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Associations Between Cardiac Troponin, Mechanism of Myocardial Injury, and Long-Term Mortality After Noncardiac Vascular Surgery

Grant W. Reed, MD; Samuel Horr, MD; Laura Young, MD; Joshua Clevenger, MD; Umair Malik, MD; Stephen G. Ellis, MD; A. Michael Lincoff, MD; Steven E. Nissen, MD; Venu Menon, MD

Background—The time-sensitive hazard of perioperative cardiac troponin T (cTnT) elevation and whether long-term mortality differs by mechanism of myocardial injury are poorly understood.

Methods and Results—In this observational study of 12 882 patients who underwent noncardiac vascular surgery, patients were assessed for cTnT sampling within 96 hours postoperatively. Mortality out to 5-years was stratified by cTnT level and mechanism of myocardial injury. During a median follow-up of 26.9 months, there were 2149 (16.7%) deaths. By multivariable Cox proportional hazards analysis, there was a graded increase in mortality with any detectable cTnT compared to <0.01 ng/mL; cTnT 0.01 to 0.029 ng/mL hazard ratio (HR) 1.54 (95% CI 1.18–2.00, P=0.002), 0.03 to 0.099 ng/mL HR 1.86 (95% CI 1.49–2.31, P<0.001), 0.10 to 0.399 ng/mL HR 1.83 (95% CI 1.46–2.31, P<0.001), ≥0.40 ng/mL HR 2.62 (95% CI 2.06–3.32, P<0.001). Mortality for each mechanism of injury was greater than for patients with normal cTnT; baseline cTnT elevation HR 1.71 (95% CI 1.31–2.24; P<0.001), Type 2 myocardial infarction HR 1.88 (95% CI 1.57–2.24; P<0.001), Type 1 MI HR 2.56 (95% CI 2.56, 1.82–3.60; P<0.001). On Kaplan–Meier analysis, long-term survival did not differ between mechanisms. The hazard of mortality was greatest within the first 10 months postsurgery. Consistent results were obtained in confirmatory propensity-score matched analyses.

Conclusions—Any detectable cTnT ≥0.01 ng/mL is associated with increased long-term mortality after vascular surgery. This risk is greatest within the first 10 months postoperatively. While short-term mortality is greatest with Type 1 myocardial infarction, long-term mortality appears independent of the mechanism of injury. (*J Am Heart Assoc*. 2017;6:e005672. DOI: 10.1161/JAHA.117.005672.)

Key Words: mortality • myocardial infarction • postoperative • surgery • troponin T • type 2 MI • type I MI

Perioperative myocardial injury detectable by cardiac troponin elevation is estimated to occur in 5% to 25% of the over 200 million patients who undergo noncardiac surgery annually.[1–4] The association between postoperative troponin elevation and short-term mortality is established.[2–8] However, how this hazard changes over time, and whether it persists long term are not well defined. Further, whether outcomes differ by the underlying mechanism leading to perioperative troponin elevation is unknown.[9,10]

Many patients have detectable troponin following noncardiac surgery, but only ≈40% meet the universal definition of Type 1 myocardial infarction (MI) because of an acute coronary syndrome (ACS).[2,3,6,7,11] It is presumed that most of these events are Type 2 MI, commonly referred to as "demand ischemia," caused by an imbalance of myocardial oxygen supply in the setting of a fixed coronary artery stenosis and increased demand from perioperative stressors.[11] The term "myocardial injury after noncardiac surgery" (MINS) has been used by some to describe events in which patients may be asymptomatic, without ECG changes, but still experience low-grade troponin elevation.[3] There exists an unmet need to examine associations between Type 2 MI or baseline troponin elevation and mortality, as there remains a lack of evidence on how to manage patients with perioperative myocardial injury not attributable to ACS.[9]

To address this, we performed a large observational study to define the association between postoperative cTnT level and mortality after noncardiac vascular surgery, and how this hazard changes over time. Robust multivariable adjustment and propensity score matching were both used to adjust for patient characteristics. We further sought to compare the long-term mortality risk of various mechanisms of myocardial

injury including Type 1 MI attributable to ST-segment myocardial infarction (STEMI) or non-STEMI (NSTEMI) from intraluminal thrombus, Type 2 MI attributable to demand ischemia or MINS, or baseline troponin elevation.

Methods

Study Population and Data Collection

This was a retrospective, observational cohort study of patients who underwent intermediate- or high-risk vascular surgery at a large tertiary care hospital between January 1, 2010 and May 1, 2015. The institutional surgical administrative database was screened to capture all episodes of vascular surgery during the study time period. Intermediate- or high-risk surgeries or endovascular procedures were identified by Current Procedure Terminology code (listed in Table S1); low-risk surgeries or minor nonsurgical procedures including diagnostic angiography were excluded. For patients who underwent more than 1 surgery, only the first surgery was included.

Baseline medical comorbidities, medication use, and laboratory values within 1 month before surgery were obtained by review of International Statistical Classification of Diseases-9 codes and electronic medical record notes. The presence or absence of cTnT sampling and peak cTnT value within 96 hours of surgery was recorded. The Roche 4th generation cTnT assay was utilized, which has an imprecision of <10% (measured as the coefficient of variation) at the 99th percentile of 0.01 ng/mL as per the manufacturer.

Degree of and Mechanisms of Myocardial Injury

Univariate Cox regression was performed to decide on cTnT cut points for stratified analyses; cTnT was considered the continuous independent variable utilizing restricted cubic splines with 6 knots, and mortality was the outcome. The log relative hazard of mortality increased until ≈0.4 ng/mL, and thus this value was used as a cut point in stratified analysis (Figure S1). We further utilized cut points of 0.01 ng/mL as this is the lowest detectable value for the assay (99th percentile normal value), 0.03 ng/mL as it is a commonly used threshold to define cTnT "elevation," and 0.1 ng/mL as it has been used as a cut point in other studies of perioperative myocardial injury.[2,5] The presence and level of myocardial injury was thus classified as "Not Sampled," "<0.01 ng/mL," "0.01 to 0.029 ng/mL," "0.03 to 0.099 ng/mL," "0.1 to 0.399 ng/mL," or "≥0.4 ng/mL."

The mechanism of myocardial injury was determined in each patient with an elevated cTnT (≥0.03 ng/mL) by chart review by 2 experienced physicians blinded to the study outcome. This was adjudicated based on the reviewer's expert opinion after assessment of all relevant notes, ECGs,

Table 1. Baseline Characteristics, Medications, and Laboratory Values

Variable	Not Sampled (N=9594)	Sampled (N=3288)	P Value
Baseline characteristics			
Age, y—mean (SD)	64.8 (14.9)	70.3 (11.8)	<0.001
Sex, male—n (%)	5516 (57.5)	2163 (65.8)	<0.001
Ischemic heart disease*, n (%)	5539 (57.7)	2207 (67.1)	<0.001
Heart failure (current or prior)*, n (%)	1791 (18.7)	620 (18.9)	0.837
Diabetes mellitus (any), n (%)	3211 (33.5)	853 (25.9)	<0.001
Prior stroke/TIA*, n (%)	1230 (12.8)	421 (12.8)	1
High-risk surgery*†, n (%)	4354 (45.4)	2119 (64.4)	<0.001
Medications, n (%)			
β-Blocker	7056 (73.5)	2624 (79.8)	<0.001
ACE or ARB	6166 (64.3)	2191 (66.6)	0.016
CCB	5052 (52.7)	1517 (46.1)	<0.001
Thiazide diuretic	2230 (23.2)	752 (22.9)	0.673
Aldosterone antagonist	803 (8.4)	257 (7.8)	0.335
Nitrates	4849 (50.5)	1696 (51.6)	0.321
Loop diuretic	1909 (19.9)	477 (14.5)	<0.001
Oral hypoglycemic	2622 (27.3)	696 (21.2)	<0.001
Insulin*	4406 (45.9)	1241 (37.7)	<0.001
Statin	6437 (67.1)	2443 (74.3)	<0.001
Aspirin	6912 (72.0)	2522 (76.7)	<0.001
P2Y$_{12}$ inhibitor	2926 (30.5)	1116 (33.9)	<0.001
Warfarin	2213 (23.1)	740 (22.5)	0.52
Laboratory values			
Total cholesterol, mean (SD)	165.7 (50.2)	160.1 (48.6)	<0.001
LDL, mean (SD)	93.4 (40.8)	90.1 (39.9)	<0.001
HDL, mean (SD)	47.4 (17.8)	45.2 (16.7)	<0.001
Hemoglobin, mean (SD)	12.0 (2.3)	12.4 (2.2)	<0.001
HbA1c, median [IQR]	6.0 [5.5, 6.7]	5.9 [5.5, 6.4]	<0.001
Cr, median [IQR]	1.09 [0.82, 2.42]	1.04 [0.83, 1.41]	<0.001
Cr ≥2.0*, n (%)	2652 (27.6)	438 (13.3)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; Cr, creatinine; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; TIA, transient ischemic attack.
*Variables included in calculation of Revised Cardiac Risk Index score.
†High-risk surgery denotes any high-risk aortic or peripheral vascular surgery.
Significance determined at α<0.05 by Student *t* test or Wilcoxon test for continuous variables, or Pearson's χ^2 or Fisher exact test for categorical variables.
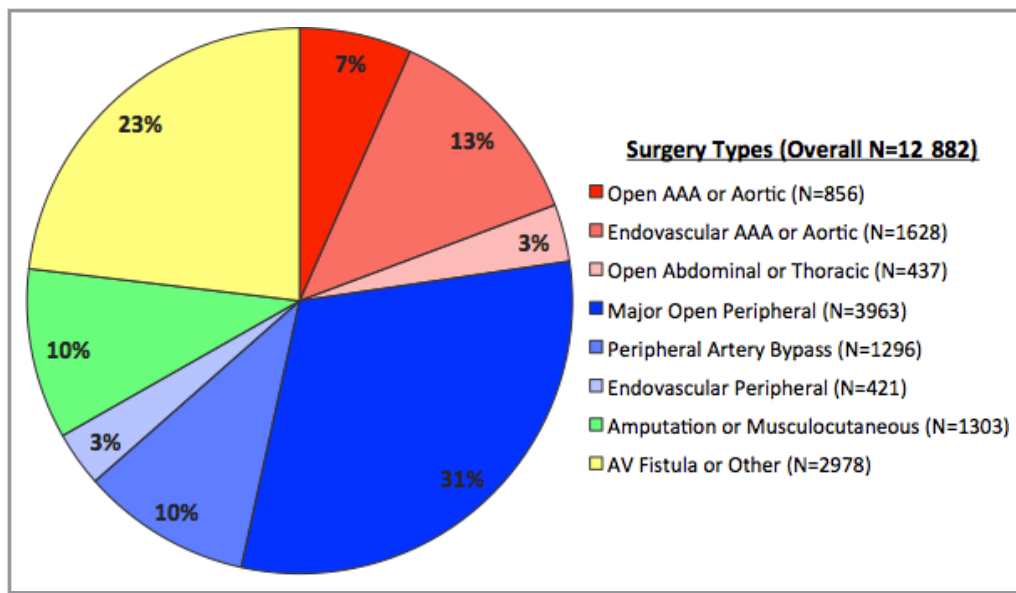
Figure 1. Frequency of types of vascular surgery in the study population. Most patients had a major aortic or peripheral vascular procedure (63% of total); endovascular peripheral procedures, amputation, AV, fistula, and other minor vascular surgeries were less common. See Table S1 for a comprehensive list of the various surgeries in each of the larger categories summarized above. AAA indicates abdominal aortic aneurysm; AV, arteriovenous.

laboratory values, stress tests, and coronary angiograms (when available). There was near complete (>95%) agreement between adjudicators for every case, and in the case of a disagreement, a third physician was used as a tie-breaker.

The mechanism was defined as "Type 1 MI (NSTEMI or STEMI due to intraluminal thrombus)," "Type 2 MI (Demand ischemia or MINS)," or "Baseline elevation." The definition of MINS used included all patients with myocardial injury because of an ischemic event that does not fulfill the Universal Definition of MI. Patients were considered to have a baseline cTnT elevation if they had a similar cTnT value before the start of the study on their last available laboratory testing. Any increase in cTnT >10% higher than the previous cTnT value was not considered a baseline elevation, and instead adjudicated as a Type 1 or Type 2 MI event.

Study End Point

The study's end point was all-cause mortality within 5 years of the index surgery. Mortality data were obtained via electronic medical record, Social Security Death Index, Ohio Death Index query, and search of public records. Mortality was chosen as the study end point as it is objective, clinically important, and easily obtainable.

Statistical Analyses

Continuous variables are presented as mean (SD) and compared with Student t test if parametric, or median (interquartile range) and compared with the Wilcoxon rank-sum test if nonparametric. Categorical variables are presented as number (percentage) and compared using Pearson's χ^2 test or Fisher exact test (if frequency <10). Continuous baseline characteristics with missing values were imputed using multivariate imputation by chained equations where appropriate.

Multivariable Cox proportional hazards models were built using mortality as the dependent variable, patient character-istics, and cTnT level or mechanism of myocardial injury as independent variables. Terms from Table 1 were selected for inclusion in the model based on a backwards selection algorithm, minimizing Akaike information criterion. Colinearity was avoided by choosing between terms with elevated variance inflation factor values. Overfitting was avoided in the final model by following a 15 event:1 variable maximum ratio. The proportional hazards assumption was tested for each final Cox model by plotting the Schoenfeld residuals versus log (time). Hazard functions were also plotted to discern whether the instantaneous hazard rate varied over time. Survival analysis was subsequently performed via the Kaplan–Meier method utilizing the log-rank comparison, stratifying long-term mortality by cTnT level and mechanisms of myocardial injury.

Next, a separate set of sensitivity analyses was performed using propensity score matching techniques. First, a propen-sity score for cTnT level was created utilizing all variables included (Table 1). Patients with each level of cTnT were 1:1 Greedy matched without replacement to patients with
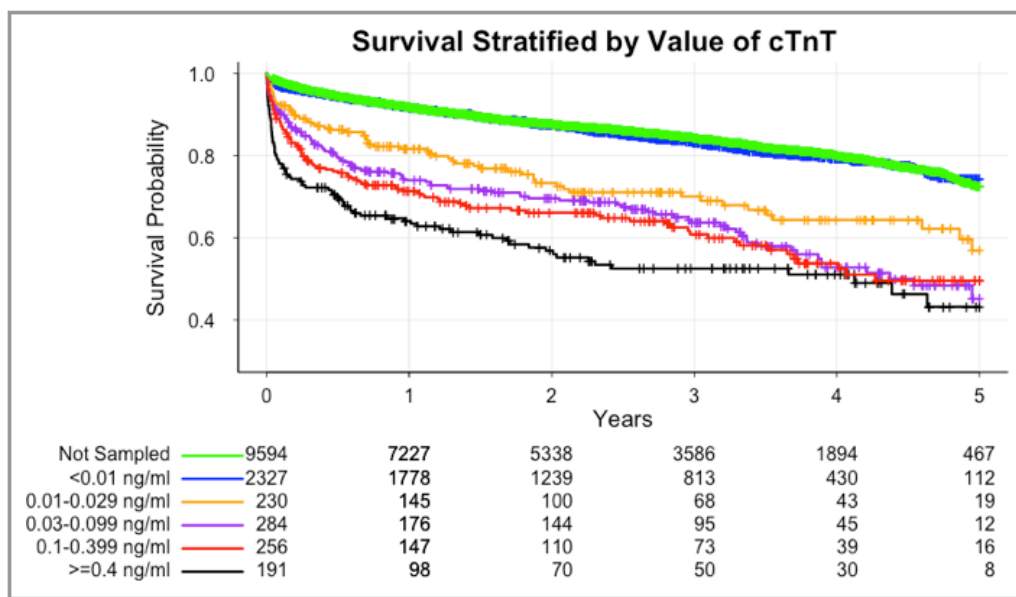
Figure 2. Kaplan–Meier survival curves for long-term mortality stratified by cTnT level. Long-term mortality was similar in patients not sampled and those not detectable (<0.01 ng/mL), whereas there was a graded decline in the probability of survival with any detectable cTnT level, even below the threshold for cTnT elevation (0.03 ng/mL). Log-rank *P*<0.001 for the entire model. Values are reported as ng/mL. cTnT indicates cardiac troponin T.

sampled but cTnT <99th percentile (<0.01 ng/mL) via nearest propensity score. In a separate set of analyses, patients with each mechanism of myocardial injury were 1:1 Greedy matched without replacement to patients with a normal cTnT (<0.03 ng/mL) via nearest propensity score. Covariate balance was assessed with an assessment of standardized differences before and after matching. Cox proportional hazards and Kaplan–Meier survival analyses were then performed after matching as previously described.

Statistical significance was defined as a 2-sided *P*<0.05 for all analyses. Data were analyzed with R version 3.1.0 statistical software. All patients provided consent to participate in the study. This study was approved by the Institutional Review Board before data collection.

Results

Baseline Characteristics and Surgery Prevalence

A total of 13 702 unique patients were identified via the inclusion criteria. Following review, 820 patients were excluded as they only had a diagnostic peripheral angiogram or nonvascular surgical procedure; 12 882 patients comprised the final cohort.

Overall as part of routine clinical practice, 3288 patients (25.52%) had cTnT sampled within 96 hours of surgery. Baseline characteristics stratified by whether patients had cTnT sampled are provided in Table 1. Patients who had cTnT

sampled were more likely to be older, male, have a history of ischemic heart disease, have underwent a high-risk surgery, but were less likely to be diabetic (*P*<0.001 for all comparisons). While statistically significant differences in medication use and certain laboratory values were observed, there were few clinically meaningful differences aside from a higher frequency of statin use in sampled patients and a higher frequency of insulin use and creatinine ≥2.0 mg/dL in those not sampled (*P*<0.001 for all comparisons).

The frequencies of the different surgeries in the study population are provided in Figure 1. The majority of patients had major or high-risk vascular surgery (64%); aortic surgery and aortic endovascular intervention were common (23% combined), as were peripheral bypass and other major peripheral vascular surgeries (41% combined). A full list of surgeries in each category is provided in Table S1.

Degree of cTnT Elevation and Long-Term Mortality

The median follow-up was 26.9 (11.7–43.4) months. A total of 2149 patients died during the follow-up period (16.7% of total). Among the 3288 patients who had cTnT sampled, cTnT was above the 99th percentile (ie, ≥0.01 ng/mL) in 961 patients (29.2% of those sampled, 7.5% of total), and cTnT was elevated (ie, ≥0.03 ng/mL) in 746 (22.7% of those sampled, 5.8% of total). In unadjusted analysis, having an elevated cTnT was strongly associated with an increased risk of long-term

Table 2. Multivariable Proportional Hazards Model for Mortality Including Degree of cTnT

Variables	HR (95% CI)	P Value
Degree of cTnT		
Not sampled	0.83 (0.74–0.94)	0.003
Undetectable (<0.01 ng/mL)	Reference	…
Minimal detection (0.01–0.029 ng/mL)	1.54 (1.18–2.00)	0.002
Mild elevation (0.03–0.099 ng/mL)	1.86 (1.49–2.31)	<0.001
Moderate elevation (0.10–0.399 ng/mL)	1.83 (1.46–2.31)	<0.001
High elevation (≥0.40 ng/mL)	2.62 (2.06–3.32)	<0.001
Clinical variables		
Age*	2.04 (1.86–2.45)	<0.001
Creatinine ≥2.0	1.27 (1.15–1.41)	<0.001
Congestive heart failure	1.27 (1.14–1.41)	<0.001
Ischemic heart disease	1.22 (1.09–1.37)	0.001
Hemoglobin†	0.58 (0.52–0.64)	<0.001
Medications		
Insulin	1.41 (1.27–1.57)	<0.001
Loop diuretic	1.30 (1.17–1.45)	<0.001
Warfarin	1.29 (1.17–1.42)	<0.001
β-Blocker	1.25 (1.08–1.44)	0.002
Aldosterone antagonist	1.22 (1.06–1.39)	0.004
Oral hypoglycemic	0.90 (0.81–1.00)	0.045
Thiazide diuretic	0.89 (0.80–0.99)	0.023
ACE inhibitor or ARB	0.88 (0.79–0.98)	0.019
Statin	0.75 (0.68–0.84)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; cTnT, cardiac troponin T; HR, hazard ratio.
*Age dichotomously stratified as above median—66 years.
†Preoperative hemoglobin dichotomously stratified as above sample median—12.1 g/dL. Significance determined at α<0.05.

mortality compared to those sampled with normal cTnT (ie, <0.03 ng/mL) (hazard ratio [HR] 2.86, 95% CI 2.46–3.32; $P<0.001$).

The cohort was further stratified by the degree of cTnT, with the number of patients with each level provided in Figure 2. After multivariable adjustment, there remained a graded, independent association between increased mortality and postoperative cTnT level ($P<0.01$ for all levels compared with cTnT <0.01 ng/mL) (Table 2). This was observed with any detectable cTnT value, even at minimally detectable levels considered "normal" (0.01–0.029 ng/mL).

On Kaplan–Meier analysis, there was no difference in the probability of long-term survival between patients not sampled and those with cTnT <0.01 ng/mL (Figure 2). However, there was a graded, stepwise decline in survival with increasing cTnT (Log-rank $P<0.001$ for any detectable cTnT compared with cTnT <0.01 ng/mL). This was similarly seen even at minimally detectable cTnT values (0.01–0.029 ng/mL). The mortality hazard appeared to be predominantly early, as the hazard rate gradually declined until ≈10 months follow-up, but did not completely abate. Illustrating this, there was a gradual divergence of survival curves over time (Figure 2), and while there was some variability, the hazard for each cTnT level tended to remain above patients without sampling or cTnT <0.01 ng/mL during follow-up (Figure 3).

Propensity-score matched analyses were performed to obtain a more robust adjustment for all patient comorbidities in Table 1. All patients within each level of cTnT were successfully matched 1:1 to a patient with cTnT <0.01 ng/mL. There was acceptable improvement of covariate balance after matching in every case (Figure S2). After propensity-score matching, the risk of mortality similarly increased with rising level of cTnT compared to <0.01 ng/mL. Specifically, for cTnT 0.01 to 0.29 ng/mL HR 1.57 (95% CI 1.07–2.31, $P=0.022$; Kaplan–Meier Log-rank $P=0.021$), for 0.03 to 0.099 ng/mL HR 1.75 (95% CI 1.28–2.39, $P<0.001$; Kaplan–Meier Log-rank $P<0.001$), for 0.1 to 0.399 ng/mL HR 1.67 (95% CI 1.22–2.29, $P=0.001$; Kaplan–Meier Log-rank $P=0.001$), and for ≥0.40 ng/mL HR 3.00 (95% CI 2.03–4.44, $P<0.001$; Kaplan–Meier Log-rank $P<0.001$).

Mortality and Mechanism of Myocardial Injury

When adjudicated by type of myocardial injury, 88 patients had a Type 1 MI, 162 patients had a Type 2 MI, and 482 patients had baseline cTnT elevation. The median cTnT value was 0.13 ng/mL (interquartile range 0.07–0.25 ng/mL) for patients with baseline elevation, 0.11 ng/mL (interquartile range 0.05–0.28 ng/mL) for patients with Type 2 MI, and 1.42 ng/mL (interquartile range 0.59–2.74 ng/mL) for Type 1 MI ($P<0.001$ overall). On multivariable analysis, there was an independent association between increased mortality and each mechanism of myocardial injury ($P<0.001$ for all comparisons; Table 3). While the mortality risk was numerically greater with Type 1 MI compared with Type 2 MI or baseline elevation, the hazards were not statistically different comparing any 2 mechanisms ($P=NS$ for all comparisons).

Similarly, by Kaplan–Meier analysis, the probability of long-term survival was significantly lower with each mechanism of myocardial injury compared with patients with a normal cTnT value (log-rank $P<0.001$ for each) (Figure 4). However, long-term survival did not differ by mechanism of injury ($P=NS$ comparing each group). While the hazard of mortality was higher with Type 1 MI in the short term, after ≈10 months the
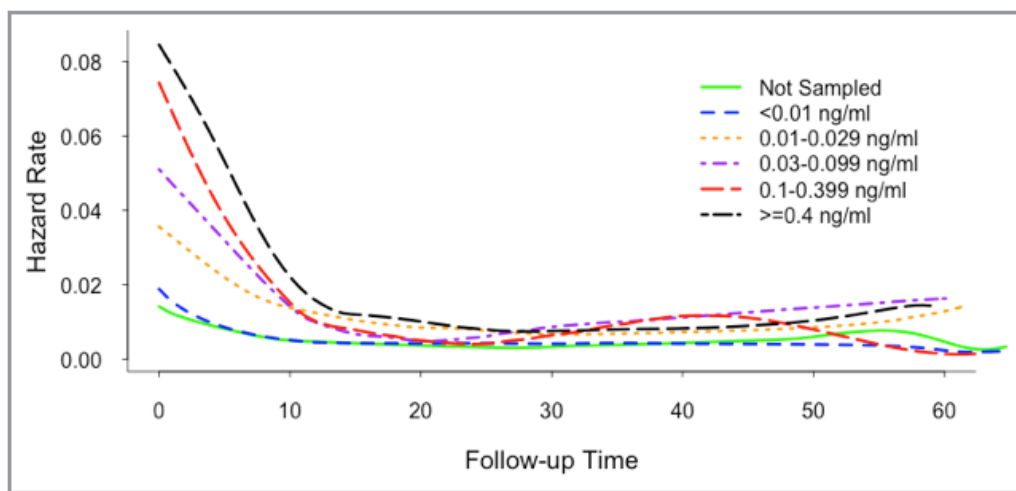
Figure 3. Plot of hazard rate over time stratified by cTnT level. There was a graded increase in the instantaneous hazard of mortality with increasing cTnT level. This risk was apparent immediately postoperatively, greatest within the first 10 months after surgery, but persisted during long-term follow-up for all levels of cTnT. cTnT indicates cardiac troponin T.

hazard of mortality appeared to equalize between groups (Figure 5). Over the long term, patients with demand Type 2 MI had similar survival and mortality hazards as patients with Type 1 MI (Figures 4 and 5).

As was done with cTnT level, propensity-score matched analyses were performed to further adjust for all comorbidities in Table 1. All patients within each mechanism of myocardial injury were successfully matched 1:1 to a patient with a normal cTnT (except 1 patient in the Type 1 MI group). There was acceptable improvement in standardized differences after matching in every case (Figure S3). After propensity-score matching, the risk for mortality remained significantly elevated for each mechanism of myocardial injury compared with normal cTnT; for baseline elevation HR 1.52 (95% CI 1.04–2.22, P=0.030; Kaplan–Meier Log-Rank P=0.029), for Type 2 MI HR 1.74 (95% CI 1.38–2.21, P<0.001; Kaplan–Meier Log-rank P<0.001), and for Type 1 MI HR 2.72 (95% CI 1.51–4.89, P<0.001; Kaplan–Meier Log-Rank P<0.001).

Provider Response to Type 1 and Type 2 MI

Tables 4 and 5 describe the treatment patterns of the patients with Type 2 MI in this study. The majority of patients with Type 1 MI underwent a stress test or left heart catheterization (61%); those who did not were because of the nature of their surgery or medical comorbidities. In contrast, very few patients with Type 2 MI were offered stress test or left heart catheterization (5%) before hospital discharge (Table 4). The majority of patients with Type 1 MI were initiated on a β-blocker, aspirin, and/or clopidogrel if they were not on one already. Most patients

with Type 2 MI were already on these medications (Table 1); however, among those who were not, fewer were initiated on these medications than patients with Type 1 MI (Table 5).

Discussion

In this study, we demonstrate that there is an independent, graded relationship between perioperative cTnT level and long-term mortality after intermediate- or high-risk noncardiac vascular surgery. This emerges immediately, is mostly an early hazard, but persists over time with any detectable cTnT value above the 99th percentile (≥0.01 ng/mL), even at levels typically considered below elevated (0.01–0.029 ng/mL). We further demonstrate that patients with Type 1 MI attributable to intraluminal thrombosis have a greater early mortality hazard than patients with Type 2 MI attributable to demand ischemia/MINS, but that the risk is roughly equivalent over time (Figures 4 and 5). Together, these results suggest that the degree of postoperative myocardial injury appears to be more important than the underlying pathogenic mechanism. Our results support the premise that patients with perioperative Type 2 MI are at high risk for mortality, and confirm that this risk persists well beyond the immediate postoperative time period of 30 days or 1 year.

Our study has several strengths. While other studies have demonstrated there is an association between perioperative cTnT elevation and mortality, we show that this is a long-term risk independent of mechanism of myocardial injury, and have been able to define how this hazard changes over time in our study. Previously, VISION (Vascular Events In Noncardiac Surgery Patients Cohort Evaluation) prospectively studied

Table 3. Multivariable Proportional Hazards Model for Mortality Including Mechanism of Myocardial Injury

Variables	HR (95% CI)	P Value
Mechanism of myocardial injury		
Not sampled	0.79 (0.70–0.88)	<0.001
Normal	Reference	…
Baseline elevation	1.71 (1.31–2.24)	<0.001
Demand ischemia/MINS	1.88 (1.57–2.24)	<0.001
ACS (NSTEMI or STEMI)	2.56 (1.82–3.60)	<0.001
Clinical variables		
Age*	2.04 (1.86–2.24)	<0.001
Ischemic heart disease*	1.23 (1.09–1.37)	<0.001
Heart failure (current or prior)*	1.27 (1.14–1.42)	<0.001
Creatinine ≥2.0	1.27 (1.15–1.40)	<0.001
Hemoglobin†	0.57 (0.52–0.64)	<0.001
Medications		
Insulin	1.41 (1.27–1.57)	<0.001
Loop diuretic	1.30 (1.17–1.45)	<0.001
β-Blocker	1.24 (1.08–1.43)	0.003
Warfarin	1.29 (1.18–1.42)	<0.001
Aldosterone antagonist	1.22 (1.07–1.39)	0.004
Oral hypoglycemic	0.93 (0.82–1.04)	0.191
Thiazide diuretic	0.89 (0.81–0.99)	0.039
ACE inhibitor or ARB	0.90 (0.81–0.99)	0.020
Statin	0.75 (0.68–0.84)	<0.001

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; HR, hazard ratio; MINS, myocardial injury after noncardiac surgery; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

*Age dichotomously stratified at above median—66 years.

†Preoperative hemoglobin dichotomously stratified at above median—12.1 g/dL. Significance determined at α<0.05.

15 093 patients who underwent noncardiac surgery, and demonstrated a similar graded increase in 30-day mortality with cTnT elevation stratified by cTnT but using different strata of ≤0.01, 0.02, 0.03 to 0.29, or ≥0.3 ng/mL.[2] While an important study, VISION only evaluated outcomes to 30 days, and did not investigate mechanisms of myocardial injury. We have addressed both of these issues, and performed propensity score adjustments for comorbidities in the current study. Further, our work improves upon a study of 447 patients who underwent major vascular surgery that found a similar graded increase in the hazard of long-term mortality with cTnT elevation cut points of ≥0.03, ≥0.1, and ≥0.2 ng/mL.[5] In addition, a meta-analysis by Levy et al found that among patients with postoperative troponin elevation, the pooled hazard ratio for mortality beyond 12 months (out to 2 years) was 1.8 (95% CI 1.4–2.3).[8] We were able to expand on both of
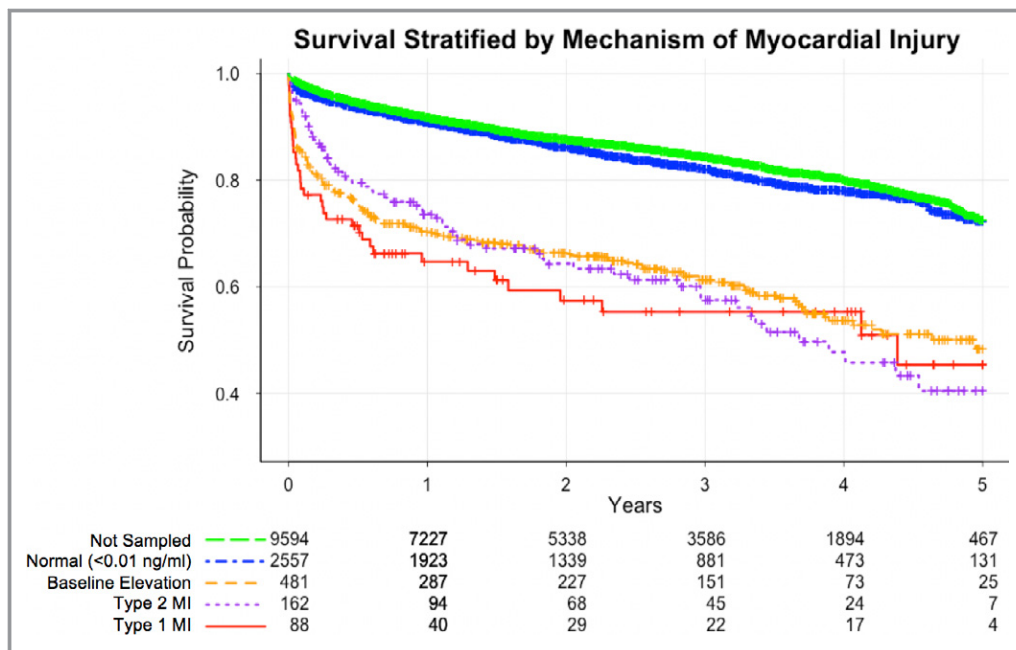
these studies, as our sample size is several times larger, and both our multivariable and propensity score adjustments for possible cofounders are more robust.

This is the largest study to evaluate the mechanisms of cTnT elevation in a surgical population to date. Importantly, we show that while the short-term hazard of mortality is higher with Type 1 than Type 2 MI, over the long term the risk of Type 2 MI is significant and approximates true ACS. Illustrating this, on Kaplan–Meier analysis, patients with Type 1 MI do appear to have worse survival immediately following surgery; however, the survival curve for patients with Type 2 MI gradually converges with the Type 1 curve over time. This similar mortality hazard lends credence to the premise that although presentations may somewhat differ between Type 1 and Type 2 MI, cTnT is specific for myocardial injury, and thus there may be a similar pathophysiology driving both types of MI. While sequelae of acute plaque rupture likely drive the early mortality hazard associated with Type 1 MI, it is likely that underlying coronary artery disease and perhaps other comorbidities (congestive heart failure, valvular disease, atrial fibrillation, etc) influence long-term mortality regardless of whether classified as Type 1 or Type 2 MI.

In support of this concept, there is emerging evidence that patients with demand ischemia may have mortality rates equivalent to or perhaps exceeding patients with true ACS across a variety of clinical circumstances.[12–15] This may be driven by underlying medical comorbidities,[16] or perhaps misclassification of a subset of these patients as type 2 MI, when in fact they had type 1 MI.[17] To this point, in a recent study of 217 patients with presumed type 2 MI who underwent angiography, 29% had evidence of acute plaque rupture.[18] The prevalence of misclassified type 2 MI may be even higher in surgical patients, as 2 angiographic studies have demonstrated thrombotic occlusion to be the cause of perioperative MI in between 26% and 60% of patients.[19,20]

Despite this, few patients with Type 2 MI were offered left heart catheterization or stress testing before hospital discharge in our study. Further, fewer patients with Type 2 MI had aspirin, clopidogrel, statin, and/or a β-blocker introduced than patients with Type 1 MI. This may represent an opportunity to improve patient outcomes; however, prospective studies and randomized trials are indicated to evaluate whether these interventions may reduce mortality.

Though infrequent, patients with proven baseline cTnT elevation before surgery were also at increased risk of long-term mortality, to a degree indistinguishable from Type 2 or Type 1 MI. Baseline troponin elevation in patients with chronic kidney disease has been poorly studied in the perioperative space; however, it is known to be a risk factor for major adverse cardiac events out to 30 days or 1 year after ACS, as demonstrated in a substudy of the ACUITY (Acute Catheterization and Urgent Intervention Triage

Survival Stratified by Mechanism of Myocardial Injury

Not Sampled	9594	7227	5338	3586	1894	467
Normal (<0.01 ng/ml)	2557	1923	1339	881	473	131
Baseline Elevation	481	287	227	151	73	25
Type 2 MI	162	94	68	45	24	7
Type 1 MI	88	40	29	22	17	4

Figure 4. Kaplan–Meier survival curves for long-term mortality stratified by mechanism of myocardial injury. Long-term survival was decreased in all patients with myocardial injury, regardless of myocardial injury. Survival was similar for patients with baseline elevation, Type 2 MI or Type 1 MI. Log-rank *P*<0.001 for the entire model. MI indicates myocardial infarction.

Strategy) trial. In addition, troponin elevation >99th percentile is commonly observed in acute and chronic heart failure. It is plausible that baseline cTnT elevation is likely more of a representation of underlying comorbidities than myocardial ischemia.[21] That said, studies of preoperative

Holter monitoring demonstrate that up to 27% of adults have reversible ST-segment changes in the 2 days before surgery, suggestive that some perioperative cTnT elevation is indeed attributable to acute ischemia rather than chronic cTnT elevations.[22,23] Strategies to reduce mortality in this patient
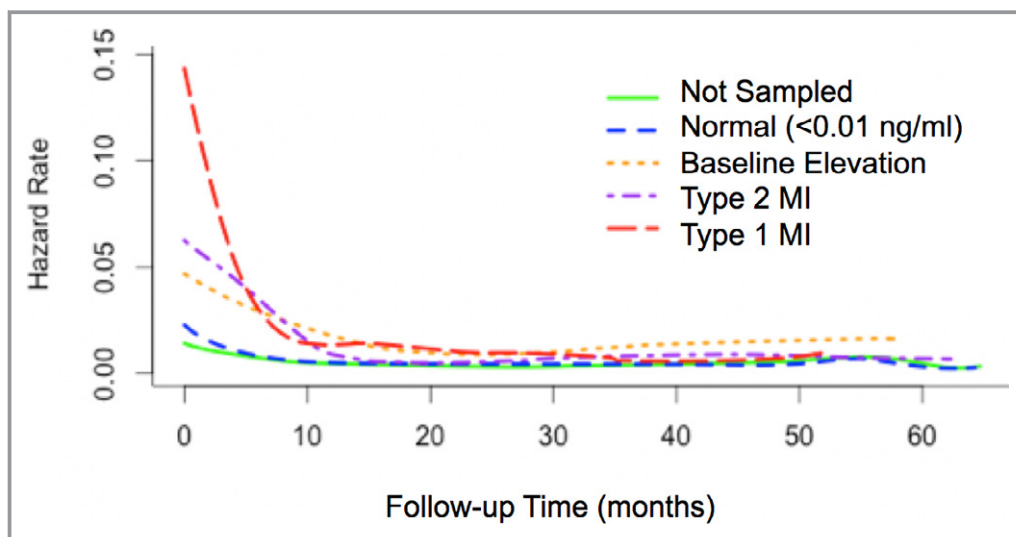
Figure 5. Plot of hazard rate over time stratified by mechanism of myocardial injury. Patients with Type 1 MI had the highest hazard of mortality in the short term after noncardiac surgery. However, patients with Type 2 MI and baseline cTnT elevation still had a higher risk than patients with a normal cTnT, and the risk was similar to that of patients with Type 1 MI after ≈10 months. cTnT indicates cardiac troponin T; MI, myocardial infarction.

Table 4. Procedures in Patients With Type 1 and Type MI

	Type 1 MI (N=88)	Type 2 MI (N=482)
Ischemic evaluation		
Stress test (nuclear or echocardiographic)	8 (9)	8 (2)
Left heart catheterization	49 (56)	16 (3)
Stress test or left heart catheterization	54 (61)	23 (5)

Results reported as N (%) out of total. MI indicates myocardial infarction.

population deserve further study, and should extend beyond the perioperative space.[24]

Current guidelines from the American College of Cardiology/American Heart Association advise measuring troponin levels in patients undergoing noncardiac surgery with signs of symptoms of ischemia (Class I recommendation), and both these American College of Cardiology/American Heart Association and the European Society of Cardiology/Heart Association Guidelines give a weak recommendation for routine troponin screening in patients at high risk for perioperative cardiovascular events (Class IIb recommendation).[25,26] While in our study the hazard of mortality was similar in patients not sampled compared to those who were sampled but below the 99th percentile (<0.01 ng/mL), these results are contrary to strong evidence that in the absence of routine troponin sampling, 85% of prognostically important myocardial injuries after noncardiac surgery may be undetected.[3] In recognition of this, the most recent Canadian Cardiovascular Society perioperative guidelines give a strong recommendation on moderate-quality data to obtaining daily troponin measurements for 48 to 72 hours after noncardiac surgery in patients with a baseline risk >5% of cardiovascular death or nonfatal MI at 30 days after surgery.[27]

Table 5. Medication Management in Patients With Types 1 and 2 MI

	Type 1 MI (N=88)		Type 2 MI (N=482)	
	Started	Total	Started	Total
Medications started				
β-Blocker	41 (47)	81 (91)	75 (16)	413 (86)
Aspirin and/or clopidogrel	28 (32)	82 (92)	63 (13)	385 (80)
Statin	34 (39)	78 (89)	53 (11)	359 (74)
Any medication change	53 (60)	…	103 (21)	…

Results reported as N (%) out of total. MI indicates myocardial infarction.

Despite its strengths, there are certain limitations of the current study. This was a single-center study, which limits generalizability. We cannot rule out the influence of unmeasured confounders on our results; however, our large sample size, robust multivariable adjustment, and separate propensity score adjustments limit this concern. All-cause mortality was used as our end point as it was readily available and objective, and cause of death was not available in all patients. While we did not compare mortality rates across various surgical types, we did adjust for high-risk surgery in the propensity-score matched analysis. Further, as a minority of patients underwent angiography or stress testing, it is possible that a subset of patients may have had their mechanism of myocardial injury misclassified. However, this is unlikely to have biased our results, as every patient was adjudicated by 2 physicians blinded to the study outcome with near complete agreement between adjudicators in every case, and the median cTnT in each group was consistent with what would be expected based on the mechanism of injury. In addition, we used imputed data for missing values where appropriate; however, this allowed us to maximize sample size and use each variable collected. Each analysis was carried out in the imputed and not-imputed samples to verity that imputation did not significantly impact our results.

Conclusions

Any degree of perioperative myocardial injury detected by serum cTnT is independently associated with long-term mortality after noncardiac vascular surgery. This risk emerges with any detection of cTnT above the 99th percentile (≥0.01 ng/mL), and rises in a stepwise manner as cTnT level increases. While the short-term hazard of mortality is greater in patients with Type 1 MI (NSTEMI or STEMI attributable to intraluminal thrombus), the long-term risk of mortality appears to be independent of mechanism of myocardial injury, as patients with Type 2 MI (demand ischemia) have long-term mortality equivalent to that of patients with Type 1 MI. Although typically neglected in clinical practice, low-grade perioperative cTnT elevation is a major risk factor for long-term adverse outcomes. Future prospective studies and clinical trials are needed to determine whether this risk is modifiable.

Acknowledgments

Disclosures

None.

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Supplemental Material

Table S1. Comprehensive List of the Various Surgeries in Each Surgical Category.

Study Category	Specific Surgeries
Open AAA or Aortic	Open AAA repair / grafting Aortic or aortoiliac stent graft explant and repair Aortic thrombectomy or endartectomy Aorto-mesenteric, -renal, -spleno, -iliac, or -femoral bypass
Endovascular AAA or Aortic	Endovascular aortic repair (EVAR); FEVAR and TEVAR Endovascular aorto-mesenteric or aorto-iliac repair Aortic angioplasty
Open Abdominal or Thoracic	Exploratory laparotomy or laporoscopy Exploratory thoracotomy, sternotomy, related surgeries Renal artery aneurysm resection Solid organ removal (i.e. splenectomy, nephrectomy) Bowel resection IVC reconstruction Other peritoneal, peroneal, or inguinal surgery Vagus or other neurostimulator surgery
Peripheral Artery Bypass	Iliofemoral, femoral-femoral, femoral-popliteal (or other) bypass Axillary-axillary, axillary-femoral (or other) bypass Upper extremity (i.e. subclavian) bypass Carotid-subclavian (or other) artery bypass Any peripheral bypass graft revision or removal
Other Major Open Peripheral	Carotid endartectomy, carotid body tumor excision Iliac, femoral, popliteal, or below knee endaterectomy Subclavian, axillary, or upper extremity endarterectomy Arterial transposition (i.e. vertebral, subclavian, carotid) Venous transposition Other open peripheral arterial or venous stenting, exploration, repair or resection
Endovascular Peripheral	Iliac, femoral, popliteal, or below-knee angioplasty/stenting Peripheral bypass graft angioplasty/stenting Carotid artery stenting Upper extremity (i.e. subclavian) angioplasty/stenting Peripheral catheter-directed thrombolysis Other endovascular peripheral interventions
Amputation or Musculocutaneous	Above the knee amputation (or revision) Below the knee amputation (or revision) Minor amputation (i.e. digital, TMA) Skin grafting or other related cutaneous surgery Fasciotomy, myocutaneous, or related orthopedic surgery Complex debridement and cutdown procedures
AV Fistula or Other	AV fistula creation, removal, or revision AV fistula thrombectomy, or other related surgery

Uncommon surgeries low in frequency (N≤10) were not included separately in the list above. Abbreviations: AAA, abdominal aortic aneurysm; FEVAR, fenestrated EVAR; TEVAR, thoracic EVAR; IVC, inferior vena cava; TMA, transmetatarsal amputation; AV, arteriovenous.

Figure S1. Log Relative Hazard of Mortality by cTnT Value (Modeled Continuously)
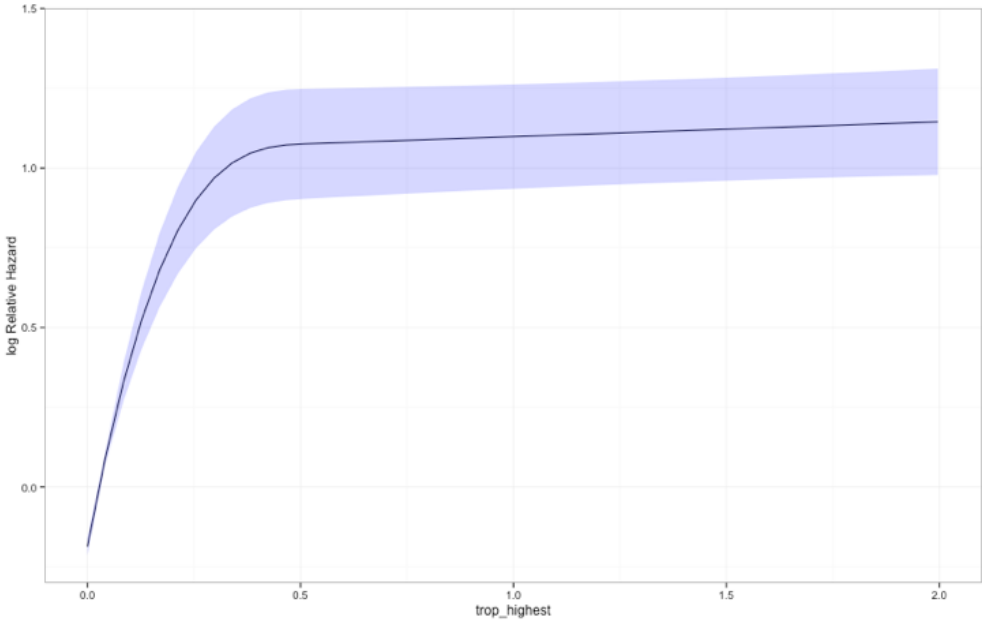
There was an increase in the relative hazard of mortality for cTnT values, which appeared to plateau at approximately 0.4 ng/ml. Thus, a value of 0.4 ng/ml was utilized as a cut-point in stratified analyses.
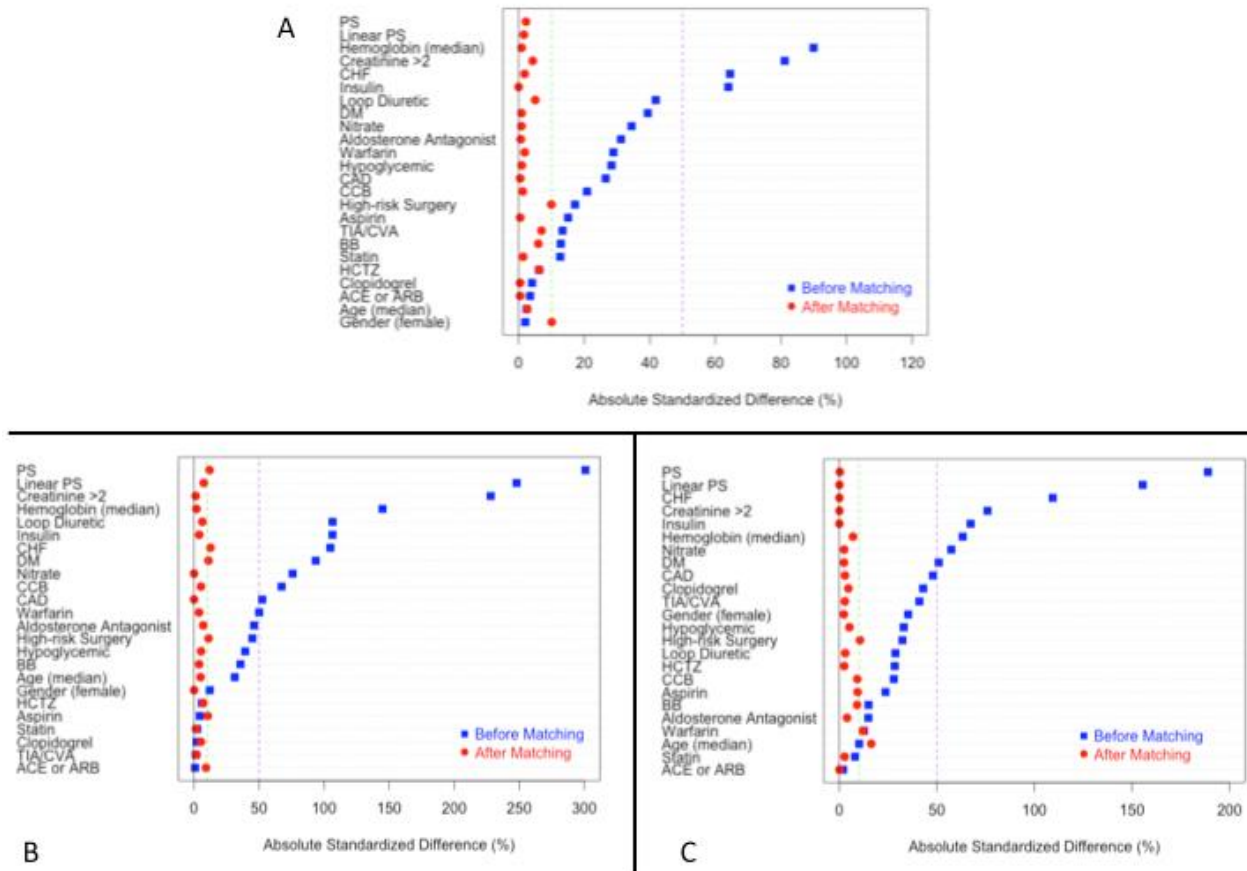
Figure S2. Plot of Standardized Differences for Propensity-Matched Analyses Stratified by

cTnT Level.
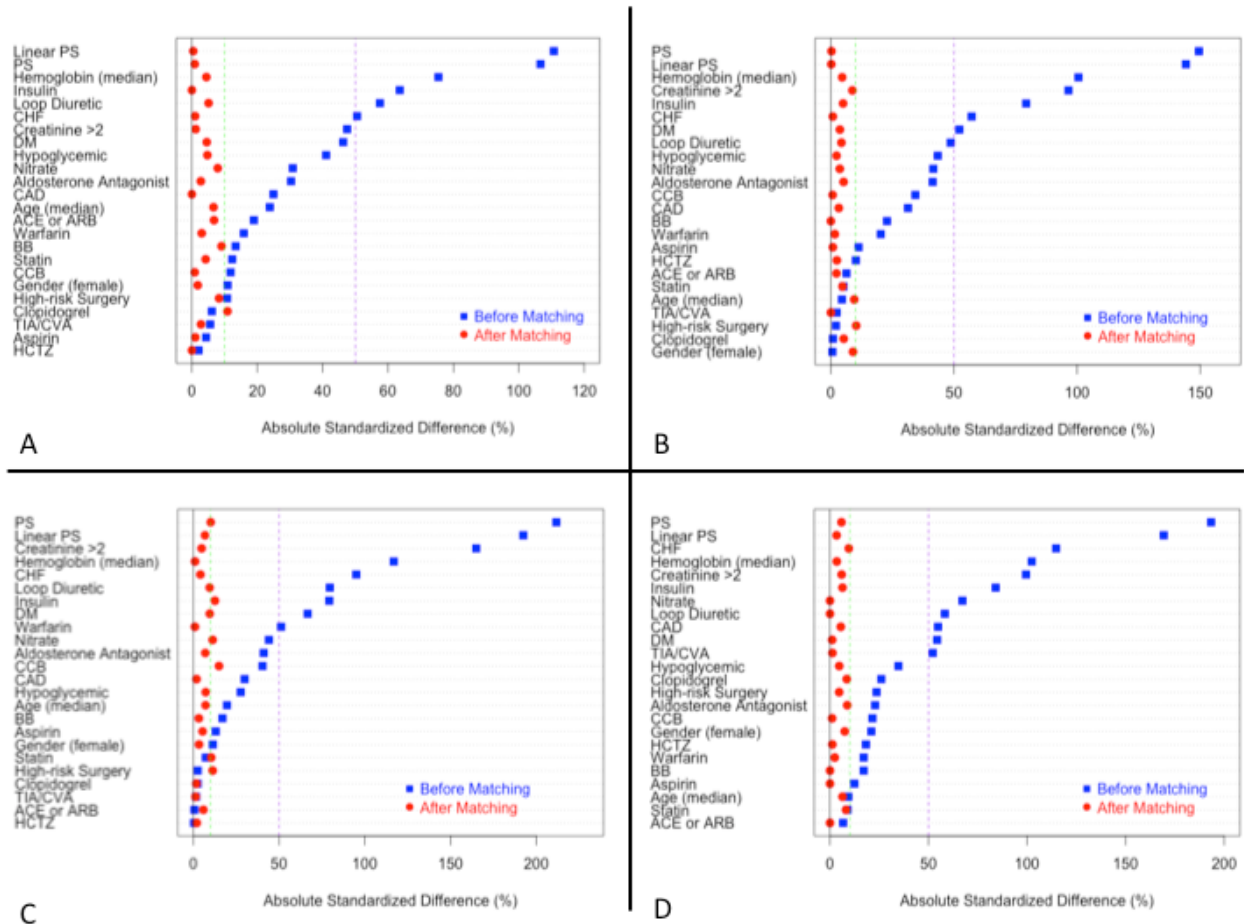
There was acceptable improvement in covariate balance with each propensity score match.

Patients in each cTnT level were Greedy matched 1:1 without replacement and no caliper to a

patient with a normal cTnT value (<0.03 ng/ml). A – cTnT 0.01-0.029 ng/ml; B – cTnT 0.03-

0.099 ng/ml; C – cTnT 0.1-0.399 ng/ml; D – cTnT ≥ 0.4 ng/ml.

Figure S3. Plot of Standardized Differences for Propensity-Matched Analyses Stratified by
Mechanism of Myocardial Injury.

There was acceptable improvement in covariate balance with each propensity score match.
Patients in each cTnT level were matched 1:1 to a patient with a normal cTnT (<0.03 ng/ml). No
caliper was used, except for the ACS match, in which a 0.2 standardized difference caliper was
used to improve covariate balance (excluding 1 patient). cTnT <0.01 ng/ml. A – cTnT 0.01-
0.029 ng/ml; B – cTnT 0.03-0.099 ng/ml; C – cTnT 0.1-0.399 ng/ml; D – cTnT ≥ 0.4 ng/ml.