Peri-operative Cardiovascular Risk and the General Internist

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About the Author
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Summary
Peri-operative cardiovascular risk assessment and management remain important and challenging tasks for the general internist. Since the 1999 publication of the now-widely-used revised cardiac risk index assessment model, there have been further risk factor qualifiers identified and newer predictive models developed. These include patient and surgical characteristic qualifiers, biomarkers, and new predictive models for non-cardiac and vascular surgery patients. These qualifiers and models inform improvements to our risk predictive performance and better guide our peri-operative surveillance and care. New evidence also reinforces the need for judicious and timelier preoperative consultation and medical management, and supports the targeted use of biomarker surveillance in the post-operative period to detect important but often otherwise-asymptomatic cardiovascular events. On the basis of this evidence review, the author invites discussion, debate, and the development of a more comprehensive and collaborative approach and guide to peri-operative risk assessment and management.

Résumé
L’évaluation et la gestion des risques cardiovasculaires peropératoires sont des tâches importantes et complexes pour l’interniste généraliste. Depuis la publication, en 1999, de l’indice de risque cardiaque modifié (indice de Lee), aujourd’hui largement utilisé, on a défini de nouvelles caractéristiques des facteurs de risques et élaboré de nouveaux modèles prédictifs; il s’agit notamment de caractéristiques relatives au patient ou à la chirurgie, de biomarqueurs et de nouveaux modèles prédictifs pour les patients qui subissent une chirurgie non cardiaque. Ces caractéristiques et modèles permettent d’améliorer la prédiction des risques ainsi que la surveillance et le soin peropératoires. Les nouveaux éléments confirment également la nécessité de mener avec discernement et en temps opportun les consultations préopératoires et la prise en charge, et étayent l’utilisation ciblée de la surveillance des biomarqueurs dans la période postopératoire afin de repérer des incidents cardiovasculaires importants, mais souvent asymptomatiques. En se fondant sur ces nouveaux éléments, l’auteur invite ses collègues à la discussion, au débat et à l’élaboration d’une approche plus exhaustive et plus collaborative pour l’évaluation et la gestion des risques peropératoires.
The expertise of the general internist is well suited to the tasks of preoperative assessment and management of patients who are to undergo elective non-cardiac surgery. These tasks include cardiovascular risk stratification, risk reduction, event surveillance, and the provision of general medical advice and management. The American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology guidelines\textsuperscript{1,2} initially separate out the preoperative cardiac risk assessment and management of patients undergoing urgent or emergent surgery, as well as patients with active or unstable cardiac conditions that would require particular management on their own account. This article reviews current evidence and recommendations for the assessment and management of the remaining group of patients: those without active or unstable cardiac conditions who are undergoing non-urgent non-cardiac surgeries.

**What Is the Evidence for Existing Risk Prediction Models?**

**Predictive Performance of the Revised Cardiac Risk Index**

The revised cardiac risk index (RCRI), published in 1999, remains the most commonly used prediction model for peri-operative cardiac risk stratification in patients undergoing non-cardiac surgery.\textsuperscript{3} This single-centre study derived and validated a model based on 4,315 patients undergoing elective non-cardiac surgery. Identified independent risk factors were dichotomized by assigning one point each for the presence of six readily available factors, and providing estimates for overall risk of cardiovascular events based on the point total (Table 1). Using the same data set, the RCRI had superior predictive performance as per receiver operating characteristics/area under the curve (ROC-AUC) to that of other existing risk assessment models including the Original Cardiac Risk Index (Goldman index),\textsuperscript{4} the Modified Cardiac Risk Index (Detsky score),\textsuperscript{5} and the American Society of Anesthesiologists (ASA) score.\textsuperscript{6}

A systematic review of newer studies using the RCRI shows that it continues to discriminate moderately well between low- and high-risk patients for mixed non-cardiac surgery (ROC-AUC of 0.75), and it appears better at “ruling out” than “ruling in” the risk of peri-operative major cardiac events. However, it does not accurately predict outcomes in certain high-risk groups such as vascular surgery patients.\textsuperscript{7}

Numerous reasons have been proposed for the model’s underperformance. The RCRI study population was from one centre, and despite the large study size it was underpowered, with only 56 cardiac events in the derivation cohort. Low event rates and excessive analysis of variables may have resulted in model over-fitting, with a subsequent reduction in strength of the association between risk factors and adverse cardiovascular outcomes, and in reduced model applicability to other populations. Although the demographic characteristics of the study population were comparable to current ones for non-cardiac surgery, the methods used to detect myocardial infarction (MI) included creatine kinase (CK) and CK MB bioassays, which are far less sensitive and specific than contemporary troponin-based event surveillance protocols.

The RCRI uses “cut points” to create dichotomous risk factors (present or absent) and assigns equal weight to each risk factor. This makes the model easier to use, but it does not allow for the potential differences in risk resulting from varying severity of clinical risk factors in a given patient. For example, the risk attributable to diabetes on insulin likely varies depending on the duration of the disease. Additionally, the use of cut points forces trade-offs between sensitivity and specificity, and potentially reduces the predictive power of the model in populations with low- versus high-risk pre-test probabilities.\textsuperscript{8}

**Not All Risk Factors Are Created Equal**

Results of a recent consecutive cohort study using population-based data on patients undergoing non-cardiac surgery (n = 19,949) suggest that patients with ischemic or non-ischemic heart failure or atrial fibrillation may have a significantly higher risk of 30-day post-operative mortality than patients with coronary artery disease (CAD), and that even minor procedures carry a higher risk than previously appreciated.\textsuperscript{9} Although the observed mortality rate may have been elevated by addressing a

### Table 1. The Revised Cardiac Risk Index

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Number of Predictors Present</th>
<th>Predicted % Post-Operative Cardiovascular Event\textsuperscript{1}</th>
<th>Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk surgery\textsuperscript{*}, ischemic heart disease, congestive heart failure, cerebrovascular disease, insulin therapy for diabetes, preoperative creatinine level &gt; 177 µmol/L</td>
<td>0</td>
<td>0.4 (0.05–1.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.9 (0.3–2.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6.6 (3.9–10.3)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td></td>
<td>11.0 (5.8–18.4)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{*}Intraperitoneal, intrathoracic, and suprainguinal vascular procedures.

\textsuperscript{†}Cardiac death, non-fatal myocardial infarction, cardiac arrest, pulmonary edema, ventricular fibrillation, complete heart block.

Source: Data from Lee et al.\textsuperscript{3}
slightly older population and by including patients undergoing emergent or urgent procedures, as well as some critically ill patients, the 4-week post-procedural mortality rates in heart failure and atrial fibrillation patients undergoing strictly outpatient minor procedures (such as colonoscopy or cystoscopy) were still in excess of 4% and 2%, respectively. Mortality rates were particularly high for those patients undergoing surgery within 4 weeks of an incident diagnosis of heart failure or atrial fibrillation. This suggests that such patients with existing heart failure or atrial fibrillation are not at low risk of adverse post-operative events, even when they undergo low-risk outpatient surgical procedures, and that existing models underestimate the risk.

What about Newer Cardiovascular Risk Prediction Models?

The Vascular Study Group of New England (VSGNE)\textsuperscript{10} produced its Cardiac Risk Index (VSG-CRI) prediction model, based on the study of adverse cardiac outcomes in large (8,200) derivation and validation (1,870) cohorts of vascular surgery patients. The model requires historical and simple laboratory data (i.e., creatinine level) (Table 2). It may be more appropriate for cardiovascular risk assessment in patients undergoing vascular surgery. Its discriminatory performance is modest (ROC-AUC of 0.71) but significantly greater than that of the RCRI when used for vascular surgery patients (ROC-AUC of 0.54–0.64).

Qualifying the RCRI with Surgical Risk, Increasing Age, and Comorbidities

Subsequent research has retrospectively applied the RCRI to other large non-cardiac surgery databases and found that the predictive utility of the RCRI can be improved by more detailed stratification for the type of surgery, and by factoring in age greater than 70 years.\textsuperscript{11} Among patients who have undergone hip fracture surgery, the presence of three or more other comorbidities (e.g., respiratory disease, current smoking, malignancy, renal disease, rheumatological diseases, and Parkinson’s disease) is also predictive of post-operative congestive heart failure (CHF), respiratory infections, and increased 30-day mortality.

Of note, age remains a factor in the VSG-CRI and the National Surgical Quality Improvement Program (NSQIP) model (described below). It is possible that increasing age is a surrogate marker for the duration or severity of co-morbidities and is capturing what the RCRI does not; that is, a condition’s contribution to risk increases as the duration of the condition increases. For example, the prevalence of cardiovascular disease in diabetes is approximately 26% after 5 years of diabetes but 71% after 20 years.\textsuperscript{13}

The National Surgical Quality Improvement Program

Most recently, researchers used medical chart abstraction from the large NSQIP prospective database of peri-operative and surgical data to identify predictors for post-operative cardiac events in patients undergoing surgery.\textsuperscript{14} Investigators created two cohorts from 2007 (derivation cohort, \(n = 211,410\)) and 2008 (validation cohort, \(n = 257,385\)). They identified five multivariate

<table>
<thead>
<tr>
<th>Risk Factors*</th>
<th>No. of Points Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 80 years</td>
<td>4</td>
</tr>
<tr>
<td>Age 70–79 years</td>
<td>3</td>
</tr>
<tr>
<td>Age 60–69 years</td>
<td>2</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine level &gt;159 (\mu\text{mol/L} (1.8 \text{mg/dL}))</td>
<td>2</td>
</tr>
<tr>
<td>Smoking</td>
<td>1</td>
</tr>
<tr>
<td>Insulin-dependent diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Long term (\beta)-blockade</td>
<td>1</td>
</tr>
<tr>
<td>History of coronary artery bypass grafting or percutaneous coronary intervention</td>
<td>-1</td>
</tr>
</tbody>
</table>

\*Myocardial infarction, clinically significant arrhythmia, congestive heart failure, or pulmonary edema.

Source: Adapted from Bertges et al.\textsuperscript{10}

<table>
<thead>
<tr>
<th>No. of Points</th>
<th>Risk of Major Adverse Cardiac Outcomes (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3</td>
<td>2.6</td>
</tr>
<tr>
<td>4</td>
<td>3.5</td>
</tr>
<tr>
<td>5</td>
<td>6.0</td>
</tr>
<tr>
<td>6</td>
<td>6.6</td>
</tr>
<tr>
<td>7</td>
<td>8.9</td>
</tr>
<tr>
<td>≥8</td>
<td>14.3</td>
</tr>
</tbody>
</table>

*Myocardial infarction, clinically significant arrhythmia, congestive heart failure, or pulmonary edema.

Source: Data from Gupta et al.\textsuperscript{14}

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Dependent functional (ADL) status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal creatinine level (&gt;132 (\mu\text{mol/L} or 1.5 \text{mg/dL})</td>
<td>Increasing ASA class</td>
</tr>
<tr>
<td>Increasing age</td>
<td>Increasing age</td>
</tr>
</tbody>
</table>

ADL = activities of daily living; ASA = American Society of Anesthesiologists; NSQIP = National Surgical Quality Improvement Program.

Source: Data from Gupta et al.\textsuperscript{14}
What Is the Role for Additional Testing?

Non-Invasive Cardiovascular Testing

Given the limitation of existing risk stratification models, ancillary methods for such as non-invasive cardiovascular testing have been extensively studied. Nuclear stress testing and dobutamine stress echocardiography studies have uniformly reported high negative predictive values, and may be useful in reducing the estimated risk in patients otherwise classified as intermediate risk by the RCRI. Semi-quantitative analysis of results stratifying by the percentage of ischemic myocardium may further improve positive predictive value. There is evidence that the use of such tests in lower-risk populations has been associated with delays in surgery without observable improvement (or some harm) in cardiac death and survival. The 2007 AHA/ACC guideline recommendations remain appropriate: to limit use of these tests to preoperative patients with symptoms of angina or dyspnea on exertion, or if exercise capacity is poor or unknown and associated with at least one clinical risk factor and only if the results may change management.

Biomarkers

There is a growing literature on the preoperative use of biomarkers, including B-type natriuretic peptide (BNP) and N-terminal (NT) proBNP, to help stratify peri-operative cardiac event risk. Two recent meta-analyses have demonstrated significant between-study variability in characteristics of the populations studied, including ages and types of surgery undertaken, types and timing of BNP or NT-proBNP assays (and thresholds) used, outcome criteria used, timing for event surveillance, employment of blinding, observed peri-operative mortality rates (1–20%), and validation of derived models. The meta-analyses suggest that these tests may be most useful for their negative predictive value, but their prognostic contribution independent of and in addition to the RCRI and other prognostic models remains unclear. Their contribution to routine assessment may be further elucidated by the Vascular Events in Non-cardiac Surgery Patient Cohort Evaluation (VISION) study.

What about Prophylactic Measures to Reduce Risk?

Prophylactic Revascularization

The Coronary Artery Revascularization Prophylaxis (CARP) and Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) trials were conducted on vascular surgery patients with stable CAD to determine whether prophylactic coronary revascularization improves post-operative outcomes in high-risk patients with multiple risk factors and extensive stress-induced ischemia. Both studies showed no difference in rates of death or MI between revascularized and non-revascularized groups. Major guidelines addressing this topic presently recommend offering revascularization to only patients who would benefit from the
procedure for reasons unrelated to any upcoming surgery.

**β-Blockers**

On a background of mixed and conflicting evidence, the well-designed, large \( n = 8,351 \), multicentre, randomized, controlled, double-blinded POISE (peri-operative ischemia evaluation) trial was conducted to study the peri-operative prophylactic use of extended-release metoprolol.\(^{26} \) Patients randomized to the extended-release metoprolol group received 100 mg 2–4 hours preoperatively, another 100 mg orally within 6 hours post-operatively (or an equipotent intravenous dose if unable to swallow), and then 200 mg of oral sustained-release metoprolol daily thereafter for a total of 30 days.

The main composite outcome at 30 days (cardiovascular death, non-fatal MI, and non-fatal cardiac arrest) was lower in the metoprolol group, but this was largely driven by the reduction in non-fatal MIs, of which fewer than one third had any complications. This benefit was achieved at the cost of increased all-cause mortality (of which 50% was cardiovascular death), stroke (often with significant residual incapacity), and clinically significant hypotension and bradycardia. Post hoc analysis demonstrated that intra-operative or post-operative hypotension was the strongest independent predictor for stroke.

The study had a number of limitations. Its inclusion criteria allowed for the entry of lower-risk patients, and it gave high-dose metoprolol to patients who were β-blocker naive (half of whom were aged 70 years or greater) without a period of titration. Most trials previously showing benefit with β-blockers included higher-risk populations (with a higher proportion of subjects with an RCRI score \( \geq 3 \)), and used lower doses that were gradually titrated for at least a week in advance of surgery.

However, these results suggested that the harms of β-blocker prophylaxis outweigh the benefits in patients at lower risk (those with RCRI scores of 2 or less), and this treatment should not be offered to this group. The 2009 ACC/AHA guidelines suggest β-blockers should be continued in the peri-operative period without interruption in those who are already taking these drugs for existing indications such as coronary heart disease, hypertension, or CHF or for stress test–induced ischemia.\(^{27} \) Management is unclear for patients deemed to be at higher risk for adverse peri-operative cardiac events and who would otherwise have no indications for these drugs. If β-blocker prophylaxis is used, it is should only be done for individuals who are not deemed at increased risk for stroke, hypotension, or bradycardia, and by using a protocol that allows sufficient time preoperatively to start and safely titrate the drugs.

**Statins**

A recent meta-analysis of studies of peri-operative statin treatment in statin-naive patients undergoing cardiac or non-cardiac surgery shows these regimens appear to reduce the incidence of atrial fibrillation and MI, as well as duration of hospital stay. Wider use of statins to improve cardiac outcomes in patients undergoing high-risk procedures may be warranted.\(^{28} \)

**Primus Non Nocere: Does Peri-operative Consultation Improve Outcomes?**

We generally assume that the process of peri-operative consultation improves outcomes in patients undergoing non-cardiac surgery who are deemed intermediate to high risk. Seemingly to the contrary, a single-centre observational cohort study\(^{29} \) and a subsequent much larger \( n = 269,866 \) retrospective cohort study\(^{30} \) suggest that the peri-operative consultative process, in comparison to no preoperative consultation, may have a negative effect, including increased 30-day mortality (number needed to harm \([\text{NNH}] = 516\)), increased 1-year mortality \([\text{NNH} = 227]\), increased hospital stay (by a mean of 0.6 days), and increased preoperative testing and pharmacological interventions. However, sensitivity analysis showed that this risk was only increased if patients were seen by specialists (versus general internists) or if they were seen within 7 days of surgery.

In addition, being seen by a specialist was associated with more diagnostic and therapeutic interventions.

This suggests that the consultative process may lose utility and even cause harm if the focus of interest is narrowed, interventions are more aggressive, or interventions occur too close to the time of surgery. Of interest, the study period was during a time of increasing use of β-blockade for peri-operative risk reduction but prior to the results of the POISE trial, which demonstrated the harms of β-blocker institution in patients at low risk or too close to the time of surgery.

**Are We Paying Attention to the Right Things and at the Right Times?**

Compared with a decade ago,\(^{31} \) there has been increasing concordance in general internists’ methods for preoperative cardiovascular risk assessment but there remains considerable variability in determination of which patients should undergo preoperative consultation.\(^{32} \) For any predictive process, the shorter the time interval between making a prediction and the event, the more accurate the prediction will be.\(^{6} \) This is especially true in situations with multiple contributing factors to risk and outcome. Various database studies suggest both intraoperative and post-operative factors are important modifiers of peri-operative cardiovascular risk.
This limitation to predictive power should be addressed by repeated surveillance and re-adjustment of risk estimates throughout the peri-operative period. This contrasts with current peri-operative cardiovascular risk prediction models and management that assume single data sampling events will suffice to predict future events.

The manner by which we assess for post-operative outcomes should also be questioned. Preliminary results of the VISION trial also suggest that major vascular events (vascular deaths, non-fatal MIs, and stroke) not only remain common (total event rate of 6.3%, 30-day mortality rate of 1.9%) but would not be detected by typical post-operative surveillance methods.\textsuperscript{16,23} For example, 66.7% of cases of MI detected by a rise in troponin with subsequent electrocardiograms (ECGs) or echocardiographic confirmation had no ischemic symptoms to suggest MI, and would probably have been missed without the routine post-operative monitoring with troponins. Similar findings were seen in the POISE trial, where more than 50% of the non-fatal MIs occurred in asymptomatic patients and were detected only by the study’s protocol of surveillance with serial ECGs and biomarkers. In addition, troponin elevation appears to be a statistically significant independent predictor of intermediate and long-term outcomes (i.e., mortality and major cardiac events), with a demonstrated a dose-response relation – the higher the peak troponin value, the higher the post-operative mortality.\textsuperscript{25,33,34}

Detection and subsequently directed long-term management of such events is therefore an important and appropriate role of the general internist. Observational data suggest that administration of acetylsalicylic acid and statins may benefit patients in whom troponin elevations are detected.\textsuperscript{35}

**Summary: Given the Current Evidence, What Should We Do?**

**In Clinical Practice**

As general internists we should maintain and develop a comprehensive and collaborative approach to risk assessment and management in the peri-operative period, and carefully weigh the benefits versus harms of any preoperative diagnostic or therapeutic intervention. Active cardiac conditions, including CHF and atrial fibrillation, should be stabilized if possible for a month or more prior to elective surgery.\textsuperscript{9} We should focus our preoperative consultations and interventions on those individuals most likely to benefit, and therefore continue to follow the ACC/AHA guidelines, forgoing preoperative cardiac evaluation of low-risk patients without active cardiac conditions who also have >4 METS exercise capacity, low risk scores and surgery types, and no co-morbidities requiring control preoperatively. Patients undergoing emergent or urgent surgery may benefit from consultation for management of acute issues, but are unlikely to benefit from an extensive preoperative risk-stratification process.

No single existing risk prediction model or set of risk factors appears to be of sufficient predictive power. Given the suboptimal capacity of our predictive models, we should avoid exclusive investment in overly standardized risk prediction, and allow medical conditions of concern – which are not presently addressed by the risk models – to challenge pre-specified scoring. In addition, more resources should be directed (or redirected) to post-operative surveillance. Each practitioner should consider which patients need careful and explicit follow-up, even though they may be asymptomatic. Pending further research and development, we should continue to use the RCI but with qualification, using increasing age, duration and severity of risk factors and other co-morbid conditions, more detailed stratification for the type of surgery, and functional capacity and status (ADL). We can supplement this with selective use of biomarkers and noninvasive exercise testing, especially to help stratify intermediate-risk populations into higher or lower risk. For patients undergoing vascular surgery, the VSG-CRI may be used instead.

Presently there are few preoperative risk prophylaxis strategies. Prophylactic revascularization appears not to benefit, the role for any \( \beta \)-blocker prophylaxis remains unclear, and the role for statin prophylaxis appears promising.

**As the Canadian Society of Internal Medicine**

As advocates, we should lobby for appropriate timing of referrals to allow the lead time necessary for effective and safe application of any diagnostic or risk reduction intervention. We should expand our role to explicitly include peri-operative surveillance and care by ensuring the collaboration, communication, and continuity of care among care providers throughout this continuum. We should develop routine and effective surveillance methods to improve our detection of variably manifest post-operative cardiovascular outcomes and coordinate this detection and management with the long-term care that addresses the prognosis.

This article is also an invitation to interested members of the general internal medicine community to discuss, debate, and reconsider the most appropriate and effective role for the general internist in evaluating and managing patients in the peri-operative period. We believe that a new national guideline is needed; one that reflects this newer evidence, more comprehensively considers all health conditions affected by surgery that the internist might care for, and provides guidance for evaluation and management for not only the preoperative...
period but the post-operative period as well. We may be contacted at bruce.fisher@ualberta.ca and va.palda@utoronto.ca.

References


