

# N-Terminal Pro-brain Natriuretic Peptide Identifies Patients at High Risk for Adverse Cardiac Outcome after Vascular Surgery

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**Background:** Preoperative N-terminal pro-BNP (NT-proBNP) is independently associated with adverse cardiac outcome but does not anticipate the dynamic consequences of anesthesia and surgery. The authors hypothesized that a single postoperative NT-proBNP level provides additional prognostic information for in-hospital and late cardiac events.

**Methods:** Two hundred eighteen patients scheduled to undergo vascular surgery were enrolled and followed up for 24–30 months. Logistic regression and Cox proportional hazards model were performed to evaluate predictors of in-hospital and long-term cardiac outcome. The optimal discriminatory level of preoperative and postoperative NT-proBNP was determined by receiver operating characteristic analysis.

**Results:** During a median follow-up of 826 days, 44 patients (20%) experienced 51 cardiac events. Perioperatively, median NT-proBNP increased from 215 to 557 pg/ml (interquartile range, 83/457 to 221/1178 pg/ml;  $P < 0.001$ ). The optimum discriminate threshold for preoperative and postoperative NT-proBNP was 280 pg/ml (95% confidence interval, 123–400) and 860 pg/ml (95% confidence interval, 556–1,054), respectively. Adjusted for age, previous myocardial infarction, preoperative fibrinogen, creatinine, high-sensitivity C-reactive protein, type, duration, and surgical complications, only postoperative NT-proBNP remained significantly associated with in-hospital (adjusted hazard ratio, 19.8; 95% confidence interval, 3.4–115) and long-term cardiac outcome (adjusted hazard ratio, 4.88; 95% confidence interval, 2.43–9.81).

**Conclusion:** A single postoperative NT-proBNP determination provides important additional prognostic information to preoperative levels and may support therapeutic decisions to prevent subsequent structural myocardial damage.

PATIENTS undergoing vascular surgery have a high prevalence of coronary artery disease<sup>1</sup> and are at substantial risk for myocardial infarction (MI) and death associated

with the occurrence of prolonged perioperative ischemia.<sup>2–5</sup> Preoperative risk evaluation and optimized medical stress protection may improve cardiac outcome,<sup>3,6,7</sup> whereas withdrawal of medication and difficulties in proper diagnosis of myocardial ischemia and myocardial dysfunction in the postoperative period expose the patient to additional cardiac risk. Therefore, early and reliable postoperative risk stratification is an important issue to identify patients at high cardiac risk and implement appropriate therapy.<sup>8</sup>

Brain natriuretic peptide (BNP) and its inactive cleavage product N-terminal pro-BNP (NT-proBNP) are released from cardiac myocytes in response to ischemia<sup>9</sup> and myocardial stretch.<sup>10,11</sup> Plasma levels of these peptides correlate well with the extent of inducible ischemia<sup>12–14</sup> and are powerful predictors of death and hospital admission in patients with stable coronary artery disease<sup>15,16</sup> and acute coronary syndromes.<sup>17–20</sup> In these patients, BNP and NT-proBNP provide prognostic information beyond clinical risk factors, high-sensitivity C-reactive protein (hs-CRP), left ventricular function, and troponins.<sup>17,21</sup> In addition, BNP and NT-proBNP are valuable tools in the emergency department to establish the diagnosis of heart failure in patients with acute dyspnea.<sup>10,22,23</sup>

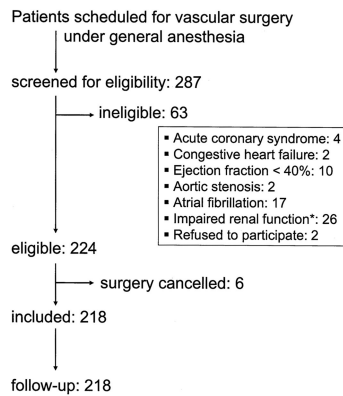
Despite evidence of their prognostic power for non-surgical<sup>10,19,20,23</sup> and preoperative patients,<sup>24–28</sup> the value of postoperative natriuretic peptides as markers of in-hospital and long-term cardiac events currently is unknown. This differentiation between preoperative and postoperative peptide levels is important, because restriction to a single preoperative value does not reflect the variable dynamic consequences of anesthesia and different risk surgery<sup>8</sup> exerted by intraoperative and postoperative catecholamine surges<sup>29</sup> and hypercoagulability with their potential to precipitate prolonged postoperative ischemia, myocardial necrosis, and myocardial dysfunction after major surgery.<sup>2,30</sup> Whether postoperative BNP or NT-proBNP levels indicate myocardial dysfunction and prove as reliable indicators of cardiac stress and outcome is unknown. Because attenuation of perioperative myocardial stress substantially reduces postoperative BNP release after major abdominal surgery<sup>29</sup> and also decreases the incidence of myocardial infarctions,<sup>31</sup> the question arises whether postoperative BNP or NT-proBNP levels are also associated with early and late cardiac outcome. Considering the

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**Fig. 1. Diagram of the patient flow through the study. \* Preoperative creatinine greater than 1.4 mg/dl.**

longer half-life of NT-proBNP (60–120 min) compared with that of BNP (20 min),<sup>32</sup> NT-proBNP may be superior in the perioperative setting although impaired renal function may reduce specificity.<sup>33,34</sup>

We therefore hypothesized that postoperative NT-proBNP levels provide additional prognostic power for in-hospital and long-term cardiac events when compared with preoperative NT-proBNP levels in patients undergoing elective major surgery.

## Materials and Methods

### Patient Selection

After institutional review board approval (Medical University of Graz, Graz, Austria), all patients scheduled to undergo major elective vascular surgery between October 2002 and June 2003 were screened for eligibility (fig. 1) for this prospective observational study. All patients gave written informed consent before participating. Patients were included if they had sinus rhythm, had a left ventricular ejection fraction of at least 40%, and were scheduled to undergo elective abdominal aortic aneurysm surgery, infrainguinal arterial reconstruction, or carotid endarterectomy during general anesthesia. Patients with unstable coronary syndromes (acute or recent MI with evidence of important ischemic risk by clinical symptoms or stress testing or unstable or severe angina pectoris<sup>8</sup>) or decompensated heart failure (new onset shortness of breath and rales together with echocardiographic evidence of cardiac dysfunction or deterioration of chronic heart failure despite heart failure therapy<sup>35</sup>) were excluded. Because chronic atrial fibrillation,<sup>36</sup> aortic stenosis,<sup>37</sup> and impaired renal function<sup>33</sup> are associated with increased serum levels of natriuretic peptides, patients with these diagnostic findings were also excluded to reduce possible confounders. Although exact sample size calculation was not feasible because of unknown means/medians and distribution of perioperative NT-proBNP levels in patients with and without cardiovascular events, we expected inclusion of approximately 200 patients during a 9-month period and anticipated a 20% combined event rate.

Before surgery, patients underwent a routine clinical evaluation, including detailed medical history, physical evaluation, routine laboratory tests, 12-lead electrocardiography, and chest radiography. Patients with coronary artery disease who were stable on any chronic antianginal medication proceeded to surgery without further noninvasive testing. Standardized perioperative stress protection with  $\beta$ -blockers was instituted in all patients without chronic  $\beta$ -blocker therapy and continued at least until hospital discharge unless contraindicated due to severe irreversible obstructive airway disease,<sup>38</sup> hypotension (systolic blood pressure less than 100 mmHg), or bradycardia (heart rate of 50 beats/min or less).

### Determination of Biochemical Markers

Blood samples were collected after 20 min of supine bed rest from an antecubital vein and centrifuged within 60 min. After determination of troponin T serum was frozen and stored in aliquots at  $-80^{\circ}\text{C}$ . NT-proBNP and hs-CRP were measured and analyzed after completion of the active inclusion period of the study. Troponin T and NT-proBNP analyses were performed using the Roche Elecsys 2010 (Roche Diagnostics GmbH, Mannheim, Germany).

Troponin T (electrochemiluminescence sandwich immunoassay, Elecsys Troponin T STAT; Roche Diagnostics; 99th percentile of the distribution in healthy population:  $< 0.01$  ng/ml; sensitivity: 0.01 ng/ml; intraassay and interassay coefficients of variance:  $< 5\%$ ; cutoff: 0.03 ng/ml) was determined on the day before surgery, on postoperative day 1, once between postoperative days 3 and 5, on the day of hospital discharge, and whenever clinically indicated by signs and symptoms of myocardial ischemia or surgical complications.

NT-proBNP determinations (electrochemiluminescence sandwich immunoassay, Elecsys ProBNP; Roche Diagnostics; sensitivity: 5 pg/ml, intraassay and interassay coefficients of variance:  $< 3\%$ ) were performed on the day before surgery and once between postoperative days 3 and 5. Because at this time most patients no longer receive intravenous infusion therapy, a possible influence of increased filling pressures on NT-proBNP levels was diminished.<sup>23</sup>

Hs-CRP (particle-enhanced immunonephelometry, CardioPhase hs-CRP; Dade Behring GmbH, Marburg, Germany; sensitivity: 0.175 mg/l; intraassay and interassay coefficient of variation:  $< 5\%$ ) was determined preoperatively.

### Perioperative Management

Serial 12-lead electrocardiogram recordings were performed on the day before surgery, once between postoperative days 3 and 5, and whenever clinically indicated.

Standard two-dimensional, M-mode and Doppler echocardiography (GE Vingmed; System Five, Holten, Norway) was performed by a cardiologist in all patients on the day before surgery, and postoperatively in case of a

troponin T greater than 0.03 ng/ml and a nondiagnostic electrocardiogram, and whenever clinically indicated to diagnose heart failure and to guide therapeutic interventions. Parasternal long- and short-axis views and apical two-, three-, and four-chamber views were obtained for the assessment of left ventricular ejection fraction. Anesthetic management, perioperative care, and intensive care unit referral were at the discretion of the attending physicians. Preoperative  $\beta$ -blockers and statins were reassumed postoperatively either orally or *via* nasogastric tube. Postoperative analgesia was performed using intravenous infusions of 0.1–0.2 mg/kg piritramide four to six times daily, supplemented by intravenous nonsteroidal antiinflammatory drugs (75 mg diclofenac and 30 mg orphenadrine citrate; Neodolpasse®; Fresenius Kabi, Austria GmbH, Graz, Austria) twice daily. The analgesic regimen was adjusted to achieve a visual analog scale score of 3 or less and was adjusted by the physicians from the acute pain service.

Perioperative anticoagulation was standardized: Intraoperatively, all patients received unfractionated heparin (30 U/kg intravenously) before vascular clamping but did not receive protamine after vascular declamping. In patients undergoing carotid endarterectomy or infringuinal bypass surgery, chronic antiaggregatory therapy with aspirin or clopidogrel was maintained perioperatively. In contrast, in patients undergoing elective abdominal aortic aneurysm surgery, chronic antiaggregatory medication was discontinued 5–7 days preoperatively, replaced with low-molecular-weight heparin, and reassumed on postoperative day 3 when justified by uneventful clinical course. In case of postoperative MI, patients received heparin (1 mg/kg enoxaparin twice daily or unfractionated heparin titrated to an activated partial thromboplastin time of 1.5 normal) and clopidogrel (300-mg bolus, continued by 75 mg/day), unless contraindicated by an increased risk of bleeding.

The perioperative hematocrit was maintained between 30% and 33%. The attending physicians were aware of the patients' perioperative echocardiographic data and troponin T levels but were unaware of NT-proBNP levels. During hospitalization, a study protocol and the patients' records were used for data documentation and collection.

#### Follow-up

Patients were monitored for in-hospital and long-term cardiac events. The primary outcome variable was a combined endpoint of nonfatal MI, emergent coronary artery revascularization, or cardiac death after index surgery. In case of two or more cardiac events, the first event was considered the endpoint of interest. The planned long-term follow-up was performed at 24–30 months after index surgery and included a telephone interview conducted by an investigator unaware of the patients' history and the aim of the study. In case of hospital readmission or death since index surgery, hos-

pital charts, death certificates, and autopsy reports were reviewed. In addition, time, number, and cause of noncardiac deaths were recorded. *Nonfatal MI* was diagnosed by a typical increase and decrease of troponin T to greater than 0.03 ng/ml together with clinical signs, symptoms, or electrocardiographic or echocardiographic findings that suggest the presence of acute myocardial ischemia.<sup>39</sup> *Acute coronary revascularization* was defined as acute percutaneous transluminal coronary angioplasty/stenting or coronary artery bypass grafting due to persistent myocardial ischemia and hemodynamic compromise refractory to medical therapy. *Cardiac death* was defined as death secondary to myocardial infarction, arrhythmia or heart failure.

#### Statistics

All data were tested for normal distribution by Shapiro-Wilk test. Results are presented as mean  $\pm$  SD, medians and interquartile range [25th–75th percentile], or absolute and relative frequencies as appropriate. Preoperative NT-proBNP values as well as their perioperative changes were compared by Mann-Whitney U test. To identify the best discriminatory level of NT-proBNP associated with the primary endpoint, receiver operating characteristic curves were analyzed, and the best cutoff was defined as a value providing equal sensitivity and specificity. The 95% confidence interval (CI) for the best threshold was determined by TG-ROC software (Matthias Greiner, Institute for Parasitology and Tropical Veterinary Medicine, Freie Universitaet Berlin, Berlin, Germany).<sup>40</sup> Sensitivity, specificity, and positive and negative predictive values were calculated. To assess event-free survival, a Kaplan-Meier analysis was performed. The event-time curve was separated into two curves according to the discriminatory postoperative NT-proBNP, and these curves were compared by log-rank test. Univariate comparisons between patients with and without events were performed using the chi-square test, Fisher exact test, Mann-Whitney U test, or Student *t* test as appropriate. Variables with *P* values below 0.25 in the univariate analysis were entered by stepwise forward selection in a multivariate Cox proportional hazards model. Subgroup analysis of in-hospital events was performed by logistic regression analysis. The level of significance was set at a two-tailed *P* value less than 0.05. The statistical software package NCSS 2004 (NCSS, Kaysville, UT) was used for analysis.

#### Results

The patient flow through the study is shown in figure 1. Baseline characteristics of the 218 included patients, troponin T, and NT-proBNP levels (preoperative and postoperative) are presented in table 1. No patient had coronary artery stenting less than 1 yr preoperatively. Ninety-six percent of the patients were successfully ex-



**Table 1. Baseline Characteristics of All Patients (n = 218) and Separated by the Occurrence of Cardiovascular Events during Follow-up**

	All Patients	Cardiovascular Events		P Value
		Yes (n = 44)	No (n = 174)	
Age, yr	70 ± 9	73 ± 9	69 ± 9	0.017
Sex, M/F	170/48	33/11	137/37	NS
Comorbidities				
Angina pectoris	80 (37)	22 (50)	58 (33)	NS
Previous MI	57 (26)	19 (43)	38 (22)	0.007
Previous CABG	15 (7)	5 (11)	10 (6)	NS
Previous coronary stent	9 (4)	3 (7)	6 (3)	NS
Previous HF	10 (5)	4 (9)	6 (3)	NS
Previous stroke/TIA	37 (17)	4 (9)	33 (19)	NS
Diabetes	78 (36)	19 (43)	59 (34)	NS
Hypertension	164 (75)	31 (71)	133 (76)	NS
LV ejection fraction	61 ± 9	60 ± 10	61 ± 9	NS
Fibrinogen preoperative, mg/dl	441 ± 240	477 ± 169	433 ± 254	0.046
Creatinine preoperative, mg/dl	1.1 ± 0.2	1.2 ± 0.2	1.1 ± 0.2	0.002
hs-CRP > 3 mg/l preoperative	147 (67)	36 (82)	111 (64)	0.030
NT-proBNP preoperative, pg/ml	215 [83–457]	551 [245–1,188]	179 [76–386]	<0.001
NT-proBNP PODs 3–5, pg/ml	557 [221–1,178]	1,612 [779–4,325]	420 [172–1,014]	<0.001
TnT > 0.03 ng/ml PODs 3–5	17 (8)	15 (34)	2 (1)	<0.001
Medication perioperative				
β-Blockers	167 (77)	30 (68)	137 (79)	NS
ACE inhibitors	110 (51)	23 (52)	87 (50)	NS
Ca antagonists	34 (16)	8 (18)	26 (15)	NS
Statins	78 (36)	15 (34)	63 (36)	NS
Aspirin	187 (86)	38 (86)	149 (86)	NS
Clopidogrel	18 (8)	5 (11)	13 (8)	NS
Surgery				
AAA	52 (24)	16 (36)	36 (21)	0.032
Infringuinal	129 (60)	24 (55)	105 (60)	NS
Carotid TEA	37 (17)	4 (9)	33 (19)	NS
Duration of surgery, min	155 ± 69	176 ± 69	149 ± 68	0.014
Surgical complications	17 (8)	7 (16)	10 (6)	0.033

Data are expressed as number (percentage), mean ± SD, or median [interquartile range] as appropriate. P value indicates differences between patients with and without cardiovascular events. Surgical complications: reoperation because of hemorrhage (n = 3) or graft thrombosis (n = 6), amputation (n = 3), wound infection needing prolonged healing with necrectomy (n = 5).

AAA = abdominal aortic aneurysm; ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; HF = heart failure; hs-CRP = high-sensitivity C-reactive protein; LV = left ventricular; MI = myocardial infarction; NT-proBNP = N-terminal pro-brain natriuretic peptide; POD = postoperative day; TEA = thromboendarterectomy; TIA = transient ischemic attack; TnT = troponin T.

tubated in the operating room, and 3% were extubated within the first 24 h postoperatively. Two patients required prolonged ventilation for 5 and 6 days, respectively, because of respiratory insufficiency.

*Cardiac Events*

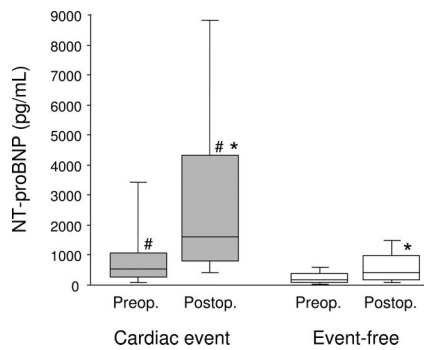
During a median follow-up of 826 days (interquartile range, 684–1,063), 44 patients (20%) experienced a total of 51 cardiac events, including 32 nonfatal myocardial infarctions (15%), 3 acute coronary revascularizations (1%), and 16 cardiac deaths (7%). Overall mortality (cardiac and noncardiac) was 14%, including 8 cases of cancer, 5 cases of sepsis, and 1 accident. Nineteen patients sustained in-hospital myocardial infarctions.

*Association of Perioperative NT-proBNP and Cardiovascular Events*

Median NT-proBNP increased significantly from 215 to 557 pg/ml (interquartile range, 83/457 to 221/1178 pg/ml;

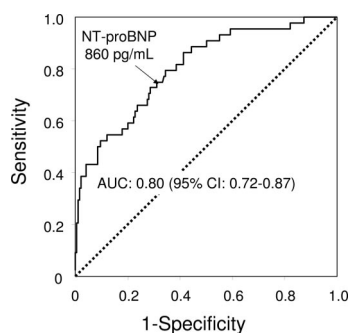
*P* < 0.001). Preoperatively, median NT-proBNP levels were higher in patients who experienced postoperative cardiovascular events as compared with event-free patients (551 vs. 179 pg/ml; *P* < 0.001). In addition, the median perioperative NT-proBNP increase was greater in patients sustaining cardiovascular events as compared with those event free (609 vs. 183 pg/ml; *P* < 0.001; fig. 2).

The association of postoperative NT-proBNP and cardiovascular events was assessed with a receiver operating characteristic curve (fig. 3). The area under the curve was 0.80 (95% CI, 0.72–0.87) for postoperative NT-proBNP. The optimum discriminate threshold for postoperative NT-proBNP was 860 pg/ml (95% CI, 556–1,054), yielding a sensitivity of 73%, a specificity of 71%, a positive predictive value of 39%, and a negative predictive value of 86% (positive likelihood ratio: 2.53). In univariate analysis, a postoperative NT-proBNP exceeding 860 pg/ml was associated with a 5.3-fold (95% CI, 2.8- to 10.4-fold) relative risk of adverse cardiac events.

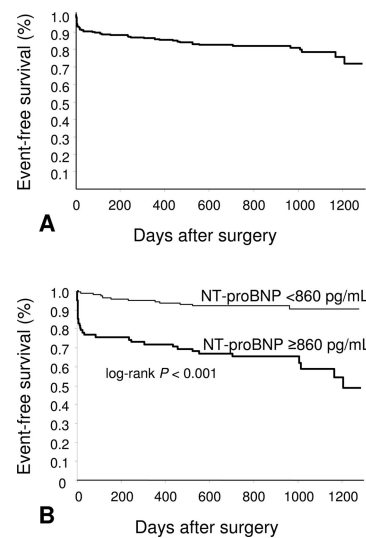


**Fig. 2.** Box-and-whisker plots of preoperative (Preop.) and postoperative (Postop.) N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in the 44 patients with cardiac events after index surgery (gray bars) compared with the 174 event-free patients (open bars). \*  $P < 0.001$  versus preoperative. #  $P < 0.001$  versus event-free patients.

Conversely, for preoperative NT-proBNP, the area under the curve was 0.74 (95% CI, 0.64–0.82), and the optimum discriminate threshold of 280 pg/ml (95% CI, 123–400) was associated with a 4.1-fold (95% CI, 2.1- to 7.9-fold) relative risk for adverse cardiac events in the univariate analysis. The occurrence of cardiac events over time is depicted in a Kaplan–Meier event-time curve (fig. 4A). Separating the initial event-time curve of figure 4A by the two levels of postoperative NT-proBNP (< 860 pg/ml and  $\geq$  860 pg/ml) demonstrates the association of postoperative NT-proBNP levels and cumulative event rate (fig. 4B). The separation of the event-time curve occurred early, indicating a different risk *a priori* that persists until late follow-up. Age, previous MI, preoperative fibrinogen, preoperative creatinine, preoperative hs-CRP greater than 3 mg/l, abdominal aortic aneurysm resection, duration of surgery, and surgical complications were significantly associated with adverse cardiac events in the univariate analysis (table 1). Adjusted for these univariate correlates by Cox proportional hazard model, postoperative but not preoperative NT-proBNP remained significantly and independently associated with adverse cardiac events (table 2). Similarly,



**Fig. 3.** Receiver operating characteristic curve for postoperative N-terminal pro-brain natriuretic peptide (NT-proBNP) levels for the prediction of the combined endpoint of nonfatal myocardial infarction, emergent coronary artery revascularization, or cardiac death after index surgery. The dotted line presents the no-discrimination curve. AUC = area under the curve; CI = confidence interval.



**Fig. 4.** Overall event-free survival (A) and event-free survival divided by postoperative N-terminal pro-brain natriuretic peptide (NT-proBNP) levels (B) during the 24–30 months of postoperative follow-up among the 218 patients.

in a subgroup analysis, only postoperative NT-proBNP remained significantly and independently associated with in-hospital cardiac events after adjustment for the above univariate correlates by logistic regression analysis (table 3).

## Discussion

In patients undergoing vascular surgery, compromised coronary perfusion and perioperative stress may precipitate prolonged postoperative myocardial ischemia and dysfunction, which adversely affect prognosis.<sup>2,4,30</sup> Therefore, early diagnosis, risk stratification, and modification are essential.<sup>8</sup> In the nonsurgical setting, BNP and NT-proBNP are equally powerful diagnostic and prognostic markers in patients with heart failure and coronary artery disease,<sup>10,15–17,19,20,22,34,41,42</sup> although BNP is considered superior to NT-proBNP in elderly patients with impaired renal function.<sup>33,34</sup> Perioperatively, however, determination of NT-proBNP may be preferred in patients with preserved renal function because of a longer half-life and a lower susceptibility to the rapid hemodynamic changes adherent with anesthesia and surgery.

**Table 2.** Significant Correlates of Cardiovascular Events and Adjusted Hazard Ratios Calculated by Multivariate Cox Proportional Hazards Model

Variable	Adjusted HR (95% CI)	P Value
NT-proBNP $\geq$ 860 pg/ml, postoperative	4.88 (2.43–9.81)	<0.001
Surgical complications	2.56 (1.11–5.90)	0.027
Creatinine preoperative > 1.2 mg/dl	1.92 (1.02–3.62)	0.044

CI = confidence interval; HR = hazard ratio; NT-proBNP = N-terminal pro-brain natriuretic peptide.

**Table 3. Significant Correlates of In-hospital Cardiovascular Events and Adjusted Odds Ratios Calculated by Multivariate Logistic Regression Model**

Variable	Adjusted OR (95% CI)	P Value
NT-proBNP $\geq$ 860 pg/ml, postoperative	19.8 (3.4–115.0)	<0.001
Surgical complications	7.5 (1.6–34.9)	0.010
Creatinine preoperative > 1.2 mg/dl	3.4 (1.0–11.4)	0.042

CI = confidence interval; NT-proBNP = N-terminal pro-brain natriuretic peptide; OR = odds ratio.

The results of the current investigation in patients undergoing vascular surgery demonstrate the prognostic value of a single postoperative NT-proBNP determination for adverse in-hospital and long-term cardiac outcome. In addition, the study also confirms the rationale of preoperative NT-proBNP determination,<sup>25,27,28</sup> because patients with higher initial NT-proBNP also had higher postoperative NT-proBNP elevations and sustained substantially more cardiovascular complications during 3 yr of follow-up as compared with patients with lower NT-proBNP levels.

The value of perioperative assessment of brain natriuretic peptides is incompletely evaluated. In patients undergoing vascular and noncardiac surgery, several recent studies demonstrated the prognostic superiority of preoperative BNP<sup>24,26</sup> and NT-proBNP levels,<sup>25,27,28</sup> as compared with traditional cardiac risk factors. Furthermore, Feringa *et al.*<sup>27,28</sup> recently suggested that preoperative NT-proBNP outweighs the prognostic power of inducible ischemia for in-hospital<sup>27</sup> and long-term cardiac events.<sup>28</sup>

In contrast, the role of postoperative BNP determination is less clear. Postoperatively elevated BNP levels indicated increased right ventricular afterload in patients after thoracic surgery.<sup>43</sup> In addition, Suttner *et al.*<sup>29</sup> demonstrated substantial BNP elevations lasting for at least 72 h after major abdominal surgery that were attenuated by continuous intraoperative and postoperative thoracic epidural analgesia. Although the substantial postoperative BNP elevations in latter two studies<sup>29,43</sup> suggest myocardial impairment, neither was designed to address diagnostic and prognostic value for adverse cardiac outcome.

The current investigation extends these findings by demonstrating for the first time that elevated postoperative NT-proBNP levels are associated with a substantially increased risk of adverse cardiac outcome after vascular surgery and that postoperative determination of this parameter helps in identifying patients at risk. When selecting a postoperative NT-proBNP cutoff of 860 pg/ml, 90% of the patients with NT-proBNP levels below this value remained free from cardiac events, whereas 50% of patients equal to or above this level sustained a cardiovascular event. In a subsequent multivariate analysis that was adjusted for well-known clinical and bio-

chemical outcome predictors and surgical specifics,<sup>3,5,44–47</sup> a high postoperative NT-proBNP level remained an independent prognostic marker associated with 20- and 5-fold increases of in-hospital and long-term adverse cardiac events, respectively.

Other multivariate predictors of adverse cardiovascular outcome included preoperative creatinine levels and postoperative surgical complications. The association between cardiac complications and surgical complications has been demonstrated previously<sup>48</sup> and emphasizes the impact of the dynamic postoperative period on cardiac outcome. In contrast, preoperative hs-CRP added no incremental prognostic power in the current investigation, a finding that is discordant with the cardiologic literature<sup>49</sup> and with a previous investigation evaluating preoperative risk factors for adverse cardiac outcome in patients undergoing vascular surgery.<sup>47</sup>

Although our study and others<sup>29,43</sup> consistently demonstrate high postoperative BNP and NT-proBNP levels after major surgery in high-risk patients, the reasons for these elevations remain speculative. BNP and NT-proBNP are expressed from cardiac myocytes to reduce ventricular wall stress in ischemic and nonischemic ventricles. It is therefore attractive to speculate that a postoperative increase of NT-proBNP reflects an impaired ischemic or nonischemic cardiac performance with a prognostic power beyond that of a single preoperative determination because it incorporates the dynamic intraoperative and postoperative stress exposure. Notably, a correlation between prestress and poststress levels of BNP and NT-proBNP and the risk and extent of inducible ischemia has been demonstrated previously, in both the nonsurgical setting<sup>12–14</sup> and the noninvasive risk stratification before vascular surgery.<sup>27,28</sup>

Although currently no consensus exists regarding the reference range of NT-proBNP values, we identified 860 pg/ml as the optimal postoperative NT-proBNP level associated with adverse in-hospital and long-term cardiac events. Our findings therefore suggest incorporation of NT-proBNP determinations in the diagnostic procedure both before and after surgery in high-risk patients. In accord with our results, patients with high preoperative levels of BNP<sup>24,26</sup> and NT-proBNP<sup>25,27,28</sup> sustained increased postoperative cardiac complications, indicating an elevated baseline risk. In contrast, early recognition of prolonged postoperative ischemia or heart failure is challenging in routine clinical practice,<sup>2,35</sup> because ischemia often presents silent in this period and is frequently skewed by parallel administration of analgetics or dyspnea of pulmonary origin. In the setting of major vascular surgery, postoperative NT-proBNP levels above 860 pg/ml were associated with substantially higher cardiac events that occurred earlier and more frequently as compared with patients with lower levels of this parameter. Therefore, determination of this parameter adds incremental prognostic information and may guide early ther-



apeutic decisions by addressing both anti-ischemic and heart failure therapy.

The results of this investigation must be interpreted with the constraints of several possible limitations. First, the overall adverse event rate in our study was 20%, which is somewhat less than that reported in the recent literature.<sup>5,45,46</sup> Because of the advanced age and the comorbidity of patients presenting for vascular surgery, we suspected a substantial proportion of noncardiac deaths before starting the study and therefore, in contrast to others,<sup>5,45,46</sup> only included cardiac death in the combined endpoint. In fact, almost half of our patients died of noncardiac causes. Second, several additional factors, including volume therapy<sup>23</sup> and pain,<sup>29</sup> may influence postoperative NT-proBNP levels. Therefore, we tried to eliminate these possible confounders by a standardized  $\beta$ -blockade, pain management, and determination on postoperative days 3–5, when patients are usually no longer receiving infusion therapy. However, because of the single postoperative measurement of NT-proBNP, we cannot determine whether the elevation of NT-proBNP between postoperative days 3 and 5 reflects the maximum increase of this parameter. Although there are age-dependent cutoffs for establishing the diagnosis of heart failure,<sup>10,35,42,50</sup> there are currently no such cutoffs for establishing postoperative prognosis. Because of the minimal, although statistically significant, difference in age between patients with and without events, we did not adjust NT-proBNP cutoff for increasing age. The discriminate value of 860 pg/ml in our study, however, is comparable with NT-proBNP levels associated with a 7- to 10-fold increased risk of short- and long-term mortality in patients presenting with acute coronary syndromes<sup>17</sup> but refers only to patients with preoperatively preserved renal function. In patients with impaired renal function, the diagnostic properties of NT-proBNP have been demonstrated to be less accurate when compared with those of BNP.<sup>34</sup> Third, we do not know whether NT-proBNP declined or returned to preoperative baseline values. This might be important because recent cardiologic investigations demonstrated that NT-proBNP level measured during a chronic, relatively stable phase is a better predictor of long-term cardiac outcome than that obtained during the acute, unstable phase.<sup>19</sup> Fourth, we only included patients with a preoperatively preserved ejection fraction of greater than 40%. Although this does not exclude heart failure, our study does not address high-risk patients<sup>51</sup> who might particularly benefit from early NT-proBNP determinations and subsequent therapeutic consequences.

In conclusion, a single postoperative NT-proBNP determination provides important additional prognostic information to preoperative levels and may support early therapeutic decisions to prevent subsequent structural myocardial damage, which ultimately leads to in-hospital and long-term cardiac complications. Further studies in

larger patient populations are required to establish age-adjusted cutoffs of brain natriuretic peptides and to compare perioperative diagnostic and prognostic properties of BNP and NT-proBNP, particularly with respect to the substantial incidence of renal dysfunction in cardiac risk patients.

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