Biomarkers and Risk Models in Cardiac Surgery

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Early risk models in cardiac surgery focused exclusively on coronary artery bypass grafting surgery (CABG), using pre-procedural variables to estimate the likelihood of in-hospital or 30-day mortality. These models were initially developed to assess provider performance, but they have subsequently been used for patient counseling, shared decision-making, and a variety of other applications. For provider profiling, the expected outcomes for all patients of a given hospital or surgeon, estimated from regional or national benchmarks, are aggregated to calculate the expected outcomes for their overall practice. These expected rates are compared with the observed outcomes to calculate standardized mortality ratios or rates.

Cardiothoracic risk models have evolved to include procedures other than isolated CABG and outcomes other than postoperative death, such as complications (e.g., reoperation, renal failure, stroke), readmissions, reinterventions, functional recovery (patient reported outcomes), costs, and long-term survival. These risk models may be helpful in identifying patients at higher than average risk of early and late adverse postoperative outcomes, some of which may be potentially prevented or at least mitigated with treatment modifications and enhanced follow-up. These might include more extensive evaluation prior to discharge; post-discharge phone calls or home visits by a nurse or PA; frequent communication between the patient’s primary care physician and the hospital team; and early postoperative follow-up appointments.

As the science of cardiothoracic surgery has evolved, risk models have kept pace, refining clinical predictor variables or adding new ones, allowing increasingly accurate risk estimation. For example, the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD) added both a qualitative variable for the presence of liver disease and a quantitative measure of liver dysfunction, the MELD score, in its version 2.73 update. A frailty score was also added, which substantially increases estimated risk when abnormal.¹
An even more recent trend in risk modeling has been the addition of various biomarkers to supplement clinical risk predictors. Because of their exquisite sensitivity, these biomarkers may provide incremental predictive value beyond that available from clinical data, thus facilitating the detection of subclinical phenomena or providing objective confirmation of clinical impressions. Two such biomarkers—Troponin T (TNT) and Beta-Type Natriuretic Peptide (BNP)—are the subject of a study by Lurati-Buse and colleagues in the current issue of Circulation. The authors should be acknowledged for their leadership in this important new area of investigation.

TNT is a sensitive marker of myocardial cell injury, often used in the evaluation and risk stratification of patients with acute coronary syndromes. TNT has also been studied in patients undergoing CABG, including previous investigations by the authors of the current study, and elevated levels are associated with less favorable short and long-term outcomes. In CABG patients, TNT levels may be elevated preoperatively due to acute coronary syndromes of varying severity and acuity. Even when preoperative levels are normal, as in many elective surgical patients, postoperative elevations of this sensitive biomarker occur due to cardiac incisions or manipulation, defibrillation, reperfusion, or myocardial injury from inadequate protection. Substantially elevated postoperative levels in some patients may alert providers to the need for enhanced follow-up in an attempt to mitigate short and long-term consequences, and they may also suggest the need to re-evaluate surgical strategies (e.g., myocardial protection).

BNP is released in response to ventricular volume or pressure overload or ischemia. Clinically, BNP elevations are most commonly associated with ventricular dysfunction or heart failure and portend a worse prognosis. In CABG, Fox et al showed that increased preoperative and peak postoperative BNP levels (especially the former) were independently
associated with early cardiac dysfunction, longer length of stay, and decreased long-term survival and physical functioning. As with TNT, it is possible that we may be able to provide more than just enhanced follow-up of patients with elevated perioperative BNP levels. For example, at least for elective procedures, might there be an opportunity to use preoperative BNP as a marker of increased risk and to modify perioperative management accordingly. In ambulatory heart failure, for example, numerous studies have shown that BNP-guided medical management designed to blunt BNP increases may improve outcomes and overall functioning.\textsuperscript{7,11-14}

In the current study, Lurati-Buse and colleagues\textsuperscript{2} report that addition of these two biomarkers augments the performance of a cardiac surgery risk model containing preoperative clinical risk factors (EuroSCORE), supplemented with clinical data on selected postoperative complications. Among 1559 patients enrolled in this prospective single center study between January 2007 and January 2010, follow up was 99.1\% at one year; 11.3\% of patients experienced the composite endpoint (death or major adverse cardiac events [MACE: myocardial infarction, cardiac arrest, need for subsequent surgical or percutaneous coronary intervention, and congestive heart failure requiring hospitalization] within 1 year); and 6.6\% of patients died. Based on biomarker levels from 6 AM on postoperative days one and two, the adjusted hazard ratio (HR) for a TNT level exceeding their threshold of 0.8 \(\mu\)g/L was 2.13 (95\% CI, 1.47-3.15), and the corresponding HR for BNP exceeding their threshold of 790 ng/L was 2.44 (95\% CI, 1.65-3.62). Compared to patients with no events during 12 month follow up, those who had an event had a higher EuroSCORE, TNT, and BNP, and more postoperative complications. Troponin and BNP were higher after procedures other than isolated CABG, although non-isolated CABG procedures were not further subdivided. Patients with elevated biomarkers experienced the composite outcome after a median of 22 days, compared with patients without
elevated biomarkers whose events occurred at a median of 87 days ($p < 0.001$), suggesting to the authors an opportunity for intervention such as “more stringent in-hospital monitoring in step-down units or systematic telemetry monitoring on the regular ward, dedicated post-cardiac surgery outpatients clinics, or virtual wards”\textsuperscript{2}.

Although the current study adds some new information, such as adjustment for complications, it also presents methodological concerns and opportunities for future investigation. For example, the authors regard it as a strength of their study that they included all consecutive cardiac surgery patients, ranging from isolated CABG to CABG plus valve and multiple valve procedures. Heterogeneous study cohorts such as this are often chosen in order to increase sample size and statistical power. The STS National Database has generally taken a different tact in developing and applying risk models, believing it is preferable to create more homogeneous patient cohorts (e.g., isolated CABG, isolated AVR)\textsuperscript{15-18}. This reduces extraneous sources of variation--noise--resulting from the aggregation of highly disparate procedures, and instead allows the analyses to focus on the source of variation that is of real interest, in this case the association of biomarkers with clinical outcomes. We might expect, for example, that the relative elevations of TNT and BNP would be quite different among the diverse group of procedures included in the current study\textsuperscript{2}. In CABG patients with acute coronary syndromes, TNT elevation might predominate, whereas in patients with chronic aortic regurgitation and heart failure, BNP elevations might be more prominent. Using homogeneous procedure cohorts would allow a more critical examination of these two biomarkers.

Use of the original Euroscore as the benchmark risk model in this study is also somewhat problematic\textsuperscript{19}. If the goal is to assess the incremental benefit of biomarkers to the predictive accuracy of existing clinical risk models, then it is only fair that the most contemporary and best
available risk models be used as the baseline for comparison. Although the authors supplemented
the original EuroSCORE with several new variables from EuroSCORE II, it would be interesting
to repeat this study using alternative risk models such as the STS ACSD, which is updated with
new and more granular data elements every three years. Version 2.81 of the ACSD includes
specific fields for 6 preoperative biomarkers (BNP, NTproBNP, hsTNT, hsCRP, and GDF-15) so
that their associations with outcomes may be explicitly studied.

Another major objective of the current study was to evaluate whether postoperative
biomarkers provide incremental predictive value to clinical risk models that were already
supplemented by data regarding postoperative complications. However, the only complications
included in this study (which were generally coded at the discretion of the surgeon and not
adjudicated) were sepsis, sternal infection without sepsis, respiratory infections (pneumonia,
ventilator associated pneumonia, or purulent tracheobronchitis without sepsis), and acute kidney
injury (AKI) classification. Stroke was not recorded, nor were hemodynamic complications such
as postoperative low cardiac output syndrome, requirement for inotropic support or IABP, or
potentially lethal ventricular arrhythmias, all of which might impact long-term MACE. If these
clinical complications had been included, the additive value of biomarkers might have been less.
Subsequent studies including these additional complications would be useful to more
convincingly validate the additive value of biomarkers.

The timing of biomarker collection in the current investigation—6 AM on postoperative
days 1 and 2—may not be optimal, and this also provides fertile opportunities for additional
study. Previous reports by Fox and colleagues demonstrated that postoperative BNP
increased significantly for the first 3 days postoperatively, then plateaus or decline by days 4
and 5, leading them to use peak rather than early postoperative BNP levels for their analyses.
Collection of specimens only on the first two postoperative mornings would therefore potentially miss the peak values.

In addition to obtaining additional postoperative biomarker samples beyond day 2, it would also be interesting to repeat these studies with adjustment for preoperative TNT or BNP, or to design analyses that compare the added predictive value of preoperative and postoperative determinations. Early postoperative biomarker elevations may reflect residually elevated preoperative levels due to myocardial injury or heart failure; elevations due to intraoperative management or events; or a combination of both. Studies by Fox and colleagues suggest that preoperative BNP may be a better predictor of length of stay and longer term mortality after CABG than peak postoperative BNP, although postoperative BNP may be useful if preoperative values are not available. From a pathophysiologic perspective, it would certainly be more satisfying to know the temporal pattern of biomarker elevations, which may help to better understand both causality and potential mitigation.

Finally, the authors use Net Reclassification Improvement (NRI) as one method to assess the added predictive value of the two biomarkers, a widely used approach since the pioneering report of Pencina and colleagues. NRI addresses the observation that even seemingly important biomarkers often add little to the area under the curve (AUC, or c-index) of predictive models, and thus perhaps underestimate their true importance. Reclassification takes a different approach, assessing the impact of a new predictor on correctly moving patients to a different risk category. Quoting from the original article: “The reclassification of people who develop and who do not develop events should be considered separately. Any ‘upward’ movement in categories for event subjects (i.e. those with the event) implies improved classification, and any ‘downward movement’ indicates worse reclassification. The interpretation is opposite for people who do not
develop events. The improvement in reclassification can be quantified as a sum of differences in proportions of individuals moving up minus the proportion moving down for people who develop events, and the proportion of individuals moving down minus the proportion moving up for people who do not develop events. We call this sum the NRI.\textsuperscript{20} The theoretical range of each of these two components of the overall NRI is – 1 (or -100%) to + 1 (or +100%), and the theoretical range of the overall NRI is thus -2 to +2 \textsuperscript{21}.

Despite its growing popularity, NRI has not always been applied or interpreted correctly, and some even question its theoretical foundation \textsuperscript{21-23}. The current study illustrates one important feature of this method--the importance of always considering the two components of the overall NRI (NRI for events and non-events) separately. The overall NRI associated with addition of TNT and BNP to the EuroSCORE was 0.276. Decomposing the two components of the overall NRI, as described above, there was reasonably strong performance of the new biomarker in detecting increased risk in patients who actually sustained an event (NRI\textsubscript{events} 0.696) but very poor performance in correctly reclassifying non-event patients (NRI\textsubscript{non-events} -0.420). In other words, among 100 patients not suffering MACE, a net of 42 would be misclassified “up” by the biomarker-augmented model, which is not reassuring performance.

In conclusion, the study of Lurati Buse and colleagues \textsuperscript{2} is an interesting addition to the growing literature on the utility of biomarkers in CABG risk prediction, and the authors are to be congratulated for their pioneering work in this area. Subsequent studies should address the methodological issues discussed in this review, which would add even more to our understanding of this complex issue. Finally, although identification of patients at higher risk for short and long term problems, and increased attention to such patients, are laudable goals, perhaps we now need to move to a more proactive approach. Future research should be aimed at identifying when and
why these molecules are released in cardiac surgery patients (the contributions of a patient’s presenting disease state versus the effects of surgery and anesthesia). Ultimately, the goal is to mitigate, when possible, the factors that lead to biomarker elevations, thereby potentially improving outcomes.

**Conflict of Interest Disclosures**: David Shahian reports the following uncompensated positions: Chair, STS National Database Workforce, Chair, STS Quality Measurement Task Force, Steering Committee, STS-ACC TVT Registry, Executive Committee, AMA PCPI, Board of Directors, National Quality Forum, and Co-Chair, National Quality Registry Network. Frederick L. Grover is a consultant without pay for Somahlution. He is also a Past Chair of STS Council of Quality, Research and Patient Safety, Past member of ACC NCDR Board, Vice Chair of STS/ACC TVT Steering Committee and is on the National Quality Forum Surgery Standing Committee.

**References**:


2. Lurati Buse GA. Troponin T and Brain Natriuretic Peptide after on-pump cardiac surgery: prognostic impact on 12-month mortality and major cardiac events after adjustment for postoperative complications. *Circulation*. 2014;130:XX-XXX.


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