N-terminal pro-B-type natriuretic peptide concentrations and long-term outcome after cardiac surgery: a prospective cohort study


1 Department of Critical Care, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Room D128, Toronto, Canada
2 Department of Clinical Biochemistry, 3 Department of Medical Genetics, and 4 Department of Cardiology, Aberdeen Royal Infirmary, Aberdeen, UK
5 Section of Population Health, University of Aberdeen, Foresterhill, Aberdeen, UK
6 Cardiovascular Division, The George Institute, Royal Prince Alfred Hospital, Sydney, Australia

* Corresponding author. E-mail brian.cuthbertson@sunnybrook.ca

Editor’s key points
• High B-type natriuretic peptide (BNP) concentrations are associated with worse long-term cardiovascular outcome.
• This study evaluated BNP concentrations and the EuroSCORE for risk prediction after cardiac surgery.
• NT-proBNP and the EuroSCORE both predicted mortality at 3 yr with moderate and similar accuracy, but combining the two was not additive.
• Patient age, history of heart failure, and duration of surgery are more important long-term outcome predictors.

Background. N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations predict cardiovascular outcome in many settings. There are very few data assessing the utility of NT-proBNP concentrations in the prediction of long-term outcome after cardiac surgery. We assessed the ability of NT-proBNP to predict 3 yr mortality compared with validated clinical risk prediction tools.

Methods. A secondary analysis of a prospectively recruited patient cohort of 1010 patients undergoing cardiac surgery. Baseline clinical details were obtained including EuroSCORE. Multi-variable modelling, area under the receiver operating characteristic curves (AUCs), and net reclassification improvement were utilized.

Results. NT-proBNP was a univariable predictor of 3 yr mortality but was no longer a significant predictor in a multivariable model (hazard ratio 1.00 per 250 ng litre$^{-1}$, 95% confidence interval 0.98–1.02, $P=0.80$). The relative and additive predictive values of the preoperative EuroSCORE (both additive and logistic versions) and NT-proBNP concentrations were compared. All were predictive of 3 yr mortality ($P<0.001$) with almost identical AUCs (0.71 for EuroSCORE, 0.70 for NT-proBNP). When either the EuroSCORE or NT-proBNP concentrations are known, the addition of the other does not improve the ability to predict 3 yr mortality.

Conclusions. Preoperative NT-proBNP concentrations and the EuroSCORE have equivalent, and moderate, predictive accuracy for mortality 3 yr after cardiac surgery. EuroSCORE uses clinical data but is not routinely used for individual clinical risk prediction. NT-proBNP measurement would incur additional costs but can be measured quickly and objectively. With such similar predictive accuracy, factors such as the ease of calculation and cost will likely determine their use in clinical practice.

Keywords: assessment; patient outcomes; cardiac surgical procedures; morbidity; mortality; natriuretic peptides

Accepted for publication: 4 August 2012

Coronary artery bypass graft (CABG) and heart valve replacement surgery play an important role in the management of patients with coronary, valvular, or both heart disease.1 2 The risks of cardiac surgery are well documented. Indeed, an ageing population and increased use of percutaneous coronary intervention means that cardiac surgery is now performed on patients with higher co-morbidity and more complex disease, resulting in a greater risk of major complications.

With high-quality alternatives (such as percutaneous techniques) increasingly available, there is an urgent need to correctly quantify the risk of patients being considered for cardiac surgery. Accurate risk prediction guides clinicians in identifying individuals who may benefit from further...
screening and follow-up, helps to target appropriate preventive management strategies that can be initiated early after surgery, assists in the effective use of healthcare resources, and facilitates clinical audit and research. Importantly, it also allows patients and their relatives to make more informed decisions regarding their management. Several systems have been developed in an effort to predict early outcome from cardiac surgery, of which the European System for Cardiac Operative Risk Evaluation (EuroSCORE) is one of the best validated. This was originally derived as a predictor in hospital outcome after cardiac surgery but is also a predictor of long-term survival. A patient’s EuroSCORE can be calculated using either the additive or logistic versions, the former being easier to derive, but potentially less accurate in high-risk patients. Although widely used in research work and for clinical audit, the EuroSCORE has significant limitations. In addition, the need to combine research work and for clinical audit, the EuroSCORE has significantly limited its utilization in some centres. An inexpensive biochemical test that, either alone or in combination with existing clinical tools, could improve the accuracy of risk prediction for individual patients would be of considerable value to patients, clinicians, and healthcare funders.

The natriuretic peptides are produced in the myocardium in response to pressure loading, volume loading, or both. Myocyte stretch leads to the release of a precursor molecule (proBNP), which is subsequently split into B-type natriuretic peptide (BNP) and an N-terminal pro-peptide (NT-proBNP). BNP release causes natriuresis, diuresis, and vasodilatation; NT-proBNP is a biologically inactive molecule. Blood concentrations of BNP and NT-proBNP are raised in patients with heart failure but are also elevated in patients with raised left ventricular (LV) filling pressure due to valvular heart disease, diastolic dysfunction, and myocardial ischaemia. It is thought to be the ability of the BNPs to integrate the risk attributable to all of these factors that underpins their prognostic utility in many settings.

Several studies have confirmed that BNP concentrations predict cardiovascular outcome in patients undergoing non-cardiac surgery. There are fewer data in patients undergoing cardiac surgery, but several studies have suggested that preoperative natriuretic peptide concentrations predict short-term outcome after cardiac surgery. Using the cohort presented in this article, we demonstrated that preoperative NT-proBNP concentrations predicted early (30 day) outcome after cardiac surgery, but that their prognostic utility at this time-point was modest, although independent of traditional indicators and conventional risk prediction scores. Only one prior study has assessed the ability of BNP to predict long-term mortality after CABG and reported that BNP was an independent predictor of 5 yr mortality. In the current study, we have assessed the ability of NT-proBNP to predict mortality within 3 yr of open cardiac surgery in a large unselected cohort. In addition, we have compared the prognostic utility of NT-proBNP with that of the EuroSCORE, explored the independence of the information provided, and evaluated the clinical value of the combination when compared with either alone.

Methods

Patients and measures

This is a secondary long-term follow-up analysis of a cohort of patients whose short-term outcomes have been previously reported. The study protocol was approved by the local research ethics committee and written informed consent was obtained from all patients. The study was a prospective single-centre observational cohort study of 1010 consecutively recruited adult patients undergoing non-emergent cardiac surgery in a tertiary referral cardiac surgery centre in Scotland.

Preoperative data collection included patient characteristics, cardiovascular risk factors, medication, and prior medical history. A baseline 12-lead electrocardiogram was recorded and reported by a cardiologist, blinded to NT-proBNP levels. LV function was assessed by echocardiography, ventriculography, or both. It was classified as normal (LV ejection fraction ≥50%), mildly impaired (LV ejection fraction 40% but <50%), or moderately to severely impaired (LV ejection fraction <40%), on the basis of visual assessment by a cardiologist, again blinded to NT-proBNP results. New York Heart Association (NYHA) functional class was determined and the logistic and additive EuroSCORE were calculated.

Plasma NT-proBNP concentrations were determined before operation using an electro-chemiluminescence immunoassay, performed on a Roche Elecsys 2010 automated platform (Roche Diagnostics, Basel, Switzerland). The assay has an effective measuring range of 5–35 000 ng litre⁻¹. The within-run coefficient of variation was 2.7% at a concentration of 175 ng litre⁻¹ and 1.9% at 1068 ng litre⁻¹. The between-run coefficients of variation were 13.4%, 5.4%, and 4.3% at concentrations of 37.8, 236.3, and 473.2 ng litre⁻¹, respectively.

Clinicians responsible for patient care were blinded to the preoperative NT-proBNP levels. All preoperative data were also collected by individuals blinded to these levels. Preoperative glomerular filtration rate was estimated (eGFR) using the Modification of Diet in Renal Disease equation.

Endpoints

Vital status was established using data collected by the General Register Office for Scotland. The primary study endpoint was all-cause mortality within 3 yr of surgery.

Statistics

Descriptive statistics of the characteristics of the entire cohort are presented, and also separately for those patients who were alive and dead at 3 yr after surgery. Categorical data are summarized as absolute values (percentage). Continuous data are presented as median [inter-quartile ranges (IQR)] or, when normally distributed, as mean [standard deviation (sd)]. The Cox proportional hazards regression models were used to estimate the risk of mortality within 3 yr after surgery for each baseline characteristic individually.
Hazard ratios (HRs) and asymptotic (standard) 95% confidence intervals (CIs) are reported, along with P-values.

The multivariable Cox regression models were used to explore the independent prognostic utility of NT-proBNP and, in separate models, the additive and logistic EuroSCORE. In addition, the value of NT-proBNP was assessed in a model containing significant preoperative clinical predictors, preoperative investigations, and factors that reflect the complexity of the surgical procedure. Co-variables for this model were selected on the basis of being strong univariable predictors and well-recognized determinants of outcome. In addition, where univariable predictors were closely related (e.g. creatinine and eGFR, bypass time and cross-clamp time, NYHA functional class III or IV, and history of heart failure), the more powerful univariable predictor was used. Secondary analyses were also performed assessing the ability of preoperative NT-proBNP concentrations to predict outcome from 30 days to 3 yr. These analyses included only patients who survived beyond 30 days.

The prognostic value of using different cut-off points of preoperative NT-proBNP to classify the cohort into low- and high-risk patients was explored. The probability of death, sensitivity, specificity, and positive and negative predictive values of each decile of NT-proBNP level are presented. 95% CIs for each of these statistics were calculated using the percentile bootstrapping method, based on 2000 re-samples of the data. In addition, the survival rates of patients with concentrations at or below the median were compared with those with higher concentrations using a log-rank test and illustrated using a Kaplan–Meier curve. Further Kaplan–Meier curves were derived comparing the survival of patients who underwent only isolated CABG surgery, dichotomized around the median NT-proBNP level for this group, and for patients who underwent valve, aortic, or both surgery (+ CABG), again dichotomized around the median level.

The ability of NT-proBNP and the EuroSCORE to discriminate between participants who died during follow-up and those who did not was assessed using area under the receiver operating characteristic curves (AUC) and the net reclassification improvement (NRI) method. AUC comparisons used non-parametric methods. The AUC is a very conservative statistic. The NRI method has, therefore, been proposed as a more sensitive measure for comparing the discriminatory power of prediction models. It assesses the ability of a potential predictor to correctly reclassify individuals with and without a subsequent event into high- and low-risk groups. NRI measures the percentage of correct change in risk category (an increase in risk category for participants who had the event or a decrease for those who did not). To compute the NRI, participants were divided into three risk categories: <8%, 8–10%, and >10% 3 yr predicted risk of death. The 10% 3 yr risk was chosen assuming a 10 yr higher risk threshold of about 30%, and 8–10% chosen to indicate intermediate risk, accounting for the distribution of predicted probabilities in our sample. Power calculations based on 30 day mortality have been previously published. We did not perform an a priori power calculation for mortality within 3 yr of surgery.

All analyses were performed using the software packages SPSS Statistics 17.0.01 (IBM Corp., Somers, NY, USA) and SAS/STAT 9.1.9 (SAS Institute Inc., Cary, NC, USA) for Windows.

Results

Patient population

Baseline characteristics are shown in Table 1, presented for patients who survived 3 yr, those who died within this period, and all patients. The cohort was predominantly male with a mean (sd) age of 66 (9) yr. NT-proBNP concentrations were obtained with a median (IQR) of 1 (3) day before surgery. Seven hundred and thirty-two (72%) patients underwent isolated CABG. Of the remaining patients, 225 received an aortic valve replacement (97 with concomitant CABG, three with associated aortic root replacement, and 16 with concurrent mitral valve surgery) and 50 patients underwent mitral valve surgery (23 with CABG and four with tricuspid valve annuloplasty). One patient had isolated tricuspid annuloplasty in addition to CABG and two patients had aortic root replacement (plus CABG).

Vital status was recorded for all patients. After 30 days, 29 (2.9%) of the study population had died and by 3 yr, 79 (8%). The univariable relationship between baseline characteristics and death at 3 yr is demonstrated in Table 1. The survival of patients with NT-proBNP concentrations above and below the median (289 ng litre$^{-1}$) is shown in Figure 1.

The median NT-proBNP level in patients undergoing isolated CABG was 203 (IQR 96–513) ng litre$^{-1}$, and in patients undergoing valve or aortic surgery (+ CABG), it was 992 (IQR 405–2195) ng litre$^{-1}$. There was no evidence of a statistical interaction between NT-proBNP and the nature of surgery (isolated CABG or valve/aortic surgery (CABG)) for the risk of death at 3 yr; $P=0.693$ for interaction. The hazard associated with increasing NT-proBNP concentrations was similar among patients who underwent isolated CABG (HR 1.02 per 250 ng litre$^{-1}$, 95% CI 0.99–1.04, $P=0.22$) and those who underwent valve or aortic surgery (HR 1.02 per 250 ng litre$^{-1}$, 95% CI 1.00–1.04, $P=0.02$). Figure 2 shows the survival of patients who underwent isolated CABG dichotomized around the median NT-proBNP level for this group (203 ng litre$^{-1}$, Fig. 2a) and the outcome of patients who underwent valve and/or aortic root surgery (+ CABG) dichotomized around the median NT-proBNP value for this group (992 ng litre$^{-1}$, Fig. 2b).

Predictive utility of NT-proBNP in multivariable modelling

In a multivariable model that included selected univariable clinical predictors of outcome (age, history of heart failure), other preoperative investigations (eGFR, LV ejection fraction <50%), and indicators of the complexity of the surgical procedure (prior cardiac surgery, the need for valve and/or aortic surgery (with or without concomitant CABG), and the duration of cardiopulmonary bypass), NT-proBNP was no...
NT-pro-BNP and long-term outcome after cardiac surgery

Table 1 Baseline patient characteristics and survival 3 yr after cardiac surgery. HRs, CIs, and P-values represent the univariate probability of the characteristic predicting mortality. ACE, angiotensin-converting enzyme; CABB, coronary artery bypass grafting; CI, confidence interval; ECG, electrocardiogram; EuroSCORE, European System for Cardiac Operative Risk Evaluation; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; IQR, interquartile range; LV, left ventricular; n, number; NT-proBNP, N-terminal proB-type natriuretic peptide; NYHA, New York Heart Association; so, standard deviation. *Missing values: abnormal preoperative ECG: alive = 6, dead = 0; creatinine, eGFR, NT-proBNP: alive = 1, dead = 0; 1 HR per 10 mmol litre⁻¹; 2 HR per 5 mm; 3 HR per 250 ng litre⁻¹.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 1010)</th>
<th>Alive (n = 931)</th>
<th>Dead (n = 79)</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) [mean (so)]</td>
<td>66 [22–89 (9)]</td>
<td>65 [22–86 (9)]</td>
<td>70 [48–89 (9)]</td>
<td>1.08 (1.05, 1.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>774 (77)</td>
<td>720 (77)</td>
<td>54 (68)</td>
<td>0.65 (0.40, 1.04)</td>
<td>0.070</td>
</tr>
<tr>
<td>Smoker (prior or current) [n (%)]</td>
<td>424 (42)</td>
<td>391 (42)</td>
<td>33 (42)</td>
<td>0.99 (0.63, 1.54)</td>
<td>0.952</td>
</tr>
<tr>
<td>Body mass index (kg m⁻²) [mean (so)]*</td>
<td>28.7 (4.4)</td>
<td>28.7 (4.4)</td>
<td>29.2 (4.4)</td>
<td>1.02 (0.98, 1.08)</td>
<td>0.338</td>
</tr>
<tr>
<td>Diabetes [n (%)]</td>
<td>177 (18)</td>
<td>163 (18)</td>
<td>14 (18)</td>
<td>1.03 (0.58, 1.83)</td>
<td>0.933</td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>748 (74)</td>
<td>681 (73)</td>
<td>67 (85)</td>
<td>2.02 (1.09, 3.73)</td>
<td>0.025</td>
</tr>
<tr>
<td>Prior myocardial infarction [n (%)]</td>
<td>403 (40)</td>
<td>369 (40)</td>
<td>34 (43)</td>
<td>1.14 (0.73, 1.78)</td>
<td>0.572</td>
</tr>
<tr>
<td>History of cardiac failure [n (%)]</td>
<td>93 (9)</td>
<td>72 (8)</td>
<td>21 (27)</td>
<td>3.99 (2.42, 6.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior cardiac surgery [n (%)]</td>
<td>28 (3)</td>
<td>22 (2)</td>
<td>6 (7)</td>
<td>3.18 (1.38, 7.31)</td>
<td>0.006</td>
</tr>
<tr>
<td>Abnormal preoperative ECG [n (%)]*</td>
<td>533 (53)</td>
<td>476 (51)</td>
<td>57 (73)</td>
<td>2.45 (1.49, 4.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV ejection fraction &lt;50% [n (%)]</td>
<td>340 (34)</td>
<td>300 (32)</td>
<td>40 (51)</td>
<td>2.08 (1.34, 3.23)</td>
<td>0.001</td>
</tr>
<tr>
<td>LV ejection fraction &lt;40% [n (%)]</td>
<td>127 (13)</td>
<td>112 (12)</td>
<td>15 (19)</td>
<td>1.64 (0.94, 2.88)</td>
<td>0.084</td>
</tr>
<tr>
<td>β-Blocker [n (%)]</td>
<td>698 (69)</td>
<td>651 (70)</td>
<td>47 (59)</td>
<td>0.63 (0.40, 0.99)</td>
<td>0.045</td>
</tr>
<tr>
<td>ACE inhibitor [n (%)]</td>
<td>473 (47)</td>
<td>434 (47)</td>
<td>39 (49)</td>
<td>1.10 (0.71, 1.71)</td>
<td>0.672</td>
</tr>
<tr>
<td>Statin [n (%)]</td>
<td>868 (86)</td>
<td>801 (86)</td>
<td>67 (85)</td>
<td>0.91 (0.49, 1.68)</td>
<td>0.757</td>
</tr>
<tr>
<td>Creatinine (mmol litre⁻¹) [median (IQR)]*</td>
<td>102 (93, 115)</td>
<td>102 (92, 115)</td>
<td>109 (97, 126)</td>
<td>1.05 (1.03, 1.08) †</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (ml min 1.73 m⁻²) [mean (so)]*</td>
<td>63 (14)</td>
<td>63 (13)</td>
<td>56 (15)</td>
<td>0.97 (0.95, 0.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA functional class III/IV [n (%)]</td>
<td>117 (12)</td>
<td>98 (11)</td>
<td>19 (24)</td>
<td>2.60 (1.55, 4.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative IABP [n (%)]</td>
<td>125 (12)</td>
<td>111 (12)</td>
<td>14 (18)</td>
<td>1.53 (0.86, 2.72)</td>
<td>0.150</td>
</tr>
<tr>
<td>Valve/aortic surgery (+ CABG) [n (%)]</td>
<td>278 (28)</td>
<td>237 (25)</td>
<td>41 (52)</td>
<td>3.03 (1.95, 4.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bypass time (min) [median (IQR)]</td>
<td>86 (69–111)</td>
<td>85 (68–108)</td>
<td>111 (84–172)</td>
<td>1.07 (1.05, 1.09) ‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cross-clamp time (min) [median (IQR)]</td>
<td>50 (37–72)</td>
<td>49 (37–67)</td>
<td>75 (45–113)</td>
<td>1.07 (1.05, 1.10) †</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP (ng litre⁻¹) [median (IQR)]*</td>
<td>289 (120, 847)</td>
<td>268 (114, 765)</td>
<td>932 (309, 1719)</td>
<td>1.03 (1.01, 1.04) ‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP ≥ 289 ng litre⁻¹ [n (%)]</td>
<td>505 (50)</td>
<td>444 (48)</td>
<td>61 (77)</td>
<td>3.52 (2.08, 5.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Logistic EuroSCORE [median (IQR)]</td>
<td>2.9 (1.6, 5.4)</td>
<td>2.7 (1.5, 4.8)</td>
<td>5.8 (3.0, 9.8)</td>
<td>1.05 (1.03, 1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additive EuroSCORE [median (IQR)]</td>
<td>4 (2–6)</td>
<td>4 (2–6)</td>
<td>6 (4–8)</td>
<td>1.24 (1.17, 1.33)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

longer a significant predictor (HR 1.00 per 250 ng litre⁻¹, 95% CI 0.98–1.02, P = 0.80) of 3 yr mortality. In this multivariable model, the significant predictors of death were age (HR 1.05 per yr, 95% CI 1.01–1.08, P = 0.005), a history of heart failure (HR 2.21, 95% CI 1.20–4.09, P = 0.01), bypass time (HR 1.05 per 5 min, 95% CI 1.03–1.07, P < 0.001), and a history of prior cardiac surgery (HR 2.75, 95% CI 1.07–7.05, P = 0.03).

Relative and additive value of NT-proBNP and EuroSCORE in the prediction of 3 yr mortality

In further models, only NT-proBNP and the relevant EuroSCORE were entered. When both the logistic EuroSCORE and NT-proBNP were entered into a regression model, they remain powerful and independent predictors of 3 yr mortality (HR for EuroSCORE 1.05 per point, 95% CI 1.03–1.07, P < 0.001 and HR for NT-proBNP 1.02 per 250 ng litre⁻¹, 95% CI 1.01–1.03, P = 0.02). When NT-proBNP was entered into similar models as a dichotomous variable, the independent hazard associated with a level at or above the median (≥289 ng litre⁻¹) was 3.09 (95% CI 1.83–5.24) in a model including the logistic EuroSCORE and 2.22 (95% CI 1.27–3.90) in a model with the additive EuroSCORE.

Comparison of the ROC curves suggests that the logistic EuroSCORE, additive EuroSCORE, and BNP were very similar in their ability to predict 3 yr mortality. The AUCs for both the logistic and additive EuroSCOREs are identical at 0.71 (95% CI for both 0.65–0.77). For NT-proBNP, the AUC was 0.70 (95% CI 0.63–0.76, P < 0.001; P = 0.70 for comparison with logistic EuroSCORE AUC and P = 0.61 for comparison with additive EuroSCORE AUC). When NT-proBNP concentrations were combined with either the logistic or the additive EuroSCORE, the AUC was 0.72 (0.66–0.78; P = 0.30 and 0.35, respectively, for comparison with NT-proBNP concentrations alone and P > 0.05 for comparisons with appropriate form of EuroSCORE alone).

Assessment of the NRI based on risk thresholds confirms that knowledge of one adds very little prognostic information
when the other was known. When NT-proBNP concentrations were used to reclassify the risk determined by the logistic EuroSCORE, the NRI was \(2.0.8\%\), \(P=0.91\). When a model that includes both NT-proBNP and logistic EuroSCORE was compared with NT-proBNP alone, there was a modest, and non-significant, improvement in the NRI (6.8%, \(P=0.34\)). Likewise, when this combined model was compared with the logistic EuroSCORE alone, the NRI was 7.2% (\(P=0.09\)).

At the median for our cohort (NT-proBNP 289 ng litre\(^{-1}\)), the sensitivity was 78% (95% CI 68–87%), specificity of 52% (43–54%), positive predictive accuracy of 13 (9–16%) and negative predictive accuracy of 96 (94–98%), and a 6% (4–8%) risk of death (Table 2). Patients with NT-proBNP concentrations in the lowest decile had a 2% chance of dying at 3 yr, compared with a 19% chance in the highest decile.

**NT-proBNP concentrations as predictors of outcome in patients surviving at least 30 days after surgery**

In 981 patients who survived >30 days, the unadjusted HR for each 250 ng litre\(^{-1}\) increase in NT-proBNP was 1.02, 95% CI 1.00–1.04, \(P=0.045\), and for concentrations >289 ng litre\(^{-1}\), it was 4.17, 95% CI 2.03–8.59, \(P<0.001\). When adjusted for additive EuroSCORE, the HR for each 250 ng litre\(^{-1}\) increase in NT-proBNP was 1.01, 95% CI 0.99–1.03, \(P=0.49\), and for concentrations >289 ng litre\(^{-1}\), it was 2.77, 95% CI 1.30–5.92, \(P=0.009\). The results of this sensitivity analysis considering only patients surviving >30 days are consistent in size and direction with those for all patients. Given the relatively small number of events in this subgroup (\(n=50\)), no further multivariable analyses were performed.

**Discussion**

In this study of 1010 non-selected patients undergoing cardiac surgery, we found that NT-proBNP was a univariable predictor of 3 yr mortality but was no longer a significant predictor in a multivariable model. The EuroSCORE and pre-operative NT-proBNP concentrations have moderate and very similar predictive accuracy for all-cause mortality at 3 yr. Assessment of the NRI based on risk thresholds suggests that knowledge of one result adds little prognostic information when the other is known.

**EuroSCORE and long-term risk of death**

EuroSCORE is a reasonably accurate predictor of short-term morbidity and mortality after cardiac surgery.\(^5\) This tool is
used to allow risk-adjusted comparison of mortality outcomes between cardiac units. Anecdotal evidence suggests, however, that it is less commonly used in mortality prediction for individual patients. There is growing evidence that EuroSCORE is also predictive of longer term mortality in this patient group, although there is little evidence that this long-term prognostic utility is widely used in clinical practice either. We have confirmed that in a non-selected group of patients undergoing cardiac surgery, EuroSCORE predicts 3 yr all-cause mortality with moderate accuracy. Potentially, such information, or preoperative concentrations of NT-proBNP, could be used to identify a group of patients who may benefit from closer follow-up and intensive medical management after surgery, although this remains unproven.

**NT-proBNP and long-term risk of death**

NT-proBNP has been shown to have moderate predictive accuracy for early morbidity and mortality in this setting, including our prior publication in this cohort of patients. There is one existing study looking at the predictive accuracy of NT-proBNP in longer term mortality after cardiac surgery.

The results of this study suggested that BNP was predictive of 5 yr mortality after CABG surgery. In this study, the authors dichotomized BNP around a median value of 292 ng litre$^{-1}$ and found an HR of 1.89 (CI 1.08–3.33) for 5 yr mortality. They also presented ROC data with an AUC of 0.63 for 5 yr mortality compared with our AUC of 0.70 for 3 yr mortality using NT-proBNP. In this analysis, we have shown that NT-proBNP predicts mortality at 3 yr with moderate accuracy and is almost identical in this regard to EuroSCORE. However,
knowledge of one does not improve the predictive accuracy of the other. Likewise, the results of our multivariable analyses suggest that factors such as the age of the patient, a history of heart failure, and the duration of surgery are more important predictors of long-term outcome than NT-proBNP.

Comparison of EuroSCORE and NT-proBNP

Although the ability of either NT-proBNP or EuroSCORE to predict mortality at 3 yr is only modest, it could be argued that since this is such a clearly defined and important outcome even moderate predictive accuracies are useful when making such important treatment-based decisions. In addition, given that both methods provide similar long-term prognostic information, it is appropriate to consider other aspects of the clinical utility of these tools in practice. EuroSCORE is derived using nine patient-related, four cardiac-related, and four operative-related factors that are routinely available in clinical practice. There is no additional cost in acquiring the data used to calculate this score and in many centres the EuroSCORE is commonly calculated for clinical audit purposes. The calculation of logistic EuroSCORE cannot, however, be easily performed at the bedside or in the clinic as it requires a mathematical calculation. This can be completed using freely available calculators—but does require the data to be retrieved and entered, at a moderate cost in terms of staff time. The additive EuroSCORE is somewhat easier to calculate, but available evidence suggests it is slightly less accurate, especially in high-risk patients.

NT-proBNP is a simple blood test, which can easily be performed in most biochemistry laboratories as part of a routine preoperative assessment or using a near patient desk-top analyser. It can be measured quickly and objectively. The cost per test is approximately UK £25, but this is negligible when compared with the costs incurred during surgery and follow-up. It could be argued that a single numerical and objective blood test result that can be rapidly available at a pre-admission clinic may have even higher clinical utility than calculation of a clinical risk prediction score. The costs and a variety of other local factors would, however, have to be weighed up in deciding the relative usefulness of these measures in each cardiac centre. In addition, it is important to recognize that appropriate thresholds will vary depending on the assay and marker (BNP or NT-proBNP) that is used. In addition, suitable cut-off concentrations of natriuretic peptides will be influenced by the case mix, and in particular the prevalence of valvular heart disease. Local thresholds need, therefore, to be identified and validated, taking such factors into account.

This study is the largest to date assessing the utility of natriuretic peptides in patients undergoing cardiac surgery. Patients were unselected, our primary outcome was objective, and the use of Scottish national vital statistics ensures comprehensive follow-up. In addition, the relative and combined values of NT-proBNP and the logistic EuroSCORE were comprehensively assessed. The study was performed in a single centre. This has inherent limitations. The study cohort was heterogeneous and included patients undergoing CABG, valve surgery, or both. Although the median NT-proBNP concentrations were lower among patients undergoing isolated CABG than in those undergoing valve, aortic, or both surgery (with or without CABG), the hazard associated with increasing concentrations is similar in both groups and there is no evidence of statistical interaction. This suggests that NT-proBNP concentrations have similar prognostic utility in both of these settings. Any threshold used would, however, need to take the type of surgery into account, and further studies may be warranted specifically in these important subgroups.

Conclusions

We conclude that both EuroSCORE and NT-proBNP have moderate and similar accuracy in predicting mortality at 3 yr in a non-selected group of cardiac surgery patients. The information they provide is not additive and, therefore,
combining these tools does not improve prognostic accuracy, when compared with either alone. The clinical applicability of both of these measures is reasonable and the choice of which strategy to use in clinical practice may depend on the balance of cost and local logistical factors.

**Declaration of interest**

None declared.

**Funding**

The initial study was funded by the British Heart Foundation. The funding organization approved the initial study design, but not the follow-up study design and had no role in data collection, analysis, or interpretation. Likewise, it had no role in the preparation or approval of the current manuscript.

**References**

10. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical practice. Heart 2006; 92: 843–9