Preoperative Serum Brain Natriuretic Peptide and Risk of Acute Kidney Injury After Cardiac Surgery

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Background—Acute kidney injury (AKI) after cardiac surgery is associated with poor outcomes and is difficult to predict. We conducted a prospective study to evaluate whether preoperative brain natriuretic peptide (BNP) levels predict postoperative AKI among patients undergoing cardiac surgery.

Methods and Results—The Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) study enrolled 1139 adults undergoing cardiac surgery at 6 hospitals from 2007 to 2009 who were selected for high AKI risk. Preoperative BNP was categorized into quintiles. AKI was defined with the use of the Acute Kidney Injury Network (AKIN) criteria; at least mild AKI was a ≥0.3-mg/dL or 50% rise in creatinine (n=407, 36%), and severe AKI was either a doubling of creatinine or the requirement of acute renal replacement therapy (n=58, 5.1%). In analyses adjusted for preoperative characteristics, preoperative BNP was a strong and independent predictor of mild and severe AKI. Compared with the lowest BNP quintile, the highest quintile had significantly higher risk of at least mild AKI (risk ratio, 1.87; 95% confidence interval, 1.40–2.49) and severe AKI (risk ratio, 3.17; 95% confidence interval, 1.06–9.48). After adjustment for clinical predictors, the addition of BNP improved the area under the curve to predict at least mild AKI (0.67–0.69; P=0.02) and severe AKI (0.73–0.75; P=0.11). Compared with clinical parameters alone, BNP modestly improved risk prediction of AKI cases into lower and higher risk (continuous net reclassification index; at least mild AKI: risk ratio, 0.183; 95% confidence interval, 0.061–0.314; severe AKI: risk ratio, 0.231; 95% confidence interval, 0.067–0.506).

Conclusions—Preoperative BNP level is associated with postoperative AKI in high-risk patients undergoing cardiac surgery. If confirmed in other types of patients and surgeries, preoperative BNP may be a valuable component of future efforts to improve preoperative risk stratification and discrimination among surgical candidates.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00774137. (Circulation. 2012;125:1347-1355.)

Key Words: acute kidney injury, cardiac surgical procedures, creatinine, natriuretic peptide, brain

Acute kidney injury (AKI) is a common complication during the early postoperative period after cardiac surgery, with rates up to 40% depending on how AKI is defined.1,2 Even mild elevations in serum creatinine (0.3 mg/dL [26 μmol/L]) are independently associated with adverse outcomes, including prolonged length of hospitalization and short- and long-term mortality.3–5 Consequently, there has been a renewed effort toward better understanding the risk factors of AKI to develop potential preventive and therapeutic strategies. Several risk-stratification algorithms exist that identify such risk factors in the preoperative (demographics, comorbid conditions), intraoperative (type of surgery, acuity of surgery), and postoperative (cardiovascular complications) periods.6–9 In addition, recent studies suggest...
Clinical Perspective on p 1355

Cardiovascular disease and heart failure are highly prevalent among those who undergo cardiac surgery, contributing to hemodynamic stress that may be poorly characterized by clinical history. Consequently, natriuretic peptide biomarkers that better characterize this underlying physiology have become well established in the diagnosis and management of patients with heart failure. These biomarkers provide important prognostic information across a variety of clinical settings, including stable and unstable coronary disease, valvular disease, and cardiac surgery. Preoperative elevations of B-type natriuretic peptide (BNP) and its precursor, N-terminal pro–B-type natriuretic peptide (NTproBNP), before cardiac10–12,14–20 and noncardiac21,22 surgeries are strongly predictive of postoperative events, including cardiovascular complications (myocardial infarction, heart failure, arrhythmias, cardiogenic shock), prolonged length of stay (intensive care unit and hospital), and mortality (short and long term). However, associations between natriuretic peptides and AKI remain unclear because previous studies are limited by small sample sizes, retrospective study designs, and suboptimal characterization of AKI.10–12 In the present study, we evaluated whether BNP elevations both before and after surgery are associated with AKI.

Methods

Study Sample

We conducted a prospective cohort study of adults undergoing cardiac surgery (coronary artery bypass grafting, surgery for valve disease, and both) at 6 academic medical centers in North America between July 2007 and December 2009. To include sufficient study outcomes, all enrolled patients were at high risk for AKI defined by the presence of 1 or more of the following criteria: preexisting renal impairment (baseline serum creatinine >2 mg/dL [177 μmol/L]), ejection fraction <35% or grade 3 or 4 left ventricular dysfunction, age >70 years, diabetes mellitus, concomitant coronary artery bypass grafting and valve surgery, or repeat revascularization surgery. Adult patients were excluded if they had evidence of AKI before surgery, prior kidney transplantation, preoperative serum creatinine level >4.5 mg/dL (400 μmol/L) or end-stage renal disease. All participants provided written informed consent, and the study was approved by each institution’s research ethics board. This clinical study was registered at www.clinicaltrials.gov as NCT00774137.

Study Protocol

Preoperatively, a blood sample was collected, centrifuged, processed, divided into aliquots in 0.5-cm³ vials, and stored at −80°C. Because many studies evaluating BNP used postoperative levels,12,14,15,18–20 we also conducted secondary analyses to evaluate whether relative or absolute increases in postoperative BNP levels independently predict subsequent AKI (postoperative level minus preoperative level). The first postoperative samples were collected soon after admission to the intensive care unit (mean±SD, 0.6±1.6 hours postoperatively), and the day 1 postoperative samples were collected on the morning of the first postoperative day in the intensive care unit (mean±SD, 16.0±5.0 hours postoperatively). These samples were also centrifuged, processed, divided into aliquots, and stored. One preoperative sample vial and each postoperative sample vial were used for biomarker measurements without any additional freeze-thaw. BNP measurements were conducted in a large batch with a Biosite Triage meter (Biosite Corp, San Diego, CA). Preoperative creatinine was measured as part of routine clinical care in the clinical laboratory of each hospital. Estimated glomerular filtration rates were calculated with the Chronic Kidney Disease Epidemiology Collaboration equation.23 Secondary postoperative predictors were used for multivariable adjustment and were obtained from the patient and the clinical record by use of the standardized definitions of the Society of Thoracic Surgeons data collection tool. We chose all variables that had been included in the prior Society of Thoracic Surgeons registry risk assessment tool for predicting AKI after cardiac surgery and others related to kidney function estimation. These included demographics (age, sex, race), comorbidities (hypertension, diabetes mellitus, heart failure, prior myocardial infarction), and surgery characteristics (elective or urgent; bypass, valvular surgery, or both; prior cardiac operation). Patients requiring emergent surgery were excluded from this study.

AKI was determined by the daily creatinine measurements during the entire hospital stay. At least mild AKI was defined by creatinine criteria for Acute Kidney Injury Network (AKIN) stage 1 or higher: an absolute creatinine increase ≥0.3 mg/dL or a ≥50% relative increase.24 Severe AKI was defined by AKIN stage 2 or higher: either a doubling of creatinine or the requirement of acute renal replacement therapy. Although AKIN criteria define creatinine changes occurring within a 48-hour period, the time required for creatinine elevations to occur depends on the half-life of excretion; ie, patients with lower levels of kidney function require longer periods of time to reach a new equilibrium state after a decrease in kidney function after acute injury. Because patients in this study included those at high risk for AKI, many of whom have lower levels of kidney function, we defined AKI according to AKIN criteria for creatinine changes that occurred during the entire hospital stay. Nonetheless, a sensitivity analysis using AKI events within the first 48 hours postoperatively was also conducted. Additional outcomes collected during the study included in-hospital death or requirement of acute renal replacement therapy and lengths of stay in the intensive care unit and hospital.

Statistical Analysis

We graphically evaluated the functional relationship of BNP with each outcome (at least mild AKI and severe AKI) using restricted cubic splines. On the basis of the spline regression, we used log-transformed serum BNP when it was included continuously in models (preoperative BNP [Figure 1] and postoperative BNP [Figure 1 in the online-only Data Supplement]). Using preoperative BNP values, we categorized our cohort into quintiles. We assessed linear trends by the Cochran-Armitage test for dichotomous outcomes and the Jonckheere-Terpstra test for continuous outcomes. We compared continuous variables with the 2-sample t test or Wilcoxon rank-sum test and dichotomous variables with the χ² test or Fisher exact test. We determined the crude and adjusted relative risks of AKI with multivariable Poisson regression.25 We adjusted for covariates that have been used in previous studies for prediction of AKI after cardiac surgery,8 including patient demographics (age [per year], sex, race), clinical risk factors (eg, baseline estimated glomerular filtration rate, hypertension, diabetes mellitus), and operative characteristics (eg, elective or urgent procedure and use of cardiopulmonary bypass). In addition, site was included as a fixed effect in multivariable models. We tested for interactions for chronic kidney disease, diabetes mellitus, chronic heart failure, elective/urgent, and age. The area under the receiver-operating characteristic curve (AUC) was used to determine the ability of the multivariable models to discriminate between AKI cases and noncases. We used likelihood ratio tests to evaluate whether the addition of serum BNP to the clinical model improved the accuracy of AKI risk prediction.26 As a second step to evaluate the impact of BNP on AKI risk prediction, we determined the continuous net reclassification index (NRI) and the integrated discrimination improvement (IDI) index.27–29 Log-transformed continuous BNP values were used to assess its discriminatory ability (receiver-operating characteristic curve analysis) and impact on risk prediction (continuous NRI and IDI analysis). Bootstrap confidence intervals were reported for AUCs and reclassification indexes (continuous NRI, IDI, relative IDI). All analyses
were completed separately for each outcome (at least mild AKI and severe AKI). Although urine albumin-to-creatinine ratio may be an important risk factor for AKI, existing risk models for AKI have not included it; thus, we did not include urine albumin-to-creatinine ratio in our primary models. However, all analyses were repeated with the addition of this ratio to our clinical model to demonstrate the improvement in AKI risk classification conferred by BNP even when we accounted for this important emerging AKI risk factor (Tables I and II and Figure II in the online-only Data Supplement).

In secondary analyses, we evaluated postoperative BNP independently, as absolute change from preoperative levels, and as a relative change from preoperative levels. This was done to determine whether postoperative BNP levels independently predict subsequent AKI. We performed all analyses in SAS version 9.2 (SAS Institute, Cary, NC) and R 2.11.0 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

Among the 1219 adults enrolled in this study, 76 participants did not have preoperative serum BNP results and 4 patients underwent emergent surgery, leaving 1139 subjects for analysis. The average age was 72 years (SD, 10 years), and 68% (n=776) were men. Most subjects were white (94%; n=1100). Among the surgical procedures, 48% (n=548) were coronary artery bypass grafting only, 29% (n=331) were valve only, and 23% (n=260) were both; 80% of surgeries were primary elective operations and 13% were reoperations. Preoperative kidney function was not decreased for most participants (creatinine, 1.09±0.34 mg/dL [96±30 μmol/L]; estimated glomerular filtration rate, 67±19 mL·min⁻¹·1.73 m⁻² [mean±SD]). Heart failure was common with ejection fraction <40% in 21% and diagnosis of heart failure in 26% (both characteristics were present in 11% of participants). When we compared baseline characteristics across quintiles of BNP (Table 1), the most striking differences were that persons in the highest BNP quintiles were older; were more likely to have hypertension, heart failure, reduced ejection fraction, and reduced kidney function; and were more likely to undergo a combined bypass and valve surgery. Those in the highest BNP quintile were less likely to be male or to have diabetes mellitus.

During the postoperative period, 407 patients (36%) had at least mild AKI and 58 (5.1%) patients had severe AKI. Patients who developed AKI were more likely to have a history of congestive heart failure, to undergo combined coronary artery bypass grafting and valve repair surgery, to have longer cardiopulmonary bypass time, to require a postoperative intra-aortic balloon pump, and to have a higher preoperative serum creatinine. The incidence of both at least mild AKI and severe AKI increased across quintiles of BNP (P for trend <0.001 and 0.002 for AKI and severe AKI, respectively; Figure 2). The risk of at least mild AKI increased across quintiles of BNP, with an approximate doubling in AKI risk for the highest compared with the lowest BNP quintile (Table 2). This relationship was only minimally attenuated after adjustment for patient demographics, clinical risk factors, and operative characteristics. Quintiles 3 through 5 remained independently associated with at least mild AKI and had BNP cut-point values similar to those identified in prior studies (≈50, 100, and 250 pg/mL). Associations between BNP quintiles and at least mild AKI did not differ significantly when stratified by those with...
varying degrees of kidney function (low versus high creatinine or chronic kidney disease versus no chronic kidney disease; \( P \) for interaction 0.9 and 0.06, respectively) or type of surgery (intra-aortic balloon pump versus no intra-aortic balloon pump, pump surgery versus no pump surgery, and elective versus nonelective surgery; all \( P \) for interaction >0.3). Restricting at least mild AKI events to the first 48 hours postoperatively also did not alter the associations observed with quintiles of BNP.

The risk of severe AKI increased across the first 3 BNP quintiles and then plateaued (Table 2). This corresponded to a 4-fold risk among the highest compared with the lowest BNP quintile. This relationship was attenuated slightly after adjustment for patient demographics, clinical risk factors, and operative characteristics. Quintiles 3 through 5 remained independently associated with severe AKI. When examining the association with other postoperative outcomes, we found that the fifth quintile was associated with the greatest risk of in-hospital death or dialysis. In addition, BNP quintiles were associated with linear increases for lengths of stay in both the intensive care unit and hospital.

The receiver-operating characteristic curve for the outcome of AKI had an AUC of 0.60 (SE, 0.02) when BNP levels alone were used and 0.67 (SE, 0.02) when the preoperative risk variables of the clinical model (Table 3) were used. The addition of BNP to the clinical model provided a modest incremental increase to 0.68 (SE, 0.02; likelihood ratio test, \( P \) = 0.01). When stratified by time after cardiac surgery (\( \geq 3 \) days \( n = 160 \), \( \leq 5 \) days \( n = 85 \)), risk prediction improved (AUC for \( \geq 3 \) days, 0.74 [SE, 0.02]; for \( \leq 5 \) days, 0.79 [SE, 0.03]). For the severe AKI outcome, the AUC was 0.63 (SE, 0.03) for BNP alone and 0.73 (SE, 0.04) for preoperative risk

<table>
<thead>
<tr>
<th>Quintile 1 (&lt;28 pg/mL; n=227)</th>
<th>Quintile 2 (28 – 56 pg/mL; n=228)</th>
<th>Quintile 3 (56–105 pg/mL; n=228)</th>
<th>Quintile 4 (105–241 pg/mL; n=228)</th>
<th>Quintile 5 (&gt;241 pg/mL; n=228)</th>
<th>( P ) for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>66.6 (11.6)</td>
<td>71.1 (8.7)</td>
<td>72.8 (8.4)</td>
<td>72.8 (9.8)</td>
<td>74.5 (9.6)</td>
</tr>
<tr>
<td>(&lt;65) y, n (%)</td>
<td>86 (38)</td>
<td>50 (22)</td>
<td>40 (18)</td>
<td>42 (18)</td>
<td>28 (12)</td>
</tr>
<tr>
<td>(65–75) y, n (%)</td>
<td>85 (37)</td>
<td>100 (44)</td>
<td>90 (39)</td>
<td>81 (36)</td>
<td>75 (33)</td>
</tr>
<tr>
<td>(75–85) y, n (%)</td>
<td>53 (23)</td>
<td>73 (32)</td>
<td>88 (39)</td>
<td>91 (40)</td>
<td>101 (44)</td>
</tr>
<tr>
<td>(&gt;85) y, n (%)</td>
<td>3 (1)</td>
<td>5 (2)</td>
<td>10 (4)</td>
<td>14 (6)</td>
<td>24 (11)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>177 (78)</td>
<td>156 (68)</td>
<td>154 (68)</td>
<td>140 (61)</td>
<td>149 (65)</td>
</tr>
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<td>White, n (%)</td>
<td>212 (93)</td>
<td>212 (93)</td>
<td>211 (93)</td>
<td>219 (96)</td>
<td>212 (93)</td>
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<td>Diabetes mellitus, n (%)</td>
<td>118 (52)</td>
<td>93 (41)</td>
<td>90 (39)</td>
<td>87 (38)</td>
<td>81 (36)</td>
</tr>
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<td>Hypertension, n (%)</td>
<td>170 (75)</td>
<td>177 (78)</td>
<td>188 (82)</td>
<td>183 (80)</td>
<td>178 (78)</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>42 (19)</td>
<td>54 (24)</td>
<td>62 (27)</td>
<td>65 (29)</td>
<td>70 (31)</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>26 (11)</td>
<td>32 (14)</td>
<td>50 (22)</td>
<td>76 (33)</td>
<td>108 (47)</td>
</tr>
<tr>
<td>Ejection fraction &lt;40%, n (%)</td>
<td>18 (9)</td>
<td>19 (10)</td>
<td>42 (21)</td>
<td>43 (20)</td>
<td>98 (46)</td>
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<td>Operative characteristics, n (%)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Prior cardiac surgery</td>
<td>29 (13)</td>
<td>26 (11)</td>
<td>25 (11)</td>
<td>29 (13)</td>
<td>38 (17)</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>192 (85)</td>
<td>193 (85)</td>
<td>180 (79)</td>
<td>178 (78)</td>
<td>164 (72)</td>
</tr>
<tr>
<td>Cardiac catheterization in last 48 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Surgery, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CABG</td>
<td>144 (63)</td>
<td>132 (58)</td>
<td>113 (50)</td>
<td>91 (40)</td>
<td>68 (30)</td>
</tr>
<tr>
<td>Valve</td>
<td>41 (18)</td>
<td>57 (25)</td>
<td>65 (29)</td>
<td>79 (35)</td>
<td>89 (39)</td>
</tr>
<tr>
<td>CABG and valve</td>
<td>42 (19)</td>
<td>39 (17)</td>
<td>50 (22)</td>
<td>58 (25)</td>
<td>71 (31)</td>
</tr>
<tr>
<td>Renal function (mean, SD)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative serum creatinine, mg/dL ( * )</td>
<td>1.03 (0.26)</td>
<td>1.01 (0.27)</td>
<td>1.09 (0.31)</td>
<td>1.09 (0.32)</td>
<td>1.21 (0.46)</td>
</tr>
<tr>
<td>Preoperative eGFR, mL·min(^{-1})·1.73 m(^2) ( * )</td>
<td>74.3 (19.6)</td>
<td>73.0 (19.5)</td>
<td>67.0 (18.7)</td>
<td>66.7 (18.6)</td>
<td>63.0 (24.5)</td>
</tr>
<tr>
<td>(&lt;30), n (%)</td>
<td>1 (0)</td>
<td>2 (1)</td>
<td>3 (1)</td>
<td>5 (2)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>(\geq30) and &lt;60, n (%)</td>
<td>56 (25)</td>
<td>57 (25)</td>
<td>86 (38)</td>
<td>76 (33)</td>
<td>100 (44)</td>
</tr>
<tr>
<td>(\geq60) and &lt;90, n (%)</td>
<td>127 (56)</td>
<td>130 (57)</td>
<td>119 (52)</td>
<td>128 (56)</td>
<td>78 (34)</td>
</tr>
<tr>
<td>(\geq90), n (%)</td>
<td>43 (19)</td>
<td>39 (17)</td>
<td>20 (9)</td>
<td>19 (8)</td>
<td>35 (15)</td>
</tr>
<tr>
<td>Preoperative serum BNP, median (IQR), pg/mL</td>
<td>16.8 (10.0–23.1)</td>
<td>40.8 (34.7–48.3)</td>
<td>77.6 (66.2–88.6)</td>
<td>151.2 (133.1–196.7)</td>
<td>422.8 (322.8–599.2)</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; and IQR, interquartile range.

\( * \)To convert serum creatinine values to millimoles per liter, multiply by 88.4.
variables alone. The AUC improved moderately to 0.74 (SE, 0.03) with the addition of BNP to the clinical model, although the P value for the likelihood ratio test was not significant (P = 0.06).

In addition to the AUC, we used the continuous NRI and IDI to determine whether BNP materially affected at least mild AKI risk classification. For patients with and without at least mild AKI, a scatterplot of these results (Figure 3) demonstrates the higher or lower predicted risks according to the clinical model alone versus the model with preoperative serum BNP included. Among the patients with AKI, 206 had higher predicted risk (above the diagonal line) and 193 had lower predicted risk in the new model. Among the patients without AKI, 412 had lower risk and 304 had higher risk in the new model. The continuous NRI is calculated by the net reclassification of the proportion of patients who move toward the correct direction indicated by the actual outcome: (206−193)/399+ (412−304)/716 = 0.183 (0.006−0.314). Continuous NRI among those with at least mild AKI (0.033; −0.043 to 0.110) was smaller than among those without at least mild AKI (0.151; 0.068−0.226), providing an improvement in risk prediction among controls compared with cases, although the overall performance was weak.28 The IDI was 0.014 (0.004−0.031) and relative IDI was 16.3% (9.3−21.8%). Similarly, the continuous NRI for severe AKI was 0.231 (−0.067−0.506), the IDI was 0.004 (−0.001−0.023), and the relative IDI was 8.8% (2.6−16.5%). Additional analyses demonstrated that the addition of urine albumin-to-creatinine ratio to our clinical model did not substantively alter the improvement in AKI risk classification conferred by BNP (Tables I and II and Figure II in the online-only Data Supplement).

In secondary analyses to evaluate the association between postoperative BNP levels and AKI, immediate (0−6 hours; Figure 4) and day 1 (data not shown) postoperative levels differed significantly between cases and noncases for both at least mild and severe AKI. Despite these differences, median changes in BNP levels between preoperative and immediate postoperative levels differed slightly for at least mild AKI (cases, −23.4 versus noncases, −15.5 pg/mL; P = 0.024) and were similar for severe AKI (cases, −32.8 versus noncases, −17.0 pg/mL; P = 0.62), suggesting that the association between postoperative BNP and AKI may be largely dependent on preoperative BNP levels. Similarly, median changes in BNP levels between preoperative and day 1 postoperative levels were similar for at least mild AKI (cases, 127.3 pg/mL versus noncases, 114.2 pg/mL; P = 0.31) and severe AKI (cases, 166.7 pg/mL versus noncases, 118.7 pg/mL; P = 0.10). Finally, the AUCs for the outcomes of at least mild and severe AKI were all <0.60 with the use of either absolute or relative changes in serum BNP between preoperative levels and both the immediate and day 1 postoperative levels.

Table 2. Association of Brain Natriuretic Peptide Quintiles With Risk for at Least Mild and Severe Acute Kidney Injury and Other Postoperative Outcomes

<table>
<thead>
<tr>
<th>BNP Quintile</th>
<th>At Least Mild AKI</th>
<th>Severe AKI</th>
<th>Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td>AKI Cases, %</td>
<td>RR (95% CI)</td>
<td>AKI Cases, %</td>
</tr>
<tr>
<td>1 (&lt;28 pg/mL)</td>
<td>24.7</td>
<td>1 (Referent)</td>
<td>1.8</td>
</tr>
<tr>
<td>2 (28–56 pg/mL)</td>
<td>28.5</td>
<td>1.16 (0.85–1.57)</td>
<td>3.1</td>
</tr>
<tr>
<td>3 (56–105 pg/mL)</td>
<td>37.3</td>
<td>1.51 (1.14–2.01)</td>
<td>7.0</td>
</tr>
<tr>
<td>4 (105–241 pg/mL)</td>
<td>39.5</td>
<td>1.60 (1.21–2.11)</td>
<td>6.1</td>
</tr>
<tr>
<td>5 (&gt;241 pg/mL)</td>
<td>48.7</td>
<td>1.97 (1.52–2.57)</td>
<td>7.5</td>
</tr>
</tbody>
</table>

BNP indicates brain natriuretic peptide; AKI, acute kidney injury; RR, relative risk; CI, confidence interval; and ICU, intensive care unit. Adjusted for age (per year), sex, race, nonselective surgery, type of surgery, cardiac catheterization in the last 48 hours, diabetes mellitus, hypertension, myocardial infarction, chronic heart failure, preoperative estimated glomerular filtration rate (continuous), and site. The number of patients per quintile is as follows, quintile 1, n = 227; quintile 2, n = 228; quintile 3, n = 228; quintile 4, n = 228; and quintile 5, n = 228.

Figure 2. Incidence of at least mild acute kidney injury (AKI; A) and severe AKI (B) by quintiles of preoperative brain natriuretic peptide (BNP). AKI was defined as during entire hospitalization; at least mild AKI (A), as ≥50% or < 0.3 mg/dL or dialysis; and severe AKI (B), as ≥100% or dialysis. BNP was measured in picograms per milliliter.
Table 3. Areas Under the Receiver-Operating Characteristic Curve and Continuous Net Reclassification Index of Preoperative Brain Natriuretic Peptide and Clinical Risk Factors for Acute Kidney Injury Risk After Cardiac Surgery

<table>
<thead>
<tr>
<th>Area under the ROC curve (95% CI)</th>
<th>At Least Mild AKI</th>
<th>Severe AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum BNP*</td>
<td>0.604 (0.569–0.639)</td>
<td>0.628 (0.562–0.695)</td>
</tr>
<tr>
<td>Clinical model†</td>
<td>0.667 (0.635–0.699)</td>
<td>0.725 (0.659–0.793)</td>
</tr>
<tr>
<td>Serum BNP and clinical model</td>
<td>0.682 (0.650–0.714)</td>
<td>0.736 (0.670–0.802)</td>
</tr>
<tr>
<td>Continuous net reclassification index (95% CI)</td>
<td>0.183 (0.061–0.314)</td>
<td>0.231 (–0.067 to 0.506)</td>
</tr>
</tbody>
</table>

AKI indicates acute kidney injury; ROC, receiver-operating characteristic; CI, confidence interval; and BNP, brain natriuretic peptide. AKI was defined as during entire hospitalization; at least mild AKI, as ≥50% or ≥0.3 mg/dL; and severe AKI, as ≥100% or dialysis.

*Log-transformed continuous BNP.
†Clinical model includes age (per year), sex, race, nonelective surgery, type of surgery, cardiac catheterization in the last 48 hours, diabetes mellitus, hypertension, myocardial infarction, chronic heart failure, preoperative estimated glomerular filtration rate (continuous), and site.

Discussion

In this large, contemporary, multicenter, prospective study of patients undergoing cardiac surgery who were selected for high AKI risk, the incidence of AKI was high, particularly among patients with greater comorbidity and impaired baseline kidney function. Although there are several well-known risk factors for AKI, associations between natriuretic peptides and AKI remain unclear. We found that preoperative BNP, a biomarker of hemodynamic stress, is a strong and independent predictor of at least mild and severe AKI. The addition of BNP to known clinical parameters provided modest improvements in risk discrimination, as demonstrated by absolute increases in the AUCs of 0.02 to 0.03. Similarly risk classification was only modestly improved, as demonstrated by continuous NRI of 0.23 to 0.38. These findings inform the role of BNP when considering how best to stratify the risk of AKI in the cardiac surgery setting.

The prognostic importance of natriuretic peptides has been well described in both the noncardiac and cardiac surgery settings. The results from 16 unique studies were reported in 2 separate systematic reviews that identified strong associations of elevated BNP and NTproBNP levels with cardiac events and mortality. Although various cut points were used to define elevated BNP levels, the average number of patients with elevated BNP levels was 1 in 4. Despite some differences in study inclusion criteria, outcome definitions, and analytic methods, both reviews estimated that elevated preoperative BNP levels were associated with higher risk of cardiovascular outcomes (including cardiac death) to a similar extent. Furthermore, this association appeared independent of conventional risk factors, although the moderate heterogeneity in past study results limits inferences in this regard. Despite differences in analytic methods that may preclude direct comparisons with noncardiac surgery studies, similar findings were observed among studies of patients undergoing cardiac surgery. The majority of these studies evaluated associations between BNP and mortality and cardiovascular complications, whereas some also examined length of stay. Most past studies were limited to <200 patients, with only 1 large study including >1000 patients. In the present study, we found that higher levels of preoperative BNP were associated with a higher incidence of postoperative mortality and longer lengths of stay in both the intensive care unit and hospital.

Few studies have examined the association between natriuretic peptides and risk of AKI after cardiac surgery. Although postoperative renal impairment is described as a study outcome in 2 recent studies, the findings are limited by small study sizes (both <500 patients) and incomplete information on the observed incidence or associations with BNP levels. However, in 1 small study (n = 135), preoperative NTproBNP levels were significantly higher among those who developed postoperative renal failure (defined as a ≥50% increase in serum creatinine; median, 1728 versus 194 ng/L; P < 0.001). When AUCs were examined for predicting renal failure, preoperative NTproBNP (AUC, 0.86; 95% confidence interval, 0.78–0.94) was more predictive than either the EuroSCORE or ejection fraction. Similarly, we found that preoperative BNP levels were significantly higher among those who developed postoperative AKI. Quintiles of BNP were linearly associated with risk of at least mild AKI,
whereas a risk threshold was observed above intermediate BNP levels when severe AKI was evaluated.

Because patients in our cohort were selected for high AKI risk, they represent a relatively homogenous high-risk population. It is possible that BNP may provide greater risk discrimination in more heterogeneous populations such as in past studies that enrolled individuals at low and medium risk of AKI.34 Although many studies evaluating BNP in cardiac surgery have examined both preoperative and postoperative levels,12,14,15,18–20 the relative advantages of each remain unclear. Consequently, we also assessed associations with postoperative BNP levels and found that preoperative levels were more informative in predicting AKI.

The prognostic value of natriuretic peptide levels in the preoperative setting is most likely related to their ability to measure small changes in right or left ventricular function among those with systolic or diastolic abnormalities, whether or not they are symptomatic. Ventricular myocardial wall stress stimulates natriuretic peptide secretion in the setting of volume expansion or pressure overload. Consequently, natriuretic peptides have prognostic abilities across a variety of conditions involving hemodynamic stress in addition to heart failure, including stable and acute coronary artery disease, sudden cardiac death, cardiac arrhythmias, pulmonary embolism, stroke, and septic shock.13 Our findings add to these prior observations by demonstrating that preoperative BNP levels also independently predict post–cardiac surgery AKI. Furthermore, this relationship is supported by early physiological studies and recent clinical observations. In classic physiological experiments, increased venous pressure reduced renal blood flow and urine flow.35 The magnitude of this effect proved even greater than equivalent decreases in arterial pressure.35 More recently, venous congestion has been demonstrated to be strongly associated with AKI among patients with heart failure36–38 and those with atherosclerotic cardiovascular disease.39 Because of greater recognition of the importance of venous congestion, the clinical trial focus is shifting from addressing impaired cardiac output and inadequate arterial filling to renal-sparing treatment strategies that reduce venous congestion.40,41

Within the perioperative setting, reducing the risk of AKI after cardiac surgery has been a focus of growing importance. The primary emphasis has been on optimization of hemodynamic status throughout the perioperative course because a variety of studies have suggested that such measures decrease the risk of AKI.42 Despite the perceived importance of intraoperative hypoperfusion as the dominant mechanism behind AKI after cardiac surgery, tight control of mean arterial pressure has not consistently been shown to reduce the risk of AKI. As observed in physiological studies outside the surgical setting, increased venous pressure may confer greater risk of postoperative AKI than decreased arterial pressure. Thus, reductions in elevated venous congestion before or during cardiac surgery may provide a novel approach to reducing the risk of AKI after cardiac surgery. Outpatient natriuretic-guided therapies have been effective in reducing heart failure deaths and rehospitalizations.43 Similarly, serum BNP may provide a noninvasive indicator to evaluate the efficacy of perioperative reductions in hemodynamic stress related to either volume-expansion or pressure-overload conditions.

This study is the largest multicenter study to date to assess the association between BNP and postoperative AKI risk. Although our evaluation focused on the relationship between preoperative BNP and AKI, the risks associated with postoperative BNP and corresponding changes from preoperative levels were also assessed. The diverse settings of the 6 institutions also ensured a broad inclusion of high-risk cardiac surgery patients. However, this study does have important limitations. Many studies evaluating natriuretic peptides have used NTproBNP instead of BNP, which may be more influenced by factors such as body mass index. However, because BNP is less influenced by kidney function, it is the more reliable natriuretic peptide in this setting.44 We were also able to account for the factors that strongly affect BNP levels such as age, sex, and kidney disease. However, other factors could not be accounted for, including pulmonary disease, severity of cardiac disease (eg, severity of preoperative myocardial infarction, hypotension, or atrial fibrillation), and body mass index. Limited cases of AKI requiring dialysis, the lack of data on pulmonary disease, and the limited data on heart failure classification precluded application of our study data to existing risk models.7,8 In addition, our patients were mostly white, limiting the generalizability of these findings to other populations. Nonetheless, all studies using natriuretic peptides suffer from limitations related to the
biological variability and intridual variation. Although our study had a very large number of at least mild AKI cases, we had few patients with severe AKI, including dialysis-requiring AKI (n=17, 1.5%). Therefore, the ability of BNP to predict risk for these outcomes could not be assessed reliably in our study. Finally, some predictors of AKI (preoperative cardiogenic shock, intra-abdominal pressure) were not available, limiting our ability to determine whether BNP levels remain independent of these factors. To develop the best AKI risk model, future efforts should simultaneously evaluate markers of kidney filtration (eg, serum creatinine, cystatin C, urine albumin-to-creatinine ratio), injury (urine neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, interleukin-18, etc), and hemodynamics (eg, BNP). This multimarker approach will then establish whether BNP is associated with AKI after simultaneously accounting for changes in other biomarkers that reflect different aspects of the AKI process. Our present results suggest that BNP will certainly need to be included in that development process.

Conclusions

We found that elevated preoperative BNP levels were strongly associated with greater AKI risk. BNP was linearly associated with risk of at least mild AKI, whereas for evaluating severe AKI, a risk threshold was observed above intermediate levels of BNP. If confirmed in other populations not selected for high AKI risk, BNP may be a valuable component of future efforts to improve preoperative risk stratification and discrimination among surgical candidates. These findings raise the possibility that preoperative therapies to reduce hemodynamic stress indicated by elevated BNP levels may be effective in mitigating the high risk of AKI among select patients.

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Disclosures

Dr Devarajan is a consultant to Abbott Diagnostics and Biosite, Inc. The other authors report no conflicts.

References


CLINICAL PERSPECTIVE
Cardiovascular disease and heart failure are highly prevalent among those who undergo cardiac surgery, contributing to hemodynamic stress that may be poorly characterized by clinical history. Consequently, natriuretic peptide biomarkers that better characterize this underlying physiology have become well established in the diagnosis and management of patients with heart failure. In this study, 1139 adults who underwent cardiac surgery were evaluated from 6 centers to establish whether preoperative brain natriuretic peptide (BNP) levels predict postoperative acute kidney injury (AKI; defined by Acute Kidney Injury Network definitions; at least mild AKI was a $>0.3$-mg/dL [26 μmol/L] or 50% rise in creatinine, and severe AKI was either a doubling of creatinine or the requirement of acute renal replacement therapy). In this high-risk cohort, AKI was common (at least mild AKI, n = 407 [36%]; severe AKI, n = 58 [5.1%]). After adjustment for different preoperative characteristics, preoperative BNP was a strong and independent predictor of mild and severe AKI. Compared with the lowest BNP quintile, the highest quintile had significantly higher risk of at least mild AKI (risk ratio, 1.87) and severe AKI (risk ratio, 3.17). After adjustment for clinical predictors, the addition of BNP improved the area under the curve to predict at least mild AKI and severe AKI. Compared with clinical parameters alone, BNP also improved risk prediction of AKI cases into lower and higher risk. Preoperative BNP level is associated with postoperative AKI in high-risk patients undergoing cardiac surgery and may be a valuable component of future efforts to improve preoperative risk stratification among surgical candidates.

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Preoperative Serum Brain Natriuretic Peptide and Risk of Acute Kidney Injury After Cardiac Surgery

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Supplemental Tables

Supplemental Table 1. Association of BNP Quintiles with Risk for At Least Mild and Severe Acute Kidney Injury and Other Post-operative Outcomes with the Clinical Model Including Pre-operative Albuminuria

<table>
<thead>
<tr>
<th>BNP Quintile (cut points, pg/mL)</th>
<th>At Least Mild AKI</th>
<th>Severe AKI</th>
<th>Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% AKI cases</td>
<td>Unadjusted RR (95% CI)</td>
<td>Adjusted RR* (95% CI)</td>
</tr>
<tr>
<td>Q1 (&lt;28)</td>
<td>24.7</td>
<td>1 (referent)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>Q2 (28, 56)</td>
<td>28.5</td>
<td>1.16 (0.85, 1.57)</td>
<td>1.26 (0.93, 1.70)</td>
</tr>
<tr>
<td>Q3 (56, 105)</td>
<td>37.3</td>
<td>1.51 (1.14, 2.01)</td>
<td>1.43 (1.06, 1.91)</td>
</tr>
<tr>
<td>Q4 (105, 241)</td>
<td>39.5</td>
<td>1.60 (1.21, 2.11)</td>
<td>1.46 (1.10, 1.96)</td>
</tr>
<tr>
<td>Q5 (&gt;241)</td>
<td>48.7</td>
<td>1.97 (1.52, 2.57)</td>
<td>1.65 (1.23, 2.23)</td>
</tr>
</tbody>
</table>

Unadjusted p for trend <.0001
Unadjusted p for trend* 0.0004
Adjusted p for trend* 0.1266

* Adjusted for age (per year), gender, race, non-elective surgery, type of surgery, cardiac catheterization in the last 48 hours, diabetes, hypertension, myocardial infarction, chronic heart failure, pre-op eGFR (continuous), site and pre-op UACR (<10, 10-30, 30-300, >300 mg/g). The number of patients per quintile: Q1 n=227, Q2 n=228, Q3 n=228, Q4 n=228, Q5 n=228.

Abbreviations: Brain natriuretic peptide (BNP); acute kidney injury (AKI); relative risk (RR); confidence interval (CI); intensive care unit (ICU); standard deviation (SD); urine albumin-to-creatinine ratio (UACR)
### Supplemental Table 2. Areas Under the Receiver Operating Characteristic Curve and Continuous Net Reclassification Index of Pre-operative BNP and Clinical Risk Factors (Including Pre-operative Albuminuria) for AKI Risk Following Cardiac Surgery

<table>
<thead>
<tr>
<th></th>
<th>At least Mild AKI</th>
<th>Severe AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Area under the ROC Curve (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Serum BNP*</td>
<td>0.604 (0.569, 0.639)</td>
<td>0.638 (0.562, 0.695)</td>
</tr>
<tr>
<td>b. Clinical model†</td>
<td>0.667 (0.635, 0.699)</td>
<td>0.725 (0.659, 0.793)</td>
</tr>
<tr>
<td>c. Serum BNP &amp; clinical model†</td>
<td>0.682 (0.650, 0.714)</td>
<td>0.736 (0.670, 0.802)</td>
</tr>
<tr>
<td>d. Clinical model† with albuminuria‡</td>
<td>0.693 (0.662, 0.723)</td>
<td>0.753 (0.678, 0.827)</td>
</tr>
<tr>
<td>e. Serum BNP &amp; clinical model† with albuminuria‡</td>
<td>0.702 (0.671, 0.732)</td>
<td>0.771 (0.701, 0.841)</td>
</tr>
<tr>
<td><strong>Continuous Net Reclassification Index (95% CI)§</strong></td>
<td>0.079 (-0.037, 0.233)</td>
<td>0.158 (-0.132, 0.461)</td>
</tr>
</tbody>
</table>

* log transformed continuous BNP
† Clinical model includes age (per year), gender, race, non-elective surgery, type of surgery, cardiac catheterization in the last 48 hours, diabetes, hypertension, myocardial infarction, chronic heart failure, pre-op eGFR (continuous), and site.
‡ Pre-op UACR categories (<10 mg/g, 10-30, 30-300, and >300 mg/g).
§ Continuous NRI is quantifying the improvement in reclassification after the addition of Serum BNP to the clinical model with albuminuria.

AKI defined as during entire hospitalization, at least mild AKI defined as ≥50% or ≥0.3mg/dL, severe AKI defined as ≥100% or dialysis.

**Abbreviations:** Acute kidney injury (AKI), brain natriuretic peptide (BNP); urine albumin-to-creatinine ratio (UACR); confidence interval (CI).

When UACR is added to the clinical model, the predictive accuracy for both at least mild and severe AKI was increased (row b vs row d). To evaluate whether the main findings with BNP were independent and not strongly confounded by albuminuria, we examined the incremental change in AUC with addition of BNP to our clinical model with albuminuria (row d vs row e). The predictive accuracy increased little for at least mild AKI (0.693 to 0.702) and somewhat more for severe AKI (0.753 to 0.771).
Supplemental Figures

Supplemental Figure 1. Post-operative Serum BNP and AKI, by Spline Regression Models

The relationship between post-operative serum BNP and AKI (at least mild AKI, a and b; severe AKI, c and d) by spline regression modeling. Serum BNP was log-transformed in b and d. The curves represent restricted cubic splines with knots estimated by the arrows on the abscissa. Triangles denote the empirical logits.

Abbreviations: Acute kidney injury (AKI); brain natriuretic peptide (BNP)
Supplemental Figure 2. Reclassification Plot of Predicted Probabilities of At Least Mild AKI Based on the Clinical Model (Including Pre-operative Albuminuria) with and without Pre-operative BNP, by AKI status

(a) AKI Cases

(b) AKI Non-cases

Predicted risks for at least mild AKI according to the clinical model (x-axis) and according to the clinical model with pre-op serum BNP included (y-axis) for AKI cases (panel a; red) and non-cases (panel b; blue). The diagonal line indicates a line of identity, such that for points above this line the predicted risk is higher in the new model (improved reclassification for AKI cases) and for points below this line the predicted risk is lower (improved reclassification for non-AKI cases). With the addition of UACR to the clinical model, the NRI for mild AKI and severe AKI did not change significantly.

Abbreviations: Acute kidney injury (AKI); brain natriuretic peptide (BNP); urine albumin-to-creatinine ratio (UACR); net reclassification index (NRI)