Can J Anesth/J Can Anesth (2012) 59:1013–1022
DOI 10.1007/s12630-012-9782-9

REPORTS OF ORIGINAL INVESTIGATIONS

Use of clinically based troponin underestimates the cardiac injury in non-cardiac surgery: a single-centre cohort study in 51,701 consecutive patients

L'utilisation de la troponine en clinique sous-estime les lésions cardiaques en chirurgie non cardiaque : étude de cohorte monocentrique de 51 701 patients consécutifs

W. Scott Beattie, MD, PhD · Keyvan Karkouti, MD · Gordon Tait, PhD · Andrew Steel, MBCH · Paul Yip, PhD · Stuart McCluskey, MD, PhD · Michael Farkouh, MD · Duminda N. Wijeysundera, MD, PhD

Received: 5 June 2012 / Accepted: 20 August 2012 / Published online: 8 September 2012
© Canadian Anesthesiologists' Society 2012

Abstract

Purpose *Postoperative myocardial infarction causes hundreds of thousands of deaths annually, and "failure to rescue" is a leading cause of hospital mortality. Strategies to recognize cardiac injury are important to reduce the burden of cardiac-related morbidity. For these reasons, we chose to assess the association between postoperative troponin I elevations and 30-day in-hospital mortality and, secondarily, to compare the predictive value of regularly scheduled troponin estimates with troponin ordered in response to clinical indications.*

Methods *We carried out a retrospective cohort analysis of 51,701 consecutive patients throughout 2003 to 2009. All patients were from a single university referral hospital and included all non-cardiac non-transplant surgery patients requiring overnight admission. Logistic regression was used to assess the risk-adjusted associations between troponin I and 30-day in-hospital mortality.*

Results *The multivariable predictive model for death improved after troponin I was included. The receiver operating characteristic was 0.902 before troponin I vs 0.934 after troponin I ($P < 0.0001$). The likelihood ratio for troponin was 3.0 (95% confidence interval 2.8 to 3.2) and evident in each surgical service. Increasing troponin I showed a dose-response associated with increased mortality, and compared with clinically based measurements, a regularly scheduled postoperative troponin protocol*

Author contributions *W. Scott Beattie* conceived of the study, supplied the funding for this study through the R. Fraser Elliot Chair of Cardiac Anesthesia, supervised the acquisition of data, and wrote the initial manuscript. *Andrew Steele* and *Duminda N. Wijeysundera* were also involved in the conception of the study. *Keyvan Karkouti, Gordon Tait, Andrew Steele, Paul Yip, Stuart McCluskey, Michael Farkouh,* and *Duminda N. Wijeysundera* supplied revisions to the manuscript. *Gordon Tait* supervised the acquisition of the data from the electronic data warehouse and oversaw the validity checks of the data. *W. Scott Beattie, Keyvan Karkouti, Stuart McCluskey,* and *Michael Farkouh* were involved in the data analysis. *Duminda N. Wijeysundera* supplied critical revisions to the analysis of the data. *Paul Yip* supplied intellectual knowledge pertaining to the troponin assays and measurement.

W. S. Beattie, MD, PhD (✉) · K. Karkouti, MD · G. Tait, PhD · A. Steel, MBCH · S. McCluskey, MD, PhD · D. N. Wijeysundera, MD, PhD
Department of Anesthesia and Pain Management, University Health Network, Toronto, ON, Canada
e-mail: scott.beattie@uhn.ca

P. Yip, PhD
Department of Anesthesia, University of Toronto, Toronto, ON, Canada

P. Yip, PhD
Department of Lab Medicine, University Health Network, Toronto, ON, Canada

W. S. Beattie, MD, PhD · K. Karkouti, MD · M. Farkouh, MD
Department of Medicine, Peter Munk Cardiac Centre, University Health Network, Toronto, ON, Canada

K. Karkouti, MD · D. N. Wijeysundera, MD, PhD
Li Ka Shing Knowledge Institute of St. Michael's Hospital, Department of Health Policy Management and Evaluation, University of Toronto, Toronto, ON, Canada

showed a threefold increase in the probability of detecting myocardial injury. However, troponin I was not found to improve the risk prediction model in the lowest risk patients (n = 18,953; probability of death < 0.02%) with one cardiac death.

Conclusions *Postoperatively elevated troponin I is associated with 30-day in-hospital mortality in a dose-dependent manner. A postoperative measurement protocol provides a threefold increase in the ability to detect myocardial injury. Conversely, in patients with a low mortality risk, cardiac injury is low; there is minimal improvement in the ability to detect cardiac injury, and the rescue rates from cardiac injury are excellent. These findings suggest that a surveillance protocol of troponin I would be optimal when limited to moderate to high-risk patients.*

Résumé

Objectif *L'infarctus du myocarde postopératoire provoque des centaines de milliers de décès chaque année et « l'échec du sauvetage » est une des principales causes de mortalité à l'hôpital. Les stratégies visant à identifier une lésion cardiaque sont importantes pour réduire le fardeau de la morbidité d'origine cardiaque. Pour ces raisons, nous avons choisi d'évaluer l'association entre l'élévation de la troponine-I et la mortalité hospitalière à 30 jours et, secondairement, de comparer la valeur prédictive des dosages de troponine planifiés régulièrement avec les dosages prescrits dans le cas d'indications cliniques.*

Méthodes *Nous avons effectué une analyse rétrospective de cohorte de 51 701 patients entre 2003 et 2009. Tous les patients provenaient d'un seul hôpital universitaire de référence et incluaient tous les patients nécessitant une hospitalisation d'au moins une nuit, à l'exclusion des patients de chirurgie cardiaque ou de greffe. Une analyse de régression logistique a servi à évaluer les associations ajustées pour le risque entre la troponine I et la mortalité hospitalière à 30 jours.*

Résultats *Le modèle prédictif multivarié pour les décès s'est amélioré après l'inclusion de la troponine I. L'aire sous la courbe ROC (Receiver Operating Characteristic) était de 0.902 avant la troponine I contre 0.934 après la troponine I (P < 0.0001). Le rapport de probabilité pour la troponine était de 3.0 (intervalle de confiance à 95 % : 2.8 à 3.2) et évident dans chaque service de chirurgie. Une élévation de la troponine I montrait une relation dose-réponse associée à une plus grande mortalité et, comparé avec des dosages reposant sur la clinique, un protocole postopératoire avec dosage régulier de la troponine multipliait par trois la probabilité de détecter une lésion myocardique. Il n'a cependant pas été montré que la troponine I améliorait le modèle de prédiction du risque chez les patients à risque le plus faible (n = 18 953; probabilité de décès < 0.02%), avec un décès d'origine cardiaque.*

Conclusions *L'augmentation postopératoire de la troponine I est associée à la mortalité hospitalière à 30 jours de façon dose-dépendante. Un protocole de dosages postopératoires permet de multiplier par trois la capacité de détection d'une lésion myocardique. À l'inverse, chez des patients ayant un faible risque de mortalité, les lésions cardiaques sont peu fréquentes; il existe une minime amélioration de la capacité à détecter une lésion et les taux de sauvetage en cas de lésion cardiaque sont excellents. Ces constatations suggèrent qu'un protocole de surveillance de la troponine I serait optimal s'il était limité aux patients à risque modéré ou élevé.*

Postoperative myocardial infarction (POMI) is a serious public health issue.[1] The World Health Organization estimates that more than 230 million surgeries are performed annually, and half of these are moderate to high risk.[2] Postoperative myocardial infarction occurs in approximately 2% of all non-cardiac surgeries,[3] with evidence suggesting a mortality rate ranging from 29-40% in patients who sustain POMI.[4] Thus, this public health issue is associated with millions of deaths annually.

Effective prophylaxis of POMI,[5-7] while controversial,[7] reduces the incidence by approximately 30%; therefore, even with prophylaxis, POMI remains a significant perioperative issue. "Failure to rescue" from serious postoperative complications, such as POMI, is the leading cause of mortality,[8] which makes it necessary and critically important to develop strategies for the recognition and appropriate management of POMI.[9] However, recognizing a POMI is exceedingly difficult since it frequently occurs without signs or symptoms.[9] An elevated troponin level is central to the diagnosis of POMI, and given the lack of signs and symptoms, universal surveillance with troponin measurements has been advocated.[10] Before instituting such measurements, however, it is important to determine the prognostic value of routine troponin measurements across a heterogeneous population and further to identify subgroups most likely to benefit from these processes of care.

Consequently, we conducted a retrospective observational study of non-cardiac surgical patients. In some patients, troponin levels were drawn at regular intervals as a result of postoperative management protocol, and in other patients, troponin levels were drawn on the basis of clinical indicators. Our primary objective was to assess the incremental value of adding troponin measurements to a clinically based risk prediction model for postoperative mortality. Our secondary objective was to determine if a protocol for routine postoperative troponin is warranted in all patients.

Methods

Study setting and patient sample

After we received institutional ethics approval and the requirement for informed consent was waived, we conducted a single-centre retrospective observational study in accordance with the STROBE statement.[A] The University Health Network (UHN), a teaching hospital affiliated with the University of Toronto, offers a full range of adult non-cardiac surgery which is performed at three sites. Inclusion criteria for our study consisted of adult patients having non-cardiac non-transplant surgery with overnight admittance during January 1, 2003[B] to December 31, 2009. Patients with same day discharge or eye surgery were excluded due to the low risk,[11] and if patients underwent multiple surgical procedures, only data from their first procedure were used.

Perioperative data were prospectively collected in institutional databases as previously described.[12-15] The patient characteristics, laboratory values, and postoperative events were retrieved from the hospital electronic charting system, MISYS CPR (QuadraMed Corp, Reston, VA, USA). Surgical information was obtained from ORSOS (McKesson Corp, San Francisco CA, USA), and data regarding drug administration were obtained from the institutional pharmacy database. The data were linked using the patient's unique hospital visit number– the accuracy of these data had previously been confirmed.[12] The primary outcome was in-hospital death within 30 days of the index surgery.

Myocardial injury was assessed using troponin I with the Dade Behring Dimension® assay (detection limit 0.07 $\mu g \cdot mL^{-1}$) (Siemens Healthcare Diagnostics, Deerfield, IL, USA). In May 2008, the institution changed to the Abbott ARCHITECT i2000 analyzer (Abbott Diagnostics, Abbott Park, IL, USA). Internal correlation studies showed a 1:1 correlation with the Dade Behring assay, and the changeover did not affect the interpretation of the results presented here. We assessed the peak postoperative troponin level, defined as the highest level at any time in the 30 days after surgery. The covariates in the mortality model included 1) preoperative patient characteristics (age, sex)[12]; 2) a list of the 17 comorbidities constructed from the International Classification of Diseases (ICD) 10 codes[16]; 3) preoperative laboratory values (creatinine, hemoglobin, international normalized ratio); 4) preoperative cardiovascular drugs (statins, beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, acetylsalicylic acid, and anti-coagulants)[13,17-19]; 5) surgical characteristics (year of surgery, site, surgical service, duration, and emergent status); and 6) transfusion status.

Statistical analyses

Primary Mortality Model

We used variables previously associated with mortality in our assessment[14] and excluded peak troponin in the primary model. Direct associations were tested in univariate analysis using Chi square for categorical variables and Student's *t* test or Wilcoxon rank sum test for continuous variables. During the development of the model describing mortality, the linearity assumptions for continuous variables were assessed using a cubic spline function. A multivariable logistic regression model was then developed to predict 30-day in-hospital mortality using the variables previously identified. All candidate variables were included in the preliminary model, and then a backward elimination procedure was employed. Covariates were retained in the final multivariable model if the P value was ≤ 0.05 for categorical variables and if any member of that category had a P value ≤ 0.05. We refer to the final model as the primary model. The goodness-of-fit of the model was evaluated by the Hosmer-Lemeshow test, and the discriminative ability of the model was assessed with a receiver operating characteristic (ROC) curve.

Incremental value of the addition of peak troponin

We assessed the incremental value of including peak troponin in the mortality model by adding this variable (positive/negative) to the primary model and assessing the area under the ROC curve. In addition, we compared the primary model with the secondary (peak troponin added) model by recalibrating at five clinically relevant increasing levels of risk. These divisions were utilized because the population was severely skewed in the direction of the lowest risk.

Assessment of a biologic gradient: troponin and 30-day mortality

Peak troponin was assessed as a categorical variable because there was no linear relationship between it and the log odds of the probability of 30-day mortality.[C]

Assessment of detection bias

In order to assess detection bias between per protocol measurements and clinically based troponin, we compared

[A] www.strobestatement.com

[B] January 2003 is the point when we began to store electronic data prospectively.

[C] The log odds of the probability of death and troponin were not linear (seen in Web appendix); thus, peak troponin was expressed as a categorical variable with five tiers: 1) Unmeasured; 2) Undetected, < 0.2; 3) > 0.2-0.7; 4) 0.7-7.0; and 5) > 7.0.

the frequency of positive troponin measurements across the risk spectrum of postoperative death. This planned secondary analysis compared the cubic spline relationships and the associated 95% confidence intervals (CI) for each of the two groups. This relationship displays the probability of detection of troponin > 0.07 $\mu g \cdot mL^{-1}$ across all levels of mortality risk, as expressed by the primary model. All analyses were performed using SAS^{TM} version 9.1 (SAS Institute, Cary, NC, USA).

Results

This analysis was conducted in 51,701 consecutive moderate to high-risk non-cardiac surgical patients. We excluded 61,952 same-day patients, 14,141 cardiac patients, 1,924 transplant patients, 1,033 ophthalmologic patients, and 5,619 duplicate surgeries from the original population of 136,371 procedures. At least one troponin measurement was ordered postoperatively for 10,534 (20.4%) patients. In vascular surgical patients, troponin measurement was routinely ordered immediately postoperatively and on the mornings of the first and second postoperative days. Seventy-four percent of all troponin measurements were ordered within the first 72 postoperative hours. The characteristics of the remaining population are presented in Table 1. Typically, troponin was measured in older males with multiple comorbidities, after longer and/or emergent surgical procedures or procedures with blood loss, and in high cardiac risk scenarios. Troponin elevations occurred within 48 hrs in 811 (69.2%) of patients (Fig. 1).

The in-hospital 30-day mortality was 2.1% (1,072 deaths); 1,173 (11.1%) patients with a troponin measurement had troponin elevations > 0.7 $\mu g \cdot L^{-1}$, and 285 (24.3%) patients with troponin elevations died. Furthermore, 880 (8.4%) patients had detectable troponin but below the threshold associated with myocardial infarction (MI), and 142 (16.1%) of these patients died. Troponin was detected in 427 (38.9%) of the patients who died. In-hospital 30-day mortality was independently associated with advanced age, male sex, several comorbidities, anemia, blood loss, the need for transfusion, and surgical factors (Table 2). In contrast, several drugs were associated with decreased mortality. The model showed good discriminative ability (C-statistic $= 0.902$) and improved with the addition of troponin (ROC $= 0.930$) (Fig. 2). The addition of troponin had a small recalibration effect when the calculated risk of mortality was $< 0.6\%$. In addition, there was virtually no cardiac mortality in these risk strata (Table 3). A positive troponin was independently associated with a mortality likelihood ratio of 3.0 (95% CI 2.8 to 3.2). The likelihood ratio for a positive troponin was significant in all ten surgical services and ranged from 1.9 (95% CI 1.5 to 2.5) in thoracic surgery to 4.4 (95% CI 3.0 to 6.3) in ear, nose, and throat surgery (Table 4). As increasing amounts of troponin were detected, a biologic gradient (dose-response) showed both an increased strength in the association with mortality and a decrease in the time to death (Fig. 3). Fig. 4 shows the cubic spline relationship between the two groups (the vascular surgery troponin protocol *vs* clinically based measurements), describing the association between the risk of death and the probability of detecting elevated troponin. At any level of estimated mortality risk (shown as the x-axis), the vascular surgery troponin protocol was associated with a threefold increase in the frequency of detecting elevated troponin.

Discussion

In this study, elevated troponin was associated with mortality in a dose-dependent manner. The clinical decision to measure troponin was related to surgical type and baseline cardiovascular risk. More importantly, the clinical practice of ordering troponin tests based on these characteristics underestimated myocardial injury. The association between troponin elevations and mortality occurred predominately within the first two days of surgery and was seen across all surgical types. The failure to detect troponin with the current standard of care raises serious questions about our ability to administer rescue therapy.

Our primary objective draws attention to the association between all levels of troponin and postoperative mortality. We have been careful not to characterize these troponin elevations as a MI. Currently, the proposed definitions of perioperative MI require additional criteria beyond biomarkers alone,[20] including symptoms of electrocardiogram (ECG) changes and/or abnormal ventricular imaging. However, considering the secondary POISE analysis,[10] where small troponin rises devoid of signs or symptoms were associated with increased 30-day mortality, as well as considering our results, where minimal elevations in troponin alone were also associated with mortality, at the very least, we would submit that the definition for POMI should be revised.[21]

This investigation also addresses the need for universal cardiac surveillance after non-cardiac surgery. This study showed that 1) elevated troponin I increased the likelihood of mortality across all types of surgery; 2) troponin elevation was seen in almost 40% of all postoperative deaths; 3) troponin was associated with death in a dose-dependent fashion; 4) the association was almost non-existent in patients with a low probability of death; and 5) the incidence of MI was underestimated when surveillance was not regularly scheduled. Critically, others have shown POMI as

Table 1 Population characteristics

	Total Population		
	Troponin Not Ordered $n = 41,167$	Troponin Ordered $n = 10,534$	Standardized Difference
Age (yr) mean	55.0	66.0	−0.708
Sex (male)	51.2%	56.1%	−0.098
General Surgery	17.9%	21.1%	−0.081
Neurosurgery	18.0%	13.8%	0.115
Thoracic Surgery	8.1%	8.0%	0.004
Emergent	23.6%	38.2%	−0.320
General Anesthesia	86.4%	88.6%	−0.067
Hospital (TWH)	50.3%	43.2%	0.143
Duration of Surgery (minutes)	134.4	179.3	−0.349
Year Surgery Performed			
2003	11.8%	12.1%	−0.009
2006	14.0%	14.1%	−0.003
2009	16.5%	14.3%	0.061
Coronary Artery Disease	1.0%	6.4%	−0.289
Cerebral Vascular Disease	3.6%	13.4%	−0.357
Peripheral Vascular Disease	0.6%	14.3%	−0.540
History of Congestive Heart Failure	60.0%	5.9%	1.407
Diabetes	6.1%	12.4%	−0.219
Diabetes with Complications	1.6%	9.2%	−0.341
Chronic Renal Failure	1.2%	6.8%	−0.289
Preoperative Creatinine ($mmol \cdot L^{-1}$)	85.30	98.30	−0.159
Chronic Obstructive Pulmonary Disease	3.7%	8.7%	−0.208
CANCER	29.3%	27.9%	0.031
Cancer with Metastatic Spread	10.5%	11.9%	−0.044
ASA class III	39.2%	49.4%	−0.206
ASA class IV	5.9%	39.0%	−0.864
RCRI class 2 or greater	2.6%	21.6%	−0.609
Charlson Comorbitiies (3 or more)	2.6%	12.5%	−0.381
Anemia (WHO)	16.5%	30.9%	−0.344
Nadir Hgb < 90 $g \cdot L^{-1}$	13.9%	40.2%	−0.620
INR	1.0	1.1	−0.290
% Transfused	6.0%	26.5%	0.818
Preoperative Hgb $g \cdot L^{-1}$	134.8	127.2	0.395
Postoperative Hgb $g \cdot L^{-1}$	107.7	98.9	0.488
Units of RBC transfused on the first postoperative day	0.2	1.0	−0.396
Beta Blockers	11.1%	37.1%	−0.638
STATINS	12.1%	29.2%	−0.432
ACE Inhibitors	10.9%	21.3%	−0.286
ARB	4.9%	7.5%	−0.108
Calcium Channel Blockers	8.9%	21.1%	−0.347
Acetylsalicylic Acid	4.4%	21.1%	−0.517
Non-Cardiac Mortality	0.6%	4.0%	−0.229

Table 1 continued

	Total Population		
	Troponin Not Ordered $n = 41,167$	Troponin Ordered $n = 10,534$	Standardized Difference
LOS	0.8	1.8	−0.166

ACE = angiotensin-converting-enzyme inhibitors; ARB = angiotensin receptor blockers; ASA = American Society of Anesthesiologists' Classification; INR = international normalized ratio; LOS = length of stay; RBC = concentrated red blood cells; RCRI = revised cardiac risk index; TWH = Toronto Western Hospital; Hemoglobin $\geq$ 120 g·L^{-1} for women and $\geq$ 130 g·L^{-1} for men; WHO = World Health Organization definition of anemia; Nadir hemoglobin refers to the lowest recorded hemoglobin in the first seven postoperative days; Charlson comorbidities are derived from the method of Quan *et al.*[16]

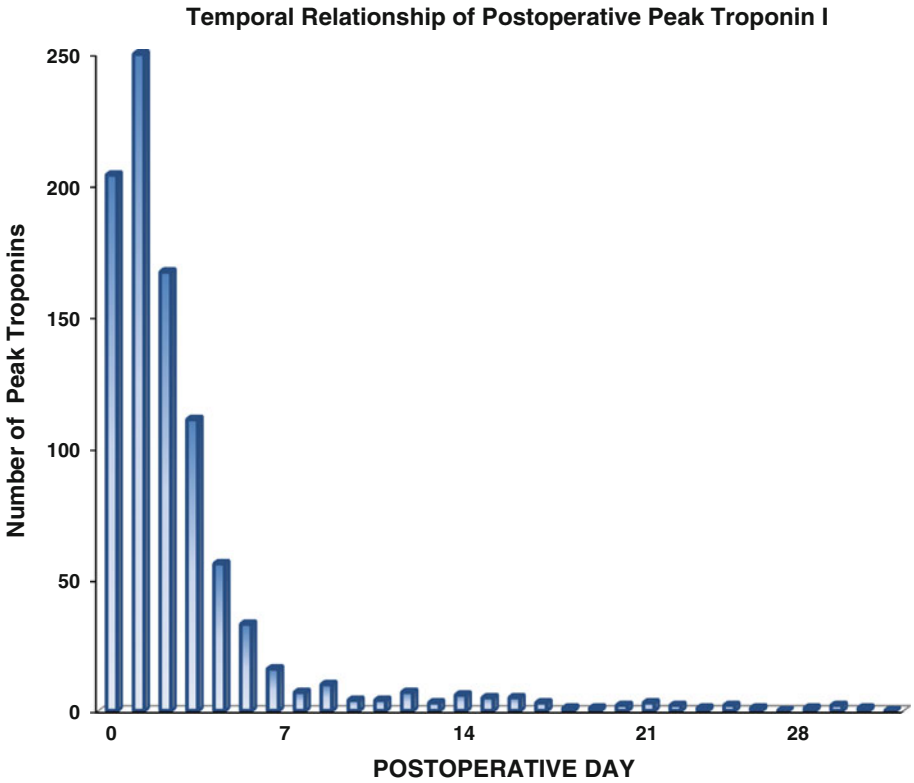

Fig. 1 Temporal relationship of postoperative peak troponin The most frequent peak elevations are seen on postoperative day 1, and they are slightly higher than the elevations seen on the day of surgery (day 0). Seventy percent of the elevations are seen within the first three postoperative days

being predominately clinically silent,[9] rendering detection of myocardial injury on clinical grounds "hit and miss". Thus, our results suggest that scheduled troponin measurements are imperative for a screening protocol.

The VISION study was published during the review process.[22] This multi-centred prospective cohort of 15,133 moderate to high-risk non-cardiac surgical patients also found that a positive troponin T assay improved the prediction for 30-day mortality. Furthermore, and similar to the present study, a biologic gradient showed that higher troponin T elevations correspond with an incremental increase in the probability of mortality. Importantly, these two studies show the need for routine postoperative cardiac surveillance in patients at an elevated risk for mortality. However, both studies also indicated that measuring troponin in patients at low risk would have a low yield. When the VISION study includes troponin in the mortality prediction, (Table 2) the net reclassification of risk portrays the lowest risk strata as $< 1\%$ and includes 56% of their patient population. In this group, the VISION study found that 6.5% were reclassified to a higher risk stratum due to positive troponin assay results, and this accounted for an increased mortality rate of 0.2% (an increase in deaths at a rate of two per thousand patients). Our results show a similar very small increase in the accuracy of the prediction model in the 50% of patients at low baseline risk. In addition, the results of the present study showed that virtually all of these low-risk patients with troponin elevations survived to 30 days, further decreasing the utility of monitoring troponin in this risk stratum. Furthermore, there may be other limitations to testing in low-risk populations, including the incremental costs of testing. Previous studies,

Table 2 Mortality models

	Primary Model		Troponin Added	
	OR	95% CI	OR	95% CI
2003	Reference			
2004	0.90	0.58 to 1.4	0.91	0.61 to 1.3
2005	0.87	0.42 to 1.06	0.92	0.71 to 1.2
2006	0.84	0.55 to 1.3	0.86	0.67 to 1.1
2007	0.84	0.56 to 1.3	1.1	0.82 to 1.3
2008	0.81	0.64 to 1.0	0.85	0.65 to 1.1
2009	0.72	0.57 to 0.93	0.78	0.61 to 1.0
Age (per year)	1.03	1.02 to 1.04	1.03	1.02 to 1.04
Sex (male)	1.5	1.3 to −1.7	1.4	1.2 to 1.7
General	Reference			
Urology	0.29	0.20 to 0.45	0.32	0.47 to 0.89
Ear Nose & Throat	0.73	0.45 to 1.2	0.74	0.53 to 1.04
Gynecology	0.67	0.44 to 1.1	0.69	0.45 to 1.07
Plastic	0.34	0.19 to 0.62	0.39	0.21 to 0.71
Neurologic	1.8	1.5 to 2.3	2.0	1.6 to 2.5
Spinal	0.41	0.18 to 0.91	0.40	0.30 to 0.58
Orthopedic	0.37	0.21 to 0.66	0.47	0.37 to 0.62
Vascular	0.73	0.40 to 1.3	0.64	0.47 to 0.89
Thoracic	1.3	1.1 to 1.7	1.3	1.01 to 1.67
Emergent Procedure	4.6	3.9 to 5.3	4.5	3.8 to 5.2
Metastatic Disease	1.5	1.2 to 1.8	1.6	1.3 to 2.0
Diabetes with Complications	1.4	1.1 to 2.6	1.4	1.1 to 1.8
Renal Disease	2.5	1.6 to 3.8	1.7	1.3 to 2.2
Cerebral Vascular Disease	1.9	1.2 to 2.9	1.6	1.3 to 2.0
Peripheral Vascular Disease	2.3	1.3 to 4.1	1.5	1.1 to 2.1
Congestive Heart Disease	2.6	2.0 to 3.4	2.0	1.6 to 2.7
Hepatic Disease	1.9	1.4 to 2.6	2.0	1.5 to 2.8
Anemia (WHO)	1.2	1.1 to 1.4	1.3	1.1 to 1.6
Nadir Hemoglobin > 90	2.4	2.1 to 2.9	2.1	1.8 to 2.5
Transfusion	3.2	2.1 to 2.9	2.0	1.7 to 2.4
Renin-Angiotensin Inhibition	0.50	0.40 to 0.61	0.50	0.40 to 0.60
Statins	0.56	0.46 to 0.69	0.52	0.42 to 0.64
Troponin (>0.7)		NA	6.5	5.4 to 7.9
	C-statistic = 0.902		C-statistic = 0.930	

OR = odds ratio; CI = confidence interval; WHO = World Health Organization

although in preoperative patients, suggest that cardiac testing in a low-risk population may actually have increased morbidity.[23-25]

The derivation of a postoperative cardiac screening algorithm should also consider that commercially available postoperative electrocardiogram (ECG) monitoring lacks the necessary sensitivity owing to the preexisting ST-T wave changes, both left and right bundle branch blocks, and atrial fibrillation, abnormalities that pre-exist in > 30% of moderate-risk surgical populations.[26]

Perioperative medications and electrolyte imbalances also interfere with interpretation of the ST segments. Moreover, the biologic gradient shows that small rises, which have previously gone unattended, are associated with doubling the mortality rate. These small elevations likely constitute epiphenomena, but they are associated with death and thus are an indication for some form of rescue therapy and follow-up. Still higher troponin values were associated with a sevenfold increase in mortality and may dictate the need for urgent cardiac interventions. Finally, this investigation confirms previous findings[9,10] that the bulk of myocardial injury occurs within the first 72 postoperative hours, limiting the need for longer-term biomarker surveillance.

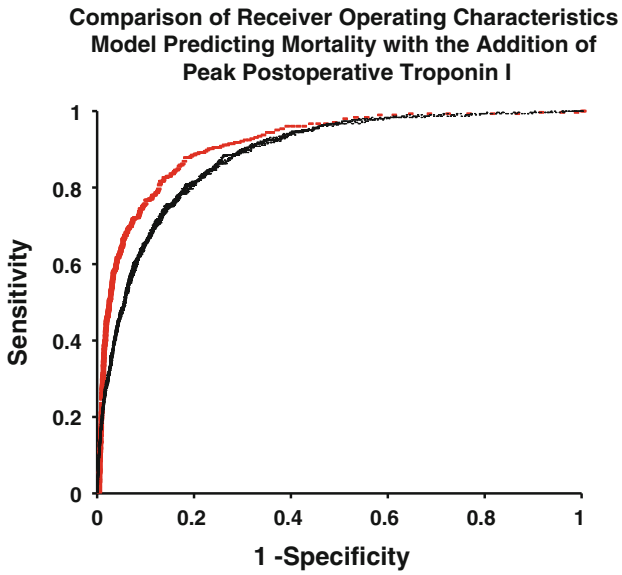

Fig. 2 Receiver operating characteristic of the postoperative mortality model The solid dark line represents the primary model derived without using elevated troponin; C-statistic = 0.902. The red line represents the secondary model where peak troponin, as a dichotomous variable defined as a level > 0.7 $\mu g \cdot L^{-1}$, was added to the model; C-statistic = 0.930

This study has numerous limitations. It is a retrospective analysis and unknown potential confounders, such as the reason to measure troponin, cannot be quantified. The clinical decision to measure troponin, irrespective of the result, is associated with a fourfold increase in death. Despite this limitation, we have shown that per protocol troponin is associated with an increase in the detection of injury, and thus our current practice is underestimating a critically important clinical event. We suggest caution when interpreting our "detection bias" since troponin measurement was not based on random allocation; the per protocol measurements occurred because vascular patients have typically been considered at the highest cardiac risk,[27,28] and we cannot exclude the possibility of selection bias. In our view, selection bias is unlikely because vascular patients in our hospital have the same mortality risk as the entire surgical population. Also, risk-adjusted mortality includes major components of the Revised Cardiac Risk Index (e.g., diabetes, congestive heart failure, cerebral vascular disease, and renal failure), which is both accurate and generalizable in elective surgery.[29]

Further, we cannot comment on the etiology of the troponin elevations as troponin release is also associated with increased creatinine levels.[30,31] While these are important considerations, in our opinion, they do not explain our results. First, creatinine levels were elevated in < 10% of the patients. Second, troponin remained associated with death in all patients with an elevated creatinine level (analysis not shown). Sepsis is similarly associated with release of troponin.[32] Again, we consider this unlikely since the main association between troponin and mortality is retained in elective surgery where the measurement is taken in the first 48 hr after surgery, a situation where the overwhelming presence of sepsis is rare.

In conclusion, a detectable postoperative troponin level showed an independent association with mortality and improved the multivariable prediction of in-hospital 30-day mortality. This investigation confirms and quantifies a detection bias that is an impediment to the effective surveillance of POMI and secondarily limits our ability to rescue patients without delay and to treat patients in the

Table 3 Pre-test and post-test probability (troponin elevation increases probability of mortality)

	Risk Class 1 (<.0.2%) n = 13,976	Risk Class 2 (0.2-0.6%) n = 15,172	Risk Class 3 (0.6-1.25%) n = 8,266	Risk Class 4 (1.25-3.75%) n = 7,640	Risk Class 5 (>3.75%) n = 6,647
Troponin measured, n (%)	948 (6.8%)	1,764 (11.6%)	1,656 (20%)	2,599 (34%)	3,414 (36.2%)
Troponin elevations, % (SD) (as percent of # measured)	71 (7.5)	215 (12.2)	244 (14.7)	569 (21.8)	1,236 (18.6)
All-cause Mortality, n (%)	3 (0.021%)	34 (0.22%)	54 (0.7%)	189 (2.5%)	794 (11.9%)
Cardiac Mortality*, n (%) (as a percent of ACM)	1 (33%)	12 (34%)	11 (20.4%)	80 (42.3%)	353 (59.9%)
Cardiac Rescue Rate**	99%	94.4%	94.4%	86%	71.5%
Likelihood Ratio* (95% CI)	6.7 (1.66 to 27.5)	5.4 (3.76 to 7.84)	3.01 (1.97 to 4.60)	2.83 (2.40 to 3.34)	1.76 (1.61 to 1.92)
Post-test Probability (of a positive troponin)***	0.14%	1.12%	2.1%	7.1%	20.3%

CI = confidence interval; SD = standard deviation; *Cardiac mortality is expressed as a percentage of the ALL CAUSE MORTALITY (ACM)

** Cardiac Rescue Rate is defined as the percentage of patients with a troponin rise (>0.02 $mg \cdot mL^{-1}$ or above the detection limit) who were discharged from hospital alive / all patients with a troponin elevation

*** Post-test Probability is the product of All Cause Mortality and the likelihood ratio of a positive test

Table 4 Effect of troponin measurement by surgical type

	ALL $n = 51,701$	General $n = 9,574$	ENT $n = 5,031$	Gyn $n = 3,378$	Plastics $n = 2,545$	Neuro $n = 6,467$	Ortho $n = 8,839$	Spinal $n = 3,518$	Thoracic $n = 4,159$	Urology $n = 5,775$	Vascular $n = 2,420$
Troponin ordered	10,534 (20.4)	2,220 (23.1)	503 (10)	363 (10.7)	145 (5.7)	1,537 (23.7)	1,449 (16.4)	767 (21.8)	676 (19.1)	551 (9.5)	2,158 (89.1)
Charlson (2 or more)	9,903 (19.2)	2,255 (23.6)	1,132 (22.5)	1,032 (30.5)	140 (5.5)	1,272 (19.7)	687 (7.8)	407 (11.5)	1,145 (27.5)	764 (13.2)	1,069 (44.2)
Myocardial Infarcts	2,055 (4.0)	451 (4.7)	83 (1.6)	55 (1,6)	24 (0.9)	320 (4.9)	291 (3.7)	92 (2.9)	237 (5.7)	70 (1.2)	229 (13.9)
Mortality (cardiac)	427 (0.8)	130 (1.4)	19 (0.4)	8 (0.3)	4 (0.1)	95 (1.5)	47 (0.6)	11 (0.3)	36 (0.9)	6 (0.1)	52 (2.4)
Mortality (all cause)	1,074 (2.1)	282 (2.9)	45 (0.8)	27 (0.8)	10 (0.4)	246 (3.8)	102 (1.2)	30 (0.8)	109 (2.6)	14 (0.2)	128 (5.2)
Likelihood ratio * (95% CI)	3.0 (2.8 to 3.2)	3.4 (2,9 to 4.0)	4.4 (3.0 to 6.3)	3.7 (2.1 to 6.5)	2.7 (1.1 to 6.4)	2.2 (1.8 to 2.7)	2.63 (2.1 to 3.3)	3.3 (2.0 to 5.6)	1.9 (1.5 to 2.5)	3.6 (1.9 to 6.8)	3.2 (2.7 to 3.8)

*Likelihood Ratio is calculated on the basis of mortality only in patients in whom a troponin was ordered

Numbers in brackets denote the percent of the population unless otherwise specified

Cardiac mortality is seen in patients with a documented rise in troponin

Mortality is defined as in-hospital mortality within 30 days of the index surgery

ENT = ear, nose, and throat; CI = confidence interval

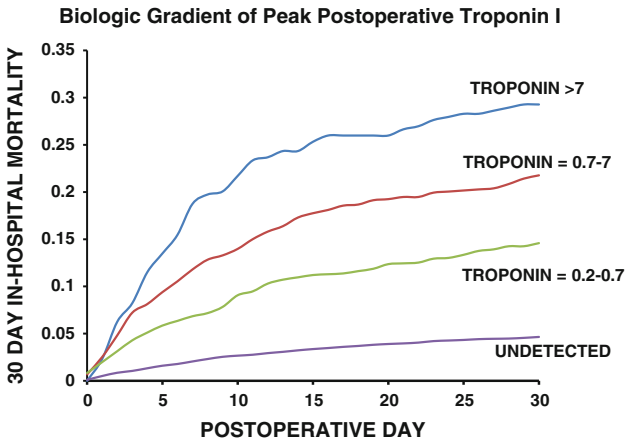

Fig. 3 Biologic gradient of peak postoperative troponin This illustration shows the risk-adjusted comparison of the four levels of troponin and mortality. The bottom line represents the patients in whom troponin was undetectable. The green line represents patients with detected troponin levels of 0.07-0.70 $\mu g \cdot L^{-1}$ compared with the baseline odds ratio of mortality at 30 days (OR 2.6; 95% CI 2.1 to 3.3). The red line represents patients with a troponin levels of 0.7-7.0 $\mu g \cdot L^{-1}$ compared with baseline (OR 4.6; 95% CI 3.7 to 5.6). The top blue line represents peak troponins > 7.0 $\mu g \cdot L^{-1}$ (OR 7.8; 95% CI 5.7 to 10.7). All odds ratios are for mortality at 30 days and compared with baseline. OR = odds ratio; CI = confidence interval

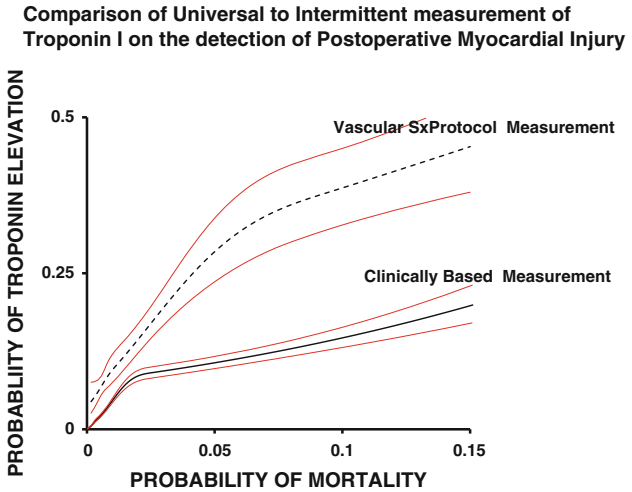

Fig. 4 Comparison of universal to intermittent troponin measurement Troponin measured as per protocol in vascular patients is compared with troponin measured in response to a clinical indication. The curves were constructed using restricted cubic splines with simultaneous 95% confidence intervals. The probability of finding an elevated troponin as seen along the y-axis is expressed as a function of the probability of 30-day in-hospital mortality. For the probabilities of mortality of 0-15%, which comprises 95% of the study population, routine measurement of postoperative troponin increased the chance of detecting myocardial injury from 12.0 (2.3)% to 31.3 (2.1)%. *Note that the risk of cardiac death is the same in both groups*

long term. There is an obvious need for further investigation and an urgent need to rethink the way we identify and treat POMI.

The investigation is supported in part by the Research and Innovation Funds of the University Health Network Department of Anesthesia and Pain Management. Dr. Beattie is supported by the R. Fraser Elliot Chair in Cardiac Anesthesia Research. Drs Beattie, Karkouti, and

Wijeysundera receive funding support from the University Department of Anesthesia Merit Awards.

Competing interests The Department of Anesthesia Research and Innovation Fund has received donations from Abbott Corp, BMS, Baxter, Bayer, Fresenius Kabi, and GE Healthcare. None of these companies has participated in any aspect of this report.

References

1. *Fleisher LA*, *Beckman JA*, *Brown KA*, *et al*. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) Developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. J Am Coll Cardiol 2007; 50: 1707-32.
2. *Weiser TG*, *Regenbogen SE*, *Thompson KD*, *et al*. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet 2008; 372: 139-44.
3. *Devereaux PJ*, *Goldman L*, *Cook DJ*, *Gilbert K*, *Leslie K*, *Guyatt GH*. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ 2005; 173: 627-34.
4. *Regenbogen SE*, *Lancaster RT*, *Lipsitz SR*, *Greenberg CC*, *Hutter MM*, *Gawande AA*. Does the Surgical Apgar Score measure intraoperative performance? Ann Surg 2008; 248: 320-8.
5. *Mangano DT*, *Layug EL*, *Wallace A*, *Tateo I*. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996; 335: 1713-20.
6. *Poldermans D*, *Boersma E*, *Bax JJ*, *et al*. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999; 341: 1789-94.
7. *POISE Study Group*, *Devereaux PJ*, *Yang H*, *Yusuf S*, *et al*. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008; 371: 1839-47.
8. *Ghaferi AA*, *Birkmeyer JD*, *Dimick JB*. Variation in hospital mortality associated with inpatient surgery. N Engl J Med 2009; 361: 1368-75.
9. *Devereaux PJ*, *Xavier D*, *Pogue J*, *et al*. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med 2011; 154: 523-8.
10. *Levy M*, *Heels-Ansdell D*, *Hiralal R*, *et al*. Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: a systematic review and meta-analysis. Anesthesiology 2011; 114: 796-806.
11. *Schein OD*, *Katz J*, *Bass EB*, *et al*. The value of routine preoperative medical testing before cataract surgery. Study of Medical Testing for Cataract Surgery. N Engl J Med 2000; 342: 168-75.
12. *Grewal K*, *Wijeysundera DN*, *Carroll J*, *Tait G*, *Beattie WS*. Gender differences in mortality following non-cardiovascular surgery: an observational study. Can J Anesth 2012; 59: 255-62.
13. *Beattie WS*, *Wijeysundera DN*, *Karkouti K*, *et al*. Acute surgical anemia influences the cardioprotective effects of beta-blockade: a single-center, propensity-matched cohort study. Anesthesiology 2010; 112: 25-33.
14. *Beattie WS*, *Karkouti K*, *Wijeysundera DN*, *Tait G*. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. Anesthesiology 2009; 110: 574-81.
15. *Karkouti K*, *Wijeysundera DN*, *Yau TM*, *et al*. Acute kidney injury after cardiac surgery: focus on modifiable risk factors. Circulation 2009; 119: 495-502.
16. *Quan H*, *Parsons GA*, *Ghali WA*. Validity of procedure codes in International Classification of Diseases, 9th revision, clinical modification administrative data. Med Care 2004; 42: 801-9.
17. *Beattie WS*, *Wijeysundera DN*. Statins and the "healthy user bias" in cardiac surgery. Anesth Analg 2010; 111: 261-3.
18. *Beattie WS*. How should we play our hand when holding an ACE? Can J Anesth 2010; 57: 720-4.
19. *Wijeysundera DN*, *Beattie WS*. Calcium channel blockers for reducing cardiac morbidity after noncardiac surgery: a meta-analysis. Anesth Analg 2003; 97: 634-41.
20. *Alpert JS*, *Thygesen K*, *Jaffe A*, *White HD*. The universal definition of myocardial infarction: a consensus document: ischaemic heart disease. Heart 2008; 94: 1335-41.
21. *Thygesen K*, *Mair J*, *Katus H*. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J 2010; 31: 2197-204.
22. *Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators; Devereaux PJ, Chan MT, Alonso-Coello P, et al.* Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2012; 307: 2295-304.
23. *Wijeysundera DN*, *Beattie WS*, *Karkouti K*, *Neuman MD*, *Austin PC*, *Laupacis A*. Association of echocardiography before major elective non-cardiac surgery with postoperative survival and length of hospital stay: population based cohort study. BMJ 2011; 342: d3695.
24. *Wijeysundera DN*, *Beattie WS*, *Austin PC*, *Hux JE*, *Laupacis A*. Noninvasive cardiac stress testing before elective major non-cardiac surgery: population based cohort study. BMJ 2010; 340: b5526.
25. *Wijeysundera DN*, *Austin PC*, *Beattie WS*, *Hux JE*, *Laupacis A*. Outcomes and processes of care related to preoperative medical consultation. Arch Intern Med 2010; 170: 1365-74.
26. *van Klei WA*, *Bryson GL*, *Yang H*, *Kalkman CJ*, *Wells GA*, *Beattie WS*. The value of routine preoperative electrocardiography in predicting myocardial infarction after noncardiac surgery. Ann Surg 2007; 246: 165-70.
27. *Landesberg G*, *Mosseri M*, *Shatz V*, *et al*. Cardiac troponin after major vascular surgery: the role of perioperative ischemia, preoperative thallium scanning, and coronary revascularization. J Am Coll Cardiol 2004; 44: 569-75.
28. *Biccard BM*, *Sear JW*, *Foex P*. Acute peri-operative beta blockade in intermediate-risk patients. Anaesthesia 2006; 61: 924-31.
29. *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: 26-35.
30. *Ishii J*, *Nomura M*, *Okuma T*, *et al*. Risk stratification using serum concentrations of cardiac troponin T in patients with end-stage renal disease on chronic maintenance dialysis. Clin Chim Acta 2001; 312: 69-79.
31. *Apple FS*, *Murakami MM*, *Pearce LA*, *Herzog CA*. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. Circulation 2002; 106: 2941-5.
32. *Roongsritong C*, *Warraich I*, *Bradley C*. Common causes of troponin elevations in the absence of acute myocardial infarction: incidence and clinical significance. Chest 2004; 125: 1877-84.