Published in final edited form as:

Am Heart J. 2013 August ; 166(2): 325–332.e1. doi:10.1016/j.ahj.2013.04.018.

High-Sensitivity Cardiac Troponin T in Prediction and Diagnosis of Myocardial Infarction and Long-Term Mortality after Non-Cardiac Surgery

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Abstract

Background—Perioperative myocardial infarction is a serious complication after non-cardiac surgery. We hypothesized that preoperative cardiac troponin T detected with a novel high-sensitivity (hs-cTnT) assay will identify patients at risk of acute myocardial infarction (AMI) and long-term mortality after major non-cardiac surgery.

Methods—This was a prospective cohort study within the Vitamins in Nitrous Oxide (VINO) trial (n=608). Patients had been diagnosed with or had multiple risk factors for coronary artery disease and underwent major non-cardiac surgery. Cardiac troponin I (contemporary assay) and troponin T (high-sensitivity assay), and 12-lead electrocardiograms were obtained before and immediately after surgery and on postoperative day 1, 2 and 3.

Results—At baseline before surgery, 599 patients (98.5%) had a detectable hs-cTnT concentration and 247 (41%) were above 14 ng/L (99th percentile). After surgery, 497 patients (82%) had a rise in hs-cTnT (median Δ hs-cTnT +2.7 ng/L [IQR 0.7, 6.8]). During the first three postoperative days, 9 patients (2.5%) with a preoperative hs-cTnT <14 ng/L suffered from AMI, compared to 21 patients (8.6%) with a preoperative hs-cTnT >14 ng/L (odds ratio, 3.67; 95% CI 1.65 – 8.15). During long-term follow-up, 80 deaths occurred. The 3-year mortality rate was 11% in patients with a preoperative hs-cTnT concentration <14 ng/L compared to 25% in patients with a preoperative hs-cTnT >14 ng/L (adjusted hazard ratio, 2.17; 95% CI 1.19 – 3.96).

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Conclusions—In this cohort of high-risk patients, preoperative hs-cTnT concentrations were significantly associated with postoperative myocardial infarction and long-term mortality after non-cardiac surgery.

Perioperative acute myocardial infarction (AMI) is a serious complication after non-cardiac surgery and is associated with significant mortality.^{1, 2} An estimated one million patients die yearly within the first 30-days after surgery and AMI is one of the leading causes. Reliable pre-operative identification of patients at high risk for postoperative AMI and/or death is currently inadequate, but may confer substantial benefits to patients as preventive measures could be instituted.

Cardiac troponin (cTn) assays provide rapid, specific and sensitive detection of myocardial injury and thus are essential for the diagnosis of AMI.^{3, 4} Until recently, cTn was used in the surgical setting exclusively to diagnose perioperative myocardial injury and infarction. Recent studies provide strong evidence that even minor cTn elevations after surgery are associated with increased cardiovascular morbidity and mortality.⁵⁻⁸

Recently, high-sensitivity (hs) cTn assays have been introduced that have lowered the limit of analytical detection by an order of magnitude into the ng/L range.⁹ This provides the ability to detect circulating cTn in the blood of many apparently healthy individuals at baseline. Higher levels of hs-cTn are associated with incident coronary artery disease, heart failure, cardiovascular and all-cause mortality.¹⁰⁻¹² We therefore reasoned that (1) the measurement of hs-cTnT before surgery might identify patients at increased risk for perioperative AMI and death and (2) that the measurement of the change in hs-cTnT (Δ hs-cTnT) might be useful to quantify the extent of perioperative myocardial injury.

Accordingly, we conducted a prospective cohort study within the Vitamins in Nitrous Oxide (VINO) Trial in which the effects of a common inhalational anesthetic, nitrous oxide, plus B-vitamins on the incidence of perioperative AMI were determined.

Methods

Study Population

Patients enrolled in the Vitamins in Nitrous Oxide (VINO) Trial (Clinicaltrials.gov number NCT00655980) were included. The VINO trial was a double-blind, randomized, placebo-controlled, single-center trial. A detailed description of the trial methods and main results has been published elsewhere.¹³ In short, 625 adult patients with either known coronary artery disease or multiple risk factors for coronary artery disease scheduled for major non-cardiac surgery under general anesthesia were randomly assigned to receive nitrous oxide and B-vitamins (250 patients) or nitrous oxide and placebo (250 patients). A concurrent reference group who received neither nitrous oxide nor B-vitamins was also enrolled (125 patients). The trial results were negative, i.e. B-vitamins had no effect on cardiac events.

The VINO trial was funded by a grant from the National Institute for General Medical Sciences (K23 GM087534) and a grant to Washington University Institute of Clinical and Translational Sciences (UL1RR024992), the Foundation for Anesthesia Education and Research (FAER), and the Division of Clinical and Translational Research, Department of Anesthesiology, Washington University. Roche Diagnostics provided high-sensitivity troponin T reagents and funding to cover the costs of running the assays, but had no role in the design of the study, data collection or analysis or manuscript preparation and submission. When it was learned that the hs-cTnT lots used in this study under-captured hs-cTnT; Roche Diagnostics corrected our anonymized hs-cTnT data but otherwise had no access to our results. The other funders/sponsors had no role in the collection, management,

and interpretation of the data; or preparation, review, or approval of the manuscript. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. The study was approved by the Washington University in St. Louis institutional review board, and all patients provided written, informed consent.

Biomarker Assays

Blood and 12-lead electrocardiograms were obtained at five pre-defined time points: preoperative (baseline), i.e. within 2 hours before surgery; at the end of surgery (within 30 minutes of arrival in the post-anesthesia care unit); and on the mornings of postoperative day 1, 2 and 3. Samples were collected in lithium heparin tubes, immediately put on ice and centrifuged within 30 minutes of collection. Plasma was transferred into cryogenic tubes and stored at -70°C . Biomarker measurements were performed in batches and samples had no more than two freeze-thaw cycles. They were performed by study personnel unaware of clinical outcomes.

cTnI concentrations (presented as $\mu\text{g/L}=\text{ng/mL}$) were measured with a contemporary assay on a Siemens Dimension RxL analyzer (limit of detection: $0.04 \mu\text{g/L}$; 99th percentile: $0.07 \mu\text{g/L}$; a 10% coefficient of variation (CV) at $0.14 \mu\text{g/L}$). hs-cTnT (reported as ng/L) was measured on a Roche Elecsys 2010 analyzer (limit of detection: 5.0 ng/L ; 99th percentile: 14 ng/L ; a 10% CV at 13 ng/L).¹⁴ The 99th percentile values for men is 14.5 ng/L and 10 ng/L for women.¹⁵ A manufacturers' notice to users dated May 2012 informed us that the hs-cTnT assay lots used in our study apparently under-recovered hs-cTnT at lower concentrations.¹⁶ Using original instrument readings and calibration records, Roche Diagnostics provided a numerical correction method (in a blinded fashion), that made our results equivalent to previous and the recently reformulated lots of hs-cTnT reagents.

Outcomes

AMI and cTn elevation within 72 hours after surgery were predefined study endpoints. Cardiac troponin elevations were defined as a peak postoperative cTnI concentration >99th percentile ($> 0.07 \mu\text{g/L}$). MI was defined according to the Universal Definition; i.e. arising pattern of cTnI with at least one elevation > 99th percentile plus new ECG changes indicative of myocardial ischemia and/or clinical symptoms.⁴ New Q-waves, ST-segment depression or T-wave inversion 0.1mV , or ST-elevation 0.2 mV in at least two contiguous leads were considered indicative of myocardial ischemia. ECGs were read and analyzed by investigators blinded to biomarker results (LdlF, JJ). Ambiguous cases were resolved by consensus opinion that included the PI. For most patients diagnosed with MI, additional confirmatory evidence from cardiac catheterization, echocardiography or myocardial scans was available. MIs were classified into type 1 (primary coronary event), type 2 (supply and demand mismatch) or type 4B (stent thrombosis).⁴ Patients were only classified as having a type 1 or 4B MI, if diagnosed by an interventional cardiologist after cardiac catheterization. Thus, unless intervention was pursued, in the absence of an alternative explanation for elevated cTn values, a type 2 AMI was diagnosed. Survival status was obtained from medical records or the Social Security Death Index with a cutoff date of July 1, 2012.

Statistical Analysis

All cTn values are reported as medians plus interquartile ranges. For univariate and multivariate models, cTn values were log-transformed after adding 1.5 ng/L (one half of the lower limit of the blank) to each value to avoid taking the log of 0. For univariate comparisons unpaired two-sided t-tests were used. To identify independent predictors of preoperative (log) hs-cTnT, a multivariate linear regression model was constructed that

adjusted for 14 pre-specified known predictors of cardiac risk (forced entry). The estimated glomerular filtration rate (eGFR) was calculated according to the CKD-EPI creatinine formula.¹⁷ Preoperative hs-cTnT was assessed as a categorical variable for most analyses with 14 ng/L (99th percentile URL) as the main cutoff level. Additionally, we probed sex-specific 99th percentiles: 10 ng/L for women and 15 ng/L for men.¹⁴ Changes in hs-cTnT from preoperative to postoperative (Δ hs-cTnT) were calculated either as absolute or relative changes of the difference between the peak postoperative and the baseline concentration. Several Δ hs-cTnT levels were assessed including +30%, +50%, +100%; +7 ng/L, +9 ng/L.^{18–20} Logistic regression was used to assess the association of preoperative hs-cTnT and postoperative troponin elevations and MI and ROC curves were calculated.

Exact date of death information was available for 73/80 patients; for the remaining seven only the year was known. For these patients, the date of death was coded as July 1 of the year of death. Kaplan-Meier estimates were calculated for varying preoperative hs-cTnT cutoffs and log-rank tests were used to determine statistical significance. Several Cox proportional hazard models were calculated with previously mentioned covariates. Violations of the proportional hazards assumption were checked graphically. Statistical analyses were performed on SPSS 20.0.0.1 and SAS 9.2. Graphs were constructed on GraphPad Prism 5.04 (GraphPad Software Inc., La Jolla, CA).

Results

Patients and preoperative characteristics

There were 608 patients enrolled in the VINO Trial who had a preoperative hs-cTnT measured. Most patients had several cardiac risk factors and co-morbidities and more than half had previously been diagnosed with coronary artery disease (Table 1). Many had suffered previous MIs or undergone cardiac interventions. The majority of patients were on one or more cardiovascular drugs (Table 1).

Before surgery, 599 patients (98.5%) had a detectable hs-cTnT concentration (>5 ng/L) with a median hs-cTnT of 12.0 ng/L [IQR 8.3, 19.3]. The distribution of these values is shown in Figure 1. In 41% of patients the hs-cTnT concentration was above the 99th percentile of the upper reference (URL) limit (14 ng/L; Table 1). In comparison, using the contemporary cTnI assay, only 13% (79/618) had a detectable cTnI and only 4% were above the 99th percentile value (0.07 μ g/L). Several co-morbidities were associated with an elevated preoperative hs-cTnT: coronary artery disease, congestive heart failure, diabetes, hypertension, and chronic renal failure. The preoperative hs-cTnT concentration correlated with the two most commonly used preoperative risk indices, the American Society of Anesthesiologists status and the Lee's revised cardiac risk index (Table 1).

High-sensitivity troponin T and perioperative MI

About a third of the surgical procedures were vascular and another third major orthopedic surgeries; the rest were neurosurgical, ENT, urological and gynecological surgeries (Table S1). After surgery, 497 patients (82%) had a rise in hs-cTnT (Δ hs-cTnT) with a median Δ hs-cTnT of +2.7 ng/L [IQR 0.7, 6.8] and a median peak hs-cTnT of 15.9 ng/L [IQR 10.9, 27.0]. In nearly 60%, the postoperative hs-cTnT concentration was above the 99th percentile compared to 41% who were elevated at baseline. In 24.5% of patients the absolute increase in hs-cTnT from baseline was +7 ng/L, and in 19.1% +9 ng/L. Of the 497 patients with a detectable preoperative hs-cTnT, 52% had a relative hs-cTnT rise of +30%, 34% +50%, and 16% +100% compared to baseline.

In the study population, 82 patients (13%) developed a postoperative cTnI elevation (cTnI 0.07 μ g/L) and 30 (5%) were diagnosed with an AMI during the first three postoperative

days using the contemporary cTnI assay. The majority of AMIs were type 2 (supply and demand mismatch; 26/30, 87%), three (10%) were type 1 AMI (thrombotic event) and one was type 4B AMI (stent thrombosis; 3%). Among patients who developed MI (n=30), all had detectable hs-cTnT concentrations before surgery with a median value of 18.5 ng/L [IQR 11.5, 30.2]. In contrast, only seven (23%) had detectable cTnI concentrations (>0.04 $\mu\text{g/L}$) and only 5 elevations were above the 99th percentile value. After surgery, peak hs-cTnT levels rose to a median of 165.9 ng/L [IQR 45.5, 512.2] between postoperative days two and three. However, median peak cTnI concentration amongst patients with postoperative MI was only 1.5 $\mu\text{g/L}$ [IQR 0.6, 3.5].

Preoperative high-sensitivity troponin T and outcomes

Using the 99th percentile value as preoperative hs-cTnT cutoff value, patients with values <14 ng/L before surgery (n=361; 59.6%) had a 7.8% incidence rate of postoperative cTnI elevation and a 2.5% incidence rate of postoperative AMI. In contrast, patients with a preoperative hs-cTnT >14 ng/L (n=247) had a 21.9 % incidence of postoperative cTnI elevations and a 8.6% incidence of postoperative AMI odds ratio [OR] for cTnI elevation = 3.33, 95% CI 2.04 – 5.43, $p<0.001$; OR for AMI = 3.67, 95% CI 1.65 – 8.15, $p=0.001$; Figure 2). At the median preoperative hs-cTnT concentration of 12.0 ng/L, the sensitivity and specificity for a postoperative AMI was 73% and 52% (AUC 0.693; 95% CI 0.604 – 0.782; $p<0.001$). In comparison, using the limit of detection of the contemporary cTnI assay (>0.04 $\mu\text{g/L}$), sensitivity and specificity for postoperative AMI were 20% and 92% (AUC 0.563).

Eighty deaths occurred and for most patients the cause of death could not be established. Only three patients (0.5%) died within the first 30-days after surgery; two of them of fatal MI. Mean survival was 3.8 years (95% CI 3.7 – 3.9 years). Patients with a preoperative hs-cTnT concentration <14 ng/L had a 3-year mortality rate of 11% while patients with a preoperative hs-cTnT >14 ng/L had a 3-year mortality rate of 25% (adjusted hazard ratio [aHR] = 2.11, 95% CI 1.26 – 3.53, $p=0.004$; adjusted for age and sex; Figure 3). In a second Cox proportional hazards model, adjusting for age, sex, race, eGFR, history of coronary artery disease, hypertension, and diabetes, the risk for patients with a preoperative hs-cTnT >14 ng/L remained basically unchanged (aHR 2.17; 95% CI 1.19 – 3.96, $p=0.011$). When preoperative hs-cTnT values were stratified into quartiles, patients in the top quartile (>19.3 ng/L) had a 2.4-fold increased hazard compared to patients in the lowest quartile (<8.3 ng/L) (HR 2.37, 95% CI 1.30 – 4.31, $p=0.005$; Figure S1).

When using sex-specific cutoffs for the hs-cTnT 99th percentile URL (10 ng/L for women, 15 ng/L for men), the HR for women whose preoperative hs-cTnT was above 10 ng/L (n=119/228; 52%) was 1.48 (95% CI 0.69 – 3.16, $p=0.311$) and 3.21 for men (95% CI 1.74 – 5.92, $p<0.001$) whose preoperative hs-cTnT was above 15 ng/L (n=162/379; 43%) (Figure 4). Preoperative log-transformed hs-cTnT (as a continuous variable) remained an independent predictor of survival after adjusting for age, race, sex, hypertension, diabetes, eGFR, coronary artery disease (aHR 4.08, 95% CI 1.56 – 10.71, $p=0.004$).

In unadjusted Cox proportional hazard models, patients with a postoperative cTnI elevation and patients who developed postoperative MI had statistically non-significant increased risk of long-term death after surgery (HR for cTnI elevation = 1.18, 95% CI 0.64 – 2.19, $p=0.59$; HR of MI = 1.83, 95% CI 0.80 – 4.21, $p=0.155$). In comparison, patients who had a peak postoperative hs-cTnT above 14 ng/L had a nearly 2-fold increased risk of death (unadjusted HR 1.94, 95% CI 1.19 – 3.15, $p=0.008$). Patients with a hs-cTnT rise $+9\text{ng/L}$ ($\Delta\text{hs-cTnT}$) had a 1.6-fold increased risk of death (unadjusted HR 1.58, 95% CI 0.95 – 2.64, $p=0.078$).

Discussion

This study in high-risk patients undergoing major non-cardiac surgery establishes several novel observations: First, before surgery nearly every patient had a detectable hs-cTnT concentration and nearly 40% were elevated above the 99th percentile URL of 14 ng/L. Second, most patients had significant hs-cTnT rises postoperatively. Third, preoperative hs-cTnT values were strong, independent predictors not only for postoperative cTnI elevations and AMI but also for 3-year mortality. In particular, patients with a preoperatively elevated hs-cTnT value had a markedly increased risk of postoperative AMI (3.7-fold increase) and death (2-fold increase) with a 3-year mortality rate of 25%. These findings have important implications for the preoperative screening patients, their risk for perioperative MI and long-term mortality.

Preoperative screening with high-sensitivity cardiac troponin T

Consistent with several prior studies, many more patients in our high-risk population had detectable hs-cTnT concentrations when compared to the contemporary cTnI assay used. The majority of preoperative hs-cTnT elevations levels were associated with cardiac risk factors.^{10–12} The fraction of patients having an elevated preoperative hs-cTnT (41%) is similar to other high-risk populations.^{21, 22} Preoperative hs-cTnT values showed a graded association with standard indices of preoperative cardiac risk such as the American Society of Anesthesiologists' physical status and Lee's revised cardiac risk index. Despite their usefulness, these risk indices are fairly crude with only four categories and therefore, preoperative hs-cTnT appeared useful as in providing an objective individualized cardiac risk assessment. This may be particularly important for patients who are poor historians.

Preoperative hs-cTnT and prognosis of postoperative MI and long-term mortality

Our results indicate that preoperative hs-cTnT is a strong, independent predictor for postoperative AMI as well as long-term mortality. While hs-cTnT levels probably reflect a continuum from very low to very high risk, patients with an elevated preoperative hs-cTnT above the 99th percentile appeared to be at a particularly increased risk both for postoperative AMI as well as long-term mortality. Surprisingly, our data did not support the use of sex-specific hs-cTnT cutoff levels (10 ng/L for women and 14.5 ng/L),^{9, 15, 23}

The high 3-year mortality rate of 25% among patients with a preoperative hs-cTnT > 14 ng/L is substantially higher than in comparable studies of non-surgical patients with similar cardiac risk profiles. Extrapolated from published graphs of community cohort studies, the observed 3-year mortality rates in patients with stable coronary artery disease were ~ 7% (using 16 ng/L as cutoff) in the study by Ndrepepa et al.,²⁴ and 3% (using 9.6 ng/L as a cutoff) in the study by Omland et al.¹² Why we observed a much higher 3-year mortality rate among our patient population is unclear; it probably represents a combination of cardiovascular deaths and deaths due to underlying diseases and conditions for which the patients required surgery. For example, some of our patients underwent surgery for cancer. Unfortunately, for most patients we were unable to identify the cause of death. Nevertheless, our results indicate that postoperative mortality, particularly among high-risk cardiac patients, is higher than the mortality observed in a non-surgical population. Our results add new insights regarding the usefulness of preoperative high-sensitivity troponin to an already robust literature concerning adverse prognostic significance of elevated postoperative cTn after non-cardiac surgery.^{6, 7} Future investigations may find it worthwhile to compare the role of hs-cTnT with other cardiac biomarkers, such as brain natriuretic peptide or the N-terminal fragment of brain natriuretic peptide, in perioperative cardiac risk stratification.²⁵

High-sensitivity cardiac troponin T and the diagnosis of perioperative MI

The diagnosis of myocardial infarction requires at least one cTn value to be 99th percentile URL with a rising and/or falling pattern.⁴ The fact that before surgery 41% and after surgery 60% of the study patients had a hs-cTnT concentration above the 99th percentile, confirms the importance of a changing pattern to distinguish acute events from hs-cTnT elevations that are chronic. There is an emerging consensus to focus on absolute and relative hs-cTnT changes (Δ hs-cTnT) to identify acute events.^{18, 20, 26, 27} More than 80% of our study population had a postoperative hs-cTnT rise which supports the notion of non-cardiac surgery being a “stress-test”. Several absolute and relative hs-cTnT changes have been proposed to maximize the diagnosis of AMI with the hs-cTnT assay. The use of changes + 7ng/L, + 9ng/L; + 30%, + 50%, and + 100% have been advocated for, but the field has not settled on universally accepted cutoffs. Our results indicate that patients with a postoperative hs-cTnT increase >9 ng/L had a 1.7-fold increased risk of death, which is consistent with recent findings by Devereaux et al. that even small increases in postoperative troponin predict mortality after non-cardiac surgery.^{8, 28}

Limitations of our study include the selected high-risk population that may not be representative of the general surgical population. Second, only a minority of AMIs underwent cardiac catheterization. Thus, it is possible that some of the elevations in hs-cTnT were not due to coronary artery disease despite the high risk nature of our population. However, our data are consistent with the results of others that suggest that most postoperative AMIs are caused by supply and demand mismatch.^{1, 5} We cannot rule out the possibility that more events were due to plaque rupture.²⁹ Third, our inability to identify the cause of death leaves us unable to differentiate between cardiovascular and non-cardiovascular deaths.

In conclusion, the results of our study show that in a cohort of high-risk patients preoperative hs-cTnT levels were significantly associated with postoperative MI and long-term mortality after non-cardiac surgery. This suggests that preoperatively measured hs-cTnT may be useful to identify patients at high risk for perioperative acute myocardial infarction and increased long-term mortality after non-cardiac surgery.

References

- Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. Perioperative myocardial infarction. *Circulation*. 2009; 119(22):2936–44. [PubMed: 19506125]
- Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, 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. [PubMed: 21502650]
- Adams JE 3rd, Bodor GS, Davila-Roman VG, Delmez JA, Apple FS, Ladenson JH, et al. Cardiac troponin I. A marker with high specificity for cardiac injury. *Circulation*. 1993; 88(1):101–6. [PubMed: 8319322]
- Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Circulation*. 2012; 126(16):2020–35. [PubMed: 22923432]
- 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(9):1547–54. [PubMed: 14607436]
- 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. [PubMed: 21336095]
- Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, et al. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study I. Association between postoperative

- troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA: the journal of the American Medical Association*. 2012; 307(21):2295–304. [PubMed: 22706835]
8. Nagele P, Rao LK, Penta M, Kallogjeri D, Spitznagel EL, Cavallone LF, et al. Postoperative myocardial injury after major head and neck cancer surgery. *Head & neck*. 2011; 33(8):1085–91. [PubMed: 20886662]
 9. Apple FS, Collinson PO. Ifcc Task Force on Clinical Applications of Cardiac Biomarkers. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clinical chemistry*. 2012; 58(1):54–61. [PubMed: 21965555]
 10. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA: the journal of the American Medical Association*. 2010; 304(22):2503–12. [PubMed: 21139111]
 11. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA: the journal of the American Medical Association*. 2010; 304(22):2494–502. [PubMed: 21078811]
 12. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med*. 2009; 361(26):2538–47. [PubMed: 19940289]
 13. Nagele P, Brown F, Francis A, Scott MG, Gage BF, Miller PJ. Influence of Nitrous Oxide Anesthesia, B-Vitamins, and MTHFR gene polymorphisms on Perioperative Cardiac Events: The Vitamins in Nitrous Oxide (VINO) Randomized Trial. *Anesthesiology*. 2013 in press.
 14. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clinical chemistry*. 2010; 56(2):254–61. [PubMed: 19959623]
 15. Giannitsis E, Becker M, Kurz K, Hess G, Zdunek D, Katus HA. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. *Clinical chemistry*. 2010; 56(4):642–50. [PubMed: 20167697]
 16. Apple FS, Jaffe AS. Clinical implications of a recent adjustment to the high-sensitivity cardiac troponin T assay: user beware. *Clinical chemistry*. 2012; 58(11):1599–600. [PubMed: 22968106]
 17. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009; 150(9):604–12. [PubMed: 19414839]
 18. Mueller M, Biener M, Vafaie M, Doerr S, Keller T, Blankenberg S, et al. Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. *Clinical chemistry*. 2012; 58(1):209–18. [PubMed: 22134520]
 19. Apple FS, Smith SW, Pearce LA, Murakami MM. Delta changes for optimizing clinical specificity and 60-day risk of adverse events in patients presenting with symptoms suggestive of acute coronary syndrome utilizing the ADVIA Centaur TnI-Ultra assay. *Clinical biochemistry*. 2012; 45(10–11):711–3. [PubMed: 22465126]
 20. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation*. 2011; 124(2):136–45. [PubMed: 21709058]
 21. Alcock RF, Kouzios D, Naoum C, Hillis GS, Brieger DB. Perioperative myocardial necrosis in patients at high cardiovascular risk undergoing elective non-cardiac surgery. *Heart*. 2012; 98(10):792–8. [PubMed: 22543837]
 22. Kavsak PA, Walsh M, Srinathan S, Thorlacius L, Buse GL, Botto F, et al. High sensitivity troponin T concentrations in patients undergoing noncardiac surgery: a prospective cohort study. *Clinical biochemistry*. 2011; 44(12):1021–4. [PubMed: 21640092]
 23. Saenger AK, Beyrau R, Braun S, Cooray R, Dolci A, Freidank H, et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. *Clinica chimica acta; international journal of clinical chemistry*. 2011; 412(9–10):748–54.

24. Ndrepepa G, Braun S, Mehilli J, Birkmeier KA, Byrne RA, Ott I, et al. Prognostic value of sensitive troponin T in patients with stable and unstable angina and undetectable conventional troponin. *American heart journal*. 2011; 161(1):68–75. [PubMed: 21167336]
25. Rodseth RN, Lurati Buse GA, Bolliger D, Burkhart CS, Cuthbertson BH, Gibson SC, et al. The predictive ability of pre-operative B-type natriuretic peptide in vascular patients for major adverse cardiac events: an individual patient data meta-analysis. *J Am Coll Cardiol*. 2011; 58(5):522–9. [PubMed: 21777751]
26. Jaffe AS. The 10 commandments of troponin, with special reference to high sensitivity assays. *Heart*. 2011; 97(11):940–6. [PubMed: 21558070]
27. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J*. 2012; 33(18):2252–7. [PubMed: 22723599]
28. VISION Investigators. Association Between Postoperative Troponin Levels and 30-Day Mortality Among Patients Undergoing Noncardiac SurgeryPostoperative Troponin Levels and 30-Day Mortality. *JAMA*. 2012; 307(21):2295–2304. [PubMed: 22706835]
29. 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. [PubMed: 22410124]

Figure 1.
Distribution of Preoperative High-Sensitivity Troponin T Concentrations.

Figure 2. Preoperative High-sensitivity Troponin T and Postoperative Troponin Elevation and Myocardial Infarction

Patients are grouped into two groups using the 99th percentile high-sensitivity troponin T (hs-cTnT) (14 ng/L) as a cutoff.

Figure 3. Kaplan-Meier Survival Curves for All-Cause-Mortality According to Preoperative High-Sensitivity Troponin T Concentration

Groups are indicated by color. Patients are grouped into two groups using the 99th percentile high-sensitivity troponin T (hs-cTnT) (14 ng/L) as a cutoff.

Figure 4. Kaplan-Meier Survival Curves for All-Cause-Mortality Using a Sex-Specific 99th Percentile for the Preoperative High-Sensitivity Troponin T Concentration
 The upper figure shows the survival characteristics of women using 10 ng/L as 99th percentile cutoff. The lower figure shows the survival characteristics for men using 15 ng/L as 99th percentile.

Table 1

Characteristics of the Study Population

Study sample (n=608)	Baseline hs-cTnT<14 ng/L (n=359; 59%)	Baseline hs-cTnT >14 ng/L (n=249; 41%)	Unadjusted P-Value
Mean age – yr (SD)	61.5 ± 9.7	69.6 ± 10.1	<0.001
Female Sex – no. (%)	158 (44.3%)	70 (27.9%)	<0.001
Race – no. (%)			0.40
White	283 (79.3%)	204 (81.9%)	
Black	72 (20.2%)	45 (18.1%)	
Other	2 (0.6%)	-	
Smoking history – no. (%)	280 (78.7%)	173 (68.9%)	0.01
Current smoker – no. (%)	120 (33.6%)	57 (22.7%)	0.04
Diabetes – no. (%)	103 (28.9%)	114 (45.8%)	<0.001
Insulin dependent – no. (%)	30 (8.4%)	57 (22.7%)	0.002
Hypertension – no. (%)	274 (77.0%)	215 (85.7%)	0.01
Hypercholesterolemia – no. (%)	221 (62.1%)	170 (68.3%)	0.12
Chronic renal failure – no. (%)	23 (6.5%)	42 (16.9%)	<0.001
On hemodialysis – no. (%)	1 (0.3%)	4 (1.6%)	<0.001
Coronary artery disease – no. (%)	171 (48.0%)	170 (67.7%)	<0.001
Previous MI – no. (%)	86 (24.1%)	79 (31.7%)	0.04
Previous PCI/stent – no. (%)	102 (28.8%)	100 (40.5%)	0.004
Previous CABG – no. (%)	39 (11.0%)	64 (25.5%)	<0.001
Congestive heart failure – no. (%)	31 (8.7%)	42 (16.8%)	0.003
Peripheral vascular disease – no. (%)	109 (30.6%)	94 (37.9%)	0.07
Carotid disease – no. (%)	23 (6.5%)	28 (11.2)	0.05
Stroke/TIA – no. (%)	52 (14.6%)	37 (14.9%)	1.0
Atrial fibrillation – no. (%)	28 (7.9%)	43 (17.3%)	<0.001
Lee's revised cardiac risk index			<0.001
I	127 (35.9%)	58 (23.1%)	
II	156 (44.1%)	113 (45.0%)	
III	63 (17.6%)	56 (22.3%)	
IV	8 (2.3%)	24 (9.6%)	
ASA status – no. (%)			<0.001
I	1 (0.3%)	-	
II	70 (19.7%)	27 (10.8%)	
III	278 (78.1%)	207 (82.8%)	
IV	7 (2.0%)	16 (6.4%)	
Medications			
Aspirin – no. (%)	173 (48.6%)	151 (60.4%)	0.005
Clopidogrel – no. (%)	62 (17.4%)	45 (18.0%)	0.914
Warfarin – no. (%)	33 (9.2%)	27 (10.8%)	0.581
Beta-Blocker – no. (%)	164 (46.1%)	157 (62.5%)	<0.001
Statin – no. (%)	183 (51.3%)	152 (60.6%)	0.025

Study sample (n=608)	Baseline hs-cTnT<14 ng/L (n=359; 59%)	Baseline hs-cTnT >14 ng/L (n=249; 41%)	Unadjusted P-Value
ACE-inhibitor – no. (%)	112 (31.4%)	106 (42.2%)	0.008
Calcium channel blocker	82 (23.0%)	76 (30.4%)	0.048
Angiotensin II-R blocker – no. (%)	39 (11.0%)	35 (13.9%)	0.314
Nitrates – no. (%)	19 (5.4%)	25 (10.0%)	0.038
Diuretic – no. (%)	93 (26.1%)	102 (40.6%)	<0.001