Preoperative NT-proBNP independently predicts outcome in patients with acute coronary syndrome undergoing CABG*

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Abstract

Objectives. The predictive value of preoperative N-terminal pro-B-type natriuretic peptide (NT-proBNP) was evaluated in patients with acute coronary syndrome undergoing coronary artery bypass grafting (CABG). Design. As a substudy to a clinical trial 383 patients with acute coronary syndrome undergoing CABG were studied. 17 patients had a concomitant procedure. NT-proBNP was measured immediately preoperatively and evaluated with regard to in-hospital mortality, and severe circulatory failure postoperatively according to prespecified criteria. Follow-up was 3.2 ± 0.9 years. Results. In patients with isolated CABG, receiver operating characteristics (ROC) analysis showed an area under the curve (AUC) of 0.82 for in-hospital mortality and 0.87 for severe circulatory failure respectively with a best cut-off for preoperative NT-proBNP of 1028 ng/L. This cut-off level independently predicted severe circulatory failure. Patients with NT-proBNP >1028 ng/L had significantly better long-term survival (p = 0.004). Preoperative NT-proBNP was higher in patients with concomitant procedure than isolated CABG (2146 ± 1858 v 887 ± 1635 ng/L; p = 0.0005). In patients with concomitant procedure ROC analysis showed an AUC of 0.93 for severe circulatory failure with a best cut-off for preoperative NT-proBNP of 3145 ng/L. Conclusions. Preoperative NT-proBNP predicted in-hospital mortality, severe circulatory failure postoperatively and long-term survival in patients undergoing surgery for acute coronary syndrome but a higher threshold was found in patients having concomitant procedures.

Key words: acute coronary syndrome, coronary artery bypass grafting, natriuretic peptides

Introduction

In cardiac surgery preoperative evaluation of each patient individually is vital for optimal treatment and planning of surgery as well as estimating postoperative resources, and therapeutic strategies regarding intensive care treatment and possible complications (1).

Several preoperative risk-scoring systems are available to help evaluate preoperative risk (2,3). However, every scoring system has limitations and identification of biomarkers that can contribute to risk stratification is desirable.

In cardiac dysfunction, natriuretic peptides will be secreted into the plasma as a response primarily due to myocyte stretch and increased wall tension, but also by ischemia per se (4). In patients with chronic heart failure, B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) have shown to be increased in patients with poor prognosis (5). On the other hand, a recent study suggests that elevated levels of NT-proBNP are independently associated with improved myocardial performance after revascularization for non-ST-elevation acute coronary syndrome (6). Studies available on BNP and NT-proBNP in cardiac surgery show a predictive value with regard to postoperative morbidity and mortality (7–11).

However, there is no consensus on cut-off levels for preoperative natriuretic peptides that indicate increased risk in cardiac surgery, especially for different preoperative heart conditions and surgical

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procedures. Furthermore, recent studies and review articles have highlighted the importance of further investigations evaluating the independent predictive value of natriuretic peptides, also based on the type of cardiac surgery (11,12).

Our aim was to evaluate the short- and long-term predictive value of preoperative NT-proBNP prospectively in patients with acute coronary syndrome (ACS) undergoing CABG with or without concomitant procedure.

Methods

Patients

Between May 2007 and November 2009, we prospectively included 383 patients as a prespecified sub-study of the The GLUTAMICS-trial (ClinicalTrials.gov Identifier: NCT00489827) (13). For details regarding the GLUTAMICS-trial see Supplementary Appendix. The Supplementary Appendix is only available in the online version of the journal. Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/14017431.2012.731518.

Patients were operated at three Swedish Cardiac Surgery Centers (Linköping, Örebro, and Karlskrona). Inclusion criteria were patients operated with CABG for ACS. Patients were eligible for inclusion regardless, if the procedure was done on-pump (n = 371) or off-pump (n = 12). 17 patients had a concomitant procedure (mitral valve surgery n = 8, aortic valve surgery n = 7, and ablation for atrial fibrillation n = 2). Exclusion criteria were informed consent not possible because of critical condition or other reason, preoperative use of inotropes or mechanical circulatory assist, preoperative dialysis, redo-procedure, unexpected intraoperative finding event that increased the magnitude of the procedure to overshadow the originally planned operation, aged > 85 years, body weight > 125 kg.

Study design

A prospective longitudinal sub-study evaluating the predictive value of preoperative NT-proBNP in patients undergoing surgery for ACS. By using receiver-operating characteristics (ROC) analysis we wanted to identify the cut-off level of preoperative NT-proBNP with regard to in-hospital mortality and circulatory failure postoperatively. Data on late mortality were retrieved from the Swedish Civil Registry. Sampling for NT-proBNP was done in the operating room immediately before induction of anesthesia and plasma levels were analyzed using electro-chemoiluminescence immunoassay on a Roche Elecsys 2010 automated platform (Roche Diagnostics, Basel, Switzerland).

Clinical endpoints committee

Due to the lack of generally accepted criteria for postoperative heart failure in association with cardiac surgery a blinded clinical endpoints committee relying on prespecified criteria was considered necessary. All cases with suspected postoperative heart failure based on SvO₂ and other hemodynamic data, use of inotropic drugs or mechanical circulatory support, extended ICU stay, circulatory problems reported by anesthesiologists or surgeons in the clinical database were reviewed. The endpoints committee was blinded to the results of NT-proBNP analyses, which were kept in safe custody at the laboratory unavailable to the investigators until the trial was terminated.

Definitions

In-hospital mortality was defined as mortality during the first hospitalization period including stay at the referral hospital after discharge from the cardiac surgical unit.

Prespecified criteria and data definition available in the Supplementary Appendix were used by a blinded endpoints committee to determine if heart failure was present. Severe circulatory failure was defined as circulatory failure leading to death or requiring ICU stay ≥ 48 hours with intraaortic balloon pump for ≥ 24 hours or inotropic agents in dosages according to Supplementary Appendix for ≥ 24 hours. The Supplementary Appendix is only available in the online version of the journal. Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/14017431.2012.731518.

Clinical management

Clinical management was standardized and similar at the three participating centers with minor differences concerning choice of anesthetic drugs. Standard surgical techniques were employed. 12 patients were operated off-pump without aortic cross-clamping. In the other patients standard use of cardiopulmonary bypass and aortic cross-clamping was employed. Crystalloid or blood cardioplegia was used for myocardial protection. Intraoperatively a surgical pulmonary artery catheter was introduced in all patients for measurement of mixed venous oxygen saturation and pressure (14,15). For details on clinical management see Supplementary Appendix. The Supplementary Appendix is only available in the online version of the journal.
Ethics

After written informed consent the patients were enrolled in the study. The study was performed according to the Helsinki Declaration of Human Rights and was approved by the Swedish Medical Products Agency (151:2003/70403) and the Regional Ethical Review Board in Linköping (M76-05).

Statistics

ROC analysis was carried out to calculate the area under the curve (AUC) and to evaluate prognostic performance of NT-proBNP with regard to in-hospital mortality and severe circulatory failure postoperatively. Equal weight to specificity and sensitivity was given for calculation of best cut-off point by choosing the point on the ROC-curve closest to 100% sensitivity and 100% specificity. Fisher’s exact test or chi-square test was used when appropriate for comparison of dichotomous variables. Students t-test or Mann-Whitney U test was used when appropriate for comparison of continuous variables. Multivariable analysis of independent predictors for severe circulatory failure postoperatively taking the intervention into account (to adjust for a possible treatment effect) was done with forward stepwise multiple logistic regression. Hosmer–Lemeshow goodness-of-fit statistics was calculated for the final model. The Kaplan–Meier estimator and Log-rank test were used for assessment of long-term survival. Results are given as percentages or mean ± standard deviation. Statistical significance was defined as \( p < 0.05 \). Statistical analyses were performed with Statistica 10.0, StatSoft Inc., Tulsa, OK, and SPSS 17.0 (SPSS Inc.).

Results

The mean age of the whole study population (n = 383) was 68 ± 9 years and 20% were females. Additive EuroSCORE was 5.2 ± 2.7. 30-day mortality was 1.0%. In-hospital mortality was 1.3%. Left ventricular failure at weaning from cardiopulmonary bypass was found in 5.7% and 2.6% developed severe circulatory failure. The mean value of preoperative NT-proBNP was 943 ± 1664 ng/l (range 10–15900 ng/l) with a median value of 440 ng/L.

Mean preoperative NT-proBNP was significantly higher in patients with concomitant procedure than in those having isolated CABG (2146 ± 1858 v 887 ± 1635 ng/L; \( p = 0.0005 \)).
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in the operating room (37.8% v 12.1%, p < 0.0001) and left ventricular failure at weaning from CPB was more common (12.1% v 2.8%, p = 0.002) (Table III).

Postoperatively the patients with NT-proBNP values ≥ 1028 ng/l had significantly higher incidence of severe circulatory failure (7.2% v 0.4%; p < 0.001) and in-hospital mortality (4.8% v 0.4%; p = 0.01). Patients with NT-proBNP values ≥ 1028 ng/l also had a higher incidence of stroke, renal dysfunction, prolonged ICU stay and ventilator treatment (Table IV).

Multivariable analysis taking the glutamate intervention into account identified preoperative NT-proBNP ≥ 1028 ng/l as the only independent predictor of severe circulatory failure postoperatively (OR 24.9; 95% confidence interval 2.9–214; p = 0.004). The final model adjusted for additive EuroSCORE and the intervention is presented in Table V.

CABG with associated procedure

ROC-analysis. In patients with concomitant procedure ROC analysis showed an AUC of 0.93 for severe circulatory failure postoperatively with a best cut-off value for preoperative NT-proBNP of 3145 ng/l (Table I, Figure 3).

Eight patients underwent concomitant mitral valve surgery and 5 of them had NT-proBNP value ≥ 3145 ng/l. Seven patients underwent concomitant aortic valve replacement and 2 patients had concomitant ablation for atrial fibrillation and none of them had NT-proBNP value ≥ 3145 ng/l.

All of the 5 patients with NT-proBNP value ≥ 3145 ng/l received inotropic drugs intraoperatively and a significantly higher proportion (3/5 v 0/12; p < 0.05) developed severe circulatory failure. Average ICU stay was markedly prolonged (4.3 ± 1.8 days v

### Table I. ROC-analysis with AUC, sensitivity and specificity for isolated CABG and CABG with concomitant procedure. Evaluation based on optimal cut-off value in relation to preoperative NT-proBNP and postoperative mortality/morbidity.

| Characteristics                  | Isolated CABG – severe circulatory failure postoperatively | Isolated CABG – In-hospital mortality | Concomitant procedure – severe circulatory failure postoperatively |
|----------------------------------|----------------------------------------------------------|--------------------------------------|---------------------------------------------------------------|
| AUC                              | 0.87                                                     | 0.82                                 | 0.93                                                          |
| 95% CI                           | 0.79–0.96                                                | 0.73–0.91                            | 0.80–1.0                                                     |
| p-value                          | 0.001                                                   | 0.01                                 | 0.02                                                         |
| NT-proBNP cut-off                | 1028 ng/l                                                | 1028 ng/l                            | 3145 ng/l                                                    |
| Sensitivity                      | 0.86                                                     | 0.80                                 | 1.0                                                          |
| Specificity                      | 0.79                                                     | 0.78                                 | 0.86                                                         |

AUC = area under curve; CI = confidence interval.

### Table II. Preoperative characteristics in patients with NT-proBNP < 1028 ng/L and ≥ 1028 ng/L. Isolated CABG.

| Characteristics                  | NT-proBNP < 1028 ng/L n = 283 | NT-proBNP ≥ 1028 ng/L n = 83 | p-value         |
|----------------------------------|-------------------------------|-----------------------------|----------------|
| Age (years)                      | 67 ± 9                        | 72 ± 8                      | <0.0001        |
| Female gender                    | 17.0%                         | 28.9%                       | 0.019          |
| BMI (kg/m²)                      | 27.5 ± 4.5                    | 26.1 ± 4.1                  | 0.012          |
| p-Creatinine (µmol/L)            | 92 ± 20                       | 106 ± 43                    | <0.0001        |
| p-Troponin T (µg/L)              | 0.086 ± 0.28                  | 0.36 ± 0.82                 | <0.0001        |
| Hb (g/l)                         | 139 ± 13                      | 127 ± 13                    | <0.0001        |
| EuroSCORE                        | 4.5 ± 2.3                     | 6.0 ± 2.8                   | <0.0001        |
| Hypertension                     | 59.6%                         | 65.1%                       | 0.37           |
| Diabetes                         | 23.0%                         | 26.5%                       | 0.56           |
| Chronic obstructive pulmonary disease | 5.7%                       | 10.8%                       | 0.14           |
| Cerebrovascular disease          | 8.8%                          | 8.5%                        | 1.0            |
| CCS class IV                    | 59.7%                         | 61.4%                       | 0.80           |
| 3 vessel disease                 | 71.4%                         | 92.8%                       | <0.0001        |
| Left main stenosis               | 32.9%                         | 42.2%                       | 0.15           |
| Recent Myocardial infarction (<3 weeks) | 61.8%                     | 77.1%                       | 0.012          |
| Severe LV dysfunction            | 1.4%                          | 12.1%                       | 0.0001         |
| Preoperative iv nitroglycerine   | 5.7%                          | 10.8%                       | 0.13           |
None of the 17 patients having a concomitant procedure died within 30 days or in-hospital.

**Long-term follow-up.** Follow-up time was $3.2 \pm 0.9$ years. Kaplan–Meier curve for isolated CABG showed significantly better long-term survival for patients with NT-proBNP $< 1028$ ng/L ($p = 0.004$) (Figure 4). Also after excluding in-hospital and 30 day mortality Kaplan–Meier curve still showed significantly better survival in patients with NT-proBNP $< 1028$ ng/L ($p = 0.046$). During follow-up time, no deaths were reported in the small group with concomitant procedure.

**Discussion**

The main finding of this study was that preoperative NT-proBNP predicted severe circulatory failure, in-hospital death and long-term survival in patients undergoing surgery for ACS. In patients undergoing isolated CABG multivariable analysis identified the cut-off level of 1028 ng/L suggested by ROC analysis to be independently predictive of severe circulatory failure postoperatively even after adjustment for EuroSCORE. A markedly higher threshold level of preoperative NT-proBNP predicting severe circulatory failure postoperatively was found in patients with ACS having concomitant procedures compared to those having isolated CABG.

In cardiac surgery preoperative evaluation and risk stratification is essential in order to accurately prepare and tailor optimal timing and strategy for the surgical procedure (1). Adequate preoperative evaluation may also contribute to improved medical resource utilization. With this background it is important to constantly evaluate and develop preoperative scoring systems and identify parameters that can give guidance in expectations concerning each individual patient.

Table IV. Postoperative characteristics in patients with NT-proBNP $< 1028$ ng/L and $\geq 1028$ ng/L.

| Characteristics                       | NT-proBNP $< 1028$ ng/L | NT-proBNP $\geq 1028$ ng/L | p-value |
|---------------------------------------|-------------------------|----------------------------|---------|
| CKMB day 1 (µg/L)                     | 21.0 ± 22.2             | 20.0 ± 16.3                | 0.27    |
| p-Troponin T day 3–4 (µg/L)           | 0.34 ± 0.34             | 0.62 ± 0.82                | 0.0007  |
| NT-proBNP day 1 (ng/L)                | 2086 ± 1283             | 6286 ± 4701                | $< 0.0001$ |
| NT-proBNP day 3 (ng/L)                | 3771 ± 3133             | 9159 ± 7247                | $< 0.0001$ |
| SvO2 arrival in ICU (%)               | 65.4 ± 6.6              | 63.1 ± 7.9                 | 0.0089  |
| Perioperative myocardial infarction    | 0.4% (1/183)            | 2.4% (2/83)                | 0.13    |
| Perioperative stroke CT-verified       | 0.4% (1/183)            | 4.8% (4/83)                | 0.01    |
| Confusion                              | 4.2% (12/283)           | 8.4% (7/83)                | 0.16    |
| Increase of p-Creatinine by $> 50\%$  | 3.9% (11/283)           | 15.7% (13/83)              | 0.0005  |
| Dialysis (new onset)                  | 0%                      | 11.0% (9/83)               | 0.23    |
| Time in ICU (hours)                   | 24.3 ± 30.8             | 50.0 ± 91.8                | 0.0004  |
| ICU stay $> 48$ hours                  | 5.0% (14/283)           | 18.1%                      | 0.0003  |
| Severe circulatory failure            | 0.4% (1/283)            | 7.2% (6/83)                | 0.0007  |
| 30 day mortality                      | 0.7% (2/283)            | 2.4% (2/83)                | 0.22    |
| In-hospital mortality                 | 0.4% (1/283)            | 4.8% (4/83)                | 0.01    |
The prognostic value of BNP and NT-proBNP has been well documented in cardiology among patients with heart failure and ischemic heart disease (5). Also in cardiac surgery increasing data on prognostic value of both pre- and postoperative BNP and NT-proBNP are gathering (7–11). In agreement with other cardiac surgical studies natriuretic peptides measured preoperatively were independently predictive of postoperative outcome even when adjusted for EuroSCORE (7,16–18). However, there is no consensus on specific preoperative risk levels for natriuretic peptides and how to relate these values with regard to preoperative patient status and type of cardiac procedure.

To our knowledge this study is the first prospective study with prespecified criteria for postoperative severe circulatory failure to show different cut-off levels for BNP in different cardiac procedures. In this study, we have been able to compare isolated CABG with combined procedures. Although the group with concomitant surgery is small it is apparent that this subgroup had markedly higher level of preoperative NT-proBNP than patients with isolated CABG. Also it appears that the group with combined procedures had a markedly higher threshold level of preoperative NT-proBNP for being at risk of developing severe circulatory failure postoperatively. One explanation for this could be that the surgery itself addresses the driving factor for BNP production, for example a valve procedure might give momentary relief of the factor that sustain the relatively high preoperative level of BNP and NT-proBNP. In contrast, the revascularization by CABG might not momentarily affect the “myocardial factor” that promotes BNP production in patients with coronary artery disease. The importance of evaluating the level of preoperative natriuretic petide in relation to different type of cardiac surgery has been stated before (12).

Analysis with Kaplan–Meier curve for isolated CABG showed significantly better long-term survival for patients with lower values of preoperative NT-proBNP. This was also true for survival after discharge and beyond 30 days postoperatively. This finding is also in-line with previous studies (16). We studied the metabolic fragment NT-proBNP instead of the active substance BNP. The reason for this was that NT-proBNP is analyzed by a standardized method making it suitable for a multicenter study. Also, this should make the results obtained more generally applicable compared to analyses of BNP for which there are several different methods available (19).

This study has limitations. The group with concomitant surgery was small and heterogeneous and the results have to be interpreted cautiously. However, the markedly higher preoperative NT-proBNP level in this group compared with isolated CABG patients is apparent and should be hypothesis generating for future studies which should include larger cohorts and more precisely differentiate between various cardiac surgical procedures.

The study involved an intervention, which influenced the number of events with regard to severe circulatory failure postoperatively described in the Supplementary Appendix. This did not influence the cut-off for the whole cohort. In the interest of statistical power, we therefore chose to include the intervention group (data in Supplementary Appendix). To adjust for a possible treatment effect the multivariable analysis was adjusted for the intervention. The criteria used for heart failure at weaning from bypass and severe circulatory failure postoperatively are inevitably debatable given the lack of generally accepted criteria for this condition. Our aim was to provide the blinded clinical endpoints committee with strict pre-specified criteria based on easily available variables to minimize bias from individual clinical judgement. The endpoint severe circulatory failure was chosen to discriminate mild short-lasting heart failure at weaning from cardiopulmonary bypass from clinically significant heart failure requiring substantial circulatory

Table V. Multivariable analysis of risk factors for severe circulatory failure in patients with undergoing isolated CABG adjusted for the intervention and additive EuroSCORE.

| Variables                        | Adjusted OR | CI (95%) | p-value |
|----------------------------------|-------------|----------|---------|
| Preoperative NT-proBNP ≥ 1028 ng/L | 10.7        | 1.3–112  | 0.047   |
| EuroSCORE*                       | 1.3         | 1.0–1.7  | 0.05    |
| Intravenous glutamate infusion   | 0.2         | 0.2–1.4  | 0.10    |

Hosmer–Lemeshow goodness-of-fit test-$\chi^2$ (df 8) = 4.0, $p = 0.86$. CI = confidence interval; OR = odds ratio; *per unit change.

Figure 3. **CABG + associated procedure**: Preoperative NT-proBNP vs severe circulatory failure postoperatively. Best cut-off: 3145 ng/L. Sensitivity 1.0, Specificity 0.86.
support and leading to prolonged ICU stay or death. The Supplementary Appendix is only available in the online version of the journal. Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/14017431.2012.731518.

To conclude preoperative NT-proBNP ≥ 1028 ng/L is a strong predictor for severe circulatory failure postoperatively, in-hospital mortality and long-term survival in patients undergoing isolated CAbG for ACS. However, a markedly higher threshold was found in patients having concomitant procedures suggesting that risk stratification based on preoperative NT-proBNP has to be made with regard to type of cardiac disease and surgical procedure. Further studies are warranted to address these issues.

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Figure 4. Cumulative long-term survival according to Kaplan–Meier related to NT-proBNP level preoperatively in patients undergoing isolated CABG for acute coronary syndrome.

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Supplementary material available online

The Supplementary Appendix.