Utility of clinical risk predictors for preoperative cardiovascular risk prediction

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Summary. Cardiovascular risk prediction using clinical risk factors is integral to both the European and the American algorithms for preoperative cardiac risk assessment and perioperative management for non-cardiac surgery. We have reviewed these risk factors and their ability to guide clinical decision making. We examine their limitations and attempt to identify factors which may improve their performance when used for clinical risk stratification. To improve the performance of the clinical risk factors, it is necessary to create uniformity in the definitions of both cardiovascular outcomes and the clinical risk factors. The risk factors selected should reflect the degree of organ dysfunction rather than a historical diagnosis. Parsimonious model design should be applied, making use of a minimal number of continuous variables rather than creating overfitted models. The inclusion of age in the model may assist partly in controlling for the duration of risk factor exposure. Risk assignment should occur throughout the perioperative period and the risk factors chosen for model inclusion should vary depending on when the assignment occurs (before operation, intraoperatively, or after operation).

Keywords: clinical risk factors; complications, myocardial infarction; modelling; risk

Preoperative risk stratification as stated by the American College of Cardiology/American Heart Association (ACC/AHA) in their ‘Perioperative cardiovascular evaluation and care for noncardiac surgery’ is aimed at ‘providing a risk profile’ while the European Society of Cardiology/European Society of Anaesthesiology’s (ESC/ESA) guidelines for preoperative cardiac risk assessment aim to generate an ‘individualized cardiac risk assessment’. These risk assessments are then used to assist with both short- and long-term patient investigation and to direct further perioperative management.

Clinical risk factors play an important role in this process, providing a cheap and readily accessible tool by which to perform preoperative risk stratification. The first major contribution to perioperative cardiovascular risk prediction was made when Goldman and colleagues developed the original perioperative cardiovascular risk index, later modified by Detsky and colleagues. Subsequent indices showed similar performance in predicting cardiovascular risk until the development of Lee’s Revised Cardiac Risk Index (RCRI). The RCRI performed significantly better than previous indices and was validated outside its derivation population (Table 1). This led to its incorporation into the ACC/AHA perioperative algorithm, and also into the ESC/ESA guidelines for preoperative cardiac risk assessment and management for non-cardiac surgery. This has established the RCRI as the primary clinical cardiovascular risk stratification tool in perioperative medicine.

The aim of this review is to evaluate the utility and limitations of the RCRI clinical risk factors as they are currently used in preoperative evaluation guidelines for risk stratification and directing further preoperative investigation. We have attempted to identify areas of clinical risk prediction which could be improved on in the future.

Performance of the current clinical risk stratification tools

The goal of preoperative risk assessment is to assess an individual patient’s cardiac risk in order to direct further testing and treatment, and to perform this process as cost-effectively as possible. Current perioperative cardiovascular evaluation algorithms follow a stepwise process making use of clinical factors and test results together with an estimation of the size of the surgical stress response to arrive at an ‘individualized cardiac risk assessment’.

The first four steps in both the European and American guidelines are directed at assessing patient-specific risk. These steps determine (i) the presence of active or unstable cardiac conditions, (ii) the patient’s functional capacity, (iii) the urgency, and (iv) associated cardiac risk of the surgery. They are tailored to the individual patient and the surgery they have to undergo. The presence of active cardiac conditions, high-risk surgery, or poor effort tolerance all greatly increases a patient’s risk for a postoperative cardiac complication.

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Patients are then clinically stratified using the RCRI clinical risk factors. In contrast to the preceding steps of the algorithms, the RCRI is a population-derived risk index. As a result, it cannot be used to assign individual patient risk but is rather used to stratify patients into risk categories, which forms the basis for further perioperative management. To perform this role adequately, the RCRI risk factors must successfully discriminate higher risk from lower risk patients in this already triaged population.

Two statistical methods may be used to evaluate the discrimination of the RCRI. The first is by means of likelihood ratios (LRs). LRs reflect a test’s ability to create risk categories, by expressing these categories as ratios. Clinically useful discrimination is seen with ratios <0.2 or >10. An added advantage of the LR is that it may be used to determine post-test probability, using Fagan’s nomogram.

The second commonly used method is the area under the receiver-operating characteristic (ROC) curve (AUC). The AUC (also known as the c-statistic) is expressed as a percentage and reflects the probability that a positive test will experience an event when compared with a negative test. The ACC/AHA guidelines use the RCRI to create three risk categories (3 or more, 1 or 2, no risk factors) to guide further investigation, while the ESC guidelines make use of only two risk categories (≥3 risk factors or <3 risk factors). An assessment of the RCRI determined that the only clinically significant LRs were achieved when a patient had no clinical risk factors (LR of 0.16). The presence of one risk factor fell just outside the clinically useful range with a negative LR of 0.34. For patients with either two, or three and more risk factors, the discrimination was found to be poor with an LR of 2.7 and 4.8, respectively. When applied to a large retrospective database study (108 593 patients) of non-cardiac surgery population, the RCRI was able to discriminate four individual risk groups in which the risk of cardiac death was statistically different (0.3%, 0.7%, 1.7%, 3.6%). However, the clinical utility of these findings is questionable as the resultant c-statistic for the AUC was only 0.63.

To improve on this discriminatory ability, patients have been grouped into low (0 or 1 risk factors) and intermediate–high (≥2 risk factors) risk categories. The ability of the RCRI to predict perioperative cardiac complications [cardiac death, myocardial infarction (MI), non-fatal cardiac arrest] or death within 30 days of surgery was reviewed in a recent large meta-analysis of predominantly observational cohort studies (792 740 patients in 24 studies). It found moderate discrimination between patients at high vs low risk for cardiac events [AUC 0.75 (95% CI 0.72–0.79), with a positive LR of 2.78 (95% CI 1.74–4.45) and a negative LR of 0.45 (95% CI 0.31–0.67)].

When used for vascular surgery alone, the RCRI showed significantly poorer discrimination for predicting cardiac events in this meta-analysis, than with other types of non-cardiac surgery, with an AUC of 0.64 (95% CI 0.61–0.66), a positive LR of 1.56 (95% CI 1.42–1.73), and a negative LR of 0.55 (95% CI 0.53–0.82). Interestingly, these findings echo those in Lee’s original prospective observational study of 4315 non-cardiac surgical patients aged ≥50 yr, where they identified the limited discriminative utility of the RCRI in aortic surgery [AUC 0.543 (0.092)]. Other data also suggest that the performance of the RCRI is influenced by the nature of the surgical procedure and is particularly compromised by higher risk surgeries. A retrospective database review found that the separation of low-to-intermediate risk surgeries from the intermediate-to-high-risk surgeries changed the AUC from 0.68 to 0.56, respectively. A recent prospective observational study of 10 081 vascular surgical patients, which evaluated the same patient outcomes of the original RCRI confirmed that with vascular surgical procedures of increasing cardiovascular risk, the RCRI progressively underestimated the associated cardiovascular complications.

Thus, the RCRI, as a preoperative population-derived risk stratification tool, is at best able to crudely risk stratify patients. In addition, the RCRI’s discrimination is best in patients with no risk factors, and not in the higher risk categories as used in the ACC/AHA or the ESC guidelines, or in vascular surgical patients. It would seem that the RCRI’s greatest utility lies in its ability to exclude low-risk patients rather than in predicting events in intermediate-to-high-risk patients. Indeed, the need to undertake high-quality studies to evaluate the RCRI’s ability to predict perioperative cardiac risk has been suggested, and Goldman in his editorial on the paper suggests that the RCRI is accurate enough for preoperative risk stratification, although he too suggests that it may benefit from an improvement in its diagnostic accuracy.

The poor discrimination in high-risk (≥3 risk factors) patients would not be a concern, if subsequent non-invasive testing was able to reliably risk stratify these patients. Unfortunately, the evidence suggests that non-invasive investigations are not able to do this. A single, prospective, randomized trial of 208 vascular surgical patients has addressed this issue. In patients with ≥2 RCRI risk factors, one group was managed as per the AHA/ACC preoperative cardiovascular algorithm and selectively underwent coronary angiography following non-invasive testing. All the patients in the other arm of the study had preoperative coronary angiography. While the groups were clinically similar, the myocardial revascularization

<table>
<thead>
<tr>
<th>Number of CVS risk factors</th>
<th>Major CVS complications (95% CI) (%)</th>
<th>Cardiovascular death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5 (0.2–1.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>1</td>
<td>1.3 (0.7–2.1)</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>3.6 (2.1–5.6)</td>
<td>1.7</td>
</tr>
<tr>
<td>≥3</td>
<td>9.1 (5.5–13.8)</td>
<td>3.6</td>
</tr>
</tbody>
</table>
rate and survival at 58 (17) months was significantly better in the group randomized to routine coronary angiography.\textsuperscript{14} Essentially, non-invasive testing was unable to identify those patients who may have benefited from coronary angiography and revascularization.

Meta-analyses of studies of non-invasive testing suggest that the discriminatory performance of these tests is clinically poor with LR ranging from 2 to 6.\textsuperscript{15, 16} While a number of the studies included in the meta-analyses of non-invasive tests were not necessarily done after RCRI specific risk stratification, many used clinical risk factors to risk stratify before non-invasive tests.

There are clearly limitations to non-invasive tests. As we have shown, the positive LR for patients with $\geq 3$ risk factors decreases below the clinically significant threshold. In addition, the pretest probability of the populations selected by the algorithm for further testing is probably lower than expected and it is possible that this may be further contributing to their poor performance. If we could improve the performance of clinical risk prediction, we may also improve the performance of preoperative non-invasive tests. Unfortunately, we are unaware of any perioperative study which has tested this hypothesis. With our current approach to risk stratification, it is true that ‘we are not yet near the situation where we can give a specific risk value for an individual’,\textsuperscript{17} although this is what we should strive for.

\section*{Reasons for the poor performance of current preoperative clinical risk prediction models}

There are three broad categories of shortcomings that underlie the current poor performance of clinical cardiovascular risk prediction models. These include: (i) the definition of both clinical risk factors and adverse cardiovascular outcomes, (ii) the limitations of identified risk factors, and (iii) the statistical flaws in model derivation. These shortcomings can be identified in many aspects of the original work on cardiovascular risk prediction and are discussed below.

\section*{Shortcomings in definitions}

\subsection*{Clinical risk factor definitions}

Risk factor definition has varied between derivation studies and the subsequent application of these models. The classic example is the risk factor ‘preoperative treatment with insulin’ adopted by Lee and colleagues\textsuperscript{6} in the RCRI. It has been changed to ‘insulin-dependent diabetes mellitus’\textsuperscript{18} and in the ACC/AHA guidelines to ‘diabetes mellitus’.\textsuperscript{1} These variations make comparisons between different studies difficult and may hamper model performance and applicability.\textsuperscript{15} Fortunately, the ESC guidelines have adopted the definition of diabetes as used by Lee and colleagues.\textsuperscript{6}

As has been highlighted in this and other papers,\textsuperscript{13, 19} it is imperative that we clearly define both preoperative risk factors and perioperative event endpoints and standardize reporting of these events. This will allow meaningful interpretation of study outcomes and also facilitating meta-analysis. Steps should be taken to build on the definitions used by the AHA/ACC and the ESC and to adopt definitions such as the universal definition for MI\textsuperscript{20} for perioperative use. Consensus reporting statements should be drawn up defining not only perioperative cardiac events, but also pulmonary, renal, gastrointestinal, and thrombotic events.

\subsection*{Adverse cardiovascular outcome definitions}

There is no standard definition of an adverse perioperative cardiovascular outcome. This has resulted in risk derivation studies using a diverse range of outcomes with widely differing definitions. In addition, some studies may have defined their outcomes in such a manner as to increase the positive event rate within the study population, which would allow for more data interrogation (Table 2). For example, in the original RCRI study, 64% of the cardiac complications were due to cardiac death or non-fatal MI, with the remainder being cardiac arrest, heart block, and pulmonary oedema.\textsuperscript{6} If cardiac death and MI were the only study endpoints, a third of the variables would not have been interrogated in the logistic regression.

The inconsistency in definition of an adverse cardiovascular outcome may affect which risk factors may be included in a model, and also the ability of the model to predict the incidence of a specific cardiovascular complication. It is likely that different outcome definitions will alter which variables are included in a derived model. This was evident in the evaluation of cardiac outcomes using a vascular surgical registry,\textsuperscript{21} where the outcomes of MI and cardiac death evaluated separately resulted in different independent predictors. A history of coronary artery disease [odds ratio (OR) 3.16, 95% confidence interval (CI) 1.59–6.29] and valvular heart disease (OR 2.07, 95% CI 1.09–3.94) were

\begin{table}[h]
\centering
\small
\begin{tabular}{|l|c|c|c|c|}
\hline
 & Goldman\textsuperscript{3} & Detsky\textsuperscript{4} & Lee\textsuperscript{6} & Welten\textsuperscript{14} \\
\hline
Cardiac death & X & X & X & X \\
Non-fatal myocardial infarction & X & X & X & X \\
Postoperative pulmonary oedema/ congestive cardiac failure & X & X & X & X \\
Ventricular tachycardia & X & X & X & X \\
Ventricular fibrillation & X & X & X & X \\
Primary cardiac arrest & X & X & X & X \\
Complete heart block & X & X & X & X \\
Coronary revascularization & X & X & X & X \\
Other minor complications & X & X & X & X \\
\hline
\end{tabular}
\caption{Cardiovascular outcomes reported in studies of clinical cardiovascular risk factors}
\end{table}
independent predictors of perioperative MI, while a history of congestive heart failure within the year before surgery (OR 13.6, 95% CI 3.57–58.6) and the number of perioperative blood transfusion units (OR 1.24, 95% CI 1.08–1.5) were independent predictors of cardiac death.\(^2\) It is likely that the independent predictors identified in the major studies in Table 2 may have been partly determined by the definitions of an adverse cardiovascular outcome adopted in each study. This would have implications for subsequent non-invasive investigation, as the subsequent identification of myocardial ischaemia or insipid cardiac failure is a very different clinical endpoint which may require different pre-operative non-invasive investigation.

Therefore, to improve model performance, the outcome should reflect the endpoint of a single pathophysiological process. Ideally, we would like to be able to confidently predict either perioperative MI or perioperative cardiac failure. Comparison of patients with ischaemic heart disease and heart failure in database reviews has shown a significantly different burden of other cardiovascular comorbidities (\(P<0.001\)), and a significantly different perioperative outcome.\(^2\) In a systematic review of the outcomes of major cardiac events after non-cardiac surgery, 66% of cardiac death was attributed to MI and the remaining 34% unrelated to adverse coronary events.

Limitations of identified clinical risk factors

There are four main problems associated with the clinical risk factors and their utility in cardiovascular risk prediction models.

Difficulty with risk factor identification

Risk factors which present a subtle clinical continuum may make it difficult for clinicians to consistently identify or acknowledge their presence. Cardiac failure is a diagnosis that is notoriously difficult to make clinically. For example, a cross-sectional observational study of 5434 patients attending community health-care centres found objective echocardiographic evidence of cardiac dysfunction in only 54% of patients clinically diagnosed with heart failure.\(^2\) On the other hand, symptoms such as pulmonary oedema, orthopnoea, and dyspnoea (sensitivity <36%) and signs such as a raised jugular venous pressure with lower limb oedema and rales on pulmonary auscultation (sensitivity <10%) were infrequent in the 551 patients objectively diagnosed with cardiac failure. This, coupled with variations in the ability of clinicians to interpret clinical signs and patients to accurately convey a history of cardiac failure, adds to the difficulty of accurately making the diagnosis of heart failure. A cross-sectional study of 621 patients assessing the accuracy of the primary care diagnosis of cardiac failure found that symptoms and signs were not an accurate predictor of left ventricular systolic dysfunction and that ‘clinical features cannot be relied upon to achieve accurate diagnosis (of heart failure)’.

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It is important to consider other markers of cardiac dysfunction such as the New York Heart Association (NYHA) functional classification, the Duke Activity Status Index, an ejection fraction, or brain natriuretic peptide (BNP), which may remove some of the subjectivity of a difficult diagnosis. A prospective observational study has shown good correlation between the Duke Activity Status Index and maximum oxygen consumption in preoperative patients.\(^2\) Models to predict major cardiac complications in patients undergoing non-cardiac surgery that incorporated echocardiographic data performed statistically better than those that only made use of clinical variables (AUC 0.73 vs 0.68; \(P<0.05\)).\(^2\) The incorporation of biomarkers such as NT-proBNP and C-reactive protein (CRP) into an RCRI model to predict MI, pulmonary oedema, or cardiovascular death improved the adjusted relative risk categorization from 1.5 to 4.6 (\(P<0.001\)).\(^2\) Importantly, the addition of BNP significantly improves the RCRI risk stratification in a prospective observational study of vascular surgical patients for post-operative troponin elevation above the upper reference limit (net reclassification improvement 38.3%, 95% CI 9.3–67.3%, \(P=0.01\) for the entire cohort).\(^2\)
Using risk factors as a dichotomy or as a continuum

Clinical risk factors present as a continuum, but are reflected in the RCRI as dichotomous risk factors. While a dichotomous approach is useful when attempting to define risk factors in large populations, the disease severity as it relates to the individual patient is lost. This approach ignores the fact that as the severity of a risk factor increases, there is a proportional ‘semi-logarithmic’ increase in patient risk.\(^{32}\) For example, when using the Seattle Heart Failure Model, a 50-yr-old female with heart failure of ischaemic aetiology, NYHA grade 2, and an ejection fraction of 55% has an expected 1 yr mortality of 12% and a mean life expectancy of 6.2 yr.\(^{33}\) In contrast, a 75-yr-old male with heart failure of ischaemic aetiology, NYHA grade 3, and an ejection fraction of 30% has an expected 1 yr mortality of 21% and a mean life expectancy of 3.9 yr. Despite this difference in risk, the RCRI would allocate an equal risk score to both these patients. Thus, the risk associated with the diagnosis of heart failure in the individual patient has been replaced by a generic risk factor describing the risk associated with the diagnosis of heart failure in a population. The effect of decreasing functional capacity on mortality associated with heart failure is illustrated in Figure 1.

In addition, there are other statistically compelling reasons to retain such risk factors as a continuum or to classify them into risk categories as has been done in the Risk Injury Failure Loss End-stage classification of renal dysfunction.\(^{24}\) Avoiding the use of a dichotomous yes/no cut point allows the risk factor to be used across a range of clinical scenarios. By choosing a classification system that maximizes sensitivity within lower risk categories, the risk factor can be used for screening purposes. Similarly, maximizing specificity in the higher risk categories allows its use as a diagnostic tool while reducing the likelihood of false

![Figure 1: One year mortality stratified according to NYHA functional classification in a simulated heart failure patient. (Calculated with Seattle Heart Failure Model: 50 yr male with ischaemia, 80 kg, ejection fraction 45%, systolic AP 140 mm Hg, no medication, Hb 12 g dl\(^{-1}\), lymphocytes 24%, uric acid 9 mg dl\(^{-1}\), total cholesterol 190 mg dl\(^{-1}\), sodium 137 mmol litre\(^{-1}\), no devices, no interventions); http://depts.washington.edu/shfm/app.php.](image)

Table 3 The additive predictive value of adding biomarkers to the RCRI.\(^{30}\) Perioperative cardiac complications; acute myocardial infarction, pulmonary oedema, cardiovascular death, RCRI \(\geq 2\), CRP \(\geq 3.4\) mg litre\(^{-1}\), and NT pro-BNP \(\geq 301\) ng litre\(^{-1}\). AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; BNP, brain natriuretic peptide

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC</th>
<th>95% CI</th>
<th>Approximate specificity to nearest 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCRI</td>
<td>0.592 (0.019)</td>
<td>0.570–0.615</td>
<td>70%</td>
</tr>
<tr>
<td>RCRI + CRP</td>
<td>0.694 (0.019)</td>
<td>0.673–0.715</td>
<td>60%</td>
</tr>
<tr>
<td>RCRI + BNP</td>
<td>0.735 (0.018)</td>
<td>0.714–0.754</td>
<td>50%</td>
</tr>
<tr>
<td>RCRI + CRP+ BNP</td>
<td>0.772 (0.017)</td>
<td>0.752–0.790</td>
<td>40%</td>
</tr>
</tbody>
</table>
risk factors for cardiovascular disease and the current consequences of these risk factors. This is analogous to a hierarchy of exposure to cardiovascular risk factors which are ultimately responsible for an adverse cardiovascular outcome. Risk factors early in the hierarchy are classically exposure (or presence) factors, while risk factors later in the hierarchy are often characterized by complications or consequence of the cardiovascular disease. For example, a patient's risk for a perioperative cardiovascular event will not be determined by the presence of hypertension, but rather by the degree of end-organ damage sustained as a consequence of hypertension. This explains how factors such as cardiac and renal failure feature prominently in most perioperative risk scores, while factors such as smoking, hypertension, and even diabetes show variable utility. A systematic review of hypertension suggests that its importance as a clinical risk factor is still controversial. A recent prospective observational study supports this concept. When the independent risk factors of perioperative cardiovascular complications were proportionally weighted according to individual β-coefficients, the cardiovascular ‘exposure’ variables of smoking and diabetes carried half the points, of the ‘consequence’ variables of coronary artery disease, heart failure, and renal failure.

Therefore, the first principle in selecting risk factors for a cardiovascular risk prediction model would be to consider those factors which quantify the known complications of the disease of interest. In the case of perioperative MACE, it is the presence of the complications of significant atherosclerosis such as stroke, renal dysfunction, and heart failure that become important; as opposed to risk factors associated with the development of atherosclerosis, such as diabetes and hypertension.

The second principle to consider is that causal factors are not necessarily constant over time, an aspect not considered in the RCRI. A history of diabetes will contribute a single point to the RCRI irrespective of the duration of the disease. This is illogical when patients with diabetes have a cardiovascular disease prevalence of 71% after 20 yr of diabetes, compared with 26% in those with a diagnosis of <5 yr (Fig. 2). The principle is further supported when one considers the frequency of Lee’s risk factors in relation to patient age. A retrospective study of 2298 vascular surgical patients suggests that with the possible exception of ischaemic heart disease (P = 0.05), the frequency of clinical risk factors does not seem to increase with age (P > 0.05), yet age appears to be an important modifier of risk. The ability of the RCRI to predict MACE in vascular surgery patients was reduced from an AUC of 0.76 in patients <55 yr to 0.62 in those >75 yr of age.

A retrospective study of more than 108 000 patients found that the addition of age to an adapted RCRI resulted in an improvement in cardiovascular mortality prediction from an AUC of 0.79-0.85, once again suggesting that it is not the prevalence of the disease, but rather the duration of disease exposure that is important. Indeed, in a prospective observational study, the age of the patient was 1.5- to 2-fold higher predictor of cardiovascular risk, than cardiovascular risk factors such as coronary artery disease, heart failure, and renal dysfunction. It is likely that including age in a cardiovascular risk prediction model will control for some of the increasing morbidity associated with an increased duration of exposure to a known cardiovascular risk factor.

Thirdly, the distribution of a chosen risk factor must be significantly different between the healthy and sick populations in order for it to have adequate clinical utility. Depending on the population presenting for surgery, cardiovascular risk factors will show variable utility in their ability to perform this differentiation. In certain types of surgery, the prevalence of a risk factor may be very high, thus eroding its ability to discriminate and subsequently predict an adverse outcome. A history of diabetes, coronary artery disease, cardiac failure, or cerebrovascular disease may become meaningless in a population where individuals have most or all of these factors. This may account for the findings of a meta-analysis where the discriminatory ability of the RCRI was eroded when applied to a vascular surgery population. The higher prevalence of Lee’s RCRI risk factors in vascular surgical patients compared with other non-cardiac surgeries is evident in a recent publication of a population registry from the Netherlands (Table 4), although the significance of this observation cannot be determined from the published study.

In the derivation of Lee’s RCRI, all risk factors were deemed to be of almost equal prognostic importance, and hence were all ‘weighted’ evenly in the risk prediction model. However, this equal weighing may be inappropriate when applied to vascular surgical patients. Risk factors such as IHD, DM, and CVA may be of less prognostic importance in a vascular surgical population, while renal dysfunction and heart failure may be more so (Table 5). The Vascular Study Group of New England Cardiac Risk Index (VSG-CRI) suggests that coronary
artery disease, renal dysfunction, and heart failure have odds ratios for cardiovascular complications after vascular surgery, which are double that of diabetes.\(^{12}\)

Other risk simulations have shown that the removal of a single risk factor from an equally weighted four risk factor model decreased the AUC from 0.72 to 0.65.\(^{45}\) This may be similar to the degradation in performance of the RCRI when it is applied to a vascular surgical population,\(^{11}\) as opposed to other non-cardiac surgical populations. It is possible that the loss (or decrease) in the utility of diabetes (Table 5) as a risk predictor in vascular surgical patients may adversely affect the performance of the RCRI. Thus, the variable weighting of risk factors, and the inclusion of age in the model, may partly explain the better performance of the VSG-CRI when compared with the RCRI.\(^{12}\)

### Statistical shortcomings in the risk factor derivation papers

#### Events per variable in derivation models

For every variable analysed for possible use in a predictive model, the population must have a certain number of positive events. To derive an optimal model and to avoid ‘overfitting’, 12–15 events per variable (EPV) have been suggested.\(^{46}\) Study cohorts examining preoperative risk have been plagued by low event rates and excessive analysis of variables, all resulting in model overfitting. For example, in Goldman’s original preoperative prediction model, all 45 variables, including an undisclosed number of laboratory values, were entered into the analysis. The total number of major cardiovascular complications in the cohort was only 58, with an EPV approaching 1.\(^{3}\) The RCRI derivation model examined six independent variables with 56 events in the cohort, with a low event per variable of 9.3. In the original paper, the total number of variables entered into the multivariate logistic regression was not specified, although it is possible that as many as 29 variables were eligible for inclusion, which would give 1.9 EPV.\(^{6}\) Overfitting has also occurred in studies examining perioperative haemodynamics with EPV ratios of 6.9,\(^{47}\) 3.1,\(^{48}\) and 3.6.\(^{49}\)

It is unlikely that a low EPV will change which variables are identified as significant, although it will certainly change the strength of the association with an adverse cardiovascular outcome.\(^{46}\) This is important, as it is likely that the equal ‘weighting’ of Lee’s RCRI risk factors is questionable, especially in the light of the low EPV and our understanding of some of the shortcomings of the included risk factors. While the use of an equally ‘weighted’ score is convenient, it does not make statistical sense.

A recent cardiac surgical model\(^{50}\) illustrates the success of adopting some of these principles in the development of a risk prediction model. A model was developed which included only three continuous variables, of which two reflected end-organ dysfunction (ejection fraction and serum creatinine) and the third was age. In a validation cohort, the model had an AUC exceeding 0.8 and was either equivalent or better than the EuroSCORE,\(^{51, 52}\) the Parsonnet score,\(^{53}\) the Cleveland Clinic score,\(^{54}\) and the Northern New England score.\(^{55}\)

### Table 4 The prevalence of Lee’s risk factors in Dutch non-cardiac surgical patients\(^{43}\)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Vascular surgical patients</th>
<th>Other non-cardiac surgical patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>5.5% &lt;1.7%, except thoracics (2.9%)</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.7% &lt;0.7%</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.6% &lt;2.7%</td>
<td></td>
</tr>
<tr>
<td>Renal disease</td>
<td>2.9% &lt;0.3% except urology (1.6%)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>11.2% &lt;0.8% except neurosurgery (6.4%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5 The trends associated with Lee’s RCRI risk factors in vascular surgical patients and possible explanations for these associations. IHD, ischaemic heart disease; DM, diabetes mellitus; renal dysfunction Cr>2 mg dl\(^{-1}\); CVA, cerebrovascular accident; CCF, congestive cardiac failure

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio for cardiovascular complications or death(^{44})</th>
<th>Trend associated with outcome in vascular surgical patients</th>
<th>Possible explanation of trend in vascular surgical patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All non-cardiac surgery(^{6})</td>
<td>Vascular surgery(^{44})</td>
<td>IHD 2.4 (1.3 – 4.2)</td>
<td>2.0 (1.3 – 3.2)</td>
</tr>
<tr>
<td>DM</td>
<td>3.0 (1.3 – 7.1)</td>
<td>2.0 (1.3 – 3.2)</td>
<td>0.2 (0.1 – 2.2)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>3.0 (1.4 – 6.8)</td>
<td>5.7 (3.1 – 10.7)</td>
<td>Trend to more importance</td>
</tr>
<tr>
<td>CVA</td>
<td>3.2 (1.8 – 6.0)</td>
<td>2.8 (1.7 – 4.6)</td>
<td>Trend to less importance</td>
</tr>
<tr>
<td>CCF</td>
<td>1.9 (1.1 – 3.5)</td>
<td>6.3 (3.4 – 11.6)</td>
<td>Possibly significantly more important</td>
</tr>
</tbody>
</table>
Importance of considering time in cardiovascular risk prediction

Prognostic models are different from diagnostic models, in that they introduce time, which introduces a stochastic or random element into the model. Prognostication is usually used for risk stratification (risk categories) when an outcome is both unknown and has not yet occurred, as opposed to a predicted binary outcome. Current perioperative models have generally avoided incorporating time into models. In model predictions, the shorter the time between making a prediction and the event, the more accurate the prediction becomes. Vital to this process is the repeated re-sampling of data points. A key pitfall in current perioperative cardiovascular risk prediction models is the expectation that a single data sampling event will suffice to predict future events and subsequently a large proportion of the published literature has dealt with preoperative risk predictors only. Various database studies have suggested that both intraoperative and postoperative factors are important modifiers of perioperative cardiovascular risk.

This understanding of time horizons is encapsulated in the theory of general relativity and its central concept; the light cone (Fig. 3) which can be extrapolated to clinical risk prediction (Fig. 4). At the moment of assessment, we attempt to determine risk as completely as possible, creating a risk assessment point (R). The accuracy of our risk assessment will be determined by how well our sampling tool reflects the R point. If we use a history of cardiac failure at point A, there is a wide range of varying probability in predicting point R. If we perform an echocardiogram or do a BNP level for the diagnosis of cardiac failure (point B), this would more closely reflect the R point. Our ability to predict future events is determined by how well we define the R point. Similarly, the accuracy of our prediction will degrade as we move away from the R point to point C (30 day mortality) and outward to point D (180 day mortality). It follows then that sequential modelling throughout the perioperative period will improve risk prediction.

The inclusion of intraoperative risk predictors into a risk stratification model has been shown to improve the prediction of adverse cardiac events with an improvement in the AUC for adverse cardiac events from 0.77 (0.3) to 0.81 (0.2) when intraoperative variables were included in the model. This performance was also improved to 0.79 for perioperative mortality when surgical data were further subclassified in addition to Lee’s RCRI. When multiple pre- and intraoperative predictors are used, the AUC has been shown to approach 0.86. Intraoperative risk factors which appear to modify perioperative cardiac adverse events include: the type of operation, operative severity (duration of surgery and blood loss), and the age of the patient. Intraoperative haemodynamics may also be important predictors, although no models have identified them as independent predictors of adverse cardiac events.

Interplay exists between pre- and intraoperative risk factors whereby intraoperative factors may increase or decrease the importance of preoperative clinical risk factors. When including intraoperative factors into risk models, certain preoperative factors such as ischaemic heart disease and diabetes lose their prognostic value and are removed from the model, while cerebrovascular disease, renal dysfunction, and cardiac failure are retained. Intraoperative blood loss, mean arterial
pressure, and heart rate may reduce the predicted odds of major complications by a half and increase them by as much as three-fold. A model that includes intraoperative risk factors once again retains risk factors that represent the complications of atherosclerotic disease, although the severity of risk associated with these factors is modulated by the intraoperative period.

A number of the observations in this review are theoretical. While we have attempted to provide clinical evidence for some of the shortcomings of the current clinical risk predictors, most of this evidence is purely observational. Our recommendations cannot therefore be currently validated from the literature. However, we would recommend that the following principles are considered in future investigation of clinical risk predictors, which would then need to be validated: (i) risk factors which represent the current degree of organ dysfunction, (ii) include age, (iii) and the type of surgery (vascular surgery). Time should be considered in modelling, and sequential models should be developed with risk factors specific to each perioperative period. Statistically, model overfitting should be avoided; multiple risk factors which all reflect a single organ dysfunction should be clustered to assist in parsimonious model development and the use of categorical or continuous risk factors should be adopted.

There have been significant advances in our understanding of risk predictors and the statistics of risk prediction. It is incumbent upon us to now take up the challenge and integrate this knowledge into the future investigation of perioperative cardiovascular risk prediction to the point where we are able to provide a patient with his or her own specific risk assessment for a perioperative cardiac event.

Acknowledgements

We thank Dr Santosh Persad for stimulating discussion and insightful comments during the preparation of this manuscript. Any shortcomings of this review are, however, entirely of our own making.

Conflict of interest

None declared.

Funding

This work was supported by departmental funds. B.M.B. is supported by an MRC self-initiated research grant. R.N.R. is supported by a CIHR Scholarship (the Canada-HOPE Scholarship).

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