Myocardial injury after noncardiac surgery: facts, fallacies and how to approach clinically

Michelle Chew and Christian Puelacher

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https://doi.org/10.1097/MCC.0000000000000885

Original publication available at:
https://doi.org/10.1097/MCC.0000000000000885

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http://www.lww.com/
Identification of myocardial injury using perioperative troponin surveillance in major noncardiac surgery and net benefit over the Revised Cardiac Risk Index

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<tr>
<th>Journal:</th>
<th><em>British Journal of Anaesthesia</em></th>
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<tbody>
<tr>
<td>Manuscript ID</td>
<td>BJA-2021-00464-PM022.R3</td>
</tr>
<tr>
<td>Article Type:</td>
<td>Clinical Investigation</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>n/a</td>
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</table>
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**Keywords:** biomarker, cardiac troponins, MINS, myocardial injury, perioperative
Identification of myocardial injury using perioperative troponin surveillance in major noncardiac surgery and net benefit over the Revised Cardiac Risk Index

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Short running title: Troponin surveillance in major noncardiac surgery

Key words: biomarker, cardiac troponins, MINS, myocardial injury, perioperative

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT03436238

Total word count: 4109
ABSTRACT

Background: The optimal approach for identifying patients with perioperative myocardial injury and at risk of death and Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) is unknown. The primary aim of this study was to determine optimal thresholds of preoperative and perioperative changes in hs-cTnT to predict MACCE and mortality.

Methods: Prospective, observational, cohort study in patients ≥50 years of age undergoing elective major non-cardiac surgery at seven hospitals in Sweden. The exposures were hs-cTnT measured before and days 0 to 3 after surgery. Two previously published thresholds for myocardial injury and two thresholds identified using ROC analyses were evaluated using multivariable logistic regression models and externally validated. The weighted comparison net benefit method was applied to determine the additional value of hs-cTnT thresholds when compared to the revised cardiac risk index (RCRI). The primary outcome was a composite of 30-day all-cause mortality and MACCE.

Results: We included 1291 patients between April 2017-Dec 2020. The primary outcome occurred in 124 patients (9.6%). Perioperative rise in hs-cTnT≥14ng L⁻¹ above preoperative values provided statistically optimal model performance and was associated with the highest risk for the primary outcome (aOR 2.9, 95% CI 1.8-4.7). Validation in an independent, external cohort confirmed these findings. A net benefit over RCRI was demonstrated across a range of clinical thresholds.

Conclusions: Perioperative rises in hsTnT≥14ng L⁻¹ above baseline values identifies acute perioperative myocardial injury and provides a net benefit when added to RCRI for the identification of patients at high risk of death and MACCE.
Introduction

Cardiac troponins (cTns), as quantitative markers of cardiomyocyte injury, are commonly elevated after non-cardiac surgery.\textsuperscript{1-6} The vast majority of patients do not fulfil the universal definition of myocardial infarction or experience ischaemic symptoms.\textsuperscript{1-3, 7} Yet, increased perioperative levels of cTns independently increase the risk of 30-day and long-term mortalities, and postoperative elevations are important indicators of poor outcome in otherwise asymptomatic patients.\textsuperscript{1-8} Current guidelines recommend screening patients at high-risk of cardiovascular complications by measurement of cTns.\textsuperscript{9-11} However, screening is hampered by the lack of guidance regarding appropriate cut-off levels, the timing of measurements, and available interventions.

Limited data exist for the value of cTns when added on to the Revised Cardiac Risk Index (RCRI) for preoperative risk stratification. The independent prognostic value of increased cTns in the presence of other determinants of perioperative outcomes are also poorly investigated.\textsuperscript{12,13,14} Although there is a general consensus favouring the high-sensitivity troponin assays, various definitions and cut-off values have been applied in previous studies. Elevations in preoperative cTns also occur commonly\textsuperscript{1-5, 8, 12} and may portend significant morbidity and mortality postoperatively.\textsuperscript{3, 8, 12-17} This raises concerns for preoperative risk stratification and a potential dilemma for the management of these patients prior to surgery.

Measurement of pre- and postoperative cTns are advocated for perioperative screening to differentiate acute perioperative myocardial injury from pre-existing chronic myocardial injury. The association of acute perioperative myocardial injury with mortality and/or major adverse cardiovascular and cerebrovascular events (MACCE) has been demonstrated in several studies.\textsuperscript{1-4, 6, 8, 13} Puelacher et al. found that the combination of increased preoperative high-sensitivity troponin T (hs-cTnT) and a perioperative change of $\geq 14$ ng L$^{-1}$ were associated with the highest risks for short- and long-term mortalities.\textsuperscript{3} Other studies
emphasize the role of postoperative cTn surveillance.\textsuperscript{1, 2, 6} Notably, all studies have applied different criteria to define perioperative myocardial injury and none have derived or externally validated diagnostic thresholds for the prediction of major adverse cardiovascular and cerebrovascular events and mortality.

Thus, ambiguity still exists regarding timing and optimal threshold values of cTns for prediction of adverse cardiovascular outcomes. There are no comparative studies of perioperative cTn thresholds for the diagnosis of myocardial injury, and none of the established thresholds have been externally validated.

The primary aim of this study was to determine optimal thresholds of preoperative hs-cTnT and perioperative changes in hs-cTnT for the prediction of MACCE and mortality within 30 days after surgery. A secondary aim was to provide an external validation for the identified thresholds. Finally, we aimed to provide a decision analysis that may help clinicians compare the net benefit of using hs-cTnT when added to the RCRI.
Methods

We adhered to the STROBE and STARD reporting guidelines (Supplementary Table 1). The study was approved by the Regional Ethical Review Committee (Linköping, Sweden; 29 March 2017) and registered at clinicaltrials.gov (NCT 03436238). All participants gave written informed consent.

We conducted a multicentre, prospective cohort study of patients aged ≥50 years undergoing elective, major abdominal surgery and requiring at least one overnight hospital stay.

Consecutive patients from 7 hospitals in Sweden (3 university and 4 regional hospitals) were included between April 2017-December 2020. Major abdominal surgery was defined as major or complex major, according to the Surgical Outcome Risk Tool. Baseline characteristics, intraoperative and postoperative variables were recorded and RCRI calculated for all patients (Table 1). Preoperative anaemia was defined as Hb <130 g L\(^{-1}\) for men and <120 g L\(^{-1}\) for women, preoperative increased creatinine was defined as plasma levels of creatinine ≥100 µmol L\(^{-1}\) for men and ≥90 µmol L\(^{-1}\) for women, intraoperative transfusion was defined as intraoperative transfusion of any blood product and intraoperative hypotension was defined as MAP<55 mmHg at any time intraoperatively (regardless of duration). The presence of ischaemic symptoms and 12-lead ECGs were recorded up to 24h prior to surgery, after surgery at the postoperative care unit (PACU), and on days 1,2 and 3 after surgery or until discharge from hospital (for definition, see Supplementary Table 2). Blood was collected at these sampling points, plasma aliquoted and stored at -80°C until batch analysis. Hs-cTnT was measured by an electrochemiluminescence-immunoassay on a Cobas e602/Cobas e601/Cobas e411 analyzer (Roche Diagnostics, Mannheim, Germany). The lower limit of detection for hs-cTnT was 3 ng L\(^{-1}\) with a 10% coefficient of variation at 13 ng L\(^{-1}\). The 99th percentile for a normal health population for this assay is 14 ng L\(^{-1}\).
Collection of ECGs, plasma samples and clinical symptom assessment were conducted by trained research staff outside of routine care. In order to mitigate the risk of detection and reporting bias these were collected, analysed and interpreted blindly. Plasma samples were analysed in batch by a central laboratory without knowledge of clinical status and ECG findings; and clinical data were collected by without knowledge of ECG and hs-cTnT findings. Treating teams were not given access to these non-routine investigations. However, routine care may have included the measurement of hs-cTnT and ECGs, and these results were not available to study assessors. Data entry into a centralised General Data Protection Regulation-compliant secure electronic database was conducted by investigators at each site and validated by the study coordinators.

The primary outcome was the composite of all-cause mortality and MACCE at 30 days after surgery. MACCE was defined as non-fatal cardiac arrest, acute myocardial infarction, congestive heart failure, new cardiac arrhythmia, angina and/or stroke (Supplementary Table 3).  

**Statistical analysis**

Sample size was calculated assuming a prevalence of elevated hs-cTnT of 10% with an estimated incidence of the primary outcome of 6.8% in the non-elevated hs-cTnT group. The calculation was powered to detect a relative difference of 10% between elevated and non-elevated hs-cTnT groups, for both primary and secondary (one year mortality) outcomes. Secondary outcomes are not presented in this study. The largest calculated sample size was 1142. Sample size was increased to 1600 patients to account for a missing data rate of 33%. On 18 June 2019, interim data was submitted (716 patients) to an independent Data Safety and Monitoring Board (DSMB). Since the frequencies of the outcomes were in line with original expectations and the missing data rate was low, the DSMB allowed a sample size
revision to 1269 patients. This sample size also allowed for adjustment of 10 independent
factors in a multivariable analysis, assuming an event rate of 8% in the whole population.
Patients with missing preoperative hs-cTnT or without at least one postoperative hs-cTnT
measurement, and those with missing follow-up at 30 days were not included in the analysis.
Summary statistics are presented as mean (SD), median (IQR) or number (%). The magnitude
of the exposure effect estimate was reported as an adjusted odds ratio (OR) with 95%
confidence intervals. P-values were two-sided with a significance level of 5%. We used the
Chi² test to compare patients with or without the primary outcome. Analyses were conducted
using Stata Statistical Software, StataCorp, Release 14.
Receiver operating characteristic (ROC) analysis was conducted to identify the optimal cut-
off concentrations for preoperative levels and perioperative increases (peak postoperative
minus preoperative value) in hs-cTnT, defined according to Youden's J-index for best
discrimination of the primary outcome. For each hs-cTnT threshold we summarized
sensitivity, specificity, positive and negative predictive values (Supplementary Table 4).
We investigated four thresholds for perioperative myocardial injury: 1) preoperative hs-cTnT
defined by ROC analysis 2) perioperative increase defined by the Basel-PMI study,³ i.e. an
increase in perioperative hs-cTnT of ≥14 ng L⁻¹ above preoperative values 3) perioperative
change defined by the VISION study,² i.e. a postoperative concentration 20 to <65 ng L⁻¹ with
an absolute change of ≥5 ng L⁻¹ or a postoperative concentration of ≥65 ng L⁻¹ and 4)
perioperative increase defined by ROC analysis. Peak postoperative values regardless of the
day of sampling were used in these calculations.
Univariable analyses were conducted to identify possible associations between a priori
defined predictor variables and the primary outcome and multivariable logistic regression was
applied to test their independent associations. Predictor variables were chosen based on
clinical plausibility and previous evidence and entered into the final model using backward
stepwise elimination. Collinearity was assessed using the variance inflation factor (VIF), and only variables with VIFs ≤10 were entered into the models (Table 3).

Model performance was assessed using ROC analyses with the probability of the outcome calculated from the logistic regression analysis. Discrimination of the model was reported as the c-index. Overall calibration and goodness of fit was assessed with the Hosmer-Lemeshow test, plots of predicted vs observed probabilities of the outcome and the Akaike Information Criterion (AIC, lower scores indicate better fit). The Brier score was used to indicate accuracy of prediction. Net reclassification indices for each of the four hs-cTnT thresholds were calculated (Supplementary Table 5).

To explore the value of adding perioperative hs-cTnT to the RCRI, the weighted comparison (WC) net benefit method was used that takes into account the prevalence of outcome. ‘Extended RCRI’ was calculated by adding +1 to the RCRI score, when the hs-cTnT test was ‘positive’ as defined by the various thresholds. Because all patients in this study had a RCRI score of at least one (major surgery), an extended RCRI score ≥2 was considered ‘test positive’. WC for the extended RCRIIs compared to RCRI alone were calculated as:

\[ \Delta \text{Sensitivity} + [(1 - \text{prevalence}/\text{prevalence}) \times \text{clinical threshold} \times \Delta \text{Specificity}] \]

where

\[ \Delta \text{Sensitivity} = \text{Sensitivity}_{\text{extended RCRI}} - \text{Sensitivity}_{\text{RCRI alone}} \]

and

\[ \Delta \text{Specificity} = \text{Specificity}_{\text{extended RCRI}} - \text{Specificity}_{\text{RCRI alone}} \]

The clinical threshold is the ratio of true positives to false positives (TP:FP). Thus, the WC method weights differences in sensitivity and specificity by a trade-off of acceptable clinical TP:FP ratios, and takes into account disease prevalence. Positive WC values indicate a net benefit and negative values indicate a net loss. We extended the WC method by constructing...
weighted comparison curves to aid clinicians in making informed choices regarding the net
benefit of measuring hs-cTnT in this population across a range of clinical thresholds.

Two sensitivity analyses were conducted. The first was restricted to patients with preoperative
creatinine within the normal range reported for Swedish laboratories (male≤100 µmol L⁻¹, 
female≤90 µmol L⁻¹); in the second analysis patients with increased perioperative troponins
due to non-ischaemic causes (e.g., pulmonary emboli, sepsis) were excluded.

The four hs-cTnT thresholds obtained in our population were externally validated in an
independent population consisting of 271 patients undergoing major abdominal surgery at the
University Hospital Basel, Switzerland. Although the same inclusion and outcome criteria
were applied in both populations, the Basel cohort was retrospective and consisted entirely of
patients with or at risk of cardiovascular disease. Also, hs-cTnT was measured within 30 days
before surgery and on postoperative days 1 and 2, according to perioperative routine in Basel.

We calculated sensitivities, specificities, PPV, NPV and the c-statistics for the different hs-
cTnT thresholds in this population. Finally, we applied logistic regression analysis to
calculate the ORs for 30-day mortality and MACCE in this external cohort.
Results

A total of 1368 patients were recruited to the study, of which 1291 were included in the final analysis (Figure 1). Population characteristics are shown in Table 1. The primary outcome occurred in 9.6% (124 patients) of patients, with a mortality rate of 1.1% (14 patients) and MACCE of 9.3% (120 patients). The missing data rate was very low (approx. 1%, Table 1).

Preoperative and at least one postoperative hsTnT measurement was available for all patients. Peak hs-cTnT levels occurred on day 2 (median 12.1 ng L$^{-1}$, IQR 8.2-19.9).

We performed ROC analyses to identify the best thresholds in hs-cTnT when measured preoperatively or as perioperative change (peak postoperative-preoperative value). The ROC analysis identified that a preoperative hs-cTnT of $\geq 14$ ng L$^{-1}$ (AUC 0.64, CI 0.58-0.69) and a perioperative increase in hs-cTnT of $\geq 5$ ng L$^{-1}$ (AUC 0.67, CI 0.62-0.72) provided best discriminatory values for the primary outcome. The incidence of MACCE and all-cause mortality at 30 days after surgery stratified by the two hs-cTnT thresholds as well as two previously published thresholds for myocardial injury (Basel-PMI study and VISION study) are shown in Table 2. Sensitivities, specificities, positive and negative predictive values for all four hs-cTnT thresholds are provided in the Supplementary table 4, and their net reclassification indices are reported in Supplementary table 5.

Univariable analyses were applied to investigate the association of the four thresholds as well as a priori defined predictor variables with the primary outcome (Supplementary table 6). Age, sex, ASA-PS class, cardiovascular medications, comorbidities, preoperative anemia, preoperative increased creatinine, surgical category, intraoperative transfusion, length of surgery, RCRI and hs-cTnT were associated with 30-day MACCE and all-cause mortality.

We tested the independent association of the pre- and perioperative increases in hs-cTnT with the primary outcome using multivariable regression (Table 3). Performance statistics are given in Table 4 and calibration plots are provided in Supplementary Figure 1. The Basel-
PMI definition (Perioperative increase ≥14 ng L\(^{-1}\) above preoperative value) had the highest prediction accuracy (Brier 0.080), provided the best fit among the 4 tested models (AIC 746) and was associated with the highest aOR for the primary outcome, thus we considered this to be statistically optimal among the 4 thresholds tested.

The majority of myocardial injuries were detected by Day 2 postoperatively (Table 5), and 1281 (99.2%) of all patients did not have ischaemic symptoms. For hs-cTnT, there were 1250 PACU measurements and 1244 day 1 measurements, 1102 day 2 measurements, and 816 day 3 measurements; and a total of 752 patients had measurement for all 5 sampling points. The majority of unavailable hs-cTnT data for days 2 and 3 were due to discharge. Although all 1291 patients fulfilled our prespecified criteria of a preoperative and at least one postoperative hsTnT measurement for inclusion in the study, we cannot exclude that the true incidence of myocardial injury may have been underestimated. Preoperative increased hsTnT was detected in 349 (27%) and perioperative increases in 11.2-34.2% depending on the threshold used.

Sensitivity analyses

In order to evaluate the effect of preoperative renal dysfunction, we restricted the multivariable model to patients without preoperative creatinine increases (Supplementary Table 7). We further evaluated the independent association between hs-cTnT and the primary outcome excluding patients with non-ischemic causes of troponin elevation (eg. sepsis and pulmonary embolus) (Supplementary table 8). Both analyses confirmed the results of the primary model.

Net benefit of hs-cTnT beyond RCRI

Weighted comparisons were calculated and plotted across a range of clinical thresholds (Figure 2). Extrapolation of all WC curves show that measurement of perioperative hs-cTnT changes was associated with a net benefit compared to RCRI alone for clinical thresholds
<0.29, corresponding to >3.4 false positives for each true positive. At clinical thresholds
≥0.18 (≤5.6 false positives for each true positive), the Basel-PMI definition provided the best
net benefit. At clinical thresholds between 0.18 and 0.03 (5.6 to 33.3 false positives for each
ture positive) the VISION definition provided the best net benefit. At clinical thresholds
≤0.03 (≥33.3 false positives for each true positive) the definition determined by ROC analysis
in this population provided the best net benefit.

7 External validation

We externally validated the hs-cTnT thresholds in an independent population (n=271).
Population characteristics for this independent cohort are shown in Supplementary table 9.
Odds ratios and performance characteristics of the different hs-cTnT thresholds are shown in
Supplementary table 10. The odds ratio for the primary outcome was highest when applying a
threshold of perioperative increase in hs-cTnT of ≥14 ng L⁻¹, even after adjustment for RCRI
and other factors (aOR 11.2, 95% CI 4.9-25.5).
Discussion

An increase in hs-cTnT≥14 ng L\(^{-1}\) above preoperative values identified acute perioperative myocardial injury, demonstrated the highest risk estimates for the primary outcome and provided a net benefit across a wide range of clinical thresholds.

All four thresholds for acute perioperative myocardial injury were independently associated with 30-day MACCE and all-cause mortality. When model performance was assessed using c-statistics, Brier scores and the AIC, the model incorporating the Basel-PMI threshold provided best performance characteristics, although the differences were modest. In a multivariable model, patients with elevated hs-cTnT before surgery were at increased risk of the primary outcome, and this risk was amplified if hs-cTnT was elevated further. Further, the model with the Basel-PMI threshold provided highest adjusted odds ratio for mortality and MACCE, a finding confirmed in the external validation cohort and sensitivity analyses. The weighted comparisons analysis demonstrated that all tested thresholds for perioperative myocardial injury provided a net benefit over RCRI alone. However, the model using a dynamic change in hs-cTnT, with increases ≥14 ng L\(^{-1}\) above preoperative values performed best.

Our findings add to previous studies that often do not take into account RCRI, ASA-PS class, preoperative anaemia, intraoperative transfusion, intraoperative hypotension (IOH) and length of surgery that are known risk factors for poor perioperative outcomes\(^{10,11,21-28}\). The independent association between hs-cTnT and the primary outcome was confirmed by sensitivity analyses excluding patients with pre-existing renal dysfunction and non-cardiac causes of hs-cTnT increases (e.g., sepsis and pulmonary emboli). Preoperative anaemia, the presence of 3 or more comorbidities, length of surgery, RCRI and hs-cTnT were the most important risk factors for 30-day mortality and MACCE.
Our study highlights the presence of modifiable risk factors such as preoperative anaemia and length of surgery, where targeted management may improve outcomes. We provide support for the value of enhanced preoperative risk stratification with the addition of hsTnT to the RCRI to identify a group of very high-risk patients. While no evidence-based guidance exists to support any preoperative strategy to improve outcomes in such a risk group, identification of increased risk may provide incentives for meticulous perioperative management such as patient blood management, increased haemodynamic monitoring, increased postoperative monitoring and optimization of cardiovascular medications.

The strength of association with the primary outcome was most marked when perioperative changes in hs-cTnT are considered, and preoperative measurements alone do not provide information on acute perioperative events. Thus, our results support the measurement of perioperative hs-cTnT increases, rather than preoperative hs-cTnT alone. These findings are congruent with an earlier study that demonstrated a stepwise increase in risk of adverse cardiovascular events when perioperative changes occur in addition to increased preoperative hsTnT levels.

Ambiguity regarding appropriate cut-off values for defining acute perioperative myocardial injury has led to considerable difficulty in evaluating the utility of hs-cTnT in perioperative care. We derived and externally validated two hs-cTnT thresholds based on ROC analysis in the current population, as well as provide an external validation for two previously published definitions. We also make head to head comparisons of 4 multivariable models that included each of the hs-cTnT thresholds, and a model without hs-cTnT. Although summary statistics such as sensitivity, specificity, negative and positive predictive values and c-indices are informative, they provide limited value for implementation in clinical practice.
Difficulties in determining optimal sensitivity and specificity trade-offs, and lack of a nuanced consideration between clinical benefit vs risk are limitations with these performance statistics. We also note that ROC curves provided only modest values of the c-index, in line with previous studies. However, ROC curves do not provide an adequate summary statistic since they combine accuracies across a wide range of thresholds and may not highlight thresholds that are most clinically relevant. Calculation of the net reclassification index (NRI) may be misleading, since it does not account for disease prevalence. The net absolute reclassification index (NARI) is an adjustment of NRI to include disease prevalence, however true positive classifications are still weighted equally as true negative classifications, which may be unreasonable within the perioperative context where correct classification of true positives may be more meaningful. We assume that most clinicians (and patients) would value missing a life-threatening disease higher than diagnosing a healthy patient as positive.

We used the weighted comparison net benefit method to provide an aid to clinical decision making since this method takes into account both disease prevalence and TP:FP ratios (clinical threshold). Rather than choosing an arbitrary TP:FP ratio, we plotted the net benefit over a range of clinical thresholds (Figure 2). All four thresholds including preoperatively elevated hs-cTnT, demonstrated net benefits compared to RCRI alone when the clinical threshold was <0.29. Perioperative hs-cTnT measurement, when using the Basel-PMI definition, provided a net benefit compared to RCRI alone at clinical thresholds between 0.18-0.29. The other definitions also provided a net benefit compared to RCRI alone but incurred a higher cost in terms of decreased TP:FP ratios. Thus, increased detection of disease should be weighed against increased probability of false positives, and the distress and unnecessary investigations that this may entail. For risk averse clinicians, where many more false positives than true positives are accepted, the net benefit was highest for increased hs-cTnT ≥5 ng L⁻¹, that provided a net benefit at clinical thresholds ≤0.03. For clinical thresholds
>0.29, accepting less than 3.4 false positives to each true positive, there was no net benefit of adding hs-cTnT measurement to the RCRI.

The present results fill a gap in knowledge regarding the utility of cardiac troponins in perioperative care. We obtained pre- and postoperative troponin measurements, ECGs and clinical information regarding ischaemic symptoms in all patients, regardless of clinical indication. Thus, we provide an unbiased indication of the true incidence of acute myocardial infarction, that has been a limitation in previous studies. The most appropriate thresholds to apply for perioperative hs-cTnT surveillance have not been previously investigated and our study provides an analysis of 2 previous definitions for perioperative hs-cTnT changes and 2 data-derived thresholds. The optimal threshold was comprehensively tested by multiple methods and their predictive value identified after careful adjustment for pre and perioperative risk factors. Further, our findings were externally validated. We present evidence for the use of acute perioperative hs-cTnT changes, rather than pre- or postoperative measurements alone, in line with the recently published recommendations of the StEP COMPAC: cardiovascular outcomes initiative. A decision analysis is provided to help clinicians consider the risk and benefits of hsTnT measurements across a wide range of clinical thresholds. We suggest that hsTnT measurements may be used as a 2-step risk management process: a first step with preoperative hsTnT measurement for the identification of high-risk patients beyond the RCRI, that may be subject to enhanced perioperative management strategies; a second step with perioperative hsTnT changes for the early detection of myocardial injury.

The implementation of hs-cTnT surveillance is costly and many clinicians argue that this may be futile in the absence of evidence-based guidelines for management. However, we argue that clinically accepted risk stratification tools such as the RCRI are also not coupled to...
specific perioperative management strategies. Recent studies suggest that MINS is amenable
to treatment. In order to minimize the cost and inconvenience of blood sampling our data
suggests that a minimum of 3 measurements, taken preoperatively and on days 1 and 2
postoperatively (earlier if the patient is discharged), would detect the majority of myocardial
injuries. Measurement of both pre- and postoperative hs-cTnT will also differentiate between
acute and chronic myocardial injury, consistent with the recommendation of the consensus
statement issued by the Joint European Society of Cardiology/American College of
Cardiology/American Heart Association/World Heart Federation Task Force for the Universal
Definition of Myocardial Infarction.

Several limitations of this study should be mentioned. Firstly, the findings of this study only
apply to hs-cTnT and not troponin I. Although we have included the most important
independent variables in the multivariable analysis, the possibility of unadjusted factors
remains. None of our patients underwent further cardiac assessments within the context of our
study, thus it is not possible to attribute a cause for increased hs-cTnT. Whilst our study
provides evidence for hs-cTnT surveillance, we stress that net benefit is highly dependent on
clinically acceptable levels of TP:FP ratios. Although hs-cTnT screening will detect
perioperative myocardial injury, only one in 4.4 patients will develop MACCE or die within
30 days of surgery when using the best-performing of the evaluated hs-cTnT thresholds in
addition to the RCRI.

This is especially important when considering future management of patients with increased
perioperative hs-cTnT. In MANAGE, the only trial investigating treatment of patients with
MINS, Dabigatran reduced the risk of major vascular complications without increasing the
risk of major bleeding. However, the hs-cTnT criterion for defining MINS was an absolute
change of at least 5 ng L\(^{-1}\) between any two (mostly postoperative) measurements. Whether
the application of the thresholds defined in the present study may more adequately select patients at increased risk, and whether this translates to better post-interventional outcomes would be relevant questions for future research. Finally, there is still no consensus on management of patients with perioperative myocardial injury.

Conclusions

An increase in hs-cTnT ≥14 ng L⁻¹ above preoperative values identified acute perioperative myocardial injury and was independently associated with 30-day all-cause mortality and MACCE. Perioperative hs-cTnT surveillance provided a net benefit over RCRI for the identification of patients at high risk of death and MACCE.
1 Authors’ contributions

2 Drs Chew and H Andersson had full access to all data in the study and take responsibility for
3 the integrity of the data and the accuracy of the data analysis. Concept and design: Chew, H
4 Andersson, Fredriksson, Pearse, Puelacher. Acquisition: Chew, Puelacher, Hammarskjöld,
5 Lyckner, Kollind, Jawad, U Andersson, Sperber, Johnsson, Elander, Zeuchner, Lindhart, De
6 Geer, Gääw Rolander, Gagnö, Didriksson, H Andersson, Puelacher, Muller. Analysis and
7 data interpretation: H Andersson, Patel, Fredriksson, Puelacher, Chew, Muller. Drafting of the
8 manuscript: Chew, H Andersson, Pearse, Puelacher.
9 Critical revision of manuscript for important intellectual content: all
10 Obtained funding: Chew, H Andersson

12 Acknowledgements

13 We wish to acknowledge all staff at the Department of Anaesthesiology and Intensive Care
14 and Department of Surgery at participating hospitals for their care of patients and their
15 contribution to our study. We also thank Martin Golster, Anna Oscarsson Tibblin, Anneli
16 Reinhöldsson, Carina Blomqvist, and Jonas Andersson for excellent study support.

18 Declaration of interests

19 Dr. Chew has received speaker’s fees and honoraria from B Braun AB and Edwards
20 Lifesciences outside the submitted work and holds editorial roles with the European Journal
21 of Anaesthesiology. Dr. Mueller has received research support from the Swiss National
22 Science Foundation, the Swiss Heart Foundation, the KTI, the University Hospital Basel, the
23 University of Basel, Abbott, Astra Zeneca, Beckman Coulter, Idorsia, Novartis, Ortho
Clinical Diagnostics, Quidel, Roche, Siemens, as well as speaker honoraria/consulting
honoraria from Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo,
Idorsia, Novartis, Osler, Roche, and Sanofi, outside the submitted work. Dr. Puelacher reports
research funding from Roche Diagnostics, the University of Basel, the University Hospital
Basel, for the submitted work, as well as chaired an advisory board on perioperative
myocardial injury for Roche Diagnostics. Dr. Pearse reports grants from NIHR, grants and
personal fees from Edwards Life Sciences, outside the submitted work; and has given lectures
and/or performed consultancy work for Nestle Health Sciences, BBraun, Intersurgical,
GlaxoSmithKline and Edwards Lifesciences, and holds editorial roles with the British Journal
of Anaesthesia, and the British Journal of Surgery.

Funding
Funded by the Swedish Research Council grants 2019-02833, South Eastern Sweden
Research Council grants 746981, 712291 and Linköping University-Region Östergötland
ALF grants 687681, 792291. The BASEL-PMI study was supported by research grants from
the Swiss National Science Foundation grants 320030-179362, Swiss Heart Foundation,
University of Basel, University Hospital of Basel, Astra Zeneca, and Roche.
Role of funder: The funding organizations had no role in the design and conduct of the study;
collection, management, analysis, and interpretation of the data; preparation, review, or
approval of the manuscript; and decision to submit the manuscript for publication.

Appendices
Supplementary Table 1, STROBE and STARD documents
Supplementary Tables 2-3, definitions
1. Supplementary Figure 1, calibration plots
2. Supplementary Table 4, Sensitivities, specificities, positive and negative predictive values for each of the hsTnT thresholds
3. Supplementary Table 5, Net reclassification index for all tested thresholds of hs-cTnT
4. Supplementary Table 6, Univariable analysis
5. Supplementary Tables 7-8, Sensitivity analyses
6. Supplementary Tables 9-10, Results external validation cohort
References


Table 1. Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number with data (%)</th>
<th>Whole population</th>
<th>With primary outcome (n=124)</th>
<th>Without primary outcome (n=167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years, IQR)</td>
<td>1291 (100%)</td>
<td>70 (63-76)</td>
<td>73.5 (68-78)</td>
<td>70 (63-76)</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>1291 (100%)</td>
<td>592 (45.9%)</td>
<td>40 (32.3%)</td>
<td>552 (47.3%)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1291 (100%)</td>
<td>168 (13.0%)</td>
<td>34 (27.4%)</td>
<td>134 (11.5%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1291 (100%)</td>
<td>69 (5.3%)</td>
<td>18 (14.5%)</td>
<td>51 (4.4%)</td>
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<tr>
<td>Atrial fibrillation</td>
<td>1291 (100%)</td>
<td>123 (9.5%)</td>
<td>20 (16.1%)</td>
<td>103 (8.8%)</td>
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<tr>
<td>Hypertension</td>
<td>1289 (99.8%)</td>
<td>636 (49.3%)</td>
<td>64 (51.6%)</td>
<td>572 (49.1%)</td>
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<tr>
<td>Stroke or TIA</td>
<td>1291 (100%)</td>
<td>107 (8.3%)</td>
<td>13 (10.5%)</td>
<td>94 (8.1%)</td>
</tr>
<tr>
<td>IDDM</td>
<td>1290 (99.9%)</td>
<td>101 (7.8%)</td>
<td>12 (9.7%)</td>
<td>89 (7.6%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>1290 (99.9%)</td>
<td>217 (16.8%)</td>
<td>16 (12.9%)</td>
<td>201 (17.2%)</td>
</tr>
<tr>
<td>COPD</td>
<td>1291 (100%)</td>
<td>169 (13.1%)</td>
<td>19 (15.3%)</td>
<td>150 (12.9%)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>1291 (100%)</td>
<td>7 (0.5%)</td>
<td>1 (0.8%)</td>
<td>6 (0.5%)</td>
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<tr>
<td>Chronic kidney disease</td>
<td>1291 (100%)</td>
<td>15 (1.2%)</td>
<td>3 (2.4%)</td>
<td>12 (1.0%)</td>
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<tr>
<td>Metastatic cancer</td>
<td>1290 (99.9%)</td>
<td>163 (12.6%)</td>
<td>15 (12.1%)</td>
<td>148 (12.7%)</td>
</tr>
<tr>
<td>RCRI (no. of risk factors)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1291 (100%)</td>
<td>929 (72.0%)</td>
<td>68 (54.8%)</td>
<td>861 (73.8%)</td>
</tr>
<tr>
<td>2</td>
<td>278 (21.5%)</td>
<td>36 (29.0%)</td>
<td>242 (20.7%)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>84 (6.5%)</td>
<td>20 (16.1%)</td>
<td>64 (5.5%)</td>
<td></td>
</tr>
<tr>
<td>ASA-PS class</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>I</td>
<td>1291 (100%)</td>
<td>157 (12.2%)</td>
<td>10 (8.1%)</td>
<td>147 (12.6%)</td>
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<tr>
<td>II</td>
<td>726 (56.2%)</td>
<td>52 (41.9%)</td>
<td>674 (57.8%)</td>
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<td>III</td>
<td>399 (30.9%)</td>
<td>58 (46.8%)</td>
<td>341 (29.2%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>9 (0.7%)</td>
<td>4 (3.2%)</td>
<td>5 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;1</td>
<td>1290 (99.9%)</td>
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<td>7 (5.7%)</td>
<td>38 (3.3%)</td>
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<tr>
<td>1-4</td>
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<td>66 (53.2%)</td>
<td>552 (47.3%)</td>
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<tr>
<td>≥4</td>
<td>627 (48.6%)</td>
<td>51 (41.1%)</td>
<td>576 (49.4%)</td>
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<tr>
<td>Preoperative medications</td>
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<td>Platelet inhibitors</td>
<td>1289 (99.8%)</td>
<td>191 (14.8%)</td>
<td>27 (21.8%)</td>
<td>164 (14.1%)</td>
</tr>
<tr>
<td>Statins</td>
<td>1290 (99.9%)</td>
<td>345 (26.7%)</td>
<td>38 (30.6%)</td>
<td>307 (26.3%)</td>
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<tr>
<td>B-blockers</td>
<td>1289 (99.8%)</td>
<td>366 (28.4%)</td>
<td>51 (41.1%)</td>
<td>315 (27.0%)</td>
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<td>Ca-channel inhibitors</td>
<td>1288 (99.8%)</td>
<td>222 (17.2%)</td>
<td>21 (16.9%)</td>
<td>201 (17.3%)</td>
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<tr>
<td>ACEi or ARBs</td>
<td>1289 (99.8%)</td>
<td>446 (34.6%)</td>
<td>42 (33.9%)</td>
<td>404 (34.7%)</td>
</tr>
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<td>Surgical category</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Upper gastrointestinal</td>
<td>1289 (99.8%)</td>
<td>109 (8.5%)</td>
<td>17 (13.7%)</td>
<td>92 (7.9%)</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td></td>
<td>242 (18.8%)</td>
<td>18 (14.5%)</td>
<td>224 (19.2%)</td>
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<tr>
<td>Pancreas</td>
<td></td>
<td>193 (15.0%)</td>
<td>27 (21.8%)</td>
<td>166 (14.2%)</td>
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<tr>
<td>Colorectal</td>
<td></td>
<td>466 (36.2%)</td>
<td>39 (29.0%)</td>
<td>430 (36.9%)</td>
</tr>
<tr>
<td>Urology (not renal)</td>
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<td>68 (5.3%)</td>
<td>4 (3.2%)</td>
<td>64 (5.5%)</td>
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<tr>
<td>Renal</td>
<td></td>
<td>118 (9.2%)</td>
<td>9 (7.3%)</td>
<td>109 (9.4%)</td>
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<tr>
<td>Gynaecology</td>
<td></td>
<td>72 (5.6%)</td>
<td>9 (7.3%)</td>
<td>63 (5.4%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>21 (1.6%)</td>
<td>4 (3.2%)</td>
<td>17 (1.46%)</td>
</tr>
<tr>
<td>Preoperative anaemia</td>
<td>Male&lt;130 g L⁻¹, Female&lt;120 g L⁻¹</td>
<td>1286 (99.6%)</td>
<td>522 (40.6%)</td>
<td>73 (59.3%)</td>
</tr>
<tr>
<td>Preoperative increased creatinine</td>
<td>Male≥100 μmol L⁻¹, Female≥90 μmol L⁻¹</td>
<td>1272 (98.5%)</td>
<td>216 (17.0%)</td>
<td>30 (24.8%)</td>
</tr>
<tr>
<td>Length of surgery</td>
<td>Mean±SD (h)</td>
<td>1289 (99.8%)</td>
<td>4.11±2.54</td>
<td>4.69±2.83</td>
</tr>
<tr>
<td>Intraoperative blood loss</td>
<td>Median (IQR) (ml)</td>
<td>1288 (99.8%)</td>
<td>150 (50-400)</td>
<td>300 (100-500)</td>
</tr>
<tr>
<td>Intraoperative transfusion</td>
<td></td>
<td>1289 (99.8%)</td>
<td>145 (11.2%)</td>
<td>23 (18.5%)</td>
</tr>
<tr>
<td>Intraoperative hypotension</td>
<td></td>
<td>1286 (99.6%)</td>
<td>675 (52.5%)</td>
<td>656 (52.4%)</td>
</tr>
<tr>
<td>Discharge destination</td>
<td>PACU</td>
<td>1290 (99.9%)</td>
<td>1259 (97.6%)</td>
<td>113 (91.1%)</td>
</tr>
<tr>
<td>ICU (planned)</td>
<td></td>
<td>13 (1.0%)</td>
<td>5 (4.0%)</td>
<td>8 (0.7%)</td>
</tr>
<tr>
<td></td>
<td>ICU (unplanned)</td>
<td>18 (1.40%)</td>
<td>6 (4.8%)</td>
<td>12 (1.0%)</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------</td>
<td>------------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Ischaemic symptoms*</td>
<td>PACU-30d</td>
<td>1289 (99.8%)</td>
<td>148 (11.5%)</td>
<td>46 (37.1%)</td>
</tr>
<tr>
<td>Ischaemic ECG*</td>
<td>PACU-30d</td>
<td>1280 (99.1%)</td>
<td>269 (21.0%)</td>
<td>42 (34.7%)</td>
</tr>
<tr>
<td>Ischaemic symptom or</td>
<td>PACU-30d</td>
<td>1281 (99.2%)</td>
<td>385 (30.1%)</td>
<td>65 (52.8%)</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day MACCE</td>
<td>1291 (100%)</td>
<td>120 (9.3%)</td>
<td>120 (96.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>1291 (100%)</td>
<td>14 (1.1%)</td>
<td>14 (11.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>30-day MACCE and/or</td>
<td>1291 (100%)</td>
<td>124 (9.6%)</td>
<td>124 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 *postoperatively, suggestive of ischaemia.
2 ASA-PS=American Society of Anesthesiologists Physical Status, ACEi=angiotensin converting enzyme inhibitors, ARBs=angiotensin receptor blockers, MET=Metabolic Equivalents, ICU=Intensive Care Unit, IDDM=Insulin Dependent Diabetes Mellitus, COPD=chronic obstructive pulmonary disease, MACCE=Major Adverse Cardiovascular and Cerebrovascular Events, MINS=Myocardial injury in noncardiac surgery, PACU=postoperative care unit, RCRI=Revised Cardiac Risk Index
Table 2. 30-day MACCE and all-cause mortality in the whole population and stratified according to various hs-cTnT thresholds

<table>
<thead>
<tr>
<th>Definition</th>
<th>Preoperative increase (ROC analysis)</th>
<th>Perioperative increase (Basel-PMI)</th>
<th>Perioperative change (VISION)</th>
<th>Perioperative increase (ROC analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole population (n=1291)</td>
<td>With increase (n=349)</td>
<td>With increase (n=144)</td>
<td>With increase (n=357)</td>
</tr>
<tr>
<td></td>
<td>With increase (n=942)</td>
<td>Without increase (n=942)</td>
<td>Without increase (n=1147)</td>
<td>Without increase (n=934)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>30 day</td>
<td>124 (9.6%)</td>
<td>61 (17.5%)</td>
<td>63 (6.7%)</td>
<td>36 (25.0%)</td>
</tr>
<tr>
<td>mortality+MACCE</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>30 day MACCE</td>
<td>120 (9.3%)</td>
<td>60 (17.2%)</td>
<td>60 (6.4%)</td>
<td>36 (25.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MACCE: major adverse cardiac events; ROC: receiver operating characteristic; Basel-PMI: Basle-Permutt-Moncada Index; VISION: very important clinical events in non-inferior surgery.
Table 3. Multivariable analysis with and without the 4 different hs-cTnT thresholds

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without hs-cTnT but including RCRI</th>
<th>Preoperative (ROC analysis)</th>
<th>Perioperative increase (Basel-PMI)</th>
<th>Perioperative change (VISION)</th>
<th>Perioperative increase (ROC analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (CI) p-value</td>
<td>OR (CI) p-value</td>
<td>OR (CI) p-value</td>
<td>OR (CI) p-value</td>
<td>OR (CI) p-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.0 (1.0-1.1) 0.038</td>
<td>1.0 (0.99-1.1) 0.156</td>
<td>1.0 (1.0-1.1) 0.040</td>
<td>1.0 (0.99-1.0) 0.211</td>
<td>1.0 (1.0-1.1) 0.108</td>
</tr>
<tr>
<td>Sex</td>
<td>1.5 (1.0-2.3) 0.049</td>
<td>1.4 (0.92-2.2) 0.114</td>
<td>1.4 (0.92-2.2) 0.116</td>
<td>1.3 (0.87-2.1) 0.184</td>
<td>1.4 (0.93-2.2) 0.103</td>
</tr>
<tr>
<td>ASA-PS</td>
<td>1.7 (1.0-2.7) 0.034</td>
<td>1.6 (0.97-2.5) 0.069</td>
<td>1.6 (1.0-2.6) 0.048</td>
<td>1.5 (0.92-2.4) 0.111</td>
<td>1.6 (0.98-2.5) 0.062</td>
</tr>
<tr>
<td>MET</td>
<td>0.93 (0.6-1.4) 0.728</td>
<td>0.93 (0.61-1.4) 0.753</td>
<td>0.9 (0.61-1.4) 0.762</td>
<td>0.96 (0.63-1.5) 0.867</td>
<td>0.92 (0.60-1.4) 0.684</td>
</tr>
<tr>
<td></td>
<td>No. of chronic comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.0 (0.6-1.8) 0.976</td>
<td>1.0 (0.57-1.8) 0.995</td>
<td>0.99 (0.56-1.7) 0.958</td>
<td>0.98 (0.56-1.7) 0.948</td>
<td>0.97 (0.56-1.7) 0.924</td>
</tr>
<tr>
<td>2</td>
<td>0.80 (0.41-1.6) 0.505</td>
<td>0.80 (0.41-1.6) 0.505</td>
<td>0.73 (0.37-1.5) 0.366</td>
<td>0.76 (0.38-1.5) 0.420</td>
<td>0.72 (0.36-1.4) 0.348</td>
</tr>
<tr>
<td>≥3</td>
<td>0.44 (0.18-1.1) 0.064</td>
<td>0.42 (0.17-1.0) 0.049</td>
<td>0.43 (0.18-1.0) 0.058</td>
<td>0.42 (0.17-1.0) 0.050</td>
<td>0.43 (0.18-1.0) 0.062</td>
</tr>
<tr>
<td>Preoperative anemia*</td>
<td>1.6 (1.1-2.5) 0.020</td>
<td>1.5 (1.0-2.3) 0.052</td>
<td>1.6 (1.0-2.4) 0.040</td>
<td>1.5 (0.95-2.2) 0.085</td>
<td>1.6 (1.0-2.4) 0.032</td>
</tr>
<tr>
<td>Preoperative increased P-creatinine†</td>
<td>1.2 (0.77-2.0) 0.380</td>
<td>1.1 (0.70-1.9) 0.588</td>
<td>1.2 (0.75-2.0) 0.414</td>
<td>1.0 (0.62-1.7) 0.936</td>
<td>1.1 (0.66-1.8) 0.768</td>
</tr>
<tr>
<td>Intraoperative transfusion‡</td>
<td>1.2 (0.68-2.0) 0.553</td>
<td>1.1 (0.66-2.0) 0.633</td>
<td>1.1 (0.64-2.0) 0.684</td>
<td>1.1 (0.64-1.9) 0.722</td>
<td>1.1 (0.63-1.9) 0.738</td>
</tr>
<tr>
<td>Intraoperative hypotension§</td>
<td>0.98 (0.66-1.5) 0.011</td>
<td>0.99 (0.67-1.5) 0.958</td>
<td>0.91 (0.61-1.4) 0.630</td>
<td>0.99 (0.66-1.5) 0.942</td>
<td>0.93 (0.62-1.4) 0.715</td>
</tr>
<tr>
<td>Length of surgery (min)</td>
<td>1.1 (1.0-1.2) 0.007</td>
<td>1.1 (1.0-1.2) 0.007</td>
<td>1.1 (1.0-1.2) 0.020</td>
<td>1.1 (1.0-1.2) 0.016</td>
<td>1.1 (1.0-1.2) 0.029</td>
</tr>
<tr>
<td>RCRI</td>
<td>0.013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 risk factors</td>
<td>1.8 (0.97-3.2) 0.063</td>
<td>1.8 (0.98-3.2) 0.058</td>
<td>1.8 (0.95-3.2) 0.070</td>
<td>1.8 (0.97-3.2) 0.063</td>
<td>1.8 (0.97-3.2) 0.064</td>
</tr>
<tr>
<td>≥3 risk factors</td>
<td>3.9 (1.6-9.4) 0.002</td>
<td>3.8 (1.6-9.1) 0.003</td>
<td>3.7 (1.5-9.0) 0.004</td>
<td>3.7 (1.5-9.1) 0.004</td>
<td>3.8 (1.6-9.2) 0.003</td>
</tr>
<tr>
<td>Change in hs-cTnT</td>
<td>-</td>
<td>1.7 (1.0-2.6) 0.035</td>
<td>2.9 (1.8-4.7) &lt;0.001</td>
<td>2.4 (1.5-3.7) &lt;0.001</td>
<td>2.2 (1.4-3.3) &lt;0.001</td>
</tr>
</tbody>
</table>

* Defined as Hb <130 g L\(^{-1}\) for men and <120 g L\(^{-1}\) for women
† Defined as plasma levels of creatinine ≥100 µmol L\(^{-1}\) for men and ≥90 µmol L\(^{-1}\) for women
‡ Defined as intraoperative transfusion of any blood product
§ Defined as MAP ≤55 mmHg at any time intraoperatively
Table 4. Performance statistics for the 4 models including different thresholds of hs-cTnT and for a model excluding hs-cTnT.

<table>
<thead>
<tr>
<th>hsTnT Threshold</th>
<th>Definition</th>
<th>AUC (95%CI)</th>
<th>Brier score</th>
<th>Hosmer Lemeshow</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>c-statistic p-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative (ROC analysis)</td>
<td>According to ROC analysis; ≥14 ng L⁻¹</td>
<td>0.72 (0.68-0.77) &lt;0.0001</td>
<td>0.082</td>
<td>10.9</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Perioperative increase (Basel-PMI)</td>
<td>0.73 (0.68-0.78) &lt;0.0001</td>
<td>0.080</td>
<td>8.9</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>Perioperative change (VISION)</td>
<td>0.73 (0.69-0.78) &lt;0.0001</td>
<td>0.081</td>
<td>5.7</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>Perioperative increase (ROC analysis)</td>
<td>0.73 (0.68-0.78) &lt;0.0001</td>
<td>0.081</td>
<td>7.4</td>
<td>0.50</td>
</tr>
<tr>
<td>No hs-cTnT measurement</td>
<td>-</td>
<td>0.71 (0.66-0.76) &lt;0.0001</td>
<td>0.082</td>
<td>6.5</td>
<td>0.59</td>
</tr>
</tbody>
</table>

ROC= Receiver operating characteristic, Sens=sensitivity, Spec=specificity, PPV=positive predictive value, NPV=negative predictive value, AUC=area under the ROC curve, 95%CI=95% confidence intervals, AIC=Akaike Information Criterion. Model performance was assessed by a combination of the C-statistic, Brier score (lower values=higher predictive accuracy) and the AIC (lower score=better model fit)
Table 5. Timing of myocardial injury diagnosis, according to the different hs-cTnT thresholds

<table>
<thead>
<tr>
<th>Dataset Description</th>
<th>PACU (n=1250)</th>
<th>Day 1 (n=1244)</th>
<th>Day 2 (n=1102)</th>
<th>Day 3 (n=816)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative increase (Basel-PMI), n=144</td>
<td>31 (21.5%)</td>
<td>51 (35.4%)</td>
<td>47 (32.6%)</td>
<td>15 (10.4%)</td>
</tr>
<tr>
<td>Perioperative change (VISION), n=357</td>
<td>158 (44.6%)</td>
<td>134 (37.9%)</td>
<td>52 (14.7%)</td>
<td>11 (3.1%)</td>
</tr>
<tr>
<td>Perioperative increase (ROC analysis), n=442</td>
<td>104 (23.5%)</td>
<td>189 (42.8%)</td>
<td>122 (27.6%)</td>
<td>27 (6.1%)</td>
</tr>
</tbody>
</table>
Figure Legends

Figure 1. Study Flowchart.

Figure 2. Weighted comparison (WC) curves for extended RCRI incorporating each of the hs-cTnT thresholds.

The clinical threshold represents the chosen ‘acceptable’ ratio of true positives to false positives (TP:FP) that may be considered reasonable in a clinical setting. Extended RCRI = RCRI score +1 when the hs-cTnT test was ‘positive’ according to the four thresholds:

- Preoperative ≥ 14 ng L⁻¹ (ROC analysis), VISION definition, Basel-PMI definition and
- Perioperative increase ≥ 5 ng L⁻¹ (ROC analysis). Positive WC values indicate a net benefit for extended RCRI compared to RCRI alone.
Patients ≥ 50 years old undergoing major abdominal surgery (n=1368)

Did not fulfill inclusion criteria (n=1)
Surgery cancelled (n=13)

Surgery rescheduled (n=16)
Consent withdrawn (n=12)

No available study nurse (n=13)
Changed surgical category (n=1)

Deceased before surgery (n=1)
Missing preoperative hsTnT (n=20)

Patients included in analysis (n=1291)
Figure 2. Weighted comparison (WC) curves for each of the hsTnT diagnostic thresholds. The clinical threshold represents the chosen 'acceptable' ratio of true positives to false positives (TP:FP) that may be considered reasonable in a clinical setting. Extended RCRI = RCRI score +1 when the hsTnT test was 'positive' according to the four diagnostic thresholds: preoperative ≥14 ng L-1 (ROC analysis), VISION definition, Basel-PMI definition and perioperative increase ≥5 ng L-1 (ROC analysis). Positive WC values indicate a net benefit for extended RCRI compared to RCRI alone.