TnT

Blowing the Cover from Perioperative Myocardial Injury

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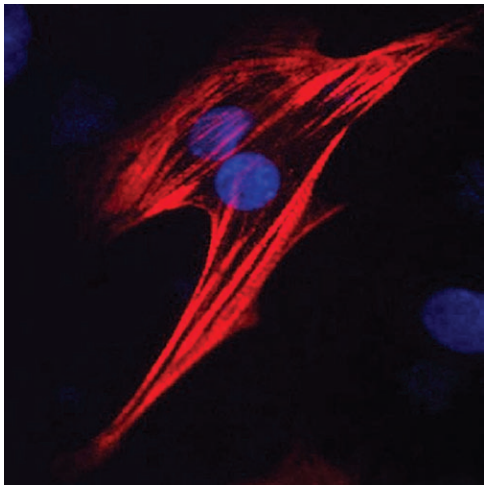
CME This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

PREVENTION, detection, and therapy of myocardial infarction have been fundamental goals of perioperative medicine for many years. As one of the first monitors dedicated to detecting myocardial ischemia, continuous electrocardiography for patients undergoing surgery became more commonly used in the 1950s. Indeed, by 1978, guidelines recommended routine baseline electrocardiogram testing for all adult patients before undergoing surgery.[1] However, given that preoperative electrocardiographic abnormalities are not necessarily predicative of postoperative myocardial infarction,[2] current practice advisories recognize that preoperative testing should rather be considered for patients with cardiovascular risk factors.[3] Intraoperative echocardiography is routinely used for diagnosis and therapy in cardiac surgery.[4,5] In addition, it can also be used safely in noncardiac surgery for the detection of new regional wall motion abnormalities indicative of myocardial ischemia.[6,7] However, given the resources required for a complete diagnostic echocardiographic examination, its use as a screening tool for myocardial injury in noncardiac surgery is likely limited. A common test used for the diagnosis of perioperative myocardial injury is the measurement of plasma troponin levels. In the past, minor increases in serum troponin levels have often clinically been dismissed as less relevant cases of supply/demand mismatch. This is likely related to the fact that a troponin increase itself does not meet definition criteria for myocardial infarction and a lack of consensus on the most appropriate therapeutic approach. Although it seems intuitive that myocardial infarction leading to cell death is of greater consequence than myocardial ischemia without necrosis, the relevance of minor myocardial injury is not well defined. Furthermore, the progression from reversible ischemic damage to necrosis occurs on a biologic continuum, making cutoffs based on the presumed degree of cellular injury impractical at best. Defining clinical relevance of biomarkers such as Troponin T (TnT) according to their association with meaningful outcomes, such as 30-day mortality, adds substantial value for the practicing clinician. The significance of creatine muscle and brain isoenzyme and TnT to predict mortality and major cardiovascular events has previously been highlighted in a meta-analysis.[8] The current study by the VISION Writing Group[9] underlines the fundamental importance of even subtle perioperative TnT increases for morbidity and mortality in surgical patients. The current findings are a *post hoc* analysis of prospectively collected data from *The Vascular events In noncardiac Surgery patIents cOhort evaluatioN* trial.[10] The reported analyses extend the interpretation of the *The Vascular events In noncardiac Surgery patIents cOhort evaluatioN* study, as they confirm the independent association of a TnT value of 0.03 ng/ml or greater with all-cause 30-day mortality after adjusting for preoperative risk factors and perioperative events.



"The current study … underlines the fundamental importance of even subtle perioperative TnT increases for morbidity and mortality in surgical patients."

In a diverse cohort comprising 15,065 patients with age 45 years or older undergoing noncardiac surgery requiring at least overnight hospitalization, the authors observed a 30-day mortality rate of 1.7%. This is consistent with previously reported death rates within 30 days of surgery. In fact, the magnitude

Image: Silvia Martín-Puig (immunofluorescent monoclonal antibody staining of cardiac Troponin T in human fetal cardiomyocytes). Used with permission.

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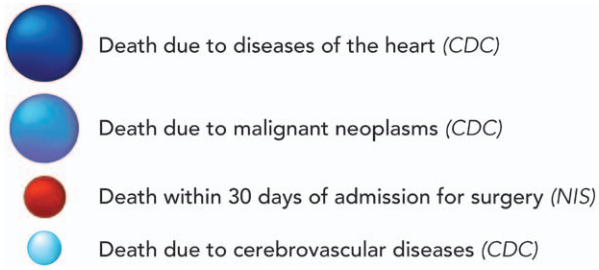

Fig. 1. Magnitude of perioperative mortality. The three leading causes of death in the Center for Disease Control's (CDC) annual death table for the United States in 2006 were: (1) diseases of heart (n = 631,636), (2) malignant neoplasms (n = 559,888), and (3) cerebrovascular diseases (n = 137,119). By using the Nationwide Inpatient Sample (NIS) for the same year, Semel *et al.*[13] reported 189,690 deaths within 30 days of admission for inpatients having a surgical procedure. In magnitude, all-cause 30-day inpatient mortality after surgery approximated the third leading cause of death in the United States. Figure adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health. Bartels K, Karhausen J, Clambey ET, Grenz A, Eltzschig HK: Perioperative organ injury. Anesthesiology 2013, copyright 2013.[11]

of all-cause perioperative mortality would make it the number three cause of death in the United States (fig. 1).[11] The current study suggests that this staggeringly high rate of death after surgery is in many circumstances preceded by often subclinical myocardial injury.[9] The authors used regression analysis to validate a cutoff value for TnT of 0.03 ng/ml or greater to define myocardial injury after noncardiac surgery. Moreover, they discovered that of the 8% of patients who developed myocardial injury after noncardiac surgery, 58.2% would not have fulfilled the universal definition for myocardial infarction. By using data from the 8,351 patients included in the PeriOperative ISchemic Evaluation trial, Devereaux *et al.*[12] previously reported a mortality rate of 11.6% in patients affected by perioperative myocardial infarction. Even when applying less rigorous criteria for myocardial injury such as a peak TnT value of 0.03 ng/ml, the current study found affected patients to be 4.3 times as likely to die within 30 days.[9] Furthermore, 1 of 10 patients with myocardial injury after noncardiac surgery did not survive 30 days after surgery. The combination of the high incidence of myocardial injury after noncardiac surgery, its prognostic relevance for 30-day mortality, and the ease and feasibility of the test to detect it (using TnT) point to tremendous opportunities for design of clinical studies to test novel interventions to attenuate myocardial injury and perioperative mortality.

Although the need for new cardio-protective therapies has been convincingly demonstrated, causality of myocardial injury and mortality has not. Perioperative ischemia and inflammation are likely to lead to injury in other organs too. Similar to low-level myocardial injury, hypoxia-sensitive tissues such as kidney are also prone to ischemic damage. Although preoperative estimated glomerular filtration rate was not associated with mortality in the current study, it seems conceivable that more sensitive markers of renal injury, such as insulin-like growth factor-binding protein 7 or tissue inhibitor of metalloproteinases-2, could have shown a comparable response pattern to TnT. Hence, the observed mortality could have been due to multiorgan injury rather than isolated myocardial injury. Therefore, interventional clinical trials focused solely on prevention of myocardial infarction might not be successful. Clearly, the development of innovative, mechanism-based approaches to prevent or treat perioperative organ injury, including myocardial injury, is paramount. These will then need to be tested in rigorous clinical trials to translate the results of this study into improved patient outcomes.

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Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Longnecker's Trade Card against the "Asphyxie" of "The Old Way"

In decrying "The Old Way" of nearly asphyxiating patients with brief administrations of 100% nitrous oxide, dentist F. C. Longnecker advertised images of a patient before and after receiving laughing gas *via* a mouthpiece from a large bag (*above*). According to Dr. Longnecker:

With your fingers your nose compress,
The real natural place of breath,
Then by swallowing, you will see
The cause of so much "asphyxie" [sic]
Now laid to my pure gas
With this nose compress and thermometer too,
You will always know how much will do.

This trade card is part of the Wood Library-Museum's Ben Z. Swanson Collection. (Copyright © the American Society of Anesthesiologists, Inc.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.

The Conundrum of Care in Perioperative Stress

American Society of Anesthesiologists Article

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The Conundrum of Care in Perioperative Stress Myocardial Ischemia, the Importance of 30-Day Outcomes and the Perioperative Surgical Home

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The Perioperative Surgical Home (PSH) is an innovative method of delivering health care during the entire patient care experience, from the time of decision for surgery, throughout preoperative, intraoperative and postoperative care, beyond discharge, until full patient recovery.[1] The goal of the PSH includes better care coordination and increased standardization while still allowing for patient variability, which has been shown to result in better clinical outcomes. An added benefit of the PSH model is the reduction of costs associated with health care by eliminating unnecessary tests, improving efficiencies, and reducing postoperative complications and hospital readmissions through coordination of care and transition planning.[2]

It is hard to imagine a more immediate anesthesia patient safety and coordination of care issue than the identification and management of relatively healthy patients recently identified to be at risk for postoperative morbidity and mortality. Analyses of the VISION cohort study, published in 2012 and 2014, prospectively studied perioperative patients, revealing a markedly high incidence of silent postoperative myocardial ischemia, infarction and mortality.[3] These patients did not fall into the category typically reserved for high-risk patients.[4]

The 2014 VISION study examined outcomes of 15,065 patients over age 45 who had major non-cardiac surgery and required an overnight stay. Vascular, colorectal or major orthopedic joint replacements were the majority of procedures performed. Plasma troponin T (TnT) concentrations were initially obtained within six to 12 hours after surgery and again on each of the first three postoperative days. Eight percent of patients had elevated postoperative TnT concentrations(TnT) >0.03 ng/mL, consistent with myocardial injury after non-cardiac surgery (MINS).

Ischemic Features of Patients with MINS

Only 15 percent of patients with MINS reported ischemic symptoms. However, 35 percent of MINS patients had ischemic electrocardiographic (EKG) changes, a majority of which were in the anterior chest leads. Combining those who reported ischemic symptoms and those who had ischemic changes on EKG, only 42 percent of patients with MINS showed an ischemic feature that met the criteria for diagnosis of myocardial infarction.[5] Since EKGs were largely obtained only because of elevated TnT concentrations, it is apparent that nearly all infractions would have been missed without biomarker monitoring.

Ten percent of patients with MINS were dead within 30 days of surgery, with most mortality occurring in-hospital. The death rate was nearly identical in patients with asymptomatic MINS and in those with ischemic symptoms. Most patients who died thus did not meet the universal definition of myocardial infarction criteria because of lack of some clinical feature.[5] Death in MINS patients is by far a leading cause of 30-day postoperative mortality. It is not widely recognized that this postoperative mortality is actually the third-leading cause of death nationwide.[6]

Identification of Perioperative Patients at Risk of Active Ischemia

Identifying perioperative patients "at risk" of having active ischemia is the first and substantial challenge for perioperative physicians. Among patients with active ischemia, 80-85 percent will have silent ischemia that is not accompanied by typical symptoms or symptom complexes suggestive of angina pectoris. Absent daily postoperative troponin testing for the first three days, most patients with active myocardial ischemia will thus be missed.[7,8] Why lethal myocardial ischemia does not produce symptoms in the perioperative period remains unknown, but the administration of potent analgesics may contribute.

Improving or Verifying the Quality of EKG Data

Applying simple quality controls may help in interpreting and comparing EKGs. In 12-lead EKGs, negative "P" waves in lead I may suggest limb lead reversal, congenital dextrocardia or acquired dextrotorsion. Leads I, AVL and V6 share the same sagittal plane, with the size of the "R" waves increasing from AVL to 1 to V6 following their relative proximity to the left ventricle. Prominent "S" waves in V6, not seen in leads I and AVL, usually indicate misplaced

lateral chestleads, where lead V6 is located anterior to the midaxillary line. This will help ensure both EKGs were properly obtained before comparison.

It is difficult to make good judgments from faulty data. EKG leads are often misplaced.[9] Proper EKG lead placement is important, and it should follow bony landmarks. Lead placement for 12-lead EKG studies and all perioperative monitoring should adhere to standard anatomic landmarks to permit comparison of intraoperative and postoperative tracings to baseline EKG studies. The V5 lead should be placed where the fifth intercostal space intersects with the anterior-axillary line, overlaying the LV. EKG changes consistent with ischemia are more commonly noted in the anterior chest leads compared to inferior limb leads.[3] This is not surprising. The closer the inferior leads (RL and LL) are to the heart, the less likely inferior ischemia will be detected. Surgical procedures on a hip, abdomen or groin may preclude placing the lower limb leads in a standard position on the leg or thigh. To optimize detection of myocardial ischemia, correct lead placement should be maintained in PACU, telemetry, intermediate care and ICU settings. EKG changes may trigger earlier-than-planned troponin studies.

Observation of technical aspects when obtaining EKG studies may identify opportunities for improvement in ischemia detection and lead to technically correct studies for later comparison in all postsurgical patients. Improving EKG quality, while valuable, is not a substitute for biomarker testing.

Management of Silent Myocardial Ischemia

Eighty-seven percent of MINS events, TnT elevations, were noted by the end of the second postoperative day.[3] Acute inferior wall myocardial ischemia may present as postoperative gastrointestinal complaints, such as severe or unrelenting nausea or belching. MINS placed patients at higher risk for other outcomes, including non-fatal cardiac arrest, congestive heart failure and stroke.[3]

The imbalance of myocardial oxygen demand and supply, including plaque rupture, thrombosis and spasm, must be corrected with the goal of adequate myocardial tissue perfusion and preservation. A cardiology consultation may be in order for both management and future continuity of care within the context of the PSH care model. Aspirin and statins to prevent coronary thrombosis and stabilize coronary plaques are often included in current outpatient therapy. Pharmacological interventions may suffice; however, correction of anatomic obstructions may be required.

Post-discharge management is at the discretion of the cardiologist, surgeon and primary care doctors, in conjunction with the perioperative physician in a PSH model. Patient education and directed risk reduction strategy for known risk factors such hypertension and hyperlipidemia are indicated and may be best accomplished by the perioperative physician and team upon discharge planning.

The silent nature of most episodes of perioperative myocardial ischemia and the frequent adverse outcomes associated with them, even in the setting of higher than normal, yet low troponin levels, demands our attention to identify, educate and provide continuing and competent perioperative care well beyond the time of discharge.[10] Economically, the laboratory costs of four troponin levels is approximately the same as one dose of intravenous acetaminophen; the former has the potential to prevent myocardial infarction and death.

This patient population, previously thought to be at “low cardiac risk” for surgery and anesthesia, may best be diagnosed, treated and managed through the continuum of care model provided by the PSH. Preoperative optimization, appropriate baseline EKGs, appropriate consults, accurate perioperative monitoring for ischemic changes, daily follow-up with troponin levels, postoperative consultation, management, patient education and continued follow-up visits may lead to reduced incidence of myocardial ischemia, infarction and 30-day mortality.

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Myocardial Injury after Noncardiac Surgery

A Large, International, Prospective Cohort Study Establishing Diagnostic Criteria, Characteristics, Predictors, and 30-day Outcomes

The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Writing Group, on behalf of The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Investigators

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ABSTRACT

Background: Myocardial injury after noncardiac surgery (MINS) was defined as prognostically relevant myocardial injury due to ischemia that occurs during or within 30 days after noncardiac surgery. The study's four objectives were to determine the diagnostic criteria, characteristics, predictors, and 30-day outcomes of MINS.

Methods: In this international, prospective cohort study of 15,065 patients aged 45 yr or older who underwent in-patient noncardiac surgery, troponin T was measured during the first 3 postoperative days. Patients with a troponin T level of 0.04 ng/ml or greater (elevated "abnormal" laboratory threshold) were assessed for ischemic features (*i.e.*, ischemic symptoms and electrocardiography findings). Patients adjudicated as having a nonischemic troponin elevation (*e.g.*, sepsis) were excluded. To establish diagnostic criteria for MINS, the authors used Cox regression analyses in which the dependent variable was 30-day mortality (260 deaths) and independent variables included preoperative variables, perioperative complications, and potential MINS diagnostic criteria.

Results: An elevated troponin after noncardiac surgery, irrespective of the presence of an ischemic feature, independently predicted 30-day mortality. Therefore, the authors' diagnostic criterion for MINS was a peak troponin T level of 0.03 ng/ml or greater judged due to myocardial ischemia. MINS was an independent predictor of 30-day mortality (adjusted hazard ratio, 3.87; 95% CI, 2.96–5.08) and had the highest population-attributable risk (34.0%, 95% CI, 26.6–41.5) of the perioperative complications. Twelve hundred patients (8.0%) suffered MINS, and 58.2% of these patients would not have fulfilled the universal definition of myocardial infarction. Only 15.8% of patients with MINS experienced an ischemic symptom.

Conclusion: Among adults undergoing noncardiac surgery, MINS is common and associated with substantial mortality. **(Anesthesiology 2014; 120:564-78)**

WORLDWIDE, millions of patients die annually within 30 days of noncardiac surgery;[1,2] myocardial ischemia is a frequent cause.[3,4] Most studies on noncardiac surgery addressing cardiac complications focus on perioperative myocardial infarction.[5–7] The "conventional" definition and diagnostic criteria of myocardial infarction in the perioperative period come from the joint task force (European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, and World Heart Federation) for the universal definition of myocardial infarction.[7] This document defines myocardial infarction as myocardial necrosis in a clinical setting consistent with acute myocardial ischemia, and the most common diagnostic criteria consist of an elevated troponin value with either

What We Already Know about This Topic

- Emerging evidence suggests that many patients sustain myocardial injury in the perioperative period which will not satisfy the diagnostic criteria for myocardial infarction
- Myocardial injury after noncardiac surgery was defined as prognostically relevant myocardial injury due to ischemia that occurs during or within 30 days after noncardiac surgery
- This study then determined the diagnostic criteria, characteristics, predictors, and 30-day outcomes of myocardial injury after noncardiac surgery

What This Article Tells Us That Is New

- Myocardial injury after noncardiac surgery is common among adults undergoing noncardiac surgery and associated with substantial mortality

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 533. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication April 19, 2013. Accepted for publication October 30, 2013. From the Hamilton General Hospital, David Braley Cardiac, Vascular, and Stroke Research Institute, Population Health Research Institute, Hamilton, Ontario, Canada (P.J.D.); and Members of The VISION Writing Group and VISION Investigators, who are listed in appendix 1 and appendix 2, respectively.

 Anesthesiology 2014; 120:564-78

an ischemic symptom or an ischemic electrocardiographic finding.

Emerging evidence suggests that many patients sustain myocardial injury in the perioperative period which will not satisfy the diagnostic criteria for myocardial infarction.[8] Nevertheless, these events portend a poor prognosis that timely and appropriate intervention could potentially improve.[4] This suggests that a new diagnosis of Myocardial Injury after Noncardiac Surgery (MINS) may be useful to patients and clinicians. Our proposed definition of MINS is as follows: myocardial injury caused by ischemia (that may or may not result in necrosis), has prognostic relevance and occurs during or within 30 days after noncardiac surgery. The definition of MINS is broader than the definition of myocardial infarction in that it includes not only myocardial infarction but also the other prognostically relevant perioperative myocardial injuries due to ischemia. MINS does not include perioperative myocardial injury which is due to a documented nonischemic etiology (*e.g.*, pulmonary embolism, sepsis, cardioversion). No study has established the diagnostic criteria, characteristics, predictors, and 30-day outcomes of MINS.

The *V*ascular events *I*n noncardiac *S*urgery pat*I*ents c*O*hort evaluatio*N* (VISION) study is a large, international, prospective cohort study evaluating complications after noncardiac surgery (clinicaltrials.gov, identifier NCT00512109). A previous publication of the VISION study demonstrated that after adjustment of preoperative clinical variables (*e.g.*, age), peak troponin T (TnT) values of 0.02 μg/l, 0.03 to 0.29 μg/l, and 0.30 μg/l or greater in the first 3 days after noncardiac surgery were independent predictors of 30-day mortality.[3] These analyses established the prognostic relevance of troponin measurements after surgery without taking into account whether the troponin elevations were due to an ischemic or nonischemic etiology. These analyses did not evaluate troponin elevations that occurred beyond day 3 after surgery. Finally, these analyses adjusted for only preoperative variables and did not assess for confounding through other perioperative complications. For this current publication, our primary objective was to inform the diagnostic criteria of MINS, and our secondary objectives were to determine the characteristics, predictors, and 30-day outcomes of MINS. To do this, we analyzed the VISION data, evaluated troponin elevations until day 30 after surgery, excluded nonischemic troponin elevations, and adjusted for perioperative complications.

Materials and Methods

Study Design

We have previously described the methodology of the VISION Study.[3] This is an ongoing, international, prospective cohort study of a representative sample of adults undergoing noncardiac surgery. At the beginning of this study, patients had fourth-generation TnT measurements after noncardiac surgery. The first 15,000 patients had event rates approximately three times higher than expected. Recognizing that we had sufficient events to address our objectives related to the fourth-generation TnT measurements, the Operations Committee decided to subsequently monitor the fifth-generation high-sensitivity TnT assay. This publication is restricted to patients enrolled during the period of fourth-generation TnT use.

Patients

Eligible patients for the VISION study had noncardiac surgery, were aged 45 yr or older, received a general or regional anesthesia, and underwent elective or urgent/emergency surgery during the day or at night, during a weekday or the weekend. Patients were excluded who did not require an overnight hospital admission after surgery, who were previously enrolled in the VISION Study, or who declined informed consent. Additional exclusion criteria for the MINS study were: patients not having a fourth-generation TnT measurement after surgery; patients having a TnT measurement reported as less than 0.04 ng/ml, less than 0.03 ng/ml, or less than 0.02 ng/ml, instead of the absolute value; patients whose troponin elevation was adjudicated as resulting from a nonischemic etiology (*e.g.*, sepsis, pulmonary embolism, cardioversion); and patients with incomplete data for the preoperative predictors of 30-day mortality.

Research personnel primarily obtained consent before surgery. For those from whom we could not obtain consent preoperatively (*e.g.*, emergency case), study personnel obtained consent within the first 24 h after surgery. Eight centers used a deferred consent process for patients unable to provide consent (*e.g.*, patients sedated and mechanically ventilated) and for whom no next-of-kin was available.[3]

Procedures

Trained research personnel interviewed and examined patients and reviewed charts to obtain information on potential preoperative predictors of major perioperative complications by using standardized definitions. Patients had blood collected to measure a Roche fourth-generation Elecsys TnT assay 6 to 12 h postoperatively and on the first, second, and third days after surgery. Patients enrolled between 12 and 24 h after surgery had a TnT drawn immediately, and testing continued as indicated in the preceding sentence. All TnT measurements were analyzed at the participating hospitals, and the TnT results were reported to the attending physicians.

A TnT of 0.04 ng/ml or greater was the laboratory threshold considered abnormal at the time the study began. Therefore, we only obtained electrocardiography on patients who had a TnT of 0.04 ng/ml or greater, and we only assessed these patients for ischemic symptoms. When a patient had a TnT measurement of 0.04 ng/ml or greater, physicians were encouraged to obtain additional TnT measurements (to determine the peak) and electrocardiograms for several days. If a patient developed an ischemic symptom

at anytime during the first 30 days after surgery, physicians were encouraged to obtain TnT measurements and electrocardiograms. We defined an ischemic feature as the presence of any ischemic symptom or ischemic electrocardiographic finding, defined in appendix 1, Supplemental Digital Content 1, http://links.lww.com/ALN/B26.

Outcomes

The primary outcome was mortality at 30 days after surgery. Centers also reported the cause of death (vascular or nonvascular, definitions in appendix 2, Supplemental Digital Content 1, http://links.lww.com/ALN/B26). Throughout patients' hospital stay, research personnel evaluated patients clinically, reviewed hospital charts, ensured patients had TnT measurements drawn, and documented outcome events (defined in appendix 3, Supplemental Digital Content 1, http://links.lww.com/ALN/B26). We contacted patients 30 days after surgery; if patients (or next-of-kin) indicated that they had experienced an outcome, we contacted their physicians to obtain documentation.

Adjudicators evaluated all patients with an elevated troponin measurement that occurred anytime during the first 30 days after surgery to determine the presence of any ischemic features (*i.e.*, whether a patient would have fulfilled the universal definition of myocardial infarction),[7] the presence of a nonischemic etiology that could explain the elevated troponin measurement, and that the myocardial injury had occurred during or after surgery (*i.e.*, no evidence to support it was due to a preoperative event). Their decisions were used in the statistical analyses.

Data Quality

At each site, an investigator reviewed and approved all data. Research personnel at participating centers submitted the case report forms and supporting documentation directly to the data management system (iDataFax; coordinating center, McMaster University, Hamilton, Ontario, Canada). Data monitoring in VISION consisted of central data consistency checks, statistical monitoring, and on-site monitoring for all centers.[3]

Statistical Analyses

A statistical analysis plan outlining the analyses in this article was written before undertaking the following analyses. For our primary objective (*i.e.*, to establish the MINS diagnostic criteria), we undertook Cox proportional hazards models in which the dependent variable was death up to 30 days after noncardiac surgery (using a time-to-event analysis). In these models, the independent variables were: (1) nine preoperative patient characteristics that a previous VISION analysis demonstrated were independent predictors of 30-day mortality[3] (defined in appendix 4, Supplemental Digital Content 1, http://links.lww.com/ALN/B26); (2) six time-dependent perioperative adverse complications, which included the outcomes sepsis and pulmonary embolus that were not accompanied by a TnT elevation (defined in appendix 3, Supplemental Digital Content 1, http://links.lww.com/ALN/B26); and (3) potential MINS diagnostic criteria. In the first model, two potential time-dependent MINS diagnostic criteria were evaluated (*i.e.*, a peak TnT of ≥0.04 ng/ml with one or more ischemic features and a peak TnT of ≥0.04 ng/ml without an ischemic feature). The reference group was patients with a TnT of 0.01 ng/ml or less. For this first model, we excluded patients with a peak TnT equal to 0.02 or 0.03 ng/ml, because a previous VISION analysis demonstrated that these thresholds were independent predictors of 30-day mortality,[3] and we did not prospectively collect data to determine whether these patients had experienced an ischemic feature (*i.e.*, these patients did not have electrocardiography and were not assessed for ischemic symptoms).

We prespecified two potential findings that would result in different MINS diagnostic criteria. First, if both a peak TnT of 0.04 ng/ml or greater with and without ischemic features independently predicted mortality, then the MINS diagnostic criteria would only require a peak TnT of 0.04 ng/ml or greater that was judged as due to myocardial ischemia (*i.e.*, no evidence of a nonischemic etiology causing the TnT elevation) without requiring the presence of an ischemic feature. If this proved the case, we planned to repeat the MINS diagnostic criteria Cox proportional hazards model, as described in the first paragraph of the statistical analysis section, including all patients and adding two more potential MINS diagnostic criteria (*i.e.*, a peak TnT = 0.02 ng/ml and a peak TnT = 0.03 ng/ml without knowledge of whether these patients experienced an ischemic feature).

Second, if only a peak TnT of 0.04 ng/ml or greater with one or more ischemic features but not a peak TnT of 0.04 ng/ml or greater without an ischemic feature independently predicted mortality, then the MINS diagnostic criteria would require a peak TnT of 0.04 ng/ml or greater with an ischemic feature. This result would have prompted a repeated MINS diagnostic criteria Cox proportional hazards model with exploration of the impact of each individual ischemic feature (*e.g.*, chest pain) on 30-day mortality to determine which ischemic features should be included in the MINS diagnostic criteria.

After establishing the MINS diagnostic criteria, we determined the incidence and 95% CIs of patients fulfilling these criteria. We repeated the initial Cox proportional hazards model and included MINS as a time-dependent perioperative adverse complication. For this model, we determined the population-attributable risk for the independent predictors of 30-day mortality.[9,10] The population-attributable risk represents the proportion of all deaths potentially attributable to the relevant risk factor (*e.g.*, MINS). We undertook a sensitivity analysis restricted to patients in whom a preoperative estimated glomerular filtration rate (eGFR) was available, which included eGFR as a candidate-independent variable.

We compared the baseline characteristics between patients who did and did not develop MINS. Across the

groups, proportions were compared using Fisher exact test and continuous variables using the Student *t* or Wilcoxon rank sum test, as appropriate. A Cox proportional hazards model was undertaken to determine independent predictors of MINS up to 30 days after surgery. Potential independent variables in this model included 15 baseline clinical variables and seven types of surgeries (defined in appendix 5, Supplemental Digital Content 1, http://links.lww.com/ALN/B26). This analysis was restricted to patients in whom a preoperative eGFR was available. A sensitivity analysis omitting eGFR included all the patients.

Among patients who developed MINS, we determined the incidence of each individual ischemic feature. This analysis was restricted to patients who had a peak TnT of 0.04 ng/ml or greater, because patients with a peak TnT = 0.03 ng/ml were not assessed for ischemic features.

We compared the cardiovascular outcomes at 30 days after surgery (defined in appendix 6, Supplemental Digital Content 1, http://links.lww.com/ALN/B26) for patients who did and did not suffer MINS. For the cardiovascular outcomes, we determined the odds ratio (OR) and 95% CI. By using Fisher exact test, we compared the 30-day outcomes among patients who developed MINS with patients who did not develop MINS.

To develop a clinical risk score to predict short-term mortality among patients who suffered MINS, we conducted logistic regression analysis. The dependent variable was mortality at 30 days, and we evaluated the following candidate-independent variables: preoperative variables (*i.e.*, age, sex); and characteristics of the MINS outcome (*i.e.*, presence of individual ischemic symptoms, presence of individual ischemic electrocardiographic findings, location of the ischemic electrocardiographic finding, and peak TnT ≥0.30 ng/ml). Our choice of candidate-independent variables was on the basis of our hypotheses regarding which variables were likely to be most predictive and the results of previous nonoperative myocardial infarction 30-day mortality risk-prediction models.[11] In this logistic regression analysis, we included only patients with peak TnT of 0.04 ng/ml or greater, because we did not know whether patients with a peak TnT of 0.03 ng/ml had ischemic features. We further included the identified significant predictors in a separate model to determine their adjusted ORs. A scoring system was developed by assigning weighted points to each statistically significant predictor based on their log ORs, and the expected 30-day mortality risk was determined for potential risk scores using the method outlined by Sullivan *et al.*[12] Bootstrapping was performed to obtain 95% CIs around the expected 30-day mortality risk for each potential risk score.

For all our regression models, we used forced simultaneous entry (all candidate variables remained in the models regardless of statistical significance).[13,14] If an adjudicator determined that a patient had suffered more than one episode of MINS throughout the first 30 days after surgery, we evaluated only the first episode in all analyses. We reported adjusted ORs (for logistic regression) and adjusted hazard ratios (for Cox proportional hazard regression), 95% CI, and associated *P* values to three decimal places with *P* values less than 0.001 reported as *P* value less than 0.001. For all tests, we used alpha = 0.05 level of significance. In our models, we validated the ORs and hazard ratios and their 95% CIs through bootstrapping. For our Cox proportional hazards models, we assessed discrimination through evaluation of the C index, and we conducted sensitivity analyses in which we used frailty models to assess for center effects. For the logistic regression model, we assessed collinearity using the variance inflation factor, and we considered variables with a variance inflation factor greater than 10 to be collinear.[15] For our logistic regression model, we assessed discrimination through evaluation of the area under the receiver-operating characteristic curve, calibration with a Hosmer–Lemeshow goodness-of-fit test, and conducted sensitivity analysis in which we used a mixed model to adjust for potential clustering by center.

Our sample size was based on our model to determine the diagnostic criteria of MINS. We evaluated 19 variables in this model and simulation studies demonstrate that regression models require 12 events per variable evaluated.[16,17] Therefore, we required 228 deaths in our study. All analyses were performed using SAS version 9.2 (Cary, NC).

Ethical Considerations and Funding Sources

The Research Ethics Board at each site approved the protocol before patient recruitment. Funding for this study comes from more than 60 grants for VISION and its substudies.

Results

Figure 1 reports the patient flow. Of the 15,065 patients included in the MINS study, 99.7% of the patients completed the 30-day follow-up. Patients were recruited at 12 centers in eight countries in North and South America, Australia, Asia, and Europe, from August 6, 2007 to January 11, 2011.

Diagnostic Criteria of MINS (Primary Objective)

Table 1, Supplemental Digital Content 2, http://links.lww.com/ALN/B27, reports the results of the initial Cox proportional hazards model demonstrating that a peak TnT of 0.04 ng/ml or greater with and separately without an ischemic feature were independent predictors of 30-day mortality. The full model that explored all the considered diagnostic criteria for MINS demonstrated that a peak TnT of 0.04 ng/ml or greater with one or more ischemic features (adjusted hazard ratio, 4.82; 95% CI, 3.40–6.84), a peak TnT of 0.04 ng/ml or greater without an ischemic feature (adjusted hazard ratio, 3.30; 95% CI, 2.26–4.81), and a peak TnT of 0.03 ng/ml (adjusted hazard ratio, 4.30; 95% CI, 2.68–6.91) all independently predicted 30-day mortality (Table 2, Supplemental Digital Content 2, http://links.lww.com/ALN/B27). Therefore, after adjustment for

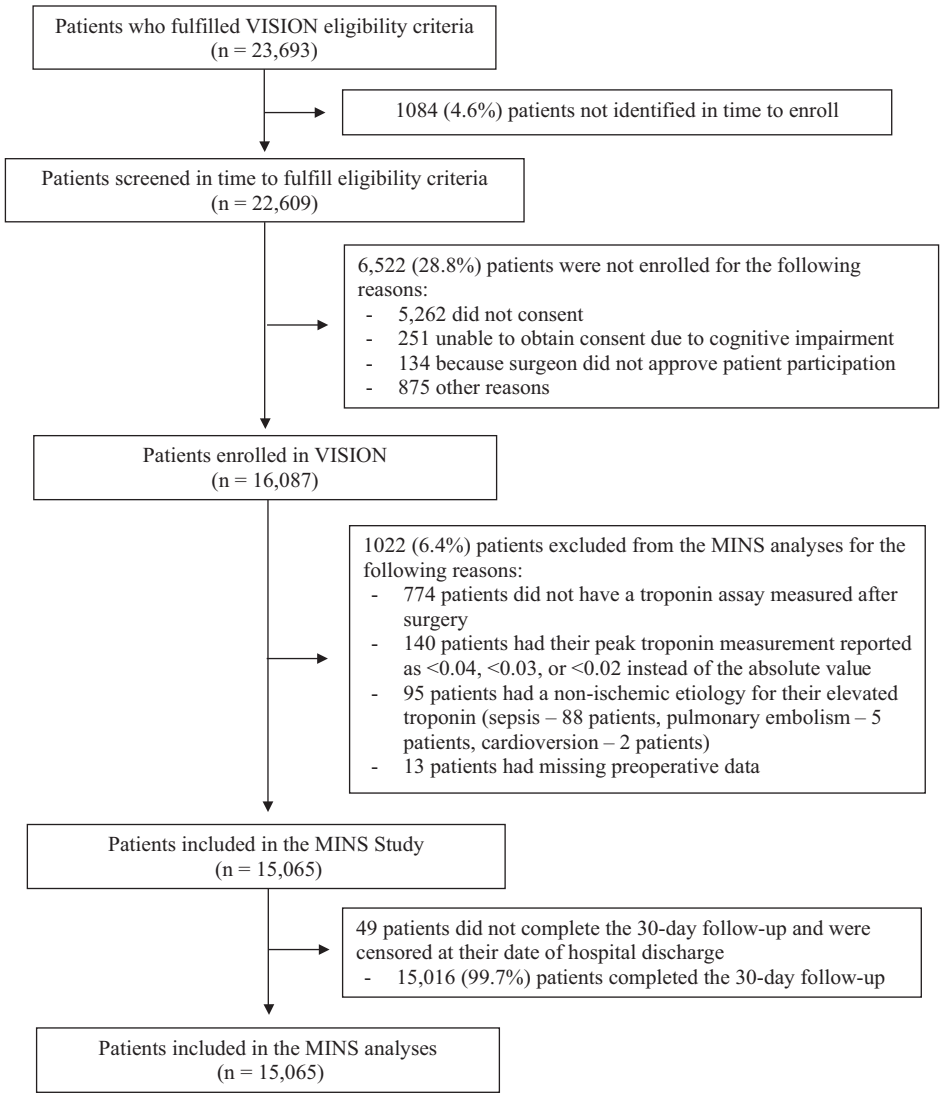

Fig. 1. Patient flow chart. MINS = myocardial injury after noncardiac surgery; VISION = *V*ascular events *I*n noncardiac *S*urgery pat*I*ents c*O*hort evaluatio*N*.

preoperative patient characteristics and perioperative complications, a peak TnT of 0.03 ng/ml or greater was an independent predictor of 30-day mortality. On the basis of these analyses, our diagnostic criterion for MINS was any peak TnT of 0.03 ng/ml or greater that was judged as resulting from myocardial ischemia (*i.e.*, no evidence of a nonischemic etiology causing the TnT elevation).

A total of 1,200 patients (8.0%; 95% CI, 7.5–8.4) fulfilled the MINS diagnostic criterion. Table 1 reports the predictors of 30-day mortality in the model that included preoperative variables and perioperative adverse complications, including MINS. Four perioperative complications (*i.e.*, MINS, sepsis, stroke, and pulmonary embolus) were independent predictors of 30-day mortality. The independent prognostic factors identified in this model potentially explain the majority of the deaths that occurred (*i.e.*, the total population-attributable risk was 92.6%; 95% CI, 89.6–95.2); among the perioperative complications, MINS had the largest population-attributable risk (34.0%; 95% CI, 26.6–41.5). Our 30-day mortality sensitivity analysis, restricted to patients for whom a preoperative eGFR was available, demonstrated that MINS was not confounded by eGFR (*i.e.*, MINS remained an independent predictor of 30-day mortality adjusted hazard ratio, 3.66; 95% CI, 2.71–4.93), but preoperative eGFR was not an independent predictor of 30-day mortality, $P = 0.480$ (Table 3, Supplemental Digital Content 2, http://links.lww.com/ALN/B27).

Characteristics and Predictors of MINS

Figure 1, Supplemental Digital Content 3, http://links.lww.com/ALN/B28, depicts that 87.1% of MINS events occurred within the first 2 days after surgery. Supplemental Digital Content 4 (table), http://links.lww.com/ALN/B29, presents the baseline characteristics of patients who did and did not suffer MINS. Patients with MINS were older, had more cardiovascular risk factors, and had known

Table 1. Model to Predict 30-day Mortality*

Predictor	Prevalence of Predictors (%)	Patients Dying within 30 Days after Surgery		Model Derivation		Model Validation		Population-attributable Risk (95% CI‡)
		n	% (95% CI)	Adjusted HR (95% CI)	*P* Value	Adjusted HR† (95% CI)	*P* Value	
Preoperative risk factors								
Age								
45–64 yr old	7,682 (51.0)	64	0.8 (0.7–1.1)	1.00		1.00		
65–74 yr old	3,756 (24.9)	60	1.6 (1.2–2.1)	1.62 (1.14–2.32)	0.008	1.61 (1.10–2.40)	0.013	42.1% (27.8–55.2)
≥75 yr old	3,627 (24.1)	136	3.7 (3.2–4.4)	2.66 (1.95–3.64)	<0.001	2.69 (1.95–3.80)	<0.001	
Urgent/emergent surgery	2,121 (14.1)	114	5.4 (4.5–6.4)	3.58 (2.73–4.68)	<0.001	3.66 (2.69–5.00)	<0.001	33.3% (25.8–40.8)
Cancer	3,993 (26.5)	102	2.6 (2.1–3.1)	2.17 (1.63–2.90)	<0.001	2.20 (1.57–3.08)	<0.001	22.7% (13.9–31.2)
General surgery	3,033 (20.1)	98	3.2 (2.7–3.9)	1.58 (1.18–2.10)	0.002	1.57 (1.14–2.18)	0.005	15.7% (6.0–24.7)
History of COPD	1,262 (8.4)	60	4.8 (3.7–6.1)	1.79 (1.33–2.41)	<0.001	1.79 (1.28–2.41)	<0.001	10.8% (4.2–17.3)
History of stroke	693 (4.6)	40	5.8 (4.3–7.8)	1.72 (1.20–2.45)	0.003	1.70 (1.13–2.47)	0.009	7.5% (2.3–12.7)
History of PVD	793 (5.3)	39	4.9 (3.6–6.7)	1.89 (1.31–2.71)	<0.001	1.89 (1.22–2.66)	0.002	6.9% (1.8–12.0)
Neurosurgery	888 (5.9)	26	2.9 (2.0–4.3)	2.03 (1.31–3.15)	0.001	2.04 (1.20–3.35)	0.007	5.6% (1.4–9.8)
Recent high-risk CAD	171 (1.1)	16	9.4 (5.8–14.7)	2.51 (1.49–4.21)	<0.001	2.50 (1.29–4.34)	0.007	4.1% (0.9–7.3)
Perioperative adverse complications‖								
MINS	1,200 (8.0)	115	9.6 (8.0–11.4)	3.87 (2.96–5.08)	<0.001	3.90 (2.90–5.27)	<0.001	34.0% (26.6–41.5)
Sepsis/infection								
Sepsis	812 (5.4)	96	11.8 (9.8–14.2)	7.18 (5.17–9.97)	<0.001	7.31 (5.13–10.35)	<0.001	30.5% (23.7–37.2)§
Infection, not sepsis	902 (6.0)	15	1.7 (1.0–2.7)	1.33 (0.77–2.30)	0.303	1.33 (0.65–2.18)	0.309	
Neither	13,351 (88.6)	149	1.1 (1.0–1.3)	1.00		1.00		
Stroke	81 (0.5)	16	19.8 (12.5–29.7)	3.50 (2.05–5.97)	<0.001	3.56 (1.78–6.77)	0.001	4.5% (1.3–7.8)
Pulmonary embolus	95 (0.6)	11	11.6 (6.6–19.6)	6.11 (3.18–11.74)	<0.001	6.15 (2.28–13.77)	<0.001	3.5% (0.9–6.2)
Deep venous thrombosis	89 (0.6)	8	9.0 (4.6–16.7)	1.47 (0.68–3.19)	0.327	1.64 (0.44–4.62)	0.514	NA
Pneumonia	345 (2.3)	50	14.5 (11.2–18.6)	1.25 (0.86–1.84)	0.248	1.24 (0.81–1.89)	0.304	NA

* C index = 0.90 (95% CI, 0.88–0.92). † Obtained from 1,000 bootstrap samples. ‡ Only variables that are significant predictors in the Cox model are included in the population-attributable risk model, and 95% CIs were determined through 10,000 bootstrap samples. § Populational-attributable risk is based on sepsis *vs.* no sepsis. ‖ Complications occurring during or within 30 days after the primary noncardiac surgery.

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; MINS = myocardial injury after noncardiac surgery; NA = not applicable; PVD = peripheral vascular disease.

cardiovascular disease. Table 2 reports the ischemic features of patients suffering MINS of whom 84.2% (95% CI, 81.7–86.4) did not experience an ischemic symptom. A total of 34.9% (95% CI, 31.9–38.0) of patients with MINS had an ischemic electrocardiographic finding, of which T-wave inversion (23.3%; 95% CI, 20.7–26.1) and ST depression (16.4%; 95% CI, 14.1–18.9) were the most common. Among patients with MINS, 41.8% had an ischemic feature and would have fulfilled the universal definition of myocardial infarction; however, 58.2% of these patients did not experience an ischemic feature and would therefore not have fulfilled the universal definition of myocardial infarction.

We identified 12 independent predictors of MINS that included the following: age 75 yr or older, cardiovascular risk factors (*e.g.*, renal insufficiency, diabetes), known cardiovascular disease (*e.g.*, peripheral vascular disease, coronary artery disease), and surgical factors (*e.g.*, urgent/emergent surgery) (table 3). The sensitivity analysis, which included all the patients and did not assess eGFR as a potential independent predictor of MINS, demonstrated similar findings to table 3 except that low-risk surgery was no longer predictive (adjusted hazard ratio, 0.77; 95% CI, 0.56–1.07).

Prognostic Impact of MINS

Patients with MINS were at higher risk of a nonfatal cardiac arrest (OR, 14.58; 95% CI, 5.75–37.02; $P < 0.001$), congestive heart failure (OR, 10.34; 95% CI, 7.99–13.37; $P < 0.001$), and stroke (OR, 4.66; 95% CI, 2.87–7.58; $P < 0.001$) compared with patients who did not suffer MINS (table 4). The 30-day mortality rate was 9.8% among patients who suffered MINS and 1.1% among patients who did not suffer MINS (OR, 10.07; 95% CI, 7.84–12.94; $P < 0.001$). Among the patients suffering MINS, 115 died within 30 days of surgery, centers reported a vascular cause of death in 62 (53.9%) patients and nonvascular in 53 (46.1%). The composite of nonfatal cardiac arrest, nonfatal congestive

Table 2. Ischemic Features of Patients Suffering Myocardial Injury after Noncardiac Surgery

	Prevalence		Mortality at 30 days	
Ischemic Feature*	n	% (95% CI)	n	% (95% CI)
Ischemic symptoms				
Chest discomfort	85	9.0 (7.4–11.0)	17	20.0 (12.9–29.7)
Neck, jaw, or arm discomfort	5	0.5 (0.2–1.2)	0	0.0 (0.0–43.4)
Dyspnea	66	7.0 (5.6–8.8)	10	15.2 (8.4–25.7)
Pulmonary edema	46	4.9 (3.7–6.5)	8	17.4 (9.1–30.7)
Any of the above	149	15.8 (13.6–18.3)	22	14.8 (10.0–21.3)
Ischemic electrocardiographic findings				
Q waves	13	1.4 (0.8–2.3)	1	7.7 (1.4–33.3)
ST elevation	22	2.3 (1.5–3.5)	7	31.8 (16.4–52.7)
LBBB	5	0.5 (0.2–1.2)	3	60.0 (23.1–88.2)
ST depression	154	16.4 (14.1–18.9)	21	13.6 (9.1–19.9)
T-wave inversion	219	23.3 (20.7–26.1)	31	14.2 (10.2–19.4)
Any of the above	328	34.9 (31.9–38.0)	47	14.3 (10.9–18.5)

* Analysis restricted to patients with a peak troponin T ≥0.04 ng/ml (*i.e.*, 941 patients) because patients with a peak troponin T equal to 0.03 ng/ml were not assessed for ischemic features.

LBBB = left bundle branch block; n = number of patients.

heart failure, nonfatal stroke, and mortality occurred more frequently in patients who suffered MINS (OR, 9.59; 95% CI, 7.99–11.51; $P < 0.001$). In those with and without an ischemic feature, 30-day mortality rates were 13.5% (95% CI, 10.5–17.3%) and 7.7% (95% CI, 5.7–10.2%), respectively.

Predictors of Mortality among Patients Suffering MINS

Age 75 yr or older, ST elevation or new left bundle branch block, and anterior ischemic electrocardiographic findings were independent predictors of 30-day mortality among patients who suffered MINS (table 5). Our scoring system to predict 30-day mortality in patients suffering MINS assigned the following points to the independent predictor of mortality: age 75 yr or older (1 point), ST elevation or new left bundle branch block (2 points), and anterior ischemic electrocardiographic findings (1 point). Figure 2 presents the expected and observed risk of 30-day mortality among the patients with MINS based on the scoring system. Patients with a score of 0, 1, 2, 3, or 4 had expected 30-day

Table 3. Independent Preoperative Predictors of Myocardial Injury after Noncardiac Surgery*

	Model Derivation		Model Validation
Analyses Based on 13,948 Patients	Adjusted HR (95% CI)	*P* Value	Adjusted HR† (95% CI)
Age ≥75 yr old	1.73 (1.48–2.03)	<0.001	1.74 (1.48–2.05)
Females	0.72 (0.64–0.81)	<0.001	0.72 (0.63–0.82)
Current atrial fibrillation	1.47 (1.20–1.81)	<0.001	1.48 (1.18–1.84)
History of			
Diabetes	1.34 (1.18–1.53)	<0.001	1.34 (1.17–1.53)
Hypertension	1.32 (1.14–1.52)	<0.001	1.32 (1.14–1.54)
Congestive heart failure	1.37 (1.14–1.65)	<0.001	1.38 (1.12–1.68)
Coronary artery disease	1.27 (1.09–1.47)	0.002	1.27 (1.08–1.48)
High-risk coronary artery disease	1.63 (1.21–2.19)	0.001	1.64 (1.16–2.29)
Peripheral vascular disease	1.92 (1.60–2.29)	<0.001	1.92 (1.58–2.31)
Stroke	1.36 (1.13–1.64)	0.001	1.36 (1.10–1.65)
Preoperative eGFR, ml/min/1.73 m^2			
<30	7.85 (6.66–9.25)	<0.001	7.93 (6.64–9.53)
30–44	2.39 (1.98–2.89)	<0.001	2.39 (1.95–2.92)
45–59	1.69 (1.41–2.01)	<0.001	1.69 (1.40–2.02)
>60	1.00	—	1.00
Low-risk surgery	0.72 (0.51–0.99)	0.049	0.71 (0.49–0.99)
Urgent/emergent surgery	1.83 (1.59–2.11)	<0.001	1.83 (1.57–2.13)

* C index = 0.79 (95% CI, 0.78–0.81). † Obtained from 10,000 bootstrap samples.

eGFR = estimated glomerular filtration rate; HR = hazard ratio.

Table 4. 30-day Outcomes

	Patients without MINS (n = 13,822)	Patients Suffering MINS (n = 1,194)	
Outcome*	n (%)	n (%)	Unadjusted OR (95% CI)
Nonfatal cardiac arrest	8 (0.06)	10 (0.8)	14.58 (5.75–37.02)
Congestive heart failure	137 (1.0)	112 (9.4)	10.34 (7.99–13.37)
Stroke	58 (0.4)	23 (1.9)	4.66 (2.87–7.58)
Mortality	147 (1.1)	117 (9.8)	10.07 (7.84–12.94)
Composite of major events†	325 (2.4)	224 (18.8)	9.59 (7.99–11.51)

* Among the 15,065 patients, 49 patients did not complete the 30-day follow-up and were not included in these analyses except for the outcome mortality in which we did not know 30-day vital status on 27 patients who were not included in the mortality analysis. † Composite of major events = composite of mortality, nonfatal cardiac arrest, nonfatal congestive heart failure, and nonfatal stroke.

MINS = myocardial injury after noncardiac surgery; n = number of patients; OR = odds ratio.

mortality rates of 5.2% (95% CI, 3.3–7.4), 10.2% (95% CI, 6.5–11.9), 19.0% (95% CI, 8.7–24.3), 32.5% (95%, 10.6–45.9), and 49.8% (95% CI, 12.0–65.5), respectively.

The random-effect (frailty) Cox models that adjusted for potential clustering-by-center effects produced similar results. Each variable included in the logistic regression models demonstrated a variance inflation factor less than 10 suggesting no collinearity. The mixed model that adjusted for any potential clustering by center in the logistic regression model produced similar results.

Discussion

Principal Findings

In this international cohort study of 15,065 patients 45 yr of age or older undergoing noncardiac surgery, we determined that the optimal diagnostic criterion for MINS is a peak TnT of 0.03 ng/ml or greater judged due to myocardial ischemia (*i.e.*, no evidence of a nonischemic etiology causing the TnT elevation). This criterion does not require the presence of an ischemic feature. MINS was common (8.0%), associated with substantial mortality and cardiovascular complications at 30 days, and the population-attributable risk suggests that MINS explains 34.0% of the deaths that occur in adults during the first 30 days after noncardiac surgery.

A minority of patients with MINS experienced an ischemic symptom; only 41.8% of patients with MINS fulfilled the universal definition of myocardial infarction. Among the 58.2% of patients with MINS who did not experience an ischemic feature and thus would not have fulfilled the universal definition of myocardial infarction, 1 in 13 died within 30 days.

Our Study in Relation to Other Studies

In a previous VISION publication, we demonstrated that the peak troponin measurement during the first 3 days after noncardiac surgery was an independent predictor (based on adjustment of only preoperative patient characteristics) of 30-day mortality.[3] Our current publication adds important new information by focusing on troponin elevations that were adjudicated as resulting from myocardial ischemia, evaluating all troponin elevations until day 30 after surgery, and taking into account potential confounding through risk adjustment of other perioperative complications. This is the first study to evaluate diagnostic criteria for MINS, independent predictors of MINS, and predictors of mortality in patients suffering MINS. LeManach *et al.* conducted a consecutive cohort study of 1,136 patients undergoing abdominal aortic surgery in which they excluded septic patients with an elevated troponin I (Dade-Behring).[18] Consistent with our findings, they demonstrated that an elevated troponin I after surgery was an independent predictor of in-hospital mortality.[18] A limitation of this study is that they did not adjust for any perioperative complications (*e.g.*, stroke).

A multivariable analysis of data from the PeriOperative ISchemic Evaluation Trial (an international, randomized, controlled trial comprising 8,351 patients) that adjusted for preoperative factors and perioperative complications demonstrated

Table 5. Independent Predictors of 30-day Mortality in Patients Suffering Myocardial Injury after Noncardiac Surgery*

		Model Derivation		Model Validation	
	Number of Patients	Adjusted OR (95% CI)	*P* Value	Adjusted OR† (95% CI)	*P* Value
Age ≥75 yr old	454 (48.3%)	2.06 (1.31–3.22)	0.002	2.06 (1.33–3.37)	0.003
ST elevation or new LBBB	27 (2.9%)	3.97 (1.70–9.27)	0.002	3.96 (1.54–9.14)	0.005
Anterior ischemic electrocardiographic findings	200 (21.3%)	2.32 (1.46–3.70)	<0.001	2.33 (1.42–3.70)	<0.001

* Analysis restricted to patients with a peak troponin T ≥0.04 ng/ml (*i.e.*, 940 patients) because patients with a peak troponin T equal to 0.03 ng/ml were not assessed for ischemic features; area under the receiver-operating characteristic curve = 0.651 (95% CI, 0.592–0.711); goodness-of-fit test *P* = 0.555, indicating no evidence of a lack of fit. † Obtained from 10,000 bootstrap samples.

LBBB = left bundle branch block; OR = odds ratio.

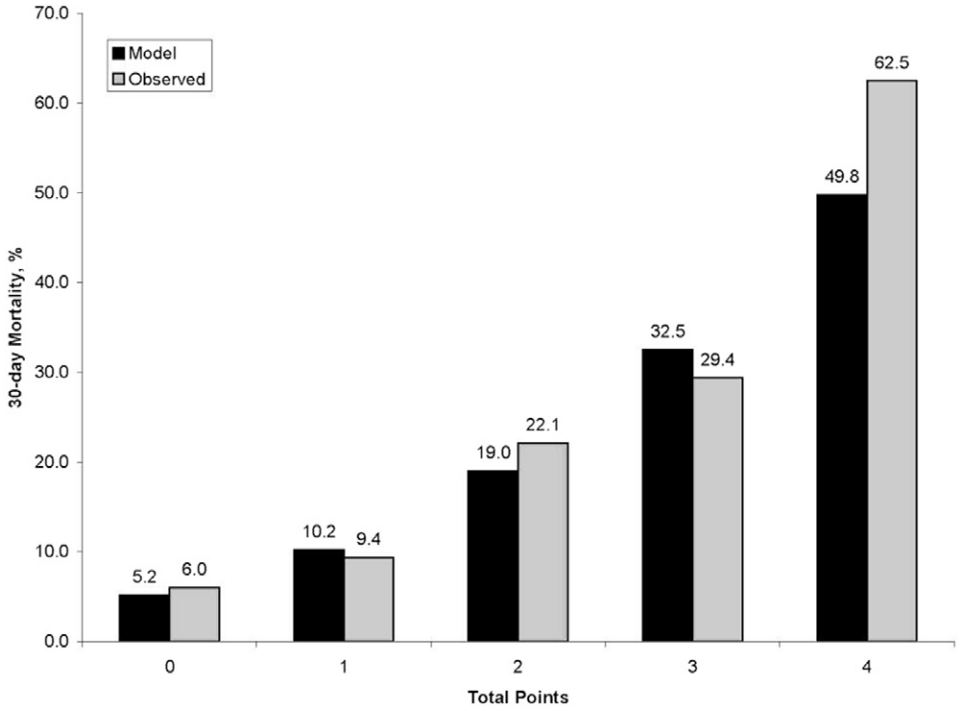

Fig. 2. Risk of mortality based on scoring system for independent predictors of 30-day mortality in patients suffering myocardial injury after noncardiac surgery.

that the highest quartile of a cardiac biomarker or enzyme elevation (*i.e.*, a troponin or creatine kinase–myocardial band value 3.6 times or greater the upper limit of normal) in patients without an ischemic feature was an independent predictor of 30-day mortality (adjusted OR, 2.54; 95% CI, 1.65–3.90).[4] Although the foregoing PeriOperative ISchemic Evaluation analysis supports our finding that an elevated troponin after surgery without an ischemic feature increases short-term mortality, many different troponin assays were evaluated and data were insufficient to determine prognostically relevant thresholds for the individual troponin assays.

Strengths and Limitations of Our Study

Strengths of our study included evaluation of a large contemporary representative sample of adults who underwent noncardiac surgery in five continents with complete follow-up data on 99.7% of the patients. All patients underwent troponin monitoring after surgery using the same troponin assay, and all patients with a TnT of 0.04 ng/ml or greater were prospectively assessed for ischemic symptoms and ischemic electrocardiographic findings. Our 30-day mortality model that included MINS (based on our diagnostic criterion) demonstrated good calibration, and the results were consistent across centers.

Our study had several limitations. We systematically monitored troponin measurements only until day 3 after surgery. Therefore, after day 3, we may have missed additional MINS events in patients who did not experience an ischemic symptom. The substantial decline in MINS events by postoperative day 3 (Figure 1, Supplemental Digital Content 3, http://links.lww.com/ALN/B28) suggests, however, that we were not likely to have missed many MINS events. We determined the MINS diagnostic threshold only for the fourth-generation TnT assay; thus, evaluation of other troponin assays will require further research.

We did not assess patients for the presence of ischemic features if their peak TnT was 0.03 ng/ml. At the start of the study, we did not know that patients with a TnT of 0.03 ng/ml had an increased risk of 30-day mortality, and we assessed patients for ischemic features only if they met the laboratory threshold considered abnormal (*i.e.*, TnT ≥0.04 ng/ml). It is possible among patients with a peak TnT of 0.03 ng/ml that only those patients who also had an ischemic feature were at increased risk of 30-day mortality. Given that patients with a peak TnT of 0.04 ng/ml or greater did not require an ischemic feature to impact 30-day mortality, we believe it is unlikely that a peak TnT of 0.03 ng/ml requires an ischemic feature to impact mortality. Our model to predict 30-day mortality in patients suffering MINS did not include patients who had a peak TnT of 0.03 ng/ml. Although it is possible that our model will not predict mortality in patients with a TnT of 0.03 ng/ml, this is unlikely given that a previous VISION publication did not demonstrate any difference in the risk of mortality across peak TnT values of 0.03 to 0.29 ng/ml.[3] Although experienced physicians in perioperative medicine adjudicated all elevated troponin measurements to ensure there was no evidence of a nonischemic cause, it is possible some nonischemic etiologies were missed and that some events were not due to ischemic myocardial injury.

Implications

Most studies on noncardiac surgery evaluating cardiac complications focus on perioperative myocardial infarction. Our results show that focusing on this complication would result in missing 58.2% of the prognostically relevant perioperative myocardial ischemic events. On the basis of these results and the rationale presented in our introduction, we advocate assessing surgical patients for the diagnosis of MINS. Although no randomized, controlled trial has established an effective treatment for patients suffering MINS, the prognosis of these patients may be modifiable. The high-quality evidence for acetyl-salicylic acid and statin therapy in the nonoperative setting,[19,20] and encouraging observational data from a large international perioperative trial (*i.e.*, PeriOperative ISchemic Evaluation) showing an association with use of these drugs and decreased 30-day mortality in patients who have suffered a perioperative myocardial injury,[4] suggests that acetyl-salicylic acid and statin therapy may benefit patients who suffer MINS.

In our study of patients 45 yr of age or older undergoing noncardiac surgery, 8.0% of patients suffered MINS. It is estimated that worldwide more than 100 million adults 45 yr of age or older undergo major noncardiac surgery each year.[1,21] This suggests that 8 million adults may suffer MINS annually. The frequency of this perioperative complication, and the associated 30-day risk of cardiovascular complications and mortality, highlights the urgent need for clinical trials to establish strategies to prevent and treat this important complication.

A minority (15.8%) of patients suffering MINS experienced an ischemic symptom. Therefore, 84.2% of MINS probably would have gone undetected without systematic troponin monitoring after surgery. Consistent with our finding, the third universal definition of myocardial infarction consensus statement recommends monitoring perioperative troponin measurements in high-risk patients undergoing noncardiac surgery.[7]

Conclusions

Evaluating patients for the diagnosis of MINS compared with myocardial infarction will allow physicians to avoid missing the majority of the patients who develop a prognostically relevant perioperative myocardial injury. Among adults undergoing noncardiac surgery, MINS is common (8%), and 1 in 10 patients suffering MINS will die within 30 days. Failure to monitor troponin measurements after noncardiac surgery will result in missing more than 80% of MINS events.

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Competing Interests

The VISION Study funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation or approval of the article. Roche Diagnostics provided the troponin T assays and some financial support for the VISION Study. Dr. Devereaux has received other funding from Roche Diagnostics and Abbott Diagnostics for investigator initiated studies. Dr. Peter Kavsak has received a reagents grant from Roche Diagnostics.

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TnT

Blowing the Cover from Perioperative Myocardial Injury

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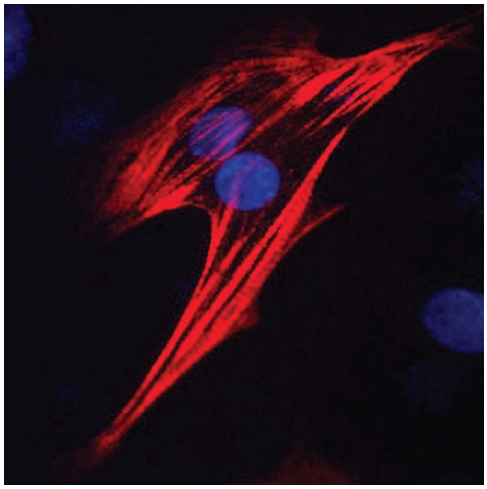
CME This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

PREVENTION, detection, and therapy of myocardial infarction have been fundamental goals of perioperative medicine for many years. As one of the first monitors dedicated to detecting myocardial ischemia, continuous electrocardiography for patients undergoing surgery became more commonly used in the 1950s. Indeed, by 1978, guidelines recommended routine baseline electrocardiogram testing for all adult patients before undergoing surgery.[1] However, given that preoperative electrocardiographic abnormalities are not necessarily predicative of postoperative myocardial infarction,[2] current practice advisories recognize that preoperative testing should rather be considered for patients with cardiovascular risk factors.[3] Intraoperative echocardiography is routinely used for diagnosis and therapy in cardiac surgery.[4,5] In addition, it can also be used safely in noncardiac surgery for the detection of new regional wall motion abnormalities indicative of myocardial ischemia.[6,7] However, given the resources required for a complete diagnostic echocardiographic examination, its use as a screening tool for myocardial injury in noncardiac surgery is likely limited. A common test used for the diagnosis of perioperative myocardial injury is the measurement of plasma troponin levels. In the past, minor increases in serum troponin levels have often clinically been dismissed as less relevant cases of supply/demand mismatch. This is likely related to the fact that a troponin increase itself does not meet definition criteria for myocardial infarction and a lack of consensus on the most appropriate therapeutic approach. Although it seems intuitive that myocardial infarction leading to cell death is of greater consequence than myocardial ischemia without necrosis, the relevance of minor myocardial injury is not well defined. Furthermore, the progression from reversible ischemic damage to necrosis occurs on a biologic continuum, making cutoffs based on the presumed degree of cellular injury impractical at best. Defining clinical relevance of biomarkers such as Troponin T (TnT) according to their association with meaningful outcomes, such as 30-day mortality, adds substantial value for the practicing clinician. The significance of creatine muscle and brain isoenzyme and TnT to predict mortality and major cardiovascular events has previously been highlighted in a meta-analysis.[8] The current study by the VISION Writing Group[9] underlines the fundamental importance of even subtle perioperative TnT increases for morbidity and mortality in surgical patients. The current findings are a *post hoc* analysis of prospectively collected data from *The Vascular events In noncardiac Surgery patIents cOhort evaluatioN* trial.[10] The reported analyses extend the interpretation of the *The Vascular events In noncardiac Surgery patIents cOhort evaluatioN* study, as they confirm the independent association of a TnT value of 0.03 ng/ml or greater with all-cause 30-day mortality after adjusting for preoperative risk factors and perioperative events.



"The current study … underlines the fundamental importance of even subtle perioperative TnT increases for morbidity and mortality in surgical patients."

In a diverse cohort comprising 15,065 patients with age 45 years or older undergoing noncardiac surgery requiring at least overnight hospitalization, the authors observed a 30-day mortality rate of 1.7%. This is consistent with previously reported death rates within 30 days of surgery. In fact, the magnitude

Image: Silvia Martín-Puig (immunofluorescent monoclonal antibody staining of cardiac Troponin T in human fetal cardiomyocytes). Used with permission.

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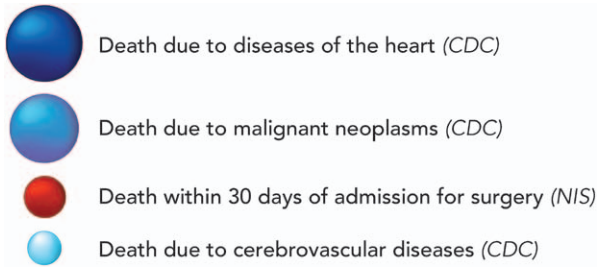

Fig. 1. Magnitude of perioperative mortality. The three leading causes of death in the Center for Disease Control's (CDC) annual death table for the United States in 2006 were: (1) diseases of heart (n = 631,636), (2) malignant neoplasms (n = 559,888), and (3) cerebrovascular diseases (n = 137,119). By using the Nationwide Inpatient Sample (NIS) for the same year, Semel *et al.*[13] reported 189,690 deaths within 30 days of admission for inpatients having a surgical procedure. In magnitude, all-cause 30-day inpatient mortality after surgery approximated the third leading cause of death in the United States. Figure adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health. Bartels K, Karhausen J, Clambey ET, Grenz A, Eltzschig HK: Perioperative organ injury. Anesthesiology 2013, copyright 2013.[11]

of all-cause perioperative mortality would make it the number three cause of death in the United States (fig. 1).[11] The current study suggests that this staggeringly high rate of death after surgery is in many circumstances preceded by often subclinical myocardial injury.[9] The authors used regression analysis to validate a cutoff value for TnT of 0.03 ng/ml or greater to define myocardial injury after noncardiac surgery. Moreover, they discovered that of the 8% of patients who developed myocardial injury after noncardiac surgery, 58.2% would not have fulfilled the universal definition for myocardial infarction. By using data from the 8,351 patients included in the PeriOperative ISchemic Evaluation trial, Devereaux *et al.*[12] previously reported a mortality rate of 11.6% in patients affected by perioperative myocardial infarction. Even when applying less rigorous criteria for myocardial injury such as a peak TnT value of 0.03 ng/ml, the current study found affected patients to be 4.3 times as likely to die within 30 days.[9] Furthermore, 1 of 10 patients with myocardial injury after noncardiac surgery did not survive 30 days after surgery. The combination of the high incidence of myocardial injury after noncardiac surgery, its prognostic relevance for 30-day mortality, and the ease and feasibility of the test to detect it (using TnT) point to tremendous opportunities for design of clinical studies to test novel interventions to attenuate myocardial injury and perioperative mortality.

Although the need for new cardio-protective therapies has been convincingly demonstrated, causality of myocardial injury and mortality has not. Perioperative ischemia and inflammation are likely to lead to injury in other organs too. Similar to low-level myocardial injury, hypoxia-sensitive tissues such as kidney are also prone to ischemic damage. Although preoperative estimated glomerular filtration rate was not associated with mortality in the current study, it seems conceivable that more sensitive markers of renal injury, such as insulin-like growth factor-binding protein 7 or tissue inhibitor of metalloproteinases-2, could have shown a comparable response pattern to TnT. Hence, the observed mortality could have been due to multiorgan injury rather than isolated myocardial injury. Therefore, interventional clinical trials focused solely on prevention of myocardial infarction might not be successful. Clearly, the development of innovative, mechanism-based approaches to prevent or treat perioperative organ injury, including myocardial injury, is paramount. These will then need to be tested in rigorous clinical trials to translate the results of this study into improved patient outcomes.

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Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Longnecker's Trade Card against the "Asphyxie" of "The Old Way"

In decrying "The Old Way" of nearly asphyxiating patients with brief administrations of 100% nitrous oxide, dentist F. C. Longnecker advertised images of a patient before and after receiving laughing gas *via* a mouthpiece from a large bag (*above*). According to Dr. Longnecker:

With your fingers your nose compress,
The real natural place of breath,
Then by swallowing, you will see
The cause of so much "asphyxie" [sic]
Now laid to my pure gas
With this nose compress and thermometer too,
You will always know how much will do.

This trade card is part of the Wood Library-Museum's Ben Z. Swanson Collection. (Copyright © the American Society of Anesthesiologists, Inc.)

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The Conundrum of Care in Perioperative Stress

American Society of Anesthesiologists Article

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The Conundrum of Care in Perioperative Stress Myocardial Ischemia, the Importance of 30-Day Outcomes and the Perioperative Surgical Home

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Committee on Patient Safety and Education

The Perioperative Surgical Home (PSH) is an innovative method of delivering health care during the entire patient care experience, from the time of decision for surgery, throughout preoperative, intraoperative and postoperative care, beyond discharge, until full patient recovery.[1] The goal of the PSH includes better care coordination and increased standardization while still allowing for patient variability, which has been shown to result in better clinical outcomes. An added benefit of the PSH model is the reduction of costs associated with health care by eliminating unnecessary tests, improving efficiencies, and reducing postoperative complications and hospital readmissions through coordination of care and transition planning.[2]

It is hard to imagine a more immediate anesthesia patient safety and coordination of care issue than the identification and management of relatively healthy patients recently identified to be at risk for postoperative morbidity and mortality. Analyses of the VISION cohort study, published in 2012 and 2014, prospectively studied perioperative patients, revealing a markedly high incidence of silent postoperative myocardial ischemia, infarction and mortality.[3] These patients did not fall into the category typically reserved for high-risk patients.[4]

The 2014 VISION study examined outcomes of 15,065 patients over age 45 who had major non-cardiac surgery and required an overnight stay. Vascular, colorectal or major orthopedic joint replacements were the majority of procedures performed. Plasma troponin T (TnT) concentrations were initially obtained within six to 12 hours after surgery and again on each of the first three postoperative days. Eight percent of patients had elevated postoperative TnT concentrations(TnT) >0.03 ng/mL, consistent with myocardial injury after non-cardiac surgery (MINS).

Ischemic Features of Patients with MINS

Only 15 percent of patients with MINS reported ischemic symptoms. However, 35 percent of MINS patients had ischemic electrocardiographic (EKG) changes, a majority of which were in the anterior chest leads. Combining those who reported ischemic symptoms and those who had ischemic changes on EKG, only 42 percent of patients with MINS showed an ischemic feature that met the criteria for diagnosis of myocardial infarction.[5] Since EKGs were largely obtained only because of elevated TnT concentrations, it is apparent that nearly all infractions would have been missed without biomarker monitoring.

Ten percent of patients with MINS were dead within 30 days of surgery, with most mortality occurring in-hospital. The death rate was nearly identical in patients with asymptomatic MINS and in those with ischemic symptoms. Most patients who died thus did not meet the universal definition of myocardial infarction criteria because of lack of some clinical feature.[5] Death in MINS patients is by far a leading cause of 30-day postoperative mortality. It is not widely recognized that this postoperative mortality is actually the third-leading cause of death nationwide.[6]

Identification of Perioperative Patients at Risk of Active Ischemia

Identifying perioperative patients "at risk" of having active ischemia is the first and substantial challenge for perioperative physicians. Among patients with active ischemia, 80-85 percent will have silent ischemia that is not accompanied by typical symptoms or symptom complexes suggestive of angina pectoris. Absent daily postoperative troponin testing for the first three days, most patients with active myocardial ischemia will thus be missed.[7,8] Why lethal myocardial ischemia does not produce symptoms in the perioperative period remains unknown, but the administration of potent analgesics may contribute.

Improving or Verifying the Quality of EKG Data

Applying simple quality controls may help in interpreting and comparing EKGs. In 12-lead EKGs, negative "P" waves in lead I may suggest limb lead reversal, congenital dextrocardia or acquired dextrotorsion. Leads I, AVL and V6 share the same sagittal plane, with the size of the "R" waves increasing from AVL to 1 to V6 following their relative proximity to the left ventricle. Prominent "S" waves in V6, not seen in leads I and AVL, usually indicate misplaced

lateral chestleads, where lead V6 is located anterior to the midaxillary line. This will help ensure both EKGs were properly obtained before comparison.

It is difficult to make good judgments from faulty data. EKG leads are often misplaced.[9] Proper EKG lead placement is important, and it should follow bony landmarks. Lead placement for 12-lead EKG studies and all perioperative monitoring should adhere to standard anatomic landmarks to permit comparison of intraoperative and postoperative tracings to baseline EKG studies. The V5 lead should be placed where the fifth intercostal space intersects with the anterior-axillary line, overlaying the LV. EKG changes consistent with ischemia are more commonly noted in the anterior chest leads compared to inferior limb leads.[3] This is not surprising. The closer the inferior leads (RL and LL) are to the heart, the less likely inferior ischemia will be detected. Surgical procedures on a hip, abdomen or groin may preclude placing the lower limb leads in a standard position on the leg or thigh. To optimize detection of myocardial ischemia, correct lead placement should be maintained in PACU, telemetry, intermediate care and ICU settings. EKG changes may trigger earlier-than-planned troponin studies.

Observation of technical aspects when obtaining EKG studies may identify opportunities for improvement in ischemia detection and lead to technically correct studies for later comparison in all postsurgical patients. Improving EKG quality, while valuable, is not a substitute for biomarker testing.

Management of Silent Myocardial Ischemia

Eighty-seven percent of MINS events, TnT elevations, were noted by the end of the second postoperative day.[3] Acute inferior wall myocardial ischemia may present as postoperative gastrointestinal complaints, such as severe or unrelenting nausea or belching. MINS placed patients at higher risk for other outcomes, including non-fatal cardiac arrest, congestive heart failure and stroke.[3]

The imbalance of myocardial oxygen demand and supply, including plaque rupture, thrombosis and spasm, must be corrected with the goal of adequate myocardial tissue perfusion and preservation. A cardiology consultation may be in order for both management and future continuity of care within the context of the PSH care model. Aspirin and statins to prevent coronary thrombosis and stabilize coronary plaques are often included in current outpatient therapy. Pharmacological interventions may suffice; however, correction of anatomic obstructions may be required.

Post-discharge management is at the discretion of the cardiologist, surgeon and primary care doctors, in conjunction with the perioperative physician in a PSH model. Patient education and directed risk reduction strategy for known risk factors such hypertension and hyperlipidemia are indicated and may be best accomplished by the perioperative physician and team upon discharge planning.

The silent nature of most episodes of perioperative myocardial ischemia and the frequent adverse outcomes associated with them, even in the setting of higher than normal, yet low troponin levels, demands our attention to identify, educate and provide continuing and competent perioperative care well beyond the time of discharge.[10] Economically, the laboratory costs of four troponin levels is approximately the same as one dose of intravenous acetaminophen; the former has the potential to prevent myocardial infarction and death.

This patient population, previously thought to be at “low cardiac risk” for surgery and anesthesia, may best be diagnosed, treated and managed through the continuum of care model provided by the PSH. Preoperative optimization, appropriate baseline EKGs, appropriate consults, accurate perioperative monitoring for ischemic changes, daily follow-up with troponin levels, postoperative consultation, management, patient education and continued follow-up visits may lead to reduced incidence of myocardial ischemia, infarction and 30-day mortality.

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Myocardial Injury after Noncardiac Surgery

A Large, International, Prospective Cohort Study Establishing Diagnostic Criteria, Characteristics, Predictors, and 30-day Outcomes

The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Writing Group, on behalf of The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Investigators

CME This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Background: Myocardial injury after noncardiac surgery (MINS) was defined as prognostically relevant myocardial injury due to ischemia that occurs during or within 30 days after noncardiac surgery. The study's four objectives were to determine the diagnostic criteria, characteristics, predictors, and 30-day outcomes of MINS.

Methods: In this international, prospective cohort study of 15,065 patients aged 45 yr or older who underwent in-patient noncardiac surgery, troponin T was measured during the first 3 postoperative days. Patients with a troponin T level of 0.04 ng/ml or greater (elevated "abnormal" laboratory threshold) were assessed for ischemic features (*i.e.*, ischemic symptoms and electrocardiography findings). Patients adjudicated as having a nonischemic troponin elevation (*e.g.*, sepsis) were excluded. To establish diagnostic criteria for MINS, the authors used Cox regression analyses in which the dependent variable was 30-day mortality (260 deaths) and independent variables included preoperative variables, perioperative complications, and potential MINS diagnostic criteria.

Results: An elevated troponin after noncardiac surgery, irrespective of the presence of an ischemic feature, independently predicted 30-day mortality. Therefore, the authors' diagnostic criterion for MINS was a peak troponin T level of 0.03 ng/ml or greater judged due to myocardial ischemia. MINS was an independent predictor of 30-day mortality (adjusted hazard ratio, 3.87; 95% CI, 2.96–5.08) and had the highest population-attributable risk (34.0%, 95% CI, 26.6–41.5) of the perioperative complications. Twelve hundred patients (8.0%) suffered MINS, and 58.2% of these patients would not have fulfilled the universal definition of myocardial infarction. Only 15.8% of patients with MINS experienced an ischemic symptom.

Conclusion: Among adults undergoing noncardiac surgery, MINS is common and associated with substantial mortality. **(Anesthesiology 2014; 120:564-78)**

WORLDWIDE, millions of patients die annually within 30 days of noncardiac surgery;[1,2] myocardial ischemia is a frequent cause.[3,4] Most studies on noncardiac surgery addressing cardiac complications focus on perioperative myocardial infarction.[5–7] The "conventional" definition and diagnostic criteria of myocardial infarction in the perioperative period come from the joint task force (European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, and World Heart Federation) for the universal definition of myocardial infarction.[7] This document defines myocardial infarction as myocardial necrosis in a clinical setting consistent with acute myocardial ischemia, and the most common diagnostic criteria consist of an elevated troponin value with either

What We Already Know about This Topic

- Emerging evidence suggests that many patients sustain myocardial injury in the perioperative period which will not satisfy the diagnostic criteria for myocardial infarction
- Myocardial injury after noncardiac surgery was defined as prognostically relevant myocardial injury due to ischemia that occurs during or within 30 days after noncardiac surgery
- This study then determined the diagnostic criteria, characteristics, predictors, and 30-day outcomes of myocardial injury after noncardiac surgery

What This Article Tells Us That Is New

- Myocardial injury after noncardiac surgery is common among adults undergoing noncardiac surgery and associated with substantial mortality

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 533. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication April 19, 2013. Accepted for publication October 30, 2013. From the Hamilton General Hospital, David Braley Cardiac, Vascular, and Stroke Research Institute, Population Health Research Institute, Hamilton, Ontario, Canada (P.J.D.); and Members of The VISION Writing Group and VISION Investigators, who are listed in appendix 1 and appendix 2, respectively.

 Anesthesiology 2014; 120:564-78

an ischemic symptom or an ischemic electrocardiographic finding.

Emerging evidence suggests that many patients sustain myocardial injury in the perioperative period which will not satisfy the diagnostic criteria for myocardial infarction.[8] Nevertheless, these events portend a poor prognosis that timely and appropriate intervention could potentially improve.[4] This suggests that a new diagnosis of Myocardial Injury after Noncardiac Surgery (MINS) may be useful to patients and clinicians. Our proposed definition of MINS is as follows: myocardial injury caused by ischemia (that may or may not result in necrosis), has prognostic relevance and occurs during or within 30 days after noncardiac surgery. The definition of MINS is broader than the definition of myocardial infarction in that it includes not only myocardial infarction but also the other prognostically relevant perioperative myocardial injuries due to ischemia. MINS does not include perioperative myocardial injury which is due to a documented nonischemic etiology (*e.g.*, pulmonary embolism, sepsis, cardioversion). No study has established the diagnostic criteria, characteristics, predictors, and 30-day outcomes of MINS.

The *V*ascular events *I*n noncardiac *S*urgery pat*I*ents c*O*hort evaluatio*N* (VISION) study is a large, international, prospective cohort study evaluating complications after noncardiac surgery (clinicaltrials.gov, identifier NCT00512109). A previous publication of the VISION study demonstrated that after adjustment of preoperative clinical variables (*e.g.*, age), peak troponin T (TnT) values of 0.02 μg/l, 0.03 to 0.29 μg/l, and 0.30 μg/l or greater in the first 3 days after noncardiac surgery were independent predictors of 30-day mortality.[3] These analyses established the prognostic relevance of troponin measurements after surgery without taking into account whether the troponin elevations were due to an ischemic or nonischemic etiology. These analyses did not evaluate troponin elevations that occurred beyond day 3 after surgery. Finally, these analyses adjusted for only preoperative variables and did not assess for confounding through other perioperative complications. For this current publication, our primary objective was to inform the diagnostic criteria of MINS, and our secondary objectives were to determine the characteristics, predictors, and 30-day outcomes of MINS. To do this, we analyzed the VISION data, evaluated troponin elevations until day 30 after surgery, excluded nonischemic troponin elevations, and adjusted for perioperative complications.

Materials and Methods

Study Design

We have previously described the methodology of the VISION Study.[3] This is an ongoing, international, prospective cohort study of a representative sample of adults undergoing noncardiac surgery. At the beginning of this study, patients had fourth-generation TnT measurements after noncardiac surgery. The first 15,000 patients had event rates approximately three times higher than expected. Recognizing that we had sufficient events to address our objectives related to the fourth-generation TnT measurements, the Operations Committee decided to subsequently monitor the fifth-generation high-sensitivity TnT assay. This publication is restricted to patients enrolled during the period of fourth-generation TnT use.

Patients

Eligible patients for the VISION study had noncardiac surgery, were aged 45 yr or older, received a general or regional anesthesia, and underwent elective or urgent/emergency surgery during the day or at night, during a weekday or the weekend. Patients were excluded who did not require an overnight hospital admission after surgery, who were previously enrolled in the VISION Study, or who declined informed consent. Additional exclusion criteria for the MINS study were: patients not having a fourth-generation TnT measurement after surgery; patients having a TnT measurement reported as less than 0.04 ng/ml, less than 0.03 ng/ml, or less than 0.02 ng/ml, instead of the absolute value; patients whose troponin elevation was adjudicated as resulting from a nonischemic etiology (*e.g.*, sepsis, pulmonary embolism, cardioversion); and patients with incomplete data for the preoperative predictors of 30-day mortality.

Research personnel primarily obtained consent before surgery. For those from whom we could not obtain consent preoperatively (*e.g.*, emergency case), study personnel obtained consent within the first 24 h after surgery. Eight centers used a deferred consent process for patients unable to provide consent (*e.g.*, patients sedated and mechanically ventilated) and for whom no next-of-kin was available.[3]

Procedures

Trained research personnel interviewed and examined patients and reviewed charts to obtain information on potential preoperative predictors of major perioperative complications by using standardized definitions. Patients had blood collected to measure a Roche fourth-generation Elecsys TnT assay 6 to 12 h postoperatively and on the first, second, and third days after surgery. Patients enrolled between 12 and 24 h after surgery had a TnT drawn immediately, and testing continued as indicated in the preceding sentence. All TnT measurements were analyzed at the participating hospitals, and the TnT results were reported to the attending physicians.

A TnT of 0.04 ng/ml or greater was the laboratory threshold considered abnormal at the time the study began. Therefore, we only obtained electrocardiography on patients who had a TnT of 0.04 ng/ml or greater, and we only assessed these patients for ischemic symptoms. When a patient had a TnT measurement of 0.04 ng/ml or greater, physicians were encouraged to obtain additional TnT measurements (to determine the peak) and electrocardiograms for several days. If a patient developed an ischemic symptom

at anytime during the first 30 days after surgery, physicians were encouraged to obtain TnT measurements and electrocardiograms. We defined an ischemic feature as the presence of any ischemic symptom or ischemic electrocardiographic finding, defined in appendix 1, Supplemental Digital Content 1, http://links.lww.com/ALN/B26.

Outcomes

The primary outcome was mortality at 30 days after surgery. Centers also reported the cause of death (vascular or nonvascular, definitions in appendix 2, Supplemental Digital Content 1, http://links.lww.com/ALN/B26). Throughout patients' hospital stay, research personnel evaluated patients clinically, reviewed hospital charts, ensured patients had TnT measurements drawn, and documented outcome events (defined in appendix 3, Supplemental Digital Content 1, http://links.lww.com/ALN/B26). We contacted patients 30 days after surgery; if patients (or next-of-kin) indicated that they had experienced an outcome, we contacted their physicians to obtain documentation.

Adjudicators evaluated all patients with an elevated troponin measurement that occurred anytime during the first 30 days after surgery to determine the presence of any ischemic features (*i.e.*, whether a patient would have fulfilled the universal definition of myocardial infarction),[7] the presence of a nonischemic etiology that could explain the elevated troponin measurement, and that the myocardial injury had occurred during or after surgery (*i.e.*, no evidence to support it was due to a preoperative event). Their decisions were used in the statistical analyses.

Data Quality

At each site, an investigator reviewed and approved all data. Research personnel at participating centers submitted the case report forms and supporting documentation directly to the data management system (iDataFax; coordinating center, McMaster University, Hamilton, Ontario, Canada). Data monitoring in VISION consisted of central data consistency checks, statistical monitoring, and on-site monitoring for all centers.[3]

Statistical Analyses

A statistical analysis plan outlining the analyses in this article was written before undertaking the following analyses. For our primary objective (*i.e.*, to establish the MINS diagnostic criteria), we undertook Cox proportional hazards models in which the dependent variable was death up to 30 days after noncardiac surgery (using a time-to-event analysis). In these models, the independent variables were: (1) nine preoperative patient characteristics that a previous VISION analysis demonstrated were independent predictors of 30-day mortality[3] (defined in appendix 4, Supplemental Digital Content 1, http://links.lww.com/ALN/B26); (2) six time-dependent perioperative adverse complications, which included the outcomes sepsis and pulmonary embolus that were not accompanied by a TnT elevation (defined in appendix 3, Supplemental Digital Content 1, http://links.lww.com/ALN/B26); and (3) potential MINS diagnostic criteria. In the first model, two potential time-dependent MINS diagnostic criteria were evaluated (*i.e.*, a peak TnT of ≥0.04 ng/ml with one or more ischemic features and a peak TnT of ≥0.04 ng/ml without an ischemic feature). The reference group was patients with a TnT of 0.01 ng/ml or less. For this first model, we excluded patients with a peak TnT equal to 0.02 or 0.03 ng/ml, because a previous VISION analysis demonstrated that these thresholds were independent predictors of 30-day mortality,[3] and we did not prospectively collect data to determine whether these patients had experienced an ischemic feature (*i.e.*, these patients did not have electrocardiography and were not assessed for ischemic symptoms).

We prespecified two potential findings that would result in different MINS diagnostic criteria. First, if both a peak TnT of 0.04 ng/ml or greater with and without ischemic features independently predicted mortality, then the MINS diagnostic criteria would only require a peak TnT of 0.04 ng/ml or greater that was judged as due to myocardial ischemia (*i.e.*, no evidence of a nonischemic etiology causing the TnT elevation) without requiring the presence of an ischemic feature. If this proved the case, we planned to repeat the MINS diagnostic criteria Cox proportional hazards model, as described in the first paragraph of the statistical analysis section, including all patients and adding two more potential MINS diagnostic criteria (*i.e.*, a peak TnT = 0.02 ng/ml and a peak TnT = 0.03 ng/ml without knowledge of whether these patients experienced an ischemic feature).

Second, if only a peak TnT of 0.04 ng/ml or greater with one or more ischemic features but not a peak TnT of 0.04 ng/ml or greater without an ischemic feature independently predicted mortality, then the MINS diagnostic criteria would require a peak TnT of 0.04 ng/ml or greater with an ischemic feature. This result would have prompted a repeated MINS diagnostic criteria Cox proportional hazards model with exploration of the impact of each individual ischemic feature (*e.g.*, chest pain) on 30-day mortality to determine which ischemic features should be included in the MINS diagnostic criteria.

After establishing the MINS diagnostic criteria, we determined the incidence and 95% CIs of patients fulfilling these criteria. We repeated the initial Cox proportional hazards model and included MINS as a time-dependent perioperative adverse complication. For this model, we determined the population-attributable risk for the independent predictors of 30-day mortality.[9,10] The population-attributable risk represents the proportion of all deaths potentially attributable to the relevant risk factor (*e.g.*, MINS). We undertook a sensitivity analysis restricted to patients in whom a preoperative estimated glomerular filtration rate (eGFR) was available, which included eGFR as a candidate-independent variable.

We compared the baseline characteristics between patients who did and did not develop MINS. Across the

groups, proportions were compared using Fisher exact test and continuous variables using the Student *t* or Wilcoxon rank sum test, as appropriate. A Cox proportional hazards model was undertaken to determine independent predictors of MINS up to 30 days after surgery. Potential independent variables in this model included 15 baseline clinical variables and seven types of surgeries (defined in appendix 5, Supplemental Digital Content 1, http://links.lww.com/ALN/B26). This analysis was restricted to patients in whom a preoperative eGFR was available. A sensitivity analysis omitting eGFR included all the patients.

Among patients who developed MINS, we determined the incidence of each individual ischemic feature. This analysis was restricted to patients who had a peak TnT of 0.04 ng/ml or greater, because patients with a peak TnT = 0.03 ng/ml were not assessed for ischemic features.

We compared the cardiovascular outcomes at 30 days after surgery (defined in appendix 6, Supplemental Digital Content 1, http://links.lww.com/ALN/B26) for patients who did and did not suffer MINS. For the cardiovascular outcomes, we determined the odds ratio (OR) and 95% CI. By using Fisher exact test, we compared the 30-day outcomes among patients who developed MINS with patients who did not develop MINS.

To develop a clinical risk score to predict short-term mortality among patients who suffered MINS, we conducted logistic regression analysis. The dependent variable was mortality at 30 days, and we evaluated the following candidate-independent variables: preoperative variables (*i.e.*, age, sex); and characteristics of the MINS outcome (*i.e.*, presence of individual ischemic symptoms, presence of individual ischemic electrocardiographic findings, location of the ischemic electrocardiographic finding, and peak TnT ≥0.30 ng/ml). Our choice of candidate-independent variables was on the basis of our hypotheses regarding which variables were likely to be most predictive and the results of previous nonoperative myocardial infarction 30-day mortality risk-prediction models.[11] In this logistic regression analysis, we included only patients with peak TnT of 0.04 ng/ml or greater, because we did not know whether patients with a peak TnT of 0.03 ng/ml had ischemic features. We further included the identified significant predictors in a separate model to determine their adjusted ORs. A scoring system was developed by assigning weighted points to each statistically significant predictor based on their log ORs, and the expected 30-day mortality risk was determined for potential risk scores using the method outlined by Sullivan *et al.*[12] Bootstrapping was performed to obtain 95% CIs around the expected 30-day mortality risk for each potential risk score.

For all our regression models, we used forced simultaneous entry (all candidate variables remained in the models regardless of statistical significance).[13,14] If an adjudicator determined that a patient had suffered more than one episode of MINS throughout the first 30 days after surgery, we evaluated only the first episode in all analyses. We reported adjusted ORs (for logistic regression) and adjusted hazard ratios (for Cox proportional hazard regression), 95% CI, and associated *P* values to three decimal places with *P* values less than 0.001 reported as *P* value less than 0.001. For all tests, we used alpha = 0.05 level of significance. In our models, we validated the ORs and hazard ratios and their 95% CIs through bootstrapping. For our Cox proportional hazards models, we assessed discrimination through evaluation of the C index, and we conducted sensitivity analyses in which we used frailty models to assess for center effects. For the logistic regression model, we assessed collinearity using the variance inflation factor, and we considered variables with a variance inflation factor greater than 10 to be collinear.[15] For our logistic regression model, we assessed discrimination through evaluation of the area under the receiver-operating characteristic curve, calibration with a Hosmer–Lemeshow goodness-of-fit test, and conducted sensitivity analysis in which we used a mixed model to adjust for potential clustering by center.

Our sample size was based on our model to determine the diagnostic criteria of MINS. We evaluated 19 variables in this model and simulation studies demonstrate that regression models require 12 events per variable evaluated.[16,17] Therefore, we required 228 deaths in our study. All analyses were performed using SAS version 9.2 (Cary, NC).

Ethical Considerations and Funding Sources

The Research Ethics Board at each site approved the protocol before patient recruitment. Funding for this study comes from more than 60 grants for VISION and its substudies.

Results

Figure 1 reports the patient flow. Of the 15,065 patients included in the MINS study, 99.7% of the patients completed the 30-day follow-up. Patients were recruited at 12 centers in eight countries in North and South America, Australia, Asia, and Europe, from August 6, 2007 to January 11, 2011.

Diagnostic Criteria of MINS (Primary Objective)

Table 1, Supplemental Digital Content 2, http://links.lww.com/ALN/B27, reports the results of the initial Cox proportional hazards model demonstrating that a peak TnT of 0.04 ng/ml or greater with and separately without an ischemic feature were independent predictors of 30-day mortality. The full model that explored all the considered diagnostic criteria for MINS demonstrated that a peak TnT of 0.04 ng/ml or greater with one or more ischemic features (adjusted hazard ratio, 4.82; 95% CI, 3.40–6.84), a peak TnT of 0.04 ng/ml or greater without an ischemic feature (adjusted hazard ratio, 3.30; 95% CI, 2.26–4.81), and a peak TnT of 0.03 ng/ml (adjusted hazard ratio, 4.30; 95% CI, 2.68–6.91) all independently predicted 30-day mortality (Table 2, Supplemental Digital Content 2, http://links.lww.com/ALN/B27). Therefore, after adjustment for

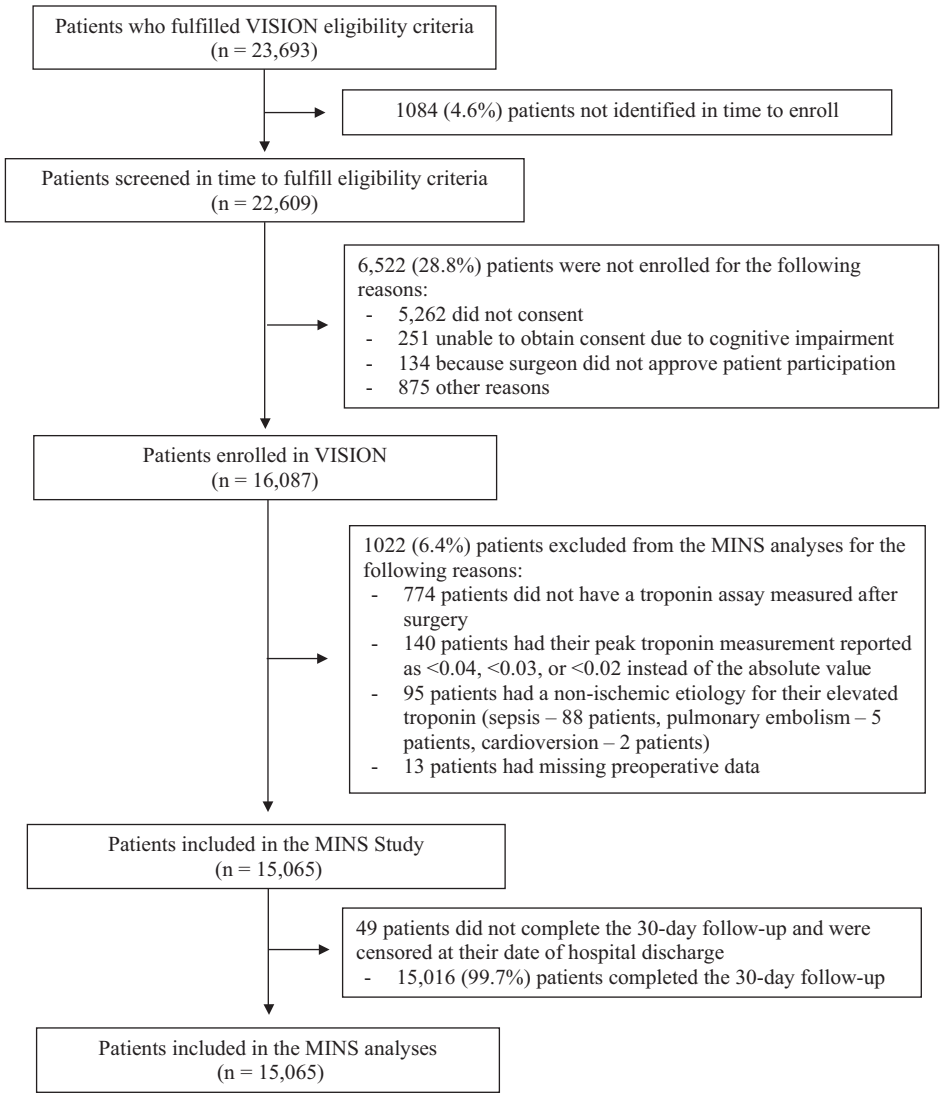

Fig. 1. Patient flow chart. MINS = myocardial injury after noncardiac surgery; VISION = *V*ascular events *I*n noncardiac *S*urgery pat*I*ents c*O*hort evaluatio*N*.

preoperative patient characteristics and perioperative complications, a peak TnT of 0.03 ng/ml or greater was an independent predictor of 30-day mortality. On the basis of these analyses, our diagnostic criterion for MINS was any peak TnT of 0.03 ng/ml or greater that was judged as resulting from myocardial ischemia (*i.e.*, no evidence of a nonischemic etiology causing the TnT elevation).

A total of 1,200 patients (8.0%; 95% CI, 7.5–8.4) fulfilled the MINS diagnostic criterion. Table 1 reports the predictors of 30-day mortality in the model that included preoperative variables and perioperative adverse complications, including MINS. Four perioperative complications (*i.e.*, MINS, sepsis, stroke, and pulmonary embolus) were independent predictors of 30-day mortality. The independent prognostic factors identified in this model potentially explain the majority of the deaths that occurred (*i.e.*, the total population-attributable risk was 92.6%; 95% CI, 89.6–95.2); among the perioperative complications, MINS had the largest population-attributable risk (34.0%; 95% CI, 26.6–41.5). Our 30-day mortality sensitivity analysis, restricted to patients for whom a preoperative eGFR was available, demonstrated that MINS was not confounded by eGFR (*i.e.*, MINS remained an independent predictor of 30-day mortality adjusted hazard ratio, 3.66; 95% CI, 2.71–4.93), but preoperative eGFR was not an independent predictor of 30-day mortality, $P = 0.480$ (Table 3, Supplemental Digital Content 2, http://links.lww.com/ALN/B27).

Characteristics and Predictors of MINS

Figure 1, Supplemental Digital Content 3, http://links.lww.com/ALN/B28, depicts that 87.1% of MINS events occurred within the first 2 days after surgery. Supplemental Digital Content 4 (table), http://links.lww.com/ALN/B29, presents the baseline characteristics of patients who did and did not suffer MINS. Patients with MINS were older, had more cardiovascular risk factors, and had known

Table 1. Model to Predict 30-day Mortality*

Predictor	Prevalence of Predictors (%)	Patients Dying within 30 Days after Surgery		Model Derivation		Model Validation		Population-attributable Risk (95% CI‡)
		n	% (95% CI)	Adjusted HR (95% CI)	*P* Value	Adjusted HR† (95% CI)	*P* Value	
Preoperative risk factors								
Age								
45–64 yr old	7,682 (51.0)	64	0.8 (0.7–1.1)	1.00		1.00		
65–74 yr old	3,756 (24.9)	60	1.6 (1.2–2.1)	1.62 (1.14–2.32)	0.008	1.61 (1.10–2.40)	0.013	42.1% (27.8–55.2)
≥75 yr old	3,627 (24.1)	136	3.7 (3.2–4.4)	2.66 (1.95–3.64)	<0.001	2.69 (1.95–3.80)	<0.001	
Urgent/emergent surgery	2,121 (14.1)	114	5.4 (4.5–6.4)	3.58 (2.73–4.68)	<0.001	3.66 (2.69–5.00)	<0.001	33.3% (25.8–40.8)
Cancer	3,993 (26.5)	102	2.6 (2.1–3.1)	2.17 (1.63–2.90)	<0.001	2.20 (1.57–3.08)	<0.001	22.7% (13.9–31.2)
General surgery	3,033 (20.1)	98	3.2 (2.7–3.9)	1.58 (1.18–2.10)	0.002	1.57 (1.14–2.18)	0.005	15.7% (6.0–24.7)
History of COPD	1,262 (8.4)	60	4.8 (3.7–6.1)	1.79 (1.33–2.41)	<0.001	1.79 (1.28–2.41)	<0.001	10.8% (4.2–17.3)
History of stroke	693 (4.6)	40	5.8 (4.3–7.8)	1.72 (1.20–2.45)	0.003	1.70 (1.13–2.47)	0.009	7.5% (2.3–12.7)
History of PVD	793 (5.3)	39	4.9 (3.6–6.7)	1.89 (1.31–2.71)	<0.001	1.89 (1.22–2.66)	0.002	6.9% (1.8–12.0)
Neurosurgery	888 (5.9)	26	2.9 (2.0–4.3)	2.03 (1.31–3.15)	0.001	2.04 (1.20–3.35)	0.007	5.6% (1.4–9.8)
Recent high-risk CAD	171 (1.1)	16	9.4 (5.8–14.7)	2.51 (1.49–4.21)	<0.001	2.50 (1.29–4.34)	0.007	4.1% (0.9–7.3)
Perioperative adverse complications‖								
MINS	1,200 (8.0)	115	9.6 (8.0–11.4)	3.87 (2.96–5.08)	<0.001	3.90 (2.90–5.27)	<0.001	34.0% (26.6–41.5)
Sepsis/infection								
Sepsis	812 (5.4)	96	11.8 (9.8–14.2)	7.18 (5.17–9.97)	<0.001	7.31 (5.13–10.35)	<0.001	30.5% (23.7–37.2)§
Infection, not sepsis	902 (6.0)	15	1.7 (1.0–2.7)	1.33 (0.77–2.30)	0.303	1.33 (0.65–2.18)	0.309	
Neither	13,351 (88.6)	149	1.1 (1.0–1.3)	1.00		1.00		
Stroke	81 (0.5)	16	19.8 (12.5–29.7)	3.50 (2.05–5.97)	<0.001	3.56 (1.78–6.77)	0.001	4.5% (1.3–7.8)
Pulmonary embolus	95 (0.6)	11	11.6 (6.6–19.6)	6.11 (3.18–11.74)	<0.001	6.15 (2.28–13.77)	<0.001	3.5% (0.9–6.2)
Deep venous thrombosis	89 (0.6)	8	9.0 (4.6–16.7)	1.47 (0.68–3.19)	0.327	1.64 (0.44–4.62)	0.514	NA
Pneumonia	345 (2.3)	50	14.5 (11.2–18.6)	1.25 (0.86–1.84)	0.248	1.24 (0.81–1.89)	0.304	NA

* C index = 0.90 (95% CI, 0.88–0.92). † Obtained from 1,000 bootstrap samples. ‡ Only variables that are significant predictors in the Cox model are included in the population-attributable risk model, and 95% CIs were determined through 10,000 bootstrap samples. § Populational-attributable risk is based on sepsis *vs.* no sepsis. ‖ Complications occurring during or within 30 days after the primary noncardiac surgery.

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; MINS = myocardial injury after noncardiac surgery; NA = not applicable; PVD = peripheral vascular disease.

cardiovascular disease. Table 2 reports the ischemic features of patients suffering MINS of whom 84.2% (95% CI, 81.7–86.4) did not experience an ischemic symptom. A total of 34.9% (95% CI, 31.9–38.0) of patients with MINS had an ischemic electrocardiographic finding, of which T-wave inversion (23.3%; 95% CI, 20.7–26.1) and ST depression (16.4%; 95% CI, 14.1–18.9) were the most common. Among patients with MINS, 41.8% had an ischemic feature and would have fulfilled the universal definition of myocardial infarction; however, 58.2% of these patients did not experience an ischemic feature and would therefore not have fulfilled the universal definition of myocardial infarction.

We identified 12 independent predictors of MINS that included the following: age 75 yr or older, cardiovascular risk factors (*e.g.*, renal insufficiency, diabetes), known cardiovascular disease (*e.g.*, peripheral vascular disease, coronary artery disease), and surgical factors (*e.g.*, urgent/emergent surgery) (table 3). The sensitivity analysis, which included all the patients and did not assess eGFR as a potential independent predictor of MINS, demonstrated similar findings to table 3 except that low-risk surgery was no longer predictive (adjusted hazard ratio, 0.77; 95% CI, 0.56–1.07).

Prognostic Impact of MINS

Patients with MINS were at higher risk of a nonfatal cardiac arrest (OR, 14.58; 95% CI, 5.75–37.02; $P < 0.001$), congestive heart failure (OR, 10.34; 95% CI, 7.99–13.37; $P < 0.001$), and stroke (OR, 4.66; 95% CI, 2.87–7.58; $P < 0.001$) compared with patients who did not suffer MINS (table 4). The 30-day mortality rate was 9.8% among patients who suffered MINS and 1.1% among patients who did not suffer MINS (OR, 10.07; 95% CI, 7.84–12.94; $P < 0.001$). Among the patients suffering MINS, 115 died within 30 days of surgery, centers reported a vascular cause of death in 62 (53.9%) patients and nonvascular in 53 (46.1%). The composite of nonfatal cardiac arrest, nonfatal congestive

Table 2. Ischemic Features of Patients Suffering Myocardial Injury after Noncardiac Surgery

	Prevalence		Mortality at 30 days	
Ischemic Feature*	n	% (95% CI)	n	% (95% CI)
Ischemic symptoms				
Chest discomfort	85	9.0 (7.4–11.0)	17	20.0 (12.9–29.7)
Neck, jaw, or arm discomfort	5	0.5 (0.2–1.2)	0	0.0 (0.0–43.4)
Dyspnea	66	7.0 (5.6–8.8)	10	15.2 (8.4–25.7)
Pulmonary edema	46	4.9 (3.7–6.5)	8	17.4 (9.1–30.7)
Any of the above	149	15.8 (13.6–18.3)	22	14.8 (10.0–21.3)
Ischemic electrocardiographic findings				
Q waves	13	1.4 (0.8–2.3)	1	7.7 (1.4–33.3)
ST elevation	22	2.3 (1.5–3.5)	7	31.8 (16.4–52.7)
LBBB	5	0.5 (0.2–1.2)	3	60.0 (23.1–88.2)
ST depression	154	16.4 (14.1–18.9)	21	13.6 (9.1–19.9)
T-wave inversion	219	23.3 (20.7–26.1)	31	14.2 (10.2–19.4)
Any of the above	328	34.9 (31.9–38.0)	47	14.3 (10.9–18.5)

* Analysis restricted to patients with a peak troponin T ≥0.04 ng/ml (*i.e.*, 941 patients) because patients with a peak troponin T equal to 0.03 ng/ml were not assessed for ischemic features.

LBBB = left bundle branch block; n = number of patients.

heart failure, nonfatal stroke, and mortality occurred more frequently in patients who suffered MINS (OR, 9.59; 95% CI, 7.99–11.51; $P < 0.001$). In those with and without an ischemic feature, 30-day mortality rates were 13.5% (95% CI, 10.5–17.3%) and 7.7% (95% CI, 5.7–10.2%), respectively.

Predictors of Mortality among Patients Suffering MINS

Age 75 yr or older, ST elevation or new left bundle branch block, and anterior ischemic electrocardiographic findings were independent predictors of 30-day mortality among patients who suffered MINS (table 5). Our scoring system to predict 30-day mortality in patients suffering MINS assigned the following points to the independent predictor of mortality: age 75 yr or older (1 point), ST elevation or new left bundle branch block (2 points), and anterior ischemic electrocardiographic findings (1 point). Figure 2 presents the expected and observed risk of 30-day mortality among the patients with MINS based on the scoring system. Patients with a score of 0, 1, 2, 3, or 4 had expected 30-day

Table 3. Independent Preoperative Predictors of Myocardial Injury after Noncardiac Surgery*

	Model Derivation		Model Validation
Analyses Based on 13,948 Patients	Adjusted HR (95% CI)	*P* Value	Adjusted HR† (95% CI)
Age ≥75 yr old	1.73 (1.48–2.03)	<0.001	1.74 (1.48–2.05)
Females	0.72 (0.64–0.81)	<0.001	0.72 (0.63–0.82)
Current atrial fibrillation	1.47 (1.20–1.81)	<0.001	1.48 (1.18–1.84)
History of			
Diabetes	1.34 (1.18–1.53)	<0.001	1.34 (1.17–1.53)
Hypertension	1.32 (1.14–1.52)	<0.001	1.32 (1.14–1.54)
Congestive heart failure	1.37 (1.14–1.65)	<0.001	1.38 (1.12–1.68)
Coronary artery disease	1.27 (1.09–1.47)	0.002	1.27 (1.08–1.48)
High-risk coronary artery disease	1.63 (1.21–2.19)	0.001	1.64 (1.16–2.29)
Peripheral vascular disease	1.92 (1.60–2.29)	<0.001	1.92 (1.58–2.31)
Stroke	1.36 (1.13–1.64)	0.001	1.36 (1.10–1.65)
Preoperative eGFR, ml/min/1.73 m^2			
<30	7.85 (6.66–9.25)	<0.001	7.93 (6.64–9.53)
30–44	2.39 (1.98–2.89)	<0.001	2.39 (1.95–2.92)
45–59	1.69 (1.41–2.01)	<0.001	1.69 (1.40–2.02)
>60	1.00	—	1.00
Low-risk surgery	0.72 (0.51–0.99)	0.049	0.71 (0.49–0.99)
Urgent/emergent surgery	1.83 (1.59–2.11)	<0.001	1.83 (1.57–2.13)

* C index = 0.79 (95% CI, 0.78–0.81). † Obtained from 10,000 bootstrap samples.

eGFR = estimated glomerular filtration rate; HR = hazard ratio.

Table 4. 30-day Outcomes

	Patients without MINS (n = 13,822)	Patients Suffering MINS (n = 1,194)	
Outcome*	n (%)	n (%)	Unadjusted OR (95% CI)
Nonfatal cardiac arrest	8 (0.06)	10 (0.8)	14.58 (5.75–37.02)
Congestive heart failure	137 (1.0)	112 (9.4)	10.34 (7.99–13.37)
Stroke	58 (0.4)	23 (1.9)	4.66 (2.87–7.58)
Mortality	147 (1.1)	117 (9.8)	10.07 (7.84–12.94)
Composite of major events†	325 (2.4)	224 (18.8)	9.59 (7.99–11.51)

* Among the 15,065 patients, 49 patients did not complete the 30-day follow-up and were not included in these analyses except for the outcome mortality in which we did not know 30-day vital status on 27 patients who were not included in the mortality analysis. † Composite of major events = composite of mortality, nonfatal cardiac arrest, nonfatal congestive heart failure, and nonfatal stroke.

MINS = myocardial injury after noncardiac surgery; n = number of patients; OR = odds ratio.

mortality rates of 5.2% (95% CI, 3.3–7.4), 10.2% (95% CI, 6.5–11.9), 19.0% (95% CI, 8.7–24.3), 32.5% (95%, 10.6–45.9), and 49.8% (95% CI, 12.0–65.5), respectively.

The random-effect (frailty) Cox models that adjusted for potential clustering-by-center effects produced similar results. Each variable included in the logistic regression models demonstrated a variance inflation factor less than 10 suggesting no collinearity. The mixed model that adjusted for any potential clustering by center in the logistic regression model produced similar results.

Discussion

Principal Findings

In this international cohort study of 15,065 patients 45 yr of age or older undergoing noncardiac surgery, we determined that the optimal diagnostic criterion for MINS is a peak TnT of 0.03 ng/ml or greater judged due to myocardial ischemia (*i.e.*, no evidence of a nonischemic etiology causing the TnT elevation). This criterion does not require the presence of an ischemic feature. MINS was common (8.0%), associated with substantial mortality and cardiovascular complications at 30 days, and the population-attributable risk suggests that MINS explains 34.0% of the deaths that occur in adults during the first 30 days after noncardiac surgery.

A minority of patients with MINS experienced an ischemic symptom; only 41.8% of patients with MINS fulfilled the universal definition of myocardial infarction. Among the 58.2% of patients with MINS who did not experience an ischemic feature and thus would not have fulfilled the universal definition of myocardial infarction, 1 in 13 died within 30 days.

Our Study in Relation to Other Studies

In a previous VISION publication, we demonstrated that the peak troponin measurement during the first 3 days after noncardiac surgery was an independent predictor (based on adjustment of only preoperative patient characteristics) of 30-day mortality.[3] Our current publication adds important new information by focusing on troponin elevations that were adjudicated as resulting from myocardial ischemia, evaluating all troponin elevations until day 30 after surgery, and taking into account potential confounding through risk adjustment of other perioperative complications. This is the first study to evaluate diagnostic criteria for MINS, independent predictors of MINS, and predictors of mortality in patients suffering MINS. LeManach *et al.* conducted a consecutive cohort study of 1,136 patients undergoing abdominal aortic surgery in which they excluded septic patients with an elevated troponin I (Dade-Behring).[18] Consistent with our findings, they demonstrated that an elevated troponin I after surgery was an independent predictor of in-hospital mortality.[18] A limitation of this study is that they did not adjust for any perioperative complications (*e.g.*, stroke).

A multivariable analysis of data from the PeriOperative ISchemic Evaluation Trial (an international, randomized, controlled trial comprising 8,351 patients) that adjusted for preoperative factors and perioperative complications demonstrated

Table 5. Independent Predictors of 30-day Mortality in Patients Suffering Myocardial Injury after Noncardiac Surgery*

		Model Derivation		Model Validation	
	Number of Patients	Adjusted OR (95% CI)	*P* Value	Adjusted OR† (95% CI)	*P* Value
Age ≥75 yr old	454 (48.3%)	2.06 (1.31–3.22)	0.002	2.06 (1.33–3.37)	0.003
ST elevation or new LBBB	27 (2.9%)	3.97 (1.70–9.27)	0.002	3.96 (1.54–9.14)	0.005
Anterior ischemic electrocardiographic findings	200 (21.3%)	2.32 (1.46–3.70)	<0.001	2.33 (1.42–3.70)	<0.001

* Analysis restricted to patients with a peak troponin T ≥0.04 ng/ml (*i.e.*, 940 patients) because patients with a peak troponin T equal to 0.03 ng/ml were not assessed for ischemic features; area under the receiver-operating characteristic curve = 0.651 (95% CI, 0.592–0.711); goodness-of-fit test *P* = 0.555, indicating no evidence of a lack of fit. † Obtained from 10,000 bootstrap samples.

LBBB = left bundle branch block; OR = odds ratio.

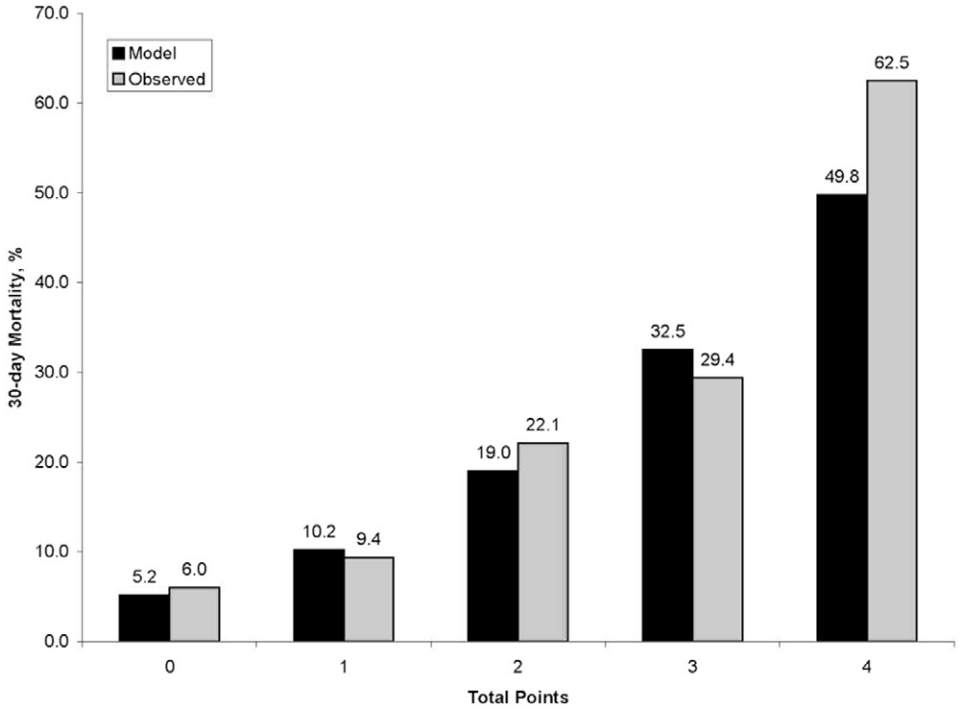

Fig. 2. Risk of mortality based on scoring system for independent predictors of 30-day mortality in patients suffering myocardial injury after noncardiac surgery.

that the highest quartile of a cardiac biomarker or enzyme elevation (*i.e.*, a troponin or creatine kinase–myocardial band value 3.6 times or greater the upper limit of normal) in patients without an ischemic feature was an independent predictor of 30-day mortality (adjusted OR, 2.54; 95% CI, 1.65–3.90).[4] Although the foregoing PeriOperative ISchemic Evaluation analysis supports our finding that an elevated troponin after surgery without an ischemic feature increases short-term mortality, many different troponin assays were evaluated and data were insufficient to determine prognostically relevant thresholds for the individual troponin assays.

Strengths and Limitations of Our Study

Strengths of our study included evaluation of a large contemporary representative sample of adults who underwent noncardiac surgery in five continents with complete follow-up data on 99.7% of the patients. All patients underwent troponin monitoring after surgery using the same troponin assay, and all patients with a TnT of 0.04 ng/ml or greater were prospectively assessed for ischemic symptoms and ischemic electrocardiographic findings. Our 30-day mortality model that included MINS (based on our diagnostic criterion) demonstrated good calibration, and the results were consistent across centers.

Our study had several limitations. We systematically monitored troponin measurements only until day 3 after surgery. Therefore, after day 3, we may have missed additional MINS events in patients who did not experience an ischemic symptom. The substantial decline in MINS events by postoperative day 3 (Figure 1, Supplemental Digital Content 3, http://links.lww.com/ALN/B28) suggests, however, that we were not likely to have missed many MINS events. We determined the MINS diagnostic threshold only for the fourth-generation TnT assay; thus, evaluation of other troponin assays will require further research.

We did not assess patients for the presence of ischemic features if their peak TnT was 0.03 ng/ml. At the start of the study, we did not know that patients with a TnT of 0.03 ng/ml had an increased risk of 30-day mortality, and we assessed patients for ischemic features only if they met the laboratory threshold considered abnormal (*i.e.*, TnT ≥0.04 ng/ml). It is possible among patients with a peak TnT of 0.03 ng/ml that only those patients who also had an ischemic feature were at increased risk of 30-day mortality. Given that patients with a peak TnT of 0.04 ng/ml or greater did not require an ischemic feature to impact 30-day mortality, we believe it is unlikely that a peak TnT of 0.03 ng/ml requires an ischemic feature to impact mortality. Our model to predict 30-day mortality in patients suffering MINS did not include patients who had a peak TnT of 0.03 ng/ml. Although it is possible that our model will not predict mortality in patients with a TnT of 0.03 ng/ml, this is unlikely given that a previous VISION publication did not demonstrate any difference in the risk of mortality across peak TnT values of 0.03 to 0.29 ng/ml.[3] Although experienced physicians in perioperative medicine adjudicated all elevated troponin measurements to ensure there was no evidence of a nonischemic cause, it is possible some nonischemic etiologies were missed and that some events were not due to ischemic myocardial injury.

Implications

Most studies on noncardiac surgery evaluating cardiac complications focus on perioperative myocardial infarction. Our results show that focusing on this complication would result in missing 58.2% of the prognostically relevant perioperative myocardial ischemic events. On the basis of these results and the rationale presented in our introduction, we advocate assessing surgical patients for the diagnosis of MINS. Although no randomized, controlled trial has established an effective treatment for patients suffering MINS, the prognosis of these patients may be modifiable. The high-quality evidence for acetyl-salicylic acid and statin therapy in the nonoperative setting,[19,20] and encouraging observational data from a large international perioperative trial (*i.e.*, PeriOperative ISchemic Evaluation) showing an association with use of these drugs and decreased 30-day mortality in patients who have suffered a perioperative myocardial injury,[4] suggests that acetyl-salicylic acid and statin therapy may benefit patients who suffer MINS.

In our study of patients 45 yr of age or older undergoing noncardiac surgery, 8.0% of patients suffered MINS. It is estimated that worldwide more than 100 million adults 45 yr of age or older undergo major noncardiac surgery each year.[1,21] This suggests that 8 million adults may suffer MINS annually. The frequency of this perioperative complication, and the associated 30-day risk of cardiovascular complications and mortality, highlights the urgent need for clinical trials to establish strategies to prevent and treat this important complication.

A minority (15.8%) of patients suffering MINS experienced an ischemic symptom. Therefore, 84.2% of MINS probably would have gone undetected without systematic troponin monitoring after surgery. Consistent with our finding, the third universal definition of myocardial infarction consensus statement recommends monitoring perioperative troponin measurements in high-risk patients undergoing noncardiac surgery.[7]

Conclusions

Evaluating patients for the diagnosis of MINS compared with myocardial infarction will allow physicians to avoid missing the majority of the patients who develop a prognostically relevant perioperative myocardial injury. Among adults undergoing noncardiac surgery, MINS is common (8%), and 1 in 10 patients suffering MINS will die within 30 days. Failure to monitor troponin measurements after noncardiac surgery will result in missing more than 80% of MINS events.

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Competing Interests

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Does Continuous Electronic ST-Segment Monitoring Enhance Prediction of Postoperative Troponin Elevation?

To the Editor:

Various baseline characteristics,[1] biomarkers,[2] and intraoperative blood pressure[3] predict myocardial injury after noncardiac surgery (MINS). Maile et al[4] asked whether adding automated intraoperative ST-segment analysis to selected clinical factors improves prediction of MINS. The question is reasonable because troponin elevation (with or without symptoms) has a 10% 30-day mortality[5] and can promote interventions, including (1) informing patients that they had myocardial injury and are thus at risk for future heart attacks; (2) starting aspirin; (3) initiating statin and/or angiotensin-converting enzyme inhibitor therapy; (4) improving hypertension control; and (5) using a "teachable moment" to encourage lifestyle changes including smoking cessation, sensible diet, and enhanced exercise.[6]

Curiously, the analysis is presented as a "case-control study design." Although ST-segment characteristics are presented in patients with and without troponin elevation, the thrust of the analysis is to add ST-segment characteristics to clinical information in an effort to better predict MINS. For example, "the relationships between individual subject characteristics and postoperative troponin elevation were summarized using logistic regression" and "to isolate independent predictors of postoperative troponin elevation, variables from each lead were entered into a nonparsimonious logistic regression predicting postoperative myocardial injury." The investigators thus used exposure (clinical characteristics and ST-segment abnormalities) to predict outcome (troponin elevation)—which is a retrospective cohort design.[7]

A limitation the investigators acknowledge is that troponin screening was not routine; instead, the biomarker usually was evaluated in response to symptoms or signs of myocardial injury. A consequence is that only 5.6% of their patients had even a single postoperative troponin measurement, and only 14% of those patients had elevated concentrations. The overall incidence of MINS was thus only 0.8%. For perspective, the multinational incidence among inpatients older than 45 years of age is 8%.[5]

We were struck by the investigators' statement that selection bias (in choosing to monitor troponin) "may have led to an underestimation of the association between ST segment depression and postoperative troponin elevation." To the extent that ST-segment depression increases both the likelihood of troponin monitoring and the risk of MINS—which is surely the case—selection bias will most likely lead to overestimation of the association between ST-segment depression and postoperative troponin elevation.

Adding ST-segment abnormalities and variability to readily available clinical data improved the area under the receiver operating characteristics curve from 0.68 to 0.71—an increase of only 3%. Although highly statistically significant, 3% represents a trivial improvement and offers little support for the investigators' conclusion that "automated ST-segment monitoring obtained during surgery is possibly useful for the detection of patients at risk for postoperative myocardial injury." A more reasonable conclusion might be that ST segment analysis is not especially helpful.

Furthermore, an area under the curve of only about 0.7 indicates that discrimination was poor—with or without ST-segment analysis. Even assuming excellent calibration (not reported), clinicians thus cannot reliably predict which patients will experience postoperative myocardial injury. And precisely because MINS cannot be reliably predicted, troponin screening should be routine for most patients older than 45 years of age having inpatient surgery.[6]

In summary, it was possible and perhaps even probable that automated intraoperative ST-segment analysis would substantially enhance clinicians' ability to predict myocardial injury after noncardiac surgery. Maile et al[4] present an elegant analysis showing that adding ST-segment analysis only trivially improves discrimination compared with a model based on clinical characteristics alone. The presented results thus appear to directly contradict the authors' conclusion that "automated ST segment values obtained during anesthesia may be useful for improving the prediction of postoperative troponin elevation." In fact, their results show that ST-segment analysis adds little value.

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In Response

We thank Sessler[1] for his interest in our recent article on the utility of intraoperative ST segment values for predicting postoperative troponin elevation.[2] It is an honor to receive these comments from an expert in the field of myocardial injury after noncardiac surgery, and we are grateful to have the opportunity to reply.

In response to his first point, we concur that our study design is better described as a retrospective cohort study. The next topic, which pertains to the possible impact that selection bias had on our results, requires more discussion. We acknowledged in our article that selection bias may have influenced the analysis because the decision to measure postoperative troponin levels was made using clinical judgment. As pointed out by Sessler, ST segment depression is commonly used to justify measuring postoperative troponin levels. On the basis of this, if our study only examined ST segment depression, it would be expected that the association between intraoperative ST segment values and postoperative troponin elevation would be overestimated. However, our study included other characteristics of ST segments and demonstrated that these other features may be more important.

This highlights one of the most intriguing finding of this study, namely, that the variability of ST segments had a greater impact than ST segment depression with increased standard deviation being associated with decreased risk of postoperative troponin elevation. For example, if 2 individuals were otherwise identical, more epochs of ST segment depression usually result in less risk because of the concurrent increase in standard deviation. Therefore, if new ST segment depression was the major reason for measuring troponin levels (which we agree is likely), then the study would tend to exclude those at higher risk (those with a small standard deviation). This could lead to an underestimation of the association between intraoperative ST segment values and postoperative troponin elevation. However, selection bias can produce both overestimation and underestimation of risk, and additional prospective studies in which all subjects are screened for troponin elevation are needed to clarify the relationship among ST segment elevation, depression, and variability.

The final point concerns the overall usefulness of intraoperative ST segments for predicting postoperative myocardial injury. It is true that the ST segment measures examined in our study, along with many of the other features commonly used to predict risk for postoperative troponin elevation, did not discriminate extremely well between those with and without postoperative troponin elevation. Despite this, it did provide a small improvement (net reclassification improvement of 0.0345; 95% confidence interval, 0.00016–0.0591, $P = .0474$). This is similar to many other patient characteristics, which, by themselves, cannot predict adverse events, but when integrated with other clinical variables, can be used to guide our care of patients. Although the suggested strategy of monitoring postoperative troponin levels for all patients older than the age of 45 years who are admitted to the hospital after noncardiac surgery would clearly be more sensitive, algorithms that use pre-existing data to identify high-risk individuals for screening may be more cost-effective. Therefore, we believe our findings support additional studies aimed at finding ways to use intraoperative ST segments to identify patients at risk for myocardial injury. Hopefully, each additional little improvement will move us closer to understanding and reducing the impact of perioperative myocardial injury.

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