British Journal of Anaesthesia **113** (1): 75–82 (2014)
Advance Access publication 11 April 2014 · doi:10.1093/bja/aeu088

BJA

EuroSCORE II and N-terminal pro-B-type natriuretic peptide for risk evaluation: an observational longitudinal study in patients undergoing coronary artery bypass graft surgery

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Editors' key points

- EuroSCORE II provided excellent predictive value with regard to severe circulatory failure after operation and in-hospital mortality in patients undergoing coronary artery bypass graft surgery for acute coronary syndromes.
- N-terminal pro-B-type natriuretic peptide ≥1028 ng litre^{-1} provided additional prognostic information regarding postoperative morbidity in patients considered to be at intermediate risk according to EuroSCORE II.

Background. Postoperative heart failure remains the major cause of death after cardiac surgery. As N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a predictor for postoperative heart failure, the aim was to evaluate if preoperative NT-proBNP could provide additional prognostic information to the recently launched EuroSCORE II.

Methods. A total of 365 patients with acute coronary syndrome (ACS) undergoing isolated coronary artery bypass graft (CABG) surgery were studied prospectively. Preoperative NT-proBNP and EuroSCORE II were evaluated with regard to severe circulatory failure after operation according to prespecified criteria. To assess what clinical outcomes are indicated by NT-proBNP levels in different risk categories, the patients were stratified according to EuroSCORE II. Based on receiver operating characteristics analysis, these cohorts were assessed with regard to preoperative NT-proBNP below or above 1028 ng litre^{-1}. The follow-up time averaged 4.4 (0.7) yr.

Results. Preoperative NT-proBNP≥1028 ng litre^{-1} [odds ratio (OR) 9.9, 95% confidence interval (CI) 1.01–98.9; P=0.049] and EuroSCORE II (OR 1.24, 95% CI 1.06–1.46; P=0.008) independently predicted severe circulatory failure after operation. In intermediate-risk patients (EuroSCORE II 2.0–10.0), NT-proBNP≥1028 ng litre^{-1} was associated with a higher incidence of severe circulatory failure (6.6% *vs* 0%; P=0.007), renal failure (14.8% *vs* 5.4%; P=0.03), stroke (6.6% *vs* 0.7%; P=0.03), longer intensive care unit stay [37 (35) *vs* 27 (38) h; P=0.002], and worse long-term survival.

Conclusions. Combining EuroSCORE II and preoperative NT-proBNP appears to improve risk prediction with regard to severe circulatory failure after isolated CABG for ACS. NT-proBNP may be particularly useful in patients at intermediate risk according to EuroSCORE II.

Clinical trial registration. NCT00489827.

Keywords: acute coronary syndrome; coronary artery bypass surgery; natriuretic peptides; risk assessment

Accepted for publication: 29 December 2013

Postoperative heart failure remains the major cause of death after coronary artery bypass graft (CABG) surgery.[1] Natriuretic peptides, represented by B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), have proven to be valuable tools when evaluating heart failure.[2] Elevated levels of NT-proBNP in patients with heart failure are associated with poor prognosis.[2 3] Also, in cardiac surgery, several studies point out the value of preoperative natriuretic peptides as independent risk predictors.[4 5] A recent systematic review and meta-analysis on preoperative BNP and NT-proBNP as predictors of adverse outcome after cardiac surgery revealed that there are still limited data available, and that studies differ considerably in sample size, inclusion criteria, endpoints, and quality.[6] It concluded that BNP and NT-proBNP have a moderate ability to predict short- and long-term mortality and morbidity.

In a study on patients operated with CABG for acute coronary syndrome (ACS), we identified a cut-off value for preoperative NT-proBNP of 1028 ng litre^{-1} as a predictor of both postoperative severe circulatory failure and in-hospital mortality.[7] In that study, NT-proBNP≥1028 ng litre^{-1} emerged as an independent risk factor for severe circulatory failure after operation. Preoperative NT-proBNP≥1028 ng litre^{-1} was more predictive of severe circulatory problems after operation than echocardiographic assessment of left ventricular function. NT-proBNP≥1028 ng litre^{-1} remained an independent risk

factor for severe circulatory failure after operation even after adjustment for EuroSCORE.[7]

When designing the recently launched EuroSCORE II model, the relevance of natriuretic peptides as an independent factor in predicting cardiac surgical outcome was acknowledged.[8] However, this biochemical marker was not included in the risk calculation because the BNP data were too limited. Therefore, the primary aim of this study was to examine if preoperative NT-proBNP and our previously identified cut-off level of NT-proBNP$\geq$1028 ng litre^{-1} could provide prognostic information in addition to EuroSCORE II in predicting severe circulatory failure after operation in patients with ACS undergoing isolated CABG.

Methods

Ethics approval

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).

Patients

Between May 2007 and November 2009, we prospectively included 366 patients in a prespecified substudy of the GLUTAMICS trial (ClinicalTrials.gov Identifier: NCT00489827). The trial was originally powered for 2214 patients with regard to the intervention but was terminated after interim analysis as prespecified stopping criteria per protocol were fulfilled.[9] For details regarding the GLUTAMICS trial, see Supplementary material.

Patients were operated at three Swedish cardiac surgery centres (Linköping, Örebro, and Karlskrona). Inclusion criteria were patients operated with isolated CABG for ACS. Patients were eligible for inclusion regardless if the procedure was done on-pump (n=354) or off-pump (n=12). Exclusion criteria are presented in the Supplementary material.

Study design

An observational longitudinal study to evaluate EuroSCORE II and preoperative NT-proBNP for prediction of severe circulatory failure after operation in patients undergoing isolated CABG for ACS. Patients were included prospectively and based on our original database, we retrospectively calculated EuroSCORE II for each patient. Calculation was done with the EuroSCORE II interactive calculator at www.euroscore.org. One patient was excluded due to missing data for adequate EuroSCORE II calculation, leaving 365 patients for final analysis (Fig. 1).

Sampling for NT-proBNP was done in the operating theatre immediately before induction of anaesthesia and plasma levels were analysed using electro-chemiluminescence immunoassay on a Roche Elecsys 2010 automated platform (Roche Diagnostics, Basel, Switzerland). The results of NT-proBNP were released from the laboratory when the trial was terminated.

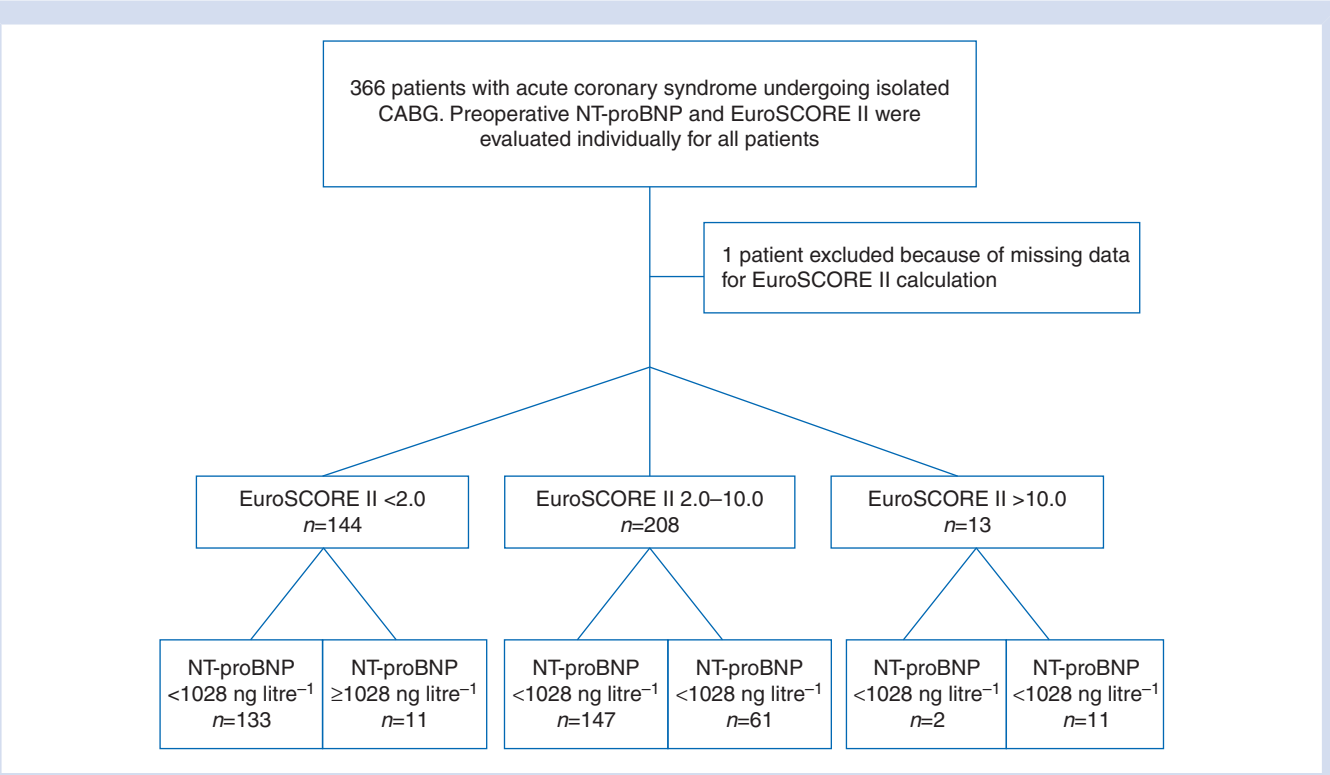

Fig 1 Flow chart of study design and stratification.

Stratification

The patients were stratified into three risk categories based on a recent evaluation of EuroSCORE II, patients with low risk (EuroSCORE II <2.0; $n=144$), intermediate risk (EuroSCORE II 2.0–10.0; $n=208$), and high risk (EuroSCORE II >10.0; $n=13$).[10] These risk groups were then assessed with regard to NT-proBNP below or above the previously identified cut-off level of 1028 ng litre^{-1} for predicting in-hospital mortality and severe circulatory failure after operation[7] (Fig. 1).

Study endpoints

The primary endpoint was severe circulatory failure after operation during the first hospitalization. The secondary endpoints were in-hospital mortality and late mortality. Mortality was divided into cardiac or non-cardiac-related cause of death. Assessments were done according to prespecified criteria by an endpoints committee consisting of consultants in cardiothoracic anaesthesia and cardiothoracic surgery from the three centres participating in the study. The committee was blinded to the results of the NT-proBNP analyses. For details, see Supplementary material. Data on late mortality were retrieved from the Swedish Civil Registry and the cause for late mortality was retrieved from the Causes of Death Registry at the Swedish National Board of Health and Welfare.

Definitions

Severe circulatory failure was defined as circulatory failure leading to death or requiring stay in the intensive care unit (ICU) $\geq$48 h with intra-aortic balloon pump for $\geq$24 h or inotropic agents for $\geq$24 h in dosages described in the Supplementary material.

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. Cardiac cause of death was defined as death caused by or initiated by a cardiac event such as heart failure or myocardial infarction.

Definitions for left ventricular failure at weaning from cardiopulmonary bypass (CPB), perioperative myocardial infarction, postoperative renal dysfunction, and stroke are given in the Supplementary material.

Peroperative management

Clinical management was standardized and similar at the three participating centres with minor differences concerning choice of anaesthetic drugs. Standard surgical techniques were used. Twelve patients were operated off-pump without aortic cross-clamping. In the other patients, standard use of CPB and aortic cross-clamping was used. 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 as previously described.[11] For details on clinical management, see Supplementary material.

Statistics

Multivariable analysis of independent predictors for severe circulatory failure after operation was done with forward stepwise multiple logistic regression. The Hosmer–Lemeshow goodness-of-fit statistics were calculated for the final model. Variables with a P-value of <0.25 in the univariable analysis were tested in the multivariable model.

Receiver operating characteristics (ROC) analysis was carried out to calculate the area under the curve (AUC) and to evaluate discrimination of NT-proBNP and EuroSCORE II with regard to severe circulatory failure after operation. Multivariable logistic regression was used to build a model with EuroSCORE II and NT-proBNP after log transformation of both variables. Areas under ROC curves were compared using a non-parametric approach.[12] Fisher's exact test or χ^2 test was used when appropriate for comparison of dichotomous variables. Student's t-test or Mann–Whitney U-test was used when appropriate for comparison of continuous variables. The Kaplan–Meier estimator and log-rank test was 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, USA), SPSS 17.0 (SPSS Inc.) and STATA/SE 12 (Stata Corp., College Station, TX, USA).

Results

The mean age of the whole study population ($n=365$) was 68 (9) yr and 19% were females. EuroSCORE II was 3.3 (2.7) (range 0.85–20.2) with a median value of 2.4. The mean value of preoperative NT-proBNP was 889 (1637) ng litre^{-1} (range 10–15 900 ng litre^{-1}) with a median value of 420 ng litre^{-1}. Severe circulatory failure after operation developed in 1.9% (7/365). In-hospital mortality was 1.4% (5/365), 30 day mortality was 1.1% (4/365), and in-hospital plus 30 day mortality was 1.6% (6/365). Among the six patients with in-hospital or 30 day mortality, five died of cardiac causes and one due to gastrointestinal bleeding.

Predictive value of EuroSCORE II and NT-proBNP with regard to severe circulatory failure after operation

Multivariable analysis identified the cut-off level of NT-proBNP $\geq$1028 ng litre^{-1} [odds ratio (OR)=9.94: 95% confidence interval (CI) 1.01–98.9; $P=0.049$] and EuroSCORE II (OR=1.24: 95% CI 1.06–1.46; $P=0.008$) as independent risk factors for severe circulatory failure after operation. The Hosmer–Lemeshow goodness-of-fit test χ^2 (df 8)=1.44, $P=0.99$, for this analysis.

Discrimination with regard to severe circulatory failure after operation was almost identical for EuroSCORE II and preoperative NT-proBNP (as a continuous variable) with an AUC of 0.87 for both variables (Table 1). Discrimination did not improve significantly with the combined model of EuroSCORE II and preoperative NT-proBNP compared with EuroSCORE II alone ($P=0.14$). The ROC curve for the combined model is shown in Figure 2.

Table 1 ROC analysis of preoperative NT-proBNP and EuroSCORE II with regard to severe circulatory failure after operation. Patients with isolated CABG $n=365$. AUC, area under the curve; CI, confidence interval

Characteristics	NT-proBNP	EuroSCORE II	Combined model NT-proBNP and EuroSCORE II
AUC	0.87	0.87	0.93
95% CI	0.79–0.96	0.76–0.98	0.87–0.98
P-value	0.001	0.001	<0.001

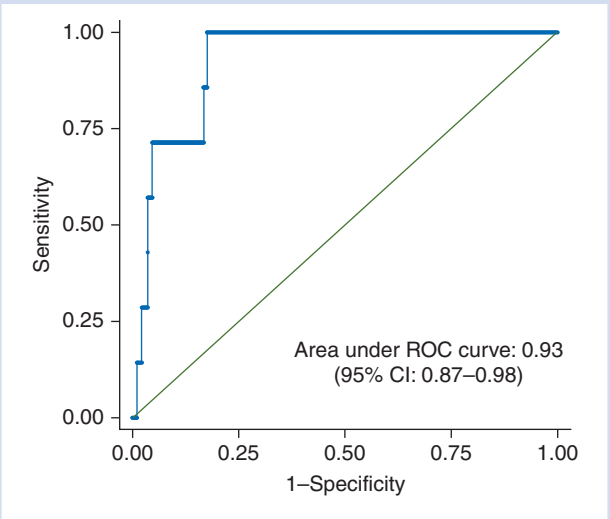

Fig 2 ROC analysis to evaluate the discrimination of the combined model of EuroSCORE II and preoperative NT-proBNP (as a continuous variable) with regard to severe circulatory failure after operation.

Predictive value of EuroSCORE II and NT-proBNP with regard to in-hospital mortality

ROC analysis with regard to in-hospital mortality showed an AUC for EuroSCORE II of 0.94 (95% CI 0.87–1.0; $P=0.001$), for NT-proBNP 0.82 (95% CI 0.73–0.91; $P=0.014$), and for the combined model 0.94 (95% CI 0.88–1.00).

Clinical outcome with regard to NT-proBNP above or below 1028 ng litre^{-1} in different risk categories according to EuroSCORE II

An overview of the perioperative characteristics in patients stratified according to EuroSCORE II is presented in Table 2.

Low-risk group: EuroSCORE II<2.0

The mean value of preoperative NT-proBNP was 421 (654) ng litre^{-1} (range 10–5880 ng litre^{-1}) with a median value of 198 ng litre^{-1}. No patient developed severe circulatory failure after operation or died in-hospital. One patient in the low-risk group died out of hospital but within 30 days (sudden death). Characteristics are presented in Table 2. Eleven patients had high NT-proBNP ≥1028 ng litre^{-1} and 133 patients low NT-proBNP <1028 ng litre^{-1}. EuroSCORE II did not differ significantly between these subgroups [1.5 (0.3) *vs* 1.4 (0.3), $P=0.37$]. Before operation, patients with NT-proBNP ≥1028 ng litre^{-1} had significantly lower haemoglobin and higher plasma-troponin T (Table 3). The group with high NT-proBNP had significantly more inotropic support intraoperatively (36% *vs* 10%, $P=0.026$) and on arrival in the ICU (36% *vs* 5.3%, $P=0.0047$) (Table 3).

Table 2 Perioperative characteristics for the low-, intermediate-, and high-risk groups based on EuroSCORE II. *M*, median value; LV, left ventricular; CPB, cardiopulmonary bypass. Number of patients in parentheses

	EuroSCORE II<2.0 ($n=144$)	EuroSCORE II 2.0–10.0 ($n=208$)	EuroSCORE II>10.0 ($n=13$)
Age (yr) (range)	62 (42–79)	72 (44–84)	78 (75–82)
Females	7.6%	25%	69%
EuroSCORE (additive)	2.9 (1.5)	6.1 (1.9)	10.6 (2.2)
EuroSCORE II	1.5 (0.3)	3.9 (1.7)	13.3 (2.9)
NT-proBNP preop. (ng litre^{-1})	421 (654), $M=198$	1030 (1650), $M=545$	3837 (4112), $M=2910$
NT-proBNP day 1 (ng litre^{-1})	1804 (1075), $M=1545$	3451 (2743), $M=2870$	10 049 (7367), $M=8570$
NT-proBNP day 3 (ng litre^{-1})	2861 (1881), $M=2460$	5773 (4957), $M=4580$	15 370 (9433), $M=14\,100$
LV failure at weaning from CPB	2.1% ($n=3$)	5.3% ($n=11$)	31% ($n=4$)
Severe circulatory failure after operation	0	1.9% ($n=4$)	23.1% ($n=3$)
In-hospital mortality	0	1.0% ($n=2$)	23.1% ($n=3$)
30 day mortality	0.7% ($n=1$)	1.0% ($n=2$)	7.7% ($n=1$)
1 yr mortality	1.4% ($n=2$)	1.4% ($n=3$)	30.8% ($n=4$)

Intermediate-risk group: EuroSCORE II 2.0–10.0

The mean value of preoperative NT-proBNP was 1030 (1650) ng litre^{-1} (range 19–15 900 ng litre^{-1}) with a median value of 545 ng litre^{-1}. Perioperatively, 5.3% ($n=11$) had circulatory failure at weaning from bypass. After operation, 1.9% ($n=4$) developed severe circulatory failure. In-hospital, 30 day mortality, and in-hospital plus 30 day mortality was 1.0% ($n=2$). Characteristics are presented in Table 2.

Sixty-one patients had high NT-proBNP ≥1028 ng litre^{-1} and 147 patients had low NT-proBNP <1028 ng litre^{-1}. The difference in preoperative EuroSCORE II between these subgroups did not reach statistical significance [4.2 (1.7) *vs* 3.8 (1.7), $P=0.07$]. Before operation, patients with high NT-proBNP had significantly lower haemoglobin, higher plasma-troponin T, and higher prevalence of severe left ventricular dysfunction (11% *vs* 2.7%, $P=0.016$) (Table 3).

Intraoperatively, patients with high NT-proBNP had longer CPB time [86 (27) *vs* 79 (33) min; $P=0.042$], mainly due to

Table 3 Characteristics of patients undergoing isolated CABG for ACS stratified by EuroSCORE II and NT-pro BNP <1028 and ≥ 1028 ng litre^{-1}. BMI, body mass index; CCS, Canadian Cardiovascular Society; LV, left ventricular; CPB, cardiopulmonary bypass; OT, operating theatre; RV, right ventricular; ICU, intensive care unit. Number of patients in parentheses

Variable	EuroSCORE II <2.0			EuroSCORE II 2.0–10.0		
	NT-proBNP <1028 ng litre^{-1}, $n=133$	NT-proBNP≥1028 ng litre^{-1}, $n=11$	*P*-value	NT-proBNP <1028 ng litre^{-1}, $n=147$	NT-proBNP≥1028 ng litre^{-1}, $n=61$	*P*-value
Preoperative NT-pro BNP (ng litre^{-1})	280 (264)	2128 (1310)	<0.0001	409 (269)	2525 (2449)	<0.0001
EuroSCORE II	1.4 (0.3)	1.5 (0.3)	0.37	3.8 (1.7)	4.2 (1.7)	0.07
Age (yr) (range)	61 (42–79)	62 (45–74)	0.65	71.3 (44–84)	73.2 (55–84)	0.08
Female gender	8.3% (11)	0%	1.0	24% (35)	26% (16)	0.71
BMI (kg m^{-2})	28.0 (4.1)	27.6 (3.7)	0.81	27.0 (4.7)	26.2 (4.1)	0.25
Hypertension	52% (68/132)	36% (4)	0.37	66% (96/145)	64% (39)	0.75
Chronic obstructive pulmonary disease	1.5% (2)	0%	1.0	9.0% (13/145)	8.2% (5)	0.86
Diabetes	16% (21)	0%	0.37	29% (43)	31% (19)	0.79
Cerebrovascular disease	2.3% (3)	0%	1.0	15% (22)	10% (6)	0.32
CCS class IV	47% (62)	36% (4)	0.55	71% (104)	61% (37)	0.16
Three vessel disease	70% (93)	100% (11)	0.35	72% (106)	92% (56)	0.0018
Left main stenosis	30% (40)	18% (2)	0.51	35% (51)	43% (26)	0.28
Recent myocardial infarction (<3 weeks)	53% (71)	73% (8)	0.35	69% (102)	75% (46)	0.38
Severe LV dysfunction	0%	0%	ns	2.7% (4)	11% (7)	0.016
Preoperative i.v. nitroglycerine	5.3% (7)	0%	1.0	6.1% (9)	9.8% (6)	0.36
Haemoglobin (g litre$^{-1)}$	142 (13)	113 (13)	0.016	137 (12)	129 (12)	<0.0001
Plasma creatinine (μmol litre^{-1})	86 (15)	91 (19)	0.47	97 (23)	104 (47)	0.71
Troponin T (μg litre^{-1})	0.11 (0.31)	0.63 (1.1)	0.003	0.068 (0.24)	0.29 (0.76)	0.0004
Aortic cross-clamp time (min)	48 (16)	55 (21)	0.33	51 (19)	54 (16)	0.22
CPB time (min)	76 (24)	87 (31)	0.28	79 (33)	86 (27)	0.042
Reperfusion time (min)	23 (13)	28 (11)	0.13	21 (9)	27 (17)	0.039
Peripheral anastomoses	3.7 (1.2)	4.3 (0.9)	0.12	3.7 (1.2)	4.1 (1.0)	0.033
Sv_{O_2} at weaning from CPB (%)	72.0 (7.8)	69.5 (6.7)	0.24	71.9 (6.9)	70.8 (7.2)	0.33
Sv_{O_2} 5 min after protamin (%)	72.1 (7.6)	67.9 (9.2)	0.24	71.7 (6.6)	69.5 (7.6)	0.045
Epinephrine at weaning from CPB	1.5% (2)	18% (2)	0.029	6.8% (10)	8.2% (5)	0.72
Milrinone at weaning from CPB	2.3% (3)	9.1% (1)	0.27	5.4% (8)	14.8% (9)	0.026
Inotropic support in the OT	10% (13)	36% (4)	0.026	13% (19)	33% (20)	0.0008
LV failure at weaning from CPB	1.5% (2)	9.1% (1)	0.21	2.7% (4)	11.5% (7)	0.016
RV failure in the OT	3.0% (4)	9.1% (1)	0.33	0.7% (1/146)	6.7% (4/60)	0.026
Sv_{O_2} on arrival in ICU (%)	66.1 (6.2)	61.9 (8.6)	0.16	64.9 (6.9)	63.0 (7.3)	0.07
NT-pro BNP day 1 (ng litre^{-1})	1662 (943)	3391 (1236)	<0.0001	2476 (1436)	5744 (3611)	<0.0001
NT-pro BNP day 3 (ng litre^{-1})	2705 (1808)	4774 (1776)	<0.001	4622 (3617)	8685 (6514)	<0.0001
CKMB day 1 (μg litre^{-1})	19.4 (20.3)	11.0 (4.1)	0.14	22.4 (24)	20.3 (17)	0.40
Troponin T day 3 (μg litre^{-1})	0.30 (0.32)	0.52 (0.56)	0.13	0.38 (0.34)	0.53 (0.72)	0.20
Myocardial infarction	0%	0%	NS	0.7% (1)	1.6% (1)	0.50
Perioperative stroke CT-verified	0%	0%	NS	0.7% (1)	6.6% (4)	0.027
Increase of plasma creatinine by >50%	2.3% (3)	9.1% (1)	0.27	5.4% (8)	14.8% (9)	0.026
New postop. atrial fibrillation	23% (30)	30% (3)	0.71	39% (57)	41% (25)	0.77
Inotropic support on admission to ICU	5.3% (7)	36% (4)	0.0047	11% (16)	21% (13)	0.048
Time in ICU (h)	21 (13)	17 (11)	0.11	27 (38)	37 (35)	0.0023
ICU stay >48 h	2.3% (3)	0%	1.0	6.8% (10)	18% (11)	0.014
Time on ventilator (h)	4.4 (5.5)	4.2 (2.5)	0.64	9 (34)	11 (22)	0.51
Severe circulatory failure	0%	0%	ns	0%	6.6% (4)	0.007
In-hospital mortality	0%	0%	1.0	0%	3.3% (2)	0.08
30 day mortality	0.8% (1)	0%	1.0	0%	3.3% (2)	0.08
In-hospital plus 30 day mortality	0.8% (1)	0%	1.0	0%	3.3% (2)	0.08
1 yr mortality	1.5% (2)	0%	1.0	0%	4.9% (3)	0.024

longer reperfusion time [27 (17) *vs* 21 (9) min, $P=0.039$]. Also, patients with high NT-proBNP had significantly more left ventricular failure at weaning from bypass (11.5% *vs* 2.7%, $P=0.016$) and more inotropic support intraoperatively (33% *vs* 13%, $P=0.0008$) (Table 3).

After operation, severe circulatory failure was only observed in patients with high preoperative NT-proBNP (6.6% *vs* 0%, $P=0.007$). Patients with high NT-proBNP also had significantly more stroke (6.6% *vs* 0.7%, $P=0.027$), renal failure (15% *vs* 5.4%, $P=0.026$), and longer ICU stay [37 (35) *vs* 27 (38) h, $P=0.002$]. In-hospital plus 30 day mortality (3.3% *vs* 0%, $P=0.08$) and 1 yr mortality (4.9% $n=3$, *vs* 0%, $P=0.024$) was only observed in the high NT-proBNP group (Table 3).

High-risk group: EuroSCORE II>10.0

The mean value of preoperative NT-proBNP was 3837 (4112) ng litre^{-1} (range 660–15 847 ng litre^{-1}) with a median value of 2910 ng litre^{-1}. Eleven patients had high NT-proBNP≥1028 ng litre^{-1} and two patients had low NT-proBNP <1028 ng litre^{-1}. Three patients developed severe circulatory failure after operation. Three patients (23%) died in-hospital, one of them within 30 days. Characteristics are presented in Table 2.

Long-term follow-up

The follow-up time for the whole study population ($n=365$) was 4.4 (0.7) yr (range 3.1–5.6 yr). Cause of death could be established in 37 out of 39 patients. Cumulative freedom from cardiac death according to Kaplan–Meier was significantly worse for those with NT-proBNP≥1028 ng litre^{-1} ($P=0.002$) (Fig. 3).

Discussion

EuroSCORE II provided excellent predictive value with regard to severe circulatory failure after operation and in-hospital mortality in patients undergoing CABG for ACSs. In spite of this, preoperative NT-proBNP≥1028 ng litre^{-1} emerged as an independent risk factor for developing severe circulatory failure even after adjusting for EuroSCORE II. NT-proBNP≥1028 ng litre^{-1} provided additional prognostic information regarding postoperative morbidity in patients considered to be at intermediate risk according to EuroSCORE II.

Complications to perioperative heart failure are the leading causes for adverse outcome after cardiac surgery.[1 13] Consequently, it is important to identify patients with increased risk for developing postoperative heart failure before operation. Owing to the lack of generally accepted criteria for postoperative heart failure in association with cardiac surgery, a clinical endpoints committee relying on prespecified criteria was considered necessary in the study to get a robust evaluation on severe circulatory failure after operation.

Natriuretic peptides are well-known markers for heart failure, and the prognostic value of preoperative NT-proBNP

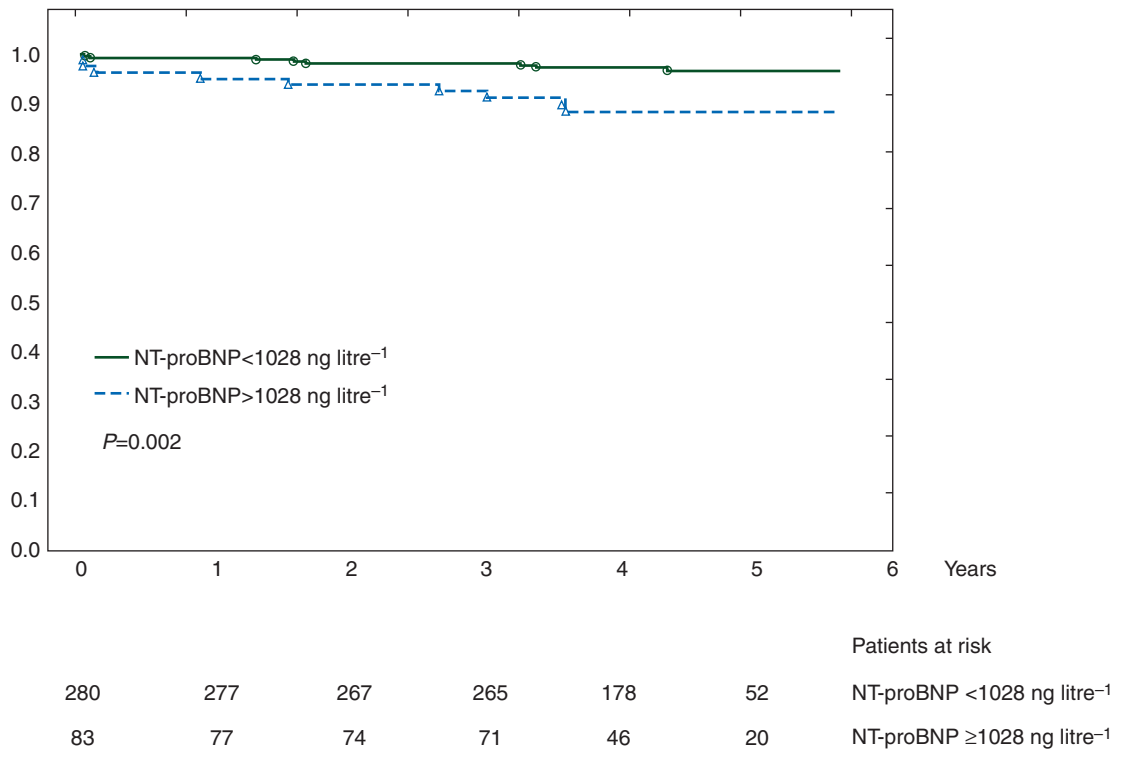

Fig 3 Cumulative freedom from cardiac death (Kaplan–Meier) related to preoperative NT-proBNP in patients undergoing isolated CABG for ACS ($n=363$).

has been well documented in cardiac surgery.[4–6] In a recent study on patients undergoing isolated CABG, we found a cut-off level for preoperative NT-proBNP of 1028 ng litre^{-1} to be independently predictive of severe circulatory failure after operation, according to strict prespecified criteria, even after adjustment for EuroSCORE.[7] This finding was in agreement with other cardiac surgical studies where natriuretic peptides measured before operation were independently predictive of postoperative outcome even when adjusted for EuroSCORE.[14 15]

However, the recently launched EuroSCORE II has been recalibrated and includes some different predictors and introduces new classifications of already existing predictors.[8] It has been suggested that a combination of biomarkers and clinical assessment could prove the most useful means to determine preoperative risk in cardiac surgery.[4] However, natriuretic peptides were not included in the EuroSCORE II risk calculation as data were only available for a small proportion of the patients. In light of this, new evaluations of NT-proBNP in relation to EuroSCORE II are desirable. Multivariable analysis in the present study on patients undergoing isolated CABG for ACS support claims that NT-proBNP can provide additional prognostic information to EuroSCORE II. According to ROC analysis, the ability to recognize patients who developed severe circulatory failure after operation was excellent and almost identical for EuroSCORE II and preoperative NT-proBNP. Combining these variables improved AUC slightly but not significantly. However, the cut-off value for NT-proBNP$\geq$1028 ng litre^{-1} emerged as an independent risk factor in the multivariable analysis in contrast to NT-proBNP as a continuous variable. For the ROC analyses, NT-proBNP was analysed as a continuous variable.

EuroSCORE II was designed to predict in-hospital mortality, but in this study, it also demonstrated excellent predictive value for severe circulatory failure after operation. This could be explained by the major role of heart failure for postoperative mortality. Vice versa, this could explain the predictive value of NT-proBNP$\geq$1028 ng litre^{-1} with regard to in-hospital mortality. We have previously reported that preoperative NT-proBNP was more predictive of severe circulatory problems after operation than echocardiographic assessment of left ventricular function.[7] NT-proBNP provides an objective measurement also taking diastolic dysfunction into account even in the absence of impaired systolic function assessed by echocardiography.[16] This does not necessarily imply that NT-proBNP should be evaluated for inclusion in risk models as it might be more useful as a complement to clinical assessment.

To assess what clinical outcomes NT-proBNP$\geq$1028 ng litre^{-1} might be associated with we stratified patients into three risk categories based on a recent evaluation of EuroSCORE II.[10] The results of our study suggest that NT-proBNP can add information to EuroSCORE II in identifying patients who carry an increased risk of developing severe circulatory problems during the perioperative period. In the low-risk group with EuroSCORE II$<$2.0, there were few patients with high NT-proBNP. In spite of this, NT-proBNP provided prognostic information to EuroSCORE II regarding the use of intraoperative inotropic support.

In the intermediate-risk group with EuroSCORE II 2.0–10.0, the additive value of NT-proBNP was more evident. Severe circulatory failure and serious adverse outcomes such as renal failure, stroke, and prolonged ICU stay were more common in patients with NT-proBNP$\geq$1028 ng litre^{-1}. Owing to a limited number of events, the mortality difference did not reach statistical significance in-hospital or at 30 days, but was statistically significant at 1 yr.

In the high-risk group (EuroSCORE II $>$10.0), there were only two patients with NT-proBNP$<$1028 ng litre^{-1} and therefore, a statistical analysis was not performed in relation to NT-proBNP level.

Cumulative freedom from cardiac death according to Kaplan–Meier was significantly worse for patients with preoperative NT-proBNP$\geq$1028 ng litre^{-1}. This finding supports a recent study that found increased perioperative BNP concentrations to be associated with hospitalization or death related to heart failure during the 5 yr after primary CABG.[17] Furthermore, in a non-selected group of cardiac surgery patients, it has been shown that preoperative NT-proBNP had moderate accuracy in predicting mortality at 3 yr.[18]

Apart from identifying high-risk patients, it is also desirable to identify patients who can undergo open cardiac surgery with a lower risk than indicated by conventional risk scoring. A notable finding was that, regardless of EuroSCORE II, only one of the 282 patients with NT-proBNP$<$1028 ng litre^{-1} developed severe circulatory failure or died in hospital. This information could be particularly useful in high-risk patients with regard to operability and choice of procedure. Further studies are warranted to address this issue.

The major limitation of this study is the retrospective calculation of EuroSCORE II in a relatively small sample size, but the study was prospective and unique in the sense that postoperative heart failure was determined by a blinded endpoints committee relying on strict prespecified criteria.

In conclusion, our results indicate that NT-proBNP provides additional prognostic information to EuroSCORE II in patients with ACS undergoing isolated CABG, particularly in those considered to be at intermediate risk.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

J.H.: study design, patient recruitment, data analysis, endpoint committee, and writing first draft of the paper. M.V.: patient recruitment, endpoint committee, and co-author. F.V.: patient recruitment, endpoint committee, and co-author Ö.F.: patient recruitment, endpoint committee, and co-author. E.H.: patient recruitment, endpoint committee, and co-author. S.W.: study design, statistical analysis, and co-author. R.S.: principal investigator, study design, patient recruitment, endpoint committee, and senior author.

Acknowledgements

We are indebted to research nurses Inger Huljebrant, Sara Thybell, Anna Krantz, and Ann-Kristin Olsson for assistance with data collection.

Declaration of interest

None declared.

Funding

This work was supported by grants from the Swedish Heart–Lung Foundation (20030595), Capio Research Foundation (2005-1021;2006-1203), Linköping University, and Östergötlands Läns Landsting.

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Handling editor: M. M. R. F. Struys