CARDIOVASCULAR SURGERY

Plasma N-terminal pro-B-type natriuretic peptide as long-term prognostic marker after major vascular surgery

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Objective: To assess the long-term prognostic value of plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) after major vascular surgery.

Design: A single-centre prospective cohort study.

Patients: 335 patients who underwent abdominal aortic aneurysm repair or lower extremity bypass surgery.

Interventions: Prior to surgery, baseline NT-proBNP level was measured. Patients were also evaluated for cardiac risk factors according to the Revised Cardiac Risk Index. Dobutamine stress echocardiography (DSE) was performed to detect stress-induced myocardial ischaemia.

Main outcome measures: The prognostic value of NT-proBNP was evaluated for the endpoints all-cause mortality and major adverse cardiac events (MACE) during long-term follow-up.

Results: In this patient cohort (mean age: 62 years, 76% male), median NT-proBNP level was 186 ng/l (interquartile range: 65–444 ng/l). During a mean follow-up of 14 (SD 6) months, 49 patients (15%) died and 50 (15%) experienced a MACE. Using receiver operating characteristic curve analysis for 6-month mortality and MACE, NT-proBNP had the greatest area under the curve compared with cardiac risk score and DSE. In addition, an NT-proBNP level of 319 ng/l was identified as the optimal cut-off value to predict 6-month mortality and MACE. After adjustment for age, cardiac risk score, DSE results and cardioprotective medication, NT-proBNP ≥ 319 ng/l was associated with a hazard ratio of 4.0 for all-cause mortality (95% CI: 1.8 to 8.9) and with a hazard ratio of 10.9 for MACE (95% CI: 4.1 to 27.9).

Conclusion: Preoperative NT-proBNP level is a strong predictor of long-term mortality and major adverse cardiac events after major non-cardiac vascular surgery.

Assessment of short- and long-term risk in patients undergoing major vascular surgery is regarded by the American College of Cardiology/American Heart Association as one of the most important initial steps in the evaluation and treatment of these patients.¹ Risk stratification is especially important given the substantial risk of perioperative and long-term morbidity and mortality.^{2–5} To identify high-risk patients prior to surgery, several risk stratification scores have been developed and adjusted using the patient's history and type of surgery to predict postoperative outcome.^{6–9} In patients with multiple risk factors undergoing high-risk surgery, preoperative non-invasive stress testing provides additional prognostic information.¹⁰

The natriuretic peptides are endogenous cardiac hormones that include atrial natriuretic peptide (A-type), brain natriuretic peptide (B-type or BNP), and its amino-terminal portion N-terminal pro-B-type natriuretic peptide (NT-proBNP).^{11–12} NT-proBNP is synthesised in the ventricular myocardium and released in response to ventricular wall stress.^{13–14} NT-proBNP has been demonstrated to be an important diagnostic and prognostic marker in patients with heart failure.^{15–16} The diagnostic and prognostic value of elevated levels of NT-proBNP has more recently been shown in patients with acute coronary syndromes and stable coronary artery disease.^{17–18} It has also recently been demonstrated that elevated NT-proBNP levels predict short-term adverse cardiovascular events in patients undergoing elective non-cardiac surgical procedures.¹⁹ Unfortunately, the long-term prognostic value of elevated baseline NT-proBNP levels evaluated together with clinical risk factors and dobutamine stress echocardiography results is not yet known.

The present prospective study was conducted to determine whether preoperative plasma NT-proBNP levels have significant

long-term prognostic value when evaluated with conventional cardiac risk factors and dobutamine stress echocardiography in patients undergoing elective abdominal aortic aneurysm repair or lower extremity revascularisation procedures.

METHODS

Study population

Patients scheduled for elective abdominal aortic aneurysm repair or lower extremity bypass surgery at the Erasmus University Medical Center in Rotterdam, the Netherlands, were prospectively included in the study from October 2003 to August 2005 after giving informed consent. Patients who underwent preoperative coronary artery revascularisation were excluded. Prior to surgery, baseline clinical data were collected by structured interviews with the patients and by reviewing their medical records. Based on the Revised Cardiac Risk Index by Lee *et al*,⁸ information on each of the following cardiac risk factors was obtained: history of coronary artery disease, history of congestive heart failure, history of cerebrovascular accident or transient ischaemic attack, diabetes mellitus (fasting glucose level ≥ 7.0 mmol/l or treatment with insulin) and renal dysfunction (preoperative serum creatinine level >2.0 mg/dl (177 μ mol/l) or treatment with renal dialysis). A cardiac risk score was calculated by assigning one point to each of these risk factors when present in the patient. Coronary artery disease was indicated if patients presented with current stable or unstable angina pectoris or if patients had a history of

Abbreviations: AUC, area under the curve; CK, creatine kinase; DSE, dobutamine stress echocardiography; MACE, major adverse cardiac events; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ROC, receiver operating characteristic

myocardial infarction. A preoperative electrocardiogram was obtained and evaluated. Patients were also screened for hypertension (blood pressure $\geq 140/90$ mm Hg or antihypertensive drugs), hypercholesterolaemia (plasma cholesterol level ≥ 5.5 mmol/l or treatment with cholesterol lowering drugs), smoking and use of cardiac medication, including statins, β -blockers, aspirin, angiotensin-converting enzyme inhibitors and calcium channel blocking agents.

Measurement of plasma N-terminal pro-B-type natriuretic peptide

The mean time of venous blood sampling prior to surgery was 24 (SD 12) days and all samples were collected before dobutamine stress echocardiography (DSE). The samples were centrifuged and plasma was frozen at -80°C until assay. NT-proBNP was measured with an electrochemiluminescence immunoassay kit (Elecsys 2010, Roche, Mannheim, Germany). This sandwich-type quantitative immunoassay is based on polyclonal antibodies against epitopes in the N-terminal part of proBNP. The lower detection limit was 5 ng/l. Intra-assay coefficients of variance at 271 and 6436 ng/l were 1.9% and 0.9%, respectively. Assays were performed by a laboratory technician blinded to the patient's baseline clinical data.

Dobutamine stress echocardiography

Patients underwent a resting two-dimensional precordial echocardiographic examination and standard apical and parasternal views were recorded on videotape. Dobutamine hydrochloride was then administered intravenously by infusion pump, starting at $10\text{ }\mu\text{g/kg/min}$ for 3 min ($5\text{ }\mu\text{g/kg/min}$ for 5 min, followed by $10\text{ }\mu\text{g/kg/min}$ for 5 min in patients with resting wall motion abnormalities), and increased by $10\text{ }\mu\text{g/kg/min}$ every 3 min to a maximum of $40\text{ }\mu\text{g/kg/min}$. The dobutamine infusion was stopped if a target heart rate (85% of a theoretical maximal heart rate) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischaemia, atropine sulphate (starting with 0.25 mg, increased to a maximum of 2.0 mg) was given intravenously while the administration of dobutamine was continued. Metoprolol was administered ($1.0\text{--}5.0$ mg intravenously) to reverse the side effects of the administration of dobutamine or the dobutamine-atropine combination if the side effects did not revert spontaneously and quickly. Two experienced independent investigators, blinded to the clinical data, performed off-line assessment of echocardiographic images. The left ventricle was divided into 17 segments, and wall motion was scored on a 5-point scale (1, normal; 2, mild hypokinesis; 3, severe hypokinesis; 4, akinesis; and 5, dyskinesis). Ischaemia was defined as new or worsening wall-motion abnormalities (compared with resting images of the same test) as indicated by an increase in regional wall motion score ≥ 1 grade(s) with stress. Akinesis becoming dyskinesis was not considered an ischaemic response. When there was disagreement between the two assessors, a third investigator viewed the images knowing the previous assessments, and a majority decision was reached.

Outcomes

Patients were monitored for all-cause mortality and major adverse cardiac events (MACE) (cardiac death or non-fatal myocardial infarction) during the perioperative period and during long-term follow-up after hospital discharge. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias or congestive heart failure. Non-fatal myocardial infarction was diagnosed when at least two of the following were present: 1) elevated cardiac enzyme levels (creatinine kinase (CK) level >190 U/l and CK-MB >14 U/l,

or CK-MB fraction $>10\%$ of total CK, or cardiac troponin T >0.1 ng/ml); 2) development of typical electrocardiographic changes (new Q waves >1 mm or >30 ms); and 3) typical symptoms of angina pectoris. All patients had at least 6 months of follow-up.

Statistical analysis

Normally distributed, continuous data were expressed as mean (SD) and compared using Student's *t* test. Non-normally distributed continuous data were expressed as median (25th and 75th percentile) and compared using the Mann Whitney U test. Categorical data were presented as per cent frequencies and differences between proportions were compared using the χ^2 test with Yates' correction. In an initial analysis, we included patients who had perioperative and long-term events and in a sub-analysis, we have excluded the patients who had perioperative events. To compare the predictive value of NT-proBNP, cardiac risk score and DSE results for 6-month outcome, receiver operating characteristic (ROC) curve analysis was performed and the area under the curve was calculated. The 6-month outcome was used since all patients had a complete follow-up status at this time. The optimal cut-off value of NT-proBNP for mortality and MACE at 6 months was determined and was defined as the NT-proBNP value providing the maximal sum of sensitivity and specificity. Age, cardiac risk score, DSE results, NT-proBNP values (dichotomised according to the optimal cut-off value for 6-month outcome) and cardioprotective medication (statins, β -blockers, aspirin, angiotensin-converting enzyme inhibitors, calcium-channel blockers) were then entered in a multivariable Cox hazard regression model to identify independent predictors of long-term mortality and MACE. Hazard ratios are given with 95% confidence intervals (CI). For all tests, a *p* value less than 0.05 (two-sided) was considered significant. All analysis was performed using SPSS 11.0 statistical software (SPSS, Chicago, Illinois, USA).

RESULTS

Baseline characteristics

The study population consisted of 335 patients (76.4% male) with a mean age of 62.2 (SD 12.4) years. Abdominal aortic aneurysm repair was performed in 155 patients (46.3%) and lower extremity revascularisation in 180 patients (53.7%). The NT-proBNP level ranged from 4 to 8257 ng/l, with a mean of 473 (SD 881) ng/l, a median of 186 ng/l, and 25th and 75th percentile values of 65 and 444 ng/l, respectively. Baseline clinical characteristics of the patients, divided according to an NT-proBNP level of 319 ng/l (optimal cut-off value to predict 6-month mortality), are presented in table 1. Patients with NT-proBNP levels above 319 ng/l were more likely to be older and to present with coronary artery disease, history of heart failure, diabetes, renal dysfunction, hypertension, Q-waves and ST segment changes on electrocardiography than patients with NT-proBNP levels below 319 ng/l. These patients were also more likely to be treated with angiotensin-converting enzyme inhibitors, β -blockers and digoxin.

DSE results

The mean maximal dobutamine dose used during stress echocardiography was 35.3 (SD 8) $\mu\text{g/kg/min}$. Atropine was used in 134 patients (40%). Stress induced myocardial ischaemia occurred in 67 patients (20%) and the mean number of ischaemic segments in patients with stress induced myocardial ischaemia was 3.3 (SD 1.6). No fatal complications occurred during or immediately after the stress test. The median NT-proBNP level was significantly higher in patients with a positive test (479 ng/l, IQ range: 172–1523 ng/l)

Table 1 Baseline clinical characteristics according to the median of N-terminal pro-B-type natriuretic peptide

Characteristic		NT-proBNP (ng/l)		p Value
		<319 ng/l (n = 216)	≥319 ng/l (n = 119)	
Age (years), mean (SD)	62.2 (12.4)	59.2 (12.1)	67.3 (11.2)	<0.001
Male gender, n (%)	256 (76.4)	158 (73.1)	98 (82.4)	0.058
Medical history				
Current stable or unstable angina pectoris, n (%)	85 (25.4)	34 (15.7)	51 (42.9)	<0.001
Previous myocardial infarction, n (%)	135 (40.3)	58 (26.9)	77 (64.7)	<0.001
Coronary artery disease (summary variable), n (%)	165 (49.3)	74 (34.3)	91 (76.5)	<0.001
History of congestive heart failure, n (%)	57 (17.0)	22 (10.2)	35 (29.4)	<0.001
Previous cerebrovascular event, n (%)	56 (16.7)	30 (13.9)	26 (21.8)	0.06
Diabetes mellitus, n (%)	68 (20.3)	28 (13.0)	40 (33.6)	<0.001
Renal dysfunction, n (%)	20 (6.0)	2 (0.9)	18 (15.1)	<0.001
Hypertension, n (%)	117 (34.9)	62 (28.7)	55 (46.2)	0.001
Hypercholesterolaemia, n (%)	131 (39.1)	85 (39.4)	46 (38.7)	0.90
Current smoking, n (%)	109 (32.5)	71 (32.9)	38 (31.9)	0.86
Cardiac risk score, mean (SD)	1.0 (0.9)	0.7 (0.9)	1.7 (1.3)	<0.001
Electrocardiography				
Q waves, n (%)	91 (27.2)	41 (19.0)	50 (42.0)	<0.001
ST-segment changes, n (%)	35 (10.4)	14 (6.5)	21 (17.6)	0.001
Medication				
Aspirin, n (%)	140 (41.8)	82 (38.0)	58 (48.7)	0.056
Angiotensin converting enzyme inhibitor, n (%)	113 (33.7)	58 (26.9)	55 (46.2)	<0.001
β-Blocker, n (%)	236 (70.4)	143 (66.2)	93 (78.2)	0.022
Calcium channel blocker, n (%)	60 (17.9)	33 (15.3)	27 (22.7)	0.090
Digoxin, n (%)	19 (5.7)	4 (1.9)	15 (12.6)	<0.001
Statin, n (%)	180 (53.7)	113 (52.3)	67 (56.3)	0.48
Abdominal aortic aneurysm repair, n (%)	155 (46.3)	108 (50.0)	47 (39.5)	0.07
Lower extremity revascularisation, n (%)	180 (53.7)	108 (50.0)	72 (60.5)	0.07

Values are expressed in number (%) or mean (SD).

compared with those with a negative stress test (134 ng/l, IQ range: 52–334 ng/l) ($p < 0.001$).

Outcome and ROC curve analysis

During a mean follow-up of 14 (SD 6) months, all-cause mortality occurred in 49 patients (15%) and MACE in 50 patients (15%) (cardiac death in 31 patients and non-fatal myocardial infarction in 19 patients). Perioperative events included all-cause mortality in 16 patients, cardiac death in 7 patients and non-fatal myocardial infarction in 13 patients. In the 305 patients who were successfully discharged from hospital, all-cause mortality occurred in 33 patients (11%) and MACE in 30 (10%) (cardiac death in 24 patients and non-fatal myocardial infarction in 6 patients). NT-proBNP had a greater area under the ROC curve (AUC) for the endpoint 6-month mortality (AUC = 0.73) compared with the cardiac risk score (AUC = 0.64) and DSE (AUC = 0.67) (fig 1A). Also for MACE, the area under the curve was greater for NT-proBNP (AUC = 0.83) compared with cardiac risk score (AUC = 0.66) and DSE (AUC = 0.67) (fig 1B). An NT-proBNP level of 319 ng/l was identified as the optimal cut-off value to predict both mortality and cardiac events at 6-month follow-up. Using this cut-off value, the sensitivity and specificity for 6-month mortality were 69% and 70%, respectively. Sensitivity and specificity for 6-month MACE were 88% and 71%, respectively.

In a sub-analysis of patients who were successfully discharged from hospital, results were comparable to the total study population. NT-proBNP had a greater area under the ROC curve for 6-month mortality (AUC = 0.72) compared with the cardiac risk score (AUC = 0.64) and DSE (AUC = 0.66). Also for MACE, the area under the curve was greater for NT-proBNP (AUC = 0.81) compared with cardiac risk score (AUC = 0.65) and DSE (AUC = 0.66). An NT-proBNP level of 315 ng/l was the optimal cut-off value to predict both 6-month mortality and MACE. Using this cut-off value, the sensitivity and specificity for 6-month mortality were 69% and 70%, respectively.

Sensitivity and specificity for 6-month MACE were 83% and 70%, respectively.

Prognostic value of NT-proBNP

Kaplan-Meier survival curves demonstrate that patients with an NT-proBNP level ≥ 319 ng/l had lower survival and more MACE compared with patients with NT-proBNP levels < 319 ng/l (fig 2). Independent predictors of all-cause mortality and MACE were identified by Cox hazard regression analysis, which demonstrated that NT-proBNP was the strongest predictor for all-cause mortality and MACE (fig 3). The adjusted hazard ratio for all-cause mortality in patients with baseline NT-proBNP levels ≥ 319 ng/l was 4.0 (95% CI: 1.8 to 8.9; $p < 0.001$). The adjusted hazard ratio for MACE in patients with baseline NT-proBNP levels ≥ 319 ng/ml was 10.9 (95% CI: 4.1 to 27.9; $p < 0.001$). Notably, β -blockers and statin therapy were significantly associated with an improved long-term outcome (fig 3).

In a subgroup analysis of patients who were successfully discharged from hospital, the adjusted hazard ratio for all-cause mortality in patients with baseline NT-proBNP levels ≥ 315 ng/l was 3.4 (95% CI: 1.3 to 8.9; $p = 0.009$). The adjusted hazard ratio for MACE in patients with baseline NT-proBNP levels ≥ 315 ng/ml was 8.7 (95% CI: 2.6 to 27.6; $p < 0.001$).

DISCUSSION

This study demonstrates that a single measurement of NT-proBNP, obtained prior to surgery, provides powerful information for use in risk stratification in patients undergoing abdominal aortic aneurysm repair or lower extremity bypass surgery. Patients with higher NT-proBNP levels were more likely to be older and to present with coronary artery disease, history of heart failure, diabetes, renal dysfunction, hypertension and Q-waves and ST segment changes on electrocardiography compared with those with lower NT-proBNP levels. This finding suggests that high baseline NT-proBNP levels due to

Figure 1 Receiver operating characteristic curves of plasma N-terminal pro-B-type natriuretic peptide against 6-month mortality (A) and major adverse cardiac events (B) in 335 patients who underwent major vascular surgery.

activation of the cardiac neurohormonal system may be a unifying feature in patients at high risk for late mortality or major adverse cardiac events.

NT-proBNP as a prognostic marker in non-surgical patients

NT-proBNP is the physiologically inactive 1–76 amino acid fragment that is secreted along with the 32 amino acid brain natriuretic peptide after cleavage from the pro-hormone pro-BNP.^{11–14} Considering its longer half life and superior in vitro stability, NT-proBNP may be a better target for assay than BNP.^{11–14} The long-term prognostic value of NT-proBNP has been evaluated in non-surgical patients with congestive heart failure, demonstrating that higher levels of NT-proBNP were associated with adverse outcome.^{20–21} In our study cohort, only 17% of the patients presented with a history of congestive heart failure; however, a history of coronary artery disease was much more frequently observed (49%). Recent studies have shown the prognostic value of NT-proBNP in non-surgical patients

with acute and stable coronary artery disease. In a sub-study of the Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV trial with 6809 patients with non-ST-segment elevation acute coronary syndromes, NT-proBNP was the strongest predictor of death at 1 year, among other biochemical and clinical markers.²² The prognostic value of NT-proBNP was also proved in a group of patients presenting with a full range of severities of acute coronary syndromes (from unstable angina pectoris, through non-ST segment elevation myocardial infarction, to ST-segment elevation myocardial infarction).²³ In 755 patients with symptoms suggestive of an acute coronary syndrome and no ST-segment elevation, Jernberg and colleagues demonstrated that NT-proBNP levels were independently associated with long-term prognosis.²⁴ Finally, NT-proBNP has been proven to provide long-term prognostic information above and beyond that provided by conventional cardiac risk factors and the degree of left ventricular systolic dysfunction in 1034 patients referred for angiography because of symptoms or signs of coronary heart disease.¹⁸

Patients at risk:

NT-proBNP < 319 ng/l	216	205	190	165	140	84	54
NT-proBNP ≥ 319 ng/l	119	93	82	76	58	30	24

Patients at risk:

NT-proBNP < 319 ng/l	216	204	189	163	138	82	51
NT-proBNP ≥ 319 ng/l	119	90	80	74	53	25	20

Figure 2 Kaplan-Meier curves showing the cumulative incidence of death (A) and major adverse cardiac events (B) during follow-up, according to N-terminal pro-B-type natriuretic peptide level. MACE, major adverse cardiac events.

Figure 3 Multivariate Cox regression model showing independent predictors of all-cause mortality (A) and major adverse cardiac events (B). DSE, dobutamine stress echocardiography.

NT-proBNP as a promising prognostic marker in major vascular surgery

The substantial postoperative mortality rate in patients undergoing major vascular surgery has led researchers and physicians to search for strategies that identify high risk patients.^{2–5} In the investigated study cohort, more than one out of 10 patients died from all causes after surgery during a mean follow-up of 14 months. The Revised Cardiac Risk Index is considered the best available cardiac risk index in non-cardiac surgery.⁸ This index uses the patient's history to predict major cardiac complications during the perioperative period. Stress induced myocardial ischaemia during DSE has also been shown to be a strong predictor of early and late cardiac events.¹⁰ The American College of Cardiology/American Heart Association guidelines for perioperative cardiovascular evaluation for non-cardiac surgery recommend preoperative clinical evaluation to identify high risk patients and recommend further cardiac stress testing in selected patients.¹

Few data are available on whether NT-proBNP levels provide additional prognostic information in vascular surgery patients. A recently published study including 190 patients undergoing elective non-cardiac surgery demonstrated that an NT-proBNP level >450 ng/l was predictive of perioperative cardiac complications.¹⁹ Although there is no consensus of what normal NT-proBNP values are, we have identified 319 ng/l as an optimal cut-off value to predict 6-month mortality and MACE, using ROC curve analysis. Our study extends currently available information about the value of NT-proBNP as a risk marker and suggests that NT-proBNP may be a superior long-term prognostic marker compared with conventional cardiac risk scores and DSE. It should be noted that the Revised Cardiac Risk Index has been used in the current study as the scoring system for long-term outcome, although this index has only been validated in the perioperative setting. Measurement of plasma NT-proBNP concentration is an objective, convenient and inexpensive test. For the purpose of optimal risk stratification and for targeting treatment strategies, our results suggest that NT-proBNP measurement should be incorporated into the management of major vascular surgery patients. However, more studies should be conducted to evaluate the cost-effectiveness of NT-proBNP measurement, to determine a subset of patients who may benefit most from NT-proBNP measurement and to assess whether incorporation of NT-proBNP measurement may improve preventive strategies for postoperative complications.

Perioperative management of patients at risk

Although the current study has shown the NT-proBNP levels have an additional value in defining risk, the management of patients at risk remains a challenge. In patients presenting with multiple cardiac risk factors with no or limited stress induced myocardial ischaemia, β -blockers and statins have been associated with a reduced rate of perioperative and long-term mortality after major non-cardiac surgery.^{3–25} A small number of patients may present with extensive myocardial ischaemia. The optimal treatment of these patients has not yet been defined, although retrospective studies suggested previous revascularisation confers a benefit.²⁶ In the randomised Coronary Artery Revascularization Prophylaxis trial, however, no benefit following prophylactic revascularisation was observed.²⁷ The optimal treatment strategy in patients with high NT-proBNP levels has still to be determined in future studies.

CONCLUSION

Patients undergoing major vascular surgery are at increased risk of late cardiac morbidity and mortality. The present study demonstrates that an elevated preoperative plasma NT-proBNP level is associated with an increased risk of late all-cause mortality and MACE after successful major vascular surgery, independent of cardiac risk factors and DSE results. Using ROC curve analysis, a level of 319 ng/ml of NT-proBNP was identified as the optimal cut-off value to predict 6-month mortality and MACE. NT-proBNP levels above these cut-off values may be a promising marker of long-term prognosis and can be incorporated into preoperative risk stratification.

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