Use of Guidelines-Recommended Management and Outcomes Among Women and Men With Low-Level Troponin Elevation
Insights From CRUSADE

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Background—Troponin elevation above the upper limit of normal (ULN) is diagnostic of myocardial infarction, but interpretation of “gray-zone” troponin elevations (1 to 1.5 × ULN) remains uncertain. Using the CRUSADE database, we explored relationships between sex and treatment and outcomes among patients with troponin 1 to 1.5 × ULN.

Methods and Results—We compared treatment and outcomes among women and men using logistic generalized estimating equation method. Overall, 5049 of 85 671 (5.9%) non–ST-segment elevation acute coronary syndromes patients (2156 women, 2893 men) had troponin 1 to 1.5 × ULN within 24 hours of presentation. Compared with troponin >1.5 × ULN, “gray-zone” patients less often received all guidelines-indicated acute (mean composite score, 63% versus 72%) and discharge therapies (mean composite score, 73% versus 78%), but received them more frequently than patients with troponin <1 × ULN (mean composite scores, 58% acute and 67% discharge). Among “gray-zone” patients, acute and discharge therapy use was similar between women and men, except acute aspirin (adjusted odds ratio, 0.80 [95% CI, 0.65 to 0.98]) and discharge angiotensin-converting enzyme inhibitors (adjusted odds ratio, 0.77 [95% CI, 0.67 to 0.88]). “Gray-zone” patients had lower mortality (2.3%) than the >1.5 × ULN (4.5%) group but higher than the <1 × ULN group (1.1%). Outcomes were similar among “gray-zone” women and men (adjusted odds ratios: death, 0.88 [95% CI, 0.58 to 1.35]; death/myocardial infarction, 0.77 [95% CI, 0.55 to 1.06]; transfusion, 1.04 [95% CI, 0.85 to 1.27]).

Conclusions—Patients with non–ST-segment elevation acute coronary syndromes and low-level troponin elevations had lower overall risk and received less aggressive guidelines-based treatment than those with greater troponin elevations, but treatment patterns were largely similar by sex across troponin elevation groups. (Circ Cardiovasc Qual Outcomes. 2009;2:199-206.)

Key Words: troponin ▪ acute coronary syndrome ▪ outcomes

The relationship between troponin positivity and clinical outcomes among patients with non–ST-segment elevation acute coronary syndromes (NSTE ACS) is clear,1,2 and the extent of risk is related to the degree of troponin elevation above the upper limit of normal (ULN). In addition, studies have highlighted that treatment benefit from several intensive therapeutic interventions for patients with NSTE ACS is enhanced among troponin-positive compared with troponin-negative patients, and failure to use guidelines-recommended treatment in patients deemed “high risk” based on troponin status is associated with higher mortality.3-9 Particularly for the small-molecule glycoprotein IIb/IIIa inhibitors, the relationship between troponin elevation and treatment effect appears to be greatest among patients with low-level elevations in the 1 to 2 × ULN range.7,10 The universal definition of myocardial infarction (MI) places increased emphasis on low-level troponin elevation by declaring that, in the context of ischemic symptoms, any troponin elevation above the 99th percentile of a reference control population should be regarded as MI,11 potentially increasing the pool of patients appropriate for treatment. However, for a number of reasons related to suboptimal assay precision and diagnostic specificity for many assays, the validity of such low-level elevations in clinical practice is frequently questioned, yielding uncertainty regarding treatment.

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We and others have previously reported on treatment disparities among women and men with NSTE ACS but posited that where greater uncertainty in diagnosis exists—such as with interpretation of low-level troponin elevation—these disparities might be even more dramatically manifest. Therefore, we used the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) National Quality Improvement Initiative database to explore the relationship between sex and use of guidelines-recommended acute and discharge interventions and in-hospital outcomes among women and men with low-level (1 to 1.5× ULN) troponin elevation. To place these “gray-zone” findings in better context, we also explored differences between women and men within cohorts with normal troponins (<1× ULN) and large troponin elevations (>1.5× ULN).

WHAT IS KNOWN
- “Grey-zone” troponin elevations (1–1.5× ULN) often lead to uncertainty among physicians in the treatment of NSTE ACS.
- Treatment disparities in use of guidelines-recommended ACS therapies have been observed.

WHAT THE STUDY ADDS
- While use of guidelines-recommended therapies was lower in the “grey-zone” group compared with larger troponin elevations, treatment was largely similar between women and men within this group.
- Regardless of level of troponin elevation, women consistently less often received an early invasive strategy compared with men.
- Standardized approaches need to be developed that better identify those patients with troponin elevations and NSTE ACS who will benefit most from evidence-based therapies.

Methods

Patient Population
The starting population for our analyses comprised 165,498 patients with NSTE ACS enrolled in CRUSADE at 550 US hospitals from its inception in 2001 through 2005. Participation in CRUSADE was approved by the institutional review board of each participating institution. The criteria for inclusion in CRUSADE have been described in detail previously. Briefly, patients at participating hospitals were enrolled in CRUSADE if they had ischemic symptoms lasting ≥10 minutes within 24 hours of presentation and had at least one of the following: ST-segment depression >0.5 mm, transient ST-segment elevation of 0.5 to 1.0 mm lasting <10 minutes, or positive cardiac markers (elevated troponin T or I or creatine kinase-MB >ULN for the local laboratory). Because we were interested in the association of the magnitude of peak troponin elevation within the first 24 hours with use of acute therapies (guidelines-recommended medications administered within the first 24 hours of hospitalization and early invasive strategy within 48 hours of presentation) and in-hospital clinical events by sex, we excluded patients with missing information for time of peak troponin (n=28,112), missing peak troponin value or ULN (n=1082), time from arrival to peak troponin >24 hours (n=18,267), peak troponin recorded after hospitalization (n=658), patients who transferred in or out to other hospitals (n=31,437), and missing sex information (n=271), leaving 85,671 patients. From this group, we identified 2156 of 35,916 (6.0%) women and 2893 of 49,755 (5.8%) men with peak troponin ratios 1 to 1.5× ULN within 24 hours of presentation. To best reflect conditions of clinical decision-making, we elected to define troponin elevation relative to the ULN set by the hospital for its specific assay, as there is substantial variability between troponin assays, both among troponin T and I as well as different manufacturers of troponin I assays.

Baseline demographics and clinical history, presenting clinical characteristics, in-hospital laboratory parameters, medical and procedural management, and clinical outcomes were collected using standardized data collection forms. Acute use of medications was defined as within the first 24 hours of hospitalization; use of an early invasive strategy was defined as receiving cardiac catheterization within 48 hours. In-hospital MI was investigator-reported and defined according to the specific instructions provided with the data collection forms (see online-only Data Supplement). Rates of transfusion reflect the use of any red blood cell (RBC) transfusion.

Statistical Methods
Baseline characteristics, use of treatments and interventions, and clinical outcomes were summarized as medians with interquartile ranges for continuous variables and percentages for categorical variables.

To account for differences in baseline characteristics and within-hospital clustering, we determined adjusted associations of sex with use of guidelines-recommended treatments and interventions and in-hospital outcomes using logistic generalized estimating equation method as described previously. Our model adjusted for patient-specific variables (age, body mass index [BMI], race, family history of coronary disease, hypertension, recent/current smoker, hypercholesterolemia, prior MI, prior percutaneous coronary intervention [PCI], prior coronary bypass graft surgery, history of heart failure, history of stroke, renal insufficiency, ST-segment depression, transient ST-segment elevation, positive cardiac markers, signs of heart failure, heart rate, systolic blood pressure, insurance status, physician specialty) and hospital characteristics (total number of hospital beds; region of the country; availability of cardiac catheterization, PCI, or bypass surgery; and type of hospital—academic or nonacademic). Furthermore, an interaction between troponin level and sex was explored in each model.

To determine mean composite scores for use of acute and discharge therapies, we determined the number of opportunities for receiving therapies (range, 0 to 5 for both acute and discharge medications) and number of therapies received (range, 0 to 5 for both acute and discharge medications) for each eligible patient. If a specific therapy was contraindicated, it was excluded from the opportunities to receive therapy (denominator). Each patient had a composite percent rate of adherence calculated as: (received/opportunities)×100. The acute medications were aspirin, clopidogrel, β-blockers, glycoprotein IIb/IIIa inhibitors, and any heparin; discharge medications included aspirin, β-blockers, clopidogrel, angiotensin-converting enzyme inhibitors, and lipid-lowering medications (for recommended patients only).

Adjusted associations are displayed as odds ratios (ORs) with 95% CIs. A probability value <0.05 was considered significant for all tests. All analyses were performed using SAS software (version 9.1, SAS Institute).

Results

Patient Population
Of 85,671 patients, 35,916 (41.9%) were women and 49,755 (58.1%) were men. In 11.5% of women and 11.0% of men, troponin elevations were <1× ULN; 6.0% of women and 5.8% of men had troponin elevations 1 to 1.5× ULN; and
82.5% of women and 83.2% of men had troponin elevations >1.5× ULN.

Table 1 shows baseline characteristics of women and men with “gray-zone” troponin elevation (1 to 1.5× ULN), as well as the <1× ULN and >1.5× ULN groups. Overall, compared with the >1.5× ULN group, the “gray-zone” group was younger, had higher BMI, more often had hypertension and prior MI and revascularization, but less often had renal insufficiency. They were less frequently cared for by cardiologists or in full-service hospitals. Compared with the <1× ULN troponin group, “gray-zone” patients were older and more often had a history of stroke, peripheral arterial disease,
and history or signs of heart failure. Additionally, the “gray-zone” group less often had prior revascularization.

Within the low-level troponin group, compared with men, women were older and more often had hypertension and diabetes as well as a history of heart failure, but less frequently were current/recent smokers, had prior MI, or prior revascularization. Women presented more frequently with signs of heart failure, but were less frequently cared for by cardiologists or in full-service hospitals. After adjustment, women remained less likely to be cared for by cardiologists.

A number of patients were excluded from our analysis because of missing information to determine peak troponin status within 24 hours. In general, the excluded patients were younger, more frequently male, and had less comorbidity than our study population, but slightly higher unadjusted rates of in-hospital death and death or MI (data not shown).

### Use of Guidelines-Recommended Medications and Interventions

Rates of use of guidelines-recommended therapies and interventions, with highlight for measures that are performance indicators, are displayed in Table 2 for the “gray-zone” troponin elevation groups as well as the <1× ULN and >1.5× ULN groups. Additionally, the adjusted ORs for use among women compared with men in the 1 to 1.5× ULN group are presented in the Figure. Table 3 displays adjusted ORs for use of guidelines-recommended therapies for all troponin elevation categories.

### Acute Therapies and Procedures

In general, within the “gray-zone” group, both sexes received fewer guidelines-recommended acute therapies and less use of an early invasive strategy within 48 hours than those within the >1.5× ULN group. Overall, compared with troponin >1.5× ULN, the “gray-zone” group less often received guidelines-indicated acute therapies (mean composite score 63% versus 72%) but received these therapies more frequently than did patients with troponin <1× ULN (mean composite score 58%). However, within the “gray-zone” group, application of guidelines-recommended acute therapies was statistically similar among women and men after adjustment, with the exception that women less often received aspirin acutely (OR, 0.80 [95% CI, 0.65 to 0.98]).

Although the point estimates of the adjusted ORs for glycoprotein IIb/IIIa inhibitors, any heparin use, and cardiac catheterization within 48 hours suggested lower use among “gray-zone” women than men, they did not reach statistical significance. The adjusted ORs were similar by troponin

### Table 2. Unadjusted Rates for the Use of Guidelines-Recommended Therapies and Interventions

<table>
<thead>
<tr>
<th>Troponin</th>
<th>Women (n=4115)</th>
<th>Men (n=5458)</th>
<th>Women (n=2156)</th>
<th>Men (n=2893)</th>
<th>Women (n=29 645)</th>
<th>Men (n=41 404)</th>
</tr>
</thead>
</table>
| Acute interventions, %
| Aspirin* | 91.2 | 92.4 | 91.4 | 93.4 | 93.2 | 94.6 |
| Clopidogrel | 33.7 | 37.0 | 35.8 | 39.1 | 44.0 | 50.5 |
| Glycoprotein IIb/IIIa inhibitor | 14.5 | 19.7 | 19.2 | 26.2 | 34.8 | 46.4 |
| Heparin, any | 65.0 | 71.8 | 74.9 | 78.5 | 85.0 | 87.9 |
| β-blocker | 74.0 | 75.0 | 79.8 | 81.2 | 85.0 | 86.2 |
| Cardiac catheterization <48 hours | 34.7 | 42.3 | 37.5 | 47.2 | 45.7 | 58.3 |
| Cardiac catheterization | 54.6 | 62.7 | 57.9 | 68.1 | 67.7 | 79.2 |
| PCI | 23.2 | 29.4 | 25.6 | 35.0 | 34.0 | 45.8 |
| Coronary artery bypass surgery | 5.2 | 8.5 | 6.0 | 10.8 | 8.3 | 13.2 |
| Discharge medications, %
| Aspirin* | 84.9 | 88.1 | 86.9 | 90.3 | 90.4 | 93.0 |
| Clopidogrel | 42.0 | 47.5 | 46.9 | 53.1 | 58.6 | 65.4 |
| β-blocker* | 76.0 | 77.5 | 82.2 | 84.6 | 87.8 | 89.7 |
| Angiotensin-converting enzyme inhibitor
| Overall | 47.5 | 51.1 | 54.5 | 58.9 | 59.5 | 60.9 |
| Recommended patients only* | 50.8 | 55.6 | 58.2 | 63.5 | 62.3 | 64.9 |
| Statin* | 56.6 | 64.7 | 61.6 | 68.2 | 66.1 | 74.3 |
| Any lipid-lowering agent
| Overall | 59.7 | 68.7 | 63.4 | 71.0 | 67.7 | 76.4 |
| Recommended patients only | 74.9 | 81.4 | 78.1 | 83.0 | 81.0 | 85.8 |
| Discharge recommendations, %
| Smoking cessation counseling* | 59.9 | 63.1 | 71.2 | 67.7 | 72.1 | 76.2 |
| Dietary modification | 64.8 | 69.8 | 71.0 | 72.6 | 72.3 | 78.0 |
| Cardiac rehabilitation referral* | 29.0 | 31.7 | 33.6 | 39.5 | 45.3 | 52.1 |

*Performance measure as defined by ACC/AHA 2008 Performance Measures for Adults with ST-Elevation and Non-ST-Elevation Myocardial Infarction.16
elevation category but were significant for the $<1 \times$ and $>1.5 \times$ ULN groups. In general, the point estimates of the adjusted ORs for comparisons of use of other acute therapies among women versus men were also similar by troponin elevation category. Although not measures of guidelines recommendations, any cardiac catheterization and use of revascularization were less frequent among women than men after adjustment for differences in baseline characteristics in all troponin elevation categories. Formal statistical testing confirmed a significant interaction between troponin level and sex differences in acute clopidogrel use, but interaction testing for other acute treatments was not significant.

### Discharge Therapies

As with acute therapies and procedures, patients within the “gray-zone” troponin elevation group less frequently received guidelines-recommended discharge therapies (mean composite score 73%) than those with troponin elevations $>1.5 \times$ ULN (mean composite score 78%), but they received these therapies more frequently than patients with troponin $<1 \times$

### Table 3. Adjusted ORs with 95% CIs (Women Versus Men) for the Use of Guidelines-Recommended Therapies and Interventions

<table>
<thead>
<tr>
<th>Troponin</th>
<th>Acute Interventions</th>
<th>Discharge Therapies</th>
<th>Discharge Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin</td>
<td>Aspirin*</td>
<td>Clopidogrel</td>
<td>Glycoprotein IIb/IIIa inhibitor</td>
</tr>
<tr>
<td>&lt;1.0×ULN</td>
<td>0.96 (0.81–1.13)</td>
<td>0.99 (0.91–1.08)</td>
<td>0.82 (0.75–0.90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.87 (0.74–1.01)</td>
</tr>
<tr>
<td>1.0–1.5×ULN</td>
<td>1.01 (0.89–1.14)</td>
<td>1.01 (0.89–1.14)</td>
<td>0.87 (0.74–1.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.92 (0.88–0.96)</td>
</tr>
<tr>
<td>&gt;1.5×ULN</td>
<td>0.96 (0.81–1.14)</td>
<td>0.96 (0.81–1.14)</td>
<td>0.96 (0.91–1.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.87 (0.84–0.90)</td>
</tr>
<tr>
<td></td>
<td>Cardiac catheterization &lt;48 hours</td>
<td>0.81 (0.73–0.90)</td>
<td>0.87 (0.74–1.01)</td>
</tr>
<tr>
<td></td>
<td>PCI</td>
<td>0.80 (0.70–0.90)</td>
<td>0.82 (0.70–0.96)</td>
</tr>
<tr>
<td></td>
<td>Coronary artery bypass surgery</td>
<td>0.53 (0.44–0.65)</td>
<td>0.54 (0.42–0.69)</td>
</tr>
<tr>
<td></td>
<td>0.53 (0.44–0.65)</td>
<td>0.54 (0.42–0.69)</td>
<td>0.58 (0.55–0.62)</td>
</tr>
<tr>
<td>Discharge medications</td>
<td>Aspirin*</td>
<td>0.88 (0.75–1.03)</td>
<td>0.85 (0.69–1.04)</td>
</tr>
<tr>
<td></td>
<td>0.89 (0.81–1.01)</td>
<td>0.91 (0.80–1.04)</td>
<td>0.96 (0.92–1.00)</td>
</tr>
<tr>
<td></td>
<td>0.80 (0.84–1.10)</td>
<td>0.85 (0.72–1.00)</td>
<td>0.85 (0.81–0.89)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>Overall</td>
<td>0.83 (0.76–0.92)</td>
<td>0.77 (0.67–0.88)</td>
</tr>
<tr>
<td></td>
<td>Recommended patients only*</td>
<td>0.85 (0.76–0.95)</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td></td>
<td>Statin*</td>
<td>0.83 (0.74–0.92)</td>
<td>0.93 (0.80–1.08)</td>
</tr>
<tr>
<td></td>
<td>Any lipid-lowering agent</td>
<td>Overall</td>
<td>0.79 (0.71–0.88)</td>
</tr>
<tr>
<td></td>
<td>Recommended patients only</td>
<td>0.79 (0.68–0.93)</td>
<td>0.88 (0.73–1.07)</td>
</tr>
<tr>
<td>Discharge recommendations</td>
<td>Smoking cessation counseling*</td>
<td>0.97 (0.78–1.20)</td>
<td>1.32 (0.96–1.82)</td>
</tr>
<tr>
<td></td>
<td>Dietary modification</td>
<td>0.85 (0.76–0.96)</td>
<td>1.01 (0.88–1.14)</td>
</tr>
<tr>
<td></td>
<td>Cardiac rehabilitation referral*</td>
<td>0.89 (0.76–1.04)</td>
<td>0.93 (0.82–1.06)</td>
</tr>
</tbody>
</table>

*Performance measure as defined by ACC/AHA 2008 Performance Measures for Adults with ST-Elevation and Non-ST-Elevation Myocardial Infarction.16
ULN (mean composite score 67%). Within the “gray-zone” group, there was a significant difference in use among women compared with men in adjusted analyses only for discharge use of angiotensin-converting enzyme inhibitors: overall (OR, 0.77 [95% CI, 0.67 to 0.88]) and recommended patients (OR, 0.78 [95% CI, 0.67 to 0.91]). The lower point estimate of the adjusted OR for use of β-blockers at discharge among women compared with men was of borderline statistical significance. After adjustment for baseline characteristics and hospital-related features, there were no significant differences in discharge recommendations for smoking cessation, cardiac rehabilitation, or dietary modification between women and men in the “gray-zone” group.

In general, the point estimates of the adjusted ORs for comparisons of use of discharge therapies and interventions in women versus men were similar by troponin elevation category. Only for smoking cessation and dietary counseling were directions of the ORs different for the “gray-zone” category. Only for smoking cessation and dietary counseling in women versus men were similar by troponin elevation

<table>
<thead>
<tr>
<th>Troponin &lt;1.0× ULN</th>
<th>Troponin 1.0–1.5× ULN</th>
<th>Troponin &gt;1.5× ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (n=4115)</td>
<td>Men (n=5548)</td>
<td>Women (n=2156)</td>
</tr>
<tr>
<td>Death</td>
<td>1.4%</td>
<td>0.9%</td>
</tr>
<tr>
<td></td>
<td>1.19 (0.78–1.80)</td>
<td></td>
</tr>
<tr>
<td>Death or MI</td>
<td>1.7%</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td>0.98 (0.70–1.39)</td>
<td></td>
</tr>
<tr>
<td>RBC transfusion</td>
<td>8.4%</td>
<td>7.4%</td>
</tr>
<tr>
<td></td>
<td>0.95 (0.81–1.13)</td>
<td></td>
</tr>
</tbody>
</table>

ULN indicates upper limit of normal.

ULN (mean composite score 67%). Within the “gray-zone” group, there was a significant difference in use among women compared with men in adjusted analyses only for discharge use of angiotensin-converting enzyme inhibitors: overall (OR, 0.77 [95% CI, 0.67 to 0.88]) and recommended patients (OR, 0.78 [95% CI, 0.67 to 0.91]). The lower point estimate of the adjusted OR for use of β-blockers at discharge among women compared with men was of borderline statistical significance. After adjustment for baseline characteristics and hospital-related features, there were no significant differences in discharge recommendations for smoking cessation, cardiac rehabilitation, or dietary modification between women and men in the “gray-zone” group.

In general, the point estimates of the adjusted ORs for comparisons of use of discharge therapies and interventions in women versus men were similar by troponin elevation category. Only for smoking cessation and dietary counseling were directions of the ORs different for the “gray-zone” group than the <1× ULN or >1.5× ULN groups. However, none of these relationships were statistically significant. Formal statistical testing found no significant interactions between troponin level and sex differences in use of discharge therapies or interventions.

**Clinical Outcomes**

Overall, “gray-zone” patients had lower in-hospital mortality (2.3%) than those with troponin elevation >1.5× ULN (4.5%), but higher in-hospital mortality than those with troponin elevation <1× ULN (1.1%). Unadjusted in-hospital clinical event rates among women and men as well as adjusted ORs for in-hospital clinical outcomes among women compared with men for all troponin groups are shown in Table 4. After adjustment, there were no significant differences in in-hospital clinical outcomes among women and men with “gray-zone” troponin elevations.

For the “gray-zone” and >1.5× ULN troponin elevation groups, the magnitude of the point estimates of the adjusted ORs for mortality are similar, though for the >1.5× ULN group it was of borderline statistical significance. Although the point estimate of the adjusted OR for death or MI was lower for the “gray-zone” group than the >1.5× ULN troponin elevation group, neither was statistically significant. The adjusted use of RBC transfusions for women compared with men increased as troponin elevation category increased, and for the group with troponin >1.5× ULN, this difference between women and men was significant. Formal statistical testing confirmed a significant interaction between troponin level and sex differences in RBC transfusion. Interaction testing for death and death or MI was not significant.

**Discussion**

In this analysis of more than 5000 patients with low-level troponin elevations—which have been shown to have prognostic implications and to convey potentially important information for guiding the use of aggressive therapeutic interventions—guidelines-recommended therapies and interventions were used less frequently than among patients with greater troponin elevations but with few exceptions were applied to similar extents among women and men across troponin elevation categories. Further, after adjustment for differences in baseline characteristics, clinical outcomes in this “gray-zone” group were not significantly different among women and men. These observations suggest that opportunity exists to improve outcomes among patients with NSTE ACS of both sexes by more effectively treating patients with positive troponin, but low-level “gray-zone” elevation, with acute and discharge guidelines-recommended therapies.

Our results have important implications. First, they suggest that for a given level of troponin elevation, women and men have similar risks of in-hospital ischemic events or death after adjustment for differences in baseline characteristics. In other words, the prognostic implications of troponin positivity do not appear to vary by sex. Second, although we hypothesized that treatment disparities between men and women might be magnified with troponin elevations in a range of clinical uncertainty regarding their validity, our results do not support this. Both women and men in the “gray-zone” group received fewer guidelines-recommended therapies than their counterparts with greater troponin elevation. However, adjusted relative use of guidelines-recommended therapies among women compared with men in this group was similar to that across other troponin elevation categories. In general, except for acute clopidogrel use, formal statistical testing for interactions revealed that treatment use according to patient sex was similar across troponin elevation categories. These findings suggest that no additional bias was introduced by patient sex in the setting of uncertainty as to the meaning of the low-level positivity.

Troponin positivity in ACS has been associated with worse outcomes, as well as with identification of a group that has enhanced benefit with particular therapies. With respect to low-level troponin elevations, there is evidence that this
troponin elevations are treated less aggressively than patients with other symptoms suggestive of ischemia and troponin elevation greater than the 99th percentile of a reference control population as having an MI. Although there are questions regarding the clinical implications of this new definition, this more sensitive definition identifies more patients with MI. Although investigators were given explicit instructions to include only cases that would be classified as NSTE ACS and, thus, would be eligible to receive guidelines-recommended therapies and interventions, there may still be some cases of MI or other causes of troponin elevation that were reported but had underlying pathophysiologic mechanisms that may have affected treatment decisions, and that cannot be further dissected from the CRUSADE database.

Although absolute differences in ischemic event rates increased as degree of troponin elevation increased, after adjusting for differences in baseline characteristics, there were no differences in mortality or death or MI between women and men in any troponin category. The disparity in use of transfusion (greater among women than men) did not appear to increase as troponin elevation level increased, and was statistically significant in the >1.5 × ULN troponin elevation group. The underpinnings of this observation are unknown but may reflect the combination of increasing use of both antithrombin therapy and invasive cardiac procedures as troponin elevation category increased combined with the known higher likelihood of bleeding among women than men with the use of these therapies. There have been other reports questioning the effective use of guidelines-recommended therapies in appropriate high-risk individuals. Our results indicate that patients with minor troponin elevations are treated less aggressively than patients with larger troponin positivity. These findings are similar to those demonstrated in another report that suggested the need for a troponin group remains uncertain. However, our observations suggest that a patient’s sex is not a major factor. Although our results indicate that there is opportunity for a greater level of adherence to guidelines-recommended therapies in this “gray-zone” group, implementation in practice relies heavily on clinical recognition of the true meaning of troponin positivity. Ongoing efforts such as the global definition of MI consensus statement and National Academy of Clinical Biochemistry guidelines aim to facilitate accurate and systematic identification of those patients with low-level troponin elevation who will benefit from effective use of guidelines-recommended therapies.11,20

Limitations
We restricted our population to those with peak troponin occurring within the first 24 hours with a goal to assess initial use of acute therapies and outcomes based on varying levels of troponin in the early period after presentation. A number of patients were excluded from our analysis because of lack of information needed to assess troponin status within the first 24 hours or because peak reported troponin occurred after 24 hours. To the extent that there were differences in baseline characteristics between the excluded and included patients, care must be taken in generalizing the results of our study, though there is no a priori reason to suspect that “gray-zone” troponins would be acted on differently in these patients were they available. Because this is a registry of patients managed according to local practice, selection of the troponin assay was not standard across sites. The 1 to 1.5 × ULN troponin-positive status used to identify women and men for this study was determined by comparison of the actual reported troponin value to the ULN for that assay locally. Although this does not account for the actual 99th percentile of the assay or assay precision or type, it does reflect a clinically relevant categorization used by the practicing clinician to make decisions in actual practice. Composite adherence scores were greater as troponin elevation category increased; however, no formal statistical testing was performed for differences between groups. In addition, all analyses in this report should be considered exploratory. Finally, this analysis did not assess long-term outcomes, as outcomes data from the CRUSADE initiative are limited to the period of hospitalization only.

Conclusions
The prognostic implications of a given level of troponin positivity do not appear to vary by sex. Further, sex-related differences in use of guidelines-recommended therapies do not appear to be enhanced in the setting of the diagnostic uncertainty that is often raised by minor elevations of troponin in clinical practice. Standardized approaches, including response to low-level troponin elevation, that eliminate treatment bias based on the presence or absence of other
clinical features will be needed to improve use of evidence-based therapies in this cohort.

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References
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Supplemental Material

CRUSADE Instructions for Investigator-defined Myocardial Infarction

**Post-admission infarction:** Clinical signs and symptoms of a new infarction or repeat infarction that is distinct from the presenting ischemic event and meeting at least one of the definitions below. If “Yes,” check if event was related to procedure.

**In patients presenting without an MI**
- CK-MB or troponin values above the ULN
- New, significant Q waves in at least two contiguous leads of an ECG

**In patients presenting with an MI**

**Prior to revascularization**
- New, significant Q waves in at least two contiguous leads of an ECG
- An increase in CK-MB or troponin above the ULN (if most recent cardiac markers prior to the event were normal)
- An increase in CK-MB or troponin by 50% above the most recent value (if most recent cardiac markers prior to the event were above the ULN)

**Within 24 hours of PCI**
- Increase in CK-MB 50% over the level preceding the procedure (if most recent cardiac markers prior to procedure were above the ULN)
- Increase in CK-MB to a value at least 3x the ULN (if most recent cardiac markers prior to procedure were normal)
- New, significant Q waves in at least two contiguous leads of an ECG

**Within 24 hours of CABG**
- Increase in CK-MB to a value at least 5x the ULN
- New, significant Q waves in at least two contiguous leads of an ECG