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Prognostic Value of Brain Natriuretic Peptide in Noncardiac Surgery

A Meta-analysis

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Background: **The prognostic role of brain natriuretic peptide (BNP) measurement before noncardiac surgery is unclear. The authors therefore performed a meta-analysis of studies in patients undergoing noncardiac surgery to assess the prognostic value of elevated BNP or *N*-terminal pro-BNP (NT-proBNP) levels in predicting mortality and major adverse cardiovascular events (MACE) (cardiac death or nonfatal myocardial infarction).**

Methods: **Unrestricted searches of MEDLINE and EMBASE bibliographic databases were performed using the terms "brain natriuretic peptide," "b-type natriuretic peptide," "BNP," "NT-proBNP," and "surgery." In addition, review articles, bibliographies, and abstracts of scientific meetings were manually searched. The meta-analysis included prospective studies that reported on the association of BNP or NT-proBNP and postoperative major adverse cardiovascular event (MACE) or mortality. The study endpoints were MACE, all-cause mortality, and cardiac mortality at short-term (less than 43 days after surgery) and longer-term (more than 6 months) follow-up. A random-effects model was used to pool study results; funnel-plot inspection was done to evaluate publication bias; Cochrane chi-square test and I^2 testing was used to test for heterogeneity.**

Results: **Data from 15 publications (4,856 patients) were included in the analysis. Preoperative BNP elevation was associated with an increased risk of short-term MACE (OR 19.77; 95% confidence interval [CI] 13.18–29.65; $P < 0.0001$), all-cause mortality (OR 9.28; 95% CI 3.51–24.56; $P < 0.0001$), and cardiac death (OR 23.88; 95% CI 9.43–60.43; $P < 0.00001$). Results were consistent for both BNP and NT-proBNP. Preoperative BNP elevation was also associated with an increased risk of long-term MACE (OR 17.70; 95% CI 3.11–100.80; $P < 0.0001$) and all-cause mortality (OR 4.77; 95% CI 2.99–7.46; $P < 0.00001$).**

Conclusions: **Elevated BNP and NT-proBNP levels identify patients undergoing major noncardiac surgery at high risk of cardiac mortality, all-cause mortality, and MACE.**

CARDIOVASCULAR complications are a leading cause of perioperative death after major noncardiac surgery.[1,2] Impaired left ventricular function and inducible myocardial ischemia are strong predictors of perioperative cardiovascular complications, and current methods of risk stratification before surgery rely on the identification of clinical risk factors for heart disease.[1] Patients identified as high risk may require more detailed preoperative cardiac evaluation (*e.g.*, echocardiography, stress testing, or cardiac catheterization) and perioperative optimization. This approach lacks objectivity, and significant cardiovascular disease may be missed. There is therefore a need for a reliable objective screening test to risk-stratify patients and to identify those requiring more detailed preoperative investigation.

Brain natriuretic peptide (BNP) is a hormone with natriuretic and vasodilator properties. It is synthesized by cardiomyocytes in response to elevated ventricular wall stress or ischemia[3,4]; it is therefore associated with a variety of cardiac pathologies such as left ventricular dysfunction, valvular heart disease, and acute coronary syndromes.[5] Both BNP and its inactive precursor *N*-terminal proBNP (NT-proBNP) can be measured in plasma using automated immunoassays costing approximately US $20 per test. These assays are frequently used as screening tests in hospital and community settings to identify patients who may have heart failure and require further definitive investigation, such as echocardiography.[5]

A number of observational studies have recently examined the hypothesis that preoperative BNP elevation identifies patients at risk of adverse events after major noncardiac surgery. Most but not all have demonstrated an association with postoperative major adverse cardiovascular events (MACE: cardiac death, nonfatal myocardial infarction), but this risk varies widely among studies, and there is little consensus. In addition there are virtually no data on the association between BNPs and postoperative mortality because no studies have been powered to examine this. Furthermore, it is not clear if there are significant differences in the predictive value of BNP and NT-proBNP. We therefore undertook a meta-analysis to test the hypothesis that elevated preoperative BNPs predict postoperative MACE, cardiac mortality, and all-cause mortality during both short (less than 43 days) and longer-term (more than 6 months) follow-up after noncardiac surgery.

Materials and Methods

The methods for this meta-analysis conform to those proposed by Stroup *et al.*[6]

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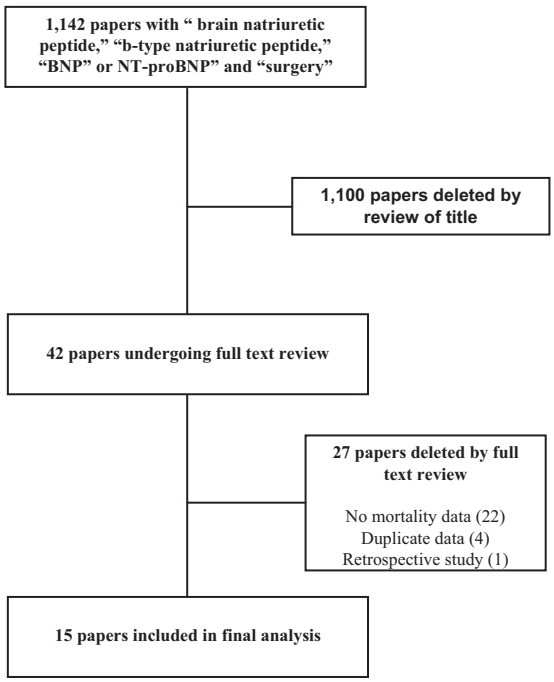

Fig. 1. Flow diagram for study selection.

Study Objectives and Definitions

The primary objectives of this analysis were to assess whether elevated preoperative plasma BNPs predict short-term MACE, cardiac mortality, and all-cause mortality in patients undergoing noncardiac surgery. The secondary objectives were to determine the relationship between preoperative BNPs and longer-term major adverse cardiovascular event (MACE) and all-cause mortality. On the basis of the range of timepoints in published studies, we defined short-term outcomes as less than 43 days after surgery, whereas longer-term outcomes were defined as 6 months or more after surgery. MACE was defined as cardiac death or nonfatal myocardial infarction. Cardiac death required evidence of myocardial infarction, cardiac arrhythmia, or congestive cardiac failure, and it was adjudicated by the authors of individual studies.

Study Selection

Studies were included in this analysis if they had prospectively collected data on perioperative mortality or MACE in adult patients undergoing noncardiac surgery with either preoperative BNP or NT-proBNP measurement. Study authors were contacted to confirm outcomes data, allowing the creation of a 2×2 table based on BNP and NT-proBNP levels (normal and elevated) and outcome (mortality or MACE).

Identification of Relevant Studies

We searched MEDLINE (1966–2008) and EMBASE (1996–2008) databases, using the search terms "brain natriuretic peptide," "b-type natriuretic peptide," "BNP,"

Table 1. Studies of Short-term Mortality

First Author	Year	N	Type of Surgery	ß-blocker Use, %	Follow-up
Berry[20]	2006	41	Elective major vascular surgery: amputation 46%, revascularisation 18%, AAA repair 18%	15	48 h
Cho[15]	2006	1,002	Elective noncardiac surgery	NR	5 days
Cuthbertson[16]‡	2007	204	Elective major noncardiac surgery: major vascular 34%, major abdominal 41%, major pelvic 25%	21	3 days
Cuthbertson[12]	2007	40	Emergency major non-cardiac surgery: Hip surgery 48%, laparotomy 52%	0	In hospital
Dernellis[17]	2006	1,590	Elective noncardiac surgery	NR	In hospital
Descamps[13]	2007	98	Emergency fractured neck of femur	NR	30 days
Feringa[21]	2006	170	Elective major vascular surgery: AAA repair 40%, infrainguinal revascularisation 60%	64	30 days
Gibson[18]*	2007	41	Elective major vascular surgery: AAA repair 27%, infrainguinal revascularisation 41%, amputation 32%	17	42 days
Gibson[18]†	2007	149	Elective major noncardiac surgery: laparotomy 33%, peripheral bypass 26%, amputation 17%, aortic repair 16%, nephrectomy 5%, esophagectomy 3%	20	42 days
Goei[23]	2008	356	Elective major vascular surgery: carotid 29%, lower limb revascularization 29%, AAA repair 42%	NR	30 days
Leibovitz[14]	2008	44	Elective high-risk noncardiac surgery: aortic 18%, orthopedic 73%, other 9%	59	30 days
Riemersma[25]	2008	19	Elective lower limb amputation	NR	30 days
Yun[19]	2008	279	Elective noncardiac surgery: orthopedic 26%, retroperitoneal 22%, TURP 20%, endoscopic 13%, head and neck 5%, intraperitoneal 2%, thoracic 0.3%, other 12%	NR	30 days

* Derivation cohort. † Validation cohort. ‡ Data provided as age (yr), range.

AAA = abdominal aortic aneurysm; ACS = acute coronary syndrome; APO = acute pulmonary oedema; BNP = brain natriuretic peptide; EKG = electrocardiograph; LVF = left ventricular failure; MACE = major adverse cardiovascular event; MI = myocardial infarction; n = number; NR = not reported; NT-proBNP = *N*-terminal brain natriuretic peptide; SD = standard deviation; TURP = transurethral resection of prostate; VT = ventricular tachycardia.

"NT-proBNP," and "surgery." Abstracts from the scientific sessions of the American Heart Association, American College of Cardiology, European Society of Cardiology, British Cardiac Society, American Society of Anesthesiology, and European Society of Anaesthesiology (2004–2008) were searched manually, as were the references of individual papers. The last search was performed on June 11, 2008.

One author (Dr. Ryding) performed the electronic and manual searches and listed the trials that were eligible for inclusion in the study. Study selection was initially performed by review of title. Candidate abstracts were then reviewed and selected for data retrieval. Only prospective studies were considered eligible for inclusion. Two authors (Dr. Ryding and Dr. Kumar) independently reviewed each study for quality assessment and extracted data on studies and patient characteristics, as well as outcomes, using standardized extraction forms. Data quality was verified by an additional reviewer (Dr. Worthington), and disagreements were resolved by discussion. Because no standardized quality scoring system exists for quality assessment of observational studies, the components of the quality review were derived largely from the Cochrane quality checklist for prognostic studies.[7] Studies were assessed for the presence of ten features: type of study, description of patient sample characteristics, description of inclusion and exclusion criteria, potential selection bias, *a priori* definition of study outcomes, objectivity of outcomes, completeness of follow-up, missing data, evidence of selective reporting of data, and completeness of follow-up.

For each study, the following individual data were extracted: general data (study design), patients (number of included patients, mean age, gender, type of surgery, β-blocker usage), BNP assays (name of the assay, type of BNP measured [NT-proBNP or BNP], cutoff level, timing of determination, and overall BNP-positive patients), deaths (cardiac or all cause mortality), and MACE among BNP-positive or -negative patients.

Statistical Analysis

Unadjusted data were used exclusively in all meta-analyses. Outcomes are reported using random-effects models to allow for interstudy variability. Cochrane chi-square test and the I^2 test for heterogeneity were used to assess between-study heterogeneity. Statistically significant heterogeneity was considered present at $P < 0.10$ and $I^2 > 50\%$. Pooled odds ratios (ORs) were reported with 95% confidence intervals (CI). Publication bias was assessed visually by the use of funnel plots by using the method of Sterne and Egger.[8]

Separate analyses were performed for MACE, all-cause mortality, and cardiac mortality, BNP, or NT-proBNP and duration of follow up. The association between cutoff and the OR was assessed using meta-regression.[9] Analyses were performed with Review Manager (RevMan)

Table 1. Continued

Age (yr), SD	Male, %	BNP Type	Mortality Data	MACE
68	66 NR	BNP	Cardiac	Fatal + nonfatal MI
NR	NR	NT-proBNP	NR	Cardiac death, nonfatal MI, APO
66, 28–79	61	BNP	All-cause	Death, myocardial injury
74, 68–83	38	BNP	Cardiac	Cardiac death, myocardial injury, EKG changes
70, 63–77	60	BNP	Cardiac	Cardiac death, nonfatal MI, APO, VT
82, 74–90	25	BNP	All-cause	NR
59	71	NT-proBNP	Cardiac	Cardiac death, nonfatal MI
68	61	BNP	Cardiac	Cardiac death, nonfatal MI
68, 58–78	66	BNP	Cardiac	Cardiac death, nonfatal MI
69, 61–75	77	NT-proBNP	Cardiac + all-cause	Cardiac death, MI, Troponin elevation
77, 65–89	41	BNP	All-cause	All-cause mortality, ACS, LVF
69, 57–82	68	NT-proBNP	All-cause	NR
68, 60–76	52	NT-proBNP	Cardiac	Cardiac death, nonfatal MI, APO, stroke

Table 2. Studies of Long-term Mortality

First Author	Year	n	Type of Surgery	ß-blocker Use, %	Follow-up	Age, yrs (SD), Range	Male, %	BNP Type	Mortality Data	MACE
Cuthbertson[16]	2006	204	Elective major noncardiac surgery: major vascular 34%, major abdominal 41%, major pelvic 25%	15	Median 654 days	66, 57–74	61	BNP	Cardiac	NR
Cuthbertson[12]	2006	40	Emergency major noncardiac surgery: Hip surgery 48%, laparotomy 52%	NR	6 months	74, 68–83	38	BNP	Cardiac	NR
Feringa[22]	2007	335	Vascular surgery: AAA 46%, lower limb revascularisation 54%	21	6 months	62, 50–74	71	NT-proBNP	Cardiac	Cardiac death, nonfatal MI
Mahla[24]	2007	218	Elective major vascular surgery: AAA repair 24%, infrainguinal 60%, CEA 16%	0	Median 826 days	70, 61–79	78	NT-proBNP	Cardiac + all-cause	Cardiac death, nonfatal MI, emergent coronary revascularisation

AAA = abdominal aortic aneurysm; BNP = brain natriuretic peptide; CEA = carotid endarterectomy; MACE = major adverse cardiovascular event; MI = myocardial infarction; N = number; NR = not reported; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; SD = standard deviation.

Version 5.0.12 (The Cochrane Collaboration, 2008, The Nordic Cochrane Centre, Copenhagen, Denmark) and meta-regression was performed with MIX software (Kisato Clinical Research Centre, Sagamihara, Kanagawa, Japan).[10] The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A total of 792 articles and 350 abstracts were retrieved with the search strategy. From these, 757 papers and 343 abstracts were excluded on the basis of the title (fig. 1); 35 papers and 7 abstracts were identified that studied BNPs in the context of noncardiac surgery; 21 papers and 1 abstract did not report mortality data, and these were excluded; 4 abstracts were subsequently published in full and were therefore not included; 1 paper was excluded because it was a retrospective analysis.[11] Therefore, 15 publications, involving 4,856 individual patients, were selected for analysis.

Selected Studies

The characteristics of the studies are described in table 1 and 2. The demographic data of the study populations were similar in terms of age and gender, except for three studies that involved predominantly elderly female patients.[12–14] Mixed noncardiac surgery was reported in seven studies,[14–19] fractured neck of femur surgery was reported in one,[13] and vascular surgery was reported in seven.[18,20–25] Two studies looked at patients undergoing emergency surgery,[12,13] and the remainder were nonemergent. Reported perioperative β-blockade use ranged between 0% and 77% (table 1 and 2). Follow-up varied among publications; 11 reported short-term mortality data (in hospital or 2–42 days after operation),[13–21,25] 3 reported only longer-term data (6 months or greater),[22,24,26] and 1 reported both short-term and longer-term data.[12]

BNP Assays and Sampling

Three different assays were used to measure BNP or NT-proBNP (table 3). Most studies measured BNPs the day before surgery (range: day of surgery to 24 days before surgery), and one reported both preoperative and postoperative measurements.[24] Analyses were restricted to preoperative BNP data only. In general, optimal cutoff values were derived by the authors of the studies from the receiver operator curve characteristics for MACE. There was wide variation in cutoff values between studies, with those for NT-proBNP being higher than for BNP (NT-proBNP range 201–791 pg/ml *vs.* BNP range 35–255 pg/ml).

Study Quality and Publication Bias

We only included prospective observational studies. All studies were conducted in a blinded fashion, except one in which the BNP values were known to the clinicians treating the patients: this led to cancellation of surgery in 2% of patients.[17] Furthermore, systematic screening for asymptomatic postoperative cardiac events was not carried out, which may have led to bias in this study. Otherwise, there was no evidence of selective reporting of data or systematic bias in the other studies.

A funnel plot was used to assess for publication bias. This is a scatter plot of treatment effect (OR) on the horizontal axis against study size (variance) on the vertical axis. Publication bias (*i.e.*, exclusion of negative studies from the literature) or systematic bias is suggested when the scatter plot is unevenly distributed within the 95% CI funnel. No evidence of publication bias was found (fig. 2).

Major Adverse Cardiovsacular Events

Data for short-term MACE was available for 10 studies comprising 11 patient cohorts (table 1). MACE occurred in 283 of 862 patients (32.83%; 95% CI 29.78–36.04) with elevated BNPs compared to 119 of

Table 3. Assay Characteristics

First Author	Year	BNP Type	Assay Name, Manufacturer	Cutoff, pg/ml	Positive, %	Mean Preoperative Sample Timing, Days
Berry[20]	2006	BNP	ADVIA Centaur, Bayer	> 100	27	1
Cho[15]	2006	NT-proBNP	Elecsys, Roche	> 340	24	< 14
Cuthbertson[16]	2007	BNP	ADVIA Centaur, Bayer	> 40	33	1
Cuthbertson[26]	2007	BNP	ADVIA Centaur, Bayer	> 170	38	1
Cuthbertson[12]	2007	BNP	ADVIA Centaur, Bayer	> 35	38	0
Dernellis[17]	2006	BNP	AxSYM, Axis-Shield Diagnostics	> 200	18	3
Descamps[13]	2007	BNP	ADVIA Centaur, Bayer	> 255	30	1
Feringa[21]	2006	NT-proBNP	Elecsys, Roche	≥ 533	15	21
Feringa[22]	2007	NT-proBNP	Elecsys, Roche	≥ 319	36	24
Gibson[18]*	2007	BNP	ADVIA Centaur, Bayer	≥ 100	34	1
Gibson[18]†	2007	BNP	ADVIA Centaur, Bayer	> 108.5	21	1
Goei[23]	2008	NT-proBNP	Elecsys, Roche	≥ 478	27	3
Leibovitz[14]	2008	BNP	ADVIA Centaur, Bayer	> 165	55	1
Mahla[24]	2007	NT-proBNP	Elecsys, Roche	≥ 280	38	1
Riemersma[25]	2008	NT-proBNP	Elecsys, Roche	≥ 791	47	1
Yun[19]	2008	NT-proBNP	Elecsys, Roche	> 201	24	1

* Derivation cohort. †Validation cohort.

BNP = brain natriuretic peptide; NT-proBNP = *N*-terminal pro-brain natriuretic peptide.

3,049 patients (3.9%; 95% CI 3.27–4.65) that did not (OR 19.77; 95% CI 13.18–29.65; $P < 0.0001$) (fig. 3). There was no significant heterogeneity ($P = 0.13$; $I^2 = 30\%$). Sensitivity analysis did not significantly alter the result. The association was consistent for BNP (OR 25.45; 95% CI 12.46–51.97; $P < 0.00001$) and NT-proBNP (OR 15.65; 95% CI 10.39–25.37; $P < 0.00001$). We sought to determine whether study differences in cutoff values for BNP and NT-proBNP were associated with the outcome because higher cut offs might be related to worse outcomes. No significant association was found using meta-regression ($P = 0.2182$).

Only two studies reported longer-term data: MACE occurred in 76 of 202 patients (37.62%; 95% CI 31.23–44.49) with elevated NT-proBNP compared to 18 of 351 who did not have NT-proBNP elevation (OR 17.70; 95% CI 3.11–100.80; $P < 0.00001$) (fig. 4).

All-cause Mortality

Short-term all-cause mortality data were available for five studies (table 1). Overall, 26 of 221 patients (11.76%; 95% CI 8.17–16.69) with elevated BNPs died compared to 4 of 494 (0.81%; 95% CI 0.3–32.1) who did not. Elevated BNPs were associated with an increased risk of death (OR 9.28; 95% CI 3.51–24.56; $P < 0.0001$) with no evidence of heterogeneity ($P = 0.49$; $I^2 = 0\%$) (fig. 5).

Longer-term all-cause mortality data were available for four studies (table 2). Of 294 patients with elevated BNPs, 71 (24.15%; 95% CI 19.61–29.36) died

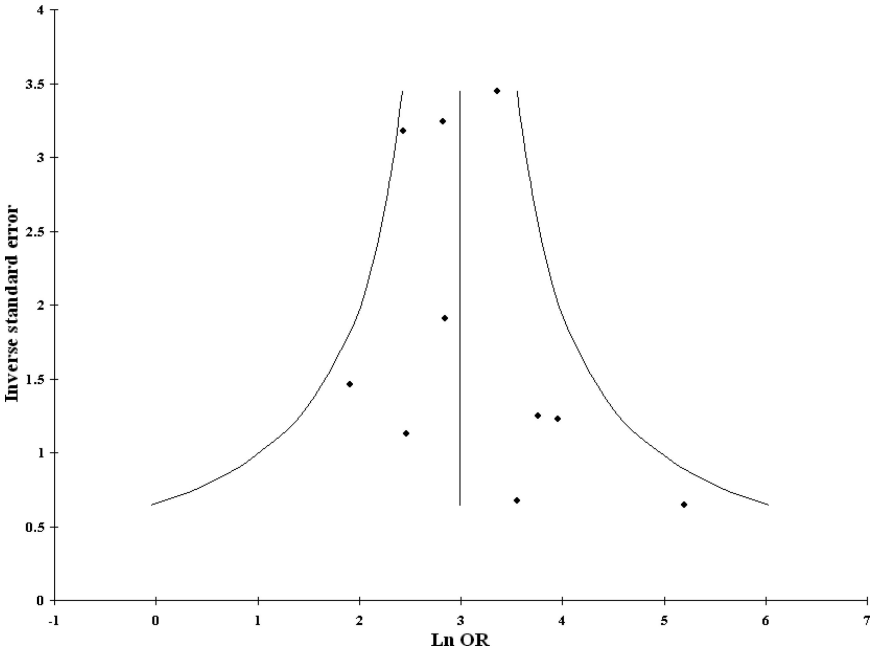

Fig. 2. Funnel plot of publications. This plots association effect (Ln OR) for MACE on the *horizontal axis* against variance (inverse SE) on the *vertical axis*. The symmetric scatter of points within the 95% confidence margins suggests that there is no publication bias. MACE = major adverse cardiovascular event; OR = odds ratio.

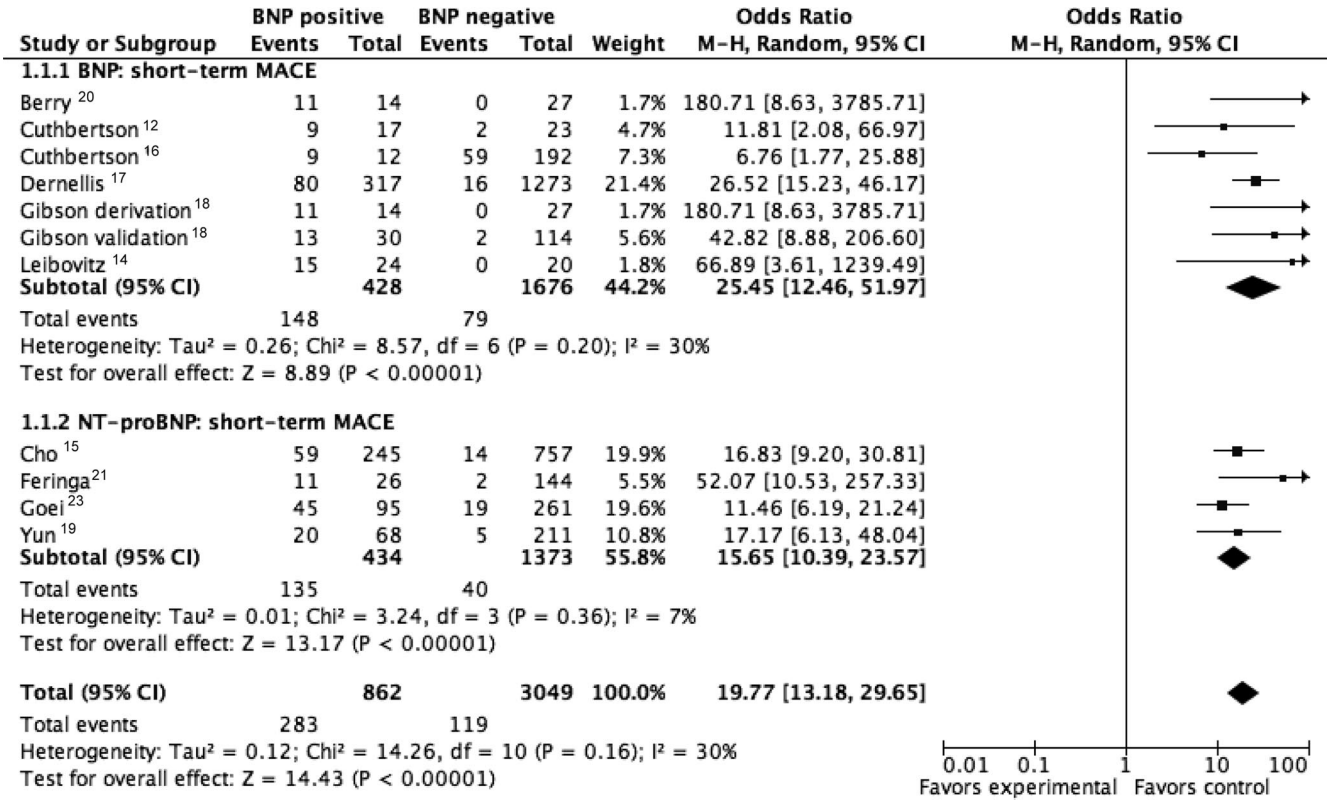

Fig. 3. Prediction of short-term major adverse cardiovascular events (MACE). BNP = brain natriuretic peptide; CI = confidence interval; NT-proBNP = *N*-terminal probrain natriuretic peptide; M-H = Mantel-Haenszel.

compared to 31 of 503 (6.16%; 95% CI 4.38–8.62) who had normal BNP levels. Elevated BNPs were associated with an increased risk of all-cause mortality (OR 4.72; 95% CI 2.99–7.46; $P < 0.00001$) with no evidence of heterogeneity ($P = 0.45$, $I^2 = 0\%$) (fig. 6). Serial exclusion of each study did not significantly alter the result.

Cardiac Mortality

Short-term cardiac mortality data were available for six studies comprising seven patient cohorts. Of 482 patients with elevated BNPs, 45 (9.34%; 95% CI 7.06–12.27) suffered cardiac death compared to 3 of 1,905 (0.16%; 95% CI 0.06–0.46) who did not. Elevated BNPs were associated with an increased risk of cardiac death (OR 23.88; 95% CI 9.43–60.43; $P < 0.00001$) with no evidence of heterogeneity ($P = 0.44$, $I^2 = 0\%$) (fig. 7). Sensitivity analysis by sequential exclusion of individual studies yielded similar results. The association was consistent for both BNP (OR 30.17; 95% CI 11.16–81.53) and NT-proBNP (OR 39.07; 95% CI 11.63–131.25) (fig. 5). No data were available for longer-term cardiac mortality.

Discussion

The main conclusions of our meta-analysis are that preoperative plasma BNP elevation is associated with a

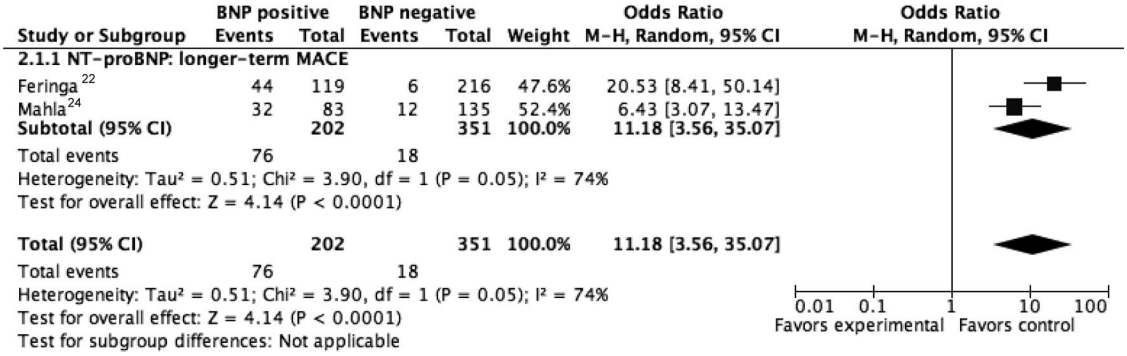

Fig. 4. Prediction of longer-term major adverse cardiovascular events (MACE). BNP = brain natriuretic peptide; CI = confidence interval; NT-proBNP = *N*-terminal probrain natriuretic peptide; M-H = Mantel-Haenszel.

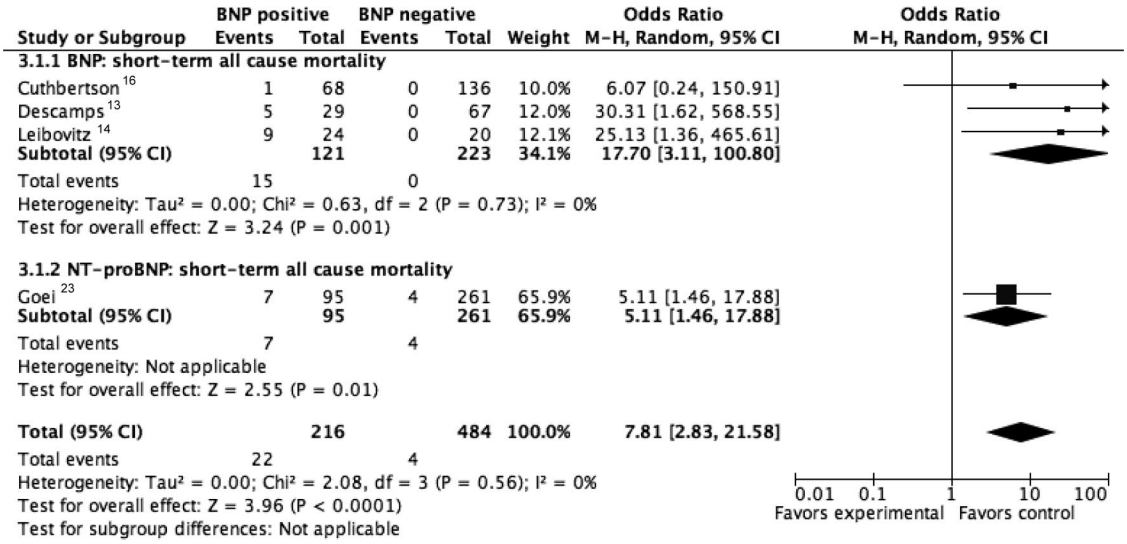

Fig. 5. Prediction of short-term all-cause mortality. BNP = brain natriuretic peptide; CI = confidence interval; NT-proBNP = *N*-terminal probrain natriuretic peptide; M-H = Mantel-Haenszel.

greatly increased risk of short-term MACE, cardiac mortality, and all-cause mortality, as well as longer-term MACE and all cause mortality after major noncardiac surgery. These findings are consistent for both BNP and NT-proBNP. Although these conclusions echo those of individual studies, this meta-analysis pools data from over 4,000 patients and, therefore, provides a greater insight into the strength of the associations. Furthermore, the analysis of mortality data in this context is novel. As such, measurement of BNPs may be a simple method of risk stratifying patients before noncardiac surgery.

To put the risk of adverse events in context, the relative risk of short-term all cause mortality in patients with elevated BNPs in this study is 6.9, which is similar to studies of myocardial infarction.[27] Likewise, the relative risk of longer-term all-cause mortality is 3.8, which is concordant with studies of stable heart failure or coronary artery disease.[28,29] This suggests that our estimates of risk are plausible.

The precise reason for the strong association between BNPs and postoperative outcome is not addressed by this analysis, but it is likely that BNP elevation identifies patients with impaired cardiac function or a significant ischemic burden who may not be able to withstand the hemodynamic and pro-inflammatory stresses of general anesthesia and major surgery. This is consistent with our observation that preoperative BNP measurement predicted short-term cardiac death more strongly than all-cause mortality.

An important question is whether BNP measurement has any incremental value over existing methods of preoperative assessment. Some studies have compared BNP and NT-proBNP to clinical risk scores, echocardiography and dobutamine stress echocardiography. However, in-

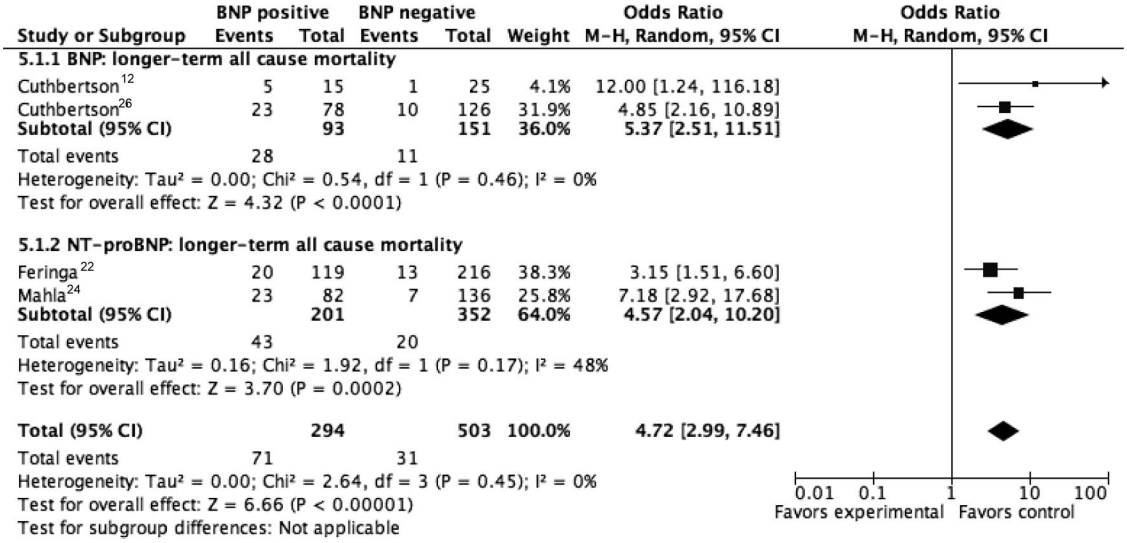

Fig. 6. Prediction of short-term cardiac mortality. BNP = brain natriuretic peptide; CI = confidence interval; NT-proBNP = *N*-terminal probrain natriuretic peptide; M-H = Mantel-Haenszel.

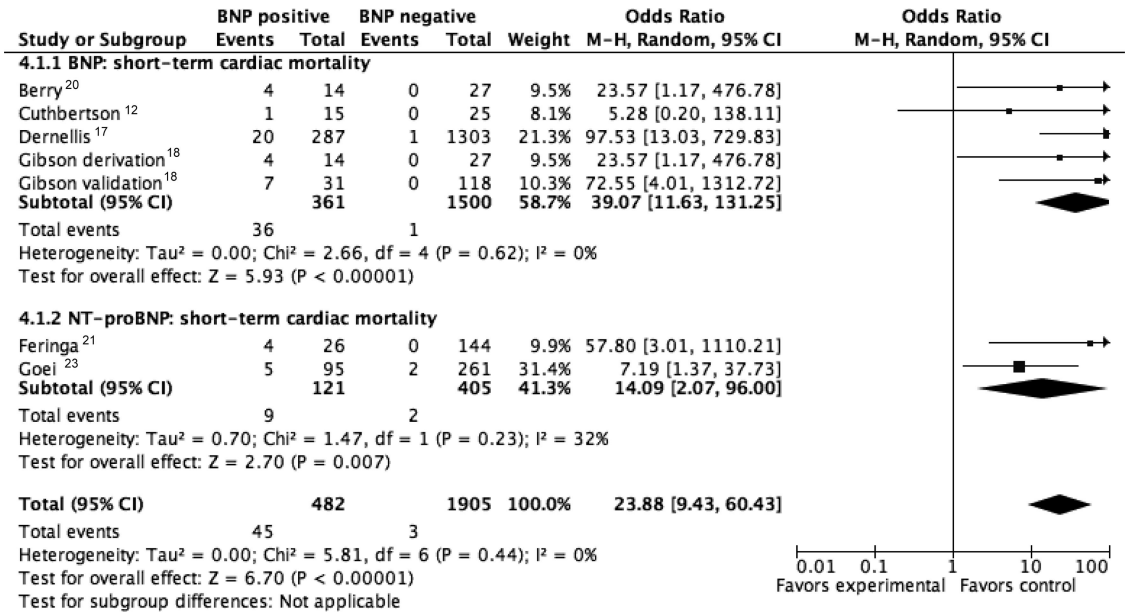

Fig. 7. Prediction of longer-term all-cause mortality. BNP = brain natriuretic peptide; CI = confidence interval; NT-proBNP = *N*-terminal probrain natriuretic peptide; M-H = Mantel-Haenszel.

sufficient data are available to allow comparison to be made in this analysis.

A limitation of this study is that the optimal cutoff values for plasma BNP and NT-proBNP cannot be defined because there was wide variation between studies. In the absence of definitive cutoffs for use in the noncardiac surgery setting, it may be reasonable to apply standard thresholds defined from heart failure studies. Generally accepted normal values for BNP (less than 100 pg/ml) and NT-Pro-BNP (less than 300 pg/ml)[5] would have a negative predictive value of at least 95% for short-term MACE if applied to these studies as a whole, and more than 99% excluding two studies that had particularly low cutoffs.[16,26] In other words, preoperative BNP measurement could be used to rule out the need for further cardiac investigation, unless there were other clinical grounds to strongly suspect a significant cardiac disorder. On the other hand, a raised BNP level should prompt further investigation to assess left ventricular function and or inducible ischemia. Unfortunately, none of the studies included in this analysis actually addressed the issue of how to use BNP levels in practice, so it remains to be proven whether triage of patients by this method can improve patient outcomes, and if so, how best to do this.

Certain factors may have affected the results of our analyses. Although we sought to minimize the possibility of publication bias by using a comprehensive search strategy, it is possible that this may be present because we did not identify any negative studies. There were differences between studies in terms of population characteristics that might affect BNP levels as well as outcomes, such as left ventricular function, age, gender, medication, renal function, obesity, and hemodynamic stress.[5,30–32] Adjusted odds ratios were reported by some studies for MACE, but mortality data were not, so we chose to use unadjusted outcome data for our analyses because this was available for all studies. It is possible that confounders may have influenced postoperative outcomes, although the magnitude of this effect is likely to be small because the adjusted and unadjusted OR were very similar where these were reported for individual studies.[16,17,21] Furthermore, in the absence of specific cutoffs for mortality outcomes, we used cutoffs derived from MACE data. Although these may not be optimal for predicting mortality outcomes, studies that have examined MACE and death found similar cutoffs for both,[22,26] suggesting that this approach is valid. Finally, the use of study-specific cutoff points introduces bias favoring a positive result, which is reflected in the very low heterogeneity in each analysis. For these reasons, it is difficult to be certain whether a particular BNP or NT-proBNP level actually carries the estimated risk reported in this study. This uncertainty can only be overcome with patient-level data for every study. Nevertheless, there is remarkable consistency between studies, lending credence to the notion that BNP levels are predictive of postoperative mortality and MACE.

In conclusion, preoperative plasma brain natriuretic pepide elevation identifies a subgroup of patients at high risk of death and MACE from major noncardiac surgery; as such, it has promise as a preoperative risk stratification tool. Current data are insufficient to define the exact role of BNP and NT-proBNP testing in preoperative patients, and large adequately powered prospective studies are required to clarify the best assay, the optimal cutoff, and the incremental value compared to standard preoperative assessment tools.

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