Will the Universal Definition of Myocardial Infarction Criteria Result in an Overdiagnosis of Myocardial Infarction?

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The Universal Definition of Myocardial Infarction (acute myocardial infarction [AMI]) requires detection of increasing or decreasing cardiac biomarkers (preferably cardiac troponin) with ≥1 value >99th percentile, together with either clinical symptoms, new ischemic electrocardiographic changes, or typical imaging findings indicative of myocardial necrosis as diagnostic criteria for AMI. However, a small cardiac troponin elevation together with ST-T segment abnormalities may also occur in clinically stable populations. Accordingly, 0.6% of elderly subjects from a community sample (PIVUS Study) and 6.7% of patients stabilized after an acute coronary syndrome (FRISC II Study) would have been labeled AMI following the Universal Definition of AMI when diagnostic classification had been based on a single cardiac troponin I result. In conclusion, our results emphasized the importance of a significant change in cardiac troponin to avoid misdiagnosis of AMI. © 2009 Elsevier Inc. (Am J Cardiol 2009;103:588–591)

During the past decade, increasing knowledge of the role of biomarkers in patients with unstable coronary artery disease has had major influences on the perception of what is regarded as an acute myocardial infarction (AMI). The World Health Organization guidelines from 1979 defined AMI as the combination of 2 of 3 criteria of typical symptoms, ischemic electrocardiographic (ECG) changes, or an increase or decrease in cardiac enzymes, usually creatine kinase or creatine kinase-MB. In 2000, the European Society of Cardiology/American College of Cardiology recommended the use of the 99th percentile for cardiac troponin determined using an assay with a coefficient of variation <10% at this level as the biochemical gold standard for AMI. Applying these criteria increased the proportion of patients with a diagnosis of AMI in patients with unstable coronary artery disease by approximately 30% compared with World Health Organization criteria.

Recently, the European Society of Cardiology/American College of Cardiology/American Heart Association/World Heart Federation Task Force for the Redefinition of AMI recommended in their universal definition of AMI evidence of an increase or decrease in cardiac troponin in a clinical setting suggestive of myocardial ischemia with ≥1 result >99th percentile, together with either clinical symptoms, new ischemic ECG changes, or imaging findings of new loss of myocardium, as criteria for non–procedure-related AMI. However, troponin may be increased in patients with a variety of chronic conditions, such as left ventricular hypertrophy, heart failure, stable coronary artery disease, and, to a lesser extent, also in apparently healthy persons. This evoked the question whether strict adherence to the universal AMI criteria might classify some clinically stable patients with a small troponin elevation not related to acute ischemia as having an AMI if 1 of the required complementary criteria was present.

To address this issue, we evaluated the prevalence of cardiac troponin I (cTnl) >99th percentile together with ECG abnormalities suggestive of myocardial ischemia in 2 stable populations: first, in elderly subjects participating in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) Study, and second, in patients from the FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) Study who had been stabilized after an episode of acute coronary syndrome 3 months ago.

Methods

In the PIVUS Study, all subjects aged 70 years and living in the community of Uppsala, Sweden, were eligible for participation. Subjects were chosen in a randomized way from the register of community inhabitants. Of 2,025 subjects invited, 1,016 participated in the study from April 2001 to June 2005. cTnl results were available for 1,005 study subjects. Of these, 10 subjects were excluded because of confounding ECG findings (left branch bundle block and pacing), leaving 995 subjects eligible for the present analysis.
In the FRISC II trial, 3,489 patients with non-ST-elevation acute coronary syndrome were randomly assigned from 1996 to 1998 in a factorial design to an early invasive or noninvasive strategy and to 3-month treatment with dalteparin or placebo. At 6 (range 4 – 7) weeks, 3 and 6 months after randomization, 1,380 patients included at selected study centers participated in a blood sampling program. For the present analysis, cTnI results obtained at 3 months were used. Because we aimed to evaluate stable subjects, all patients with an AMI or revascularization procedure during the 14 days before blood sampling were excluded. cTnI results were thus available for 1,016 patients. All these patients underwent exercise testing at 3 months. However, 111 subjects were excluded because of confounding ECG findings (e.g., left branch bundle block and pacing), leaving 905 patients eligible for this analysis. Follow-up was performed at the 3 measurement times and by telephone contacts at 12 and 24 months. Thereafter and up to 5 years after randomization, all information for events was based on National Registries run by the Swedish Health Authority. Mortality, AMI, and its composite occurring after blood sampling at 3 months were used as end points for the present analysis.

Written informed consent had been obtained from all participants in the PIVUS and FRISC II Studies, the study protocols were approved by the local ethics committees, and studies complied with the Declaration of Helsinki.

cTnI was measured in frozen EDTA plasma samples using the high-sensitive Access AccuTnI assay (Beckman Coulter Inc., Fullerton, California). The lower limit of detection of this assay was 0.006 μg/L, the lowest concentration measurable with a coefficient of variation <10% was 0.014 μg/L, and the 99th percentile in elderly subjects without evidence of cardiovascular disease was 0.028 μg/L. Conventional 12-lead electrocardiograms were recorded in the PIVUS Study at baseline and in the FRISC II Study before exercise testing at 3 months and analyzed regarding the presence of ST-T segment abnormalities (ST-segment depression, Minnesota codes 4-1 or 4-2; T-wave inversion, Minnesota codes 5-1, 5-2, or 5-3). As described previously, exercise testing in the FRISC II Study was performed using a bicycle ergometer with continuous 12-lead ECG monitoring during and up to 10 minutes after exercise and subjective symptom rating according to the Borg scale.

Continuous variables were described as median and 25th and 75th percentiles. Categorical variables were expressed as frequencies and percentages. Differences between categorical variables were analyzed using the chi-square test. For all comparisons, a 2-sided p < 0.05 was considered statistically significant. All data analysis was performed using the Statistical Package for Social Sciences (SPSS 14.0) software program (SPSS Inc., Chicago, Illinois).

Results

Clinical characteristics of the subjects included in the PIVUS and FRISC II Studies are listed in Table 1. For PIVUS subjects, cTnI >99th percentile of 0.028 μg/L was found in 15 subjects (1.5%), and 6 subjects (0.6%) had both cTnI >0.028 μg/L and significant ST-T segment abnormalities.

In the FRISC II Study, 93 patients (10%) had cTnI >0.028 μg/L, of whom 61 also had significant ST-T segment abnormalities on the electrocardiogram at rest (6.7% of the entire sample population). Compared with the remaining 32 patients with cTnI >0.028 μg/L, these 61 pa-

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Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>PIVUS (n = 995)</th>
<th>FRISC II (n = 905)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yrs)</td>
<td>70.0</td>
<td>67.1 (59.2–73.6)</td>
</tr>
<tr>
<td>Men</td>
<td>499 (50.2%)</td>
<td>647 (71.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>718 (72.2%)</td>
<td>287 (31.7%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>128 (12.9%)</td>
<td>181 (20.0%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>32 (3.2%)</td>
<td>133 (14.7%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>623 (62.6%)</td>
<td>751 (83.0%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>107 (10.8%)</td>
<td>204 (22.5%)</td>
</tr>
<tr>
<td>Previous smoker</td>
<td>411 (41.3%)</td>
<td>334 (36.9%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>69 (6.9%)</td>
<td>732 (80.9%)</td>
</tr>
<tr>
<td>Previous coronary revascularization</td>
<td>52 (5.2%)</td>
<td>497 (54.9%)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>35 (3.5%)</td>
<td>43 (4.8%)</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>69 (6.9%)</td>
<td>146 (16.1%)</td>
</tr>
<tr>
<td>T-Wave inversion</td>
<td>89 (8.9%)</td>
<td>422 (46.6%)</td>
</tr>
<tr>
<td>ST-T segment abnormalities</td>
<td>120 (12.1%)</td>
<td>450 (49.7%)</td>
</tr>
</tbody>
</table>

Hyperlipidemia defined as low-density lipoprotein cholesterol >3.5 mmol/L, serum triglycerides >1.7 mmol/L, or antihyperlipidemic treatment (PIVUS Study) or total cholesterol >5.0 mmol/L or antihyperlipidemic treatment at 3-month follow-up (FRISC II Study).
patients did not have a higher prevalence of anginal symptoms (23% vs 28%; p = 0.62) or provocative angina on exercise testing (16% vs 22%; p = 0.58). After blood sampling at 3 months, 76 patients (8.4%) from the FRISC II Study died, 100 patients (11%) had an AMI, and 148 patients (16%) had the composite end point of death or AMI during 5-year follow-up. Event rates in relation to cTnI increase >0.028 μg/L together with the presence or absence of ST-T segment abnormalities are shown in Figure 1. Patients with cTnI >0.028 μg/L had increased mortality compared with patients with cTnI ≤0.028 μg/L (13 patients [14%] vs 63 [7.8%]; p = 0.048). Rates for any other end point were not significantly different between patients with and without cTnI >0.028 μg/L and with and without ST-T segment abnormalities. The presence of ST-T segment abnormalities did not identify patients with further increased risk in those with cTnI >0.028 μg/L (p = 1.00 for any end point).

Discussion

Our results highlighted an important issue that needs to be addressed with regard to the recently published universal definition of AMI consensus document. These guidelines required an increase or decrease in cardiac troponins with ≥1 value >99th percentile, together with an additional indicator of new myocardial necrosis as criteria for non–procedure-related AMI. However, our results showed that increased cTnI also was detectable in apparently stable populations, such as elderly subjects from the community and patients with an acute coronary syndrome 3 months ago.⁵,¹⁰ According to current evidence, troponin increase in these populations primarily reflects left ventricular hypertrophy and/or myocardial pump failure with a continuous loss of viable cardiac myocytes caused by increased myocardial wall strain, chronic ischemia, or apoptosis.⁵–⁷ These conditions are often associated with ST-T segment abnormalities that may mimic changes related to acute coronary ischemia.¹⁸ Accordingly, cTnI >99th percentile in combination with significant ST-T segment abnormalities were present in 0.6% and 6.7% of subjects from the PIVUS and FRISC II Studies, respectively. Noteworthy, the presence of ST-T segment abnormalities in cTnI-positive FRISC II patients was not associated with clinical or prognostic features indicative of an ongoing acute coronary syndrome. These results indicated a risk of misdiagnosis of AMI in troponin-positive patients with preexisting ST-T segment abnormalities in case of admittance for nonischemic chest pain or other symptoms indicative of myocardial ischemia. This in turn may have important consequences regarding the initial management of these patients and hospital resource use. Of note, the universal definition of AMI requires that ischemic ECG changes be new to fulfill the criteria for AMI. However, a recently recorded electrocardiogram may not be available for many patients. Detection of a true and significant increase and/or decrease in serially measured troponin will therefore be of critical importance to correctly establish the diagnosis of AMI and discriminate ischemic or other acute causes from chronic causes of troponin increase. However, as noted in a recent article by Wu et al,⁹ timing of sampling and required degree of troponin changes were unresolved issues yet. The National Academy of Clinical Biochemistry recently recommended a 20% change.²⁰ Applied to the 99th percentile for the Access AccuTnI assay, this corresponds to cTnI of 0.006 μg/L. However, such subtle changes may also be related to biologic intraindividual variability in cTnI that has not been described before, but may be detectable with the use of highly sensitive assays. This indicates that a degree of troponin changes >20% probably might be more appropriate for clinical purposes to avoid diagnostic misclassification.