Association Between Postoperative Troponin Levels and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery

The Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators

WORLDWIDE, MORE THAN 200 MILLION ADULTS HAVE MAJOR NONCARDIAC SURGERY ANNUALLY.1-3 Despite benefits associated with surgery, major perioperative complications, including death, occur.3 More than 1 million adults worldwide will die within 30 days of noncardiac surgery each year.1,2

Perioperative risk estimation identifies patients who require more intensive monitoring and management in the postoperative period. Current perioperative risk prediction models for 30-day mortality have limitations.4,5 Some clinicians advocate monitoring troponin measurements after vascular surgery,6 and inconclusive evidence suggests that troponin measurements after abdominal aortic surgery may enhance prediction of short-term mortality.7 Little is known about optimal troponin threshold(s) for predicting mortality after noncardiac surgery.

A large international study called the VISION Study (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation; clinicaltrials.gov identifier, NCT00512109) is evaluating major complications after noncardiac surgery. Participating patients have troponin T (TnT) levels measured after noncardiac surgery. We assessed the relationship between the peak fourth-generation TnT measurement after noncardiac surgery and 30-day mortality.

Context Of the 200 million adults worldwide who undergo noncardiac surgery each year, more than 1 million will die within 30 days.

Objective To determine the relationship between the peak fourth-generation troponin T (TnT) measurement in the first 3 days after noncardiac surgery and 30-day mortality.

Design, Setting, and Participants A prospective, international cohort study that enrolled patients from August 6, 2007, to January 11, 2011. Eligible patients were aged 45 years and older and required at least an overnight hospital admission after having noncardiac surgery.

Main Outcome Measures Patients' TnT levels were measured 6 to 12 hours after surgery and on days 1, 2, and 3 after surgery. We undertook Cox regression analysis in which the dependent variable was mortality until 30 days after surgery, and the independent variables included 24 preoperative variables. We repeated this analysis, adding the peak TnT measurement during the first 3 postoperative days as an independent variable and used a minimum P value approach to determine if there were TnT thresholds that independently altered patients' risk of death.

Results A total of 15,133 patients were included in this study. The 30-day mortality rate was 1.9% (95% CI, 1.7%-2.1%). Multivariable analysis demonstrated that peak TnT values of at least 0.02 ng/mL, occurring in 11.6% of patients, were associated with higher 30-day mortality compared with the reference group (peak TnT ≤ 0.01 ng/mL): peak TnT of 0.02 ng/mL (adjusted hazard ratio [aHR], 2.41; 95% CI, 1.33-3.77); 0.03 to 0.29 ng/mL (aHR, 5.00; 95% CI, 3.72-6.76); and 0.30 ng/mL or greater (aHR, 10.48; 95% CI, 6.25-16.62). Patients with a peak TnT value of 0.01 ng/mL or less, 0.02-0.29, and 0.30 or greater had 30-day mortality rates of 1.0%, 4.0%, 9.3%, and 16.9%, respectively. Peak TnT measurement added incremental prognostic value to discriminate those likely to die within 30 days for the model with peak TnT measurement vs without (C index=0.85 vs 0.81; difference, 0.4; 95% CI, 0.2-0.5; P<.001 for difference between C index values). The net reclassification improvement with TnT was 25.0% (P<.001).

Conclusion Among patients undergoing noncardiac surgery, the peak postoperative TnT measurement during the first 3 days after surgery was significantly associated with 30-day mortality.

METHODS

Study Design and Eligibility Criteria

The VISION Study is a prospective cohort study of a representative sample of patients undergoing noncardiac surgery. VISION was designed to recruit 40,000 patients in North and South America, Africa, Asia, Australia, and Europe to evaluate major complications after noncardiac surgery. At the beginning of this study, patients had fourth-generation TnT measurements after noncardiac surgery. The first 15,000 pa...
patients experienced event rates at approximately 3 times what was ex-
pected. Recognizing that we had sufficient events to address our objec-
tives related to the fourth-generation TnT measurements, the operations
committee decided to henceforth monitor the fifth-generation high-
sensitivity TnT assay. This publication is restricted to patients during
the period of fourth-generation TnT use.

Eligible patients for the VISION Study had noncardiac surgery, were at
least 45 years of age, received a gen-
eral or regional anesthetic, and under-
went elective, urgent, or emergency sur-
urgery during the day or at night on a
weekday or weekend. Additional eligi-
bility criteria restricting patients to
those with data allowing prognostic
evaluation of fourth-generation TnT
included patients who had a fourth-
generation TnT assay measurement and
deploy data for the 24 potential pre-
operative predictors of 30-day morta-
ality that we evaluated. Patients were ex-
cluded if they did not require an
overnight hospital admission after sur-
ery, were previously enrolled in the
VISION Study, or declined consent.
The research ethics board at each site
approved the protocol prior to patient
recruitment.

Patient Recruitment
Patients gave consent prior to surgery or, for those from whom we could not
obtain consent prooperatively (eg,
emergency night surgical case), re-
search personnel obtained consent
within the first 24 hours after surgery.
Eight centers used a deferred consent
process for patients unable to provide consent (eg, patients sedated and me-
chanically ventilated) and for whom no
next of kin was available. This al-
lowed collection of TnT measure-
ments while awaiting patient or next-
of-kin consent.

Patients were identified by screen-
ing daily patient lists in preoperative as-
essment clinics, on surgical wards, and
in intensive care units; daily and pre-
vieous-day surgical lists; and patients in
the preoperative holding area. In some
centers, surgical volume exceeded the
capacity of research staff to enroll all
eligible patients on consecutive weeks.
In these centers, the project office either
created a recruitment schedule consist-
ing of random weeks of nonrecruit-
ment or randomly selected surgical ser-
dices. At the end of each week, research
personnel reviewed the surgical log-
book and reported the number of pa-
tients eligible but not enrolled.

Procedures
Research personnel interviewed and ex-
amined patients and reviewed medi-
cal records to obtain information on po-
tential predictors of major perioperative
complications. At each site, an inves-
tigator reviewed and approved all data.
Patients had blood collected to mea-
sure a Roche 4th-generation Elecsys
TnT assay 6 to 12 hours postopera-
tively and on the first, second, and third
days after surgery. Patients enrolled be-
 tween 12 and 24 hours after surgery had
a TnT drawn immediately, and testing
continued as previously reported. All
TnT measurements were analyzed at the
participating hospitals. TnT results were
reported to the attending physicians.

Throughout each patient’s hospital
stay, research personnel performed
clinical evaluations, reviewed medical
records, ensured patients had TnT mea-
surements drawn, and noted outcome
events. The primary outcome was mor-
tality at 30 days after surgery. Centers
also reported the cause of death (vas-
cular or nonvascular, definitions in eAp-
pendix 2 available at http://www.jama.
com). Patients were phoned at 30 days
after surgery. If patients (or next of kin)
indicated the occurrence of an out-
come, their physicians were contacted
to obtain documentation. Research per-
sonnel at participating centers submit-
ted the case report forms and support-
ing documentation directly to the data
management system (iDataFax, coor-
dinating center, McMaster University,
Hamilton, Ontario, Canada).

Data monitoring in VISION con-
sisted of central data consistency
checks, statistical monitoring, and on-
site monitoring for all centers. For the
on-site monitoring, the central coordi-
nator randomly selected participants
with and without a perioperative com-
pliation, and independent monitors
audited their medical records and all
other supporting documents. No cen-
ter stood out regarding results from cen-
tral data consistency checks or statis-
tical monitoring. On-site monitoring
demonstrated no major discrepancies
between the submitted data and the
monitoring findings, except for a sys-
tematic error in recording the dura-
tion of perioperative hemodynamic
compromise at 2 centers. This was cor-
corrected and subsequent on-site moni-
toring at these 2 centers demonstrated
no substantial errors.

Statistical Analyses
The analyses related to the association
between TnT and 30-day mortality were
planned prior to evaluating any of the
data. Patients who did not com-
plete the 30-day follow-up were cens-
sored on the last day their vital status
was known. We determined the per-
centage of patients who died within
30 days after surgery and the associ-
ated 95% CI. We undertook a Cox
proportional hazards model in which
the dependent variable was mortality
until 30 days after surgery, and the
independent variables included 24
preoperative variables (eAppendix 3).
The model was repeated adding the peak
fourth-generation TnT measurement
during the first 3 days after surgery as
an independent variable and a mini-
mum P value approach was used to de-
termine if there were TnT threshold val-
ues that independently altered the
patients’ risk of mortality.5 This ap-
proach evaluated every possible thresh-
hold of TnT (eg, ≤0.01 vs >0.01; ≤0.02
vs >0.02) in the multivariable model
with the 24 preoperative variables.
This analysis showed the TnT value that
demonstrated the smallest statistically
significant P value was a TnT threshold that
independently predicted 30-day mor-
tality. Subsequently, this threshold was
fixed and the multivariable analysis was
repeated to determine if there was an-
other statistically significant threshold

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in addition to the first threshold. The multivariable analysis was repeated until we were no longer able to identify another statistically significant TnT threshold. The Kruskal-Wallis test was used to identify any statistically significant differences in the median time from the peak TnT value to death across the TnT thresholds that independently predicted mortality.

For all independent predictors of 30-day mortality, we report the adjusted hazard ratio (aHR), 95% CI, and associated P value (a priori 2-sided α = 0.05 was designated as statistically significant). For the TnT thresholds that independently predicted 30-day mortality, we determined the aHRs and their 95% CIs through bootstrapping 1000 samples. We undertook a random-effects (frailty) Cox model to adjust for any potential site-clustering effect.9 We calculated the population attributable risk for the independent predictors of 30-day mortality.10 11 The population attributable risk represents the proportion of all deaths potentially attributable to the relevant risk factor (eg, an elevated TnT measurement) if causality were proven. For the TnT thresholds that independently predicted 30-day mortality, we determined the likelihood ratios. For the model that included the peak TnT measurement, discrimination was assessed through evaluation of the C index and calibration with a goodness-of-fit test.12 14 The difference in the C index between the model that included the peak TnT measurement and the model that only included preoperative variables was examined using 1000 bootstrap samples. Assessment of improved risk classification, as demonstrated in the model that included the peak TnT measurement vs the model that only included preoperative variables, was made by calculating the net reclassification improvement.13 For this analysis we classified 30-day mortality as low risk (<1%), intermediate risk (1%-5%), high risk (>5%-10%), and very high risk (>10%).

In patients for whom preoperative creatinine was measured, we analyzed whether there was an interaction between patients’ preoperative estimated glomerular filtration rate (eGFR) (<30 mL/min per 1.73 m² or receiving dialysis), 30 to 44 mL/min per 1.73 m², 45 to 59 mL/min per 1.73 m², and ≥60 mL/min per 1.73 m²)15 16 and the TnT thresholds that independently predicted 30-day mortality. For these analyses, we used a Cox proportional hazard model that incorporated a test for interaction and a priori α = 0.01 was designated as statistically significant.

We undertook sensitivity analyses that excluded patients with a preoperative history of coronary artery disease, recent high-risk coronary artery disease, or congestive heart failure and a separate analysis excluding patients who died within 36 hours after surgery. In the sensitivity analyses that included the other preoperative variables, we determined if the TnT thresholds established in our model that included the peak TnT measurement continued to predict 30-day mortality. Additional sensitivity analyses were used to determine if the TnT thresholds that independently predict overall 30-day mortality predicted both vascular mortality and nonvascular mortality, based on the center’s determination of the cause of death.

For all models, forced simultaneous entry (all candidate variables remained in the models) was used rather than automated stepwise selection because simulations demonstrate a higher risk of overfitting with the latter approach.18 19 We assessed collinearity using the variance inflation factor that measures the extent to which the variance of the model coefficients are inflated (because of the correlation of a variable with other predictor variables) if that variable is included in the model. We considered variables with a variance inflation factor of greater than 10 to be colinear.20 All analyses were performed using SAS version 9.2, except for the random-effect (frailty) Cox model that was performed using R, version 2.14.1.

RESULTS

Figure 1 reports the patient flow. Of the 15 133 patients included in the VISION fourth-generation TnT prognostic study, 99.7% of the patients completed the 30-day follow-up. Centers that recruited patients from August 6, 2007 to January 11, 2011, are listed by location and number of patients in eTable 1.

eTable 2 reports the preoperative patient characteristics and the type of surgery. Approximately 1 in 4 patients (24.2%) were at least 75 years of age and 51.5% were women. The most common vascular risk factors were hypertension (50.9%) and diabetes (19.5%), and 26.5% of the patients had active cancer. The most common surgeries were major orthopedic surgery (20.4%), major general surgery (20.3%), and low-risk surgeries (39.4%). The median number of fourth-generation TnT measurements in the first 3 days after surgery was 3 (interquartile range [IQR] 2-4).

The 30-day mortality rate was 1.9% (282 deaths; 95% CI, 1.7%-2.1%), with 26.6% dying after hospital discharge (median time from discharge to death was 11.0 days; IQR, 4.0-15.0 days). Table 1 presents the results of the preoperative Cox proportional hazards model. Eleven of the 24 variables assessed were independent predictors of 30-day mortality. Urgent/emergency surgery was the strongest preoperative predictor of 30-day mortality (aHR, 4.62; 95% CI, 3.57-5.98).

Using a minimum P value approach, multivariable analysis demonstrated that peak TnT threshold values of 0.02 ng/mL, 0.03 ng/mL, and 0.30 ng/mL were independently associated with 30-day mortality (Table 1). The random-effects (frailty) Cox model that adjusted for any potential site clustering effect produced similar results. A history of congestive heart failure and major vascular surgery independently predicted mortality in the preoperative model, but not in the model in-
The strongest independent predictors of 30-day mortality were a peak TnT value of 0.03 to 0.29 ng/mL (aHR, 5.00; 95% CI, 3.72-6.76) and 0.30 ng/mL or greater (aHR, 10.48; 95% CI, 6.25-16.62). The independent prognostic factors identified in this model potentially explain the majority of the deaths that occurred (ie, the total population attributable risk was 89.0%; 95% CI, 85.3-92.4); the prognostically relevant peak TnT values had the largest population attributable risk (41.8%).

Peak TnT values of 0.01 ng/mL or less, 0.02 to 0.29 ng/mL, and 0.30 ng/mL or greater occurred in 9.4%, 3.3%, 7.4%, and 0.9% of the patients, respectively. The incidence of 30-day mortality was 1.0%, 4.0%, 9.3%, and 16.9% in patients with a peak TnT value of 0.01 or less, 0.02 to 0.29, and 0.30 ng/mL or greater, respectively. eTable 3 reports the likelihood ratios for these TnT thresholds. Patients with TnT values that were independently associated with mortality demonstrated the following median times from the peak TnT measurement to death: 0.02 ng/mL (13.5 days; IQR, 8.5-20 days); 0.03 to 0.29 ng/mL (9.0 days; IQR, 3.5-16 days); and 0.30 ng/mL or greater (6.5 days; IQR, 1.5-15 days), P = .01 for differences among time to death. Figure 2 reports Kaplan-Meier estimates for death based on the peak TnT values. eTable 4 reports the results of our sensitivity analysis that excluded patients who had a preoperative history of coronary artery disease, recent high-risk coronary artery disease, or congestive heart failure, and eTable 5 reports the results of our sensitivity analysis that excluded patients who had a preoperative creatinine level of less than 10, suggesting no colinearity.

Each variable included in the models demonstrated a variance inflation factor of less than 10, suggesting no colinearity. The model that included the peak TnT measurement demonstrated good calibration (goodness-of-fit test P = .43). The model that included the peak TnT measurement demonstrated good discrimination, as did the preoperative model without TnT measurement (C index=0.85 vs 0.81; [difference, 0.4; 95% CI, 0.2-0.5] P < .001 for difference between C index values). Among the patients who died, the percentage correctly reclassified to a higher risk category with the model that included the peak TnT measurement compared with the model that only included preoperative risk factors was 18.8% (Table 2). Among the patients who survived, the percentage correctly reclassified to a lower risk category with the model that included the peak TnT measurement compared with the model that only included preoperative risk factors was 6.2%. The net reclassification improvement associated with TnT measurement was 25.0% (95% CI, 17.2%-32.8%; P < .001).

Of the 14 008 (92.6%) patients in whom preoperative creatinine levels were measured, 520 patients (3.7%) had an eGFR of less than 30 mL/min per 1.73 m² or were receiving dialysis; 760 patients (5.4%) had an eGFR of 30 to 44 mL/min per 1.73 m²; 1496 patients (10.7%) had an eGFR of 45 to 59 mL/min per 1.73 m²; and 11 232 patients (80.2%) had an eGFR of at least 60 mL/min per 1.73 m². There was no interaction between preoperative eGFR and the TnT thresholds (P = .5).

Among the 282 patients who died within 30 days of surgery, centers reported a vascular cause of death in 127 patients (45.0%) and a nonvascular cause in 155 patients (55.0%). Table 3 reports the independent predictors of 30-day vascular mortality and nonvascular mortality separately. The results for the TnT thresholds that independently predicted 30-day mortality were not appreciably different for vascular and nonvascular mortality. Among patients who experienced a TnT elevation 0.02 ng/mL or greater, this occurred at 6 to 12 hours after surgery, post-

**Figure 1. Patient Flow Chart**

- 23680 Patients fulfilled VISION eligibility criteria
- 1084 Not identified in time to enroll
- 22609 Screened in time
- 6522 Excluded
  - 5262 Did not consent
  - 251 Cognitive impairment (unable to provide consent)
  - 875 Other reasons
- 16087 Enrolled in VISION
- 954 Excluded from the fourth-generation Troponin T Prognostic Study
  - 779 No troponin assay measured after surgery
  - 29 Died before a troponin assay was measured
  - 750 No troponin assay measured before discharge
  - 146 Had peak troponin measurement reported as <0.04, <0.03, or <0.02 instead of the absolute value
  - 29 Missing data on ≥1 of 24 clinical variables assessed in model
- 15133 Included in the VISION fourth-generation Troponin T Prognostic Study
- 15093 Completed the 30-day follow-up
  - 40 Did not complete the 30-day follow-up and were censored at the time of last contact
- 15133 Patients included in the final analyses

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operative day 1, postoperative day 2, and postoperative day 3 in 45.9%, 28.3%, 17.7%, and 8.2% of these patients, respect-
ively. Considering the most serious non-
vascular complications, the median time to a diagnosis of pneumonia was 6 days
(IQR, 3.0-12.0 days), and the median time to a diagnosis of sepsis was 7.0 days (IQR,
4.0-12.0 days).

Table 1. Models to Predict 30-Day Mortality

<table>
<thead>
<tr>
<th>Potential Risk Factor</th>
<th>Death Within 30 Days Postsurgery</th>
<th>Preoperative Variables Only</th>
<th>Preoperative Variables and Peak TnT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Died/Total No.</td>
<td>% (95% CI)</td>
<td>aHR (95% CI)</td>
</tr>
<tr>
<td>Age, y</td>
<td>45-64</td>
<td>68/7697</td>
<td>0.9 (0.7-1.1)</td>
</tr>
<tr>
<td>65-74</td>
<td>68/7379</td>
<td>1.8 (1.4-2.3)</td>
<td>1.67 (1.18-2.36)</td>
</tr>
<tr>
<td>≥75</td>
<td>146/3657</td>
<td>4.0 (3.4-4.7)</td>
<td>3.03 (2.20-4.18)</td>
</tr>
<tr>
<td>Recent high-risk CAD</td>
<td>No recent high-risk CAD</td>
<td>15/173</td>
<td>8.7 (5.3-13.8)</td>
</tr>
<tr>
<td>No PVD history</td>
<td>No PVD history</td>
<td>45/809</td>
<td>5.6 (4.2-7.4)</td>
</tr>
<tr>
<td>Current history No stroke history</td>
<td>No stroke history</td>
<td>43/896</td>
<td>6.0 (5.8-6.1)</td>
</tr>
<tr>
<td>COPD</td>
<td>No COPD</td>
<td>65/1282</td>
<td>5.1 (4.0-6.4)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>No active cancer</td>
<td>106/4015</td>
<td>2.6 (2.2-3.2)</td>
</tr>
<tr>
<td>Urgent/emergency surgery*</td>
<td>No urgent/emergency surgery*</td>
<td>123/2142</td>
<td>5.7 (4.8-6.8)</td>
</tr>
<tr>
<td>Major general surgery</td>
<td>No major general surgery</td>
<td>113/2076</td>
<td>3.7 (3.1-4.4)</td>
</tr>
<tr>
<td>Major neurosurgery</td>
<td>No major neurosurgery</td>
<td>25/888</td>
<td>2.8 (1.9-4.1)</td>
</tr>
<tr>
<td>Peak TnT measurement</td>
<td>No major neurosurgery</td>
<td>25/888</td>
<td>2.8 (1.9-4.1)</td>
</tr>
<tr>
<td>0.02 ng/mL</td>
<td>0.03-0.29 ng/mL</td>
<td>104/1121</td>
<td>9.3 (7.7-11.1)</td>
</tr>
<tr>
<td>0.03-0.29 ng/mL</td>
<td>0.03-0.29 ng/mL</td>
<td>104/1121</td>
<td>9.3 (7.7-11.1)</td>
</tr>
<tr>
<td>≥0.30 ng/mL</td>
<td>≥0.30 ng/mL</td>
<td>24/142</td>
<td>16.9 (11.6-23.9)</td>
</tr>
</tbody>
</table>

Predictive in the Preoperative Model but Not Predictive in the Model That Included TnT Measurements

| CHF history | No CHF history | 37/703 | 5.3 (3.8-7.2) | 1.60 (1.09-2.36) | .02 | 1.20 (0.82-1.77) | .35 |
| No major vascular surgery | No major vascular surgery | 19/504 | 3.8 (2.4-5.8) | 2.38 (1.04-5.47) | .04 | 2.10 (0.92-4.72) | .08 |

Not Predictive in the Preoperative Model or the Model That Included TnT Measurements

| Men | Women | 151/7339 | 2.1 (1.8-2.4) | 1.01 (0.79-1.29) | .96 | NA |
| 131/7794 | 1.7 (1.5-2.0) | 0.93 (0.72-1.21) | .37 | 0.73 (0.51-1.05) | .09 | NA |
| No CAD History | No CAD History | 56/1832 | 3.1 (2.4-3.9) | 0.85 (0.60-1.21) | 1 [Reference] | .37 | 0.73 (0.51-1.05) | .09 |
| No cardiac arrest history | No cardiac arrest history | 1/88 | 1.5 (0.3-7.9) | 0.63 (0.09-6.42) | 1 [Reference] | .65 | 0.70 (0.50-1.05) | .05 |
| No TIA history | No TIA history | 217/4757 | 1.9 (1.7-2.1) | 0.54 (0.25-1.15) | 1 [Reference] | .11 | 0.48 (0.22-1.04) | .06 |
| No DVT or PE history | No DVT or PE history | 114/875 | 2.3 (1.3-4.1) | 1.08 (0.59-2.01) | 1 [Reference] | .78 | 1.03 (0.56-1.93) | .92 |
| No diabetes | No diabetes | 74/2952 | 2.5 (2.0-3.1) | 1.16 (0.88-1.54) | 1 [Reference] | .29 | 1.08 (0.81-1.43) | .60 |
| Hypertension | No hypertension | 180/7079 | 2.3 (2.0-2.7) | 1.05 (0.80-1.38) | 1 [Reference] | .71 | 0.93 (0.71-1.22) | .61 |
| Current atrial fibrillation | No current atrial fibrillation | 102/7424 | 1.4 (1.1-1.7) | 0.98 (0.60-1.68) | 1 [Reference] | .92 | 1.02 (0.63-1.68) | .91 |
| Obstructive sleep apnea | No obstructive sleep apnea | 11/773 | 1.4 (0.8-2.5) | 0.90 (0.49-1.65) | 1 [Reference] | .73 | 0.94 (0.51-1.72) | .83 |
| Major orthopedic surgery | No major orthopedic surgery | 63/3094 | 2.0 (1.6-2.6) | 1.74 (0.84-3.63) | 1 [Reference] | .12 | 1.64 (0.79-3.41) | .18 |
| Major URO/GYN surgery | No URO/GYN surgery | 10/1888 | 0.5 (0.3-1.0) | 0.99 (0.27-3.17) | 1 [Reference] | .18 | 0.56 (0.26-1.16) | .12 |
| Major thoracic surgery | No major thoracic surgery | 7/376 | 1.9 (0.9-3.8) | 1.70 (0.64-4.49) | 1 [Reference] | .28 | 1.61 (0.60-4.33) | .34 |

Abbreviations: aHR, adjusted hazard ratio; AR, attributable risk; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; GYN, gynecological; NA, not applicable; PE, pulmonary embolus; PVD, peripheral vascular disease; TnT, troponin T; URO, urological.

* First, urgent and emergency surgery variables were evaluated separately, giving very similar hazard ratios. Next, these 2 surgical categories were combined.

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COMMENT
In this international prospective cohort study of 15,133 patients who were at least 45 years of age and underwent noncardiac surgery that required hospital admission, multivariable analysis demonstrated that fourth-generation peak TnT thresholds of 0.02 ng/mL, 0.03 ng/mL, and 0.30 ng/mL independently predicted 30-day mortality. Peak TnT values after noncardiac surgery proved the strongest predictors of 30-day mortality, and the population attributable risk analysis suggested elevated TnT measurements after surgery may explain 41.8% of the deaths. Based on the identified peak TnT values, there were marked increases in the absolute risk of 30-day mortality (ie, 1.0% for a TnT value ≤0.01 ng/mL; 4.0% for a value of 0.02 ng/mL; 9.3% for a value of 0.03-0.29 ng/mL; and 16.9% for a value ≥0.30 ng/mL). 11.6% of patients had a prognostically relevant peak TnT value of at least 0.02 ng/mL. The higher the peak TnT value, the shorter the median time to death. Our net reclassification improvement analysis demonstrated that monitoring TnT values for the first 3 days after surgery substantially improved 30-day mortality risk stratification compared with assessment limited to preoperative risk factors.

Strengths and Limitations
Strengths of this study include the large sample of patients undergoing noncardiac surgery from 8 countries in 5 continents. Our results were consistent across sites for the TnT thresholds, suggesting they are relevant to contemporary surgery worldwide. All patients had the same fourth-generation TnT assay measured after surgery. A total of 99.7% of the patients completed the 30-day follow-up. We had complete data on the 24 preoperative variables that we evaluated. The model that included the peak TnT measurement demonstrated good discrimination and calibration.

Rather than evaluating predetermined values, we statistically identified prognostically relevant TnT thresholds. Thresholds based on 99th percentiles or coefficients of variation of less than 10%, although commonly used, are arbitrary. Studies that demonstrate worse prognosis above these thresholds do not confirm these thresholds are where risk is actually changing. Such results may be driven by the poor outcomes of patients with TnT measurements substantially above these thresholds. Further, some patients with troponin values immediately below these thresholds may have poor outcomes, but their signal may get washed out by the larger patient population with even lower troponin values who have few or no events. It is for this reason that we believe statistically
identifying prognostically relevant TnT thresholds based on the actual data are a more appropriate method.

This study also has limitations. We did not measure a TnT value prior to surgery and cannot comment on how a preoperative value would impact risk prediction. We only measured the fourth-generation TnT assay, and therefore cannot comment on the prognostic relevance of other troponin assays. Despite our large sample size, only 1263 patients had a peak troponin threshold of 0.03 ng/mL or greater. Therefore, it is possible with an even larger cohort that we may have identified another statistically significant and prognostically relevant TnT threshold between 0.03-0.29 ng/mL and at greater than 0.30 ng/mL. Although we did not demonstrate an interaction between preoperative eGFR and the TnT thresholds, we cannot exclude an interaction, especially at lower levels of renal function. Our results are, however, consistent with a prior large (N=7033) acute coronary syndrome study that demonstrated TnT levels predicted 30-day mortality regardless of patients’ baseline eGFR.21 We did not capture whether patients were recruited prior to or after surgery, and therefore we cannot evaluate these subgroups of patients separately. We did not record whether any actions were taken based on the TnT values reported to physicians, and therefore we cannot comment on the potential impact of any such interventions. If physicians implemented therapies based upon these TnT measurements and these interventions impacted 30-day mortality, then our 30-day mortality rates associated with elevated TnT measurements likely represent the mortality rates future unblinded physicians can expect in their clinical practice.

Comparison to Other Studies

Levy et al22 undertook a meta-analysis of 10 studies (N=1728 patients) that assessed the independent prognostic capabilities of an elevated troponin measurement after noncardiac surgery to predict intermediate-term (<12 months) mortality and demonstrated an odds ratio of 6.7 (95% CI, 4.1-10.9; I=0%).22 The studies in this meta-analysis used several different troponin assays, numerous different troponin thresholds, and did not evaluate the impact on short-term mortality (<30 days). Le Manach et al demonstrated in a study of 1136 abdominal aortic surgical cases that a Dade-Behring Troponin I measurement of greater than 1.5 ng/mL was an independent predictor of in-hospital mortality. Our study included a much broader spectrum of noncardiac surgeries and a much larger sample size.

Interpretation

We have demonstrated that the peak fourth-generation TnT measurement in the first 3 days after surgery strongly

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Table 3. Perioperative Independent Predictors of 30-Day Causes of Death (Vascular and Nonvascular) as Reported by Centers

<table>
<thead>
<tr>
<th>Vascular Mortality (n = 127)</th>
<th>Nonvascular Mortality (n = 155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No./No. a</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Agg, y</td>
<td>45-64</td>
</tr>
<tr>
<td>65-75</td>
<td>25/3779</td>
</tr>
<tr>
<td>≥75</td>
<td>79/3657</td>
</tr>
<tr>
<td>Recent high-risk CAD</td>
<td>11/173</td>
</tr>
<tr>
<td>No recent high-risk CAD</td>
<td>116/14960</td>
</tr>
<tr>
<td>History of PVD</td>
<td>23/809</td>
</tr>
<tr>
<td>No history of PVD</td>
<td>104/14324</td>
</tr>
<tr>
<td>History of stroke</td>
<td>28/696</td>
</tr>
<tr>
<td>No history of stroke</td>
<td>99/14437</td>
</tr>
<tr>
<td>COPD</td>
<td>36/1282</td>
</tr>
<tr>
<td>No COPD</td>
<td>91/13851</td>
</tr>
<tr>
<td>Active cancer</td>
<td>29/4015</td>
</tr>
<tr>
<td>No active cancer</td>
<td>98/11118</td>
</tr>
<tr>
<td>Urgent/emergency surgery</td>
<td>54/2124</td>
</tr>
<tr>
<td>No urgent/emergency surgery</td>
<td>69/12991</td>
</tr>
<tr>
<td>Major general surgery</td>
<td>36/3076</td>
</tr>
<tr>
<td>No major general surgery</td>
<td>91/12057</td>
</tr>
<tr>
<td>Major neurosurgery</td>
<td>12/888</td>
</tr>
<tr>
<td>No major neurosurgery</td>
<td>115/14245</td>
</tr>
<tr>
<td>Peak TnT measurement</td>
<td>≤0.01 ng/mL</td>
</tr>
<tr>
<td>&gt;0.02 ng/mL</td>
<td>7/494</td>
</tr>
<tr>
<td>&gt;0.03-0.29 ng/mL</td>
<td>51/1121</td>
</tr>
<tr>
<td>≥0.30 ng/mL</td>
<td>13/142</td>
</tr>
</tbody>
</table>

Abbreviations: aHR, adjusted hazard ratio; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; TnT, troponin T.

No./No., number of patients who died in subgroup/total number of patients in subgroup.

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POSTOPERATIVE TROPONIN LEVELS AND 30-DAY MORTALITY

predicts 30-day mortality and may explain a substantial proportion of the deaths (41.8%). Compared with our preoperative model, the model that included the peak TnT measurement demonstrated an absolute increase in the C index value of 0.04. We also classified 30-day mortality as low risk (<1%), intermediate risk (1%-5%), high risk (5%-10%), and very high risk (>10%) and with our model that included the peak TnT measurement, we demonstrated among patients who died and also among those who survived an improvement in reclassification of 18.8% and 6.2%, respectively. Although these data suggest improvement in risk classification with postoperative troponin measurements, what is now required is to undertake clinical trials to determine if this risk is modifiable.

Based on the guideline recommendation that abnormal troponin values should have a coefficient of variation less than 10%, many laboratories consider a fourth-generation TnT measurement of at least 0.04 ng/mL abnormal.23,24 Our study suggests that TnT values of less than the commonly used threshold of 0.04 ng/mL (ie, 0.02 ng/mL and 0.03 ng/mL) are, in the context of noncardiac surgery, strongly associated with 30-day mortality. Given that troponin biomarkers have nearly absolute myocardial tissue specificity and the median time to death from a peak TnT value of 0.02 ng/mL (ie, 13.5 days) and 0.03 ng/mL (9.0 days), these lower TnT values may represent a warning myocardial insult.23,25

Consideration that more than 200 million adults undergo major noncardiac surgery annually,1 potentially half of these patients are at least 45 years of age,2 and 11.6% of the patients in our study had a peak TnT value of at least 0.02 ng/mL, suggests that worldwide more than 10 million adults may have prognostically relevant troponin values after noncardiac surgery each year. Although no randomized controlled trial has established an effective treatment for patients with an elevated troponin measurement after noncardiac surgery, the prognosis of these patients may be modifiable. First, the high-quality evidence for acetylsalicylic acid (ASA) and statin therapy in the nonoperative setting26,27 and encouraging observational data from a large international perioperative trial showing an association with use of these drugs and decreased 30-day mortality in patients who have experienced a perioperative myocardial injury,28 suggests that ASA and statin therapy may benefit patients with an elevated perioperative troponin measurement. We have previously demonstrated that a substantial proportion of patients experiencing a myocardial injury after noncardiac surgery do not receive these drugs.29 Second, the timeline from the peak TnT value until death demonstrates that there is time to intervene.

Third, although study centers deemed approximately half the deaths as having nonvascular causes, it is possible that these events may also be modifiable through enhanced cardiovascular management. Because the majority of patients who experience a perioperative myocardial infarction after noncardiac surgery do not experience ischemic symptoms,28 physicians may have missed diagnosing some of the patients with a prognostically relevant TnT value after surgery as having a cardiac event. Further, undiagnosed and untreated myocardial injury may decrease the likelihood of surviving a nonvascular complication. For example, although pneumonia is a serious complication that can result in death after noncardiac surgery,30 it is possible that patients who first experience a myocardial injury may have a higher likelihood of developing pneumonia, a greater risk of dying if they do develop pneumonia, or both. In this study, 74.2% of patients who would develop an elevated TnT measurement did so within the first 24 hours after surgery, whereas the median time to develop pneumonia was 6 days after surgery. These considerations may explain the association between the prognostically relevant TnT thresholds and nonvascular death in our sensitivity analysis, and suggest that intervention in those with elevated troponin could decrease deaths classified as nonvascular.

Although noncardiac surgery has enormous potential to help patients, many patients die within 30 days of surgery (1.9% in VISION). Our study demonstrates that prognostically relevant TnT measurements after surgery strongly predict who will die within 30 days of surgery. Although at present, troponin measurements are not commonly measured after noncardiac surgery, the simplicity of this test and its prognostic power suggest it may have substantial clinical utility. There is now a need for large randomized controlled trials to evaluate potential interventions to mitigate the high risk of death in patients who have an elevated troponin measurement after noncardiac surgery.

CONCLUSIONS

The peak fourth-generation TnT measurement in the first 3 days after noncardiac surgery is strongly associated with 30-day mortality. Our data suggest that 1 in 25 patients with a peak TnT measurement of 0.02 ng/mL, 1 in 11 patients with a peak TnT measurement of 0.03 to 0.29 ng/mL, and 1 in 6 patients with a peak TnT measurement of at least 0.30 ng/mL will die within 30 days of surgery. Monitoring postoperative TnT measurements can enhance risk stratification after noncardiac surgery. Although there are some encouraging observational data, clinical trials are needed to establish whether interventions can alter patients' risk of death based on an elevated troponin measurement after surgery.

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Drugs or devices: Hielscher.

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