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

A Systematic Review and Meta-analysis


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 (I² = 56%). The

* 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; §§§ Assistant Professor, Department of Medicine, McMaster University; §§§ Associate Professor, Department of Anaesthesiology and Critical Care Medicine, Hebrew University—Hadassah Medical Center, Jerusalem, Israel; ¶¶ Associate Professor, Departments of Anaesthesiology and Intensive Care, Pontchaillau Hospital, France; ¶¶¶ Professor, Department of Anaesthesiology, 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 Medicine 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, 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.

Copyright © 2011, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anesthesiology 2011; 114: 796–806
What We Already Know about This Topic

- Increased troponin or creatine 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.

ONCOCARDIAC 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-term (≤ 12 months) mortality was an OR = 6.7 (95% CI 4.1–10.9, I² = 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, I² = 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, I² = 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.

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 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?
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 $\kappa$ 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). 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. 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. One of these studies also performed a logistic regression analysis, but did not report the numerical results. 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:

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

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

We pooled ORs using the DerSimonian and Laird random-effects model. 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. 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).

**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).

Interobserver agreement for study eligibility was excellent ($\kappa$, 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, seven studies included pa-
patients 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 troponin measurement.
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 2 reports the adjusted ORs for the studies that had at least one patient who suffered a major cardiovascular complication.

### Table 2. Troponin Measurements

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

* 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.
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 studies6,10 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 3. CK-MB Measurements

<table>
<thead>
<tr>
<th>Study</th>
<th>Manufacturer</th>
<th>CK-MB Threshold</th>
<th>Timing and Frequency of CK-MB Measurement</th>
<th>Patients with Elevated CK-MB n/N (%)</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filipovic18</td>
<td>Abbott AxsYM</td>
<td>&gt; 10.4 mcg/l</td>
<td>Postoperative days 1 or 2</td>
<td>20/173 (11.6)</td>
<td>28</td>
</tr>
<tr>
<td>Landesberg6</td>
<td>Vitros dry chemistry</td>
<td>CK &gt; 170 IU and a relative index</td>
<td>Immediately after surgery and postoperative days 1, 2, and 3</td>
<td>34/447 (7.6)</td>
<td>82</td>
</tr>
<tr>
<td>Kertai11</td>
<td>Roche/Hitachi 747</td>
<td>&gt; 5%</td>
<td>Postoperative days 2, 3, and 7 (or discharge)</td>
<td>31/393 (7.9)</td>
<td>80</td>
</tr>
</tbody>
</table>

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.

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 a major cardiovascular event. Four of the studies included myocardial infarction in their composite outcome;12,14,21,22 and three of these studies12,14,22 used the European Society of Cardiology/American College of Cardiology definition of myocardial infarction.24

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; I² = 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; I² = 0%).
Table 4. Study Quality Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with Complete Follow-up n/N (%)</th>
<th>Blinded Outcome Assessment (Y/N)</th>
<th>Method of Patient Follow-up</th>
<th>Variables Adjusted for in Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim8</td>
<td>226/229 (99)</td>
<td>Y</td>
<td>Direct patient follow-up and for patients with inaccurate phone numbers they searched the Social Security death index</td>
<td>Age, history of CHF, TAA repair, perioperative β-blocker (defined as morning of surgery, during surgery, and/or first 48 h after surgery)</td>
</tr>
<tr>
<td>Filipovic18</td>
<td>173/173 (100)</td>
<td>N</td>
<td>Telephone interview and hospital charts</td>
<td>LF/HF &lt; 2 (low- to high-frequency power ratio: measure of heart rate variability), revised cardiac risk index</td>
</tr>
<tr>
<td>Landesberg6</td>
<td>447/447 (100)</td>
<td>Y</td>
<td>Administrative data</td>
<td>Age, type of vascular surgery, previous myocardial infarction, renal insufficiency</td>
</tr>
<tr>
<td>Kertai11</td>
<td>393/393 (100)</td>
<td>N</td>
<td>Administrative data and hospital records</td>
<td>ST segment changes, cardiac risk factors, chronic cardiac medications (ASA, BB), type of surgery</td>
</tr>
<tr>
<td>Oscarsson7</td>
<td>161/161 (100)</td>
<td>Y</td>
<td>Administrative data and chart review</td>
<td>BMI, ASA status, chronic BB use, chronic diuretic use, reoperation, tachycardia</td>
</tr>
<tr>
<td>Lopez-Jiminez21</td>
<td>722/772 (94)</td>
<td>Y</td>
<td>Telephone interview and administrative database</td>
<td>CK-MB, type of operation, age, gender, previous cardiac history, smoking history, use of aspirin or BB, diabetes</td>
</tr>
<tr>
<td>Godet9</td>
<td>315/315 (100)</td>
<td>Y</td>
<td>Direct patient follow-up</td>
<td>CAD</td>
</tr>
<tr>
<td>Higham10</td>
<td>154/154 (100)</td>
<td>N</td>
<td>Direct patient follow-up and patient chart review</td>
<td>CAD</td>
</tr>
<tr>
<td>Bursi12</td>
<td>190/190 (100)</td>
<td>Y</td>
<td>Direct patient follow-up, patient chart review, and administrative data</td>
<td>Age, CAD, renal failure</td>
</tr>
<tr>
<td>Blecha13</td>
<td>373/373 (100)</td>
<td>N</td>
<td>Administrative data, direct patient follow-up, and patient charts</td>
<td>Type of surgery, ECG change (postop), diabetes, CAD, age, preop cardiac catheter, preop PCI, preop CABG surgery, postop ischemic symptoms</td>
</tr>
<tr>
<td>Ausset14</td>
<td>88/88 (100)</td>
<td>N</td>
<td>Direct patient follow-up and patient charts</td>
<td>Age, ASA score, revised cardiac risk index</td>
</tr>
<tr>
<td>McFalls15</td>
<td>377/377 (100)</td>
<td>Y</td>
<td>Administrative data</td>
<td>Age, elevated creatinine, preop history of CHF, diabetes</td>
</tr>
<tr>
<td>Chong22</td>
<td>102/102 (100)</td>
<td>N</td>
<td>Telephone interview and patient charts</td>
<td>Premorbid ischemic heart disease, premorbid CHF, postop transfusion, postop cardiac event</td>
</tr>
<tr>
<td>Oscarrson23</td>
<td>186/211 (88)</td>
<td>N</td>
<td>Administrative data, telephone interview, and patient charts</td>
<td>Malignancy, perioperative inotropes, aspirin use</td>
</tr>
<tr>
<td>Bolliger16</td>
<td>133/133 (100)</td>
<td>Y</td>
<td>Administrative data, telephone interview, and patient charts</td>
<td>Age, gender, revised cardiac risk index</td>
</tr>
</tbody>
</table>

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.
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

<table>
<thead>
<tr>
<th>Study</th>
<th>Composite Cardiac Outcome</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Adjusted Odds Ratio 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopez-Jimenez21</td>
<td>Cardiac death, nonfatal myocardial infarction, and admission for unstable angina</td>
<td>722</td>
<td>19</td>
<td>4.6</td>
<td>NR</td>
</tr>
<tr>
<td>Bursi12</td>
<td>Death and myocardial infarction</td>
<td>391</td>
<td>83</td>
<td>4.7*</td>
<td>2.9–7.7</td>
</tr>
<tr>
<td>Ausset14</td>
<td>Cardiac death, myocardial infarction, congestive heart failure, need for coronary revascularization, or unstable angina</td>
<td>88</td>
<td>8</td>
<td>17.4*</td>
<td>3.7–82</td>
</tr>
<tr>
<td>Chong22</td>
<td>Myocardial infarction, congestive cardiac failure, atrial fibrillation, or major arrhythmia</td>
<td>102</td>
<td>33</td>
<td>3.9</td>
<td>1.4–10.7</td>
</tr>
<tr>
<td>Bolliger16</td>
<td>Hospitalization for myocardial revascularization, acute coronary syndrome, acute congestive heart failure, or death</td>
<td>133</td>
<td>19</td>
<td>13.1</td>
<td>3.8–44.6</td>
</tr>
</tbody>
</table>

* Adjusted hazard ratio.
NR = not reported.
perioperative myocardial infarction will die before hospital discharge,30,32,33 and it is logical to assume that early detection of 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 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 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.
References


805

Anesthesiology 2011; 114:796–806

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

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)

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

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