Biomarkers to Personalize Preoperative Cardiovascular Risk Stratification: Ready for Prime Time?

Globally, more than 200 million adults have major noncardiac surgery each year (1). Although advances in anesthesia, surgical techniques, and postoperative care have improved outcomes, cardiovascular complications remain the most common causes of postoperative morbidity and mortality. Among patients having elective noncardiac surgery, greater than 5% have a major cardiac complication within the first 30 days, resulting in death, disability, prolonged hospitalization, and increased health care expenditure (2). Several preoperative factors are associated with more cardiac events, including high-risk coronary artery disease, recent stroke, congestive heart failure, renal insufficiency, uncontrolled hypertension, valvular heart disease, and diabetes mellitus. In addition, the risk for cardiac complications is increased in the setting of hemodynamic compromise, increased sympathetic activation, inflammation, bleeding, or hypercoagulability. Several approaches have been examined to predict the risk for cardiac complication after major noncardiac surgery, including assessment of clinical risk factors, noninvasive cardiac testing, and biomarkers.

Clinical risk indices are used to assess the risk for cardiac complications after noncardiac surgery. Of these, the Revised Cardiac Risk Index (RCRI) is most frequently used and recommended by clinical practice guidelines (2, 3). This index predicts the risk for cardiac complications on the basis of the risk associated with the procedure and presence of clinical risk factors (ischemic heart disease, prior congestive heart failure, stroke or transient ischemic attack, use of insulin therapy, and serum creatinine level of >2 mg/dL [>176.8 μmol/L]) established to be independently associated with perioperative cardiac complications. Although the RCRI has been considered a gold standard for cardiovascular risk prediction after noncardiac surgery, several validation studies of large cohorts have shown that it underestimates risk by as much as 50% (1). The National Surgical Quality Improvement Program Myocardial Infarction and Cardiac Arrest Risk Index is the second most widely used perioperative cardiac risk calculator. It includes age and functional status in addition to clinical risk factors and has discriminative ability superior to the RCRI (3). However, this risk index has been shown to underestimate perioperative myocardial infarction. Many clinical practice guidelines recommend preoperative noninvasive cardiac testing (for example, cardiac stress test and coronary computed tomographic angiography) to improve cardiac risk stratification (2, 3). However, these diagnostic tests have been shown to overestimate cardiac risk, resulting in such unintended consequences as additional diagnostic testing (including invasive coronary angiography), increased health care costs, and delays in planned surgery. Consequently, efforts have been made to develop novel approaches of risk stratification that improve the current perioperative cardiac risk calculators. To this end, early developments have shown a potential role for cardiac biomarkers (4). Although these markers are commonly used in the diagnosis and prognostication of patients with cardiovascular disease, they are rarely used for preoperative cardiac risk stratification in patients having surgery.

In this context, Duceppe and colleagues (5) report the role of *N*-terminal pro–B-type natriuretic peptide (NT-proBNP), a biomarker of myocardial wall stress and structural changes, in risk stratification of patients having noncardiac surgery. In their analysis of 10 402 patients having noncardiac surgery, the investigators examined whether the addition of preoperative NT-proBNP levels to the RCRI improves risk prediction for the primary composite outcome of vascular mortality, myocardial infarction, and ischemic myocardial injury at 30 days after surgery. An independent and incremental association between preoperative NT-proBNP levels and higher rates of cardiovascular events was found, such that patients with NT-proBNP levels greater than 1500 pg/mL had a more than 5-fold higher risk for the primary outcome relative to those with levels less than 100 pg/mL. Furthermore, adding NT-proBNP levels to the RCRI improved risk prediction and reclassification compared with the RCRI alone (c-statistic increased from 0.65 to 0.73). Of note, an NT-proBNP concentration of 200 pg/mL or greater was associated with risk for a primary outcome exceeding 5%. These findings are consistent with several smaller studies and meta-analyses that have shown improved perioperative cardiac risk stratification with the addition of NT-proBNP levels to clinical risk indices (6, 7). The association of increased NT-proBNP levels with higher rates of cardiovascular events in apparently healthy persons and patients with stable coronary artery disease, acute coronary syndrome, and heart failure is well established (8). The ability of NT-proBNP to predict cardiac events relates to its sensitivity to detect myocardial wall stress and structural changes even in the absence of clinical manifestations. Thus, the findings by Duceppe and colleagues are not surprising and demonstrate the biological underpinnings of NT-proBNP. Nonetheless, this study is a major step forward in advancing the use of biomarkers for preoperative cardiac risk assessment.

There are several notable strengths of this work compared with prior studies. First, it is the largest study evaluating NT-proBNP in a preoperative setting. Second, the investigators examined the risk for events across a wide range of NT-proBNP values compared with dichotomized values in prior studies, providing more precision in risk prediction. Finally, in addition to hard clinical end points, the authors evaluated rates of

This article was published at Annals.org on 24 December 2019.

myocardial injury, a proven risk marker of short- and long-term outcomes.

Individualized and precise preoperative cardiac risk assessment should be a major component of elective noncardiac surgery planning. An effective risk stratification achieves several goals, including facilitation of shared decision making for surgery and optimization of intra- and postoperative care. Although there is unquestionable evidence about the prognostic significance of NT-proBNP in preoperative risk stratification, these breakthroughs have not translated into routine clinical practice. As such, the European Society of Cardiology and European Society of Anaesthesiology and the American College of Cardiology and American Heart Association 2014 guidelines do not recommend routine use of NT-proBNP for preoperative cardiac risk stratification (2, 3). Thus, given the well-known limitations of clinical risk indices and noninvasive cardiac diagnostic testing in preoperative risk prediction, evaluation of NT-proBNP in addition to clinical factors offers a readily available, precise, and inexpensive tool for risk stratification. However, whether NT-proBNP–driven perioperative management reduces the risk for cardiovascular events is unknown and should be investigated.

The role of biomarkers in routine preoperative cardiac risk stratification is still in its infancy and further study is needed. This field is wide open to investigation to find a suitable position for biomarkers in this setting; for example, a randomized trial of biomarker-guided preoperative risk assessment versus RCRI alone may answer whether this approach results in meaningful improvement in outcomes. Until then, data support the use of NT-proBNP to personalize cardiac risk stratification in patients having noncardiac surgery.

Arman Qamar, MD, MPH
Sripal Bangalore, MD, MHA
New York University Grossman School of Medicine
New York, New York

Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-3718.

Corresponding Author: Sripal Bangalore, MD, MHA, New York University Grossman School of Medicine, 550 First Avenue, SKI9R/109, New York, NY 10016; e-mail, sripalbangalore@gmail.com.

Current author addresses are available at Annals.org.

Ann Intern Med. 2020;172:149-150. doi:10.7326/M19-3718

References

1. **Devereaux PJ, Sessler DI.** Cardiac complications in patients undergoing major noncardiac surgery. N Engl J Med. 2015;373:2258-69. [PMID: 26630144] doi:10.1056/NEJMra1502824
2. **Kristensen SD, Knuuti J, Saraste A, et al; Authors/Task Force Members.** 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J. 2014;35:2383-431. [PMID: 25086026] doi:10.1093/eurheartj/ehu282
3. **Fleisher LA, Fleischmann KE, Auerbach AD, et al.** 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:2215-45. [PMID: 25085962] doi:10.1161/CIR.0000000000000105
4. **Clerico A, Emdin M, Passino C.** Cardiac biomarkers and risk assessment in patients undergoing major non-cardiac surgery: time to revise the guidelines? Clin Chem Lab Med. 2014;52:959-63. [PMID: 24501160] doi:10.1515/cclm-2013-0900
5. **Duceppe E, Patel A, Chan MTV, et al.** Preoperative *N*-terminal pro–B-type natriuretic peptide and cardiovascular events after noncardiac surgery. A cohort study. Ann Intern Med. 24 December 2019. [Epub ahead of print]. doi:10.7326/M19-2501
6. **Karthikeyan G, Moncur RA, Levine O, et al.** Is a pre-operative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. J Am Coll Cardiol. 2009;54:1599-606. [PMID: 19833258] doi:10.1016/j.jacc.2009.06.028
7. **Rodseth RN, Biccard BM, Le Manach Y, et al.** The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: a systematic review and individual patient data meta-analysis. J Am Coll Cardiol. 2014;63:170-80. [PMID: 24076282] doi:10.1016/j.jacc.2013.08.1630
8. **Kragelund C, Grønning B, Køber L, et al.** N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. N Engl J Med. 2005;352:666-75. [PMID: 15716560]

Current Author Addresses: Drs. Qamar and Bangalore: New York University Grossman School of Medicine, 550 First Avenue, SKI9R/109, New York, NY 10016.