,5 %, 2,6 %, 7,2 %, et 14,4 %, respectivement, dans notre cohorte de patients, comparativement à 0,4 %, 1,1 %, 4,6 %, et 9,7 %, respectivement, dans la cohorte originale. Tout comme dans le compte rendu original, l'analyse de régression logistique binaire a montré que ni un traitement préopératoire avec de l'insuline (rapport de cotes [RC] 1,4; intervalle de confiance [IC] 95 % 0,7 à 2,6), ni un taux de créatinine préopératoire > 176,8 mmol·L^{-1} (RC 1,7; IC 95 % 0,8 à 3,6) n'amélioraient la capacité prédictive de l'indice. L'analyse des quatre autres facteurs a donné une surface sous la courbe (SSC) identique à celle observée pour l'IRCM à six facteurs reconstruit (SSC = 0,79). Nous avons observé qu'un débit de filtration glomérulaire (DFG) < 30 mL·min^{-1} était un meilleur prédicteur de complications cardiaques majeures (RC 2,2; IC 95 % 1,2 à 4,3) qu'un taux de créatinine > 176,8 mmol·L^{-1}. L'analyse de la courbe ROC de ce modèle à 5 facteurs a donné une SSC de 0,79, avec 0, 1, 2, ≥ 3 prédicteurs représentant un risque de 0,5 %, 2,9 %, 7,4 %, et 17,0 %, respectivement, dans notre cohorte de patients.*

Conclusion *Par rapport à l'IRCM, un modèle simplifié à 5 facteurs utilisant un type de chirurgie à risque élevé, des antécédents de cardiopathie ischémique, une insuffisance cardiaque congestive, une maladie cérébrovasculaire et un DFG préopératoire < 30 mL·min^{-1} donne une meilleure prédiction de complications cardiaques majeures après une chirurgie non cardiaque non urgente.*

The most frequent cause of postoperative morbidity and mortality is as a direct result of an adverse cardiac event.[1] This is a major public health issue since mortality rates remain in excess of 2%[1,2] in the more than 200 million surgical procedures that occur annually around the world.[3] In an effort to reduce this burden, the American College of Cardiology/American Heart Association guidelines committee[4] has adopted the Revised Cardiac Risk Index (RCRI)[5] to preoperatively identify elective patients at risk of major cardiac complications. The RCRI has subsequently been found to be practicable, accurate, and generalizable.[6]

The RCRI was derived from a prospective cohort of elective surgical patients and used creatinine kinase-MB (CK-MB) to identify postoperative cardiac events. The "revised" nomenclature specified that the RCRI built on and simplified an earlier index.[7] The RCRI was derived from a cohort of 4,315 patients, where 2,893 were used to derive the index, i.e., the "derivation set", and 1,422 patients were assigned to the "validation set". The index is composed of six predictive factors: high-risk type of surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine > 177 mmol·L^{-1}. Each factor in the model is equally weighted with one point assigned per predictor and with increasing point totals corresponding to an increase in the patient's overall postoperative cardiac risk. Interestingly, the risk factors "preoperative treatment with insulin" and "preoperative serum creatinine > 177 mmol·L^{-1}" did not remain significant in the validation process of the original communication. Nevertheless, these factors were included in the model and have remained in the index because comparison of the odds ratios in the derivation and validations sets were "not statistically different". The original description did show that exclusion of these two factors, i.e., diabetes and chronic renal failure, resulted in a model with superior discrimination. Presently, almost a quarter century after the first patients were entered in the model, use of the RCRI is now widespread.[8-11] In this interval, the diagnostic criteria

for myocardial infarction have changed,[12] and we are unaware of any studies that have re-examined the two factors, diabetes and chronic renal failure. As a result, we submit there is a need to re-examine the accuracy and clinical utility of the index.

The primary objective of this study was to re-examine the validity of the inclusion of the two predictors, diabetes and chronic renal failure, in the RCRI using a large modern prospectively collected data set. Our hypothesis was that neither diabetes nor this definition of chronic renal failure improved the accuracy or discrimination of the RCRI. The secondary objectives of this study were to evaluate alternative definitions of preoperative renal function and diabetes or glucose tolerance on the predictive accuracy of the RCRI.

Methods

The University Health Network (UHN) Research Ethics Board approved this study and waived the need for informed consent. The UHN is a university-based tertiary care hospital that performs a full range of adult surgical procedures. Our goal *a priori* was to reproduce, as closely as possible, the conduct of the original investigation.[4] We therefore included consecutive elective patients, over the age of 50, who were screened in the preoperative assessment clinic for elective inpatient non-cardiac surgery with a length of stay of at least two days. The preoperative data were prospectively collected from April 1, 2008 to December 31, 2010 and extracted from two separate electronic databases. Preoperative data were collected from our Clinical Anesthesia Information System (CAIS) (Adjuvant Informatics, Freelton, ON, Canada). The CAIS is a standardized web-based preoperative assessment tool developed by the UHN to evaluate all elective surgical patients. Patient information was entered into the CAIS by advanced practice nurses at pre-scheduled appointments. The CAIS collects information using standardized branched logic. The collected data include patient demographics, vital signs, detailed histories (and their treatments), including the components of the RCRI, preoperative lab values, results of noninvasive tests, and a full medication history, including instructions of when to stop or continue the medications. Postoperative data were extracted from the institutional electronic data warehouse (EDW) and included data relating to the surgical procedure, postoperative laboratory values, as well as postoperative patient outcomes. The EDW data are largely obtained from the International Classification of Diseases tenth revision (ICD-10) codes. Myocardial injury was assessed using troponin I on the Abbott ARCHITECT i2000SR® analyzer (Abbott Diagnostics Abbott Park, IL, USA). The peak postoperative troponin level—defined as the highest level at any time postoperative until discharge—was assessed. We have recently shown an error rate of $< 2\%$ in a direct comparison of the patient chart *vs* the EDW data at the UHN.[13]

During the study period, the UHN preoperative assessment clinics evaluated 15,597 consecutive patients, each having a complete CAIS data set. We excluded 4,073 patients who were under the age of 50 or had either urgent or emergent procedures. A further 2,005 patients were excluded due to a hospital length of stay that was less than two days, leaving a final study population of 9,519 patients. The six RCRI predictors and the outcome variable, major cardiac complications (MCCs), were reconstructed using the original criteria. We therefore defined MCCs using a definition similar to the original RCRI as the postoperative occurrence of any or all of myocardial infarction, pulmonary edema, or primary cardiac arrest. This differs from the primary paper in the following ways:

1) Due to limitations within the CAIS data, a history of paroxysmal nocturnal dyspnea was excluded.
2) The term "pulmonary edema" was based on ICD-10 codes instead of a formal reading of the chest radiograph.
3) The terms "complete heart block" and "ventricular fibrillation" were not available and are thus excluded from the derivation of MCCs (Table 2).

All other predictors used were derived as outlined in the original investigation. Using the reproduced risk predictors, the eligible patients in the study database were then individually categorized as per the RCRI scoring system.

Statistical analysis was conducted with SPSS® version 19 (IBM, Armonk, NY, USA). A reproduced RCRI model using the CAIS data was generated in a fashion identical to the original RCRI using the original predictors and forced entry binary logistic regression. Next, to test the importance of the six factors to the overall quality of the model, a forward conditional entry model was generated, again using binary logistic regression. Finally, the addition of supplementary predictors to the simplified model was tested using individual substitution into the model and a forward conditional build. The candidate variables assessed in this aspect of the analysis were alternative definitions of diabetes. For diabetes, we sequentially assessed the terms "diabetic yes or no", "preoperative glucose $>$ 11.1 mmol·L^{-1}", and "glucose categories ($<$ 7.8, 7.8 to 11.1, and $>$ 11.1 mmol·L^{-1}). For renal failure, we also assessed two levels of glomerular filtration rate (GFR) (30 and 60 mL·min^{-1}), calculated using the Cockcroft-Gault

Table 1 Study cohort comparison between RCRI and CAIS data: includes percentage breakdown by individual surgical category for the CAIS data

	Women, %	Mean age, yr	High Risk Surgery,[1] %	CAD,[2] %	Diabetes,[3] % (% on insulin)	CHF,[4] %	CVD,[5] %	Renal Insufficiency,[6] %	Hypertension,[7] %
Lee *et al*., 1999	51.4	NR	32.1	33.1	NR (4.0)	16.0	10.0	3.7	NR
CAIS data overall	48.5	66.0	26.3	18.5	17.0 (2.4)	3.0	7.2	1.4	52.4
Surgical Subtype									
Abdominal (n = 1,318, 14%)	47.4	65.7	97.1	18.2	22.3 (4.7)	3.8	6.1	1.8	51.4
Orthopedic (n = 2,264, 24%)	60.0	67.5	0.0	17.0	15.6 (1.2)	2.9	5.2	0.5	56.5
Thoracic (n = 1,011, 11%)	49.0	65.6	99.1	20.1	12.8 (1.5)	2.3	4.5	0.9	46.2
Vascular (n = 461, 5%)	24.5	72.0	47.1	52.7	27.5 (5.4)	9.8	27.5	4.8	82.0
Other (n = 4,465, 47%)*	45.4	64.9	0.0	15.5	16.0 (2.2)	2.2	7.1	1.4	49.0

CAIS = Clinical Anesthesia Information System; RCRI = original dataset for derivation and validation of the Revised Cardiac Risk Index; NR = not reported

[1] Defined as intraperitoneal, intrathoracic or suprainguinal vascular procedures, cardiac ischemia, use of nitrate therapy

[2] Defined as coronary artery disease

[3] Defined as total % diabetics (CAIS), of this 2.4% are on insulin therapy (CAIS)

[4] Defined as history of congestive heart failure (CAIS), excluded pulmonary edema on chest *x-ray*, paroxysmal nocturnal dyspnea, physical exam showing bilateral rales or S3 gallop

[5] Cardiovascular disease - defined as history of either stroke or transient ischemic attack (CAIS)

[6] Defined as preoperative serum creatinine > 176.6 mmol·L^{-1} (CAIS)

[7] Defined as history of hypertension (CAIS) or hypertension requiring medical control of blood pressure (CAIS)

*"Other" category composed of gastrointestinal, ear nose and throat, neurological surgeries

equation.[A] The threshold for inclusion was $P < 0.05$ for all models generated. The generated models were then compared using receiver operating characteristic (ROC) curves and area under the curve (AUC) analysis and using the net reclassification index.[14] Odds ratios for each of the original six factors and the additional factors tested were also calculated, and the discrimination of the new models (ROC and 95% confidence interval [CI]) was compared with those in the original report.

Results

The two study populations, the original RCRI description of 4,315 elective patients and the CAIS population of 9,519, are compared in Table 1. Of importance is the slightly higher percentage of males in the CAIS data. The original data did not report the mean age of the study population or the percentage of the study population with hypertension. Each of six component risk factors is less frequent in the CAIS data compared with the original description. Table 1 also includes a subset breakdown by surgical classification that is different from the original RCRI data. The present study had more abdominal surgeries but fewer orthopedic and vascular procedures. The category "Other" surgery included genitourinary, neurosurgery, and ear nose and throat surgeries and included significantly more than in the original RCRI manuscript.

The prevalence of MCCs in each of the six component risk factors is compared with the original RCRI in Table 2. The CAIS and RCRI data sets show that events occurred more often in patients with a "history of ischemic heart disease" and "congestive heart failure". The remaining four risk factors had similar rates of MCCs. The rates of myocardial infarction (MI) are measured by troponin I as compared with creatine kinase in the original RCRI description. The terms "complete heart block", which was recorded in only 0.1% of the RCRI population (4/4,315), and "ventricular fibrillation", were not available in the CAIS data. Ventricular fibrillation was combined with cardiac arrest in the RCRI data (0.4%, 16/4,315), but in the CAIS data, cardiac arrest was recorded alone (0.3%, 34/9,519) (relative risk [RR] 0.96; 95% CI 0.53 to 1.74). The overall rate of MCCs did not differ between the two studies (Table 3).

[A] The Cockcroft-Gault equation is generated using age, weight, sex, and serum creatinine level *g*lomerular filtration rate ($GFR = (140 - age \times weight\ [kg] \times constant) / serum\ creatinine\ (umol \cdot L^{-1})$). The constant is 1.23 for men and 1.04 for women. This estimated *g*lomerular filtration rate (eGFR) is automatically calculated in the Clinical Anesthesia Information System using this equation. Available from URL: http://en.wikipedia.org/wiki/Renal_function (accessed May 10, 2013).

Table 2 Comparison of the components of RCRI: CAIS *vs* original (4): The occurrence of major cardiac complications (MCCs) postoperatively

Revised Cardiac Risk Index: predictors	CAIS data		RCRI data		Relative risk of MCCs (95% CI)
	MCCs / *n*	(%)	MCCs / *n*	(%)	
1. High-risk surgery type	87 / 2,499	(3.4)	27 / 894	(3.0)	1.15 (0.75 to 1.76)
2. History of ischemic heart disease	104 / 1,762	(5.9)	34 / 951	(3.6)	1.65 (1.13 to 2.41)
3. History of congestive heart failure	33 / 284	(11.6)	23 / 434	(5.3)	2.12 (1.35 to 3.65)
4. History of cerebrovascular disease	41 / 685	(6.0)	17 / 291	(5.8)	1.02 (0.59 to 1.77)
5. Preoperative treatment with insulin	12 / 225	(5.3)	7 / 112	(6.3)	0.85 (0.35 to 2.10)
6. Preoperative creatinine > 176 mmol·L^{-1}	9 / 131	(6.9)	9 / 103	(8.7)	0.78 (0.32 to 1.91)

The relative risk compares the outcomes (MCCs) between CAIS and original data for each component risk factor

RCRI data = original derivation and validation of the Revised Cardiac Risk Index; CAIS = Clinical Anesthesia Information System; CI = confidence interval

Table 3 Primary outcome: comparison of the components of the composite

Major cardiac complications	CAIS data (Total = 9,519) *n* (%)	RCRI data (Total = 4,315) *n* (%)	*P* value
Major cardiac complication	200 (2.1)	92 (2.1)	0.957
Myocardial *infarction*	163 (1.7)	46 (1.1)	0.005
Pulmonary edema	19 (0.2)	42 (1.0)	< 0.001
Cardiac arrest/ventricular	34 (0.3)	16 (0.4)	0.795
Fibrillation*			
Complete heart block	Not Available	4 (0.1)	

*CAIS data did not include ventricular fibrillation data;

CAIS = Clinical Anesthesia Information System; RCRI data = original derivation and validation data for the Revised Cardiac Risk Index

Table 4 Comparison of the original RCRI model with models generated using CAIS data: Individual risk stratification by point score and resultant model AUC

Model	Events/Total, by Model Score, *n*/*n* (%)				AUC (95% CI)	NRI
	0 Points	1 Point	2 Points	≥ 3 Points		
RCRI data 1999[1]	7 / 1,559 (0.4)	19 / 1,673 (1.1)	35 / 764 (4.6)	31 / 319 (9.7)	0.78 (0.73 to 0.82)	
CAIS data (Reconstructing RCRI)	25 / 5,276 (0.5)	81 / 3,145 (2.6)	65 / 897 (7.2)	29 / 201 (14.4)	0.79 (0.76 to 0.83)	
4-Factor model* (CAIS data)	25 / 5,397 (0.5)	87 / 3,156 (2.8)	70 / 842 (8.3)	18 / 124 (14.5)	0.79 (0.76 to 0.82)	−5.2%, $P = 0.246$
5-Factor model (Using eGFR < 30 mL·min^{-1})**	21 / 4,446 (0.5)	78 / 2,693 (2.9)	56 / 753 (7.4)	23 / 135 (17.0)	0.79 (0.75 to 0.82)	−0.4%, $P = 0.049$

*Original RCRI predictors, including high-risk type of surgery, a history of ischemic heart disease, congestive heart failure, cerebrovascular disease, but removing "insulin therapy for diabetes" and "preoperative serum creatinine > 176.8 mmol·L^{-1}"

**4-Factor model with the addition of glomerular filtration rate (GFR) < 30 mL·min^{-1}. Not all patients had data necessary to calculate GFR (n = 8,027 used, total MCCs n = 178). RCRI = Revised Cardiac Risk Index; CAIS = Clinical Anesthesia Information System; AUC = area under the curve; CI = confidence interval; NRI = net reclassification index; eGFR = estimated glomerular filtration rate; The NRI tables are in the Appendix

The rates of MCCs in the original RCRI model were 0.4%, 1.1%, 4.6%, and 9.7% for 0, 1, 2, and ≥ 3 points, respectively, with an AUC value of 0.78 (95% CI 0.73 to 0.82). The comparable rates using the CAIS data were 0.5%, 2.6%, 7.2%, and 14.4% risk of MCCs, respectively, for the same categories. The AUC was 0.79 (95% CI 0.76 to 0.83) (Table 4). When the model was re-calculated using forward conditional entry, the terms "insulin therapy for diabetes" and "preoperative creatinine > 176 mmol·L^{-1}" did not remain in the model, creating the "4-Factor model". The percentages of predicted MCCs by point class remain essentially the same, and the AUC value is unchanged in this model.

Evaluation of the alternative definitions of diabetes and renal failure were attempted after finding that "preoperative treatment with insulin" (odds ratio [OR]

1.4; 95% confidence interval [CI] 0.7 to 2.6) and "preoperative creatinine > 177 mmol·L^{-1}" (OR 1.7; 95% CI 0.8 to 3.6) were not significant and did not improve the discrimination of the index. The terms "diabetic yes or no" (OR 1.4; 95% CI 1.0 to 2.0), "preoperative glucose > 11.1 mmol·L^{-1}" (OR 1.5; 95% CI 0.8 to 2.6), and "glucose categories (< 7.8, 7.8-11.1, > 11.1 mmol·L^{-1})" (OR 1.2; 95% CI 1.0 to 1.6) were evaluated, but none of these definitions improved the discrimination of the index (Table A2). Furthermore, two alternative models were then generated. In the model with five variables, the fifth variable used GFR < 30 mL·min^{-1}. This model showed the same percent of predicted MCCs as the model without GFR but improved calibration. The relative variances between the RCRI point categories resulting from the above modifications and the original reconstructed RCRI model are detailed in Table A1. The 4-Factor model shifts both MCCs and overall patients in the 2 and ≥ 3 point categories to lower point ranges and results in no significant change in the net reclassification index. The 5-Factor model with GFR < 3 0 mL·min^{-1} also loses patients from the 2 and ≥ 3 categories but to a less extent than the 4-Factor model and to a significantly less extent than patients who experienced MCCs in the ≥ 3 category; therefore, the net reclassification index is marginally improved.

Discussion

This study reinforces the importance and validity of the RCRI as a means of predicting major cardiac events after elective surgery. Almost two decades later, in spite of rapidly changing surgical techniques[15,16] and improvements to clinical diagnostic testing,[11,17,18] the factors identified in the original report are relevant in a modern elective surgical patient population. Through all of the modelling procedures, any combination of the terms (high-risk type of surgery, history of ischemic heart disease, history of congestive heart failure, and history of cerebrovascular disease) remained discriminatory.

The results of the present study are remarkably similar to those in the original description, and in its current form, the model contains two factors, documented in this analysis, that do not improve its risk prediction. As in the original description, the removal of these factors does not affect the final risk stratification or the improved discrimination of the index. A recent large retrospective analysis of the Veterans Affairs Medical Center surgical database also failed to find diabetes as a significant predictor of cardiac outcomes.[19] Focused attempts to include modified terms related to diabetes mellitus or preoperative blood sugar levels could not significantly improve the ability to predict the risk of MCCs or improve the accuracy or the discrimination of the index. Glycosylated hemoglobin has been advocated as an important risk factor in diabetic outcomes and may be a factor that could potentially improve the index;[20-22] however, the data in our database were insufficient to assess this variable. In our view, it would be important to drop the diabetes terminology from the RCRI; inclusion has the potential to create patient safety issues. We consider this an important issue, even though investigation shows that inclusion of diabetes does not influence the overall statistical integrity of the predictive model. We do not debate that diabetes continues to be highly associated with cardiac disease, renal failure, and cerebral vascular disease, all of which remain highly predictive of postoperative major cardiac events. When diabetes is the ONLY risk factor, we are concerned that it may lead to an inappropriate intervention. Consider the pay per performance guidelines that were implemented in the USA making beta-blockers a quality of care indicator. In response, all patients with a cardiac risk were required to have beta-blockers administered perioperatively. Subsequently, at least two investigations have shown a 30% increase in mortality when beta-blockers were administered to patients where diabetes was the ONLY risk factor.[9,23]

Our investigation did identify a potential alternative definition of chronic renal failure, specifically, a preoperative GFR of < 30 mL·min^{-1}. A reconstituted 5-Factor model, including cardiovascular disease, coronary artery disease, congestive heart failure, high-risk surgery, and GFR < 30 mL·min^{-1}, maintained the same discrimination value and slightly improved the net reclassification, mostly in patients at higher risk for MCCs. The addition of a calculated GFR of < 60 mL·min^{-1} resulted in less improvement in either the discrimination or the calibration. This definition does have the advantage of being the threshold for chronic kidney disease as defined by the National Kidney Foundation.[19] On the basis of these considerations, we would advocate for a 5-Factor model where the renal component is denoted by a low GFR and diabetes is dropped from the index.

This evaluation of a prospectively collected moderate-risk elective non-cardiac surgical population has several important differences compared with the original population derived for the RCRI. All six RCRI predictors are less prevalent in our study population compared with the original derivation. In addition, the number of patients at lowest risk of MCCs in our evaluation represents 55% of the study population, whereas this risk stratum represents 27% of the original study population. In fact, in the original study population, there were more patients in the second risk stratum than in the first. This difference between two consecutive patient populations is difficult to explain; we

can only reiterate that our series represents a consecutive series of patients from an organized central clinic using a universal web-based interrogation system. In contrast, the original data were derived from several different specialty clinics, resulting in variable entry to the study. Even so, the rate of MCCs are similar in the lowest risk stratum, and the overall rate of MCCs within our data is comparable with that seen in the RCRI data.

There were, however, important differences in the components of the composite outcome. The prevalence of myocardial infarction within the CAIS data was almost twice that seen in the original derivation. We suspect this is related to the use of high-sensitivity serum troponin measurements that are now the gold standard for the diagnosis of perioperative myocardial infarction[24,25] and superior for the diagnosis of acute myocardial infarction.[12] The absolute number of pulmonary edema events is the same, but this represents an increased prevalence in our more recent data, since the number of patients with pre-existing congestive heart failure is one-quarter that of the original study. This lower incidence of preoperative congestive heart failure likely represents the improved chronic management of cardiac diseases in the 25 years between the two studies. Neither data set can comment on the severity of congestive heart failure; however, we would point out that the highest incidence of pre-existing congestive heart failure is in vascular surgical patients who are a decade older than the other surgical groups. Over this same time period, there have been improvements in perioperative fluid and transfusion therapy that have been shown to improve postoperative outcomes.[26]

The rates of MCCs for each of the RCRI predictive variables show that the rates within the CAIS data are similar to those measured in the original descriptive data. The major differences (outlined above) are shown for "history of ischemic heart disease" and "history of cerebrovascular disease", which are increased in the CAIS data compared with the RCRI data; however, the overall rates are similar.

The surgical subtypes differ from the RCRI data as well. The CAIS data encompass a greater number of "other" surgeries (genitourinary, neurosurgery, and ear nose and throat surgeries), and although the rate of abdominal surgeries is increased, there are fewer orthopedic and vascular procedures than in the RCRI data. This likely represents both a difference in the surgical emphasis at the study hospitals and factors such as vascular surgery and changes in preferred surgical practices over time (endovascular rather than open procedures.[7] The accuracy and discrimination of vascular surgery in the RCRI has been questioned. A recent meta-analysis[3] of the RCRI found that the area under curve for RCRI ranged from 0.60-0.74 with a pooled estimate of 0.64 (95% CI 0.61 to 0.68), which was less than that found in nonvascular surgery (ROC 0.75; 95% CI 0.72 to 0.79) A subgroup analysis in our population found a similar decrease in discrimination (ROC 0.73 for vascular patients compared with ROC 0.79 for non-vascular patients; data not shown).

Limitations

As outlined, the CAIS data did not include data relating to the outcomes for complete heart block and ventricular fibrillation. Nevertheless, in the original descriptive data, these variables were small contributors to the total prevalence of MCCs and were often present in patients who concurrently suffered one of the other three complications. Also, a few differences existed in the factors used to categorize patients into the six risk predictors as outlined in the Methods section. A major limitation in both the original descriptive study and our study is the lack of universal serial monitoring for cardiac damage. In the original series, creatine kinase surveillance was not universal and measured only in patients who provided *a priori* consent. In the present study, troponin was systematically measured only in the vascular population, and the remainder of the troponin measurements were based on underlying risk and clinical signs. As a result, troponin was measured more frequently in patients with elevated RCRI scores, and we have previously documented and shown that this clinically based measurement can deliver up to a threefold underestimation of the rate of myocardial damage.[20]

In conclusion, the four validated terms from the original RCRI (i.e., high-risk type of surgery, history of ischemic heart disease, history of congestive heart failure, and history of cerebrovascular disease) should continue to be used to estimate risk and allocate resources in elective surgical patients. The elimination of diabetes from the index would have little effect on the performance of the "index" except to move more patients to a lower risk category. Replacing the term for chronic renal failure with GFR < 30 mL·min^{-1} results in a 5-factor index that has good discrimination and better calibration than all other alternatives. Future research should aim to validate these findings within similar consecutive cohorts of elective non-cardiac surgery.

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Competing interests The Department of Anesthesia Research and Innovation Fund has received donations from Abbott Corp, BMS, Baxter, Bayer, Fresenius Kabi, and GE Healthcare. None of these companies have participated in the any aspect of this report.

Appendix

Table A1 Reclassification comparison between the six-variable RCRI model and the model derived from the significant 4-Factors ($n = 9{,}519$)

Original model (6 factors)		Patients with MCCs				Patients without MCCs			
		RCRI 0	RCRI 1	RCRI 2	RCRI ≥ 3	RCRI 0	RCRI 1	RCRI 2	RCRI ≥ 3
4-Factor model	0	25	0	0	0	5,251	116	5	0
	1	0	81	6	0	0	2,948	117	4
	2	0	0	59	11	0	0	710	62
	≥ 3	0	0	0	18	0	0	0	106

The net reclassification index is the sum of the patients who had MCCs correctly reclassified to a higher risk category ($-17/200 = -8.5\%$) and the patients without MCCs correctly changed to a lower risk category ($304/9{,}319 = 3.3\%$)

Reclassification index for the 4-Factor model was -5.2% ($P = 0.246$). RCRI = Revised Cardiac Risk Index; MCCs = major cardiac complications

Table A2 Reclassification comparison between the six-variable RCRI model and the model derived from the 5-Factors with GFR < 30 mL·min^{-1} ($n = 8{,}027$)

Original model (6 factors)		Patients with MCCs				Patients without MCCs			
		RCRI 0	RCRI 1	RCRI 2	RCRI ≥ 3	RCRI 0	RCRI 1	RCRI 2	RCRI ≥ 3
5-Factor model (GFR < 30 mL·min^{-1})	0	21	0	0	0	4,353	70	2	0
	1	1	74	3	0	20	2,514	80	1
	2	0	0	50	6	0	23	630	44
	≥ 3	0	0	4	19	0	0	9	103

The net reclassification index is the sum of the patients who had MCCs correctly reclassified to a higher risk category ($-4/178 = -2.2\%$) and the patients without MCCs correctly changed to a lower risk category ($145/7{,}849 = 1.8\%$). Reclassification index for the 5-Factor model was -0.4% ($P = 0.049$)

RCRI = Revised Cardiac Risk Index; MCCs = major cardiac complications; GFR = glomerular filtration rate

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Biomarkers

The Predictive Ability of Pre-Operative B-Type Natriuretic Peptide in Vascular Patients for Major Adverse Cardiac Events

An Individual Patient Data Meta-Analysis

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Objectives The aims of this study were to perform an individual patient data meta-analysis of studies using B-type natriuretic peptides (BNPs) to predict the primary composite endpoint of cardiac death and nonfatal myocardial infarction (MI) within 30 days of vascular surgery and to determine: 1) the cut points for a natriuretic peptide (NP) diagnostic, optimal, and screening test; and 2) if pre-operative NPs improve the predictive accuracy of the revised cardiac risk index (RCRI).

Background NPs are independent predictors of cardiovascular events in noncardiac and vascular surgery. Their addition to clinical risk indexes may improve pre-operative risk stratification.

Methods Studies reporting the association of pre-operative NP concentrations and the primary study endpoint, post-operative major adverse cardiovascular events (defined as cardiovascular death and nonfatal MI) in vascular surgery, were identified by electronic database search. Secondary study endpoints included all-cause mortality, cardiac death, and nonfatal MI.

Results Six data sets were obtained, 5 for BNP ($n = 632$) and 1 for N-terminal pro-BNP ($n = 218$). An NP level higher than the optimal cut point was an independent predictor for the primary composite endpoint (odds ratio: 7.9; 95% confidence interval: 4.7 to 13.3). BNP cut points were 30 pg/ml for screening (95% sensitivity, 44% specificity), 116 pg/ml for optimal (highest accuracy point; 66% sensitivity, 82% specificity), and 372 pg/ml for diagnostic (32% sensitivity, 95% specificity). Subsequent to revised cardiac risk index stratification, reclassification using the optimal cut point significantly improved risk prediction in all groups (net reclassification improvement 58%, $p < 0.000001$), particularly in the intermediate-risk group (net reclassification improvement 84%, $p < 0.001$).

Conclusions Pre-operative NP levels can be used to independently predict cardiovascular events in the first 30 days after vascular surgery and to significantly improve the predictive performance of the revised cardiac risk index. (J Am Coll Cardiol 2011;58:522–9) © 2011 by the American College of Cardiology Foundation

More than 200 million major surgical procedures are performed annually worldwide. This is equivalent to 1 procedure for every 25 human beings and increases to 1 procedure for every 10 persons in developed countries (1),

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with the majority of these procedures being noncardiac surgery. In a recent international randomized controlled study (8,351 patients, 190 hospitals in 23 countries), 6.9% of patients age 45 years or older with or at risk of cardiovascular disease who were hospitalized for noncardiac surgery had cardiovascular events (cardiovascular death, nonfatal myocardial infarction [MI], nonfatal cardiac arrest) within 30 days (2). Patients presenting for vascular surgery have a particularly high cardiovascular disease burden. As a result, they experience higher rates of perioperative mortality, adverse cardiovascular events, and rehospitalizations than patients undergoing other noncardiac procedures (3,4).

Pre-operative risk stratification enables both patients and physicians to make informed decisions regarding the appropriateness of surgery when considering the risk for a perioperative cardiovascular event. In addition, the identification of high-risk patients allows targeted resource allocation during the perioperative period by directing additional pre-operative testing and perioperative monitoring.

Current guidelines make use of clinical risk factors, exercise tolerance, and type of surgery to estimate perioperative cardiovascular risk and direct pre-operative investigation (5). These clinical risk factors, which include a history of ischemic heart disease, compensated or prior heart failure, cerebrovascular events, diabetes mellitus, and renal insufficiency, have been derived from a set of risk factors known as the revised cardiac risk index (RCRI) (6). To date, the use of the RCRI and the performance of noninvasive tests and imaging studies as directed by the guidelines have not provided good discrimination when applied to patients undergoing vascular surgery (7–9).

Ventricular cardiomyocytes secrete B-type natriuretic peptide (BNP), a prohormone, and its inactive cleavage product N-terminal fragment (N-terminal pro-B-type natriuretic peptide [NT-proBNP]), into the blood in response to atrial or ventricular wall stretch. Preoperative elevations of BNP or NT-proBNP have consistently and independently been associated with adverse cardiovascular events in noncardiac and particularly major vascular surgery (10–23). We aimed to study the following questions: 1) What is the optimal BNP cutoff to predict cardiovascular events after vascular surgery? 2) Does the use of pre-operative natriuretic peptides (NPs), BNP or NT-proBNP, improve upon current risk stratification tools?

Methods

We aimed to perform an individual patient data meta-analysis of studies using NPs to predict major adverse cardiac events (MACE) and all-cause mortality within 30 days of vascular surgery. MACEs were defined as the composite of cardiac death and nonfatal MI. In addition, we aimed to determine the NP cutoffs for: 1) a diagnostic test; 2) a general optimal test; and 3) a screening test (24), as well as to determine if the pre-operative use of NP assessment improves the predictive performance of the RCRI (6).

Abbreviations and Acronyms

AUC = area under the receiver-operating characteristic curve
BNP = B-type natriuretic peptide
CI = confidence interval
MACE = major adverse cardiac event(s)
MI = myocardial infarction
NP = natriuretic peptide
NRI = net reclassification improvement
NT-proBNP = N-terminal pro-B-type natriuretic peptide
OR = odds ratio
RCRI = revised cardiac risk index
ROC = receiver-operating characteristic

Study identification and selection. Studies reporting on the association of pre-operative NP concentrations and post-operative cardiovascular events in adults undergoing noncardiac vascular surgery were identified by electronic searches of the MEDLINE (July 5, 2010) and EMBASE (week 26 of 2010) databases. The electronic searches were completed by manual search of the reports' reference lists. The terms used in the search strategy were "natriuretic peptides," "surgery or surgical procedures," and validated combinations of prognostic terms (25) and diagnostic terms (26,27). No language restriction was applied.

Congress abstracts, studies in cardiac surgery populations, and studies in which BNP administration was part of an interventional algorithm were excluded. To avoid the inclusion of duplicate study data from reports publishing partial results, the study with the most complete follow-up or largest sample size was included. Study quality issues in the study selection process were not considered. Working as 2 groups (C.S.B. and G.A.L.B., R.N.R. and G.A.L.B.), we independently selected studies according to predefined eligibility criteria. Selections inconsistencies were resolved by consensus.

Data collection. The investigators of eligible studies were contacted by e-mail a maximum of 3 times to obtain individual patient data for pre-operative BNP or NT-proBNP concentrations and the type of noncardiac surgery conducted, history of coronary artery disease, congestive cardiac failure, cerebrovascular disease, diabetes mellitus, and renal failure (creatinine >2 mg/dl) to obtain the individual RCRI for each patient. Information on all patients who had undergone vascular surgery was extracted from the individual databases as supplied by the investigators of each study and subsequently merged. After merging, a random sample of 20% of the cases were checked for accuracy against the original data sets provided by the investigators, and no errors were detected (kappa = 1).

Study quality assessment. All studies included for methodological and reporting quality were evaluated according to the Quality Assessment of Diagnostic Accuracy Studies checklist (28), adapting the checklist for the purposes of this review because all the included studies were prognostic in nature (Online Appendix). In the adapted checklist's for-

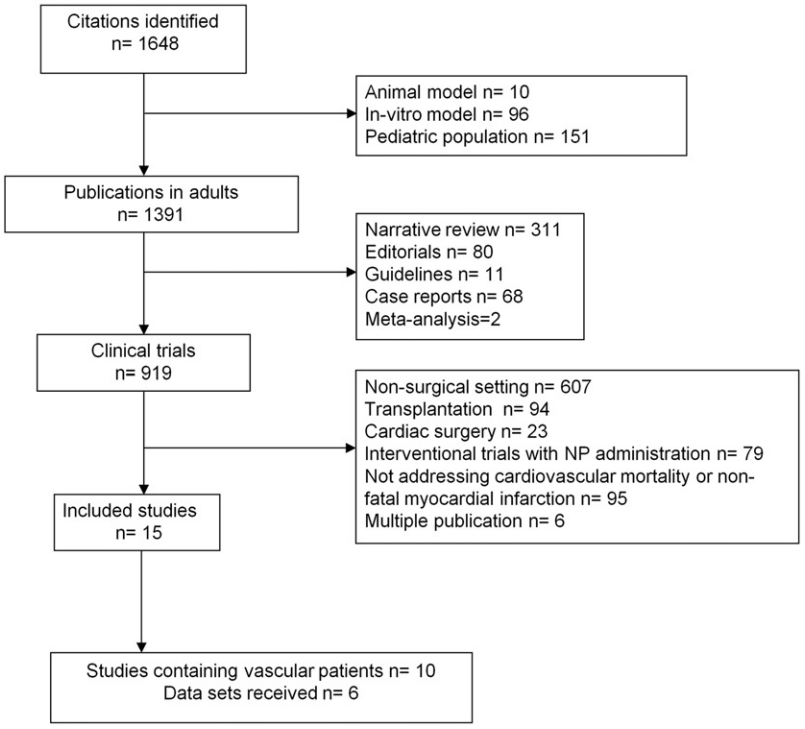

Figure 1 **Flow Chart of Included and Excluded Studies**

Flow chart demonstrating the results of a structured electronic database search of MEDLINE and EMBASE conducted to identify studies reporting on the association of pre-operative natriuretic peptide (NP) concentration and post-operative cardiovascular events in adults undergoing noncardiac vascular surgery. The terms used in the search strategy were "natriuretic peptides," "surgery or surgical procedures," and validated combinations of prognostic and diagnostic terms.

mulation, "index test," "target condition," and "reference standard" were replaced by "natriuretic peptide concentrations," "all-cause mortality," and "outcome," respectively. Criteria 3, 4, 7, and 13 of the original checklist (28) were regarded as not applicable in this context. Criterion 9 (execution of outcome assessment) of the original checklist was considered as not applicable for the studies addressing in-hospital all-cause mortality only. Two authors (G.A.L.B. and C.S.B.) independently rated study quality.

Statistical analysis. Frequencies are described as numbers and/or percents. Age is described as a mean and agreement between the authors for eligibility of the retrieved studies as a kappa value.

Before merging study data, the association between BNP concentration and MACE heterogeneity across studies was assessed using chi-square analysis, and a meta-analysis was conducted using Review Manager version 4.3 for Windows (The Cochrane Collaboration, Copenhagen, Denmark).

Table 1 **Characteristics of Studies Identified as Including Vascular Surgery Cases**

First Author, Year (Ref. #)	Proportion Vascular Surgery (%)	Male (%)	Mean Age (yrs)	Patients With NP Levels Above Thresholds* (%)	Individual Patient Data Available
Yeh et al., 2005 (31)	6/190 (3)	50	57	Not reported	No
Cuthbertson et al., 2007 (30)	61/204 (30)	61	66	38	Yes
Feringa et al., 2007 (15)	335 (100)	76	62	35	No
Gibson et al., 2007 (16)	88/190 (59)	65	68	21	Yes
Mahla et al., 2007 (20)	218 (100)	78	70	Not reported	Yes
Leibowitz et al., 2008 (19)	3/44 (7)	41	77	41	Yes
Riemersma et al., 2008 (32)	19 (100)	68	69	89	No
Bolliger et al., 2009 (10)	133 (100)	85	68	57	Yes
Choi et al., 2009 (12)	534/2,054 (26)	61	68	27	Yes
Goei et al., 2009 (17)	592 (100)	76	70	35	No
Biccard et al., 2011 (33)	297 (100)	64	59	44	Yes

*Thresholds reflect the optimal general cut point as defined in each individual study.
NP = natriuretic peptide.

Table 2 Characteristics of the Vascular Studies From Which Data Were Received

First Author, Year (Ref. #)	Patients Contributed	Biomarker	Diagnostic Assay	Cutoff (pg/ml)
Mahla et al., 2007 (20)	218	NT-proBNP	Elecsys (Roche Diagnostics, Mannheim, Germany)	280
Cuthbertson et al., 2007 (30)	70	BNP	ADVIA Centaur (Bayer Diagnostics, Leverkusen, Germany)	35
Gibson et al., 2007 (16)	129	BNP	Shinoria BNP kit, Shionogi & Company, Ltd., Osaka, Japan)	108.5
Leibowitz et al., 2008 (19)	3	BNP	ADVIA Centaur	165
Bolliger et al., 2009 (10)	133	BNP	AxSYM BNP (Abbott Laboratories, Abbott Park, IL)	50
Biccard et al., 2011 (33)	297	BNP	ADVIA Centaur Xp	39

BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Random-effects or fixed-effects models were used according to the presence or absence of significant heterogeneity between studies, respectively.

The association between NP concentration and MACEs at 30 days was determined using backward stepwise logistic regression, and pooled dichotomous outcomes are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical analysis was performed using SPSS version 15.0 for Windows (SPSS, Inc., Chicago, Illinois).

The general optimal test cutoff value, also known as the optimal diagnostic point, is the point that optimizes the rate of true-positive results while minimizing the rate of false-positive results, thereby reflecting the point with the highest accuracy for the prediction of study endpoints. For both NT-proBNP and BNP, this was defined by receiver-operating characteristic (ROC) statistics using a 1:1 weighting of sensitivity and specificity and the point determined by the value with the minimal distance when using the formula distance = $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$ (24). The screening cutoff point was chosen at a sensitivity of 95% while optimizing specificity. Similarly, the diagnostic cutoff point was chosen at a specificity of 95% while optimizing sensitivity (24).

Patients were categorized according to their RCRI risk groups (0 = low risk; 1 or 2 = intermediate risk; 3, 4, or 5 = high risk) and then reclassified according to their pre-operative NP concentrations (above or below the general optimal test cutoff) (29). The reclassification by net reclassification improvement (NRI) was then tested for discrimination and reclassification calibration statistics.

Two-sided p values were used in all analyses, and values <0.05 were considered significant.

EpiCalc 2000 version 1.02 (Brixton Books, London, U.K.), SAS version 9.1 (SAS Institute Inc., Cary, North Carolina) and Excel 2007 (Microsoft Corporation, Redmond, Washington) were used for statistical analysis.

Results

Study identification and selection. The literature search retrieved 1,648 citations, of which 15 noncardiac surgery studies fulfilled the eligibility criteria (Fig. 1). The kappa value for eligibility was 0.809.

Of these 15 studies, 10 were identified as containing vascular surgery patients (10,12,15–17,19,20,30–32) (Table 1). Individual datasets were obtained from 6 studies, 5 datasets reporting BNP values in 632 vascular patients (10,13,16,19,30)

Table 3 Patient Characteristics of Merged Datasets

Variable	All Patients (n = 850)	MACE at 30 Days (n = 75)	No MACE at 30 Days (n = 775)	p Value
Age (yrs)	65.3 ± 12.1	69.4 ± 8.8	65.0 ± 12.3	0.003
Men	561 (66%)	49 (65.3%)	512 (66.1%)	1.00
Type of surgery				
Vascular, infrainguinal	629 (74%)	50 (66.7%)	579 (74.7%)	0.572
Vascular, aortoiliac	217 (25.5%)	25 (33.3%)	192 (24.8%)	0.24
Vascular, not specified	4 (0.5%)	0	4 (0.5%)	1.00
RCRI class				
Low (RCRI 0)	320 (37.6%)	19 (25.3%)	301 (38.8%)	0.117
Intermediate (RCRI 1 or 2)	476 (56%)	45 (60%)	431 (55.6%)	0.691
High (RCRI ≥3)	54 (6.4%)	11 (14.7%)	43 (5.5%)	0.01
RCRI components				
Coronary artery disease	327 (38.5%)	42 (56%)	285 (36.8%)	0.05
Congestive heart failure	64 (7.5%)	14 (18.7%)	50 (6.5%)	0.003
Cerebrovascular disease	145 (17.1%)	8 (10.7%)	137 (17.7%)	0.254
Diabetes mellitus	204 (24%)	25 (33.3%)	179 (23.1%)	0.143
Creatinine ≥2 mg/dl	28 (3.3%)	6 (8%)	22 (2.8%)	0.037

Values are mean ± SD or as n (%).
MACE = major adverse cardiac event(s); RCRI = revised cardiac risk index.

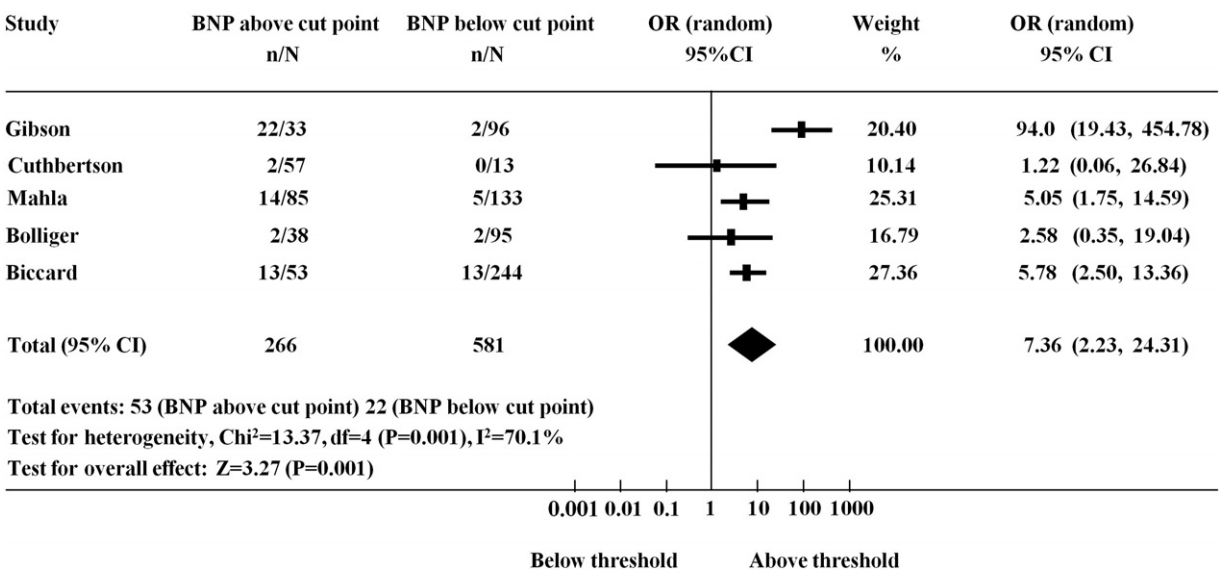

Figure 2 **Unadjusted ORs for a Pre-Operative BNP or NT-proBNP Concentration Above the Optimal General Cut Point (BNP 116 pg/ml, NT-proBNP 277.5 pg/ml) in Predicting Cardiovascular Outcomes 30 Days After Surgery**

Forest plot showing the individual and pooled unadjusted odds ratios (ORs) from the included studies.
BNP = B-type natriuretic peptide; CI = confidence interval; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

and 1 study measuring NT-proBNP concentrations in 218 vascular patients (20), for a total dataset of 850 patients having undergone both open and catheter-based vascular surgery. A study that has recently been accepted for publication and fulfilled the criteria was also included (33). The characteristics of the studies for which data were received are shown in Table 2. On analysis, the included studies showed significant heterogeneity (chi-square = 13.37, I^2 = 70.1%) in the unadjusted association between BNP and 30-day MACEs. The characteristics for the merged patient population are shown in Table 3.

Study quality. All of the 11 included studies fulfilled the requirements of a representative spectrum of patients by having clearly defined inclusion and exclusion criteria, outcome verification of the whole cohort, equal outcome evaluation regardless of the NP results, sufficient description of NP measurement, and availability of clinical data. We considered the description of the NP measurement (index test) sufficient for replication in 9 of the studies (10,15–17,19,20,30,31,33). Of the 6 studies (10,15,16,20,30,32) that monitored for MACEs after discharge, 3 provided detailed descriptions of their follow-up methods (10,20,30). In only 2 studies were the NP results interpreted without knowledge of outcome (15,16), and only 5 stated that outcomes were determined without knowledge of the NP results (10,16,20,30,31). Two of the 7 studies that lost patients from follow-up provided reasons for this loss or withdrawal (30,34).

Predictive value of NPs. Figure 2 indicates the results of the meta-analysis of the individual studies in predicting MACEs before the merging of the datasets using a random-effects model. The 3 patients from the study by Leibowitz et al. (19) were not included in the analysis, because they provided only true-positive results.

Using the merged dataset, the general optimal test cut points for the BNP (116 pg/ml) and NT-proBNP (277.5 pg/ml) groups were determined as described in our "Methods" section. Patients were then classified as falling above or below this point.

The following independent predictors of MACEs were identified by backward stepwise logistical regression analysis: NP level higher than the optimal cut point (OR: 7.9; 95% CI: 4.7 to 13.3), aortoiliac surgery (OR: 2.1; 95% CI: 1.2 to 3.6), and diabetes mellitus (OR: 1.9; 95% CI: 1.1 to 3.3). The ORs for NP higher than the threshold were 4.3 (95% CI: 1.7 to 11.3) for cardiac death, 7.5 (95% CI: 4.1 to 13.6) for nonfatal MI, and 3.1 (95% CI: 1.4 to 6.7) for all-cause mortality within 30 days of vascular surgery.

Because only 1 NT-proBNP dataset was available, a ROC analysis for pre-operative BNP and the RCRI (n = 632) in

Table 4 **AUCs for BNP and the RCRI in Predicting Perioperative Outcomes (n = 632)**

	BNP		RCRI	
Outcome	AUC (%)	95% CI (%)	AUC (%)	95% CI (%)
MACEs	80.5	75.1–85.8	64.5	56.6–72.3
Cardiac death	80.0	71.5–88.6	67.1	53.8–80.5
Nonfatal MI	78.6	72.2–85.5	62.3	52.8–71.7
All-cause mortality	71.4	60.7–82.2	63.8	53.2–74.3

AUC = area under the receiver-operating characteristic curve; BNP = B-type natriuretic peptide; CI = confidence interval; MI = myocardial infarction; other abbreviations as in Table 3.

Table 5 Test Characteristics at 3 BNP Cutoff Points in Predicting 30-Day MACEs

Cutoff Point	BNP (pg/ml)	Sensitivity (%)	Specificity (%)	+LR	−LR
Screening	30	95	44	1.69	0.11
General optimal	116	66	82	3.6	0.41
Diagnostic	372	32	95	6.4	0.71

BNP = B-type natriuretic peptide; LR = likelihood ratio; MACE = major adverse cardiac event.

predicting perioperative events was performed on the BNP dataset alone (Table 4).

Determination of BNP screening and diagnostic cutoff points. Because there was only a single study in the NT-proBNP group, we calculated screening and diagnostic cut points for the BNP group only (n = 632). Having determined the optimal general cutoff point for BNP to be 116 pg/ml, the BNP level for a screening test with 95% sensitivity was determined to be 30 pg/ml, and a BNP level of 372 pg/ml was determined for a diagnostic test with 95% specificity. Table 5 shows the test characteristics at these 3 cutoff concentrations in predicting MACE at 30 days.

The area under the ROC curve (AUC) for BNP as a continuum in predicting MACE was 80.5% (95% CI: 75.1% to 85.8%). A reduced ROC curve using only these 3 cutoff points resulted in an AUC of 80.1% (95% CI: 74.3% to 80%). The incidence of MACE stratified according to these 3 cut points is shown in Table 6.

RCRI reclassification. Per the American College of Cardiology and American Heart Association guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery (5), all 850 patients were classified into 3 risk groups according to their RCRI scores. A reclassification was performed on the basis of the patients' NP levels. If levels fell below the optimal general cut point, patients were moved down 1 risk category, and if levels fell above the optimal general cut point, patients were moved up 1 risk category (29).

Table 7 shows the results of the reclassification process. In patients classified as low risk by the RCRI, 20% were reclassified as intermediate by the use of NP concentration. In patients classified as intermediate risk by the RCRI, 71% were reclassified as low risk and 28.5% as high risk. In those classified as high risk by the RCRI, 54% were reclassified as intermediate risk. Overall, the use of NP resulted in a statistically significant improvement in discrimination, with an NRI of 58% ($z = 5.48$, $p < 0.001$). In patients classified as intermediate risk by the RCRI, the NRI was 84% ($z = 5.37$, $p < 0.001$). Applying this cutoff point to the entire population, without predefining risk categories, results in a "continuous" NRI. This can be used to compare the predictive performance of BNP with other pre-operative risk predictors that may be identified in the future. The continuous NRI was 96.4% ($z = 6.89$, $p < 0.000001$).

Discussion

Predictive value of NP. This meta-analysis shows that among patients undergoing vascular surgery, elevated NPs were independently predictive of MACEs at 30 days in patients undergoing vascular surgery and that the addition of BNP to the widely used RCRI risk stratification system significantly improves risk discrimination in a large proportion of these patients.

This finding supports previous evidence of the independent significant association between pre-operative BNP concentrations and the occurrence of cardiovascular events after vascular surgery (18). The validity of this association between NP and MACEs was supported by evidence of a biological gradient, with increasing concentrations of NP being associated with an increase in the risk for MACEs.

As an individual patient data meta-analysis, this study enabled us to determine cutoff values for pre-operative BNP, thereby overcoming the limitations of previous meta-analyses (18,22,23). Previous studies have focused on the identification of a single optimal discrimination cut point with which to direct patient management. Although this single value is appealing, it may be more logical to make use of a categorical classification system. When used as a continuous variable to predict MACEs, BNP has an AUC of 80.5% which falls to 74.1% when the single optimal cutoff point is used.

We propose that a categorical classification system based on BNP cutoff points reflecting the clinical goals of screening and general optimal and diagnostic testing (24) be investigated for use in pre-operative risk stratification. The use of a categorical system would allow the maximization of sensitivity within the lower risk groups while maximizing specificity in the higher risk groups (35), while maintaining a high degree of diagnostic accuracy. Future studies should not focus on the identification of a single cutoff point alone.

Table 6 Incidence of Adverse Cardiac Events Stratified According to the Screening, General Optimal, and Diagnostic BNP Values (n = 632)

NP Threshold (pg/ml)	MACEs (%)	Cardiac Death (%)	Nonfatal MI (%)	OR (95% CI)
Below screening (0–29)	1.2	0	1.2	—
Between screening and general optimal diagnostic (30–115)	6.5	2.8	3.6	5.6 (1.6–19.6)
Between general optimal and diagnostic (116–370)	20.9	5.5	15.4	21.0 (6.0–72.9)
Above diagnostic (>372)	36.7	12.2	24.5	45.4 (12.7–162.7)

Abbreviations as in Tables 1, 3, and 4.

Table 7 Change in Risk Stratification and its Relationship to Frequency of MACEs Following the Application of an NP Threshold

RCRI Risk Category	MACE	No MACE	Total	NP-Reclassified Risk Category	MACE	No MACE	Total
Low risk	19 (5.9%)	301 (94.1%)	320	Low risk	22 (3.7%)	574 (96.3%)	596
Intermediate risk	45 (9.5%)	431 (90.5%)	476	Intermediate risk	14 (15.1%)	79 (84.9%)	93
High risk	11 (20.4%)	43 (79.6%)	54	High risk	39 (24%)	122 (76%)	161

Abbreviations as in Tables 1 and 3.

Further work to define these cutoff points for NT-proBNP is required.

Risk stratification in vascular surgery. Previously, the RCRI has shown only modest performance in predicting perioperative cardiac events in vascular surgery (36). Similarly, this study has shown similar performance of the RCRI in predicting both MACEs (AUC: 61.6%; 95% CI: 54.6% to 68.6%) and all-cause mortality (AUC: 65.8%; 95% CI: 55.7% to 75.9%) in patients undergoing vascular surgery. This is probably due to the RCRI's having been derived from a population of predominantly noncardiac nonvascular surgery patients. In fact, in the original study in which the RCRI was derived, the index did not perform well in patients undergoing abdominal aortic aneurysm surgery (AUC: 54.3 ± 9.2%) (6).

The addition of pre-operative NP concentration to the RCRI risk stratification resulted in the correct reclassification of 58% of patients. A correct reclassification occurs when a patient who had an event moves up into a higher risk category once restratified with NP concentration, or a patient who did not have an event is moved down a risk category. These results suggest that in patients risk stratified with the RCRI, the optimal BNP cutoff point should be used to reclassify patients, thereby obtaining a more accurate risk assessment. This would improve not only risk assessment accuracy but also the identification of high-risk patients who may benefit from further noninvasive testing. Further work should be undertaken to determine whether the RCRI improves pre-operative risk stratification in patients primarily risk stratified using NPs and to examine the role of the individual RCRI factors together with NPs in improving pre-operative risk stratification. The findings of this meta-analysis, together with the other studies in this area (36), raise concerns regarding the use of the RCRI in isolation in vascular surgery populations as proposed by the American College of Cardiology and American Heart Association algorithm.

Study limitations. First, individual patient data could not be obtained for all studies that the search strategy retrieved. In particular, the available datasets that measured NT-proBNP were under-represented; as such, we chose to limit the calculation of screening and diagnostic cutoff points to the BNP dataset only. Second, 3 different BNP assay methods were used in the studies included in this analysis (Table 2), with a lack of standardization between assays. The degree of imprecision is 3.5% to 4.4% for the ADVIA system (Bayer Diagnostics, Leverkusen, Germany), 5.5% for the AxSYM system (Abbott Laboratories, Abbott Park, Illinois), and 8% for the Shionogi system (Shionogi & Company, Ltd., Osaka, Japan) (37–39) The ADVIA and Shionogi systems recognize similar BNP epitopes that differ from those identified by the AxSYM system. As a result, when compared with the AxSYM system, the ADVIA system on average results in lower BNP values (38). However, all 3 BNP assays make use of a cut point of 100 pg/ml (39), and the degree of imprecision around this shared cut point is consistently acceptable (37–39).

Third, the I^2 statistic of 70.1% indicates significant heterogeneity in the unadjusted OR between the studies. The incidence of MACEs is significantly different between the NP study groups but correlated with the degree of disease burden, as indicated by those patients with scores of 3 or more on the RCRI (Pearson's correlation $p = 0.01$). It would seem that as the event rate within the surgical population increases, so does the predictive value of NP concentration.

Conclusions

Pre-operative NP levels are able to independently predict MACEs (OR: 7.9; 95% CI: 4.7 to 13.3), cardiac death (OR: 4.3; 95% CI: 1.7 to 11.3), and nonfatal MI (OR: 7.5; 95% CI: 4.1 to 13.6) in the first 30 days after vascular surgery. The cutoff points for pre-operative BNP when used as a screening, optimal general, and diagnostic test for MACEs in a vascular surgical population are 30, 116, and 372 pg/ml, respectively. Pre-operative NP levels are able to significantly improve on the predictive performance of the RCRI; their inclusion in existing pre-operative evaluation algorithms should be considered, and the role of the RCRI in vascular surgery should be reviewed.

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Key Words: BNP ■ N-terminal pro-B-type natriuretic peptide ■ perioperative myocardial infarction ■ perioperative risk.

APPENDIX

For a description of study quality assessment, please see the online version of this article.