European Journal of Cardio-Thoracic Surgery 41 (2012) 525–534
doi:10.1093/ejcts/ezr007 Advance Access publication 20 October 2011

REVIEW

ADULT CARDIAC

The use of pre-operative brain natriuretic peptides as a predictor of adverse outcomes after cardiac surgery: a systematic review and meta-analysis

Edward Litton[a,b,*] and Kwok M. Ho[a,c]

[a] Department of Intensive Care Medicine, Royal Perth Hospital, Perth, WA, Australia
[b] School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia
[c] School of Population Health, University of Western Australia, Perth, WA, Australia

* Corresponding author. Intensive Care Unit, Royal Perth Hospital, Wellington Street, Perth, WA 6000, Australia. Tel: +61-8-92242244; fax: +61-8-92243668; e-mail: ed.litton@health.wa.gov.au (E. Litton).

Received 21 April 2011; received in revised form 7 August 2011; accepted 10 August 2011

Summary

The objective of this systematic review was to assess whether pre-operative brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT pro-BNP) are independent predictors of adverse outcomes after cardiac surgery. MEDLINE, Embase and the Cochrane Controlled Trials Register databases were searched. Eligible studies included observational or randomized control trials measuring natriuretic peptide concentrations before induction of anaesthesia for cardiac surgery. Two investigators independently extracted the data and assessed the validity of the included studies. The predictive ability of pre-operative BNP or NT pro-BNP on mortality, post-operative atrial fibrillation (AF) and intra-aortic balloon pump (IABP) requirement was meta-analysed. The association between BNP or NT pro-BNP and other outcomes was systematically summarized. A total of 4933 patients from 22 studies were considered in the systematic review. Ten studies with one or more outcomes of interest were included in the meta-analyses. The strength of association between pre-operative natriuretic peptide levels and adverse outcomes after surgery was variable, as was the size and quality of the included studies. The summary areas under the receiver operating characteristic curve for mortality, post-operative AF and post-operative IABP requirement were 0.61 (95% confidence interval [CI] 0.51–0.70), 0.61 (95% CI 0.58–0.64) and 0.81 (95% CI 0.73–0.89), respectively. With the limited data available, the associations between pre-operative natriuretic peptide levels and adverse outcomes after cardiac surgery were moderate. Future studies should assess whether pre-operative natriuretic peptides can provide additional independent predictive information to well-validated prognostic scores of cardiac surgery.

Keywords: Cardiac surgery • Mechanical circulatory assistance

BACKGROUND

Brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT pro-BNP) are synthesized and released by ventricular cardiomyocytes in response to myocardial wall stress and ischaemia [1]. Elevated levels of BNP and NT pro-BNP have been shown to be associated with adverse outcomes in a number of settings, including acute coronary syndrome, congestive heart failure and patients undergoing major non-cardiac surgery [2–4].

In patients undergoing cardiac surgery, pre-operative scoring systems such as EuroSCORE have been well validated and are used extensively to predict post-operative risk of death [5]. However, these scoring systems are limited by their complexity, subjective calculation, suboptimal performance in predicting major post-operative morbidity, as well as the potential for deterioration in discrimination and calibration over time, and may not be generalizable to some patient cohorts [6, 7].

The number of patients undergoing high-risk cardiac surgery is increasing [8]. Accurate risk assessment for cardiac surgery is of paramount importance both for clinical audit and in considering prophylactic interventions to reduce adverse post-operative outcomes [9, 10].

We hypothesized that BNP and NT pro-BNP are independent predictors of adverse outcomes after adjusting for standard clinical risk factors for cardiac surgery. We conducted a systematic review and meta-analysis to assess the ability of pre-operative BNP or NT pro-BNP in predicting adverse outcomes after cardiac surgery.

MATERIALS AND METHODS

Eligibility criteria

We searched for randomized controlled trials and observational studies in which BNP or NT pro-BNP was measured before the induction of anaesthesia in patients undergoing cardiac surgery. The post-operative outcomes of interest included short- and long-term mortality, post-operative atrial fibrillation (AF), acute myocardial infarction (AMI), cardiogenic shock, requirement for intra-aortic balloon pump (IABP) and intensive care unit (ICU) or hospital length of stay (LOS). Studies in which natriuretic peptide levels were measured only after the induction of anaesthesia were excluded to prevent the potential for the results to be affected by haemodynamic disturbances associated with induction, cardiac canulation and the dilutional effects of cardiopulmonary bypass. Furthermore, by excluding post-induction measurements, the results remain generalizable to a population potentially amenable to pre-operative intervention and optimization. Studies that reported only a composite end-point of all adverse outcomes, or did not include a clearly defined cohort of cardiac surgical patients were also excluded.

Search strategy

The primary electronic search was conducted using MEDLINE, Embase and the Cochrane Central Register of Controlled Trials databases. We used medical subject headings and keyword searches for the terms BNP or N-terminal pro-BNP (NT pro-BNP) combined with medical subject headings and keyword searches for the terms surgery, cardiac surgery, pre-operative, or post-operative. The search included the time period between 1966 and October 2010 and was conducted without language restrictions. We searched the reference lists of all included studies as well as relevant review articles. Where uncertainty existed on study eligibility, the corresponding author was contacted for clarification or to request further information.

Study selection

Both authors screened the results of the search and one author (E.L.) retrieved all potentially relevant articles. Both authors independently applied the inclusion and exclusion criteria, and disagreement was resolved by consensus.

Data extraction and validity appraisal

Both investigators extracted the data and assessed study validity independently; disagreement was resolved by consensus. The outcomes of interest included short-term mortality (≤60 days or in hospital), long-term mortality (>60 days), post-operative AF, AMI, cardiogenic shock, requirement for IABP and ICU or hospital LOS. Assessment of the validity of the observational studies was based on five criteria: whether the study was prospective or retrospective, inclusion of an *a priori* definition of outcome measures, description of inclusion and exclusion criteria, the completeness of follow-up and assessment of important co-variables in a multivariable analysis.

Data analysis

Sensitivity and specificity of BNP or NT pro-BNP to predict outcomes were extracted from the included studies. Where these data were not directly provided, they were calculated from the data in the reports when feasible. For outcomes in which data were available from more than three studies, pooled diagnostic odds ratios (DORs) and areas under the receiver operating characteristic (ROC) curve were calculated using a fixed-effect model. I^2 was used to quantify heterogeneity, and all calculations were conducted using Meta-DiSc Version 1.4 [11].

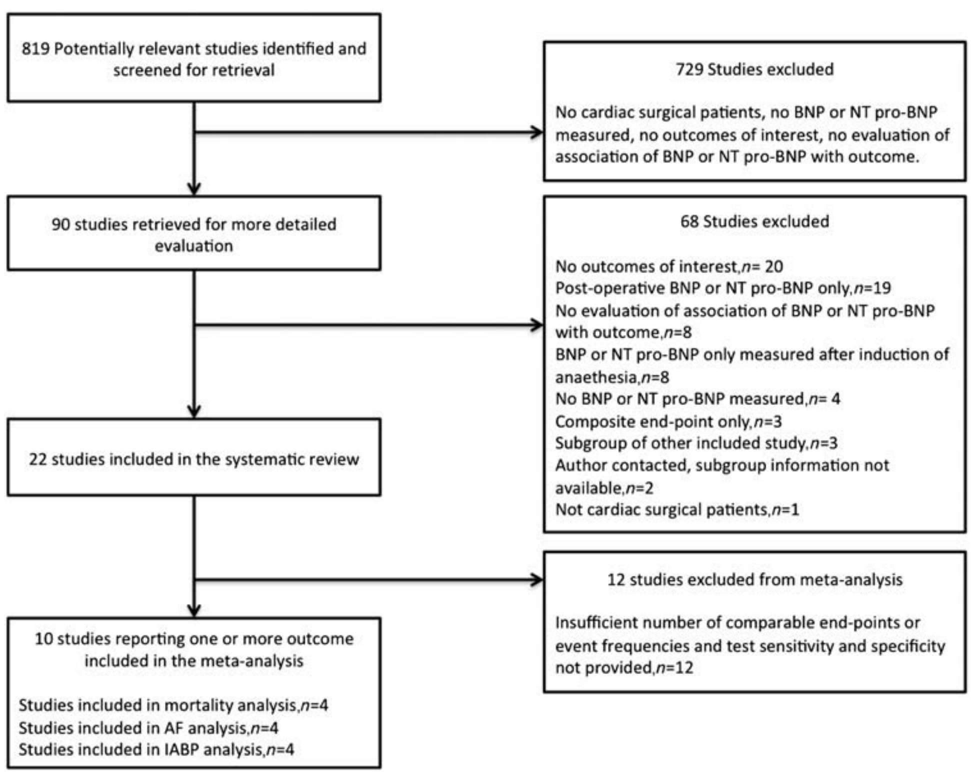

Figure 1: Flow chart of study inclusion.

Table 1: Characteristics of the included studies

Study number, author, year and number of participants (n)	Study design and setting	Duration of follow-up	Inclusion criteria	Exclusion criteria
1. Akazawa 2008, n = 150	Prospective single-centre cohort study, Juntendo University, Tokyo, Japan	Duration of hospital admission	Consecutive patients without pre-operative AF undergoing elective isolated off-pump CABG	Significant valve disease, AMI <1/52 pre-operative, CRF or haemodialysis, minimally invasive bypass operation
2. Ata 2009, n = 144	Prospective single-centre cohort study, Bursa Yuksek Ihtisas Education and Research Hospital, Bursa, Turkey	Duration of hospital admission	Elective first-time isolated CABG	Urgent operation, off-pump surgery, creatinine >1.5 mg/dl, AMI <1 month pre-operative, MV insufficiency, history of AF
3. Attaran 2009, n = 141	Prospective single-centre cohort study, King's College, London, UK	30 days post-operative	First-time elective and urgent CABG and valve surgery	Intubated patients, patients who did not agree to study participation
4. Ballotta 2010, n = 31	Retrospective single-centre cohort study, IRRCS Policlinico San Donato, Italy	Not stated	Elective patients undergoing surgical ventricular restoration with CABG	No pre-operative BNP available
5. Bergler-Klein 2007, n = 29 (subgroup of 69 total study population)	Prospective two-centre cohort study, Laval Hospital/Quebec Heart Institute Ontario Canada and Medical University of Vienna, Austria	2 years post-operative	AVR for AS with valve area <1.2 cm, mean gradient <40 mmHg and LVEF <40%, urgency not stated	AR >2+, MV area <2 cm or MR >2+, AF, paced rhythm, pulmonary oedema, pregnancy or lactation, CRF creatinine >3 mg dl
6. Cerrahoglu 2007, n = 52	Observational single-centre study, University Hospital, Turkey	Duration of hospital stay	Elective CABG	CRF, AMI, valvular disease, severe COAD
7. Cuthbertson 2005, n = 46	Prospective single-centre cohort study, Aberdeen Royal Infirmary, Scotland, UK	30 days	Consecutive patients undergoing elective CABG	Emergency CABG, concomitant valve surgery, pre-operative inotropes or IABP, serum creatinine >200 µmol/l
8. Cutherbertson 2009, n = 1010	Prospective single-centre cohort study, Aberdeen Royal Infirmary, Scotland, UK	30 days	Non-emergent CABG (on and off pump) and valve surgery	Not stated
9. Eliasdottir 2008, n = 135	Retrospective single-centre cohort study, Landspitali University Hospital, Iceland	28 days	Elective CABG (on and off pump) and valve surgery	Not stated
10. Fellahi 2010, n = 208	Prospective single-centre cohort study, Saint-Martin Hospital, Caen, France	In-hospital	Consecutive adult patients undergoing elective on-pump CABG and valve surgery	Emergency surgery (<24 h), redo operation, unusual complex cardiac surgical procedures
11. Fox 2010, n = 1519	Prospective two-centre cohort study, Brigham and Women's Hospital Massachusetts and Texas Heart Institute, TX, USA	Mean follow-up 4.3 years	Consecutive patients undergoing non-emergent isolated on-pump CABG surgery	Hct <0.25, transfusion of leucocyte-rich blood <30 days before surgery, prior cardiac surgery, emergency surgery, valve surgery, aorta not cross-clamped, pre-operative IABP, VAD or inotropes, serum creatinine >3 mg/dl
12. Hutfless 2004, n = 98	Prospective single-centre cohort study, San Diego Veterans Affairs Hospital, CA, USA	Duration of hospital stay	Male patients undergoing open heart surgery, urgency not stated	Female patients
13. Jogia 2007, n = 118	Prospective single-centre cohort study, Waikato Hospital, New Zealand	6 months	Consecutive patients undergoing non-emergent CABG and valve surgery	Cardiac instability requiring urgent operation
14. Pedrazzini 2008, n = 144	Prospective single-centre cohort study, Fondazione Cardiocentro Ticino, Lugano, Switzerland	Median follow-up 17 months, maximum 36 months	Symptomatic AS undergoing AVR, peak velocity >4 m/s or trans-valvular gradient >50 mmHg or aortic valve area <1 cm^2, urgency not stated	Nil
15. Pfister 2010, n = 31	Prospective single-centre cohort study, University of Cologne, Italy	2 months	Symptomatic severe aortic stenosis unsuitable for AVR, urgency not stated	Not stated
16. Saribulbul 2003, n = 26	Prospective single-centre cohort study, Celal Bayar University, Manisa, Turkey	Post-operative period in ICU	Non-urgent CABG surgery	AMI in past 3 weeks, unstable angina
17. Sezai 2009, n = 234	Single-centre cohort study, Nihon University, School of Medicine, Tokyo	Duration of hospital stay	Elective and emergency isolated CABG surgery	AMI, history of arrhythmia

Continued

Table 1: Continued

Study number, author, year and number of participants (*n*)	Study design and setting	Duration of follow-up	Inclusion criteria	Exclusion criteria
18. Sodeck 2008, $n = 104$	Prospective single-centre cohort study, Medical University, Vienna, Austria	30 days	Consecutive patients undergoing emergency surgical repair of non-traumatic aortic dissection	Not stated
19. Tavakol 2009, $n = 328$	Retrospective single-centre cohort study, New York Methodist Hospital, NY, USA	7 days	Consecutive patients undergoing elective or emergency CABG and/or valve surgery	Prior AF, permanent pacemaker, sepsis
20. Turk 2008, $n = 85$	Prospective single-centre cohort study, Bursa Yuksek Ihtisas Education and Research Hospital, Bursa, Turkey	Duration of hospital stay	Elective first-time isolated CABG	Urgent operation, off-pump surgery, creatinine >1.5 mg/dl, AMI <1 month, mitral valve insufficiency
21. Wang 2010, $n = 112$	Prospective single-centre cohort study, Tiajin Medical University Hospital, China	Duration of hospital stay	Primary off-pump CABG, urgency not stated	Liver failure, renal failure, pre-existing autoimmune disease, severe infection
22. Wazni 2004, $n = 187$	Retrospective single-centre cohort study, Cleveland Clinic, OH, USA	Duration of hospital stay	Non-emergent CABG and/or valve surgery with pre-operative BNP available	De-compensated heart failure or AMI <60 days of surgery, history of atrial arrhythmia, anti-arrhythmic medication, PPM, emergency surgery

BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; AVR, aortic valve replacement; AS, aortic valve replacement; AMI, acute myocardial infarction; MVR, mitral valve replacement; AF, atrial fibrillation; IABP, intra-aortic balloon pump; VAD, ventricular assist device; COAD, chronic obstructive airway disease; PPM, permanent pacemaker.

RESULTS

The initial electronic search returned 819 records. After examination of the titles and abstracts, 90 studies were retrieved for more detailed evaluation. A total of 22 studies including 4933 participants met the inclusion criteria of this systematic review [12–33], and 10 studies provided sufficient data for one or more outcomes to be included in the meta-analyses. The flowchart of the search and reasons for study exclusion are presented in Fig. 1. The sample size of the included studies ranged between 29 and 1519 participants. All the included studies were observational, 16 were prospective, 4 were retrospective and 2 did not report the methodology undertaken. The characteristics of the included studies are described in Table 1.[1] Details of the assay, cut-off levels and timing are available in the supplementary material.

Study characteristics and validity assessment

There was considerable variation in sample size, natriuretic peptide laboratory test and BNP or NT pro-BNP threshold used in the included studies. Indications for surgery also differed between studies and included patients who had on or off-bypass surgery, elective or emergency surgery for a variety of indications including coronary artery bypass grafting, valve repair or replacement, ventricular reduction and aortic dissection. None of the included studies used an external sample or cohort to validate the diagnostic accuracy of BNP and NT pro-BNP or assessed the calibration of BNP or NT pro-BNP as a prognostic factor. The overall quality of the included studies was only modest and also varied considerably between studies. The results of the validity assessment are shown in Table 2.

Qualitative data synthesis

Pre-operative BNP and NT pro-BNP were associated with a moderate accuracy in predicting a variety of post-operative adverse events including short- and long-term mortality, AF, cardiogenic shock, IABP requirement, ICU and hospital LOS. The correlation between EuroSCORE and pre-operative natriuretic peptide levels was moderate ($r = 0.52–0.66$) and did not appear to cause collinearity during the multivariate analysis. In the nine studies (41% of all included studies) in which an appropriate multivariable analysis was performed, the ability of BNP or NT pro-BNP to predict adverse outcomes persisted after adjusting for EuroSCORE or other risk prediction models. The variability in adverse outcomes explained by BNP or NT pro-BNP, as measured by its chi-square contribution in the multivariate models, was not reported in the included studies. No clear differences were apparent between the prognostic ability of BNP and NT pro-BNP. The results for short-term mortality, post-operative AF and post-operative shocked state of all the included studies are summarized in Table 3.[2] Details of any additional outcome measures assessed in each study are available in the supplementary material.

[1]Additional study characteristics including population demographics, details of the urgency and type of surgery as well as the natriuretic peptide assay and cut-off levels are available as supplementary material.
[2]Results for additional outcomes including long-term mortality, post-operative AMI, length of ICU and hospital stay and any other reported outcome are available upon request.

Table 2: Validity assessment of the included studies

Study ID, author and year of publication	Prospective or retrospective	Representative and well-defined cohort—description of inclusion and exclusion criteria	Adequate follow-up	Objective outcome criteria clearly defined	Appropriate variables included in adjusted analysis
1. Akazawa 2008	Prospective	Yes	Yes	Yes	Yes
2. Ata 2009	Prospective	Yes	Yes	Yes	Multivariable analysis did not include EuroSCORE or equivalent
3. Attaran 2009	Prospective	Yes	Yes	AF and cardiac events not clearly defined	No multivariable analysis performed
4. Ballotta 2010	Retrospective	14 out of 45 no pre-operative BNP available	Yes	Yes	Only ejection fraction and EuroSCORE explicitly included
5. Bergler-Klein 2007	Prospective	Yes	Yes	Yes	No multivariable analysis performed
6. Cerrahoglu 2007	Not stated	Inclusion criteria not specified	Yes	Yes	No multivariable analysis performed
7. Cuthbertson 2005	Prospective	Yes	Yes	No	No multivariable analysis performed
8. Cutherbertson 2009	Prospective	Yes	Yes	Yes	Yes
9. Eliasdottir 2008	Retrospective	Exclusion criteria not clearly defined	Data missing in 44 out of 179 cases	Yes	No multivariable analysis performed
10. Fellahi 2010	Prospective	Yes	23 patients excluded	Yes	Yes
11. Fox 2010	Prospective	Yes	336 patients excluded	Yes	Yes
12. Hutfless 2004	Prospective	Yes	Yes	Yes	No multivariable analysis performed
13. Jogia 2007	Prospective	Yes	Yes	AF determined by ICU chart recording	Yes
14. Pedrazzini GB 2008	Prospective	Yes	Yes	Mortality cause and duration of the perioperative period not defined	Yes
15. Pfister 2010	Prospective	Yes	Yes	Yes	No multivariable analysis performed
16. Saribulbul 2003	Prospective	Timeframe and number screened not provided	Follow-up period not stated	Definitions not provided for post-operative inotropes	No multivariable analysis performed
17. Sezai 2009	Not stated	History of AMI or arrhythmia excluded, definitions and timeframes not provided	Yes	Yes	Multivariable analysis did not report covariables initially analysed
18. Sodeck 2008	Prospective	Yes	14 of 118 with missing data excluded	Yes	Yes
19. Tavakol 2009	Retrospective	Yes	33 of 361 with missing data excluded	Yes	EuroSCORE or equivalent not included in the multivariable model
20. Turk 2008	Prospective	Yes	Yes	Yes	EuroSCORE or equivalent not included in the multivariable model
21. Wang 2010	Prospective	Yes	Yes	Rationale for choosing ICU stay >3 days not stated	Yes
22. Wazni 2004	Retrospective	Uncertain number of patients excluded due to lack of BNP availability or other reasons	Yes	Yes	Yes

AF, atrial fibrillation; ICU, intensive care unit; AMI, acute myocardial infarction.

Table 3: Selected outcomes reported by the included studies

Study ID, author, number of participants (*n*) and test (units)	Short-term mortality	Post-operative atrial fibrillation	Post-operative shocked state
1. Akazawa, *n* = 150, BNP (pg/ml)		BNP cut-off 78.9, sensitivity 77% (56–91%), specificity 72% (63–80%); univariate BNP OR 7.336 (2.401–22.409), $P < 0.001$; multivariate BNP OR 6.272 (1.980–19.861), $P = 0.002$, ROC AUC 0.74; age and BNP the only independent predictors of post-operative AF	
2. Ata, *n* = 144, BNP (pg/ml)		BNP cut-off 135, sensitivity 72% (55–86%), specificity 71% (62–80%); ROC AUC 0.75 (0.65–0.85)	
3. Attaran, *n* = 141, BNP (ng/l)	30-day mortality; 6 patients died, BNP 1018[a]; 135 patients survived, BNP 132[a]; $P = 0.019$	38 patients with AF, BNP 237[a]; 103 patients with no AF, BNP 145[a]; $P = 0.109$	21 patients with IABP or inotropes, BNP 452[a]; 120 patients with no IABP or inotropes, BNP 120[a]; $P = 0.0015$
4. Ballotta, *n* = 31, NT pro- BNP, (pg/ml)	In-hospital mortality; 13 patients with NT pro-BNP >1304, 1 died; 18 patients with NT pro-BNP <1304, 0 died, $P = 0.232$; NT pro-BNP cut-off 1304, sensitivity 100% (3–100%), specificity 60% (41–77%)		62% with NT pro-BNP >1304 had low CO; 22% with NT pro-BNP <1304 did not have low CO, $P = 0.027$; 38% of patients with NT pro-BNP >1304 had IABP; 11% of patients with NT pro-BNP <1304 did not have IABP, $P = 0.072$, BNP cut-off 1304, sensitivity 71% (29–96%), specificity 67% (45–84%)
5.Bergler-Klein, *n* = 29, BNP (pg/ml)	30-day mortality; 16 patients with BNP >550, 3 died; 13 patients with BNP <550, 1 died; BNP cut-off 550, sensitivity 75% (19–94%), specificity 48% (28–69%)		
6. Cerrahoglu, *n* = 52, NT pro-BNP (pg/ml)			80.8% with NT pro-BNP >220 received post-operative inotropes, 15.4% with NT proBNP <220 received post-operative inotropes, $P < 0.05$
7. Cuthbertson, *n* = 46, BNP (ng/l)			Required inotropes NT pro-BNP 356[b]; did not require inotropes NT pro-BNP 207[b], $P = 0.002$; required IABP NT pro-BNP 456[b]; did not require IABP NT pro-BNP 266[b], $P = 0.18$; ROC AUC for cardiovascular support 0.75 (0.59–0.91)
8. Cuthbertson, *n* = 1010, NT pro-BNP (ng/l)	30-day mortality; NT pro-BNP cut-off 289, sensitivity 69% (49–85%), specificity 51% (48–54%); univariable analysis: OR for below median vs. above median 2.27 (1.02–5.03), $P = 0.04$; multivariable analysis: OR 1.03 (1.00–1.05), $P = 0.04$ (OR per 250 ng/ml increment)	NT pro-BNP with AF 388[b]; NT pro-BNP without AF 246[b]; OR 1.02 (1.00–1.03), $P = 0.02$; NT pro-BNP cut-off 289, sensitivity 59% (53–64%), specificity 55% (51–59%)	
9. Eliasdottir, *n* = 135, NT pro-BNP (ng/l)	28-day mortality; 8 patients died, NT pro-BNP 1420[b]; 127 patients survived, NT pro-BNP 2184[b]; $P = 0.001$; correlation between NT pro-BNP and EuroSCORE $r = 0.658$, $P < 0.001$		Required inotropes >1 day NT pro-BNP 964[b]; did not require inotropes >1 day NT pro-BNP 119[b], $P < 0.001$; NT pro-BNP cut-off 376, sensitivity 79%, specificity 75%, ROC AUC 0.84 (0.77–0.91), EuroSCORE 0.77 (0.68–0.91), EF 0.38 (0.26–0.49); required IABP >1 day NT pro-BNP 1795[b]; did not require IABP >1 day NT pro-BNP 208[b], $P < 0.001$; NT pro-BNP cut-off 396, sensitivity 79%, specificity 66%, ROC AUC NT pro-BNP 0.79 (0.68–0.91); EuroSCORE 0.74 (CI 0.59–0.89)
10. Fellahi, *n* = 209, BNP (pg/ml)	Composite in-hospital major adverse cardiac event or death; BNP cut-off 317, sensitivity 77% (60–89%), specificity 75% (68–81%); BNP ROC AUC 0.76 (0.68–0.85), $P < 0.001$; EuroSCORE 0.59 (0.48–0.69), $P = 0.05$; multivariable analysis pre-operative BNP independent risk factor for major adverse cardiac event or death; OR 10.7 (4.1–27.8), $P < 0.001$; rank correlation between BNP and EuroSCORE $r = 0.52$ (0.41–0.61)		
11. Fox, *n* = 1519, BNP (pg/ml)			Post-operative LV dysfunction, need for two inotropes IABP or VAD OR = 1.92 (1.12–3.29), $P = 0.018$; ROC AUC 0.67 (0.62–0.73)

12. Hutfless, *n* = 98, BNP (pg/ml)			10 patients with post-operative IABP BNP 387[a]; 88 patients without post-operative IABP BNP 181[a]; BNP cut-off 120, sensitivity 70%, specificity 62%; BNP cut-off 280, sensitivity 50%, specificity 79%; BNP cut-off 385, sensitivity 50%, specificity 90%; ROC AUC 0.70 (0.51–0.87)
13. Jogia, *n* = 118, NT pro-BNP (pmol/l)			Required post-operative milronone NT pro-BNP 860[a]; did not require post-operative milronone NT pro-BNP 122[a], $P = 0.004$; significant positive correlation between pre-operative NT pro-BNP and total perioperative noradrenaline dose $r = 0.55$, $P = 0.003$
14. Pedrazzini, *n* = 144, BNP (pg/ml)	Perioperative mortality; univariable analysis: BNP >312; OR 19.0 (2.30–157), $P < 0.001$; *C*-statistic 0.75; bivariate analysis: (with EuroSCORE); OR 21.99 (2.51–192), $P = 0.003$		
15. Pfister, *n* = 31, NT pro-BNP, (pg/ml)	2-month mortality; 15 patients with NT pro-BNP >1975, 3 died, 16 patients with NT pro-BNP <1975, 5 died, $P = 0.47$, sensitivity 38% (9–76%), specificity 48% (27–69%)		
16. Saribulbul, *n* = 26, BNP (pg/ml)			14 patients required post-operative inotropes BNP 78[a]; 12 patients did not require post-operative inotropes BNP 33[a], $P = 0.027$
17. Sezai, *n* = 234, BNP and ANP (pg/dl)		73 with AF BNP 137.2[a]; 161 with no AF BNP 149.7[a], $P = 0.751$; multivariable analysis BNP *P*-value not significant, EuroSCORE >7, OR 6.37 (1.16–34.98), $P = 0.033$	
18. Sodeck, *n* = 104, NT pro-BNP (pg/ml)	30-day mortality; 23 died NT pro-BNP 2240[b]; 81 survived NT pro-BNP 328[b], $P = 0.001$; multivariable analysis NT pro-BNP > 647 compared with lowest tertile OR 11.67 (2.61–52.09), $P = 0.001$		Post-operative heart failure; multivariable analysis NT-proBNP >647; OR 9.08 (CI 2.06–40.07), $P = 0.004$
19. Tavakol, *n* = 328, BNP (mg/dl)		57 patients with AF BNP 361[a]; 261 patients with no AF BNP 302[a], $P = 0.30$; multivariable analysis pre-operative log BNP OR 0.9 (0.34–2.4), *P*-value not significant	
20. Turk, *n* = 85, BNP (pg/ml)		Post-operative AF data reported in the larger cohort of Study 2 [13]	Six required post-operative IABP BNP 325[b]; 79 did not require post-operative IABP BNP 68[b], $P = 0.021$; BNP cut-off 235, sensitivity 83% (36–100%), specificity 84% (74–91%), ROC AUC 0.79 (0.56–1.01); 25 required post-operative inotropes BNP 189[b]; 60 did not require post-operative inotropes BNP 65, $P = 0.004$, BNP cut-off 185, sensitivity 52%, specificity 82%, ROC AUC 0.70 (CI 0.58–0.82)
21. Wang, *n* = 112, BNP (pg/ml)			
22. Wazni, *n* = 187, BNP (pg/ml)		80 patients with AF BNP 615[b]; 107 patients with no AF BNP 444[b], $P = 0.005$; BNP cut-off 50th centile, sensitivity 60% (48–71%), specificity 38% (29–48%); multivariable analysis: BNP >50th centile, OR 2.5 (1.12–5.39), $P = 0.025$	

BNP, brain natriuretic peptide; AMI, acute myocardial infarction; AF, atrial fibrillation; IABP, intra-aortic balloon pump; LOS, length of stay in days; CO, cardiac output; ROC, receiver operating characteristic curve; AUC, area under the curve; OR, odds ratio. Range in brackets refers to 95% confidence intervals unless otherwise stated.
[a]Mean.
[b]Median.

Table 4: Summary DOR for BNP and NT pro-BNP in predicting short-term mortality, post-operative atrial fibrillation (AF) and post-operative IABP requirement

Study	DOR	95% CI	% Weight
Short-term mortality			
Ballotta[b]	4.4	0.2–118.0	2.8
Bergler Klein[a]	2.8	0.3–30.4	6.6
Cuthbertson 2009[b]	2.3	1.0–5.1	62.5
Pfister[b]	0.6	0.1–2.9	28.2
Pooled DOR	1.9	1.0–3.5	Inconsistency (I^2) = 0.0%
Post-operative AF			
Akazawa[a]	8.5	3.1–22.9	2.3
Ata[a]	6.5	2.8–15.0	3.8
Cuthbertson 2009[b]	1.8	1.4–2.3	74.2
Wazni[a]	0.9	0.5–1.7	19.6
Pooled DOR	1.9	1.6–2.4	Inconsistency (I^2) = 86.8%
Post-operative IABP			
Ballotta[b]	5.0	0.8–31.7	25.3
Eliasdottir[b]	7.2	1.9–27.1	44.7
Hutfless[a]	8.8	2.1–36.3	22.5
Turk[a]	25.4	2.7–235.6	7.5
Pooled DOR	8.3	3.9–17.9	Inconsistency (I^2) = 0.0%

[a]BNP.
[b]NT pro-BNP.

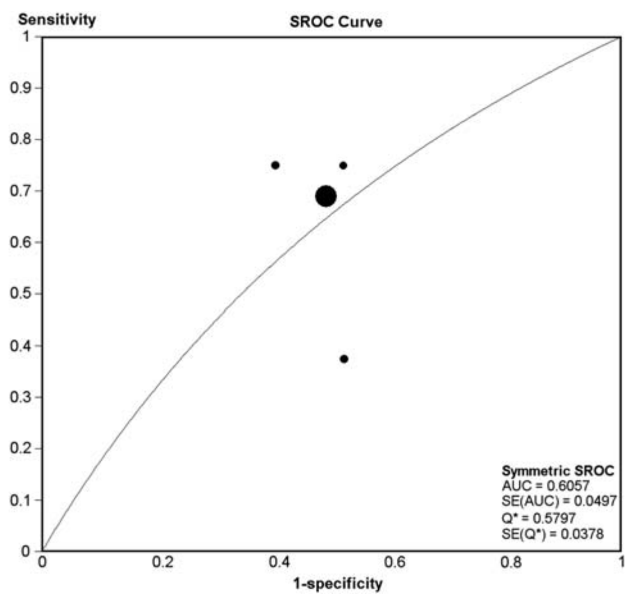

Figure 2: The ROC curve for post-operative mortality.

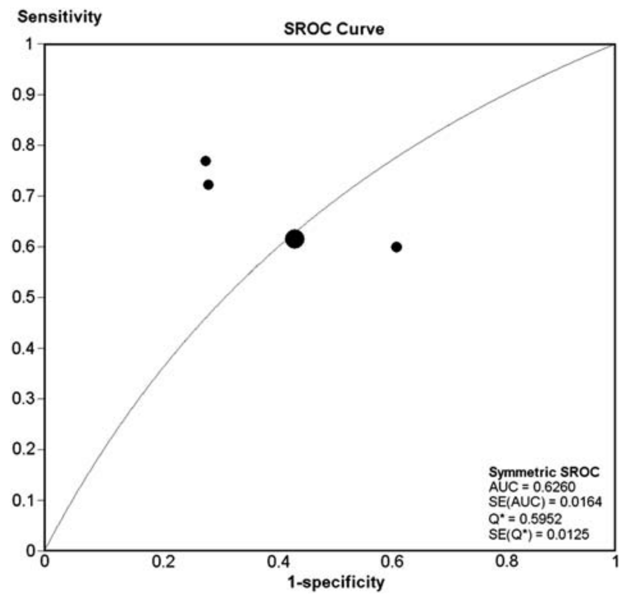

Figure 3: The ROC curve for post-operative atrial fibrillation.

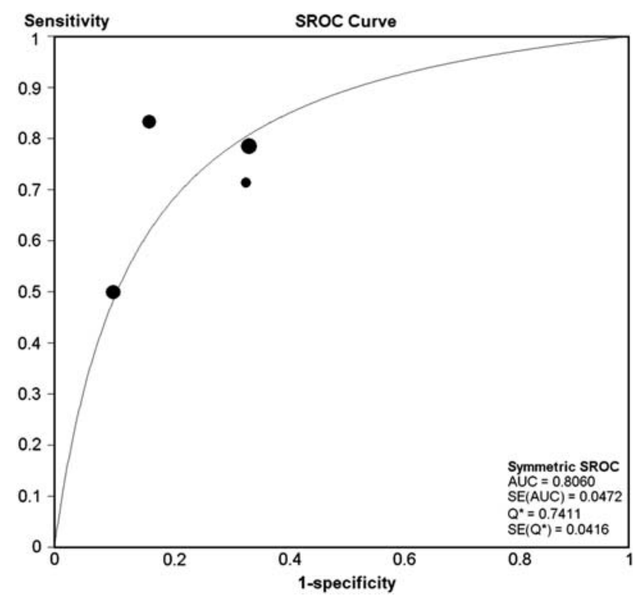

Figure 4: The ROC curve for post-operative IABP requirement.

Quantitative data synthesis

A total of 10 studies reported sufficient and comparable outcome data to provide pooled summary estimates of the association between pre-operative natriuretic peptide levels and post-operative short-term mortality (four studies including 1101 participants), AF (four studies including 1491 participants) and IABP requirement (four studies including 349 participants). The DOR and the area under the ROC curve of BNP and NT pro-BNP to predict short-term mortality were: DOR 1.9 (95% confidence interval [CI] 1.0–3.5) and ROC area 0.61 (95% CI 0.51–0.70, I^2 = 0%), respectively (Table 4 and Fig. 2). The DOR and the area under the ROC curve to predict post-operative AF were: DOR 1.9 (95% CI 1.6–2.4) and ROC area 0.61 (95% CI 0.55–0.64, I^2 86%), respectively (Table 4 and Fig. 3). The DOR and the area under the ROC curve to predict post-operative IABP requirement were: DOR 8.3 (95% CI 3.9–17.9) and ROC area 0.81 (95% CI 0.73–0.89, I^2 = 0%), respectively (Table 4 and Fig. 4).

DISCUSSION

In this systematic review, all the studies assessing pre-operative BNP or NT pro-BNP to predict outcomes after cardiac surgery were observational in nature and differed considerably in their sample sizes, inclusion criteria and quality. With the limited data available, pre-operative BNP and NT pro-BNP had a moderate ability to discriminate between patients that did and did not have adverse outcomes after cardiac surgery. BNP and NT pro-BNP also appeared to provide prognostic information about the risk of adverse outcomes after cardiac surgery when combined with established risk prediction models such as EuroSCORE.

In patients undergoing cardiac surgery, accurate risk adjustment is of paramount importance for clinical audit, benchmarking and research and to identify high-risk patients that may benefit from prophylactic interventions to reduce post-operative adverse outcomes. Our results showed that BNP and NT pro-BNP concentrations had a moderate ability to predict post-operative adverse outcomes and appeared to provide additional prognostic information, especially on the risk of requiring IABP after surgery, which was not fully captured by standard clinical scoring systems such as EuroSCORE [5]. These results require careful consideration. Firstly, BNP and NT pro-BNP are synthesized and released by ventricular cardiomyocytes in response to myocardial wall stress and ischaemia and as such, it is not surprising that they could have an ability to predict a post-operative requirement for IABP. BNP and NT pro-BNP are relatively inexpensive tests, the results are rapidly available, and measurement does not involve subjective assessment. As such, they may be particularly useful in the immediate pre-operative period to stratify patients into different risk categories, or to alert the surgical, anaesthesia and intensive care team that a patient's condition may have changed since previous BNP or NT pro-BNP measurements or after the most recent echocardiography or comprehensive risk assessment.

Secondly, in high-risk patients undergoing cardiac surgery, prophylactic interventions including pre-operative levosimendan and IABP may reduce the incidence of post-operative adverse outcomes [9, 10]. Limitation to widespread adoption of these interventions includes the difficulty in accurately identifying those high-risk patients most likely to benefit. Incorporating BNP or NT pro-BNP as a recruitment criterion or as a baseline characteristic in a randomized controlled trial on effectiveness of a new intervention should be seriously considered, especially if high-risk patients are the targeted participants.

Finally, although many existing clinical prognostic models such as EuroSCORE are very useful, further refinement, update or recalibration are needed to maintain their utility. Most of these clinical prognostic scores for cardiac surgery are only useful in predicting mortality but not adverse events such as AF or cardiogenic shock requiring IABP [6, 7]. Perhaps, incorporating pre-operative BNP or NT pro-BNP may improve the performance and generalizability of these prognostic scores and should be seriously considered in the development of new prognostic models for cardiac surgery.

This study has some limitations. Firstly, although we have included all potential studies without language restrictions, there is still a risk of publication bias when investigators do not report their results on outcomes that are negative. Secondly, although the total number of patients considered was not small, the variations in the type of natriuretic peptide assays used, study inclusion criteria and outcomes measured limited the ability to include many studies in the meta-analysis, and hence the precision of the pooled results. Finally, many studies did not report the additive and independent predictive ability of BNP or NT pro-BNP when used with an established risk prediction model, and this merits further investigation and external validation in a large multicentre observational study.

In summary, the strength of associations between pre-operative natriuretic peptide levels and adverse outcomes after cardiac surgery varied between different studies. With the limited evidence available from the larger and higher quality studies, pre-operative natriuretic peptide levels were associated with a moderate ability to predict post-operative adverse outcomes. The additive value of combining natriuretic peptides with an established cardiac surgical risk prediction model deserves further investigation.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

REFERENCES

[1] Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998;339:321–8.
[2] Di Angelantonio E, Chowdhury R, Sarwar N, Ray KK, Gobin R, Saleheen D *et al*. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. Circulation 2009;120: 2177–87.
[3] Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 2004;110:2168–74.
[4] Karthikeyan G, Moncur RA, Levine O, Heels-Ansdell D, Chan MT, Alonso-Coello P *et al*. 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. J Am Coll Cardiol 2009;54:1599–606.
[5] Nashef SA, Roques F, Hammill BG, Peterson ED, Michel P, Grover FL *et al*. Validation of European System for Cardiac Operative Risk Evaluation (EuroSCORE) in North American cardiac surgery. Eur J Cardiothorac Surg 2002;22:101–5.
[6] Yap CH, Mohajeri M, Ihle BU, Wilson AC, Goyal S, Yii M. Validation of EuroSCORE model in an Australian patient population. ANZ J Surg 2005; 75:508–12.
[7] Toumpoulis IK, Anagnostopoulos CE, Swistel DG, DeRose JJ Jr. Does EuroSCORE predict length of stay and specific postoperative complications after cardiac surgery? Eur J Cardiothorac Surg Official J Eur Assoc Cardiothorac Surg 2005;27:128–33.
[8] Ferguson TB Jr, Hammill BG, Peterson ED, DeLong ER, Grover FL. A decade of change—risk profiles and outcomes for isolated coronary artery bypass grafting procedures, 1990–1999: a report from the STS National Database Committee and the Duke Clinical Research Institute. Society of Thoracic Surgeons. Ann Thorac Surg 2002;73:480–9; discussion 9–90.
[9] Landoni G, Mizzi A, Biondi-Zoccai G, Bruno G, Bignami E, Corno L *et al*. Reducing mortality in cardiac surgery with levosimendan: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth 2010;24:51–7.
[10] Field ML, Rengarajan A, Khan O, Spyt T, Richens D. Preoperative intra aortic balloon pumps in patients undergoing coronary artery bypass grafting. Cochrane Database Systemic Reviews (Online) 2007:CD004472.
[11] Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol 2006;6:31.
[12] Akazawa T, Nishihara H, Iwata H, Warabi K, Ohshima M, Inada E. Preoperative plasma brain natriuretic peptide level is an independent predictor of postoperative atrial fibrillation following off-pump coronary artery bypass surgery. J Anesth 2008;22:347–53.
[13] Ata Y, Turk T, Ay D, Eris C, Demir M, Ari H *et al*. Ability of B-type natriuretic peptide in predicting postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting. Heart Surg Forum 2009;12:E211–6.

[14] Attaran S, Sherwood R, Desai J, Langworthy R, Mhandu P, John L *et al*. Brain natriuretic peptide a predictive marker in cardiac surgery. Interact Cardiovasc Thorac Surg 2009;9:662–6.

[15] Ballotta A, Ranucci M, Kunkl A, El Baghdady H, Bossone E, Castelvecchio S *et al*. N-terminal pro-brain natriuretic peptide and outcomes in patients undergoing surgical ventricular restoration. Am J Cardiol 2010; 105:640–4.

[16] Bergler-Klein J, Mundigler G, Pibarot P, Burwash IG, Dumesnil JG, Blais C *et al*. B-type natriuretic peptide in low-flow, low-gradient aortic stenosis: relationship to hemodynamics and clinical outcome: results from the Multicenter Truly or Pseudo-Severe Aortic Stenosis (TOPAS) study. Circulation 2007;115:2848–55.

[17] Cerrahoglu M, Iskesen I, Tekin C, Onur E, Yildirim F, Sirin BH. N-terminal ProBNP levels can predict cardiac failure after cardiac surgery. Circ J 2007;71:79–83.

[18] Cuthbertson BH, McKeown A, Croal BL, Mutch WJ, Hillis GS. Utility of B-type natriuretic peptide in predicting the level of peri- and postoperative cardiovascular support required after coronary artery bypass grafting. Crit Care Med 2005;33:437–42.

[19] Cuthbertson BH, Croal BL, Rae D, Gibson PH, McNeilly JD, Jeffrey RR *et al*. N-terminal pro-B-type natriuretic peptide levels and early outcome after cardiac surgery: a prospective cohort study. Br J Anaesth 2009;103:647–53.

[20] Eliasdottir SB, Klemenzson G, Torfason B, Valsson F. Brain natriuretic peptide is a good predictor for outcome in cardiac surgery. Acta Anaesthesiol Scand 2008;52:182–7.

[21] Fellahi JL, Daccache G, Rubes D, Massetti M, Gerard JL, Hanouz JL. Does preoperative B-type natriuretic peptide better predict adverse outcome and prolonged length of stay than the standard European system for cardiac operative risk evaluation after cardiac surgery? J Cardiothorac Vasc Anesth 2010;25:256–62.

[22] Fox AA, Muehlschlegel JD, Body SC, Shernan SK, Liu KY, Perry TE *et al*. Comparison of the utility of preoperative versus postoperative B-type natriuretic peptide for predicting hospital length of stay and mortality after primary coronary artery bypass grafting. Anesthesiology 2010;112: 842–51.

[23] Hutfless R, Kazanegra R, Madani M, Bhalla MA, Tulua-Tata A, Chen A *et al*. Utility of B-type natriuretic peptide in predicting postoperative complications and outcomes in patients undergoing heart surgery. J Am Coll Cardiol 2004;43:1873–9.

[24] Jogia PM, Kalkoff M, Sleigh JW, Bertinelli A, La Pine M, Richards AM *et al*. NT-pro BNP secretion and clinical endpoints in cardiac surgery intensive care patients. Anaesth Intens Care 2007;35:363–9.

[25] Pedrazzini GB, Masson S, Latini R, Klersy C, Rossi MG, Pasotti E *et al*. Comparison of brain natriuretic peptide plasma levels versus logistic EuroSCORE in predicting in-hospital and late postoperative mortality in patients undergoing aortic valve replacement for symptomatic aortic stenosis. Am J Cardiol 2008;102:749–54.

[26] Pfister R, Wahlers T, Baer FM, Scherner M, Strauch J, Erdmann E. Utility of NT-pro-BNP in patients undergoing transapical aortic valve replacement. Clin Res Cardiol 2010;99:301–7.

[27] Saribulbul O, Alat I, Coskun S, Apaydin AZ, Yagdi T, Kiliccioglu M *et al*. The role of brain natriuretic peptide in the prediction of cardiac performance in coronary artery bypass grafting. Tex Heart Inst J 2003;30:298–304.

[28] Sezai A, Hata M, Niino T, Kasamaki Y, Nakai T, Hirayama A *et al*. Study of the factors related to atrial fibrillation after coronary artery bypass grafting: a search for a marker to predict the occurrence of atrial fibrillation before surgical intervention. J Thorac Cardiovasc Surg 2009;137:895–900.

[29] Sodeck G, Domanovits H, Schillinger M, Janata K, Thalmann M, Ehrlich MP *et al*. Pre-operative N-terminal pro-brain natriuretic peptide predicts outcome in type A aortic dissection. J Am Coll Cardiol 2008;51:1092–7.

[30] Tavakol M, Hassan KZ, Abdula RK, Briggs W, Oribabor CE, Tortolani AJ *et al*. Utility of brain natriuretic peptide as a predictor of atrial fibrillation after cardiac operations. Ann Thorac Surg 2009;88:802–7.

[31] Turk T, Ata Y, Ay D, Ozkan H, Vural H, Yavuz S *et al*. Plasma brain natriuretic Peptide after isolated on-pump coronary artery bypass grafting: prediction of postoperative adverse outcomes. Heart Surg Forum 2008;11:E84–9.

[32] Wang Z, Liang D, Fu Q, Jia L, Men J, Wei M. Perioperative brain natriuretic peptide in off-pump coronary artery bypass. Acta Cardiol 2010;65: 297–301.

[33] Wazni OM, Martin DO, Marrouche NF, Latif AA, Ziada K, Shaaraoui M *et al*. Plasma B-type natriuretic peptide levels predict postoperative atrial fibrillation in patients undergoing cardiac surgery. Circulation 2004;110: 124–7.