MINS=
myocardial injury following non cardiac surgery

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

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, 0.03-0.29, 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.

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Worldwide, more than 200 million adults have major noncardiac surgery annually.[1,2] 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 preoperative 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.

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-

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tients experienced event rates at approximately 3 times what was expected. Recognizing that we had sufficient events to address our objectives 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 general or regional anesthetic, and underwent elective, urgent, or emergency surgery during the day or at night on a weekday or weekend. Additional eligibility 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 complete data for the 24 potential preoperative predictors of 30-day mortality that we evaluated. Patients were excluded if they did not require an overnight hospital admission after surgery, 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 preoperatively (eg, emergency night surgical case), research 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 mechanically ventilated) and for whom no next of kin was available. This allowed collection of TnT measurements while awaiting patient or next-of-kin consent.

Patients were identified by screening daily patient lists in preoperative assessment clinics, on surgical wards, and in intensive care units; daily and previous-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 consisting of random weeks of nonrecruitment or randomly selected surgical services. At the end of each week, research personnel reviewed the surgical logbook and reported the number of patients eligible but not enrolled.

Procedures

Research personnel interviewed and examined patients and reviewed medical records to obtain information on potential predictors of major perioperative complications. At each site, an investigator reviewed and approved all data. Patients had blood collected to measure a Roche 4th-generation Elecsys TnT assay 6 to 12 hours postoperatively and on the first, second, and third days after surgery. Patients enrolled between 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 measurements drawn, and noted outcome events. The primary outcome was mortality at 30 days after surgery. Centers also reported the cause of death (vascular or nonvascular, definitions in eAppendix 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 outcome, their physicians were contacted to obtain documentation. Research personnel at participating centers submitted the case report forms and supporting documentation directly to the data management system (iDataFax, coordinating center, McMaster University, Hamilton, Ontario, Canada).

Data monitoring in VISION consisted of central data consistency checks, statistical monitoring, and on-site monitoring for all centers. For the on-site monitoring, the central coordinator randomly selected participants with and without a perioperative complication, and independent monitors audited their medical records and all other supporting documents. No center stood out regarding results from central data consistency checks or statistical monitoring. On-site monitoring demonstrated no major discrepancies between the submitted data and the monitoring findings, except for a systematic error in recording the duration of perioperative hemodynamic compromise at 2 centers. This was corrected and subsequent on-site monitoring 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 complete the 30-day follow-up were censored on the last day their vital status was known. We determined the percentage of patients who died within 30 days after surgery and the associated 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 minimum *P* value approach was used to determine if there were TnT threshold values that independently altered the patients' risk of mortality.[8] This approach evaluated every possible threshold of TnT (eg, $\leq$0.01 vs $>$0.01; $\leq$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 mortality. Subsequently, this threshold was fixed and the multivariable analysis was repeated to determine if there was another statistically significant threshold

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 $\alpha = .05$ 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.[15] 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 m^2 or receiving dialysis, 30 to 44 mL/min per 1.73 m^2, 45 to 59 mL/min per 1.73 m^2, and ≥60 mL/min per 1.73 m^2)[16,17] 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 $\alpha = .01$ 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 colinearity 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

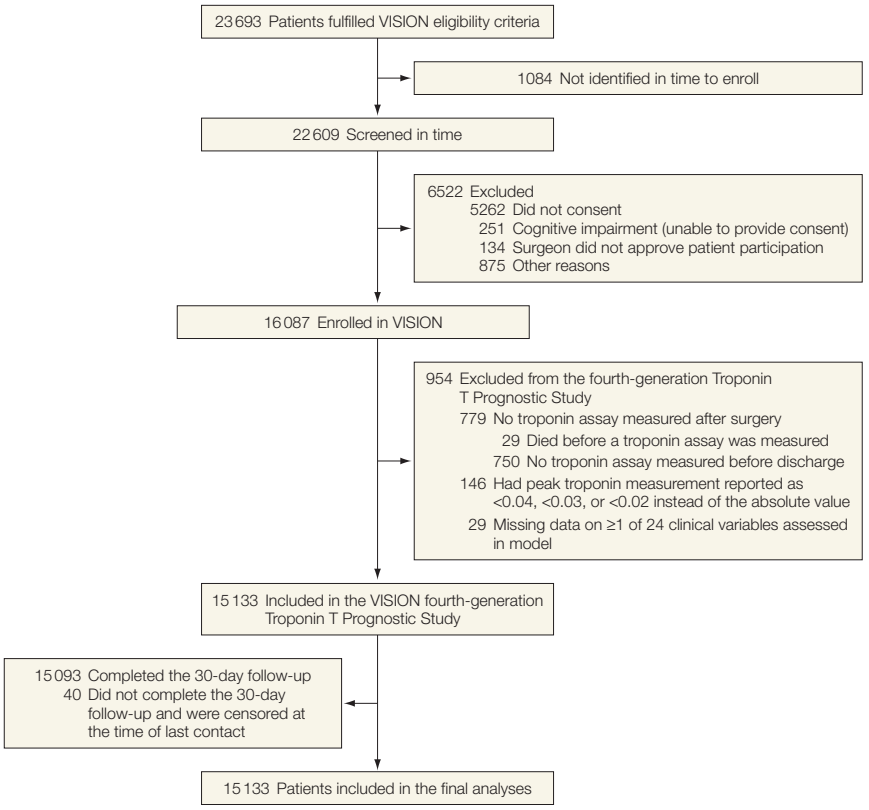
FIGURE 1 reports the patient flow. Of the 15 133 patients included in the VISION fourth-generation TnT prognostic study, 99.7% of the patients completed the 30-day follow-up. Centers that recruited patients from August 6, 2007 to January 11, 2011, are listed by location and number of patients in eTable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

Figure 1. Patient Flow Chart



cluding the peak TnT measurement. 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 ng/mL, 0.03 to 0.29 ng/mL, and 0.30 ng/mL or greater occurred in 88.4%, 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 values of 0.01 or less, 0.02, 0.03 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 died within the first 36 hours after surgery. Both sensitivity analyses demonstrated that results for the TnT thresholds did not appreciably differ from the model that included all 15 133 patients.

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 m^2 or were receiving dialysis; 760 patients (5.4%) had an eGFR of 30 to 44 mL/min per 1.73 m^2; 1496 patients (10.7%) had an eGFR of 45 to 59 mL/min per 1.73 m^2; and 11 232 patients (80.2%) had an eGFR of at least 60 mL/min per 1.73 m^2. There was no interaction between preoperative eGFR and the TnT thresholds ($P=.05$).

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-

operative day 1, postoperative day 2, and postoperative day 3 in 45.9%, 28.3%, 17.7%, and 8.2% of these patients, respectively. Considering the most serious nonvascular complications, the median time to a diagnosis of pneumonia was 6.0 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

			Model				
	Death Within 30 Days Postsurgery		Preoperative Variables Only		Preoperative Variables and Peak TnT		
Potential Risk Factor	No. Died/Total No.	% (95% CI)	aHR (95% CI)	*P* Value	aHR (95% CI)	*P* Value	Population AR (95% CI)
Age, y							
45-64	68/7697	0.9 (0.7-1.1)	1 [Reference]		1 [Reference]		39.7 (26.2-52.8)
65-74	68/3779	1.8 (1.4-2.3)	1.67 (1.18-2.36)	.004	1.57 (1.11-2.23)	.01	
≥75	146/3657	4.0 (3.4-4.7)	3.03 (2.20-4.18)	<.001	2.37 (1.71-3.28)	<.001	
Recent high-risk CAD	15/173	8.7 (5.3-13.8)	3.12 (1.71-5.68)	<.001	2.13 (1.17-3.88)	.01	2.4 (0.0-5.4)
No recent high-risk CAD	267/14 960	1.8 (1.6-2.0)	1 [Reference]		1 [Reference]		
PVD history	45/809	5.6 (4.2-7.4)	2.13 (1.47-3.10)	<.001	1.83 (1.27-2.66)	.001	7.9 (2.8-13.0)
No PVD history	237/14 324	1.7 (1.5-1.9)	1 [Reference]		1 [Reference]		
Stroke history	42/696	6.0 (4.5-8.1)	2.01 (1.42-2.84)	<.001	1.82 (1.29-2.57)	<.001	7.2 (2.5-12.1)
No stroke history	240/14 437	1.7 (1.5-1.9)	1 [Reference]		1 [Reference]		
COPD	65/1282	5.1 (4.0-6.4)	2.15 (1.61-2.89)	<.001	2.07 (1.54-2.78)	<.001	12.6 (6.7-18.5)
No COPD	217/13 851	1.6 (1.4-1.8)	1 [Reference]		1 [Reference]		
Active cancer	106/4015	2.6 (2.2-3.2)	2.38 (1.79-3.18)	<.001	2.32 (1.74-3.10)	<.001	20.6 (12.6-28.6)
No active cancer	176/11 118	1.6 (1.4-1.8)	1 [Reference]		1 [Reference]		
Urgent/emergency surgery[a]	123/2142	5.7 (4.8-6.8)	4.62 (3.57-5.98)	<.001	3.55 (2.73-4.60)	<.001	32.9 (25.8-40.1)
No urgent/emergency surgery	159/12 991	1.2 (1.0-1.4)	1 [Reference]		1 [Reference]		
Major general surgery	113/3076	3.7 (3.1-4.4)	3.25 (1.64-6.45)	<.001	3.16 (1.59-6.29)	.001	23.6 (15.9-31.3)
No major general surgery	169/12 057	1.4 (1.2-1.6)	1 [Reference]		1 [Reference]		
Major neurosurgery	25/888	2.8 (1.9-4.1)	3.72 (1.68-8.20)	.001	3.44 (1.55-7.62)	.002	5.6 (2.3-9.2)
No major neurosurgery	257/14 245	1.8 (1.6-2.0)	1 [Reference]		1 [Reference]		
Peak TnT measurement							
≤0.01 ng/mL	134/13 376	1.0 (0.8-1.2)	1 [Reference]		1 [Reference]		41.8 (34.5-49.0)
0.02 ng/mL	20/494	4.0 (2.6-6.2)			2.41 (1.33-3.77)	<.001	
0.03-0.29 ng/mL	104/1121	9.3 (7.7-11.1)			5.00 (3.72-6.76)	<.001	
≥0.30 ng/mL	24/142	16.9 (11.6-23.9)			10.48 (6.25-16.62)	<.001	
Predictive in the Preoperative Model but Not Predictive in the Model That Included TnT Measurements							
CHF history	37/703	5.3 (3.8-7.2)	1.60 (1.09-2.36)	.02	1.20 (0.82-1.77)	.35	NA
No CHF history	245/14 430	1.7 (1.5-1.9)	1 [Reference]		1 [Reference]		
Major vascular surgery	19/504	3.8 (2.4-5.8)	2.38 (1.04-5.47)	.04	2.10 (0.92-4.79)	.08	NA
No major vascular surgery	263/14 629	1.8 (1.6-2.0)	1 [Reference]		1 [Reference]		
Not Predictive in the Preoperative Model or the Model That Included TnT Measurements							
Men	151/7339	2.1 (1.8-2.4)	1 [Reference]	.55	1 [Reference]	.96	NA
Women	131/7794	1.7 (1.4-2.0)	0.93 (0.72-1.19)		1.01 (0.79-1.29)		
CAD history	56/1832	3.1 (2.4-3.9)	0.85 (0.60-1.21)	.37	0.73 (0.51-1.05)	.09	NA
No CAD history	226/13 301	1.7 (1.5-1.9)	1 [Reference]		1 [Reference]		
Cardiac arrest history	1/68	1.5 (0.3-7.9)	0.63 (0.09-4.62)	.65	0.70 (0.10-5.05)	.72	NA
No cardiac arrest history	281/15 065	1.9 (1.7-2.1)	1 [Reference]		1 [Reference]		
TIA history	7/376	1.9 (0.9-3.8)	0.54 (0.25-1.15)	.11	0.48 (0.22-1.04)	.06	NA
No TIA history	275/14 757	1.9 (1.7-2.1)	1 [Reference]		1 [Reference]		
DVT or PE history	11/475	2.3 (1.3-4.1)	1.09 (0.59-2.01)	.78	1.03 (0.56-1.90)	.92	NA
No DVT or PE history	271/14 658	1.8 (1.6-2.1)	1 [Reference]		1 [Reference]		
Diabetes	74/2952	2.5 (2.0-3.1)	1.16 (0.88-1.54)	.29	1.08 (0.81-1.43)	.60	NA
No diabetes	208/12 181	1.7 (1.5-2.0)	1 [Reference]		1 [Reference]		
Hypertension	180/7709	2.3 (2.0-2.7)	1.05 (0.80-1.38)	.71	0.93 (0.71-1.22)	.61	NA
No hypertension	102/7424	1.4 (1.1-1.7)	1 [Reference]		1 [Reference]		
Current atrial fibrillation	20/504	4.0 (2.6-6.0)	0.98 (0.60-1.59)	.92	1.03 (0.63-1.66)	.91	NA
No current atrial fibrillation	262/14 629	1.8 (1.6-2.0)	1 [Reference]		1 [Reference]		
Obstructive sleep apnea	11/773	1.4 (0.8-2.5)	0.90 (0.49-1.65)	.73	0.94 (0.51-1.72)	.83	NA
No obstructive sleep apnea	271/14 360	1.9 (1.7-2.1)	1 [Reference]		1 [Reference]		
Major orthopedic surgery	63/3094	2.0 (1.6-2.6)	1.74 (0.84-3.63)	.12	1.64 (0.79-3.41)	.18	NA
No major orthopedic surgery	219/12 039	1.8 (1.6-2.1)	1 [Reference]		1 [Reference]		
Major URO/GYN surgery	10/1888	0.5 (0.3-1.0)	0.59 (0.27-1.27)	.18	0.55 (0.26-1.18)	.12	NA
No URO/GYN surgery	272/13 245	2.1 (1.8-2.3)	1 [Reference]		1 [Reference]		
Major thoracic surgery	7/376	1.9 (0.9-3.8)	1.70 (0.64-4.49)	.28	1.61 (0.60-4.33)	.34	NA
No major thoracic surgery	275/14 757	1.9 (1.7-2.1)	1 [Reference]		1 [Reference]		

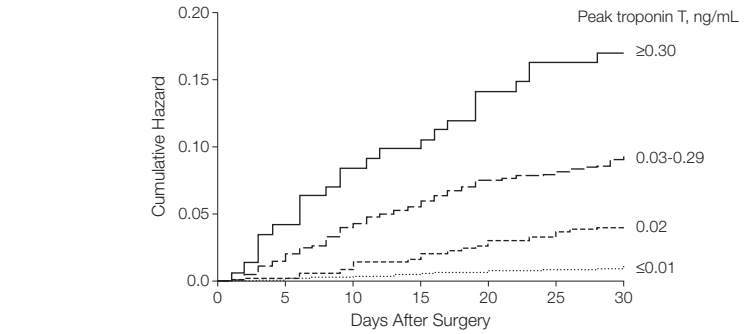
Abbreviations: aHR, adjusted hazard ratio; AR, attributable risk; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; GYN, gynecological; NA, not applicable; PE, pulmonary embolus; PVD, peripheral vascular disease; TnT,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

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

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.

Figure 2. Kaplan-Meier Estimates of 30-Day Mortality Based on Peak Troponin T Values



No. at risk

Peak troponin T, ng/mL							
≥0.30	142	136	129	127	121	118	117
0.03-0.29	1121	1103	1075	1058	1036	1030	1018
0.02	494	492	489	485	480	477	473
≤0.01	13376	13348	13300	13271	13250	13230	13209

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

Table 2. Net Reclassification Improvement of Predicted Probability of 30-Day Mortality With the Model That Included the Peak TnT Measurement Compared With the Model Based Only on the Preoperative Risk Factors[a]

	Models for 30-Day Probability of Death							
	Includes Peak TnT Measurement							
	Died, No.				Survived, No.			
Preoperative Risk Factors Only	<1%	1%-5%	>5%-10%	>10%	<1%	1%-5%	>5%-10%	>10%
<1%	25	16	0	0	8014	496	15	0
1%-5%	10	68	21	22	1488	3398	290	183
>5%-10%	0	20	13	30	0	419	148	133
>10%	0	1	5	51	0	35	92	140

Abbreviation: TnT, troponin T.

[a] The number of patients who were reclassified to a higher risk category based on the model that included the peak TnT measurement compared with the model that only included preoperative risk factors was 89 among the patients who died and 1117 among those who survived. The number of patients who were reclassified to a lower risk category based on the model that included the peak TnT measurement compared with the model that only included preoperative risk factors was 36 among the patients who died and 2034 among those who survived. Among the patients who died, the percentage correctly reclassified to a higher risk category when both models were compared was 89 minus 36, divided by the total number of patients who died (282), which equals 18.8%. Among the patients who survived, the percentage correctly reclassified to a lower risk category when both models were compared was 2034 minus 1117, divided by the total number of patients who survived (14 851), which equals 6.2%. The net reclassification improvement is the sum of the percentages of correctly reclassified individuals who did and did not survive (ie, 18.8% + 6.2% = 25.0% [95% CI, 17.2%-32.8%] $P<.001$).

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 al[22] 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^2=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[7] 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

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

	Vascular Mortality (n = 127)			Nonvascular Mortality (n = 155)		
Potential Independent Predictors	No./No.[a]	% (95% CI)	Adjusted HR (95% CI)	No./No.[a]	% (95% CI)	aHR (95% CI)
Age, y						
45-64	24/7697	0.3 (0.2-0.5)	1 [Reference]	44/7697	0.6 (0.4-0.8)	1 [Reference]
65-75	25/3779	0.7 (0.4-1.0)	1.59 (0.90-2.81)	43/3779	1.1 (0.8-1.5)	1.56 (1.02-2.38)
≥75	78/3657	2.1 (1.7-2.7)	3.29 (2.03-5.35)	68/3657	1.9 (1.5-2.4)	1.83 (1.22-2.74)
Recent high-risk CAD	11/173	6.4 (3.6-11.0)	2.48 (1.30-4.73)	4/173	2.3 (0.9-5.8)	0.95 (0.34-2.60)
No recent high-risk CAD	116/14 960	0.8 (0.6-0.9)	1 [Reference]	151/14960	1.0 (0.9-1.2)	1 [Reference]
History of PVD	23/809	2.8 (1.9-4.2)	1.66 (1.03-2.67)	22/809	2.7 (1.8-4.1)	2.07 (1.29-3.32)
No history of PVD	104/14 324	0.7 (0.6-0.9)	1 [Reference]	133/14324	0.9 (0.8-1.1)	1 [Reference]
History of stroke	28/696	4.0 (2.8-5.8)	2.66 (1.72-4.10)	14/696	2.0 (1.2-3.3)	1.15 (0.66-2.03)
No history of stroke	99/14 437	0.7 (0.6-0.8)	1 [Reference]	141/14437	1.0 (0.8-1.2)	1 [Reference]
COPD	36/1282	2.8 (2.0-3.9)	2.65 (1.78-3.95)	29/1282	2.3 (1.6-3.2)	1.63 (1.07-2.47)
No COPD	91/13 851	0.7 (0.5-0.8)	1 [Reference]	126/13851	0.9 (0.8-1.1)	1 [Reference]
Active cancer	29/4015	0.7 (0.5-1.0)	1.14 (0.72-1.79)	77/4015	1.9 (1.5-2.4)	3.17 (2.22-4.53)
No active cancer	98/11 118	0.9 (0.7-1.1)	1 [Reference]	78/11118	0.7 (0.6-0.9)	1 [Reference]
Urgent/emergency surgery	58/2142	2.7 (2.1-3.5)	3.26 (2.24-4.75)	65/2142	3.0 (2.4-3.8)	4.26 (3.00-6.04)
No urgent/emergency surgery	69/12 991	0.5 (0.4-0.7)	1 [Reference]	90/12991	0.7 (0.6-0.9)	1 [Reference]
Major general surgery	36/3076	1.2 (0.8-1.6)	1.57 (1.04-2.38)	77/3076	2.5 (2.0-3.1)	3.04 (2.15-4.31)
No major general surgery	91/12 057	0.8 (0.6-0.9)	1 [Reference]	78/12057	0.6 (0.5-0.8)	1 [Reference]
Major neurosurgery	12/888	1.4 (0.8-2.3)	2.46 (1.32-4.58)	13/888	1.5 (0.9-2.5)	2.74 (1.49-5.03)
No major neurosurgery	115/14 245	0.8 (0.7-1.0)	1 [Reference]	142/14245	1.0 (0.8-1.2)	1 [Reference]
Peak TnT measurement						
≤0.01 ng/mL	56/13 376	0.4 (0.3-0.5)	1 [Reference]	78/13376	0.6 (0.5-0.7)	1 [Reference]
0.02 ng/mL	7/494	1.4 (0.7-2.9)	1.65 (0.74-3.67)	13/494	2.6 (1.5-4.4)	3.25 (1.78-5.94)
0.03-0.29 ng/mL	51/1121	4.5 (3.5-5.9)	4.81 (3.18-7.25)	53/1121	4.7 (3.6-6.1)	5.06 (3.47-7.38)
≥0.30 ng/mL	13/142	9.2 (5.4-15.0)	10.01 (5.30-18.90)	11/142	7.7 (4.4-13.3)	9.20 (4.79-17.65)

Abbreviations: aHR, adjusted hazard ratio; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; TnT, troponin T.
[a]No./No., number of patients who died in subgroup /total number of patients in subgroup.

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.[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 setting,[26,27] 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.[28] 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,[29] 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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Online-Only Material: eAppendixes 1 through 3 and eTables 1 through 5 are available at http://www.jama.com.

REFERENCES

1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery. *Lancet*. 2008;372(9633):139-144.

2. Devereaux PJ, Chan M, Eikelboom J. Major vascular complications in patients undergoing noncardiac surgery: the magnitude of the problem, risk prediction, surveillance, and prevention. In: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, eds. *Evidence-Based Cardiology*. 3rd ed. London, England: BMJ Books; 2009:47-62.

3. Devereaux PJ, Yang H, Yusuf S, et al; POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial. *Lancet*. 2008;371(9627):1839-1847.

4. Ford MK, Beattie WS, Wijeysundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. *Ann Intern Med*. 2010;152(1):26-35.

5. Gordon HS, Johnson ML, Wray NP, et al. Mortality after noncardiac surgery: prediction from administrative versus clinical data. *Med Care*. 2005;43 (2):159-167.

6. Kim LJ, Martinez EA, Faraday N, et al. Cardiac troponin I predicts short-term mortality in vascular surgery patients. *Circulation*. 2002;106(18):2366-2371.

7. Le Manach Y, Perel A, Coriat P, Godet G, Bertrand M, Riou B. Early and delayed myocardial infarction after abdominal aortic surgery. *Anesthesiology*. 2005; 102(5):885-891.

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

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

10. Engel LS, Chow WH, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. *J Natl Cancer Inst*. 2003;95(18):1404-1413.

11. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. *Am J Epidemiol*. 1985;122(5):904-914.

12. Parzen M, Lipsitz SR. A global goodness-of-fit statistic for Cox regression models. *Biometrics*. 1999; 55(2):580-584.

13. May S, Hosmer DW. A simplified method of calculating an overall goodness-of-fit test for the Cox proportional hazards model. *Lifetime Data Anal*. 1998; 4(2):109-120.

14. Kremers WK. Concordance for survival time data: fixed and time-dependent covariates and possible ties in predictor and time. Rochester, MN: Mayo Clinic; 2007. Technical Report Series #80.

15. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker. *Stat Med*. 2008;27(2):157-172.

16. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease. *Kidney Int*. 2005;67(6):2089-2100.

17. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9): 604-612.

18. Derksen S, Keselman H. Backward, forward and stepwise automated subset selection algorithms. *Br J Math Stat Psychol*. 1992;45:265-282 doi:10.1111/j .2044-8317.1992.tb00992.x.

19. Steyerberg EW, Eijkemans MJ, Harrell FE Jr, Habbema JD. Prognostic modeling with logistic regression analysis. *Med Decis Making*. 2001;21 (1):45-56.

20. Kline R. Data preparation and screening. In: Kline R, ed. *Principles and Practice of Structural Equation Modeling*. New York, NY: The Guilford Press; 1998: 67-94.

21. Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med*. 2002; 346(26):2047-2052.

22. Levy M, Heels-Ansdell D, Hiralal R, et al. Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery. *Anesthesiology*. 2011;114(4):796-806.

23. Thygesen K, Alpert JS, White HD, et al; Joint ESC /ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation*. 2007;116(22):2634-2653.

24. Panteghini M, Pagani F, Yeo KT, et al; Committee on Standardization of Markers of Cardiac Damage of the IFCC. Evaluation of imprecision for cardiac troponin assays at low-range concentrations. *Clin Chem*. 2004;50(2):327-332.

25. Jaffe AS, Ravkilde J, Roberts R, et al. It's time for a change to a troponin standard. *Circulation*. 2000; 102(11):1216-1220.

26. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002; 324(7329):71-86.

27. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments. *J Am Coll Cardiol*. 2008;52(22):1769-1781.

28. Devereaux PJ, Xavier D, Pogue J, et al; POISE (Peri-Operative ISchemic Evaluation) Investigators. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery. *Ann Intern Med*. 2011;154(8):523-528.

29. Qaseem A, Snow V, Fitterman N, et al; Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery. *Ann Intern Med*. 2006;144(8):575-580.