NARRATIVE REVIEW ARTICLE

Myocardial Injury After Noncardiac Surgery: Preoperative, Intraoperative, and Postoperative Aspects, Implications, and Directions

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Myocardial injury after noncardiac surgery (MINS) differs from myocardial infarction in being defined by troponin elevation apparently from cardiac ischemia with or without signs and symptoms. Such myocardial injury is common, silent, and strongly associated with mortality. MINS is usually asymptomatic and only detected by routine troponin monitoring. There is currently no known safe and effective prophylaxis for perioperative myocardial injury. However, appropriate preoperative screening may help guide proactive postoperative preventative actions. Intraoperative hypotension is associated with myocardial injury, acute kidney injury, and death. Hypotension is common and largely undetected in the postoperative general care floor setting, and independently associated with myocardial injury and mortality. Critical care patients are especially sensitive to hypotension, and the risk appears to be present at blood pressures previously regarded as normal. Tachycardia appears to be less important. Available information suggests that clinicians would be prudent to avoid perioperative hypotension. (Anesth Analg XXX;XXX:00–00)

GLOSSARY

ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program Surgical Risk Calculator; **ASA** = American Society of Anesthesiologists; **BNP** = B-type natriuretic peptides; **CABG** = coronary artery bypass surgery; **CCTA** = coronary computed tomography angiography; **CI** = confidence interval; **CPT** = current procedural terminology; **ECG** = electrocardiogram; **ENIGMA** = Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia; **HR** = hazard ratio; **hsTnT** = high-sensitivity troponin T; **ICU** = intensive care unit; **MANAGE** = Management of Myocardial Injury After Noncardiac Surgery Trial; **MAP** = mean arterial pressure; **MI** = myocardial infarction; **MINS** = myocardial injury after noncardiac surgery; **NSQIP MICA** = National Surgical Quality Improvement Program for Myocardial Infarction and Cardiac Arrest risk index; **NT-proBNP** = N-terminal pro b-type natriuretic peptide; **OR** = odds ratio; **PCI** = percutaneous coronary intervention; **POISE** = PeriOperative ISchemic Evaluation trial; **RCRI** = revised cardiac risk index; **VISION** = Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Trial

Anesthesia-related intraoperative mortality is now so rare that it is difficult to quantify.[1,2] In contrast, almost 1% of surgical patients in the United States die within a month of noncardiac surgery. Among inpatients, mortality is about 2%.[3,4] If the 30 days after noncardiac surgery were considered a disease, it would be the third-leading cause of death in the United States.[5] About two-thirds of deaths occur during the initial hospitalization, that is, under physician care in high-level health care facilities. Deaths are most strongly associated with major bleeding or myocardial injury.[6]

The goal of this narrative review is to offer an updated clinical perspective on myocardial injury after noncardiac surgery (MINS) during the perioperative period. We summarize pertinent terminology, pathophysiology, and the role of troponin monitoring. We discuss the epidemiology of MINS in the postoperative period. We also explore the potential role of conventional preoperative cardiac risk stratification tools and cardiac biomarkers in predicting MINS, prevention and management strategies for MINS, and finally, the association between perioperative hypotension and myocardial injury.

MYOCARDIAL INFARCTION VERSUS MYOCARDIAL INJURY

Myocardial Infarction

According to the Fourth Universal Definition of Myocardial Infarction, myocardial injury is defined as

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troponin elevation thought to be of ischemic origin, with or without clinical signs.[7] Postoperative myocardial infarction (MI) requires myocardial injury and at least one of the following: symptoms of acute myocardial ischemia, new ischemic electrocardiogram (ECG) changes, development of pathological Q waves, imaging evidence of a new regional wall motion abnormality in the pattern consistent with an ischemic etiology, or identification of a coronary thrombus on angiography including intracoronary imaging or by autopsy.[7]

The Fourth Universal Definition of Myocardial Infarction categorizes MI into 5 different types (Table 1).[7] Acute MI types 1–3 are defined as acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of an increase in troponin concentrations with at least 1 value exceeding the 99th percentile. Types 4 and 5 MIs must meet the criteria for a >5 (type 4) or >10-fold (type 5) increase of cardiac biomarkers (in patients with normal baseline concentrations) and manifest a change from baseline value >20% (in patients with an elevated baseline).

In the nonsurgical setting, myocardial injury typically presents as acute coronary syndrome, which is manifested as MI or unstable angina, and is typically accompanied by chest pain and or shortness of breath.[8] The etiology is usually either thrombotic (type I) or demand ischemia (type II).[8–11]

Perioperative MIs after noncardiac surgery are apparently largely caused by supply-demand mismatch and are considered type II infarctions.[8,11] Perioperative infarctions are usually clinically silent, with symptoms such as chest pain and shortness of breath being rare.[9] In fact, most present as isolated troponin elevation after surgery that is typically accompanied by neither symptoms nor signs.[12,13]

Table 1. Types of Myocardial Infarction

Type I	Caused by atherothrombotic coronary artery disease and usually precipitated by atherosclerotic plaque disruption (rupture or erosion)
Type II	Based on a mismatch between oxygen supply and demand, such as coronary spasm, coronary embolism, arrhythmia, anemia, or hypotension
Type III	Sudden cardiac death, having typical signs and symptoms of myocardial infarction, but patient may succumb soon. Death may occur before elevation in serum biomarkers
Type IV	Related to coronary revascularization procedures, whether percutaneous coronary intervention or coronary artery bypass grafting, may be temporally related to the procedure itself, reflecting periprocedural issues, or may occur later reflecting complications of a device, like early or late stent thrombosis or in-stent restenosis for PCI, or graft occlusion or stenosis with CABG
Type V	Myocardial infarction that occurs during coronary artery bypass grafting, and is mostly related to the details of cardiac preservation, the extent of the direct traumatic injury to the myocardium, as well as any potential ischemic injury

Source: American Heart Association, Inc.[7]
Abbreviations: CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention.

Myocardial Injury After Noncardiac Surgery

Because isolated troponin elevations are associated with death, a new syndrome was defined by the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) investigators: MINS.[12] MINS is a myocardial injury that occurs postoperatively. It differs from MI, in being defined by troponin elevation apparently from cardiac ischemia with or without signs and symptoms. It does not include perioperative myocardial injury due to nonischemic causes such as sepsis, rapid atrial fibrillation, pulmonary embolism, or renal failure; nor does it include chronically elevated troponin concentrations. MINS occurs in about 8 million patients worldwide yearly and is independently associated with risk of death and cardiovascular complications over the initial postoperative year.[14] Throughout this review, we will focus on MINS and distinguish MINS from MI, which will be restricted to events that are accompanied by myocardial symptoms or signs, thus meeting the Fourth Universal Definition of Myocardial Infarction.

TROPONIN MONITORING

Troponins are a family of proteins found in skeletal and cardiac muscle fibers that contribute to contraction. There are 3 subgroups of troponin: C, T, and I. Troponin T and troponin I are both integral parts of the cardiac muscle infrastructure and each contributes to excitation-contraction coupling.[15] The skeletal and cardiac versions of these proteins differ, which led to the development of assays specific to cardiac troponin, although even cardiac-specific assays can rarely cross-react with skeletal muscle proteins released after major muscle injury.[16,17]

Normally, cardiac-specific troponin is undetectable or only barely detectable in blood. But after cardiomyocyte necrosis, troponin is released and can be detected in circulating blood, typically after 3–4 hours. Blood concentrations typically remain elevated for 10–14 days.[18] In the setting of acute coronary syndrome, even slight troponin elevations are strongly associated with mortality.[19]

Types of Cardiac Troponin and Thresholds

Troponin I tests are generic and vary depending on the test in use. The harm thresholds must therefore be determined in consultation with local laboratories. In contrast, troponin T is a branded product (Roche Diagnostics, Basel, Switzerland), and the assay is the same worldwide.

There are 2 versions of troponin T in current use: fourth- and fifth-generation high-sensitivity troponin. Most of the world now use high-sensitivity troponin,

but the test was only recently approved in the United States. Consequently, many centers in the United States still use the fourth-generation test. Changes in fourth troponin T were most comprehensively evaluated in the initial VISION cohort.[12] A peak postoperative concentration ≥0.03 ng/mL predicted a nearly 4-fold increase in 30-day mortality and is therefore now considered the harm threshold.

Because many patients have detectable troponin concentrations preoperatively, the harm threshold for high-sensitivity troponin depends on the baseline concentration. Specifically, high-sensitivity troponin T is considered to be elevated when the peak postoperative concentration increases by at least 5 ng/L from the preoperative concentration to at least 20 ng/L, or when the concentration exceeds 65 ng/L irrespective of baseline concentration.[13] An important proviso and clinical corollary is that it is difficult to reliably assess MINS without a baseline troponin concentration.

Elevated Baseline Troponin

High-sensitivity troponin T concentrations are elevated preoperatively (>14 ng/L) in 2% of patients aged 50 years and almost 40% of patients >70 years of age.[20,21] Elevated baseline high-sensitivity troponin is common in patients with end-stage renal disease, which is consistent with renal excretion of the protein—although chronic kidney disease per se has remarkably little effect on serum troponin concentration.[22,23] Instead, it is likely that many of these patients have concurrent myocardial dysfunction.

Other nonischemic etiologies for high-sensitivity elevations include chronic elevation (64%), sepsis (11%), atrial fibrillation (9%), pulmonary embolus (3%), and cardioversion (1%).[13] But whatever the etiology, preoperative troponin elevation is a poor prognostic sign and is associated with substantially increased mortality over at least 3 postoperative years.[24] For example, noncardiac surgical patients with baseline troponin elevations have an adjusted hazard ratio (HR) for 1-year mortality of 2.5 (95% confidence interval [CI], 2.0–3.2; $P < .001$).[25] Preoperative troponin elevation thus identifies patients who are at high risk of both short-term and long-term mortality.

Routine Troponin Monitoring

It is now clear that without routine troponin screening, most MINS is undetected because nearly all such patients are asymptomatic.[12,13] Consequently, the 2017 Canadian Cardiovascular Society guidelines recommend "daily troponin measurements for 2–3 days in patients with moderate cardiovascular risk."[26] The recent Fourth Universal Definition of Myocardial Infarction international consensus statement, which included the European Society of Cardiology, American College of Cardiology, American Heart Association, and World Heart Federation, recommends "postoperative troponin surveillance in high-risk surgical patients."[7] A useful empirical and practical approach is to monitor troponin in noncardiac surgical inpatients who are 45–64 years old and have at least 1 cardiovascular risk factor, and in all surgical inpatients ≥65 years old. An alternative approach is to restrict troponin monitoring to surgical inpatients who have preoperative N-terminal pro b-type natriuretic peptide (NT-proBNP) concentrations exceeding 300 ng/mL.[27]

Generally, troponin screening should start preoperatively and continue for the first 2 days after surgery—an approach that will identify <95% of MINS.[28] Meta-analysis also suggests that routine troponin measurement is cost-effective, although cost varies considerably from country to country and depends on the specific troponin assay used.[29] Currently, there is no reliable way besides troponin screening to detect either MINS or postoperative MI.

EPIDEMIOLOGY OF MINS

Incidence and Etiology

The incidence of perioperative MI ranges from 3% to 6%, and these events are fatal at least as often as nonoperative MIs.[30,31] The etiology and pathophysiology of MINS is incompletely understood and it remains unclear whether thrombosis or demand ischemia dominants[8]—although most occur in patients who have underlying atheroma. Much postoperative myocardial ischemia is nonetheless probably consequent to supply-demand mismatch.[32,33]

In the nonsurgical setting, approximately 38% of patients who present to the hospital with acute coronary syndrome have an ST-elevation MI.[34] More than 90% of patients with MINS do not display ST segment elevation or any other ischemic symptom.[13] Some patients with perioperative infarctions have angiographic evidence of coronary plaque rupture consistent with type 1 MI. However, few patients with MINS have coronary angiography, and those with ST segment elevation and regional wall motion abnormalities are probably overrepresented.[35,36] The difficulty is that only about 20% of cases of MINS meet the Fourth Universal Definition criteria for MI—although mortality with MINS is nearly as high as it is for MI.[13]

Presentation

Approximately 40% of MINS occurs on the day of surgery, 40% on the first postoperative day, and 15% on the second postoperative day. Thus, while some perioperative myocardial injury presumably occurs during surgery, most apparently develops postoperatively. Only about 14% of patients who experience perioperative MIs report chest pain and 65% of these events are entirely clinically silent. Consequently, 93% of MINS and 68% of MIs are typically unrecognized without

troponin screening.[13,14] Postoperative analgesics might explain why some patients with troponin elevation do not experience chest or arm pain, but a more likely explanation is that the etiology and pathology of postoperative myocardial injury differs from conventional infarctions.[28,37] Key features of MINS are listed in Table 2.

Consequences

VISION, a prospective cohort study, initially evaluated fourth-generation troponin T at 6–12 hours after surgery and on the first 3 postoperative days while patients remained hospitalized.[38] The initial VISION cohort, published in 2012, included 15,133 patients of whom 8% experienced MINS. Overall mortality in patients experiencing MINS was 9.8% compared to 1.1% patients without MINS.[38] Patients with MINS were also at increased risk of 30-day mortality (adjusted HR, 3.3 [95% CI, 2.3–4.8]), and the population-attributable risk was 34% (95% CI, 27–42).[12]

Importantly, the vast majority (84%) of patients remained asymptomatic, and only 42% of the patients fulfilled the formal criteria for MI. Fourth-generation troponin T concentrations that even only slightly exceeded 0.03 ng/mL were prognostic. But the prognosis for cardiac death depended on the magnitude of the perioperative troponin rise, with higher concentrations also corresponding to a shorter median time to death—most of which occurred during the initial hospitalization.

The second phase of the VISION cohort study prospectively enrolled 21,842 patients >45 years of age who were scheduled for noncardiac surgery. Troponin T was again measured 6–12 hours after surgery and on the first 3 postoperative days while patients remained hospitalized. Most patients also had troponin measured preoperatively. The critical distinction from the initial VISION cohort is that high-sensitivity troponin T (hsTnT) was measured, rather than fourth-generation troponin.[13]

Among 21,842 enrolled patients, 266 died within 30 days after surgery (1.2%; 95% CI, 1.1%–1.4%). Mortality increased markedly from 0.1% at a troponin T concentration <5 ng/L to 30% when troponin T exceeded 1000 ng/L (Figure 1). Any change in hsTnT of 5 ng/L or more in absolute terms was associated with an increased risk of 30-day mortality (adjusted HR 4.7, 95% CI, 3.5–6.2). A total of 3633 of 3904 patients with MINS (93.1%, 95% CI, 92.2%–93.8%) did not experience an ischemic symptom. Nevertheless, even in these patients, an elevated postoperative hsTnT (ie, 20–<65 ng/L with an absolute change ≥5 ng/L or hsTnT ≥65 ng/L) was associated with 30-day mortality (adjusted HR 3.2, 95% CI, 2.37–4.32).

Use of high-sensitivity troponin T resulted in several important distinctions from the initial VISION cohort. About 18% of the enrolled surgical patients had at least slightly elevated preoperative troponin concentrations. Consequently, preoperative values need to be considered in defining MINS (see proceeding section for details). Ninety-three percent of MINS was asymptomatic, and 94% occurred within the initial 2 postoperative days. The risk of cardiac death at 1 year in patients having MINS was 4.1% compared to 0.6% in patients without MINS. The adjusted HR for 30-day mortality was 55% greater in patients having ischemic symptoms than those without, a difference that is small compared with the 8.5 increase in odds between patients without and with MINS.

Table 2. Perioperative Myocardial Injury Is Common, Silent, and Deadly

4% of inpatients >45 y have a postoperative MI
MINS
8 million adults/y worldwide
93% without symptoms
80% do not meet third universal definition of MI
Typically type-2 events (supply-demand mismatch)
Mortality is 4% at 30 d
It is not just "troponitis"
8.5% have an MI, cardiac arrest, or death in 30 d
1 in 7 has a major vascular event within 16 mo

Data primary from the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Trial cohort study. MINS is defined by postoperative troponin elevation apparently due to myocardial ischemia. The threshold depends on the type and generation of troponin.[13]

Abbreviations: MI, myocardial infarction; MINS, myocardial injury after noncardiac surgery.

CARDIAC RISK STRATIFICATION FOR MINS

Postoperative myocardial injury does not occur randomly; it is most likely in patients who have preexisting cardiovascular disease. While type, duration, and extent of surgery contribute, baseline risk is a far stronger determinant of both myocardial risk and mortality.[39–41] Perioperative cardiac risk prediction may help guide patient choices, treatment decisions (eg, open versus endoscopic procedure), and intensity and duration of postoperative monitoring. Risk prediction generally uses a combination of clinical risk tools, noninvasive cardiac testing, and, more recently and seemingly most promising, cardiac biomarkers. Table 3 summarizes the advantages, disadvantages, and evidence supporting various risk assessment tools.

Anesthesiologists frequently use patient-reported exercise tolerance as a rough index of fitness. But patients generally have a poor ability to estimate their exercise tolerance, and perhaps consequently, physicians also poorly estimate patient's exercise tolerance. Poor estimates of exercise tolerance probably do not much matter though because even formal cardiopulmonary testing poorly predicts perioperative cardiovascular risk.[42]

Clinical Cardiac Risk Assessment Tools

Many tools for predicting cardiac risk and outcomes after noncardiac surgery have been proposed

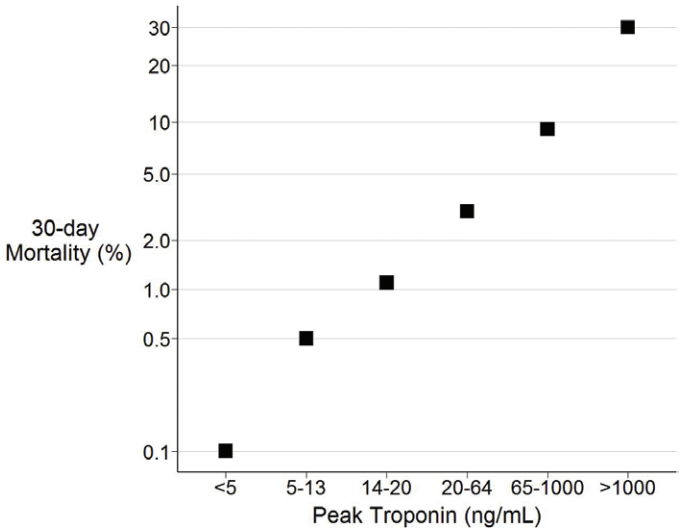

Figure 1. Thirty-day mortality as a function of postoperative peak high-sensitivity troponin T. Mortality increases markedly from 0.1% at a troponin T concentration <5 ng/L to 30% mortality when troponin T exceeds 1000 ng/L. Adapted with permission from the Writing Committee for the Vision Study Investigators, Devereaux PJ, Biccard BM, et al, "Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-day Mortality Among Patients Undergoing Noncardiac Surgery." *JAMA*. 2017;317:1642–1651.[13]

Table 3. Advantages, Disadvantages, and Evidence Supporting Each Risk Assessment Tool for Cardiac Outcomes After Noncardiac Surgery

Assessment	Advantages	Disadvantages	Evidence
RCRI	Ease of use	May not predict risk as well in nonvascular, nonorthopedic and nonthoracic surgery. Assigns most patients to intermediate risk—offers minimal guidance to clinicians Uses only electrocardiographic changes to diagnose myocardial infarction—under estimates risk	Single-center with 4315 patients; last patient enrolled in 1994; 92 events[43]
ACS NSQIP	More accurate than RCRI	Needs online calculator Uses electrocardiographic changes to diagnose myocardial infarction—under estimates risk	400 hospitals with 1414,006 patients covering 1557 unique CPT codes[45]
NSQIP MICA	More accurate than RCRI	Needs online calculator Uses electrocardiographic changes to diagnose myocardial infarction—under estimates risk	>250 centers, with 468,795 patients; last patient enrolled in 2008; 2772 events[90]
Stress test	Useful in patients who are immobile for reasons other than cardiovascular insufficiency	A third of cardiovascular complications occur with normal preoperative stress tests. Prophylactic preoperative revascularization in addition to recommended medical therapy does not improve outcomes in patients with positive stress tests	1179 patients with 82 cardiac events with semiquantitative dipyridamole myocardial perfusion scintigraphy[91]
CCTA	Noninvasive evaluation of coronary vasculature	Expensive Radiation exposure Risk reclassification worsens predictions compared to RCRI/NSQIP	955 at risk patients who had noncardiac surgery. Composite of cardiovascular death and nonfatal myocardial infarction occurred in 74[92]
Focused echocardiogram	Easily available Inexpensive	No evidence to suggest improvement in clinical outcomes	100 moderate-to-high-risk patients in a preoperative clinic[93–95]
BNP and NT-proBNP	Highly predictive	May also be elevated in inflammatory states and certain neuroendocrine disorders	2179 patients; preoperative BNP (and NT-proBNP) correctly reclassified 16% more high-risk patients and 15% more low-risk patients than a model based on preoperative baseline risk factors alone[50]

Abbreviations: ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program Surgical Risk Calculator; BNP, B-type natriuretic peptides; CCTA, coronary computed tomography angiography; CPT, current procedural terminology; NSQIP MICA, National Surgical Quality Improvement Program for Myocardial Infarction and Cardiac Arrest risk index; NT-proBNP, N-terminal pro b-type natriuretic peptide; RCRI, revised cardiac risk index.

over the past 40 years, often for specific populations or procedures. The 3 best-validated and most widely used tools are the Revised Cardiac Risk Index (RCRI), the American College of Surgeons National Surgical Quality Improvement Program Surgical Risk Calculator (ACS NSQIP), and the National Surgical Quality Improvement Program for Myocardial Infarction and Cardiac Arrest (NSQIP MICA) risk index.

The RCRI is a well-validated cardiovascular risk prediction model based on a combination of the risk of surgery, preexisting medical disease, and laboratory values.[43,44] The original derivation and test datasets included many patients who had thoracic, vascular, and orthopedic surgery. Unsurprisingly, subsequent validation in broader surgical populations found that the RCRI does not predict cardiac events as well in patients having other types of noncardiac surgery.[44]

The ACS NSQIP surgical risk calculator was first reported in 2013, based on standardized clinical data from nearly 400 hospitals.[45] The model included >1,400,000 patients who had procedures represented by 1557 unique current procedural terminology codes. The web-based calculator requires users to enter 21 preoperative factors, including demographic characteristics, comorbidities, and procedure details.

The NSQIP MICA risk index, also known as Gupta's index, is a risk prediction model that uses patient age, American Society of Anesthesiologist's physical status, preoperative creatinine, functional status, and procedure type.[46] Currently, none of these 3 best-validated and widely used tools for predicting cardiac risk and outcomes after noncardiac surgery has been shown to have adequate predictive strength and applicability for MINS.

Cardiac Biomarkers

B-type natriuretic peptides (BNPs) are biomarkers that are released into the systemic circulation in response to left atrial myocardial stretching. They are also released in response to ischemia, inflammation, and neuroendocrine stimuli.[47,48] Point-of-care tests are available for natriuretic proteins. Preoperative BNP concentrations are strong predictors of perioperative cardiac events, including mortality, MI, and heart failure.[49,50] In patients having vascular surgery, preoperative BNP risk assessment substantially improves predictions based on the RCRI.[51]

Rodseth et al[27] performed a systematic review of 2179 patients and individual-patient meta-analysis. Elevated preoperative BNP at concentrations >92 ng/L or preoperative NT-proBNP concentrations >300 ng/L were strong predictors of death or nonfatal MI at 180 days or more after surgery (odds ratio [OR], 2.6 [95% CI, 2.0–3.4; $P < .001$]) and within 30 days of surgery (OR, 3.4 [95% CI, 2.6–4.5; $P < .001$]). A model using preoperative BNP correctly reclassified 16% more high-risk patients and 15% more low-risk patients than a model based on preoperative baseline risk factors alone.[27,50] Adding postoperative BNP and N-terminal fragment of proBNP (NT-proBNP) concentrations to preoperative concentrations increases the predictive ability for a composite of death and nonfatal MI at 30 days (adjusted OR, 3.7 [95% CI, 2.2–6.2]) and 180 days (adjusted OR, 2.2 [95% CI, 1.9–2.7]) after noncardiac surgery.[27]

The European Society of Anesthesiology guidelines for preoperative risk assessment for noncardiac surgery recommend preoperative measurement of natriuretic peptides in high-risk patients scheduled for major general or orthopedic surgery (level of evidence 2C) and in intermediate- and high-risk patients scheduled for vascular or major thoracic surgery (level of evidence 1C).[52] The Canadian Cardiovascular Society Guidelines for noncardiac surgery recommend measuring brain natriuretic peptide or NT-proBNP before surgery to enhance perioperative cardiac risk estimation in patients who are 65 years of age or older, are 45–64 years of age with significant cardiovascular disease, or have a RCRI score ≥1. In addition, patients who have elevated biomarker concentrations should have troponin measured on the first 2 postoperative days.[26]

POSSIBLE ASSOCIATION BETWEEN HYPOTENSION AND TACHYCARDIA AND MINS

Intraoperative Hypotension and Tachycardia

Even brief periods of intraoperative hypotension, at thresholds that until recently were considered acceptable by many anesthesiologists, are associated with myocardial injury, renal injury, and mortality.[53–55]

Absolute mean arterial pressure (MAP) <65 mm Hg and a relative decrease of about 30% from baseline are both comparably associated with myocardial injury (Figure 2).[56] Severity and duration of hypotension are key determinants of cardiac injury and mortality. For example, once mean pressure decreases to 55 mm Hg, a duration of only a few minutes is associated with increased mortality.[54,57] A systematic review of reported associations of relative and absolute blood pressure values concluded that the first indication of organ injury occurs when mean arterial pressure decreases <80 mm Hg for ≥10 minutes and that risk increases at progressively lower blood pressures.[58]

We note that adjusted associations between intraoperative hypotension and myocardial injury are considerably weaker than those with many baseline clinical factors. As noted earlier, perioperative myocardial injury does not occur randomly; it is largely restricted to patients with preexisting cardiovascular risk. Baseline risk is thus a far stronger predictor of cardiovascular outcomes than intraoperative hypotension.[59,60] But the possible association between hypotension and MINS is nonetheless important because, unlike baseline patient characteristics, blood pressure can largely be controlled. For example, about a third of all hypotension occurs between anesthetic induction and incision and is independently associated with acute kidney injury.[61] Hypotension during and shortly after induction results from anesthetic drugs and is presumably largely preventable. Continuous intraoperative monitoring (including the use of arterial catheters) reduces episodes of hypotension.[62,63]

Futier et al[64] performed an elegant parallel-group randomized trial that compared tight intraoperative blood pressure control (norepinephrine infusion to maintain systolic pressure within 10% of baseline) versus minimal control (ephedrine for systolic pressure <80 mm Hg or <40% below baseline) in 298 high-risk surgical patients.[64] The primary outcome, a collapsed composite of systemic inflammatory

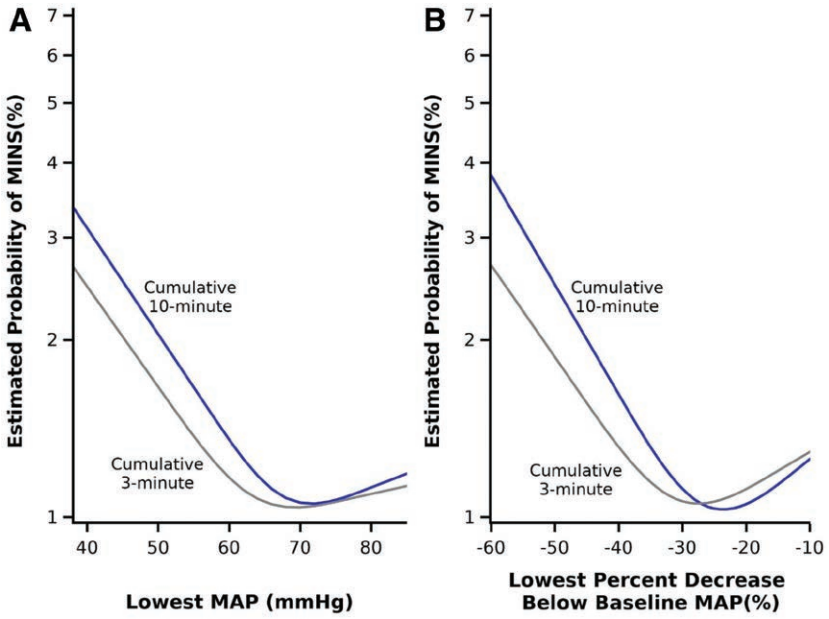

Figure 2. Lowest MAP thresholds for MINS. The left graph shows the relationship between the lowest cumulative absolute MAP maintained for 3 and 10 min and myocardial injury. The right graph shows the relationship between the lowest cumulative relative MAP maintained for 3 and 10 min and myocardial injury. Both graphs are multivariable logistic regression smoothed by restricted cubic spline with 3 degrees and knots at 10th, 50th, and 90th percentiles of given exposure variable. MAP indicates mean arterial pressure; MINS, myocardial injury after noncardiac surgery. Data were derived with permission from Salmasi V, Maheshwari K, Yang D, et al, "Relationship Between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury After Noncardiac Surgery: A Retrospective Cohort Analysis." *Anesthesiology*. 2017;126:47–65. Available at: https://anesthesiology.pubs.asahq.org/article.aspx?articleid=2579833.[56]

response syndrome and/or at least 1 organ failure, occurred in 56/147 patients in the norepinephrine group versus 75/145 patients in the minimal control group: relative risk 0.73 (95% CI, 0.56–0.94).

The intervention threshold in the minimal control group was a systolic pressure of just 80 mm Hg. Presumably, a higher intervention pressure would reduce the observed 25% benefit. Curiously, only 1 MI was reported, which is many times fewer than would be expected in a high-risk population.[13] Futier et al[64] also report a very small actual difference in mean pressure (6.5 mm Hg) and have not reported the amount of hypotension below critical thresholds where most myocardial injury presumably occurs. An additional limitation is that the protocol focused on vasopressor infusions rather than fluid administration. Nonetheless, this is an important study because it suggests that at least some of the observed association between intraoperative hypotension and organ injury is causal and therefore amenable to intervention. Larger robust trials are clearly needed to establish causality.

Tachycardia increases myocardial oxygen demand and impairs diastolic filling time. Chronic tachycardia, including paroxysms of tachycardia with superimposed rhythm disturbances, may contribute to nonoperative MI.[33,65] Given the contribution of tachycardia to nonoperative MIs, clinicians might reasonably assume that intraoperative tachycardia would similarly contribute to MINS, which is thought to be largely consequent to supply-demand mismatch.[32] Consistent with this theory, there is an association between preoperative ambulatory tachycardia and postoperative MINS.[66] Such a relationship has been reported in small cohorts having noncardiac surgery.[67] But interestingly, in nearly 3000 noncardiac surgical patients at Cleveland Clinic, various degrees of tachycardia including the highest individual rate and rates exceeding 100 beats/min were not associated with myocardial injury.[68] Similarly, Abbott et al[69] report that although myocardial injury was associated with tachycardia, harm was most apparent when heart rate exceeded 100 beats/min for prolonged periods.

While there are surely degrees and durations of tachycardia that promote MINS, tachycardia appears to contribute considerably less than hypotension. Available data suggest that heart rates up to 100 beats/min rarely require treatment. Sustained higher rates probably should be treated, but cautiously avoid consequent hypotension. Causing hypotension in an effort to treat tachycardia will likely worsen overall cardiac risk.

Postoperative Hypotension and Tachycardia

Most postoperative MIs and MINS occur postoperatively, nearly all within 48 hours. There is thus considerable reason to be concerned about hemodynamic control in patients recovering from surgery. Nonetheless, vital signs are infrequently measured on surgical wards, typically only at 4- to 8-hour intervals. Consequently, ward hypotension can be sustained for hours without recognition.

A recent analysis of continuous untethered blinded hypotension monitoring on surgical wards at the Cleveland Clinic showed that 24% of all patients had continuous episodes of mean arterial pressure <70 mm Hg for at least 30 minutes, and 14% had continuous pressures <65 mm Hg for at least 15 minutes. Seventy percent of these patients, all of whom had vital signs measured at 4-hour intervals, had no mention of hypotension in their electronic records (Figure 3).[70]

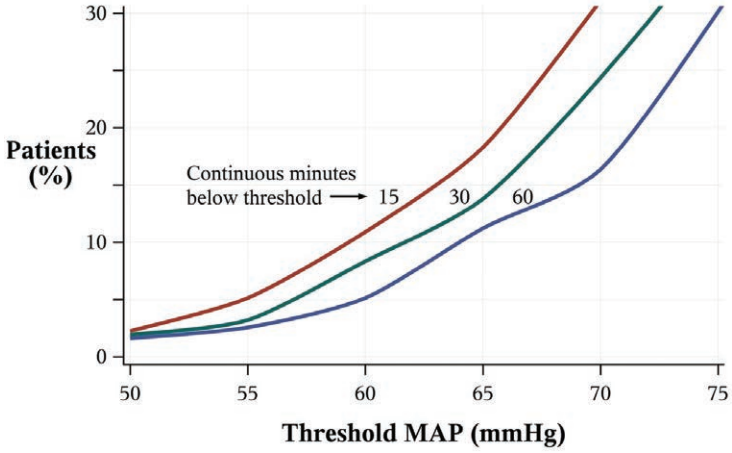

Figure 3. Continuous hypotensive episodes of various durations under various thresholds. For each patient, the total time of the observed longest continuous hypotensive episode (ie, no gap) with MAP readings below various thresholds was computed. The percentage of patients with at least that many minutes below the threshold is plotted. For example, the green line shows that 24% of patients had a continuous episode of MAP <70 mm Hg lasting at least 30 min. MAP indicates mean arterial pressure. Data were derived with permission from Turan A, Chang C, Cohen B, et al. "Incidence, Severity, and Detection of Blood Pressure Perturbations After Abdominal Surgery: A Prospective Blinded Observational Study," *Anesthesiology*. 2019;130:550–559. Available at: https://anesthesiology.pubs.asahq.org/article.aspx?articleid=2723777.[70]

The current approach to ward monitoring was developed decades ago when surgery was largely restricted to relatively healthy patients who all stayed at least a night before surgery and then remained hospitalized long after surgery. Now, we operate on remarkably fragile patients, never even admit 60% in the United States, and send others home early. A consequence is that hospitalized surgical patients are now much sicker than in past decades. To the extent that postoperative hypotension (and perhaps tachycardia) contributes to myocardial injury, current sparse ward monitoring probably misses many potentially important hemodynamic events. The obvious solution is continuous hemodynamic monitoring, which seems likely to reduce the amount of hypotension and may improve outcomes[71]—although this theory remains speculative pending larger randomized trials.

As on surgical wards, hypotension in critical care units is often marked and more sustained than during surgery. Furthermore, intensive care unit (ICU) patients are inherently unstable and have ongoing organ system injury, which may be worsened by hypotension. A strong association of MINS with hypotension at pressures previously regarded as normal and higher than the traditional threshold mean pressure of 65 mm Hg has been seen in large cohorts of medical and surgical ICU patients.[72,73] An important caveat is that this relationship is also complicated by several known and presumably some unknown confounders, which may be difficult to adjust for. Therefore, it currently remains difficult to precisely define thresholds of hypotension associated with myocardial damage in critically ill patients. Further defining blood pressure harm thresholds in critical care patients remains a priority.

PREVENTION OF MINS

Published data are currently lacking on how to safely and effectively prevent MINS. Yet some inferences can perhaps be drawn from 3 large trials that have evaluated potential ways of preventing perioperative myocardial events. PeriOperative ISchemic Evaluation trial (POISE)-I,[74] POISE-2,[75,76] and Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA-2)[77] each included MI as defined by the Third Universal Definition of Myocardial Infarction as their primary outcomes. They thus required an elevated cardiac biomarker and 1 or more ischemic symptoms including pathological Q waves, electrocardiographic changes indicative of ischemia, coronary artery intervention, or new wall motion abnormality on echocardiography or scanning, or autopsy finding of MI.

The POISE trial randomized 8351 patients with known or suspected atherosclerotic disease to receive extended-release metoprolol or placebo for inpatient noncardiac surgery. Perioperative β blockers prevented nonfatal MIs. However, extended-release metoprolol increased the risk of stroke; the strokes were devastating and increased overall mortality. Metoprolol therefore worsened overall perioperative outcomes.[74] Patients who routinely take β blockers should be restarted by the first postoperative day to reduce the risk of atrial fibrillation,[78] but β blockers should not be started de novo in the hopes of preventing postoperative myocardial ischemia and infarction.

The ENIGMA-2 trial also enrolled surgical inpatients with known or suspected cardiovascular disease (n = 7112), who were randomized to either nitrous oxide or nitrogen during anesthesia. The primary outcome was cardiac morbidity defined as a composite of death and cardiovascular complications (nonfatal MI, stroke, pulmonary embolism, or cardiac arrest) within 30 days of surgery. Nitrous oxide had neither beneficial nor substantive harmful effects (Figure 4).[79]

Death or nonfatal MI was also the primary outcome of the POISE-2 trial (n = 10,010). The study population also had known or suspected cardiovascular disease, were scheduled for noncardiac surgery, and were factorially randomized to receive aspirin or

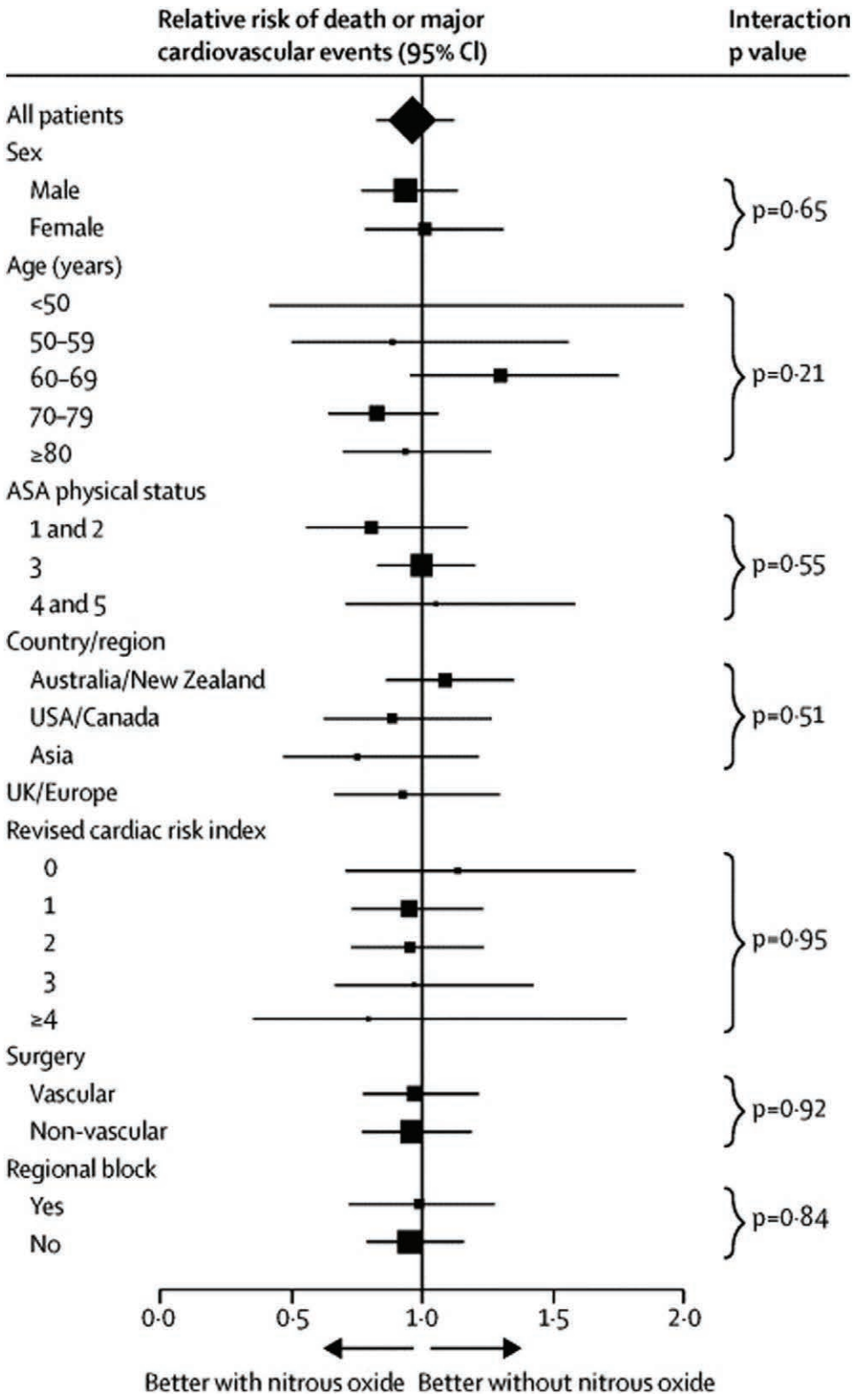

Figure 4. The ENIGMA-II trial randomly assigned 7112 non-cardiac surgery patients at risk of perioperative cardiovascular events to 70% N_2O or 70% N_2 groups. Exposure to nitrous oxide did not increase the risk of the primary outcome (odds ratio [OR], 1.08; 95% CI, 0.94–1.25; *P* = .27), disability or death (OR, 1.07; 95% CI, 0.90–1.27; *P* = .44), death (hazard ratio, 1.17; 95% CI, 0.97–1.43; *P* = .10), myocardial infarction (OR, 0.97; 95% CI, 0.81–1.17; *P* = .78), or stroke (OR, 1.08; 95% CI, 0.74–1.58; *P* = .70). Relative risk for the primary end point (death and cardiovascular complications) associated with the use of nitrous oxide in selected subgroups is shown. ASA indicates American Society of Anesthesiologists; ENIGMA-II, Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia; CI, confidence interval. Reprinted from *The Lancet*, 384, Myles PS, Leslie K, Chan MT, et al, "The Safety of Addition of Nitrous Oxide to General Anaesthesia in At-Risk Patients Having Major Non-Cardiac Surgery (ENIGMA-II): A Randomised, Single-Blind Trial," 1446–1454, 2014, with permission from Elsevier.[79]

placebo and simultaneously to clonidine or placebo. Neither aspirin nor clonidine reduced the incidence of MI and death. However, clonidine was associated with bradycardia and hypotension, and aspirin with increased bleeding.[75,76] A caveat is that few patients in the trial had coronary artery stents; the results of POISE-2 should therefore not be considered an indication for stopping aspirin in patients who have stents or other indications for platelet inhibition. But it does indicate that aspirin or clonidine should not be started

de novo in the hopes of reducing perioperative cardiovascular risk.

MANAGEMENT OF MINS

Some believe that there is no need for troponin screening because nothing can be done for patients with elevated levels. Actually, there is much that can be done (Table 4). Failing to screen and to act on screening results is a missed opportunity to treat patients—and for anesthesiologists to act as perioperative physicians.

Patients with MINS have at least a 3% chance of dying within 30 days,[13] and increased mortality risk continues for at least 1 year.[80] An anesthesiologist, intensivist, or hospitalist serving as the perioperative physician thus ideally engages with MINS patients and explains what has happened, the prognostic implications, and therapeutic options. Cardiologists may be best suited for these discussions; furthermore, patients with MINS need long-term follow-up that few anesthesiologists can provide. A cardiology consult is therefore probably the best initial response to postoperative troponin elevations. But that said, there are cardiologists who remain unfamiliar with MINS and inappropriately dismiss asymptomatic troponin elevations as unimportant "troponitis." Perioperative physicians may thus need to guide cardiologists to the relevant literature.[12,13,81]

Aspirin is not helpful for primary prevention of perioperative infarctions,[75] although it should usually be continued in patients who had previous percutaneous coronary interventions.[81] But at least for nonoperative MIs, there is strong evidence that low-dose aspirin reduces the risk of secondary infarctions by 23%.[82] Angiotensin-converting enzyme inhibitors,[83] angiotensin receptor blockers,[80] and statins[84,85] also reduce secondary vascular complications. In an observational subanalysis of POISE patients, those who were started on aspirin and/or statins had markedly lower risk of 30-day mortality.[74] Clinicians should at least consider these treatments in patients who experience MINS.

It is already well established that the perioperative period constitutes a "teachable moment" during which patients are especially receptive to lifestyle advice.[86] Presumably, patients are even more receptive than usual after an operation complicated by a cardiovascular event. It is therefore an unfortunate missed opportunity when clinicians fail to use MINS as an opportunity to discuss smoking cessation, healthful eating, and exercise.

And finally, there is a specific treatment that has been shown to benefit MINS patients. Prolonged anticoagulation is a well-established treatment for nonoperative MIs.[87,88] The Management of Myocardial Injury After Noncardiac Surgery (MANAGE) trial randomized patients who had MINS to dabigatran or placebo for up to 2 years. The primary outcome was a composite of vascular complications, primarily reinfarction. Dabigatran reduced the HR 28%, with a number-needed-to-treat of 24 (Figure 5).[81] Dabigatran

Table 4. Clinical Considerations When Patients Have Elevated Postoperative Troponin Concentrations

Cardiology consultation
Occasional patients need catheterization and angioplasty
Patients will benefit from long-term care and monitoring
Aspirin reduces secondary infarctions by 23%
Consider statins and angiotensin-converting enzyme inhibitors
Heart rate and hypertension control
Lifestyle interventions (teachable moment)
Smoking cessation
Healthful diet
Exercise
Anticoagulation: 28% hazard reduction

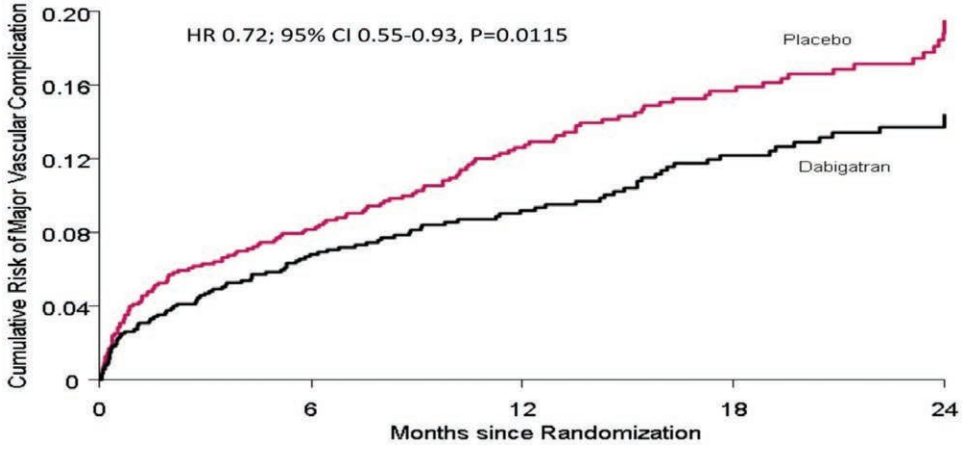

Figure 5. The MANAGE trial randomized 1754 patients who had MINS to dabigatran or placebo for up to 2 y. The primary outcome was a composite of vascular complications, primarily reinfarction. Dabigatran reduced the hazard ratio 28%, with a number-needed-to-treat of 24. Major bleeding was similar in each group. CI indicates confidence interval; HR, hazard ratio; MANAGE, Management of Myocardial Injury After Noncardiac Surgery trial; MINS, myocardial injury after noncardiac surgery. Adapted from *The Lancet*, 391, Devereaux PJ, Duceppe E, Guyatt G, et al, "Dabigatran in Patients with Myocardial Injury After Noncardiac Surgery (MANAGE): An International, Randomized, Placebo-Controlled Trial," 2325–2334, 2018, with permission from Elsevier.[95]

increased minor bleeding, but not major bleeding, which was comparable in the treatment and placebo groups. This is consistent with a previous study showing that the drug is safer than warfarin.[89]

SUMMARY

Perioperative MIs are usually clinically silent, with symptoms such as chest pain and shortness of breath being rare. Troponin elevation after surgery—an indication of myocardial injury—is typically accompanied by neither symptoms nor signs—but the association between troponin elevation and mortality is nearly as strong without as with symptoms and signs. MINS differs from MI in being defined by troponin elevation apparently from cardiac ischemia, with or without signs and symptoms.

Perioperative myocardial injury (distinct from MI) is common, typically silent, and strongly associated with mortality. Myocardial injury is usually asymptomatic and only detected by routine troponin monitoring. A reasonable strategy is to determine serum troponin concentrations preoperatively and on the first 2 postoperative mornings in surgical inpatients >45 years old who have at least 1 cardiovascular risk factor, and in all surgical inpatients over the age of 65 years.

There is currently no known safe prophylaxis for perioperative MI and injury. Beta blockers significantly reduce MI risk, but with a concomitant increase in stroke and mortality. Avoiding nitrous oxide does not reduce cardiovascular risk. Clonidine and aspirin do not reduce risk and both cause complications.

Intraoperative and postoperative hypotension is associated with MINS, acute kidney injury, and death. In contrast, tachycardia appears to be considerably less important. Limited randomized data suggest that preventing hypotension reduces a composite of serious complications by about 25%. Large trials of hypotension prevention are clearly needed. But meanwhile, it seems prudent to avoid intraoperative and postoperative hypotension when practical.

DISCLOSURES

Name: Kurt Ruetzler, MD.
Contribution: This author helped to conduct the literature search, write the manuscript, and approved the final version of the manuscript.
Conflicts of Interest: None.
Name: Ashish K. Khanna, MD, FCCP, FCCM.
Contribution: This author helped to conduct the literature search, write the manuscript, and approved the final version of the manuscript.
Conflicts of Interest: A. K. Khanna is a consultant for Edwards Lifesciences.
Name: Daniel I. Sessler, MD.
Contribution: This author helped to conduct the literature search, write the manuscript, and approved the final version of the manuscript.
Conflicts of Interest: D. I. Sessler is a consultant for Edwards Lifesciences. D. I. Sessler also participated in the development of the 2017 Canadian Cardiovascular Society guidelines.
This manuscript was handled by: Richard C. Prielipp, MD, MBA.

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