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The prognostic value of preoperative and postoperative B-type natriuretic peptides (BNP and NT proBNP) in patients having noncardiac surgery: A systematic review and individual patient data meta-analysis

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Structured Abstract

Objectives – To determine if measuring postoperative B-type natriuretic peptides (NP, i.e., B-type natriuretic peptide [BNP] and N-terminal fragment of proBNP [NT-proBNP]) enhances risk stratification, in adult patients undergoing noncardiac surgery, in whom a preoperative NP has been measured.

Background – Preoperative NP concentrations are powerful independent predictors of perioperative cardiovascular complications, but recent studies have reported that elevated postoperative NP concentrations are independently associated with these complications. It is not clear if there is value in measuring postoperative NP when a preoperative measurement has been done.

Methods - We conducted a systematic review and individual patient data meta-analysis to determine if the addition of postoperative NP enhanced the prediction of the composite of death and nonfatal myocardial infarction (MI) at 30 and ≥180 days after surgery.

Results- 18 eligible studies provided individual patient data (n=2179). Adding postoperative NP to a risk prediction model containing preoperative NP improved model fit and risk classification at both 30 days (QICu 1280 to 1204; NRI 20%; p<0.001) and at ≥180 days (QICu 1320 to 1300; NRI 11%; p=0.003). Elevated postoperative NP was the strongest independent predictor of the primary outcome at 30 days (odds ratio [OR] 3.7; 95% CI 2.2–6.2; p<0.001) and ≥180 days (OR 2.2; 95% CI 1.9–2.7; p<0.001) after surgery.

Conclusions- Additional postoperative NP measurement enhanced risk stratification for the composite outcomes of death or nonfatal MI 30 days and ≥180 days after noncardiac surgery as compared to a preoperative NP measurement alone.

Key words: anesthesia, myocardial infarction, natriuretic peptides, risk factors, surgery

Abbreviations List

NP – B-type natriuretic peptides
MI – myocardial infarction
BNP - B-type natriuretic peptide
NT-proBNP - N-terminal fragment of proBNP
RCRI - Revised Cardiac Risk Index
GEE – generalized estimating equations
QICu – corrected quasi-likelihood under the independence model criterion
NRI – net reclassification index
ROC – receiver operating characteristic
AUC – area under the curve

Introduction

Worldwide, an estimated 10 million adults annually experience significant myocardial injury after noncardiac surgery, as suggested by the postoperative peak troponin T measurement in a large (n= 15.133 patients) international cohort study (1). To mitigate this risk, strategies are needed that provide appropriate preoperative medical investigation and preparation, surgical interventions (e.g. open vs. endoscopic surgery), and postoperative surveillance and management. However, the success of such interventions depends largely on the ability of clinicians to accurately identify patients at risk of cardiovascular complications.

B-type natriuretic peptides (NP) are released from the myocardium in response to multiple physiological stimuli including ischemia, myocardial stretch, inflammation and other neuro-endocrine stimuli (2,3) and multiple studies have demonstrated that elevated preoperative NP concentrations are powerful independent predictors of perioperative cardiovascular complications (i.e., mortality, myocardial infarction, and heart failure) (4,5). In vascular surgical patients preoperative NP risk stratification outperforms traditional clinical risk stratification (6) and the European Society of Cardiology and European Society of Anesthesiology guidelines for preoperative cardiac risk assessment have recommended that preoperative NP measurement be considered in high-risk noncardiac surgery patients (7).

However, recently studies have reported that elevated postoperative NP concentrations are independently associated with postoperative cardiovascular complications (8,9). Considering the improved preoperative risk stratification provided by preoperative NP measurement it is not clear whether there would be any advantage to measuring postoperative NP in these patients.

We conducted a systematic review and individual patient meta-analysis to determine, in adults undergoing noncardiac surgery, whether adding postoperative NP measurements to preoperative values enhances a clinicians' ability to predict a composite of death and nonfatal myocardial infarction (MI) at 30 days and ≥ 180 days after noncardiac surgery. The study protocol (CRD42012002683) was registered with an international prospective register of systematic reviews (PROSPERO).

Methods

Systematic review methodology

Studies were considered eligible if they measured B-type natriuretic peptide (BNP) or N-terminal fragment of proBNP (NT-proBNP) preoperatively and postoperatively (i.e., < 8 days after noncardiac surgery) on the same patient. Our primary outcome was a composite of mortality or nonfatal MI. Studies were included regardless of language, design, sample size, publication status, or date of publication. We excluded cardiac surgery studies, pediatric studies, and studies where NP were used as therapy (e.g. nesiritide). Studies collecting relevant data but not reporting outcomes of interest were included if outcomes could be obtained from study authors.

The methodology used for this meta-analysis is reported in Appendix 1.

Statistical analysis

The baseline characteristics of the included patients are reported as mean (standard deviation [SD]) for continuous variables and count (percent) for categorical variables. To identify preoperative BNP and NT-proBNP thresholds we used the approach described by Mazumdar et al. to identify the values corresponding to the smallest p-values that are associated with statistically significant association between the outcome of mortality and nonfatal MI at 30 days after surgery (10). To categorize postoperative NP we used thresholds previously identified as

predicting mortality or nonfatal MI 30 days after surgery (i.e., BNP ≥245 ng/L and NT-proBNP ≥718 ng/L) (9). Patients with a measurement below these thresholds were classified as low risk. Patients with a measurement greater than or equal to these thresholds were classified as high risk. BNP and NT-proBNP data sets were then merged and used for further analyses. NP measurements obtained using fluoroimmunoassay methods may differ from those obtained using radioimmunoassay methods and may affect the homogeneity of the results (11,12). We therefore assessed the heterogeneity between BNP and NT-proBNP studies for the outcome of 30 day mortality or nonfatal MI.

In addition we explored preoperative NP using thresholds previously identified in patients with cardiac failure (i.e., BNP <100 ng/L and 250 ng/L; NT-proBNP <300, 300 - 900, 900 – 3000, and >3000 ng/L) to determine if they separated patients into clinically useful risk groups for the primary outcome (13-16). The thresholds were explored for the entire cohort of patients, as well as in vascular and non-vascular patients.

To identify independent predictors of the primary outcome at 30 days and ≥180 days after surgery we used generalized estimating equations (GEE) with an exchangeable correlation structure to take into account study clustering (17). The baseline model included the following variables: age, RCRI score ≥ 3, type of surgery (vascular vs. non-vascular), urgency of surgery (urgent/emergent vs. elective), and study as a clustering variable. We assessed co-linearity using the variance inflation factor. Variables with a variance inflation factor >10 were considered to be collinear, and we then excluded one of these variables from the analysis.

We evaluated preoperative NP by adding preoperative NP measurement to the baseline model to create a preoperative NP model. The variables in this model included: age, RCRI score ≥ 3, type of surgery (vascular vs. nonvascular), urgency of surgery (urgent/emergent vs. elective), and

preoperative NP. We evaluated postoperative NP by adding a postoperative NP measurement to the preoperative NP model.

We used the corrected quasi-likelihood under the independence model criterion (QICu) statistic to compare all model fits (18). The model with the lowest QICu was considered preferable. We used reclassification statistics (net reclassification index [NRI]) to evaluate how the addition of NP variables to the baseline model changed risk classification (19). Based on the NP measurement patient were reclassified into different risk categories. The NRI provides a summary statistic describing this change in risk classification, where a positive NRI reflects an improvement in risk stratification and a negative NRI a worsening in risk stratification. For NRI analyses patients were risk stratified as <5%, 5-10%, >10-15%, >15% risk for the primary outcome at 30 days after surgery (1). To determine the influence of postoperative NP drawn later than one day after surgery, we conducted a sensitivity analysis by excluding such studies and repeating these analyses.

For both BNP and NT-proBNP data sets we evaluated the NP change, from preoperative to postoperative, to determine if this added additional prognostic information for the prediction of the primary outcome at 30 days after surgery. The change variables evaluated were: 1) absolute NP change (i.e. postoperative NP – preoperative NP); 2) absolute change in the log transformed NP value (i.e. log[postoperative NP]– log[preoperative NP]), 3) fractional change ($\frac{Postoperative\ NP - preoperative\ NP}{Preoperative\ NP}$); and 4) log fractional change ($(Log(postoperative\ NP) - \log(preoperative\ NP))/(Preoperative\ NP)$). These four change variables were separately each evaluated in a model containing the preoperative and postoperative NP threshold variables.

We report adjusted odd ratios (AOR), corresponding 95% confidence interval (CI) and associated p-values. All p-values are reported to three decimal places. The criterion for statistical significance was set *a priori* at alpha = 0.05. We used IBM SPSS Statistics 21.0 (Chicago, IL) for all analyses except for the derivation of the NP thresholds where we used R software version 2.14.1 (http://www.R-project.org).

Results

Study identification and selection

The study selection process is shown in Figure 1. We identified 918 citations, from which 56 were selected for full-text evaluation. From these we identified 25 eligible citations (8,20-43). Seven of these studies were not included in the analysis: data from four papers were included in larger subsequent publications that we included (29,40-42); one study did not collect data on death or nonfatal MI (32); we were unable to contact the authors of one study (28); and one study has been discredited and was therefore not included (Erasmus Investigational Committee, 2012) (26). Individual patient data were received from all remaining 18 studies, and are included in this systematic review (8,20-25,27,30,31,33-39,43). Inter-observer agreement for study eligibility was excellent (kappa = 0.86).

Study characteristics and data collection

The characteristics of the 18 studies included in this systematic review are reported in Table 1. All studies were prospective observational cohort studies. Their sample sizes ranged from 22 to 400 patients and included: 4 mixed or major general surgery studies (n = 745); 3 orthopedic studies (n = 309); 3 thoracic studies (n = 471); 2 urological studies (n = 77); and 6 vascular studies (n = 688). All studies measured postoperative NP within the first day after surgery except for Mahla et al. (8) (measured day 3 – 5 after surgery) and Walszek et al. (measured day 7 after

surgery) _ENREF_40(43). Study quality is reported in Table 2. Data collection and outcome assessment was blinded in 17 of the 18 studies, and all used a consistent outcome definition over the course of the study. Fourteen studies conducted surveillance for postoperative myocardial infarction by measuring postoperative troponins.

Data were received on 2477 patients from 18 studies. We excluded 298 patients across all studies who did not have both a preoperative and postoperative NP measurement. A total of 2179 patients were included; 8 studies evaluated BNP (n = 619), and 10 studies evaluated NT-proBNP (n = 1560). A postoperative sample was drawn within the first day after surgery from 88% of these patients (1921/2179), and within the first three days after surgery in 98% of patients (2139/2179). The mean (SD) age was 68 (12) years. Sixty-five percent of patients were male, 31% of patients had a history of coronary artery disease and the most commonly performed surgery was vascular (40% of the sample). Appendix 2 shows the characteristics of all 2179 patients. This is subdivided into the patients who did and did not suffer death or nonfatal MI at 30 days after surgery.

Study outcome and determination of preoperative NP cut-points

Within 30 days of surgery 2.8% of patients had died (n=62/2179) and 10.8% had died or suffered nonfatal MI (n=235/2179). At ≥180 days 8.4% of patients had died (n=182/1605) and 16.8% had died or suffered nonfatal MI (n=366/1617).

The preoperative NP threshold associated with the lowest p-value for the outcome of death and non-fatal MI at 30 days after surgery was 92 ng/L (95% CI 38 - 133) for BNP (receiver operating characteristic [ROC] area under the curve [AUC] 0.71; 95% CI 0.63 – 0.78) and 300 ng/L (95% CI 240 -540) for NT-proBNP (ROC AUC 0.69; 95% CI 0.65 – 0.73). For the merged data set the ROC AUC was 0.70; 95% CI 0.66 – 0.74. There was no heterogeneity between the BNP or the

NT-proBNP studies for the outcome of 30 death and non-fatal MI (I2=0) despite two (35, 39) of the eight BNP studies having used a radioimmunoassay method.

Death or nonfatal MI at 30 days after surgery occurred in 21.8% of patients with a preoperative NP measurement above the threshold (n = 166/763; likelihood ratio 2.3) as compared to 4.9% in patients with a measurement below the threshold (n = 69/1416; likelihood ratio 0.42). An elevated preoperative NP (OR 3.4 95% CI 2.57 – 4.47; p<0.001), RCRI ≥ 3 (OR 2.7, 95% CI 1.81 – 3.96; p<0.001) and urgent/emergency surgery (OR 1.6 95% CI 0.75 – 3.53; p=0.216) all predicted 30-day death or nonfatal MI (Appendix 3).

Death or nonfatal MI at ≥180 days after surgery occurred in 37% of patients with a preoperative NP measurement above the threshold (n = 235/635; likelihood ratio 2.0) as compared to 13.3% in patients with a measurement below the threshold (n = 131/982; likelihood ratio 0.53). As shown in Appendix 3 an elevated preoperative NP measurement was the strongest predictor of ≥180-day death or nonfatal MI with an OR 2.6 (95% CI 2.0 – 3.43; p<0.001).

Risk prediction improvement with the addition of NP

Adding a preoperative NP measurement to the baseline model improved model fit and risk classification for the prediction of the primary outcome at 30 days (QICu 1352.95 to 1280.16; NRI 32%, p<0.001) and at ≥180 days (QICu 1376 to 1320.42; NRI 18%, p<0.001) after surgery (Table 3). Adding a postoperative NP measurement to the preoperative NP model further improved model fit and risk classification at both 30 days (QICu 1280.16 to 1204.06; NRI 20%; p<0.001) and at ≥180 days (QICu 1320.42 to 1300.09; NRI 11%; p=0.003) (Table 4). The results of the sensitivity analysis that excluded the two studies measuring postoperative NP after the first postoperative day did not differ appreciably from the primary results (Appendix 4).

In the final model independent predictors for the study outcome at 30 days were elevated postoperative NP (OR 3.7; 95% CI 2.18 – 6.24; p<0.001), RCRI ≥ 3 (OR 2.3; 95% CI 1.59 – 3.19; p<0.001), and elevated preoperative NP (OR 1.9; 95% CI 1.44 – 2.40; p<0.001). At ≥180 days the independent predictors were elevated postoperative NP (OR 2.2; 95% CI 1.85 – 2.65; p<0.001), RCRI ≥ 3 (OR 2.2; 95% CI 1.87 – 2.52; p<0.001), elevated preoperative NP (OR 1.9; 95% CI 1.38 – 2.58; p<0.001), and age (OR 1.01; 95% CI 1 – 1.02; p=0.016). These results are reported in Table 5. We identified no significant collinearity between variables.

NP change

After surgery NP measurements increased in 76% (n = 1653) of patients, with a median BNP increase of 66 ng/L (inter quartile range [IQR] 123 ng/L) and a NT-proBNP increase of 323 ng/L (IQR 874 ng/L). NP decreased in 23% (n = 507) of patients, with a median BNP decrease of 15 ng/L (IQR 64) and a NT-proBNP decrease of 53 ng/L (IQR 153). In both BNP and NT-proBNP data sets the four change variables were each separately evaluated in a GEE model containing the derived pre and postoperative NP thresholds. In both data sets none of the change variables were significant predictors of the primary study outcome at 30 days after surgery (Appendix 5). Our exploration of traditional NP thresholds found that patients with preoperative BNP values of 0-100, >100–250, >250 ng/L suffered the composite of 30-day mortality or nonfatal MI at a rate of 5.1%, 11.6%, and 26.3%, respectively. Patients with preoperative NT-proBNP values of 0-300, >300–900, >900-3000, and >3000 ng/L suffered the same outcome at a rate of 5.2%, 16.1%, 26%, and 39.5% respectively. These BNP and NT-proBNP results, together with the breakdown for vascular and non-vascular surgery patients, are shown in Appendix 6.

Discussion

This systematic review and individual patient level data analysis demonstrates that adding a

postoperative NP measurement to a preoperative risk model which included preoperative NP measurement improved the prediction of mortality or nonfatal MI at 30 or ≥180 days after noncardiac surgery.

The potential for NP measurement in preoperative risk stratification lies in its ability to integrate the impact of multiple preoperative pathophysiological processes into a single measurement (2,3). Previous meta-analyses suggest that a single elevated preoperative NP measurement is highly predictive of serious cardiovascular complications after noncardiac surgery, and may be a better predictor of these events than the RCRI (4,5). Measuring NP in adults having major noncardiac surgery thus significantly improves preoperative risk stratification and could easily be incorporated into clinical practice; particularly in patients having major vascular, intrathoracic, orthopaedic or intra-peritoneal surgery, and would allow physicians to plan prophylactic strategies in patients identified as high risk.

In our analysis a postoperative NP measurement was the strongest predictor of mortality or nonfatal MI after noncardiac surgery and the addition of a postoperative NP measurement augmented identification of at-risk patients. It is possible that postoperative NP elevations may identify patients who will develop major cardiovascular complications allowing physicians to intervene by administering beta-blockers, aspirin or statins. However, further studies are required to ascertain whether interventions in response to NP measurements will improve patient outcomes. What remains unclear, and what could not be determined from this analysis, is the extent to which postoperative NP elevation correlates with postoperative troponin elevation. NP elevation may precede troponin elevation, as for example when the patient is fluid overloaded and in cardiac failure, or NP elevation may occur together with troponin elevation when the

myocardium is exposed to ischemia. In such cases it remains unclear whether measuring NP provides additional information to that provided by postoperative troponin alone (1,44).

The strengths of this review lie in its rigorous methodology which includes a published review protocol, an extensive literature search, and adherence to reporting standards for systematic reviews. A particular strength is our success in obtaining individual level patient data on 2179 patients. Further, our analysis has accounted for the clustering effect of the contributing studies, and we surpassed 10 events per variable in all our regression models thus ensuring stable measures of association (45).

A limitation of this analysis is that postoperative NP sampling was not performed at the same time point in all studies. More than 90% of patients included in the primary analysis had NP drawn within the first day after surgery, and 98% within the first three days after surgery. The results of the sensitivity analysis conducted using only studies where NP were drawn within the first day of surgery were not appreciably different from the primary analysis. It is therefore likely that these results are representative of what can be expected with by sampling NP early after surgery. No other postoperative variables besides NP could be evaluated in this analysis and as a result we are unable to adjust for factors such as postoperative renal dysfunction known to elevate NP. Two BNP studies used radioimmunoassay analysis methods (35,39) and the remaining six BNP studies used fluoroimmunoassay. While our analysis found no heterogeneity between the BNP studies for the primary outcome our choice to pool BNP concentrations obtained from diverse assays with varying degrees of precision (11,12) should be seen as a limitation.

Four studies (n=496) did not conduct routine postoperative troponin surveillance and so it is possible that the incidence of postoperative MI may be higher than what we have reported. Most

postoperative troponin elevations occur within the first 48-72 hours after surgery (46). While 88% of postoperative NP measurements were made within the first day after surgery we are unable to determine the exact relationship between postoperative NP elevation and postoperative troponin elevation. All studies used an elevated troponin as part of their definition of postoperative MI with two studies making the diagnosis on the basis of troponin elevation alone (30, 37).

Conclusion

The addition of a postoperative NP measurement to a preoperative risk model which includes preoperative NP measurement significantly improves the prediction of the composite outcome of mortality or nonfatal MI within 30 days or ≥180 days after noncardiac surgery.

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Table 1. Characteristics of included studies

Author, Year	Patient population, type of surgery	No. of patients	Mean age of study patients (SD)	Type of natriuretic peptide	Assay, manufacturer	Timing and frequency of samples	Length of follow-up (days)
Manikandan, 2005 (31)	Elective, urological	52	72 (9.0)	BNP	Elecsys ProBNP, Roche Diagnostics	Preoperative; Postoperative: day 1	30
Cardinale, 2007 (21)	Elective, thoracic	400	62 (9.9)	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Preoperative; Postoperative: 1 hour after surgery	In-hospital
Hoksch, 2007 (27)	Elective, thoracic	22	67 (11.1)	BNP	Triage BNP-Test, Biosite Diagnostic	Preoperative; Postoperative: days 1-5	270
Mahla, 2007 (8)	Elective, major vascular	218	70 (9.3)	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Preoperative; Postoperative: days 3-5	826
Schutt, 2009 (38)	Elective & urgent/emergent, mixed (60% orthopedic)	75	69 (11.0)	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Preoperative; Postoperative: days 1-3	30
Chong 2010 (23)	Urgent/emergent, orthopedic	33	86 (9.7)	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Preoperative; Postoperative: days 1-3	180
Chong 2010 (22)	Urgent/emergent, orthopedic	89	80 (9.9)	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Preoperative; Postoperative: days 1-3	730

Cagini, 2011 (20)	Elective, thoracic	149	66 (12.5)	BNP	Triage BNP, Biosite	Preoperative; Postoperative: days 1,3 and 7	360
Cnotliwy, 2011 (25)	Elective, vascular	100	69 (8.5)	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Preoperative; Postoperative: day 1	30
Radović, 2011 (35)	Elective, urological	25	56 (8.0)	BNP	BNP 2, IRMA	Preoperative; Postoperative: days 1 and 7	180
Rajagopalan, 2011 (36)	Elective, major vascular	136	69 (9.7)	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Preoperative; Postoperative: day 1	654
Suttie, 2011 (39)	Elective, major vascular	45	72 (10.4)	BNP	BNP, Peninsula Laboratories	Preoperative; Postoperative: immediately after surgery, and days 1 - 4	365
Waliszek, 2011 (43)	Elective, vascular	40	63.1 (10.6)	NT-proBNP	Elecsyst ProBNP, Roche Diagnostics	Preoperative; Postoperative: day 7	7
Lurati Buse, 2012 (30)	Elective, mixed (58% vascular)	380	72 (7.9)	NT-proBNP	Elecsyst ProBNP, Roche Diagnostics	Preoperative; Postoperative: day 1 and 2	365
Mercantini, 2012 (33)	Elective, general and orthopedic	205	64 (16.3)	BNP	Triage BNP, Biosite	Preoperative; Postoperative: day 1	30

Chong 2012 (24)	Emergency, orthopedic	187	77 (9.3)	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Preoperative; Postoperative: days 1-3	365
Park, 2012 (34)	Elective, mixed (46% orthopedic)	85	69 (14.8)	BNP	Advia Centaur Xp, Siemens (Bayer)	Preoperative; Postoperative: day 1	30
Rodseth, 2012 (37)	Elective, vascular	149	59 (12.2)	BNP	Advia Centaur Xp, Siemens (Bayer)	Preoperative; Postoperative: day 1	30

BNP indicates B-type natriuretic peptide; NT-proBNP, N-terminal fragment of proBNP; SD, standard deviation.

Table 2. Study quality characteristics

Author, Year	Data collection blinded to NP value	Outcome assessment blinded to NP	Consistent outcome definition	Diagnostic troponin threshold used during postoperative screening	Myocardial infarction criteria
Manikandan, 2005 (31)	Blinded	Blinded	Yes	4th gen Troponin T (≥0.03 ng/ml)	Elevated troponin, and one or more of: ECG changes or anginal symptoms
Cardinale, 2007 (21)	Blinded	Blinded	Yes	No screening performed	Not a predefined study endpoint
Hoksch, 2007 (27)	Blinded	Blinded	Yes	No screening performed	Not a predefined study endpoint
Mahla, 2007 (8)	Blinded	Blinded	Yes	4th gen Troponin T (≥0.03 ng/ml)	Elevated troponin and ECG changes indicative of ischemia[47]
Schutt, 2009 (38)	Blinded	Blinded	Yes	4th gen Troponin T (≥003 ng/ml)	Elevated troponin, and one or more of: ECG changes or anginal symptoms
Chong, 2010 (20)	Blinded	Blinded	Yes	Troponin I (≥0.03 ng/ml)	Universal definition of myocardial infarction[48]
Chong, 2010 (23)	Blinded	Blinded	Yes	Troponin I (≥0.03 ng/ml)	Universal definition of myocardial infarction[48]
Cagini,	Blinded	Blinded	Yes	No screening performed	Not a predefined study endpoint

2011 (20)					
Cnotliwy, 2011 (25)	Blinded	Unblinded	Yes	Troponin I (≥0.01 ng/mL)	Universal definition of myocardial infarction[48]
Radović, 2011 (35)	Blinded	Blinded	Yes	No screening performed	Not a predefined study endpoint
Rajagopalan, 2011 (36)	Blinded	Blinded	Yes	Troponin-I (≥0.1 ng/mL)	Elevated troponin only
Suttie, 2011 (39)	Blinded	Blinded	Yes	Troponin T (≥0.01 ng/mL)	Elevated troponin, and one or more of: ECG changes or anginal symptoms
Waliszek, 2011 (43)	Blinded	Blinded	Yes	Troponin I (≥0.3ng/ml)	Elevated troponin, and one or more of: ECG changes or anginal symptoms
Lurati Buse, 2012 (30)	Blinded	Blinded	Yes	2006-2009: 4th gen Troponin T (≥0.03 ng/ml) 2010 onwards: 5th gen Troponin T (≥0.013 ng/ml)	Elevated troponin only
Mercanti, 2012 (33)	Blinded	Blinded	Yes	4th gen Troponin T (≥003 ng/ml)	Elevated troponin, and one or more of: ECG changes or anginal symptoms
Chong 2012 (24)	Blinded	Blinded	Yes	Troponin I	Universal definition of myocardial infarction[48]

				(≥0.03 ng/ml)	
Park, 2012 (34)	Blinded	Blinded	Yes	Troponin T (≥0.01 ng/ml)	Elevated troponin and ECG changes indicative of ischemia
Rodseth , 2012 (37)	Blinded	Blinded	Yes	Troponin I (≥0.1 ng/ml)	Elevated troponin only

NP = B-type natriuretic peptides

Table 3. Change in risk classification for the probability of mortality or nonfatal MI at 30 days using a model including preoperative NP as compared with a model using baseline factors only.

Risk classification using baseline factors	**Risk classification using baseline and preoperative NP**				**Reclassified † as:**		**Net correctly reclassified‡ %**	**Net reclassification improvement§ %**
	<5%	5% to 10%	>10% to 15%	>15%	Higher risk	Lower risk		
Patients **with** primary outcome*								
<5%	12	8	0	0	91	53	16.2%	31.6%
5 – 10%	29	7	32	8				
>10 – 15%	2	15	14	43				
> 15% - 65	0	4	3	58				
Patients **without** primary outcome*								
<5%	676	61	0	0	342	641	15.4%	
5 – 10%	425	77	159	15				
>10 – 15%	33	126	49	107				
> 15%	0	44	13	159				

MI = myocardial infarction; NP = B-type natriuretic peptide

Key

	Improved classification
	No classification change
	Worse classification

*Primary outcome = composite of mortality of nonfatal MI at 30 days after surgery.

†The addition of NP to the baseline risk model reclassified: 91 patients with the primary outcome and 342 patients without the primary outcome to a higher risk category; and 53 patients with the primary outcome and 641 patients without the primary outcome to a lower risk category.

‡In patients with the primary outcome 16.2% were correctly reclassified ([91 – 53] / 235). In patients without the primary outcome 15.4% were correctly reclassified ([641 – 342] / 1944).

[§]The net reclassification improvement is the sum of the correctly reclassified patients who did and did not survive (i.e., 16.2% + 15.4% = 31.6%)

Table 4. Change in risk classification for the probability of mortality or nonfatal MI at 30 days using a model including pre- and postoperative NP as compared with baseline and preoperative NP model only.

Risk classification using baseline factors and preoperative NP	**Risk classification using baseline, with pre- and postoperative NP**				**Reclassified[†] as:**		**Net correctly reclassified[‡] %**	**Net reclassification improvement[§] %**
	<5%	5% to 10%	>10% to 15%	>15%	Higher risk	Lower risk		
Patients **with** primary outcome*								
<5%	30	9	4	0	74	28	19.6%	20.2%
5 – 10%	7	8	4	15				
>10 – 15%	0	7	0	42				
> 15% - 65	0	9	5	95				
Patients **without** primary outcome*								
<5%	1033	46	55	0	305	316	0.6%	
5 – 10%	139	87	33	49				
>10 – 15%	6	92	1	122				
> 15%	0	70	15	196				

MI = myocardial infarction; NP = B-type natriuretic peptide

	Improved classification
	No classification change
	Worse classification

*Primary outcome = composite of mortality of nonfatal MI at 30 days after surgery.

[†]The addition of NP to the baseline risk model reclassified: 74 patients with the primary outcome and 305 patients without the primary outcome to a higher risk category; and 28 patients with the primary outcome and 316 patients without the primary outcome to a lower risk category.

[‡]In patients with the primary outcome 19.6% were correctly reclassified ([74 – 28] / 235). In patients without the primary outcome 0.6% were correctly reclassified ([316 – 305] / 1944).

[§]The net reclassification improvement is the sum of the correctly reclassified patients who did and did not survive (i.e., 19.6% + 0.6% = 20.2%)

Table 5. Variables evaluated in the final GEE model for an association with the composite outcome of mortality or nonfatal MI after surgery.

Outcome	Variable	Adjusted OR (95% CI)	P
Death or nonfatal MI 30 days after surgery	Postoperative elevated NP	3.7 (2.18 – 6.24)	<0.001*
	RCRI ≥ 3	2.3 (1.59 – 3.19)	<0.001*
	Preoperative elevated NP	1.9 (1.44 – 2.40)	<0.001*
	Urgent/emergent surgery	1.4 (0.72 – 2.64)	0.337
	Vascular surgery	1.3 (0.63 – 2.62)	0.484
	Age (per year)	1.0 (0.99 – 1.03)	0.096
Death or nonfatal MI ≥180 days after surgery	Postoperative elevated NP	2.2 (1.85 – 2.65)	<0.001*
	RCRI ≥ 3	2.1 (1.87 – 2.52)	<0.001*
	Preoperative elevated NP	1.9 (1.38 – 2.58)	<0.001*
	Age (per year)	1.01 (1 – 1.02)	0.016*
	Vascular surgery	1.4 (0.77 – 2.47)	0.590
	Urgent/emergent surgery	0.6 (0.22 – 1.86)	0.545

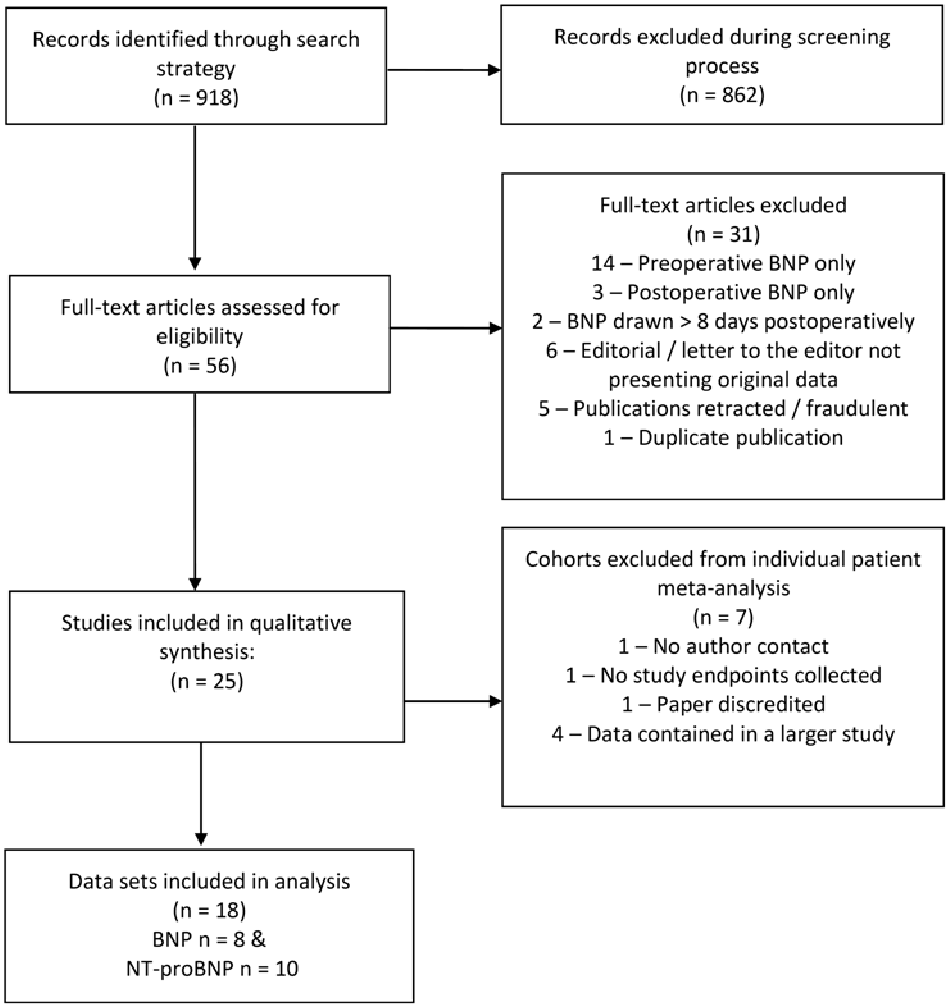
MI = myocardial infarction; NP = B-type natriuretic peptides; OR = odds ratio; CI = confidence interval; GEE = generalized estimating equation; RCRI = revised cardiac risk index.

Figure legend

Figure 1. Study selection process

Flow chart demonstrating the results of a structured electronic database search of 6 databases and grey literature conducted to identify studies reporting on the association of pre- and postoperative NP concentrations and post-operative cardiovascular events in adults undergoing noncardiac surgery.

Figure 1. Study selection process



Appendix 1. Meta-analysis methodology

Study identification

On June 21, 2012 we searched 6 databases (EMBASE, OVID Health Star, Ovid Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, ProQuest Dissertations and Theses A&I), abstracts from meetings of the American Heart Association and the American Society of Anesthesiologists, consulted with experts, reviewed reference lists from identified articles, and searched for cited references of key publications in Web of Science. No language filters were used. To avoid inclusion of duplicate study data from reports publishing partial results the study with the largest, most complete follow-up was included.

Search strategy and databases

The search terms, including validated prognostic search terms_ENREF_7 and databases used are listed as follows: Database searches were conducted on June 21 2012 using the OvidSP search engine (Ovid Technologies, Inc., New York, NY 2009) for the following databases:

1. EMBASE 1980 to 2012 Week 24
2. OVID Health Star (1966 to May 2012)
3. Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and OVID MEDLINE(R) 1946 to present
4. Cochrane Central Register of Controlled Trials (June 2012)
5. Cochrane Database of Systematic Reviews (June 2012)
6. ProQuest Dissertations and Theses A&I (June 2012)

Example of search conducted on MEDLINE

	Search terms
1	(Natriuretic peptide [MESH] OR natriureti*).mp.
2	(BNP OR B type natriureti* OR B-type natriureti* OR Brain natriureti*).mp.

3	(NT-pro BNP OR NT-proBNP OR NT-pro-BNP OR N terminal proBNP OR N terminal pro-BNP OR N-terminal proBNP N terminal pro-BNP OR N-terminal pro-brain natriureti* OR N-terminal pro-B-type natriureti* OR N-terminal pro-B type natriureti*).mp
4	(Surgery [MESH] OR operative OR noncardiac).mp.
5	1 or 2 or 3
6	4 and 5
7	prognosis.sh. or diagnosed.tw. or cohort:.mp. or predictor:.tw. or death.tw. or exp models, statistical/
8	6 and 7
9	remove duplicates from 8

No additional search filters were used.

For the EMBASE search the EMTree term “Brain natriuretic peptide” was used**.**

Eligibility Assessment

The title and abstract of each citation was independently screened by both BB and RR to identify potentially eligible studies. If either reviewer felt the citation may contain a relevant study, the article was retrieved to undergo full text evaluation. Full texts of all citations identified as being potentially relevant were then independently evaluated by both BB and RR to determine eligibility. Disagreements were solved by consensus and where this could not be reached a third reviewer (GL) made the final eligibility decision. Chance corrected inter-observer agreement for study eligibility was tested using kappa statistics.

Data collection and assessment of study quality

A standardized extraction form was used to record: study design, year of publication, sample size, type of surgery, length of follow-up, method of follow-up, type of NP assay used, and

measurement frequency. Study quality was evaluated based on data collection, assessment of outcome, use of a consistent outcome definition, diagnostic troponin threshold used during postoperative screening, and MI criteria.

All authors from eligible studies were contacted and invited to provide anonymous individual patients data using standardized Excel spreadsheets. Age, gender, either the individual Revised Cardiac Risk Index (RCRI) components (49) or the cumulative RCRI score if the individual factors were not available, type (vascular or non-vascular) and urgency of surgery, pre and postoperative NP value, and predefined outcomes at 30 days and ≥180 days were obtained. Only studies supplying individual patient data were included in this review. Individual patients were only included in the analysis if both a pre- and postoperative NP measurement were obtained. Where more than one postoperative NP measurement was available we used the sample drawn closest to the time of surgery in the analysis.

Appendix 2. Overall patient characteristics and by subgroups according to whether patients did or did not experience the primary outcome

Variable	All patients n=2179	Patients who did not experience death or nonfatal MI at 30 days n=1944	Patients who experienced death or nonfatal MI at 30 days n=235	P
Age, mean, (SD) years	68.2 (12)	67.6 (12)	73.2 (11)	<0.001
Male, n (%)	1409 (64.7)	1247 (64.1)	162 (68.9)	0.083
Vascular surgery, n (%)	878 (40.4)	733 (37.7)	145 (61.7)	<0.001
Urgent/ emergent surgery, n (%) (n=2111)	342 (15.7)	303 (15.6)	39 (16.6)	0.366
RCRI components				
Coronary artery disease, n (%) (n=2050)	682 (31.3)	534 (27.5)	148 (63)	<0.001
Congestive heart failure, n (%) (n=2063)	104 (4.8)	79 (4.1)	25 (10.6)	<0.001
Cerebrovascular disease, n (%) (n=1663)	255 (11.7)	220 (11.3)	35 (14.9)	0.303
Diabetes mellitus, n (%) (n=1779)	306 (14)	248 (12.8)	58 (24.7)	<0.001
Creatinine ≥2 mg/dl, n (%) (n=2126)	73 (3.4)	56 (2.9)	17 (7.2)	0.002

MI = myocardial infarction; SD = standard deviation; RCRI = revised cardiac risk index

Appendix 3. Preoperative variables evaluated in multivariable GEE model for an association with the composite outcome of death or nonfatal MI after surgery

Outcome	Model variable	OR (95% CI)	P	QICu
Death or nonfatal MI 30 days after surgery	Preoperative elevated NP	3.4 (2.57 – 4.47)	<0.001*	1151.30
	RCRI ≥ 3	2.7 (1.81 – 3.96)	<0.001*	
	Vascular surgery	1.1 (0.58 – 2.10)	0.767	
	Urgent/emergent surgery	1.6 (0.75 – 3.52)	0.216	
	Age (per year)	1.02 (1.01 – 1.03)	<0.001*	
Death or nonfatal MI ≥180 days after surgery	Preoperative elevated NP	2.6 (2.0-3.43)	<0.001*	1083.96
	RCRI ≥ 3	2.4 (2.02 – 2.9)	<0.001*	
	Vascular surgery	1.3 (0.73 – 2.43)	0.348	
	Urgent/emergent surgery	0.6 (0.22 – 1.81)	0.386	
	Age (per year)	1.02 (1.01 – 1.03)	<0.001*	

GEE = generalized estimating equation; MI = myocardial infarction; OR = odds ratio; RCRI = revised cardiac index

Appendix 4. Sensitivity analysis conducted using only studies that measured postoperative NP within the first day after surgery that evaluated the improvement in risk prediction with the addition of preoperative NP to the baseline risk model; and postoperative NP to the preoperative NP model.

Death or nonfatal MI at 30 days after surgery		
Model	**QICu**	**NRI**
Baseline	1222.59	-
Baseline with preoperative NP	1151.30	30% (p<0.001)
Baseline with pre- and postoperative NP	1083.96	14% (p = 0.004)
Death or nonfatal MI at 180 days after surgery		
Model	**QICu**	**NRI**
Baseline	1132.54	-
Baseline with preoperative NP	1099.06	25% (p<0.001)
Baseline with pre- and postoperative NP	1079.7	9% (p = 0.03)

NP = B-type natriuretic peptides; QICu = quasi-likelihood under the independence model criterion statistic; NRI = net reclassification index.

Appendix 5. The significance and odds ratio associated with the addition of a change variable to a GEE model containing preoperative and postoperative NP thresholds for the prediction of death or nonfatal MI at 30 days after surgery

Assay	Change variables							
	Absolute change		Log absolute change		Ratio change		Log ratio change	
	P value	OR	P value	OR	P value	OR	P value	OR
BNP	0.689	1 (1-1)	0.499	1.1 (0.88–0.31)	0.214	1 (0.99 – 1)	0.108	0.78 (0.58 – 1.06)
NT-proBNP	0.347	1 (1–1)	0.390	1.2 (0.82–1.67)	0.276	1.0 (0.99-1.02)	0.538	1.6 (0.39 – 6.21)

OR = odds ratio; GEE = generalized estimating equation; NP = natriuretic peptides; MI = myocardial infarction; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal fragment of proBNP

Appendix 6. Preoperative BNP thresholds and the incidence of death or nonfatal MI at 30 days after surgery

Type of NP	NP thresholds (pg/ml)	Mortality or MI for all types of surgery		Patients without events	Multilevel Likelihood Ratios
		n/N*	% (95% CI)		
BNP Studies	0 – 100	25/475	5.3% (3.2 – 7.2)	450	0.58
	≥100 – 250	8/69	11.6% (4.3 – 18.8)	61	1.38
	≥250	21/78	26.9% (17.1 – 35.5)	57	3.88
	Total	54/622	8.7% (6.3 – 10.7)	568	-
NT-proBNP studies	0 – 300	50/957	5.2% (4 – 6.8)	907	0.42
	>300 – 900	57/355	16.1% (12 – 20.2)	298	1.46
	>900 – 3000	44/169	26% (18.3 – 33.7)	125	2.68
	>3000	30/76	39.5% (26.3 – 52.6)	46	4.97
	Total	181/1560	11.6% (10.2 – 13.4)	1379	-

* n/N=number of patients who died in subgroup/ total number of a patients in subgroup

MI = myocardial infarction; BNP = B-type natriuretic peptide; CI = confidence interval; NT-proBNP = N-terminal fragment of proBNP

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