

# Comparison of the Utility of Preoperative *versus* Postoperative B-type Natriuretic Peptide for Predicting Hospital Length of Stay and Mortality after Primary Coronary Artery Bypass Grafting

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## ABSTRACT

**Background:** Preoperative B-type natriuretic peptide (BNP) is known to predict adverse outcomes after cardiac surgery. The value of postoperative BNP for predicting adverse outcomes is less well delineated. The authors hypothesized that peak postoperative plasma BNP (measured postoperative days 1–5) predicts hospital length of stay (HLOS) and mortality in patients undergoing primary coronary artery bypass grafting, even after adjusting for preoperative BNP and perioperative clinical risk factors.

**Methods:** This study is a prospective longitudinal study of 1,183 patients undergoing primary coronary artery bypass grafting surgery. Mor-

tality was defined as all-cause death within 5 yr after surgery. Cox proportional hazards analyses were conducted to separately evaluate the associations between peak postoperative BNP and HLOS and mortality. Multivariable adjustments were made for patient demographics, preoperative BNP concentration, and clinical risk factors. BNP measurements were  $\log_{10}$  transformed before analysis.

**Results:** One hundred fifteen deaths (9.7%) occurred in the cohort (mean follow-up = 4.3 yr, range = 2.38–5.0 yr). After multivariable adjustment for preoperative BNP and clinical covariates, peak postoperative BNP predicted HLOS (hazard ratio [HR] = 1.28, 95% CI = 1.002–1.64,  $P = 0.049$ ) but not mortality (HR = 1.62, CI = 0.71–3.68,  $P = 0.25$ ), whereas preoperative BNP independently predicted HLOS (HR = 1.09, CI = 1.01–1.18,  $P = 0.03$ ) and approached being an independent predictor of mortality (HR = 1.36, CI = 0.96–1.94,  $P = 0.08$ ). When preoperative and peak postoperative BNP were separately adjusted for within the clinical multivariable models, each independently predicted HLOS (preoperative BNP HR = 1.13, CI = 1.05–1.21,  $P = 0.0007$ ; peak postoperative BNP HR = 1.44, CI = 1.15–1.81,  $P = 0.001$ ) and mortality (preoperative BNP HR = 1.50, CI = 1.09–2.07,  $P = 0.01$ ; peak postoperative BNP HR = 2.29, CI = 1.11–4.73,  $P = 0.02$ ).

**Conclusions:** Preoperative BNP may be better than peak postoperative BNP for predicting HLOS and longer term mortality after primary coronary artery bypass grafting surgery.

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## What We Already Know about This Topic

- ❖ Preoperative B-type natriuretic peptide (BNP) predicts adverse outcomes after cardiac surgery
- ❖ Postoperative BNP may reflect worsening cardiac function, but whether it provides additional prognostic value beyond assessment of preoperative BNP is uncertain

## What This Article Tells Us That Is New

- ❖ In more than 1,100 patients undergoing coronary artery bypass graft surgery, peak postoperative BNP adds little to the value of preoperative BNP measurement alone for predicting hospital stay and mortality

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**P**LASMA B-type natriuretic peptide (BNP) is secreted primarily by cardiac ventricular myocytes in response to increased ventricular wall stress related to volume expansion, pressure overload, or ischemia.<sup>1,2</sup> In addition to having compensatory diuretic, natriuretic, and vasodilatory properties, plasma BNP is an established diagnostic and prognostic biomarker in both ambulatory heart failure and acute coronary syndrome patients.<sup>2–11</sup> Similarly, elevations in preoperative BNP have been shown to predict increased morbidity or mortality after cardiac surgery,<sup>12–17</sup> even after adjusting for clinical risk factors.<sup>13–15</sup> Postoperative BNP has the potential to reflect both the preoperative condition of the heart and myocardial insults induced by intraoperative and early postoperative cardiac stress. However, the utility of postoperative plasma BNP for perioperative risk stratification has not been as clearly delineated, possibly because previous studies have used small cohorts or have enrolled subjects undergoing diverse surgeries.<sup>12,16–22</sup> Furthermore, previous studies have not directly compared the predictive value of preoperative *versus* postoperative plasma BNP. Therefore, using a prospectively enrolled cohort of 1,183 subjects undergoing primary coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB), we hypothesized that peak postoperative plasma BNP independently predicts increased hospital length of stay (HLOS) and up to 5 yr all-cause mortality, even after adjusting for preoperative BNP concentration and clinical risk factors.

## Materials and Methods

### Study Population

Between August 2001 and September 2006, 1,519 men and women aged 20 to 89 yr scheduled for isolated primary CABG surgery with CPB at Brigham Women's Hospital, Boston, Massachusetts, and Texas Heart Institute, St. Luke's Episcopal Hospital, Houston, Texas, were prospectively enrolled in an ongoing parent study known as the CABG Genomics Study.<sup>††23,24</sup> Respective institutional review board approval and written informed consent of the subjects was obtained. CABG Genomics Study exclusion criteria included a preoperative hematocrit less than 25% or transfusion of leukocyte-rich blood products within 30 days before surgery. Enrolled subjects were, in addition, prospectively excluded from the analysis of this study if they had undergone previous cardiac surgery, if they underwent emergency surgery or concurrent valve surgery, if they received a preoperative inotrope, intraaortic balloon pump, or ventricular assist device support, or if they were missing preoperative or peak postoperative plasma BNP measurements. Patients with severe renal dysfunction (requiring preoperative hemodialysis or having preoperative serum creatinine > 3 mg/dl) were also excluded from analysis because severe renal dys-

function and perioperative dialysis can variably affect perioperative plasma BNP concentrations.<sup>25,26</sup>

### Data and Blood Collection

Data were collected for each enrolled subject during primary hospitalization using a detailed prospectively designed study case report form that included (1) preoperative demographic characteristics, comorbidities, and medications; (2) surgical characteristics; and (3) postoperative in-hospital events. Data were subjected to automated range and logic checking and an additional manual audit of a proportion of records. Postoperative patient survival was assessed annually by mail or telephone interviews, and by examination of the Social Security Death Index. Death events were assessed through February 1, 2009.

Plasma samples obtained preoperatively and on postoperative days (PODs) 1–5 were stored in vapor-phase liquid nitrogen until analysis. BNP and cardiac troponin I were measured for all time points at a single core laboratory using sandwich immunoassays on a Triage<sup>®</sup> platform (Biosite, San Diego, CA).

### Definitions

Study predictor covariates were prospectively defined as follows. Peak postoperative plasma BNP was assessed if a subject had at least three POD 1–5 measures and was defined as the highest of the measured POD 1–5 values. Creatinine clearance was estimated for all subjects using the four variable estimated glomerular filtration rate equation from the Modification of Diet in Renal Disease Study Group.<sup>27,28</sup> Postoperative creatinine clearance was estimated using each subject's peak postoperative creatinine from routine measurements made during primary hospitalization. Postoperative ventricular dysfunction was defined as a new requirement for two or more inotropes or as a new placement of an intraaortic balloon pump or ventricular assist device either during the intraoperative period after the patient separated from CPB or postoperatively in the intensive care unit. Inotrope support was defined as continuous infusion of amrinone, milrinone, dobutamine, dopamine (>5  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ), epinephrine, isoproterenol, norepinephrine, or vasopressin. New onset postoperative atrial fibrillation was defined as the occurrence of atrial fibrillation in patients who did not present for surgery in atrial fibrillation but who developed atrial fibrillation postoperatively as identified from nursing, physician, or electrocardiogram reports during primary hospitalization.

Mortality was defined as all-cause death within 5 yr after primary CABG surgery. HLOS was assessed as a continuous outcome for all analyses except receiver operating characteristic (ROC) curve analysis. For ROC analysis, extended HLOS was defined as primary hospitalization longer than 12 days after surgery (90th percentile for the study cohort).

### Statistical Analysis

Statistical analyses were conducted using SAS (version 9.1; SAS Institute, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria). The R statistical package powerSur-

†† <http://clinicaltrials.gov/show/NCT00281164>. Accessed July 10, 2009.

**Table 1.** Patient Demographics, Medications, and Perioperative Clinical Risk Factors for Increased Hospital Length of Stay and Mortality after Primary Coronary Artery Bypass Grafting

Preoperative Demographics and Risk Factors (n = 1,183)	Mean or Proportion	Univariate Association with HLOS (Hazard Ratio, <i>P</i> Value)	Univariate Association with All-cause Mortality (Hazard Ratio, <i>P</i> Value) 115 Death Events
Age (yr)	63.8 ± 10.1	1.01, < 0.0001	1.08, < 0.0001
Female gender	213 (18.0)	1.10, 0.20	0.93, 0.76
Institution			
Brigham and Women's Hospital	879 (74.3)	1.31, < 0.0001	0.75, 0.21
Texas Heart Institute	304 (25.7)		
Ethnicity (minority)	190 (16.1)	1.13, 0.12	0.51, 0.04
Diabetes mellitus (n = 1,182)	344 (29.1)	1.14, 0.04	1.32, 0.16
Hypertension (n = 1,180)	882 (74.7)	1.21, 0.004	1.00, 0.99
Hypercholesterolemia (n = 1,178)	886 (75.2)	0.85, 0.02	0.49, 0.0002
Obesity (BMI > 30 kg/m <sup>2</sup> )	471 (39.8)	1.18, 0.006	1.23, 0.28
Smoking, > 30-pack-year history (n = 1,135)	305 (26.9)	1.16, 0.03	2.36, < 0.0001
Preoperative creatinine clearance (ml · min <sup>-1</sup> · 1.73 m <sup>-2</sup> ) (n = 1,182)	74.7 ± 20.7	0.995, < 0.0001	0.99, 0.02
Myocardial infarction ≤ 2 wk preoperatively (n = 1,181)	206 (17.4)	1.28, 0.002	1.38, 0.15
Left ventricular ejection fraction (%) (n = 1,130)	52.7 ± 12.4	0.99, < 0.0001	0.97, < 0.0001
Coronary artery regions with > 50% stenosis		Overall <i>P</i> value 0.01	Overall <i>P</i> value 0.03
0–1 Region	87 (7.3)	1	1
2 Regions	390 (33.0)	0.74	0.43
3 Regions	706 (59.7)	0.85	0.47
Mitral insufficiency (moderate or severe) (n = 1,142)	25 (2.2)	1.30, 0.20	3.34, 0.002
Past arrhythmia	118 (10.0)	1.57, < 0.0001	2.23, 0.0009
Anemia (n = 1,180)	391 (33.1)	1.27, 0.0001	1.94, 0.0004
Median preoperative BNP (pg/ml) (10th and 90th percentile), mean preoperative BNP (pg/ml) ± SD	16.4, [1.5, 122.8], 47.6 ± 92.8	1.22 for log <sub>10</sub> increase, < 0.0001	1.99 for log <sub>10</sub> increase, < 0.0001
Preoperative cTnI > 0.1 μg/l	173 (14.6)	1.11, 0.21	0.91, 0.72
Preoperative medications			
ACE inhibitor (n = 1,182)	549 (46.4)	1.10, 0.09	0.84, 0.34
Diuretic (n = 1,182)	249 (21.1)	1.42, < 0.0001	1.33, 0.18
Statin	915 (77.3)	0.87, 0.04	0.55, 0.002
Digoxin	32 (2.7)	1.81, 0.002	3.94, < 0.0001
β blocker	913 (77.2)	0.87, 0.05	0.67, 0.04
Aspirin	899 (76.0)	0.89, 0.10	0.73, 0.12
Nonaspirin platelet inhibitor (n = 1,182)	257 (21.7)	1.29, 0.0003	0.83, 0.45
Nitroglycerin intravenous (n = 1,178)	120 (10.2)	1.04, 0.67	0.87, 0.67
Heparin intravenous	267 (22.6)	1.10, 0.16	1.13, 0.58

(continued)

Table 1. Continued

Preoperative Demographics and Risk Factors (n = 1,183)	Mean or Proportion	Univariate Association with HLOS (Hazard Ratio, <i>P</i> Value)	Univariate Association with All-cause Mortality (Hazard Ratio, <i>P</i> Value) 115 Death Events
Surgical risk factors			
Urgent surgery (n = 1,181)	647 (54.8)	1.02, 0.71	1.20, 0.33
Cardiopulmonary bypass time > 120 min	257 (21.7)	1.20, 0.01	0.58, 0.04
No. coronary grafts (n = 1,182)		Overall <i>P</i> value 0.65	Overall <i>P</i> value 0.003
1–2 Grafts	176 (14.9)	1	1
3 Grafts	533 (45.1)	0.97	1.05
≥ 4 Grafts	473 (40.0)	1.03	0.51
In-hospital postoperative outcomes			
Ventricular dysfunction	138 (11.7)	2.33, < 0.0001	2.75, < 0.0001
New onset atrial fibrillation	340 (28.7)	1.81, < 0.0001	2.14, < 0.0001
Postoperative creatinine clearance (ml · min <sup>-1</sup> · 1.73 m <sup>-2</sup> ) (n = 1,182)	68.3 ± 21.5	0.99, < 0.0001	0.98, < 0.0001
Peak postoperative cTnI (μg/l)	1.25 [0.37, 7.49]	1.32 for log <sub>10</sub> increase, < 0.0001	0.90 for log <sub>10</sub> increase, 0.56

Data are shown as n (%) for dichotomous variables and mean ± SD or median (10th and 90th percentiles) for continuous variables. ACE = angiotensin converting enzyme; BMI = body mass index; BNP = B-type natriuretic peptide; HLOS = hospital length of stay.

vEpi (Channing Laboratory, Boston, MA) was used for Cox proportional hazards model-based power calculations.<sup>29</sup> After excluding subjects from analysis according to prospectively defined exclusion criteria, assuming 80% power and a type I error rate = 0.05, we estimated a minimum detectable unadjusted hazard ratio (HR) of 2.28 for the association between a 1 unit change in log<sub>10</sub> peak postoperative BNP and risk of mortality during 5 yr postoperative follow-up.

The Wilcoxon signed-rank test was used to compare differences in BNP concentrations between the different study time points. The Wilcoxon rank sum test was used to conduct between group comparisons of BNP levels measured at each time point after stratifying subjects by occurrence of extended HLOS or by mortality during up to 5 yr follow-up. Because preoperative and peak postoperative BNP data were right skewed, continuous plasma BNP was log<sub>10</sub> transformed to normalize distribution before regression analyses. Linear regression was used to determine the square of Pearson correlations (*r*<sup>2</sup>), reflecting association between log<sub>10</sub> preoperative and log<sub>10</sub> postoperative BNP (peak postoperative and POD 1) measurements. Categorical and continuous patient and clinical characteristics (table 1) were assessed for univariate association with HLOS or mortality using Cox proportional hazards regression analyses.

Using covariates listed in table 1, multivariable prediction models for HLOS and up to 5 yr mortality were separately developed using Cox proportional hazards regression with a semiparsimonious stepwise selection approach (two-tailed nominal *P* value thresholds for model entry and exit were 0.15 and 0.05, respectively). Age, gender, institution, and

ethnicity were locked into the multivariable HLOS and mortality models before stepwise selection. Despite dropping out of the models during stepwise selection, the left ventricular ejection fraction covariate was subsequently forced back into both the HLOS and the mortality models because of perceived potential for this covariate to confound associations between BNP and the study outcomes. To avoid excessive influence of subjects who were outliers for HLOS, subjects who had HLOS greater than 30 days were censored at 30 days. For seven subjects who died during primary hospitalization within 30 days of surgery, HLOS was censored on the day of death. To assess whether peak postoperative BNP independently predicted HLOS or mortality after adjusting for preoperative BNP and perioperative clinical risk factors, peak postoperative BNP was added into both the HLOS and the mortality multivariable Cox proportional hazards models. To secondarily assess whether peak postoperative BNP predicted HLOS and mortality after adjusting for perioperative clinical risk factors but not adjusting for preoperative BNP, peak postoperative BNP was added into both the HLOS and the mortality models without preoperative BNP being included in the models. Because several previous studies have only assessed the predictive value of postoperative BNP measured approximately 24 h after cardiac surgery,<sup>12,17,18,20,21</sup> we in addition used the same approach that we used for assessing peak postoperative BNP to assess the independent value of BNP measured on POD 1 for predicting HLOS and mortality.

Akaike information criteria (AIC) were used to compare goodness of fit for the multivariable HLOS and mortality models including (1) clinical covariates without any BNP covariates, (2) clinical covariates with preoperative



BNP added, (3) clinical covariates with peak postoperative BNP added, and (4) clinical covariates with preoperative and peak postoperative BNP added simultaneously. The AIC is a statistical criterion used to compare how well different multivariable regression models that contain data from the same exact patients predict an outcome. A multivariable model is considered better for predicting a study outcome if it has a lower AIC. ROC curves were used to assess the relationship between peak postoperative BNP concentrations and both extended HLOS and mortality through 2.38 yr of follow-up (the minimum duration of study follow-up that all study subjects had reached). Both the HLOS and the mortality outcomes were dichotomized before ROC assessment because ROC analyses should not be conducted for time-censored outcome data. Areas under the ROC curves with 95% CIs and related specificities and sensitivities for the 75th percentile of peak postoperative BNP were calculated.

## Results

Of the 1,519 subjects enrolled into the source cohort during the study period, 336 were prospectively excluded from the analysis for one or more of the following exclusion criteria: no CABG surgery performed ( $n = 16$ ), previous cardiac surgery ( $n = 6$ ), concurrent valve surgery performed ( $n = 61$ ), emergency surgery ( $n = 4$ ), CPB not used ( $n = 52$ ), aortic cross-clamp not used ( $n = 76$ ), preoperative intraaortic balloon pump ( $n = 39$ ), preoperative inotropes ( $n = 8$ ), preoperative hemodialysis ( $n = 2$ ), preoperative serum creatinine more than 3 mg/dl ( $n = 4$ ), no preoperative BNP ( $n = 98$ ), or no peak postoperative BNP measurement ( $n = 166$ ). Three of the subjects excluded for missing peak postoperative BNP died during the first five PODs (two died on POD 1 and one died on POD 4).

### Patient Characteristics

Perioperative demographic, medical, and surgical characteristics of the 1,183 subjects included in the study analysis are listed in table 1 along with their univariate associations with HLOS and mortality during up to 5 yr of follow-up. Log<sub>10</sub> preoperative plasma BNP concentration was univariately associated with both HLOS (HR = 1.22, 95% CI = 1.15–1.28,  $P < 0.0001$ ) and mortality (HR = 1.99, 95% CI = 1.53–2.60,  $P < 0.0001$ ).

### Changes in Perioperative Plasma BNP Concentrations through POD 5

POD 1–5 plasma BNP concentrations were all significantly increased compared with preoperative plasma BNP concentration ( $P < 0.0001$ ; fig. 1). Preoperative plasma BNP measurements significantly associated with peak postoperative plasma BNP ( $r^2 = 0.30$ ,  $P < 0.0001$ ). Median peak postoperative BNP concentration = 177.6 pg/ml, with a 10th to 90th percentile range of 77.7–475.6 pg/ml. Mean peak postoperative BNP is  $246.5 \pm 229.5$  pg/ml. Plasma BNP levels

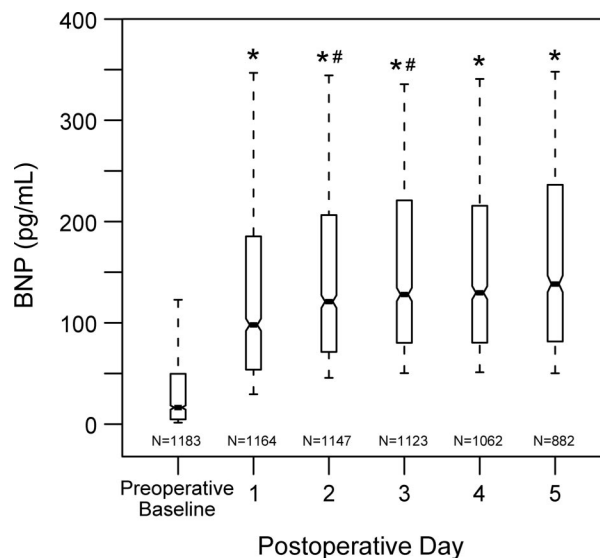


Fig. 1. Perioperative plasma B-type natriuretic peptide (BNP) concentrations for 1,183 subjects undergoing primary coronary artery bypass graft surgery with 10th, 25th, 50th, 75th, and 90th percentile values shown for each time point. \*  $P < 0.0001$  compared with preoperative baseline. #  $P < 0.0005$  compared with previous postoperative day.

rose consecutively and significantly during PODs 1–3 ( $P < 0.0005$ ), whereas POD 3–5 BNP measurements plateaued and did not increase significantly ( $P > 0.05$ ) (fig. 1). Patients with extended HLOS had significantly higher BNP concentrations at all perioperative time points ( $P < 0.0001$ ). Patients who died during the 5-yr follow-up period had significantly higher BNP concentrations at all perioperative time points ( $P < 0.0001$ ).

### Relationship of Peak Postoperative BNP to Hospital Stay

Seven subjects died in hospital within 30 days of surgery, and 12 subjects had HLOS longer than 30 days. Only four subjects were discharged on POD 4. Median HLOS was 7 days (10th and 90th percentiles: 5 and 12 days, respectively). One hundred thirteen subjects had extended HLOS (*i.e.*, greater than 12 days).

Peak postoperative plasma BNP concentrations are univariately associated with HLOS (HR = 2.04, 95% CI = 1.71–2.43,  $P < 0.0001$ ). The value of peak postoperative BNP concentration for predicting HLOS was evaluated after adjusting for preoperative BNP concentration, demographic characteristics (age, sex, institution, and ethnicity), and other clinical predictors including: preoperative medications, history of preoperative arrhythmia treatment, extended CPB time, preoperative left ventricular ejection fraction, new onset postoperative atrial fibrillation, postoperative ventricular dysfunction, and decreased postoperative creatinine clearance (table 2). After multivariable adjustment for preoperative BNP and clinical covariates, peak postoperative BNP predicted HLOS (HR = 1.28, 95% CI = 1.002–1.64,  $P = 0.049$ ). In this multivariable clinical model containing preoperative and peak postoperative BNP together, preoperative BNP also independently predicted HLOS (HR = 1.09, 95% CI = 1.01–1.18,  $P = 0.03$ ). When

**Table 2.** Proportional Hazards Model of Hospital Stay after Primary Coronary Artery Bypass Graft Surgery with Preoperative and Postoperative B-type Natriuretic Peptide Measures Alone and Together in the Model (n = 1,131\*)

AIC = 4,641.79 for Clinical Model without BNP Covariates	Model Including Log <sub>10</sub> Preoperative BNP AIC = 4,632.84		Model Including Log <sub>10</sub> Peak Postoperative BNP AIC = 4,633.60		Model Including Both Log <sub>10</sub> Preoperative BNP and Log <sub>10</sub> Peak Postoperative BNP AIC = 4,630.94	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Predictor						
Log <sub>10</sub> preoperative BNP	1.13 (1.05–1.21)	0.0007	—	—	1.09 (1.01–1.18)	0.03
Log <sub>10</sub> peak postoperative BNP	—	—	1.44 (1.15–1.81)	0.001	1.28 (1.002–1.64)	0.049
Age (10-yr increment)	1.07 (1.003–1.14)	0.04	1.07 (1.003–1.14)	0.04	1.06 (0.994–1.13)	0.08
Gender (female)	1.08 (0.92–1.27)	0.32	1.05 (0.89–1.24)	0.55	1.05 (0.89–1.23)	0.59
Institution	1.63 (1.40–1.90)	< 0.0001	1.70 (1.45–1.98)	< 0.0001	1.69 (1.45–1.98)	< 0.0001
Ethnicity (minority)	1.20 (1.01–1.43)	0.04	1.20 (1.01–1.43)	0.03	1.20 (1.01–1.43)	0.03
Preoperative nonaspirin platelet inhibitor	1.22 (1.05–1.41)	0.01	1.24 (1.07–1.44)	0.004	1.23 (1.06–1.43)	0.007
Preoperative $\beta$ blocker	0.84 (0.72–0.97)	0.02	0.84 (0.72–0.97)	0.02	0.83 (0.72–0.96)	0.01
History of preoperative arrhythmia treatment	1.24 (1.01–1.52)	0.04	1.26 (1.02–1.55)	0.03	1.24 (1.01–1.52)	0.04
Cardiopulmonary bypass time > 120 min	1.21 (1.04–1.41)	0.01	1.22 (1.05–1.42)	0.009	1.21 (1.04–1.41)	0.01
Preoperative left ventricular ejection fraction (%)	0.999 (0.994–1.004)	0.72	0.998 (0.993–1.003)	0.49	1.000 (0.994–1.005)	0.88
New onset postoperative atrial fibrillation	1.81 (1.57–2.08)	< 0.0001	1.78 (1.54–2.04)	< 0.0001	1.79 (1.55–2.05)	< 0.0001
Postoperative ventricular dysfunction	2.16 (1.76–2.65)	< 0.0001	2.08 (1.69–2.55)	< 0.0001	2.09 (1.70–2.56)	< 0.0001
Postoperative creatinine clearance (ml · min <sup>-1</sup> · 1.73 m <sup>-2</sup> )	0.988 (0.985–0.991)	< 0.0001	0.988 (0.985–0.991)	< 0.0001	0.989 (0.986–0.992)	< 0.0001

\* Fifty-two subjects missing one or more of the model's predictor variables and are not included in this analysis; 18 subjects censored for hospital length of stay more than 30 days or for in-hospital death within 30 days of surgery.

AIC = Akaike information criterion; BNP = B-type natriuretic peptide; CI = confidence interval.

preoperative BNP concentration was not included in the multivariable model, peak postoperative BNP continued to be an independent predictor of HLOS (HR = 1.44, 95% CI = 1.15–1.81,  $P$  = 0.001).

To assess the goodness of fit of multivariable models for predicting HLOS, AIC were compared for each of the four multivariable models that contained clinical covariates alone or in combination with preoperative or peak postoperative BNP (table 2). The AICs from highest to lowest (worst to best fit) were as follows: 4,641.79 (clinical covariates without BNP covariates), 4,633.60 (clinical covariates with peak postoperative BNP), 4,632.84 (clinical covariates with preoperative BNP), and 4,630.94 (clinical covariates with both preoperative and peak postoperative BNP). Therefore, preoperative BNP alone improved model fit more than peak postoperative BNP alone, but adding peak postoperative BNP to the model together with preoperative BNP additionally improved the model fit for HLOS.

Area under the ROC curve describing the relationship between peak postoperative BNP and occurrence of extended HLOS was 0.69 (95% CI: 0.63–0.74;  $P$  < 0.0001). Associated specificity and sensitivity for the peak postopera-

tive BNP cutoff of 303.7 pg/ml (75th percentile) were 77 and 46%, respectively.

### Relationship of Peak Postoperative BNP to Postoperative Mortality

During the 5-yr postoperative follow-up period, 115 subjects died (9.7%), with the mean time between surgery and death being  $2.5 \pm 1.6$  yr (range 6 days–5 yr). Because only seven subjects died within 30 days of surgery, we did not assess the predictors of short-term postoperative mortality. Mean follow-up for the 1,068 living patients was  $4.3 \pm 0.9$  yr (range 2.38–5.0 yr).

Peak postoperative plasma BNP concentrations univariately associated with mortality during up to 5 yr postoperative follow-up (HR = 5.89, 95% CI = 3.38–10.28,  $P$  < 0.0001). The value of peak postoperative BNP concentration for predicting mortality was evaluated after adjusting for preoperative BNP concentration, demographic characteristics (age, sex, institution, and ethnicity) and other likely clinical predictors including: preoperative medications, preoperative left ventricular ejection fraction, greater than 30 pack year history of smoking, and decreased postoperative

**Table 3.** Proportional Hazards Model of up to 5-yr All-cause Mortality after Primary Coronary Artery Bypass Graft Surgery with Preoperative and Postoperative BNP Measures Alone and Together in the Model (n = 1,089\*)

AIC = 1,267.26 for Clinical Model without BNP Covariates	Model Including Log <sub>10</sub> Preoperative BNP AIC = 1,262.21		Model Including Log <sub>10</sub> Peak Postoperative BNP AIC = 1,264.21		Model Including Both Log <sub>10</sub> Preoperative BNP and Log <sub>10</sub> Peak Postoperative BNP AIC = 1,262.89	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Predictor						
Log <sub>10</sub> preoperative BNP	1.50 (1.09–2.07)	0.01	—	—	1.36 (0.96–1.94)	0.08
Log <sub>10</sub> peak postoperative BNP	—	—	2.29 (1.11–4.73)	0.02	1.62 (0.71–3.68)	0.25
Age (10-yr increment)	1.65 (1.32–2.06)	< 0.0001	1.67 (1.34–2.09)	< 0.0001	1.63 (1.31–2.04)	< 0.0001
Gender (female)	0.81 (0.48–1.36)	0.42	0.77 (0.45–1.31)	0.33	0.76 (0.45–1.30)	0.31
Institution	1.42 (0.80–2.51)	0.23	1.49 (0.83–2.67)	0.18	1.51 (0.84–2.70)	0.17
Ethnicity (minority)	0.68 (0.33–1.43)	0.31	0.70 (0.34–1.47)	0.35	0.69 (0.33–1.45)	0.33
Preoperative digoxin	2.67 (1.32–5.38)	0.006	2.79 (1.39–5.62)	0.004	2.69 (1.34–5.43)	0.006
Preoperative beta blocker	0.63 (0.41–0.96)	0.03	0.66 (0.43–1.02)	0.06	0.63 (0.41–0.98)	0.04
> 30-pack-year history of smoking	1.73 (1.15–2.61)	0.009	1.68 (1.11–2.54)	0.01	1.70 (1.12–2.56)	0.01
Preoperative left ventricular ejection fraction (%)	0.99 (0.97–1.01)	0.19	0.99 (0.97–1.001)	0.07	0.99 (0.97–1.01)	0.24
Postoperative creatinine clearance (ml · min <sup>-1</sup> · 1.73 m <sup>-2</sup> )	0.987 (0.977–0.998)	0.02	0.987 (0.977–0.998)	0.02	0.988 (0.977–0.999)	0.03

\* Ninety-four subjects missing one or more of the model's predictor variables and are not included in this analysis; 100 death events included in the analysis.

AIC = Akaike information criterion; BNP = B-type natriuretic peptide; CI = confidence interval.

creatinine clearance (table 3). After these multivariable adjustments neither peak postoperative BNP concentration (HR = 1.62, 95% CI = 0.71–3.68,  $P = 0.25$ ) nor preoperative BNP concentration (HR = 1.36, 95% CI = 0.96–1.94,  $P = 0.08$ ) independently predicted mortality. When preoperative BNP concentration was not included in the multivariable model, peak postoperative BNP was an independent predictor of mortality (HR = 2.29, 95% CI = 1.11–4.73,  $P = 0.02$ ).

To assess which model had the most goodness of fit for predicting mortality, AIC were compared with the four multivariable models that contained clinical covariates alone or in combination with preoperative or peak postoperative BNP (table 3). The AICs from highest to lowest (worst to best fit) were as follows: 1,267.26 (clinical covariates without BNP covariates), 1,264.21 (clinical covariates with peak postoperative BNP), 1,262.89 (clinical covariates with both preoperative and peak postoperative BNP), and 1,262.21 (clinical covariates with preoperative BNP). Therefore, preoperative BNP alone improved model fit for predicting mortality more than peak postoperative BNP alone or peak postoperative BNP considered in combination with preoperative BNP.

Fifty-seven death events occurred during the first 2.38 yr of follow-up (the minimal duration that all subjects in the cohort had been followed). Area under the ROC curve describing the relationship between peak postoperative BNP and mortality up to 2.38 yr of postoperative follow-up = 0.64 (95% CI: 0.57–

0.72;  $P = 0.0002$ ). Associated specificity and sensitivity for the peak postoperative BNP cutoff of 303.7 pg/ml (75th percentile) were 76 and 46%, respectively.

### Relationship of POD 1 BNP to Postoperative Hospital Stay and Survival

Although post-CABG BNP measurements typically peak later than POD 1 (fig. 1), because several previous studies have assessed the utility of POD 1 BNP for perioperative risk stratification, we in addition assessed the predictive value of POD 1 BNP in our study cohort.<sup>12,17,18,20,21</sup> Preoperative plasma BNP measurements are significantly associated with POD 1 plasma BNP ( $r^2 = 0.23$ ,  $P < 0.0001$ ). Median POD 1 BNP concentration = 98.2 pg/ml, with a 10th to 90th percentile range of 29.5–347.9 pg/ml. POD 1 BNP concentrations were univariately associated with HLOS (HR = 1.29, 95% CI = 1.16–1.43,  $P < 0.0001$ ) and with mortality during up to 5 yr postoperative follow-up (HR = 2.94, 95% CI = 1.87–4.61,  $P < 0.0001$ ). However, POD 1 BNP was not significantly associated with either outcome after multivariable adjustments were made for the clinical covariates in tables 2 and 3, respectively (HR<sub>HLOS</sub> = 1.08, 95% CI = 0.94–1.24,  $P = 0.27$ ; HR<sub>mortality</sub> = 1.58, 95% CI = 0.91–2.74,  $P = 0.10$ ). This remained true when preoperative BNP was, in addition, included in the multivariable adjustments (HR<sub>HLOS</sub> = 0.99; 95% CI = 0.85–1.16,  $P = 0.92$ ; HR<sub>mortality</sub> = 1.19, 95% CI = 0.66–2.17,  $P = 0.56$ ).

## Discussion

Elevations in BNP are known to predict morbidity and mortality in both ambulatory cohorts and noncardiac surgical populations.<sup>1–11,30–33</sup> Preoperative BNP is also known to predict adverse outcomes after cardiac surgery, even after adjusting for known clinical risk factors such as preoperative left ventricular ejection fraction.<sup>13–15</sup> However, the utility of postoperative plasma BNP for perioperative risk stratification has yet to be clearly delineated,<sup>12,16–22</sup> particularly with regard to understanding the additional value it may provide over assessing preoperative BNP alone.

In the current study, after multivariable adjustment for preoperative BNP and clinical covariates, elevated peak postoperative BNP was a weak but significant predictor of HLOS and was not associated with mortality. In these same multivariable models, preoperative BNP independently predicted HLOS and approached being an independent predictor of mortality. The ability of the study's multivariable clinical model to predict mortality was improved (as assessed by AIC) when preoperative BNP was added to the clinical model alone compared with when it was added to the clinical model together with peak postoperative BNP.

Although we hypothesized that peak postoperative BNP would add significantly to the utility of preoperative BNP and clinical risk factors for predicting HLOS and mortality after CABG surgery, our study results suggest that there is little added benefit to assessing peak postoperative BNP either instead of or in addition to preoperative BNP. Our HLOS results suggest a small additional predictive value that was derived from assessing peak postoperative BNP and preoperative BNP together compared with assessing preoperative BNP alone. However, we do not believe that this finding is sufficiently strong to warrant measuring both preoperative and peak postoperative BNP together for the purposes of risk stratifying primary CABG patients.

Another finding of our study is that when preoperative and peak postoperative BNP were separately entered into the multivariable clinical prediction models for HLOS and mortality, both the preoperative and the peak postoperative BNP measurements independently predict each study outcome. This indicates that peak postoperative BNP could be useful for postoperative risk stratification, particularly if a preoperative BNP measurement is not available. This also supports the findings of a recent smaller study of mixed cardiac surgical patients that did not adjust for preoperative BNP but did find that peak postoperative BNP significantly predicted occurrence of major adverse cardiovascular events during the first postoperative year, even after adjusting for subjects' Euroscores.<sup>22</sup> That study assessed postoperative BNP values immediately after surgery and on PODs 1 and 5, and, consistent with our findings, postoperative BNP was significantly more elevated at later postoperative time points.<sup>22</sup> Approximately 20% of our primary CABG subjects were discharged on POD 5, and so assessing the peak of at least three POD 1–5 BNP measurements allowed us a high likelihood of cap-

turing an approximate peak postdischarge measurement without limiting us to biases induced by assessing only the latest postoperative time points (*i.e.*, assessing POD 5 BNP instead of peak postoperative BNP would have biased the analysis by eliminating those patients who did well enough to be discharged on POD 5 or earlier).

Although POD 1 BNP is clinically convenient to measure for immediate postoperative risk stratification, we found that it does not significantly predict HLOS and mortality after adjusting for clinical risk factors. This supports the findings of Provenchere *et al.*<sup>20</sup> who reported that POD 1 BNP did not independently predict 1-yr mortality in a smaller cohort of CABG and valve surgery patients after adjusting for clinical risk factors. This suggests that future investigations of the predictive value of BNP measured after cardiac surgery should focus on peak postoperative BNP measurements. In our primary CABG cohort, peak postoperative BNP tends to occur later in the postoperative course (POD 3–5) after the initial postoperative rise in BNP release begins to plateau.

BNP cut-points for predicting adverse outcomes in various cardiac or general population cohorts are often substantially lower than BNP levels observed in patients with acute heart failure, suggesting that even mild elevations in BNP may reflect subclinical myocardial pathology that puts patients at risk beyond what can be predicted using clinical signs and symptoms alone.<sup>1,11,30</sup> In our study, the CIs surrounding the HRs for peak postoperative BNP's associations with HLOS and with mortality are wider than those surrounding the HRs for preoperative BNP. This reflects greater variation in the range of postoperative *versus* preoperative BNP measurements (fig. 1) and may explain why we found preoperative BNP to be a more significant predictor of both HLOS and mortality despite preoperative BNP having smaller associated HRs than those observed for peak postoperative BNP. Although our study's findings suggest that preoperative BNP may be better than peak postoperative BNP for predicting HLOS and mortality, future studies of peak postoperative BNP that focus on prediction of longer term cardiac-specific outcomes such as heart failure may have narrower CIs surrounding HRs related to postoperative BNP, because the cardiac outcome is more strongly associated with peak postoperative BNP. Furthermore, although the areas under the ROC curves that we derived for the relationship between peak postoperative BNP and both extended HLOS and mortality (2.38 yr follow-up) indicate only moderate discriminatory ability of the peak postoperative BNP measurement, these areas are similar to the area under the curve reported by Fellahi *et al.*<sup>22</sup> for the ROC curve relating peak postoperative BNP to occurrence of 1 yr postoperative major adverse cardiovascular events. Future studies of peak postoperative BNP in relation to development of longer term heart failure-specific outcomes may reveal improved areas under associated ROC curves. Results to date suggest that although peak postoperative BNP adds to what can be predicted by clinical risk factors alone, it should not be used as a "stand-alone" predictor of adverse outcome after CABG surgery but



should be considered in conjunction with important clinical predictors.

Fellahi *et al.*<sup>22</sup> recently reported significant improvement in 1 yr major adverse cardiovascular events prediction in 224 subjects undergoing elective CABG or valve surgeries when subjects' Euroscores and peak postoperative BNP, cardiac troponin I, and C-reactive protein measurements were assessed together *versus* separately. One drawback to this multimarker approach is that the three measured biomarkers peak at different postoperative time points, necessitating the need for multiple postoperative measurements of three different postoperative biomarkers. The authors state that they did not analyze the value of simultaneous preoperative measurements of the three biomarkers because most of the preoperative biomarker assessments in their cohort were within the normal range and would, thus, warrant a larger sample size for assessment. The goal of our current study was to assess whether peak postoperative BNP added to what could be practically assessed by a single preoperative BNP measurement and routinely assessed clinical risk factors. However, given that we found preoperative BNP to be a more significant predictor of HLOS and mortality than peak postoperative BNP, a future study hypothesis could focus on the predictive value of simultaneous assessment of preoperative BNP, cardiac troponin I, and CRP measurements.

Several limitations of our study deserve consideration. First, this study included patients undergoing nonemergency primary CABG-only surgery with CPB. Therefore, caution should be taken in extrapolating these results to other surgical populations. However, the fact that perioperative BNP associates with HLOS and mortality in our study, even after excluding higher risk CABG patients, suggests that perioperative BNP can help to identify CABG patients who are at increased risk of adverse outcomes but who may not be clearly at risk based on clinical risk factors alone. Second, although we may not be able to completely account for institutional variations in perioperative management, we did statistically adjust for potential confounding related to institutional practice by including institution as a covariate in the study's multivariable HLOS and mortality models. Third, there are multiple commercially available BNP and N-terminal proBNP assays. Although both BNP and N-terminal proBNP measurements generally correlate well with each other and both have been used successfully for perioperative risk stratification, the absolute values of BNP and N-terminal proBNP are not interchangeable.<sup>31,32</sup> Furthermore, there is a variability in absolute values of measurements made with various commercially available BNP assays.<sup>33</sup> Thus, although results of this study, particularly with regard to cut-points in peak postoperative BNP, should be considered specific to the BNP assay used in this study, future studies should focus on risk stratification cutoffs for different BNP and N-terminal proBNP assays in both primary CABG and other cardiac surgical cohorts. Fourth, although this is the largest study to date of the value of in-hospital postoperative BNP for risk stratification of cardiac surgical patients, it is possible that a much larger study

with greater power might find that both preoperative BNP and peak postoperative BNP are independent predictors of up to 5-yr mortality. Finally, the outcomes of this study are limited to HLOS and all-cause mortality. Future studies may be warranted to assess the association between peak postoperative BNP and other longer term cardiac specific adverse outcomes such as development of postoperative heart failure, particularly because our HLOS results suggest that peak postoperative BNP may be able to detect additional intraoperative and postoperative cardiac insults that cannot be assessed using preoperative BNP.

## Conclusions

Early identification of cardiac surgical patients at risk for developing shorter and longer term adverse postoperative outcomes is important for initiating and developing preventive therapies and interventions that improve patient outcomes. In this study of primary CABG surgery patients, preoperative BNP concentration seems to be better than peak postoperative BNP for predicting hospital stay or all-cause mortality after primary CABG surgery.

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