

# Pre-Operative N-Terminal Pro-Brain Natriuretic Peptide Predicts Outcome in Type A Aortic Dissection

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<b>Background</b>	Acute Stanford type A aortic dissection (AAD) is associated with substantial perioperative mortality and morbidity.
<b>Objective</b>	N-terminal pro-brain natriuretic peptide (NT-proBNP) is a prognostic biomarker of outcome in cardiovascular disease. Its predictive power in patients undergoing emergency surgery for acute type A aortic dissection is yet unknown.
<b>Methods</b>	We prospectively measured pre-operative NT-proBNP in 104 patients (39 female, 35%; median age 61 years) undergoing emergency surgery for AAD during a 6-year study period. European System for Cardiac Operative Risk Evaluation risk scores were recorded and patients were followed for 30-day mortality and major adverse events (MAEs) as defined by the need for rethoracotomy, occurrence of postoperative heart failure, neurologic deficit, lung failure, renal failure, or sepsis.
<b>Results</b>	Median logistic European System for Cardiac Operative Risk Evaluation in the cohort was 12 (interquartile range 7 to 19). During the first 30 days, 23 patients (22%) died, and 53 patients (51%) experienced MAEs. Median (interquartile range) NT-proBNP levels in survivors versus nonsurvivors were 328 pg/ml (157 to 569) versus 2,240 pg/ml (515 to 4,734; $p < 0.001$ ), and in patients without versus with MAEs, 227 pg/ml (107 to 328) and 719 pg/ml (442 to 2,287; $p < 0.001$ ), respectively. Adjusted odds ratios for increasing tertiles of NT-proBNP compared with the lowest tertile were 0.98 (95% confidence interval [CI] 0.18 to 5.33; $p = 0.98$ ) and 11.67 (95% CI 2.61 to 52.09; $p = 0.001$ ) for 30-day mortality and 9.07 (95% CI 2.58 to 31.83; $p = 0.001$ ) and 50.21 (95% CI 10.85 to 232.45; $p < 0.001$ ) for MAEs, respectively, indicating a significant association between pre-operative NT-proBNP levels and outcome.
<b>Conclusions</b>	Pre-operative NT-proBNP predicts outcome in patients undergoing surgery of AAD. (J Am Coll Cardiol 2008;51:1092–7) © 2008 by the American College of Cardiology Foundation

Emergency surgery of patients with acute Stanford type A aortic dissection is associated with high morbidity and mortality rates (1–3). Although substantial advances in surgical techniques such as selective cerebral perfusion and deep hypothermic circulatory arrest have helped to improve early and long-term outcome, in-hospital mortality rates remain excessively high (1–3).

A variety of multifactorial risk indexes have been described to help delineate pre-operative risk assessment of patients undergoing cardiac surgery (4–6) and, particularly, the European System for Cardiac Operative Risk Evaluation Euro-Score (EuroSCORE) (4) is frequently used.

However, the ability to effectively predict post-operative complications and mortality in acute aortic dissection remains uncertain, and no gold standard exists (7). Furthermore, many of these assessment tools are not routinely used in pre-operative evaluation because of complexity, inaccuracy when applied to individuals, unavailability of important variables, or time constraints (8–12).

A valuable addition to the pre-operative evaluation would therefore be a clinical routine biomarker capable of predicting patients' perioperative and early post-operative risk. Within this context, N-terminal pro-brain natriuretic peptide (NT-proBNP) has become a recent focus of common interest in the diagnosis, risk stratification, and assessment of mortality of cardiovascular diseases (13–15).

We speculated that pre-operative NT-proBNP may predict 30-day mortality and major adverse events in patients undergoing emergency repair of Stanford type A aortic

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Table 1 EuroSCORE Logistic Regression Model	
Variables (X1)	β-Coefficient
Age (continuous)	0.0666354
Female	0.3304052
Serum creatinine >200 μmol/l	0.6521653
Extracardiac arteriopathy	0.6558917
Pulmonary disease	0.4931341
Neurological dysfunction	0.841626
Previous cardiac surgery	1.002625
Recent myocardial infarct	0.5460218
Left ventricular ejection fraction 30%–50%	0.4191643
Left ventricular ejection fraction <30%	1.094443
Systolic pulmonary pressure >60 mm Hg	0.7676924
Active endocarditis	1.101265
Unstable angina	0.5677075
Emergency operation	0.7127953
Critical pre-operative state	0.9058132
Ventricular septal rupture	1.462009
Other than isolated coronary surgery	0.5420364
Thoracic aortic surgery	1.159787
Constant β0	−4.789594

For a given patient, the logistic EuroSCORE, which is the predicted mortality according to the logistic regression equation, is achieved with the following formula: predicted mortality =  $e^{(\beta_0 + \sum \beta_1 X_1)} / 1 + e^{(\beta_0 + \sum \beta_1 X_1)}$ .  
EuroSCORE = European System for Cardiac Operative Risk Evaluation.

dissection. Therefore, we investigated the association between NT-proBNP measured upon arrival of the patient in the emergency department and peri- and post-operative outcome within 30 days.

Methods

**Design.** The study was designed as a prospective cohort study, including consecutive patients undergoing emergency surgical repair of nontraumatic Stanford type A aortic dissection during a 6-year study period (from January 2000 to December 2006). Acute aortic dissection was diagnosed at the Department of Emergency Medicine at our institution and classified according to the guidelines published by the European Society of Cardiology (7). All study related procedures were in accordance with the ethical standards of the responsible committee of the Vienna Medical School.

**Patient data.** Cardiovascular risk factors and comorbidities, as the time point of onset of symptoms, were assessed on admission. Pre-operatively, the additive and the logistic EuroSCORE were applied to estimate the individual patient's outcome (for details, refer to Table 1). In brief, EuroSCORE identifies a number of risk factors that help to predict mortality from cardiac surgery. The predicted mortality (in %) is calculated by adding the weights assigned to each pre-operative risk factor. EuroSCORE has now been extensively tested and found to be valid worldwide (4–6). Additionally, C-reactive protein and total leukocyte count, as established surrogate markers of adverse outcome, were obtained at the time of hospital admission.

**End points.** As the primary end point, all-cause 30-day mortality was defined. The secondary objective was the

occurrence of major adverse events (MAEs) within the 30-day post-operative phase, as is classified according to criteria of the critical care society and to the guidelines of the Society of Thoracic Surgeons: acute respiratory distress syndrome; acute heart failure; diffuse or focal neurologic ischemic damage, such as persistent paraparesis or paraplegia due to impairment of blood supply to the spinal cord or signs of central neurological damage after cerebral hypoperfusion; and septicemia. Acute renal failure was defined as an increase in serum creatinine 44 mmol/l (0.5 mg/dl) over the baseline value (serum creatinine on admission) or the need for renal replacement therapy until day 30. Rethoracotomy was defined as the need of surgical reintervention for bleeding complications. When patients fulfilled at least one criterion, they were classified as suffering from post-operative MAEs.

**NT-proBNP measurements.** Arterial blood samples were collected pre-operatively into tubes containing potassium ethylene diamine tetraacetic acid. After centrifugation at 3,000 g, the supernatants were frozen at −80°C until use for pooled analysis. Pre-operative NT-proBNP was measured by chemiluminescence (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany) according to the manufacturer's recommendations. The test uses 2 polyclonal antibodies, which bind to the NT-proBNP peptide and form a stable sandwich complex. The sensitivity of the test is 5 pg/ml. Intraassay and interassay coefficients of variance at 175 pg/ml are 2.7% and 3.2%, respectively, without cross reactivities with other hormones.

**Statistical methods.** Continuous data are presented as the median and interquartile range (range from the 25th to the 75th percentile). Discrete data are given as counts and percentages. Univariate comparisons of continuous data were performed with Mann-Whitney *U* tests. Groups of categorical data were compared with the Fisher exact tests. Spearman correlation was applied to test for correlation between admission levels and time of onset of symptoms. Levels of NT-proBNP were grouped in tertiles to achieve clinically meaningful effect sizes by multivariable analysis; a multivariate logistic regression model was applied to assess the independent predictive value of NT-proBNP for the primary and secondary study end points and to adjust for possible confounding factors. We adjusted the logistic regression model for the EuroSCORE and time interval of onset of specific symptoms to account for the potentially confounding effect of patients' baseline morbidity. Results of the logistic regression model are given as the odds ratio (OR) and the 95% confidence interval (CI). Regression diagnostics and overall model-fit were performed according to standard procedures. A 2-sided *p* < 0.05 was considered

Abbreviations and Acronyms
CI = confidence interval
EuroSCORE = European System for Cardiac Operative Risk Evaluation
IQR = interquartile range
MAE = major adverse event
NT-proBNP = N-terminal pro-brain natriuretic peptide
OR = odds ratio

**Table 2** Distribution of Patients by Different Chronic Health Conditions and In-Hospital Risk Assessment Stratified to Their Individual Post-Operative Course

	No Event (n = 51)	MAE/Death (n = 53)	p Value
<b>Demographics</b>			
Age, yrs, median (IQR)	56 (50–66)	62 (54–68)	0.19
Female, n (%)	26 (51)	13 (25)	0.016
<b>Chronic health conditions and risk factors, n (%)</b>			
Extracardiac arteriopathy	3 (6)	2 (4)	0.68
Neurological dysfunction	1 (2)	2 (4)	1.00
Previous cardiac surgery	0 (0)	4 (7)	0.12
Serum creatinine >200 mmol/l	0 (0)	9 (17)	0.0027
Pulmonary hypertension	0 (0)	4 (7)	0.12
Recent myocardial infarction	0 (0)	3 (6)	0.24
<b>In-hospital assessment</b>			
Critical pre-operative state, n (%)	8 (16)	17 (32)	0.067
Left ventricular dysfunction, n (%)	4 (8)	20 (38)	0.0004
Unstable angina, n (%)	0 (0)	3 (6)	0.24
NT-proBNP, median (IQR) (pg/ml)	227 (107–328)	719 (442–2,287)	<0.0001
C-reactive protein, median (IQR) (mg/dl)	0.3 (0.0–1.5)	1.9 (0.0–9.3)	0.0029
Total leukocyte count, median (IQR) (g/l)	9.7 (7.7–16.0)	13.9 (10.2–16.3)	0.013
<b>EuroSCORE risk score, median (IQR)</b>			
Additional	7 (5–9)	9 (7–12)	0.0021
Logistic	10 (6–17)	16 (9–32)	0.0021

Unless otherwise indicated, data are numbers (percentages). Classification of chronic health conditions and risk factors according to EuroSCORE criteria. Critical pre-operative state defined any one or more of the following conditions: ventricular tachycardia or fibrillation or aborted sudden death, pre-operative cardiac massage, pre-operative ventilation before arrival in the anesthesia room, pre-operative inotropic support, or pre-operative acute renal failure.

EuroSCORE = European System for Cardiac Operative Risk Evaluation; IQR = interquartile range; MAE = major adverse event; NT-proBNP = N-terminal pro-brain natriuretic peptide.

statistically significant. Calculations were performed with SPSS for Windows (version 12.0, Microsoft, Seattle, Washington).

## Results

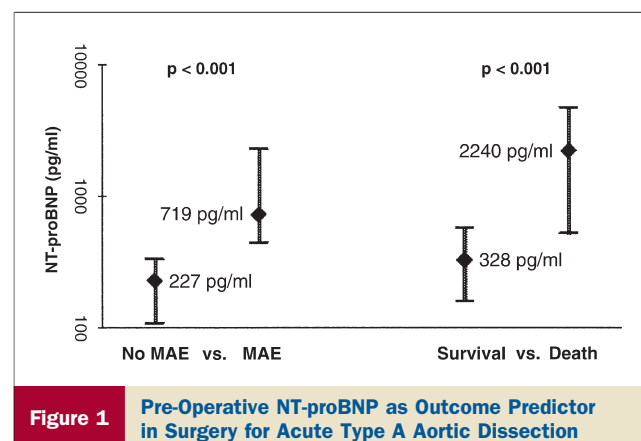
**Patient data.** During a 6-year period, we included 104 of 118 consecutive patients with acute aortic dissection in the present study (39 female, 35%; median age 61 years, interquartile range [IQR] 51 to 67). Fourteen patients had to be excluded because of missing data. Demographic data and clinical characteristics of these patients were not significantly different to patients included in the study (data not shown).

The median pre-operative NT-proBNP level was 413 pg/ml (IQR 182 to 947). We found a significant correlation between admission levels and time of onset of symptoms (median 6.5 h, IQR 4 to 19.5;  $r = 0.31$ ,  $p = 0.001$ ). Detailed demographic data of the study cohort is provided in Table 2.

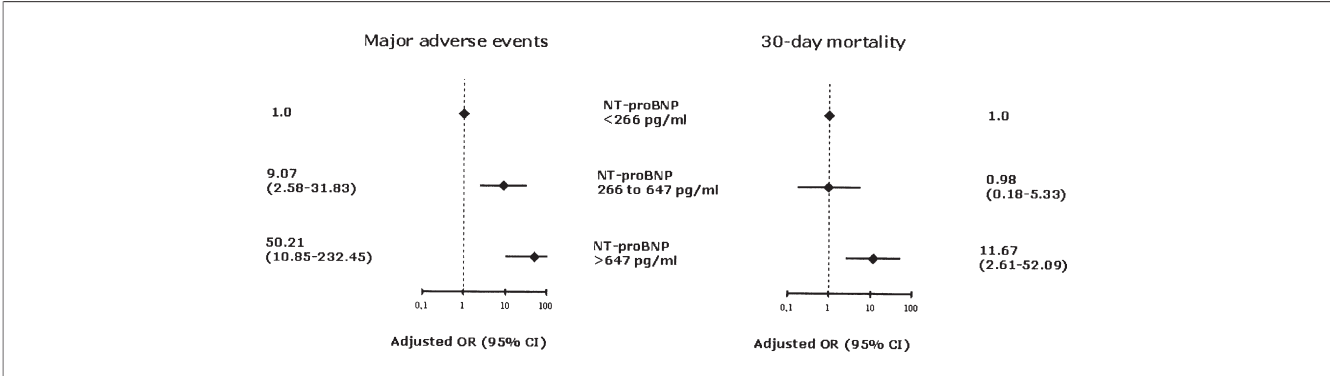
**Outcome after emergency surgery.** A total of 23 deaths (22%) occurred during the first 30 days. Major adverse events during postoperative course were documented in 53 patients (51%): occurrence of postoperative heart failure in 19 (18%), neurologic deficit in 14 (13%), need for rethoracotomy due to severe bleeding complications in 9 (9%), postoperative renal failure in 5 (5%), acute lung failure in 4 (4%), and sepsis in 2 patients (2%), respectively. A comparison of demographic data and clinical characteristics of patients is given in Table 2. Median NT-proBNP level (IQR) in 30-day survivors versus nonsurvivors was 328

pg/ml (157 to 569) versus 2,240 pg/ml (515 to 4,734;  $p = 0.001$ ), and in patients without versus with major adverse events 227 pg/ml (107 to 328) and 719 pg/ml (442 to 2,287;  $p = 0.001$ ), respectively (Fig. 1).

**Pre-operative NT-proBNP and outcome prediction.** We applied a multivariate model to assess the independent



Pre-operative NT-proBNP in 104 patients undergoing emergency surgical repair of type A aortic dissection with respect to post-operative occurrence of major adverse events and 30-day mortality. Plots indicate median and interquartile range (range from the 25th to the 75th percentile). Major adverse event was defined as composite end point, including need for rethoracotomy, occurrence of post-operative heart failure, neurologic deficit, lung failure, renal failure, or sepsis. MAE = major adverse event; NT-proBNP = N-terminal pro-brain natriuretic peptide.



**Figure 2** Pre-Operative NT-proBNP Predicts 30-Day Post-Operative Outcome After Adjustment for the Time Onset of Symptoms and the Logistic EuroSCORE

Adjusted odds ratios (OR) (diamonds) and 95% confidence intervals (CIs) (solid lines) comparing N-terminal pro-brain natriuretic peptide (NT-proBNP) levels on admission (in tertiles) and occurrence of major adverse events or death within a 30-day post-operative observation period. Major adverse event was defined as composite end point, including need for rethoracotomy, occurrence of post-operative heart failure, neurologic deficit, lung failure, renal failure, or sepsis. Final models were adjusted for logistic EuroSCORE and time of onset of symptoms. EuroSCORE = European System for Cardiac Operative Risk Evaluation.

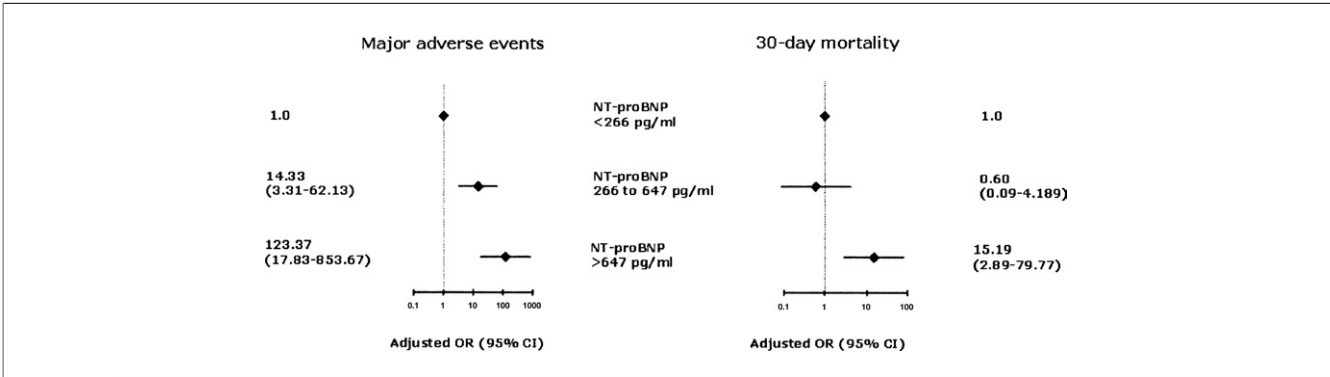
predictive value of pre-operative BNP-levels for outcome in patients with acute aortic dissection adjusting for the logistic EuroSCORE and time of onset of symptoms: we grouped baseline NT-proBNP levels in tertiles to obtain clinically meaningful effect sizes for the risk of death and MAEs (Fig. 2). Adjusted ORs for increasing tertiles of NT-proBNP compared with the lowest tertile were 0.98 (95% CI 0.18 to 5.33;  $p = 0.98$ ) and 11.67 (95% CI 2.61 to 52.09;  $p = 0.001$ ) for 30-day mortality, and 9.07 (95% CI 2.58 to 31.83;  $p = 0.001$ ) and 50.21 (95% CI 10.85 to 232.45;  $p < 0.001$ ) for MAEs, respectively, indicating a significant association between pre-operative NT-proBNP levels and outcome.

Comparable figures were obtained when adjusting for the additive EuroSCORE instead of the logistic EuroSCORE. Adjusted ORs for increasing tertiles of NT-proBNP compared with the lowest tertile were 1.03 (95% CI 0.19 to 5.75;  $p = 0.97$ ) and 12.18 (95% CI 2.68 to 55.38;  $p =$

0.001) for 30-day mortality and 9.63 (95% CI 2.72 to 34.04;  $p < 0.001$ ) and 52.87 (95% CI 11.47 to 243.79;  $p < 0.001$ ) for MAEs, respectively.

We further performed a second set of multivariable analysis, adjusting for potential confounders as indicated by univariate analyses instead of using only the logistic EuroSCORE and the "time onset of symptoms." By using univariate analysis, we found that "gender," "time onset of symptoms," "pulmonary hypertension," "impaired left ventricular function," "critical pre-operative state," and "impaired renal function" were significant predictors of outcome. Adjusting for these factors, risk estimates for tertiles of NT-proBNP were even greater than for the EuroSCORE-adjusted model, indicating that the latter one does not overestimate the effect (Fig. 3).

In final subgroup analysis, we further found NT-proBNP levels  $>647$  pg/ml to be significantly associated with occurrence of postoperative heart failure (adjusted OR [logistic]



**Figure 3** Pre-Operative NT-proBNP Predicts 30-Day Postoperative Outcome After Adjustment for the Time Onset of Symptoms and the Individual Patient's Risk Profile

Adjusted ORs (diamonds) and 95% CIs (solid lines) comparing NT-proBNP levels on admission (in tertiles) and occurrence of major adverse events or death within a 30-day post-operative observation period. Major adverse event was defined as composite end point, including need for rethoracotomy, occurrence of post-operative heart failure, neurologic deficit, lung failure, renal failure, or sepsis. Final models were adjusted for "gender," "time onset of symptoms," "pulmonary hypertension," "impaired left ventricular function," "critical pre-operative state," and "impaired renal function." Abbreviations as in Figure 2.



9.08 95% CI 2.06 to 40.07;  $p = 0.004$ ). For other MAEs, however, no significant correlation was observed.

## Discussion

The present study demonstrates that pre-operative NT-proBNP provides valuable information for risk stratification of patients with acute type A aortic dissection. In this patient population, concentrations of BNP  $>266$  pg/ml were highly predictive for postoperative complications. Moreover, we found that a NT-proBNP level  $>647$  pg/ml on admission was a powerful predictive factor of 30-day survival.

So far, pre-operative NT-proBNP has not been evaluated for its ability to predict postoperative complications after emergency surgery for acute type A aortic dissection, nor has NT-proBNP ever been part of the standard pre-operative work-up. Furthermore, none of the risk assessment indices incorporate pre-operative BNP levels into their calculations despite its proven correlation with outcome in both surgical and nonsurgical critically ill patients (4–12). In review of the literature, we have found one single study, reporting about increased pre-operative levels in acute aortic disease (16).

Several studies have convincingly demonstrated that a sepsis-like state substantially contributes to morbidity and mortality in acute aortic disease (17,18). Severe systemic inflammatory response syndrome is further associated with cardiovascular dysfunction. Cardiac dysfunction is a frequent and important factor in determining outcome of critically ill patients associated with poor prognosis (13,14). Previous examinations demonstrated that increased plasma levels of NT-proBNP are related to cardiovascular dysfunction in both surgical and nonsurgical critical ill patients (19–22). Thus, the levels of NT-proBNP observed in our cohort may be attributed either to inflammation-induced, cytokine-mediated NT-proBNP up-regulation, or to myocardial dysfunction. Increased plasma levels of NT-proBNP may reflect not only the severity of myocardial depression but also the disease severity.

Another important finding of the present study is that NT-proBNP levels show a significant correlation with the time of onset of symptoms of acute aortic dissection. This fact again underlines the importance of early diagnosis and intervention in treatment of acute Stanford type A aortic dissection in improving survival (2).

Multiple factors have shown to contribute to outcomes after emergency surgery of acute aortic dissection (3,8–12); thus, although a strong outcome predictor, pre-operative NT-proBNP may not be used as a “stand-alone” test in clinical routine but will substantially improve outcome prediction in combination with existing risk indices. An integrated approach would increase accuracy of pre-operative risk assessment predicting morbidity and mortality. Risk stratification might allow identifying patients not suitable for conventional surgical repair in circulatory arrest; in those, endovascular treatment of type A dissection may

be a new promising therapeutic option trying to reduce high perioperative mortality in emergency surgery of acute aortic dissection (23,24).

**Study limitations.** Some limitations of the present study have to be acknowledged. Although we could demonstrate that pre-operative NT-proBNP levels represent a powerful predictor for outcome in patients undergoing surgical repair of acute Stanford type A aortic dissection, sample size is modest when it comes to random variability, resulting in wide confidence intervals. From these data, a reliable cutoff therefore cannot be derived and interrogation of larger databases will be necessary. Because of its low incidence—previous studies suggest an incidence of 2.6 to 3.5 cases per 100,000 person-years (2,7)—our findings from a single-center study will ideally need confirmation in multicenter studies.

Although prospective, a remaining risk of selection bias cannot be excluded because only 88% of eligible patients could be included. However, considering overall death, our main end point, this bias appears to be negligible. Confounding by patient-management at the emergency department, operating theater, and intensive care unit, however, may be still present. Such confounders are impossible to control in an observational study.

Opposing these limitations, some arguments support our hypothesis: first, we found an overall strong effect size both for the primary and the secondary study end point; second, there was a clear biological gradient; third, there is a plausible pathophysiological background; and fourth, our findings are in line with similar investigations in the field.

## Conclusions

Considering the variety of factors that might influence mortality and morbidity following emergency surgery of acute type A aortic dissection, pre-operative NT-proBNP-measurement may represent a biomarker approach to estimate outcome. Increased levels of NT-proBNP ( $>647$  pg/ml in our observation) indicate unfavorable outcome. Future studies should assess possible treatment strategies relying on risk stratification derived from pre-operative NT-proBNP measurement.

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