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CME

Is a Pre-Operative Brain Natriuretic Peptide or N-Terminal Pro–B-Type Natriuretic Peptide Measurement an Independent Predictor of Adverse Cardiovascular Outcomes Within 30 Days of Noncardiac Surgery?

A Systematic Review and Meta-Analysis of Observational Studies

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Objectives We conducted a systematic review and meta-analysis to determine if pre-operative brain natriuretic peptide (BNP) (i.e., BNP or N-terminal pro–B-type natriuretic peptide [NT-proBNP]) is an independent predictor of 30-day adverse cardiovascular outcomes after noncardiac surgery.

Background Pre-operative clinical cardiac risk indices have only modest predictive power. BNP predicts adverse cardiovascular outcomes in a variety of nonsurgical settings and may similarly predict these outcomes in the perioperative setting.

Methods We employed 5 search strategies (e.g., searching bibliographic databases), and we included all studies that assessed the independent prognostic value of pre-operative BNP measurement as a predictor of cardiovascular complications after noncardiac surgery. We determined study eligibility and conducted data abstraction independently and in duplicate. We calculated a pooled odds ratio using a random effects model.

Results Nine studies met eligibility criteria, and included a total of 3,281 patients, among whom 314 experienced 1 or more perioperative cardiovascular complications. The average proportion of patients with elevated BNP was 24.8% (95% confidence interval [CI]: 20.1 to 30.4%; $I^2 = 89\%$). All studies showed a statistically significant association between an elevated pre-operative BNP level and various cardiovascular outcomes (e.g., a composite of cardiac death and nonfatal myocardial infarction; atrial fibrillation). Data pooled from 7 studies demonstrated an odds ratio (OR) of 19.3 (95% CI: 8.5 to 43.7; $I^2 = 58\%$). The pre-operative BNP measurement was an independent predictor of perioperative cardiovascular events among studies that only considered the outcomes of death, cardiovascular death, or myocardial infarction (OR: 44.2, 95% CI: 7.6 to 257.0, $I^2 = 51.6\%$), and those that included other outcomes (OR: 14.7, 95% CI: 5.7 to 38.2, $I^2 = 62.2\%$); the p value for interaction was 0.28.

Conclusions These results suggest that an elevated pre-operative BNP or NT-proBNP measurement is a powerful, independent predictor of cardiovascular events in the first 30 days after noncardiac surgery. (J Am Coll Cardiol 2009; 54:1599–606) © 2009 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

BNP = brain natriuretic peptide

LVEF = left ventricular ejection fraction

MI = myocardial infarction

NT-proBNP = N-terminal pro–B-type natriuretic peptide

OR = odds ratio

A recent study used surgical data from 56 countries to estimate that >230 million major surgical procedures are undertaken annually worldwide (1). Given that cardiac and pediatric surgery account only for a minority of major surgical cases, at least 200 million adults annually undergo major noncardiac surgery. Several million of these patients suffer a major cardiovascular complication within 30 days of their surgery (2).

Establishing a method to facilitate accurate pre-operative assessment of major perioperative cardiovascular risk serves a number of important purposes. Accurate risk estimates provide guidance to physicians for perioperative management, including the choice of anesthetic techniques and the location and intensity of post-operative care. Accurate pre-operative risk assessment also allows patients and physicians to make informed decisions about the appropriateness of surgery. For example, some patients may find their risk of a major perioperative cardiac complication unacceptable and may choose to forgo or defer surgery (e.g., to experience an important life event).

See page 1607

Many surgical patients have limited activity levels because of their underlying disease states (e.g., arthritis, peripheral vascular disease, cancer). These patients may have underlying cardiac disease but are not sufficiently active to exhibit symptoms. Consequently, clinical cardiovascular risk indices have only modest predictive power in patients undergoing major noncardiac surgery (2,3). To enhance risk prediction, researchers have assessed the added value of noninvasive cardiac testing (e.g., dobutamine echocardiography, dipyridamole stress perfusion imaging) before noncardiac surgery (4,5). Although data are limited, these tests appear to provide additional predictive value beyond clinical variables, but are costly and time consuming (4,5). Therefore, there remains a need for a fast, simple, and cost-effective method to enhance pre-operative cardiovascular risk assessment.

Ventricular cardiomyocytes secrete brain natriuretic peptide (BNP), a prohormone, and its inactive cleavage product N-terminal fragment (N-terminal-pro–B-type natriuretic peptide [NT-proBNP]) into the blood in response to atrial or ventricular wall stretch (6), or myocardial ischemia (7). Throughout the rest of the paper, we will use the term BNP to represent either BNP or NT-proBNP unless otherwise stated.

Plasma BNP is a powerful predictor of death and major adverse cardiovascular events in patients with stable coronary artery disease (8), acute coronary syndromes (9), and congestive heart failure (10). A few recent studies have suggested that pre-operative elevation of BNP predicts major perioperative cardiovascular complications in patients undergoing noncardiac surgery. An accurate understanding of this potential association requires a comprehensive, systematic, and unbiased assessment of the literature. We therefore undertook a systematic review and meta-analysis to address the following question: in patients undergoing noncardiac surgery, is pre-operative BNP blood concentration an independent predictor of adverse cardiovascular outcomes within 30 days of surgery?

Methods

Study eligibility. We included studies of noncardiac surgery patients who had a BNP measurement before surgery, and the authors reported the independent association between a pre-operative BNP measurement and a perioperative cardiovascular event up to 30 days after surgery. A priori we defined a perioperative cardiovascular event as 1 or more of the following events: death, cardiac death, cardiovascular death, myocardial infarction (MI), acute coronary syndrome, unstable angina, coronary artery revascularization, cardiac arrest, cardiac arrhythmia resulting in hemodynamic compromise or requiring an intervention, congestive heart failure, or rehospitalization due to a cardiac cause.

Studies were excluded if they involved patients under 18 years of age. If studies did not restrict outcomes to the first 30 days after surgery, did not report the independent association of an elevated BNP level with cardiovascular events, or did not report BNP results based on a threshold value (i.e., they only reported results for BNP as a continuous variable), we attempted to contact the authors to obtain these missing data. If we were unable to obtain these data, the study was excluded.

Search strategy. We undertook 5 strategies to identify potentially eligible studies. Our search included the following: 5 electronic bibliographic databases; hand searching abstracts of the annual meetings of the American College of Cardiology, American Heart Association, and European Society of Cardiology between 1997 and 2007; reference

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lists of the retrieved articles, review articles, and practice guidelines; our own files; and contact with experts.

Using all the studies of which we were initially aware, we identified medical subject heading terms and key words for the search. In each database, we undertook an iterative process to refine the search strategy through testing of several search terms and incorporation of new search terms as new relevant citations were identified. We searched the Ovid version of MEDLINE (Ovid MEDLINE in-process and other nonindexed citations and Ovid MEDLINE, 1950 to third week of April, 2008), EMBASE (1980 to 2008, week 15), the Cochrane Central Register of Controlled Trials (first quarter 2008), the Cochrane Database of Systematic Reviews (first quarter 2008), and the ACP Journal Club (1991 to March/April 2008). No language restrictions were applied. All searches were performed using the OvidSP search engine (Ovid Technologies, Inc., New York, New York). The search strategy is detailed in the Online Appendix.

Eligibility assessment. Teams of 2 persons independently screened the title and abstract of each citation identified in our search. They selected any citation that they suspected had any possibility of fulfilling our eligibility criteria to undergo full review. If either of the 2 reviewers of a citation identified a citation as potentially relevant, we obtained the full-text article for full review.

Teams of 2 persons independently determined the eligibility of all studies identified to undergo full text evaluation in our screening process. Disagreements were resolved by a consensus process of having the 2 reviewers discuss their rationale regarding the study's eligibility, and when this did not resolve differences, a third person made a final decision on the study's eligibility.

Data abstraction and validity assessment. We abstracted the following descriptive data from all eligible studies: study design, study period, sample size, patient population, type of surgery, number of participants, length of follow-up, outcome, marker evaluated (i.e., BNP or NT-proBNP), assay manufacturer, BNP threshold, timing of BNP measurement, and the proportion of patients with an elevated BNP measurement. We evaluated the following validity criteria: blinding of data collectors and outcome adjudicators to BNP values, consistency of outcome assessment (whether the outcome assessment was the same for all study participants), and variables adjusted for in the analyses.

Two persons independently abstracted data from all studies that fulfilled our eligibility criteria, and we resolved disagreements using the same consensus process discussed above. We contacted the authors of all eligible studies to obtain missing data or confirm the accuracy of the abstracted data.

Statistical analyses. Interobserver agreement of study eligibility and the validity criteria between reviewers was assessed using a weighted kappa (determined by the PC-Agree Program, McMaster University, Hamilton, Ontario, Canada).

Three of the studies that we included in our meta-analysis did not report the odds ratio we required. The authors of 1 study (Gibson et al. [11]) provided their raw data, and we were thus able to perform a logistic regression analysis, adjusting for sex, ischemic heart disease, heart failure, cerebrovascular disease, renal impairment, type of surgery, and the prescription of beta-blockers and statins. These were the variables they had used in their reported analysis based upon a continuous BNP value. The study by Mahla et al. (12) focused on post-operative BNP, but they had also collected a pre-operative BNP sample. Dr. Mahla performed a multivariable logistic regression using pre-operative BNP instead of post-operative BNP and provided us with the results. In the paper by Yeh et al. (13), only the p value for the pre-operative BNP measurement was reported from their multivariable analysis but not the odds ratio. The authors were contacted, and they provided us with the odds ratio (13).

To determine the proportion of patients with an elevated BNP value across studies, we used the inverse-variance method to pool the results across studies. The outcomes varied among the studies, and were mostly composite outcomes. One person (P.J.D.), blinded to the study and study results, assessed the prognostic similarity of the each study's outcome and decided whether it was reasonable to include the study results in a pooled analysis. For the studies selected, we pooled the adjusted odds ratios using the DerSimonian and Laird random effects model (14). We calculated the I^2 statistic to assess heterogeneity between studies. An I^2 value $>25\%$ was considered to represent significant heterogeneity (15). Our a priori hypotheses to explain significant heterogeneity in the direction and magnitude of effect were: 1) BNP type (BNP vs. NT-proBNP); 2) type of surgery (major vascular, intra-abdominal, or intrathoracic vs. other); 3) blinding of data collectors (yes vs. no); 4) blinding of outcome adjudicators (yes vs. no); and 5) number of known predictors (i.e., diabetes mellitus, renal failure, coronary artery disease, congestive heart failure, stroke/transient ischemic attack, or high-risk surgery [intra-abdominal, intrathoracic, or vascular surgery]) adjusted for in analysis (2 or fewer vs. other).

We also performed sensitivity analyses to determine if the predictive power of BNP varied between studies that evaluated the outcomes of death, cardiovascular death, or MI, compared to studies that evaluated outcomes that only, or also, evaluated other less prognostically important events as part of their outcome. All p values were 2-sided and a value <0.05 was considered statistically significant. Analyses were performed using S-PLUS version 8.0 (TIBCO, Seattle, Washington).

Results

Our initial search yielded 564 references. We eliminated 529 citations after preliminary screening. The full texts of the remaining 35 articles were scrutinized to determine eligibility. Nine studies fulfilled our eligibility criteria and are

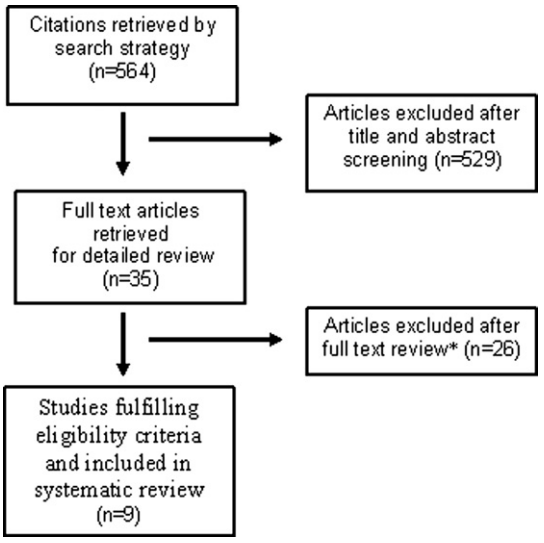

Figure 1 Flow Chart Showing Selection of Studies

*Independent association of pre-operative brain natriuretic peptide (BNP) levels not reported with outcomes of interest, n = 14; data overlapped with other reports, n = 4; 30-day outcomes not available, n = 3; patients did not undergo a surgical procedure, n = 1; patients underwent cardiopulmonary bypass as part of surgery, n = 1; no pre-operative BNP value available, n = 1; BNP analyzed as a continuous variable, n = 1; case report, n = 1.

included in this systematic review (Fig. 1) (11–13,16–21). Twenty-six studies were excluded during the full text review; reasons for exclusions are reported in Figure 1.

Data from a preliminary study of a small number of patients (22) was also reported in a subsequent larger study by the same group of investigators (11). Only the latter study was included in our analysis. There were 4 studies from 1 group of investigators reporting data from the same centers and across overlapping periods, and what appeared to be overlapping patient populations (16,23–25). We included the largest of these reports, which fulfilled our eligibility criteria (16). Interobserver agreement for the decisions around study eligibility was good (weighted kappa 0.64). We were able to contact an author for 7 of the 9 studies that fulfilled our eligibility criteria to confirm abstracted or obtain missing data. We sent the 2 remaining authors information on the data we abstracted from their studies and asked them to contact us if we had misunderstood any of their data.

Characteristics of included studies. All studies were prospective cohort studies. Table 1 presents the details of the included studies. The average age of the patients enrolled in these studies ranged between 57 and 74 years. Eight of the eligible studies included elective surgery patients, and the ninth study included emergent surgery patients (19). Patients underwent a wide range of different surgical procedures across the included studies. Two studies included only patients who underwent vascular surgery (12,16), and vascular surgery constituted a major proportion of the surgeries in 3 other studies (11,13,18).

Pre-operative BNP/NT pro-BNP measurement. The timing of pre-operative BNP measurement ranged from 21 days before surgery to immediately before the procedure. Five of the 9 studies used the NT-proBNP assay from Roche Diagnostics (Hoffmann-La Roche Ltd., Basel, Switzerland). The decision threshold used in the studies varied widely between 40 and 189 pg/ml for BNP and between 201 and 533 pg/ml for NT-proBNP (Table 2). The pooled analysis demonstrated that the proportion of patients with an elevated BNP value across studies was 24.8% (95% confidence interval [CI]: 20.1 to 30.4%; I^2 = 89%).

Methodologic quality of included studies. Table 3 reports the study validity criteria that we assessed. Interobserver agreement for the various validity criteria that we assessed was very good (weighted kappa values ranged from 0.71 to 1.00). Considering the issue of ascertainment bias, the data collectors and outcome adjudicators were blinded in most of the included studies. With the exception of 1 study, all studies explicitly defined the criteria used for assessing outcomes (21). No patients were lost to follow-up. Most of the included studies were at risk of overfitted models, because the number of events per variable included in the multivariable analyses was

Table 1 Characteristics of Included Studies

Author, Year (Ref. #)	Study Period*	Patient Population	Mean Age of Patients in Study (yrs)	Types of Surgery	Length of Follow-Up
Dernellis and Panaretou, 2006 (20)	Not reported	Elective	70	Abdominal, genitourinary, orthopedic, head and neck	3–17 days
Cuthbertson et al., 2007 (18)	Sept 2004 to Dec 2005	Elective	66	Major vascular, abdominal, genitourinary	72 h
Cuthbertson et al, 2007 (19)	Jan 2006 to June 2006	Emergent	74†	Abdominal, orthopedic	72 h
Yun et al., 2008 (21)	Jan 2006 to Dec 2006	Elective	68	Thoracic, abdominal, genitourinary, orthopedic, head and neck, other	30 days
Mahla et al., 2007 (12)	Oct 2002 to June 2003	Elective	70	Major vascular	30 days‡
Yeh et al., 2005 (13)	Nov 2002 to Aug 2003	Elective	57	Thoracic, major vascular, abdominal	30 days
Gibson et al., 2007 (11)	April 2004 to Oct 2005	Elective	68†	Thoracic, major vascular, abdominal	30 days‡
Feringa et al., 2006 (16)	Oct 2003 to Dec 2004	Elective	59	Major vascular	30 days
Cardinale et al., 2007 (17)	Oct 2004 to Dec 2005	Elective	62	Thoracic	8 days

*Study period is the time across which included patients underwent surgery. †Median. ‡As per separate analysis provided by study author.

Table 2 BNP and NT-proBNP Measurements

Author, Year (Ref. #)	Marker	Assay Manufacturer	BNP Threshold (pg/ml)	Timing of BNP Measurement	Proportion of Patients With Elevated BNP (%)
Dernellis and Panaretou, 2006 (20)	BNP	AxSYM system Axis Shield Diagnostics	189	Up to 3 days pre-operative	19.9
Cuthbertson et al., 2007 (18)	BNP	ADVIA Centaur Bayer	40	Within 24 h pre-operative	33.3
Cuthbertson et al., 2007 (19)	BNP	ADVIA Centaur Bayer	170	Immediately pre-operative	37.5
Yun et al., 2008 (21)	NT-proBNP	Elecsys 2010 Roche Diagnostics	201	Pre-operative*	24.4
Mahla et al., 2007 (12)	NT-proBNP	Elecsys ProBNP Roche Diagnostics	280	1 day pre-operative	38.1
Yeh et al., 2005 (13)	NT-proBNP	Elecsys 2010 Roche Diagnostics	450	Immediately pre-operative	23.7
Gibson et al., 2007 (11)	BNP	Shinoria BNP Shinogi & Co.	108.5	1 day pre-operative	23.7
Feringa et al., 2006 (16)	NT-proBNP	Elecsys 2010 Roche Diagnostics	533	21 ± 11 days pre-operative	15.3
Cardinale et al., 2007 (17)	NT-proBNP	Elecsys 1010 Roche Diagnostics	Various†	24 h pre-operative	17.8

*Exact timing of measurement not reported. †Authors employed 6 age- and sex-dependent thresholds.
BNP = brain natriuretic peptide; NT-proBNP = N-terminal pro–B-type natriuretic peptide.

<10, a minimum threshold established in simulation studies (Tables 3 and 4) (26).

Adjusted association between pre-operative BNP or NT-proBNP and 30-day cardiovascular outcomes. All adjusted associations were generated through multivariable logistic regression analyses (Table 4). The 9 eligible studies included a total of 3,281 patients, among whom 314 experienced a perioperative cardiovascular complication. All the included studies demonstrated that a pre-operative BNP or NT-proBNP measurement was an independent predictor of cardiovascular outcomes within 30 days of noncardiac surgery. Three studies in our systematic review adjusted for left ventricular ejection fraction (LVEF) and still reported a statistically significant association between a pre-operative BNP

Table 3 Study Quality Characteristics

Author, Year (Ref. #)	Blinded Data Collection (Yes/No)	Blinded Outcome Assessment (Yes/No)	Consistent Outcome Assessment* (Yes/No)	Method of Patient Follow-Up	Variables Adjusted for in Analyses
Dernellis and Panaretou, 2006 (20)	Not reported	No	Yes	Chart review	DM, CAD (past MI, CABG/PCI, angina as independent variables), CHF, type of surgery, hypertension, dyslipidemia, smoking, aortic stenosis, arrhythmia on last pre-operative ECG, ST-segment or T-wave changes or left bundle branch on baseline ECG, LVH on echo, LVEF, A:E ratio on transmitral Doppler >1, drug use (including beta-blocker, ACE inhibitor, diuretic), Goldman index, signs of chronic liver disease, family history of CAD, sex, age
Cuthbertson et al., 2007 (18)	Yes	Yes	Yes	Direct patient follow-up	Revised cardiac risk index;† age and prior use of cardiac medication in a second model
Cuthbertson et al., 2007 (19)	Yes	Yes	Yes	Direct patient follow-up	RCRI, ASA scoring system
Yun et al., 2008 (21)	Not reported	Not reported	No	Direct patient follow-up	History of CAD, history of CHF, intermediate-risk surgery, RCRI ≥2, left atrial enlargement, hemoglobin, LVEF, age, operation time >60 min, diastolic dysfunction, atrial fibrillation, transfusion, regional wall motion abnormality
Mahla et al., 2007 (12)	Yes	Yes	Yes	Direct patient follow-up	CAD, pre-operative creatinine, high-risk surgery (abdominal aortic aneurysm resection), age, pre-operative fibrinogen, pre-operative high sensitivity C-reactive protein, duration of surgery, surgical complications
Yeh et al., 2005 (13)	Yes	Yes	Yes	Direct patient follow-up	ASA grade, pre-operative cardiac impairment, age
Gibson et al., 2007 (11)	Yes	Yes	Yes	Direct patient follow-up	CAD, CHF, CVA/TIA, renal impairment, type of surgery, sex, beta-blocker and statin use
Feringa et al., 2006 (16)	Yes	Yes	Yes	Direct patient follow-up; chart review	DM, renal failure, DSE WM abnormalities (both new and at rest)
Cardinale et al., 2007 (17)	Yes	Yes	Yes	Direct patient follow-up	CAD, high-risk surgery, age, sex, hypertension, COPD, left atrial size, LVEF, beta-blocker use

*Consistent outcome assessment is whether the outcome assessment was the same for all study participants. †Variables in the Revised Cardiac Risk Index (RCRI) include high-risk type of surgery, ischemic heart disease, history of congestive heart failure or cerebrovascular disease, insulin therapy for diabetes mellitus, and pre-operative serum creatinine >2.0 mg/dl.
ASA = American Society of Anesthesiologists; CABG = coronary artery bypass graft; CAD = coronary artery disease (including past myocardial infarction); CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CVA = cerebrovascular accident; DM = diabetes mellitus; DSE = dobutamine stress echocardiography; ECG = electrocardiography; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; WM = wall motion.

Table 4 Adjusted Association Between Pre-Operative BNP/NT-proBNP Level and Cardiovascular Events at 30 Days

Author, Year (Ref. #)	Outcome Events	Number of Patients	Number of Events	Adjusted OR	95% CI	p Value
Dernellis and Panaretou, 2006 (20)	Cardiac death, nonfatal MI, pulmonary edema, ventricular tachycardia	1,590	96	34.52	17.08–68.62	0.00001
Cuthbertson et al., 2007 (18)	Myocardial injury, death, arrhythmia*	204	12	7.5	1.9–29.4	0.004
Cuthbertson et al., 2007 (19)	Cardiac death, myocardial injury	40	11	13.6	1.9–97.8	0.009
Yun et al., 2008 (21)	Cardiac death, nonfatal MI, pulmonary edema, nonfatal stroke	279	25	7.6	2.2–26.6	0.003
Mahla et al., 2007 (12)	Nonfatal MI, acute coronary revascularization, cardiac death	218	44	5.34	1.04–27.50	0.045
Yeh et al., 2005 (13)	Cardiac death, ACS, heart failure, arrhythmia*	190	15	76.3	8.8–661.8	<0.001
Gibson et al., 2007 (11)	Cardiac death, nonfatal MI	190 (41+149)	26 (11+15)	104.0	20.0–540.0	<0.001
Feringa et al., 2006 (16)	Death, nonfatal MI	170	13	17.2	2.8–106.4	0.002
Cardinale et al., 2007 (17)	Atrial fibrillation	400	72	27.9	13.2–58.9	<0.001

*Resulting in hemodynamic compromise or requiring intervention.
ACS = acute coronary syndrome; CI = confidence interval; LR = logistic regression; MI = myocardial infarction; OR = odds ratio.

measurement and a perioperative cardiovascular outcome (17,20,21). These studies suggest that a pre-operative BNP measurement provides independent prognostic information beyond LVEF.

We were able to obtain data on events occurring up to 30 days after noncardiac surgery for all 9 studies, either from the published reports or by contacting the authors. Death, cardiac death, and nonfatal MI were part of the composite outcome in all but 1 of the studies (17). The primary outcome in this study, by Cardinale et al. (17), was the occurrence of atrial fibrillation. This outcome was judged to be prognostically distinct from the outcomes in the other studies (i.e., it was thought that this outcome did not pose an immediate threat of mortality, unlike the other study outcomes) and was not included in the pooled analysis. In the study by Cuthbertson et al. (19), patients could satisfy the definition for myocardial injury if they had significant new post-operative electrocardiographic changes. Because of concerns about the prognostic dissimilarity of this outcome to the outcomes in the other trials, we did not include the data from this study in the pooled analysis. The results of the pooled estimate of the remaining 7 studies were included in our meta-analysis and are presented in Figure 2. An elevated pre-operative

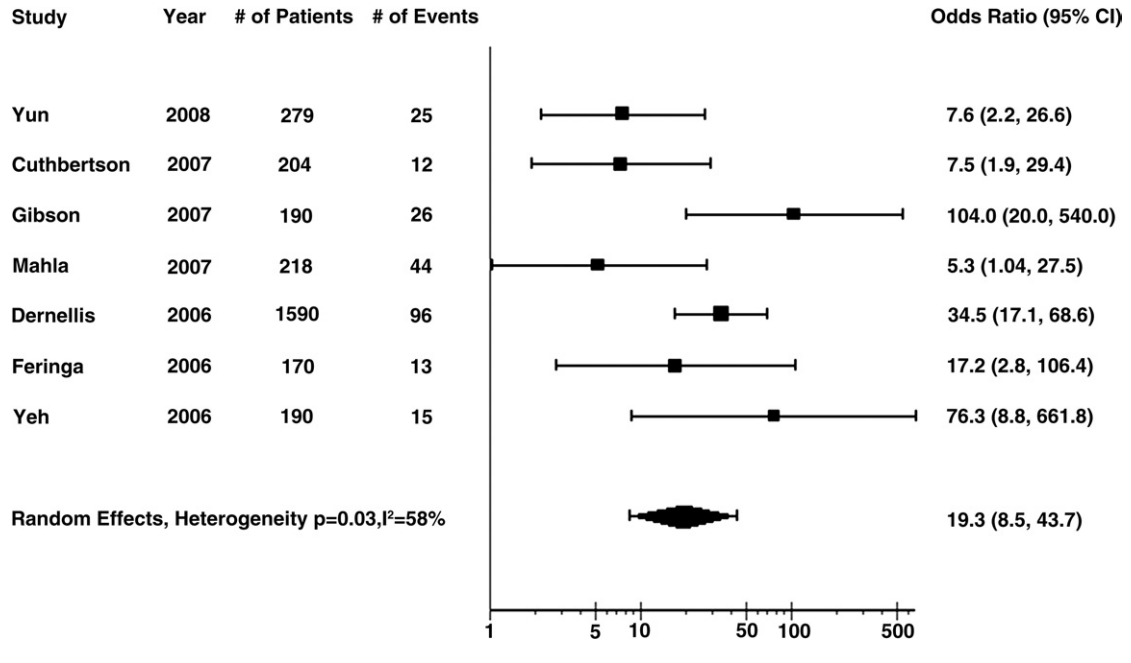

Figure 2 Adjusted Odds Ratios for Pre-Operative BNP/NT-proBNP to Predict Cardiovascular Outcomes at 30 Days After Surgery

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

BNP measurement was strongly predictive of cardiovascular outcomes at 30 days (odds ratio [OR]: 19.3, 95% CI: 8.5 to 43.7). There was, however, a moderate amount of heterogeneity across study results (I^2 = 58%, p = 0.03). Our a priori hypotheses (i.e., type of BNP, type of surgery, blinding of data collectors and outcome adjudicators, number of known predictors adjusted for in analysis) did not explain the demonstrated heterogeneity.

The pre-operative BNP measurement was an independent predictor of perioperative cardiovascular events among studies that only considered the outcomes of death, cardiovascular death, or MI (OR: 44.2, 95% CI: 7.6 to 257.0, I^2 = 51.6%) (11,16) and studies that included other outcomes (OR: 14.7, 95% CI: 5.7 to 38.2, I^2 = 62.2%) (12,13,18,20,21); p value for interaction was 0.28.

Discussion

Statement of principal findings. This meta-analysis suggests that a pre-operative BNP or NT-proBNP measurement may facilitate risk stratification of patients undergoing noncardiac surgery. An elevated BNP measurement was a powerful predictor of adverse cardiovascular outcomes at 30 days, independent of conventional risk factors. There was, however, a moderate amount of heterogeneity that we could not explain, and that weakens the inferences of our findings.

Strengths and weaknesses of our systematic review. Our systematic review has several strengths. We undertook a comprehensive search, conducted eligibility decisions and data abstraction in duplicate and demonstrated a high degree of agreement, and obtained or confirmed data with authors from 7 of the 9 included studies.

There are several limitations to our systematic review. The majority of studies included too many variables in their multivariable analyses for the number of events in the study, and that may have resulted in unreliable models. Furthermore, the underlying studies did not evaluate a consistent outcome, and there was marked heterogeneity across study results that we could not explain. Each of the individual odds ratios were, however, statistically significant. This finding indicates that the heterogeneity was entirely quantitative, and although there is uncertainty regarding the strength of the association, the evidence strongly suggests that there is an independent association between an elevated pre-operative BNP level and an increased risk of an adverse perioperative cardiovascular outcome. This relationship is robust both for the outcomes of total mortality, cardiovascular death, or MI and for the other adverse cardiovascular outcomes assessed.

Studies reported results as an adjusted OR instead of an adjusted likelihood ratio, which is required to allow physicians to use the BNP results to move from a pre-test probability to a post-test probability. Further, the wide confidence intervals associated with the pooled estimates (e.g., OR: 44.2; 95% CI: 7.6 to 257.0 for the outcomes of death, cardiovascular death, or MI) highlight why further research is needed before physicians can reliably use the results of a pre-operative BNP measurement to enhance perioperative risk prediction.

Our systematic review in relation to other systematic reviews. Our systematic review extends the results reported in a recent systematic review that demonstrated an association between elevated pre-operative BNP measurement and perioperative cardiovascular outcomes in patients having vascular surgery (27). However, that review pooled the unadjusted odds ratios. In contrast, we pooled the adjusted odds ratios from the eligible studies to evaluate whether an elevated pre-operative BNP measurement is an independent predictor of perioperative cardiovascular events. This is an important distinction because the cost associated with measuring a pre-operative BNP level is only justifiable if it provides prognostic information in addition to that available from established clinical risk factors. Therefore, we focused on determining whether a pre-operative BNP measurement is an independent predictor of a perioperative cardiovascular event. Further, this recent systematic review only included studies involving patients who underwent vascular surgery.

How does pre-operative BNP predict risk? The ability of BNP levels to predict outcomes in the perioperative setting likely relates to its exquisite sensitivity to changes in ventricular function, both systolic and diastolic. Even the small changes in ventricular function induced by transient myocardial ischemia produce measurable changes in plasma BNP (7,28), and proportionately higher levels are found in patients with poorer left ventricular function (29). Recent evidence also suggests that plasma BNP levels reflect the presence and severity of coronary artery disease among patients with chronic stable coronary disease (30). Thus, it is perhaps not surprising that elevated BNP measurements proved a powerful predictor of cardiovascular outcomes at 30 days, independent of conventional risk factors.

What is the level of BNP that should be considered abnormal? The studies we evaluated used different thresholds for BNP and NT-proBNP assays to represent an abnormal value. Because of the limited number of studies, our systematic review cannot provide clear guidance on the level of BNP or NT-proBNP that may be considered abnormal. Moreover, it is unlikely that there is a dichotomous threshold that defines a normal or abnormal BNP value. More probably, perioperative cardiovascular risk increases as BNP concentrations increase.

To establish whether there is a single threshold or a few important BNP thresholds requires the evaluation of a large number of patients across the spectrum of perioperative risk undergoing a broad range of surgical procedures. We are currently conducting a substudy in the 40,000 patient international VISION (Vascular events In noncardiac Surgery patIents cOhort evaluatioN) study. This substudy of 10,000 patients is evaluating whether NT-proBNP is an independent predictor of major vascular complications in the first 30 days after surgery, and we will also determine if there is 1 or multiple NT-proBNP thresholds that substantially influence risk prediction.

Conclusions

This systematic review and meta-analysis suggests that a pre-operative BNP or NT-proBNP concentration is a powerful, independent predictor of cardiovascular events in the first 30 days after noncardiac surgery. This test appears to represent a rapid and relatively inexpensive method to enhance pre-operative cardiovascular risk prediction. Results from the ongoing VISION NT-proBNP study will help clarify the value of a pre-operative NT-proBNP measurement in a large adequately powered prospective cohort study.

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Key Words: perioperative myocardial infarction ■ brain natriuretic peptide ■ perioperative risk.

APPENDIX

For the search strategy, please see the online version of this article.