Differential Expression of Cardiac Biomarkers by Gender in Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction

A TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction 18) Substudy

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Background—Diagnosis of coronary artery disease in women is more difficult because of lower specificity of symptoms and diagnostic accuracy of noninvasive testing. We sought to examine the relationship between gender and cardiac biomarkers in patients with unstable angina (UA)/non–ST-segment elevation myocardial infarction (NSTEMI).

Methods and Results—In the TACTICS-TIMI 18, OPUS-TIMI 16, and TIMI 11 studies, baseline samples were analyzed in the Thrombolysis In Myocardial Infarction (TIMI) biomarker core laboratory. We examined the relationship between gender and elevated biomarkers. Of 1865 patients from TACTICS-TIMI 18, 34% were women. Fewer women had elevated creatine kinase-MB or troponins, whereas more had elevated high-sensitivity C-reactive protein or brain natriuretic peptide. Presence of ST-segment deviation and TIMI risk scores were not significantly different. This pattern was confirmed in TIMI 11 and OPUS-TIMI 16. The prognostic value of the markers in TACTICS-TIMI 18 was similar in women and men. When a multimarker approach was examined, a greater proportion of high-risk women were identified. Marker-positive patients of both genders had improved outcome with an invasive strategy; however, marker-negative women appeared to have improved outcomes with a conservative strategy.

Conclusions—In patients with UA/NSTEMI, there was a different pattern of presenting biomarkers. Men were more likely to have elevated creatine kinase-MB and troponins, whereas women were more likely to have elevated C-reactive protein and brain natriuretic peptide. This suggests that a multimarker approach may aid the initial risk assessment of UA/NSTEMI, especially in women. Further research is necessary to elucidate whether gender-related pathophysiological differences exist in presentation with acute coronary syndromes. (Circulation. 2004;109:580-586.)

Key Words: cardiovascular diseases ■ natriuretic peptides ■ creatine kinase ■ inflammation ■ women

Coronary heart disease is the leading cause of death for women in the western world.1 Many gender differences exist among patients with coronary artery disease (CAD), including risk factor profiles, predictive characteristics of stress testing, clinical presentations, and patient outcomes in acute coronary syndromes (ACS).2-4 Diagnosis and risk assessment of CAD in women has traditionally been more difficult than in men. The sensitivity and specificity of stress testing is lower in women.5 Although not an entirely consistent finding,6 prior studies have shown that women have higher rates of in-hospital complications and risk of death after ACS than men.4,7

Cardiac biomarkers play an important role in the risk stratification and choice of treatment strategies for patients...
with ACS. Cardiac troponins, sensitive markers of myocardial necrosis, are an important component of risk stratification and are useful in the prediction of therapeutic efficacy for pharmacological and percutaneous interventions (PCI). Brain natriuretic peptide (BNP) is associated with heart failure in patients with shortness of breath and is an indicator of short- and long-term prognosis in patients with ACS. High-sensitivity C-reactive protein (hs-CRP), a measure of inflammation, provides powerful prognostic information for the development of cardiovascular events in men and women. hs-CRP also predicts outcome in patients with ACS or those undergoing PCI. A multimarker approach to the evaluation of ACS has demonstrated that these markers provide independent, complementary information regarding prognosis of patients presenting with a spectrum of ACS.

Because of the differences in presentation between men and women and reliance on cardiac biomarkers for risk stratification of patients with ACS, we examined the relationship between gender and cardiac biomarkers in patients enrolled in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-TIMI 18 study.

Methods

The primary analysis was performed with data from TACTICS-TIMI 18, a randomized trial in patients with unstable angina (UA)/non-ST-segment elevation myocardial infarction (NSTEMI). All patients were treated with tirofiban and randomized to either an early invasive or early conservative strategy. Inclusion criteria included accelerating or prolonged (≥20 minutes) angina, eligibility for PCI, and the presence of at least 1 objective marker of ischemia. A total of 2220 patients were enrolled and followed up for 6 months. Baseline blood samples were drawn in 1865 patients for biomarker analysis. Cardiac markers, including troponin I (TnI; Roche Diagnostics), troponin I (TnI; Bayer), hs-CRP (Dade Behring), and BNP (Biosite), were analyzed in the Thrombolysis In Myocardial Infarction (TIMI) biomarker core laboratory. Creatine kinase-MB (CK-MB) measurement was performed locally. The TIMI risk score for UA/NSTEMI was ascertained for all patients. The primary end point in the present study was the combined incidence of death, myocardial infarction (MI), and rehospitalization for ACS. Each of the components of this end point was adjudicated by an independent clinical events committee using standard TIMI definitions.

Baseline biomarkers were considered positive if above an accepted, prespecified cut point based on prior work. Specifically, cut points for positive biomarkers were 0.01 ng/mL for cardiac TnT, 0.1 ng/mL for TnI, 15 mg/L for hs-CRP, and 80 pg/mL for BNP.

No distinction was made between treatment groups because we have previously reported no treatment interaction with invasive therapy and gender. Patients were included if complete marker and outcome data were available. Comparisons were made between genders for mean levels of biomarkers and the proportion of patients presenting with biomarkers above the defined decision limits.

It was determined whether each patient had 0, 1, 2, or 3 positive biomarkers. The effect of gender was assessed with logistic regression, modeling the odds of death and MI with the number of positive biomarkers, gender, and the interaction term. Composite end-point outcomes were examined for treatment strategies. Patients were stratified by gender and presence/absence of elevated biomarkers (number of positive markers ≥1).

The possibility of unrecognized confounding in this analysis related specifically to features of TACTICS-TIMI 18 was handled with marker data from additional clinical trials of UA/NSTEMI: TIMI 11A (CRP, TnT), TIMI 11B (TnI, CK-MB), and OPUS-TIMI 16 (BNP). Details of the TIMI 11 studies have been published elsewhere; each compared unfractionated heparin to enoxaparin. Details of the OPUS-TIMI 16 trial, a randomized, placebo-controlled trial of orbofiban (oral glycoprotein IIb/IIIa inhibitor) in ACS have also been published previously. The present analysis was limited to patients with UA/NSTEMI. Baseline biomarkers were analyzed at the TIMI core laboratory for the markers listed. Identical cut points for positive markers were used.

Gender comparisons were made with respect to mean levels of cardiac biomarkers and the proportion of patients presenting with biomarkers above the defined cut points. Proportions were compared with the chi-squared test. Continuous variables were compared with the Student’s t test. Multivariable analyses were performed with logistic regression that controlled for univariate differences between genders. The association of clinical outcomes, gender, and the number of positive biomarkers was evaluated with logistic regression that included terms for the main effects and the interaction between gender and number of positive biomarkers.

Results

Elevation of Biomarkers in Women Versus Men

Baseline characteristics are reported in Table 1. Women in TACTICS-TIMI 18 were more likely to be older or hypertensive. Men were more likely to be smokers and to have

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n=1227)</th>
<th>Women (n=638)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>60.2</td>
<td>64.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>25th Percentile</td>
<td>52</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>75th Percentile</td>
<td>69</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>88.2</td>
<td>75.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race, % white</td>
<td>79.1</td>
<td>75.2</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>62.0</td>
<td>72.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>61.0</td>
<td>64.1</td>
<td>NS</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>29.8</td>
<td>24.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Family history of CAD, %</td>
<td>45.6</td>
<td>41.1</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>26.3</td>
<td>30.4</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic renal insufficiency, %</td>
<td>1.8</td>
<td>1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>41.8</td>
<td>34.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Prior CHF, %</td>
<td>6.5</td>
<td>8.7</td>
<td>NS</td>
</tr>
<tr>
<td>Prior CABG, %</td>
<td>24.3</td>
<td>16.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior PTCA, %</td>
<td>28.4</td>
<td>28.5</td>
<td>NS</td>
</tr>
<tr>
<td>Prior CAD, %</td>
<td>60.7</td>
<td>53.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Prior aspirin use, %</td>
<td>67.9</td>
<td>66.5</td>
<td>NS</td>
</tr>
<tr>
<td>ST-segment deviation, %</td>
<td>37.8</td>
<td>39.5</td>
<td>NS</td>
</tr>
<tr>
<td>TIMI risk score, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>25</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>3–4</td>
<td>59</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>5–7</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Biomarker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB, ng/mL</td>
<td>16.0±0.95</td>
<td>9.5±0.92</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TnT, ng/mL</td>
<td>0.39±0.03</td>
<td>0.28±0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>TnI, ng/mL</td>
<td>6.3±0.4</td>
<td>4.1±0.5</td>
<td>0.0018</td>
</tr>
<tr>
<td>hs-CRP, mg/dL</td>
<td>1.32±0.07</td>
<td>1.59±0.12</td>
<td>0.043</td>
</tr>
<tr>
<td>BNP, ng/mL</td>
<td>46.1±2.4</td>
<td>68.4±4.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure.
prior MI, CABG, or documented CAD. There was no significant difference in ST-segment deviation or TIMI risk score. For patients who underwent coronary angiography, women were more likely to have no significant CAD (17% versus 9%, \( P < 0.0001 \)). Women had lower CK-MB (\( P < 0.001 \)), TnT (\( P = 0.01 \)), and TnI (\( P = 0.0018 \)) levels but higher hs-CRP (\( P = 0.043 \)) and BNP (\( P < 0.0001 \)). Similar results were seen when cut points were used (Figure 1A).

In multivariable analyses that controlled for age, weight, hypertension, hypercholesterolemia, smoking, aspirin use, and prior MI, CABG, PTCA, or CAD, women were less likely to have positive TnT (OR 0.53 [95% CI 0.43 to 0.68]).
and TnI (OR 0.58 [95% CI 0.46 to 0.73]). Women were more likely to have elevated hs-CRP (OR 1.49 [95% CI 1.16 to 1.92]) when controlling for age, weight, hypertension, diabetes mellitus, smoking, race, renal insufficiency, and history of congestive heart failure, MI, CAGB, PCI, or any known CAD. Women were also more likely to have elevated BNP (OR 1.33 [95% CI 1.02 to 1.75]) when controlling for age, hypertension, prior CAD, and chronic renal failure. However, although the addition of adjustment for history of congestive heart failure attenuated this association (OR 1.28 [95% CI 0.97 to 1.67]) only slightly, with the addition of this covariate, the association was no longer statistically significant.

Markers were evaluated in additional ACS trials (Figure 1B). Men were more likely to have elevated CK-MB (TIMI 11B, \( P < 0.005 \)), TnI (TIMI 11B, \( P < 0.002 \)), and TnT (TIMI 11A, \( P = 0.001 \)), and women were more likely to have elevated hs-CRP (TIMI 11A, \( P = 0.095 \)) and BNP (OPUS-TIMI 16, \( P = 0.039 \)). When combined across trials (Figure 2), these results persisted.

### TABLE 2. Interaction Between Gender, Positive Markers, and Outcome

<table>
<thead>
<tr>
<th>Death</th>
<th>OR for Interaction</th>
<th>95% CI for Interaction</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>TnI +</td>
<td>1.33</td>
<td>0.4–4.4</td>
<td>0.46</td>
</tr>
<tr>
<td>TnT +</td>
<td>2.1</td>
<td>0.54–7.7</td>
<td>0.29</td>
</tr>
<tr>
<td>CRP +</td>
<td>1.6</td>
<td>0.54–5.0</td>
<td>0.38</td>
</tr>
<tr>
<td>BNP +</td>
<td>2.1</td>
<td>0.64–7.2</td>
<td>0.22</td>
</tr>
</tbody>
</table>

### Elevated Biomarkers and Outcome

Elevated biomarkers predicted adverse outcomes in TACTICS-TIMI 18 in both genders. Overall, cardiac TnI and TnT predicted death or MI (TnI, OR 3.9; TnT, OR 4.0; \( P < 0.001 \) for each) and the composite outcome of death, MI, or readmission for ACS (OR, 2.1 and 1.8, respectively; \( P < 0.005 \)). Elevated hs-CRP was a significant predictor of death or MI (OR 1.9, \( P < 0.03 \)) but not for the composite end point. Elevated BNP predicted all-cause mortality (OR 3.1, \( P < 0.03 \)).

A significant gender interaction did not exist between positive markers and the prediction of death or death and MI (Table 2), which suggests that the predictive value of positive biomarkers is similar in men and women. When MI was examined separately, women with positive troponins were more likely to have recurrent MI at 180 days (OR for TnI interaction of gender and positive marker was 0.30 [95% CI 0.10 to 0.86], \( P = 0.046 \); for TnT, OR was 0.35 [95% CI 0.11 to 1.13], \( P = 0.08 \). There was no significant gender interaction for BNP and all-cause mortality (OR 2.1 [95% CI 0.63 to 7.2], \( P = 0.22 \)) or for hs-CRP and death or MI (OR 0.97 [95% CI 0.45 to 2.06], \( P = 0.93 \)).

With a multimarker approach in TACTICS-TIMI 18 (Table 3), more patients were identified as having increased risk (men 73%, women 63% with positive markers) than when CK-MB (men 42%, women 29%) or troponins (men 63%, women 54%) were used. When examined by gender, an increasing number of

### TABLE 3. Multimarker Approach Compared by Gender

<table>
<thead>
<tr>
<th>No. of Positive Biomarkers</th>
<th>Women (n=549)</th>
<th>Men (n=1088)</th>
<th>Overall (n=1637)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>31.5</td>
<td>27.3</td>
<td>28.7</td>
</tr>
<tr>
<td>1</td>
<td>38.4</td>
<td>48.4</td>
<td>45.1</td>
</tr>
<tr>
<td>2</td>
<td>23.5</td>
<td>18.8</td>
<td>20.4</td>
</tr>
<tr>
<td>3</td>
<td>6.6</td>
<td>5.4</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Values are percentages.
positive markers conferred an increasing risk of death or MI at 180 days (Figure 3; males, \( P_{\text{trend}} < 0.0001 \); females, \( P_{\text{trend}} = 0.009 \)). Neither a significant difference between men and women nor a gender interaction (\( P = 0.42 \)) existed.

**Invasive Versus Conservative Strategy**

Elevated cardiac biomarkers were associated with a benefit from invasive strategy in both genders (Figure 4). For men with at least 1 positive biomarker, 22.1% of patients assigned to the conservative strategy reached the primary end point compared with 14.2% assigned to the invasive strategy (OR 0.58 [95% CI 0.41 to 0.82]). Similarly, 25.8% of women assigned to the conservative strategy versus 17.5% assigned to the invasive strategy reached the primary end point (OR 0.61 [95% CI 0.38 to 0.96]). In both genders, this difference was predominantly mediated by troponins, because there was no statistical differ-
ence in outcomes by treatment strategy for troponin-negative patients who were BNP or CRP positive (women, OR 0.54 [95% CI 0.12 to 16.6]; men, OR 1.12 [95% CI 0.36 to 3.5]). In men without marker elevation, no significant difference existed by strategy for the primary end point (OR 1.2 [95% CI 0.64 to 2.25]). However, in women without marker elevation, the invasive strategy was associated with an increased risk of death, MI, or hospitalization for ACS (OR 3.1 [95% CI 1.17 to 8.31]). In both genders, when all markers were negative, there were nonsignificant trends toward increased death or MI in the invasive group (Figure 4; women, OR 1.36 [95% CI 0.22 to 8.4]; men, OR 1.38 [95% CI 0.45 to 4.2]).

Discussion
Several important findings regarding the effect of gender on the profile of cardiac biomarkers in patients presenting with UA/NSTEMI have emerged from this analysis. Women were less likely to have biomarker evidence of myocyte necrosis, elevated CK-MB, or troponins but more likely to have elevations in newer markers used for risk stratification in ACS: hs-CRP and BNP. Despite differences in biomarker profiles, individual markers were predictive of outcome in both genders. A significant gender interaction did not exist between biomarkers in the prediction of death or death and MI, although troponins appeared to predict the risk of recurrent MI in women more than men.

The use of a multimarker panel identified more patients, especially more women, at elevated risk than a strategy that used CK-MB or cardiac troponins. Because the diagnosis and risk stratification of ACS is more difficult in women, the present findings suggest that a broader, multimarker approach may be appropriate for risk stratification of women with ACS.

Marker elevation had different implications for response to treatment. As reported previously, both women and men had an overall benefit from an invasive treatment strategy, with no gender interaction with treatment strategy. From previous reports in TACTICS-TIMI 18, patients with positive troponins benefited from an early invasive strategy, and no significant benefit was seen with negative troponins. No group had been previously demonstrated to have significantly worse outcomes with the invasive strategy. In the present analysis, women without positive biomarkers were more likely to have death, MI, or rehospitalization for ACS with the invasive strategy.

Previous studies have examined the relationship of selected cardiac biomarkers and gender. In the FRISC II trial, women had lower median levels of cardiac TnT than men and were less likely to have a TnT level above the limit for MI.

In population studies, there have been reports of gender and age differences in hs-CRP and BNP. Levels of hs-CRP are higher in women in healthy populations and in patients with stable angina. BNP levels are also higher in older subjects and healthy women than in men. Debate continues about age- and gender-specific decision limits for biomarker elevation.

Possible Mechanisms of Gender Differences in Biomarker Levels
Gender differences in pathophysiological mechanisms may have existed among the subjects. More men may have presented with atherosclerotic plaque rupture, platelet-rich thrombus, and microembolization (accounting for elevated troponins), and more women may have presented with small-vessel coronary disease, vascular inflammation, or congestive heart failure (resulting in elevated levels of CRP and BNP). This hypothesis is supported by the higher proportion of women without significant epicardial coronary lesions seen on angiography. Despite this, each patient who was enrolled in TACTICS-TIMI 18 was judged by the enrolling physician to have ACS. That patterns of markers were similar across ACS trials makes it less likely that this observation is related to unaccounted patient variables in TACTICS-TIMI 18.

It is also possible that women were a lower-risk population, accounting for lower troponins. Elevations in BNP and hs-CRP may have been related to higher gender-specific baseline levels. However, the TIMI risk scores for UA/NSTEMI were nearly identical, which suggests that there was a similar profile for ACS risk between genders. The possibility that elevated hs-CRP and BNP in women were purely related to gender differences in the baseline distribution of these markers is reduced by the lack of statistical interaction between positive marker and clinical end points. Although these cutoffs have been derived from predominantly male populations, this lack of interaction supports the use of a single biomarker cut point for both genders in this analysis.

Study Limitations
This type of analysis is not designed to answer pathophysiological questions, such as differential release of cardiac markers from cardiac muscle, differential levels of platelet aggregation, platelet embolization, response of the myocardium to ischemia or wall stress, differences in inflammation, inflammatory responses to ischemia, or differential clearance of cardiac markers after release, although any of these mechanisms could account for dissimilar patterns of marker elevation. Furthermore, the present analysis was performed among patients with a high probability of ACS, and results should not be generalized for diagnosis or risk stratification of patients presenting with atypical chest pain.

In the present analysis, as in clinical practice, single cut points were used to determine whether biomarkers were elevated; however, the clinician should recognize that additional information can be obtained from examining biomarker levels as a continuum, and prognostic information can be obtained even within the normal range. The use of a combination of multiple biomarkers in the present analysis is a convenient, although simplified way of integrating disparate information that is provided by individual markers. Different biomarkers are related to different pathophysiological processes, with troponins being markers of necrosis, natriuretic peptides being markers of hemodynamic stress, and hs-CRP being a marker of inflammation. Studies have shown that different markers offer different prognostic information, with cardiac troponins being predominantly predictive of reinfarction and natriuretic peptides being predictive of mortality. Increasing knowledge of the individual predictive characteristics of biomarkers may someday allow for biomarker profiles of individual patients to assess the contribution of different pathophysiological mechanisms and to personalize prognosis. The present analysis highlights the principle that different subsets of patients (in this case, by gender) may have different biomarker patterns.
Conclusions

Despite gender differences in cardiac markers in the present study, elevated markers predicted adverse outcomes in both men and women with ACS. Recognition of different patterns of elevated markers and the gender neutrality of a multmarker strategy could have an impact on the evaluation and management of patients with ACS. These data suggest that a broader, multimarker approach to risk stratification should be applied to women presenting with a high probability of ACS, with measurement of troponins, hs-CRP, and BNP as an adjunct to clinical data. Furthermore, if these data are corroborated in future studies, the multimarker approach may help to identify a subgroup of women (with no elevated markers) of sufficiently low risk who may benefit from an initial conservative strategy. Further research is necessary to elucidate gender-related pathophysiological differences in ACS.

Acknowledgments

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References

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