JAMA | Original Investigation

Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery

Writing Committee for the VISION Study Investigators

IMPORTANCE Little is known about the relationship between perioperative high-sensitivity troponin T (hsTnT) measurements and 30-day mortality and myocardial injury after noncardiac surgery (MINS).

OBJECTIVE To determine the association between perioperative hsTnT measurements and 30-day mortality and potential diagnostic criteria for MINS (ie, myocardial injury due to ischemia associated with 30-day mortality).

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study of patients aged 45 years or older who underwent inpatient noncardiac surgery and had a postoperative hsTnT measurement. Starting in October 2008, participants were recruited at 23 centers in 13 countries; follow-up finished in December 2013.

EXPOSURES Patients had hsTnT measurements 6 to 12 hours after surgery and daily for 3 days; 40.4% had a preoperative hsTnT measurement.

MAIN OUTCOMES AND MEASURES A modified Mazumdar approach (an iterative process) was used to determine if there were hsTnT thresholds associated with risk of death and had an adjusted hazard ratio (HR) of 3.0 or higher and a risk of 30-day mortality of 3% or higher. To determine potential diagnostic criteria for MINS, regression analyses ascertained if postoperative hsTnT elevations required an ischemic feature (eg, ischemic symptom or electrocardiography finding) to be associated with 30-day mortality.

RESULTS Among 21 842 participants, the mean age was 63.1 (SD, 10.7) years and 49.1% were female. Death within 30 days after surgery occurred in 266 patients (1.2%; 95% CI, 1.1%-1.4%). Multivariable analysis demonstrated that compared with the reference group (peak hsTnT <5 ng/L), peak postoperative hsTnT levels of 20 to less than 65 ng/L, 65 to less than 1000 ng/L, and 1000 ng/L or higher had 30-day mortality rates of 3.0% (123/4049; 95% CI, 2.6%-3.6%), 9.1% (102/1118; 95% CI, 7.6%-11.0%), and 29.6% (16/54; 95% CI, 19.1%-42.8%), with corresponding adjusted HRs of 23.63 (95% CI, 10.32-54.09), 70.34 (95% CI, 30.60-161.71), and 227.01 (95% CI, 87.35-589.92), respectively. An absolute hsTnT change of 5 ng/L or higher was associated with an increased risk of 30-day mortality (adjusted HR, 4.69; 95% CI, 3.52-6.25). An elevated postoperative hsTnT (ie, 20 to <65 ng/L with an absolute change ≥5 ng/L or hsTnT ≥65 ng/L) without an ischemic feature was associated with 30-day mortality (adjusted HR, 3.20; 95% CI, 2.37-4.32). Among the 3904 patients (17.9%; 95% CI, 17.4%-18.4%) with MINS, 3633 (93.1%; 95% CI, 92.2%-93.8%) did not experience an ischemic symptom.

CONCLUSIONS AND RELEVANCE Among patients undergoing noncardiac surgery, peak postoperative hsTnT during the first 3 days after surgery was significantly associated with 30-day mortality. Elevated postoperative hsTnT without an ischemic feature was also associated with 30-day mortality.

JAMA. 2017;317(16):1642-1651. doi:10.1001/jama.2017.4360

Supplemental content

The Authors/Writing Committee and the VISION Investigators are listed at the end of this article.

Corresponding Author: P. J. Devereaux, MD, PhD, Population Health Research Institute, David Braley Cardiac, Vascular, and Stroke Research Institute, Perioperative Medicine and Surgical Research Unit, Hamilton General Hospital, McMaster University, 237 Barton St E, Room C1-116, Hamilton, ON L8L 2X2, Canada (philipj@mcmaster.ca).

Large observational studies suggest that among patients aged 45 years or older undergoing major noncardiac surgery, more than 1% die in hospital or within 30 days of surgery.[1,2] Myocardial injury after noncardiac surgery (MINS) is defined as myocardial injury caused by ischemia that occurs during or within 30 days after surgery and is independently associated with mortality.[3] Diagnostic criteria for MINS, based on the non-high-sensitivity troponin T assay, have been identified[3]; however, the US Food and Drug Administration recently approved use of the high-sensitivity troponin T (hsTnT) assay, and globally, many hospitals are using high-sensitivity troponin assays.

Little is known about the relationship between perioperative hsTnT measurements and 30-day mortality. A large international study, the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study, was undertaken to assess perioperative complications. Among adults who underwent noncardiac surgery and had a postoperative hsTnT measurement, the primary objective was to determine the association between perioperative hsTnT measurements and 30-day mortality and potential diagnostic criteria for MINS based on hsTnT. The secondary objectives were to (1) determine if there was an interaction between the lowest prognostically important postoperative hsTnT threshold (ie, the lowest hsTnT threshold that was independently associated with patients' risk of 30-day mortality and had an adjusted hazard ratio [HR] ≥3.0 and a risk of 30-day mortality ≥3%) and estimated glomerular filtration rate (eGFR) or sex; (2) describe the characteristics of patients experiencing MINS and their outcomes; and (3) determine the proportion of MINS that might go undetected without troponin monitoring.

Key Points

Question What is the relationship between perioperative high-sensitivity troponin T (hsTnT) measurements and 30-day mortality and myocardial injury after noncardiac surgery?

Findings In this prospective cohort study of 21 842 patients, elevated postoperative hsTnT measured 6 to 12 hours after surgery and daily for 3 days with and without an ischemic feature (eg, ischemic symptom, ischemic electrocardiography finding) was significantly associated with an increased risk of 30-day mortality (0.5% for <20 ng/L, 3.0% for 20 to <65 ng/L, 9.1% for 65 to <1000 ng/L, and 29.6% for ≥1000 ng/L).

Meaning Among patients undergoing noncardiac surgery, peak postoperative hsTnT was significantly associated with 30-day mortality, even in the absence of an ischemic feature.

Methods

Study Design and Participants

The VISION Study was a prospective cohort study of a representative sample of adults who underwent noncardiac surgery. In the first 15 000 patients, non-hsTnT was measured and its association with 30-day mortality and MINS was evaluated and reported.[2,3] In the second half of the study, hsTnT measurements were obtained in more than 21 000 patients. This represents the focus of this article.

Eligible patients were aged 45 years or older, underwent noncardiac surgery under general or regional anesthesia, and stayed at least 1 night in the hospital after surgery. Patients were excluded if they were previously enrolled in VISION or did not provide informed consent. eAppendix 1 in the Supplement reports additional exclusion criteria related to the secondary objectives.

The institutional/ethics review board at each site approved the protocol before patient enrollment commenced. Patients provided written informed consent before surgery unless they were unable (eg, emergency surgery), in which case research personnel obtained consent within the first 24 hours after surgery. Seven centers used a deferred consent process for patients unable to provide consent (eg, patients sedated and mechanically ventilated) and for whom no designated decision maker was available. This allowed collection of data while awaiting the patient's or designated decision maker's consent.

Procedures

Details regarding participant screening and procedures to ensure a representative sample are reported in eAppendix 2 in the Supplement. Research personnel interviewed and examined patients and reviewed charts to obtain data on variables potentially associated with perioperative complications. Patients had blood collected for measurement by the Roche fifth-generation Elecsys hsTnT assay 6 to 12 hours postoperatively and on days 1, 2, and 3 after surgery. Patients enrolled between 12 and 24 hours after surgery had blood drawn for hsTnT measurement immediately, and testing continued as described above. During the later phase of the study, hsTnT measurement was added before surgery. The majority of hospitals analyzed the hsTnT measurements of their patients and reported the results to clinicians. Two UK centers blinded clinicians to hsTnT results. In the United States, where hsTnT was not approved for clinical use at the time of conducting the VISION Study, blood samples were collected, processed, frozen, and analyzed for hsTnT at a later date. For US participants, the fourth-generation non-hsTnT assay was used and clinicians received these results; however, analyses for this study are restricted to the hsTnT measurements.

Throughout hospital stay, research personnel evaluated patients, reviewed hospital charts, ensured that patients had hsTnT measurements completed, and noted outcomes (eAppendix 3 in the Supplement). Patients with an hsTnT level of at least 14 ng/L (ie, threshold considered abnormal by manufacturer)[4] were assessed for ischemic features (eg, ischemic symptoms, ischemic electrocardiographic findings; defined in eAppendix 4 in the Supplement). Centers were encouraged to obtain electrocardiograms for several days after an hsTnT measurement result of at least 14 ng/L and to obtain hsTnT measurements and electrocardiograms if patients experienced an ischemic symptom. Exceptions to these procedures occurred in the 2 centers that blinded clinicians to the hsTnT results and among US participants with an hsTnT level of at least 14 ng/L but a non-hsTnT level of less than 0.04 ng/mL (ie, threshold considered abnormal by manufacturer). For these

patients, study personnel reviewed clinical notes for ischemic symptoms, but no electrocardiograms were obtained.

Study personnel telephoned patients at 30 days after surgery; documentation was obtained if patients (or next of kin) indicated that they had experienced an outcome. At each site, an investigator reviewed and approved all data. Research personnel submitted the case report forms and supporting documentation to the data management system (iDataFax, coordinating center, McMaster University, Hamilton, Canada). Data monitoring in VISION consisted of central data consistency checks and on-site monitoring.

Expert unblinded physician adjudicators evaluated all patients with an elevated hsTnT level. They assessed the clinical notes and laboratory data related to elevated hsTnT measurements to determine the presence of an ischemic feature (ie, whether a patient fulfilled the universal definition of myocardial infarction),[5] for evidence that the hsTnT elevation was due to a nonischemic etiology (eg, sepsis, pulmonary embolus, atrial fibrillation, cardioversion, chronic elevation), and to confirm that the myocardial injury had occurred during or after surgery rather than before surgery. Their decisions were used in the statistical analyses.

Statistical Analyses

A statistical analysis plan was written before undertaking the analyses. For the analyses to determine the association between perioperative hsTnT measurements and 30-day mortality, patients were excluded if they did not have an hsTnT measurement during the first 3 days after surgery, if the hospital laboratory reported their hsTnT as less than 10 ng/L or less than 14 ng/L instead of an absolute value, or if they were missing data on a baseline clinical variable included in the multivariable model. A Cox proportional hazards model was undertaken in which the dependent variable was mortality up to 30 days after surgery and the independent variables included preoperative and surgical variables previously associated with 30-day mortality (eAppendix 5 in the Supplement)[2] and peak postoperative hsTnT thresholds from the first 3 days after surgery (ie, 0 to 100 ng/L in increments of 5 ng/L [except that 14 ng/L was used instead of 15 ng/L because 14 ng/L represents the 99th percentile], 100 to 200 ng/L in increments of 10 ng/L, and 200 to 1000 ng/L in increments of 100 ng/L).

A modified Mazumdar approach (ie, an iterative process that explored potential hsTnT thresholds)[2,6] was used to determine if there were prognostically important postoperative hsTnT thresholds that were independently associated with patients' risk of 30-day mortality and had an adjusted HR of at least 3.0 and a risk of 30-day mortality of at least 3% (these requirements were determined a priori based on feedback from international perioperative researchers and an anticipated 1% 30-day mortality rate in the overall cohort). Through this iterative process, prognostically important hsTnT thresholds were identified until the *P* value from the likelihood ratio test was greater than .01 or the hsTnT threshold had an adjusted HR of less than 3. After establishing the prognostically important peak postoperative hsTnT thresholds, a Kaplan-Meier curve was constructed. The modified Mazumdar approach was also used to determine if there were absolute changes between preoperative and postoperative hsTnT values that were independently associated with 30-day mortality. Using the lowest significant change threshold identified in this analysis, subsequent analyses evaluated the association between the highest and lowest perioperative hsTnT measurements (eg, change between postoperative hsTnT measurements) and 30-day mortality.

To determine if there was a significant interaction (ie, interaction $P < .05$) between the lowest prognostically important postoperative hsTnT threshold and eGFR or sex, the Cox model was repeated that included the lowest prognostically important postoperative hsTnT threshold and preoperative eGFR (ie, <30 mL/min/1.73 m^2 or undergoing dialysis, 30-44 mL/min/1.73 m^2, 45-59 mL/min/1.73 m^2, and ≥60 mL/min/1.73 m^2) and the interaction between the hsTnT threshold and eGFR. The model was repeated substituting sex for eGFR.

For the analyses to determine potential diagnostic criteria for MINS, patients with the following were excluded: no hsTnT measurement during the first 30 days after surgery; a peak hsTnT level of at least 20 ng/L adjudicated as resulting from a nonischemic etiology (eg, chronic elevation) other than a nonischemic postoperative complication (eg, sepsis, pulmonary embolus, atrial fibrillation); a peak preoperative hsTnT level of at least 20 ng/L and the preoperative measurement was the peak measurement or equal to the peak postoperative measurement; a peak postoperative hsTnT of 20 to less than 65 ng/L and no ability to assess change (ie, only 1 hsTnT measurement); or missing data on a baseline clinical variable or perioperative outcome included in the multivariable model.

To evaluate potential diagnostic criteria for MINS, based on hsTnT measurements, Cox proportional hazards models were undertaken in which the dependent variable was 30-day mortality. Independent variables included preoperative and surgical variables (eAppendix 5 in the Supplement),[2] postoperative outcomes (ie, major bleeding, sepsis, new clinically important atrial fibrillation, stroke, pulmonary embolus, deep venous thrombosis, and pneumonia as time-dependent covariates), and potential MINS diagnostic criteria (ie, an elevated postoperative hsTnT measurement with an ischemic feature and an elevated postoperative hsTnT measurement without an ischemic feature). If the elevated postoperative hsTnT measurement with and without ischemic features was significantly associated with 30-day mortality, the MINS diagnostic criteria would require only an elevated hsTnT, without the need for presence of an ischemic feature. Patients with an elevated postoperative hsTnT measurement that adjudicators attributed to a nonischemic postoperative complication (eg, sepsis) were included in these analyses but were not counted as having an elevated postoperative hsTnT measurement due to ischemia.

For the Cox model in which the dependent variable was 30-day mortality and the independent variables included preoperative and surgical variables and postoperative complications (eg, MINS, major bleeding) as time-dependent covariates, several sensitivity analyses and analyses to assess for interactions were undertaken. The first sensitivity analysis was restricted to centers with at least 95% complete follow-up. The second sensitivity analysis included all patients who had a peak hsTnT level of at least 20 ng/L adjudicated as resulting from

a nonischemic etiology—including chronic elevations—and a peak preoperative hsTnT level of at least 20 ng/L, in whom the preoperative measurement was the peak measurement or equal to the peak postoperative measurement, and all of these patients were counted as non-MINS patients. For the third sensitivity analysis, the second sensitivity analysis was repeated, but patients with a peak preoperative hsTnT level of at least 20 ng/L and in whom the preoperative measurement was the peak measurement or equal to the peak postoperative measurement were counted as having had MINS. An analysis was undertaken based on the 2 sites that blinded clinicians to hsTnT results and a separate analysis based on all other sites and tested for an interaction between MINS diagnostic criteria and these groups of centers. To determine if there was an interaction between MINS and the presence of a preoperative hsTnT measurement, the Cox model was repeated and incorporated a test of interaction between MINS and the presence of a preoperative hsTnT measurement.

After identifying the MINS diagnostic criteria for this study, the proportion of patients experiencing MINS with ischemic features was determined (eAppendix 4 in the Supplement). The proportion of MINS that might have gone undetected without troponin monitoring (ie, MINS without an ischemic symptom) was also determined.

Random-effects (frailty) Cox models to adjust for potential site-clustering effects were undertaken.[7] The adjusted HRs and 95% confidence intervals were reported, and discrimination was assessed through evaluation of the C statistic. All tests were 2-sided and a $P < .05$ was designated as statistically significant; however, the likelihood ratio test required a $P \leq .01$. Analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.3.2 (R Project).

Results

Patients were recruited at 23 centers in 13 countries in North America, South America, Africa, Asia, Australia, and Europe from October 2008 to November 2013 (eTable 1 in the Supplement). Of the 21 842 patients included in these analyses (mean age, 63.1 [SD, 10.7] years; 49.1% female), 21 050 (96.4%) completed the 30-day follow-up; the remaining patients were censored at the time of hospital discharge. The **Figure** shows participant study flow.

Table 1 reports patients' preoperative characteristics and the surgery performed (for definitions, see eAppendix 6 in the Supplement); approximately half were women. The most common types of surgery were major orthopedic (16.5%), major general (20.2%), and low-risk (35.5%). The median number of hsTnT measurements after surgery was 3 (interquartile range, 2-4), and 40.4% had a preoperative hsTnT measurement. eTable 2 in the Supplement reports the timing of preoperative hsTnT measurements. eTable 3 in the Supplement reports the baseline characteristics of patients who did and did not have a preoperative hsTnT measurement.

Death within 30 days after surgery occurred in 266 patients (1.2%; 95% CI, 1.1%-1.4%). Multivariable analyses demonstrated that compared with the reference group (peak hsTnT level <5 ng/L), peak postoperative hsTnT levels of 20 to less than 65 ng/L, 65 to less than 1000 ng/L, and 1000 ng/L or more had adjusted HRs of 23.63 (95% CI, 10.32-54.09), 70.34 (95% CI, 30.60-161.71), and 227.01 (95% CI, 87.35-589.92), with corresponding 30-day mortality rates of 3.0%, 9.1%, and 29.6%, respectively (**Table 2**). The random-effects Cox model that adjusted for any potential site-clustering effect produced similar results (eTable 4 in the Supplement). The eFigure in the Supplement presents the Kaplan-Meier estimates for 30-day mortality based on the peak postoperative hsTnT thresholds identified through the modified Mazumdar approach. Cox models demonstrated no interaction between the lowest prognostically important postoperative hsTnT threshold (ie, ≥20 ng/L) and eGFR or sex (interaction P=.83 and P=.20, respectively). A sensitivity analysis that assessed eGFR as a continuous variable demonstrated an interaction P = .89.

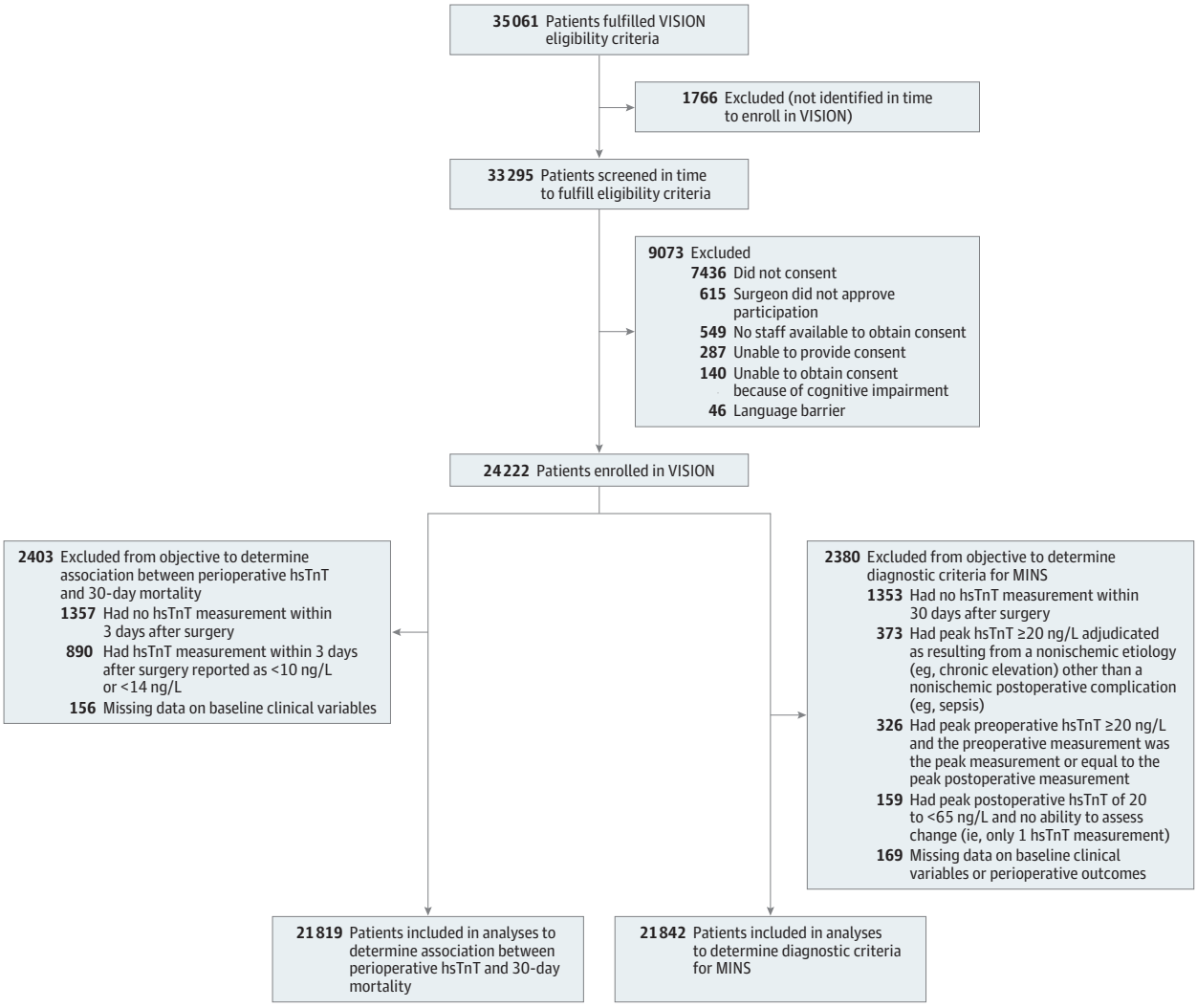
The modified Mazumdar approach identified that absolute changes of at least 5 ng/L and at least 40 ng/L between preoperative and postoperative hsTnT measurements were independently associated with risk of 30-day mortality (**Table 3**). The lower change value (≥5 ng/L) across any hsTnT measurements was associated with risk of 30-day mortality (30-day mortality rates in patients with changes of <5 ng/L and ≥5 ng/L were 0.5% and 3.0%, respectively; adjusted HR, 4.69; 95% CI, 3.52-6.25). Few patients who had an hsTnT level of at least 65 ng/L did not have a change of at least 5 ng/L, and these patients had a high risk of death (eTable 5 in the Supplement). Analyses restricted to patients with a peak postoperative hsTnT level of less than 65 ng/L demonstrated that an absolute change of at least 5 ng/L was associated with 30-day mortality (adjusted HR, 3.28; 95% CI, 2.38-4.53) (eTable 6 in the Supplement).

Based on these results, an elevated postoperative hsTnT measurement was defined as 20 to less than 65 ng/L with an absolute change of at least 5 ng/L or an hsTnT level of at least 65 ng/L. Among the 4385 patients (19.7%) with an elevated postoperative hsTnT level, 481 (11.0%; 95% CI, 10.1%-11.9%) were adjudicated as having nonischemic, non-MINS hsTnT elevations (eg, sepsis) (eTable 7 in the Supplement). Among the 9494 patients with a preoperative hsTnT measurement, 2355 patients (24.8%) had an elevated perioperative hsTnT, of whom 326 (13.8%; 95% CI, 12.5%-15.3%) had a preoperative hsTnT that was greater than or equal to the peak postoperative hsTnT measurement.

eTable 8 in the Supplement reports the 30-day mortality rates among patients who did not have MINS (0.6%), who had MINS without an ischemic feature (2.9%), and who had MINS with an ischemic feature (8.5%). The results of the Cox proportional hazards model demonstrated that an elevated postoperative hsTnT level without an ischemic feature (adjusted HR, 3.20; 95%, CI, 2.37-4.32) and with an ischemic feature (adjusted HR, 5.04; 95% CI, 3.56-7.12) were independently associated with 30-day mortality. Based on this analysis, the diagnostic criteria for MINS were an elevated postoperative hsTnT level judged as resulting from myocardial ischemia (ie, no evidence of nonischemic etiology for the hsTnT elevation) without the requirement of an ischemic feature.

eTable 9 in the Supplement reports the sensitivity analysis restricted to centers with at least 95% complete follow-up,

Figure. Participant Flow in the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study



VISION indicates Vascular Events in Noncardiac Surgery Patients Cohort Evaluation; MINS, myocardial injury after noncardiac surgery; hsTnT, high-sensitivity troponin T.

which demonstrated similar findings to the results in eTable 8. The second sensitivity analysis (ie, the Cox model that included and designated as non-MINS patients all those who had a peak hsTnT level ≥20 ng/L adjudicated as resulting from a nonischemic etiology and those with a peak preoperative hsTnT level ≥20 ng/L, with the preoperative measurement as the peak measurement or equal to the peak postoperative measurement) demonstrated that MINS was independently associated with 30-day mortality (adjusted HR, 3.10; 95% CI, 2.39-4.02). The third sensitivity analysis (ie, the analysis that repeated the second sensitivity analysis but designated patients with a peak preoperative hsTnT level ≥20 ng/L, with the preoperative measurement as the peak measurement or equal to the peak postoperative measurement, as MINS patients) demonstrated that MINS was associated with 30-day mortality (adjusted HR, 3.34; 95% CI, 2.57-4.34). Cox models demonstrated that there was no interaction between the MINS diagnostic criteria and the centers that blinded the hsTnT results vs the centers that did not blind the hsTnT results (interaction $P = .67$) or between MINS and the presence vs absence of a preoperative hsTnT measurement (interaction $P = .24$).

A total of 3904 patients (17.9%; 95% CI, 17.4%-18.4%) fulfilled the MINS diagnostic criteria. **Table 4** reports the variables independently associated with 30-day mortality in the model that included preoperative variables and perioperative complications, including MINS (C statistic, 0.89; 95% CI, 0.87-0.91). Five perioperative complications (ie, MINS, major bleeding, sepsis, new atrial fibrillation, and stroke) were independently associated with 30-day mortality. eTable 10 in the Supplement reports when MINS was diagnosed; 94.1% of diagnoses occurred by day 2 after surgery.

Among 3904 patients who had MINS, 846 (21.7%; 95% CI, 20.4%-23.0%) fulfilled the universal definition of myocardial infarction (ie, an elevated hsTnT with ≥1 ischemic feature),[5] of whom 575 (68.0%; 95% CI, 64.7%-71.0%) did not experience an ischemic symptom. These asymptomatic patients who

fulfilled the universal definition of myocardial infarction had another ischemic feature, most commonly an ischemic electrocardiography finding. eTable 11 in the Supplement reports the ischemic features of patients experiencing MINS; 3.6% experienced chest discomfort. A total of 3633 patients (93.1%) who had MINS did not experience an ischemic symptom, and MINS might have gone undetected without troponin monitoring. eTable 12 in the Supplement reports cardiovascular outcomes among patients who had MINS, did not have MINS, and had MINS and a postoperative hsTnT level of at least 65 ng/L. All cardiovascular complications were increased among patients who had MINS, including a composite of nonfatal cardiac arrest, congestive heart failure, coronary revascularization, and mortality (30-day risk among patients who did not and did have MINS was 0.9% and 7.3%, respectively; unadjusted odds ratio, 8.47; 95% CI, 6.94-10.34).

Discussion

A postoperative hsTnT measurement of at least 20 ng/L was associated with 30-day mortality, and there was no interaction based on eGFR or sex. An absolute hsTnT change of at least 5 ng/L across any hsTnT measurements was also associated with an increased risk of 30-day mortality. Only 11.0% of elevated postoperative hsTnT measurements (ie, an hsTnT level of 20 to <65 ng/L with an absolute change ≥5 ng/L or an hsTnT level ≥65 ng/L) were adjudicated as having a nonischemic etiology. Based on the study analyses, the MINS diagnostic criteria were an elevated postoperative hsTnT, judged as resulting from myocardial ischemia (ie, no evidence of a nonischemic etiology) not requiring an ischemic feature. MINS was associated with an increased risk of major cardiovascular complications.

A study of 599 patients who had noncardiac surgery demonstrated in an unadjusted analysis that a peak postoperative hsTnT level of at least 14 ng/L was associated with an increased risk of 3-year mortality (HR, 1.94; 95% CI, 1.19-3.15).[8] In contrast, the current study identified through adjusted analyses multiple hsTnT thresholds that were associated with 30-day mortality. In another study of 455 vascular surgery patients who had preoperative and postoperative hsTnT measurements, an absolute hsTnT change of at least 6.3 ng/L independently improved risk estimation of a composite of myocardial infarction and cardiovascular death at 30 days compared with the revised cardiac risk index alone (P = .002).[9] The current study had substantially more patients and events and found that an absolute change of at least 5 ng/L was associated with 30-day mortality.

Although troponin thresholds associated with mortality and diagnostic criteria for MINS have been identified in prior studies, these studies were restricted to the non-hsTnT assay.[2,3] Given the recent US Food and Drug Administration approval of hsTnT and the common use of this assay globally, the current study provides important information regarding the hsTnT thresholds associated with 30-day mortality and diagnostic criteria for MINS. Moreover, the current study provides data supporting that MINS does not require the presence of an ischemic feature.

Table 1. Participant Baseline Characteristics and Type of Anesthesia and Surgery

Characteristics	No. of Participants With Data	Participants With Characteristic, No. (%)[a]
Age, y	21 842	
45-64		12 770 (58.5)
65-74		5694 (26.1)
≥75		3378 (15.5)
Women	21 838	10 714 (49.1)
History of		
Diabetes	21 838	4508 (20.6)
Hypertension	21 839	10 869 (49.8)
Congestive heart failure	21 835	551 (2.5)
Coronary artery disease	21 831	2821 (12.9)
High-risk coronary artery disease	21 842	164 (0.8)
Coronary revascularization	21 808	1283 (5.9)
Coronary revascularization within 6 mo	21 803	68 (0.3)
Cardiac arrest	21 834	145 (0.7)
Peripheral vascular disease	21 842	2031 (9.3)
Stroke	21 842	762 (3.5)
Chronic obstructive pulmonary disease	21 842	1638 (7.5)
Active cancer	21 842	5237 (24.0)
In atrial fibrillation just before surgery	21 837	496 (2.3)
Preoperative estimated glomerular filtration rate, mL/min/1.73 m^2	20 411	
<30 or receiving dialysis		745 (3.6)
30-44		810 (4.0)
45-59		1912 (9.4)
≥60		16 944 (83.0)
Type of surgery[b]	21 842	
Major vascular		1873 (8.6)
Major general		4422 (20.2)
Major thoracic		737 (3.4)
Major urology or gynecology		2703 (12.4)
Major orthopedic		3598 (16.5)
Major neurosurgery		1243 (5.7)
Low-risk surgery		7759 (35.5)
Urgent or emergent surgery	21 842	1613 (7.4)
Type of anesthesia	21 836	
General only		11 493 (52.6)
Neuroaxial (spinal or epidural) only		5012 (23.0)
General and nitrous oxide only		1781 (8.2)
General and thoracic epidural only		1075 (4.9)
General and nerve block only		768 (3.5)
Other		1707 (7.8)

[a] Some percentages may add up to more than 100% because of rounding.

[b] Some patients may have had more than 1 type of surgery; for definitions, see eAppendix 6 in the Supplement.

Although anesthetic and surgical advances have improved surgical safety, more than 1% of patients aged 45 years or older undergoing major noncardiac surgery die in the hospital or within 30 days of surgery.[1,2] The current study has

Table 2. Peak Postoperative hsTnT Thresholds Associated With 30-Day Mortality[a]

	hsTnT Thresholds, ng/L					
	<5	5 to <14	14 to <20	20 to <65	65 to <1000	≥1000
Patients, No. (%)	5318 (24.4)	8750 (40.1)	2530 (11.6)	4049 (18.6)	1118 (5.1)	54 (0.2)
Deaths, No. (%)	6 (0.1)	40 (0.5)	29 (1.1)	123 (3.0)	102 (9.1)	16 (29.6)
Adjusted hazard ratio (95% CI)	1 [Reference]	3.73 (1.58-8.82)	9.11 (3.76-22.09)	23.63 (10.32-54.09)	70.34 (30.60-161.71)	227.01 (87.35-589.92)
P Value		.003	<.001	<.001	<.001	<.001

Abbreviation: hsTnT, high-sensitivity troponin T.

[a] A total of 21 819 patients were included in this analysis. The Cox proportional hazards model includes the following preoperative variables: active cancer, general surgery, urgent/emergent surgery, history of peripheral vascular disease, history of chronic obstructive pulmonary disease, age, recent high-risk coronary artery disease, history of stroke, and neurosurgery. Postoperative hsTnT measurements during the first 3 days after surgery were assessed in these analyses.

Table 3. Association Between Absolute Changes in hsTnT Values and 30-Day Mortality[a]

	Absolute Change Between Preoperative and Peak Postoperative hsTnT Values Among 7857 Patients With Preoperative and Postoperative Measurements					Absolute Change Between Postoperative hsTnT Values Among 18 023 Patients With ≥2 Postoperative Measurements		Absolute Change Between hsTnT Values Among 19 373 Patients With ≥2 Measurements	
	Analysis 1			Analysis 2					
	<5 ng/mL	≥5 to <40 ng/mL	≥40 ng/mL	<5 ng/mL	≥5 ng/mL	<5 ng/mL	≥5 ng/mL	<5 ng/mL	≥5 ng/mL
Patients, No. (%)	5116 (65.1)	2369 (30.2)	372 (4.7)	5116 (65.1)	2741 (34.9)	11 542 (64)	6481 (36)	11 950 (61.7)	7423 (38.3)
30-d mortality, No. (%)	23 (0.4)	35 (1.5)	36 (9.7)	23 (0.4)	71 (2.6)	62 (0.5)	217 (3.3)	64 (0.5)	226 (3)
Adjusted hazard ratio (95% CI)	1 [Reference]	2.81 (1.63-4.82)	15.68 (8.94-27.51)	1 [Reference]	4.53 (2.77-7.39)	1 [Reference]	5.24 (3.92-7.01)	1 [Reference]	4.69 (3.52-6.25)
P Value		<.001	<.001		<.001		<.001		<.001

Abbreviation: hsTnT, high-sensitivity troponin T.

[a] The models include the following preoperative variables: active cancer, general surgery, urgent/emergent surgery, history of peripheral vascular disease, history of chronic obstructive pulmonary disease, age, recent high-risk coronary artery disease, history of stroke, and neurosurgery. Preoperative hsTnT measurements were obtained on the day of surgery before the operation started to 28 days before surgery (eTable 2 in the Supplement), and postoperative hsTnT measurements during the first 3 days after surgery were assessed in these analyses.

established that elevated postoperative hsTnT levels were significantly associated with death. Although most patients experiencing MINS do not receive secondary-prevention cardiovascular drugs (eg, aspirin, statins),[10] observational studies suggest that these medications prevent mortality and major cardiac complications.[11,12]

Given that the current study is the second large study reporting that the diagnostic criteria for MINS do not require an ischemic feature, this finding supports the MINS diagnostic criteria of an elevated postoperative hsTnT judged as resulting from myocardial ischemia (ie, no evidence of a nonischemic etiology for hsTnT elevation) without the requirement of an ischemic feature. Without perioperative troponin monitoring, 93.1% of MINS and 68.0% of myocardial infarctions might go unrecognized because these patients do not experience ischemic symptoms. Most patients (94%) experience MINS within 2 days of surgery, a period when analgesic medications can mask cardiac symptoms. Given the relevance of absolute change in hsTnT measurements in diagnosing MINS and that 13.8% of patients with an elevated perioperative hsTnT had their peak value before surgery, physicians should consider obtaining a preoperative hsTnT measurement in patients in whom they plan to measure hsTnT after surgery.

Strengths of this study include a large, international, representative sample of adults undergoing noncardiac surgery; 96.4% of the participants completed 30-day follow-up. All elevated hsTnT measurements were adjudicated to determine the presence of ischemic features and for evidence of a nonischemic etiology.

This study has several limitations, including the arbitrariness of the criteria for a prognostically important hsTnT elevation (ie, adjusted HR ≥3.0 and 30-day risk of mortality ≥3%). This decision was made a priori based on feedback from many international investigators. Mortality data based on independent hsTnT thresholds that did not fulfill this definition of prognostic importance were reported (Table 2).

The adjusted HRs' 95% confidence intervals were wide for the peak postoperative hsTnT thresholds that were independently associated with 30-day mortality; however, even for the lowest threshold (ie, an hsTnT of 20 to <65 ng/L), the lower limit of the 95% confidence interval of the adjusted HR was 10.32. Although this large international study identified hsTnT thresholds that were associated with 30-day mortality in adjusted analyses, and the frailty model demonstrated no site-clustering effect, further research evaluating the identified thresholds would be of value.

Obtainment of preoperative hsTnT measurements was implemented after the study had started, and only 40.4% of patients had a preoperative measurement. Given that 13.8% of patients with an elevated perioperative hsTnT measurement had a preoperative hsTnT value that was greater than or equal to the postoperative hsTnT peak measurement, there may have been an overestimation of the incidence of MINS among the 59.6% of patients who did not have a preoperative hsTnT measurement.

Table 4. 30-Day Mortality Model[a]

	No. (%)			
	Patients (n = 21 842)	30-Day Deaths	Adjusted Hazard Ratio (95% CI)	*P* Value
Perioperative complications				
MINS	3904 (17.9)	162 (4.1)	3.69 (2.80-4.85)	<.001
No MINS	17 938 (82.1)	104 (0.6)	1 [Reference]	
Major bleeding	3101 (14.2)	139 (4.5)	2.77 (2.11-3.62)	<.001
No major bleeding	18 741 (85.8)	127 (0.7)	1 [Reference]	
Sepsis	886 (4.1)	82 (9.3)	4.96 (3.54-6.96)	<.001
No sepsis	20 956 (95.9)	184 (0.9)	1 [Reference]	
New atrial fibrillation	273 (1.2)	29 (10.6)	1.85 (1.19-2.87)	.007
No new atrial fibrillation	21 569 (98.8)	237 (1.1)	1 [Reference]	
Stroke	69 (0.3)	11 (15.9)	5.19 (2.75-9.78)	<.001
No stroke	21 773 (99.7)	255 (1.2)	1 [Reference]	
Pulmonary embolus	92 (0.4)	4 (4.3)	1.19 (0.42-3.34)	.75
No pulmonary embolus	21 750 (99.6)	262 (1.2)	1 [Reference]	
Deep venous thrombus	76 (0.3)	2 (2.6)	1.07 (0.26-4.37)	.93
No deep venous thrombus	21 766 (99.7)	264 (1.2)	1 [Reference]	
Pneumonia	392 (1.8)	37 (9.4)	1.21 (0.80-1.84)	.37
No pneumonia	21 450 (98.2)	229 (1.1)	1 [Reference]	
Preoperative variables				
Active cancer	5237 (24.0)	113 (2.2)	1.94 (1.47-2.57)	<.001
No active cancer	16 605 (76.0)	153 (0.9)	1 [Reference]	
General surgery	4422 (20.2)	96 (2.2)	1.58 (1.18-2.11)	.002
Other surgeries	17 420 (79.8)	170 (1.0)	1 [Reference]	
Urgent or emergent surgery	1613 (7.4)	50 (3.1)	2.39 (1.73-3.29)	<.001
Elective surgery	20 229 (92.6)	216 (1.1)	1 [Reference]	
History of PVD	2031 (9.3)	55 (2.7)	1.81 (1.30-2.52)	<.001
No history of PVD	19 811 (90.7)	211 (1.1)	1 [Reference]	
History of COPD	1638 (7.5)	46 (2.8)	1.56 (1.12-2.18)	.009
No history of COPD	20 204 (92.5)	220 (1.1)	1 [Reference]	
Age, y				
45-64	12 770 (58.5)	114 (0.9)	1 [Reference]	
65-74	5694 (26.1)	70 (1.2)	0.95 (0.70-1.29)	.73
≥75	3378 (15.5)	82 (2.4)	1.17 (0.86-1.59)	.32
Recent high-risk CAD	164 (0.8)	7 (4.3)	1.83 (0.86-3.92)	.12
No recent high-risk CAD	21 678 (99.2)	259 (1.2)	1 [Reference]	
History of stroke	762 (3.5)	17 (2.2)	0.93 (0.56-1.55)	.79
No history of stroke	21 080 (96.5)	249 (1.2)	1 [Reference]	
Neurosurgery	1243 (5.7)	14 (1.1)	1.41 (0.81-2.46)	.22
Other surgeries	20 599 (94.3)	252 (1.2)	1 [Reference]	

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; hsTnT, high-sensitivity troponin T; MINS, myocardial injury after noncardiac surgery; PVD, peripheral vascular disease.

[a] For these analyses to determine potential diagnostic criteria for MINS, we excluded patients with no hsTnT measurement during the first 30 days after surgery, with a peak hsTnT level ≥20 ng/L adjudicated as resulting from a nonischemic etiology (eg, chronic elevation) other than a nonischemic postoperative complication (eg, sepsis, pulmonary embolus, atrial fibrillation), with a peak preoperative hsTnT level ≥20 ng/L and the preoperative measurement was the peak measurement or equal to the peak postoperative measurement; a peak postoperative hsTnT level of 20 to <65 ng/L and no ability to access change (ie, only 1 hsTnT measurement), or with missing data on a baseline clinical variable or perioperative outcome included in the multivariable model. The preoperative hsTnT measurements were obtained on the day of surgery before the operation started up to 28 days before surgery (eTable 2 in the Supplement), and postoperative hsTnT measurements during the first 30 days after surgery were assessed in these analyses. All of the perioperative complications and preoperative variables listed in the table were included in the model.

Some elevated postoperative hsTnT measurements were due to nonischemic etiologies; independent adjudicators were relied on to identify such situations. They likely missed some of these, leading to an overestimation of the incidence of MINS. However, given that adjudicators had access to all of the patients' clinical notes and laboratory data, they had the opportunity to identify most nonischemic etiologies. Moreover, the most common nonischemic etiology was chronic hsTnT elevation, and 79.6% of patients with this had a change of at least 5 ng/L. Although adjudicators made their decisions before analyses established that an absolute hsTnT change of at least 5 ng/L was independently associated with a patient's risk of 30-day mortality, the adjudicators' decisions were accepted and these cases were treated as nonischemic hsTnT elevations. This may have led to an underestimation of the incidence of MINS.

Conclusions

Among patients undergoing noncardiac surgery, peak postoperative hsTnT during the first 3 days after surgery was significantly associated with 30-day mortality. Elevated postoperative hsTnT without an ischemic feature was also associated with 30-day mortality.

ARTICLE INFORMATION

Authors/Writing Committee for the VISION Study Investigators: P. J. Devereaux, MD, PhD; Bruce M. Biccard, MBChB, MMedSci, PhD; Alben Sigamani, MD, MSc; Denis Xavier, MD, MSc; Matthew T. V. Chan, MBBS, PhD; Sadeesh K. Srinathan, MD, MSc; Michael Walsh, MD, PhD; Valsa Abraham, MD, DA; Rupert Pearse, MD; C. Y. Wang, MBChB; Daniel I. Sessler, MD; Andrea Kurz, MD; Wojciech Szczeklik, MD, PhD; Otavio Berwanger, MD, PhD; Juan Carlos Villar, MD, PhD; German Malaga, MD, MSc; Amit X. Garg, MD, PhD; Clara K. Chow, MBBS, PhD; Gareth Ackland, PhD, MD; Ameen Patel, MB; Flavia Kessler Borges, MD, PhD; Emilie P. Belley-Cote, MD, MSc; Emmanuelle Duceppe, MD; Jessica Spence, MD; Vikas Tandon, MD; Colin Williams, MbChB; Robert J. Sapsford, MBBS, MD; Carisi A. Polanczyk, MD, ScD; Maria Tiboni, MD; Pablo Alonso-Coello, MD, PhD; Atiya Faruqui, MD; Diane Heels-Ansdell, MSc; Andre Lamy, MD; Richard Whitlock, MD, PhD; Yannick LeManach, MD, PhD; Pavel S. Roshanov, MD, MSc; Michael McGillion, RN, PhD; Peter Kavsak, PhD; Matthew J. McQueen, MBChB, PhD; Lehana Thabane, PhD; Reitze N. Rodseth, MBChB, PhD; Giovanna A. Lurati Buse, MD; Mohit Bhandari, MD, PhD; Ignacia Garutti, MD, PhD; Michael J. Jacka, MD, MSc, MBA; Holger J. Schünemann, MD, PhD; Olga Lucía Cortes, RN, PhD; Pierre Coriat, MD; Nazari Dvirnik, MD; Fernando Botto, MD, MSc; Shirley Pettit, RN; Allan S. Jaffe, MD; Gordon H. Guyatt, MD, MSc.

Affiliations of Authors/Writing Committee for the VISION Study Investigators: McMaster University, Hamilton, Ontario, Canada (Devereaux, Walsh, Patel, Belley-Cote, Duceppe, Spence, Tandon, Tiboni, Heels-Ansdell, Lamy, Whitlock, LeManach, Roshanov, McGillion, Kavsak, McQueen, Thabane, Bhandari, Schünemann, Dvirnik, Pettit, Guyatt); University of Cape Town, Cape Town, South Africa (Biccard); Narayana Hrudayalaya Limited, Bangalore, Karnataka, India (Sigamani); St John's Medical College and Research Institute, Bangalore, India (Xavier, Faruqui); Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (Chan); Winnipeg Health Sciences Centre, University of Manitoba, Winnipeg, Manitoba, Canada (Srinathan); Christian Medical College, Ludhiana, Punjab, India (Abraham); Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, England (Pearse); University of Malaya, Kuala Lumpur, Malaysia (Wang); Cleveland Clinic, Cleveland, Ohio (Sessler, Kurz); Jagiellonian University Medical College, Krakow, Poland (Szczeklik); Research Institute Hcor (Hospital do Coracao), Sao Paulo, Brazil (Berwanger); Universidad Autónoma de Bucaramanga and Fundación Cardioinfantil–Instituto de Cardiología, Bogotá, Colombia (Villar); Universidad Peruana Cayetano Heredia, Lima, Peru (Malaga); Western University, London, Ontario, Canada (Garg); The George Institute for Global Health, Westmead Hospital, University of Sydney, Sydney, Australia (Chow); University College Hospital NHS Trust and William Harvey Research Institute, Queen Mary University of London, London, United Kingdom (Ackland); Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil (Borges); Royal Liverpool and Broadgreen University Hospitals, Liverpool, England (Williams); Leeds Teaching Hospitals NHS Trust, Leeds, England (Sapsford); Federal University of Rio Grande do Sul and Hospital Moinhos de Vento, Porto Alegre, Brazil (Polanczyk); Iberoamerican Cochrane Center (IIB Sant Pau–CIBERESP), Hospital Sant Pau, Barcelona, Spain (Alonso-Coello); University of KwaZulu-Natal, Pietermaritzburg, South Africa (Rodseth); University Hospital Düsseldorf, Düsseldorf, Germany (Buse); Hospital Universitario Gregorio Marañón, Madrid, Spain (Garutti); University of Alberta, Edmonton, Alberta, Canada (Jacka); Fundación Cardioinfantil–Instituto de Cardiología, Bogotá, Colombia (Cortes); Universite Pierre et Marie Curie, Paris, France (Coriat); Hospital Universitario Austral, Pilar, Buenos Aires, Argentina (Botto); Mayo Clinic, Rochester, Minnesota (Jaffe).

Author Contributions: Dr Devereaux and Ms Heels-Ansdell had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.
Study concept and design: Devereaux, Xavier, Chan, Walsh, Abraham, Pearse, Sessler, Szczeklik, Berwanger, Villar, Alonso-Coello, McGillion, Thabane, Rodseth, Jacka, Schünemann, Botto, Guyatt.
Acquisition, analysis, or interpretation of data: Devereaux, Biccard, Sigamani, Xavier, Chan, Srinathan, Walsh, Pearse, Wang, Sessler, Kurz, Szczeklik, Berwanger, Villar, Malaga, Garg, Chow, Ackland, Patel, Kessler Borges, Belley-Cote, Duceppe, Spence, Tandon, Williams, Sapsford, Polanczyk, Tiboni, Alonso-Coello, Faruqui, Heels-Ansdell, Lamy, Whitlock, Le Manach, Roshanov, Kavsak, McQueen, Thabane, Rodseth, Lurati-Buse, Bhandari, Garutti, Schünemann, Cortes, Coriat, Dvirnik, Pettit, Jaffe, Guyatt.
Drafting of the manuscript: Devereaux.
Critical revision of the manuscript for important intellectual content: Devereaux, Biccard, Sigamani, Xavier, Chan, Srinathan, Walsh, Abraham, Pearse, Wang, Sessler, Kurz, Szczeklik, Berwanger, Villar, Malaga, Garg, Chow, Ackland, Patel, Kessler Borges, Belley-Cote, Duceppe, Spence, Tandon, Williams, Sapsford, Polanczyk, Tiboni, Alonso-Coello, Faruqui, Heels-Ansdell, Lamy, Whitlock, Le Manach, Roshanov, McGillion, Kavsak, McQueen, Thabane, Rodseth, Lurati-Buse, Bhandari, Garutti, Jacka, Schünemann, Cortes, Coriat, Dvirnik, Botto, Pettit, Jaffe, Guyatt.
Statistical analysis: Devereaux, Srinathan, Kessler Borges, Belley-Cote, Duceppe, Heels-Ansdell, Le Manach, Thabane, Pettit.
Obtained funding: Devereaux, Biccard, Sigamani, Chan, Srinathan, Walsh, Wang, Szczeklik, Berwanger, Villar, Chow, Ackland, Williams, Alonso-Coello, Whitlock, Cortes.
Administrative, technical, or material support: Devereaux, Biccard, Sigamani, Xavier, Chan, Srinathan, Walsh, Pearse, Wang, Kurz, Villar, Ackland, Patel, Kessler Borges, Belley-Cote, Duceppe, Spence, Tandon, Williams, Sapsford, Tiboni, Whitlock, Roshanov, Kavsak, McQueen, Rodseth, Lurati-Buse, Jacka, Schünemann, Cortes, Pettit, Guyatt.
Study supervision: Devereaux, Biccard, Sigamani, Xavier, Srinathan, Abraham, Sessler, Szczeklik, Malaga, Ackland, Patel, Kessler Borges, Tandon, Williams, Polanczyk, Garutti, Cortes, Botto.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Devereaux reports receipt of grants from Abbott Diagnostics, Boehringer Ingelheim, Covidien, Octapharma, Philips Healthcare, Roche Diagnostics, and Stryker. Dr Xavier reports receipt of grants from Cadila Pharmaceuticals, Boehringer Ingelheim, AstraZeneca India, Sanofi-Aventis, Pfizer, and the National Heart, Lung, and Blood Institute. Dr Pearse reports receipt of grants or personal fees from GlaxoSmithKline, Medtronic, Edwards Lifesciences, and Nestle Health Sciences. Dr Ackland reports receipt of consultancy fees from GlaxoSmithKline. Dr Whitlock reports receipt of personal fees from Boehringer Ingelheim, Daiichi Sankyo, and Armetheon Inc. Dr Kavsak reports receipt of grants and/or personal fees from Abbott Laboratories, Beckman-Coulter, Ortho Clinical Diagnostics, Randox Laboratories, and Siemens Healthcare. Dr Jaffe reports receipt of consulting fees from Beckman-Coulter, Alere, Abbott, Siemens, Roche, ET Healthcare, Outpost Medical, Sphingotec, Singulex, Novartis, and NeurogenomeX. No other disclosures were reported.

VISION Study Investigators: North America: **Canada:** *Hamilton:* Juravinski Hospital and Cancer Centre: Justin DeBeer, MD, Clive Kearon, MD, Richard Mizera, MD, Jehonathan Pinthus, MD, Sebastian Ribas, MD, Tej Sheth, MD, Marko Simunovic, MD, Vikas Tandon, MD, Tomas VanHelder, MD, Mitchell Winemaker, MD, James Paul, MD, Zubin Punthakee, MD, Karen Raymer, MD; Saint Joseph's Healthcare: Anthony Adili, MD, Catherine Clase, MD, Deborah Cook, MD, Mark Crowther, MD, James Douketis, MD, Hugh Fuller, MD, Azim Gangji, MD, Paul Jackson, MD, Wendy Lim, MD, Peter Lovrics, MD, Sergio Mazzadi, MD, William Orovan, MD, Jill Rudkowski, MD, Mark Soth, MD, Maria Tiboni, MD; Hamilton General Hospital: John Eikelboom, MD, Javier Ganame, MD, James Hankinson, MD, Stephen Hill, MD, Sanjit Jolly, MD, Elizabeth Ling, MD, Patrick Magloire, MD, Guillaume Pare, MD, David Szalay, MD, Jacques Tittley, MD, Omid Salehian, MD, Hertzel Gerstein, MD; *Winnipeg:* Health Sciences Centre Winnipeg: Sadeesh K. Srinathan, MD, Clare Ramsey, MD, Philip St John, MD, Laurel Thorlacius, PhD, Faisal S. Siddiqui, MD, Hilary P. Grocott, MD, Andrew McKay, MD, Trevor W. R. Lee, MD, Ryan Amadeo, MD, Duane Funk, MD, Heather McDonald, MD, James Zacharias, MD; *London:* Victoria Hospital: Rey Acedillo, MD, Amit Garg, MD, Ainslie Hildebrand, MD, Ngan Lam, MD, Danielle MacNeil, MD, Marko Mrkobrada, MD, Pavel Roshanov, MD; **United States:** *Cleveland:* Cleveland Clinic: Daniel I Sessler, MD, Andrea Kurz, MD, Emre Gorgun, MD, Amanda Naylor, MD, Matt Hutcherson, MD, Zhuo Sun, MD, Bianka Nguyen, MD, Michael Palma, MD, Avis Cuko, MD, Aram Shahinyan, MD, Vinayak Nadar, MD, Mauricio Perilla, MD, Kamal Maheshwari, MD, Alparslan Turan, MD; Europe: **United Kingdom:** *London:* Barts and the London: Rupert Pearse, MD, Edyta Niebrzegowska, MSc, Andrew Wrag, PhD, Andrew Archbold, MD, Elisa Kam, Kirsty Everingham, PhD, Phoebe Bodger, BSc, Thais Creary, BSc, Ben Bloom, MBChB, Alice Carter, MBChB, Tom E. F. Abbott, BMBCh, Nirav Shah, MBChB, Katarzyna Mrozek, MBBS, Amy Richardson, BSc, Alex Fowler, MBBS, Zakaria Rob, BSc; University College Hospital: Gareth Ackland, MD, Robert Stephens, FRCA, Anna Reyes, BSc, Laura Gallego Paredes, BSc, Pervez Sultan, FRCA,

David Cain, FRCA, John Whittle, FRCA, Ana Gutierrez del Arroyo, FRCA, Shamir Karmali, FRCA; *Liverpool:* Royal Liverpool University Hospital: C. Williams, MD, A. Rushton, MD, I. Welters, MD, M. Leuwer, MD, Jane Parker, RGN; *Leeds:* Leeds Teaching Hospitals: Robert J. Sapsford, MD, Julian Barth, MBBS, Julian Scott, MBBS, Alistair Hall, MBBS, Simon Howell, MBBS, Michaela Lobley, RGN, Janet Woods, RGN, Susannah Howard, RGN, Joanne Fletcher, RGN, Nikki Dewhirst, RGN. **Poland:** *Krakow*: Jagiellonian University Medical College: Wojciech Szczeklik, MD, Jacek Gorka, MD, Karolina Gorka, MD, Bogusz Kaczmarek, MD, Kamil Polok, MD, Jolanta Gasior, MD, Anna Włudarczyk, MD, Magdalena Duchińska, MD, Jakub Fronczek, MD, Aleksandra Wojnarska, MD, Mateusz Kozka, MD, Andrzej Halek, MD; **France:** *Paris*: Pitie-Salpetriere Hospital: Pierre Coriat, MD, Denis Monneret, PharmD, Marie-Hélène Fléron, MD, Jean Pierre Goarin, MD, Cristina Ibanez Esteve, MD, Catherine Royer, MD, Georges Daas, MD; Asia: **India:** *Ludhiana*: Christian Medical College: Valsa Abraham, MD, Preetha George; *Bangalore:* St John's Medical College Hospital: Denis Xavier, MD, Alben Sigamani, MD, Atiya Faruqui, MD, Radhika Dhanpal, MD, Smitha Almeida, MD, Joseph Cherian, MS, Sultana Furruqh, MD; **Malaysia:** *Kuala Lumpur*: University Malaya Medical Centre: C. Y. Wang, MBChB, G. S. Y. Ong, MBBS, M. Mansor, MBBS, Alvin S. B. Tan, MBBS, I. I. Shariffuddin, MBChB, N. H. M. Hashim, MBBS, A. Wahab Undok, MBBS, H. Y. Lai, MBBS, W. A. W. Ahmad, MBBS, P. S. Loh, MBBS, C. Y. Chong, BSc, A. H. A. Razack, MBBS; **China**: *Hong Kong SAR:* Chinese University of Hong Kong: Matthew T. V. Chan, MBBS, PhD, Gordon Y. S. Choi, MBBS, Lydia C. W. Lit, PhD, Tony Gin, MD, Alex Wan, MBBS, Linda Lai, MBChB, MSc, Polly Chan, MBChB; South America: **Peru:** *Lima*: Hospital Nacional Cayetano Heredia: German Malaga, MD, Vanessa Valderrama-Victoria, MD, Javier D. Loza-Herrera, MD, Maria De Los Angeles Lazo, MD, Aida Rotta-Rotta, MD; **Brazil:** *São Paulo*: Hospital do Coracao: Otavio Berwanger, MD, Erica Suzumura, PT, Eliana Santucci, PT, Katia Leite, MSc, Jose Amalth do Espirirto Santo, MD, Cesar A. P. Jardim, MD, Alexandre Biasi Cavalcanti, MD, Helio Penna Guimaraes, PhD; *Porto Alegre:* Hospital de Clinicas de Porto Alegre: Carisi A. Polanczyk, MD, Mariana V. Furtado, MD; **Colombia:** *Bogota:* Foundation CardioInfanil: Olga Lucía Cortés, PhD, Félix R. Montes, MD, Paula A. Alvarado, RN; *Bucamaranga:* Hospital Universitario de Santander: Juan Carlos Villar, MD, Skarlett Vásquez, RN, MSc; Africa: **South Africa:** *Durban:* Inkosi Albert Luthuli Hospital: Bruce Biccard, PhD, Hussein Cassimjee, MBChB, Dean Gopalan, MBChB, Theroshnie Kisten, MBChB, Aine Mugabi, MBChB, Prebashini Naidoo, MBBCh, Rubeshan Naidoo, Reitze Rodseth, PhD, David Skinner, MBChB, Alex Torborg, MBChB; **Australia:** *Sydney*: Westmead Hospital: Clara K. Chow, MBBS, Graham S. Hillis, MBBS, Richard Halliwell, MBBS, Stephen Li, MBBS, Vincent W. Lee, PhD, John Mooney, MBBS. Study coordination: This study was coordinated by the Clinical Advances Through Research and Information Translation (CLARITY) project office in the Department of Clinical Epidemiology and Biostatistics at McMaster University and the Population Health Research Institute at Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada.

Funding/Support: Roche Diagnostics provided the troponin T assays as well as financial support for the VISION Study. Funding for this study came from more than 60 grants for VISION and its substudies. Canada: Canadian Institutes of Health Research (7 grants); Heart and Stroke Foundation of Ontario (2 grants); Academic Health Science Centres Alternative Funding Plan Innovation Fund Ontario; Population Health Research Institute; CLARITY Research Group; McMaster University Department of Surgery Surgical Associates; Hamilton Health Science New Investigator Fund; Hamilton Health Sciences; Ontario Ministry of Resource and Innovation; Stryker Canada; McMaster University, Department of Anesthesiology (2 grants); St Joseph's Healthcare, Department of Medicine (2 grants); Father Sean O'Sullivan Research Centre (2 grants); McMaster University Department of Medicine (2 grants); Roche Diagnostics Global Office (5 grants); Hamilton Health Sciences Summer Studentships (6 grants); McMaster University Department of Clinical Epidemiology and Biostatistics; McMaster University, Division of Cardiology; Canadian Network and Centre for Trials Internationally; Winnipeg Health Sciences Foundation; University of Manitoba Department of Surgery (2 grants); Diagnostic Services of Manitoba Research; Manitoba Medical Services Foundation; Manitoba Health Research Council; University of Manitoba Faculty of Dentistry Operational Fund; University of Manitoba Department of Anesthesia; University Medical Group, Department of Surgery, University of Manitoba, Start-up Fund. Australia: National Health and Medical Research Council Program. Brazil: Projeto Hospitais de Excelência a Serviço do SUS (PROADI-SUS) grant from the Brazilian Ministry of Health in partnership with Hcor (Cardiac Hospital Sao Paulo-SP); National Council for Scientific and Technological Development (CNPq) grant from the Brazilian Ministry of Science and Technology. China: Public Policy Research Fund (grant CUHK-4002-PPR-3), Research Grant Council, Hong Kong SAR; General Research Fund (grant 461412), Research Grant Council, Hong Kong SAR; Australian and New Zealand College of Anaesthetists (grant 13/008). Colombia: School of Nursing, Universidad Industrial de Santander; Grupo de Cardiología Preventiva, Universidad Autónoma de Bucaramanga; Fundación Cardioinfantil–Instituto de Cardiología; Alianza Diagnóstica SA. France: Université Pierre et Marie Curie, Département d'anesthésie Réanimation, Pitié-Salpêtrière, Assistance Publique–Hôpitaux de Paris. India: St John's Medical College and Research Institute; Division of Clinical Research and Training. Malaysia: University of Malaya (grant RG302-14AFR); University of Malaya, Penyelidikan Jangka Pendek. Poland: Polish Ministry of Science and Higher Education (grant NN402083939). South Africa: University of KwaZulu-Natal. Spain: Instituto de Salud Carlos III; Fundació La Marató de TV3. United States: American Heart Association; Covidien. United Kingdom: National Institute for Health Research.

Role of the Funder/Sponsor: The VISION Study funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation or approval of the manuscript; or decision to submit the manuscript for publication.

REFERENCES

1. Smilowitz NR, Gupta N, Ramakrishna H, Guo Y, Berger JS, Bangalore S. Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. *JAMA Cardiol*. 2017;2(2):181-187.

2. Devereaux PJ, Chan MT, Alonso-Coello P, et al; Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study Investigators. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA*. 2012;307(21):2295-2304.

3. Botto F, Alonso-Coello P, Chan MT, et al; Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Writing Group. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology*. 2014;120(3):564-578.

4. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem*. 2010;56(2):254-261.

5. Thygesen K, Alpert JS, Jaffe AS, et al; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Circulation*. 2012;126(16):2020-2035.

6. Mazumdar M, Smith A, Bacik J. Methods for categorizing a prognostic variable in a multivariable setting. *Stat Med*. 2003;22(4):559-571.

7. Hougaard P. *Shared Frailty Models: Analysis of Multivariate Survival Data: Statistics for Biology and Health*. New York, NY: Springer; 2000:215-262.

8. Nagele P, Brown F, Gage BF, et al. High-sensitivity cardiac troponin T in prediction and diagnosis of myocardial infarction and long-term mortality after noncardiac surgery. *Am Heart J*. 2013;166(2):325-332.

9. Gillmann HJ, Meinders A, Grohennig A, et al. Perioperative levels and changes of high-sensitivity troponin T are associated with cardiovascular events in vascular surgery patients. *Crit Care Med*. 2014;42(6):1498-1506.

10. van Waes JA, Nathoe HM, de Graaff JC, et al; Cardiac Health After Surgery Investigators. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation*. 2013;127(23):2264-2271.

11. Foucrier A, Rodseth R, Aissaoui M, et al. The long-term impact of early cardiovascular therapy intensification for postoperative troponin elevation after major vascular surgery. *Anesth Analg*. 2014;119(5):1053-1063.

12. Devereaux PJ, Xavier D, Pogue J, et al; Perioperative Ischemic Evaluation Investigators. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med*. 2011;154(8):523-528.