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

Results From a Randomized Trial

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Because of the wide spectrum of risk among patients with unstable angina and non–ST-segment elevation myocardial infarction (UA/NSTEMI), the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the management of this condition recommend risk stratification as one of the most important initial steps in evaluating and treating these patients.1 Routine risk assessment is especially important given the approximately 1.4 million hospital admissions annually in the United States for UA/NSTEMI.1 Baseline levels of cardiac specific troponin I (cTnI) and T (cTnT) have been shown to be useful for assessing prognosis in patients with unstable angina and non–ST-segment elevation myocardial infarction (UA/NSTEMI). However, the use of cardiac troponins for predicting benefit of an invasive vs conservative strategy in this patient population is not clear.

Objective To prospectively test whether an early invasive strategy provides greater benefit than a conservative strategy in acute coronary syndrome patients with elevated baseline troponin levels.

Design Prospective, randomized trial conducted from December 1997 to June 2000.

Setting One hundred sixty-nine community and tertiary care hospitals in 9 countries.

Participants A total of 2220 patients with acute coronary syndrome were enrolled. Baseline troponin level data were available for analysis in 1821, and 1780 completed the 6-month follow-up.

Interventions Patients were randomly assigned to receive (1) an early invasive strategy of coronary angiography between 4 and 48 hours after randomization and revascularization when feasible based on coronary anatomy (n=1114) or (2) a conservative strategy of medical treatment and, if stable, predischarge exercise tolerance testing (n=1106). Conservative strategy patients underwent coronary angiography and revascularization only if they manifested recurrent ischemia at rest or on provocative testing.

Main Outcome Measure Composite end point of death, MI, or rehospitalization for acute coronary syndrome at 6 months.

Results Patients with a cTnI level of 0.1 ng/mL or more (n=1087) experienced a significant reduction in the primary end point with the invasive vs conservative strategy (15.3% vs 25.0%; odds ratio [OR], 0.54; 95% confidence interval [CI], 0.40-0.73). Patients with cTnI levels of less than 0.1 ng/mL had no detectable benefit from early invasive management (16.0% vs 12.4%; OR, 1.4; 95% CI, 0.89-2.05; P<.001 for interaction). The benefit of invasive vs conservative management through 30 days was evident even among patients with low-level (0.1-0.4 ng/mL) cTnI elevation (4.4% vs 16.5%; OR, 0.24; 95% CI, 0.08-0.69). Directionally similar results were observed with cTnT.

Conclusion In patients with clinically documented acute coronary syndrome who are treated with glycoprotein IIb/IIa inhibitors, even small elevations in cTnI and cTnT identify high-risk patients who derive a large clinical benefit from an early invasive strategy.
in numerous studies to be potent predictors of risk in this population. In addition, several groups have shown that the troponins can identify patients who derive particular benefit from treatment with glycoprotein IIb/IIIa inhibitors and low-molecular-weight heparin. However, few data are available on the ability of troponin to predict the benefit of an invasive vs conservative management strategy. In a prespecified secondary analysis, we prospectively tested the hypothesis that the early invasive strategy would provide a greater benefit in patients with elevated baseline levels of troponin, and have reported initial dichotomous results with cTnT. We now extend upon these results with an assessment of the usefulness of cTnI for selecting appropriate patients for an early invasive strategy, and take an additional important step toward clinical application by evaluating the significance of low levels of troponin elevation with respect to prognosis and the effect of early invasive vs conservative management.

**METHODS**

**Study Population**

Between December 18, 1997, and December 22, 1999, 2220 patients were enrolled in TACTICS-TIMI 18 at 169 community and tertiary care hospitals in 9 countries and followed up for 6 months. The study design and primary results have been published. Briefly, inclusion criteria were: men or women at least 18 years old who experienced an episode of angina (with an accelerating pattern or prolonged [>20 minutes] or recurrent episodes at rest or with minimal effort) within the preceding 24 hours, who were candidates for coronary revascularization, and who had at least 1 of the following: ST-segment depression (0.05 mV), transient (<20 min) ST-segment elevation (≥0.1 mV) or T-wave (≥0.3 mV) inversion in 2 or more leads not known to be old; elevated cardiac markers; or documented coronary disease.

Exclusion criteria included persistent ST-segment elevation, secondary angina, percutaneous coronary intervention or coronary artery bypass graft surgery within 6 months, factors associated with increased risk of bleeding, left bundle branch block or paced rhythm, severe congestive heart failure or cardiogenic shock, important systemic disease, serum creatinine levels greater than 2.5 mg/dL (221 µmol/L), or concurrent treatment with warfarin, ticlopidine, or clopidogrel.

**Medical Management**

The protocol specified that patients receive 325 mg of aspirin daily (unless contraindicated) and intravenous unfractionated heparin and tirofiban (Aggrastat, Merck and Co, Inc, West Point, Pa), administered as an intravenous loading infusion of 0.4 µg/kg per minute over 30 minutes followed by a maintenance infusion of 0.1 µg/kg per minute, for a minimum of 48 hours, including 12 hours or more following PCI. Use of other medications, such as β-blockers or angiotensin-converting enzyme inhibitors, was left to the discretion of treating physicians.

**Treatment Strategy**

Patients were randomized via a centralized system to an early invasive or conservative strategy (FIGURE 1). Patients in the early invasive strategy were to undergo coronary angiography between 4 and 48 hours after randomization and revascularization when feasible based on assessment of coronary anatomy. Patients in the conservative strategy were treated medically; if stable, they underwent a predischarge exercise tolerance test. These patients were to undergo coronary angiography and revascularization as appropriate only if they manifested recurrent ischemia at rest, or on provocative testing.

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**Figure 1. Flow of Patients Through Study**

![Diagram showing the flow of patients through the study](image-url)
Troponin Testing
A baseline blood sample was obtained and serum stored at -20°C or colder at the enrolling site until shipped to the TIMI Core Laboratory at Children’s Hospital Medical Center (Boston, Mass), where samples were stored at -80°C. Samples were later analyzed in batches after a single thaw. Cardiac troponin I was measured using the ACS-180 Chemiluminescence cTnI Immunoassay (Bayer Diagnostics, Tarrytown, NY). The ACS-180 assay for cTnI is an automated system using a 2-site sandwich immunoassay and direct chemiluminesmetric technology. The manufacturer reports the minimum detectable concentration as 0.03 ng/mL. The total imprecision determined in the TIMI Core Laboratory was characterized by a coefficient of variation (CV) (ratio of the SD to the mean) of 10% at 0.4 ng/mL, 15% at 0.2 ng/mL, and 20% at 0.1 ng/mL. Cardiac troponin T was measured on the Elecsys 10/10 (Roche Diagnostics, Indianapolis, Ind). The manufacturer has reported the minimal detectable concentration as 0.01 ng/mL, and a CV of 10% at 0.05 ng/mL.

Statistical Methods
The primary end point of the study was the combined incidence of death, MI, and rehospitalization for an acute coronary syndrome at 6 months. All primary end points were adjudicated by an independent clinical endpoints committee, blinded to treatment assignment. The major secondary end point was death or new MI. The primary decision limit for cTnI (0.1 ng/mL) was based on prior work with the assay used in this study.11 A secondary cutpoint was prospectively specified for cTnI, corresponding to the diagnostic limit for MI reported by the manufacturer (1.5 ng/mL). The established clinical threshold for cTnT is 0.1 ng/mL. We also evaluated an additional cutpoint corresponding to a total CV of 10% for both cTnI (0.4 ng/mL) and cTnT (0.05 ng/mL) in accord with recent expert recommendations.12 In supplementary analyses, we divided patients with cTnI levels of 0.1 ng/mL or greater into quartiles of cTnI level. This enabled us to evaluate the behavior of cTnI as a semicontinuous variable.

Evaluation of the risk associated with an elevated level of cardiac troponin was performed using the χ² test for dichotomized cTnI and cTnT results. The risk associated with each stratum of troponin elevation was then tested compared with those in the reference group (cTnI <0.1 ng/mL, cTnT <0.01 ng/mL) in logistic regression models that included the main effects of troponin status, invasive vs conservative management strategies, and an interaction term. Potential confounders considered included age, ST-segment change, creatine kinase MB fraction (CK-MB), and patient’s sex. Given the multiple testing against the single reference group, a Bonferroni correction was applied and a P value of less than .017 was considered to indicate statistical significance.

The primary analysis in the troponin study was based on the dichotomous comparison of patients with positive or negative troponin results using the lower cutoffpoints of 0.1 ng/mL and 0.01 ng/mL for cTnI and cTnT, respectively. Testing for heterogeneity in the degree of cTnI elevation revealed a stable pattern of increased risk of death or MI, including those patients with low-level elevations of cTnI (Table 1). The lowest cutoffpoint, 0.1 ng/mL, provided the best dichotomous discrimination of risk as compared with 0.4 and 1.5 ng/mL. If the decision limit had instead been set at the concentration corresponding to the level of 10% total imprecision (0.4 ng/mL), 181 additional patients (10% of the population) would have been classified as “troponin negative,” but these patients had a 30-day risk for death or MI comparable with that for patients with cTnI levels of 1.5 ng/mL or greater. Thus, as reflected by the respective χ² statistics and odds ratios (ORs), the predictive capacity of cTnI for death or recurrent ischemic events would have been diminished by increasing the prognostic decision limit from 0.1 to 0.4 ng/mL (χ²; 23.7 vs 14.5; OR, 3.4 [95% CI, 2.01-5.51] vs 2.2 [95% CI, 1.48-3.39]).
Table 1. Outcomes by Baseline Levels of Cardiac Troponin I (cTnI)*

<table>
<thead>
<tr>
<th>cTnI Level, ng/mL</th>
<th>&lt;0.1 (n = 734)</th>
<th>0.1 to &lt;0.4 (n = 181)</th>
<th>0.4 to &lt;1.5 (n = 213)</th>
<th>≥1.5 (n = 693)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Days Primary end point, %</td>
<td>5.5</td>
<td>10.5</td>
<td>11.3</td>
<td>12.1</td>
</tr>
<tr>
<td>OR (95% CI) Reference</td>
<td>2.0 (1.3-3.6)</td>
<td>2.2 (1.3-3.7)</td>
<td>2.4 (1.6-3.5)</td>
<td></td>
</tr>
<tr>
<td>P value Reference</td>
<td>.11</td>
<td>.02</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Death or MI, %</td>
<td>2.5</td>
<td>8.3</td>
<td>7.0</td>
<td>7.9</td>
</tr>
<tr>
<td>OR (95% CI) Reference</td>
<td>3.6 (1.8-7.3)</td>
<td>3.0 (1.5-6.1)</td>
<td>3.4 (2.0-5.9)</td>
<td></td>
</tr>
<tr>
<td>P value Reference</td>
<td>.002</td>
<td>.03</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Death, %</td>
<td>1.6</td>
<td>0.6</td>
<td>3.3</td>
<td>2.6</td>
</tr>
<tr>
<td>OR (95% CI) Reference</td>
<td>0.6 (0.7-4.6)</td>
<td>3.5 (1.3-9.6)</td>
<td>2.8 (1.2-6.4)</td>
<td></td>
</tr>
<tr>
<td>P value Reference</td>
<td>.60</td>
<td>.01</td>
<td>.02</td>
<td></td>
</tr>
</tbody>
</table>

*P values are adjusted for treatment group and interaction. MI indicates myocardial infarction; OR, ratio; and CI, confidence interval.

When concentrations of cTnT are evaluated in the same manner, consistent results are observed (Table 2). In particular, those patients with cTnT levels between 0.01 and 0.05 ng/mL were at increased risk of death or MI at 30 days (P < .001) and 6 months (P = .002) compared with cTnT-negative patients. Again, the optimal troponin threshold for predicting the benchmark end point of death or MI at 30 days was at the lowest of the 3 decision limits evaluated (6.3, 20.8 vs 15.7; OR, 2.8 [95% CI, 1.80-4.36] vs 2.0 [95% CI, 1.31-2.93] vs 2.2 [95% CI, 1.47-3.25]).

Interaction With Therapy

Using the previously established cut-point (0.1 ng/mL),11 a significantly greater benefit of the early invasive vs the conservative management strategy was seen in patients with positive (vs negative) cTnI results (Table 3). Among patients with cTnI levels of 0.1 ng/mL or greater, there was a 30% relative risk reduction in the primary end point with the invasive vs the conservative strategy, whereas patients with a negative troponin had similar outcomes with either treatment approach (P < .001 for interaction). The capacity of cTnI to predict a benefit of invasive strategy with respect to the primary end point (χ² for interaction, 12.0; P < .001) compared favorably with other important risk factors, such as ST-segment deviation (χ² for interaction, 5.7; P = .02) and CK-MB (χ² for interaction, 2.3; P = .13). Moreover, the ability of cTnI to identify patients who derived a greater reduction in the primary end point with early invasive management was evident after controlling for the effects of age, ST-segment depression, and the baseline level of CK-MB (adjusted P for interaction, < .001). An identical 39% relative risk reduction was observed among patients with cTnI levels greater than 0.01 ng/mL (P = .003 for interaction) with no benefit among those with negative cTnI.12 The particular advantage of the early invasive strategy among troponin-positive patients was observed as early as 7 days for both cTnI and cTnT.
(FIGURE 2) with respect to the occurrence of death or MI. At 30 days, there was a significant 53% relative reduction in the risk of death or MI (P = .001) among those with elevated cTnI (Table 3) that was comparable to the 50% relative risk reduction in patients with elevated cTnT.8

As such, the risk of recurrent events associated with elevated cardiac troponin was substantially attenuated by the early invasive strategy. For example, the 30-day risk of death or MI associated with a cTnI level greater than 0.1 ng/mL was reduced and no longer statistically significant among those treated in the invasive group (N=917; OR, 1.7; 95% CI, 0.8-3.4), compared with patients managed conservatively (N=904; OR, 6.3; 95% CI, 3.1-12.7; P = .02 for interaction).

Evaluation of the benefits of the early invasive strategy according to the degree of troponin elevation showed a consistently lower OR favoring the invasive strategy among those with low-level as well as higher degrees of troponin elevation (FIGURE 3). Notably, patients with cTnI elevation in the range of 0.1 to 0.4 ng/mL experienced a statistically significant reduction in the risk of the primary end point (OR, 0.24; 95% CI, 0.08-0.69; P = .008) with early invasive vs conservative management, and a corresponding strong trend with respect to the risk of death or MI (OR, 0.34; 95% CI, 0.11-1.06; P = .06). A similar pattern was evident for patients with low levels of cTnT elevation, though not achieving statistical significance (Figure 3B). Similar results were noted when troponin levels were split into quartiles.

**COMMENT**

This prospective evaluation of the “troponin hypothesis” demonstrates the potential usefulness of baseline determination of cTnI or cTnT for identifying patients with UA/NSTEMI who should be managed with an early invasive strategy. In patients with elevated levels of troponin, the early invasive strategy using upstream GpIIb/IIIa inhibition with tirofiban reduced event rates to levels near those seen in troponin-negative patients. The benefit was a 10% absolute and a 39% relative reduction in risk of the primary end point at 6 months. We also demonstrate that among patients with clinically documented UA/MI.
NT-AMI even “minor” elevation of cardiac troponin confers increased risk and predicts significant benefit of an early invasive strategy. These findings were consistent between cTnI and cTnT. Thus, even low-level elevation of cardiac troponin in patients with a good clinical history for unstable angina should be an indication for the strategy of early GpIIb/IIIa inhibition and routine invasive management.

**Cardiac Troponins for Therapeutic Decision Making**

Elevated levels of cardiac troponins identify patients with UA/NSTEMI with more complicated coronary lesions, greater burden of intracoronary thrombus, and impaired tissue-level myocardial flow. It was thus anticipated that cTnI and cTnT would be useful for selecting patients most likely to benefit from potent antiplatelet and antithrombin therapy. For example, in the PRISM (Platelet Receptor Inhibition in Ischemic Syndrome Management) Trial, therapy with tirofiban was associated with a nearly 70% relative reduction in the 30-day risk of death or MI among patients with elevated cTnI or cTnT levels compared with no detectable benefit among those with normal levels. Multiple studies have now shown a consistent 40% to 70% reduction in death or MI with GpIIb/IIIa inhibition among patients with elevated baseline troponins, with the most convincing benefit among patients undergoing invasive therapy. Our data from TACTICS-TIMI 18 extend these observations with medical therapy and clearly demonstrate the usefulness of cTnI and cTnT for identifying patients who are likely to benefit from an early invasive strategy with upstream GpIIb/IIIa inhibition. They also add to subgroup analyses from the Fragmin and Fast Revascularisation during Instability in Coronary artery disease (FRISC II) Trial that demonstrated a reduction in mortality at 1 year among patients with baseline levels of cTnT higher than 0.1 ng/mL.

While other clinical indicators, such as ST-segment depression, also appear to be useful for stratifying patients with respect to the benefit of an invasive management strategy, cardiac troponins appear to confer additional information. Specifically, they identify a greater number of patients (60% of the population for cTnI, 54% for cTnT, and 38% for ST-segment depression) who appear to benefit from invasive vs conservative management while maintaining similar, if not stronger, discrimination between the reduction in clinical events in the 2 treatment groups. Our data thus support the incorporation of the cardiac troponins into current management strategies for triage of patients to an early invasive strategy. In this analysis, no benefit of the early invasive strategy was detected among patients with negative troponin results. Future work will continue to evaluate other risk indicators or biomarkers that may identify patients with negative troponin results who are still at high risk and may benefit from early invasive management.

**Decision Limits for Troponins in UA/NSTEMI**

This study also evaluated several prospectively defined ranges of troponin elevation with respect to prognosis and utility for clinical decision-making. The optimal troponin thresholds for risk stratification and therapeutic decision making remain a subject of debate. The development of troponin assays with increasingly lower detection limits has led...
to frequent reporting of mildly elevated troponin levels in patients with chest pain and suspected acute coronary syndromes, and created the need for careful prospective evaluation of the prognostic and therapeutic implications of such troponin results. Recently, a joint committee from the European Society of Cardiology and the American College of Cardiology (ESC/ACC) convened to formulate diagnostic criteria for MI, taking into account the introduction of cardiac troponins. The committee has recommended use of a diagnostic threshold for MI based on the 99th percentile of troponin levels among normal controls, but not to go below a specific level of assay precision (coefficient of variation [CV], 10%). In addition, the committee has supported the use of a single clinical threshold for each troponin assay for risk stratification and diagnosis.

Importantly, we found that patients with a clinical history consistent with UA/NSTEMI and low levels of troponin elevation were not only at significantly increased risk for death or recurrent ischemic events, but also derived a substantial benefit from an early invasive management strategy. Such “minor” elevations of cTnT (≥ 0.1–0.4 ng/mL) are above the prognostic decision limit established in prior work, but fall below the 10% level of imprecision recommended by the joint ESC/ACC committee as the lower bounds for a diagnostic cutpoint for MI. Our results suggest that a decision limit of 0.1 ng/mL, for the cTnT assay we studied, provides superior predictive capacity to the higher threshold despite the lower precision of the assay in this range. Coupled with the consistent observations with cTnT, these data indicate that troponin elevations below the level of a 10% CV may offer important prognostic information among patients with a typical clinical history of UA/NSTEMI, and support the use of a decision limit for prognosis and therapy that may be lower than the diagnostic threshold for MI. These findings also reinforce the need to take an evidence-based approach to the establishment of decision limits for risk assessment and therapy.

Although these findings are relevant to patients with a typical clinical presentation for UA/NSTEMI, caution should be exercised in generalizing the results to patients with a low clinical suspicion of acute myocardial ischemia. Particularly when considering low-level elevation of cardiac troponins, the patient’s pretest probability of having an acute coronary syndrome must play an important role in determining the clinical response to “positive” test results. Elevation of cardiac troponins may also result from nonischemic mechanisms of myocardial injury (eg, myocarditis, severe heart failure, cardiac contusion), or rare false-positive results that must be distinguished from MI. Moreover, patients enrolled in TACTICS-TIMI 18 were free from significant renal insufficiency or recent coronary intervention, 2 settings in which the prognostic implications of elevated troponin levels remain to be fully evaluated. Repeat testing may be useful in discriminating between nonischemic and ischemic causes of elevation, as well as suspected false-positive results. As emphasized in the ACC/AHA guidelines for the management of UA/NSTEMI, clinical information from the history and electrocardiogram must be integrated with data from cardiac troponins to effectively assess the risk of these patients. Furthermore, these data do not negate the importance of continued efforts by manufacturers of troponin assays to improve precision at the low end, and thereby reduce the probability of falsely positive or negative dichotomous results.

The troponin measurements used for this analysis were obtained in an experienced central laboratory. Nevertheless, the assays were run on the standard platforms commonly available in general clinical chemistry laboratories, using standard calibration methods described in the package inserts. Thus, we do not anticipate any substantial differences in the performance characteristics of the assays or results of this study when applied in clinical practice. However, given differences in standardization between cTnI assays, the specific decision-limits studied in our report should not be applied to other cTnI assays without supportive clinical data.

### Critical Pathways and Quality Improvement

Even in the face of widespread dissemination of clinical trial results, many patients with UA/NSTEMI do not receive evidence-based therapies. Critical pathways based on careful review of clinical studies and expert guidelines may help to improve triage procedures, and lead to appropriate use of medications and management strategies. The present study provides strong evidence for the integration of cardiac troponins into clinical algorithms that guide the management of patients with UA/NSTEMI, including decisions regarding use of early invasive evaluation. Moreover, in guiding the future development of performance measures for UA/NSTEMI, these data strongly support the use of an invasive strategy for patients with a typical history of unstable angina and elevated cardiac troponins.

### Conclusion

Cardiac troponin I and T are potent tools for risk stratification and clinical decision-making with respect to the potential benefits of early invasive management for patients with UA/NSTEMI. Even low-level elevations of cardiac troponins help identify patients who benefit from a strategy of early GpIIb/IIIa inhibition in combination with an early invasive approach. These results provide an evidence-based guide for integration of cardiac troponins into critical pathways for early management of patients with non-ST-segment elevation acute coronary syndromes.

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TROTONIN IN ACUTE CORONARY SYNDROMES

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REFERENCES


Truth may be stretched but cannot be broken, and always gets above falsehood, as oil does above water.
—Miguel de Cervantes Saavedra (1547-1616)