Cardiac Risk of Non-Cardiac Surgery

Roman Kluger

Department of Anaesthesia, St. Vincent's Hospital

Is it a problem?

Yes – death directly due to anaesthesia is less than 1 in a few hundred thousand. However 30 day mortality and morbidity following surgery is common and much of it is cardiac. Worldwide more than 200 million adults have major non-cardiac surgical procedures annually. Millions of these patients will have a major vascular complication (vascular death, nonfatal myocardial infarction [MI], nonfatal cardiac arrest, or nonfatal stroke) within 30 days after surgery. Myocardial infarction is the most common major peri-operative vascular complication. For example in the original POISE (PeriOperative ISchemic Evaluation) study[1] 1.6% died of vascular causes, 0.7% had a stroke, 0.5% had a non-fatal cardiac arrest, and 5.0% had an MI in the first 30 days. Overall postoperative vascular events account for one third of perioperative deaths and are associated with increased hospital stay and long-term mortality rates.

Why estimate risk?

1. To inform patient and surgeon decision making. Most surgery is elective and often can be postponed or even cancelled. Less invasive surgical alternatives may be available and more appropriate.

2. To inform peri-operative management. Risk reduction strategies must aim at high risk patients. For example pre-operative troponins, BNP levels and stress testing; invasive haemodynamic monitoring and tighter blood pressure and heart rate control during surgery; and postoperative monitoring in high dependency /ICU, postoperative troponins and long term follow-up and prophylactic cardiac medications. However at this stage none of these strategies have been convincingly shown to safely decrease morbidity or mortality.

Peri-operative Myocardial Infarction

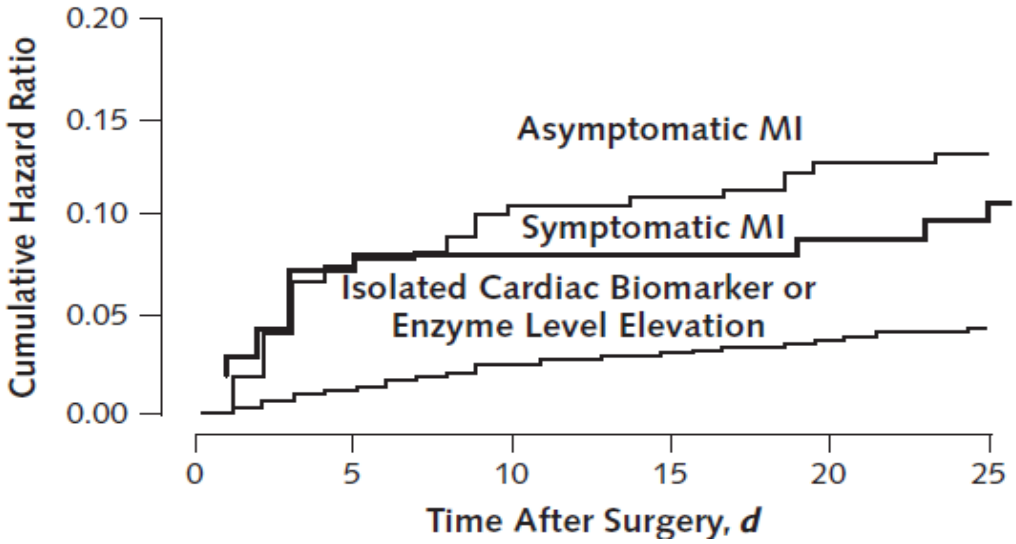
The risk of an MI in the postoperative period is far higher than at any other period and its prognosis is worse (approximately double the mortality of an outpatient MI) because the postoperative period is a period of inflammation, hypercoagulability, stress, hypoxia and anaemia.

Analysis of the POISE data, where all patients had daily cardiac enzymes, ECGs and clinical evaluations provided much information regarding postoperative MIs[2].

5% of the patients had a postoperative MI and the 30 day mortality was higher for patients who had an MI (11.6%) than for those who did not (2.2%). 74% of MIs occurred within 48 hours of surgery. 58% of patients who had an MI died with 48 hours of the event.

Of the patients who had an MI 65% did not have ischaemic symptoms, and the mortality rate was similar between those who did and did not have symptoms.
8.3% of patients had elevated levels of cardiac enzymes (but did not fulfil MI definition) and were also at higher risk of adverse cardiac events. See figure 1.
Only 10.6 % of the MIs had ST elevation.

Figure 1: Cumulative hazard ratios for mortality among patients who had symptomatic or asymptomatic MI or an isolated elevated level of a cardiac biomarker or enzyme after surgery.



Pre-operative Risk Prediction

Several risk indices have been developed during the past 30 years, based on multivariate analyses of observational data, to represent the relationship between clinical characteristics and peri-operative cardiac mortality and morbidity. The indices developed by Goldman et al. (1977), Detsky et al. (1986), and Lee et al. (1999) have become well-known.

RCRI

The Lee index or 'revised cardiac risk' index (RCRI)[3], a modified version of the original Goldman index, was designed to predict major adverse cardiac outcomes (defined as post-operative myocardial infarction, pulmonary oedema, ventricular fibrillation or cardiac arrest, and complete heart block) and until recently was considered by many to be the best and most widely used index in non-cardiac surgery (ref x). It was developed on a cohort of nearly 3000 patients aged >50 years who underwent non-emergent non-cardiac procedures with an expected length of stay 2 or more days at Brigham and Women's Hospital in early 1990s and validated on another cohort.

This risk index comprises six variables:

1. High risk surgery - intra peritoneal, intrathoracic or supra-inguinal vascular
2. History of IHD - history of myocardial infarction, positive exercise test result, current ischemic chest pain or nitrate use, pathological Q waves on ECG (patients who had undergone prior coronary bypass surgery or angioplasty were included only if they had such findings after their procedure)
3. History of heart failure - defined as a history of heart failure, pulmonary oedema, paroxysmal nocturnal dyspnoea; an S3 gallop or bilateral rales on physical examination; or chest radiograph showing pulmonary congestion
4. History of cerebrovascular disease, stroke or transient ischemic attack
5. Pre-operative treatment with insulin
6. Pre-operative creatinine > 175 mmol/L (> 2.0 mg/dL)

Estimated risk of a major adverse cardiac event in based on predictors in the Lee index

No. of risk factors	Risk of major perioperative cardiac event, % (95% CI)
0	0.4 (0.05-1.5)
1	0.9 (0.3-2.1)
2	6.6 (3.9-10.3)
≥3	11.0 (5.8-18.4)

This index is poorer at estimating risk in vascular surgery and especially open aortic procedures.

The following website provides these RCRI risks when the predictors are input:
http://www.mdcalc.com/revised-cardiac-risk-index-for-pre-operative-risk/

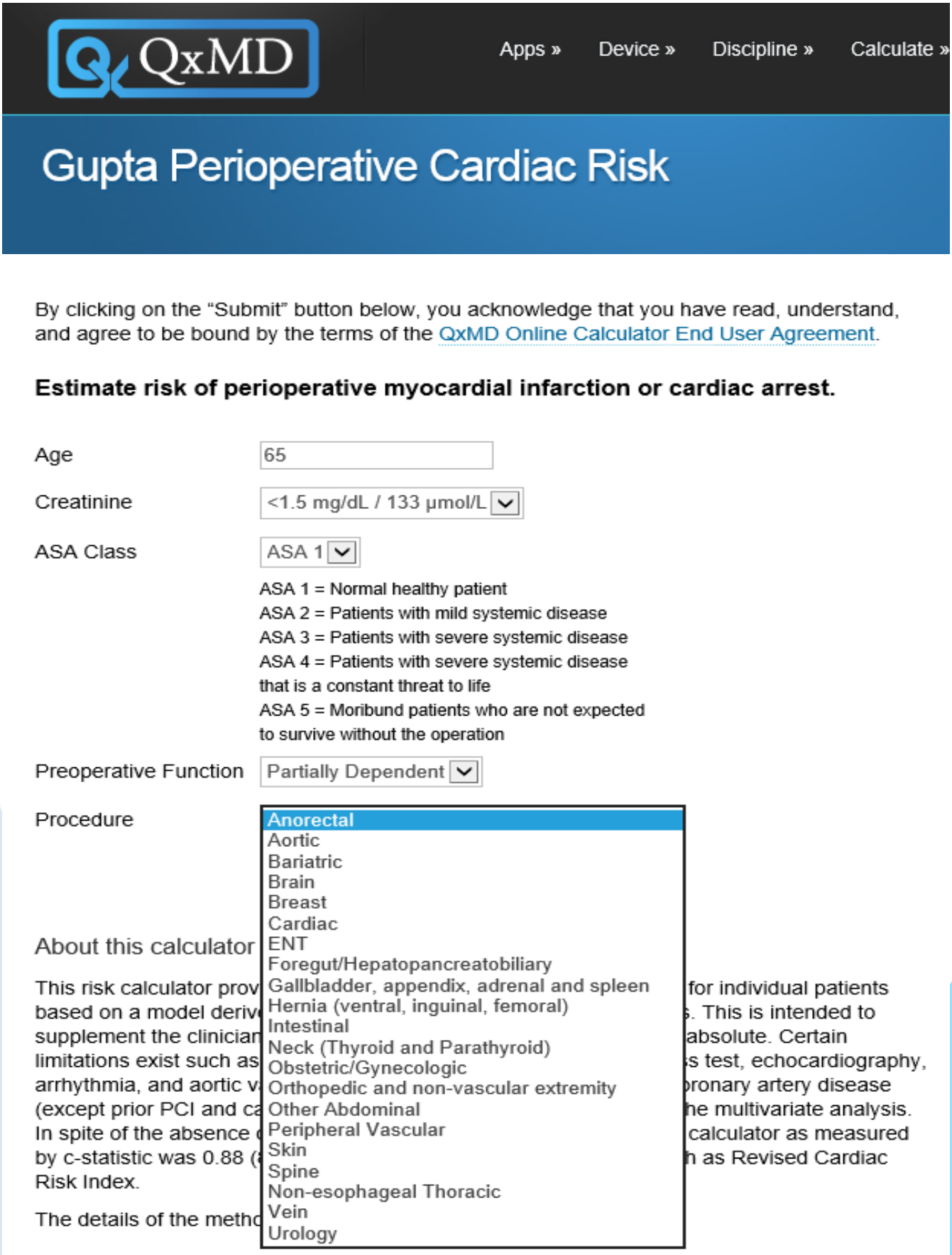
NSQIP MICA model[4]

A new predictive model was recently developed using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database. This NSQIP MICA model was built on the 2007 data set, based on patients from 180 hospitals, and was validated with the 2008 data set, both containing 200,000 patients. The primary endpoint was intra-operative/post-operative myocardial infarction or cardiac arrest (MICA) up to 30 days after surgery. Five predictors of perioperative myocardial infarction/cardiac arrest were identified:

1. Type of surgery,
2. Functional status,
3. Elevated creatinine (>130 mmol/L or >1.5 mg/dL),
4. American Society of Anesthesiologists (ASA) Physical Status Classification
5. Age.

This model is presented as an interactive risk calculator at http://www.surgicalriskcalculator.com/miorcardiacarrest. This tool is also available on a mobile app 'Calculate by QxMD'. Unlike the Lee index it is not a simple scoring system, but outputs a probability of MICA for an individual patient depending on values of the 5 variables above.

Figure 2: A screen shot from the NSQIP MICA model website.



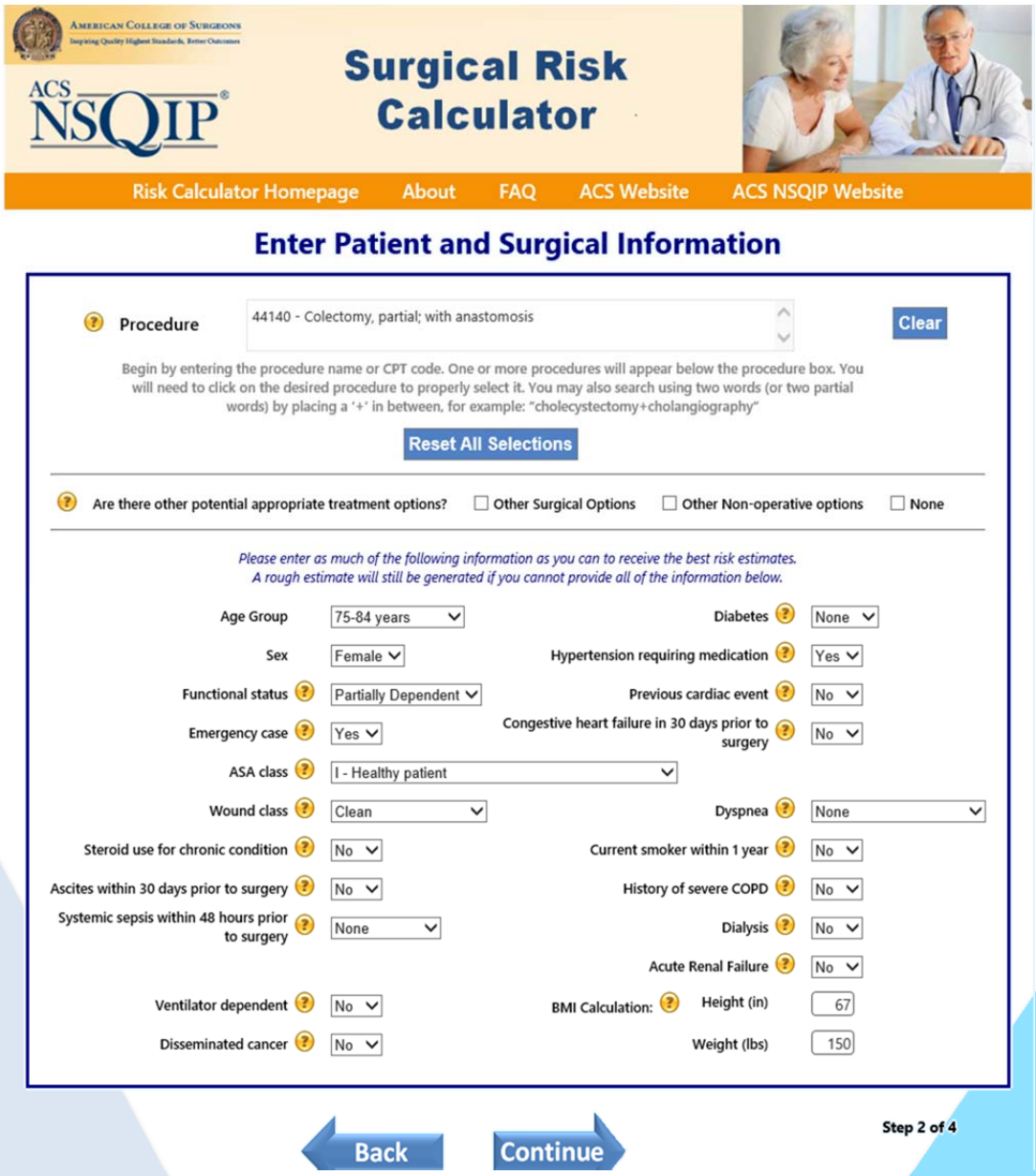
It performed better than the Lee risk index, with some reduction in performance in vascular patients, although it was still superior. However, some perioperative cardiac complications of interest to clinicians, such as pulmonary oedema and complete heart block, were not considered in the NSQIP model because those variables were not included in the NSQIP database. Furthermore daily postoperative ECGs and troponins are not mandated (cf. Lee's study creating the RCRI, and the POISE studies). In other words silent MIs could be missed, so rates may be underestimated.

NSQIP Surgical Risk Calculator[5]

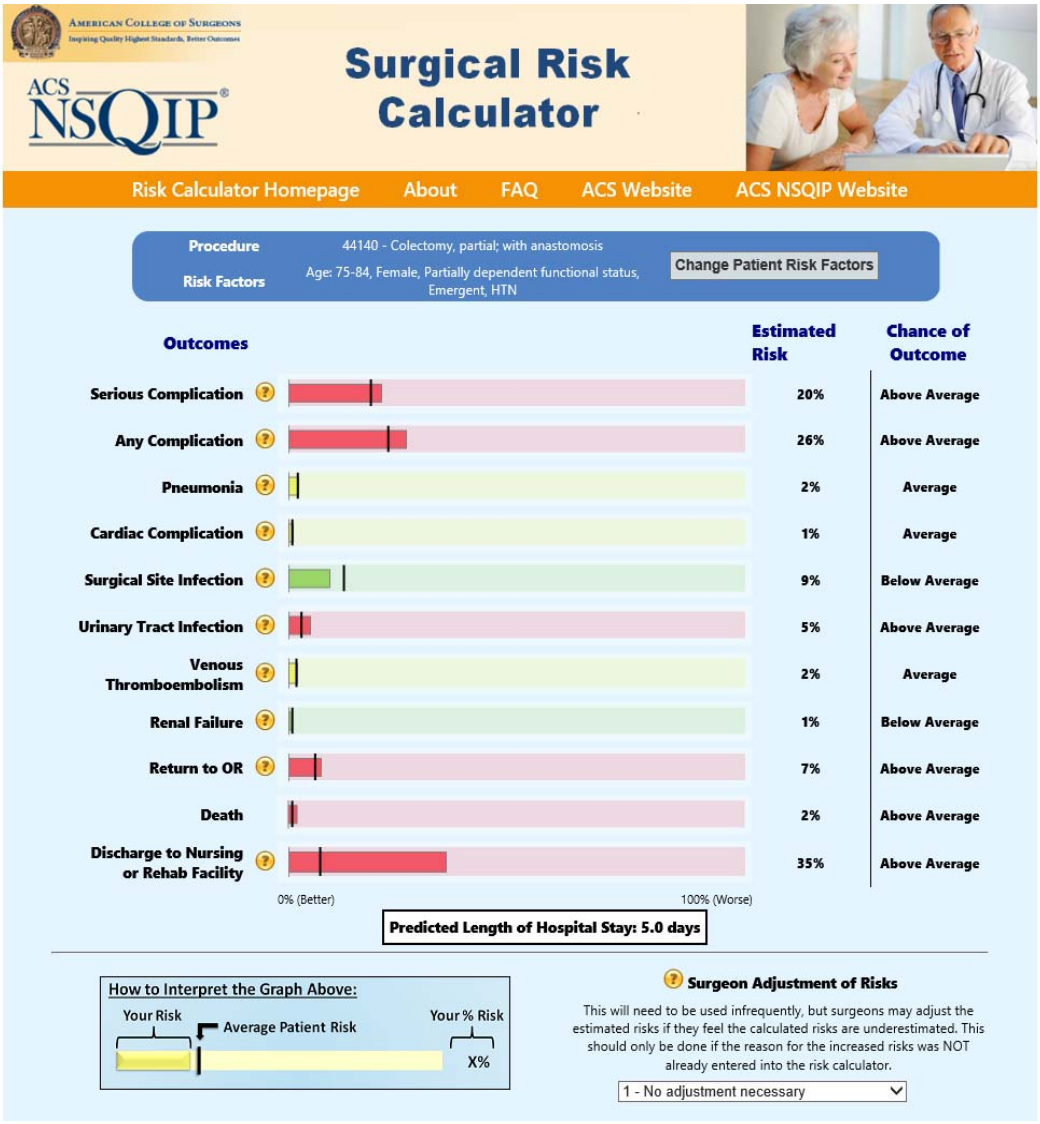
Over 1.4 million patients in the NSQIP database have been used to create probably the best estimator of surgery-specific risk of MICA, death and 8 other adverse outcomes. The NSQIP Surgical Risk Calculator (found at http://riskcalculator.facs.org) calculates these risks based on 21 patient specific variables (eg, age, sex, body mass index, dyspnoea, previous MI, functional status) and the actual operation.

Figures 3: Screenshots of the ACS NSQIP Surgical Risk Calculator website

(A) Risk factor entry screen.



(B) Report screen



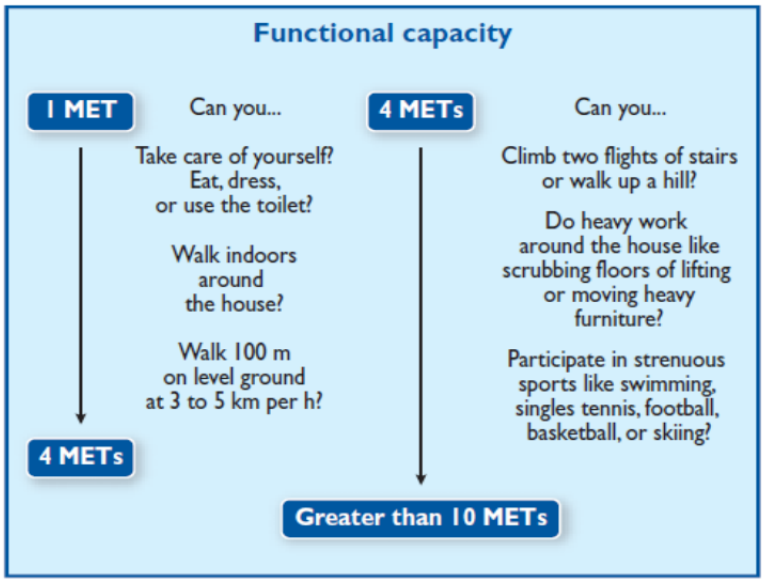
Reference Information for National Surgical Quality Improvement Program (NSQIP) such as data field definitions can be found at the following website:

http://www.google.com.au/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&sqi=2&ved=0CB0QFjAAahUKEwiGtpfO_IPHhXDF5QKHdPSDVE&url=http%3A%2F%2Fbcpsqc.ca%2Fdocuments%2F2012%2F11%2FNSQIP-FAQ-2012-forSurgeons.doc&ei=iq66VYbJEsOv0ATTpbeIBQ&usg=AFQjCNGQah6KT7xmo6HcOPNoOj53Clxhiw&bvm=bv.99261572,d.dGo

Functional status

The two risk calculators above take into account patient's functional capacity as a 3 point scale (independent, partially dependent and totally dependent) and indirectly via the ASA physical status. Furthermore in both the European[6] and American Heart Association guidelines[7] determination of functional capacity is an important step in preoperative cardiac risk assessment algorithms and is measured in metabolic equivalents (METs). One MET equals the basal metabolic rate. Exercise testing provides an objective assessment of functional capacity. Without testing, functional capacity can be estimated from the ability to perform the activities of daily living (see figure 4). Climbing two flights of stairs demands 4 METs, and inability to achieve this indicates poor functional capacity and is associated with an increased incidence of post-operative cardiac events. However, this appears to be a poorer predictor than other inputs into the risk models such as ASA status.

Figure 4: Estimated energy requirements for various activities.



The European guidelines use the grading of surgical risk shown in Figure 5 in their algorithm. The American guidelines use risks estimated from one of the NSQIP models discussed earlier in their most recent algorithm.

Figure 5: Surgical risk estimate

Low-risk: < 1%	Intermediate-risk: 1–5%	High-risk: > 5%
• Superficial surgery • Breast • Dental • Endocrine: thyroid • Eye • Reconstructive • Carotid asymptomatic (CEA or CAS) • Gynaecology: minor • Orthopaedic: minor (meniscectomy) • Urological: minor (transurethral resection of the prostate)	• Intraperitoneal: splenectomy, hiatal hernia repair, cholecystectomy • Carotid symptomatic (CEA or CAS) • Peripheral arterial angioplasty • Endovascular aneurysm repair • Head and neck surgery • Neurological or orthopaedic: major (hip and spine surgery) • Urological or gynaecological: major • Renal transplant • Intra-thoracic: non-major	• Aortic and major vascular surgery • Open lower limb revascularization or amputation or thromboembolectomy • Duodeno-pancreatic surgery • Liver resection, bile duct surgery • Oesophagectomy • Repair of perforated bowel • Adrenal resection • Total cystectomy • Pneumonectomy • Pulmonary or liver transplant

CAS = carotid artery stenting; CEA = carotid endarterectomy.
[a]Surgical risk estimate is a broad approximation of 30-day risk of cardiovascular death and myocardial infarction that takes into account only the specific surgical intervention, without considering the patient's comorbidities.
[b]Adapted from Glance *et al.*[11]

Pre-operative Biomarkers

Cardiac troponins T and I (cTnT and cTnI, respectively) are the preferred markers for the diagnosis of myocardial infarction because they demonstrate sensitivity and tissue specificity better than other available biomarkers. Troponin release and thus "myocardial injury" can be the result of non-coronary factors such as a high adrenergic drive, sepsis, inflammation, myocarditis, renal failure or right ventricular failure secondary from aetiologies such as pulmonary embolism. As more sensitive troponin assays become available it is clear that even normal individuals have detectable levels and elevations above the 99th percentile can be due to structural heart disease in the absence of any acute process. Hence the latest definition of acute MI[8] mandates ischaemic symptoms or ECG changes in addition to troponin levels above the 99th percentile.

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. Recent studies demonstrated that among individuals in

the general population and among patients with chronic vascular disease, measurable circulating TnT and TnI levels reflect chronic sources of subclinical myocardial injury, rather than acute processes, and predict long-term adverse cardiac outcomes and death.

Existing evidence suggests that even small increases in cTnT in the peri-operative period reflect clinically relevant myocardial injury with worsened cardiac prognosis and outcome. In one series of 1,041 consecutive patients undergoing endovascular peripheral revascularization measurable cTnT levels (> 0.01 ng/ml) were detected pre-operatively in 21.3% of individuals and were strongly associated with adverse cardiovascular event rates and mortality, independent of impaired renal function[9]. In another series of 979 patients undergoing non-cardiac surgery pre-operative hsTnT levels above 0.014 g/ml provided strong prognostic information incremental to Lee's RCRI[10].

B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are produced in cardiac myocytes in response to increases in myocardial wall stress. This may occur at any stage of heart failure, independently of the presence or absence of myocardial ischaemia. Multiple studies[11-14] have demonstrated that elevated pre-operative NP concentrations are powerful independent predictors of perioperative cardiovascular complications (i.e. mortality, MI and heart failure). In vascular surgical cases, it appears pre-operative BNP risk stratification outperforms traditional clinical risk stratification[15].

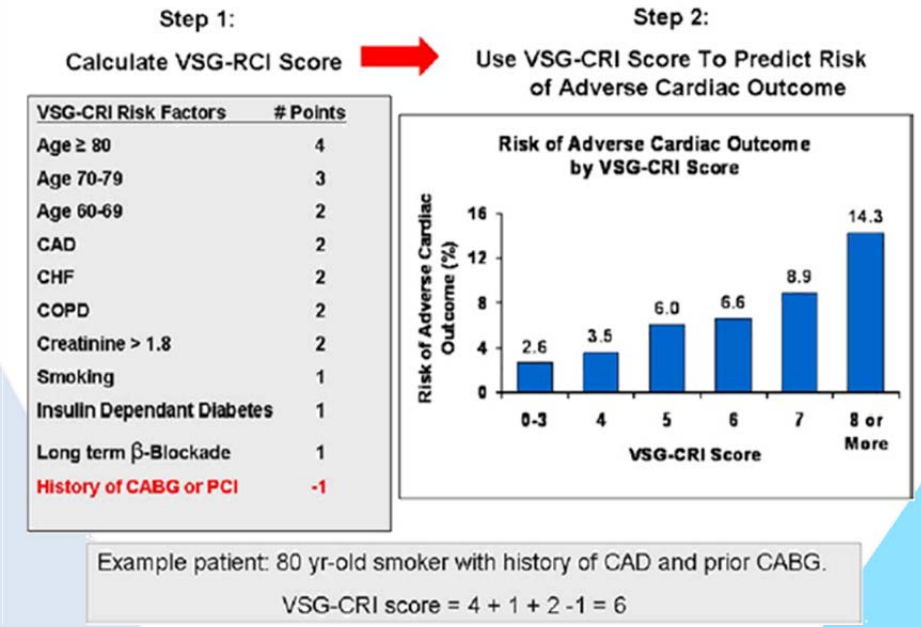
American and European guidelines suggest that based on the existing data, assessment of serum biomarkers for patients undergoing non-cardiac surgery cannot be proposed for routine use, but may be considered in high-risk patients.

Miscellaneous

Frailty is an increasingly used concept in the geriatric medicine and a number of 'frailty scores' exist. Increasing frailty has been associated with increased complications (including cardiac) and length of hospital stays in medically stable older adults undergoing non-cardiac surgery[16].

Although not mentioned in the American or European guidelines the Vascular Study group of New England developed a cardiac risk index based on over 10,000 patients undergoing vascular surgery[17] (see figure 6). This Vascular Study Group of New England Cardiac Risk Index (VSG-CRI) more accurately predicts in-hospital cardiac events after vascular surgery than the RCRI which substantially underestimates in-hospital cardiac events in patients undergoing elective or urgent vascular surgery, especially after lower extremity bypass, endovascular abdominal aortic aneurysm repair and open infrarenal abdominal aortic aneurysm repair.

Figure 6: Vascular Surgery Group Cardiac Risk Index



Intra-operative risk prediction

Anaesthesia providers have long assumed that a smooth intra-operative course is associated with better postoperative outcomes. Tachycardia[2], hypotension[18], bleeding [2,18], anaemia and transfusion have all been independently associated with adverse cardiac events. However they may just reflect patient characteristics or the physiological impact of surgery and may not be amenable to modification.

Two recent large studies have looked at impact of hypotension on outcomes. Monk et al[19] (over 18,000 patients) found that SBP < 70 mmHg, MAP < 50 mmHg, and DBP < 30 mmHg for over 5 minutes, were associated with increased 30 day mortality. In over 100,000 patients Mascha et al[20] found that cumulative duration of MAP less than 50, 55, 60, 70, and 80 mmHg was associated with increased odds of 30-day mortality.

Gawende et al[21] published an interesting approach to using intra-operative parameters to predict adverse outcomes. They developed a 10-point (Apgar like) score based on a patient's estimated amount of blood loss, lowest heart rate, and lowest mean arterial pressure during general or vascular operations. This score (see figure 7) was significantly associated with major complications or death within 30 days. For example, those with scores of 4 or less had a greater than 50% risk of major complications, including a 14% mortality rate.

Figure 7: A 10-Point Surgical Outcomes Score

	0 points	1 point	2 points	3 points	4 points
Estimated blood loss (mL)	> 1,000	601–1,000	101–600	≤ 100	—
Lowest mean arterial pressure (mmHg)	< 40	40–54	55–69	≥ 70	—
Lowest heart rate (beats/min)	> 85	76–85	66–75	56–65	≤ 55†

Surgical score = sum of the points for each category in the course of a procedure.
*Based on model 1 from cohort 1.
†Occurrence of pathologic bradyarrhythmia, including sinus arrest, atrioventricular block or dissociation, junctional or ventricular escape rhythms, and asystole also receive 0 pts for lowest heart rate.

Post-operative prediction

Increases in postoperative levels of troponins and BNP are both independently associated with adverse cardiac outcomes and mortality.

Troponins

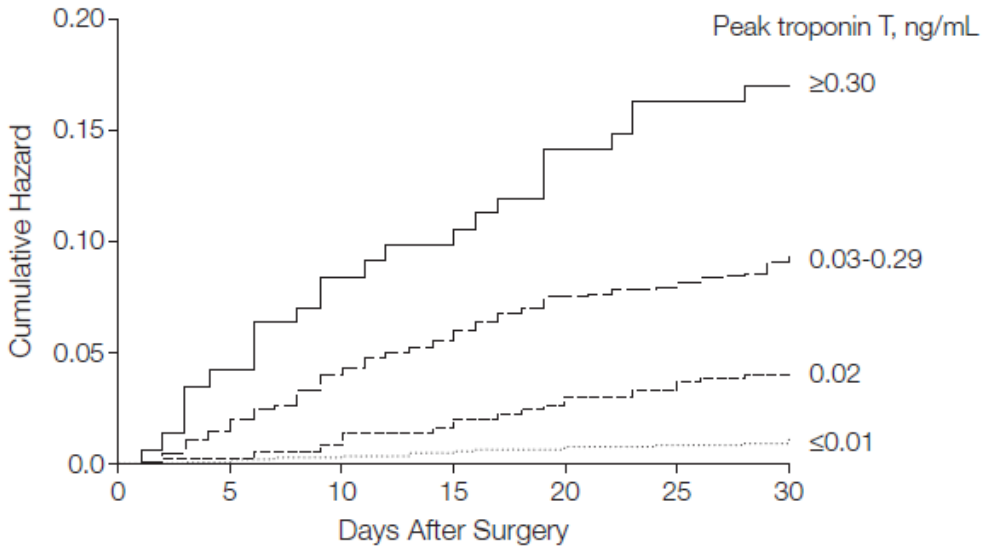
Many studies have confirmed the association between elevated troponin levels and adverse outcomes in a variety of settings, however the results from the first 15,000 patients in the VISION study have provided the most extensive and generalisable information regarding postoperative troponins and adverse vascular outcomes and mortality.

The VISION Study (Vascular Events in Non-cardiac Surgery Patients Cohort Evaluation) [22] is a large international prospective study evaluating major complications after non-cardiac surgery. Eligible patients are aged 45 and over undergoing non-cardiac surgery requiring at least overnight admission. Patients' TnT levels were measured 6 to 12 hours after surgery and on days 1, 2, and 3 after surgery. 24 pre-operative variables were documented and there were daily clinical assessments. The primary outcome was mortality at 30 days and whether the cause was vascular or non-vascular. 45% of deaths were vascular. They found that Peak TnT measurement added incremental prognostic value (to the clinical variables) to discriminate those likely to die within 30 days for both vascular and nonvascular mortality. Peak TnT values after non-cardiac surgery proved the strongest predictors of 30-day mortality, and the population attributable risk analysis suggested elevated TnT measurements after surgery may explain 41.8% of the deaths.

Multivariable analysis demonstrated that peak TnT threshold values of 0.02 ng/mL, 0.03 ng/mL, and 0.30 ng/mL were independently associated with 30-day mortality (the commonly accepted upper limit for this assay is 0.04 ng/ml). See table below and figure 8.

Peak TnT measurement	% of cohort	30 day mortality	30 day vascular mortality	Time to death
≤ 0.01 ng/ml	88.4%	1%	0.4%	
0.02 ng/ml	3.3%	4.0%	1.4%	13 days
0.03 - 0.29 ng/ml	7.4%	9.3%	4.5%	9 days
≥ 0.3 ng/ml	0.9%	16.9%	9.2%	6.5 days

Figure 8: Kaplan-Meier Estimates of 30-Day Mortality Based on Peak Troponin T Values



Among patients who experienced a TnT elevation of 0.02 ng/mL or greater, this occurred at 6to12 hours after surgery, post- operative day 1, postoperative day 2,and postoperative day 3 in 45.9%, 28.3%, 17.7%, and 8.2% of these patients, respectively

A weakness of the VISION study was that they did not measure pre-operative troponins so cannot assess how a pre- operative value would impact risk prediction.

The VISION investigators published a follow-up paper [23] in which they used the VISION data to determine properties of "Myocardial Injury after Non-cardiac Surgery" (MINS) which they defined as prognostically relevant myocardial injury due to ischaemia. To do this they analysed the ischaemic symptoms and ECGs of patients who has a troponin level above 0.04 ng/ml (elevated 'abnormal' lab threshold). They also excluded 95 patients who were adjudicated to have a non-ischaemic cause for their troponin rise (e.g. sepsis, pulmonary embolism, cardioversion). Multivariable analysis (including preoperative predictors) revealed that an elevated troponin (≥ 0.03 ng/ml) after non-cardiac surgery, irrespective of the presence of an ischemic symptom or ECG, independently predicted 30-day mortality. Therefore, the authors' diagnostic criterion for MINS was a peak troponin T level of 0.03 ng/ml or greater judged due to myocardial ischemia (i.e. not sepsis etc.). MINS was an independent predictor of 30-day mortality (adjusted hazard ratio, 3.87; 95% CI, 2.96–5.08). Twelve hundred patients (8.0%) suffered MINS, and 58.2% of these patients would not have fulfilled the universal definition of myocardial infarction. Only 15.8% of patients with MINS experienced an ischemic symptom. 9.8% of MINS patients died within 30 days of surgery and an additional 9% had a non-fatal cardiac arrest, stroke or congestive cardiac failure.

BNP

Using individual patient data meta-analysis (on over 2000 patients) Reitze N et al[24] found that an elevated postoperative BNP independently associated with increased mortality, myocardial infarction, and cardiac failure at 30 days and more than 180 days after non-cardiac surgery,

In a further analysis Rodseth RN et al[25] found that post-operative BNP measurement enhanced risk stratification for the composite outcomes of death or nonfatal myocardial infarction at 30 days and more than 180 days after non-cardiac surgery compared with a pre-operative BNP measurement alone.

However the extent to which post-operative NP elevation correlates with post-operative troponin elevation and whether measuring NP provides additional information to that provided by post-operative troponin alone is unknown.

What can we do?

There is no good evidence for a safe and effective way to prevent postoperative cardiac complications or how to treat them and improve their long term prognosis. However recent large trials have clarified some issues regarding preoperative management. Clonidine is of no benefit and increases risk of hypotension (POISE-2)[18]. Aspirin is of no benefit and increases risk of bleeding (POISE-2[26]). It should be stopped prior to surgery unless minimal bleeding risk and major thrombosis risk. In general aspirin should be continued in patients with stents and recent infarcts.

Evidence regarding statins is still evolving but AHA and European guidelines suggest continuing statins in patients currently taking them and that the pre-operative initiation of statins is reasonable in patients undergoing vascular surgery and maybe other high risk situations.

A recent review of perioperative beta-blockade[27] concluded that beta blockade started within 1 day or less before non-cardiac surgery prevents nonfatal MI but increases risks of stroke, death, hypotension, and bradycardia. Without the controversial DECREASE studies, there are insufficient data on beta blockade started 2 or more days prior to surgery. Multicenter RCTs are needed to address this knowledge gap. AHA and European guidelines state that pre-existing beta-blockade should be continued and suggest that they may be initiated in high risk situations (high risk patient, high risk surgery, tachycardia) in a titrated manner.

Nitrous oxide has been cleared of increasing cardiovascular risk (ENIGMA 2).

The VISION study has confirmed the importance of measuring post-operative troponin levels to identify a poor short and long term prognosis population for which preventative strategies must be studied.

Foucrier et al[28] performed an interesting (non-randomised) study in which they compared one year freedom from adverse cardiac events in vascular surgery patients who had a peri-operative MI or significant troponin rise and had intensification of their previous medical therapy (addition of anti-platelet drug, statin, beta blocker or ACE inhibitor) to a group who had no change in their medical therapy following their MI / troponin rise. Patients not receiving intensified cardiovascular therapy had a higher risk of an adverse cardiac event compared to patients with no MI / troponin rise and those whose therapy had been intensified. Patients whose therapy was intensified had similar risk to those who had no MI / troponin rise. They concluded that in patients with elevated troponin I levels after non-cardiac surgery, long-term adverse cardiac outcomes may likely be improved by following evidence-based recommendations for the medical management of acute coronary syndromes.

Another recent study (non-randomised)[29], which reinforced the potential importance of optimal post-operative patient management, found that postoperative delay in resuming angiotensin receptor blockers (ARBs) is common, particularly in patients who are frail after surgery. However withholding ARBs was strongly associated with increased 30-day mortality.

Devereuax et al[2] also found that a substantial proportion of patients with a peri-operative MI did not receive cardiovascular medications known to be effective in managing patients with non-operative MI.

The issue of how to treat postoperative MI / troponin elevations is being studied in a large multicentre trial: Management of Myocardial Injury After Non-cardiac Surgery Trial (MANAGE). This was started in 2013 and expected to be completed by 2017. This is a factorial design in which patients who have suffered an MI or an elevated troponin measurement after surgery with no alternative explanation (e.g., pulmonary embolism, sepsis) to myocardial injury are being randomised to placebo, omeprazole (20 mg daily), dabigatran (110 mg bd) or both.

There have also been some promising small trials[30] on the pre-operative use of the anti-anginal drug, ivabradine. This is a specific inhibitor of the I_f current in sinoatrial node myocytes which reduces heart rate independently of sympathetic activation and does not cause hypotension. A large randomised trial is required.

Finally I would just to bring you attention to a recently published study. Using clinical data from the New York State Cardiac Surgery Reporting System Glance et al[31] found that the rate of death or major complications among patients undergoing coronary artery bypass graft surgery varies markedly across anesthesiologists , controlling for confounders such as patient factors and hospital quality. These findings suggest that there may be intra-operative opportunities to improve outcomes among high-risk surgical patients. This study did not collect details of peri-operative management so which aspects of anaesthesia management may have impacted outcomes is unknown.

Summary

The following 3 recommendations from the European guidelines summarise much of the material in this literature review:

1. Clinical risk indices such as the RCRI or NSQIP model are recommended for peri-operative risk stratification.
2. Assessment of cardiac troponins in high risk patients, both before, and 48-72 hours after major surgery should be considered.
3. NT-proBNP and BNP measurements may be considered for obtaining independent prognostic information for perioperative and late cardiac events in high-risk patients.

There is promising data from existing studies and extensive on-going research regarding interventions to improve peri-operative and longer term cardiac outcomes in our high risk patients.

Statistical note

Many papers quote a "c statistic" of "C-statistic" to compare models or risk indices. The c statistic, is a measure of how well a model can be used to discriminate subjects having the event from subjects not having the event. Values range from 0.5 to 1.0. A value of 0.5 indicates that the model is no better than chance at predicting the outcome. A value of 1.0 indicates that the model perfectly identifies those with and without the outcome. Models are typically considered reasonable when the c-statistic is higher than 0.7 and strong when it exceeds 0.8. The c-statistic is the same as the area under the receiver-operating characteristic curve, formed by taking the predicted values from the regression model as a diagnostic test for the outcome event in the data.

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