Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk

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Abstract

THIS IS THE FIRST OF 2 ARTICLES EVALUATING cardiac events in patients undergoing noncardiac surgery. In this article, we review the magnitude of the problem, the pathophysiology of these events, approaches to risk assessment and communication of risk. The number of patients undergoing noncardiac surgery worldwide is growing, and annually 500 000 to 900 000 of these patients experience perioperative cardiac death, nonfatal myocardial infarction (MI) or nonfatal cardiac arrest. Although the evidence is limited, a substantial proportion of fatal perioperative MIs may not share the same pathophysiology as nonoperative MIs. A clearer understanding of the pathophysiology is needed to direct future research evaluating prophylactic, acute and long-term interventions. Researchers have developed tools to facilitate the estimation of perioperative cardiac risk. Studies suggest that the Lee index is the most accurate generic perioperative cardiac risk index. The limitations of the studies evaluating the ability of noninvasive cardiac tests to predict perioperative cardiac risk reveals considerable uncertainty as to the role of these popular tests. Similarly, there is uncertainty as to the predictive accuracy of the American College of Cardiology / American Heart Association algorithm for cardiac risk assessment. Patients are likely to benefit from improved estimation and communication of cardiac risk because the majority of noncardiac surgeries are elective and accurate risk estimation is important to allow informed patient and physician decision-making.

CMAJ 2005;173(6):627-34

Throughout the last few decades noncardiac surgery has made substantial advances in treating diseases (e.g., cancer) and improving patient quality of life (e.g., arthroplasty). As a result, the number of patients undergoing noncardiac surgery is growing worldwide.[1] However, such surgery is associated with significant cardiac morbidity, mortality and consequent cost.

This is the first of 2 articles evaluating major perioperative cardiac events in patients undergoing noncardiac surgery. In this article, we review the magnitude of the problem, the pathophysiology of these events, approaches to perioperative risk assessment and the communication of risk. In the second article, we will present evidence regarding monitoring strategies for perioperative myocardial infarction (MI), propose diagnostic criteria for perioperative MI and review the evidence for perioperative prophylactic cardiac interventions.

The breadth of the topics covered in this article prohibited a fully systematic approach to this review. Although this is a narrative review, we did conduct thorough literature searches in each area and contacted the authors of relevant articles when necessary. We sought relevant systematic reviews and have highlighted their findings in our discussion. Our methods and attempt to focus on systematic reviews distinguish our review from several others,[2–4] which may explain why we often reached different conclusions.

Magnitude of risk of major perioperative cardiac events

Patients undergoing noncardiac surgery are at risk of major perioperative cardiac events (cardiac death, nonfatal MI and nonfatal cardiac arrest). Patients experiencing an MI after noncardiac surgery have a hospital mortality rate of 15%–25%,[5–8] and nonfatal perioperative MI is an independent risk factor for cardiovascular death and nonfatal MI during the 6 months following surgery (hazard ratio 18; 95% confidence interval [CI] 6–57).[9] Patients who have a cardiac arrest after noncardiac surgery have a hospital mortality rate of 65%,[10] and nonfatal perioperative cardiac arrest is a risk factor for cardiac death during the 5 years following surgery.[11]

Table 1 presents the proportion of patients undergoing noncardiac surgery who experienced a major cardiac event in prospective cohort studies with samples of more than 300 patients that did not have restrictions as to the type of surgery (e.g., vascular surgery) and that required patients to have at least 1 measurement of a cardiac enzyme or biomarker after surgery.[5–8,12–14] We included only studies that required such measurement after surgery because perioperative MI occurs primarily during the first 3 days after surgery,[7,15] a period when the majority of patients are receiving narcotic therapy and therefore may not experience cardiac symptoms during their MI.[6,7,16]

The pooled results from the studies evaluating patients who had or were at risk of cardiac disease[5–8,12,13] suggest that

DOI:10.1503/cmaj.050011

3.9% (95% CI 3.3%–4.6%) of these patients experience major perioperative cardiac events. The study by Lee and colleagues[14] is the only study in Table 1 that included relatively unselected patients (i.e., it was not limited to patients referred to a medical consult service or to patients with or at risk of coronary artery disease). Their findings suggest that major perioperative cardiac events occur in 1.4% (95% CI 1.0%–1.8%) of adults 50 years of age or older undergoing elective noncardiac surgery requiring hospital admission.

There are a number of reasons why the time frames of the studies reported in Table 1 — most were conducted over a decade ago — limit their ability to inform us about the current incidence of major perioperative cardiac events. First, patients with coronary artery disease are now living longer as a result of major medical advances.[17] Therefore, patients with high burdens of coronary artery disease are now surviving long enough for other conditions to develop that require surgical consideration, including cancer and severe osteoarthritis of the hip and knee. Second, there has been a shift in practice patterns toward advanced medical care (including surgery) for elderly patients. Third, some surgical interventions have become less invasive.

Despite these limitations, results from the study by Lee and colleagues likely represent a conservative estimate of the current incidence of major perioperative cardiac events among unselected adults undergoing noncardiac surgery that requires hospital admission. We say conservative because of the authors' exclusion of emergent surgical cases and the increasing numbers of elderly people undergoing noncardiac surgery today. Emergent cases represent about 10% of noncardiac surgeries,[18] and patients undergoing emergent surgery are at higher risk of major perioperative cardiac events than patients undergoing elective surgery (odds ratio 2.6, 95% CI 1.2–5.6).[8]

About 100 million adults worldwide undergo noncardiac surgery annually.[1] Conservative assumptions suggest that half of these patients are in an at-risk age group[1] and that the results from the study by Lee and colleagues[14] reflect their cardiac risk. Therefore, each year it is likely that 500 000 to 900 000 patients worldwide experience perioperative cardiac death, nonfatal MI or nonfatal cardiac arrest. This problem is important because of the burden of illness it represents and the health resources it consumes: perioperative cardiac complications prolong hospital stays by a mean of 11 days (95% CI 9–12 days).[15]

Pathophysiology of perioperative cardiac events

Cardiac death

In studies that examined perioperative cardiac death, authors attributed the cause to MI in 66% of the cases and to

Table 1: Outcomes of major perioperative cardiac events in patients undergoing noncardiac surgery

Study	Patient population	Enrolment years	Outcome; no. (%) of patients			
			Cardiac death	MI*	Cardiac arrest	Major cardiac outcome†
Studies evaluating patients with or at risk of cardiac disease						
Detsky et al[12]	455 consecutive patients aged > 40 yr evaluated by general medical service for perioperative cardiac risk	1983–1985	11 (2.4)	14 (3.1)	0	25 (5.5)
Shah et al[5]	688 consecutive patients aged > 70 yr with cardiac disease	1986–1987	15 (2.2)	32 (4.7)	NA	40 (5.8)
Mangano et al[13]	474 consecutive men with CAD or 2 risk factors for CAD; patients undergoing nonelective surgery were excluded	1987–1988	6 (1.3)	12 (2.5)	NR	13 (2.7)
Ashton et al[6]	835 consecutive men aged ≥ 40 yr with CAD, cerebral or peripheral atherosclerosis, or risk factors for CAD; patients undergoing emergent surgery were excluded	1987–1989	9 (1.1)	15 (1.8)	NA	20 (2.4)
Badner et al[7]	323 consecutive patients aged ≥ 50 yr with CAD	1993–1996	3 (0.9)	18 (5.6)	0	18 (5.6)
Kumar et al[8]	1121 patients with known or suspected CAD	1992–1995	8 (0.7)	31 (2.8)	7 (0.6)	36 (3.2)
All			52 (1.3)	122 (3.1)	7 (0.2)	152 (3.9)
Study evaluating relatively unselected patients						
Lee et al[14]	4315 patients aged ≥ 50 yr with expected postoperative length of stay ≥ 48 h; patients undergoing emergent surgery were excluded	1989–1994	12 (0.3)	46 (1.1)	16 (0.4)	59 (1.4)

Note: MI = myocardial infarction, CAD = coronary artery disease, NA = author contacted but unable to provide data, NR = not reported.
*Various definitions of MI were used across the studies, which may account for some of the variation in event rates.
†Composite of cardiac death, nonfatal myocardial infarction and nonfatal cardiac arrest.

arrhythmia or heart failure in 34% (Table 1). However, none of these studies used formal criteria to establish the underlying causes of cardiac death or determined intrarater reliability.[5–8,13] In addition, it is unclear whether ischemia, arrhythmia or a pre-existing cardiomyopathy caused heart failure that resulted in death. Further well-designed studies are needed to determine accurately the frequency with which these events cause perioperative cardiac death and to elucidate other causes.

Cardiac arrest

We identified only 1 study that examined the cause of cardiac arrest in patients undergoing noncardiac surgery.[10] Sprung and colleagues evaluated 223 cases of perioperative cardiac arrest that occurred between the start of anesthesia and discharge from the recovery room in patients undergoing noncardiac surgery at a single centre from 1990 to 2000. A committee of staff anesthesiologists, anesthesia chief residents, certified nurse anesthetists and recovery room nurses reviewed all cases and judged the probable cause of each cardiac arrest. The dominant causes were cardiac causes (e.g., MI) and bleeding (Table 2). Confidence in these conclusions will require a multicentre study of all cardiac arrests that occur in the postoperative period (i.e., from the start of surgery to 30 days after surgery).

Myocardial infarction

Arterial thrombosis is the underlying cause of the majority of nonoperative MIs.[19] In 64%–100% of patients with nonoperative MIs, coronary artery plaque fissuring occurs,[20,21] and in 65%–95% there is an acute luminal thrombus.[21–25] The pathophysiology underlying MIs in the operative setting is less clear.

Interpretation of coronary pathology and angiography data

Two studies of the coronary pathology underlying fatal perioperative MI revealed that two-thirds of the patients had significant left main or 3-vessel coronary artery disease.[26,27] These studies also showed that most of the patients did not exhibit plaque fissuring and only about one-third had an intracoronary thrombus. These findings suggest that a substantial proportion of these fatal perioperative MIs may have resulted from an increase in oxygen demand in the setting of fixed coronary artery stenoses.[28] In contrast, a study involving patients who underwent coronary angiography before vascular surgery revealed that the majority of nonfatal perioperative MIs occurred in arteries *without* high-grade stenoses. These findings suggest that the events may have resulted from plaque fissuring and acute coronary artery thrombosis.[29] Given the conflicting evidence, further study is needed to establish the pathophysiology of fatal and nonfatal perioperative MIs; this area of investigation would gain important insights from a study in which all patients experiencing perioperative MI underwent acute coronary angiography.

Table 2: Probable causes of perioperative cardiac arrest[10]

Probable cause	No. of patients	% (95% CI)
Bleeding	78	35 (29–42)
Cardiac*	98	44 (37–51)
Other†	47	21 (16–27)

Note: CI = confidence interval.
*Includes myocardial infarction, high-degree block and dysrhythmia from any cause (e.g., electrolyte abnormality, medication-related asystole).
†Includes pulmonary embolism (thromboembolism, air, fat or carbon dioxide embolism), anaphylactic drug reaction and hypoxia (e.g., upper airway obstruction, unrecognized tracheal extubation).

Triggers of perioperative myocardial infarction

Surgery, with its associated trauma, anesthesia and analgesia, intubation and extubation, pain, hypothermia, bleeding and anemia, and fasting, is analogous to an extreme stress test. Fig. 1 illustrates how these factors initiate inflammatory, hypercoagulable, stress and hypoxic states, which are associated with perioperative elevations in troponin levels, arterial thrombosis and mortality.[30–35]

Increasing grades of surgical trauma and general anesthesia can initiate inflammatory and hypercoagulable states.[31,36–39] The inflammatory state involves increases in tumour necrosis factor-α, interleukin (IL)-1, IL-6 and C-reactive protein; these factors may have a direct role in initiating plaque fissuring and acute coronary thrombosis.[38,40–42] The hypercoagulable state involves increases in plasminogen activator inhibitor-1, factor VIII and platelet reactivity, as well as decreases in antithrombin III; all of these factors can lead to acute coronary thrombosis.[31,43,44]

The stress state involves increased levels of catecholamines (epinephrine and norepinephrine) and cortisol. Perioperative catecholamine and cortisol levels increase with general anesthesia, anesthetic reversal, extubation, increasing pain scores, increasing grades of surgical trauma, anemia, fasting and hypothermia.[45–50] Increased stress hormone levels result in increases in blood pressure, heart rate, coronary artery sheer stress, relative insulin deficiency and free fatty acid levels.[33,50,51] Coronary artery shear stress may trigger plaque fissuring and acute coronary thrombosis.[50] The other factors increase oxygen demand and can result in perioperative myocardial ischemia, which is strongly associated with perioperative MI.[13,52,53]

Factors that can initiate a hypoxic state include anemia, hypothermia (through shivering), and anesthesia and analgesia (through suppression of breathing).[54–56] Perioperative hypoxia can result in myocardial ischemia in the setting of a hemodynamically significant coronary artery stenosis.

Further research is needed to determine which of these potential triggers are independent risk factors for perioper-

ative MI and to assess other potential triggers. To determine whether suppression of these triggers will prevent perioperative MIs will require large randomized trials.

Preoperative cardiac risk assessment

Although no research has documented its benefits, preoperative cardiac risk assessment may serve an important function. The majority of noncardiac surgeries are elective, and an accurate estimate of risk would facilitate informed patient and physician decision-making. For example, if an elderly woman with multiple risk factors undergoing hip arthroplasty for osteoarthritis were accurately informed that her risk of a major perioperative cardiac event was 10%–12%, she might decide to delay surgery and live with her suboptimal quality of life until her granddaughter graduates in 1 year. Further, accurate risk estimates provide guidance for perioperative management, including the choice of surgical techniques and the location and intensity of postoperative care.

Clinical indices

Two types of clinical indices — generic and Bayesian — exist to estimate the risk of a major perioperative cardiac event in patients undergoing noncardiac surgery. The various published generic indices (Lee, Goldman, Larsen and Gilbert indices) estimate a patient's risk through determi-

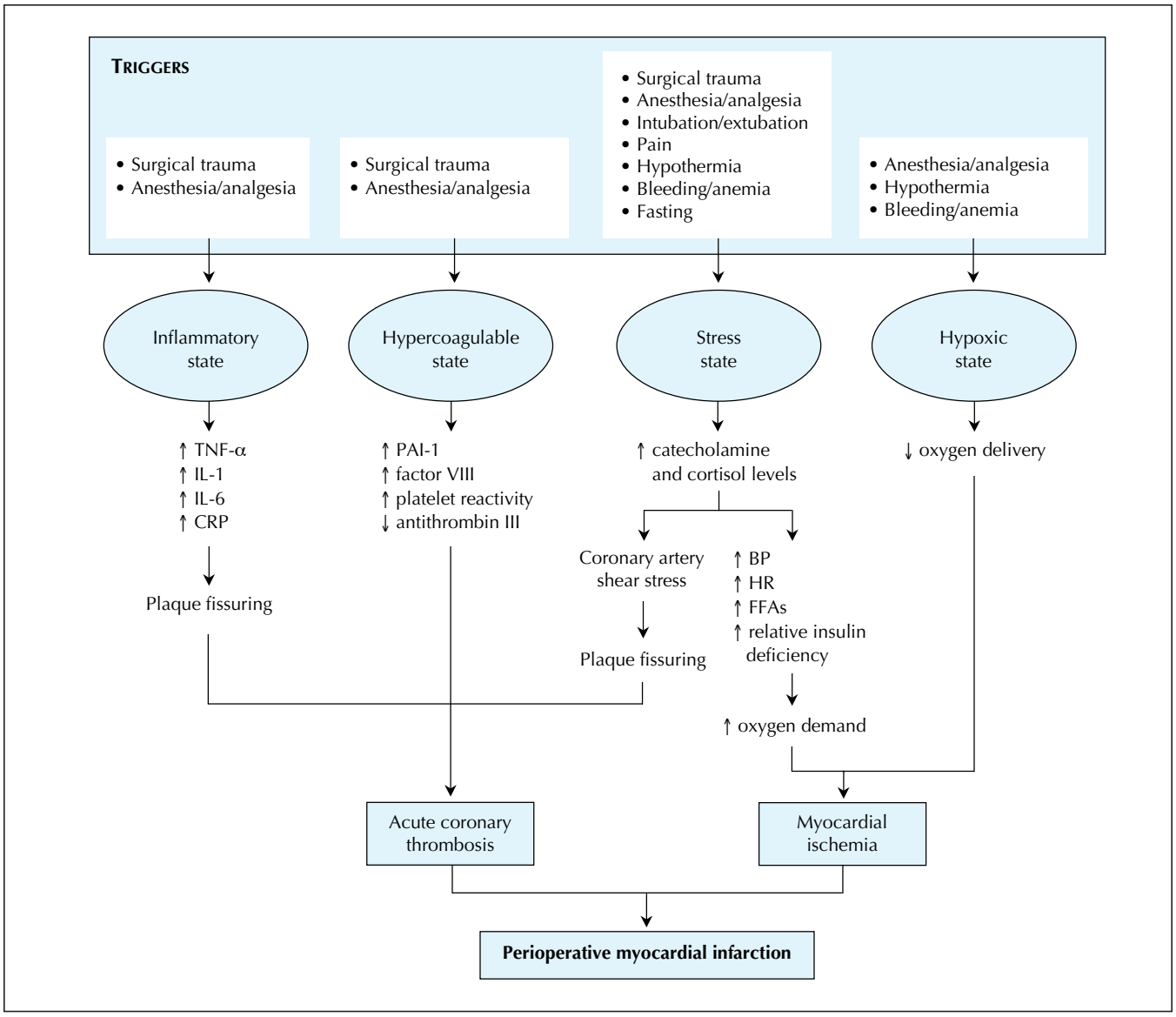

Fig. 1: Potential triggers of states associated with perioperative elevations in troponin levels, arterial thrombosis and fatal myocardial infarction. TNF-α = tumour necrosis factor-α, IL = interleukin, CRP = C-reactive protein, PAI-1 = plasminogen activator inhibitor-1, BP = blood pressure, HR = heart rate, FFAs = free fatty acids.

nation of how many predictors of risk (e.g., history of angina, diabetes, emergent surgery) the patient has.[14,57–59] The published Bayesian risk indices (Kumar and Detsky indices) modify the hospital's average cardiac event rate for a specific surgery (pretest probability) through use of a patient's individual index score (likelihood ratio), which is based on how many predictors of risk (e.g., history of angina, diabetes) the patient has; this results in an estimate of the patient's risk of a perioperative cardiac event (posttest probability).[8,12]

Although several studies have compared the predictive accuracy of the generic and Bayesian risk indices,[8,12,14,59,60] only 2 have used contemporary pretest probabilities based on data from the hospitals studied at that time.[8,12] These 2 studies revealed superior prediction capabilities of the Bayesian risk indices.[8,12] Although these studies fulfill the methodologic criteria of a clinical prediction rule study,[61] only the Detsky index has shown consistent results in a separate setting, although this validation is limited to 1 high-quality single-centre study.[8] However, the current predictive accuracy of the Detsky index is uncertain, because no high-quality studies have established contemporary complication rates for individual surgeries, and it is unknown whether contemporary complication rates at one institution are generalizable to others. Because of the limitations of the available data (e.g., most of the studies occurred at single university hospitals, and most did not focus on composite outcomes with more or less equally important components), determining the optimal risk index to predict major perioperative cardiac events will require a multicentre study that includes several university and nonuniversity hospitals.

Until more definitive research becomes available, clinicians require a practical clinical index to facilitate perioperative cardiac risk estimation. The Lee index is the best validated and most accurate predictive generic risk index, and it is simple to use in clinical practice.[14] It consists of 6 equally weighted cardiovascular risk factors: high-risk surgery (intraperitoneal, intrathoracic or suprainguinal vascular surgery), history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease (stroke or transient ischemic attack), use of insulin therapy for diabetes and a preoperative serum creatinine level of more than 175 μmol/L (> 2.0 mg/dL). Table 3 shows the estimated risk of a major perioperative cardiac event based on the number of risk factors met. Although there are many positive aspects of the Lee index, the study that derived and validated it had limitations (it excluded emergent surgeries and surgical cases with an expected length of stay of less than 2 days during the years 1989–1994).

Table 3: Estimated risk of a major perioperative cardiac event* based on predictors in the Lee index[14]

No. of risk factors†	Risk of major perioperative cardiac event, % (95% CI)
0	0.4 (0.1–0.8)
1	1.0 (0.5–1.4)
2	2.4 (1.3–3.5)
≥ 3	5.4 (2.8–7.9)

*Includes cardiac death, nonfatal myocardial infarction and nonfatal cardiac arrest. Not included in this table are postoperative cardiogenic pulmonary edema and complete heart block, which are included as outcomes in the Lee index.
†Risk factors include high-risk surgery (intraperitoneal, intrathoracic or suprainguinal vascular surgery); history of ischemic heart disease (defined as a history of myocardial infarction, positive exercise test result, current complaint of ischemic chest pain or nitrate use, or electrocardiogram showing pathological Q waves; patients who had undergone prior coronary bypass surgery or angioplasty were included only if they had such findings after their procedure); history of congestive heart failure (defined as a history of heart failure, pulmonary edema or paroxysmal nocturnal dyspnea; an S3 gallop or bilateral rales on physical examination; or chest radiograph showing pulmonary vascular resistance); history of cerebrovascular disease (stroke or transient ischemic attack); use of insulin therapy for diabetes; and preoperative serum creatinine level > 175 μmol/L (> 2.0 mg/dL).

Noninvasive testing

Table 4 presents the results from a recent meta-analysis that evaluated the prognostic accuracy of 6 noninvasive tests for predicting perioperative cardiac death or nonfatal MI in patients undergoing vascular surgery.[62] The results suggested a trend toward superior prognostic accuracy with dobutamine stress echocardiography compared with the other tests, but this trend was statistically significant only in comparison with myocardial perfusion scintigraphy. These results warrant cautious interpretation for the following reasons: the majority of studies included in the meta-analysis used weak methods (e.g., retrospective design, failure to blind individuals interpreting the test results to the clinical predictors of risk, and failure to blind the outcome assessors to the test results); the cumulative event rate for most of the tests was low; there was significant heterogeneity across the study results for

Table 4: Results of meta-analysis evaluating ability of noninvasive cardiac tests to predict risk of perioperative cardiac events in patients undergoing vascular surgery*

Test	No. of studies	No. of patients	No. of events	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Radionuclide ventriculography	8	532	54	50 (32–69)	91 (87–96)
Ambulatory electrocardiography	8	893	52	52 (21–84)	70 (57–83)
Exercise electrocardiography	7	685	25	74 (60–88)	69 (60–78)
Myocardial perfusion scintigraphy	23	3119	207	83 (77–89)	49 (41–57)
Dobutamine stress echocardiography	8	1877	82	85 (74–97)	70 (62–79)
Dipyridamole stress echocardiography	4	850	33	74 (53–94)	86 (80–93)

*This table has been modified, with permission, from the original, which appeared in reference 62 (Kertai MD, Boersma E, Bax JJ, Heijenbrok-Kal MH, Hunink MG, L'Talien GJ, et al. A meta-analysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery. *Heart* 2003;89:1327-34).

individual tests; and test results were analyzed using a single threshold (i.e., results were dichotomized as positive or negative).

The relevance of this last limitation is highlighted in another recent meta-analysis that evaluated semiquantitative dipyridamole myocardial stress perfusion imaging for predicting perioperative cardiac death or nonfatal MI in patients undergoing vascular surgery.[63] This meta-analysis included 9 studies evaluating 1179 patients, of whom 82 experienced cardiac death or nonfatal MI. Rather than considering test results as positive or negative, variation in the likelihood ratios were shown based on the extent of reversibility of myocardial defects (Table 5). In the setting of a diagnostic study, many would not consider variations in likelihood ratios of 0.42 to 2.9 of much relevance. In evaluating prognostic information, however, a patient or physician may value the ability to distinguish between a perioperative risk of a major cardiovascular outcome of 3%, 7% or 18%, so to them the test and its results are relevant (Table 5). Narrowing the confidence intervals for these results, and determining more precisely the number of patients who are likely to have the various proportions of reversible myocardial defects, will require further high-quality research.

The limitations of the studies evaluating the ability of noninvasive cardiac tests to predict perioperative risk leaves considerable uncertainty concerning the role of these popular tests before noncardiac surgery. Until investigators undertake further research, some physicians may want to consider noninvasive cardiac testing in patients who have severe exercise restrictions (e.g., patients with severe claudication) that limit the clinical assessment of symptoms suggestive of coronary artery disease.

When considering which noninvasive cardiac test to order, physicians may want to consider the following: the results of the relevant meta-analyses, and their limitations; the uncertain utility of noninvasive tests in patients undergoing nonvascular, noncardiac surgery; what tests and expertise are available at their hospital; what test a patient can undertake (e.g., patients with severe claudication are probably unable to complete an exercise electrocardiographic stress test); and the likelihood of an important change in risk estimation (e.g., physicians using the Lee index should use a noninvasive test to refine the risk estimate only if the refined risk estimate, based on the potential test results, would be interpreted by the patient or physician as important). To illustrate the last point, if the results of the meta-analysis evaluating semiquantitative dipyridamole myocardial stress perfusion imaging in patients undergoing vascular surgery (Table 5) are applicable to other types of surgery, use of this noninvasive test in patients undergoing nonvascular, noncardiac surgery with no risk factors on the Lee index (i.e., a risk estimate of 0.4% [Table 3]) may result in a refined risk estimate of less than 0.01% or 5%; for patients with 3 risk factors on the Lee index (i.e., a risk estimate of 5.4% [Table 3]), the refined risk estimate may be 2% or 14%.

American College of Cardiology / American Heart Association algorithm for preoperative cardiac risk assessment

Some authors have recommended that physicians use the American College of Cardiology / American Heart Association (ACC/AHA) algorithm to stratify patients undergoing noncardiac surgery according to their perioperative cardiac risk.[64,65] It should be noted that this algorithm was not derived from a prospective study; rather, it was derived from the interpretation of data from various studies and the judgments of the committee members.[66] The few studies that have evaluated the reliability of the ACC/AHA algorithm have limitations: they had few cardiac events; they failed to demonstrate that the algorithm is effective in stratifying cardiac risk across the 3 strata proposed in the algorithm; and they did not compare the predictive accuracy of the ACC/AHA algorithm with the most accurate clinical risk indices (i.e., the Lee and Detsky indices).[67,68] The recommendations in the ACC/AHA algorithm regarding non-

Table 5: Results of meta-analysis showing summary likelihood ratios and estimated post-test probability of perioperative cardiac complications for each scan result of dipyridamole myocardial stress perfusion imaging in patients undergoing vascular surgery*

Extent of reversibility of myocardial defects	Likelihood ratio (95% CI)	Post-test probability† of MI or cardiac death, % (95% CI)	% of scans with this result
No defects	0.42 (0.20–0.88)	3 (1–6)	30
Fixed defects only	0.51 (0.24–1.1)	4 (2–8)	30
Reversibility < 20%	1.3 (0.88–1.9)	9 (6–13)	17
Reversibility 20%–29%	1.6 (1.0–2.6)	11 (7–16)	11
Reversibility 30%–39%	2.9 (1.6–5.1)	18 (11–28)	6
Reversibility 40%–49%	2.9 (1.4–6.2)	18 (10–32)	3
Reversibility ≥ 50%	11 (5.8–20)	45 (30–60)	3

*This table has been modified from the original, which appeared in reference 63 (Etchells E, Meade M, Tomlinson G, Cook D. Semiquantitative dipyridamole myocardial stress perfusion imaging for cardiac risk assessment before noncardiac vascular surgery: a meta-analysis. *J Vasc Surg* 2002;36:534-40). © 2002, with permission from The Society for Vascular Surgery.
†Assumption of pretest probability of 7% based on mean event rate across all studies in the meta-analysis.

invasive testing ignore the issue of patient and physician values. As mentioned earlier, noninvasive testing is relevant only if patients or physicians would value the potential magnitude of changes in predicted risk.

How do clinicians define and communicate perioperative cardiac risk?

A recent survey of 104 general internists performing a high volume of preoperative consultations (mean of 17 per month) provides insights into how physicians communicate and define perioperative cardiac risk.[69] Of the respondents, 96% indicated that they informed patients of their perioperative cardiac risk, but 77% of these respondents indicated that they communicated the risk subjectively (i.e., simply telling patients that they were at low, moderate or high risk). When asked what they meant by low, moderate and high risk, respondents provided 8, 27 and 12 different definitions, respectively. The range of values provided by the respondents for the definitions demonstrated marked variation: from less than 1% to less than 20% for low risk, 1% to 50% for moderate risk, and more than 2% to more than 50% for high risk.

Given the variety of definitions used for low, moderate and high risk, physicians should avoid these terms to prevent misunderstandings. Instead, physicians can tell patients and surgeons the percentage risk of cardiac death, nonfatal MI or nonfatal cardiac arrest or the expected event rate among 100 or 1000 similar patients. Given the uncertainty around the risk estimation data, physicians may also want to present the range of risk consistent with the 95% CI. For example, a 50-year-old man receiving insulin therapy who is scheduled to undergo a bowel resection would have 2 risk factors according to the Lee index (Table 3); a consultant could convey to the patient and surgeon that the patient's risk of cardiac death, nonfatal MI or nonfatal cardiac arrest is 1.5% to 3.5%.

Conclusion

Noncardiac surgery is associated with substantial cardiac mortality, morbidity and consequent cost. Perioperative MIs likely result from triggers that initiate inflammatory, hypercoagulable, hypoxic and stress states. Because the majority of noncardiac surgeries are elective, accurate estimation of risk of perioperative cardiac events is important to allow informed patient and physician decision-making. The Lee index is a practical clinical risk index that physicians can use to facilitate risk estimation. There is significant uncertainty regarding the predictive accuracy of preoperative noninvasive cardiac tests and the ACC/AHA algorithm for cardiac risk assessment. Physicians informing a patient or surgeon about the patient's risk of a major perioperative cardiac event should provide specific risk estimates and avoid assumptions associated with subjective classifications of risk.

This article has been peer reviewed.

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Competing interests: None declared.

Contributors: P.J. Devereaux was responsible for the conception of the manuscript and analysis of the data and wrote the first draft. He and Lee Goldman were responsible for data acquisition. All of the authors contributed to the manuscript's design and interpretation of the data, provided critical revisions to the manuscript and approved the final version.

Acknowledgements: P.J. Devereaux is supported by a Senior Research Fellowship Award from the Canadian Institutes of Health Research. Deborah Cook is a Chair of the Canadian Institutes for Health Research.

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Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review

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Abstract

THIS IS THE SECOND OF 2 ARTICLES EVALUATING cardiac events in patients undergoing noncardiac surgery. Unrecognized myocardial infarctions (MIs) are common, and up to 50% of perioperative MIs may go unrecognized if physicians rely only on clinical signs or symptoms. In this article, we summarize the evidence regarding monitoring strategies for perioperative MI in patients undergoing noncardiac surgery. Perioperative troponin measurements and 12-lead electrocardiograms can detect clinically silent MIs and provide independent prognostic information. Currently, there are no standard diagnostic criteria for perioperative MIs in patients undergoing noncardiac surgery. We propose diagnostic criteria that reflect the unique features of perioperative MIs. Finally, we review the evidence for perioperative prophylactic cardiac interventions. There is encouraging evidence that some perioperative interventions (e.g., β-blockers, α_2-adrenergic agonists, statins) may prevent major cardiac ischemic events, but firm conclusions await the results of large definitive trials. The best evidence does not support a management strategy of preoperative coronary revascularization before noncardiac surgery.

CMAJ 2005;173(7):779-88

This is the second of 2 articles in which we evaluate cardiac events in patients undergoing noncardiac surgery. In the first article, we established that patients undergoing noncardiac surgery frequently experience major perioperative cardiac events (i.e., cardiac death, nonfatal myocardial infarction [MI] and nonfatal cardiac arrest).[1] We discussed the still unresolved pathophysiology of these events and suggested strategies for preoperative cardiac risk assessment and communication of risk. In this article, we summarize the evidence regarding monitoring strategies for perioperative MI, propose diagnostic criteria for perioperative MI and review the evidence for perioperative prophylactic cardiac interventions.

The breadth of the topics covered in this article prohibited a fully systematic approach to this review. Although this is a narrative review, we did conduct thorough literature searches in each area and contacted the authors of relevant articles when necessary. We sought relevant systematic reviews and have highlighted their findings in our discussion.

The difficulty in detecting perioperative myocardial infarctions

Unrecognized MIs are not restricted to the perioperative setting.[2] Eight large cohort studies (samples over 1000), which were not confined to patients undergoing surgery (e.g., the Framingham Study), evaluated the frequency of unrecognized MIs among more than 65 000 people based on the new appearance of diagnostic Q waves (typically ≥ 30 ms in 2 or more anatomically adjacent leads).[3–10] In these studies, 3237 MIs occurred, of which 945 (29%; 95% confidence interval [CI] 28%–31%) were not detected at the time of the event. These MIs were not benign: patients experiencing an unrecognized MI have a prognosis similar to that of patients experiencing a recognized MI.[11]

To estimate the frequency of perioperative clinically unrecognized MI, we evaluated all prospective cohort studies of patients undergoing noncardiac surgery that fulfilled the following criteria: sample greater than 300 patients, surgery not restricted to a specific type (e.g., vascular surgery), at least 1 measurement of a cardiac enzyme or biomarker after surgery, and an accounting of the patients experiencing a perioperative MI who had no clinical signs or symptoms suggestive of an MI (Table 1).[12–14] The pooled results from the 3 eligible studies suggest that only 14% (95% CI 3%–25%) of patients experiencing a perioperative MI will have chest pain and only 53% (95% CI 38%–68%) will have a clinical sign or symptom that may trigger a physician to consider an MI.

Although the number of events is small, the large proportion of clinically unrecognized MIs is plausible. First, the majority of perioperative MIs occur during the first 3 days after surgery,[14,15] a period when most patients receive analgesics (e.g., narcotics), which can blunt cardiac pain perception. Second, a small but high-risk group of surgical patients will require intubation and sedation during the

DOI:10.1503/cmaj.050316

highest risk period, which limits their ability to communicate symptoms. Third, surgical patients experiencing potential signs (e.g., hypotension, tachycardia) or symptoms (e.g., shortness of breath, nausea) of MI have a host of more common potential explanations (e.g., atelectasis, pneumonia, hypovolemia, bleeding, medication side effect), and physicians may therefore not consider MI.

Diagnosing perioperative MIs in patients undergoing noncardiac surgery

Currently, there are no standard diagnostic criteria for perioperative MI in patients undergoing noncardiac surgery. Optimal diagnostic criteria must consider the unique features of perioperative MIs, in particular that a large proportion are clinically silent. We propose diagnostic criteria for perioperative MIs (Box 1) that we have adapted from a recent consensus document of the joint European Society of Cardiology / American College of Cardiology (ESC/ACC) committee that redefined nonperioperative MI[16] (Box 2).

The first of our criteria requires a typical rise in troponin or a typical fall of an elevated troponin level detected at its peak after surgery in a patient without a documented alternative explanation for an elevated troponin level (e.g., pulmonary embolism) or — only if troponin measurement is unavailable — a rapid rise and fall of CK-MB. We encourage physicians to use troponin measurement, because perioperative CK-MB measurements are prone to false-positive and false-negative values. Surgical trauma can result in the release of CK-MB from skeletal muscle and a false-positive CK-MB value for MI.[17–19] A substantial proportion of perioperative MIs occur in the first 2 days after surgery, when serum CK values are high secondary to surgical trauma. These high CK values can result in a low, and thus false-negative, ratio of CK-MB to total CK.[19,20] Given the limitations of CK-MB measurement in the perioperative setting, physicians should only use CK-MB if troponin measurement is unavailable at their centre.

As troponin values rise, their variability, as measured by the coefficient of variation, decreases. The ESC/ACC guidelines define an increased troponin level as "a measurement exceeding the 99th percentile of a reference control group." At the same time, however, they specify that the coefficient of variation at the 99th percentile should be 10% or less. Unfortunately, no available troponin assay meets the 10% coefficient of variation criterion at the 99th percentile — higher levels (above the 99th percentile) are required to meet this criterion.[21,22] In keeping with previous suggestions,[21,23] until the assays are improved to meet the ESC/ACC recommendation, we define an increased troponin level as the lowest value that has a coefficient of variation equal to 10% (Appendix 1).[21]

New Q-wave changes (≥ 30 ms) present in any 2 contiguous leads fulfill the definition of the development of

Table 1: Incidence of myocardial infarction (MI) and presence of signs or symptoms among patients undergoing noncardiac surgery

Study	No. of patients	Incidence of MI; no. (%) of patients			Study definition of MI
		Total	With chest pain	With any sign or symptom	
Mangano et al[12]	474	12 (3)	1 (8)	8 (67)	Elevated CK-MB value and 1 of the following: • new Q-wave changes • persistent ST-segment and T-wave changes • autopsy evidence
Ashton et al[13]	512	8 (2)	2 (25)	5 (62)	2 of the following: • new Q-wave changes • elevated CK-MB value • positive pyrophosphate scan
Badner et al[14]	323	18 (6)	3 (17)	7 (39)	Elevated CK level and 2 of the following: • elevated CK-MB/CK ratio • new Q-wave changes • elevated troponin level • positive pyrophosphate scan
Total (pooled result)*	1 309	38 (3)	6 (14)	20 (53)	–

Note: CK-MB = creatine kinase MB isoenzyme.
*The results were pooled with the use of a fixed-effects model. The pooled results did not show significant heterogeneity (MI with chest pain, $p = 0.57$ for heterogeneity; MI with any sign or symptom, $p = 0.24$ for heterogeneity).

pathological Q waves. We define electrocardiogram (ECG) changes indicative of ischemia as ST-segment elevation (≥ 2 mm in leads V_1, V_2 or V_3 and ≥ 1 mm in the other leads) or ST-segment depression (≥ 1 mm) in at least 2 contiguous leads, or symmetric inversion of T waves (≥ 1 mm) in at least 2 contiguous leads. Coronary artery intervention includes percutaneous coronary intervention or coronary artery bypass grafting (CABG).

Because many patients will not experience symptoms, clinicians may still miss the correct diagnosis in patients with an elevated troponin level after surgery who have experienced an MI. Some of these patients will have an uninterpretable ECG (e.g., paced, left bundle-branch block, chronic ST-segment changes); some will have an infarct in a territory (e.g., posterior) where the conventional ECG lacks sensitivity;[24] and some will have significant ST-segment changes that resolve by the time the ECG is repeated the following day. To avoid missing the diagnosis of MI, we have added to the first criterion the finding of a new or presumed new wall-motion abnormality on echocardiography or a new or presumed new fixed cardiac defect on radionuclide imaging.

When physicians encounter a patient who has an elevated troponin level after surgery without either ischemic symptoms or a diagnostic ECG, the differential diagnosis includes MI and noncardiac causes (e.g., pulmonary embolism). Because MI is a probable cause of an elevated troponin level in this situation, physicians should consider obtaining an echocardiogram or radionuclide imaging.

Although physiologic studies suggest that an imaging study may be insensitive (an injury involving > 20% of myocardial wall thickness may be required to detect a wall-motion abnormality on echocardiography, and an injury of myocardial tissue > 10 g may be required to detect a radionuclide perfusion defect),[16] at least 1 clinical study has suggested that echocardiography has a high sensitivity: 108 patients had troponin levels measured before surgery and every 6 hours for the first 36 hours after surgery, as well as echocardiography before surgery and 3–5 days after surgery.[19] Echocardiography demonstrated a new wall-motion abnormality in all but 1 of the 9 patients who experienced an MI based on the diagnostic criteria of an elevated troponin level and significant ECG changes. This study also suggested excellent specificity for echocardiography. None of the remaining 99 patients had a new wall-motion abnormality. These results suggest that a wall-motion abnormality detected on an imaging study in the absence of a prior study suggests the diagnosis of perioperative MI, and a demonstrably new abnormality increases the likelihood further and thus supports our definition of a perioperative MI.

Further research is needed to evaluate the diagnostic criteria we propose.

Box 1: Proposed diagnostic criteria for perioperative myocardial infarction in patients undergoing noncardiac surgery

The diagnosis of perioperative MI requires any 1 of the following criterion:

- Criterion 1: A typical rise in the troponin level or a typical fall of an elevated troponin level detected at its peak after surgery in a patient without a documented alternative explanation for an elevated troponin level (e.g., pulmonary embolism); or a rapid rise and fall of CK-MB only if troponin measurement is unavailable.* This criterion requires that 1 of the following criteria must also exist:
  - Ischemic signs or symptoms (e.g., chest, arm or jaw discomfort, shortness of breath, pulmonary edema)
  - Development of pathological Q waves on an ECG
  - ECG changes indicative of ischemia
  - Coronary artery intervention
  - New or presumed new cardiac wall-motion abnormality on echocardiography, or new or presumed new fixed defect on radionuclide imaging
- Criterion 2: Pathological findings of an acute or healing MI
- Criterion 3: Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event

Note: CK-MB = creatine kinase MB isoenzyme, ECG = electrocardiogram
*Because CK-MB is both less sensitive and less specific in the perioperative setting compared with other settings and compared with troponin levels, it should be used for diagnostic purposes only when troponin levels are not obtainable.

Prognostic factors

Cardiac biomarkers

Perioperative measurement of cardiac enzymes or biomarkers not only can help to identify otherwise silent MI but may also contribute important prognostic information.

Box 2: Diagnostic criteria for nonperioperative myocardial infarction of the European Society of Cardiology / American College of Cardiology[16]

A. The diagnosis of acute, evolving or recent MI requires either of the following criterion:
   - Criterion 1: A typical rise and gradual fall (troponin) or a more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least 1 of the following:
     - Ischemic symptoms
     - Development of pathological Q waves on an ECG
     - ECG changes indicative of ischemia
     - Coronary artery intervention
   - Criterion 2: Pathological findings of an acute MI

B. The diagnosis of established MI requires either of the following criterion:
   - Criterion 1: Development of new pathological Q waves on serial ECGs
   - Criterion 2: Pathological findings of a healed or healing MI

Note: CK-MB = creatine kinase MB isoenzyme, ECG = electrocardiogram.

To assess the prognostic value of perioperative troponin and CK-MB measurements, we evaluated all noncardiac surgery studies that fulfilled the following criteria: at least 1 troponin or CK-MB measurement after surgery; reporting short-term (< 30 days after surgery) cardiac or total mortality, or intermediate (≤ 1 year after surgery) or long-term (> 1 year after surgery) mortality or major cardiac events; and assessment of the prognostic value of perioperative troponin and CK-MB measurements through multivariable analysis.

The 6 eligible studies,[25–30] which included a total of 2175 patients and 249 events (Table 2), evaluated CK-MB,[26,27,29,30] troponin T,[28–30] troponin I[25,27] or both troponin T and I.[26] In all 6 studies, troponin measurement proved to be a statistically significant independent predictor of intermediate and long-term outcomes (i.e., mortality and major cardiac events). This finding persisted even in the 2 studies that excluded patients who experienced a perioperative MI.[29,30] Two studies evaluated and demonstrated a dose–response relation — the higher the peak troponin value, the higher the 1-year mortality.[25,28] In contrast, 3 of the 4 studies that assessed CK-MB failed to show an association between an elevated CK-MB value and intermediate or long-term outcomes.[26,27,29,30]

The authors of one of the studies[27] published a second paper evaluating the same patients but excluding deaths in the first month after surgery and extending the follow-up period from 1 to 2 years.[31] In this second paper, an elevated perioperative troponin value did not significantly predict the few deaths between months 1 to 24 after surgery (odds ratio 2.7, 95% CI 0.7–10),[31] which suggests that an elevated perioperative troponin value more strongly predicts mortality in the first 12 months after surgery.

We did not evaluate the short-term predictive power of troponin or CK-MB values for diagnosing MI because they are now part of the diagnostic criteria. Troponin was not, however, part of the diagnostic criteria when one of the earlier studies showed its prognostic benefit.[29]

Electrocardiography

We evaluated studies using the same eligibility criteria for troponin and CK-MB measurement, made specific for electrocardiography, to assess the prognostic value of ECG evidence of perioperative ischemia. Because of the consistency with which an elevated perioperative troponin value proved to be an independent predictor of major outcomes after surgery, we also required that studies include troponin in their multivariable analysis. Three studies met our criteria (Table 3).[26,27,30]

Filipovic and colleagues[27] did not demonstrate a statistically significant association between 3-lead ECG evidence of perioperative ischemia and mortality after surgery, probably because ECG monitoring with fewer leads has lower sensitivity than monitoring with 12 leads.[32] The other 2 studies, one of which excluded patients who experienced an MI within 30 days after surgery,[30] demonstrated a statistically significant association, independent of perioperative troponin values, between perioperative ischemia on a 12-lead ECG and long-term mortality.[26,30]

Table 2: Prognostic value of perioperative troponin and CK-MB measurements in patients undergoing noncardiac surgery

Study	No. of patients	Variables adjusted for in analysis	Primary outcome	Association of elevated troponin level to outcome*	Association of elevated CK-MB level to outcome*
Kim et al[25]	229	Age, CHF, TAA surgery, perioperative β-blocker therapy	Total mortality at 6 mo (n = 18)	OR 5.9 (1.6–22)	NA
Landesberg et al[26]	447	Age, MI, renal failure, type of vascular surgery	Total mortality at 32 mo (n = 82)	OR 2.15 (1.4–3.4)	OR 2.71 (1.5–5)
Filipovic et al[27]	173	Age, renal failure, CHF, hypertension, diabetes, anesthetic used, heart rate variability, ECG evidence of ischemia, elevated CK-MB value	Mortality at 12 mo (n = 28)	OR 10.2 (2.8–37)	OR 6.9 (0.8–56)
Oscarsson et al[28]	161	BMI, ASA score, perioperative β-blocker and diuretic therapy, perioperative tachycardia	Mortality at 12 mo (n = 22)	HR 15 (4–60)	NA
Studies that excluded patients who had an MI before hospital discharge or within 30 days after surgery					
Lopez-Jimenez et al[29]	772	Age, sex, history of cardiac disease, diabetes, smoking, type of surgery, CK-MB level	Composite outcome at 6 mo (n = 19) of cardiac death (n = 14), nonfatal MI (n = 3) and unstable angina (n = 2)	OR 4.6 ($p < 0.05$)	RR 1.2 (0.5–3.2)
Kertai et al[30]	393	Clinical risk score, ECG evidence of ischemia	Mortality at 48 mo (n = 80)	HR 1.9 (1.1–3.1)	HR 1.6 (0.7–3.4)

Note: ASA = American Society of Anesthesiologists, BMI = body mass index, CHF = congestive heart failure, CK-MB = creatine kinase MB isoenzyme, ECG = electrocardiogram, HR = hazard ratio, MI = myocardial infarction, NA = not assessed, OR = odds ratio, RR = relative risk, TAA = thoracoabdominal aneurysm.
*Numbers in parentheses are 95% confidence intervals, unless stated otherwise.

The ECG, like biomarkers, is part of the diagnostic criteria for MI, but it also is often the sole criterion for myocardial ischemia in the absence of infarction. Even a single postoperative ECG demonstrating ischemia in the recovery room is predictive of a major cardiac complication later during the hospital stay.[33]

Use of diagnostic and prognostic data

If clinicians wish to avoid missing a significant proportion of perioperative MIs and identify patients at high risk of intermediate or long-term major cardiac events, they should consider monitoring troponin levels and ECGs daily during the first 3 days after surgery. Choosing whom to monitor presents a challenge. The risk of missing an asymptomatic infarct increases with increasing postoperative risk of major cardiac events. A reasonable threshold would be to obtain troponin levels and ECGs for patients with established atherosclerotic disease (i.e., coronary artery disease and peripheral vascular disease) who are undergoing surgery requiring hospital admission. An alternative threshold would be to monitor patients who have other risk factors for perioperative cardiac events (e.g., diabetes mellitus, renal insufficiency, or a history of heart failure or cerebrovascular disease).[34] Definitive recommendations await the results of further studies.

Interventions to prevent perioperative cardiac events

The multiple triggers and states (i.e., inflammatory, hypercoagulable, hypoxic and stress states) that may result in an MI in patients undergoing noncardiac surgery, which we discussed in the first article in this series,[1] open the possibility for a variety of potential prophylactic interventions. We will review the evidence for perioperative prophylactic use of β-blockers, calcium-channel blockers, α_2-adrenergic agonists, coronary revascularization, 3-hydroxy-3-methylglutaryl (HMG)–coenzyme A reductase inhibitors (i.e., statins) and acetylsalicylic acid (ASA) in patients undergoing noncardiac surgery (Table 4).[35–46]

Table 3: Prognostic value of ECG evidence of perioperative ischemia in patients undergoing noncardiac surgery

Study	ECG monitoring method	Association of ECG evidence with death after surgery*
Landesberg et al[26]	Continuous 12-lead ECG monitoring for 48–72 h after surgery	OR 2.20 ($p = 0.03$)
Filipovic et al[27]	Continuous 3-lead ECG monitoring for 48 h after surgery	OR 2.0 (0.3–12)
Kertai et al[30]	12-lead ECG on postoperative days 2, 3 and 7	HR 1.8 (1.0–3.1)

Note: ECG = electrocardiogram, OR = odds ratio, HR = hazard ratio.
*Numbers in parentheses are 95% confidence intervals, unless stated otherwise.

In considering the evidence for these interventions, readers should keep in mind 2 points. First, it is only realistic to expect moderate treatment effects (i.e., relative risk reductions of 20%–35%). Even when an intervention effectively blocks one or more pathogenic mechanisms, there will remain a number of unaffected pathogenic mechanisms; thus, large treatment effects are unlikely. Second, even assuming a high rate of perioperative cardiovascular events of 10%, trials need at least 350, and ideally 650, events to convincingly demonstrate a 25% relative risk reduction.[47]

β-Blockers

β-Blockers moderate the effects of increased catecholamine levels and therefore may prevent perioperative cardiac events.[48,49] Many authors and 2 guideline committees have recommended that patients with coronary artery disease or risk factors for coronary artery disease undergoing noncardiac surgery receive perioperative β-blocker therapy.[50–53] Important developments have occurred since these recommendations, and subsequent reviews,[54,55] were published.

Proponents of β-blocker prophylaxis have based their recommendations primarily on the results of 2 randomized controlled trials (RCTs) (Table 4).[35,37] These 2 trials have limitations. Poldermans and colleagues[35] stopped their unblinded trial after an interim analysis based on 20 outcomes, and they demonstrated an implausible relative risk reduction of 90% in the composite outcome of cardiac death and nonfatal MI. In a second trial, by Mangano and colleagues,[37] the results were no longer statistically significant when patients who died while receiving the study drug were included in the intention-to-treat analysis.[56]

In contrast, the results from 2 recent trials did not demonstrated any benefit from β-blocker therapy.[36,38] Although these 2 trials had a greater number of cardiac events and enrolled more patients than the 2 previous trials, they were nonetheless underpowered to determine the impact of β-blocker therapy on major cardiovascular outcomes. However, their findings indicate that the results from the earlier trials were overly optimistic. Ongoing trials[54] will help to resolve the inconsistency in the results of the current perioperative β-blocker trials.

Calcium-channel blockers and α_2-adrenergic agonists

Calcium-channel blockers dilate coronary arteries;[57] α_2-adrenergic agonists suppress the release of catecholamines.[42,58] These effects may prevent perioperative cardiac events. In Table 4 we present the results from 2 recent sys-

Table 4: Results of studies evaluating the effectiveness of perioperative prophylactic cardiac interventions

Intervention; study	Study design	Outcome	Group; no. of events / no. of patients		RR* (95% CI)	Comments
			Intervention	Control		
β-blocker therapy						
Short-term follow-up (30 d after surgery)						
Poldermans et al[35]	RCT	Cardiac death or nonfatal MI	2/59	18/53	0.10 (0.02–0.41)	Unblinded trial; stopped early after first interim analysis
Yang et al[36]	RCT	Cardiac death or nonfatal MI	19/246	22/250	0.88 (0.49–1.58)	Blinded trial; not stopped after interim analysis
Long-term follow-up						
Mangano et al[37]	RCT	Total mortality at 2 yr	13/99	23/101	0.58 (0.31–1.07)	Authors reported statistically significant result but excluded patients who died while taking study drug. Result was not significant after we included all deaths in intention-to-treat analysis
Juul et al[38]	RCT	Total mortality, MI, UA or CHF at 18 mo	99/462	93/459	1.06 (0.82–1.36)	Authors included all events. Total mortality was the same in both groups (16%)
Calcium-channel blocker therapy						
Short-term follow-up						
Wijeysundera et al[39]	MA of RCTs	Total mortality	5/358	12/334	0.40 (0.14–1.16)	MA included 11 RCTs, of which 8 evaluated diltiazem, 2 evaluated verapamil and 2 evaluated dihydropyridines
		MI	0/252	5/234	0.25 (0.05–1.18)	
α_2-Adrenergic agonist therapy						
Short-term follow-up						
Wijeysundera et al[40]	MA of RCTs	Total mortality (vascular surgery)	13/877	26/771	0.47 (0.25–0.90)	Results were reported separately for patients who underwent vascular surgery and those who underwent nonvascular, noncardiac surgery. MA included 12 RCTs of noncardiac surgery, of which 8 included vascular surgery
		MI (vascular surgery)	45/859	65/757	0.66 (0.46–0.94)	
		Total mortality (nonvascular, noncardiac surgery)	16/512	15/501	1.09 (0.52–2.09)	
		MI (nonvascular, noncardiac surgery)	36/502	26/491	1.35 (0.83–2.21)	
Oliver et al[41]	RCT	Total mortality	91/946	100/941	0.89 (0.67–1.18)	This trial was included in the MA by Wijeysundera et al.[40] We included it here because it accounts for 56 of the 70 deaths and 157 of the 172 MIs in the MA
		Total mortality or nonfatal MI	22/946	34/941	0.61 (0.35–1.03)	
Long-term follow-up (2 yr)						
Wallace et al[42]	RCT	Total mortality	19/125	19/65	0.43 (0.21–0.89)	The trial evaluated the effect of 4 d of perioperative clonidine therapy
Preoperative coronary artery revascularization						
Long-term follow-up [2.7 yr])						
McFalls et al[43]	RCT	Total mortality	70/258	67/252	0.98 (0.70–1.37)	Of the patients assigned to coronary artery revascularization, 38% underwent CABG, 55% underwent PCI, and 7% did not receive coronary revascularization
Statin therapy						
6-mo follow-up after surgery						
Durazzo et al[44]	RCT	Cardiac death, nonfatal MI, ischemic stroke or UA	4/50	13/50	0.31 (0.11–0.88)	None of the individual outcomes demonstrated statistically significant results
Antiplatelet therapy						
Short-term follow-up						
Robless et al[45]	MA of RCTs	Vascular death, nonfatal MI, or nonfatal stroke	76/893	92/872	OR 0.76 (0.54–1.05)	Patients underwent infra-inguinal bypass surgery. MA included 10 RCTs, 6 of which evaluated effects of ASA
PEP investigators[46]	RCT	Death from ischemic heart disease or nonfatal MI	105/6679	79/6677	HR 1.33 (1.00–1.78)	ASA therapy was evaluated in patients undergoing surgical repair of hip fracture

Note: ASA = acetylsalicylic acid, CABG = coronary artery bypass grafting, CHF = congestive heart failure, CI = confidence interval, MA = meta-analysis, MI = myocardial infarction, PCI = percutaneous coronary intervention, PEP trial = Pulmonary Embolism Prevention trial, RCT = randomized controlled trial, UA = unstable angina.
*Relative risks are reported, unless stated otherwise.

tematic reviews and meta-analyses that evaluated the effects of perioperative calcium-channel blockers and α_2-adrenergic agonists in patients undergoing noncardiac surgery.[39,40] The results of the meta-analysis of calcium-channel blockers were not statistically significant; however, there were too few events from which to draw conclusions.[39] More research is needed to determine the effect of perioperative calcium-channel blocker therapy.

A meta-analysis of α_2-adrenergic agonists demonstrated a statistically significant reduction in both mortality and incidence of MI with α_2-adrenergic agonist therapy among the patients who underwent vascular surgery.[40] The investigators, however, found no effect on mortality and MI incidence among the patients who underwent nonvascular, noncardiac surgery.

Although there were 12 RCTs included in the meta-analysis of α_2-adrenergic agonists, a single study accounted for most of the events.[41] In this trial, 2854 patients were included in the randomization, but the published report excluded 957 of them at high risk of coronary artery disease because an interim analysis showed that they had a lower than expected event rate. The investigators then focused on the remaining 1897 patients with established coronary artery disease, 52% of whom underwent thoracic, abdominal or orthopedic surgery. Mivazerol therapy resulted in a statistically significant reduction in the composite outcome of total mortality and nonfatal MI only in the subgroup of patients who underwent vascular surgery.

An RCT completed since the publication of the meta-analysis of α_2-adrenergic agonists evaluated the long-term effects of perioperative clonidine in patients undergoing noncardiac surgery.[42] Clonidine was found to have no effect on the incidence of MIs (4 events) during the original hospital admission, but the trial results suggested a mortality benefit at 2 years after surgery.

Although the results of the meta-analysis of α_2-adrenergic agonists are encouraging, they warrant a cautious interpretation. The most recent clonidine trial is also encouraging, but given there were few events, unrealistic relative risk reductions and results of borderline statistical significance, the results may represent a chance finding. Confirmation of these results is required in a large, well-designed trial.

Coronary revascularization

The use of coronary revascularization before noncardiac surgery is based on the assumption that perioperative MIs occur primarily in coronary arteries with hemodynamically significant stenoses and that revascularization may therefore prevent infarction. As we discussed in the first article in this series,[1] this assumption may be erroneous.

Although some observational studies suggested a benefit of coronary revascularization before noncardiac surgery,[59,60] a recent RCT has revealed that coronary revascularization performed in patients with chronic stable angina had no effect on outcomes after elective vascular surgery for abdominal aortic aneurysm or severe leg claudication (Table 4).[43]

This trial excluded patients with unstable angina, some of whom may benefit from coronary revascularization before noncardiac surgery. Small observational studies suggest that patients should have their noncardiac surgery delayed for at least 1 month following CABG and 6 weeks following angioplasty with a bare-metal stent.[61–64] The optimal period to delay noncardiac surgery following use of a cardiac drug-eluting stent is unknown.[65] However, it is probably substantially longer than 6 weeks, because drug-eluting stents delay endothelialization compared with bare-metal stents, and their use likely prolongs the period of risk for late stent-related thrombosis.[66]

Statins

Statins have plaque-stabilizing properties and therefore may prevent perioperative cardiac events.[67] Three observational studies suggest that statin therapy reduces the risk of perioperative death in patients undergoing noncardiac surgery.[68–70] The 1 RCT that evaluated the effects of perioperative statin therapy in patients undergoing vascular surgery demonstrated a statistically significant benefit, but there were few events (Table 4).[44]

Given the limited current evidence (i.e., 17 events in the only RCT, implausibly large relative risk reduction, borderline statistically significant result for a broad composite outcome), the effectiveness of perioperative statin therapy remains uncertain. The evidence does, however, provide the impetus for an adequately powered RCT to determine whether perioperative statin therapy prevents major perioperative cardiac events.

Acetylsalicylic acid

ASA suppresses platelet aggregation and therefore may prevent perioperative cardiac events.[71] A systematic review of antiplatelet therapy versus placebo in patients undergoing infra-inguinal bypass surgery offers encouraging evidence that antiplatelet therapy prevents vascular events (Table 4).[45] In contrast, the Pulmonary Embolism Prevention (PEP) trial suggested an increased risk of cardiac ischemic outcomes with ASA therapy in patients undergoing surgery for a hip fracture.[46] Although the PEP trial suggests that ASA therapy can prevent pulmonary emboli (hazard ratio 0.43, 95% CI 0.18–0.60), this result has failed to affect clinical practice, because only 25% of patients in the placebo group were receiving a low-molecular-weight heparin. The American College of Chest Physicians' evidence-based guidelines recommend low-molecular-weight heparin, not ASA, for prophylaxis against venous thromboembolism in patients undergoing hip fracture surgery.[72]

ASA therapy in patients undergoing noncardiac surgery is associated with an increased risk of bleeding. In the PEP trial, there were 197 postoperative bleeding episodes requiring a transfusion among the 6679 patients randomly assigned to receive ASA, compared with 157 postoperative bleeding episodes requiring a transfusion among the 6677 patients in the placebo group (relative risk increase 24%, 95% CI 1%–53%).[46] In the antiplatelet trialists' overview of RCTs of antiplatelet therapy (ASA was the intervention in a third of these trials) in surgical patients, there were 28 nonfatal bleeding episodes requiring a transfusion among the 3798 patients receiving antiplatelet therapy, compared with 15 nonfatal bleeding episodes requiring a transfusion among the 3808 control subjects ($p = 0.04$).[73]

Given the evidence that ASA prevents cardiovascular events in the nonperioperative setting,[74] the conflicting RCT evidence surrounding the impact of ASA on perioperative cardiovascular events, and the likelihood of increased risk of bleeding associated with perioperative ASA therapy, determining the balance of benefits and risk of ASA prophylaxis in patients undergoing noncardiac surgery will require a large definitive RCT. Until then, physicians must weigh the increased risk of bleeding against yet unproven cardiovascular benefits.

Acute and long-term management of major perioperative ischemic cardiac events

Unfortunately, there are no RCTs informing us how to manage perioperative ischemic cardiac events acutely or in the long term. Identifying and treating correctable causes (e.g., anemia and hypoxia) seems advisable. Although thrombolytic, antiplatelet and anticoagulant therapies are beneficial in the management of acute nonoperative MIs,[75] these therapies in the acute perioperative setting are likely to have a different risk–benefit ratio. Drugs that are efficacious in the long-term management of nonoperative MI (e.g., ASA, ACE inhibitors, β-blockers and statins) may not have the same impact in the management of perioperative MI.[76] Only RCTs specific to the perioperative period will leave us confident of generalizing results from other settings.

Conclusions

Unrecognized MIs are common, and about half of all perioperative MIs may go unrecognized if physicians rely solely on clinical signs or symptoms. Perioperative troponin measurement and 12-lead ECGs can facilitate detection of clinically silent MIs as well as provide long-term prognostic information. Although several perioperative prophylactic interventions (α_2-adrenergic agonist, β-blocker, statin, ASA and calcium-channel blocker therapies) may prevent major perioperative cardiac events, definitively establishing or refuting their benefit will require large, well-designed and conducted trials. Current evidence does not support a management strategy of preoperative coronary revascularization before noncardiac surgery.

This article has been peer reviewed.

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Competing interests: None declared.

Contributors: P.J. Devereaux was responsible for the conception of the manuscript, the acquisition and analysis of the data and the writing the first draft. All of the authors contributed significantly to the manuscript's design and interpretation of the data, provided critical revisions to the manuscript and approved the final version.

Acknowledgements: P.J. Devereaux is supported by a Senior Research Fellowship Award from the Canadian Institutes of Health Research (CIHR). Salim Yusuf holds an endowed Chair of the Heart and Stroke Foundation of Ontario and is a Senior Scientist of CIHR.

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Appendix 1: Recommended troponin threshold* for myocardial infarction based on concentrations corresponding to a coefficient of variation (CV) equal to 10%†

Manufacturer; assay	Troponin	Concentration corresponding to 10% CV imprecision, µg/L
Abbott Diagnostics		
AxSYM	I	1.22
Bayer Diagnostics		
ACS:180	I	0.37
Centaur	I	0.33
Immuno 1	I	0.34
Beckman Coulter		
Access, second generation	I	0.06
Access 2, second generation	I	0.09
BioMerieux		
Vidas	I	0.36
Byk-Sangtec Diagnostica		
Liaison	I	0.065
Dade Behring		
Dimension RxL, second generation	I	0.26
Opus, second generation	I	0.90
Stratus CS	I	0.10
Diagnostic Products Corporation		
Immulite One	I	0.32
Ortho-Clinical Diagnostics		
Vitros ECi	I	0.44
Roche Diagnostics		
E 170	T	0.04
Elecsys 1010, third generation	T	0.04
Tosoh Corporation		
AIA-21, second generation	I	0.09

*If troponin levels cannot be obtained, no creatine kinase MB isoenzyme (CK-MB) threshold is of equivalent diagnostic accuracy. A threshold that physicians may want to use, if troponin measurement is unavailable, is a CK-MB value at the 99th percentile of a reference control group.[16]
†This appendix has been modified, with permission, from Table 3 in reference 21 (Panteghini M, Pagani F, Yeo KT, Apple FS, Christenson RH, Dati F, et al. Evaluation of imprecision for cardiac troponin assays at low-range concentrations. *Clin Chem* 2004;50:327-32). © 2004 American Association for Clinical Chemistry.