Cardiac Troponin I Predicts Short-Term Mortality in Vascular Surgery Patients

Lauren J. Kim, Elizabeth A. Martinez, Nauder Faraday, Todd Dorman, Lee A. Fleisher, Bruce A. Perler, G. Melville Williams, Daniel Chan and Peter J. Pronovost

Circulation 2002;106;2366-2371; originally published online Oct 14, 2002;
DOI: 10.1161/01.CIR.0000036016.52396.BB
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Cardiac Troponin I Predicts Short-Term Mortality in Vascular Surgery Patients

Lauren J. Kim, MPH; Elizabeth A. Martinez, MD; Nauder Faraday, MD; Todd Dorman, MD; Lee A. Fleisher, MD; Bruce A. Perler, MD; G. Melville Williams, MD; Daniel Chan, PhD; Peter J. Pronovost, MD, PhD

Background—Cardiac troponin I (cTnI) is a highly sensitive and specific marker for myocardial injury that predicts outcomes in patients with acute coronary syndromes. Cardiovascular complications are the leading cause of morbidity and mortality in patients who have undergone vascular surgery. However, postoperative surveillance with cardiac enzymes is not routinely performed in these patients. We evaluated the association between postoperative cTnI levels and 6-month mortality and perioperative myocardial infarction (MI) after vascular surgery.

Methods and Results—Two hundred twenty-nine patients having aortic or infrainguinal vascular surgery or lower extremity amputation were included in this study. Blood samples were analyzed for cTnI immediately after surgery and the mornings of postoperative days 1, 2, and 3. An elevated cTnI was defined as serum concentrations >1.5 ng/mL in any of the 4 samples. Twenty-eight patients (12%) had postoperative cTnI >1.5ng/mL, which was associated with a 6-fold increased risk of 6-month mortality (adjusted OR, 5.9; 95% CI, 1.6 to 22.4) and a 27-fold increased risk of MI (OR, 27.1; 95% CI, 5.2 to 142.7). Furthermore, we observed a dose-response relation between cTnI concentration and mortality. Patients with cTnI >3.0 ng/mL had a significantly greater risk of death compared with patients with levels ≤0.35 ng/mL (OR, 4.9; 95% CI, 1.3 to 19.0).

Conclusions—Routine postoperative surveillance for cTnI is useful for identifying patients who have undergone vascular surgery who have an increased risk for short-term mortality and perioperative MI. Further research is needed to determine whether intervention in these patients can improve outcome. **(*Circulation*. 2002;106:2366-2371.)**

Key Words: cardiovascular diseases ■ complications ■ surgery

Cardiovascular disease is the leading cause of morbidity and mortality in surgical patients and are particularly common after vascular surgery.[1,2] Fifty percent to 60% of patients undergoing vascular procedures have severe coronary artery disease (CAD)[3] and <10% have normal coronary arteries.[2–4] Current risk assessment tools[5–7] can help identify patients at high risk, and perioperative blockade of β-adrenergic receptors can improve outcome.[8,9] However, morbidity and mortality are not eliminated.

Although myocardial ischemia commonly complicates vascular surgery, early detection of clinically meaningful ischemia remains a challenge in the perioperative setting. Anginal chest pain (or its equivalents), the cardinal clinical symptom of acute coronary syndromes, rarely accompanies postoperative myocardial ischemia.[10] Electrocardiographic ST-segment changes occur in one third of patients who have undergone vascular surgery and are associated with a 9- to 16-fold increase in risk of myocardial infarction (MI) and cardiac death.[11] Although the current guidelines for perioperative surveillance of myocardial ischemia and infarction include ECG monitoring, they do not include routine screening with cardiac enzymes, except in the presence of symptomatic or ECG evidence of myocardial dysfunction.[2]

Cardiac troponin I (cTnI) is a contractile protein that is released into the circulation after myocardial cell injury. Unlike creatine kinase and its MB isoenzyme (CK-MB), cTnI is not found in skeletal muscle and is therefore a highly sensitive and specific for myocardial necrosis.[12–16] During surgery, cTnI is reported to be more specific for diagnosis of MI than CK-MB.[17] In patients with acute coronary syndromes, elevated cTnI levels at the onset of symptoms are associated with an increased risk of cardiac morbidity and mortality,[18–21] and cTnI has been shown to be a useful tool for risk stratification in emergency room and inpatient settings.[20–23] However, its utility for routine surveillance and risk assessment after vascular surgery is unknown. The

Received June 26, 2002; revision received August 14, 2002; accepted August 16, 2002.

From the Johns Hopkins University School of Medicine, Departments of Anesthesiology and Critical Care Medicine (L.J.K., E.A.M., N.F., T.D., L.A.F., P.J.P.), Medicine (T.D., L.A.F.), Surgery (E.A.M., N.F., T.D., B.A.P., G.M.W., P.J.P.), and Pathology (D.C.); the Johns Hopkins University Bloomberg School of Public Health, Department of Health Policy and Management (L.A.F., P.J.P.); and the Johns Hopkins Hospital, Department of Nursing (T.D.), Baltimore, Md.

Correspondence to Peter J. Pronovost, MD, PhD, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins University School of Medicine, 600 N Wolfe St, Meyer 297A, Baltimore, MD 21287–7294. E-mail ppronovo@jhmi.edu

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000036016.52396.BB**

specific aim of this study was to evaluate the association between postoperative cTnI levels and 6-month mortality and perioperative MI in patients who have undergone vascular surgery.

Methods

Study Population

After approval from the institutional review board, informed consent was obtained from 229 patients undergoing aortic or infrainguinal vascular surgery or lower extremity amputation between June 1997 and September 1999 at the Johns Hopkins Hospital (Baltimore, Md). These patients were part of a clinical trial designed to evaluate the efficacy of early detection (using continuous 12-lead ECG monitoring) and treatment of myocardial ischemia for reducing cardiac complications. All patients were monitored for ischemia by computerized ST-segment analysis for the first 48 hours after surgery and had ECGs at baseline and for the first 2 postoperative days according to American College of Cardiology/American Heart Association guidelines.[2] Standard perioperative treatment included the routine use of β-blockers. Exclusion criteria for the trial included age <40 years, a left bundle-branch block on a preoperative ECG, a permanent pacemaker, and emergency procedures.

Outcome Variables

The main dependent variable was 6-month mortality. To evaluate this end point, patients were followed through surgery and contacted for a phone interview at 6 months. In patients who died during the index or subsequent hospitalization, cause of death was classified by 2 independent investigators as cardiovascular disease versus "other," based on a review of clinical data, including death certificates and autopsy reports. For patients whose telephone number was not accurate, we ran a search in the social security death index. The secondary dependent variable was perioperative MI. MI diagnosis was made by the primary care team according to standard World Health Organization criteria[24] or by autopsy findings during the course of routine clinical care.

Exposure Variable: Cardiac Troponin I

Blood specimens were analyzed for cTnI immediately after surgery and the morning of postoperative days 1, 2, and 3. These time points were chosen because patients are at greatest risk for cardiac complications during the first 72 hours after vascular surgery.[25] The single highest cTnI concentration was used as the exposure variable, and patients were considered to have an elevated cTnI if the peak serum level was >1.5 ng/mL, the manufacturer-recommended cutoff for MI diagnosis.[14,26] The detection limit of the immunoassay was 0.35 ng/mL. cTnI assays were performed in the hospital core laboratory with the use of the Stratus fluorometric enzyme immunoassay (Dade Pharmaceuticals), which uses two monoclonal antibodies that are specific for the cardiac isotype of troponin I. The primary clinical team was blinded to the cTnI results obtained as part of the study protocol.

In a supplementary analysis, we investigated a dose-response relation between cTnI and 6-month mortality by stratifying peak cTnI concentrations into 4 groups: ≤0.35 ng/mL (virtually no cTnI detected in serum), 0.4 to 1.5 ng/mL (moderate elevations), 1.6 to 3.0 ng/mL (significant elevations consistent with the definition of an MI), and >3.0 ng/mL (elevations more than twice that required for MI diagnosis). The ≤0.35 ng/mL group was the reference category to which the other groups were compared.

Statistical Analysis

In the univariate analysis of baseline characteristics, dichotomous variables were compared by means of a χ^2 test or Fischer's exact test where appropriate, and continuous variables were compared by means of a Student's *t* test. For the primary dependent variable, multivariate analysis was performed with logistic regression, with cTnI modeled as a dichotomous variable. Estimated odds ratios and corresponding 95% confidence intervals and probability values are reported.

We examined survival time after surgery by constructing actuarial curves using the Kaplan-Meier method. Survival at 6 months between groups with peak cTnI levels greater than and less than or equal to 1.5 ng/mL was compared by means of the log rank test. To investigate an association between postoperative cTnI levels and perioperative MI diagnosis, we created a 2×2 contingency table of the exposure and outcome variables and calculated an estimate of the odds ratio and 95% CI by using the Woolf procedure.[27] Probability values <0.05 were considered statistically significant, and all analyses were performed with STATA 6.0.

TABLE 1. Patient Characteristics

	CTnI >1.5 ng/mL (n=28)	CTnI <1.5 ng/mL (n=201)	*P*
Age, y*	70±10	69±10	0.52
Female sex, %	57	43	0.17
White race, %	68	76	0.35
Preoperative cardiac medications (%)			
β-Blocker	32	38	0.56
Calcium channel blocker	54	44	0.36
Aspirin	44	43	0.89
Cardiac risk factors, %			
Hypertension	86	80	0.45
Diabetes†	50	26	0.01
History of tobacco use	89	83	0.40
Prior cardiac history, %			
Myocardial infarction	39	35	0.64
Coronary artery bypass surgery	25	23	0.85
Congestive heart failure	18	16	0.79
Surgical procedure, %			
Thoracoabdominal aneurysm repair†	32	16	0.05
Abdominal aortic aneurysm repair	21	26	0.58
Infrainguinal bypass	46	55	0.41
Lower extremity amputation	0	2	...
Perioperative β-blockade, %§	75	76	0.90

*Age is expressed as mean±SD.
†$P<0.05$.
§Morning of surgery, during surgery, and/or first 48 hours after surgery.

Results

Baseline Characteristics

Twelve percent of patients (28 of 229) had peak cTnI levels >1.5 ng/mL after surgery. Of these patients, the majority of peak cTnI values occurred on postoperative days 1 (46%) and 3 (36%). The frequency was 11% and 7% on postoperative days 2 and 0, respectively. Of 9 patients who were dialysis-dependent before surgery, 2 had elevated cTnI levels. Comparison of baseline characteristics between patients with cTnI levels above and below the diagnostic cutoff is presented in Table 1. Diabetes was the only preoperative predictor of an elevated cTnI. Fifty percent of patients in the cTnI >1.5 ng/mL group had diabetes compared with 26% in the cTnI ≤1.5 ng/mL group (OR, 2.8; 95% CI, 1.2 to 6.2). Thoracoabdominal aortic aneurysm repair, compared with all other

TABLE 2. Predictors and Estimated Risk of Six-Month Mortality

	Death+	Death−	Unadjusted			Adjusted*	
	(n=18)	(n=208)	OR	(95% CI)	P	OR (95% CI)	P
Age <75 y, %†	50	67	1.2	(1.0–1.5)	0.03	1.2 (1.0–1.4)	0.04
Female sex, %	67	44	2.6	(0.9–7.1)	0.07	...	...
White race, %	67	77	0.6	(0.2–1.7)	0.33	...	...
Preoperative cardiac medications, %							
β-Blocker	28	38	0.6	(0.2–1.8)	0.39	...	...
Calcium channel blocker	67	44	2.5	(0.9–7.0)	0.08	...	...
Aspirin	50	43	1.3	(0.5–3.5)	0.55	...	...
Cardiac risk factors, %							
Hypertension	94	79	4.4	(0.6–34.2)	0.15	...	...
Diabetes	33	29	1.2	(0.4–3.4)	0.72	...	...
History of tobacco use	67	85	0.4	(0.1–1.0)	0.05	...	...
Prior cardiac history, %							
Myocardial infarction	28	36	0.7	(0.2–2.0)	0.51	...	...
Coronary artery bypass surgery	28	23	1.3	(0.4–3.8)	0.65	...	...
Congestive heart failure‡	50	13	6.7	(2.4–18.4)	<0.01	12.0 (3.3–44.2)	<0.01
Surgical procedure, %							
TAA repair‡	33	17	2.5	(0.9–7.0)	0.09	5.8 (1.5–23.3)	0.01
AAA repair	22	26	0.8	(0.3–2.5)	0.70	...	...
Infrainguinal bypass	39	55	0.5	(0.2–1.4)	0.20	...	...
Lower extremity amputation	6	2	3.0	(0.3–28.4)	0.34	...	...
Perioperative β-blockade, %‡§	50	78	0.3	(0.1–0.7)	0.01	0.3 (0.1–0.9)	0.03
CTnI >1.5 ng/mL, %‡	21	6	4.2	(1.4–12.4)	<0.01	5.9 (1.6–22.4)	<0.01

TAA indicates thoracoabdominal aortic aneurysm; AAA, abdominal aortic aneurysm.

*Adjusted OR presented only for variables included in multiple logistic regression model.

†Age was entered into the adjusted model as a continuous variable and a linear spline term with a break at 75 years.

‡$P<0.05$.

§Morning of surgery, during surgery, and/or first 48 hours after surgery.

surgical procedures, was also associated with elevated cTnI (OR, 2.4; 95% CI, 1.0 to 5.8).

Mortality at Six Months

Six months after surgery, there were 3 patients (1%) who were lost to follow-up and 18 deaths (8%) in the remaining cohort. Nine deaths occurred during the index hospitalization and 9 occurred after discharge. All 11 deaths for which we have cause-specific mortality data were classified as cardiovascular death. Mortality at 6 months was significantly higher among patients with cTnI >1.5 ng/mL compared with those with levels ≤1.5 ng/mL (21% [6 of 28] versus 6% [12 of 201]), for a 15% absolute increase in mortality rate.

Elevated cTnI on routine surveillance was associated with death in both univariate and multivariate analyses (Table 2). Compared with those with cTnI levels below the diagnostic threshold, patients with cTnI >1.5 ng/mL had a 4-fold increase in mortality risk (OR, 4.2; 95% CI, 1.4 to 12.4). After controlling for other covariates in the adjusted model, the risk increase was 6-fold (OR, 5.9; 95% CI, 1.6 to 22.4). Other multivariate predictors of mortality included history of congestive heart failure (OR, 12.0; 95% CI, 3.3 to 44.2), thoracoabdominal aortic aneurysm repair (OR, 5.8; 95% CI, 1.5 to 23.3), and age <75 years (OR, 1.2 per year; 95% CI, 1.0 to 1.4). Although patients who died were older than those who were alive at 6 months (76±7 years versus 69±10 years; $P<0.001$), the mortality risk was significantly greater in younger patients as the result of a nonlinear relation between age and death, with a break at 75 years. Similar to previous studies,[8,9] perioperative β-blockade was associated with a significant reduction in short-term mortality (OR, 0.3; 95% CI, 0.1 to 0.9).

There was a dose-response relation between cTnI concentration and 6-month mortality (Figure 1). Peak cTnI levels were ≤0.35 ng/mL in 57% (n=128), between 0.4 and 1.5 ng/mL in 31% (n=70), between 1.6 and 3.0 ng/mL in 4% (n=10), and >3.0 ng/mL in 8% (n=18) of patients. Six-month mortality rates in these groups were 5%, 7%, 20%, and 22%, respectively. CTnI >3.0 ng/mL was associated with a significantly increased risk for 6-month mortality compared with the lowest level group (OR, 4.9; 95% CI, 1.3 to 19.0).

A Kaplan-Meier survival curve for patients with peak cTnI levels above and below the diagnostic threshold is shown in Figure 2. Survival rates were similar in these 2 groups until ≈5 weeks after surgery, after which patients with cTnI >1.5 ng/mL had a steeper decline in survival compared with patients with cTnI ≤1.5 ng/mL. At 6 months, patients with elevated cTnI had an unadjusted hazard ratio of 3.9 (95% CI,

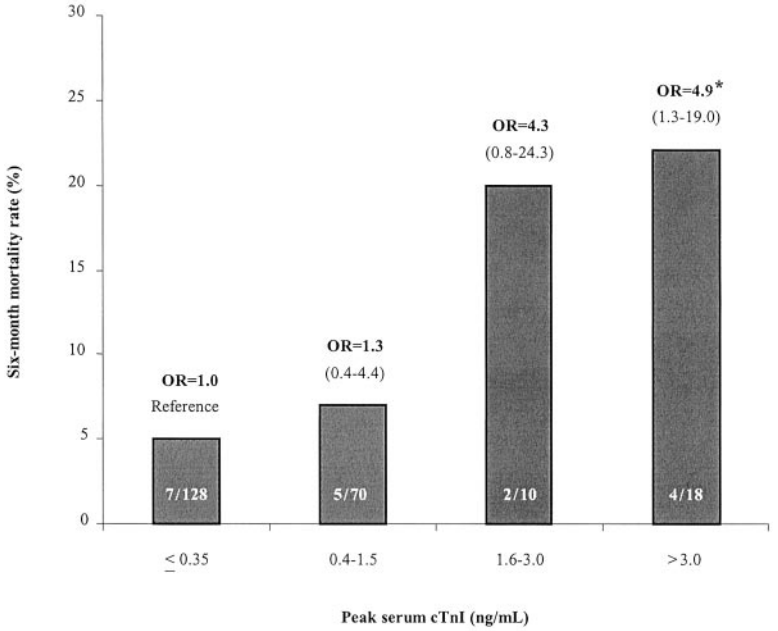

Figure 1. Dose-response relation between peak serum cTnI and 6-month mortality. Peak cTnI concentrations are categorized into 4 groups and presented with 6-month mortality rates. Numbers inside bars indicate number of deaths divided by total number of patients in each group. Odds ratios and 95% confidence intervals for mortality are shown above bars. The ≤0.35 ng/mL group is the reference category to which other groups with increasing cTnI levels are compared. *$P<0.05$.

2.0 to 37.4) for death compared with those with levels below the cutoff.

Perioperative Myocardial Infarction

Eight patients (3%) were diagnosed with a perioperative MI: 6 had elevated cardiac enzymes and diagnostic ECGs, 1 had chest pain in addition to elevated cardiac enzymes and diagnostic ECGs, and 1 MI was discovered at autopsy. Surveillance cTnI was elevated in 6 of these patients before or concurrent with clinical diagnosis, and all received medical intervention. At 6 months, 5 of these patients reported no invasive coronary interventions and 1 had an incomplete follow-up. Of the 2 patients who had surveillance cTnI ≤1.5 ng/mL, 1 ruled in with a positive troponin I on postoperative day 2 by means of a more sensitive second-generation assay that was in clinical use. The other patient was not diagnosed on clinical grounds but had a respiratory arrest on postoperative day 3 and was diagnosed with MI on postmortem examination.

Elevated surveillance cTnI levels were associated with perioperative MI in vascular surgery patients (OR, 27.1; 95% CI, 5.2 to 142.7) (Table 3). Of the 28 patients with cTnI >1.5 ng/mL, 6 were diagnosed with a clinical MI and 1 of these patients was dead at 6 months. Of the remaining 22 patients with elevated cTnI and not diagnosed with an MI, there were 5 deaths, the majority (4 of 5) of which occurred after hospital discharge.

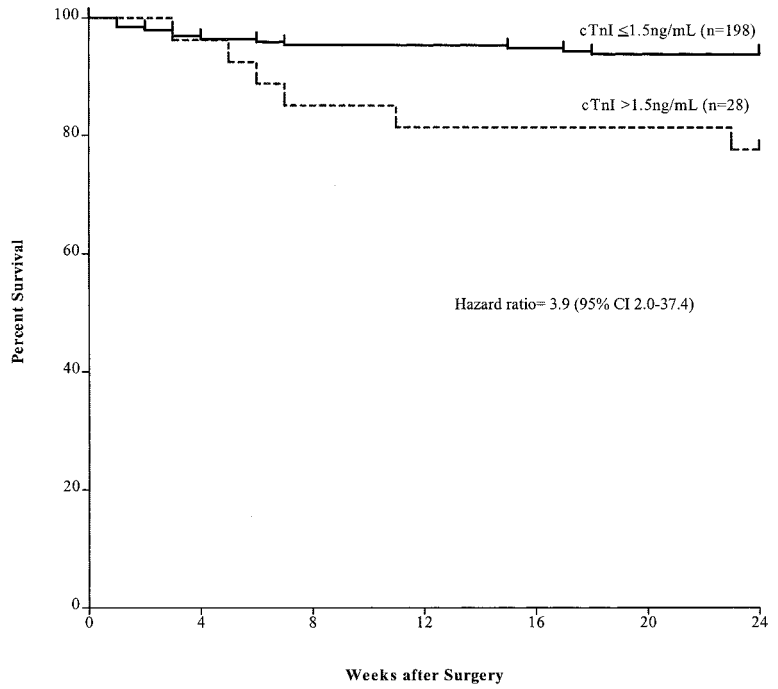

Figure 2. Kaplan-Meier survival curve of patients by postoperative cTnI levels. Six-month survival of patients with surveillance cTnI levels above and below 1.5 ng/mL was compared by means of log rank test. Hazard ratio of death between these 2 groups is presented with 95% confidence interval.

TABLE 3. Predictive Value of cTnI for Perioperative MI

cTnI	MI+ (n=8)	MI− (n=221)	Unadjusted OR (95% CI)
>1.5 ng/mL	6 (75%)	22 (10%)	27.1† (5.2–142.7)
≤1.5 ng/mL	2 (25%)	199 (90%)	...

MIs were diagnosed by the primary clinical team using standard WHO criteria or at autopsy.

†*P* value<0.01.

Discussion

Elevated cTnI levels after major vascular surgery are associated with an increased risk of short-term mortality and morbidity. Patients with postoperative cTnI >1.5 ng/mL are 6 times more likely to die within 6 months of surgery compared with patients with levels ≤1.5 ng/mL, after adjusting for age, congestive heart failure, surgical procedure, and perioperative β-blockade. Moreover, we observed a dose-response relation between cTnI concentration and death. The strong association between cTnI and short-term mortality suggests that clinically meaningful postoperative ischemia may have been missed in a significant number of vascular surgery patients. More importantly, the survival analysis demonstrates that the difference in mortality associated with an elevated cTnI does not emerge until 5 weeks after surgery. Thus, routine postoperative surveillance for cTnI may alert clinicians to patients at high risk for cardiovascular complications and death before the occurrence of a morbid event. Further research is required to determine if additional evaluation and treatment of these patients at high risk can reduce morbidity.

Twelve percent of patients had cTnI elevations during routine postoperative surveillance that were associated with an increased risk of perioperative MI. This proportion is lower than the one third of patients reported to have ECG evidence of myocardial ischemia after vascular surgery[10,11] but higher than the 5% incidence of perioperative MI previously reported.[28,29] Only 3% of patients in this study were identified as having a clinical MI defined by current guidelines for perioperative ischemia surveillance and WHO definitions of MI.[24]

Perioperative cardiac injury is associated with mortality rates of 36% to 70%.[30,31] However, its detection in surgical patients remains a challenge for several reasons: In the postoperative setting, MI and clinically important ischemia are often silent as a result of altered pain perception caused by residual anesthetics, analgesics, or competing incisional pain.[1] Additionally, skeletal muscle injury sustained during surgery increases CK-MB levels, making it difficult to distinguish myocardial from skeletal muscle injury with the use of this conventional cardiac marker. cTnI, on the other hand, is useful for confirming or excluding the diagnosis of myocardial injury. Its potential utility in the perioperative risk assessment of patients who have undergone vascular surgery is particularly good because of the high prevalence of CAD and incidence of cardiac complications. Routine cTnI surveillance may improve current strategies that are used to detect perioperative myocardial ischemia and infarction.

Consistent with previous studies, we found a relation between perioperative administration of β-blockers and reduced short-term mortality. However, there was no association between β-blocker use and elevated postoperative cTnI. Furthermore, the relation between cTnI and death persisted even after adjusting for the benefits of perioperative β-blockade. Thus, surveillance cTnI appears to be an independent predictor of morbidity and mortality even in the presence of β-blockade.

Our results in surgical patients parallel previous reports of medical patients.[12,15–18] In patients with unstable angina, elevated cTnI levels on admission are associated with a 3- to 5-fold increase in short-term morbidity and mortality.[18–21] A quantitative relation between cTnI concentration and incidence of cardiac complications guides risk stratification practices,[18–20,22] and as a screening test, cTnI has been shown to improve triage procedures for patients presenting to emergency rooms with acute chest pain.[22] Recently, investigators of the Treat Angina with Aggrastat and Determine Costs of Therapy with an Invasive or Conservative Therapy—Thrombolysis In Myocardial Ischemia/Infarction (TACTICS-TIMI) 18 trial reported a marked reduction in adverse cardiac events among cTnI-positive patients with acute coronary syndromes who were randomly assigned to an early invasive treatment strategy compared with medical treatment.[32] Moreover, the ability of cTnI to predict a benefit from more aggressive therapy was superior to that of CK-MB elevation or ST-segment deviation.[32] There is growing evidence in support of integrating cTnI into algorithms that guide risk assessment and treatment of patients with acute coronary syndromes. Our data suggest that inclusion of cTnI surveillance in such algorithms for vascular surgery patients may have utility as well.

We recognize several limitations of the present study. Because the primary outcome of the main study has not yet been reviewed, all cause-specific mortality data were not available for this analysis. However, based on physician review of clinical data, evidence from medical patients,[18–21] and the high prevalence of CAD in patients who have undergone vascular surgery,[1–4] it is likely that cardiovascular complications contributed to mortality and that additional cardiovascular evaluation would appear prudent. Furthermore, we did not determine the optimal number and timing of cTnI measurements. cTnI remains elevated for 7 to 10 days after release into circulation,[13] which may allow screening at a single postoperative time point to identify patients who had myocardial injury. It remains unclear which screening strategy would be most cost-effective for identification of high-risk surgical patients. Last, although 75% of our patients received β-blockers during surgery, β-blocker use was not universal. Thus, it is possible that the 12% incidence of elevated cTnI we observed is higher than what may occur in the presence of universal β-blockade. Nonetheless, even when β-blocker therapy has been universally applied in clinical trials, cardiac morbidity and mortality have not been eliminated.[8,9]

In conclusion, elevated cTnI levels after major vascular surgery are associated with a significantly increased risk of 6-month mortality and perioperative MI. Moreover, we ob-

served a dose-response relation between cTnI concentration and death. Postoperative cTnI levels provide important prognostic information, and routine surveillance is useful for identifying patients who have an increased risk for morbidity and mortality. Further research is needed to determine whether intervention in patients with elevated cTnI can improve outcome.

Acknowledgments

This study was supported by GCRC/NIH grant M01-RR00052, Department of Anesthesiology and Critical Care Medicine at the Johns Hopkins Medical Institutions, GE/Marquette Electronics (Milwaukee, Wis), and Dade Pharmaceuticals (Miami, Fla). Dr Pronovost was supported by the Clinician Scientist Award. Dr Faraday was supported by grants from the NIH/NHLBI and the American Heart Association.

References

1. Mangano DT. Perioperative cardiac morbidity. *Anesthesiology*. 1990;72:153–184.
2. Eagle KA, Brundage BH, Chaitman BR, et al. Guidelines for perioperative cardiovascular evaluation for noncardiac surgery: Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery *Circulation*. 1996;93:1278–1317.
3. Hertzer NR. Cardiac risk factors in peripheral vascular surgery. In: Estafanous F, ed. *Anesthesia and the Heart Patient*. Cleveland, Ohio: Butterworths; 1989.
4. Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients: a classification of 1000 coronary angiograms and results of surgical management. *Ann Surg*. 1984;199:223–233.
5. Detsky AS, Abrams HB, Forbath N, et al. Cardiac assessment for patients undergoing noncardiac surgery: a multifactorial clinical risk index. *Arch Intern Med*. 1986;146:2131–2134.
6. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med*. 1977;297:845–850.
7. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043–1049.
8. Mangano DT, Layug EL, Wallace A, et al. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery: Multicenter Study of Perioperative Ischemia Research Group. *N Engl J Med*. 1996;335:1713–1720.
9. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery: Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med*. 1999;341:1789–1794.
10. Raby KE, Barry J, Creager MA, et al. Detection and significance of intraoperative and postoperative myocardial ischemia in peripheral vascular surgery. *JAMA*. 1992;268:222–227.
11. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery: the Study of Perioperative Ischemia Research Group. *N Engl J Med*. 1990;323:1781–1788.
12. Adams JE III, Bodor GS, Davila-Roman VG, et al. Cardiac troponin I: a marker with high specificity for cardiac injury. *Circulation*. 1993;88:101–106.
13. Adams JE III, Abendschein DR, Jaffe AS. Biochemical markers of myocardial injury: Is MB creatine kinase the choice for the 1990s? *Circulation*. 1993;88:750–763.
14. Cummins B, Auckland ML, Cummins P. Cardiac-specific troponin-I radioimmunoassay in the diagnosis of acute myocardial infarction. *Am Heart J*. 1987;113:1333–1344.
15. Wu AH, Apple FS, Gibler WB, et al. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases. *Clin Chem*. 1999;45:1104–1121.
16. Apple FS, Falahati A, Paulsen PR, et al. Improved detection of minor ischemic myocardial injury with measurement of serum cardiac troponin I. *Clin Chem*. 1997;43:2047–2051.
17. Adams JE III, Sicard GA, Allen BT, et al. Diagnosis of perioperative myocardial infarction with measurement of cardiac troponin I. *N Engl J Med*. 1994;330:670–674.
18. Galvani M, Ottani F, Ferrini D, et al. Prognostic influence of elevated values of cardiac troponin I in patients with unstable angina. *Circulation*. 1997;95:2053–2059.
19. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med*. 1996;335:1342–1349.
20. Luscher MS, Thygesen K, Ravkilde J, et al. Applicability of cardiac troponin T and I for early risk stratification in unstable coronary artery disease: TRIM Study Group: Thrombin Inhibition in Myocardial ischemia. *Circulation*. 1997;96:2578–2585.
21. Christenson RH, Duh SH, Newby LK, et al. Cardiac troponin T and cardiac troponin I: relative values in short-term risk stratification of patients with acute coronary syndromes. GUSTO-IIa Investigators. *Clin Chem*. 1998;44:494–501.
22. Hamm CW, Goldmann BU, Heeschen C, et al. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med*. 1997;337:1648–1653.
23. Tanasijevic MJ, Cannon CP, Antman EM. The role of cardiac troponin-I (cTnI) in risk stratification of patients with unstable coronary artery disease. *Clin Cardiol*. 1999;22:13–16.
24. World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. *J Clin Epidemiol*. 1988;41:105–114.
25. Badner NH, Knill RL, Brown JE, et al. Myocardial infarction after noncardiac surgery. *Anesthesiology*. 1998;88:572–578.
26. Bodor GS, Porter S, Landt Y, et al. Development of monoclonal antibodies for an assay of cardiac troponin-I and preliminary results in suspected cases of myocardial infarction. *Clin Chem*. 1992;38:2203–2214.
27. Rosner B, ed. *Fundamentals of Biostatistics*. 5th ed. Boston, Mass: Duxbury; 2000.
28. Mamode N, Scott RN, McLaughlin SC, et al. Perioperative myocardial infarction in peripheral vascular surgery. *BMJ*. 1996;312:1396–1397.
29. Taylor LM Jr, Yeager RA, Moneta GL, et al. The incidence of perioperative myocardial infarction in general vascular surgery. *J Vasc Surg*. 1992;15:52–61.
30. London MJ, Mangano DT. Assessment of perioperative risk. In: Stoelting RK, ed. *Advances in Anesthesia*. Chicago, Ill: Year Book Medical; 1988:53–87.
31. Roberts SL, Tinker JH. *Cardiovascular Disease, Risk, and Outcome in Anesthesia*. Philadelphia, Pa: JB Lippincott; 1988.
32. Morrow DA, Cannon CP, Rifai N, et al. Ability of minor elevations of Troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction. *JAMA*. 2001;286:2405–2412.