Clinical Performance of Two Highly Sensitive Cardiac Troponin I Assays

Per Venge,1* Stefan James,2,3 Leif Jansson,4 and Bertil Lindahl2,3

BACKGROUND: The aim of this study was to compare the clinical performance of 2 sensitive cTnI assays with 10% CV imprecision below the 99th percentile upper reference limit.

METHODS: We measured cardiac troponin and N-terminal pro–brain natriuretic peptide (NT-proBNP) concentrations in a random sample of the Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO) IV cohort (n = 1251). Outcome data of 1-year mortality and the composite endpoint DMI [death and/or myocardial infarction (MI) within 30 days] were available in all patients. The 99th percentile of a healthy population was estimated from the Sweden Women and Men and Ischemic Heart Disease (SWISCH) cohort (n = 442). We measured cardiac troponin I (cTnI) using the Access AccuTnI (Beckman Coulter) and Centaur TnI Ultra (Siemens Healthcare Diagnostics) and NT-proBNP using the Elecsys 2010 (Roche Diagnostics).

RESULTS: Applying the 10% CV cutoff, the sensitivity of the Access AccuTnI assay in identifying DMI and death was higher than that of the Centaur TnI Ultra (P = 0.02 and P < 0.001), and the AccuTnI assay also identified more patients at risk (P < 0.001) and with poor outcome. Applying the 99th percentile cutoffs, AccuTnI identified more patients at risk than the Centaur TnI (P < 0.001) and with significant differences in outcome. Significantly more patients with cardiac troponins below the cutoffs as measured by Centaur TnI had increased NT-proBNP concentrations (P < 0.001) compared with AccuTnI.

CONCLUSIONS: The AccuTnI assay identified more patients at risk than the Centaur cTnI Ultra assay. Our results demonstrate the clinical potential of high-sensitivity cardiac troponin assays for the identification of patients at risk of dying from cardiovascular disease. © 2008 American Association for Clinical Chemistry

Measurement of cardiac troponins in blood is currently the procedure of choice for the biochemical identification of patients with myocardial cell injury (1). With the introduction of hypersensitive assays for cardiac troponin I (cTnI)5, it has become possible to measure cTnI even in healthy subjects (2). We showed previously that minor elevations of cTnI are predictive of long-term fatal outcomes, not only in subjects with diagnosed cardiovascular disease (CVD), but also in subjects with no known CVD (3). The consensus documents published by AACC and the European Society of Cardiology proposed that the 99th percentile of the upper reference limit (URL) shall be used as a cutoff for the diagnosis of myocardial infarction (4, 5), and that the analytical goal of the assay should be imprecision of ≤10% CV at the 99th percentile URL. Two commercial cTnI assays currently available seem to meet these criteria, the AccuTnI assay from Beckman Coulter and the Centaur cTnI assay from Siemens Healthcare Diagnostics (formerly Bayer). The 10% CV concentration of the AccuTnI was recently shown to be 0.014 μg/L, with age-dependent 99th percentile URLs ranging from 0.02 to 0.04 μg/L (2, 6), whereas the Centaur has a 10% CV at 0.03 μg/L, with a 99th percentile of 0.04 μg/L. The clinical performance of the Siemens Centaur cTnI assay was evaluated in a recent report (7), and the prognostic performance of the Beckman Coulter AccuTnI assay has been largely documented (3, 6, 8–11).

The aim of this study was to compare the clinical performances of 2 sensitive cTnI assays using a subsample of the Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO) IV cohort, from...
which are available outcome data of 1-year mortality
and the composite endpoint DMI [death and/or myo-
cardial infarction (MI) within 30 days] (12, 13).

Patients and Methods

PATIENT SELECTION

The GUSTO IV trial included 7800 patients with non–
ST-elevation acute coronary syndrome (ACS) from
458 centers in 24 countries during 1999 and 2000
(12, 14, 15). The detailed design and main results
of the trial have been published. Eligible patients were
\( \geq 21 \) years of age with 1 or more episodes of angina
lasting \( \geq 5 \) min, within 24 h of admission, and either a
positive cardiac TnT or TnI test (above the upper limit
of normal for the local assay) or \( \geq 0.5 \) mm transient or
persistent ST-segment depression. The study was con-
ducted in a double-blind fashion with patients ran-
domly assigned to 3 treatment groups: abciximab infu-
sion for 24 or 48 h or corresponding placebo infu-
sion. All patients received aspirin, 150–325 mg orally once a
day, for long-term treatment as well as either unfrac-
tionated heparin infusion for 48 h (n = 6826) or sub-
cutaneous dalteparin every 12th hour for 5–7 days (n =
974). Coronary angiography was not to be performed
during or within 12 h after the completion of study
agent infusion. For this study, we randomly selected
samples from a cohort of 1260 patients. Samples were
missing from 9 patients, making the final cohort
1251 patients.

The study on healthy subjects consisted of 442
men and women included in the Sweden Women and
Men and Ischemic Heart Disease (SWISCH) study
during 2000–2001 (16). SWISCH was a case-control
study on risk factors for coronary artery disease in el-
derly men and women, for which subjects were ran-
domly recruited from the population using the popu-
lation registry. Subjects were matched for age and sex,
with patients having unstable coronary artery disease
included at 6 hospitals in the Fragmin and Fast Revas-
cularisation during Instability in Coronary Artery Dis-
ease (FRISC) II trial during 1996–1998. Details of these
studies have been published (16–18).

LABORATORY ANALYSES

Venous blood samples were collected in evacuated
tubes via a direct venous puncture at baseline. An ali-
quot of the serum samples at baseline was stored at
\(-70^\circ C\) and used for the analysis of cTnl and N-
terminal pro–brain natriuretic peptide (NT-proBNP).
We measured NT-proBNP using an Elecsys 2010
(Roche Diagnostics), and the analytical range extended
from 20 to 35 000 ng/L. Our in-house total CV was
3.3% (n = 21) at a concentration of 209 ng/L and 3.0%
(n = 21) at a concentration of 7431 ng/L.

We measured cTnl using the Access AccuTnl assay
(Beckman Coulter) and the Centaur cTnl Ultra assay
commercialized by Siemens Healthcare Diagnostics.
For the AccuTnl assay, the 99th percentile URL was
0.04 \( \mu g/L \) for healthy subjects regardless of age and
0.021 \( \mu g/L \) for subjects \(<60\) years (2, 19). The lowest
concentration measurable with the previous assay with
a 10% CV was 0.06 \( \mu g/L \). Minor modifications of the
commercially available AccuTnl assay have recently
been introduced by the manufacturer, however, and we
used this modified assay in the study. These modifica-
tions resulted in more robust results at the low end,
with 10% and 20% CVs at 0.014 and 0.008 \( \mu g/L \), re-
spectively (6). The lowest concentration measurable
with the Centaur cTnl Ultra assay with a 10% CV was
0.03 \( \mu g/L \), and with a 20% CV, 0.025 \( \mu g/L \), which is in
accord with the imprecision estimates given in the
package insert of the assay. Imprecision data were de-
A

ned from imprecision profiles of duplicate samples of
large cohorts of ACS patients. cTnl on Centaur was
analyzed at the clinical chemistry laboratory, Gävle
Hospital (Gävle, Sweden) and cTnl on the Access at the
clinical chemistry laboratory, University Hospital
(Uppsala, Sweden). Analyses of cTnl in the 2 laborato-
ries were performed during the same time period, but
on separate aliquots of never-thawed freshly frozen
samples. In both laboratories, the analysis work was
performed in batch by dedicated personnel outside the
clinical workflow.

STATISTICS

We used Passing–Bablok regression analysis, Bland–
Altman bias plot, ROC curve analysis, Mann–Whitney
nonparametric test for group comparisons, McNemar
test, and test for differences in proportions. All calcu-
lations were performed using Medcalc v. 9, Statistica
for Windows v. 8, and SPSS 11.5.

Results

Fig. 1 shows the Passing–Bablok regression analysis of
the AccuTnl and Centaur cTnl assays. The \( r^2 \) was 0.83
and the equation \( y = -0.03395 + 1.7804x \). Thus,
overall the Centaur cTnl assay produced 78% higher
values (95% CI 1.74–1.82) than the AccuTnl. The re-
lationship between the assays also showed significant
deviation from linearity (\( P < 0.01 \)). The figure also
shows a Bland–Altman bias plot that indicates a sys-
tematic bias between the assays. Fig. 2 shows the cTnl
concentrations, as measured by Centaur cTnl, in the
SWISCH cohort of healthy subjects. After elimination
of 3 outliers, the 99th percentile of the whole cohort
was 0.08 \( \mu g/L \), with a clear tendency toward an age-
dependent relationship—that is, toward higher con-
centrations at higher ages. This tendency was further
Fig. 1. (A) Passing–Bablok regression analysis of the AccuTnI and Centaur cTnl Ultra assays. The inset shows the relationship between the 2 assays at the lower end of the concentrations. (B) Bland–Altman bias plot of these data.
supported by the fact that the cTnI concentrations in the 2 cohorts < or ≥60 years of age differed significantly (*P* = 0.0002).

The AccuTnI had a higher sensitivity for identifying death within 1 year (*P* = 0.001) compared with the Centaur cTnI assay when the 10% CV cutoffs were used (100% and 88% sensitivities, respectively) (Table 1). The AccuTnI assay also demonstrated a higher sensitivity for identifying the composite endpoint DMI (*P* = 0.02). When using the 99th percentile URL based on the SWISCH cohort of healthy subjects, the sensitivities of the 2 assays were nonsignificantly different. No statistically significant differences in the areas under the curve (AUCs) for ROC curves were observed between the assays. For the endpoint death within 1 year as well as the composite endpoint DMI. The comparisons based on the 99th percentile URLs showed a concordance between the 2 assays of 88.9%. In analysis of discordant results, 10.6% of the patients had increased concentrations only by the AccuTnI assay, whereas 0.6% had increased concentrations only by the Centaur assay (*P* < 0.0001). Twelve patients died within 1 year, and 7 died and/or had an MI within 30 days in the AccuTnI-only group, compared with 1 patient in the Centaur-only group (*P* = 0.0003 [deaths] and *P* = 0.07 [DMI]). When the 10% CV cutoffs were used, the concordance was 79.3%. Thus, 20.4% of the patients had concentrations above the cutoff only with the AccuTnI vs 0.2% only with the Centaur cTnI (*P* < 0.0001). In the AccuTnI-only group, 13 patients died.

The AccuTnI had a higher sensitivity for identifying death within 1 year (*P* = 0.001) compared with the Centaur cTnI assay when the 10% CV cutoffs were used (100% and 88% sensitivities, respectively) (Table 1). The AccuTnI assay also demonstrated a higher sensitivity for identifying the composite endpoint DMI (*P* = 0.02). When using the 99th percentile URL based on the SWISCH cohort of healthy subjects, the sensitivities of the 2 assays were nonsignificantly different. No statistically significant differences in the areas under the curve (AUCs) for ROC curves were observed between the assays. For the endpoint death within 1 year as well as the composite endpoint DMI. The comparisons based on the 99th percentile URLs showed a concordance between the 2 assays of 88.9%. In analysis of discordant results, 10.6% of the patients had increased concentrations only by the AccuTnI assay, whereas 0.6% had increased concentrations only by the Centaur assay (*P* < 0.0001). Twelve patients died within 1 year, and 7 died and/or had an MI within 30 days in the AccuTnI-only group, compared with 1 patient in the Centaur-only group (*P* = 0.0003 [deaths] and *P* = 0.07 [DMI]). When the 10% CV cutoffs were used, the concordance was 79.3%. Thus, 20.4% of the patients had concentrations above the cutoff only with the AccuTnI vs 0.2% only with the Centaur cTnI (*P* < 0.0001). In the AccuTnI-only group, 13 patients died.

The relative risk of having an outcome of death within 1 year was 1.136 times higher (*P* = 0.0005), and of having the composite outcome DMI, 1.069 times higher (*P* = 0.02) with a positive AccuTnI result compared to having a positive Centaur result when using the cutoffs based on the 10% CV. Using cutoffs based on the 99th percentile URLs, no differences in relative risks were observed.

The clinical performance comparisons between the AccuTnI and Centaur cTnI assays are shown in Tables 2 and 3. In the comparisons, we used the cutoffs of 10% CV and the 99th percentile URL based on the SWISCH cohort. As endpoints, we used death within 1 year as well as the composite endpoint DMI. The comparisons based on the 99th percentile URLs showed a concordance between the 2 assays of 88.9%. In analysis of discordant results, 10.6% of the patients had increased concentrations only by the AccuTnI assay, whereas 0.6% had increased concentrations only by the Centaur assay (*P* < 0.0001). Twelve patients died within 1 year, and 7 died and/or had an MI within 30 days in the AccuTnI-only group, compared with 1 patient in the Centaur-only group (*P* = 0.0003 [deaths] and *P* = 0.07 [DMI]). When the 10% CV cutoffs were used, the concordance was 79.3%. Thus, 20.4% of the patients had concentrations above the cutoff only with the AccuTnI vs 0.2% only with the Centaur cTnI (*P* < 0.0001). In the AccuTnI-only group, 13 patients died.

**Fig. 2.** cTnI concentrations, as measured by the Centaur cTnI Ultra assay, in the SWISCH cohort of healthy subjects (n = 442). The horizontal line indicates the 99th percentile after elimination of 3 outliers.
and 6 died and/or had a MI within 30 days, compared with none in the Centaur-only group \( (P = 0.0002 \) [deaths] and \( P = 0.03 \) [DMI]). It should also be noted that none of the subjects having AccuTnI concentrations \( <0.014 \mu g/L \) died within 1 year or had a MI within 30 days. Applying the 99th percentile URL, the 1-year mortality was 9.6% \( (n = 92) \) vs 5.5% \( (n = 16) \) in the cohorts with AccuTnI concentrations above and below the cutoff [odds ratio \( (OR) 1.8, 95\% CI 1.1–3.2, P < 0.029 \}], and DMI was 9.0% \( (n = 86) \) vs 2.4% \( (n = 9) \) \( (OR 4.0, 95\% CI 1.8–8.8, P < 0.001) \). Corresponding figures for Centaur Ultra cTnI results were 9.7% vs 6.5% \( (OR 1.6, 95\% CI 0.99–2.4, P = 0.053) \) and 9.6% vs 3.1% \( (OR 3.3, 95\% CI 1.8–6.0, P < 0.001) \).

A large number of patients had nonincreased concentrations with either cardiac troponin assay. To

<table>
<thead>
<tr>
<th>Table 1. Diagnostic specifics of the AccuTnI and Centaur cTnI assays in the prediction of mortality within 1 year and the composite endpoint death and/or MI within 30 days (DMI).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutoff concentration</strong></td>
</tr>
<tr>
<td>AccuTnI, 0.014 ( \mu g/L ) (10% CV)</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>Positive predictive value</td>
</tr>
<tr>
<td>Negative predictive value</td>
</tr>
<tr>
<td>Centaur, 0.03 ( \mu g/L ) (10% CV)</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>Positive predictive value</td>
</tr>
<tr>
<td>Negative predictive value</td>
</tr>
<tr>
<td>AccuTnI, 0.04 ( \mu g/L ) (99th percentile, SWISCH defined)</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>Positive predictive value</td>
</tr>
<tr>
<td>Negative predictive value</td>
</tr>
<tr>
<td>Centaur, 0.08 ( \mu g/L ) (99th percentile, SWISCH defined)</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>Positive predictive value</td>
</tr>
<tr>
<td>Negative predictive value</td>
</tr>
</tbody>
</table>

\( ^a P < 0.001; ^b P < 0.02. \)

<table>
<thead>
<tr>
<th>Table 2. Concordances between the AccuTnI and Centaur cTnI assays using cutoffs based on 10% CV.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
</tr>
<tr>
<td><strong>cTnI Centaur</strong></td>
</tr>
<tr>
<td>AccuTnI &lt;0.014 ( \mu g/L )</td>
</tr>
<tr>
<td>Death within 1 year</td>
</tr>
<tr>
<td>DMI</td>
</tr>
<tr>
<td>AccuTnI ≥0.014 ( \mu g/L )</td>
</tr>
<tr>
<td>Death within 1 year</td>
</tr>
<tr>
<td>DMI</td>
</tr>
</tbody>
</table>
understand better the relevance of nonincreased cardiac troponin concentrations, we used NT-proBNP as an alternative marker of myocardial dysfunction and compared the proportions of patients with nonincreased cardiac troponin in the patient group that had increased NT-proBNP. For this purpose, the patient cohort was divided into those with NT-proBNP higher than the median concentration for the whole cohort of 669 ng/L (high NT-proBNP) and those with concentrations less than the median for the whole cohort (low NT-proBNP). NT-proBNP concentrations in our patient cohort have been reported (20). Using the 99th percentile cutoff, only 4.4% of the patients had nonincreased AccuTnI concentrations in the high NT-proBNP cohort, compared with 9.3% for the Centaur cTnI Ultra assay (P < 0.0001). Using the 10% CV cutoff, 0.1% of the patients in the high NT-proBNP cohort had nonincreased AccuTnI concentrations, compared with 4.5% for Centaur cTnI (P < 0.0001).

**Discussion**

Only a few cTnI assays are sensitive enough to measure cardiac troponin concentrations below the 99th percentile URL with acceptable imprecision. Two such assays are available—from Siemens, the Centaur cTnI Ultra assay, and from Beckman Coulter, the Access AccuTnI assay. Although both assays are highly sensitive, significant differences were seen in their capacity to identify patients at risk of premature death from cardiovascular disease. These differences were most obvious when cutoff concentrations of 10% CV imprecision were used in the comparisons, but were also suggested when the 99th percentiles URL were used. Our study again emphasizes the importance of highly sensitive assays with low imprecision for the detection of all patients at risk.

The differences in numbers of deaths identified by the 2 assays were quite substantial and also highly dependent on the applied cutoff. As can be deduced from Tables 2 and 3, all 108 patients who died had concentrations higher than the 10% CV cutoff of AccuTnI, but only 92 patients were identified using the 99th percentile URL; thus, there was a gain in diagnostic sensitivity of 16 patients if the lower cutoff was applied. Similar (but less impressively different) figures were obtained when comparing use of the 10% CV and 99th percentile cutoffs with the Centaur cTnI Ultra assay. In previous studies, we suggested the antibody configuration of the cTnI assays to be an important factor in determining their relative clinical performance (8). Assays such as the old AxSym assay from Abbott Diagnostics, the Liaison assay from Diasorin, and the Immulite 2500 cTnI assay from former DPC (Diagnostics Products Corporation) all had an inferior clinical performance compared with the AccuTnI assay (2, 9), whereas the reconfigured cTnI Architect assay from Abbott Diagnostics achieved a performance similar to that of the AccuTnI assay (8).

The configuration of the Centaur cTnI assay is very similar to the Abbott Architect assay, with 2 antibodies directed against epitopes in the heart-specific region of troponin I, amino acids 27–40 and 41–49, and 1 directed against the epitope 87–91. The performance of the Centaur assay was therefore expected to be similar to that of the AccuTnI assay, and because we did not find this to be the case, it is important to consider possible reasons. One is the fact that the AccuTnI is more sensitive in its present setup, since we estimated the 10% CV concentration to be 0.014 μg/L and therefore well below the 99th percentile URL. From the regression analysis, this should correspond to 0.025 μg/L for the Centaur assay, which is fairly close to the 10% CV concentration of 0.03 μg/L. Also, the 99th percentile cutoffs are close to the theoretical concentrations based on comparisons from the regression analysis, since 0.04 μg/L should correspond to about 0.072 μg/L and the actual 99th percentile was 0.08 μg/L. Thus,

### Table 3. Concordances between the AccuTnI and Centaur cTnI assays using cutoffs based on 99th percentile URL (SWISCH defined).

<table>
<thead>
<tr>
<th>n (%)</th>
<th>cTnI Centaur &lt;0.08 μg/L</th>
<th>cTnI Centaur ≥0.08 μg/L</th>
<th>AccuTnI vs Centaur cTnI concordance, %</th>
<th>Differences in proportions (McNemar test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death within 1 year</td>
<td>285 (22.8)</td>
<td>7 (0.6)</td>
<td>88.9</td>
<td>P = 0.003 (death within 1 year); P = 0.07 (DMI)</td>
</tr>
<tr>
<td>DMI</td>
<td>6 (2.1)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AccuTnI ≥0.04 μg/L</td>
<td>133 (10.6)</td>
<td>827 (66.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death within 1 year</td>
<td>12 (9.0)</td>
<td>80 (9.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMI</td>
<td>7 (5.3)</td>
<td>79 (9.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
although slight differences in analytical sensitivities could explain part of the differences in clinical performance, other analytical issues may be involved as well. Beckman Coulter optimized their assay recently without changing the antibody configuration of the assay. This optimization resulted in a substantial improvement of the concentration at which 10% CV imprecision is achieved from the previous 0.06 to the current 0.014 μg/L (6, 19). Differences in choice of capture and detection antibodies are other issues that may be of importance, since the Centaur cTnI assay includes, as stated above, an antibody directed against the epitope 87–91 to which autoantibodies may be directed (21). It is therefore possible that a comparison of the Architect assay with the improved AccuTnI would have had similar results to the Centaur comparison and that the differences in the assays relate to the inclusion of this antibody in the assay and the interferences of autoantibodies.

One of the major issues raised in recent years regarding cardiac troponin measurement is how sensitive the assays should be. No clear answer to this question has yet been given, but it is quite apparent that the more sensitive the assays are, the more patients are actually identified at risk of premature death. This was clearly shown in cohorts of ACS patients (6, 22), but also in population-based studies (3, 11). In this study, we have shown in a high-risk population cohort of non–ST-elevation ACS that lowering the cutoffs allows the detection of substantially more patients at risk, since no deaths were found to occur with cTnI concentrations below the 10% CV cutoff for AccuTnI. To validate this cutoff further, we related the classification of patients by this cutoff to that of NT-proBNP as another marker of myocardial dysfunction. Interestingly, only 1 patient with cTnI below this cutoff had NT-proBNP concentrations above the median. When using the 99th percentile URL as a cutoff, an additional 54 patients below that higher cutoff also had NT-proBNP above the median. In comparison with Centaur cTnI, however, these numbers were much lower, indicating that a substantial proportion of patients may be presenting with high-risk left ventricular dysfunction and are therefore misjudged when higher cutoffs or less-sensitive troponin assays are used in risk stratification.

This study has some limitations. One is the definition of the 99th percentile of the upper reference limit. We have deliberately used the SWISCH cohort for these purposes, since its age and sex distribution is similar to that of the GUSTO IV cohort. However, it is quite likely that some of the elderly subjects had a subclinical disease with slightly increased concentrations, and that the true 99th percentile of healthy subjects has been overestimated. However, for the assay comparison it seemed important to define the cutoffs in the same cohort. Another limitation may be the fact that the samples were run in different laboratories involving different personnel with samples that had been stored frozen for a substantial length of time. Even if previous studies indicated that plasma cardiac troponin I is very stable during storage (23), we cannot exclude some alterations in the antigenicity of the molecule that may have affected the 2 assays differently. It is noteworthy that no differences were seen between the assays when compared by means of ROC-curve analyses. This inability, however, may reflect the relative insensitivity of ROC-curve analysis to identify differences in assay performances in studies with relatively few events (24). Such analysis should therefore be complemented by alternative means of comparison, as was shown in this report.

We conclude from this study that when using comparable cutoffs, the AccuTnI assay identified more patients with poor outcomes and at risk of premature death in cardiovascular disease than the Centaur cTnI Ultra assay. The differences may be partly explained by the greater analytical sensitivity of the AccuTnI assay, but are probably also related to the overall configurations of the assays, including choice of antibodies. Our study also shows the utility of highly sensitive cardiac troponin assays for the identification of patients at risk and clearly indicates that the adoption of the 99th percentile URL for risk prediction of patients with the acute coronary syndrome has major limitations and should be reevaluated.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (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: B. Lindahl: member of scientific advisory board, Beckman Coulter; member of advisory board, Siemens (both compensated).

Stock Ownership: None declared.

Honoraria: P. Venge: lecture fees from Abbott, Beckman Coulter, DPC, Siemens, Roche.

Research Funding: P. Venge: for studies on cardiac biomarkers from Abbott, Beckman Coulter, DPC, Roche, Radiometer. The study was supported by funding from Uppsala University Hospital (ALF-fundings) and from Beckman Coulter Inc.

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, or preparation or approval of manuscript.

Acknowledgments: The expert technical assistance of Charlotte Gruvestrom and Cecilia Olven is greatly appreciated.
References

1. Apple FS, Jesse RL, Newby LK, Wu AH, Christen-son RH. National Academy of Clinical Biochemis-
try and IFCC Committee for Standardization of
Markers of Cardiac Damage Laboratory Medicine
Practice Guidelines: analytical issues for bio-
chemical markers of acute coronary syndromes.
2. Venge P, Johnston N, Lagerqvist B, Wallentin L,
Lindahl B. Clinical and analytical performance of
the Liaison cardiac troponin I assay in unstable
coronary artery disease, and the impact of age on
the definition of reference limits. A FRISC II sub-
3. Zethelius B, Johnston N, Venge P. Troponin I as a
predictor of coronary heart disease and mortality
in 70-year-old men: a community-based cohort
4. Apple FS, Quist HE, Doyle PJ, Otto AP, Murakami
MM. Plasma 99th percentile reference limits for
cardiac troponin and creatine kinase MB mass for
use with European Society of Cardiology/Ameri-
can College of Cardiology consensus recommenda-
5. Thygessen K, Alpert JS, White HD, Jaffe AS, Apple
FS, Galvani M, et al. Universal definition of myo-
6. Eggers KM, Lagerqvist B, Venge P, Wallentin L,
Lindahl B. Persistent cardiac troponin I elevation
in stabilized patients after an episode of acute
coronary syndrome predicts long-term mortality.
MM. Use of the Centaur Trit-Ultra assay for de-
tection of myocardial infarction and adverse
events in patients presenting with symptoms sug-
gestive of acute coronary syndrome. Clin Chem
P. The antibody configurations of cardiac tropo-
nin I assays may determine their clinical perfor-
9. Venge P, Lagerqvist B, Diderholm E, Lindahl B,
Wallentin L. Clinical performance of three cardiac
troponin assays in patients with unstable coro-
mary artery disease (a FRISC II substudy). Am J
Cardiol 2002;89:1035–41.
10. Morrow DA, Rifai N, Sabatine MS, Ayanian S,
Murphy SA, De Lemos JA, et al. Evaluation of the
AccuTnI cardiac troponin I assay for risk assess-
ment in acute coronary syndromes. Clin Chem
11. Zethelius B, Berglund L, Sundstrom J, Ingelsson E,
Busu S, Larsson A, et al. Use of multiple bio-
markers to improve the prediction of death from
2107–16.
12. James SK, Armstrong P, Barnathan E, Califf R,
Lindahl B, Siegbahn A, et al. Troponin and C-
reactive protein have different relations to sub-
sequent mortality and myocardial infarction after
coronary artery disease: a GUSTO-IV substudy.
13. Simoons ML. Effect of glycoprotein IIb/IIIa recep-
tor blocker abciximab on outcome in patients
with acute coronary syndromes without early cor-
onary revascularization: the GUSTO IV-ACS ran-
Venge P, Wallentin L, Lindahl B. Troponin T levels
and risk of 30-day outcomes in patients with the
acute coronary syndrome: prospective verifica-
tion in the GUSTO-IV trial. Am J Med 2003;115:
178–84.
15. Ottervanger JP, Armstrong P, Barnathan ES,
Boersma E, Cooper JS, Ohman EM, et al. Long-
term results after the glycoprotein IIb/IIIa inhibi-
tor abciximab in unstable angina: one-year sur-
vival in the GUSTO IV-ACS (Global Use of
Strategies To Open Occluded Coronary Arteries
IV–Acute Coronary Syndrome) Trial. Circulation
16. Johnston N, Jernberg T, Lindahl B, Lindback J,
Stridsberg M, Larsson A, et al. Biochemical indi-
cators of cardiac and renal function in a healthy
17. Lindahl B, Toss H, Siegbahn A, Venge P, Wallen-
tin L. Markers of myocardial damage and in-
flammation in relation to long-term mortality in
unstable coronary artery disease. FRISC Study
Group. Fragmin during Instability in Coronary
18. Long-term low-molecular-mass heparin in unsta-
ble coronary-artery disease: FRISC II prospective
randomised multicentre study. FRagmin and Fast
Revascularisation during InStability in Coronary
artery disease Investigators. Lancet 1999;354:
701–7.
AW, Venge P, Olson MD, et al. Multicenter eval-
uation of an automated assay for troponin I. Clin
20. James SK, Lindahl B, Siegbahn A, Stridsberg M,
natriuretic peptide and other risk markers for the
separate prediction of mortality and subsequent
myocardial infarction in patients with unstable
coronary artery disease: a Global Utilization of
Strategies To Open occluded arteries (GUSTO)-IV
21. Eriksson S, Halkaus H, Pulkki K, Hellman J, Pet-
terson K. Negative interference in cardiac tropo-
nin I immunoassays by circulating troponin auto-
22. Kucak PA, Newman AM, Lustig V, Macae AR,
Palomaki GE, Ko DT, et al. Long-term health
outcomes associated with detectable troponin I
cardiac troponin I assay for the Access immuno-
24. Obuchowski NA, Lieber ML, Wians F, Jr. ROC
curves in clinical chemistry: uses, misuses, and