Prognostic Value of Troponin and Creatine Kinase Muscle and Brain Isoenzyme Measurement after Noncardiac Surgery

A Systematic Review and Meta-analysis

Michael Levy, M.D., M.P.H.,* Diane Heels-Ansdell, M.Sc.,† Rajesh Hiralal, M.D.,‡ Mohit Bhandari, M.D., M.Sc.,§ Gordon Guyatt, M.D., M.Sc.,‖ Salim Yusuf, M.B.B.S., D.Phil.,# Deborah Cook, M.D., M.Sc.,** Juan Carlos Villar, M.D., Ph.D.,†† Matthew McQueen, M.B., Ch.B., Ph.D.,‡‡ Edward McFalls, M.D., Ph.D.,§§ Miodrag Filipovic, M.D.,‖‖ Holger Schünemann, M.D., Ph.D.,## John Sear, M.B.B.S., Ph.D.,*** Pierre Foex, M.D., Ph.D.,††† Wendy Lim, M.D., M.Sc.,‡‡‡ Giora Landesberg, M.D., D.Sc.,§§§ Gilles Godet, M.D.,‖‖‖ Don Poldermans, M.D., Ph.D.,### Francesca Bursi, M.D., M.Sc.,**** Miklos D. Kertai, M.D., Ph.D.,†††† Neera Bhatnagar, M.L.I.S.,‡‡‡‡ P. J. Devereaux, M.D., Ph.D.§§§§

ABSTRACT

Background: There is uncertainty regarding the prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurements after noncardiac surgery.

Methods: The current study undertook a systematic review and meta-analysis. The study used six search strategies and included noncardiac surgery studies that provided data from a multivariable analysis assessing whether a postoperative troponin or creatine kinase muscle and brain isoenzyme measurement was an independent predictor of mortality or a major cardiovascular event. Independent investigators determined study eligibility and abstracted data in duplicate.

Results: Fourteen studies, enrolling 3,318 patients and 459 deaths, demonstrated that an increased troponin measurement after surgery was an independent predictor of mortality (odds ratio [OR] 3.4, 95% confidence interval [CI] 2.2–5.2), but there was substantial heterogeneity (I^2 = 56%). The

◆ This article is accompanied by an Editorial View. Please see: Muehlschlegel JD: If a troponin falls in a forest but no one measures it, does it really matter? ANESTHESIOLOGY 2011; 114:732–3.

* Clinical Scholar, Department of Medicine, McMaster University, Hamilton, Ontario, Canada; † Statistical Analyst, Department of Clinical Epidemiology and Biostatistics, McMaster University; ‡ Clinical Scholar, Department of Medicine, McMaster University; § Associate Professor, Departments of Surgery and Clinical Epidemiology and Biostatistics, McMaster University; ‖ Professor, Departments of Medicine and Clinical Epidemiology and Biostatistics, McMaster University; # Professor, Departments of Medicine and Clinical Epidemiology and Biostatistics, McMaster University, and Population Health Research Institute, Hamilton Health Sciences, McMaster University; ** Professor, Chair, Department of Medicine and Professor, Department of Clinical Epidemiology and Biostatistics, McMaster University; †† Professor, Grupo de Cardiología Preventiva, Universidad Autónoma de Bucaramanga and Department of Research, Fundación Cardioinfantil–Instituto de Cardiología, Bogotá, Colombia; ‡‡ Professor, Department of Pathology and Molecular Medicine, McMaster University and Hamilton Regional Laboratory Medicine Program, Hamilton Health Sciences and St. Joseph's Healthcare, Hamilton, Ontario, Canada; §§ Professor, Department of Medicine, University of Minnesota, Veterans Affairs Medical Center, Minneapolis, Minnesota; ‖‖ Consultant and Vice Head, Associate Professor, Department of Anaesthesia, University of Basel Hospital, Basel, Switzerland, and Institute of Anaesthesiology, Kantonsspital Steet Gallen, Steet Gallen, Switzerland; ## Chair, Professor, Departments of Medicine and Clinical Epidemiology and Biostatistics, McMaster University; *** Professor, Nuffield Department of Anaesthetics, University of Oxford, Oxford, United Kingdom; ††† Professor, Nuffield Department of Anaesthetics, University of Oxford; ‡‡‡ Assistant Professor, Department of Medicine, McMaster University; §§§ Associate Professor, Department of Anesthesiology and Critical Care Medicine, Hebrew University–Hadassah Medical Center, Jerusalem, Israel; ‖‖‖ Associate Professor, Departments of Anesthesiology and Intensive Care, Pontchaillou Hospital, Rennes, France; ### Professor, Department of Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands; **** Cardiology Consultant, Cardiology Institute, Policlinico University Hospital, Modena, Italy; †††† Assistant Professor, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina; ‡‡‡‡ Medical Librarian, Department of Library Sciences, McMaster University; §§§§ Associate Professor, Department of Medicines and Clinical Epidemiology and Biostatistics, McMaster University, and Population Health Research Institute, Hamilton Health Sciences, McMaster University.

Received from the Department of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, Ontario, Canada. Submitted for publication June 25, 2010. Accepted for publication November 4, 2010. This systematic review was funded through a Regional Medical Association grant (Hamilton, Ontario, Canada). Drs. Bhandari and Cook are supported by a Canadian Research Chair (Hamilton, Ontario, Canada). Dr. Yusuf is supported by a Heart and Stroke Foundation Endowed Chair in Cardiovascular Research (Hamilton, Ontario, Canada). Dr. Schünemann is supported by an endowed chair (Hamilton, Ontario, Canada). Dr. Devereaux is supported by a Canadian Institutes of Health Research New Investigator Award (Hamilton, Ontario, Canada). Dr. Devereaux has received a grant-in-kind from Roche Diagnostics (Mannheim, Germany) to evaluate troponin T among patients undergoing noncardiac surgery. Dr. McQueen has received grants-in-kind from Roche Diagnostics for evaluating diabetes, cardiac, and renal biomarkers in several clinical studies.

Address correspondence to Dr. Devereaux: McMaster University Health Sciences Center, Room 2C8, 1200 Main Street West, Hamilton, Ontario, Canada, L8N 3Z5. philipj@mcmaster.ca. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

 Anesthesiology 2011; 114: 796–806

What We Already Know about This Topic

- Increased troponin or creatinine kinase, muscle and brain isoenzyme (CK-MB) after surgery may independently predict a patient's intermediate or long-term risk of death or a major cardiovascular event

What This Article Tells Us That Is New

- In this systematic review, increased troponin and, to a lesser extent, CK-MB, after surgery independently predicted mortality, particularly within the first year
- These findings might be applied clinically to identify and manage patients with high risk for postoperative cardiac mortality

independent prognostic capabilities of an increased troponin value after surgery in the 10 studies that assessed intermediate-term (≤ 12 months) mortality was an OR = 6.7 (95% CI 4.1–10.9, I^2 = 0%) and in the 4 studies that assessed long-term (more than 12 months) mortality was an OR = 1.8 (95% CI 1.4–2.3, I^2 = 0%; $P < 0.001$ for test of interaction). Four studies, including 1,165 patients and 202 deaths, demonstrated an independent association between an increased creatine kinase muscle and brain isoenzyme measurement after surgery and mortality (OR 2.5, 95% CI 1.5–4.0, I^2 = 4%).

Conclusions: An increased troponin measurement after surgery is an independent predictor of mortality, particularly within the first year; limited data suggest an increased creatine kinase muscle and brain isoenzyme measurement also predicts subsequent mortality. Monitoring troponin measurements after noncardiac surgery may allow physicians to better risk stratify and manage their patients.

NONCARDIAC surgical interventions offer the ability to cure disease and improve patients' quality of life. The number of patients undergoing noncardiac surgery is growing. Worldwide estimates suggest 200 million adults annually undergo major noncardiac surgery.[1,2] Despite the procedural benefits, several million of these patients suffer a major cardiovascular complication (*i.e.*, cardiovascular death, nonfatal myocardial infarction, or nonfatal cardiac arrest) during the perioperative period (≤ 30 days after surgery),[3] and many more patients die or suffer a major cardiovascular event in the subsequent 1–2 yr after surgery.[4,5]

Recent studies suggest that a troponin or creatine kinase muscle and brain isoenzyme (CK-MB) measurement after surgery may independently predict a patient's intermediate- (≤ 12 months) or long-term (more than 12 months) risk of death or a major cardiovascular event.[6,7] Based on these findings, some investigators have advocated monitoring perioperative troponin measurements in patients undergoing noncardiac surgery to identify patients at risk.[7,8] A recommendation to monitor one of these measurements after surgery requires an accurate understanding of the prognostic value of a perioperative cardiac enzyme or biomarker through a systematic, unbiased, comprehensive assessment of the evidence. We therefore conducted a systematic review and meta-analysis to address the following question: In patients undergoing noncardiac surgery, is a troponin or CK-MB measurement after surgery an independent predictor of death or a major cardiovascular event in the years after surgery?

Materials and Methods

Study Eligibility

We included all noncardiac surgery studies that fulfilled the following criteria: Patients had at least one troponin or CK-MB measurement after surgery; the study had one or more patients who suffered a major cardiovascular event or died more than 30 days after surgery; and the study assessed the prognostic value of postoperative troponin or CK-MB measurement through multivariable analysis or provided us with the data to undertake the multivariable analysis. There were no language or publication restrictions. We excluded studies that did not evaluate adults or evaluated patients having cardiac surgery.

Study Identification

Strategies to identify studies included the following: searching six bibliographic databases (appendix 1 reports databases and search terms); searching our own files; consulting with experts; reviewing reference lists from articles fulfilling our eligibility criteria; searching PubMed using the "related articles" feature for studies fulfilling our eligibility criteria; and searching Web of Science for cited references of key publications.

Eligibility Assessment

Teams of two screeners independently screened the title and abstract of each citation identified in our search. These screeners selected any citation that they suspected had any possibility of fulfilling our eligibility criteria to undergo full review. If either of the two screeners identified a citation as potentially relevant, we obtained the full text article for detailed review.

Teams of two reviewers independently determined the eligibility of all studies that underwent full text evaluation. Disagreements were resolved through discussion between the two reviewers; when this did not resolve differences, a third reviewer made a final decision on the study's eligibility.

Data Collection and Quality Assessment

We abstracted the following data from all eligible studies: study period, type of surgery, number of patients, length of follow-up, measurement assessed (*i.e.*, troponin I or T or CK-MB), assay manufacturer, measurement threshold, frequency of measurements, proportion of patients with increased cardiac biomarker or enzyme, and number of deaths or major cardiovascular events. We abstracted the following

study quality criteria: completeness and method of patient follow-up (*e.g.*, direct patient contact), blinding of outcome adjudicators to cardiac biomarker or enzyme results, and factors adjusted for in multivariable analysis.

Two individuals independently abstracted data from all studies that fulfilled our eligibility criteria, and we resolved disagreements using the same consensus process discussed above. We contacted the authors of all eligible studies to obtain missing data or confirm the accuracy of the abstracted data.

Statistical Analysis

A κ statistic was calculated to quantify chance-corrected interobserver agreement for study eligibility decisions. We determined raw agreement for abstracted variables.

Ten of the studies included in our meta-analyses did not directly provide an adjusted odds ratio (OR).[6,7,9–16] Two of these studies did not report a multivariable analysis, but the authors provided us with the individual patient data and we conducted our own multivariable analyses to obtain adjusted ORs.[9,10] In these multivariable logistic regression analyses, we included coronary artery disease as the adjustment variable.

Eight of these 10 studies performed time-to-event analyses and reported hazard ratios (HRs) from Cox proportional hazards models.[6,7,11–16] One of these studies also performed a logistic regression analysis, but did not report the numerical results.[16] The authors of this study provided us with the ORs from this analysis. In the remaining seven studies that reported a HR, we computed the relative risk (RR) at 1 yr, using the following formula:

$$RR = \frac{1 - e^{HR \cdot \ln(1 - P_0)}}{P_0},$$

where HR is the hazard ratio at 1 yr and P_0 is the proportion of patients without an abnormal troponin level who had died within 1 yr of surgery. When contacted, the authors provided us with crude mortality rates at 1 yr. We used this to estimate P_0. Once we obtained the RR, we were able to calculate the OR at 1 yr, based on the following formula by Zhang and Yu[17]:

$$OR = \frac{RR \cdot (1 - P_0)}{1 - RR \cdot P_0},$$

One study did report a multivariable OR for troponin, but did not report one for CK-MB.[18] Upon contacting the authors, they provided us with the CK-MB multivariable OR.

We pooled ORs using the DerSimonian and Laird random-effects model.[19] An I^2 value was calculated to assess heterogeneity across study results. An I^2 value more than 25% was considered to represent substantial heterogeneity.[20] Our *a priori* hypotheses to explain substantial heterogeneity across study results were: stronger prediction in intermediate- *versus* long-term follow-up, stronger prediction in troponin T *versus* I assay, stronger prediction in early troponin measurement *versus* late troponin measurement, stronger association in vascular *versus* other types of surgery, stronger association in retrospective *versus* prospective studies, stronger association in studies without *versus* with blinding of outcome adjudicators, and stronger association without *versus* with 100% completeness of follow-up. We tested for interactions by performing a z-test on the natural logarithms of the ORs across subgroups in an attempt to explain heterogeneity. The test of interaction was statistically significant for two of our *a priori* hypotheses, and we therefore performed a metaregression analysis where we included both *a priori* hypotheses in one model to simultaneously test these two possible sources of heterogeneity. Analyses were performed using S-PLUS 8.0 (TIBCO Software, Inc., Palo Alto, CA) and Stata 8.2 (StataCorp LP, College Station, TX).

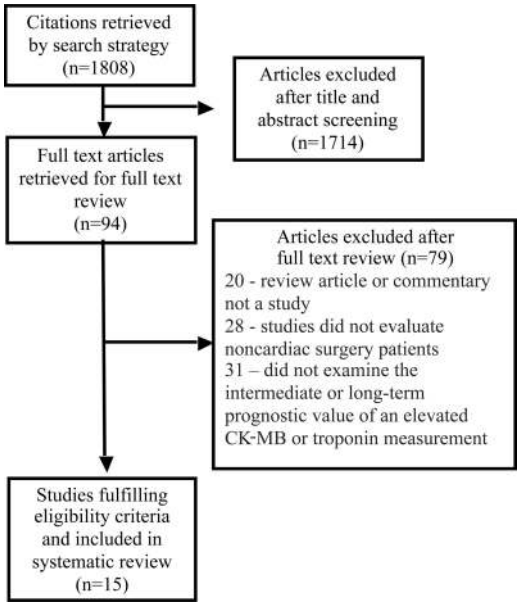

Fig. 1. Study selection process. CK-MB = creatine kinase muscle and brain isoenzyme.

Results

Our search strategy identified 1,808 citations. After an initial screening of titles and abstracts, 1,714 studies were eliminated. Of 94 studies selected for full text evaluation, 15 studies fulfilled our eligibility criteria and are included in this systematic review (fig. 1).[6–16,18,21–23]

Interobserver agreement for study eligibility was excellent (κ, 0.86). Raw agreement across individual abstracted variables ranged from 75–100%.

Characteristics of Included Studies

Table 1 presents the characteristics of the 15 included studies that enrolled 4,040 patients (minimum and maximum sample size 88 and 722 patients, respectively). The majority of studies were prospective cohort studies or clinical trials. The duration of follow-up varied from 3 to 48 months. Twelve studies included patients undergoing vascular surgery,[6–13,15,16,18,21] seven studies included pa-

Table 1. Characteristics of Included Studies

Study	Study Period*	Type of Study	No. of Patients†	Type(s) of Surgery	Length of Follow-up
Kim[8]	June 97–Sept 99	Prospective cohort study	226	Vascular, amputation	6 months
Filipovic[18]	Jan 98–Feb 01	Prospective cohort	173	General, orthopedic, thoracic, vascular	12 months
Landesberg[6]	July 97–June 01	Prospective cohort	447	Vascular	32 months (mean)
Kertai[11]	May 96–Dec 00	Retrospective cohort	393	Vascular	48 months (median)
Oscarsson[7]	Nov 98–Mar 00	Prospective cohort	161	General, gynecologic, orthopedic, urologic, vascular	12 months
Lopez-Jiminez[21]	Dec 91–June 94	Prospective cohort	722	General, gynecologic neurologic, orthopedic, thoracic, urologic, vascular	6 months
Godet[9]	Sept 95–Dec 98	Prospective cohort	315	Vascular	12 months
Higham[10]	July 96–Feb 01	Prospective cohort	154	Orthopedic, vascular	12 months
Bursi[12]	Sept 00–July 02	Prospective cohort	373	Vascular	18.9 months (mean)
Blecha[13]	June 00–Dec 03	Retrospective cohort	190	Vascular	36 months (median)
Ausset[14]	Oct 03–Oct 04	Prospective cohort	88	Orthopedic	12 months
McFalls[15]	Mar 99–Feb 03	Randomized, controlled trial	377	Vascular	30 months (median)
Chong[22]	April 06–Dec 06	Prospective cohort	102	Emergency orthopedic	12 months
Oscarrson[23]	April 07–April 08	Prospective cohort	186	Urgent/emergent surgery (abdominal, gynecologic, hand/reconstructive, neurosurgery, opthalmologic, orthopedic, spinal, urologic)	3 months
Bolliger[16]	April 02–Feb 05	Randomized, controlled trial	133	Vascular	12 months

* Time across which included patients underwent surgery. † These numbers reflect the patients that were used in the multivariable analyses.

tients undergoing orthopedic surgery,[7,10,14,18,21–23] four studies included patients undergoing general or abdominal surgery,[7,18,21,23] and three studies included patients undergoing gynecologic and urologic surgery.[7,21,23]

Troponin and CK-MB Measurements

Table 2 presents information related to the troponin measurements, and table 3 presents information related to the CK-MB measurements. All studies evaluated the prognostic properties of troponin measurement after surgery (14 evaluated mortality,[6–16,18,22,23] and five evaluated major cardiovascular events[12,14,16,21,22]), whereas only four studies evaluated the prognostic properties of CK-MB measurement.[6,10,11,18] Ten studies evaluated troponin I exclusively,[8,9,12–16,18,22,23] three evaluated troponin T exclusively,[7,11,21] and two studies evaluated troponin I and T.[6,10] There was wide variation across studies in the threshold for an increased troponin and the timing and frequency of troponin measurements. An increased troponin measurement was observed in 8.4–52.9% of patients across studies, and an increased CK-MB was observed in 7.6–23.7% of patients across studies.

Study Quality

Table 4 reports study quality. Overall completeness of follow-up was high, and 12 studies achieved complete follow-up.[6,7,9–16,18,22] Eight studies blinded outcome adjudicators to the cardiac biomarker and enzyme values.[6–9,12,15,16,21] There was substantial variation across studies regarding which variables were adjusted for in the multivariable analyses.

Prognostic Capabilities of an Increased Postoperative Troponin Measurement

Figure 2 reports the meta-analysis of the 14 studies for which we were able to obtain an adjusted OR for a postoperative increased

Table 2. Troponin Measurements

Study	Troponin Type	Manufacturer	Troponin Threshold	Timing and Frequency of Troponin Measurement	Patients with Elevated Troponin n/N (%)	No. of Deaths
Kim[8]	I	Stratus (Dade)	> 1.5 ng/l	Immediately after surgery and postoperative days 1, 2, and 3	28/229* (12.2)	18
Filipovic[18]	I	AxSYM (Abbott)	> 0.2 μg/l	Before surgery, immediately after surgery, 8 h after surgery, and postoperative days 1, 2, 3, and 6	27/173 (15.6)	28
Landesberg[6]	I and/or T	Stratus II (Dade Behring) Elecsys 2010	Tn-I > 0.6 ng/ml, Tn-T > 0.03 ng/ml	Immediately after surgery and postoperative days 1, 2, and 3	107/447 (23.9)	82
Oscarsson[7]	T	Elecsys 2010 (Roche)	> 0.02 ng/ml	Postoperative days 5–7	53/546* (9.7)	22
Lopez-Jiminez[21]	T	TnT ES-300 (Boehringer Manheim)	> 0.1 ng/ml	Immediate after surgery, 8 PM after surgery, and postoperative days 2 and 3	92/772* (11.9)	14†
Godet[9]	I	Stratus (Dade)	> 0.54 ng/ml	Postoperative days 1, 2, and 3	49/315 (15.6)	5
Higham[10]	I and T	Beckman Access Immunoassay system Roche ES 300 Analyzer	> 0.1 μg/l	Before surgery and postoperative days 1–3	13/154 (8.4)	12
Bursi[12]	I	Stratus CS STAT (Dade Behring, Inc.)	> 0.1 ng/ml	Postoperative days 1, 2, and 3	85/391* (21.7)	40
Blecha[13]	I	Abbott ASYM assay	> 2.0 ng/ml	Immediately, 8 h, and 16 h after surgery	21/190 (11.1)	52
Ausset[14]	I	Ortho Vitros Eci, Ortho-Clinical Diagnostics kit	> 0.08 ng/ml	Postoperative days 1, 2, and 3	11/88 (12.5)	9
McFalls[15]	I	Dade Behring Dimension Analyzer	> 0.01 μg/l	First 4 postoperative days	100/377 (26.5)	33
Chong[22]	I	CTnI, Abbott Diagnostics	> 0.03 μg/l	Before surgery and postoperative days 1, 2, and 3	54/102 (52.9)	21
Oscarrson[23]	I	Stratus CS Acute care diagnostic system (Dade)	> 0.06 μg/l	Before surgery and 12 and 48 h after surgery	62/186 (33.3)	43
Bolliger[16]	I	Ax SYM cTnI Abbott	> 2 ng/ml	Before surgery, immediately after surgery, and postoperative days 1, 2, 3, and 7	19/133 (14.3)	14

* In some studies, there were more patients at the time of troponin measurement than were included in the multivariable analysis. The sample sizes in other tables reflect those used in the multivariable analyses. † Cardiac deaths.

n/N = number of patients with an elevated troponin/total number of patients included in study; TnT = troponin T; cTnI = cardiac troponin I.

troponin measurement to predict all-cause mortality. The 14 studies enrolled a total of 3,318 patients, among whom 459 died during follow-up. Ten of the 14 studies had statistically significant adjusted ORs, suggesting an association between increased troponin and mortality. The remaining four studies all showed nonsignificant ORs greater than 1.0. The meta-analysis of the 14 studies demonstrated that an increased troponin measurement after surgery was an independent predictor of mortality (OR 3.4, 95% CI, 2.2–5.2), but there was substantial heterogeneity in these results ($I^2 = 56\%$).

Table 5 reports the adjusted ORs for the studies that had at least one patient who suffered a major cardiovascular com-

Table 3. CK-MB Measurements

Study	Manufacturer	CK-MB Threshold	Timing and Frequency of CK-MB Measurement	Patients with Elevated CK-MB n/N (%)	No. of Deaths
Filipovic[18]	Abbott AxSYM	> 10.4 mcg/l	Postoperative days 1 or 2	20/173 (11.6)	28
Landesberg[6]	Vitros dry chemistry analyzer (J&J)	CK > 170 IU and a relative index > 5%	Immediately after surgery and postoperative days 1, 2, and 3	34/447 (7.6)	82
Kertai[11]	Roche/Hitachi 747 analyzer and Merck	24 IU/l or relative index > 6%	Postoperative days 2, 3, and 7 (or discharge)	31/393 (7.9)	80

CK = creatine kinase; CK-MB = creatine kinase muscle and brain isoenzyme; n/N = number of patients with an elevated CK-MB/total number of patients included in study; relative index = CK-MB/total CK.

plication more than 30 days after surgery and reported the results of an adjusted analysis determining the prognostic capabilities of a postoperative increased troponin measurement to predict a major cardiovascular event. The cardiac composite outcome varied across studies, but all five studies demonstrated that an increased troponin measurement after surgery was an independent predictor of a major cardiovascular event. Four of the studies included myocardial infarction in their composite outcome,[12,14,21,22] and three of these studies[12,14,22] used the European Society of Cardiology/American College of Cardiology definition of myocardial infarction.[24]

Prognostic Capabilities of an Increased Postoperative CK-MB Measurement

Figure 3 presents the meta-analysis of the four studies for which we were able to obtain an adjusted OR for a postoperative increased CK-MB measurement to predict all-cause mortality. The four studies enrolled a total of 1,165 patients, among whom 202 died during follow-up. The pooled meta-analysis of the four studies demonstrated that an increased CK-MB measurement after surgery was an independent predictor of mortality (OR 2.5, 95% CI, 1.5–4.0), and there was minimal heterogeneity observed ($I^2 = 4\%$).

Exploring Potential Explanations of Heterogeneity in the Troponin Meta-analysis

Two of our *a priori* hypotheses (type of surgery and length of follow-up) to explain heterogeneity demonstrated a statistically significant interaction ($P = 0.001$ and $P < 0.001$, respectively). We then undertook a metaregression analysis that included both of these subgroups, and length of follow-up stayed significant ($P = 0.01$), but type of surgery did not ($P = 0.72$). Figure 4 reports the adjusted OR for an increased postoperative troponin measurement to predict all-cause mortality, based on duration of follow-up. The 10 studies with a duration of follow-up ≤12 months demonstrated a pooled OR of 6.7 (95% CI, 4.1–10.9; $I^2 = 0\%$), whereas the four studies with a duration of follow-up more than 12 months demonstrated a pooled OR of 1.8 (95% CI, 1.4–2.3; $I^2 = 0\%$).

Discussion

Statement of Principal Findings

Our meta-analysis indicates that an increased postoperative troponin measurement is an independent predictor of mortality, particularly during the first year after surgery and therefore may help physicians to risk stratify their patients after noncardiac surgery. Although fewer studies evaluated the prognostic capabilities of an increased postoperative CK-MB measurement, this also appears to provide independent prognostic information.

Strengths and Weaknesses of Our Systematic Review

Strengths of our systematic review include: a comprehensive search; conducting eligibility decisions and data abstraction in duplicate with very good agreement; obtaining data from several authors to allow inclusion of their study in our meta-analysis; and we followed reporting standards for systematic reviews.[25]

Our systematic review has several limitations. All but two studies[6,10] were at substantial risk of developing unreliable models, as they included an excess of variables in their models relative to the number of events in each study. Simulation studies demonstrate that logistic models require 12–15 events per predictor to produce stable estimates.[26,27] Most studies were small and had few events; as a result, many of the established intermediate- and long-term predictors of death were not included in the models. The studies used various types, manufacturers, and generations of troponin assays and employed various thresholds to label a value as increased. We evaluated all-cause mortality as opposed to cardiovascular mortality. If an increased troponin value after surgery does not predict noncardiovascular mortality, our results would represent an underestimation of the association between an increased troponin measurement and cardiovascular mortality. It is, however, frequently complicated to accurately discern the cause of death after surgery, and we were limited to what the eligible studies evaluated (i.*e.*, all-cause mortality).

Table 4. Study Quality Characteristics

Study	Patients with Complete Follow-up n/N (%)	Blinded Outcome Assessment (Y/N)	Method of Patient Follow-up	Variables Adjusted for in Analyses
Kim[8]	226/229 (99)	Y	Direct patient follow-up and for patients with inaccurate phone numbers they searched the Social Security death index	Age, history of CHF, TAA repair, perioperative β-blocker (defined as morning of surgery, during surgery, and/or first 48 h after surgery)
Filipovic[18]	173/173 (100)	N	Telephone interview and hospital charts	LF/HF < 2 (low- to high-frequency power ratio: measure of heart rate variability), revised cardiac risk index
Landesberg[6]	447/447 (100)	Y	Administrative data	Age, type of vascular surgery, previous myocardial infarction, renal insufficiency
Kertai[11]	393/393 (100)	N	Administrative data and hospital records	ST segment changes, cardiac risk factors, chronic cardiac medications (ASA, BB), type of surgery
Oscarsson[7]	161/161 (100)	Y	Administrative data and chart review	BMI, ASA status, chronic BB use, chronic diuretic use, reoperation, tachycardia
Lopez-Jiminez[21]	722/772 (94)	Y	Telephone interview and administrative database	CK-MB, type of operation, age, gender, previous cardiac history, smoking history, use of aspirin or BB, diabetes
Godet[9]	315/315 (100)	Y	Direct patient follow-up	CAD
Higham[10]	154/154 (100)	N	Direct patient follow-up and patient chart review	CAD
Bursi[12]	190/190 (100)	Y	Direct patient follow-up, patient chart review, and administrative data	Age, CAD, renal failure
Blecha[13]	373/373 (100)	N	Administrative data, direct patient follow-up, and patient charts	Type of surgery, ECG change (postop), diabetes, CAD, age, preop cardiac catheter, preop PCI, preop CABG surgery, postop ischemic symptoms
Ausset[14]	88/88 (100)	N	Direct patient follow-up and patient charts	Age, ASA score, revised cardiac risk index
McFalls[15]	377/377 (100)	Y	Administrative data	Age, elevated creatinine, preop history of CHF, diabetes
Chong[22]	102/102 (100)	N	Telephone interview and patient charts	Premorbid ischemic heart disease, premorbid CHF, postop transfusion, postop cardiac event
Oscarrson[23]	186/211 (88)	N	Administrative data, telephone interview, and patient charts	Malignancy, perioperative inotropes, aspirin use
Bolliger[16]	133/133 (100)	Y	Administrative data, telephone interview, and patient charts	Age, gender, revised cardiac risk index

ASA = acetyl-salicylic acid; ASA score = American Society of Anesthesiologists scoring system; BB = β-blocker; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; CK-MP = creatine kinase muscle and brain; ECG = electrocardiography; LF/HF = low-frequency/high-frequency; n/N = number of patients with complete follow-up/total number of patients included in study; N = no; PCI = percutaneous coronary intervention; postop = postoperative; preop = preoperative; TAA = thoracoabdominal aortic aneurysm; Y = yes.

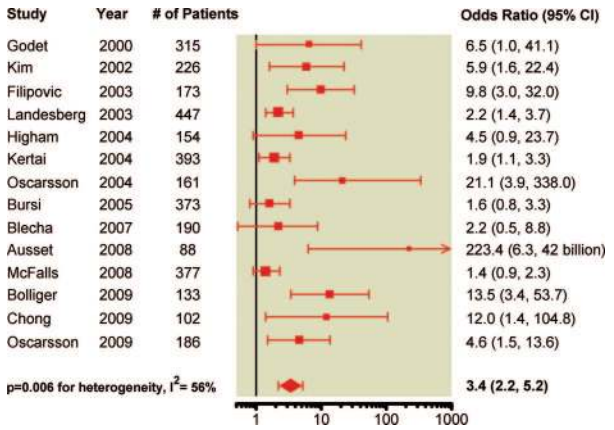

Fig. 2. Adjusted odds ratio for an increased postoperative troponin measurement to predict all-cause mortality.

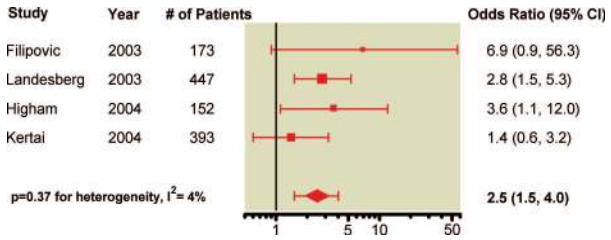

Fig. 3. Adjusted odds ratio for an increased postoperative CK-MB measurement to predict all-cause mortality. CK-MB = creatine kinase muscle and brain isoenzyme.

Our Study in Relation to Other Studies

We are unaware of any other systematic reviews that have evaluated the prognostic relevance of a troponin or CK-MB measurement after noncardiac surgery. A prior study that only followed patients to 30 days after surgery suggested an increased troponin I was an independent predictor of mortality within 30 days.[28] Our systematic review is an extension of this research, for we demonstrate an association between an increased postoperative troponin and mortality during intermediate- and long-term follow-up.

Interpretation and Implication of Our Findings

Our meta-analysis demonstrated that increased postoperative troponin is an independent predictor of mortality, but there was substantial heterogeneity across study results. Factors supporting the apparent subgroup effect suggesting a stronger association for troponin with death in the first year *versus* thereafter include the fact that it was one of a relatively small number of *a priori* hypothesis; we specified the direction of the effect *a priori*, the difference in ORs was relatively large and consistent, was biologically plausible, and the interaction was statistically significant in both univariable analysis and metaregression. It was, however, based on between- rather than within-study findings. Our findings suggest increased postoperative troponin is a strong predictor of mortality—the point estimate of effect suggests it increases the risk more than 6-fold—during the first year after surgery.

Given that the majority of patients who will develop a troponin elevation and myocardial infarction after surgery will not experience ischemic symptoms,[29–31] this supports the monitoring of troponin after surgery to enhance risk stratification. Detection of increased troponin after surgery may also provide an opportunity to change a patient's risk of death. At present, there are no randomized, controlled trials evaluating interventions among patients who have suffered an increased postoperative troponin measurement. Therefore, it remains unproven that detecting an increased tro-

Table 5. Adjusted Association between an Elevated Postoperative Troponin Measurement and Major Cardiovascular Events

Study	Composite Cardiac Outcome	No. of Patients	No. of Events	Adjusted Odds Ratio	95% CI	*P* Value
Lopez-Jimenez[21]	Cardiac death, nonfatal myocardial infarction, and admission for unstable angina	722	19	4.6	NR	< 0.05
Bursi[12]	Death and myocardial infarction	391	83	4.7*	2.9–7.7	< 0.0001
Ausset[14]	Cardiac death, myocardial infarction, congestive heart failure, need for coronary revascularization, or unstable angina	88	8	17.4*	3.7–82	NR
Chong[22]	Myocardial infarction, congestive cardiac failure, atrial fibrillation, or major arrhythmia	102	33	3.9	1.4–10.7	0.008
Bolliger[16]	Hospitalization for myocardial revascularization, acute coronary syndrome, acute congestive heart failure, or death	133	19	13.1	3.8–44.6	< 0.001

* Adjusted hazard ratio.
NR = not reported.

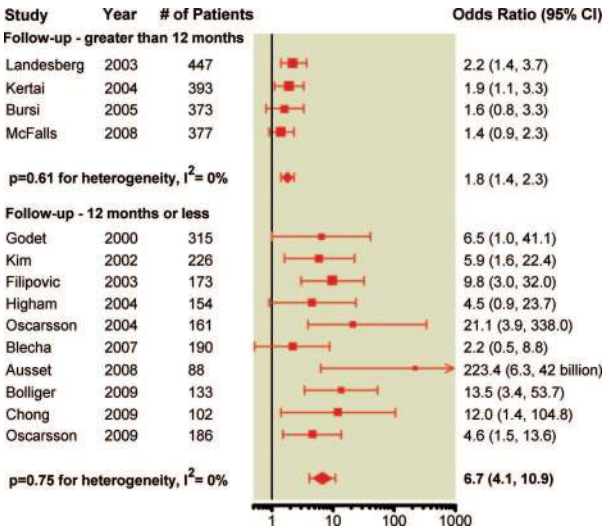

Fig. 4. Adjusted odds ratio for an increased postoperative troponin measurement to predict all-cause mortality based on duration of follow-up.

ponin after surgery can improve patient outcomes, but there is a rationale to suspect that it can enhance patient outcomes.

Most patients with an increased postoperative troponin measurement have suffered a perioperative myocardial infarction.[30] Between 10% and 20% of patients suffering a perioperative myocardial infarction will die before hospital discharge,[30,32,33] and it is logical to assume that early detection of a myocardial infarction will afford physicians the greatest opportunity to prevent death, as is the case in the nonoperative setting. Strategies for managing a patient with an increased postoperative troponin that are more likely to benefit than harm patients include: (1) more frequent monitoring of vital signs to allow early detection and reversal of cardiovascular instability; (2) management in a telemetry-monitored unit or cardiac care unit to allow early detection and treatment of serious arrythmias[34,35]; (3) vigilant screening and correction of potential contributing factors (*e.g.*, hypoxia, anemia); and (4) optimal intravascular volume management to minimize the risk of heart failure.

We believe that it is also reasonable to suspect that even patients who would survive to hospital discharge, despite having suffered an undetected perioperative troponin elevation, can benefit from detection of their increased troponin. Given that the majority of these patients likely have some degree of underlying coronary artery stenosis,[36–38] it seems prudent to consider offering these patients management with known beneficial secondary prophylactic cardiac interventions (*e.g.*, aspirin, angiotensin I–converting enzyme inhibitor, β-blocker, and statin). Studies suggest that a minority of patients who will develop a positive troponin after surgery are taking aspirin,[7,8,11,14,21,22] an angiotensin I–converting enzyme inhibitor,[7,11,14,23] a β-blocker,[7,8,14,21,22] or a statin,[11,16,22,23] highlighting that there is substantial potential for improved medical management of these patients.

In considering whether it is more appropriate to monitor CK-MB or troponin measurements after surgery, several points are relevant. First, surgical trauma can result in the release of CK-MB from skeletal muscle and a false-positive CK-MB value for myocardial infarction.[39–41] Second, a substantial proportion of perioperative myocardial infarctions occur in the first 2 days after surgery when serum CK values are high secondary to surgical trauma. The high CK values can result in a low, and thus false-negative, ratio of CK-MB to total CK.[41,42] Third, troponin is more sensitive and specific than CK-MB for myocardial infarction in patients undergoing noncardiac surgery.[41] Considering the results of our meta-analyses, these points suggest that physicians should monitor troponin values after surgery, as opposed to CK-MB values.

Future Research

Although our research demonstrates that an increased troponin value after surgery is a strong independent predictor of mortality at 1 yr, many important questions remain.[43] Although most studies have used, and guidelines have recommended, the 99th percentile for a healthy population to represent an increased troponin level, there is a need for large studies to determine what level of troponin should be considered abnormal after surgery and whether there is one or multiple troponin T thresholds that substantially influence risk. Further, there is a need for research to evaluate the new troponin high-sensitive assays that will replace the current fourth-generation troponin assays. We are currently conducting a prospective cohort study to address these questions and have enrolled a representative sample of over 20,000 adults undergoing noncardiac surgery in countries throughout the world, in the Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study.‖‖‖‖‖‖‖‖

Conclusions

The results of this systematic review suggest that an increased troponin measurement after surgery is an independent predictor of mortality, particularly within the first year. Further, our data suggest that the burden of mortality is higher within the first year after surgery for patients with a postoperative troponin rise. Physicians may find these data helpful in risk stratifying those patients who should undergo more intensive monitoring and management after noncardiac surgery.

‖‖‖‖‖‖‖‖ Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study (VISION) NCT00512109, 2009. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00512109? term=VISION&rank=2. Last updated July 22, 2010.

References

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA: An estimation of the global volume of surgery: A modelling strategy based on available data. Lancet 2008; 372:139–44
2. Alonso-Coello P, Paniagua P, Mizera R, Devereaux PJ: Should physicians initiate beta-blocker therapy in patients undergoing non-cardiac surgery? Insights from the POISE trial. Pol Arch Med Wewn 2008; 118:616–8
3. Devereaux PJ, Chan M, Eikelboom J: Major vascular complications in patients undergoing non-cardiac surgery: Magnitude of the problem, risk prediction, surveillance, and prevention, Evidence based Cardiology, 3rd Edition. Edited by Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ. West Sussex, UK, Wiley-Blackwell, 2010, pp 47–62
4. Mangano DT, Browner WS, Hollenberg M, Li J, Tateo IM: Long-term cardiac prognosis following noncardiac surgery: The Study of Perioperative Ischemia Research Group. JAMA 1992; 268:233–9
5. Pasternack PF, Grossi EA, Baumann FG, Riles TS, Lamparello PJ, Giangola G, Yu AY, Mintzer R, Imparato AM: Silent myocardial ischemia monitoring predicts late as well as perioperative cardiac events in patients undergoing vascular surgery. J Vasc Surg 1992; 16:171–9; discussion 179–80
6. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, Weissman C, Mosseri M: Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol 2003; 42:1547–54
7. Oscarsson A, Eintrei C, Anskar S, Engdahl O, Fagerstrom L, Blomqvist P, Fredriksson M, Swahn E: Troponin T-values provide long-term prognosis in elderly patients undergoing noncardiac surgery. Acta Anaesthesiol Scand 2004; 48:1071–9
8. Kim LJ, Martinez EA, Faraday N, Dorman T, Fleisher LA, Perler BA, Williams GM, Chan D, Pronovost PJ: Cardiac troponin I predicts short-term mortality in vascular surgery patients. Circulation 2002; 106:2366–71
9. Godet G, Dumerat M, Baillard C, Ben Ayed S, Bernard MA, Bertrand M, Kieffer E, Coriat P: Cardiac troponin I is reliable with immediate but not medium-term cardiac complications after abdominal aortic repair. Acta Anaesthesiol Scand 2000; 44:592–7
10. Higham H, Sear JW, Sear YM, Kemp M, Hooper RJ, Foex P: Peri-operative troponin I concentration as a marker of long-term postoperative adverse cardiac outcomes: A study in high-risk surgical patients. Anaesthesia 2004; 59:318–23
11. Kertai MD, Boersma E, Klein J, Van Urk H, Bax JJ, Poldermans D: Long-term prognostic value of asymptomatic cardiac troponin T elevations in patients after major vascular surgery. Eur J Vasc Endovasc Surg 2004; 28:59–66
12. Bursi F, Babuin L, Barbieri A, Politi L, Zennaro M, Grimaldi T, Rumolo A, Gargiulo M, Stella A, Modena MG, Jaffe AS: Vascular surgery patients: Perioperative and long-term risk according to the ACC/AHA guidelines, the additive role of post-operative troponin elevation. Eur Heart J 2005; 26:2448–56
13. Blecha MJ, Clark ET, Worley TA, Salazar MR, Podbielski FJ: Predictors of electrocardiographic change, cardiac troponin elevation, and survival after major vascular surgery: A community hospital experience. Am Surg 2007; 73:697–702
14. Ausset S, Auroy Y, Lambert E, Vest P, Plotton C, Rigal S, Lenoir B, Benhamou D: Cardiac troponin I release after hip surgery correlates with poor long-term cardiac outcome. Eur J Anaesthesiol 2008; 25:158–64
15. McFalls EO, Ward HB, Moritz TE, Apple FS, Goldman S, Pierpont G, Larsen GC, Hattler B, Shunk K, Littooy F, Santilli S, Rapp J, Thottapurathu L, Krupski W, Reda DJ, Henderson WG: Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: Results of the CARP trial. Eur Heart J 2008; 29:394–401
16. Bolliger D, Seeberger MD, Lurati Buse GA, Christen P, Rupinski B, Gurke L, Filipovic M: A preliminary report on the prognostic significance of preoperative brain natriuretic peptide and postoperative cardiac troponin in patients undergoing major vascular surgery. Anesth Analg 2009; 108: 1069–75
17. Zhang J, Yu KF: What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998; 280:1690–1
18. Filipovic M, Jeger R, Probst C, Girard T, Pfisterer M, Gurke L, Skarvan K, Seeberger MD: Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease. J Am Coll Cardiol 2003; 42:1767–76
19. DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177–88
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. BMJ 2003; 327:557–60
21. Lopez-Jimenez F, Goldman L, Sacks DB, Thomas EJ, Johnson PA, Cook EF, Lee TH: Prognostic value of cardiac troponin T after noncardiac surgery: 6-month follow-up data. J Am Coll Cardiol 1997; 29:1241–5
22. Chong CP, Lam QT, Ryan JE, Sinnappu RN, Lim WK: Incidence of post-operative troponin I rises and 1-year mortality after emergency orthopaedic surgery in older patients. Age Ageing 2009; 38:168–74
23. Oscarsson A, Fredrikson M, Sorliden M, Anskar S, Gupta A, Swahn E, Eintrei C: Predictors of cardiac events in high-risk patients undergoing emergency surgery. Acta Anaesthesiol Scand 2009; 53:986–94
24. Alpert JS, Thygesen K, Antman E, Bassand JP: Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000; 36:959–69
25. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. Ann Intern Med 2009; 151:W65–94
26. Babyak MA: What you see may not be what you get: A brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med 2004; 66:411–21
27. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR: A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996; 49:1373–9
28. Le Manach Y, Perel A, Coriat P, Godet G, Bertrand M, Riou B: Early and delayed myocardial infarction after abdominal aortic surgery. Anesthesiology 2005; 102:885–91
29. Devereaux PJ, Goldman L, Yusuf S, Gilbert K, Leslie K, Guyatt GH: Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: A review. CMAJ 2005; 173:779–88
30. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. Lancet 2008; 371:1839–47
31. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS: Perioperative myocardial infarction. Circulation 2009; 119: 2936–44

32. Badner NH, Knill RL, Brown JE, Novick TV, Gelb AW: Myocardial infarction after noncardiac surgery. ANESTHESIOLOGY 1998; 88:572–8
33. Shah KB, Kleinman BS, Rao TL, Jacobs HK, Mestan K, Schaafsma M: Angina and other risk factors in patients with cardiac diseases undergoing noncardiac operations. Anesth Analg 1990; 70:240–7
34. Christiansen I, Iversen K, Skouby AP: Benefits obtained by the introduction of a coronary-care unit. A comparative study. Acta Med Scand 1971; 189:285–91
35. Sagie A, Rotenberg Z, Weinberger I, Fuchs J, Agmon J: Acute transmural myocardial infarction in elderly patients hospitalized in the coronary care unit *versus* the general medical ward. J Am Geriatr Soc 1987; 35:915–9
36. Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA: Pathology of fatal perioperative myocardial infarction: Implications regarding pathophysiology and prevention. Int J Cardiol 1996; 57:37–44
37. Cohen MC, Aretz TH: Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 1999; 8:133–9
38. Ellis SG, Hertzer NR, Young JR, Brener S: Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. Am J Cardiol 1996; 77:1126–8
39. Healey JH, Kagen LJ, Velis KP, Levine DB: Creatine kinase MB in skeletal muscle and serum of spine-fusion patients. Clin Orthop 1985; 282–8
40. Jules-Elysee K, Urban MK, Urquhart B, Milman S: Troponin I as a diagnostic marker of a perioperative myocardial infarction in the orthopedic population. J Clin Anesth 2001; 13:556–60
41. Adams JE 3rd, Sicard GA, Allen BT, Bridwell KH, Lenke LG, Davila-Roman VG, Bodor GS, Ladenson JH, Jaffe AS: Diagnosis of perioperative myocardial infarction with measurement of cardiac troponin I. N Engl J Med 1994; 330:670–4
42. Haggart PC, Adam DJ, Ludman PF, Bradbury AW: Comparison of cardiac troponin I and creatine kinase ratios in the detection of myocardial injury after aortic surgery. Br J Surg 2001; 88:1196–200
43. Archan S, Fleisher LA. From creatine kinase-MB to troponin: The adoption of a new standard. ANESTHESIOLOGY 2010; 112: 1005–12

Appendix 1:

A medical librarian (NB) guided us in selecting relevant bibliographic databases and used all the studies of which we were initially aware to identify search terms for the search. Searches were performed using the OvidSP search engine (Ovid Technologies, Inc., New York, NY 2009) for the following databases:

1. Ovid version of MEDLINE (Ovid MEDLINE ® In-Process and other Non-Indexed Citations and Ovid MEDLINE ®, 1950 to June 11, 2009)
2. EMBASE (1980 to 2009, week 23),
3. the Cochrane Central Register of Controlled Trials (2nd quarter 2009)
4. the Cochrane Database of Systematic Reviews (2nd quarter 2009), and
5. the ACP Journal Club (1991 to May 2009)
6. Healthstar (1966 to May 2009)

	Search terms	Number of references
1	(Troponin or CK-MB).mp.	33477
2	(Surgery or non-cardiac surgery or post-operative).mp.	1767172
3	1 and 2 (articles for title and abstract screening)	3654
4	Remove duplicates from 3	1808

ACP = American College of Physicians; CK-MB = Creatine Kinase, Muscle and Brain isoenzyme; NB = Neera Bhatnagar