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Should troponin and creatinine kinase be routinely measured after vascular surgery?

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Abstract: The current guidelines for the evaluation and prediction of adverse cardiovascular events (CVEs) following vascular surgery in high-risk patients recommends serial electrocardiograms (ECGs) but not biomarkers such as cTn-I and CK-MB. The objective of this study was to determine whether biomarkers should be routinely measured in high-risk patients undergoing vascular surgery. A multicenter, prospective study with investigators blinded to core laboratory results was conducted. cTn-I and CK-MB were obtained on the day of surgery, as well as 24 hours, 72 hours and 120 hours after surgery, 24 hours prior to planned hospital discharge and at the onset of symptoms of a suspected CVE. The CVE was adjudicated by an endpoint committee using ECG, biomarker and symptoms data and was defined as cardiac death or myocardial infarction (MI) occurring up to 30 days after surgery. A total of 784 patients, with a mean age of 70.1 (SD $\pm$ 9.8), underwent vascular surgery. Of the 83 patients with a CVE, cTn-I was positive in 42 and CK-MB was positive in 29 on or before the day of the CVE. The number of patients not classified as having a CVE but positive for elevation of cTn-I or CK-MB was 64 and 20, respectively. cTn-I was more sensitive than CK-MB (50.6% versus 34.9%) for predicting a CVE. The optimum time for measuring cTn-I after surgery with the highest positive predictive value was 24 hours. In conclusion, these data support routine serial measurement of cTn-I after vascular surgery.

Key words: creatine kinase; myocardial infarction; troponin

Introduction

Perioperative myocardial ischemic injury is a major source of morbidity and mortality after vascular surgery.[1] Despite treatment with beta blockers and HMG CoA-reductase inhibitors (statins), the estimated cardiovascular events (CVEs) rate remains high.[2–5] The data supporting preoperative evaluation for high-risk patients undergoing vascular surgery continues to evolve.[1,6] A recent study indicates that preoperative revascularization does not significantly reduce postoperative CVEs.[7] This finding, coupled with frequent atypical presentations of postoperative myocardial ischemia,[8,9] necessitates increased postoperative vigilance to identify patients early in the postoperative course having a CVE.

Biomarkers such as creatine kinase (CK) and cardiac-specific troponins are proven diagnostic indicators of myocardial ischemia and predict long-term survival after vascular surgery.[10,11] Previous reports indicate that among patients with unstable angina and non-ST-segment elevation myocardial infarction (MI), even small increases in troponin are associated with worse outcome.[12] Cardiac troponin I (cTn-I) is a sensitive marker of myocardial ischemia and may be predictive of MI and death compared with creatine kinase MB fraction (CK-MB) and electrocardiogram (ECG) findings.[13] Furthermore, even low levels of troponin release may herald a delayed, greater than 24 hour, MI.[14] Although intriguing, none of the studies utilized an adjudication committee to blindly evaluate events.

A phase 2, randomized, double-blind multicenter study was conducted to determine whether zoniporide, a Na^+/H^+ exchange ion inhibitor, reduced the occurrence of perioperative mortality and cardiac events in high-risk individuals undergoing non-cardiac vascular surgery.[15] The study results are published elsewhere and indicate no significant difference in cardiovascular outcome for the drug treatment group compared to placebo. The sponsors discontinued the study enrollment early based

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on a futility analysis of the chance of demonstrating efficacy with a larger sample size.

An event committee was formed prior to study initiation with the aim of blindly adjudicating CVEs. Patients in this trial underwent a prospectively defined evaluation for biomarkers including cTn-I and CK-MB at numerous time points, including just before surgery, and at the time of a suspected MI which allowed for the evaluation of these markers as predictors of cardiovascular morbidity and mortality after vascular surgery.

The purpose of this study was to determine whether routine serial measurement of biomarkers should be done on the day of and after vascular surgery. A unique aspect of this study compared with other studies of CVEs after surgery is the multidisciplinary endpoint committee that blindly adjudicated all CVEs and the prospectively designed collection of biomarkers. This large prospective evaluation of biomarkers provides important data necessary to determine how to monitor high-risk patients after vascular surgery.

Methods

A prospective multicenter study of patients undergoing vascular surgery at high risk for vascular events was conducted in 105 sites throughout the USA, South America, Europe and Asia.[15] The study population included individuals with peripheral arterial atherosclerosis and was carried out in accordance with the ethical standards of Helsinki. All participants signed a consent form describing the study and study risks. Individuals had a history of three or more of the following; age ≥ 65 years, hypertension, documented stroke or transient ischemic attack (TIA), prior MI, medically managed coronary artery disease with active angina pectoris ($\geq$ Canadian class II), diabetes mellitus, congestive heart failure ($\geq$ NYHA class II), symptomatic cardiac arrhythmia or history of one of these risk factors and either radionuclide / echocardiographic / ECG evidence of reversible ischemia in response to exercise or pharmacologic stress or evidence of clinically significant coronary artery disease during coronary angiography. Patients with unstable angina were excluded. The diagnostic study must have been performed within the previous year, and complete revascularization must not have occurred prior to surgery. All patients underwent urgent or elective major vascular surgery involving (1) revascularization utilizing aortic or proximal lower extremity vascular cross clamp (including but not limited to abdominal aortic aneurysm repair, proximal vascular bypass procedures, and axillary-femoral bypass) or (2) infrainguinal lower extremity arterial reconstruction. Individuals were excluded if they had concurrent cardiogenic shock or pulmonary edema or current or recent history of liver disease or concurrent evidence of liver dysfunction on screening laboratory testing, renal disease requiring hemodialysis or peritoneal dialysis. Individuals were also excluded if unrevascularized left main or severe triple vessel coronary artery disease requiring imminent surgical intervention / revascularization was present.

Study design

The details of the study design are published elsewhere.[15] In brief, the study consisted of three phases: (1) screening visit; (2) an inpatient phase (treatment and post-treatment); and (3) a follow-up phase (outpatient visit 30 days after termination of study drug). Individuals were randomized to one of three dose groups of zoniporide (3 mg/kg per day, 6 mg/kg per day, or 12 mg/kg per day) or placebo given as an intravenous infusion. The intra- and postoperative management was at the discretion of the attending surgeon and anesthesiologist. The duration of treatment varied from 2 to 7 days dependent upon the participant's postoperative course.

Pre- and postoperative evaluation

cTn-I and CK-MB were obtained on the day of surgery, as well as 24, 72 and 120 hours after surgery, 24 hours prior to planned hospital discharge and at the onset of symptoms of a suspected CVE. The biomarkers used for analysis in this study were only those scheduled measurements and not those associated with symptoms since the purpose was to assess the predictive value of scheduled biomarker measurement. The investigators were blinded to biomarker results as they were evaluated in a core laboratory. A CVE was defined for analysis as cardiac death or MI. ECGs were obtained preoperatively and on a daily basis for at least 3 days after surgery as well as at the time of any CVE. The CVE was adjudicated by a multidisciplinary endpoint committee composed of cardiologists, vascular surgeons, anesthesiologists and internists who were blinded to the allocation to study drug or placebo. The determination of a MI was made using hospital records as well as biomarker and ECG results. A CVE was defined as cardiac death or MI occurring up to 30 days after surgery according to previously published criteria.[16] A new MI was defined by biomarker evidence of myocardial necrosis as well as electrocardiographic changes or symptoms of acute MI or acute coronary artery revascularization. The electrocardiographic abnormalities must have involved two or more anatomically contiguous leads comprised of new ST segment shifts with an upward-convex or downward-concave > 0.2 mV in the precordial leads or > 0.1 mV in the limb leads, measured 0.08 seconds after the j point associated with progression to either (a) symmetrical T wave inversion in at least two anatomically contiguous leads of > 0.3 mV in depth from the isoelectric line in the precordial leads or > 0.2 mV in depth in the limb leads or (b) new pathologic Q waves of > 0.04 seconds in duration. The

creatine kinase total and CK-MB isoenzyme criteria in this population are confounded by the possible coexistence of CK-MB release from skeletal muscle injury associated with the index surgical procedure. In view of this, a cardiac index was used (CK-MB CK-MB total). The baseline index was defined as the most recent CK-MB index prior to the event undergoing evaluation. In cases where the baseline index is normal ($< 5\%$), the CK-MB index must be $> 5\%$ to be considered abnormal. In cases where the baseline index is elevated, the difference between the baseline CK-MB (absolute value) and subsequent peak CK-MB (absolute value) associated with the event must be more than twice the absolute value of the upper limit of normal for CK-MB. The absolute value of the peak cTn-I level associated with the event must be > 4.0 ng/ml.

It was anticipated that some patients will undergo an 'asymptomatic' biomarker elevation and not meet criteria for a CVE. Cut-off criteria to establish the presence of an elevated cardiac biomarker of necrosis were defined as a maximal cTn-I > 3.1 ng/ml or a total CK-MB / CK-MB total index of $> 5\%$ with an absolute CK-MB more than twice the absolute value of the upper limit of normal for CK-MB. These elevations must have been present without any anginal symptoms, ischemic equivalents or ECG changes that satisfy the criteria for a MI as outlined above. Adjudication of these events will include a determination of whether or not any associated ischemia was documented on concurrent ECG tracings. A positive biomarker finding was defined as cTn-I > 3.1 ng/ml or CK-MB $> 2 \times$ ULN (upper limit of normal) with an index $> 5\%$ and all performed at a central laboratory. The ECGs were also evaluated in a central laboratory. A new MI was defined with biomarker criteria of myocardial necrosis (CK-MB index $> 5\%$ or cTn-I > 0.4 mg/ml) and one of the following: presence of left bundle-branch block, paced rhythm or non-specific ECG changes, or symptoms consistent with acute myocardial ischemia or acute coronary revascularization procedure. All participants returned for a follow-up visit 30 days after completion of study drug treatment.

Statistical analysis

Descriptive statistics were used to define sensitivity and specificity of the biomarker tests both overall and at specific time points relative to surgery. For these calculations the qualifying cardiovascular test must have occurred after the time of the biomarker measurement. Sensitivity was defined as the number of patients with a true positive biomarker test divided by the number of patients with a CVE (true positive rate). Specificity was defined as the as the number of patients who were a true negative for the test divided by the sum of the false positives and true negatives (true negative rate or 1 – false positive rate). Positive predictive values (PPVs) for the biomarker tests were defined as those patients who were true positives for the test divided by the sum of the true and false positive patients. Receiver operator curves (ROC) for cTn-I were constructed using Microsoft Excel. One ROC was constructed for all scheduled cTn-I measurements to assess the threshold for the multiple tests over time in predicting a subsequent CVE.[16] This included several biomarker measurements per patient and therefore the above definitions for sensitivity and specificity were based on the number of tests rather than participants. In addition, patient-based ROCs were constructed separately for each scheduled biomarker measurement time. The calculation of area under the curve was done according to the previously published method.[17] The estimated relative risk and odds ratio for developing a CVE after vascular surgery based on a positive cTn-I test is calculated directly from the rates of CVE after positive and negative tests at each scheduled time point.

Results

Demographics

The study population was 71% male, 84% white, and with age and weight as shown in Table 1. Drug treatments after screening but prior to the start of study treatment included antihypertensives in 71% of individuals, diuretics in 37%, beta-blockers in 57%,

Table 1 Demographics of study population.

	Zoniporide 3 mg/kg per day	Zoniporide 6 mg/kg per day	Zoniporide 12 mg/kg per day	Placebo
Total number of individuals ($n = 784$)	127	132	266	259
	M / F	M / F	M / F	M / F
Number of individuals	94 / 33	90 / 42	183 / 83	193 / 66
Age (years)				
mean	69.6 / 73.8	69.0 / 73.7	68.3 / 70.0	70.5 / 72.6
range	41–88	40–96	28–92	46–93
Weight (kg)				
mean	77.4 / 64.7	79.0 / 64.1	79.5 / 68.4	77.6 / 63.5
range	39–135	44–139	40–150	35–127

vasodilators in 31%, and drugs for hyperlipidemia in 47%. Concomitant drug treatment at any time during the study drug treatment or the follow-up period included antihypertensives in 82%, diuretics in 68%, beta-blockers in 71%, vasodilators in 52%, and drugs for hyperlipidemia in 49%. The index surgical procedures included abdominal aortic aneurysm (AAA) repair in 22% and aortofemoral and/or aortoiliac bypass in 14% of participants. Diabetes, hypertension, and ischemic heart disease were present at screening in 51%, 81% and 42% of participants, respectively. A past history of ischemic heart disease was reported in 57%.

CK-MB, cTn-I and CVEs

There were 83 patients of the 784 (10.6%) who had at least one qualifying adjudicated event of cardiac death or MI. Including the multiple events in patients, this consisted of 95 total events. There were 65 patients with an MI and one of these patients had two MIs, thus bringing the total number of MIs to 66. Twenty-nine patients suffered a cardiac death and of these, 11 had a MI. Interestingly, there were 14 participants who had Tn-I $>$ 3.1 ng/ml at baseline prior to surgery. These preoperative, asymptomatic, biomarker results were not immediately available to the investigator until after study completion as they were shipped to a core laboratory for analysis. Of these, five had adjudicated events of MI or cardiac death postoperatively. One patient who signed the consent form had an MI just prior to undergoing surgery and prior to receiving study drug. This patient was included in the study as part of an intent to treat approach.

The following are the results of patients with cardiac events who also had a positive biomarker result on the day of or prior to the day of the adjudicated event. Of the 83 patients with cardiac events, 42 had positive cTn-I, 29 had positive CK-MB, 23 had both cTn-I and CK-MB and 48 had either positive cTn-I or CK-MB. The level of CK-MB and cTn-I was compared for patients who had a CVE. Of the 699 patients who did not qualify as having an adjudicated cardiac event, 64 had a positive cTn-I and 20 had a positive CK-MB at one or more of the scheduled samplings. cTn-I was more sensitive than CK-MB (50.6% versus 34.9%) for predicting a cardiac event whereas the specificity was higher for CK-MB (97.1% versus 90.8%).

Threshold of cTn-I and diagnosis of a CVE

In order to evaluate the threshold for diagnosis of a cardiac event, an ROC curve was generated for all of the scheduled cTn-I results versus occurrence of a cardiac event (MI /cardiac death) on the day of or after the given cTn-I result (Figure 1). Note that individual patients are represented multiple times according to the number of cTn-I measurement time points. Based on this ROC analysis, the overall total test-based

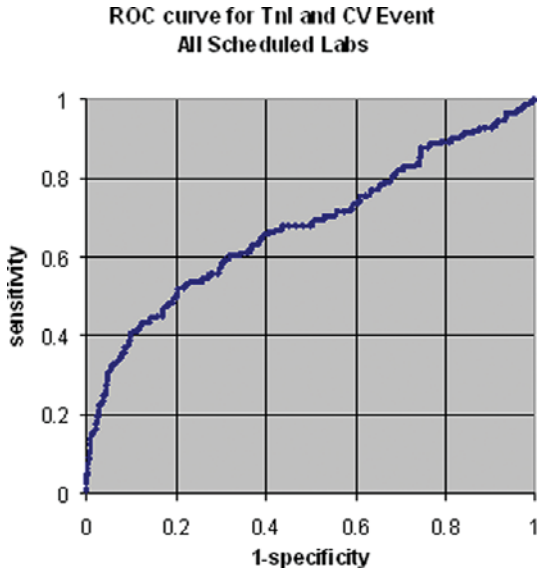

Figure 1 ROC curve for obtaining threshold diagnosis of a CVE from all scheduled cTn-I measurements. Sensitivity is plotted on the Y-axis and the false positive rate (1-specificity) on the X-axis.

sensitivity and specificity for the threshold of cTn-I $>$ 3.1 ng/ml is 30% and 95% respectively.

Temporal relationship for all cTn-I measurements and CVE

An ROC curve was constructed for cTn-I at baseline and 24, 48, 72 and 120 hours after vascular surgery (Figure 2). The 48-hour measurements were those

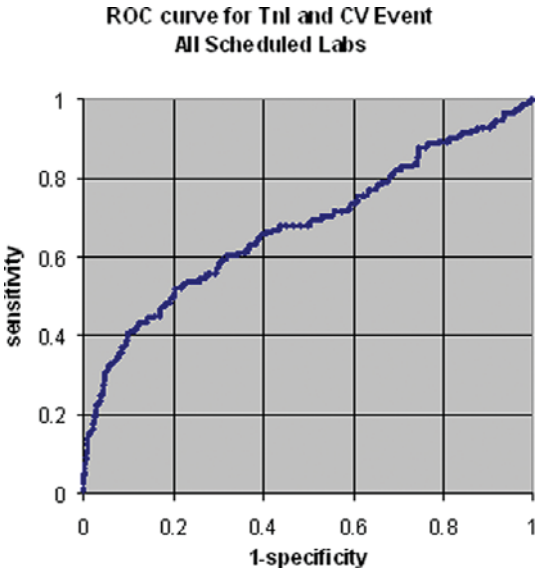

Figure 2 ROC curve for obtaining threshold diagnosis of CVE from cTn-I measured prior to surgery and at 24, 48, and 72 hours post surgery. (The curve for 120 hours was omitted due to the sparse data and few CVEs at or after that time point).

taken 24 hours prior to planned hospital discharge. The 24-hour time point had the largest positive predictive value (46.9%) and the 72-hour time point had the highest sensitivity (64%).

Odds ratio for developing a CVE after vascular surgery

The odds ratio and relative risk for developing a CVE after vascular surgery were calculated given positive (> 3.1 ng/ml) or negative cTn-I measurements as shown in Table 2 and for CK-MB as shown in Table 3. The highest relative risk occurred at 72 hours after surgery.

Discussion

Our study is the largest prospective evaluation of biomarkers in high-risk patients undergoing vascular surgery. The results indicate that cTn-I is a more sensitive biomarker for CVEs after vascular surgery than CK-MB. The optimum time, of those studied, for measuring cTn-I after surgery that provided the highest positive predictive value was 24 hours. The time point with the highest sensitivity for cTn-I was at 72 hours. There were 48 participants of the 83 with an adjudicated event that had earlier detection of this event with asymptomatic elevation in cardiac biomarkers. Surprisingly, there were patients with an elevated cTn-I just before surgery, indicating a possible high-risk group that deserves more study. The adjudication committee identified that 64/106 patients with a positive cTn-I did not have a major event, suggesting that utilization of cTn-I alone as diagnostic for a perioperative cardiac event would overestimate its occurrence. However, based upon work by others, this group likely remains at high risk for long-term cardiac events.

There are multiple factors that increase the risk of perioperative MI and those patients undergoing vascular surgery are at significant risk. Because a postoperative MI increases both short- and long-term mortality, accurate diagnosis is essential. The diagnosis of postoperative MI can include assessment of clinical symptoms, serial electrocardiography, evaluation of cardiac specific biomarkers and imaging studies before and after surgery. Current guidelines from the American College of Cardiology (ACC) recommend that patients with known or suspected coronary artery disease and undergoing high- or intermediate-risk surgical procedures should have an ECG at baseline, immediately after the surgical procedure, and daily on the first 2 days after surgery.[1] However, the majority of perioperative MI events will be non-ST segment MI and ECG monitoring may not accurately identify patients with MI if they are asymptomatic.[1] The characteristic rise and fall of cardiac biomarkers after MI differs between CK-MB and troponins. The shorter circulation levels and release from non-cardiac

Table 2 Rates of developing a cardiovascular event after vascular surgery (Tn-I).

	CVE after cTn-I +	CVE after cTn-I −	Sensitivity	Specificity	Relative risk (95% CIs)	Odds ratio (95% CIs)	LR-pos (95% CIs)	LR-neg (95% CIs)
Regardless of time	42/106 = 0.396	41/676 = 0.061	0.51 (0.40–0.61)	0.91 (0.89–0.93)	6.53 (4.47–9.54)	10.16 (6.16–16.78)	5.53 (4.03–7.58)	0.54 (0.44–0.68)
Baseline	5/14 = 0.357	72/737 = 0.097	0.06 (0.01–0.12)	0.99 (0.98–1)	3.66 (1.75–7.63)	5.13 (1.67–15.73)	4.86 (1.67–14.14)	0.95 (0.89–1.00)
24 hours	23/49 = 0.469	45/679 = 0.066	0.34 (0.23–0.45)	0.96 (0.95–0.98)	7.08 (4.70–10.67)	12.46 (6.59–23.57)	8.59 (5.19–14.19)	0.69 (0.58–0.82)
48 hours	9/26 = 0.346	5/198 = 0.025	0.64 (0.39–0.89)	0.92 (0.88–0.95)	13.71 (4.97–37.78)	20.43 (6.15–67.88)	7.94 (4.36–14.47)	0.39 (0.19–0.79)
72 hours	16/48 = 0.338	9/402 = 0.022	0.64 (0.45–0.83)	0.92 (0.9–0.95)	14.89 (6.96–31.83)	21.83 (8.94–53.31)	8.50 (5.45–13.26)	0.39 (0.23–0.66)
120 hours	2/14 = 0.143	3/148 = 0.020	0.4 (0–0.83)	0.97 (0.96–0.98)	7.05 (1.28–38.70)	8.06 (1.22–52.98)	5.23 (1.57–17.43)	0.65 (0.32–1.33)

CVE, cardiovascular events; cTn-I, troponin I; CI, confidence interval.

Table 3 Rates of developing a cardiovascular event after vascular surgery (CK).

	CVE after CK +	CVE after CK −	Sensitivity	Specificity	Relative risk (95% CIs)	Odds ratio (95% CIs)	LR-pos (95% CIs)	LR-neg (95% CIs)
Regardless of time-CK	29/49 = 0.592	54/733 = 0.074	0.35 (0.25–0.45)	0.97 (0.96–0.98)	8.03 (5.68–11.35)	18.23 (9.68–34.35)	12.21 (7.24–20.59)	0.67 (0.57–0.78)

CVE, cardiovascular events; CK, creatine kinase; CI, confidence interval; LR, likelihood ratio.

sources of ischemic limbs limits the clinical utility of CK-MB. One study of 232 mostly diabetic and hypertensive patients undergoing non-cardiac surgery found that serial CK-MB had a higher false-positive rate and without improved sensitivity than serial ECGs 2 days postoperatively.[18]

As reported by Breslow and colleagues, the use of cTn-I or cTn-T may be more clinically useful than CK-MB.[19] Cardiac troponin I was assessed every 6 hours for 36 hours postoperatively in a series of 96 individuals undergoing vascular surgery and in 12 undergoing spinal surgery. The diagnosis of postoperative MI was confirmed with the appearance of a new echocardiographic segmental wall-motion abnormality on postoperative day 3. All eight patients who underwent vascular surgery and had new postoperative segmental wall-motion abnormalities had elevated cardiac cTn-I levels whereas six had elevated CK-MB. Of 100 patients without new segmental wall-motion abnormalities, 19 had CK-MB elevations and one had cardiac cTn-I elevation.[19] In another study of 323 patients undergoing non-cardiac surgery (13.6% vascular surgery), the incident rate of perioperative MI increased significantly when the cardiac troponin T (cTn-T) was included in the diagnostic algorithm.[20] In a larger study of 772 patients who underwent major non-cardiac surgery without major cardiovascular complications during hospitalization, cTn-T was increased in 12% and CK-MB in 27%. During the 6-month follow-up, the relative risk of cardiac events was 5.4 when cardiac cTn-T was elevated, whereas CK-MB did not predict late post-discharge cardiac events.[12] Our results showing patients with elevated cTn-I and without a MI or cardiac death are consistent with this study and likely indicate a population that is at higher risk for an outpatient cardiac event. The results from a prospective study of 467 high-risk patients undergoing vascular surgery indicates that serial monitoring of cTn-I on postoperative days 1, 2, and 3 provides the strategy with the highest diagnostic yield for surveillance of MI and is also in general agreement with our study results.[16]

Are there significant numbers of patients with asymptomatic biomarker elevation on the day of surgery and postoperatively? To assess the diagnostic performance of cTn-T as a marker for myocardial injury in patients undergoing major non-cardiac surgery, Lee and colleagues prospectively collected preoperative and postoperative clinical data, including measurements for creatine kinase (CK), CK-MB, and troponin T for 1175 patients undergoing major non-cardiac surgery.[21] Acute MI was diagnosed in 1.4% by a reviewer who was blinded to troponin T data and who used CK-MB and electrocardiographic criteria to define acute MI. Troponin T elevations occurred in 87% of patients with and in 16% of patients without MI. Among patients without MI, troponin T was elevated in 62% of patients with and in 15% of patients

without major cardiac complications. Our study results showing a significant percentage of patients with elevated biomarkers before the diagnosis of MI or death occurred are complementary to the above study by Lee and colleagues supporting biomarker monitoring after vascular surgery.

The study results we report are unique as this is the first study to blindly adjudicate endpoints and compare to biomarkers at pre-specified time points and provide robust data supporting daily serial monitoring of troponin along with ECG for at least 3 days after vascular surgery. The study is limited as variables such as beta blocker, treatment with cholesterol lowering medications and comorbid states could potentially affect the predictive ability of the biomarkers studied.

The 2002 guidelines for perioperative cardiovascular evaluation for non-cardiac surgery[1] note "further evaluation regarding the optimal strategy for surveillance and diagnosis of perioperative MI is required." The results from our study and others support that routine screening of high-risk patients after vascular surgery with cTn-I at multiple time points in conjunction with the ECG identify a population at risk for cardiac events. However, prospective studies are needed to determine whether the asymptomatic biomarker group carries a clinically significant higher risk after discharge from the hospital.

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