Prognostic Implications of Elevated Troponin in Patients With Suspected Acute Coronary Syndrome But No Critical Epicardial Coronary Disease

A TACTICS-TIMI-18 Substudy

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OBJECTIVES

The purpose of this study is to determine whether there is clinical significance to elevated troponin I in patients with suspected acute coronary syndromes (ACS) with non-critical angiographic coronary stenosis.

BACKGROUND

Elevation of troponin in patients admitted with ACS symptoms with non-critical coronary artery disease (CAD) may result from coronary atherothrombosis not evident using standard angiography or from other ischemic and non-ischemic causes that may confer increased risk for future events.

METHODS

Patients with ACS enrolled in the Treat Angina With Aggrastat and Determine Cost of Therapy With Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction (TACTICS-TIMI)-18 were included. Of 2,220 patients enrolled in the trial, 895 were eligible. Patients were divided into four groups according to troponin status on admission and presence of significant angiographic stenosis. Baseline brain natriuretic peptide (BNP) and C-reactive protein (CRP) were obtained on all patients.

RESULTS

The median troponin I levels were 0.71 ng/ml in patients with CAD compared with 0.02 ng/ml in patients without CAD (p < 0.0001). Troponin-positive patients with or without angiographic CAD had higher CRP and BNP levels compared with troponin-negative patients (p < 0.01 for both). The rates of death or reinfarction at six months were 0% in troponin-negative patients with no CAD, 3.1% in troponin-positive patients with no CAD, 5.8% in troponin-negative patients with CAD, and 8.6% in troponin-positive patients with CAD (p = 0.012).

CONCLUSIONS

Elevated troponin in ACS is associated with a higher risk for death or reinfarction, even among patients who do not have significant angiographic CAD. The mechanisms conferring this adverse prognosis merit further study. (J Am Coll Cardiol 2005;45: 19–24) © 2005 by the American College of Cardiology Foundation

Cardiac troponins are independent predictors of death or reinfarction in patients presenting with acute coronary syndromes (ACS) (1–3). Moreover, troponin elevations in ACS have been associated with a higher incidence of multivessel disease, complex lesions, visible thrombus, and impaired myocardial perfusion (4–7).

The finding of elevated cardiac troponin in patients who are subsequently found not to have non-critical epicardial coronary artery disease (CAD) at angiography has been a source of confusion for clinicians, and led to concern over “false-positive” results with this biomarker (8). In this study, we address for the first time this important clinical issue by evaluating the outcome of patients with suspected ACS according to the presence or absence of significant CAD on angiography and troponin status on admission.

METHODS

Study population. The data were drawn from an 895-patient subset from the Treat Angina With Aggrastat and Determine Cost of Therapy With Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction (TACTICS-TIMI)-18 trial who were randomized to the invasive strategy, had angiographic evaluation, and baseline determination of troponin I. The design of TACTICS-TIMI-18 has been previously described (9).

Troponin testing. Cardiac troponin I (cTnI) was measured using the ACS:180 Chemiluminescensce troponin I Immunoassay (Bayer Diagnostics, Tarrytown, New York). This assay is an automated system using a two-site sandwich immunoassay and direct chemoilluminescense technology.
The manufacturer reports a lower limit of detection of 0.03 ng/ml. The total imprecision determined in the core laboratory was characterized by a coefficient of variation of 10% at 0.4 ng/ml, 15% at 0.2 ng/ml, and 20% at 0.1 ng/ml. On the basis of our prior work with this assay, the threshold used to define a positive cTnI test was 0.1 ng/ml (10,11).

**B-type natriuretic peptide (BNP) and C-reactive protein testing (CRP).** Blood samples for BNP and CRP were obtained at enrollment in citrated tubes, and plasma was isolated within 60 min of acquisition. Aliquots for BNP testing were shipped frozen to Biosite Inc. (San Diego, California), where they were thawed and analyzed using an established immunoassay by personnel blinded to clinical outcomes. The decision limit of 80 pg/ml was prespecified based on previous work with this assay (12); CRP levels were measured with the BN II Nephelometer (Dade-Behring, Deerfield, Illinois), and a prespecified decision limit of 15 mg/l was used (13).

**Angiographic analysis.** Only patients who were assigned to the invasive arm with early coronary angiography (between 4 and 48 h after randomization) are included in this analysis. Patients were determined to have significant angiographic CAD if they had ≥50% stenosis in any of their coronary arteries as assessed by the local study investigators. There were five patients who had no stenoses ≥50% but underwent percutaneous coronary intervention during the index hospitalization and were excluded from the present analysis. Investigators were not made aware of the patients’ troponin status.

**Statistical analysis.** Baseline demographics and electrocardiographic characteristics were compared between groups using Pearson’s chi-square test or Fisher exact test (if n < 5) for categorical variables and Student t test or analysis of variance for continuous variables. Continuous biomarker data are described as both median and mean values ± SD and were compared using the nonparametric Wilcoxon rank-sum test (for two-way comparisons) or Kruskal-Wallis test (for four-way comparisons). A p value of ≤0.05 was considered statistically significant. All analyses were performed using STATA v8.0 (STATA Corp., College Station, Texas).

### Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ACS</td>
<td>= acute coronary syndromes</td>
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<tr>
<td>BNP</td>
<td>= B-type natriuretic peptide</td>
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<tr>
<td>CAD</td>
<td>= coronary artery disease</td>
</tr>
<tr>
<td>CRP</td>
<td>= C-reactive protein</td>
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<tr>
<td>cTnI</td>
<td>= cardiac troponin I</td>
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<tr>
<td>TACTICS-TIMI</td>
<td>= Treat Angina With Aggrastat and Determine Cost of Therapy With Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction</td>
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**RESULTS**

**Baseline characteristics.** Baseline clinical characteristics of the study patients are shown in Table 1. Of the 895 patients who underwent angiography, 542 (61%) had elevated troponin values, and 510 (94%) of the patients with elevated troponin had evidence of significant angiographic CAD. Of the remaining 353 patients with negative troponin, 278 (79%) had evidence of significant CAD, whereas 75 (21%) did not. As shown in Table 1, there were no differences in smoking status, congestive heart failure, or renal function among the four groups.

When comparing TnI-positive patients with angiographic CAD to those without CAD, patients with elevated troponin and CAD were more likely to have a history of diabetes (p = 0.034), hypertension (p = 0.062), and hypercholesterolemia (p < 0.001). Similarly, TnI-positive patients with CAD were more likely to be white (p < 0.001) and have ST-segment depression on the initial electrocardiogram (p = 0.009). The TnI-positive patients without angiographic CAD were more likely to be females than males (p = 0.017).

**Troponin, BNP, and CRP.** The median TnI level in patients with CAD (n = 788) was 0.71 ng/ml (interquartile range 0.02 to 5.7 ng/ml), compared with 0.02 ng/ml (interquartile range 0 to 0.24 ng/ml) in patients without CAD (n = 107, p < 0.0001). Table 2 shows baseline BNP and CRP levels in the four groups of patients. There were statistically significant differences in the median BNP and CRP levels between the four groups, and in the percentage of patients with BNP levels >80 pg/ml and CRP >1.5 mg/dl. Troponin-positive patients with and without angiographic stenosis had similar BNP and CRP measurements. Both BNP and CRP levels were significantly higher in TnI-positive patients without CAD compared with TnI-negative patients without CAD (p < 0.0001).

**Six-month outcome by TnI status and CAD.** As shown in Table 3, the rate of death, reinfarction, or readmission for ACS was 15.5% for troponin-positive patients with CAD, 20.1% in troponin-negative patients with CAD, 6.3% in troponin-positive patients without CAD, and 2.7% in troponin-negative patients without CAD (p < 0.001). There was no significant difference in outcome between troponin-positive patients with CAD compared with those without CAD (p = 0.20). We then tested for interaction between troponin level and CAD for the composite outcome at six months. There was no significant interaction (odds ratio 3.35, p = 0.246). Figure 1 shows the Kaplan-Meier death or reinfarction-free survival curve at six months for the four study groups. The rate of death or reinfarction was 8.6% in patients with positive troponin and CAD compared with 5.8% in troponin-negative patients with CAD, 3.1% in troponin-positive patients without CAD, and 0% in troponin-negative patients without CAD (p = 0.012). Troponin I positivity without CAD (odds ratio
15.7, 95% confidence interval 2.05 to 120.7, p = 0.008), troponin I positivity with CAD (odds ratio 11.6, 95% confidence interval 1.48 to 90.2, p = 0.019), and gender (odds ratio 0.51, 95% confidence interval 0.32 to 0.81, p = 0.005) were all independently associated with outcome on multivariate analysis for the triple composite end point. A multivariate analysis could not be done for death or reinfarction alone because there were no events in the troponin-negative no CAD group.

**Six-month outcome by CAD and positive markers.** The incidence of death, MI, or rehospitalization according to the presence of positive markers or CAD is shown in Table 4. There was an incremental worsening in outcome among the four groups. The rate of death or reinfarction was 0% in patients with all markers negative and no CAD, 2.1% in patients with any marker positive and no CAD, 5.4% in patients with all markers negative and CAD, and 8.6% in patients with any marker positive and CAD (p = 0.023).

**DISCUSSION**

We have previously demonstrated the strong prognostic value of cardiac troponin in patients with high clinical suspicion for non–ST-segment elevation ACS (14). The present study demonstrates that, in the important group of patients presenting with symptoms of ACS who were later found to not have angiographically significant CAD, the presence of an elevated troponin is also associated with an adverse prognosis. This finding challenges the idea that these are “false-positive” troponin results and that these patients may be regarded as low-risk for subsequent cardiovascular events. Elevation of troponin in these patients may result from coronary atherothrombosis not evident using
standard angiography or from other ischemic and non-ischemic mechanisms.

In the current study, 6% of patients who satisfied clinical criteria for ACS and had elevated troponin early after presentation were found not to have significant angiographic coronary stenosis. Despite the absence of significant coronary stenosis, this group of patients had a 3.1% incidence of death, reinfarction, or rehospitalization for ACS at six months compared with 0% in troponin-negative patients without angiographic CAD. The readmission rate at six months for troponin-positive patients without CAD was 6.3% compared with 2.7% in troponin-negative patients without CAD. Despite that this analysis is post hoc and observational in nature, multiple in number, it is hypothesis-generating and not definitive.

Several mechanisms can be suggested to explain our findings. In this study, patients with significant CAD were only classified if they had angiographic evidence of >50% diameter stenosis. It is likely that some patients who were classified to not have significant CAD had clinically important coronary atherothrombosis (15). It is now recognized that angiography underestimates plaque burden. Other patients may have presented late after the onset of symptoms, at a time where troponins were tracking down and the degree of stenosis was less than expected. Finally, some patients with ACS and positive troponin without significant angiographic stenosis may have sustained myocardial ischemia secondary to coronary vasospasm.

In the current study, women comprised only 30% of the troponin-positive patients with CAD compared with 50% of the troponin-positive patients without CAD (p < 0.017). There has been much discussion in published reports about coronary microvascular dysfunction and its prevalence in women without significant obstructive CAD (16–18). Similarly, coronary erosions on mild coronary plaques have been described to occur more often in women (19). This phenomenon may represent another potential explanation for troponin release, increased CRP levels, and higher rate of future events without significant coronary stenosis.

Another novel finding in this study is that both BNP and CRP levels were increased in troponin-positive patients independent of whether they had significant angiographic disease or not. Several studies have shown that an elevated CRP or BNP in the setting of ACS is associated with worse prognosis (12,20). It is possible that the mechanisms leading to increased CRP and BNP in troponin-positive patients without significant angiographic CAD differ from those for patients with epicardial CAD, but still carry adverse consequences. It is conceivable that etiologies such pulmonary embolism, left ventricular or diastolic dysfunction, myocarditis, pericarditis, or arrhythmias may have led into elevated troponin in these patients with subsequent bad outcomes on

### Table 2. BNP and CRP by Presence of CAD on Catheterization and Troponin I Status on Admission

<table>
<thead>
<tr>
<th>Troponin I</th>
<th>Negative, No CAD on Cath</th>
<th>Negative, CAD on Cath</th>
<th>Positive, No CAD on Cath</th>
<th>Positive, CAD on Cath</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP (pg/ml), median and IQ_range</td>
<td>15 (0, 37) (n = 65)</td>
<td>16 (3, 39) (n = 252)</td>
<td>19 (3, 57) (n = 29)</td>
<td>38 (8, 81) (n = 454)</td>
<td>0.0001</td>
</tr>
<tr>
<td>BNP &gt;80 pg/ml (%)</td>
<td>6.2</td>
<td>11.1</td>
<td>24.1</td>
<td>25.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CRP (mg/l), median and IQ_range</td>
<td>0.46 (0.21, 1.13) (n = 75)</td>
<td>0.42 (0.17, 0.97) (n = 278)</td>
<td>0.58 (0.24, 1.59) (n = 32)</td>
<td>0.70 (0.28, 1.55) (n = 520)</td>
<td>0.0001</td>
</tr>
<tr>
<td>CRP &gt;15 mg/l (%)</td>
<td>16.0</td>
<td>18.4</td>
<td>25.0</td>
<td>35.5</td>
<td>0.063</td>
</tr>
</tbody>
</table>

**BNP** = B-type natriuretic peptide; **CAD** = coronary artery disease; **Cath** = coronary angiography; **CRP** = C-reactive protein; **IQ** = interquartile.

### Table 3. Six-Month Outcomes by Presence or Absence of CAD and Troponin I Status

<table>
<thead>
<tr>
<th>Troponin I</th>
<th>Negative, No CAD (n = 75)</th>
<th>Positive, No CAD (n = 32)</th>
<th>Negative, CAD (n = 278)</th>
<th>Positive, CAD (n = 510)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (%)</td>
<td>0</td>
<td>3.1</td>
<td>2.2</td>
<td>3.5</td>
<td>0.288</td>
</tr>
<tr>
<td>Re-MI (%)</td>
<td>0/75</td>
<td>1/32</td>
<td>6/278</td>
<td>18/510</td>
<td>5.9</td>
</tr>
<tr>
<td>Death/re-MI (%)</td>
<td>0/75</td>
<td>0</td>
<td>4.3</td>
<td>5</td>
<td>0.064</td>
</tr>
<tr>
<td>Death/re-MI (%)</td>
<td>0/75</td>
<td>3.1</td>
<td>5.8</td>
<td>8.6</td>
<td>0.012</td>
</tr>
<tr>
<td>Death/re-MI (%)</td>
<td>0/75</td>
<td>1/32</td>
<td>16/278</td>
<td>44/510</td>
<td>0.002</td>
</tr>
<tr>
<td>Rehospitalization for ACS (%)</td>
<td>2.7</td>
<td>3.1</td>
<td>15.8</td>
<td>10.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Death, re-MI, rehospitalization</td>
<td>2.7</td>
<td>6.3</td>
<td>20.1</td>
<td>15.5</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**ACS** = acute coronary syndromes; **CAD** = coronary artery disease; **MI** = myocardial infarction.
follow-up. It is possible that some troponin-positive patients without angiographic CAD, in particular those with increased BNP, may have suffered from other conditions resulting in acute increases in ventricular wall stress, such as non-ischemic cardiomyopathy, worsening heart failure, or pulmonary embolism (21,22).

A graded relationship between baseline troponin levels in patients with ACS and death upon intermediate follow-up has been established (23). We have now shown that ACS patients with CAD have the greatest risk for adverse outcomes, whereas patients with suspected ACS and elevated troponin but without CAD have an intermediate risk for recurrent cardiovascular events. As such, these findings underscore the notion that elevated levels of troponin in patients with suspected ACS without significant CAD (sometimes labeled as “false-positives”) are the result of myocardial injury, and that these patients are candidates for aggressive preventive therapies. The interventions offered must be guided by a clinical assessment of the probable cause of myocardial injury.

**Study limitations.** The analysis in the current study is retrospective in nature, and the study population comes from a clinical trial dataset that focused on lower-risk patients and excluded patients with renal insufficiency and other high-risk features. Troponin data were available at baseline only. The number of patients with positive troponin without CAD was small compared with the overall number of patients enrolled in the study, and, therefore, the results should be interpreted with caution. However, a similar analysis performed among patients enrolled in the TIMI-IIIB study yielded similar outcomes. Investigator-determined coronary stenosis is subjective and not very reproducible. Angiographic CAD is not an accurate assessment of underlying atherosclerosis, especially if including up to 50% stenosis. Our study was not designed to provide insight into the specific mechanisms resulting in myocardial injury.

Table 4. Six-Month Outcomes by Presence or Absence of CAD and Marker Status (Troponin I, BNP, and CRP)

<table>
<thead>
<tr>
<th>Marker Status</th>
<th>Death (%)</th>
<th>Re-MI (%)</th>
<th>Death/Re-MI (%)</th>
<th>Rehospitalization for ACS (%)</th>
<th>Death, re-MI, rehospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Markers Negative, No CAD (n = 53)</td>
<td>0.328</td>
<td>0.098</td>
<td>0.023</td>
<td>0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Any Marker Positive, No CAD (n = 48)</td>
<td>1.6</td>
<td>9.8</td>
<td>5.4</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>All Marker Negative, CAD (n = 185)</td>
<td>3.7</td>
<td>5.8</td>
<td>8.3</td>
<td>34/590</td>
<td>94/590</td>
</tr>
<tr>
<td>Any Marker Positive, CAD (n = 590)</td>
<td>22/590</td>
<td>34/590</td>
<td>51/590</td>
<td>62/590</td>
<td>94/590</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndromes; BNP = B-natriuretic peptide; CAD = coronary artery disease; CRP = C-reactive protein; MI = myocardial infarction.
injury in patients with suspected ACS and no critical epicardial CAD.

Conclusions. Elevated levels of cardiac troponin in patients with suspected ACS are associated with a significantly higher risk for death or reinfarction compared with troponin-negative patients, even among those who do not have significant epicardial CAD on angiography. The mechanism of this adverse outcome requires further study.

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REFERENCES