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UTILITY OF B-TYPE NATRIURETIC PEPTIDE IN PREDICTING MEDIUM-TERM MORTALITY IN PATIENTS UNDERGOING MAJOR NON-CARDIAC SURGERY.

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Brief title: BNP and medium term surgical outcome.

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Abstract

We assessed the ability of pre-operative B-type natriuretic peptide (BNP) levels to predict medium-term mortality in patients undergoing major noncardiac surgery. During a median 654 days follow-up 33 patients from a total cohort of 204 patients (16%) died. The optimal cut-off in this cohort, determined using a receiver operating characteristic curve, was >35pg.mL^{-1}. This was associated with a 3.47-fold increase in the hazard of death (p=0.001) and had a sensitivity of 70% and a specificity of 68% for this outcome. These findings extend recent work demonstrating that BNP levels obtained before major noncardiac surgery can be used to predict peri-operative morbidity, and indicate that they also forecast medium-term mortality.

Introduction

Major non-cardiac surgery is associated with a high risk of early cardiovascular complications.[1] In addition, there is a significant longer-term mortality in these patients. Some of these late deaths may relate to the underlying pathology, but many are due to cardiovascular disease. Peri-operative and early post-operative cardiac events predict an excess medium term mortality.[2, 3] In particular, even small elevations in markers of myocardial cell necrosis, such as cardiac troponin I (cTnI) or T, are associated with an increased risk of death.[2, 3] Recently, several relatively small studies have also demonstrated that pre-operative levels of B-type natriuretic peptide (BNP) and N-terminal pro-BNP are useful predictors of peri-operative cardiac complications in this setting.[4-8] These studies have, however, largely relied on subjective, short-term, end-points. The aim of the current study is therefore, to determine the usefulness of pre-operative BNP in predicting longer-term mortality after major non-cardiac surgery, and to

assess whether such measures provide any additional prognostic information to that afforded by post-operative troponin levels.

Methods

The study was approved by the local ethics committee and written informed consent was obtained. Consecutive patients undergoing scheduled major non-cardiac surgery were recruited. This included patients undergoing major vascular surgery, major gastrointestinal surgery and major pelvic cancer surgery. Patients requiring emergency or minor surgery were excluded. Pre-operative data collection included patient demographics, medical and drug history. In addition, the Revised Cardiac Risk Index[9] was calculated. Pre-operative blood samples were obtained for Cardiac Troponin (cTnI) and BNP and details of surgery and anesthesia were also recorded. Post operative data collection included the recording of a 12 lead Electrocardiograph (ECG) and measurement of cTnI at 24 and 72 hours after surgery. Patients were followed-up while in hospital and subsequent vital status determined using data provided by the General Register Office for Scotland. The primary endpoint was all-cause mortality. BNP and cTnI assays were measured using the Bayer ADVIA Centaur™ immunoassay. The lower limit of detection for BNP is 5pg.ml^{-1} and the coefficients of variation at 48pg.ml^{-1} and 461pg.ml^{-1} are 3.4% and 2.9% respectively.[10] The 99th percentile value for the cTnI assay is 0.16μg/L with a coefficient of variation of <10% achieved at levels ≥0.32μg/L.[11]

Categorical data are summarised using absolute values (percentage). Normally distributed continuous data are presented as mean (standard deviation) or, where skewed, as median (interquartile range). Long-term survival was described using the Kaplan-Meier method and comparisons made using the log-rank statistic. Estimations of risk were performed using Cox regression. All univariable predictors were then entered in a stepwise manner into a multivariable

model of survival, with entry and retention set at a significance level of <0.05. A receiver operating characteristic (ROC) curve, assessing the ability of pre-operative BNP to predict mortality, was plotted and the area under the curve (with 95% confidence interval) estimated. A p-value <0.05 was considered significant.

Results

From September 2004 to April 2005, 239 patients eligible to take part in the study were invited to participate. Twenty (8%) refused consent. It was not possible to obtain pre-operative blood samples from 5 patients (2%) and 10 (4%) patients did not undergo major surgery and were excluded. The remaining 204 patients completed the trial protocol. Baseline characteristics for this cohort are shown in table 1. Seventy (34%) patients underwent major vascular surgery, 84 (41%) major abdominal surgery and 50 (25%) major pelvic surgery. The utility of pre-operative BNP levels in predicting early cardiac events in this cohort has been previously reported.[8]

Vital status data were available for all study participants. One patient (0.5%) died within 30 days of surgery. During a median 654 (interquartile range 532-711) days follow-up 33 patients (16%) died. Seventeen (24%) died after major vascular surgery, 9 (11%) after major abdominal surgery and 6 (12%) after major pelvic surgery. No patients had detectable (>0.10μg/L) cTnI levels pre-operatively. In contrast, post-operative cTnI levels >0.10μg/L at 24 and/or 72 hours were observed in 12 out of 70 (17%) patients undergoing major vascular surgery and 15 out of 130 (12%) of those undergoing major abdominal/pelvic surgery. Elevated cTnI levels 24 hours after surgery were powerful predictors of long-term mortality. In contrast, cTnI levels at 72 hours were not significant predictors.

When analyzed as a continuous variable, pre-operative BNP levels did not predict long-term outcome. The relationship between BNP and subsequent death was not, however, linear – with the excess hazard primarily associated with a pre-operative BNP level in the upper quartile (table 1 and figure 1). In this cohort a ROC curve identified the optimal cut-off level of BNP for long-term mortality as 35pg.mL^{-1}, which achieved a sensitivity of 70% and a specificity of 68%. The area under the ROC curve was 0.70 (95% CI 0.61-0.79, p<0.001). Figure 2 shows the Kaplan Meier curve demonstrating survival in patients with BNP levels below and above this threshold.

To assess whether BNP levels conveyed independent prognostic information regression models were developed. In the first of these BNP dichotomised around the optimal cut-off level of 35pg.mL^{-1} was entered along with cTnI levels at 24 hours post-operatively. This demonstrated that, even after correction for cTnI levels, BNP levels >35pg.mL^{-1} remained strong predictors of subsequent death (HR 3.17, 95% CI 1.48-6.79, p=0.003). A further backward conditional model was developed including BNP levels >35pg.mL^{-1}, cTnI levels at 24 hours post-operatively, age and the Revised Cardiac Risk Index. In this model the only independent predictor of death was age (HR 1.48 per 10 year increase, 95% CI 1.04-2.12, p=0.03). However, there was a trend towards BNP levels >35pg.mL^{-1} independently predicting outcome (HR 2.25, 95% CI 0.97-5.25, p=0.06).

Discussion

The current study confirms that elevated pre-operative BNP levels in patients undergoing non-cardiac surgery are associated with an increased risk of mortality during medium-term follow-up. These results extend the findings from several recent small studies that have demonstrated that BNP levels may be used to predict an increased risk of peri-operative adverse events in this setting.[4-8] In addition, the current data suggest that BNP may provide prognostic

information that is incremental to that obtained from post-operative cardiac troponin levels. It has already been suggested that pre-operative BNP and/or levels might assist in differentiating patients who have a very low-risk of peri-operative cardiac events from those who require more detailed cardiovascular testing and optimization of therapy prior to major non-cardiac surgery.[5] The current data suggest this that this strategy might result in improved long-term outcome. This, however, requires to be tested prospectively.

The Revised Cardiac Risk Index[9] did not prove to be a useful measure of medium-term outcome in this cohort. This most likely reflects the relative homogeneity of the current cohort in terms of their clinical risk scores. Likewise, the Revised Cardiac Risk Index was developed to predict peri-operative events - including clinically defined measures of morbidity, some using outdated definitions - and not long-term mortality. It was also derived and validated in patients ≥50 years old. In addition to its superior prognostic performance in this cohort, BNP levels have several other advantages. Measurement relies on a relatively cheap and widely available blood test. A biochemical test also avoids the difficulties inherent in applying complex scoring systems and provides an objective measure without the potential for subjective interpretation.

The current study confirms that, among patients undergoing major non-cardiac surgery, cardiac troponin levels are frequently elevated after surgery, even in patients who are undergoing non-vascular surgery. It also demonstrates that patients exhibiting only minor elevations have a higher medium-term mortality.

This was a small study of patients undergoing diverse major surgical procedures. Ideally, these results should be verified in a study powered to detect hospital and longer-term mortality in all surgical subgroups. Use of all-cause mortality has the advantage of being entirely objective.

We acknowledge, however, that data relating to the cause of death and other non-fatal outcomes would have been of interest. Further work should determine the utility of BNP in combination with existing risk stratification tools and, more importantly, assess whether interventions that reduce BNP levels can prevent peri-operative and longer-term complications.

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Table 1. Baseline patient characteristics.

Patient characteristic	Total cohort (n=204)	Died during follow-up (n=33)	Survivors at time of follow-up (n=171)	Hazard ratio (95% CI)	P value
Men	125 (61%)	21 (63%)	104 (61%)	1.04 (0.51-2.12)	0.91
Age (years)	66 (57-74)	74 (68-80)	64 (57-72)	1.06 (1.03-1.09)	<0.001
Cardiac medication[†]	108 (53%)	20 (60%)	88 (52%)	1.13 (0.55-2.31)	0.74
Diabetes mellitus	30 (15%)	6 (18%)	24 (14%)	1.17 (0.48-2.83)	0.74
Hypertension	74 (36%)	15 (45%)	59 (35%)	1.45 (0.73-2.87)	0.29
Prior myocardial infarction	20 (10%)	2 (6%)	18 (10%)	0.40 (0.09-1.69)	0.21
Prior angina pectoris	47 (23%)	10 (30%)	37 (22%)	1.02 (0.47-2.24)	0.96
Prior atrial fibrillation	7 (3%)	1 (3%)	6 (3%)	0.93 (0.13-6.83)	0.94
Current smoker	48 (23%)	10 (30%)	38 (22%)	1.36 (0.64-2.86)	0.41
Prior revascularization	12 (6%)	1 (3%)	11 (6%)	0.44 (0.06-3.23)	0.42
Creatinine ($\mu mol.ml^{-1}$)	92 (82-106)	96 (85-107)	92 (82-106)	1.00 (0.99-1.02)	0.78
Revised Cardiac Risk Index ≥2	65 (32%)	14 (42%)	19 (11%)	1.37 (0.67-2.79)	0.38
Post-operative ECG changes	14 (7%)	1 (3%)	13 (8%)	0.34 (0.05-2.51)	0.29
cTnI at 24 hours ($\mu g.L^{-1}$)	0.03 ±0.15	0.10 ±0.29	0.02 ±0.11	4.84 (1.51-15.57)	0.008
cTnI at 72 hours ($\mu g.L^{-1}$)	0.09 ±0.67	0.13 ±0.40	0.08 ±0.72	0.96 (0.65-1.41)	0.84
cTnI >0.10$\mu g.L^{-1}$ at 24 +/or 72 hours	27 (13)	9 (27)	18 (11)	2.18 (1.00-4.73)	0.05
Pre-operative BNP (pg/mL^{-1})	26.6 (11.5-50.3)	50.4 (24.8-76.1)	21.5 (10.1-45.5)	1.02 (0.97-1.06)	0.50
Quartiles of BNP (pg/mL^{-1}					
Quartile 1 (0-11.4)	51 (25%)	3 (9)	48 (28)	1	-
Quartile 2 (11.5-26.4)	51 (25%)	5 (15)	46 (27)	1.66 (0.40-6.96)	0.49
Quartile 3 (26.5-49.9)	51 (25%)	8 (24)	43 (25)	2.59 (0.69-9.78)	0.16
Quartile 4 (50.0-376.0)	51 (25%)	17 (52)	34 (20)	4.92 (1.43-16.94)	0.01
Pre-operative BNP >35$pg.mL^{-1}$	78 (38%)	23 (70)	55 (32)	3.47 (1.64-7.34)	0.001

† Cardiac medication is defined as the regular prescription of a medication for a cardiovascular disease; ‖ Optimal cut-off as defined by receiver operating characteristic curve; MI = myocardial infarction, BNP = B-type natriuretic peptide.

Figure 1. Quartiles of pre-operative BNP and subsequent mortality.

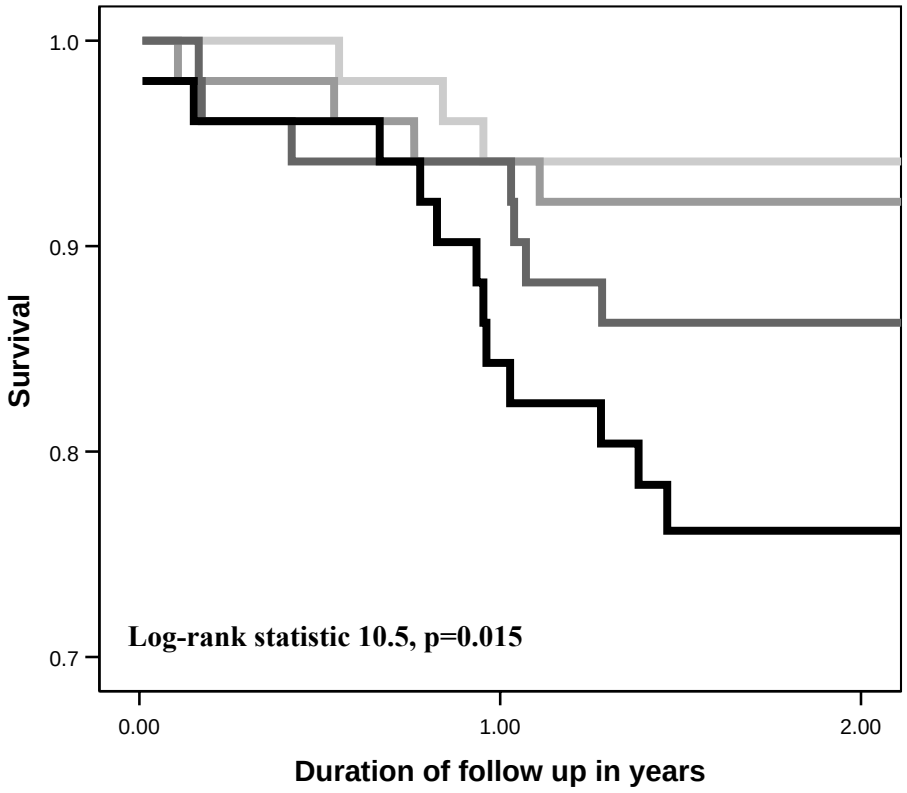

FIGURE LEGEND

BNP quartile 1

BNP quartile 2

BNP quartile 3

BNP quartile 4

Figure 2. Pre-operative BNP levels >35pg.mL^{-1} and subsequent mortality.

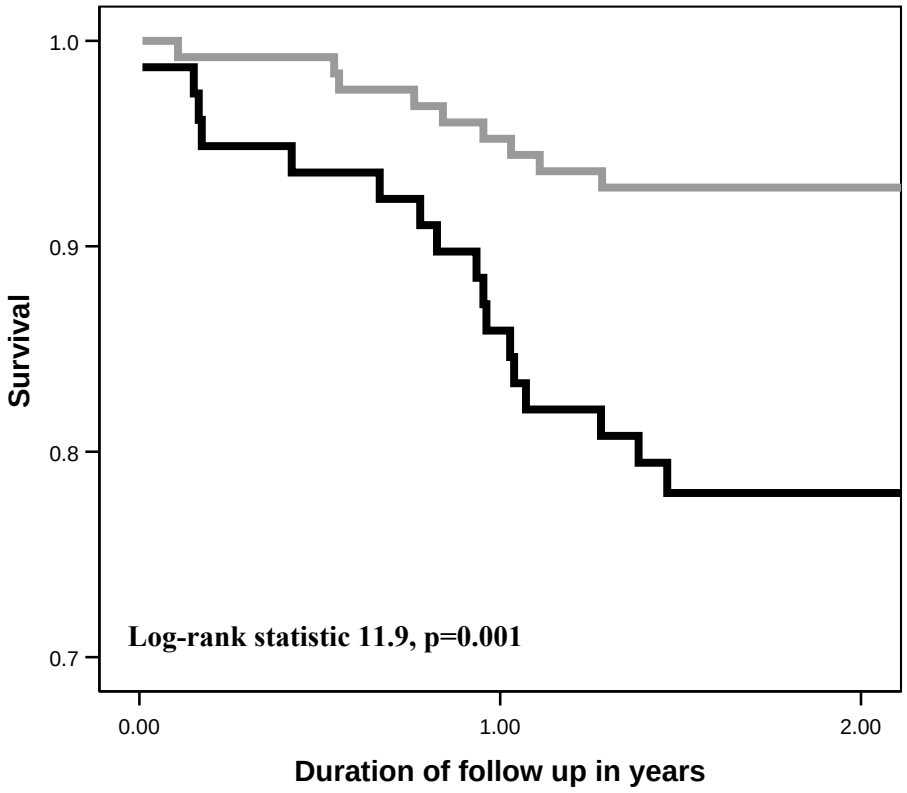

FIGURE LEGEND

BNP ≤35pg.mL^{-1}

BNP >35pg.mL^{-1}