Value of Cardiac Troponin I Cutoff Concentrations below the 99th Percentile for Clinical Decision-Making

Kai M. Eggers,1* Allan S. Jaffe,4 Lars Lind,2 Per Venge,3 and Bertil Lindahl1

BACKGROUND: The aim of this study was to evaluate factors influencing the 99th percentile for cardiac troponin I (cTnI) when this cutoff value is established on a highly sensitive assay, and to compare the value of this cutoff to that of lower cutoffs in the prognostic assessment of patients with coronary artery disease.

METHODS: We used the recently refined Access AccuTnI assay (Beckman-Coulter) to assess the distribution of cTnI results in a community population of elderly individuals [PIVUS (Prospective Study of the Vasculature in Uppsala Seniors) study; n = 1005]. The utility of predefined cTnI cutoffs for risk stratification was then evaluated in 952 patients from the FRISC II (FRagmin and Fast Revascularization during InStability in Coronary artery disease) study at 6 months after these patients had suffered acute coronary syndrome.

RESULTS: Selection of assay results from a subcohort of PIVUS participants without cardiovascular disease resulted in a decrease of the 99th percentile from 0.044 μg/L to 0.028 μg/L. Men had higher rates of cTnI elevation with respect to the tested thresholds. Whereas the 99th percentile cutoff was not found to be a useful prognostic indicator for 5-year mortality, both the 90th percentile (hazard ratio 3.1; 95% CI 1.9–5.1) and the 75th percentile (hazard ratio 2.8; 95% CI 1.7–4.7) provided useful prognostic information. Sex-specific cutoffs did not improve risk prediction.

CONCLUSIONS: The 99th percentile of cTnI depends highly on the characteristics of the reference population from which it is determined. This dependence on the reference population may affect the appropriateness of clinical conclusions based on this threshold. However, cTnI cutoffs below the 99th percentile seem to provide better prognostic discrimination in stabilized acute coronary syndrome patients and therefore may be preferable for risk stratification.

© 2008 American Association for Clinical Chemistry

The cardiac troponins are generally acknowledged as the biochemical gold standard for the detection of myocardial necrosis. Current guidelines suggest the use of the 99th percentile of troponin concentrations from a healthy reference population as a cutoff for diagnostic and prognostic assessment (1, 2). With the implementation of assays with improved analytical sensitivity, however, the reliable determination of troponin even at concentrations well below the previously defined 99th percentile values has become possible (3, 4). Concentrations below the 99th percentile measured with several different assays have been shown to provide robust prognostic information (4–7).

Determination of the previously established 99th percentile was likely influenced by the limits of sensitivity of the assays as well as the characteristics of the reference population from which it had been determined. To address this issue, we used an improved iteration of the commercially available Beckman Coulter assay to establish 75th, 90th, 97.5th, and 99th percentiles for cardiac troponin I (cTnI) in apparently healthy elderly individuals participating in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. The prevalence of cTnI elevations above these percentiles, differences potentially related to sex, and prognostic implications were then assessed in patients stabilized after a recent episode of non–ST-elevation acute coronary syndrome (ACS) who participated in the FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) trial.
Materials and Methods

The primary aim of the PIVUS study was to investigate mechanisms of endothelial function and arterial compliance in an elderly general population (8). All individuals aged 70 years living in Uppsala, Sweden, were eligible for participation. Potential study participants were chosen in a randomized way from the register of community inhabitants. Of the 2025 individuals invited, 1016 participated in the study between 2001 and 2005. All participants recorded their medical history, smoking habits, and regular medication, and underwent echocardiography.

The FRISC II trial was a prospective multicenter study, conducted between 1996 and 1998, in which a total of 3489 patients with non-ST-elevation ACS were randomized in a factorial design to an early invasive or noninvasive strategy and to 3 months treatment with aspirin and clopidogrel. Patients were eligible for study inclusion if they had symptoms of unstable coronary artery disease with objective signs of myocardial ischemia such as changes found on electrocardiography (ECG) (ST-segment depression ≥0.1 mV or T-wave inversion ≥0.1 mV) or increased biochemical markers of myocardial necrosis. Patients were followed with outpatient visits at 6 (range 4–7) weeks, and 3 and 6 months, and by telephone contacts at 12 and 24 months. Thereafter and up to 5 years after randomization, all information on events was obtained from national registries run by the Swedish Health Authority (10). The present analysis included 1380 patients who participated in a blood-sampling program in which blood samples were collected 6 weeks, 3 months, and 6 months after randomization at selected study centers. Patients with an acute myocardial infarction (AMI) or a revascularization procedure within 14 days before blood sampling at 6 months were excluded. Mortality occurring after the 6-month sampling period was used as an endpoint.

Written informed consent was obtained from all participants of both studies, and the study protocols were approved by all local ethics committees.

cTnI was determined in both studies from frozen (−70 °C), not previously thawed samples of EDTA-plasma by using the current version of the Access AccuTnI assay (Beckman Coulter). Following recent modifications by the manufacturer, the signal-to-dose relationship of this assay had been improved, thereby providing more robust results at the low end of its range compared to the previous version of the assay. Accordingly, the lower limit of detection of the assay was found to be 0.006 μg/L, and the lowest concentrations measurable with CVs of ≤10% and ≥20% were 0.014 μg/L and 0.008 μg/L, respectively (4). Measurements in unthawed duplicate cTnI samples from the FRISC II study (n = 31) showed a linear correlation to samples used in a previous analysis ($r^2 = 0.99$), indicating that no in vitro cTnI degradation processes had occurred during the time of storage (see Supplemental Fig. 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol55/issue1).

N-terminal probrain natriuretic peptide (NT-proBNP) was determined in both studies by using the Elecsys proBNP sandwich immunoassay on Elecsys 1010 instruments (Roche Diagnostics). The analytical range of this assay is 5–35 000 ng/L. Plasma creatinine was analyzed in the PIVUS by study using an Architect ci8200 analyzer (Abbott Laboratories) and locally at the time of randomization in the FRISC II-study. In both studies creatinine clearance was calculated according to the Cockcroft-Gault formula (11).

Clinical risk factors were defined as follows: Participants were considered to have hypertension if they had antihypertensive treatment or had blood pressure >140/90 mm Hg at rest (PIVUS), or if they were undergoing antihypertensive treatment (FRISC II). Diabetes was considered to be present in patients with fasting glucose >6.1 mmol/L or who had antidiabetic treatment including diet (PIVUS), or with fasting glucose >6.1 mmol/L or antidiabetic medication at 6-month follow-up (FRISC II). Hyperlipidemia was considered present in individuals with LDL-cholesterol >3.5 mmol/L, serum triglycerides >1.7 mmol/L, or with antihyperlipidemic treatment (PIVUS), or with total cholesterol >5.0 mmol/L or with antihyperlipidemic treatment at 6-month follow-up (FRISC II).

Previous AMI was identified on the basis of self-reported history (PIVUS) or history of AMI before the index event or AMI as index event, defined as cardiac troponin T >0.035 μg/L (Elecsys 2010; 10% CV level) (12), or AMI after randomization and before 6-month follow-up (FRISC II). Previous coronary revascularization was determined by self-reported history (PIVUS) or history of coronary revascularization or revascularization after randomization and before 6-month follow-up (FRISC II). Congestive heart failure was identified by self-reported history (PIVUS) or pharmacologically treated heart failure or left-ventricular ejection fraction <0.45, assessed by echocardiography during the index hospitalization (FRISC II).

For analyses in the PIVUS study, cardiovascular disease was defined by previous AMI, previous revascularization, congestive heart failure, previous stroke (self reported), or hypertension. Normal ECG was defined as no evidence of ST-segment depression (Minnesota codes 4–1 and 4–2), T-wave inversion (Minnesota codes 5–1, 5–2, or 5–3), pathologic Q-waves (Minnesota code 1–1), or left bundle-branch block (Minnesota code 7–1) (13). Left ventricular hypertrophy was defined as left ventricular mass index on echo-
Cardiography > 116 g/m² in men or > 104 g/m² in women (14). Increased NT-proBNP levels were defined as NT-proBNP > 210 μg/L in men or > 250 μg/L in women (15, 16).

We established the 75th, 90th, 97.5th, and 99th percentiles for cTnI by using the weighted average method [Statistical Package for Social Sciences (SPSS) version 14.0] in 2 different subsets from the PIVUS study, first in all participants and second in participants without cardiovascular disease, with a normal ECG, without left ventricular hypertrophy, and with nonincreased levels of NT-proBNP. The 95% CIs of the cTnI percentiles were estimated with the bootstrap (percentile) method by using 10000 bootstrap samples.

The prevalence of cTnI levels above the percentiles derived from the healthiest subset of PIVUS participants was then assessed in the FRISC II study in samples obtained at 6 months. The relative importance of sex as a contributor to detectable cTnI levels was evaluated in both studies by multivariable logistic regression analysis (model 1) with adjustment for age (FRISC II study only), congestive heart failure, diabetes, hyperlipidemia, previous smoking, previous AMI, previous coronary revascularization, creatinine clearance, and NT-proBNP levels (model 2). Because NT-proBNP values were highly skewed, we performed logarithmic transformation on these data before entering them into model 2.

Continuous variables are described as medians and 25th and 75th percentiles. Categorical variables are expressed as frequencies and percentages. Differences regarding categorical variables between groups were expressed as frequencies and percentages. Differences and 25th and 75th percentiles. Categorical variables are transformed on these data before entering them into values were highly skewed, we performed logarithmic

NT-proBNP levels (model 2). Because NT-proBNP levels was 0.028 μg/L, and the 97.5th, 90th and 75th percentiles in this subset were 0.022 μg/L, 0.013 μg/L and 0.009 μg/L, respectively. Only the 75th and 90th percentiles differed significantly between the sexes in this subset, with higher percentile values found in men.

cTnI was more often increased in men compared to women with regard to all tested cutoffs (Table 1). According to multivariable logistic regression analysis applied to the entire population from the PIVUS study (n = 1 005), male sex was also independently associated with detectable cTnI levels > 0.006 μg/L in model 1 [odds ratio (OR) 2.1 (95% CI 1.6–2.7); P < 0.001] and model 2 adjusted for several cardiovascular co-morbidities and their indicators [OR 2.2 (95% CI 1.7–2.9); P < 0.001].

FRISC II STUDY

cTnI results were available at 6 months after randomization in 952 patients. The clinical characteristics of this population are given in Table 1. cTnI levels ranged from 0.0 to 1.815 μg/L in men and from 0.0 to 1.665 μg/L in women, with a total of 588 patients (61.7%) having detectable cTnI levels > 0.006 μg/L. Application of the 99th percentile determined in the healthiest subset of PIVUS participants (i.e., cTnI > 0.028 μg/L) resulted in an increased rate of increased cTnI levels compared to the 99th percentile of 0.044 μg/L derived from the entire PIVUS population [75 patients (7.9%) vs 42 patients (4.4%); P < 0.001].

Men had higher rates of cTnI elevation compared to women with regard to the lower limit of detection and the 75th and 90th percentiles but not regarding higher percentiles (Table 1). As in the PIVUS study, male sex was independently associated with the prevalence of detectable cTnI concentrations > 0.006 μg/L [model 1, OR 1.6 (95% CI 1.2–2.1); P = 0.002; model 2, OR 2.0 (95% CI 1.4–2.9); P < 0.001].

The implications of the sex-specific cutoffs derived from the healthiest subset of PIVUS participants were evaluated by using the 90th percentiles (i.e., cTnI > 0.014 μg/L in men, cTnI > 0.011 μg/L in women) and 99th percentiles (i.e., cTnI > 0.033 μg/L in men, cTnI > 0.025 μg/L in women). We did not consider the 75th percentiles because at this low cTnI concentration...
the subtle differences between the sexes might have been influenced by the relative analytical imprecision of the AccuTnI assay. Application of the sex-specific 99th percentiles instead of an overall single 99th percentile lowered the rate of cTnI positivity at 6 months from 7.9% to 6.9% (P < 0.02). This effect was mainly due to the reclassification of 1.6% of all men included in this analysis from cTnI positive to cTnI negative, i.e., men with minor cTnI elevations who were cTnI positive by the single 99th percentile of 0.028 µg/L and cTnI negative by the sex-specific 99th percentile of 0.033 µg/L. Of all women with cTnI concentrations in the range 0.026–0.028 µg/L, 0.7% were reclassified from cTnI negative to cTnI positive on the basis of sex-specific 99th percentiles. When the sex-specific 90th percentiles were applied instead of a single 90th percentile, only a slightly lower rate of cTnI positivity was noted, a finding that was not statistically significant (25.2% vs 24.0%; P = 0.11).

The prognostic importance of increased cTnI concentrations above the lowest level of detection and the tested single and sex-specific percentiles derived from the healthiest subset of PIVUS participants is demonstrated in Fig. 1. With respect to the analytical performance of the applied assay, we considered only a single 75th percentile was used for this analysis. cTnI concentrations predicted 5-year mortality, with the 75th and 90th percentiles being most prognostically useful. The sensitivities of the 75th and 90th percentiles for mortality were 63.4% (95% CI 48.0%–71.2%) and 47.9% (95% CI 36.3%–59.5%), with corresponding specificities of 61.5% (95% CI 58.5%–65.0%) and 76.7% (95% CI 69.0%–82.5%).

The baseline characteristics of study participants are shown in Table 1.

### Table 1. Baseline characteristics of study participants.

<table>
<thead>
<tr>
<th></th>
<th>PIVUS Males (n = 502)</th>
<th>PIVUS Females (n = 503)</th>
<th>P-value</th>
<th>FRISC II Males (n = 679)</th>
<th>FRISC II Females (n = 273)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>70.0</td>
<td>70.0</td>
<td>—</td>
<td>66.2 (58.2–73.2)</td>
<td>69.5 (64.0–75.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>349 (69.5%)</td>
<td>375 (74.6%)</td>
<td>0.08</td>
<td>205 (30.2%)</td>
<td>113 (41.4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>74 (14.7%)</td>
<td>56 (11.1%)</td>
<td>0.09</td>
<td>140 (20.6%)</td>
<td>39 (14.3%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart failure</td>
<td>22 (4.4%)</td>
<td>13 (2.6%)</td>
<td>0.17</td>
<td>105 (15.5%)</td>
<td>36 (13.2%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>304 (60.6%)</td>
<td>327 (65.0%)</td>
<td>0.15</td>
<td>511 (75.3%)</td>
<td>226 (82.8%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Current smoking</td>
<td>50 (10.0%)</td>
<td>58 (11.5%)</td>
<td>0.48</td>
<td>162 (23.9%)</td>
<td>59 (21.6%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Previous smoking</td>
<td>239 (47.6%)</td>
<td>176 (35.0%)</td>
<td>&lt;0.001</td>
<td>286 (42.1%)</td>
<td>62 (22.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous AMI</td>
<td>57 (11.4%)</td>
<td>15 (3.0%)</td>
<td>&lt;0.001</td>
<td>492 (72.5%)</td>
<td>173 (63.4%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Previous PCI/CABG</td>
<td>42 (8.4%)</td>
<td>12 (2.4%)</td>
<td>&lt;0.001</td>
<td>435 (64.1%)</td>
<td>138 (50.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>25 (5.0%)</td>
<td>11 (2.2%)</td>
<td>0.02</td>
<td>35 (5.2%)</td>
<td>11 (4.0%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-I/AII antagonists</td>
<td>96 (19.1%)</td>
<td>67 (13.3%)</td>
<td>0.01</td>
<td>132 (19.4%)</td>
<td>49 (18.0%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Antithrombotics</td>
<td>108 (21.5%)</td>
<td>73 (14.5%)</td>
<td>0.004</td>
<td>644 (94.8%)</td>
<td>262 (96.3%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Betablockers</td>
<td>106 (21.1%)</td>
<td>111 (22.1%)</td>
<td>0.76</td>
<td>554 (81.6%)</td>
<td>226 (83.1%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Calcium-antagonists</td>
<td>65 (12.9%)</td>
<td>49 (9.7%)</td>
<td>0.11</td>
<td>131 (19.3%)</td>
<td>59 (21.7%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Digitalis</td>
<td>12 (2.4%)</td>
<td>6 (1.2%)</td>
<td>0.16</td>
<td>27 (4.0%)</td>
<td>6 (2.2%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Diuretics</td>
<td>58 (11.6%)</td>
<td>65 (12.9%)</td>
<td>0.56</td>
<td>104 (15.3%)</td>
<td>79 (29.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antilipids</td>
<td>89 (17.7%)</td>
<td>71 (14.1%)</td>
<td>0.12</td>
<td>357 (52.6%)</td>
<td>148 (54.2%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Nitrates</td>
<td>19 (3.8%)</td>
<td>11 (2.2%)</td>
<td>0.14</td>
<td>186 (27.4%)</td>
<td>99 (36.4%)</td>
<td>0.008</td>
</tr>
<tr>
<td>cTnI elevation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.006 µg/L</td>
<td>295 (58.8%)</td>
<td>203 (40.4%)</td>
<td>&lt;0.001</td>
<td>440 (64.8%)</td>
<td>147 (53.8%)</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt;0.009 µg/L</td>
<td>166 (33.1%)</td>
<td>115 (22.9%)</td>
<td>&lt;0.001</td>
<td>300 (44.1%)</td>
<td>85 (31.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;0.013 µg/L</td>
<td>80 (15.9%)</td>
<td>44 (8.7%)</td>
<td>0.001</td>
<td>192 (28.2%)</td>
<td>48 (17.6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt;0.022 µg/L</td>
<td>26 (5.2%)</td>
<td>7 (1.4%)</td>
<td>0.001</td>
<td>85 (12.5%)</td>
<td>24 (8.8%)</td>
<td>0.12</td>
</tr>
<tr>
<td>&gt;0.028 µg/L</td>
<td>13 (2.6%)</td>
<td>3 (0.6%)</td>
<td>0.01</td>
<td>57 (8.4%)</td>
<td>18 (6.6%)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

* PCI, percutaneous coronary intervention; CAGB, coronary artery bypass graft; ACE-I, ACE-inhibitors; AII, angiotensin II.

88 Clinical Chemistry 55:1 (2009)
CI 74.3%–79.8%), respectively. The negative predictive values were 95.4% and 94.8%, with positive predictive values of 11.7% and 14.2%, respectively. The 97.5th and 99th percentiles provided sensitivities for the 5-year mortality hazard ratios [Fig. 1; P = 1.00 for any comparison of single and sex-specific cutoffs (McNemar test)].

**Discussion**

For clinical decision-making in patients with ACS, guideline groups recommend the use of a troponin cutoff corresponding to the 99th percentile derived from a healthy reference population (1, 2). However, our data, with the use of a highly sensitive assay that allows for the reliable detection of cTnI levels below this threshold, unmask several important issues that require critical reflection.

Our results demonstrate that the cTnI 99th percentile strongly depends on the selection of individuals forming the reference population. The use of stricter criteria among apparently healthy 70-year-old individuals from the PIVUS study resulted in a decrease of the 99th percentile values from 0.044 to 0.028 µg/L.

In addition, we found 1.3-fold to 2.6-fold higher concentrations in men compared to women, depending on the chosen subset of participants from the PIVUS study. This result was mainly attributable to particularly high cTnI levels in some men with cardiovascular disease. These results are in line with those of previous studies demonstrating that mean troponin concentrations differ between the sexes when analyzed with assays with improved analytical sensitivity (18, 19). This phenomenon may depend on more pronounced myocardial apoptotic processes in men (22).

Table 2. Percentiles of cTnI in the different subsets from the PIVUS study.a

<table>
<thead>
<tr>
<th>Percentiles</th>
<th>All participants</th>
<th>75th</th>
<th>90th</th>
<th>97.5th</th>
<th>99th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 1005)</td>
<td>0.010 µg/L</td>
<td>0.015 µg/L</td>
<td>0.025 µg/L</td>
<td>0.044 µg/L</td>
<td></td>
</tr>
<tr>
<td>(0.010–0.010 µg/L)</td>
<td>(0.014–0.016 µg/L)</td>
<td>(0.022–0.028 µg/L)</td>
<td>(0.028–0.072 µg/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (n = 502)</td>
<td>0.011 µg/L</td>
<td>0.017 µg/L</td>
<td>0.031 µg/L</td>
<td>0.072 µg/L</td>
<td></td>
</tr>
<tr>
<td>(0.010–0.012 µg/L)</td>
<td>(0.015–0.019 µg/L)</td>
<td>(0.024–0.044 µg/L)</td>
<td>(0.033–0.155 µg/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women (n = 503)</td>
<td>0.009 µg/L</td>
<td>0.013 µg/L</td>
<td>0.019 µg/L</td>
<td>0.028 µg/L</td>
<td></td>
</tr>
<tr>
<td>(0.008–0.010 µg/L)</td>
<td>(0.012–0.014 µg/L)</td>
<td>(0.017–0.022 µg/L)</td>
<td>(0.019–0.036 µg/L)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Participants without cardiovascular disease, left ventricular hypertrophy, ECG abnormalities, or elevated NT-proBNP levels**

<table>
<thead>
<tr>
<th>Percentiles</th>
<th>75th</th>
<th>90th</th>
<th>97.5th</th>
<th>99th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 520)</td>
<td>0.009 µg/L</td>
<td>0.013 µg/L</td>
<td>0.022 µg/L</td>
<td>0.028 µg/L</td>
</tr>
<tr>
<td>(0.008–0.010 µg/L)</td>
<td>(0.012–0.014 µg/L)</td>
<td>(0.018–0.024 µg/L)</td>
<td>(0.022–0.033 µg/L)</td>
<td></td>
</tr>
<tr>
<td>Men (n = 249)</td>
<td>0.009 µg/L</td>
<td>0.014 µg/L</td>
<td>0.024 µg/L</td>
<td>0.033 µg/L</td>
</tr>
<tr>
<td>(0.009–0.011 µg/L)</td>
<td>(0.012–0.017 µg/L)</td>
<td>(0.019–0.031 µg/L)</td>
<td>(0.022–0.067 µg/L)</td>
<td></td>
</tr>
<tr>
<td>Women (n = 271)</td>
<td>0.008 µg/L</td>
<td>0.011 µg/L</td>
<td>0.019 µg/L</td>
<td>0.025 µg/L</td>
</tr>
<tr>
<td>(0.007–0.009 µg/L)</td>
<td>(0.010–0.013 µg/L)</td>
<td>(0.015–0.022 µg/L)</td>
<td>(0.018–0.028 µg/L)</td>
<td></td>
</tr>
</tbody>
</table>

| P-value | <0.001 | <0.001 | 0.001 | 0.03 |

*95% CIs for the cTnI percentiles are given in parentheses. P-values refer to comparisons of percentiles between men and women [bootstrap (percentile) method].
than the PIVUS participants will probably also dimin-
ish differences of cTnI concentrations between men 
and women, thereby making sex-specific cutoffs 
obsolete.

Our results highlight an additional issue, suggest-
ing that the assays currently in use are not nearly as 
sensitive as might be optimal for clinical purposes. 
That troponin levels even below the 99th percentile are 
useful for the detection of cardiac disease or definition 
of risk has been demonstrated in previous studies. 
These studies, however, applied assays with 10% CV 
levels above or in the same range as the 99th percentile 
(6, 23). Thus, some caution is required when interpret-
ing these results, owing to the imperfect analytical assay 
precision at lower troponin concentrations. Our re-
results are an important addition to the existing literature 
because the superior analytical performance of the highly sensitive assay used in our analysis allowed for 
the reliable determination of risk associated with tro-
ponin concentrations below the 99th percentile. Our 
data raise the question of what troponin cutoff should 
be regarded as the most appropriate biochemical crite-
rion for decision-making in ACS, particularly because 
recent data suggest that normal values are substantially 
lower than measured by any of the currently available 
assays (3).

For the recently modified AccuTnI assay, the 10% 
CV level is 0.014 µg/L, a value that is close to the 90th 
percentile established in the healthiest subset from the 
PIVUS study. The 90th percentile was associated with

Fig. 1. Prediction of 5-year mortality in participants from the FRISC II-study by cardiac troponin I levels at 6 months 
by applying different cutoffs. 
Estimated hazard ratios (HR) and corresponding 95% CIs for single and sex-specific cutoffs are given. LLD indicates lowest level 
of detection; perc, percentile
higher hazard ratios for 5-year mortality, suggesting an increased clinical utility to this value in a concentration range for which the sex-related differences also lost their relative importance. The failure of cutoffs below the 90th percentile to improve risk prediction may be related to the relative imprecision of the AccuTnl assay at these very low thresholds or the fact that these low cTnl concentrations represent only physiologic cardiomyocyte turnover.

Our findings are at variance with those of some other studies demonstrating an increasing mortality with higher troponin cutoffs (5, 6, 24). We can not exclude the possibility that a probable beneficial effect by coronary revascularization attenuated the prognostic value of high cTnl cutoffs in patients with more severe cardiac disease, i.e., patient subgroups known to have a higher prevalence of cTnl elevation (7, 25, 26).

Regarding the clinical utility of cTnl cutoffs below the 99th percentile, lower diagnostic cutoffs undoubtedly will result in an increased rate of detection of cTnl elevations that may be more likely to be attributable to chronic rather than acute processes (7) or be difficult to explain. This possibility is reflected by the 62% rate of detectable cTnl concentrations in FRISC II participants at 6 months after randomization and by recent data from the Val-HeFT (Valsartan Heart-Failure Pants at 6 months after randomization and by recent of detectable cTnI concentrations in FRISC II partici-
ations and the strict adherence to complementary crite-ia for defining AMI in an acute setting should be emphasized whenever the use of a lowered troponin cutoff is contemplated.

LIMITATIONS
Because we established the percentiles of cTnl in a pop-
ulation of 70-year-old individuals, we could not evalu-
ate potential influences of age on the distribution of cTnl levels, an influence that has been reported for at least 1 assay (27). Given the results of the present analy-

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 require-
ments: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data, (b) drafting or revising the article for intellectual content, and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.
Consultant or Advisory Role: A.S. Jaffe, Beckman Coulter, Siemens, Critical Diagnostics, Novartis, Bayer, and Singulex; B. Lindahl, Beck-
man Coulter and Siemens (former Dade-Behring).

Stock Ownership: None declared.
Honoraria: P. Venge, Beckman Coulter, Abbott Diagnostics, and Roche Diagnostics; this author has an immediate family member who received an honorarium from Radiometer; B. Lindahl, Abbott, Roche, Dade-Behring, and Beckman Coulter

Research Funding: This study was supported by grants from the Swedish Heart and Lung Foundation and the Erik, Karin and Gösta Selander Foundation. The reagents for the cTnl assay were provided as a gift by Beckman Coulter (Fullerton, CA). A.S. Jaffe, Beckman Coulter; L. Lind, AstraZeneca; P. Venge, Beckman Coulter, Abbott Diagnostics, Roche Diagnostics, and Radiometer.

Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, preparation or approval of manuscript.

Acknowledgments: We are indebted to Johan Lindbäck for statisti-
cal support.

References

1. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/ AHA/WHF Task Force for the Redefinition of Myocar-


7. Schulz O, Paul-Walter C, Lehmann M, Abraham K, Berg höfer G, Schimke I, et al. Usefulness of detectable levels of troponin, below the 99th per-
centile of the normal range, as a clue to the presence of underlying coronary artery disease. Am J Cardiol 2007;100:746–9.

8. Lind L, Fors N, Hall J, Marttala K, Stenborg A. A comparison of three different methods to evalu-
ate endothelium-dependent vasodilation in the elderly. The Prospective Investigation of the Vas-
culature in Uppsala Seniors (PIVUS) Study. Arte-

9. The Fragmin and Fast Revascularisation during InStability in Coronary artery disease Investiga-
tors. Invasive compared with non-invasive treat-


