

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

Copyright © 2015 Massachusetts Medical Society.

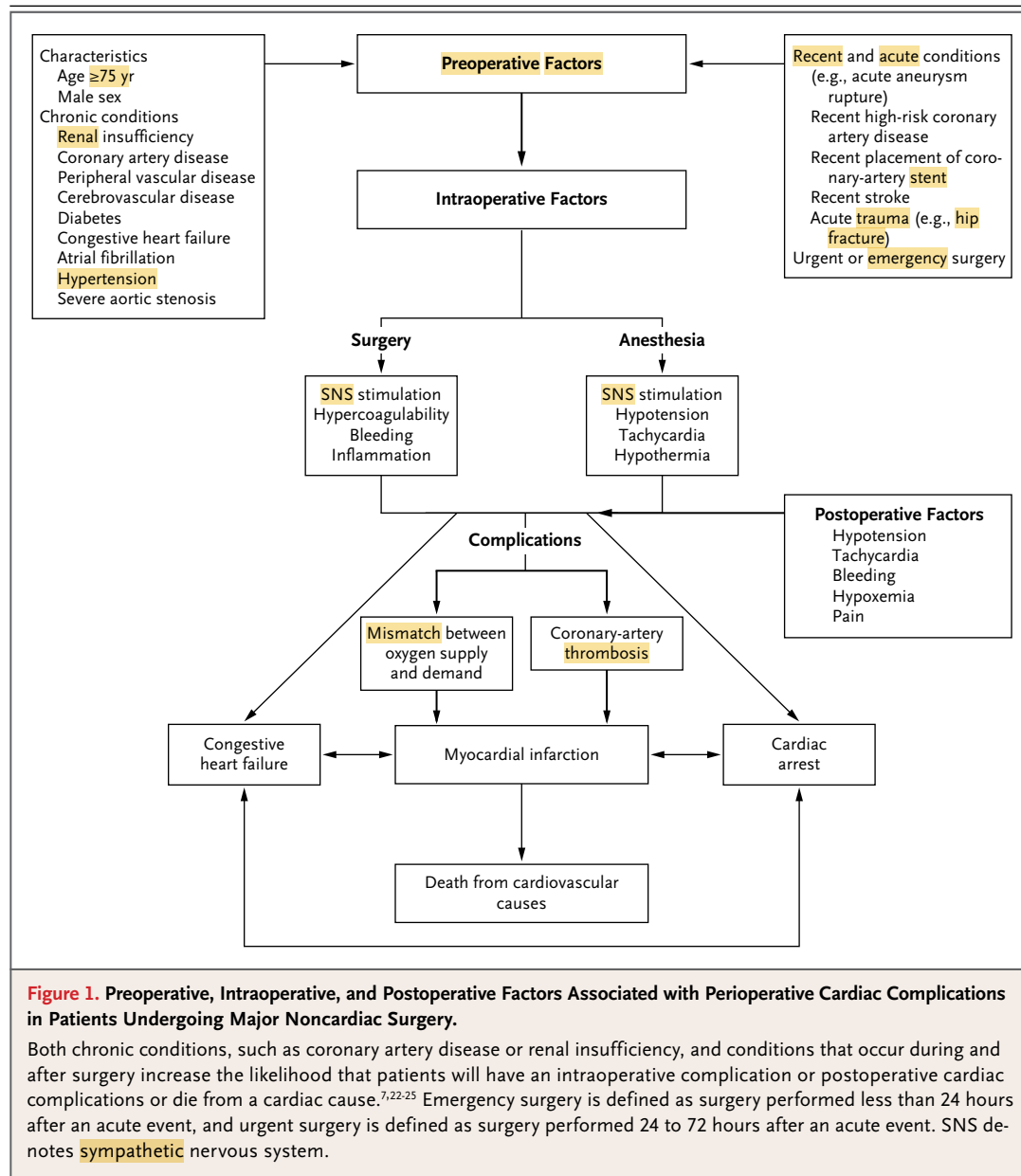
ALTHOUGH MAJOR NONCARDIAC SURGERY HAS THE POTENTIAL TO IMPROVE the quality and prolong the duration of a patient's life, surgery may also precipitate complications such as death from cardiac causes, myocardial infarction or injury, cardiac arrest, or congestive heart failure.¹ In this article, we review 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



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 patients⁶¹ 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 complication⁶³; 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 cardiovas-

cular 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 <i>net no. (95% CI)</i> | P Value | Reassignment |
|---|---|---------|---------------|
| 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 trial⁴² 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 Association⁶⁸ 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 response has 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 <i>no. of patients with event/total no.</i> | Control Group <i>no. of patients with event/total no.</i> | Relative Risk, Hazard Ratio, or Odds Ratio (95% CI)†‡ |
|---|--|--|--|---|
| 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, Wijeyesundera 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) |
| α₂-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 Wijeyesundera 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 Wijeyesundera 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 Anti-thrombotic 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 reinstate 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 usu-

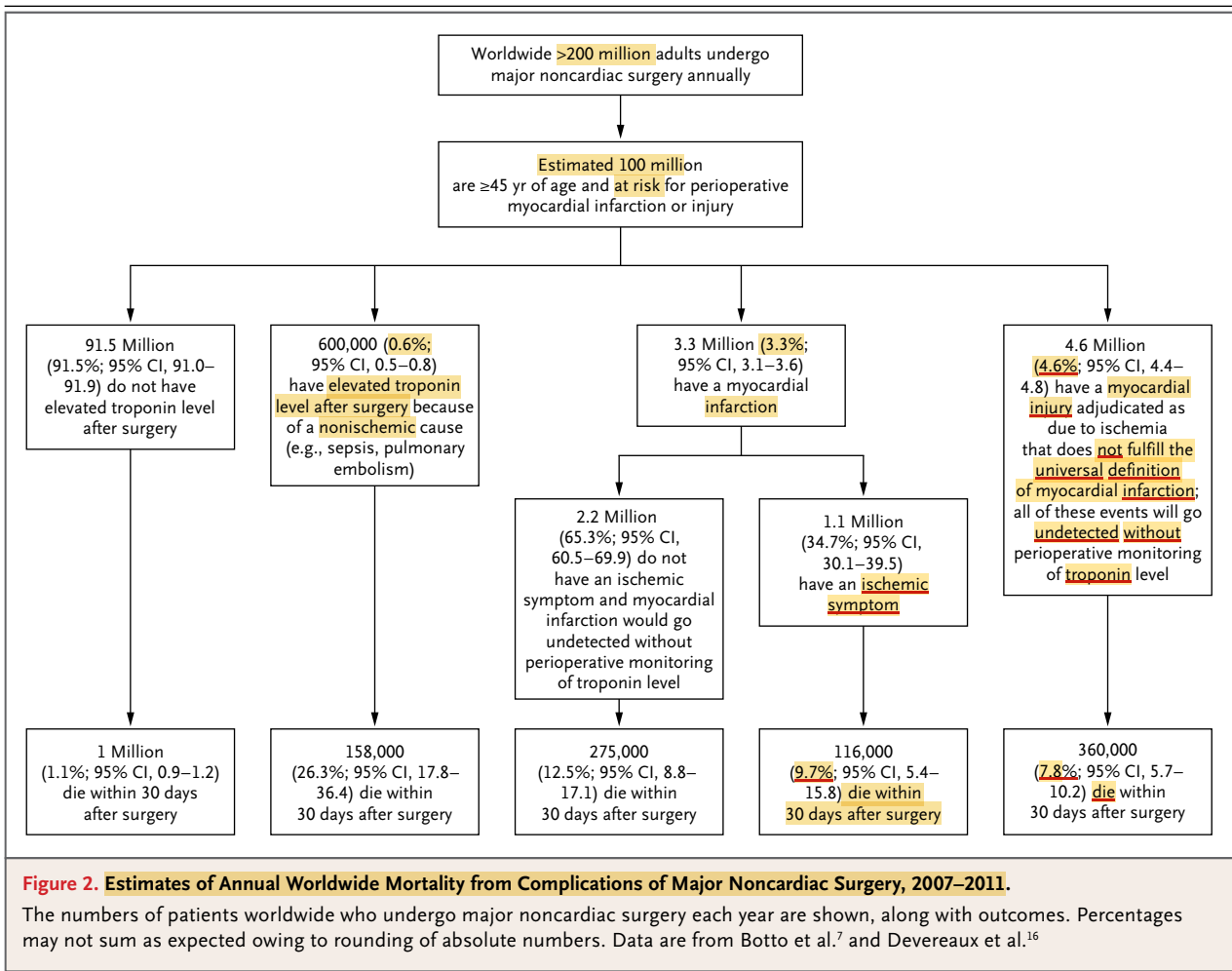
ally receive analgesic medications that can blunt their awareness and mask cardiac symptoms.^{7,16}

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.



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

- 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.
- 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.
- Bickler SW, Spiegel DA. Global surgery — defining a research agenda. *Lancet* 2008;372:90-2.
- Semel ME, Lipsitz SR, Funk LM, Badier AM, Weiser TG, Gawande AA. Rates and patterns of death after surgery in the United States, 1996 and 2006. *Surgery* 2012;151:171-82.
- 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.
- 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.
- 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.
- Bartels K, Karhausen J, Clambey ET, Grenz A, Eltzschig HK. Perioperative organ injury. *Anesthesiology* 2013;119:1474-89.
- 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.
- Rodseth RN, Biccari 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.
- 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.
- 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.
- 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.
- 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.
- Mangano DT, Browner WS, Hollenberg M, Li J, Tateo IM. Long-term cardiac prognosis following noncardiac surgery. *JAMA* 1992;268:233-9.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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. Wijesundera DN, Wijesundera 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. Baxevasis CN, Papias 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, Mrkobra 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, Wijesundera 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, Wijesundera 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. Biccari B. Proposed research plan for the derivation of a new Cardiac Risk Index. *Anesth Analg* 2015;120:543-53.
62. Wijesundera 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, Wijesundera 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 non-cardiac 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. Wijeyundera 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, Wijeyundera DN, Karakouti K, McCluskey S, Tait G. Does tight heart rate control improve beta-blocker efficacy? An updated analysis of the non-cardiac 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. Fouchier 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.

Copyright © 2015 Massachusetts Medical Society.

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.

Cardiac Complications and Major Noncardiac Surgery

TO THE EDITOR: In their review article on cardiac complications in patients undergoing major noncardiac surgery, Devereaux and Sessler (Dec. 3 issue)¹ did not mention the role of statins in the prevention of perioperative events. Statins have proved effective in the reduction of perioperative events in both prospective and retrospective studies.^{2,3} Statins appear to be able to achieve this without any increase in adverse events.⁴ The timing of initiation of preoperative statin therapy is unclear, but trials involving patients with acute coronary syndromes may lead us to believe that even a brief course before surgery may be beneficial.⁵

Patrick F. Mathias, M.D.

Osceola Regional Medical Center
Kissimmee, FL
indianpat127@yahoo.com

No potential conflict of interest relevant to this letter was reported.

1. Devereaux PJ, Sessler DI. Cardiac complications in patients undergoing major noncardiac surgery. *N Engl J Med* 2015;373:2258-69.
2. Berwanger O, Le Manach Y, Suzumura EA, et al. Association between pre-operative statin use and major cardiovascular complications among patients undergoing non-cardiac surgery: the VISION Study. *Eur Heart J* 2016;37:177-85.
3. O'Neil-Callahan K, Katsimaglis G, Tepper MR, et al. Statins decrease perioperative complications in patients undergoing noncardiac vascular surgery: the Statins for Risk Reduction in Surgery (StaRRS) study. *J Am Coll Cardiol* 2005;45:336-42.
4. Schouten O, Kertai MD, Bax JJ, et al. Safety of perioperative statin use in high-risk patients undergoing major vascular surgery. *Am J Cardiol* 2005;95:658-60.
5. Patti G, Pasceri V, Colonna G, et al. Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial. *J Am Coll Cardiol* 2007;49:1272-8.

DOI: 10.1056/NEJMc1516761

TO THE EDITOR: Devereaux and Sessler mentioned in their review that the National Surgical Quality Improvement Program risk index for Myocardial Infarction and Cardiac Arrest (NSQIP MICA) underestimated perioperative cardiac risk because the definition of myocardial infarction was based only on electrocardiographic (ECG) changes, ST-segment elevation, or new left bundle-branch block. This is a factual error, because the NSQIP MICA risk index used troponin levels in defining myocardial infarction.¹ The **Revised Cardiac Risk Index (RCRI)**, which was described

by the authors as the “best-validated” risk index, is a **15-year-old model** that **used creatine kinase levels** to define acute myocardial infarction.² Creatine kinase is less sensitive than troponin for the diagnosis of myocardial infarction.

We ask the authors to make a correction to this error. Articles in the *Journal* are read by the medical community around the world, and physicians will quote this false statement in the review as evidence of the inadequacy of the NSQIP MICA risk index.

Hussam Ammar, M.D.

Rukma Govindu, M.D.

University of Texas Health Science Center at Houston
Houston, TX
h_ammam68@yahoo.com

Ragai Fouda, M.D., Ph.D.

Kasr AlAiny School of Medicine, Cairo University
Cairo, Egypt

No potential conflict of interest relevant to this letter was reported.

1. 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.
2. 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.

DOI: 10.1056/NEJMc1516761

TO THE EDITOR: We believe that the review article by Devereaux and Sessler failed to adequately emphasize studies using **continuous perioperative 12-lead ECG monitoring**, which have shown that **most postoperative myocardial infarctions are preceded by prolonged, reversible ST-segment depression–type ischemia**, whereas postoperative ST-segment **elevation is rare** despite the high incidence of coronary artery disease in studied patients.^{1,2} Those studies led to the recognition that postoperative myocardial infarctions are identifiable, **are mainly of the type 2 variety**, and are often **driven by increased heart rates as a predominant mechanism**.^{1,3} Anemia, hypoxemia, increased myocardial oxygen demand, ventricular overload or underload, systolic or diastolic dysfunction, and neuroendocrine responses to the stresses of surgery all contribute to the decreased ischemic threshold early after surgery.³ Beta-blockers may prevent ischemia, but if used as

prophylaxis, they may cause adverse events when postoperative hypotension, anemia, or infection occurs.³ Silent (asymptomatic) elevations of troponin after surgery are common and predict not only cardiac but also noncardiac morbidity and mortality.⁴ The recurrent observations that cardiac events are preceded by detectable hemodynamic perturbations provide compelling evidence for prevention and deserved emphasis in the review.

Giora Landesberg, M.D., D.Sc.

Charles Weissman, M.D.

Hadassah—Hebrew University Medical Center
Jerusalem, Israel
gio@cc.huji.ac.il

Allan S. Jaffe, M.D.

Mayo Clinic
Rochester, MN

No potential conflict of interest relevant to this letter was reported.

1. Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol* 2003;42:1547-54.
2. 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.
3. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. Perioperative myocardial infarction. *Circulation* 2009;119:2936-44.
4. Landesberg G, Jaffe AS. 'Paradox' of troponin elevations after non-cardiac surgery. *Br J Anaesth* 2015;114:863-5.

DOI: 10.1056/NEJMc1516761

THE AUTHORS REPLY: Observational studies suggest that use of a statin around the time of noncardiac surgery may prevent cardiac complications.¹ There are, however, only a few small, randomized, controlled trials in this setting, and their data are inconclusive regarding the effect of perioperative statin therapy.² There is a need for a large trial of such therapy, to inform whether physicians should prescribe a statin in the perioperative setting.

Ammar and colleagues are correct that there was an error in our statement related to the definition of myocardial infarction in the NSQIP MICA risk index study. We stated that the definition was based only on findings of infarction on ECG; however, according to the NSQIP MICA definition, a patient with a troponin value greater than 3 times the upper level of the reference range in the context of suspected myocardial ischemia would also be deemed to have had a myocardial infarction.³ Our comment that the

NSQIP MICA risk index underestimates risk remains because patients did not undergo systematic measurements of perioperative troponin levels. Without cardiac biomarker screening, more than half of all perioperative myocardial infarctions are missed.⁴

Landesberg and colleagues point out that in their studies the majority of perioperative myocardial infarctions were preceded by ST-segment depression on 12-lead ECG monitoring, as opposed to ST-segment elevation. They state that these findings led to the recognition that postoperative myocardial infarctions are mainly of the type 2 variety (i.e., due to supply-demand mismatch). Landesberg and colleagues may be right that perioperative myocardial infarctions are primarily type 2, but we believe their position that ECG changes are pathognomonic of the cause is erroneous for the reasons outlined below.

Intracoronary optical coherence tomography (OCT) is a highly accurate imaging technique for the detection of thrombus. Ino and colleagues performed intracoronary OCT in 49 patients who had a non-ST-segment elevation (NSTEMI) acute coronary syndrome.⁵ Thrombus was detected in 32 patients (65%): 13 (27%) had a red thrombus (i.e., a red-cell-rich thrombus that is considered fresh), and 19 (39%) had a white thrombus (i.e., a platelet-rich thrombus that is considered older). Therefore, even patients with an NSTEMI acute coronary syndrome may have intracoronary thrombus.

Remote automated systems for continuous noninvasive monitoring of oxygen saturation, hemodynamic variables, and ST-segment depression or elevation in patients after surgery have the potential to identify and facilitate early management of important physiological abnormalities highlighted by Landesberg and colleagues.

P.J. Devereaux, M.D., Ph.D.

Population Health Research Institute
Hamilton, ON, Canada
philipj@mcmaster.ca

Daniel I. Sessler, M.D.

Cleveland Clinic
Cleveland, OH

Since publication of their article, the authors report no further potential conflict of interest.

1. Kapoor AS, Kanji H, Buckingham J, Devereaux PJ, McAlister FA. Strength of evidence for perioperative use of statins to reduce cardiovascular risk: systematic review of controlled studies. *BMJ* 2006;333:1149.

2. Sanders RD, Nicholson A, Lewis SR, Smith AF, Alderson P. Perioperative statin therapy for improving outcomes during and after noncardiac vascular surgery. *Cochrane Database Syst Rev* 2013;7:CD009971.
3. 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.
4. 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.
5. Ino Y, Kubo T, Tanaka A, et al. Difference of culprit lesion morphologies between ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndrome: an optical coherence tomography study. *JACC Cardiovasc Interv* 2011;4:76-82.

DOI: 10.1056/NEJMc1516761

Intensity of Chronic Pain

TO THE EDITOR: In their Perspective article, Ballantyne and Sullivan (Nov. 26 issue)¹ write that when the Joint Commission “introduced a mandate that pain be recognized and treated, numerical ratings of pain intensity were chosen as the chief metric.” This statement may perpetuate misconceptions about our pain standard, which simply says: “The hospital assesses and manages the patient’s pain.” We do not specify how assessments should be done. We state that hospitals should conduct comprehensive pain assessments using methods consistent with the patient’s age, condition, and ability to understand and should reassess and respond to patients’ pain on the basis of their reassessment criteria.² Numerical intensity scales may be helpful as part of initial comprehensive assessments, but they are not required and are usually inadequate on their own. Some patients have difficulty assigning scores to their pain, and qualitative assessments of severity may work better. We also do not specify a numerical value or other target that constitutes adequate control, especially the unrealistic and inappropriate target of zero pain. We endorse the compassionate approach that the authors recommend for assessing the complex pathologic, physiologic, and psychosocial factors that contribute to patients’ perceived pain and for determining the adequacy of pain control.

David W. Baker, M.D., M.P.H.

Mark R. Chassin, M.D., M.P.P.

Joint Commission
Oakbrook Terrace, IL
dbaker@jointcommission.org

No potential conflict of interest relevant to this letter was reported.

1. Ballantyne JC, Sullivan MD. Intensity of chronic pain — the wrong metric? *N Engl J Med* 2015;373:2098-9.
2. Joint Commission. 2015 Comprehensive accreditation manual for hospitals. Oak Brook, IL: Joint Commission Resources, 2015.

DOI: 10.1056/NEJMc1516797

THE AUTHORS REPLY: Indeed, the pain mandate from the Joint Commission did not specify that numerical ratings of pain intensity be used.¹ But the reality is that assessing and documenting pain on the basis of a 0-to-10 numerical rating scale was rapidly adopted as standard practice after the introduction of the mandate because it was a simple and practical way for institutions to comply with the mandate. The problem is that pain is not simple, especially when it is chronic, and there is no single approach to either its assessment or its treatment that is universally successful. Treatment of chronic pain according to a numerical pain score (the “titrate to effect” principle) misdirects care and has produced substantial adverse consequences for patients and society.² We commend the Joint Commission for the recent amendment to its mandate suggesting a greater emphasis on nonopioid treatments.³ However, for the reasons presented in our article, we believe that opioids will still be overprescribed unless changes are also made to the blanket requirement to treat on the basis of the report of pain.

Jane C. Ballantyne, M.D.

Mark D. Sullivan, M.D., Ph.D.

University of Washington School of Medicine
Seattle, WA

Since publication of their article, the authors report no further potential conflict of interest.

1. Phillips DM. JCAHO pain management standards are unveiled. *JAMA* 2000;284:428-9.
2. Sullivan MD, Ballantyne JC. Must we reduce pain intensity to treat chronic pain? *Pain* 2016;157:65-9.
3. The Joint Commission. Clarification of the pain management standard. Joint Commission Perspectives November 2014; 34:11 (http://www.jointcommission.org/assets/1/18/Clarification_of_the_Pain_Management_Standard.pdf).

DOI: 10.1056/NEJMc1516797