JOURNAL of ANESTHESIA and PERIOPERATIVE MEDICINE

Original Article

Postoperative High-Sensitivity Troponin Monitoring Following Noncardiac Surgery: Evaluating the Effect on Mortality of Associated Perioperative Clinical Events

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ABSTRACT

Background: The 30-day mortality following non-cardiac surgery ranges from 2%-6%. Observational studies have suggested myocardial injury following non-cardiac surgery (MINS) and subsequent vascular events are partly responsible.

Methods: Postoperative high-sensitivity troponin I levels were recorded on in-patients undergoing non-cardiac surgery. Positive results (> 17 ng/L) were categorized by the associated pathophysiological process; "secondary" if associated with sepsis, significant perioperative bleeding or prolonged pathological atrial or ventricular tachyarrhythmias and "primary" if not. The 30-day and 6-month mortality data were collected. Multivariate Cox proportional hazard modeling determined independent predictors of 6-month mortality.

Results: Of 387 patients analyzed, 125 (32%) were over 75 years of age; 192 (50%) were male. The 30-day mortality (2.8%) was comparable to the VISION study (1.9%); 30-day mortality following an elevated postoperative troponin was 5.6%, all associated with sepsis. The 6-month mortality overall was 10%; 21% following any postoperative troponin elevation, 8.6% following "primary" events, 36% and 21% following "secondary" events associated with sepsis and bleeding respectively and 3.7% with normal post-operative troponin. 5% of deaths had vascular causes identified; none had an elevated postoperative troponin. Emergency presentation, sepsis, and abnormal renal function independently predicted 6-month mortality with the emergency presentation being the strongest predictor. Troponin levels > 1000 ng/l (highly suggestive of independently predicting 6-month mortality (P = 0.06)) occurred in 13 patients (3.4% of the entire cohort); the majority of these patients were emergency admissions requiring high-dependency or intensive care unit admission and 9 had evidence of perioperative sepsis. "Primary" elevated post-operative troponins were not independent predictors of mortality.

Conclusion: Postoperative high-sensitivity troponin elevation in patients undergoing non-cardiac surgery is associated with 30-day and 6-month mortality. However, early mortality in patients with elevated troponin was largely accounted for by other non-cardiac adverse events; we suggest a mixture of pathophysiological processes are at work rather than solely indicating new vascular events. (Funded by the Regional Innovation Fund of NHS England and the South Tees NHS Foundation Trust Research and Development Fund.)

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Citation: Matthew W. P. Jackson, Mark Hammonds, Nicola Cunningham, David Austin, Neil Swanson, Mark A. de Belder, Michael J. Stewart. Postoperative High-Sensitivity Troponin Monitoring Following Noncardiac Surgery: Evaluating the Effect on Mortality of Associated Perioperative Clinical Events. *J Anesth Perioper Med* 2018;5:281-292.

doi: 10.24015/JAPM.2018.0116

Over 200 million people undergo major non-cardiac surgery worldwide every year (1). Mortality following such operations is estimated between 2% - 6% at 30 days (2, 3). The Vascular Events in Non-Cardiac Surgery Patient Cohort Evaluation (VISION) study recruited 15, 133 patients, routinely measuring post-operative troponins on all patients over the age of 45 years undergoing emergency or elective non-cardiac surgery with a length of stay more than 2 days (3). Raised troponin T was noted in 11.7% of patients and were associated with 30-day mortality, with increasing troponin levels adding additional prognostic significance.

The further analysis excluded non-ischemic etiology (sepsis, pulmonary embolism or undergoing cardioversion) and established diagnostic criteria for Myocardial Injury after Non-cardiac Surgery (MINS) events (4). Peak troponin T levels above 0.03 ng/L with or without ECG changes or ischemic symptoms were shown to be independently associated with elevated 30-day mortality. Such events were termed a MINS event, suggesting they marked cardiovascular events relating to undiagnosed or unstable atherosclerotic disease "triggered" by the stress of undergoing surgical intervention, hemodynamic fluctuations, and potentially physical maneuvering. MINS occurred without symptoms or ECG changes in 84% of patients. Routine post-operative troponin monitoring was recommended to maximize detection of such events; subsequent guidelines for perioperative cardiac risk assessment and management have adopted this strategy for selected patients felt to be at increased risk of cardiac events in the post-operative period although the optimal management of such events has not yet been established (5).

Our experience in day-to-day practice is that there is often no clear single shared mechanism that explains an elevated troponin following non-cardiac surgery, an important consideration when trying to determine therapeutic strategies. The introduction of high-sensitivity troponin assays will also dramatically increase the sensitivity for detecting myocardial injury although at the cost of reduced specificity. Through an in-depth analysis of our initial experience of post-operative high-sensitivity troponin monitoring, we aimed to further characterize the population of patients who experience raised postoperative troponins.

MATERIALS AND METHODS

Data Collection and Study Population

The James Cook University Hospital, Middlesbrough is a large NHS hospital with 250 surgical beds. It serves a population of over 1 million people in Teesside and County Durham as a regional trauma center and major cancer center. Sub-specialties include general, urological, major vascular, neuro - and orthopedic surgery (both trauma and elective) as well as plastics, otolaryngological and maxillofacial surgery.

Data were collected prospectively between September 2014 and May 2015 as part of a service evaluation project performed during this time period to gather data on the incidence of postoperative troponin elevation. Suitable elective cases were identified using the CaMIS patient identification system (EMIS Health © 2015) one month in advance. Pre-operative troponin I levels were performed on blood samples corresponding to the patient identifier if received on a pre-planned "Waiting List To-Come-In" (WL-TCI) date. Patients appeared on the TheatreMan operation record once they underwent their operation, triggering the postoperative troponin data collection. Postoperative troponins were measured on any samples taken as part of routine postoperative care within the first 72 hours postoperatively and the peak troponin measurement recorded. Only samples collected as part of routine clinical care were used; no samples were taken for research purposes alone.

Emergency cases (that is, patients requiring in-hospital surgery after urgent or emergency admission) were identified by a daily download of the TheatreMan operation recording system indicating they had undergone surgery. Preoperative troponins were performed retrospectively on the blood sample obtained on admission. Postoperative troponins were performed as described for elective patients.

All troponins were performed using the ADIVA Centaur Troponin I Ultra Assay (Siemens); this assay meets the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Task Force on Clinical Applications of Cardi-

ac Bio-markers recommendations with a coefficient of variation (CV) < 10% at the 99th centile (40 ng/L) and demonstrates clinical equivalence to high-sensitivity troponin assay (6, 7). The lower limit of detection is 6 ng/L but our laboratory reports a minimum value of 17 ng/L and therefore values < 17 ng/L were deemed to be "undetectable"; to assess percentage change in troponin, < 17 ng/L was assigned the mid-range value of 8 ng / L. Assays were performed within 24 hours of phlebotomy to maximize accuracy.

Troponins requested by the clinical team for clinical reasons were available for view on our pathology reporting system. Troponins performed for the research study were withheld to prevent clinical care being affected, given the uncertain significance of the results.

According to local research protocols, the initial data collection process was deemed a service evaluation project with specific ethical approval not required. No ethical issues were raised by reviewers as part of the funding application to NHS England and our Trust R&D lead approved the project without any governance or ethical concerns.

Definitions

Clinical records were assessed retrospectively to determine the presence of events that may be associated with troponin release including sepsis, major perioperative bleeding, pulmonary embolism, cardioversion or prolonged tachyarrhythmia. Sepsis was defined as "the presence (probable or documented) of infection together with the systemic manifestation of infection" as per the 2012 sepsis guidelines (8). Major perioperative bleeding was defined as a fall in hemoglobin greater than 5 g/dL (9), or to a minimum level under 7 g / dL, considered a suitable threshold for transfusion using a restrictive transfusion policy in the 2015 NICE guidelines (10). This was chosen to identify patients at a high risk of significant or prolonged coronary under-perfusion. If a patient experienced significant bleeding but was rapidly transfused such that serial daily hemoglobins did not detect a fall in hemoglobin, this was not included in our definition. Prolonged tachyarrhythmias were defined as a pathological atrial or ventricular tachycardia excluding sinus tachycardia, documented either in the clinical notes or on 12-lead electrocardiography; the majority of patients were not monitored continuously so only those arrhythmias triggering clinical investigation or concerns were recorded.

Post-operative troponin elevations > 17 ng/L were sub-classified by associated clinical events to allow more detailed characterization of the underlying pathophysiological process at work. Primary events did not have an associated clinical event. Secondary events had a documented associated clinical event (i. e. sepsis, bleeding or arrhythmia as defined above).

Outcomes

The 30-day and 6-month mortality outcomes were obtained from the Office of National Statistics (ONS) along with a cause of death.

Statistical Analysis

Variables were separately assessed for association with mortality at 30 days and 6 months using a Cox Proportional Hazards univariate analysis with mortality as the dichotomous dependent variable, compared to a reference group without the variable (i. e. patients with sepsis versus patients without sepsis). Variables were also analyzed in combination with a positive troponin (e. g. patients with sepsis and a positive troponin (a "secondary MINS" event) versus all other patients). For all variables, we report a hazard ratio with 95% confidence intervals and the associated P-value.

Abnormal renal function was evaluated by a variety of thresholds (eGFR > 60 mL/min vs < 60 mL/min, > 50 mL/min vs < 50 mL/min, etc.) to identify the most predictive threshold to use in subsequent multivariate analysis. Post-operative troponin level was tested as a dichotomous variable using values >17ng/l as positive. It was subsequently evaluated by a variety of thresholds (> 50 ng/L, > 100 ng/L, > 500 ng/L and every 100 ng/L to > 1000 ng/L) to identify the most predictive threshold to use in multivariate analysis.

A multivariate Cox Proportional Hazards model was then constructed to determine independent predictors of 6-month mortality. Forced simultaneous entry of all variables was used initially to determine significant variables compared to the univariate analysis. All variables with a P value less than 0.2 in either analysis

were then entered into both a forward and backward stepwise selection model to determine the independent predictors of 6-month mortality.

Kaplan-Meier survival curves were constructed comparing mortality depending on post-operative troponin level, type of postoperative troponin elevation and outcomes for each pathophysiological process associated with a "secondary" troponin elevation.

RESULTS

Of 1114 patients screened, 387 patients were identified for further analysis (Figure 1). All had a pre-operative and at least one post-operative troponin measurement; 460 (41%) patients had at least two post-operative troponin levels taken. The demographics can be seen in Table 1 with demographics from the VISION study for comparison.

Post-operative troponin elevations occurred in 141 (36%) patients; 61 patients had a postoperative troponin > 40 ng/L and 13 had a peak level > 1000 ng/L. Eighty-two (62%) of urgent/emergency patients and 59 (23%) of elective patients had an elevated post-operative troponin. Sepsis occurred in 71 (18%) patients, significant perioperative bleeding in 37 (9.6%) patients and prolonged pathological arrhythmia in 3 (0.8%) patients.

Mortality outcomes divided by underlying pathophysiology can be seen in Table 2; survival curves showing 30-day and 6-month mortality divided by normal troponin, "primary" and "secondary" troponins can be seen in Figure 2 and divided by peak post-operative troponin in Figure 3. For the whole cohort, 11 patients (2.8%) died within 30 days; eight had an elevated post-operative troponin all in the setting of peri-operative sepsis (11% of all patients with perioperative sepsis). Three deaths occurred in the 241 patients with a normal post-operative troponin. There were no early deaths amongst patients with "primary" troponin elevations or "secondary" troponin elevation in the setting of bleeding or tachycardia.

At 6 months, there were 39 deaths (10%); 29 deaths occurred following urgent/emergency surgery. Patients with a normal postoperative troponin had a mortality rate of 3.7% compared to 21% in patients with an elevated postoperative troponin. Patients with a "primary" troponin elevation suffered 8.7% mortality compared to 33% amongst patients with a "secondary" troponin elevation. The 6-month mortality was 36% and 21% following sepsis and bleeding respectively. Mortality following a "secondary" troponin elevation was significantly higher than a "primary" troponin elevation or normal postoperative troponin. There was no difference between mortality following "primary" troponin elevation and a normal postoperative troponin.

The 6-month mortality in patients with perioperative sepsis regardless of troponin was 31% (4.8% in elective patients, 42% in emergency patients); in patients with a normal post-operative troponin, this was 6.7%, 0% and 11% in the three cohorts compared to 38%, 6.7%, and 49% if an elevated troponin was present. Patients without perioperative sepsis had 6-month mortality rates of 5.4%, 3.8%, and 9.8%. Kaplan-Meier survival curves comparing 6-month mortality in patients without peri-operative sepsis, with perioperative sepsis but with a normal post-operative troponin and sepsis with an elevated postoperative troponin are shown in Figure 4.

Perioperative Troponin Trends

Perioperative trends in troponin can be seen in Table 3. Preoperative troponin exceeded peak postoperative troponin levels in 37 (9.6%) patients; one (2.7%) patient suffered 30-day mortality and eight (22%) suffered 6-month mortality. A positive preoperative troponin fell to a negative troponin in 17 (6.9%) patients; one (5.9%) suffered 6-month mortality.

The percentage change in troponin was < 20% in 63% of patients; mortality in this group was 0.8% at 30-days and 2.9% at 6-months. Large changes (> 1000%) occurred in 7% of patients; mortality was 19% at 30-days and 26% at 6-months.

Univariate and Multivariate Analysis

Univariate analysis of perioperative variables can be seen in Table 4. An urgent / emergency surgical presentation, perioperative sepsis, and post-operative troponin elevation were associated with both 30-day and 6-month mortality. Renal function was a significant predictor at all tested

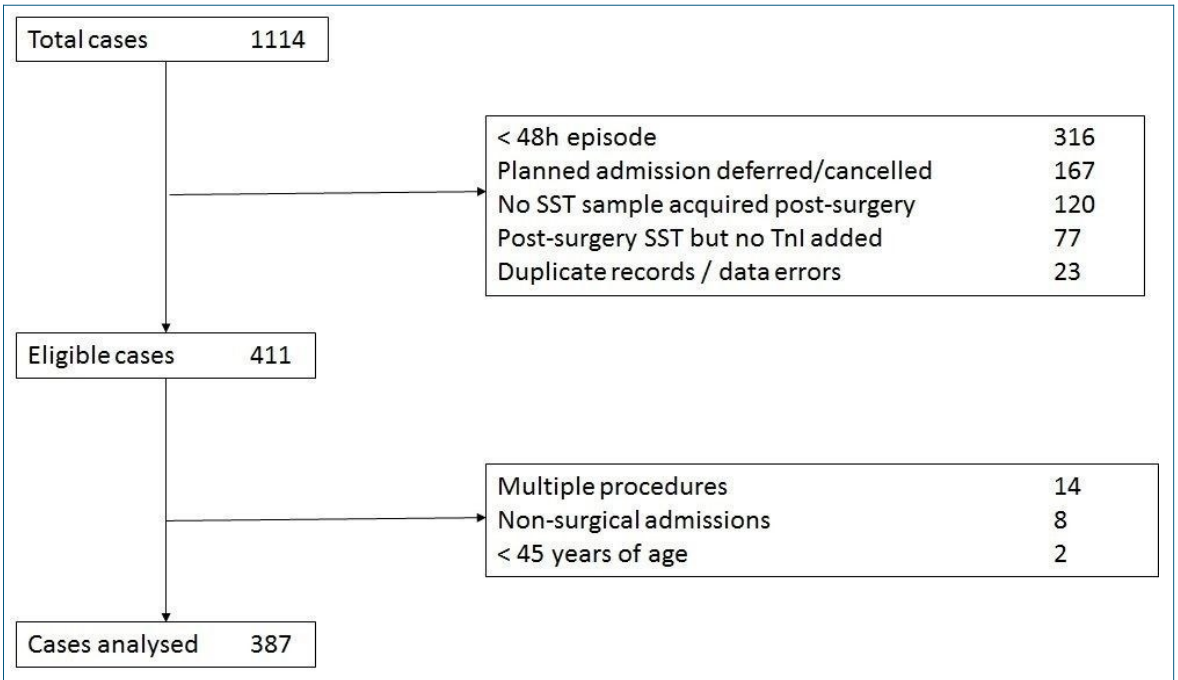

Figure 1. Patient Selection Process.

Table 1. Demographics of the JCUH Study Cohort and VISION Study Cohort.

Demographics Parameters	JCUH Study Cohort (n = 387)	VISION Study Cohort (n = 15133)	P value
Age			
45 – 64	125 (32%)	7697 (51%)	P < 0.001
65 – 74	137 (35%)	3779 (25%)	P < 0.001
75 +	125 (32%)	3657 (24%)	P = 0.001
Male	192 (50%)	7794 (52%)	P = 0.465
Urgent / Emergency Surgery	132 (34%)	2142 (14%)	P < 0.001
Types of surgery			
Orthopaedic	143 (37%)	3094 (20%)	P < 0.001
General / Vascular	146 (38%)	3580 (24%)	P < 0.001
Urology / Gynaecology	49 (13%)	1888 (13%)	P = 0.912
Neurosurgery	15 (3.9%)	888 (5.9%)	P = 0.099
Other	34 (9%)	5960 (39%)	P < 0.001

JCUH, The James Cook University Hospital; VISION, Non-Cardiac Surgery Patient Cohort Evaluation.

thresholds with a minimum P value obtained for eGFR < 60 mmol / L (P = 0.003, HR 7.338 (1.947 - 27.661); this was therefore used as the threshold in subsequent analyses. Significant peri-operative blood loss was not associated with 30-day mortality (P = 0.706, HR 1.485 (0.190 - 11.596) but was associated with 6-month mortality (P = 0.003 HR 3.412 (1.506 - 7.731)). Age at presentation was not associated with 30-day mortality but age over 75 years was associated with 6-month mortality.

The "Secondary" troponin elevations associated with sepsis and bleeding exhibit a higher hazard ratio than sepsis alone for 30-day and 6-month mortality, suggesting raised troponin as a marker of risk. The "Primary" troponin elevations were not statistically associated with 30-day or 6-month mortality (P = 0.325 HR 0.036 (0 - 26.807)).

Multivariate analysis with simultaneous entry of all variables confirmed these findings. Stepwise regression modeling determined that urgent /

Table 2. Types of Postoperative Troponin Elevations and Mortality Data.

	All surgery (n = 387)	30-day mortality**	6-month mortality**	Emergency (n = 132)	30-day mortality**	6-month mortality**	Elective (n = 255)	30-day mortality**	6-month mortality**
Total cohort	387	11 (2.8%)	39 (10%)	132	10 (7.6%)	29 (22%)	255	1 (0.4%)	10 (0.4%)
All post-operative troponin elevation	141 (36%)	8 (5.7%)	30 (21%)	82 (62%)	8 (9.8%)	24 (29%)	59 (23%)	0 (0%)	6 (10%)
Primary post-operative troponin elevation	69 (49%)	0 (0%)	6 (8.6%)	31 (37%)	0 (0%)	3 (9.6%)	38 (64%)	0 (0%)	3 (7.7%)
Secondary post-operative troponin elevation	72 (51%)	8 (11%)	24 (33%)	51 (62%)	8 (16%)	21 (41%)	21 (36%)	0 (0%)	3 (14%)
Associated with sepsis	55 (39%)	8 (15%)	20 (36%)	40 (50%)	8 (20%)	19 (46%)	15 (25%)	0 (0%)	1 (6.7%)
Associated with bleeding	14 (9.9%)	0 (0%)	3 (21%)	9 (11%)	0 (0%)	1 (11%	5 (8.5%)	0 (0%)	2 (40%)
Associated with tachycardia	3 (2.1%)	0 (0%)	1 (33%)	2 (2.4%)	0 (0%)	1 (50%)	1 (1.7%)	0 (0%)	0 (0%)
Normal post-operative troponin	246 (64%)	3 (1.2%)	9 (3.7%)	50 (38%)	2 (4%)	5 (10%)	196 (77%)	1 (0.5%)	4 (2%)

**, mortality percentage is a proportion within that category.

emergency presentation (HR 3.233 (1.453 - 7.190, P = 0.004), sepsis (HR 2.851 (1.386 - 5.861), P = 0.004) and abnormal renal function (HR 3.267 (1.678 - 6.362), P < 0.001) were significant predictors of 6-month mortality.

Various troponin thresholds were tested; only troponin > 1000 ng/L was suggestive of independently predicting 6-month mortality (HR 2.425 (0.967 - 6.079) P = 0.06). This degree of troponin elevation occurred in 13 patients (3.4% of the entire cohort); 12 were emergency admissions, 11 required admissions to high-dependency or intensive care units and 9 had evidence of perioperative sepsis with / without multi-organ failure. One patient was documented as suffering a "likely type 1 myocardial infarction" prior to admission which was managed conservatively.

DISCUSSION

The key findings of our analysis of 387 patients undergoing major non-cardiac surgery are:

1. Postoperative high-sensitive troponin elevation is associated with both 30-day and 6-month mortality. Levels > 1000 ng/L are highly suggestive of independently predicting 6-month mortality.

2. "Secondary" troponin elevations in the setting of postoperative clinical events have a significantly higher mortality than "primary" troponin elevations at both 30-day and 6-months.

3. Troponin elevation adds prognostic significance to post-operative complications that already carry significant mortality.

4. There is no significant difference in mortality between patients experiencing an isolated low-to-medium postoperative troponin elevation and a normal postoperative troponin.

The role of postoperative troponin monitoring using contemporary troponin assays has been explored in several studies previously. Landesberg and colleagues demonstrated even small elevations in postoperative cardiac biomarkers were predictive of adverse outcomes in patients undergoing major vascular surgery (11). Beattie and colleagues performed a single-center cohort analysis of over 10, 000 patients undergoing major non-cardiac surgery; an elevated postoperative troponin I > 0.07 ng/mL, found in 11% of patients, was independently associated with 30-day postoperative mortality (2.1% overall, 24.3% with elevated postoperative troponin) with incremental increases of troponin strengthening this

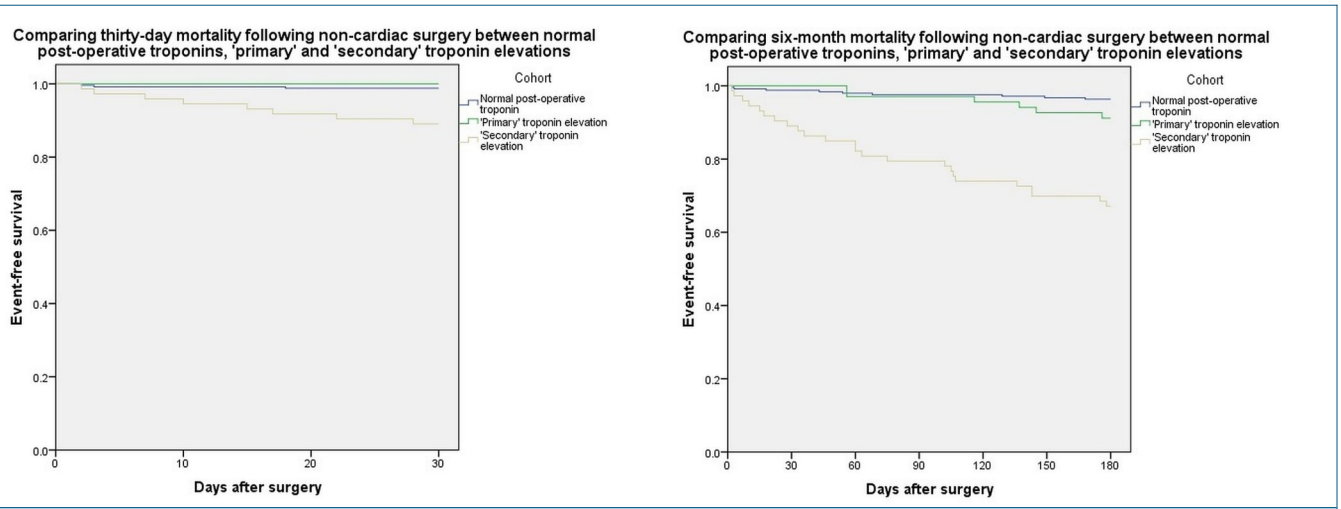

Figure 2. Kaplan Meier Survival Curves Showing 30-day and 6-month Mortality Divided by Non-MINS versus Primary MINS versus Secondary MINS Events.

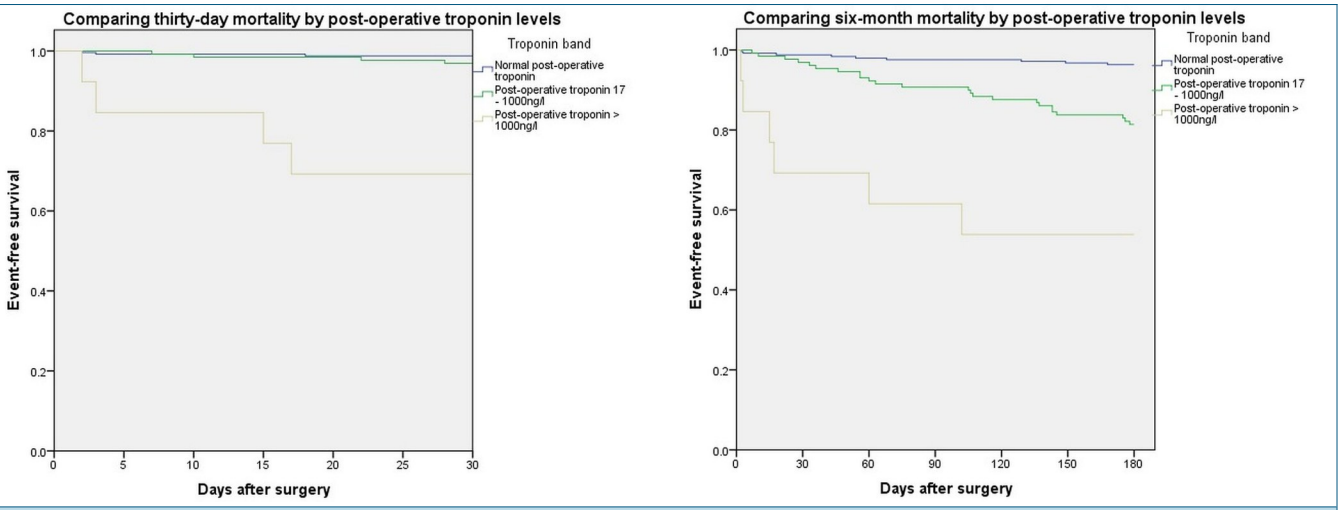

Figure 3. Kaplan Meier Survival Curves Showing 30-day and 6-month Mortality by Peak Postoperative Troponin Level.

association (12).

Van Waes and colleagues found an elevated troponin I (> 0.06 ng/mL) in 19% of patients undergoing intermediate or high-risk non-cardiac surgery with all-cause 30-day mortality of 3% (13). Elevated postoperative troponin again independently predicted 30-day mortality after non-cardiac surgery although myocardial infarction was only diagnosed in 10 (0.6%) patients.

The VISION study also demonstrated that even smaller elevations in troponin I (>0.01 ng/mL) present in 11.7% of patients were associated with adverse outcomes. Features required to meet the Universal Definition of myocardial infarction, such as ECG changes or ischemic symptoms were often absent. Routine postoperative troponin monitoring was recommended as the majority of myocardial injury and troponin release occurred in the first 72 postoperative hours (14, 15). The recent BASEL-PMI study supported these findings in a higher risk cohort (patients over 65 years of age or over 45 with a history of vascular disease; perioperative troponin elevation was associated with higher mortality and was largely asymptomatic (16). Low-risk patients, comprising 56% of the VISION cohort and 50% of patients stud-

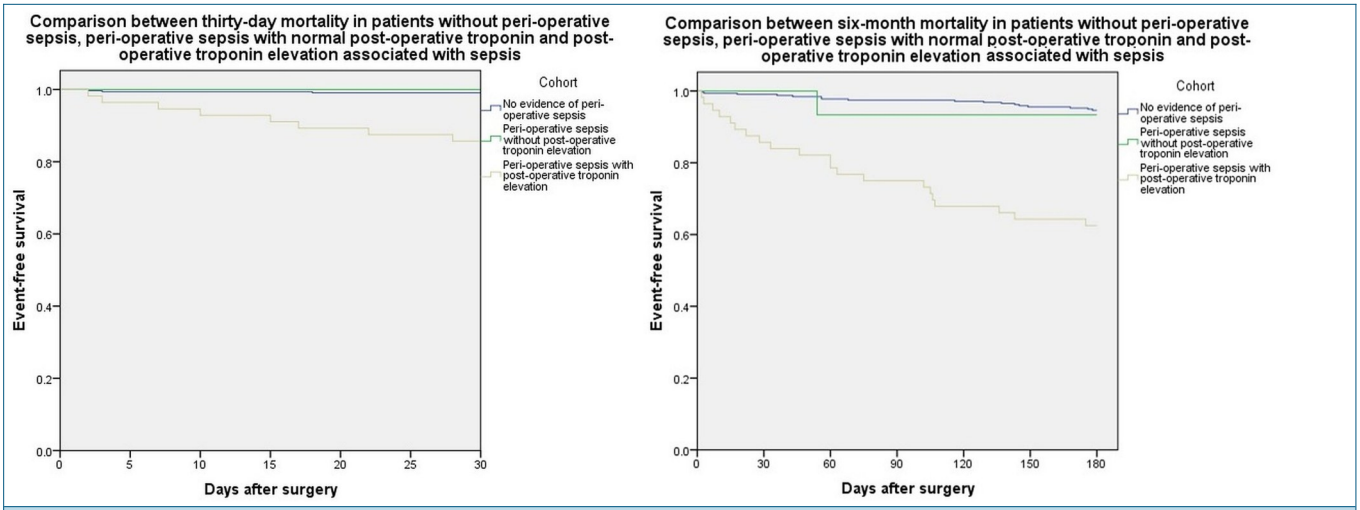

Figure 4. Kaplan Meier Survival Curve Showing 30-day and 6-month Mortality without Evidence of Perioperative Sepsis, with Perioperative Sepsis but Normal Troponin and with Perioperative Sepsis and An Elevated Postoperative Troponin in An All-Comers Cohort.

ied by Beattie et al were at low risk of adverse outcomes regardless of postoperative troponin. Of note, both VISION and BASEL-PMI report high non-cardiovascular mortality at 30-days (45% vs 55% (VISION), 41% vs 59% (BASEL-PMI) and 12-months (32% vs 68% (BASEL-PMI).

Our cohort experienced comparable 30-day mortality rates (2.8%) to the above studies; there is no published 6-month mortality data for comparison. Incidence of an elevated postoperative troponin was higher (37% vs 11.6% in VISION / 11% in Beattie et al. / 19% in Van Waes et al.); the low threshold combined with the higher-sensitivity troponin assay used will increase detection rates and recent analysis of 21,842 patients by the VISION investigators using a fifth-generation high-sensitivity troponin assay did demonstrate higher detection rates of postoperative troponin exceeding the 99th centile (35.5% vs 19% in our study) (17). Significantly raised troponins > 1000 ng/L were less common in VISION compared to our study (0.2% vs 3.4%) reflecting the lower risk patient cohort studied but experienced similarly high 30-day mortality (29.6% vs 31%). The low proportion of minor surgery and high proportion of emergency admission compared to the original VISION study (9% vs 41% and 40% vs 14% respectively) and high-sensitivity troponin VISION study (9% vs 36% and 40% vs 7.4% respectively) reflects our institution' s role as a major trauma center and will select a higher surgical risk population, potentially increasing the incidence and prognostic value of an elevated postoperative troponin.

Our cohort experienced significantly higher rates of sepsis compared to the original VISION (20% vs 5.4%), likely due to the differing definitions between the two studies. The VISION trial definition of sepsis selected patients more likely to have more severe sepsis with hemodynamic compromise. Our definition, based on blood results, positive blood cultures and clinical documentation instead of hemodynamic parameters, may include less severe infective states hence the higher incidence. However, the systemic inflammatory response associated will still be present along the possibility of associated elevations in troponin and we note that the presence of troponin significantly increases 6-month mortality in all cohorts compared to patients with sepsis but a normal post-operative troponin.

MINS – Multiple Pathophysiological Processes?

The detailed patient-level analysis permitted by our smaller study suggests that postoperative troponin elevations may represent a complex mix of multiple pathophysiological processes rather than a single disease state.

Troponin elevation may occur due to type 1 myocardial infarctions, triggered by acute coro-

Table 3. Incidence and Mortality by Peak Postoperative Troponin.

Postoperative troponin	Number of patients	30-day mortality	6-month mortality
< 17 ng/L	245 (63%)	3 / 245 (0.1%)	8 / 245 (3.3%)
17 – 40 ng/L	69 (18%)	2 / 69 (2.9%)	11 / 69 (16%)
40 – 1000 ng/L	60 (16%)	2 / 60 (3.3%)	7 / 60 (12%)
>1000 ng/L	13 (3.4%)	4 / 13 (31%)	6 / 13 (46%)
% Troponin change preop to peak postop	Number of patients	30-day mortality	6-month mortality
< 20%	242 (63%)	2 / 242 (0.8%)	7 / 242 (2.9%)
20 – 100%	49 (13%)	2 / 49 (4.1%)	10 / 49 (20%)
100 – 1000%	69 (18%)	2 / 69 (2.9%)	8 / 69 (12%)
>1000%	27 (7.0%)	5 / 27 (19%)	7 / 27 (26%)
Type of event	Falling troponin trend (of total number events)	30-day mortality (with falling troponin trend)	6-month mortality (with falling troponin trend)
All troponin elevations (i.e. > 17 ng/L)	20 / 141 (14%)	1 / 20 (5%)	7 / 20 (35%)
Primary troponin elevations	12 / 69 (17%)	0 / 12	2 / 12 (17%)
Secondary troponin elevations	8 / 72 (11%)	1 / 8 (13%)	5 / 8 (60%)
Associated with sepsis	5 / 55 (9.1%)	1 / 5 (20%)	3 / 5 (60%)
Associated with bleeding	1 / 14 (7.1%)	0 / 1 (0%)	1 / 1 (100%)
Associated with tachycardia	2 / 3 (67%)	0 / 2 (0%)	1 / 3 (33%)
No troponin elevation	17 / 246 (6.9%)	0 / 17 (0%)	1 / 17 (5.9%)

The % change between preoperative and postoperative level and associated pathophysiology with a falling troponin trend.

nary plaque rupture and thrombus formation. Gualandro et al. compared the angiographic findings of 120 patients with a perioperative acute coronary syndrome following non-cardiac surgery (PACS), 120 patients with a spontaneous ACS (SACS) and 240 patients with stable CAD (18). Complex lesions were defined by the Ambrose and Goldstein criteria (19, 20). Almost 50% of patients with PACS had evidence of plaque disruption, a finding supported by two autopsy studies (21,22) although only 7.5% had evidence of thrombus. Only patients with troponin elevation in combination with one of the ischemic symptoms, ECG changes of ischemia (ST depression or elevation) or new pathological Q waves were studied; patients with symptoms and/or ECG changes made up only 16% of the VISION cohort.

Troponin release may occur also through other mechanisms such as type 2 myocardial infarction (supply-demand imbalances along with underlying stable coronary artery disease, coronary spasm or endothelial dysfunction) or non-ischemic cardiac pathology (such as dysrhythmias, acute stress-related cardiomyopathies or inflammatory / infective processes). Altmann et al. assessed coagulation parameters in troponin-negative and troponin-positive patients with sepsis and septic shock, showing no statistical difference between the two groups (23). They suggest that mechanisms other than thrombus associated myocardial necrosis are responsible, such as reversible myocardial membrane and/or cytokine-mediated apoptosis. Raised troponin in chronic kidney disease is markedly prognostic and thought to be due to structural heart disease and/or direct toxic effects on the myocardium (25-27). In chronic left ventricular dysfunction, wall stress due to increased ventricular pressures can trigger cardiomyocyte apoptosis and autophagy causing elevated troponins (28-30), as can direct cardiac toxicity from neurohormones such as norepinephrine released peri-operatively (31). Noordzij et al. suggest that a raised troponin predisposes patients to non-cardiac complications such as bleeding, sepsis, postoperative respiratory insufficiency or wound infection although neither causality nor the underlying pathophysiology causing the tro-

Table 4. Univariate Analysis of Variables for Associations with 30-day and 6-month Mortality.

Variables	30-day Mortality		6-month Mortality	
	Hazard Ratio	P value	Hazard Ratio	P value
Age				
45 - 65	1 (Reference)		1 (Reference)	
65 – 74	2.294 (0.445 – 11.823)	P = 0.321	1.880 (0.759 – 0.466)	P = 0.173
>75	2.030 (0.372 – 11.082)	P = 0.414	2.652 (1.108 – 6.350)	P = 0.029
Male vs. Female	1.229 (0.375 – 4.029)	P = 0.733	0.778 (0.413 – 1.466)	P = 0.438
Abnormal renal function				
eGFR < 60	7.338 (1.947 – 27.661)	P = 0.003	4.734 (2.482 – 9.026)	P < 0.001
eGFR < 50	3.498 (1.067 – 11.462)	P = 0.039	4.789 (2.555 – 8.976)	P < 0.001
eGFR < 40	5.869 (1.791 – 19.233)	P = 0.003	6.030 (3.200 – 11.363)	P < 0.001
eGFR < 30	4.157 (1.103 – 15.671)	P = 0.035	3.562 (1.691 – 7.505)	P = 0.001
eGFR < 20	4.207 (0.909 – 19.473)	P = 0.066	4.599 (2.029 – 10.424)	P < 0.001
Abnormal renal function with elevated postoperative troponin	6.725 (2.052 – 22.041)	P = 0.002	7.430 (3.595 – 13.957)	P < 0.001
Emergency admission	19.9 (2.55 – 155)	P = 0.004	6.350 (3.081 – 12.982)	P < 0.001
Emergency admission with elevated post-operative troponin	10.034 (2.733 – 38.845)	P < 0.001	6.986 (3.662 – 13.325)	P < 0.001
Sepsis	11.375 (3.017 – 42.880)	P < 0.001	6.255 (3.319 – 11.790)	P < 0.001
Sepsis with elevated post-operative troponin	15.596 (4.243 – 60.308)	P < 0.001	7.856 (4.188 – 14.739)	P < 0.001
Bleeding	1.485 (0.190 – 11.596)	P = 0.706	3.412 (1.502 – 7.708)	p = 0.003
Bleeding with elevated post-operative troponin	1.799 (0.230 – 14.052)	P = 0.576	2.263 (0.697 – 7.349)	P = 0.174
Tachycardia	0	P = 0.799	2.224 (0.305 – 16.198)	P = 0.430
Tachycardia with elevated post-operative troponin	0	P = 0.820	4.196 (0.576 – 30.585)	P = 0.157
All post-operative troponin elevations	4.695 (1.246 – 17.7)	P = 0.022	6.275 (2.979 – 13.219)	P < 0.001
Primary post-operative troponin elevation	0.036 (0 – 26.807)	P = 0.325	0.802 (0.336 – 1.914)	P = 0.619

ponin elevation is established (32).

We note that the CCS guidelines recommend postoperative troponin monitoring in patients with "significant obstructive cardiac disease" (5); this definition includes severe obstructive valvular disease, hypertrophic cardiomyopathy, and pulmonary hypertension, all of which will have detectable cardiac troponin through differing non-cardiac mechanisms. To further complicate matters, sepsis and the associated systemic inflammatory response (considered a "non-ischemic" mechanism by the MINS criteria) may trigger acute plaque rupture events (33, 34).

Trials investigating therapeutic options targeting antiplatelet and anti-ischemic medications on the basis that such events represent type 1 ischemia have been negative to date (35, 36). The MANAGE trial has shown treatment with dabigatran reduces major vascular events but demonstrated no reduction in vascular or all-cause mortality with event reduction driven by less non-hemorrhagic stroke rather than the myocardial ischaemic event (37). Ausset et al. noted that optimizing factors associated with type 2 myocardial injury (hypoxemia, anemia, hypotension, tachycardia, and hyperglycemia) resulted in a 56% reduction of postoperative myocardial injury and a 75% reduction in MACE at 1 year (38).

It is not known whether elevated postoperative troponin events are more common in patients with a known obstructive coronary disease, nor whether it is worth investigating patients for

this possibility once they are stable enough postoperatively for evaluation. The investigation into the coronary anatomy of patients, either invasively or using CT coronary angiography, may determine the underlying incidence of unstable or significant coronary disease that is present in these patients and allow nuanced interpretation of these rises in troponin.

Strengths

Our sample represents an all-comer real-world population with few exclusion criteria. All suitable patients were potentially included in the study regardless of past medical history, pre-test likelihood of a positive result or nature of surgery performed.

Limitations

Our sample is much smaller than the VISION study. Data collection and troponin measurement for elective patients required a fixed operative date to trigger the process; any patients who canceled, changed their date or whose operation as delayed were lost. The retrospective nature of screening for emergency operations made data collection easier; however, patients presenting at a weekend were not included as the troponins could not be added on within 24 hours of admission and as such were not included. As such, our sample is a non-consecutive convenience sample.

As our troponin assays were performed on routinely collected blood samples, troponins were not recorded at precise intervals following surgery. Our assessment of troponin trends uses the assumption that troponins < 17 ng/L have the value of 8 ng/L. This prevents accurate calculation of trends for small values; as such, we did not include troponin trend in the univariate or multivariate analysis.

CONCLUSION

Postoperative high-sensitive troponins are associated with 30-day and 6-month mortality following non-cardiac surgery. However the picture is complex, and using troponin in isolation to guide treatment would ignore significant non-vascular pathophysiological processes that carry their own risk of mortality and require alternative therapeutic interventions. Therapeutic maneuvers aimed at atherosclerotic disease or thrombosis may have limited benefit and better methods are needed to determine which patients may benefit from conventional secondary prevention strategies. Strategies to avoid and manage both infection and renal dysfunction may have an important role to play in reducing the high mortality of these patients.

This study was supported by grants from the the Regional Innovation Fund of NHS England and internally by the South Tees NHS Foundation Trust Research and Development Fund.

The authors have no other potential conflicts of interest for this work.

References

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008; 372 (9633):139-44.
2. Devereaux PJ, Chan M, Eikelboom J. Major Vascular Complications in Patients Undergoing Non-Cardiac Surgery: Magnitude of the Problem, Risk Prediction, Surveillance, and Prevention. In: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, eds. Evidence-Based Cardiology. 3rd ed. London, UK: Blackwell Publishing Ltd, 2009:47-62.
3. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012; 307:2295-304.
4. Botto F, Alonso-Coello P, Chan M, Villar JC, Xavier D, Srinathan S, et al. Myocardial Injury after Noncardiac surgery. A Large International Prospective Cohort Study Establishing Diagnostic Criteria, Characteristics, Predictors and 30-day outcomes. *Anesthesiology* 2014;120(3):564-78.
5. Duceppe E, Parlow J, MacDonald P, Lyons K, McMullen M, Srinathan S, et al. Canadian Cardiovascular Society Guidlins on Perioperative Cadiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. *Can J Cardiol* 2017;33:17-23.
6. Apple FS, Collinson PO; IFCC Task Force on Clinical Applications of Cardiac Biomarkers. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem* 2012;58(1):54-61.
7. Sherwood MW, Kristin Newby L. High-sensitivity troponin assays: evidence, indications, and reasonable use. *J Am Heart Assoc* 2014;3(1):e000403.
8. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.
9. Mehran R, Rao SV, Bhatt L, Gibson CM, Caixeta A, Eikelboom J, et al. Standardised Bleeding Definitions for Cardiovascular Clinical Trials: A Consensus Report From the Bleeding Academic Research Consortium. *Circulation* 2011;123:2736-47.
10. The National Institute for Health and Care Excellence (NICE). NICE Guideline for Blood Transfusion (18 November 2015). (Accessed November 12, 2018, at https://www.nice.org.uk/guidance/ng24/resources/blood-transfusion-1837331897029.)
11. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, et al. 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.
12. Beattie WS, Karkouti K, Tait G, Steel A, Yip P, McCluskey S, et al. Use of clinically based troponin underestimates the cardiac injury in non-cardiac surgery: a single-centre cohort study in 51,701 consecutive patients. *Can J Anaesth* 2012;59(11):1013-22.
13. van Waes JA, Nathoe HM, de Graaff JC, Kemperman H, de Borst GJ, Peelen LM, et al. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation* 2013;127:2264-71.

14. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med* 2011;154(8):523-8.
15. Levy M, Heels-Ansdell D, Hiralal R, Bhandari M, Guyatt G, Yusuf S, 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(4):796-806.
16. Puelacher C, Lurati Buse G, Seeberger D, Sazgary L, Marbot S, Lampart A, et al. Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, and Characterization. *Circulation* 2018; 137 (12):1221-32.
17. Writing Committee for the VISION Study Investigators, Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MTV, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. *JAMA* 2017; 317(16): 1642-51.
18. Gualandro DM, Campos CA, Calderaro D, Yu PC, Marques AC, Pastana AF, et al. Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: frequent and dangerous. *Atherosclerosis* 2012;222(1):191-5.
19. Ambrose JA, Israel DH. Angiography in unstable angina. *Am J Cardiol* 1991;68(7):78B-84B.
20. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med* 2000;343(13):915-22.
21. 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(1):37-44.
22. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. *Cardiovasc Pathol* 1999;8(3):133-9.
23. Altmann DR, Korte W, Maeder MT, Fehr T, Haager P, Rickli H, et al. Elevated cardiac troponin I in sepsis and septic shock: no evidence for thrombus associated myocardial necrosis. *PLoS One* 2010;5(2): e9017.
24. Fernández-Reyes MJ, Mon C, Heras M, Guevara P, Garcia MC, Sanchez R, et al. Predictive value of troponin T levels for ischemic heart disease and mortality in patients on hemodialysis. *J Nephrol* 2004;17 (5):721-7.
25. Aviles RJ, Askari AT, Lindahl B, Wallentin L, Jia G, Ohman EM, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med* 2002;346(26): 2047-52.
26. Mallamaci F, Zoccali C, Parlongo S, Tripepi G, Benedetto FA, Cutrupi S, et al. Troponin is related to left ventricular mass and predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 2002;40(1):68-75.
27. deFilippi C, Wasserman S, Rosanio S, Tiblier E, Sperger H, Tocchi M, et al. Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. *JAMA* 2003;290(3): 353-9.
28. Canty JM, Lee TC. Troponin I Proteolysis and Myocardial Stunning: Now You See It-Now You Don't. *J Mol Cell Cardiol* 2002;34(4):375-7.
29. Feng J, Schaus BJ, Fallavollita JA, Lee TC, Canty JM Jr. Preload induces troponin I degradation independently of myocardial ischemia. *Circulation* 2001; 103(16):2035-7.
30. Shih H, Lee B, Lee RJ, Boyle AJ. The aging heart and post-infarction left ventricular remodeling. *J Am Coll Cardiol* 2011;57(1):9-17.
31. Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation* 2007; 116(11): 1242-9.
32. Noordzij PG, van Geffen O, Dijkstra IM, Boerma D, Meinders AJ, Rettig TC, et al. High-sensitive cardiac troponin T measurements in prediction of noncardiac complications after major abdominal surgery. *Br J Anaesth* 2015;114(6):909-18.
33. Madjid M, Vela D, Khalili-Tabrizi H, Casscells SW, Litovsky S. Systemic infections cause exaggerated local inflammation in atherosclerotic coronary arteries: clues to the triggering effect of acute infections on acute coronary syndromes. *Tex Heart Inst J* 2007; 34(1):11-8.
34. Kaynar AM, Yende S, Zhu L, Frederick DR, Chambers R, Burton CL, et al. Effects of intra-abdominal sepsis on atherosclerosis in mice. *Crit Care* 2014;18(5):469.
35. POISE Study Group, Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008;371(9627):1839-47.
36. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, et al. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med* 2014; 370(16):1494-503.
37. Devereaux PJ, Duceppe E, Guyatt G, Tandon V, Rodseth R, Biccard BM, et al. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. *Lancet* 2018;391(10137):2325-34.
38. Ausset S, Auroy Y, Verret C, Benhamou D, Vest P, Cirodde A, et al. Quality of postoperative care after major orthopedic surgery is correlated with both long-term cardiovascular outcome and troponin Ic elevation. *Anesthesiology* 2010;113(3):529-40.