Postoperative B-type Natriuretic Peptide for Prediction of Major Cardiac Events in Patients Undergoing Noncardiac Surgery

Systematic Review and Individual Patient Meta-analysis

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What We Already Know about This Topic

- Although preoperative B-type natriuretic peptides have been demonstrated to predict mortality and myocardial infarction in patients undergoing noncardiac surgery, the usefulness of postoperative natriuretic peptide has not been well established.

What This Article Tells Us That Is New

- Using individual patient data meta-analysis, patients with elevated postoperative natriuretic peptide were at increased risk of mortality, myocardial infarction, and cardiac failure at 30 days and more than 180 days after surgery
- The results further suggested that postoperative natriuretic peptide measurements may provide additional prognostic information and use in stratifying cardiovascular risk after noncardiac surgery

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 3A.

ABSTRACT

Background: It is unclear whether postoperative B-type natriuretic peptides (*i.e.,* BNP and *N*-terminal proBNP) can predict cardiovascular complications in noncardiac surgery.

Methods: The authors undertook a systematic review and individual patient data meta-analysis to determine whether postoperative BNPs predict postoperative cardiovascular complications at 30 and 180 days or more.

Results: The authors identified 18 eligible studies (n = 2,051). For the primary outcome of 30-day mortality or nonfatal myocardial infarction, BNP of 245 pg/ml had an area under the curve of 0.71 (95% CI, 0.64–0.78), and *N*-terminal proBNP of 718 pg/ml had an area under the curve of 0.80 (95% CI, 0.77–0.84). These thresholds independently predicted 30-day mortality or nonfatal myocardial infarction (adjusted odds ratio [AOR] 4.5; 95% CI, 2.74–7.4; $P < 0.001$), mortality (AOR, 4.2; 95% CI, 2.29–7.69; $P < 0.001$), cardiac mortality (AOR, 9.4; 95% CI, 0.32–254.34; $P < 0.001$), and cardiac failure (AOR, 18.5; 95% CI, 4.55–75.29; $P < 0.001$). For greater than or equal to 180-day outcomes, natriuretic peptides independently predicted mortality or nonfatal myocardial infarction (AOR, 3.3; 95% CI, 2.58–4.3; $P < 0.001$), mortality (AOR, 2.2; 95% CI, 1.67–86; $P < 0.001$), cardiac mortality (AOR, 2.1; 95% CI, 0.05–1,385.17; $P < 0.001$), and cardiac failure (AOR, 3.5; 95% CI, 1.0–9.34; $P = 0.022$). Patients with BNP values of 0–250, greater than 250–400, and greater than 400 pg/ml suffered the primary outcome at a rate of 6.6, 15.7, and 29.5%, respectively. Patients with *N*-terminal proBNP values of 0–300, greater than 300–900, and greater than 900 pg/ml suffered the primary outcome at a rate of 1.8, 8.7, and 27%, respectively.

Conclusions: Increased postoperative BNPs are independently associated with adverse cardiac events after noncardiac surgery.

MORE than 200 million surgeries were performed in adults globally each year and this number is increasing.[1,2] More than 10 million of these patients will suffer a major perioperative cardiovascular event (*i.e.,* cardiovascular mortality or myocardial infarction [MI]) within 30 days of surgery.[3] Effective optimization and intervention are only possible when these at-risk patients are accurately identified.

B-type natriuretic peptide (BNP) and its inactive cleavage product *N*-terminal fragment BNP (NT-proBNP) are hormones secreted from ventricular myocytes in response to ventricular wall stretch or myocardial ischemia.[4] Preoperative concentrations of BNPs are powerful predictors of mortality and MI in patients undergoing noncardiac surgery.[5] Postoperative NPs may have similar prognostic abilities,[6] but not all studies have demonstrated this signal.[7] Many of these studies have small sample sizes, ranging from 22 to 400 patients, and have been conducted on focused patient populations, such as vascular surgery. All these factors limit the generalizability of these individual studies. Furthermore, the previous individual studies have not established specific postoperative NP thresholds that define a patient at risk of an adverse postoperative cardiac event.

We undertook a systematic review and individual patient data meta-analysis to determine whether NPs, sampled less than 7 days postoperatively, are independently associated with the individual outcomes of mortality, cardiac mortality, nonfatal MI, cardiac arrest, coronary revascularization, or heart failure within 30 days and 180 days or more of adult noncardiac surgery. The study protocol (CRD42012002054) was registered with an international prospective register of systematic reviews (PROSPERO).

Materials and Methods

Study Eligibility

Studies of noncardiac surgery patients, where postoperative BNP or NT-proBNP was measured upto 7 days after surgery, were considered eligible for inclusion. Studies were

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included regardless of language, design, sample size, publication status, or date of publication. Studies were excluded if patients had cardiac surgery, included pediatric patients, or used NPs (*e.g.,* nesiritide) as therapy. Studies that met the inclusion criteria but did not report an outcome of interest (*i.e.,* mortality, cardiac mortality, nonfatal MI, cardiac arrest, coronary revascularization, or cardiac failure) were included if authors were able to provide the unpublished data for one or more of these outcomes.

Study Identification

We searched six databases (EMBASE, OVID Health Star, Ovid Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and ProQuest Dissertations and Theses A&I), used 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. The search terms, including validated prognostic search terms, and databases used are listed in Appendix 1. No language filters were used. To avoid inclusion of duplicate study data from reports publishing partial results, only the article with the largest most complete follow-up was included.

Eligibility Assessment

Drs. Biccard and Rodseth independently screened the title and abstract of each citation identifying those that potentially could fulfill the eligibility criteria. Full texts of citations identified to undergo full-text review during the screening process were obtained, and eligibility was independently evaluated by Drs. Biccard and Rodseth. Disagreements were solved by consensus, and where this could not be reached a third reviewer (Dr. Lurati Buse) made the final eligibility decision.

Data Collection and Assessment of Study Quality

Using a standardized extraction form, we recorded the following data: 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 assessed using the modified Quality Assessment of Diagnostic Accuracy Studies assessment tool.[8]

All authors from eligible studies were contacted and invited to provide anonymous individual patient data using standardized Excel (Microsoft Corp., Redmond, WA) spreadsheets. Age, sex, individual Revised Cardiac Risk Index (RCRI) risk factors[9] or if this was not available the cumulative RCRI score, type and urgency of surgery, postoperative NPs value, and predefined 30- and more than 180-day outcomes were obtained. Data sets were checked for accuracy and completeness. Only studies supplying individual patient data were included in this review. We assessed the risk of publication bias by constructing a funnel plot for the composite outcome of mortality and nonfatal MI.

Reporting of Study Outcomes

Our *a priori* individual outcomes of interest included: mortality, cardiac mortality, nonfatal MI, cardiac arrest, coronary revascularization, and cardiac failure. Four studies did not differentiate between nonfatal MI and fatal MI and did not conduct routine postoperative troponin surveillance.[10–13] For this reason, we were not able to report nonfatal MI; however, given that all trials collected data on mortality and MI, we were able to report this composite outcome of mortality or nonfatal MI. We deemed this outcome as the most clinically relevant and used it as our primary outcome.[14] The MI definitions used are shown in Appendix 2. Two studies collected data on cardiac mortality (Appendix 3).[6,15] Eleven studies collected data on cardiac failure,[7,10–13,16–20] and three of these studies explicitly defined this outcome (Appendix 4).[19,21,22] No studies collected data on coronary revascularization or cardiac arrest.

Statistical Analysis

Interobserver agreement was tested using κ statistics for study eligibility. An *a priori* decision was made that when studies measured more than one postoperative NP value within the first 48 h, the highest NP measurement would be used in the analysis. For studies measuring NPs after the first 48 h, we used the NP value closest to the time of surgery. Separate data sets were created for BNP and NT-proBNP. Using receiver operating characteristic (ROC) curves, we identified the highest ROC discriminatory threshold, using Youden Index (J = sensitivity + specificity − 1 = sensitivity − false positive rate), together with its associated 95% CIs for the composite outcome of mortality and nonfatal MI at 30 days in both data sets.[23,24] We then classified patients as falling on, above, or below this threshold, and merged the data sets.

Generalized estimating equations[25] were used to analyze each outcome. All analyses were adjusted for age, cumulative RCRI score (as a categorical variable), type of surgery (vascular *vs.* nonvascular), study as a clustering variable, and NP (above or below the highest ROC discriminatory threshold as determined above). Generalized estimating equations are special generalized linear models technique for clustered or correlated data. It allows for the specification of a correlation structure among patients within a study. We used an exchangeable correlation structure, which assumes the same correlation between any two patients within a study. The results are reported as adjusted odds ratio (AOR), corresponding 95% CI and associated *P* values. As a sensitivity analysis, we repeated this analysis using only those studies where NPs were sampled on the first day after surgery. We assessed collinearity using the variance inflation factor. Variables with a variance inflation factor greater than 10 were considered to be collinear, and if present we excluded one of these variables from the analysis.

The NT-proBNP thresholds of less than 300 pg/ml and greater than 900 pg/ml in patients aged between 50–75 years, and BNP thresholds of 250 and greater than 400 pg/ml, have been used in the diagnosis of acute cardiac failure.[26–28]

We explored these thresholds to determine whether they separated patients into clinically useful risk groups for the outcome of mortality or nonfatal MI at 30 days after surgery. To determine the clinical utility of postoperative NP reclassification, we used patient age, RCRI score, and type of surgery (vascular or nonvascular) to classify them into four preoperative risk categories (<5, 5–10, >10–15, and >15) for the outcome of 30-day mortality or nonfatal MI. We then reclassified patients using these postoperative NP thresholds and tested the results using reclassification statistics.[29]

The criterion for statistical significance was set *a priori* at $\alpha = 0.05$. We used IBM SPSS Statistics 19.0.0 (Chicago, IL) for descriptive analyses and SAS 9.2 2008 (Cary, NC) for generalized estimating equations and logistic regression.

Results

Study Identification and Selection

Our literature search identified 876 citations from which our screening process identified 53 to undergo full-text evaluation and from these we identified 28 eligible studies.[6,7,10–13,15–22,30–43] Data from five of these studies[33,39–42] were contained in larger subsequent publications that we included,[6,19,20,30] leaving 23 cohorts as shown in figure 1.[6,7,10–13,15–22,30–32,34–38,43] Five studies were not included in the analysis as we were unable to contact authors of three studies;[31,32,34] one study did not collect data on any of our outcomes of interest;[36] and data from one group is under review by an institutional research committee and could not be shared.[30] Authors of the remaining 18 studies provided individual patient data, and these data are included in this systematic review. Interobserver agreement for study eligibility was high ($\kappa = 0.84$). The funnel plot is shown in figure 2.

Study Characteristics and Data Collection

The characteristics of the 18 study cohorts are shown in table 1. All studies were prospective cohort studies of small sample sizes (smallest, 22 patients and largest, 400 patients). The type of surgery evaluated within studies included: six vascular surgery studies (679 vascular surgery patients), three thoracic studies (471 thoracic surgery patients), two

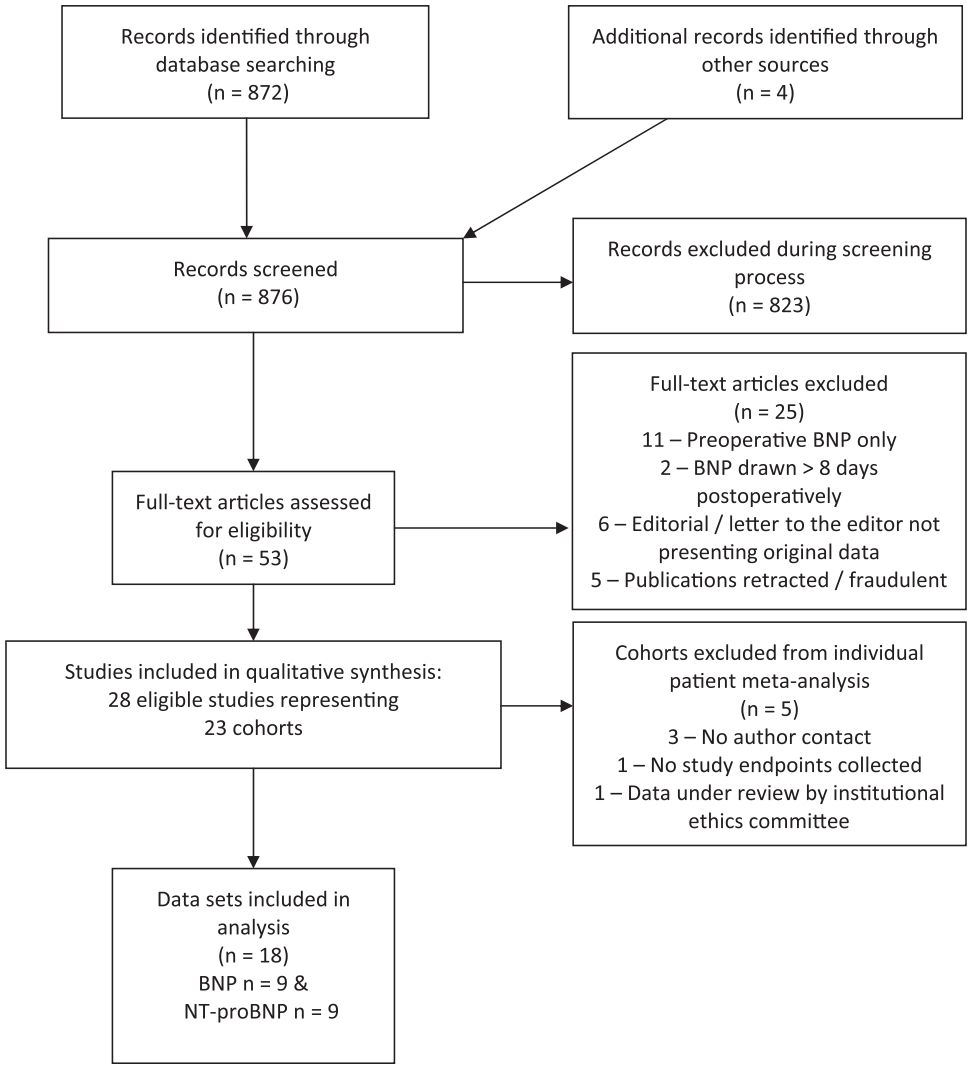

Fig. 1. Demonstrates the study selection process used for the systematic review.

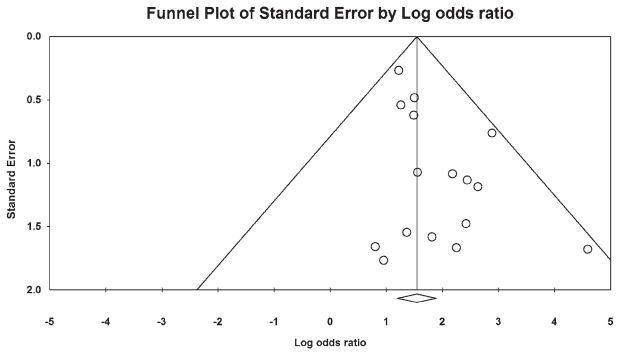

Fig. 2. Funnel plot for studies reporting the ability of postoperative natriuretic peptides to predict the composite outcome of mortality or nonfatal myocardial infarction 30 days after surgery.

orthopedic studies (122 orthopedic surgery patients), two urological studies (77 urology surgery patients), and five mixed or major general surgery studies (844 total patients). Most studies measured NP on day 1 after surgery. The quality of eligible studies was generally high (Appendix 5).

A total of 2,051 patients were included across the 19 studies. Ten studies evaluated BNP (n = 627) and nine studies evaluated NT-proBNP (n = 1,424). The mean age of the patients was 67 ± 12 (SD) years and 66% were men. The most common surgery was vascular surgery (43% underwent this surgery), and 32% of patients had a history of coronary artery disease. Table 2 shows the clinical characteristics of all 2,051 patients and for the subgroups of patients who did and did not suffer the primary outcome.

Event Rates and Determination of NPs Cut-points

The 30-day event rates were as follows: mortality or nonfatal MI, 11.6% (n = 238 of 2,051); mortality, 3.3% (n = 67 of 2,051); cardiac mortality, 1.5% (n = 5 of 337); and cardiac failure, 3% (n = 63 of 2,051). The corresponding greater than or equal to 180-day outcomes (mean follow-up of 212 days) were 33.5% (n = 480 of 1,432) for mortality or nonfatal MI, 11.1% (n = 160 of 1,432) for mortality, 9.2% (n = 31 of 337) for cardiac mortality, and 22.7% (n = 163 of 717) for cardiac failure.

For the composite outcome of mortality or nonfatal MI at 30 days, the highest ROC postoperative NP discrimination point was 245 pg/ml for BNP with a 95% CI ranging from 195 to 468 pg/ml (ROC area under the curve, 0.71; 95% CI, 0.64–0.78) and 718 pg/ml for NT-proBNP with a 95% CI ranging from 656 to 994 pg/ml (ROC area under the curve, 0.80; 95% CI, 0.77–0.84). For the merged data set with both NPs, the ROC area under the curve was 0.76; 95% CI, 0.73–0.80.

Table 3 shows the odds ratios—adjusted for age, RCRI score, and type of surgery (vascular or nonvascular)—associated with postoperative NPs increased above the highest ROC threshold for each of the study outcomes. Patients with an increased postoperative NP measurement were at

Table 1. Characteristics of Included Study Cohorts

Study	Type of Observational Study	No of Patients	Mean Patient Age, SD	Nature of Surgery	Patient Population
Manikandan, 2005[35]	Prospective	52	72 (9.0)	Urological (TURP)	Elective
Cardinale, 2007[11]	Prospective	400	62 (9.9)	Thoracic	Elective
Hoksch, 2007[12]	Prospective	22	67 (11.1)	Thoracic	Elective
Mahla, 2007[6]	Prospective	218	70 (9.3)	Major vascular	Elective
Cahill, 2009[20]	Prospective	99	69 (14.8)	Major general	Elective and urgent/emergent
Schutt, 2009[22]	Prospective	75	69 (11.0)	Mixed (60% orthopedic)	Elective and urgent/emergent
Chong, 2010[7]	Prospective	33	86 (9.7)	Orthopedic	Urgent/emergent
Chong, 2010[16]	Prospective	89	80 (9.9)	Orthopedic	Urgent/emergent
Cagini, 2011[10]	Prospective	49	66 (12.5)	Thoracic	Elective
Cnotliwy, 2011[21]	Prospective	100	69 (8.5)	Vascular (CEA)	Elective
Radović, 2011[13]	Prospective	25	56 (8.0)	Urological	Elective
Rajagopalan, 2011[15]	Prospective	136	69 (9.7)	Major vascular	Elective
Suttie, 2011[38]	Prospective	45	72 (10.4)	Major vascular	Elective
Waliszek, 2011[18]	Prospective	40	63.1 (10.6)	Vascular	Elective
Lurati Buse, 2012[43]	Prospective	380	72 (7.9)	Mixed (58% vascular)	Elective
Mercantini, 2012[19]	Prospective	205	64 (16.3)	General and orthopedic	Elective
Park, 2012[17]	Prospective	85	69 (14.8)	Mixed (46% orthopedic)	Elective
Rodseth, 2012[37]	Prospective	149	59 (12.2)	Vascular	Elective

BNP = B-type natriuretic peptide; CEA = carotid endarterectomy; NP = natriuretic peptides; NT-proBNP = *N*-terminal proBNP; postop = postoperatively; TURP = transurethral resection of the prostrate.

increased risk of 30-day mortality or nonfatal MI (AOR, 4.5; 95% CI, 2.74–7.4; $P < 0.001$) and cardiac failure (AOR, 18.5; 95% CI, 4.55–75.29; $P < 0.001$). NP increases remained predictive for greater than or equal to 180-day mortality or nonfatal MI (AOR, 3.3; 95% CI, 2.58–4.3; $P < 0.001$) and cardiac failure (AOR, 3.5; 95% CI, 1.0–9.34; $P = 0.022$).

Testing the robustness of these results by performing logistic regression in which we ignored study clustering did not appreciably change the AORs (Appendix 6). For the outcomes of mortality, and the composite of mortality and nonfatal MI, the results of the sensitivity analysis that excluded measurements obtained after the first postoperative day did not differ appreciably from the primary results (Appendix 7). For the outcomes of cardiac mortality and cardiac failure, the AOR was lower but remained significant. No variables were found to be collinear.

Patients with BNP values of 0–250, greater than 250–400, and greater than 400 pg/ml suffered the composite of 30-day mortality or nonfatal MI at a rate of 6.6, 15.7, and 29.5%, respectively. Patients with NT-proBNP values of 0–300, greater than 300–900, and greater than 900 pg/ml suffered the same composite of 30-day mortality or nonfatal MI at a rate of 1.8, 8.7, and 27%, respectively. In the NT-proBNP group, 32% (460 of 1,421) of patients had a value greater than 900 pg/ml. In a *post hoc* analysis, postoperative NP measurement improved overall net reclassification index by 20% ($P < 0.001$), with 6% of patients having an event being reclassified as higher risk and 14% of patients without an event being reclassified as lower risk (table 4). Among the 895 patients with a preoperative risk between 5 and 15% the net reclassification index improvement was 70% ($P < 0.001$) with 46% of patients having an event being reclassified to a high-risk category, and 25% of patient without an event being reclassified to a low-risk category.

Due to the number of patients with an NT-proBNP greater than 900 pg/ml we decided to undertake a *post hoc* analysis to determine the results for an additional NT-proBNP threshold of 3,000 pg/ml, which has been used in previous publications.[44] Patients with NT-proBNP values of 900–3,000 and greater than 3,000 pg/ml had an incidence of 30-day mortality or nonfatal MI of 20.9 and 38.4%, respectively. Using 3,000 pg/ml as a threshold ensured the CIs of the two new risk groups did not overlap. These NT-proBNP and BNP results together with the associated AOR and multilevel likelihood ratios are shown in tables 5 and 6.

Discussion

Summary of Evidence

Our systematic review and individual patient level meta-analysis included more than 2,000 patients who had a variety of different noncardiac surgeries. Meta-analysis indicates that an increased postoperative NP is an independent predictor of mortality, cardiac mortality, mortality or nonfatal

Table 1. (*Continued*)

Biomarker	Diagnostic Assay	Timing of Postoperative NPs Sample	Total Length of Follow-up, Days
BNP	Elecsys ProBNP; Roche Diagnostics	One sample: day 1	30
NT-proBNP	Elecsys ProBNP; Roche Diagnostics	One sample: 1 h postop	In-hospital
BNP	Triage BNP-Test; Biosite Diagnostic	One sample: days 1–5	30–270
NT-proBNP	Elecsys ProBNP; Roche Diagnostics	One sample: days 3–5	826
BNP	Abbott Architect	One sample: 12–48 h postop	90
NT-proBNP	Elecsys ProBNP; Roche Diagnostics	One sample: days 1–3	30
NT-proBNP	Elecsys ProBNP; Roche Diagnostics	One sample: days 1–3	180
NT-proBNP	Elecsys ProBNP; Roche Diagnostics	One sample: days 1–3	730
BNP	Triage BNP; Biosite	One sample: days 1, 3, and 7	7
NT-proBNP	Elecsys ProBNP; Roche Diagnostics	One sample: day 1	30
BNP	BNP 2; IRMA	One sample: days 1 and 7	180
NT-proBNP	Elecsys ProBNP; Roche Diagnostics	One sample: day 1	654
BNP	Peninsula Laboratories, Merseyside, United Kingdom	Immediately postop, and days 1–4	365
NT-proBNP	Elecsyst ProBNP; Roche Diagnostics	One sample: day 7	7
NT-proBNP	Elecsyst ProBNP; Roche Diagnostics	One sample: days 1 and 2	365
BNP	Triage BNP; Biosite	One sample: day 1	30
BNP	Advia Centaur Xp; Siemens (Bayer)	One sample: day 1	30
BNP	Advia Centaur Xp; Siemens (Bayer)	One sample: day 1	30

Table 2. Patient Characteristics in the Overall Patient Population and by Subgroups According to Whether Patients Did or Did Not Experience the Primary Outcome

Variables	All Patients n = 2,051	Patients Who Did not Experience Mortality or Nonfatal MI at 30 Days n = 1,813	Patients Who Experienced Mortality or Nonfatal MI at 30 Days n = 238	*P* Value
Age, mean (SD)	67 (12.0)	67 (12.4)	72 (11.1)	<0.001
Male, n (%)	1,350 (65.8)	1,190 (65.6)	160 (67.2)	0.663
Vascular surgery, n (%)	887 (43.2)	773 (43)	114 (60.5)	<0.001
Urgent/emergent surgery, n (%) (n = 1,980)	253 (12.8)	215 (11.8)	38 (16)	0.074
RCRI components				
Coronary artery disease, n (%) (n = 2,050)	663 (32.3)	518 (28.6)	145 (60.9)	<0.001
Congestive heart failure, n (%) (n = 1,931)	102 (5)	76 (4.2)	26 (10.9)	<0.001
Cerebrovascular disease, n (%) (n = 1,531)	245 (11.9)	211 (11.6)	34 (16)	<0.001
Diabetes mellitus, n (%) (n = 1,649)	279 (13.6)	222 (12.2)	57 (23.9)	0.003
Creatinine ≥2 mg/dl, n (%) (n = 1,998)	82 (4)	63 (3.5)	19 (8.1)	0.003

MI = myocardial infarction; RCRI = Revised Cardiac Risk Index.

MI, and cardiac failure at 30 and greater than or equal to 180 days after noncardiac surgery.

Strengths and Weaknesses

The strengths of this review lie in the: (1) rigorous systematic review methodology, (2) success in obtaining individual patient data, and (3) the quality of the included studies. Simulation studies show that logistic regression models require at least 10 events per predictor variable to produce stable estimates of association.[45] In our meta-analyses, we evaluated four independent variables, that is age, RCRI score, type of surgery (vascular *vs.* nonvascular), and peak postoperative NP measurement. We surpassed 10 events per variable for all outcomes except the 30- and greater than or equal to 180-day cardiac mortality outcomes.

Our systematic review is limited by the inability to adjust for postoperative troponin measurements, which are known to be strongly associated with postoperative mortality.[46,47] The majority of troponin increases occur within the first 48–72 h after surgery;[14] the same time period during which 16 of the studies included in this review sampled NPs. Unfortunately, the data were not available to allow us to determine the temporal relationship between NP and troponin increases. As we were limited by the inability to obtain the individual preoperative RCRI risk factors for each study it is possible that our model suffers from residual confounding. The funnel plot suggests the possibility of publication bias toward studies reporting a stronger association between increased postoperative NPs and the composite outcome of mortality and nonfatal MI. This weakens our inferences.

Preoperative NPs are useful for preoperative risk stratification. This analysis did not evaluate the interaction between preoperative and postoperative NPs. It is possible that postoperative NP increases may allow clinicians to identify the

Table 3. Odds Ratio Associated with Postoperative NPs above the Highest ROC Discriminatory Threshold after Adjusting for Age, Type of Surgery (Vascular or Nonvascular), and the RCRI Score

Days After Surgery	Outcome	Patients with Event n/N* (%)	Adjusted OR (95% CI)	*P* Value
30 days	Mortality	67/2,051 (3.3)	4.2 (2.29–7.69)	<0.001
	Cardiac mortality	5/337 (1.5)	9.4 (0.32–254.34)	<0.001
	Mortality or nonfatal MI	238/2,051 (11.6)	4.5 (2.74–7.4)	<0.001
	Cardiac failure	63/2,051 (3)	18.5 (4.55–75.29)	<0.001
≥180 days	Mortality	160/1,432 (11.1)	2.2 (1.67–2.86)	<0.001
	Cardiac mortality	31/337 (9.2)	2.1 (0.05–1,385.17)	<0.001
	Mortality or nonfatal MI	480/1,432 (33.5)	3.3 (2.58–4.3)	<0.001
	Cardiac failure	163/717 (22.7)	3.5 (1.0–9.34)	0.022

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

MI = myocardial infarction; NPs = natriuretic peptides; OR = odds ratio; RCRI = Revised Cardiac Risk Index; ROC = receiver operating curve characteristics.

Table 4. Change in Risk Stratification and Its Relationship to the Incidence of Mortality or Nonfatal MI within 30 Days Postsurgery after the Application of a Postoperative NP Measurement

	Mortality or Nonfatal MI		
Risk, %	Events (%)	No. of Events (%)	Total
Preoperative risk category*			
<5	6 (5.8)	97 (94.2)	103
5–10	34 (7.5)	419 (92.5)	453
>10–15	53 (12)	389 (88)	442
>15	145 (22.3)	506 (77.7)	651
Reclassified postoperative NP risk category			
<5	14 (2.9)	469 (97.1)	483
5–10	25 (7.5)	307 (92.5)	332
>10–15	28 (11.2)	221 (88.8)	249
>15	171 (29.2)	414 (70.8)	585

* Determined by age, RCRI score, and type of surgery (vascular or nonvascular).

NPs = natriuretic peptides; MI = myocardial infarction; RCRI = Revised Cardiac Risk Index.

most vulnerable patients among those with high preoperative NP concentrations.[37]

The large number of patients and deaths allowed us to evaluate all-cause mortality as an outcome. Unfortunately, cardiac mortality was only collected in two studies.[6,15] The small number of events analyzed for this outcome make overfitting of the results possible. This, together with the results of the sensitivity analysis, demonstrates that readers should interpret the cardiac mortality and heart failure data with caution. Evaluation of postoperative MI is hampered by the varying definitions used among the studies; however, all these studies included troponin increase as part of their definitions. The definitions of cardiac failure varied widely among studies, which may limit the validity of these results.

Postoperative NPs Thresholds

Converting a continuous variable into a categorical or dichotomous variable results in a loss of information, but it may make results more practical for clinical use. The thresholds we explored separated patients into clinically useful risk groups, but in many cases CIs overlapped. This may be due to the small sample size in some of the groups. The net reclassification results suggest that in this patient population a postoperative NP measurement is of greatest value in patients with a 5–15% preoperative baseline risk of 30-day mortality or nonfatal MI.

Recommendations and Implications for Clinical Practice

Previous studies have shown that NP concentrations are related to the extent of myocardial injury after nonoperative MI and improve prognostic scoring systems.[48,49] Our systematic review demonstrates the potential utility of postoperative NPs to identify patients at high risk of adverse cardiac events. These patients may benefit from close postoperative monitoring and more rigorous heart rate and fluid management; however, clinical trials are needed to determine whether this risk factor is modifiable. Postoperative NPs may also have a role in the diagnosis and management of patients with subclinical postoperative cardiac failure and may alert clinicians to those patients at risk of acute decompensation.

Before NPs can be incorporated into clinical practice they must demonstrate superiority to other more commonly used risk factors.[50] For this to take place studies are required to understand the relationship between postoperative troponin and NP increases. Two questions should be addressed: (1) do increased NPs in patients without early postoperative troponin increases predict postoperative cardiac complications? and (2) do increased NPs in patients with postoperative troponin increases add additional prognostic value to troponin measurement alone? Furthermore, studies to determine the optimal timing for sampling postoperative NPs would also be useful.

Conclusions

Postoperative NPs increases are associated with postoperative mortality, cardiac mortality, mortality and nonfatal MI, and cardiac failure at both 30 days and 180 days or more after surgery. Clinicians may thus find postoperative NP measurements useful in stratifying cardiovascular risk after noncardiac surgery.

Table 5. Postoperative NT-proBNP Thresholds and the Incidence of Mortality or Nonfatal MI at 30 Days after Surgery

NT-proBNP Value, pg/ml	Mortality or MI for All Types of Surgery		Adjusted Odds Ratio, 95% CI	Multilevel Likelihood Ratios
	n/N*	% (95% CI)		
0–300	11/605	1.8 (0.8–2.9)	1	0.16
>300–900	31/356	8.7 (5.8–11.7)	1.8 (0.57–5.61)	0.75
>900–3,000	63/301	20.9 (16.3–22.5)	4.7 (1.62–13.37)	1.79
>3,000	61/159	38.4 (30.7–46)	12.5 (2.85–54.89)	3.28
Total	166/1,421	11.7 (10.0–13.4)		

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

MI = myocardial infarction; NT-proBNP = *N*-terminal B-type natriuretic peptide.

Table 6. Postoperative BNP Thresholds and the Incidence of Mortality or Nonfatal MI at 30 Days after Surgery

BNP Value, pg/ml	Mortality or MI for All Types of Surgery		Adjusted Odds Ratio, 95% CI	Multilevel Likelihood Ratios
	n/N*	% (95% CI)		
0–250	31/467	6.6 (4.7–9.2)	1	0.58
>250–400	8/51	15.7 (6.4–26.1)	2.5 (1.39–4.49)	1.37
>400	33/112	29.5 (20.7–37.8)	5.9 (3.71–9.26)	2.58
Total	72/630	11.4 (8.9–13.9)		

* n/N = number of patients who died in subgroup/total number of a patients in subgroup.
BNP = B-type natriuretic peptide; MI = myocardial infarction.

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Appendix 1. Search Strategy and Databases

Database searches were conducted on January 14, 2012 using the OvidSP search engine (Ovid Technologies, Inc., New York, NY) for the following databases:

1. EMBASE 1980–2012 Week 3
2. OVID Health Star (1966 to November 2011)
3. Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and OVID MEDLINE(R) 1946 to present
4. Cochrane Central Register of Controlled Trials (January 2012)
5. Cochrane Database of Systematic Reviews (January 2012)
6. ProQuest Dissertations and Theses A&I (January 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.

Appendix 2. Cohort Definitions of Myocardial Infarction

Study	Postoperative Troponin Screening Conducted?	Troponin Threshold	Troponin Manufacturer	MI Criteria
Manikandan, 2005[35]	Yes	Troponin T (4th gen) > 0.03 ng/ml	Elecsys STAT; Roche	Increased troponin and one or more of ECG changes or anginal symptoms
Cardinale, 2007[11]	No	NA	NA	Not a predefined study endpoint
Hoksch, 2007[12]	No	NA	NA	Not a predefined study endpoint
Mahla, 2007[6]	Yes	Troponin T (4th gen) > 0.03 ng/ml	Elecsys STAT; Roche	Increased troponin and ECG changes indicative of ischemia[51]
Cahill, 2009[20]	Yes	Troponin I > 0.01 ng/ml	Abbott Architect Ci8200; Abbott	Increased troponin and one or more of ECG changes (ischemia or new pathological Q waves); anginal symptoms; evidence of MI on cardiac imaging
Schutt, 2009[22]	Yes	Troponin T (4th gen) > 003 ng/ml	Elecsys STAT; Roche	Increased troponin and one or more of ECG changes or anginal symptoms
Chong, 2010[7]	Yes	Troponin I > 0.03 ng/ml	Architect STAT; Abbott	Universal definition of myocardial infarction[52]
Chong, 2010[16]	Yes	Troponin I > 0.03 ng/ml	Architect STAT; Abbott	Universal definition of myocardial infarction[52]
Cagini, 2011[10]	No	NA	NA	Not a predefined study endpoint
Cnotliwy, 2011[21]	Yes	Troponin I > 0.01 ng/ml	VIDAS BLUE, boMerieux	Universal definition of myocardial infarction[52]
Radović, 2011[13]	No	NA	NA	Not a predefined study endpoint
Rajagopalan, 2011[15]	Yes	Troponin I > 0.1 ng/ml	ADVIA Centaur; Siemens	Increased troponin only
Suttie, 2011[38]	Yes	Troponin T > 0.01 ng/ml	Elecsys ECLI; Roche	Increased troponin and one or more of ECG changes or anginal symptoms
Waliszek, 2011[18]	Yes	Troponin I > 0.3 ng/ml	Advia Centaur; Siemens	Increased troponin and one or more of ECG changes or anginal symptoms
Lurati Buse, 2012[43]	Yes	Troponin T (4th gen) > 0.03 ng/ml (2006–2009) Troponin T (5th gen) > 0.013 ng/ml (2010 onwards)	Elecsys; Roche	Increased troponin only
Mercantini, 2012[19]	Yes	Troponin T (4th gen) > 003 ng/ml	Elecsys STAT; Roche	Increased troponin and one or more of ECG changes or anginal symptoms
Park, 2012[17]	Yes	Troponin T > 0.01 ng/ml	Cobas e 411; Roche	Increased troponin and ECG changes indicative of ischemia
Rodseth, 2012[37]	Yes	Troponin I > 0.1 ng/ml	Advia Centaur; Siemens	Increased troponin only

ECG = electrocardiogram; MI = myocardial infarction; NA = not applicable.

Appendix 3. Study Definitions of Cardiac Mortality

Study	Definition
Mahla, 2007[6]	Mortality secondary to myocardial infarction, arrhythmia, or heart failure
Rajagopalan, 2011[15]	Mortality due to an obvious cardiac cause

Appendix 4. Study Definitions of Heart Failure

Study	Definition
Schutt, 2009[22]	Congestive heart failure—Framingham Criteria[53]
Cnotliwy, 2011[21]	Acute heart failure—European Society of Cardiology[54]
Mercantini, 2012[19]	Acute heart failure—European Society of Cardiology[55]

Appendix 5. Study Quality Characteristics

Study	Is This a Population Representative of Patients Who Will Receive the Test in Practice?	Does the Diagnostic Criterion Used for the Outcome Classify the Target Condition Correctly?	Was Same Outcome Definition Used for All Patients?	Was Outcome Diagnosis Independent of NPs Results?	Were Outcomes Interpreted Independently of NPs Results	Were the NPs Results Interpreted Independently of the Outcomes?	Would the Same Clinical Data Be When Test Is Used in Practice?	Were Withdrawals from the Study Explained?
Manikandan, 2005[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cardinale, 2007[11]	Yes	No for PMI	Yes	Yes	Yes	Yes	Yes	Yes
Hoksch, 2007[12]	Yes	No for PMI	Yes	Yes	Yes	Yes	Yes	Yes
Mahla, 2007[6]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cahill, 2009[20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Schutt, 2009[22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chong, 2010[7]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chong, 2010[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cagini, 2011[10]	Yes	No for PMI	Yes	Yes	Yes	Yes	Yes	Yes
Cnotliwy, 2011[21]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Radović, 2011[13]	Yes	No for PMI	Yes	Yes	Yes	Yes	Yes	Yes
Rajagopalan, 2011[15]	Yes	No for PMI	Yes	Yes	Yes	Yes	Yes	Yes
Suttie, 2011[38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Waliszek, 2011[18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lurati Buse, 2012[43]	Yes	No for PMI	Yes	Yes	Yes	Yes	Yes	Yes
Mercanti, 2012[19]	Yes	Yes	Yes	No for cardiac failure	Yes	Yes	Yes	Yes
Park, 2012[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rodseth, 2012[37]	Yes	No for PMI	Yes	Yes	Yes	Yes	Yes	Yes

Modified from the QUADAS quality assessment tool.[9]

NP = B-type natriuretic peptides; PMI = perioperative myocardial infarction.

Appendix 6. The Adjusted ORs for Study Outcomes Associated with Increased Postoperative NPs above the ROC Highest Threshold, Calculated with Logistic Regression (Ignoring Study Clusters)

Days after Surgery	Outcome	Logistic Regression Results (Ignoring Study Clusters) Adjusted OR (95% CI)
30 days	Mortality	4.13 (2.22–7.69)
	Cardiac mortality	10.45 (1.78–109.72)
	Mortality or nonfatal MI	4.36 (3.14–6.07)
	Cardiac failure	20.41 (7.78–53.53)
≥180 days	Mortality	2.4 (1.57–3.63)
	Cardiac mortality	2.39 (1.04–5.21)
	Mortality or nonfatal MI	3.28 (2.38–4.52)
	Cardiac failure	2.98 (1.3–6.86)

MI = myocardial infarction; NPs = natriuretic peptide; OR = odds ratio; ROC = receiver operator curve.

Appendix 7. Results of the Sensitivity Analysis Including only Those Studies Where NPs Were Sampled within the First Postoperative Day

Days after Surgery	Outcome	Patients with Event n/N*, %	Adjusted OR, 95% CI	*P* Value
30 days	Mortality	58/1,391 (4.2)	4.1 (2.13–8.11)	<0.001
	Cardiac mortality	3/129 (2.3)	6.8 (3.59–18.27)	<0.001
	Mortality or nonfatal MI	217/1,391 (15.6)	4.3 (3.09–5.9)	<0.001
	Cardiac failure	55/593 (8.5)	15.54 (3.34–72.37)	<0.001
≥180 days	Mortality	110/906 (12.1)	1.9 (1.49–2.53)	<0.001
	Cardiac mortality	19/278 (6.8)	1.47 (1.02–2.12)	0.038
	Mortality or nonfatal MI	225/906 (24.8)	3.2 (2.59–4.04)	<0.001
	Cardiac failure	53/270 (19.6)	3.04 (1.1–8.79)	0.04

The table reports the adjusted odds ratio associated with postoperative NPs above the highest ROC discriminatory threshold.

* n/N = number of patients with an event in subgroup/total number of a patients in subgroup.

MI = myocardial infarction; NPs = natriuretic peptides; OR = odds ratio; ROC = receiver operating curve characteristics.

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