CME

The Prognostic Value of Pre-Operative and Post-Operative B-Type Natriuretic Peptides in Patients Undergoing Noncardiac Surgery

B-Type Natriuretic Peptide and N-Terminal Fragment of Pro-B-Type Natriuretic Peptide: A Systematic Review and Individual Patient Data Meta-Analysis

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JACC JOURNAL CME

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CME Objective for This Article: At the conclusion of this activity, the learner should be able to determine if measuring post-operative 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 pre-operative NP has been measured.

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The Prognostic Value of Pre-Operative and Post-Operative B-Type Natriuretic Peptides in Patients Undergoing Noncardiac Surgery

B-Type Natriuretic Peptide and N-Terminal Fragment of Pro-B-Type Natriuretic Peptide: A Systematic Review and Individual Patient Data Meta-Analysis

Objectives   The objective of this study was to determine whether measuring post-operative B-type natriuretic peptides (NPs) (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 pre-operative NP has been measured.

Background   Pre-operative NP concentrations are powerful independent predictors of perioperative cardiovascular complications, but recent studies have reported that elevated post-operative NP concentrations are independently associated with these complications. It is not clear whether there is value in measuring post-operative NP when a pre-operative measurement has been done.

Methods   We conducted a systematic review and individual patient data meta-analysis to determine whether the addition of post-operative NP levels enhanced the prediction of the composite of death and nonfatal myocardial infarction at 30 and $\geq$180 days after surgery.

Results   Eighteen eligible studies provided individual patient data (n = 2,179). Adding post-operative NP to a risk prediction model containing pre-operative NP improved model fit and risk classification at both 30 days (corrected quasi-likelihood under the independence model criterion: 1,280 to 1,204; net reclassification index: 20%; p < 0.001) and $\geq$180 days (corrected quasi-likelihood under the independence model criterion: 1,320 to 1,300; net reclassification index: 11%; p = 0.003). Elevated post-operative NP was the strongest independent predictor of the primary outcome at 30 days (odds ratio: 3.7; 95% confidence interval: 2.2 to 6.2; p < 0.001) and $\geq$180 days (odds ratio: 2.2; 95% confidence interval: 1.9 to 2.7; p < 0.001) after surgery.

Conclusions   Additional post-operative NP measurement enhanced risk stratification for the composite outcomes of death or nonfatal myocardial infarction at 30 days and $\geq$180 days after noncardiac surgery compared with a pre-operative NP measurement alone.   (J Am Coll Cardiol 2014;63:170–80) © 2014 by the American College of Cardiology Foundation

Worldwide, an estimated 10 million adults annually experience significant myocardial injury after noncardiac surgery, as suggested by the post-operative peak troponin T measurement in a large (n = 1,513) international cohort study (1). To mitigate this risk, strategies are needed that provide appropriate pre-operative medical investigation and preparation, surgical interventions (e.g., open vs. endoscopic surgery), and post-operative 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 (NPs) are released from the myocardium in response to multiple physiological stimuli, including ischemia, myocardial stretch, inflammation, and other neuroendocrine stimuli (2,3), and multiple studies have demonstrated that elevated pre-operative NP concentrations are powerful independent predictors of perioperative cardiovascular complications (i.e., mortality, myocardial infarction [MI], and heart failure) (4,5). In vascular surgical cases, pre-operative NP risk stratification outperforms traditional clinical risk stratification (6), and the European Society of Cardiology and European Society of Anesthesiology guidelines for pre-operative cardiac risk assessment have recommended that pre-

operative NP measurement be considered in high-risk noncardiac surgery cases (7).

However, recent studies have reported that elevated post-operative NP concentrations are independently associated with post-operative cardiovascular complications (8,9). In view of the improved pre-operative risk stratification provided by pre-operative NP measurement, it is not clear whether there would be any advantage to measuring post-operative NP in these patients.

We conducted a systematic review and individual patient meta-analysis to determine, in adults undergoing noncardiac surgery, whether adding post-operative NP measurements to pre-operative values enhances a clinician's ability to predict a composite of death and nonfatal MI at 30 days and $\geq$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 in which NPs 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 Online Appendix 1.

Statistical analysis. The baseline characteristics of the included patients are reported as mean ± SD for continuous variables and count (percent) for categorical variables. To identify pre-operative BNP and NT-proBNP thresholds, we used the approach described by Mazumdar and Glassman (10) to identify the values corresponding to the smallest p values that are associated with a statistically significant association between the outcome of mortality and nonfatal MI at 30 days after surgery. To categorize post-operative 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 pre-operative NP using thresholds previously identified in patients with cardiac failure (i.e., BNP <100 and 250 ng/l; NT-proBNP <300, 300 to 900, 900 to 3,000, and >3,000 ng/l) to determine whether they separated patients into clinically useful risk groups for the primary outcome (13–16). The thresholds were explored for the entire cohort of patients and in vascular and nonvascular groups of patients.

To identify independent predictors of the primary outcome at 30 days and ≥180 days after surgery, we used generalized estimating equations with an exchangeable correlation structure to take into account study clustering (17). The baseline model included the following variables: age, Revised Cardiac Risk Index (RCRI) score ≥3, type of surgery (vascular vs. nonvascular), urgency of surgery (urgent/emergent vs. elective), and study as a clustering variable. We assessed collinearity 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 pre-operative NP by adding pre-operative NP measurement to the baseline model to create a pre-operative 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 pre-operative NP. We evaluated post-operative NP by adding a post-operative NP measurement to the pre-operative 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). On the basis of the NP measurement, patients 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 reflects a worsening in risk stratification. For NRI analyses, patients were risk stratified as <5%, 5% to 10%, >10% to 15%, and >15% risk for the primary outcome at 30 days after surgery (1). To determine the influence of post-operative NP drawn later than 1 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 pre-operative to post-operative, to determine whether 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., post-operative NP − pre-operative NP); (2) absolute change in the log transformed NP value (i.e., log[post-operative NP] − log[pre-operative NP]); (3) fractional change $\left(\frac{post\text{-}operative\ NP - pre\text{-}operative\ NP}{pre\text{-}operative\ NP}\right)$; and (4) log fractional change $\left(\frac{log(post\text{-}operative\ NP) - log(pre\text{-}operative\ NP)}{pre\text{-}operative\ NP}\right)$. These four change variables were each evaluated separately in a model containing the pre-operative and post-operative NP threshold variables.

We report adjusted odd ratios, corresponding 95% confidence interval (CI), and associated p values. All p values are reported to 3 decimal places. The criterion for statistical significance was set a priori at alpha = 0.05. We used IBM SPSS Statistics 21.0 (Chicago, Illinois) for all analyses except for the derivation of the NP thresholds, for which we used R software version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria).

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

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Abbreviations and Acronyms

AUC = area under the curve

BNP = B-type natriuretic peptide

CI = confidence interval

IQR = interquartile range

MI = myocardial infarction

NP = natriuretic peptide

NRI = net reclassification index

NT-proBNP = N-terminal fragment of B-type natriuretic peptide

OR = odds ratio

QICu = corrected quasi-likelihood under the independence model criterion

RCRI = Revised Cardiac Risk Index

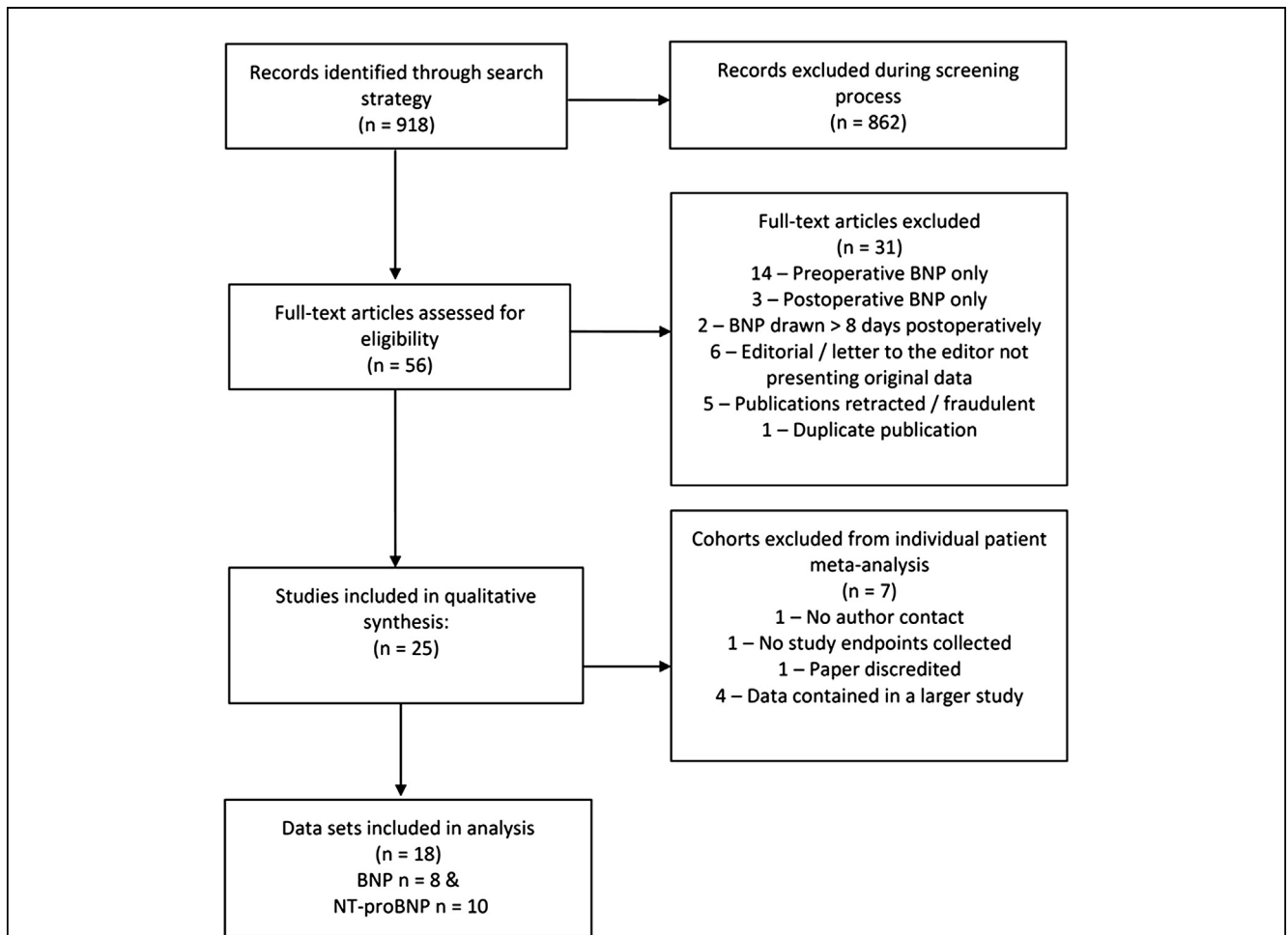**ROC** = receiver operating characteristic

these, we identified 25 eligible citations (8,20–43). Seven of these studies were not included in the analysis: Data from 4 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). Interobserver 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 the studies by Mahla et al. (8) (measured 3 to 5 days after surgery) and Waliszek et al. (43) (measured 7 days after surgery) (43). Study quality is reported in Table 2. Data collection and outcome assessment were 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 post-operative MI by measuring post-operative troponins.

Data were received on 2,477 patients from 18 studies. We excluded 298 patients, across all studies, who did not have both a pre-operative and post-operative NP measurement. A total of 2,179 patients were included; 8 studies evaluated BNP (n = 619), and 10 studies evaluated NT-proBNP (n = 1,560). A post-operative sample was drawn within the first day after surgery from 88% of these

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Table 1	**Characteristics of Included Studies**						
First Author, Year (Ref. #)	**Patient Population, Type of Surgery**	**No. of Patients**	**Age of Study Patients, mean ± SD**	**Type of Natriuretic Peptide**	**Assay, Manufacturer**	**Timing and Frequency of Samples**	**Length of Follow-up (Days)**
Manikandan et al., 2005 (31)	Elective, urological	52	72 ± 9.0	NT-proBNP	Elecsys ProBNP, Roche Diagnostics (Indianapolis, Indiana)	Pre-operative; post-operative: day 1	30
Cardinale et al., 2007 (21)	Elective, thoracic	400	62 ± 9.9	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Pre-operative; post-operative: 1 h after surgery	In-hospital
Hoksch et al., 2007 (27)	Elective, thoracic	22	67 ± 11.1	BNP	Triage BNP-Test, Biosite Diagnostic (San Diego, California)	Pre-operative; post-operative: days 1-5	270
Mahla et al., 2007 (8)	Elective, major vascular	218	70 ± 9.3	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Pre-operative; post-operative: days 3-5	826
Schutt et al., 2009 (38)	Elective and urgent/emergent, mixed (60% orthopedic)	75	69 ± 11.0	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Pre-operative; post-operative: days 1-3	30
Chong et al., 2010 (23)	Urgent/emergent, orthopedic	33	86 ± 9.7	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Pre-operative; post-operative: days 1-3	180
Chong et al., 2010 (22)	Urgent/emergent, orthopedic	89	80 ± 9.9	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Pre-operative; post-operative: days 1-3	730
Cagini et al., 2011 (20)	Elective, thoracic	149	66 ± 12.5	BNP	Triage BNP, Biosite Diagnostic	Pre-operative; post-operative: days 1,3 and 7	360
Cnotliwy et al., 2011 (25)	Elective, vascular	100	69 ± 8.5	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Pre-operative; post-operative: day 1	30
Radović et al., 2011 (35)	Elective, urological	25	56 ± 8.0	BNP	BNP 2, IRMA, CIS bio Internationale, Gif-Sur-yvette Cedex, France	Pre-operative; post-operative: days 1 and 7	180
Rajagopalan et al., 2011 (36)	Elective, major vascular	136	69 ± 9.7	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Pre-operative; post-operative: day 1	654
Suttie et al., 2011 (39)	Elective, major vascular	45	72 ± 10.4	BNP	BNP, Peninsula Laboratories, Merseyside, United Kingdom	Pre-operative; post-operative: immediately after surgery, and days 1–4	365
Waliszek et al., 2011 (43)	Elective, vascular	40	63.1 ± 10.6	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Pre-operative; post-operative: day 7	7
Lurati Buse et al., 2012 (30)	Elective, mixed (58% vascular)	380	72 ± 7.9	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Pre-operative; post-operative: day 1 and 2	365
Mercantini et al., 2012 (33)	Elective, general and orthopedic	205	64 ± 16.3	BNP	Triage BNP, Biosite Diagnostic	Pre-operative; post-operative: day 1	30
Chong et al., 2012 (24)	Emergency, orthopedic	187	77 ± 9.3	NT-proBNP	Elecsys ProBNP, Roche Diagnostics	Pre-operative; post-operative: days 1–3	365
Park et al., 2012 (34)	Elective, mixed (46% orthopedic)	85	69 ± 14.8	BNP	Advia Centaur Xp, Siemens (Bayer), Leverkusen, Germany	Pre-operative; post-operative: day 1	30
Rodseth et al., 2012 (37)	Elective, vascular	149	59 ± 12.2	BNP	Advia Centaur Xp, Siemens (Bayer)	Pre-operative; post-operative: day 1	30

BNP = B-type natriuretic peptide; IRMA = immunoradiometric assay; NT-proBNP = N-terminal fragment of pro B-type natriuretic peptide.

| Table 2 | **Study Quality Characteristics** | | | | |

First Author, Year (Ref. #)	Data Collection Blinded to NP Value	Outcome Assessment Blinded to NP	Consistent Outcome Definition	Diagnostic Troponin Threshold Used During Post-Operative Screening	MI Criteria
Manikandan et al., 2005 (31)	Blinded	Blinded	Yes	4th-generation troponin T ($\geq$0.03 ng/ml)	Elevated troponin, and $\geq$1 or more of ECG changes or anginal symptoms
Cardinale et al. 2007 (21)	Blinded	Blinded	Yes	No screening performed	Not a predefined study end point
Hoksch et al., 2007 (27)	Blinded	Blinded	Yes	No screening performed	Not a predefined study end point
Mahla et al., 2007 (8)	Blinded	Blinded	Yes	4th-generation troponin T ($\geq$0.03 ng/ml)	Elevated troponin and ECG changes indicative of ischemia
Schutt et al., 2009 (38)	Blinded	Blinded	Yes	4th-generation troponin T ($\geq$003 ng/ml)	Elevated troponin, and $\geq$1 of ECG changes or anginal symptoms
Chong et al., 2010 (20)	Blinded	Blinded	Yes	Troponin I ($\geq$0.03 ng/ml)	Universal definition of MI
Chong et al., 2010 (23)	Blinded	Blinded	Yes	Troponin I ($\geq$0.03 ng/ml)	Universal definition of MI
Cagini et al., 2011 (20)	Blinded	Blinded	Yes	No screening performed	Not a predefined study end point
Cnotliwy et al., 2011 (25)	Blinded	Unblinded	Yes	Troponin I ($\geq$0.01 ng/ml)	Universal definition of MI
Radović et al., 2011 (35)	Blinded	Blinded	Yes	No screening performed	Not a predefined study end point
Rajagopalan et al., 2011 (36)	Blinded	Blinded	Yes	Troponin-I ($\geq$0.1 ng/ml)	Elevated troponin only
Suttie et al., 2011 (39)	Blinded	Blinded	Yes	Troponin T ($\geq$0.01 ng/ml)	Elevated troponin, and $\geq$1 of ECG changes or anginal symptoms
Waliszek et al., 2011 (43)	Blinded	Blinded	Yes	Troponin I ($\geq$0.3 ng/ml)	Elevated troponin, and $\geq$1 of ECG changes or anginal symptoms
Lurati Buse et al., 2012 (30)	Blinded	Blinded	Yes	2006–2009: 4th-generation troponin T ($\geq$0.03 ng/ml) 2010 onward: 5th-generation troponin T ($\geq$0.013 ng/ml)	Elevated troponin only
Mercantini et al., 2012 (33)	Blinded	Blinded	Yes	4th-generation troponin T ($\geq$003 ng/ml)	Elevated troponin, and $\geq$1 of ECG changes or anginal symptoms
Chong et al., 2012 (24)	Blinded	Blinded	Yes	Troponin I ($\geq$0.03 ng/ml)	Universal definition of MI
Park et al., 2012 (34)	Blinded	Blinded	Yes	Troponin T ($\geq$0.01 ng/ml)	Elevated troponin and ECG changes indicative of ischemia
Rodseth et al., 2012 (37)	Blinded	Blinded	Yes	Troponin I ($\geq$0.1 ng/ml)	Elevated troponin only

ECG = electrocardiogram; MI = myocardial infarction; NP = natriuretic peptide.

patients (1,921 of 2,179) and within the first 3 days after surgery in 98% of patients (2,139 of 2,179). 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). Online Appendix 2 shows the characteristics of all 2,179 patients. This is subdivided into the patients who did and did not die or have nonfatal MI at 30 days after surgery.

Study outcome and determination of pre-operative NP cut-points. Within 30 days of surgery, 2.8% of patients had died (n = 62 of 2,179) and 10.8% had died or experienced nonfatal MI (n = 235 of 2,179). At $\geq$180 days, 8.4% of patients had died (n = 182 of 1,605) and 16.8% had died or experienced nonfatal MI (n = 366 of 1,617).

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

and nonfatal 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 pre-operative NP measurement above the threshold (n = 166 of 763; likelihood ratio: 2.3) compared with 4.9% in patients with a measurement below the threshold (n = 69 of 1,416; likelihood ratio: 0.42). An elevated pre-operative NP (odds ratio [OR]: 3.40; 95% CI: 2.57 to 4.47; p < 0.001), RCRI $\geq$3 (OR: 2.7; 95% CI: 1.81 to 3.96; p < 0.001), and urgent/emergency surgery (OR: 1.60; 95% CI: 0.75 to 3.53; p = 0.216) all predicted death or nonfatal MI at 30 days (Online Appendix 3).

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

Risk prediction improvement with the addition of NP. Adding a pre-operative NP measurement to the baseline model improved model fit and risk classification for the

Table 3 Change in Risk Classification for the Probability of Mortality or Nonfatal MI at 30 Days Using a Model Including Pre-Operative NP Compared With a Model Using Baseline Factors Only

Risk Classification Using Baseline Factors	Risk Classification Using Baseline and Pre-Operative NP				Reclassified† as		Net Correctly Reclassified‡ %	Net Reclassification Improvement§ %
	<5%	5%–10%	>10%–15%	>15%	Higher Risk	Lower Risk		
Patients With Primary Outcome*								
<5%	12	8	0	0				
5%–10%	29	7	32	8				
>10%–15%	2	15	14	43	91	53	16.2%	
>15%	0	4	3	58				31.6%
Patients Without Primary Outcome*								
<5%	676	61	0	0				
5%–10%	425	77	159	15				
>10%–15%	33	126	49	107	342	641	15.4%	
>15%	0	44	13	159				

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]/1,944). §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%).

MI = myocardial infarction; NP = natriuretic peptide.

prediction of the primary outcome at 30 days (QICu: 1,352.95 to 1,280.16; NRI: 32%; p < 0.001) and ≥180 days (QICu: 1,376 to 1,320.42; NRI: 18%; p < 0.001) after surgery (Table 3). Adding a post-operative NP measurement to the pre-operative NP model further improved model fit and risk classification at both 30 days (QICu: 1,280.16 to 1,204.06; NRI: 20%; p < 0.001) and ≥180 days (QICu: 1,320.42 to 1,300.09; NRI: 11%; p = 0.003) (Table 4). The results of the sensitivity analysis that excluded the two studies measuring post-operative NP after the first post-operative day did not differ appreciably from the primary results (Online Appendix 4).

Table 4 Change in Risk Classification for the Probability of Mortality or Nonfatal MI at 30 Days Using a Model Including Pre- and Post-operative NP Compared With Baseline and Pre-Operative NP Model Only

Risk Classification Using Baseline Factors and Preoperative NP	Risk Classification Using Baseline, With Pre- and Post-Operative NP				Reclassified† as		Net Correctly Reclassified‡ %	Net Reclassification Improvement§ %
	<5%	5%–10%	>10%–15%	>15%	Higher Risk	Lower Risk		
Patients With Primary Outcome*								
<5%	30	9	4	0				
5%–10%	7	8	4	15				
>10%–15%	0	7	0	42	74	28	19.6%	
>15%	0	9	5	95				20.2%
Patients Without Primary Outcome*								
<5%	1,033	46	55	0				
5%–10%	139	87	33	49				
>10%–15%	6	92	1	122	305	316	0.6%	
>15%	0	70	15	196				

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 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]/1,944). §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%).

MI = myocardial infarction; NP = natriuretic peptide.

Table 5	Variables Evaluated in the Final Generalized Estimating Equation Model for an Association With the Composite Outcome of Mortality or Nonfatal MI After Surgery		
Outcome	**Variable**	**Adjusted OR (95% CI)**	**p Value**
Death or nonfatal MI 30 days after surgery	Post-operative elevated NP	3.70 (2.18–6.24)	<0.001*
	RCRI ≥3	2.30 (1.59–3.19)	<0.001*
	Pre-operative elevated NP	1.90 (1.44–2.40)	<0.001*
	Urgent/emergent surgery	1.40 (0.72–2.64)	0.337
	Vascular surgery	1.30 (0.63–2.62)	0.484
	Age (per year)	1.00 (0.99–1.03)	0.096
Death or nonfatal MI ≥180 days after surgery	Post-operative elevated NP	2.20 (1.85–2.65)	<0.001*
	RCRI ≥3	2.10 (1.87–2.52)	<0.001*
	Pre-operative elevated NP	1.90 (1.38–2.58)	<0.001*
	Age (per year)	1.01 (1.00–1.02)	0.016*
	Vascular surgery	1.40 (0.77–2.47)	0.590
	Urgent/emergent surgery	0.60 (0.22–1.86)	0.545

*p < 0.05.
CI = confidence interval; GEE = generalized estimating equation; MI = myocardial infarction; NP = natriuretic peptide; OR = odds ratio; RCRI = Revised Cardiac Risk Index.

In the final model, independent predictors for the study outcome at 30 days were elevated post-operative NP (OR: 3.70; 95% CI: 2.18 to 6.24; p < 0.001), RCRI ≥3 (OR: 2.30; 95% CI: 1.59 to 3.19; p < 0.001), and elevated pre-operative NP (OR: 1.90; 95% CI: 1.44 to 2.40; p < 0.001). At ≥180 days, the independent predictors were elevated post-operative NP (OR: 2.20; 95% CI: 1.85 to 2.65; p < 0.001), RCRI ≥3 (OR: 2.20; 95% CI: 1.87 to 2.52; p < 0.001), elevated pre-operative NP (OR: 1.90; 95% CI: 1.38 to 2.58; p < 0.001), and age (OR: 1.01; 95% CI: 1.00 to 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% of patients (n = 1,653), with a median BNP increase of 66 ng/l (interquartile range [IQR]: 123 ng/l) and an NT-proBNP increase of 323 ng/l (IQR: 874 ng/l). NP decreased in 23% of patients (n = 507), with a median BNP decrease of 15 ng/l (IQR: 64 ng/l) and an NT-proBNP decrease of 53 ng/l (IQR: 153 ng/l). In both BNP and NT-proBNP data sets, the four change variables were each separately evaluated in a generalized estimating equation model containing the derived pre- and post-operative NP thresholds. In both data sets, none of the change variables were significant predictors of the primary study outcome at 30 days after surgery (Online Appendix 5).

Our exploration of traditional NP thresholds found that patients with pre-operative BNP values of 0 to 100, >100 to 250, and >250 ng/l demonstrated the composite of 30-day mortality or nonfatal MI at a rate of 5.1%, 11.6%, and 26.3%, respectively. Patients with pre-operative NT-proBNP values of 0 to 300, >300 to 900, >900 to 3,000, and >3,000 ng/l demonstrated 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 nonvascular surgery groups of patients, are shown in Online Appendix 6.

Discussion

This systematic review and individual patient-level data analysis demonstrate that adding a post-operative NP measurement to a pre-operative risk model that included pre-operative NP measurement improved the prediction of mortality or nonfatal MI at 30 or ≥180 days after noncardiac surgery.

The potential for NP measurement in pre-operative risk stratification lies in its ability to integrate the impact of multiple pre-operative pathophysiological processes into a single measurement (2,3). Previous meta-analyses suggest that a single elevated pre-operative 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 undergoing major noncardiac surgery thus significantly improves pre-operative risk stratification and could easily be incorporated into clinical practice, particularly in patients undergoing major vascular, intrathoracic, orthopedic, or intraperitoneal surgery, and would allow physicians to plan prophylactic strategies in patients identified as high risk.

In our analysis, a post-operative NP measurement was the strongest predictor of mortality or nonfatal MI after noncardiac surgery, and the addition of a post-operative NP measurement augmented the identification of at-risk patients. Post-operative NP elevations might 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 post-operative NP elevation correlates with post-operative troponin elevation.

NP elevation may precede troponin elevation, 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 post-operative troponin alone (1,44).

The strengths of this review lie in its rigorous methodology that 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 2,179 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).

Study limitations. A limitation of this analysis is that post-operative 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 3 days after surgery. The results of the sensitivity analysis conducted using only studies where NP sampling was performed within the first day of surgery were not appreciably different from the primary analysis. Therefore, it is likely that these results are representative of what can be expected by sampling NP early after surgery. No other post-operative variables besides NP could be evaluated in this analysis, and as a result we are unable to adjust for factors such as post-operative renal dysfunction, which is known to elevate NP. Two BNP studies used radioimmunoassay analysis methods (35,39), and the remaining six BNP studies used fluoroimmunoassay (20,27,31,33,34,37). Although 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 post-operative troponin surveillance (20,21,27,35); thus, it is possible that the incidence of post-operative MI may be higher than what we have reported. Most post-operative troponin elevations occur within the first 48 to 72 h after surgery (46). Although 88% of post-operative NP measurements were made within the first day after surgery, we are unable to determine the exact relationship between post-operative NP elevation and post-operative troponin elevation. All studies used an elevated troponin as part of their definition of post-operative MI, with two studies making the diagnosis on the basis of troponin elevation alone (30,37).

Conclusions

The addition of a post-operative NP measurement to a pre-operative risk model that includes pre-operative 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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▶ **APPENDIX**

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