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Expert Review

# The Increasing Perioperative Impact of Natriuretic Peptides on Cardiovascular Outcomes

Kristin Stawiarski, MD*,
Farouk Mookadam, MD, FRCP (c), FACC †,
Harish Ramakrishna, MD, FACC, FESC‡,[1]

*Department of Internal Medicine, Yale New Haven Health System, Bridgeport, CT
†Department of Cardiovascular Diseases, Mayo Clinic, Scottsdale, AZ
‡Division of Cardiovascular and Thoracic Anesthesiology, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Scottsdale, AZ

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B-TYPE NATRIURETIC PEPTIDE (BNP) belongs to a family of neurohormones responsible for circulatory homeostasis in response to volume and pressure overload within cardiac chambers. BNP levels rise in proportion to the severity of left ventricular dysfunction as seen on echocardiography.[1] Based on these properties, the monitoring of BNP levels has made its way into clinical management of patients with acute congestive heart failure (CHF). It has particular value in patients presenting with dyspnea of unclear etiology and is also a predictive marker for postoperative cardiac events in surgical patients.[2,3] Various cutoff values have been refined continually for optimal utility given the growing number of studies in this area. In this review, the authors summarize the significance of these values in the clinical and perioperative settings along with the consensus statements that guide their use.

## BNP Versus NT-proBNP

When cleaved, the prohormone proBNP produces an active 32-amino acid BNP and inactive N-terminal pro-BNP (NT-proBNP) form.[4] Both biomarkers have been used in clinical practice as diagnostic and prognostic indicators for patients with CHF. Because they both are found in similar plasma concentrations, either assay can be tracked. However, resulting values are not interchangeable. BNP carries a much shorter half-life of 21 minutes compared to 60 to 120 minutes, making it more susceptible to acute hemodynamic changes.[4]

Initial data from the 2005 N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department study identified NT-proBNP cutoff points of >450 pg/mL for patients <50 years of age and >900 pg/mL for patients ≥50 years of age for the diagnosis of acute CHF.[5] Additional dichotomous cutpoints were identified in the 2006 International Collaborative of NT-pro BNP trial where 1,256 patients across 3 continents were studied compared to the previous North American-based N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department study with only 600 patients.[5,6] The International Collaborative of NT-pro BNP trial established diagnostic cutoffs of NT-proBNP at 450, 900, and 1800 pg/mL for age categories of <50, 50 to 75, and >75 years of age, respectively.[5,6] More contemporary research from Januzzi et al. in 2018[7] validated the use of the age-stratified levels and noted that CHF can be excluded in patients with a NT-proBNP of <300 pg/mL. Of note, the current US Food and Drug Administration cutoffs for NT-proBNP are 125 pg/mL for patients <75 and 450 pg/mL for patients over age 75 (Table 1).[7]

Caution should be taken in the interpretation of BNP in the clinical environment as elevations in both natriuretic peptides (NPs) also have been associated with other cardiac and

[1]Address reprint requests to Harish Ramakrishna, MD, FACC, FASE, Division of Cardiovascular and Thoracic Anesthesiology, Mayo Clinic, 5777 East Mayo Blvd, Phoenix, AZ 85054.
*E-mail address:* ramakrishna.harish@mayo.edu (H. Ramakrishna).

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Table 1
NT-proBNP Cutpoint Variations for the Diagnosis of Acute CHF

| Study | <50 Years Old (pg/mL) | ≥50 Years Old (pg/mL) | <75 Years Old (pg/mL) | ≥75 Years Old (pg/mL) |
|---|---|---|---|---|
| 2005 PRIDE | 450 | 900 | | |
| 2006 ICON | 450 | 900 | | 1800 |
| 2018 ICON-RELOADED | 450 | 900 | | 1800 |
| Current FDA Approved | 125 | | | 450 |

Abbreviations: CHF, congestive heart failure; FDA, Food and Drug Administration; ICON, International Collaborative of NT-pro BNP; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PRIDE, N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department; RELOADED, Re-evaluation of Acute Diagnostic Cut-Offs in the Emergency Department.

noncardiac etiologies (Table 2). Increasing age and female sex have been identified as independent factors associated with increased BNP levels.[8] Similarly, a well-known inverse relationship has been established between increasing body mass index and BNP levels, which has prompted advocation for the use of a weight-specific cutoff.[9] BNP is also a substrate for neprilysin and will be elevated discriminately compared to NT-proBNP in patients taking neprilysin inhibitors.[10,11] Despite these caveats, BNP monitoring for the prevention, diagnosis, and prognostication of CHF has gained popularity (Table 3).

Table 3
Caveats to NT-proBNP Interpretation

| Factor | Effect on NP Levels |
|---|---|
| Higher BMI | ↓ |
| Older age | ↑ |
| Female sex | ↑ |
| Neprilysin inhibitor use | ↑ |
| Worsening renal function | ↑ |
| Vigorous exercise | ↑ (transient) |

Abbreviations: BMI, body mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NP, natriuretic peptide.

## Recommendations for the Use of BNP in CHF

The 2017 focused update on the management of CHF summarized society consensus statements of the utility of BNP testing at various stages of CHF (Table 4).[11] NP-based screening in patients at risk of developing CHF can be useful when followed by a team of cardiovascular specialties (class IIa, level of evidence (LOE) B-randomized). A number of single-center studies have used BNP cutoff values of as low as >50 pg/mL to guide preventative management, including patient education and medication optimization to avoid cardiac events or left ventricular dysfunction.[12,13] For patients presenting with dyspnea of unclear origin, measurement of NP is a useful aid in the diagnosis or exclusion of CHF (class I, LOE A).[11] In contrast to the 2013 CHF guideline, measurement of baseline NP levels on hospital admission now is recommended to establish the prognosis of CHF (class I, LOE A).[11,14] An additional predischarge level now also is recommended to determine the prognosis postdischarge (class IIa, LOE B-nonrandomized). Those patients who do not see a decrease in NP value across admission to time of discharge have worse outcomes.[15] However, target NP-directed therapy has not been accepted yet in clinical practice.[16]

Table 2
Differential Diagnosis of Elevated NT-proBNP Levels

| | |
|---|---|
| Cardiac | |
| | Heart failure |
| | Acute coronary syndrome |
| | Valve heart disease |
| | Atrial fibrillation |
| | Heart muscle disease, including myocarditis and left ventricular hypertrophy |
| | Cardiac surgery |
| | Cardioversion |
| Noncardiac | Renal insufficiency, older age |
| | Critical illness, including sepsis or severe burns |
| | Toxic metabolic insults |
| | Pulmonary disease, including obstructive sleep apnea and pulmonary hypertension |
| | Anemia |

Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide.

In the PRIMA II trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?), Stienen et al. randomized 405 patients with acute CHF exacerbation from European hospitals to NP-guided therapy (with a goal of >30% reduction from admission NT-proBNP levels) versus conventional therapy. Although significantly more patients in the NP-guided therapy group achieved target reductions, there was no difference between groups with regards to all-cause mortality or CHF readmissions.[17] Further studies are required to examine how great of a reduction in NT-proBNP levels (eg, >30% *v* >50%) is needed to translate into clinical effect. Elevated NP markers are associated with increased morbidity and mortality; however, these need to be interpreted in the context of each patient's clinical context.

## BNP in the Perioperative Setting

### *Cardiac Surgery*

Most cardiac risk assessments include left ventricular ejection fraction as a marker of operative morbidity and mortality.

Table 4
Indications for Natriuretic Peptide Assay

| | ACC/AHAStage A/B CHF | ACC/AHAStage C/D CHF | ACC/AHAAcute/Hospitalized |
|---|---|---|---|
| Prevention | X | | |
| Diagnosis | | X | X |
| Prognosis | | X | X (at admission and discharge) |

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; CHF, congestive heart failure.

In 2004, Hutfless et al. extrapolated this concept to the use of NP levels >385 pg/mL to predict 1-year mortality after coronary artery bypass graft (CABG) surgery.[18] Since then, several prospective cohort studies have emerged exploring the significance of preoperative and postoperative BNP levels.[1] Postoperative elevations have predicted prolonged intensive care unit stays of >4 days and in-hospital deaths in CABG patients in a male-predominant population.[19] The extended use of an intra-aortic balloon pump or inotropic support for >24 hours was correlated strongly to high BNP levels drawn postoperatively in the intensive care unit in a small cohort of 169 patients undergoing aortic or mitral valve repair or replacement ± CABG.[20] Murad et al. conducted a larger study of 499 patients after valve or CABG surgery and found that BNP values above 382 pg/mL were an independent predictor of 30-day mortality.[21] Although isolated testing of BNP postoperatively correlates with poor outcomes, trending postoperative BNP levels have not been shown to correlate with 1-year mortality.[22] Because of the variability of surgical procedures and populations studied, care should be taken in interpreting results and applying them in clinical practice.

When stratifying by the cause of underlying heart disease, preoperative BNP levels were found to be highest in patients with aortic stenosis and mitral regurgitation compared to those with coronary artery disease.[23] NT-proBNP levels were least predictive of severe postoperative heart failure in patients with aortic stenosis.[23] However, elevated discharge BNP was found to be associated with increased 2-year mortality in patients post-transcatheter aortic valve replacement.[24]

Recently, the utility of BNP monitoring has evolved into a predictor for outcomes in percutaneous intervention versus CABG for left main coronary artery revascularization and may help guide future treatment strategy selections.[25] The Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial randomized 1,037 patients with similar SYNTAX coronary artery disease scores to receive percutaneous coronary intervention versus CABG. Increased risk of cardiac endpoints of myocardial infarction, stroke, or all-cause death was highest in the 410 patients with preoperative elevations in BNP. Further, significant interaction was seen between baseline BNP and revascularization type. Event-free survival after CABG was independent of baseline BNP levels whereas an elevated BNP in the percutaneous coronary intervention patient was associated with worse outcomes. Thus, initial CABG may be favored in those with high BNP.

Widely used surgical risk models, such as the European System for Cardiac Operative Risk Evaluation II, are designed to predict postoperative mortality, but currently do not take NP biomarkers into consideration.[26] Recent work by Brynildsen et al.[27] suggests that preoperative and postoperative NT-proBNP can not only provide additive prognostic benefit to the European System for Cardiac Operative Risk Evaluation II but also may allow for the development of a more streamlined prognostic score with less variables.[27] No such combination has been studied yet with the newly revised 2018 North American-based Society of Thoracic Surgeons cardiac risk model.[28,29]

### *Noncardiac Surgery*

The concept of using NP biomarkers for postoperative cardiovascular risk assessments in noncardiac surgery first emerged in 2005.[30] Yeh et al. followed 190 patients through noncardiac surgery requiring general anesthesia.[30] Fifteen patients developed cardiac complications including acute coronary syndrome and CHF, which correlated with preoperative NT-proBNP levels of >450 ng/L.[30] Despite other clinical correlates, multivariate analysis revealed that the NT-proBNP level was the only independent predictor of cardiac events.[30] Rodseth et al. demonstrated the additive value of combining preoperative BNP with standard surgical risk scores (Revised Cardiac Risk Index) to improve significantly the operative mortality estimate.[31] Additional data have supported the use of postoperative NP measurements to predict longer-term cardiac events at 30 days and 180 days after surgery. A 2014 meta-analysis of over 2,000 participants across 18 studies showed that the addition of postoperative NP measurements to a risk-prevention model including preoperative levels enhanced risk stratification for the composite outcomes of death or nonfatal myocardial infarction after noncardiac surgery compared with a preoperative NP measurement alone.[3] Further, a recent multicenter prospective cohort of 1,401 patients compared clinicians' subjective preoperative assessment to quantitative measures of functional capacity (Duke Activity Status Index questionnaire and cardiopulmonary exercise testing), along with serum NT-proBNP concentrations.[32] NP measurements were found to outperform subjective clinician assessments as a predictor of 30-day postoperative myocardial infarction and death. Specifically, increased preoperative NT-proBNP concentrations were associated with increased risks of postoperative 30-day death or myocardial injury; increased serum concentrations also predicted increased 1-year mortality. The authors of the study support recommendations to incorporate NP in recent clinical practice guidelines for preoperative risk assessment.

The current American College of Cardiology/American Heart Association guidelines on perioperative cardiovascular evaluation for patients undergoing noncardiac surgery recognize the growing evidence in support of NP biomarker measurement.[33] However, before incorporating NP testing into routine preoperative evaluation guidelines, further randomized studies are required to determine if postoperative risk can be minimized by targeting these biomarkers for treatment in the perioperative setting.[33]

Specific surgical populations, largely those over age 65 years undergoing orthopedic interventions, have been studied further in this regard. Kim et al. analyzed the NT-proBNP levels of 506 patients older than 70 years with normal level ventricular systolic function on echocardiogram undergoing total knee arthroplasties.[34] Major adverse cardiac and cerebral vascular events occurred in 7.9% of patients with a NT-proBNP value of >425.3 pg/mL identified as an independent predictor of these events.[34] Similar results were seen with 450 patients with a mean age of 83 years undergoing hip fracture surgery.[35] NT-proBNP values of >600 pg/mL were associated with postoperative cardiac complications within 14 days of surgery.[35] As recent CHF research has adopted an age-stratified approach to dichotomizing BNP values, so too may this be a direction of further analysis in the perioperative setting.

### *Prediction of Postoperative Atrial Fibrillation*

Postoperative atrial fibrillation (POAF) occurs in as many as 60% of patients after cardiac surgery and 26% after noncardiac surgery, leading to prolonged hospital stays.[36,37] Wazni et al. reported significant preoperative NP levels of 615 pg/mL in 80 of 187 patients who developed POAF compared to those who did not (444 pg/mL) after CABG or valve surgery.[36] A similar cutoff of 629 pg/mL also was found to be predictive of POAF in patients after isolated CABG.[38] Hwang et al. followed the rhythm status of patients undergoing mitral valve surgery.[39] Not only was elevated BNP associated with AF presence, but a reduction in BNP perioperatively was seen in patients who converted from preoperative AF to postoperative sinus rhythm, further reinforcing the prognostic value of BNP.[39]

Research on noncardiac thoracic surgery, including anatomic lung resections and esophagectomy, also has shown a significant correlation between BNP levels and POAF.[40] Amar et al. reported a significant cutoff value above 30 pg/mL, which predicts POAF, whereas further studies suggests a sensitivity of 77% and a specificity of 93% with this level.[41,42] Alternatively, a level of 59 pg/mL has been considered an independent predictor of POAF, whereas levels above 113 pg/mL were associated with an 8-fold increase in POAF.[43,44] A 2015 meta-analysis revealed a 14.5% incidence of POAF with varying predictive levels of NP and a predictor odds ratio of 3.13 (95% confidence interval 1.38-7.12).[45] However, more recent studies by Brecher et al. found no correlation between BNP and POAF in similar populations.[46] Further research is required to determine if the prophylactic use of antiarrhythmic therapy is warranted in patients undergoing high-risk procedures.

## Conclusion

NP levels have proven useful in both acute CHF as well as in the perioperative setting. Over the recent American College of Cardiology/American Heart Association guideline updates, NP measurements have gained an increasing level of significance in the diagnosis, management, and prognosis of CHF. Elevated NP levels also have been linked to higher adverse cardiac outcomes perioperatively, including POAF. With additional studies, there may be a role for incorporating BNP level measurement in presurgical risk scores for both cardiac and noncardiac surgery alike. However, clinical judgment should remain the gold standard for the elevation of a patient's surgical risk and volume status in acute CHF.

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