Multimarker Approach to Risk Stratification in Non-ST Elevation Acute Coronary Syndromes

Simultaneous Assessment of Troponin I, C-Reactive Protein, and B-Type Natriuretic Peptide

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Background—In patients with acute coronary syndromes (ACS), troponin I (TnI), C-reactive protein (CRP), and B-type natriuretic peptide (BNP) each predict adverse cardiac events. Little is known, however, about the utility of these biomarkers in combination.

Methods and Results—Baseline measurements of TnI, CRP, and BNP were performed in 450 patients in OPUS-TIMI 16. Elevations in TnI, CRP, and BNP each were independent predictors of the composite of death, myocardial infarction (MI), or congestive heart failure (CHF). When patients were categorized on the basis of the number of elevated biomarkers at presentation, there was a near doubling of the mortality risk for each additional biomarker that was elevated \( (P=0.01) \). Similar relationships existed for the endpoints of MI, CHF, and the composite, both at 30 days and through 10 months. In a validation cohort of 1635 patients in TACTICS-TIMI 18, the number of elevated biomarkers remained a significant predictor of the composite endpoint after adjustment for known clinical predictors: patients with one, two, and three elevated biomarkers had a 2.1- \( (P=0.006) \), 3.1- \( (P<0.001) \), and 3.7- \( (P=0.001) \) fold increase in the risk of death, MI, or CHF by 6 months.

Conclusions—Troponin, CRP, and BNP each provide unique prognostic information in patients with ACS. A simple multimarker strategy that categorizes patients based on the number of elevated biomarkers at presentation allows risk stratification over a broad range of short- and long-term major cardiac events. (Circulation. 2002;105:1760-1763.)

Key Words: coronary disease ■ prognosis ■ myocardial infarction ■ inflammation ■ natriuretic peptides

Several new cardiac biomarkers have emerged as strong predictors of risk among patients presenting with acute coronary syndromes (ACS) and are now routinely available to clinicians. Elevated levels of troponin I (TnI), \(^1\) high-sensitivity C-reactive protein (hs-CRP), \(^2\) and B-type natriuretic peptide (BNP)\(^3\) each are associated with higher rates of death and recurrent ischemic events. Little is known, however, about the utility of these biomarkers in combination. Importantly, these 3 biomarkers assess different pathophysiological mechanisms in myocardial ischemia: elevations in troponin indicate myocardial necrosis\(^4\); CRP is a marker of inflammation\(^5\); and BNP is elevated in response to left ventricular overload.\(^6\)

We hypothesized that simultaneous assessment of all 3 biomarkers would provide complementary information and enable clinicians to stratify risk more effectively among patients with ACS. We tested this hypothesis in patients from the Orbofiban in Patients with Unstable Coronary Syndromes (OPUS)-TIMI 16 trial,\(^7\) and then validated our findings in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-TIMI 18 trial.\(^8\)

Methods

The design and results of OPUS-TIMI 16 and TACTICS-TIMI 18 have been reported.\(^7,8\) In OPUS-TIMI 16, baseline biomarkers were assessed in 450 cases and controls with non-ST elevation ACS that were randomly selected from patients assigned to the orbofiban 50 mg arm. In TACTICS-TIMI 18, baseline biomarkers were assessed in all patients for whom blood samples were available.

Blood samples were shipped to the TIMI Biomarker Core Laboratory (Children’s Hospital, Boston, Mass) for analysis. TnI was
measured using the ACS:Immunoassay (Bayer Diagnostics), and a decision limit of 0.1 ng/mL was used. Hs-CRP was measured with the BN II Nephelometer (Dade-Behring), and a decision limit of 1.5 mg/dL was used. BNP was measured using an established immunoassay (Biosite), and a decision limit of 80 pg/mL was used.

Prespecified clinical endpoints for this analysis included all-cause mortality, nonfatal MI, development of CHF, and the composite. Tests for trend were used for analysis of categorical variables. Multivariable-adjusted associations between biomarkers and endpoints were evaluated using Cox regression in OPUS-TIMI 16 and logistic regression in TACTICS-TIMI 18.

**Results**

A total of 450 patients in OPUS-TIMI 16 had assessment of all 3 biomarkers, obtained at the time of enrollment (≤72 hours after symptom onset). In a multivariable model that included each biomarker, an elevated TnI (hazard ratio [HR] 1.8, \( P=0.038 \)), CRP (HR 1.5, \( P=0.045 \)), and BNP (HR 2.1, \( P=0.001 \)) each was an independent predictor of the composite endpoint of death, MI, or CHF through 10 months. As the hazard ratios were similar for all 3 biomarkers, a simple scoring system was devised in which patients were categorized on the basis of the number of elevated biomarkers. The 30-day risk of death increased in proportion to the number of cardiac biomarkers elevated at baseline (\( P=0.014 \)), with a near doubling of the mortality risk for each additional biomarker that was elevated (Figure A). Similar relationships existed for the endpoints of MI, CHF, and the composite, both at 30 days and through 6 months (Table 1).

Adjustment for known predictors of adverse outcomes, including age, diabetes, prior MI, prior CHF, and ST depression, revealed minimal confounding. In the TACTICS-TIMI 18, 31% had elevations in none of the biomarkers, 44% had an elevation in one, 20% had elevations in 2, and 5% had elevations in all 3. A statistically significant association was observed between the number of elevated biomarkers and mortality at 30 days (\( P<0.0001 \)), again with a doubling in mortality risk for each additional biomarker that was elevated (Figure B). Similar relationships existed for the endpoints of MI, CHF, and the composite, both at 30 days and through 6 months (Table 2).

**TABLE 1. Relative Risk of Death, MI, and CHF in OPUS-TIMI 16**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>No. of Elevated Cardiac Biomarkers</th>
<th>( P ) Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0, 1, 2, 3</td>
<td>0.014</td>
</tr>
<tr>
<td>MI</td>
<td>1.0, 3.5, 4.3</td>
<td>0.0006</td>
</tr>
<tr>
<td>CHF</td>
<td>1.0, 2.7, 3.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>D/MI/CHF</td>
<td>1.0, 6.2, 8.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>10-month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1.0, 0.9, 2.3, 5.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>MI</td>
<td>1.0, 2.0, 2.3, 3.9</td>
<td>0.0004</td>
</tr>
<tr>
<td>CHF</td>
<td>1.0, 1.8, 3.9</td>
<td>0.0009</td>
</tr>
<tr>
<td>D/MI/CHF</td>
<td>1.0, 1.9, 2.5, 4.7</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**TABLE 2. Relative Risk of Death, MI, and CHF in TACTICS-TIMI 18**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>No. of Elevated Cardiac Biomarkers</th>
<th>( P ) Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1.0, 2.1, 5.7, 13.0</td>
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<tr>
<td>MI</td>
<td>1.0, 2.6, 2.9, 1.9</td>
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<tr>
<td>CHF</td>
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<tr>
<td>D/MI/CHF</td>
<td>1.0, 2.7, 3.1, 5.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>6-month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1.0, 1.4, 4.7, 12.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>MI</td>
<td>1.0, 1.8, 2.3, 1.1</td>
<td>0.06</td>
</tr>
<tr>
<td>CHF</td>
<td>1.0, 2.6, 4.7, 8.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>D/MI/CHF</td>
<td>1.0, 2.0, 3.2, 4.4</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

\( D \) indicates death; MI, myocardial infarction; and CHF, congestive heart failure.
18 validation data set, patients with 1, 2, and 3 elevated biomarkers had a 2.1- (P=0.006), 3.1- (P<0.001), and 3.6- (P=0.001) fold increase in the risk of the composite endpoint by 6 months (Table 3).

**Discussion**

In more than 2000 patients with non-ST elevation ACS from 2 contemporary clinical trials, we found TnI, CRP, and BNP each provided independent and incremental prognostic information. Using prospectively defined cutoffs and categorizing patients by the number of elevated cardiac biomarkers, we found that simultaneous assessment of these 3 pathobiologically diverse biomarkers at the time of presentation enabled powerful prediction of a patient’s risk of death, MI, and CHF both at 30 days and at ≥6 months.

Just 10 years ago, a discussion of cardiac biomarkers was limited to CK-MB, aspartate aminotransferase, and lactate dehydrogenase. These enzymes are released in the setting of myonecrosis and thus were used as tools for the diagnosis of myocardial infarction. In the intervening years, however, several new cardiac biomarkers were developed that provided insight into the pathobiology and prognosis of ACS.

Troponin I and T are more sensitive and specific markers of myocyte necrosis than CK-MB and even minor elevations convey prognostic information beyond that obtained from measuring CK-MB. CRP has been used primarily as a marker of systemic inflammation. It is now appreciated, however, that inflammation also plays a central role in atherosclerosis and its complications. Thus, CRP may not only reflect the degree of underlying inflammation predisposing to atherosclerosis, but may also play a direct role in promoting plaque rupture and thrombosis. BNP, part of the neurohormonal axis, is elevated in the setting of left ventricular overload. Recently, BNP levels have been shown to be elevated in ACS, even in the absence of infarction. As ischemia may lead to a transient decrease both in systolic function and in compliance, elevations in BNP may reflect not only the underlying impairment in left ventricular function, but also the severity of the acute ischemic insult.

Several years ago, a multiaxis framework was proposed in order to more completely appreciate the etiology of unstable angina. Given that each of these markers appears to reflect a unique axis in the pathobiology of ACS, it is not surprising that simultaneous assessment of all 3 yields independent and complementary prognostic information. By using standard, widely available assays and a simple scoring system, our multimarker approach enables clinicians to rapidly stratify patients across a 5-fold range of risk for adverse cardiac outcomes. Even after adjustment for traditional clinical predictors of adverse events, the prognostic value of our multimarker approach remained highly significant.

A potential limitation to this approach is the loss of quantitative information. For all 3 biomarkers, it has been shown that higher levels portend correspondingly greater risk. Using binary cutoffs, however, enables clinicians to integrate data rapidly from all 3 biomarkers into a simple scoring system without the need for computational support. It should also be acknowledged that elevations in each biomarker may confer different relative risks for individual components of the composite endpoint. However, viewed as a whole, the biomarkers offer complementary information and provide powerful prognostic ability for a clinically meaningful composite endpoint.

In conclusion, our findings suggest that simultaneous assessment of troponin, CRP, and BNP in acute coronary syndromes provides unique prognostic information. Using a simple multimarker strategy in which patients are categorized based on the number of elevated biomarkers, clinicians can risk stratify patients over a broad range of short- and long-term major cardiac events.

**Acknowledgments**

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**References**


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