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Troponin: An Important Prognostic Marker and Risk-Stratification Tool in Non–ST-Segment Elevation Acute Coronary Syndromes

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Over the past decade, there has been a progressive evolution of cardiac marker testing in patients with acute coronary syndromes (ACS). This has not only resulted in a dramatic shift in how we view the diagnosis of myocardial infarction (MI), but it has also extended the role of cardiac marker testing into risk stratification and guidance of treatment decisions. By the year 2000, the development of highly sensitive and cardiac-specific troponin assays had resulted in a consensus change in the definition of MI, placing increased emphasis on cardiac-marker testing with troponins as the new gold standard. Furthermore, and perhaps more importantly, the role of the troponins as superior markers of subsequent cardiac risk in ACS patients became firmly established. Most recently, the supportive role of these markers in identifying patients with ACS who may derive particular benefit from potent antithrombotic and anti-platelet therapy or early invasive treatment strategies has been demonstrated. This paper will review the evolution of these important roles of troponin testing for risk stratification in ACS. (J Am Coll Cardiol 2003;41:31S–36S) © 2003 by the American College of Cardiology Foundation

The clinical spectrum of ischemic heart disease is diverse, ranging from silent ischemia to acute myocardial infarction (MI). Initial components of assessing a patient with ischemic heart disease include the clinical history, physical examination, 12-lead electrocardiography, and measurement of biochemical markers. The gold standard for diagnosis of MI has been an elevated serum level of creatine kinase-myocardial band (CK-MB), the cardiac-specific isoform of CK. This measure satisfied one component of the diagnostic criteria for MI proposed by the World Health Organization and was later extended for the MONItoring trends and determinants in CArdiovascular disease (MONICA) study (1). However, elevated CK-MB may not detect all myocardial necrosis. In patients who die suddenly after severe or silent episodes of ischemia, autopsies frequently reveal micronecrosis that was not reflected in routine CK-MB measurements (2,3). In addition, myocardial biopsies taken during coronary artery bypass surgery in patients with unstable angina have shown platelet aggregates in the microvasculature, with associated myocardial necrosis, but without serum CK-MB elevation (4).

New cardiac markers with superior specificity and sensitivity for myocardial damage and greater ability to risk-stratify patients with ischemic myocardial necrosis are now challenging the role of CK-MB. The troponins (T, I, and C) are subunits of the thin filament-associated troponin-tropomyosin complex, which is involved in regulating striated muscle contraction. Monoclonal antibody-based assays have been developed that are specific for the cardiac isoforms of troponin (5,6). Using such assays, data are now available confirming that troponins can identify myocardial micronecrosis even when an MI diagnosis has been excluded according to the conventional definition (7,8).

In response to these and other issues, a new definition of MI was proposed in September 2000 (9) which emphasizes the use of cardiac troponins as the preferred marker of myocardial necrosis in the context of ischemic symptoms in routine clinical practice. Troponin measurement has also been included as a fundamental component of diagnosis and risk stratification in the latest revision of the American College of Cardiology/American Heart Association guidelines for management of non–ST-segment elevation acute coronary syndromes (NSTE ACS) (10). This review will describe the data that support the conversion to a "troponin gold standard."

TROPONINS FOR DIAGNOSIS AND RISK STRATIFICATION

Troponins as diagnostic markers. Compared with CK-MB measurement, troponin assays are substantially more sensitive in the detection of myocardial injury. The release kinetics of troponins T and I are similar; both are detectable in the serum within 4 to 12 h after the onset of myocardial necrosis and depending on the duration of ischemia and reperfusion status, peak values occur 12 to 48 h from symptom onset. Therefore, serial sampling, including a baseline sample and follow-up testing at 8 to 12 h after symptom onset, is recommended. Although troponin I is

Please refer to the Trial Appendix at the back of this supplement for the complete list of clinical trials.

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CK-MB = creatine kinase-myocardial band
GP = glycoprotein
LMWH = low-molecular-weight heparin
MI = myocardial infarction
NSTE = non–ST-segment elevation
PCI = percutaneous coronary intervention
RR = relative risk

cleared more quickly than troponin T, both isoforms may remain elevated in the serum for several days after myocardial injury, allowing for diagnostic confirmation even when patients delay presentation after symptom onset. Because of their long serum half-lives, however, neither troponin I nor troponin T assays are ideal for detection of re-infarction after an index event.

Troponins as prognostic indicators in NSTE ACS. Troponin measurement is also a powerful instrument for risk stratification in patients with acute cardiac ischemia. Patients with chest pain at rest, but without ST-segment elevation, are a particularly challenging group for both diagnosis and risk stratification, even when clinical or angiographic data are considered (11). Because the extent of myocardial necrosis is an important prognostic indicator in this situation (12), early identification of high-risk patients is as important as confirming a diagnosis of MI. It not only affects initial triage decisions but also can influence medical and interventional choices. As early as 1992, the prognostic value of troponin T was convincingly demonstrated (13). The rate of major cardiac events during and after hospitalization among troponin T–positive patients with Braunwald class III unstable angina was 15%, compared with only 1.9% among similar troponin T–negative patients ($p = 0.003$).

Several studies of ischemic patients without ST-segment elevation have investigated the risk of death or nonfatal MI at varying intervals after presentation. The FRagmin during InStability in Coronary artery disease (FRISC) trial investigators (14) observed a strong correlation between troponin elevation and 30-day and 5-month mortality. Stubbs et al. (15) showed a trend toward more frequent death or MI among troponin T–positive than troponin T–negative patients during a three-year follow-up (29% vs. 17%, respectively; $p = 0.07$) which reached statistical significance after adjustment for revascularization ($p = 0.042$). The Thrombolysis In Myocardial Infarction (TIMI) IIIB investigators found an increased risk for 42-day mortality among unstable angina patients who were troponin I–positive at baseline (16) which was directly proportional to troponin I elevation.

Among 855 high-risk ACS patients in the Global Utilization of Strategies To open Occluded arteries (GUSTO)-IIa troponin substudy, baseline troponin T was found to be a powerful marker of short-term mortality risk (17) and to be linearly related to increasing troponin T levels across a wide range of troponin T values. After adjustment for CK-MB level and electrocardiographic category, baseline troponin T level remained a strong predictor of 30-day mortality (chi-squared, 9.2; $p = 0.027$), while CK-MB was no longer significant. At one year, mortality among troponin T–positive patients was 14.1% compared with 4.5% among troponin T–negative patients ($p < 0.0001$) (18).

In a meta-analysis that included data from >4,000 patients in a number of studies, risk ratios for death or MI for troponin positivity were 2.7 for troponin T (95% confidence interval [CI], 2.1 to 3.4; $p < 0.001$) and 4.2 for troponin I (95% CI, 2.7 to 6.4; $p < 0.001$) (19). However, among individual studies, the odds ratios (ORs) varied considerably.

A recent meta-analysis that considered variable follow-up durations has helped to refine estimates of the level of risk associated with elevated troponins (20). Pooled ORs for death or MI at 30 days were 2.86 (95% CI, 2.35 to 3.47; $p < 0.0001$) in patients with ST-segment elevation and 4.93 (95% CI, 3.77 to 6.45; $p < 0.0001$) in patients with NSTE. This analysis emphasized the ability of troponins to detect myocardial necrosis in the absence of ST-segment elevation and to predict heightened risk in both groups of patients.

Isolated troponin elevation across the spectrum of clinical presentations. Using data from the Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON) B and GUSTO IIa troponin substudies and the CHest pain Evaluation by Creatine Kinase-MB, Myoglobin, And Troponin I (CHECKMATE) studies, Rao et al. (21) investigated the relationship of isolated troponin elevation with 24-h and 30-day clinical events across the spectrum of low- to high-risk presentations with chest pain. Patients who were both troponin- and CK-MB-positive had the highest odds of 24-h and 30-day death or MI, regardless of clinical presentation. However, isolated troponin positivity carried higher risk than isolated CK-MB positivity in both high- and low-risk patients. For patients with isolated troponin elevation, the unadjusted ORs of death or MI at 24-h were 5.2 (95% CI, 2.3 to 11.9) and 52.4 (95% CI, 17.0 to 161.4) for high- and low-risk patients, respectively. The adjusted ORs of 30-day death or MI were 1.3 (95% CI, 0.7 to 2.3) and 7.5 (95% CI, 2.6 to 21.5) for high- and low-risk patients. The risks of 24-h and 30-day death or MI were lower with isolated CK-MB elevation than with isolated troponin elevation, and they were not significantly greater than if both markers were negative.

Therapeutic potential for troponin-identified, high risk patients. Angiographic findings strongly support troponins as markers of platelet aggregation, thrombus formation, and distal embolization leading to myonecrosis in ACS patients with elevated troponins. In the Chimeric c7E3 AntiPlatelet Therapy in Unstable REfractory angina (CAPTURE) trial (22), angiograms showed increased visual thrombi in troponin T–positive patients (11.6% vs. 4.0%; $p < 0.01$). These patients also had greater thrombus resolution and reduced clinical outcomes after treatment with abciximab than

Table 1. Treatment Effect by Troponin T (TnT) Status in Various Studies (32)

	N	Study Design	Population	Death or MI, TnT (+)		Relative Reduction
				Treatment	Control	
PRISM (30)	2222	Retrospective	ACS	3.5%	13.7%	74%
CAPTURE (26,33)	1265	Retrospective	ACS + PCI	5.8%	19.6%	70%
PARAGON-B (32)	1160	Prospective	ACS	11.0%	19.0%	42%
PRISM-PLUS*	110	Retrospective	ACS	3.6%	20.6%	71%
GUSTO IV ACS†	7707	Prospective	ACS	10.5%	10.7%	—

*Januzzi JL, personal communication. February 21, 2001. †The GUSTO IV ACS Investigators; Presented at the XXII Congress of the European Society of Cardiology, August 2000. Newby LK, Ohman EM, Christenson RH, et al. Benefit of glycoprotein IIb/IIIa inhibition in patients with acute coronary syndromes and troponin T-positive status: the PARAGON-B Troponin T Substudy. Circulation 2001;103:2891–96.

ACS = acute coronary syndromes; CAPTURE = Chimeric c7E3 AntiPlatelet Therapy in Unstable REfractory angina; GUSTO = Global Utilization of Strategies To open Occluded arteries; MI = myocardial infarction; PARAGON = Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network; PCI = percutaneous coronary intervention; PRISM-PLUS = Platelet Receptor inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms.

troponin T–negative patients, suggesting a selective potential for enhanced effectiveness of anti-thrombotic and antiplatelet agents.

Troponin status and treatment benefit from low-molecular-weight heparins (LMWH). Among 976 patients in the FRISC trial who were randomized to the LMWH, dalteparin, or placebo, there was a linear relationship between baseline troponin T level and death or MI in the follow-up (23). Patients with troponin T levels of either <0.06, 0.06 to 0.18, or >0.18 ng/ml within 24 h of admission had rates of death or MI of 4.3%, 10.5%, and 16.1%, respectively. Among troponin T–positive patients only, there was a strong reduction in the rate of death or MI with dalteparin, from 6.0% to 2.4% (relative risk [RR] 0.41, 95% CI, 0.18 to 0.92), a benefit that persisted at 40 and 150 days.

Among high-risk patients with NSTE ACS and negative CK-MB measures enrolled in a TIMI 11B substudy, 50.1% were troponin I–positive (>0.1 ng/ml) (24). There was a strong association between troponin I elevation during the first 24 h and an adverse clinical outcome at 48 h and 14 days. In this study, treatment with enoxaparin conferred benefit among troponin I–positive patients, for whom a 47% reduction ($p = 0.001$) in the composite end point (death, MI, urgent revascularization) was observed at 14 days. No benefit was found in troponin I–negative patients.

Troponin status and benefit from platelet glycoprotein (GP) IIb/IIIa receptor blockade. In the CAPTURE trial, abciximab reduced MI before, during, and after angioplasty in patients with refractory unstable angina after documentation of coronary artery lesions amenable to angioplasty (25). A substudy found that abciximab was more beneficial in patients with elevated troponin T (>0.1 ng/ml) at baseline (26). The OR for death or nonfatal MI for abciximab versus placebo was 0.32 in troponin T–positive patients (95% CI, 0.12 to 0.49; $p = 0.002$) and was driven primarily by a reduction in the MI component ($p < 0.001$). No such benefit was observed in troponin T–negative patients.

In the Platelet Receptor inhibition for Ischemic Syndrome Management (PRISM) and Platelet Receptor inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms (PRISM-PLUS) trials, the small-molecule GP IIb/IIIa inhibitor, tirofiban, was shown to reduce death or nonfatal MI in patients with NSTE ACS (27,28). In PRISM-PLUS, treatment with a heparin-plus-tirofiban combination resulted in lower peak troponin T levels than heparin alone (5.2 ± 8.3 ng/ml vs. 15.5 ± 29.1 ng/ml; $p = 0.017$) (28). As in the CAPTURE study, a possible correlation between intracoronary thrombus and clinical outcome was also demonstrated (29). Patients with intracoronary thrombus had significantly higher rates of death or MI than did patients without thrombus (19% vs. 10%; $p < 0.001$). In a substudy of the PRISM trial, a preferential treatment benefit was found with tirofiban among troponin I–positive and troponin T–positive patients (30). The rate of death or MI was significantly lower among troponin I–positive patients treated with tirofiban (4.3%) than those who received placebo (13%). No treatment benefit was observed in troponin I–negative patients.

The PARAGON B Troponin T Substudy investigators recently reported a 42% reduction in death or MI ($p = 0.02$) with GP IIb/IIIa receptor inhibitor treatment in troponin T–positive ACS patients (31). The lamifiban treatment resulted in an event rate approaching that of troponin T–negative patients (32).

The PARAGON B study, along with the CAPTURE and PRISM trials, provided strong evidence that the treatment effect of GP IIb/IIIa antagonists is amplified in troponin-positive patients. As shown in Table 1 (32), however, these studies differed in several important ways, preventing their results from being generally applicable in routine clinical practice (26,30,32,33). For example, in the CAPTURE trial, only patients with documented coronary artery disease who failed medical therapy and were scheduled for percutaneous coronary intervention (PCI) were enrolled. This limits its extrapolation to current clinical

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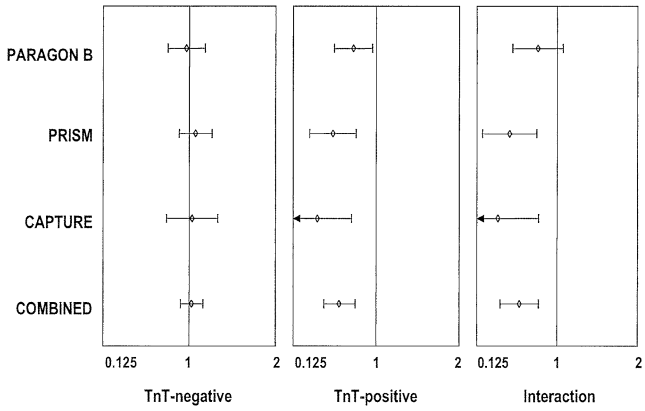

Figure 1. Odds ratios with 95% confidence interval for death or myocardial infarction among troponin-negative and troponin-positive patients and for interaction of troponin status with treatment effect for Platelet Receptor inhibition for Ischemic Syndrome Management (PRISM), Chimeric c7E3 AntiPlatelet Therapy in Unstable REfractory angina (CAPTURE), Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON-B), and combined trials. **Values to the left of 1.0** indicate a benefit of glycoprotein IIb/IIIa inhibition. TnT = troponin T. Newby LK, Ohman EM, Christenson RH, et al. Benefit of glycoprotein IIb/IIIa inhibition in patients with acute coronary syndromes and troponin T-positive status: the PARAGON-B Troponin T Substudy. Circulation 2001;103:2891–6. Reproduced with permission from Lippincott, Williams and Wilkins.

practice. In the PRISM study, tirofiban was used without concomitant heparin and was not continued for PCI. Further, the troponin substudies were initiated after the CAPTURE and PRISM main trials were completed (26,30), while the PARAGON B substudy was carried out concurrently with the main trial (32). Nevertheless, the findings in the PARAGON B study were similar to those described by previous investigators. Although the subgroup comparison was not statistically rigorous, results were also similar in medically- and interventionally-treated patients in both PRISM and PARAGON B (30,32).

We previously (32) performed a meta-analysis of the PRISM, CAPTURE, and PARAGON B troponin substudy data to better define the interaction of troponin status with treatment on the end point of death or MI. As shown in Figure 1, none of these studies revealed a treatment effect with a GP IIb/IIIa antagonist in troponin-negative patients. However, among troponin-positive patients, there was a significant treatment effect (pooled OR, 0.34; 95% CI, 0.19 to 0.58). Further, for the three studies combined, the pooled OR for interaction of treatment by troponin status was highly significant (OR, 0.33; 95% CI, 0.19 to 0.57). As in the studies of LMWHs, these findings suggest that the benefit of GP IIb/IIIa inhibitors is enhanced by troponin-positive status across a spectrum of treatment indications and use patterns.

These studies illustrate how a biochemical risk marker may be used to improve outcomes by guiding decisions to optimize anti-thrombotic therapy. However, the results of the GUSTO IV ACS trial raised questions about the particular benefit of GP IIb/IIIa blockers in patients with ACS and elevated troponin levels (34). Unlike previous studies of GP IIb/IIIa inhibitors in NSTE ACS, GUSTO IV failed to show a benefit of abciximab over placebo in either medically-managed NSTE patients overall or in troponin T–positive patients. This is particularly noteworthy, considering that the relationship of troponin elevation to risk was similar to the relationship found in previous studies. Although patients were not managed with early cardiac catheterization/intervention, it is unlikely that this factor alone accounts for the findings, because other studies showed benefits from GP IIb/IIIa blockade in patients who did not undergo revascularization.

Troponin status and benefit from early angiography. The benefit of an early choice of angiography based on troponin status has also been investigated. In the TIMI-IIIB trial, the RR for 42-day mortality among patients with troponin I levels >0.4 ng/ml, compared with troponin I–negative patients, was 1.11 (95% CI, 1.05 to 1.17; p = 0.016) (35). However, in the subgroup of troponin I–positive patients randomly assigned to the invasive strategy, mortality was similar to that of troponin I–negative patients (RR, 0.92; 95% CI, 0.86 to 0.98; p = 0.024) (35). Data from the GUSTO-IIa substudy also suggested that the treatment benefit from an early invasive strategy may be enhanced in troponin-positive patients (36). In this blinded study, troponin T–positive patients who underwent revascularization had one-year mortality similar to that of troponin T–negative patients (6.3% vs. 6.2%; p = 0.78) (36). However, one-year mortality among troponin T–positive patients who did not receive angioplasty was substantially higher than mortality in troponin T–negative patients (37% vs. 11%, p = 0.001).

The suggestion that early revascularization may result in improved outcomes was recently confirmed in both the FRISC II study and the TACTICS trials (37,38). A substudy of FRISC-II addressed the influence of troponin T elevation and ST-segment depression on the effects of an early invasive versus noninvasive strategy (39). Among troponin T–positive patients, there was a 29.7% reduction in the incidence of death or MI at one-year (RR 0.70, 95% CI, 0.55 to 0.90; p = 0.005). A similar effect was observed for troponin T elevation in combination with ST-segment depression at entry.

CONCLUSIONS

Measurement of cardiac troponins is rapidly assuming the position of gold standard for the biochemical diagnosis of myocardial necrosis, replacing conventional CK-MB measurement. The superiority of troponin T and I measurement in the diagnosis of myocardial damage, which may represent even microscopic zones of myocardial necrosis, has been clearly demonstrated in numerous studies over the past decade. The recently proposed new definition of MI (9) identifies cardiac troponin (T or I) as the preferred biomarker for routine MI diagnosis. However, retrospective con-

firmation of MI is only one function of a cardiac marker. A role in risk stratification and in therapeutic choices, such as the use of LMWHs, GP IIb/IIIa inhibitors, and coronary revascularization in accordance with treatment guidelines, is also crucially important. In this respect as well, troponin measurement has clearly demonstrated superiority over CK-MB in its usefulness as a complement to other routine assessments, including the history and electrocardiogram.

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