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RESEARCH

Preoperative B-type natriuretic peptides in patients undergoing noncardiac surgery: a cumulative meta-analysis

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Background: A plethora of studies have shown elevated preoperative natriuretic peptide measurements to predict postoperative mortality and adverse cardiac events.
Objectives: The current study aimed to demonstrate this overwhelming association and to show that further studies of this nature are unwarranted.
Methods: A cumulative meta-analysis of 28 studies was conducted where the primary outcomes of mortality and adverse cardiac events were associated with elevated preoperative natriuretic peptides.
Results: Cumulative meta-analysis demonstrated an odds ratio trending to a constant of 5.66, with a marked narrowing in the 95% confidence interval.
Conclusions: Further studies aiming only to demonstrate an association between a preoperative natriuretic peptide threshold and the risk of postoperative adverse cardiac events are not justified. Future investigation should focus on the clinical implications of these data and the application of these findings with regard to further investigation, optimisation and appropriate adaptation of perioperative management.

Keywords: BNP, major adverse cardiac event, myocardial injury, natriuretic peptides, non-cardiac surgery, NT-proBNP, outcomes

Introduction

The prediction of postoperative mortality and adverse cardiac events remains challenging, and clinical risk models and cardiac stress testing (e.g. cardiopulmonary, radioisotope and dobutamine stress testing) have met with limited success. However, over the last 10 years,[1] multiple studies have examined the ability of preoperative B-type natriuretic peptides (NP) (i.e. B-type natriuretic peptide [BNP] or N-terminal fragment of proBNP [NT-proBNP]), which are released from cardiac myocytes and fibroblasts in response to myocardial stretch, ischaemia and other neuro-endocrine stimuli,[2,3] to predict these events.

Almost uniformly every study conducted in non-cardiac surgical populations has reported that preoperative NP measurement elevations are predictive of short (≤ 30 day), intermediate (>30–180 day) and long-term (>180 day) postoperative mortality,[4] as well as major adverse cardiac events such as myocardial infarction, troponin elevation, cardiac failure, and atrial fibrillation. This signal has been repeatedly demonstrated in multiple meta-analyses.[5–8]

In the face of this consistent and overwhelming signal we believe the point has been reached where current data clearly demonstrate that elevated preoperative NP measurements are undoubtedly associated with postoperative mortality and major adverse cardiac events.

To test this hypothesis and in accordance with the Preferred Reporting Items for Reviews and Meta-Analyses (PRISMA) statement, we conducted a cumulative meta-analysis with the aim to address the question: Is the cumulative evidence for the ability of NPs to predict major adverse cardiac outcomes at 30 days after non-cardiac surgery sufficiently strong such that further studies designed to examine similar outcomes are unwarranted?

A cumulative meta-analysis can be considered a series of meta-analyses, with each subsequent analysis in the sequence including all previous studies as well as any additional studies.[9] The chronological combination of studies can track the progression of evidence over time; demonstrate consistency in results of prior and subsequent studies; and can potentially identify a point where, due to multiple studies showing the same outcomes, no further studies are necessary.[10]

Methods

We conducted a cumulative meta-analysis, including studies where the primary outcome was a composite of mortality and adverse cardiac outcomes. Adverse cardiac outcomes included: non-fatal myocardial infarction (MI), myocardial injury after non-cardiac surgery (MINS), electrocardiogram (ECG) evidence of ischaemia (new Q-waves or ST segment changes), evidence of new onset or decompensated congestive cardiac failure, new onset or haemodynamically unstable arrhythmias (atrial fibrillation/flutter or ventricular tachyarrhythmias), and the need for percutaneous coronary intervention (PCI). The protocol for this study was not published.

Databases and search strategy

In October 2014, we searched the following online databases, using the OvidSP search engine (Ovid Technologies, Inc., New York, NY, 2009): EMBASE 1980 to 2012, Week 28; OVID Health Star (1966 to June 2013); OVID MEDLINE(R) In-Process & Other Non-Indexed Citations and AVID MEDLINE(R) 1946 to present:

Cochrane Central Register of Controlled Trials (June 2012); Cochrane Database of Systematic Reviews (June 2012) and ProQuest Dissertations and Theses A&I (June 2012). The search terms and an example of the search methodology used are listed in Appendix 1. No language filters were used.

Study selection and inclusion

We included all observational studies or randomised controlled trials (RCTs) reporting on adult patients undergoing non-cardiac surgery, where NPs were measured preoperatively (up to one month prior to surgery), and where the authors reported all-cause mortality or a major adverse cardiac outcome up to 30 days after surgery. Studies were included regardless of language, sample size and publication status. We excluded studies examining cardiac surgery, paediatric studies, and those where NPs were measured postoperatively only.

Eligibility assessment

The titles and abstracts of each citation found in the search were independently screened by two people (DS, DP). These screeners noted citations they felt had a possibility of meeting the criteria for eligibility to undergo further review. If either reviewer felt the citation might contain a relevant study, the article was retrieved to undergo full text evaluation. Full texts of all citations identified as being potentially relevant were then independently evaluated by both DS and DP to determine eligibility. Disagreements were adjudicated by a third person (RR). Chance-corrected inter-observer agreement for study eligibility was tested using kappa statistics.

Data extraction

Data were extracted from the eligible studies by CR and LR and disagreements resolved by consensus. Descriptive data abstracted from all eligible studies included: year of publication, study design, sample size, patient population, type of surgery, type of NP assay used (i.e. BNP or NT-proBNP), critical NP threshold, study outcomes, and the number of events recorded. Where required, authors were contacted to confirm abstracted data, to provide missing data, and for viewing of their complete data sets.

From each study we extracted the adjusted odds ratio (OR) and 95% confidence interval (CI) associated with a preoperative NP measurement above the study-specific NP threshold for the primary composite outcome of postoperative all-cause mortality and/or adverse cardiac outcomes. In studies where the OR was not reported, we converted the hazard ratio (HR) or relative risk (RR) to odds ratio using the following formulae, where OR = odds ratio, RR = relative risk, HR = hazard ratio:

$$OR = \frac{RR.(1 - P_0)}{1 - (RR.P_0)}$$

$$RR = \frac{1 - e^{HR \,.\, ln(1-P_0)}}{P_0}$$

or extracted the OR from a previously published meta-analysis that made use of original study data to determine adjusted ORs.[6] RR commonly underestimates the OR, therefore where RR could not be converted to OR, RR was used in the analysis. We then performed a separate cumulative meta-analysis, including only the studies where only OR was reported.

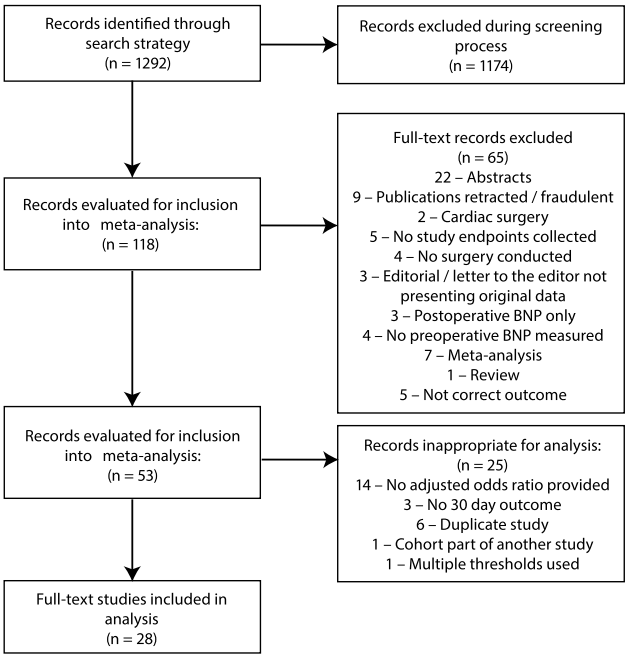
Adverse cardiac outcomes included non-fatal myocardial infarction (MI), myocardial injury after non-cardiac surgery (MINS) as evidenced by troponin elevation, ECG evidence of ischaemia (new Q-waves or ST segment changes), evidence of new onset or decompensated congestive cardiac failure, new onset or haemodynamically unstable arrhythmias (atrial fibrillation/flutter or ventricular tachyarrhythmias), or the need for percutaneous coronary intervention (PCI). Cumulative meta-analysis was conducted using Comprehensive Meta Analysis version 2.0 (Biostat, Englewood, NJ, USA) using a random effects model.

Results

Included studies

The database search using the search terms described above yielded 1 292 study citations. The initial screening process excluded 1 174 unsuitable studies, leaving 118 studies for full text evaluation. After full text evaluation 22 citations were excluded as they yielded abstracts only and nine citations were excluded because they had been retracted due to fraud. Another 34 studies were excluded for the following reasons: cardiac surgery (2); no study end-points collected (5); no surgery conducted (4); editorial or letter to the editor (3); postoperative NP measured (3); no preoperative NP measurement (4); meta-analysis (7), review article (1). Five studies were excluded as they did not examine the required outcome. Inter-observer agreement for study eligibility was good (kappa = 0.7).

The remaining 53 studies were then assessed to determine their suitability for inclusion in the meta-analysis. At this point, 14 studies were excluded as they reported no adjusted OR,[11–24] 3 studies were excluded because 30-day outcomes were not provided,[25–27] and 6 studies were excluded as they were duplications of previously included/excluded studies.[21,27–31] One study[32] was excluded because the patient cohort was part of the full cohort presented in another included paper, and one was excluded because multiple BNP thresholds were used.[33] Figure 1 summarises the studies that were excluded from the analysis, and the reasons therefor. After the above exclusions we were able to include 28 studies[29,34–60] in the cumulative meta-analysis.



BNP : B-type natriuretic peptide; NT-proBNP: N-terminal fragment of proBNP

Figure 1: Study selection process.

Table 1: Study characteristics of eligible studies

Author, year	Surgery type	Patients	Events	Outcome definitions
Yeh, 2005	Elective non-cardiac	190	15	MACE
Dernellis, 2006	Elective non-cardiac	1590	96	MACE
Cardinale, 2007	Elective thoracic	400	72	AF
Cuthbertson, 2007	Elective major non-cardiac	204	12	MACE
Cuthbertson, 2007	Emergency hip and abdominal	40	11	MACE
Gibson, 2007	Elective major non-cardiac	190	26	MACE
Mahla, 2007	Elective vascular	218	44	MACE, acute coronary revascularisation
Hou, 2007	Elective oesophagectomy	142	11	MACE
Rajagopalan, 2008	Elective major vascular	136	28	Myocardial injury
Yun, 2008	Elective non-cardiac	279	25	MACE, non-fatal stroke
Bolliger, 2009	Elective major vascular	133	19	MACE
Oscarsson, 2009	Emergency hip	69	34	MACE
Schutt, 2009	Elective & emergency non-cardiac	25	83	Heart failure, unstable angina
Breidthardt, 2010	Elective orthopaedic	270	4	MACE, troponin elevation, ECG changes
Chong, 2010	Emergency orthopaedic	89	65	MACE
Villacorta, 2010	Elective orthopaedic	208	17	MACE
Lee, 2011	Elective thoracic	98	10	MACE, ECG changes
Nojiri, 2011	Elective thoracic	80	34	Cardiorespiratory complications
Park, 2011	Elective major non-cardiac	1923	355	MACE
Payne, 2011	Elective non-cardiac	345	111	Long term all-cause mortality
Amar, 2012	Elective thoracic	415	65	AF
Biccard, 2012	Elective vascular	788	136	Mortality, troponin elevation
Mercantini, 2012	Elective major abdominal	205	31	MACE, troponin elevation
Yang, 2012	Elective vascular	365	63	MACE
Bryce, 2013	Elective abdominal aortic aneurysm	106	29	MACE, all-cause mortality
Borges, 2013	Elective non-cardiac	145	17	Vascular death, non-fatal MI, non-fatal cardiac arrest
Scrutinio, 2014	Elective vascular	411	87	Death, ACS, acute pulmonary oedema, postoperative myocardial damage
Vetrugno, 2014	Elective orthopaedic	227	14	MACE

Notes: AF: atrial fibrillation; MACE: major adverse cardiac events (cardiac death, non-fatal myocardial infarction, congestive cardiac failure, arrhythmias); ACS: acute coronary syndrome; ECG: electrocardiograph.

Study characteristics

Table 1 describes the characteristics of the studies included in this cumulative meta-analysis. The average age of the patients ranged from 57 to 87 years. In 24 of the 28 included publications (85.7%), the patients were undergoing elective surgery. Of the remaining studies, three reported exclusively on patients undergoing emergency surgery,[38,45,48] and one documented both elective and emergency surgeries that were classified as being high risk.[46]

Certain studies investigated outcomes in a specific surgical discipline, including thoracic surgery (4),[36,50,51,54] vascular (7),[29,40,42,44,55,57,59] orthopaedic (5),[45,47–49,60] major abdominal (1),[56] oesophagectomy (1),[41] while the rest documented outcomes following a variety of surgeries performed (10),[34,35,37–39,43,46,52,53,58] including a mix of general, head and neck, gynaecological, orthopaedic, vascular, urological, neurosurgery and thoracic surgery.

The study outcomes included all-cause mortality, cardiac death, non-fatal myocardial infarction (MI), myocardial injury after non-cardiac surgery (MINS) as evidenced by troponin elevation, ECG evidence of ischaemia (new Q-waves or ST segment changes), evidence of new onset or decompensated congestive cardiac failure, new onset or haemodynamically unstable arrhythmias (atrial fibrillation/flutter or ventricular tachyarrhythmias) or the need for percutaneous coronary intervention).

Primary outcome definitions, myocardial infarction criteria and cardiac troponin levels used to define myocardial injury for each study are summarised in Appendix 2.

Preoperative NP measurements

Table 2 summarises the details of the NP measured and the assays used to determine the NP levels in the included studies, the manufacturers thereof, as well as the discriminatory thresholds employed by the authors when reporting the ORs for the respective studies.

Study quality

We performed an analysis of the quality of the studies included in the cumulative meta-analysis. These findings are summarised in Table 3.

Study design

In total, 24 of the 28 studies[29,34–38,40–43,46–53,55–60] were prospective observational cohort studies. Of the remaining four studies:

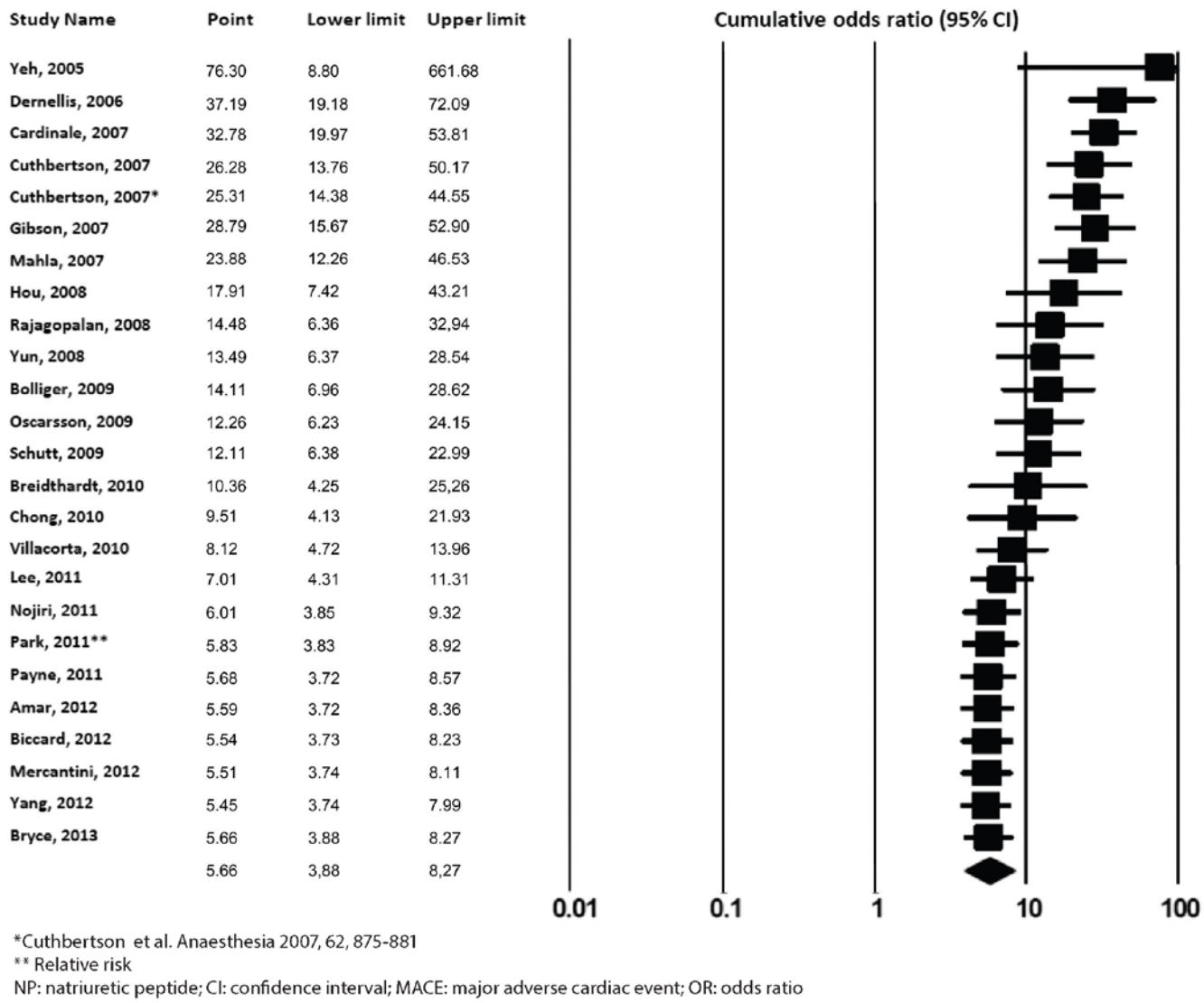


Figure 2: Cumulative risk for postoperative mortality or major adverse cardiac events associated with an elevated preoperative BNP or NT-proBNP measurement.

one[39] was a prospective derivation study with a subsequent validation study performed; one[44] was a prospective pre-specified secondary analysis of a cohort in a placebo-controlled randomised controlled trial (RCT); one[45] was a cohort extracted from a prospective observational study; and one[54] was a retrospective review of patients enrolled in a different study with prospectively collected data.

Blinding

In 13 of the 28 studies (46.4%), it was indicated that both data collection and outcome assessment were performed by investigators blinded to the NP value. Four of the studies[35,45,47,54] specifically reported that the investigators performing data collection and outcome assessment were *not* blinded, while in 10 of the studies blinding was not indicated. In one study[53] the investigators collecting the data were blinded to the NP value, while those performing outcome assessment were not.

Outcome definitions

Consistent outcome definitions were utilised in all 28 included papers.

Troponin screening

Routine postoperative troponin screening was documented in 17 of the 28 papers (60.7%) included in the analysis. In the studies where troponin screening was not routine, four studies[34,35,47,49] indicated that troponin testing was guided by clinical signs or at the discretion of the attending doctors. The specific systems and assays used to measure troponin levels are shown in Table 3.

Association between NPs and postoperative major adverse cardiac events and mortality

All associations between elevated NP levels and major adverse cardiac events were calculated using multivariate logistic regression analysis. The 28 eligible studies incorporated a total of 9291 patients, among which there were 1514 documented adverse cardiac events. All of the included studies demonstrated that an elevated preoperative NP measurement was an independent predictor of the primary study outcome.

Figure 2 presents t he results of the cumulative meta-analysis of the 28 studies reporting an adjusted OR for the composite of all-cause mortality or adverse cardiac outcomes in patients with an elevated preoperative NP measurement. These results show that, with cumulative data over time (from 2005 to 2014), the

Table 2: Natriuretic peptide assay characteristics

Author, year	Natriuretic peptide measured	Assay, Manufacturer	Threshold (pg/ml)
Yeh, 2005	NT-proBNP	Elecsys, Roche diagnostics	450
Dernellis, 2006	BNP	AxSYM, Axis Shield diagnostics	189
Cardinale, 2007	NT-proBNP	Elecsys, Roche diagnostics	204
Cuthbertson, 2007	BNP	Bayer ADVIA Centaur, Siemens medical diagnostics	40
Cuthbertson, 2007	BNP	Bayer ADVIA Centaur, Siemens medical diagnostics	170
Gibson, 2007	BNP	Not indicated	108.5
Mahla, 2007	NT-proBNP	Elecsys, Roche diagnostics	280
Hou, 2007	NT-proBNP	Elecsys, Roche diagnostics	Not indicated
Rajagopalan, 2008	NT-proBNP	Elecsys, Roche diagnostics	308
Yun, 2008	NT-proBNP	Elecsys, Roche diagnostics	201
Bolliger, 2009	BNP	AxSYM, Axis Shield diagnostics	50
Oscarsson, 2009	NT-proBNP	Stratus CS Acute Care Diagnostic System	3984
Schutt, 2009	NT-proBNP	Elecsys, Roche diagnostics	457
Breidthardt, 2010	BNP	Fluorescence immunoassay, Biosite diagnostics	174
Chong, 2010	NT-proBNP	Elecsys, Roche diagnostics	842
Villacorta, 2010	BNP	Triage, Biosite Inc	60
Lee, 2011	NT-proBNP	Elecsys, Roche diagnostics	160
Nojiri, 2011	BNP	Shionogi BNP, Shionogi Pharmaceuticals	30
Park, 2011	NT-proBNP	Elecsys, Roche diagnostics	301
Payne, 2011	BNP	Shionoria BNP Kit (Shinogi & Co)	87.5
Amar, 2012	BNP	Not indicated	30
Biccard, 2012	BNP	Bayer ADVIA Centaur, Siemens medical diagnostics	48.1
Mercantini, 2012	BNP	Triage, Biosite Inc	36
Yang, 2012	NT-proBNP	Not indicated	302
Bryce, 2013	BNP	Shinoria BNP Kit, Shinogi & Co Ltd	99.5
Borges, 2013	NT-proBNP	Elecsys, Roche diagnostics	917
Scrutinio, 2014	NT-proBNP	Not indicated	Not indicated
Vetrugno, 2014	BNP	Bayer ADVIA Centaur, Siemens medical diagnostics	39

incorporation of each subsequent study into the cumulative analysis shifts the cumulative OR progressively towards a constant number. The cumulative ORs appearing in the lower third of the forest plot demonstrate an almost vertical trend towards an OR of approximately 5.66. Second, whereas the 95% confidence interval at the start of the cumulative meta-analysis is wide, it becomes progressively narrower as additional studies are incorporated.

We conducted a sensitivity analysis that excluded the three studies where the OR was not primarily reported (one study[53] reported a HR, and two reported RR[51,52]). This analysis yielded similar results, producing a higher cumulative OR of 6.57. This is consistent with the tendency for RR to underestimate OR and the actual association, so the inclusion of these three studies in the cumulative meta-analysis probably produces a conservative estimation of the true association.

Discussion

This cumulative meta-analysis confirms that the measurement of an elevated BNP or NT-proBNP is clearly and undoubtedly associated with an increased risk of death and major adverse cardiac outcomes. Importantly, this demonstrates that with each subsequent study added into the sequential analysis, the signal becomes progressively clearer and increasingly well defined. The cumulative odds ratio (OR) for the combined studies is seen to trend towards a constant (± 5.66), with the 95% confidence intervals growing progressively smaller with the addition of subsequent studies, an indication that the cumulative OR is increasingly likely to represent the 'true' association. Indeed, we believe the data now overwhelmingly demonstrate this association, and further small studies that aim to demonstrate a similar association are unwarranted.

Rather, future studies in this field should be directed at using this information to improve patient outcome. Large studies conducted across multiple surgical populations, which make use of robust statistical methods, are required to identify clinically relevant NP risk thresholds able to change clinical decision-making. This research should focus on a number of important questions. First, is there an NP level that warrants delaying elective surgery in order to investigate and optimise coexisting medical conditions? This may include initiation of 'best medical therapy' or percutaneous coronary intervention (PCI). Second, can we demonstrate the reliability of NP changes to monitor response to PCI or medical therapy in the absence of cardiac failure? Third, is there benefit in adjusting anaesthetic or surgical technique and level of perioperative care in patients with elevated NP levels? What would the cost implications of this be and would it improve outcome? Lastly, is there an NP level at which it might be advisable to avoid surgery altogether due to an unacceptably high probability of cardiac morbidity or

Table 3: Study quality characteristics

Author, year	Study design	Data collection blinded to NP value	Outcome assessment blinded to NP value	Consistent outcome definition	Routine post-operative troponin screening	Troponin assay, manufacturer & threshold used
Yeh, 2005	Prospective observational cohort	Blinded	Blinded	Yes	No, troponin testing guided by clinical signs	Not specified
Dernellis, 2006	Prospective observational cohort	Not blinded	Not blinded	Yes	No, troponin testing guided by clinical signs	Not specified
Cardinale, 2007	Prospective observational cohort	Blinded	Blinded	Yes	No	Not applicable
Cuthbertson, 2007	Prospective observational cohort	Blinded	Blinded	Yes	Yes	2nd generation, Bayer ADVIA Centaur, Troponin I > 0.32 ng/ml
Cuthbertson, 2007	Prospective observational cohort	Blinded	Blinded	Yes	Yes	2nd generation, Bayer ADVIA Centaur, Troponin I> 0.1 ng/ml
Gibson, 2007	Prospective derivation with subsequent validation study	Blinded	Blinded	Yes	Yes	2nd generation, Bayer ADVIA Centaur, no threshold indicated
Mahla, 2007	Prospective observational cohort	Blinded	Blinded	Yes	Yes	4th generation, Roche Elecsys Troponin T STAT, > 0.03 ng/ml)
Hou, 2007	Prospective observational cohort	Not indicated	Not indicated	Yes	No	Not applicable
Rajagopalan, 2008	Prospective observational cohort	Not indicated	Not indicated	Yes	Yes	2nd generation Bayer ADVIA Centaur, Troponin I > 0.1 ng/ml
Yun, 2008	Prospective observational cohort	Not indicated	Not indicated	Yes	Yes	Troponin T, assay not specified, no threshold indicated
Bolliger, 2009	Prospective prespecified secondary analysis of cohort in a placebo-controlled RCT	Blinded	Blinded	Yes	Yes	1st generation Abbott AxSYM Troponin I, > 2 ng/ml
Oscarsson, 2009	Cohort extracted from prospective observational study	Not blinded	Not blinded	Yes	Yes	High sensitivity, Siemens Stratus CS acute care Troponin I, > 0.06 ng/ml
Schutt, 2009	Prospective observational cohort	Blinded	Blinded	Yes	No	Not specified
Breidthardt, 2010	Prospective observational cohort	Not blinded	Not blinded	Yes	No, troponin testing at discretion of treating physician	1st generation Abbott AxSYM Troponin I, > 2 ng/ml
Chong, 2010	Prospective observational cohort	Blinded	Blinded	Yes	Yes	4th generation Abbott Architect STAT Troponin I, > 0.03 ng/ml
Villacorta, 2010	Prospective observational cohort	Not indicated	Not indicated	Yes	No, troponin testing guided by clinical signs	Not specified
Lee, 2011	Prospective observational cohort	Not indicated	Not indicated	Yes	No	Not specified
Nojiri, 2011	Prospective observational cohort	Not indicated	Not indicated	Yes	No	Not specified
Park, 2011	Prospective observational cohort	Not indicated	Not indicated	Yes	Yes	Troponin I (0.78 ng/ml),assay not specified
Payne, 2011	Prospective observational cohort	Blinded	Not blinded	Yes	Yes	Troponin I, assay not specified

(*Continued*)

Table 3: (*Continued*)

Author, year	Study design	Data collection blinded to NP value	Outcome assessment blinded to NP value	Consistent outcome definition	Routine post-operative troponin screening	Troponin assay, manufacturer & threshold used
Amar, 2012	Retrospective review of patients enrolled in a different study	Not blinded	Not blinded	Yes	No	Not applicable
Biccard, 2012	Prospective observational cohort	Not blinded	Not blinded	Yes	Yes	2nd generation Siemens Advia Centaur XP, Troponin > URL
Mercantini, 2012	Prospective observational cohort	Blinded	Blinded	Yes	Yes	4th generation Troponin T(≥ 0.06 ng/ml)
Yang, 2012	Prospective observational cohort	Not indicated	Not indicated	Yes	Yes	Troponin I (0.78 ng/ml),Roche Diagnostics, assay not specified
Bryce, 2013	Prospective multi-centre observational cohort	Blinded	Blinded	Yes	Yes	4th generation Abbott Architect STAT Troponin I, no threshold specified
Borges, 2013	Prospective observational cohort	Blinded	Blinded	Yes	Yes	2nd generation Siemens cTnI Ultra, Troponin I > 0.04 ng/ml
Scrutinio, 2014	Prospective observational cohort	Not indicated	Not indicated	Yes	Yes	2nd generation Siemens RxL immunoassay, Troponin I > 0.14 ng/ml
Vetrugno, 2014	Prospective observational cohort	Blinded	Blinded	Yes	No	Not specified

Note: NP = B-type natriuretic peptides.

mortality? Should patients and families be given risk-algorithm models to empower them to assist with the decision-making process? These questions can only be answered once investigators move away from repeatedly demonstrating the already clear association between NP elevations and morbidity, and rather focus subsequent studies on using this information in order to change outcomes in the at-risk population.

Limitations

In some of the included studies, the NP thresholds were predetermined in the methodology of the study; however, the majority used the area under the receiver operator characteristic (ROC) curve to determine the NP level that best predicted the primary study outcome. Thus, the NP thresholds used varied markedly both for BNP (30–189 pg/ml) and for NT-proBNP (160–3984 pg/ml).

Our decision to make use of varying definitions of adverse cardiac outcomes allowed us to compare our results with a previous seminal BNP/NT-proBNP meta-analysis by Karthikeyan *et al*., who made use of similar varying composite outcomes.[6] Further, despite these different outcome definitions we were able to demonstrate that the signal approaches a consistent odds ratio, which we believe adds further support to our findings.

Ten studies were excluded as they did not report adjusted ORs associated with elevated NP measurements; however, all of these studies reported a positive association with an elevated preoperative MP measurement and adverse cardiovascular outcomes. Therefore, while the addition of these studies would marginally change the point estimate of our analysis, their inclusion would further narrow the associated 95% CI, thereby affirming our conclusions.

Conclusions

These results suggest that further small studies conducted solely to demonstrate an association between a study-specific preoperative NP threshold and the risk of postoperative mortality or adverse cardiac events are no longer justified. Future investigation should be focused on developing robust clinically applicable BNP or NT-proBNP thresholds from large representative perioperative populations that are adjusted for important preoperative risk factors. Attention should further be given to developing trials that demonstrate: that preoperative NP measurement is able to reduce postoperative mortality and adverse cardiovascular events; the cost effectiveness of NP measurement; and to determine if treating patients with elevated NP before surgery is able to improve patient outcomes.

Author attestations

All authors have made material contributions to this manuscript according to the rules of authorship as explained in the Instructions for Authors at http://www.springer.com/12630. Contribution to authorship is as follows:

L Ryan — Study concept and design, abstract screening, acquisition of data, analysis and interpretation of data, manuscript drafting, final approval of the version to be published.

C Rajah — Abstract screening, acquisition of data, analysis and interpretation of data, critical revision of manuscript for important intellectual content, final approval of the version to be published.

D Simmers — Abstract screening, acquisition of data, critical revision of manuscript for important intellectual content, final approval of the version to be published.

D Potgieter — Abstract screening, data extraction, critical revision of manuscript for important intellectual content, final approval of the version to be published.

RN Rodseth — Study concept and design, abstract screening and acquisition of data, analysis and interpretation of data, critical revision of the manuscript for intellectual content, final approval of the version to be published.

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Appendix 1

Search strategy and databases used

	Search terms	Number
1	(Natriuretic peptide OR natriureti*).mp.	90 064
2	(BNP OR B type natriureti* OR B-type natriureti* OR Brain natriureti*).mp.	42 364
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	13 484
4	(Surgery OR operative OR non-cardiac).mp.	3 308 271
5	1 or 2 or 3	94 975
6	4 and 5	4 456
7	prognosis.sh. or diagnosed.tw. or cohort:.mp. or predictor:.tw. or death.tw. or exp models, statistical/	4 837 473
8	6 and 7	1 433
9	remove duplicates from 8	876

Notes: No additional search filters were used.
For the EMBASE search the EMTree term 'Brain natriuretic peptide' was used.

Appendix 2

Details of outcome definitions, criteria and thresholds used

Author, year	Primary outcome definitions	Myocardial infarction criteria	Myocardial injury/damage/ necrosis criteria
Yeh, 2005	Cardiac death, ACS including MI and unstable angina, congestive cardiac failure and serious cardiac arrhythmia	Increased cardiac enzymes (creatine kinase MB isoenzyme or troponin I) and ECG evidence of myocardial infarction (new Q waves or ST-T wave changes) in at least two adjacent leads	N/A
Dernellis, 2006	Cardiac death, non-fatal MI, acute pulmonary oedema, ventricular arrhythmia	Cardiac enzyme increase greater than twice the upper limit of normal OR new Q wave on postoperative ECG plus cardiac enzyme rise consistent with necrosis	N/A
Cardinale, 2007	Atrial fibrillation	N/A	N/A
Cuthbertson, 2007	Death or myocardial injury	N/A	cTnI > 0.32 ng/ml
Cuthbertson, 2007	Cardiac death and/or new postoperative myocardial injury and/or significant postoperative ECG changes	N/A	cTnI > 0.1 ng/ml
Gibson, 2007	Non-fatal MI and cardiac death	Typical rise and fall of cTnI plus one of: ischaemic symptoms, ECG changes (new Q waves or ST segment changes), or coronary intervention (ESC/ ACC definition)	N/A
Mahla, 2007	Non-fatal MI, acute coronary revascularisation, cardiac death	Elevated cTnT and clinical or ECG changes indicative of ischaemia	N/A
Hou, 2007	Atrial fibrillation	N/A	N/A
Rajagopalan, 2008	Myocardial injury	N/A	Elevated cTnI > 0.1 ng/ml
Yun, 2008	Cardiac death, ischaemic heart disease, acute pulmonary oedema or nonfatal stroke	Not specified	Not specified
Bolliger, 2009	Any hospitalisation for myocardial revascularisation, acute coronary syndrome, acute congestive heart failure, or death by any cause	N/A	N/A
Oscarsson, 2009	Myocardial damage, acute MI, and/ or death	Not specified	cTnI > 0.06 ng/ml
Schutt, 2009	Postoperative MI heart failure, unstable angina, dysrhythmia, cardiac arrest	2 out of 3 of: symptoms consistent with myocardial infarction, elevated troponin T level, or new diagnostic changes on electrocardiogram	N/A
Breidthardt, 2010	ECG changes, significant arrhythmias, myocardial necrosis, cardiac failure	N/A	cTnI > 2 ng/ml
Chong, 2010	Acute MI, congestive cardiac failure, atrial fibrillation, major arrhythmia	Standard definition [1]	cTn I > 0.03 ng/ml
Villacorta, 2010	Acute MI, unstable angina, acute pulmonary oedema, heart failure, acute atrial fibrillation, sustained ventricular tachycardia, cardiac death	Elevation of biomarkers more than 2 x upper limit of normal plus ECG changes	N/A
Lee, 2011	Myocardial injury, ECG evidence of ischaemia or arrhythmia, heart failure	N/A	cTn T > 0.1 ng/ml
Nojiri, 2011	Arrhythmias, angina pectoris, MI, congestive cardiac failure, thrombo-embolic events	Not specified	Not specified
Park, 2011	MI, pulmonary oedema, cardiovascular death	cTnI > 0.78 ng/ml (99th centile of upper reference limit)	N/A
Payne, 2011	Perioperatve death & MACE, long-term all-cause mortality	Not specified	Not specified
Amar, 2012	Atrial fibrillation	N/A	N/A
Biccard, 2012	Mortality, troponin elevation	Not specified	cTn > URL
Mercantini, 2012	Angina pectoris, STEMI, NSTEMI, troponin elevation, cardiac failure, acute hypertensive event	ST changes in two or more contiguous leads	cTnI > 0.06 ng/ml, cTnT > 0 ng/ml
Yang, 2012	MI, aggravation of cardiac failure, cardiovascular death	cTnI > 0.78 ng/ml	N/A

(*Continued*)

Appendix 2: (*Continued*)

Author, year	Primary outcome definitions	Myocardial infarction criteria	Myocardial injury/damage/ necrosis criteria
Bryce, 2013	Non-fatal MI, cardiac death, all-cause mortality	Troponin elevation and gradual decline plus one of: ischaemic symptoms, ECG changes (new Q waves or ST changes), or coronary artery intervention	N/A
Borges, 2013	Vascular death, non-fatal MI, non-fatal cardiac arrest	Typical rise and fall of cTnI to > 0.04 ng/ml, plus one of: ischaemic symptoms, ECG changes (new Q wave, ST changes in two or more contiguous leads, or new LBBB)	N/A
Scrutinio, 2014	Death, ACS, acute pulmonary oedema, postoperative myocardial damage	Standard definition[1]	cTnI > 0.14 ng/ml
Vetrugno, 2014	New onset atrial fibrillation/flutter, acute heart failure or non-fatal/fatal MI	cTnI > 0.12 ng/ml (3 x upper reference limit)	N/A