Cardiovascular risk management in the peri-operative setting

Shehane Mahendran[1], Aravinda Thiagalingam[2], Graham Hillis[3], Richard Halliwell[2], Henry CC Pleass[4], Clara K Chow[2,5]

Summary

- Peri-operative cardiovascular events occur in up to 3% of patients undergoing non-cardiac surgery.
- Accurate cardiovascular risk assessment is important in the peri-operative setting, as it allows informed and shared decisions regarding the appropriateness of proceeding with surgery, guides surgical and anaesthetic approaches, and may influence the use of preventive medications and post-operative cardiac monitoring. Quantitative risk assessment may also inform a reconsideration of choosing a more limited lower risk type of surgery, or conservative management.
- Pre-operative cardiovascular risk assessment starts with clinical assessment and should include an estimate of functional capacity.
- Specialised cardiac investigations are rarely indicated specifically to assess pre-operative cardiovascular risk. The decision regarding cardiac investigations is influenced by the nature, extent and urgency of surgery.
- The strategy of performing pre-operative revascularisation to improve post-operative outcomes is not evidence-based and recent international guidelines recommend against this.

In Australia, there are over 2 million elective admissions into hospital each year for major non-cardiac surgery, and this number is rising. Although these operations improve symptoms and reduce premature mortality, they come with risks, of which cardiovascular complications are the most frequent, making the management of peri-operative cardiovascular risk and events a common and growing burden for health services.[1,2]

Peri-operative major adverse cardiovascular events (MACE) are estimated to occur in about 3% of patients undergoing major non-cardiac surgery, and accounts for one-third of deaths at 30 days.[3] Peri-operative MACE are regarded as those that occur within 30 days following surgery and encompass exacerbation or decompensation of existing cardiovascular disease (CVD) and first presentations of CVD, including ischaemic heart disease, stroke and transient ischaemic attack, arrhythmias, heart failure, cardiac arrest, and cardiovascular death.[4] In addition, myocardial injury after non-cardiac surgery (MINS), defined as myocardial injury within 30 days after surgery (denoted by elevated troponin above the 99th percentile of the upper reference level for the troponin assay, with a rise/fall pattern), occurs in as many as 20% of patients and is a strong marker of future MACE.[5]

Accurate peri-operative risk assessment is important to enable shared decision making and to optimise the multidisciplinary management of patients undergoing major surgery, defined as a procedure necessitating overnight hospital stay.[6] This narrative review aims to examine the evaluation of cardiovascular risk, as well as the prevention and management of cardiac complications in patients undergoing major non-cardiac surgery.

Methods

We searched the MEDLINE database to identify relevant articles on peri-operative cardiovascular risk management, using the keywords "pre-operative", "peri-operative", "major non-cardiac surgery", "cardiovascular risk assessment", "major adverse cardiovascular events", "MACE", "myocardial injury after non-cardiac surgery" and "MINS", with the most recent search done in October 2022. We also identified relevant guidelines and reviews, including the guidelines from the Canadian Cardiovascular Society (CCS),[6] the American College of Cardiology/American Heart Association (ACC/AHA),[7] and the European Society of Cardiology/European Society of Anaesthesiology (ESC/ESA),[8] and reviewed their reference lists.

Pre-operative cardiovascular risk assessment

There is considerable variation in peri-operative cardiovascular risk among patients presenting for surgery. For example, the peri-operative MACE rate is higher in adults aged 75 years and older compared with younger adults (9.5% *v* 4.8% respectively) and in patients with coronary stents compared to those without (9.5% *v* 1.5% respectively).[9,10] Regardless of their pre-existing risk profile, patients who require urgent (within six to 24 hours) or emergency (within six hours) surgery are at an increased risk of peri-operative MACE.[11] The level of cardiovascular risk is also a function of the proposed type and extent of surgery, with cataract and cosmetic surgery associated with less than 1% risk of peri-operative MACE, and peripheral vascular, thoracic and transplant surgery associated with a 5% risk or greater (Box 1).[3,7,14]

Pre-operative cardiovascular risk assessment is generally warranted in patients undergoing major elective non-cardiac surgery, with some guidelines specifically recommending this for all patients aged 45 years or older, or aged 18–44 years if they have a history of CVD. The extent of pre-operative cardiovascular risk assessment is often additionally informed by surgical factors, including the type of procedure, anaesthesia method, and the urgency of surgery.[6]

Clinical risk assessment

For all patients undergoing surgery, the pre-operative cardiovascular assessment starts with a history and examination. In both urgent and elective surgery settings, this is focused on identifying unstable cardiovascular conditions that substantially elevate a patient's risk of undergoing surgery and are considered contraindications to surgery, including acute coronary syndrome, decompensated heart failure, haemodynamically or clinically significant tachyarrhythmias or bradyarrhythmias, symptomatic severe valvular disease, or severe pulmonary hypertension.[6,10]

[1]Westmead Applied Research Centre, University of Sydney, Sydney, NSW. [2]Westmead Hospital, Sydney, NSW. [3]Royal Perth Hospital, Perth, WA. [4]Institute of Academic Surgery, Royal Prince Alfred Hospital, Sydney, NSW. [5]University of Sydney, Sydney, NSW. clara.chow@sydney.edu.au • doi: 10.5694/mja2.51988

1 Factors predictive of increased peri-operative cardiac risk

Predictive factors: patient characteristics	Predictive surgical factors

• Characteristics:[12]
  ‣ age ≥ 75 years;
  ‣ male sex;
  ‣ obesity
• Chronic conditions:
  ‣ coronary artery disease, particularly if the patient had a recent myocardial infarction with or without placement of a coronary artery stent within the past 60 days;
  ‣ haemodynamically significant valvular disease, including severe aortic stenosis;
  ‣ arrhythmias, including atrial fibrillation;[13]
  ‣ congestive heart failure;
  ‣ hypertension;
  ‣ cerebrovascular disease;
  ‣ peripheral vascular disease;
  ‣ renal insufficiency;
  ‣ diabetes
• Poor functional capacity
• Obstructive sleep apnoea
	• Types of surgery:
	  ‣ vascular (7.7%);
	  ‣ thoracic (6.5%);
	  ‣ transplant (6.2%);
	  ‣ general (3.9%)[14]
	• Emergency or urgent surgery[15]
	• Acute trauma (eg, hip fracture)[12]

2 Modified four-question Duke Activity Status Index (M-DASI-4Q)

- Are you able to climb a flight of stairs or walk up a hill?
- Are you able to do heavy work around the house (lifting and moving heavy furniture)?
- Are you able to do yard work (raking leaves or pushing a power mower)?
- Are you able to participate in strenuous sports (swimming, singles tennis, football, basketball or skiing)?

Specific symptoms that may elicit these unstable conditions include a history of exertional angina, dyspnoea, orthopnoea or recent syncope. Furthermore, the medical history should evaluate the presence of known cardiovascular conditions, including ischaemic heart disease, prior percutaneous coronary intervention, heart failure, valvular heart disease, arrhythmias, systemic or pulmonary hypertension, and risk factors for CVD, including diabetes or chronic kidney disease.[14]

Clinical examination should include assessment of haemodynamic status and examination for severe valvular disease or heart failure.[10] Examination should be supplemented with a 12-lead electrocardiogram (ECG) for patients with suspected new heart disease or exacerbation of known ischaemic heart disease. ECG is also recommended in some guidelines for all patients with known CVD or cardiovascular risk factors, or with signs or symptoms of CVD before intermediate or high risk major surgeries, but it is acknowledged that the evidence base for these recommendations is weak.[7,8] That is, pre-operative ECG abnormalities have not been consistently shown to predict peri-operative MACE in observational studies.[16-18]

Poor functional capacity, defined as an inability to perform four or more metabolic equivalents of task (roughly the equivalent of being unable to walk up a hill or climb two or more flights of stairs due to symptomatic limitation), is independently associated with a twofold increased risk of peri-operative complications.[8,19] Cardiopulmonary exercise testing is the current gold standard for functional capacity assessment but is time and resource intensive and not widely available.[20] Self-reported functional capacity has inconsistently been shown to predict peri-operative cardiovascular events.[19,21-23] Therefore, screening tools such as the Duke Activity Status Index (DASI) are used to identify individuals requiring formal assessment. The DASI has shown to be an independent predictor of death or myocardial infarction.[7,24] It gives a maximum score of 58.2, and a score below 34 is a threshold that denotes elevated cardiovascular risk based on observational evidence.[25] A simplified version of the 12-part DASI questionnaire is the modified DASI (M-DASI-4Q) consisting of four questions (Box 2). The DASI and the M-DASI-4Q have been shown in observational studies to delineate those with and without satisfactory functional capacity, defined as an anaerobic threshold greater than 11 mL/kg per minute and oxygen consumption (VO_2) peak greater than 16 mL/kg per minute.[26,27] In scenarios associated with higher risk, unknown or suspected poor functional capacity, an objective evaluation of functional capacity should be made if the results are likely to change the peri-operative management.[7,10]

Frailty, characterised by an increased vulnerability to adverse health outcomes and commonly associated with ageing, is now increasingly recognised as a significant factor in peri-operative risk assessment. Adjusting risk evaluation based on frailty assessment using a validated screening tool among patients aged 70 years or older in addition to functional capability measures, such as self-reported ability to climb two flights of stairs, carries an ESC/ESA class IIa, level B recommendation.[8,28,29]

Risk prediction tools

Risk prediction scores may assist in quantification of peri-operative cardiovascular risk. Several risk prediction indices have been proposed based on multivariate analyses of observational data.[8] These risk calculators combine a mix of clinical factors and surgery-related factors and have less emphasis on frailty and detailed functional assessment. They also do not integrate biomarkers.

The Revised Cardiac Risk Index (RCRI), a modified version of the original Goldman Risk Index, has moderate accuracy in predicting risk of acute coronary syndromes and cardiovascular mortality, but has not been calibrated to other cardiovascular endpoints.[14,23] A systematic review of 24 studies with more than 790 000 patients concluded that the RCRI is moderately effective in distinguishing between patients at low versus high risk of cardiac events after non-cardiac surgery. However, the RCRI was found to be inadequate in predicting cardiac events following vascular surgery and in predicting overall patient mortality.[30]

The National Surgical Quality Improvement Program (NSQIP) risk calculator from the American College of Surgeons (ACS) was developed based on data from over 1 400 000 patients and has been well validated.[31,32] It is designed to predict the likelihood of a negative outcome, such as a complication or death, following surgery, and provides information specific to surgery type. Some comparative studies suggest the ACS NSQIP risk calculator has greater peri-operative discriminatory ability in predicting adverse outcomes than previous indices, others suggest it may be less accurate in some surgical types, such as robot-assisted major surgery and colorectal surgery.[29,31,33,34]

The American Society of Anesthesiologists (ASA) Physical Status Classification System is a broader subjective assessment of overall physical status in the pre-operative setting.[35] In one study of 6301 patients, the risk of cardiac complications and mortality for healthy patients (ASA, class I) was 0.1%, and patients with health consistent with ASA class IV had an 18% risk (Box 3).[36] A

more recently developed risk score is the American University of Beirut (AUSB)-HAS2 Cardiovascular Risk Index, which large studies have suggested has higher accuracy compared with RCRI, but there is less experience with this to date.[37-39] The most recent ESC/ESA guidelines did not specifically recommend one risk score over another.[8]

Cardiology consultation and investigations

Current international guidelines recommend against routine specialist cardiac investigations in the work-up of patients undergoing planned non-cardiac surgery.[7,10] These infer that low risk patients on clinical risk assessment do not require further investigation. These guidelines also infer that for elevated risk patients, further testing is often for a usual clinical indication and rarely solely for pre-operative work-up, and also that consideration is given to how and whether peri-operative medical, anaesthetic or surgical approaches could be changed.[6,40]

Transthoracic echocardiography

Although routine pre-operative evaluation of left ventricular function is not recommended by current international guidelines, resting transthoracic echocardiography may be indicated to evaluate valvular function in patients with a newly detected murmur and clinical signs or symptoms of severe valvular disease, including dyspnoea, angina, oedema, recent syncope, or where there may be unexplained dyspnoea or heart failure with worsening clinical status. This is especially so in patients with poor functional capacity before high risk surgery (ESC/ESA, class I level B). Reassessment of left ventricular function in patients with clinically stable heart failure or known moderate to severe valvular disease may be reasonable if echocardiography has not been performed within the past 12 months.[6-8] Pre-operative findings of left ventricular systolic dysfunction, reduced left ventricular ejection fraction, moderate to severe left ventricular hypertrophy, moderate to severe mitral regurgitation, or aortic stenosis with a mean gradient of 40 mmHg or more have been shown in observational studies to be independently associated with worse peri-operative outcomes, particularly post-operative decompensated heart failure.[41,42]

Stress testing

Stress exercise ECG, or pharmacological stress testing in patients unable to exercise, has varied recommendations in the current major guidelines. It is not routinely recommended before non-cardiac surgery by Canadian guidelines.[16] In contrast, ACC/AHA and ESC/ESA recommend consideration of non-invasive pharmacological stress testing (dobutamine stress echocardiogram or stress myocardial perfusion imaging) in patients who have an elevated clinical risk profile and poor functional capacity (less than four metabolic equivalents of task), if it will change management. Non-invasive stress testing is not recommended by ACC/AHA in patients with a low risk profile, good to excellent exercise tolerance, or those undergoing low risk non-cardiac surgery.[7,8] Given formal exercise testing is resource intensive and not easily accessible to all, initial screening with the M-DASI-4Q is a pragmatic approach, consistent with most guidelines, with further objective assessment of functional capacity with formal exercise testing at the discretion of clinicians.[27]

Biomarker testing

Routine pre-operative biomarker assessment, including high sensitivity cardiac troponin T/I (hs-cTnT/I), B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), has varying recommendations by the major guidelines. Multiple meta-analyses and systematic reviews have demonstrated that pre-operative BNP is associated with short and long term mortality and MACE.[43-45] One such systematic review and meta-analysis of 2179 patients from 18 studies found that elevated pre-operative BNP (> 92 mg/L) or NT-proBNP (> 300 ng/L) was the strongest independent predictor of death and non-fatal myocardial infarction at 30 days (odds ratio [OR], 3.7; 95% CI, 2.2–6.2; $P < 0.001$) and at 180 days or more (OR, 2.2; 95% CI, 1.9–2.7; $P < 0.001$) after surgery.[45] Yet, there is no consensus on

3 Risk assessment scores for patients undergoing surgery

Revised Cardiac Risk Index (RCRI; 1999)*[14]	National Surgical Quality Improvement Program (NSQIP) — Surgical Risk Calculator (2013)[31]	American Society of Anesthesiologists (ASA) risk score[36]
• History of ischaemic heart disease • History of cerebrovascular disease • History of congestive heart failure • Diabetes mellitus requiring insulin therapy • Pre-operative serum creatinine level ≥ 177 µmol/L • Planned high risk procedure (intraperitoneal, intrathoracic or vascular surgery)	• Age • Sex • Pre-operative functional status • ASA class • Emergency procedure required • Diabetes • Hypertension requiring medication • Congestive cardiac failure in the 30 days before the surgery • Ascites within 30 days before the surgery • Steroid use for chronic condition • History of severe chronic obstructive pulmonary disease • Current smoker within the past 12 months • Dyspnoea • Dialysis • Acute renal failure • Systemic sepsis within 48 hours before the surgery • Ventilator-dependent • Disseminated cancer • Body mass index	• I: The patient is healthy with no systemic disease • II: The patient has mild systemic disease • III: The patient has severe systemic disease that is not incapacitating • IV: The patient has incapacitating disease that is a constant threat to life • V: A moribund patient who is not expected to live 24 hours with or without surgery • E: Emergency surgery ("E "is placed after the Roman numeral)

* Score 1 point for each risk of complications: 0 = 0.4%; 1 = 0.9%; 2 = 7%; ≥ 3 = 11%. ◆

thresholds at which increased risk is conferred and on how they add value to existing risk prediction strategies.[16,46,47] In a prospective observational study of 979 patients, elevated pre-operative hsTnT was the strongest independent predictor for the combined endpoint of in-hospital mortality, myocardial infarction, cardiac arrest, cardiopulmonary resuscitation, and acute decompensated heart failure (hazard ratio, 2.6; 95% CI, 1.3–5.3; $P = 0.01$).[48] Similarly, a systematic review of 19 studies with 13 386 patients undergoing non-cardiac surgery found that pre-operative cardiac troponin is a predictor of short (OR, 4.3; 95% CI, 2.9–6.5; $P < 0.001$) and long term (OR, 4.2; 95% CI, 1.0–17.3; $P = 0.05$) MACE and/or all-cause mortality.[49] The CCS guidelines recommend routine measurement of BNP or NT-proBNP before non-cardiac surgery in patients aged over 65 years, patients aged 45–64 years with significant CVD, or RCRI score of 1 or over, although they do not advise pre-operative troponin measurement.[6] ACC/AHA guidelines do not recommend routine pre-operative BNP measurement and suggest functional capacity as a discriminator for the need for biomarker testing.[7] ESC/ESA guidelines suggest a judicious approach with measurement of pre-operative hs-cTnT/I before intermediate and high risk non-cardiac surgery in patients with known CVD; cardiovascular risk factors, including age 65 years or older; or signs or symptoms suggestive of CVD.[8,50]

Coronary angiography and revascularisation

Coronary computed tomography angiography findings have been shown to correlate with risk of post-operative MACE.[40,51] However, there is no evidence from randomised control trials (RCTs) that routine prophylactic revascularisation to prevent ischaemia at the time of surgery improves outcomes in asymptomatic patients or in those with stable coronary artery disease. Hence, routine coronary evaluation with invasive coronary angiography or coronary computed tomography angiography is not generally recommended, and pre-operative coronary revascularisation in this setting to reduce perioperative cardiac events is also not recommended.[6-8]

However, in patients with unstable angina, an individual risk–benefit assessment is necessary to determine the value of coronary revascularisation before urgent or semi-urgent non-cardiac surgery.[6] Pre-operative percutaneous coronary intervention (PCI) before non-cardiac surgery may be considered in patients with refractory symptoms, high degree of myocardial ischaemia, or significant angiographic findings, such as left main coronary artery disease, who are unsuitable for bypass surgery. However, these recommendations are less clear-cut and require discussion between the cardiologist and the surgeon.[8]

In patients requiring PCI before non-cardiac surgery, there is an ESC/ESA class I level A recommendation for new generation drug-eluting stent over bare metal stent and balloon angioplasty. This is based on data from a subgroup analysis of 2432 patients from the LEADERS FREE trial, a randomised, double-blind control study, which demonstrated that new generation drug-eluting stents have superior safety outcomes compared with bare metal stents in patients undergoing early non-cardiac surgery (within three months) following PCI.[7,8,52] After elective PCI, it is recommended to delay time-sensitive non-cardiac surgery for a minimum of one month while dual antiplatelet therapy (DAPT; aspirin + $P2Y_{12}$ inhibitor) is given (ESC/ESA, class I level C).[8]

Among patients with recent acute coronary syndrome and/or PCI, the risk of peri-operative MACE is higher, and timing of non-cardiac surgery is a balance between the risks of delaying surgery and the risks of ischaemia and stent thrombosis. Guidelines recommend elective non-cardiac surgery be delayed for at least six months after elective PCI and 12 months after acute coronary syndrome, regardless of the revascularisation strategy (ESC/ESA, class I level A).[7]

In the event of acute coronary syndrome in a patient awaiting a time-sensitive non-cardiac procedure, if surgery can be safely postponed for at least three months, it is recommended that this is done (ESC/ESA, class I level A). In the scenario where critical non-cardiac surgery is needed simultaneously with an acute coronary event requiring revascularisation, a minimalist strategy involving plain balloon angioplasty and delayed stenting may be deemed appropriate, but it should follow a case-by-case approach (ESC/ESA, class IIa level C).[8] Our recommendation for coronary revascularisation and timing of non-cardiac surgery is in keeping with the updated 2022 ESC/ESA guidelines.

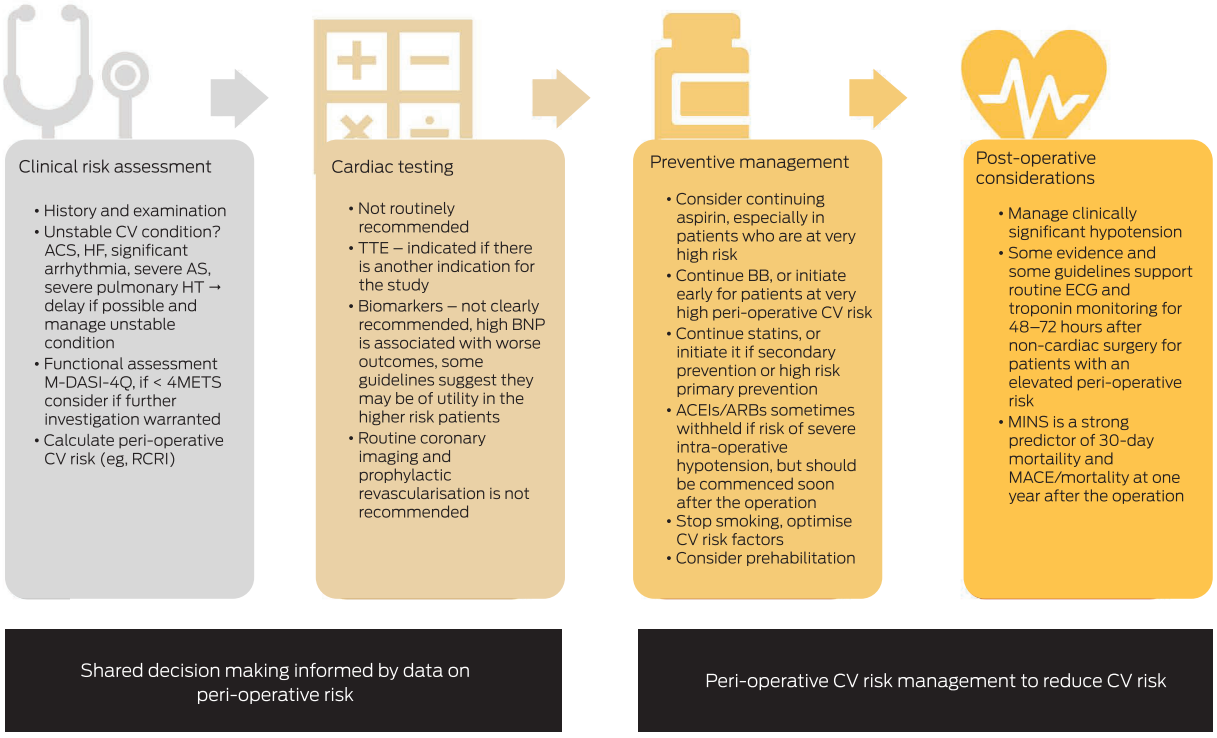
Preventive management to reduce peri-operative cardiovascular events

Peri-operative cardiovascular preventive management can best be considered a balance between risks and one that is generally optimised through a discussion of these risks in a multidisciplinary team including the patient (Box 4). When unplanned urgent or emergency surgery is required, there is obviously less time to inform these decisions or implement preventive management.

Antiplatelet therapy

A common challenge for clinical decision making is how to manage antiplatelet therapy peri-operatively. A recent systematic review identified 38 relevant studies and attempted to address timing of stopping antiplatelets, continuation versus stopping in patients with stents, and use of bridging therapies.[53] With respect to stopping antiplatelets or not, the largest body of evidence was for the question of continuing aspirin versus placebo, with three RCTS and two cohort studies including 28 062 patients, of which the most recent RCT was the POISE-2 trial published in 2014.[54] Aspirin continuation was associated with an increased risk of major bleeding (relative risk [RR], 1.31; 95% CI, 1.15–1.50) but did lower the risk of major thromboembolism (stroke, transient ischaemic attack, myocardial infarction, pulmonary embolism, venous thromboembolism, vascular death) (RR, 0.75; 95% CI, 0.59–0.95).[9,53,55-58] Among a small number of studies that examined the benefits of stopping aspirin more than seven days before surgery compared with stopping seven days or less before surgery, there was no difference in risk of bleeding or major thromboembolism.[55,59] No well powered trials directly examined continuation of aspirin versus stopping in patients with stents. One large scale secondary analysis of 28 029 patients who had undergone non-cardiac operations within 24 months of stent implantation demonstrated a strong correlation of timing of surgery with MACE (MACE rate 11.6% if < 6 weeks since stent implantation, 6.4% if 6 weeks to less than 6 months, 4.2% if 6–12 months, and 3.5% if >12–24 months).[60] The three factors most strongly associated with additional risk increases in patients with stents were non-elective operation, history of recent myocardial infarction less than 6 months, and prior RCRI score greater than 2.[60] The RCT evidence on the continuation of long term antiplatelet therapy in peri-operative patients is very limited, and thus recommendations suggest a nuanced approach guided by an accurate assessment of the competing risks of peri-operative thrombotic versus bleeding events.[61]

4 Shared decision to balance risk with surgical urgency and optimise peri-operative management to reduce cardiovascular risk



ACEIs = angiotensin-converting enzyme inhibitors; ACS = acute coronary syndrome; ARBs = angiotensin-receptor blockers; AS = aortic stenosis; BB = β-blocker; BNP = B-type natriuretic peptide; CV = cardiovascular; ECG = electrocardiogram; HF = heart failure; HT = hypertension; MACE = major adverse cardiovascular events; M-DASI-4Q = Modified four-question Duke Activity Status Index; METS = metabolic equivalents of task; MINS = myocardial injury after non-cardiac surgery; RCRI = Revised Cardiac Risk Index; TTE = transthoracic echocardiogram. ◆

The nature of surgery is also key in decision making, including taking into consideration the bleeding risk.

In patients without a history of ischaemic heart disease, or who have not had previous coronary stenting, initiation or continuation of aspirin is not beneficial in those undergoing elective non-cardiac, non-carotid surgery, based on the results from the POISE-2 study.[6,7]

Antiplatelet therapy in chronic coronary syndrome

It is strongly recommended that antiplatelet management in patients with recent PCI be discussed between the surgeon, the anaesthetist and the cardiologist.[7,8] DAPT should be continued for a minimum of one month, and ideally six months, after elective PCI. In patients with a history of PCI, aspirin is recommended to continue peri-operatively. The caveat to this is patients undergoing high bleeding risk surgery, such as intracranial, spinal neurosurgery or vitreoretinal eye surgery, in which case it is recommended to interrupt aspirin for at least seven days before the operation, given the bleeding consequences may be much more significant.[8,62]

Antiplatelet therapy in acute coronary syndrome

In general, patients with acute coronary syndrome require DAPT for 12 months, unless there is a high risk of bleeding or a need to co-administer oral anticoagulant therapy. Interruption of DAPT is associated with a significant risk of acute stent thrombosis, and such a decision should only be made after careful consideration of risks and benefits and discussion with the treating cardiologist. When requiring time-sensitive surgery following acute coronary syndrome, a minimum duration of three months for DAPT should be considered and aspirin should be continued while $P2Y_{12}$ inhibition is interrupted, unless planned for high bleeding risk surgery.[8,62,63]

If interruption of $P2Y_{12}$ inhibition is indicated, it is recommended to withhold ticagrelor for three to five days, clopidogrel for five days and prasugrel for seven days before non-cardiac surgery (ESC/ESA, class I level B).[8,50] If antiplatelet therapy has been withheld before surgery, it is recommended to recommence therapy as soon as possible, ideally within 48 hours after the procedure. However, this requires discussion of risks between the surgeon and the cardiologist (ESC/ESA and ACC/AHA, class I level C).[7,8,50]

Statin therapy

Peri-operative statin use has been shown in observational data to have a beneficial effect on the 30-day rate of MACE and mortality, as well as on long term mortality and MACE.[64] In one large retrospective analysis of 204 885 patients undergoing non-cardiac surgery, patients who were prescribed lipid-lowering therapy had reduced in-hospital mortality compared with patients who were not (2.1% *v* 3.1% respectively; adjusted OR, 0.62; 95% CI, 0.58–0.67).[65] Statin therapy is also associated with a decreased risk of complications after endovascular repair of abdominal aortic aneurysms and reduced risk of stroke after carotid stenting.[66,67]

In patients already taking statins, peri-operative continuation is strongly recommended (ESC/ESA, class I level B).[8] Peri-operative statin withdrawal more than four days after aortic surgery is associated with a threefold increased risk of post-operative myocardial ischaemia.[68]

Regarding pre-operative commencement of statin therapy in patients not previously taking them, the results from mainly small RCTs and meta-analyses have been inconsistent.[69,70] Routine peri-operative initiation of statin therapy is therefore not recommended, unless patients have coronary artery disease or raised cardiovascular risk and would hence be indicated for statins for secondary or high risk primary prevention.[8] In addition, the ACC/AHA and ESC/ESA guidelines suggest patients planned for vascular surgery should be initiated on statin therapy at least two weeks before intervention and continued for at least one month following surgery, although there is only moderate evidence to support this (ESC/ESA, class IIa, level B).[7,8] Statins with a long half-life, such as atorvastatin, are preferred in the peri-operative period when there may be limited oral intake.[8] In summary, long term statin therapy should be continued peri-operatively, and it is reasonable to commence lipid-lowering therapy in patients with high cardiovascular risk and all patients undergoing vascular surgery.

β-Blockers

There is some theoretical support for the use of β-blockers in the peri-operative setting because they reduce mismatch in myocardial oxygen supply and demand. Despite observational studies suggesting the use of β-blockers may improve outcomes in high risk patients, RCTs have found initiating β-blockers may reduce MACE, but increase total mortality, stroke and clinically significant hypotension or bradycardia.[71] Therefore, routine initiation of β-blockers peri-operatively is not recommended.[8] However, most guidelines advise continuation of β-blockers in patients taking them chronically (ESC/ESA, class I level B), as peri-operative withdrawal is associated with an increased risk of mortality.[7,72] But if patients are hypotensive, it is reasonable to reduce or withhold the dose.[6-8] In patients with a history of ischaemic heart disease, cerebrovascular disease, renal insufficiency or diabetes mellitus, or in those planned for high risk surgical procedures, including vascular surgery, the ESC/ESA guidelines suggest initiation of β-blockers at least one week before surgery.[8,73,74] The ESC/ESA guidelines also give preference to low dose atenolol or bisoprolol, with dose titration to achieve a resting heart rate between 60 and 70 beats per minute with systolic blood pressure greater than 100 mmHg.[8] The ACC/AHA and CCS guidelines are similar to the ESC/ESA guidelines.[6,7]

Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers

There is conflicting advice regarding the management of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) therapy in the peri-operative period. A pooled analysis of three RCTs with a total of 188 patients found that peri-operative continuation of ACE inhibitors or ARBs correlates with increased rates of intra-operative hypotension (pooled RR, 2.53; 95% CI, 1.08–5.93).[6,75-77] In addition, two large multicentre RCTs have demonstrated that clinically significant hypotension in patients undergoing non-cardiac surgery is independently associated with an elevated risk of death, myocardial infarction, and stroke.[71,78] Furthermore, an observational study including 4802 patients undergoing non-cardiac surgery demonstrated that interruption of ACE inhibitors or ARBs before the operation correlated with a reduced risk of clinically significant hypotension (adjusted RR, 0.80; 95% CI, 0.73–0.88) and the composite endpoint of MINS, stroke and mortality at 30 days (adjusted RR, 0.82; 95% CI, 0.70–0.96).[79] The CCS guidelines reflect these findings in their support for withholding ACE inhibitors or ARBs for 24 hours before non-cardiac surgery, particularly if there is concomitant β-blocker use.[6] The ACC/AHA guidelines recommend continuation of ACE inhibitors or ARBs peri-operatively, and, if withheld, to recommence them as soon as clinically possible after the operation.[7] The ESC/ESA guidelines suggest withholding ACE inhibitors or ARBs on the day of surgery only if they have been prescribed in patients who do not have ejection fraction reduced heart failure.[8]

Intra-operative management

Events during surgery significantly increase the risk of post-operative cardiac complications. A meta-analysis of 11 studies identified that surgical factors, such as intra-operative bleeding requiring blood transfusion, or prolonged operative time greater than 3.8 hours, as well as haemodynamic factors, including intra-operative tachycardia, hypertension or hypotension, were found to be associated with increased risk of peri-operative cardiac events.[80] Intra-operative hypotension is associated with an increased risk of cardiac complications (OR, 2.69; 95% CI, 1.31–5.55; systematic review, n = 130 862). However, there is no standard definition of intra-operative hypotension. A recently reported trial compared hypotension-avoidance (where blood pressure medicines were managed and intra-operative mean arterial pressure ≥ 80 mmHg was targeted) with hypertension-avoidance strategies (where blood pressure medicines were given and intra-operative mean arterial pressure ≥ 60 mmHg was targeted). This study found no difference on major vascular complications at 30 days after the operation.[81] The risk of adverse outcomes is related to the degree of hypotension and duration, with the threshold of potential harm beginning at mean arterial pressure below 80 mmHg and duration of more than ten minutes.[82] We recommend discussion and shared decision making with the surgeon and anaesthetist to determine the most appropriate procedural and anaesthetic approach. Furthermore, in higher risk patients requiring urgent surgery, more invasive haemodynamic monitoring, intra-operative management to minimise rapid changes in volume status, and maintaining blood pressure and heart rate within a normal range could assist.[8,83] In addition, a recent trial, the Perioperative Ischemic Evaluation-3 (POISE-3) trial, suggests the consideration of tranexamic acid intra-operatively. POISE-3 found use of tranexamic acid intra-operatively in major non-cardiac surgery reduced major bleeding (9.1% *v* 11.7%; absolute difference, –2.6%; 95% CI, –3.8 to –1.4). The non-inferiority of the primary composite cardiovascular safety outcome was not met, although the difference was small (hazard ratio, 1.02; 95% CI, 0.92–1.14).[84]

Lifestyle management, cardiovascular risk factors, and prehabilitation

Pre-operative exercise intervention, or prehabilitation, has been demonstrated to increase pre-operative functional capacity and to aid recovery following surgery.[85] Prehabilitation, in broad terms, involves exercise, nutrition and psychological counselling. Small RCTs have demonstrated improvements in the six-minute walk test, anxiety, depression, and quality of life after major non-cardiac surgery but have been insufficiently powered to examine the impact on peri-operative MACE.[86,87] This evidence has influenced guidelines recommending consideration of referral to prehabilitation. However, current access to these types of prehabilitation programs is currently limited.

It is conceivable that prehabilitation could reduce peri-operative MACE, larger scale trials are required, but it makes sense to use the opportunity that prehabilitation offers to optimise

peri-operative management and encourage lifestyle risk factor management in the multidisciplinary setting. Pre-operative smoking cessation is recommended — smokers have worse outcomes at one year after surgery and early pre-operative smoking cessation is associated with a lower likelihood of smoking resumption after the operation. In addition, optimisation of cardiovascular risk factors, including blood pressure, dyslipidaemia and diabetes, is strongly recommended before elective non-cardiac surgery.[8,88]

Post-operative monitoring and management

Peri-operative myocardial infarction, in contrast to non-operative myocardial infarction, is mostly asymptomatic. In the POISE trial, only 34.7% of patients with myocardial infarction reported chest pain.[89] In another peri-operative trial, chest pain was present in only 6% of patients with a myocardial infarction and was associated with a 30-day and one-year mortality of 9% and 22% respectively.[2] Therefore, routine post-operative clinical assessment facilitates the opportunity for early detection of cardiac complications. Severe post-operative pain increases sympathetic drive and has been shown to be significantly associated with myocardial injury. Avoidance of acute post-operative pain is recommended (ESC/ESA, class I level B).[8,90]

Electrocardiogram, biomarkers and telemetry

It is common standard of care that high risk patients are monitored closely for a period after their operation, often with a combination of frequent vital sign monitoring, telemetry, ECGs and biomarkers. However, there is a dearth of evidence to support the utility of such monitoring and, thus, guidelines interpret existing evidence differently and recommend differing practices. For example, the ACC/AHA guidelines recommend only performing post-operative ECGs if there are signs or symptoms suggestive of myocardial ischaemia, myocardial infarction, or arrhythmia.[7] However, the CCS guidelines recommended routine post-operative ECGs and daily troponin monitoring for 48–72 hours in patients at elevated risk, defined by elevated BNP or proBNP before surgery, RCRI score of 1 or more, age 45–64 years with significant CVD, or age 65 years or older.[6] Given their recommendations for daily troponin, Canadian guidelines do not recommend routine telemetry monitoring, as they propose telemetry adds no further benefit.[91] Post-operative elevated troponin T has been shown to be a strong predictor of 30-day mortality, but the ACC/AHA guidelines only recommend measuring post-operative troponin if there is clinical evidence of myocardial ischaemia or infarction.[5,7] We suggest a tailored approach of increased monitoring for high risk patients using a combination of the above in the immediate post-operative period. Further studies are required to better establish the most efficacious and cost-effective means of monitoring these patients.

Post-operative management

Management of patients with peri-operative cardiovascular complications should be tailored towards the presumed underlying mechanism. Patients who develop MINS, identified through troponin monitoring, are at increased risk for recurrent MACE and mortality in the one to two years after surgery.[92] These patients should have ongoing follow-up with a cardiologist to monitor their progress, intensify their cardiovascular medications and arrange further cardiac evaluation as appropriate.[6] Notably, in a large observational

5 Gaps in the evidence and trials underway to address them

Diagnostic tests and prediction scores for peri-operative risk evaluation

- Perioperative Inflammatory Response Assessment in High-risk Patients Undergoing Noncardiac Surgery (INSIGHT) — a prospective non-interventional observational study
  - Target enrolment: 1400 participants
  - Expected completion: 31 January 2025
  - ClinicalTrials.gov identifier NCT04753307
- Prognostic Value of the Selvester QRS Score for Perioperative Myocardial Injury Following Non-cardiac Surgery
  - Target enrolment: 400 participants
  - Expected completion: 1 May 2023
  - ClinicalTrials.gov identifier NCT05453097

Peri-operative therapeutic medications to improve post-operative outcomes

- Impact of Colchicine on Peri-Operative Major Adverse Cardiovascular Events in Patients with Prior Coronary Revascularization: the Peri-OPerative COlchicine to Reduce Negative Events (POPCORN) trial
  - Target enrolment: 700 participants
  - Expected completion: 31 December 2027
  - ClinicalTrials.gov identifier NCT05618353
- Randomized Controlled Trial of Magnesium Sulfate Versus Placebo on the Prevention of Atrial Fibrillation Post Cardiac Surgery (POMPAE)
  - Target enrolment: 530 participants
  - Expected completion: 31 January 2025
  - ClinicalTrials.gov identifier NCT05669417
- Ivabradine for PREVENTion of Myocardial Injury after Noncardiac Surgery Trial (PREVENT-MINS)
  - Target enrolment: 2500 participants
  - Expected completion: 31 March 2026
  - ClinicalTrials.gov identifier NCT05279651

Peri-operative cardiovascular medication management

- Angiotensin-converting Enzyme Inhibitors and Angiotensin Receptor Blockers During the Perioperative Period: to Withdraw or to Continue? A multicenter randomized controlled trial (AIPOP)
  - Target enrolment: 3200 participants
  - Expected completion: 1 September 2024
  - ClinicalTrials.gov identifier NCT04506372
- Safety and Efficacy of Bridging Antithrombotic Therapy During Elective Non-cardiac Surgery for Coronary Artery Disease Patients Treated with Oral Antiplatelet Agents (SAFE)
  - Target enrolment: 950 participants
  - Expected completion: June 2023
  - ClinicalTrials.gov identifier NCT04675801

Intra-operative blood pressure management

- IMPROVE trial: Effect of Personalized Perioperative Blood Pressure Management on Postoperative Complications and Mortality in High-risk Patients Having Major Abdominal Surgery: a multicenter prospective randomized controlled interventional clinical trial
  - Target enrolment: 1272 participants
  - Expected completion: May 2024
  - ClinicalTrials.gov identifier NCT05416944
- Association of Intraoperative Blood Pressure Excursions below Cerebral Autoregulatory Boundaries with Organ Injury Following Major Noncardiac Surgery (AUTOREGULATE-NONCARDIAC)
  - Target enrolment: 500 participants
  - Expected completion: June 2025
  - ClinicalTrials.gov identifier NCT05336864

Utility of prehabilitation before non-cardiac surgery*

- Prehabilitation of Elderly Frail or Pre-frail Patients Prior to Elective Surgery — a randomized controlled multicenter study (PRAEP-Go)
  - Target enrolment: 1400 participants
  - Expected completion: July 2024
  - ClinicalTrials.gov identifier NCT04418271

Continues

5 Continued

Management of peri-operative cardiovascular events

- Anticoagulation for Stroke Prevention In Patients With Recent Episodes of Perioperative Atrial Fibrillation After Noncardiac Surgery (ASPIRE-AF) trial
  - Target enrolment: 2800 participants
  - Expected completion: December 2026
  - ClinicalTrials.gov identifier NCT03968393

* There are no current large clinical trials to examine the impact of prehabilitation on major adverse cardiovascular events for patients undergoing major non-cardiac surgery. ◆

study of 667 patients with elevated serum troponin after vascular surgery, patients with MINS who were prescribed intensified medical therapy had a one-year survival free from a major cardiac event rate similar to surgical patients without MINS.[93] Commencement of aspirin and statin after MINS has been demonstrated to have a significant reduction in 30-day mortality.[89,93] In addition, evidence from an international RCT demonstrated that, in patients who had MINS after non-cardiac surgery, the commencement of dabigatran 110 mg twice a day reduced the risk of major vascular complications, without significantly increasing major bleeding.[94]

Conclusions

The literature to inform peri-operative cardiovascular risk management has grown, but there are still many unanswered questions (Box 5). Cardiac risk assessment should be communicated to the patient to allow enhanced shared decision making in the peri-operative setting.[6,8] For patients who are assessed as being at very high risk of peri-operative morbidity or mortality, this may influence the decisions regarding delaying surgery to allow optimisation or prehabilitation, cancelling or proceeding with surgery, or taking a more conservative approach. In patients at high risk of proceeding to surgery, there is limited evidence that any specific therapy or interventions can mitigate peri-operative risk, but optimal guideline-based management of cardiovascular conditions and an individualised approach are recommended. Likewise, for patients who experience peri-operative cardiovascular complications, the evidence on which to base treatment is limited and strategies need to consider individual circumstances.

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