REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Cardiac Complications in Patients Undergoing Major Noncardiac Surgery

P.J. Devereaux, M.D., Ph.D., and Daniel I. Sessler, M.D.

From the Population Health Research Institute, Hamilton Health Sciences and McMaster University (P.J.D.), and the Departments of Clinical Epidemiology and Biostatistics and Medicine (P.J.D.), McMaster University — all in Hamilton, ON, Canada; and the Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland (D.I.S.). Address reprint requests to Dr. Devereaux at the Population Health Research Institute, David Braley Cardiac, Vascular, and Stroke Research Institute, Rm. C1-116, Perioperative Medicine and Surgical Research Unit, Hamilton General Hospital, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, or at philipj@mcmaster.ca.

N Engl J Med 2015;373:2258-69.
DOI: 10.1056/NEJMra1502824

Although major noncardiac surgery has the potential to improve the quality and prolong the duration of a patient's life, surgery may also precipitate complications such as death from cardiac causes, myocardial infarction or injury, cardiac arrest, or congestive heart failure.[1] In this article, we review what is known about the epidemiology and mechanisms of perioperative cardiac complications (i.e., from induction of anesthesia to within 30 days after surgery), preoperative methods of predicting these complications, perioperative cardiac interventions, and postoperative monitoring.

Epidemiology and Mechanisms of Perioperative Cardiac Complications

Worldwide, more than 200 million adults undergo major noncardiac surgery each year,[2,3] and the number of such patients is increasing.[4] Both the average age of patients and the risk of cardiac complications are increasing in this group.[5] Each year, more than 10 million adults worldwide have a major cardiac complication in the first 30 days after noncardiac surgery.[6,7] If perioperative death were considered as a separate category, it would rank as the third leading cause of death in the United States.[8] Major perioperative cardiac complications are important because they account for at least one third of perioperative deaths,[7,9-13] result in substantial rates of complications,[7,9,14-16] prolong hospitalization,[17-19] and increase medical costs.[17,20,21]

Figure 1 shows the preoperative factors (i.e., chronic conditions, recent conditions [up to 6 months before surgery], and acute conditions that are present at the time of hospital admission), intraoperative factors, and postoperative factors that can cause perioperative cardiac complications. Large, prospective cohort studies have shown that several chronic cardiac conditions such as coronary artery disease provide a substrate for cardiac complications after surgery.[7,22-24] Several related chronic conditions (e.g., renal insufficiency) are also strongly associated with perioperative cardiac complications. This relationship may indicate that these conditions are a surrogate for an unknown cardiac condition, or the related conditions may exacerbate risk through other mechanisms, such as bleeding.[25]

Examples of recent preoperative conditions that are independently associated with perioperative cardiac complications are high-risk coronary artery disease (i.e., myocardial infarction or Canadian Cardiovascular Society class [CCSC] III or IV angina within 6 months before surgery),[1,7,26,27] stroke within 3 months before surgery,[28] and coronary-artery stenting within 6 months before surgery.[29,30] Acute conditions such as hip fracture that involve trauma and other conditions such as aortic aneurysm rupture that require urgent or emergency surgery substantially

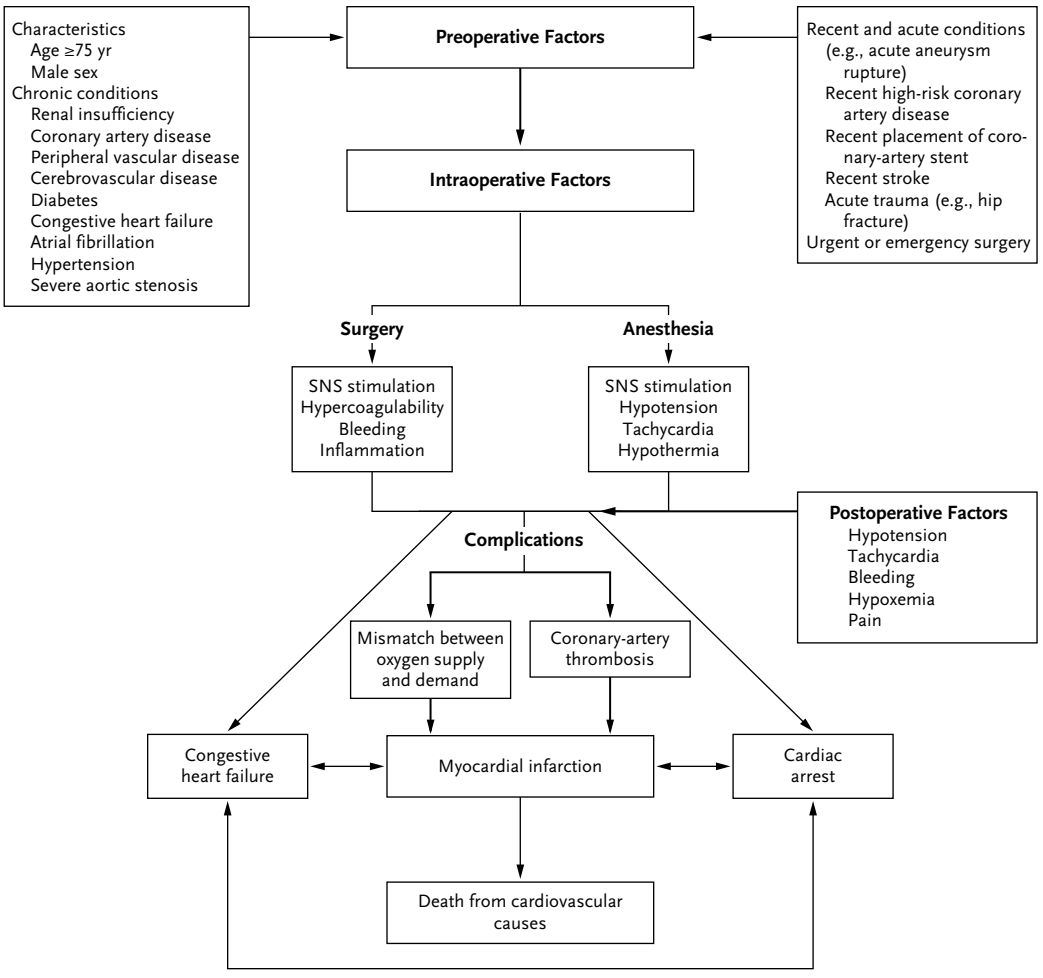

Figure 1. Preoperative, Intraoperative, and Postoperative Factors Associated with Perioperative Cardiac Complications in Patients Undergoing Major Noncardiac Surgery.

Both chronic conditions, such as coronary artery disease or renal insufficiency, and conditions that occur during and after surgery increase the likelihood that patients will have an intraoperative complication or postoperative cardiac complications or die from a cardiac cause.[7,22-25] Emergency surgery is defined as surgery performed less than 24 hours after an acute event, and urgent surgery is defined as surgery performed 24 to 72 hours after an acute event. SNS denotes sympathetic nervous system.

increase the probability of cardiac complications.[1,7,27] This effect is probably due to the harmful pathways initiated by these acute conditions. For example, a hip fracture initiates inflammation, stress, hypercoagulable, and catabolic states that increase a patient's risk of a perioperative cardiac complication.[31-33]

Surgery and anesthesia are associated with activation of the sympathetic nervous system, inflammation, hypercoagulability, hemodynamic compromise, bleeding, and hypothermia, all of which can trigger cardiac complications.[34-44] During the past several decades, developments such as less invasive surgical interventions, improved anesthetic techniques, and enhanced intraoperative monitoring have decreased the frequency of cardiac stressors initiated in response to surgery and anesthesia.[45-49] Consequently, the number of anesthesia-related deaths has decreased by at least a factor of 10 in recent decades, and these deaths now occur in less than 1 in 100,000 noncardiac operations.[47,48,50] In contrast, postoperative mortality remains substantial; 1.5% of adults who undergo inpatient noncardiac surgery

Table 1. Clinical Models for the Prediction of Cardiac Events in Patients Undergoing Major Noncardiac Surgery.*

Model Name and Study	Estimation of Risk	Definition of Outcome	Data Collection
RCRI[22,58]; single-center study; last patient enrolled in 1994; 4315 patients; 92 events	Risk factors (high-risk surgery; ischemic heart disease; prior congestive heart failure, stroke, or transient ischemic attack; use of insulin therapy; and creatinine level >2 mg/deciliter) are each assigned 1 point. The risk of an event is 0.5% with no points, 1.3% with 1 point, 3.6% with 2 points, and 9.1% with ≥3 points.	Myocardial infarction, pulmonary edema, ventricular fibrillation or primary cardiac arrest, or complete heart block	Patients were systematically monitored for myocardial infarction by means of cardiac enzyme measurements and electrocardiography during the first few days after surgery; research personnel collected data on risk factors.
NSQIP MICA Risk Index[24]; >250 centers; last patient enrolled in 2008; 468,795 patients; 2772 events	Relevant variables (age, dependent functional status [partial or total], American Society of Anesthesiologists physical-status class, creatinine level [>1.5 mg/deciliter indicates higher risk], and type of surgery) are entered into an online risk calculator (www.surgicalriskcalculator.com/miorcardiacarrest).	Myocardial infarction or cardiac arrest. Myocardial infarction could be diagnosed only on the basis of electrocardiographic findings (e.g., ST-segment elevation in ≥2 contiguous leads or new left bundle-branch block).	Patients were not systematically monitored for levels of cardiac biomarkers; decisions regarding assessment for myocardial infarction were made by the attending surgeons; trained nurses collected data on risk factors.

* NSQIP MICA denotes National Surgical Quality Improvement Program Myocardial Infarction and Cardiac Arrest, and RCRI Revised Cardiac Risk Index. High-risk surgery is defined as intraperitoneal, intrathoracic, or aortic surgery.

die during the subsequent 30 days.[4,51] Cardiac complications are the leading cause of postoperative deaths,[7] and several postoperative factors (e.g., hypotension, tachycardia, bleeding, hypoxemia, and pain) are associated with such complications.[16,42,52-56]

PREOPERATIVE PREDICTION OF CARDIAC COMPLICATIONS

Accurate preoperative estimation of the risk of perioperative cardiac events is important for several reasons. First, there is an ethical requirement to inform patients accurately about both the benefits and the risks of surgery. Patients' preferences and values may vary substantially, and patients require accurate estimates of the risks and benefits in order to make informed decisions about whether or not to undergo surgery. Accurate estimation of cardiac risk can also inform decisions about treatment (e.g., whether to use an endovascular or an open surgical approach)[46] and guide decisions about the location (e.g., recovery in a monitored setting or an unmonitored setting) and intensity (e.g., daily troponin measurements or no measurement of troponin levels) of postoperative care. Researchers have evaluated three methods for estimating perioperative cardiac risk: clinical risk indexes, noninvasive cardiac testing, and measurement of cardiac biomarker levels.

CLINICAL RISK INDEXES

Table 1 describes two preoperative cardiac risk indexes that are endorsed in various society guidelines.[6,22,24,57] The best-validated risk model is the Revised Cardiac Risk Index (RCRI).[22,58] Its advantages are that it is simple and practical and does not require a risk calculator. However, it does not inform risk among patients undergoing emergency surgery, and the original risk estimates are 50% lower than the rates of events observed in more recent cohort studies.[59,60]

In one study, the National Surgical Quality Improvement Program risk index for Myocardial Infarction and Cardiac Arrest (NSQIP MICA) was shown to have a predictive performance that was superior to that of the RCRI.[24] Although the NSQIP MICA index has the potential to improve risk estimation, it underestimates actual risk because the definition of myocardial infarction in the study was based only on electrocardiographic changes, ST-segment elevation, or new left bundle-branch block (Table 1).[24] Moreover, perioperative cardiac biomarker levels were not systematically monitored in the study that formed the basis of this index, and it is known that without such monitoring, more than half of all perioperative myocardial infarctions are not detected.[16]

NONINVASIVE CARDIAC TESTING

Clinical risk indexes are known to underestimate risk in some patients[61] because many patients are

immobile for long periods before surgery. For example, in the NSQIP MICA study, 22% of patients were completely functionally dependent (i.e., dependent on other persons for activities of daily living) and 20% were partially dependent.[24] In some patients, cardiac disease is not recognized because they have not had symptoms, owing to their immobility. Because of this limitation of clinical risk indexes, researchers have assessed whether noninvasive cardiac testing can improve the prediction of risk.

Guidelines on cardiac assessment and care of patients undergoing noncardiac surgery recommend preoperative cardiac stress testing in patients with limited functional capacity who, on the basis of clinical factors, are considered to have a risk of a major cardiac event of 1% or more and in whom the test result would influence treatment.[6,57] The results of a large, population-based cohort study showed that 9% of patients who were 40 years of age or older and who underwent elective major noncardiac surgery on an inpatient basis underwent a preoperative cardiac stress test.[62] Studies have shown that evidence of ischemia on cardiac testing indicates an increased risk of a perioperative cardiac complication[63]; however, a meta-analysis showed that one third of myocardial infarctions or deaths occurred in patients with normal results on a preoperative thallium-201 stress test (i.e., one form of stress nuclear scintigraphy).[64] These studies were limited by their small size and few events. In addition, almost half used a retrospective design, the clinicians were unaware of test results in only a minority of the studies, and systematic monitoring for myocardial infarction occurred in only a few studies.[64] Moreover, none of the studies showed the overall absolute net rate of reclassification of patients to a higher or lower risk category on the basis of cardiac stress testing, as compared with the use of a clinical risk index.

A recent international prospective cohort study conducted at 12 centers in eight countries evaluated the capacity of preoperative coronary computed tomographic angiography (CCTA) to improve perioperative risk prediction in 955 patients who had or were at risk for vascular disease.[65] Physicians were unaware of the results of the CCTA unless left main coronary-artery stenosis was detected, and the patients' troponin levels were measured daily for 3 days after surgery. The primary outcome — death from cardiovascular causes or nonfatal myocardial infarction — occurred in 74 patients (7.7%) within 30 days after surgery.

The study showed that, as compared with the RCRI alone, findings on preoperative CCTA improved the estimation of risk among patients in whom the primary outcome occurred (adjusted hazard ratio for extensive obstructive coronary artery disease, 3.76; 95% confidence interval [CI], 1.12 to 12.62). However, the study also showed that CCTA overestimated the risk among patients who did not have the primary outcome. Table 2 extrapolates these results from the study sample of 955 patients to a sample of 1000 patients and shows the net absolute numbers of patients who would be appropriately or inappropriately reassigned to a different risk category among those who had the primary outcome (i.e., who had a nonfatal myocardial infarction or died) and those who did not. The overall absolute net reclassification in a sample of 1000 patients shows that CCTA will result in an inappropriate estimate of risk in 81 patients (on the basis of risk categories of <5%, 5 to 15%, and >15% for the primary outcome) and 60 patients (on the basis of risk categories of <1%, 1 to 5%, and >5%).[65]

Overestimation of risk can have negative consequences. For example, many patients who have a positive result on preoperative cardiac stress testing are referred for invasive coronary angiography, with a plan for revascularization.[63,64] The result may be that noncardiac surgery is delayed for months, until the patient has undergone coronary revascularization that may provide no benefit.[66] Because of an overestimation of cardiac risk, some patients may decide to delay or cancel beneficial surgery because they (and their physicians) incorrectly believe the risk to be excessive. If patients are inappropriately sent to monitored beds (i.e., critical care beds or beds in a cardiac step-down unit) because their risk is overestimated, access to care may be limited for patients at greater risk.

MEASUREMENT OF CARDIAC BIOMARKER LEVELS

In a meta-analysis of individual data from 2179 patients, of whom 235 died or had a myocardial infarction (the primary outcome) within 30 days after noncardiac surgery, an elevated preoperative plasma level of natriuretic peptide (i.e., a B-type natriuretic peptide [BNP] level of ≥92 ng per liter or an N-terminal pro-BNP [NT-proBNP] level of

Table 2. Reassignment of Risk in a Sample of 1000 Patients on the Basis of Findings on CCTA, as Compared with Findings on the RCRI.*

Patient Subgroup and Risk Categories for the Primary Outcome	Patients Reassigned to a Different Risk Category	P Value	Reassignment
	net no. (95% CI)		
77 Patients in whom death from cardiovascular causes or nonfatal myocardial infarction would occur			
<5%, 5–15%, and >15%	17 (11–25)	<0.001	Appropriate
<1%, 1–5%, and >5%	10 (4–17)	0.002	Appropriate
923 Patients in whom death from cardiovascular causes or nonfatal myocardial infarction would not occur			
<5%, 5–15%, and >15%	98 (69–128)	<0.001	Inappropriate
<1%, 1–5%, and >5%	70 (44–96)	<0.001	Inappropriate

* Calculations are based on a sample of 1000 patients undergoing major noncardiac surgery; this sample was extrapolated from the data in Sheth et al.[65] The primary outcome was defined as death from cardiovascular causes or nonfatal myocardial infarction within 30 days after surgery. The net number of patients who were reassigned to a different risk category was calculated by subtracting the number of patients who were reassigned to a lower risk group from the number of patients who were reassigned to a higher risk group on the basis of results on coronary computed tomographic angiography (CCTA) relative to the RCRI. Among patients who had the primary outcome, reassignment to a higher risk category was considered appropriate if more patients were reassigned to a higher risk group than to a lower risk group and inappropriate if more patients were reassigned to a lower risk group than to a higher risk group. Among patients who did not have the primary outcome, reassignment to a higher risk category was considered appropriate if more patients were reassigned to a lower risk group than to a higher risk group and inappropriate if more patients were reassigned to a higher risk group than to a lower risk group. CI denotes confidence interval.

≥300 ng per liter) was the strongest independent preoperative predictor of the primary outcome (odds ratio, 3.40; 95% CI, 2.57 to 4.47).[10] The study showed that, as compared with a preoperative clinical model alone, preoperative measurement of natriuretic peptide levels improved risk estimation among both patients who had the primary outcome and those who did not. On the basis of the 7.7% event rate in the CCTA study, the overall absolute net reclassification of risk estimation in a sample of 1000 patients is that preoperative measurement of natriuretic peptide levels, as compared with the clinical model alone, would be projected to result in a more appropriate estimate of the risk of death or myocardial infarction in 155 patients (on the basis of risk categories of <5%, 5 to 10%, >10 to 15%, and >15%). Although a smaller meta-analysis of studies that involved only patients undergoing vascular surgery suggested that lower BNP thresholds may also provide important prognostic information, data are lacking from studies to clearly establish whether other BNP and NT-proBNP thresholds provide an independent prediction of risk.

The cost of measuring natriuretic peptide levels is much lower than the cost of a stress test. Furthermore, results can be obtained within minutes with testing at the point of care. Measurement of natriuretic peptide levels is thus preferable to stress testing because it is more accurate and convenient, faster, and less expensive. In fact, measurement of natriuretic peptide levels costs less than an internal medicine or cardiology consultation, so the test might be used to decide which patients should be referred for consultation with a specialist.

PERIOPERATIVE CARDIAC INTERVENTIONS

PREOPERATIVE CORONARY REVASCULARIZATION

The Coronary Artery Revascularization Prophylaxis trial provides the most robust data on the value of preoperative coronary-artery revascularization.[66] This trial included patients who were undergoing elective vascular surgery and who had at least one coronary artery with a stenosis of at least 70% and that was suitable for revascularization. In an article that focused on the methods in this study,[67] the authors further reported the exclusion criteria, including unstable

angina, left main coronary-artery stenosis of at least 50%, a left ventricular ejection fraction of less than 20%, or severe aortic stenosis. The 510 participants were randomly assigned to coronary-artery revascularization before vascular surgery or no coronary revascularization before vascular surgery. There was no significant effect on the primary outcome of long-term survival (Table 3). Moreover, the trial showed no short-term benefit of preoperative coronary revascularization.[66]

These data do not provide support for delaying noncardiac surgery until coronary revascularization can be performed in patients with stable coronary artery disease. In patients with CCSC III or IV angina, performing coronary revascularization before surgery may be prudent; however, an individual risk–benefit assessment is required in patients with life-threatening conditions (e.g., cancer or trauma) who require immediate noncardiac surgery. In patients who receive a coronary stent, noncardiac surgery should ideally be delayed for 6 months.[29,30]

INTERVENTIONS TARGETING THE STRESS RESPONSE

Researchers have assessed the ability of beta-blockers and α_2-adrenergic agonists to minimize the negative consequences of the perioperative sympathetic stress response. A recent meta-analysis that included data from more than 10,000 patients showed that perioperative beta-blockade reduced the risk of nonfatal myocardial infarction but increased the risk of death, nonfatal stroke, hypotension, and bradycardia (Table 3).[68] Data from the Perioperative Ischemic Evaluation (POISE) trial (a study of perioperative beta-blockers in which 8351 patients were enrolled) showed that clinically important hypotension was a strong independent predictor of stroke and death.[70]

Recognizing that clinically important hypotension was potentially responsible for the harmful effects of perioperative beta-blockade, investigators in the POISE-2 trial[42] evaluated clonidine (an α_2-adrenergic agonist) as an alternative means to control the perioperative stress response, since previous trials had suggested that low-dose clonidine produces less hypotension than beta-blockers.[68,71] The POISE-2 study, in which 10,010 patients were randomly assigned to receive clonidine or a placebo, showed that clonidine had no effect on the rates of myocardial infarction, stroke, or death (Table 3).[42]

Maintaining the most effective match between perioperative myocardial oxygen supply and demand may require a balance between decreasing the heart rate (thus minimizing demand)[72] and avoiding clinically important hypotension (ensuring supply).[42] The perioperative trials showed that beta-blockade provides substantially better heart-rate control than clonidine and only a limited increase in hypotension, and these factors may explain their differing effects on myocardial infarction.[42,68,70]

Some reviewers have suggested that the harm associated with beta-blocker use in the POISE study resulted from an excessive dose.[73] A meta-analysis of studies of beta-blockers by a task force of the American College of Cardiology and the American Heart Association[68] showed, however, that the increased risk of stroke and death was qualitatively unchanged when the POISE data were omitted. Other authors have suggested that it is more appropriate to initiate beta-blockade weeks, instead of hours, before surgery.[74] However, because most patients are seen in preoperative clinics within days or weeks before surgery, adjustment of the beta-blocker dose presents a challenge. Moreover, whatever dose of a beta-blocker a patient is able to receive without adverse events before surgery cannot be assumed to be safe for perioperative use, since hypotension is common after surgery.[42]

Controlling the perioperative sympathetic stress responsehas benefit, but it is necessary to find a way to do it safely. A strategy that holds promise is the use of personalized beta-blocker therapy to treat ischemia and tachycardia that is identified by means of a remote, automated, continuous monitoring system that noninvasively assesses a patient's hemodynamic status and ST-segments after surgery.

USE OF ASPIRIN

Although some perioperative myocardial infarctions are due to thrombosis,[75] the POISE-2 trial showed that aspirin did not reduce the risk of myocardial infarction but increased the risk of major bleeding (Table 3).[41] In this study, patients were randomly assigned to start taking aspirin or placebo just before surgery and to continue it postoperatively. POISE-2 included 5628 patients who were not previously receiving aspirin and 4382 who had been receiving aspirin for a long time but had stopped taking it a median of 7 days

Table 3. Results of Studies of the Effect of Perioperative Prophylactic Cardiac Interventions on Perioperative Cardiac Events.*

Intervention and Outcome	Study and Reference	Treatment Group	Control Group	Relative Risk, Hazard Ratio, or Odds Ratio (95% CI)†
		no. of patients with event/total no.		
Coronary revascularization before vascular surgery	CARP, McFalls et al.[66]			
Death		70/258	67/252	0.98 (0.70–1.37)
Liberal strategy for hemoglobin transfusion‡	FOCUS, Carson et al.[69]			
Death or inability to walk across a room without assistance 30 days after surgery		459/995	481/1000	0.92 (0.73–1.16)
Death		52/995	43/1000	1.23 (0.71–2.12)
Beta-blocker therapy	Meta-analysis of studies, Wijeysundera et al.[68]			
Nonfatal myocardial infarction		181/5394	256/5391	0.72 (0.59–0.86)
Nonfatal stroke		40/5274	21/5271	1.86 (1.09–3.16)
Death		161/5394	126/5391	1.30 (1.03–1.63)
Hypotension		892/5228	593/5220	1.47 (1.34–1.60)
Bradycardia		402/5227	150/5231	2.61 (2.18–3.12)
α_2-Adrenergic agonist therapy	POISE-2, Devereaux et al.[42]			
Myocardial infarction		329/5009	295/5001	1.11 (0.95–1.30)
Stroke		18/5009	17/5001	1.06 (0.54–2.05)
Death		64/5009	63/5001	1.01 (0.72–1.44)
Hypotension		2385/5009	1854/5001	1.32 (1.24–1.40)
Bradycardia		600/5009	403/5001	1.49 (1.32–1.69)
Aspirin therapy	POISE-2, Devereaux et al.[41]			
Myocardial infarction		309/4998	315/5012	0.98 (0.84–1.15)
Stroke		16/4998	19/5012	0.84 (0.43–1.64)
Death		65/4998	62/5012	1.05 (0.74–1.49)
Major bleeding		230/4998	188/5012	1.23 (1.01–1.49)

* All studies were randomized, controlled trials except for the meta-analysis of randomized, controlled trials evaluating the effects of perioperative beta-blockers at 30-day follow-up by Wijeysundera et al.[68] CARP denotes Coronary Artery Revascularization Prophylaxis, FOCUS The Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair, and POISE-2 Perioperative Ischemic Evaluation 2.

† In the CARP trial and the meta-analysis of studies by Wijeysundera et al., results were reported as relative risks. In FOCUS, results were reported as odds ratios, and in the POISE-2 trials, results were reported as hazard ratios.

‡ FOCUS evaluated the effects of a hemoglobin transfusion threshold of 10 g per deciliter (liberal strategy) as compared with a hemoglobin level of less than 8 g per deciliter (restrictive strategy and control group) in patients with a hemoglobin level below 10 g per deciliter after surgery for a hip fracture.

before surgery. The results were similar between these two subgroups of patients and also in the subgroup of 3271 patients with known vascular disease.[41]

In POISE-2, the occurrence of life-threatening or major bleeding was an independent predictor of myocardial infarction (hazard ratio, 1.82; 95% CI, 1.40 to 2.36). The incidence of myocardial infarction and the incidence of all major bleeding was similar (6.3%) — a result that may explain why aspirin was not beneficial in the perioperative period. In contrast, the Antithrombotic Trialists' Collaboration meta-analysis showed the benefits of aspirin in patients who were not undergoing surgery; in these patients, the risk of myocardial infarction is usually higher than the risk of major bleeding.[76] These data suggest that aspirin should not be administered during the perioperative period, but that it is important to reinitiate the use of aspirin 8 to 10 days

after surgery in patients with an indication for long-term aspirin use.[41]

TRANSFUSION THRESHOLD

The Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair, a major trial of noncardiac surgery, has provided important insights into the relative effects of a liberal strategy for blood transfusion (hemoglobin level, 10 g per deciliter) and a restrictive strategy (hemoglobin level, <8 g per deciliter) in patients undergoing surgery for hip fracture.[69] This trial, which included patients who had either cardiovascular disease or risk factors for it, showed no benefit associated with a liberal transfusion strategy (Table 3).

This study was limited to patients undergoing hip-fracture surgery. However, a restrictive transfusion strategy after any noncardiac surgery is probably prudent unless proved otherwise.

SHARED CARE

Surgeons are often busy in operating rooms, which limits their ability to respond rapidly to postoperative medical complications on surgical wards. For example, among the 5001 patients who received placebo in the POISE-2 trial,[42] the median duration of clinically important hypotension during surgery was 15 minutes, whereas on the first postoperative day it was 150 minutes (P<0.001). These data suggest a need for procedures to facilitate more rapid management of cardiovascular compromise on surgical wards.

Models of shared care arrangements between surgeons and readily available medical specialists have the potential to improve outcomes for patients. This idea is supported by data from a meta-analysis that showed lower mortality among patients who underwent surgery for a hip fracture and whose care was comanaged by surgeons and geriatricians, as compared with surgeons alone.[77]

POSTOPERATIVE MONITORING

MONITORING FOR HYPOXEMIA, HEMODYNAMIC COMPROMISE, AND MYOCARDIAL ISCHEMIA

Within hours after surgery, most adults return to a surgical ward, and thereafter their vital signs are evaluated only every 4 to 8 hours, in contrast to the intensity of intraoperative monitoring.[78,79] Moreover, after surgery, patients usually receive analgesic medications that can blunt their awareness and mask cardiac symptoms.[7,16]

A recent study from the Cleveland Clinic that included a representative sample of adults who underwent inpatient noncardiac surgery showed that nurses detected a 5% incidence of hypoxemia (defined as the saturation of peripheral oxygen measured by means of pulse oximetry [Spo_2] of <90%) during patients' first 48 hours on a surgical ward after surgery.[80] Among the 564 patients in whom nurses did not detect hypoxemia, pulse-oximeter recordings of which the health care providers were unaware showed that 38% of these patients had at least one continuous episode of an Spo_2 of less than 90% lasting 1 hour or more, and 10% of the patients had at least one continuous episode of an Spo_2 of less than 85% lasting 1 hour or more. Considering that hypoxemia lasting more than 5 minutes is associated with an increased risk of myocardial ischemia, these results suggest that insufficient monitoring on surgical wards poses a risk to patients.[56]

Multivariable analysis from the POISE-2 trial showed that clinically important hypotension was an independent predictor of the subsequent risk of myocardial infarction (adjusted hazard ratio, 1.37; 95% CI, 1.16 to 1.62) during a 30-day follow-up.[42] Studies have also shown that continuous ST-segment monitoring after surgery can identify asymptomatic ischemia that is independently associated with myocardial infarction.[81-83]

These data suggest that new monitoring strategies are needed on surgical wards if postoperative care is to achieve improvements similar to those that have occurred in intraoperative care. Moreover, the data suggest that remote automated systems for continuous noninvasive monitoring of oxygen saturation, hemodynamic variables, and ST-segment depression or elevation in patients after surgery can identify impending cardiac events much sooner than currently occurs in routine care.

Data are lacking from studies to establish the most appropriate thresholds for identifying hypoxemia, hemodynamic compromise, and ischemia, while minimizing the risk of false alarms and alarm fatigue. Moreover, randomized, controlled trials are lacking to establish effective treatment strategies (e.g., beta-blockade for tachycardia or ischemia in patients with an adequate blood pressure) and cost-effectiveness.

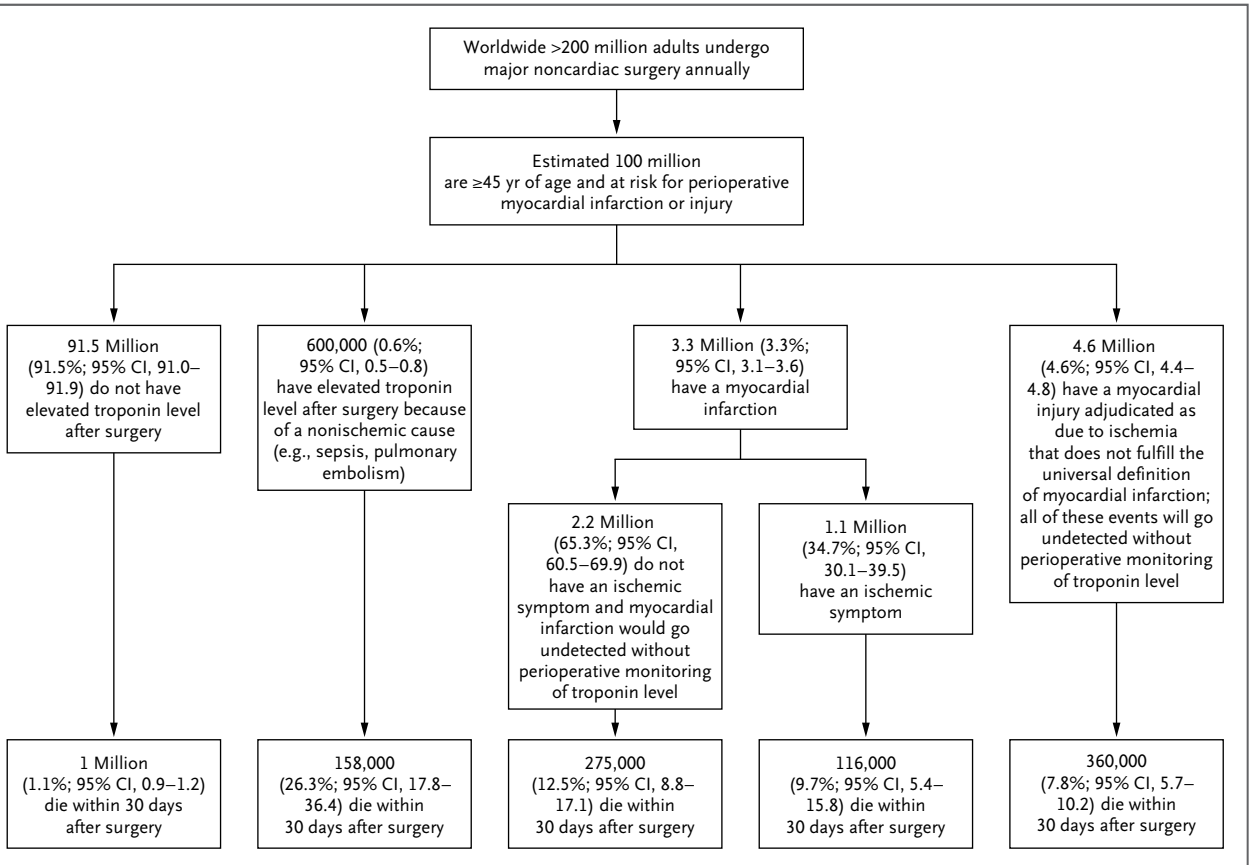

Figure 2. Estimates of Annual Worldwide Mortality from Complications of Major Noncardiac Surgery, 2007–2011.

The numbers of patients worldwide who undergo major noncardiac surgery each year are shown, along with outcomes. Percentages may not sum as expected owing to rounding of absolute numbers. Data are from Botto et al.[7] and Devereaux et al.[16]

MEASUREMENT OF TROPONIN LEVELS

Most myocardial infarctions occur within 48 hours after noncardiac surgery, when patients are receiving analgesic medications that can mask symptoms of ischemia.[16] This use of analgesic medications probably explains why 65% of patients in whom a perioperative myocardial infarction occurs do not have symptoms of ischemia. Asymptomatic myocardial infarctions are associated with an increase in the risk of death within 30 days (adjusted odds ratio, 4.00; 95% CI, 2.65 to 6.06) that is similar to that after symptomatic myocardial infarctions (adjusted odds ratio, 4.76; 95% CI, 2.68 to 8.43).[16] Moreover, asymptomatic perioperative elevations in troponin levels that are interpreted as evidence of myocardial injuries due to ischemia but that do not fulfill the universal definition of myocardial infarction are also associated with increased risk of death at 30 days (adjusted hazard ratio, 3.30; 95% CI, 2.26 to 4.81).[7] Figure 2 shows the numbers of patients worldwide who undergo major noncardiac surgery each year and, among other outcomes, the frequency of myocardial injury due to ischemia that does not fulfill the universal definition of myocardial infarction, the frequency of myocardial infarction that does not fulfill the definition, the numbers of patients who have elevation of troponin levels because of a nonischemic event, and the numbers of patients who do not have an elevated level of troponin after surgery.[7,16]

Despite observational studies that suggest that cardiovascular drugs used for secondary prevention are beneficial and cost-effective in patients in whom a perioperative myocardial infarction or injury occurs,[16,84,85] a substantial proportion of these patients are discharged with-

out receiving such drugs.[16] Without monitoring of perioperative troponin levels during the first few days after surgery in patients with known vascular disease or risk factors, the majority of myocardial infarctions and injuries will go undetected. There may also be value in obtaining a measurement of troponin levels before surgery, because it may provide independent prognostic information.[86] In addition, and in centers where a highly sensitive troponin assay is used, physicians may find it helpful to evaluate the preoperative-to-postoperative changes in these levels.[87]

CONCLUSIONS

Death during surgery is now rare, but postoperative death is not. Cardiovascular complications are the leading cause of death within 30 days after noncardiac surgery. Measurement of natriuretic peptide levels has substantial advantages over noninvasive cardiac testing (such as stress echocardiography, stress nuclear scintigraphy, and CCTA) as a means to enhance preoperative risk prediction. Although randomized, controlled trials have not identified an effective and safe intervention to prevent perioperative cardiac complications, some trials have identified ways to improve safety. Enhanced monitoring on surgical wards and rapid management of cardiac complications when they occur may improve outcomes. Because most patients in whom a perioperative myocardial infarction occurs do not have symptoms, physicians should monitor troponin levels after surgery in patients with risk factors in order to avoid missing these prognostically important events.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Dr. Erin Sloan for assistance in conceptualizing an earlier version of Figure 1.

REFERENCES

1. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 1977;297:845-50.
2. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet 2008;372:139-44.
3. Bickler SW, Spiegel DA. Global surgery — defining a research agenda. Lancet 2008;372:90-2.
4. Semel ME, Lipsitz SR, Funk LM, Bader AM, Weiser TG, Gawande AA. Rates and patterns of death after surgery in the United States, 1996 and 2006. Surgery 2012;151:171-82.
5. Siddiqui NF, Coca SG, Devereaux PJ, et al. Secular trends in acute dialysis after elective major surgery — 1995 to 2009. CMAJ 2012;184:1237-45.
6. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J 2014;35:2383-431.
7. Botto F, Alonso-Coello P, Chan MT, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology 2014;120:564-78.
8. Bartels K, Karhausen J, Clambey ET, Grenz A, Eltzschig HK. Perioperative organ injury. Anesthesiology 2013;119:1474-89.
9. Kazaure HS, Roman SA, Rosenthal RA, Sosa JA. Cardiac arrest among surgical patients: an analysis of incidence, patient characteristics, and outcomes in ACS-NSQIP. JAMA Surg 2013;148:14-21.
10. Rodseth RN, Biccard BM, Le Manach Y, et al. The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: a systematic review and individual patient data meta-analysis. J Am Coll Cardiol 2014;63:170-80.
11. Greenstein AJ, Chassin MR, Wang J, et al. Association between minor and major surgical complications after carotid endarterectomy: results of the New York Carotid Artery Surgery study. J Vasc Surg 2007;46:1138-46.
12. Beattie WS, Karkouti K, Tait G, et al. Use of clinically based troponin underestimates the cardiac injury in non-cardiac surgery: a single-centre cohort study in 51,701 consecutive patients. Can J Anaesth 2012;59:1013-22.
13. McFalls EO, Ward HB, Moritz TE, et al. Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: results of the CARP trial. Eur Heart J 2008;29:394-401.
14. Levy M, Heels-Ansdell D, Hiralal R, et al. Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: a systematic review and meta-analysis. Anesthesiology 2011;114:796-806.
15. Mangano DT, Browner WS, Hollenberg M, Li J, Tateo IM. Long-term cardiac prognosis following noncardiac surgery. JAMA 1992;268:233-9.
16. Devereaux PJ, Xavier D, Pogue J, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med 2011;154:523-8.
17. Mackey WC, Fleisher LA, Haider S, et al. Perioperative myocardial ischemic injury in high-risk vascular surgery patients: incidence and clinical significance in a prospective clinical trial. J Vasc Surg 2006;43:533-8.
18. van Waes JA, Nathoe HM, de Graaff JC, et al. Myocardial injury after noncardiac surgery and its association with short-term mortality. Circulation 2013;127:2264-71.
19. Le Manach Y, Perel A, Coriat P, Godet G, Bertrand M, Riou B. Early and delayed myocardial infarction after abdominal aortic surgery. Anesthesiology 2005;102:885-91.
20. Udeh BL, Dalton JE, Hata JS, Udeh CI, Sessler DI. Economic trends from 2003 to 2010 for perioperative myocardial infarction: a retrospective, cohort study. Anesthesiology 2014;121:36-45.
21. Dimick JB, Pronovost PJ, Cowan JA, Lipsett PA. Complications and costs after high-risk surgery: where should we focus quality improvement initiatives? J Am Coll Surg 2003;196:671-8.
22. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043-9.

23. Sabaté S, Mases A, Guilera N, et al. Incidence and predictors of major perioperative adverse cardiac and cerebrovascular events in non-cardiac surgery. Br J Anaesth 2011;107:879-90.
24. Gupta PK, Gupta H, Sundaram A, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation 2011;124:381-7.
25. Acedillo RR, Shah M, Devereaux PJ, et al. The risk of perioperative bleeding in patients with chronic kidney disease: a systematic review and meta-analysis. Ann Surg 2013;258:901-13.
26. Kumar R, McKinney WP, Raj G, et al. Adverse cardiac events after surgery: assessing risk in a veteran population. J Gen Intern Med 2001;16:507-18.
27. Detsky AS, Abrams HB, McLaughlin JR, et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. J Gen Intern Med 1986;1:211-9.
28. Jørgensen ME, Torp-Pedersen C, Gislason GH, et al. Time elapsed after ischemic stroke and risk of adverse cardiovascular events and mortality following elective noncardiac surgery. JAMA 2014; 312:269-77.
29. Hawn MT, Graham LA, Richman JS, Itani KM, Henderson WG, Maddox TM. Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. JAMA 2013;310:1462-72.
30. Wijeysundera DN, Wijeysundera HC, Yun L, et al. Risk of elective major noncardiac surgery after coronary stent insertion: a population-based study. Circulation 2012; 126:1355-62.
31. Beloosesky Y, Hendel D, Weiss A, et al. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. J Gerontol A Biol Sci Med Sci 2007; 62:420-6.
32. Chuang D, Power SE, Dunbar PR, Hill AG. Central nervous system interleukin-8 production following neck of femur fracture. ANZ J Surg 2005;75:813-6.
33. Desborough JP. The stress response to trauma and surgery. Br J Anaesth 2000;85: 109-17.
34. Chernow B, Alexander HR, Smallridge RC, et al. Hormonal responses to graded surgical stress. Arch Intern Med 1987;147: 1273-8.
35. Udelsman R, Norton JA, Jelenich SE, et al. Responses of the hypothalamic-pituitary-adrenal and renin-angiotensin axes and the sympathetic system during controlled surgical and anesthetic stress. J Clin Endocrinol Metab 1987;64:986-94.
36. Cruickshank AM, Fraser WD, Burns HJ, Van Damme J, Shenkin A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. Clin Sci (Lond) 1990;79:161-5.
37. Baxevanis CN, Papilas K, Dedoussis GV, Pavlis T, Papamichail M. Abnormal cytokine serum levels correlate with impaired cellular immune responses after surgery. Clin Immunol Immunopathol 1994;71:82-8.
38. Rosenfeld BA, Beattie C, Christopherson R, et al. The effects of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. Anesthesiology 1993;79:435-43.
39. Flinn WR, McDaniel MD, Yao JS, Fahey VA, Green D. Antithrombin III deficiency as a reflection of dynamic protein metabolism in patients undergoing vascular reconstruction. J Vasc Surg 1984;1:888-95.
40. McDaniel MD, Pearce WH, Yao JS, et al. Sequential changes in coagulation and platelet function following femorotibial bypass. J Vasc Surg 1984;1:261-8.
41. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. N Engl J Med 2014; 370:1494-503.
42. Devereaux PJ, Sessler DI, Leslie K, et al. Clonidine in patients undergoing noncardiac surgery. N Engl J Med 2014;370:1504-13.
43. Kamel H, Johnston SC, Kirkham JC, et al. Association between major perioperative hemorrhage and stroke or Q-wave myocardial infarction. Circulation 2012; 126:207-12.
44. Frank SM, Beattie C, Christopherson R, et al. Unintentional hypothermia is associated with postoperative myocardial ischemia. Anesthesiology 1993;78:468-76.
45. Lederle FA, Freischlag JA, Kyriakides TC, et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. JAMA 2009;302:1535-42.
46. Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med 2010;362:1863-71.
47. Li G, Warner M, Lang BH, Huang L, Sun LS. Epidemiology of anesthesia-related mortality in the United States, 1999-2005. Anesthesiology 2009;110:759-65.
48. Lienhart A, Auroy Y, Péquignot F, et al. Survey of anesthesia-related mortality in France. Anesthesiology 2006;105:1087-97.
49. Moller JT, Johannessen NW, Espersen K, et al. Randomized evaluation of pulse oximetry in 20,802 patients: II. Perioperative events and postoperative complications. Anesthesiology 1993;78:445-53.
50. Dripps RD, Lamont A, Eckenhoff JE. The role of anesthesia in surgical mortality. JAMA 1961;178:261-6.
51. Devereaux PJ, Chan MT, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2012;307:2295-304.
52. Goldman MD, Reeder MK, Muir AD, et al. Repetitive nocturnal arterial oxygen desaturation and silent myocardial ischemia in patients presenting for vascular surgery. J Am Geriatr Soc 1993;41:703-9.
53. Sprung J, Warner ME, Contreras MG, et al. Predictors of survival following cardiac arrest in patients undergoing noncardiac surgery: a study of 518,294 patients at a tertiary referral center. Anesthesiology 2003;99:259-69.
54. Beattie WS, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. Anesth Analg 2001;93:853-8.
55. Mangano DT, Siliciano D, Hollenberg M, et al. Postoperative myocardial ischemia: therapeutic trials using intensive analgesia following surgery. Anesthesiology 1992;76:342-53.
56. Gill NP, Wright B, Reilly CS. Relationship between hypoxaemic and cardiac ischaemic events in the perioperative period. Br J Anaesth 1992;68:471-3.
57. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:e278-e333.
58. Ford MK, Beattie WS, Wijeysundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the Revised Cardiac Risk Index. Ann Intern Med 2010;152:26-35.
59. Davis C, Tait G, Carroll J, Wijeysundera DN, Beattie WS. The Revised Cardiac Risk Index in the new millennium: a single-centre prospective cohort re-evaluation of the original variables in 9,519 consecutive elective surgical patients. Can J Anaesth 2013;60:855-63.
60. Devereaux PJ, Bradley D, et al. An international prospective cohort study evaluating major vascular complications among patients undergoing noncardiac surgery: the VISION Pilot Study. Open Med 2011; 5(4):e193-200.
61. Biccard B. Proposed research plan for the derivation of a new Cardiac Risk Index. Anesth Analg 2015;120:543-53.
62. Wijeysundera DN, Beattie WS, Austin PC, Hux JE, Laupacis A. Non-invasive cardiac stress testing before elective major non-cardiac surgery: population based cohort study. BMJ 2010;340:b5526.
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.
64. Beattie WS, Abdelnaem E, Wijeysundera DN, Buckley DN. A meta-analytic comparison of preoperative stress echocardiography and nuclear scintigraphy imaging. Anesth Analg 2006;102:8-16.
65. Sheth T, Chan M, Butler C, et al. Prognostic capabilities of coronary computed

tomographic angiography before noncardiac surgery: prospective cohort study. BMJ 2015;350:h1907.
66. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med 2004;351:2795-804.
67. McFalls EO, Ward HB, Krupski WC, et al. Prophylactic coronary artery revascularization for elective vascular surgery: study design. Control Clin Trials 1999;20:297-308.
68. Wijeysundera DN, Duncan D, Nkonde-Price C, et al. Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:2246-64.
69. Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011;365:2453-62.
70. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371:1839-47.
71. Darvish-Kazem S, Alderazi AE, Walsh M, et al. Vascular safety and efficacy of perioperative clonidine treatment in patients undergoing non-cardiac surgery: systematic review and meta-analysis. Can J Cardiol 2009;25B:158. abstract.
72. Beattie WS, Wijeysundera DN, Karkouti K, McCluskey S, Tait G. Does tight heart rate control improve beta-blocker efficacy? An updated analysis of the noncardiac surgical randomized trials. Anesth Analg 2008;106:1039-48.
73. Angeli F, Verdecchia P, Karthikeyan G, et al. Beta-blockers and risk of all-cause mortality in non-cardiac surgery. Ther Adv Cardiovasc Dis 2010;4:109-18.
74. Fleisher LA, Poldermans D. Perioperative beta blockade: where do we go from here? Lancet 2008;371:1813-4.
75. Gualandro DM, Campos CA, Calderaro D, et al. Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: frequent and dangerous. Atherosclerosis 2012;222:191-5.
76. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60.
77. Grigoryan KV, Javedan H, Rudolph JL. Orthogeriatric care models and outcomes in hip fracture patients: a systematic review and meta-analysis. J Orthop Trauma 2014;28:e49-e55.
78. Leuvan CH, Mitchell I. Missed opportunities? An observational study of vital sign measurements. Crit Care Resusc 2008;10:111-5.
79. McGain F, Cretikos MA, Jones D, et al. Documentation of clinical review and vital signs after major surgery. Med J Aust 2008;189:380-3.
80. Sun Z, Sessler DI, Dalton JE, et al. Postoperative hypoxemia is common and persistent: a prospective blinded observational study. Anesth Analg 2015;121:709-15.
81. Landesberg G, Luria MH, Cotev S, et al. Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. Lancet 1993;341:715-9.
82. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. N Engl J Med 1990;323:1781-8.
83. Mangano DT, Hollenberg M, Fegert G, et al. Perioperative myocardial ischemia in patients undergoing noncardiac surgery — I: Incidence and severity during the 4 day perioperative period. J Am Coll Cardiol 1991;17:843-50.
84. Foucrier A, Rodseth R, Aissaoui M, et al. The long-term impact of early cardiovascular therapy intensification for postoperative troponin elevation after major vascular surgery. Anesth Analg 2014;119:1053-63.
85. Torborg A, Ryan L, Kantor G, Biccard BM. The pharmacoeconomics of routine postoperative troponin surveillance to prevent and treat myocardial infarction after non-cardiac surgery. S Afr Med J 2014;104:619-23.
86. Weber M, Luchner A, Seeberger M, et al. Incremental value of high-sensitive troponin T in addition to the revised cardiac index for peri-operative risk stratification in non-cardiac surgery. Eur Heart J 2013;34:853-62.
87. Kavsak PA, Walsh M, Srinathan S, et al. High sensitivity troponin T concentrations in patients undergoing noncardiac surgery: a prospective cohort study. Clin Biochem 2011;44:1021-4.

IMAGES IN CLINICAL MEDICINE

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal*'s website at NEJM.org. At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.