Improved peri-operative risk stratification in non-cardiac surgery: going beyond established clinical scores

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This editorial refers to ‘Incremental value of high sensitive troponin T in addition to the revised cardiac index for peri-operative risk stratification in non-cardiac surgery’, by M. Weber et al., on page 853

Risk stratification represents an important clinical strategy to assess the patient’s prognosis precisely in various settings and/or tailor therapeutic interventions to his or her specific needs. Initially this was done by clinical judgement based on the patient’s history, a physical examination, and measuring select parameters from the clinical chemistry profile. In cardiovascular medicine, nowadays, there are a number of established scores available that measure the patient’s absolute risk for various cardiovascular endpoints based on traditional risk factors in primary prevention. Yet, despite the introduction of global risk assessment, e.g. by the European Society of Cardiology (ESC) SCORE, prediction of cardiovascular events is limited. This has prompted the search for novel markers to improve risk prediction in apparently healthy subjects.

Similarly, in patients with manifest cardiovascular diseases (CVDs), in particular after an acute coronary syndrome (ACS), risk stratification is an important issue. For this purpose, several scores are available: the TIMI (Thrombolysis in Myocardial Infarction)⁵ and the GRACE (Global Registry of Acute Coronary Events) Score⁶ which contain a number of clinical variables and information on renal function, blood glucose control, and cardiac enzymes. Based on such variables, fairly reliable prediction not only in the short term but even over a 5-year period can be made.⁶ In addition, other variables have been proven useful, such as global left ventricular (LV) function,⁷ results of exercise stress testing, and indicators of atherosclerotic burden such as carotid plaque and the ankle–brachial index. However, despite such routinely available variables, further improvement of risk assessment in this high-risk group is of paramount importance because available treatment options should be tailored according to the patient’s individual risk.

For cardiac surgery, most recently complex scores such as the SYNTAX score⁶ or the EURO score⁷ have been developed. For non-cardiac surgery, there are also several validated scores available such as that of Goldman et al.⁸ or the revised cardiac index of Lee et al.⁹ which has received a class IA recommendation in the ESC guidelines on pre-operative cardiac risk assessment.¹⁰ Lee’s revised cardiac risk index consists of six major criteria: four of them can be derived from the patient’s history (coronary artery disease, chronic heart failure, cerebrovascular disease, and insulin-dependent diabetes mellitus), one item refers to the risk of the planned surgical procedure, and only one laboratory parameter, creatinine, if >2 mg/dL, has made it into that score. Major complications predicted by the score of Lee et al. include myocardial infarction (MI), pulmonary embolism, ventricular fibrillation, cardiac arrest, and complete heart block, certainly all of utmost clinical importance. However, similar to other scenarios outlined above, the availability of powerful cardiovascular biomarkers such as high sensitive troponins (hsTnT or hsTnI), exquisite markers of myocyte necrosis, and markers of haemodynamic stress such as N-terminal pro brain natriuretic peptide (NT-proBNP) or BNP offer the opportunity for further refinement of these tools (Figure 1).

Epidemiological studies have convincingly shown that troponins accurately predict risk of cardiovascular ischaemia and subsequent clinical endpoints such as heart failure, stroke, MI, and death in a wide variety of clinical entities from acute-onset chest pain, to stable coronary heart disease (CHD), compensated and decompensated heart failure, and even cardiac surgery. Troponin levels detectable by the novel high sensitive troponin assays are ~ 10 times lower than those detected by conventional troponin assays, and even only slightly elevated values have been found to be associated with increased cardiovascular risk.¹¹–¹³ Recent studies demonstrated that among individuals in the general population and among patients with chronic CVD, measurable circulating TnT and TnI levels reflect chronic sources of myocardial injury, rather than acute processes, and predict long-term heart failure.

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risk. In aggregate, these findings suggest that low circulating levels of troponin reflect subclinical myocardial injury and thereby identify individuals at risk for heart failure or myocardial necrosis.

The study by Weber et al.\textsuperscript{14} assesses the performance of the revised Lee’s score without and in combination with hsTnT and NT-proBNP and finds a strong improvement in peri-operative risk prediction when adding hsTnT to the score.

For the purpose of their study, the authors enrolled 979 patients from eight hospitals in various European countries, scheduled for major non-cardiac surgery. Further inclusion criteria were age >55 years and at least one cardiovascular risk factor. The primary endpoint was all-cause mortality during hospitalization and a pre-defined combined endpoint comprising mortality, acute MI, cardiac arrest or ventricular fibrillation, CPR, and acute decompensated heart failure, thus incorporating at least three of Lee’s criteria. The median follow-up period was 11 days. During this time period, however, only very few patients either died (n = 25, 2.6%) or suffered from the combined endpoint (n = 36, 3.7%), despite 25% of patients having a history of CHD and 57% presenting with at least two cardiovascular risk factors. Those who died had higher hsTnT and NT-proBNP values. Mortality rates for hsTnT values above vs. below the 99th percentile (14 ng/L) were 6.9% vs. 1.2%, and the respective figures for NT-proBNP using a cut-off of 300 pg/mL were 4.8% vs. 1.4%, respectively. In Cox regression analyses, hsTnT was the strongest independent predictor of the combined endpoint as well as of in-hospital mortality. Furthermore, baseline levels were related to length of hospital stay and the need for intensive care treatment, two additional important clinical variables. Adding the information of hsTnT levels to the Lee index improved the area under the curve (AUC) from receiver operating characteristic (ROC) analyses for the combined endpoint substantially from 0.683 to 0.784, which showed a trend in statistical significance, and to 0.809 for in-hospital mortality. A much smaller increase was seen with NT-proBNP to 0.708, which was not significant. Nevertheless, NT-proBNP levels were also related to length of hospital stay and need for intensive care treatment.

So, what can we learn from this study? The main message certainly is that the authors provide evidence for a clinically significant improvement of an established score of cardiac risk stratification in patients scheduled for non-cardiac surgery which has received a class IA recommendation based on ESC guidelines, when hsTnT is added to the patient’s evaluation. The study has used relevant clinical outcomes and appropriate statistical methodology.

However, there are several issues that need to be considered before translation of such data into clinical practice. First, the number of endpoints is fairly low, thus overestimation of the results might be an issue. In this context, a longer follow-up period would also have been desirable. Thus, replication of the data, first and foremost, is needed, using an even larger sample comprising a truly representative population scheduled for elective non-cardiac surgery. Furthermore, in addition to performance measures such as ROC analyses, reclassification strategies have to be incorporated into the statistical analysis plan. Finally, we have to ask what are the clinical implications of such improved risk stratification? Will these patients be treated differently before the procedure? Will such data lead to additional diagnostic testing pre-operatively? If yes, which tests need to be done? Ultimately, only well-powered, randomized clinical trials will provide us with the adequate answer. Until then, we should be aware that patients with increased hsTnT outside an ACS are still at high risk for various adverse outcomes and deserve our full clinical attention and optimal medical treatment.

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References


