Biomarkers for Predicting Serious Cardiac Outcomes at 72 Hours in Patients Presenting Early after Chest Pain Onset with Symptoms of Acute Coronary Syndromes

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BACKGROUND: Most outcome studies of patients presenting early to the emergency department with potential acute coronary syndromes have focused on either the index diagnosis of myocardial infarction (MI) or a composite end point at a later time frame (30 days or 1 year). We investigated the performance of 9 biomarkers for an early serious outcome.

METHODS: Patients (n = 186) who presented to the emergency department within 6 h of chest pain onset had their presentation serum sample measured for the following analytes: creatine kinase, creatine kinase isoenzyme MB, enhanced AccuTnI troponin I (Beckman Coulter), high-sensitivity cardiac troponin T (hs-cTnT), ischemia-modified albumin, interleukin-6, investigation use only hs-cTnI (Beckman Coulter), high-sensitivity cardiac troponin T (hs-cTnT), isoenzyme MB, enhanced AccuTnI troponin I (Beckman Coulter), high-sensitivity cardiac troponin T (hs-cTnT), and cardiac troponin I (Abbott AxSym). We followed patients until 72 h after presentation and determined whether they experienced the following serious cardiac outcomes: MI, heart failure, serious arrhythmia, refractory ischemic cardiac pain, or death. ROC curves were analyzed to determine the area under the ROC curve (AUC) and optimal cutoffs for the biomarkers.

RESULTS: The AUCs for the hs-cTnI assay (0.86; 95% CI, 0.76–0.96), the AccuTnI assay (0.86; 95% CI, 0.78–0.95), and the hs-cTnT assay (0.82; 95% CI, 0.71–0.94) assays were significantly higher than those for the other 6 assays (AUC values ≤0.71 for the rest of the biomarkers, P < 0.05). The ROC curve–derived optimal cutoffs were ≥19 ng/L (diagnostic sensitivity, 80%; specificity, 88%), ≥0.018 µg/L (diagnostic sensitivity, 75%; specificity, 86%), and ≥32 ng/L (diagnostic sensitivity, 68%; specificity, 92%) for the hs-cTnI, AccuTnI, and hs-cTnT assays, respectively.

CONCLUSIONS: The optimal cutoffs for predicting serious cardiac outcomes in this low-risk population are different from the published 99th percentiles. Larger studies are required to verify these findings.

For patients presenting with chest pain to the emergency department (ED),3 the 2007 universal definition of myocardial infarction (MI) states unequivocally that cardiac troponin is the preferred biomarker and that the 99th percentile derived from a healthy population should be used as the cutoff to identify an increased cardiac troponin concentration (1). This recommendation has been substantiated in large studies that have assessed both sensitive and high-sensitivity cardiac troponin assays in both diagnostic and prognostic studies of patients with acute coronary syndromes (ACSs) (2–4). Moreover, recent data have demonstrated that high-sensitivity cardiac troponin assays can identify individuals at risk for an adverse outcome outside of the ACS setting (5–7), further supporting the notion that cardiac troponin may be the optimal biomarker for predicting a cardiac outcome.

Despite these data, it is still unclear whether cardiac troponin is the best marker for predicting a short-term cardiac event in patients presenting early after the onset of chest pain with ACS symptoms. Moreover, there is uncertainty whether high-sensitivity cardiac troponin assays provide benefit in addition to that of sensitive cardiac troponin assays in the emergency setting (8, 9). To address these issues, we evaluated different versions of the troponin assays (both sensitive and high-sensitivity assays) and other markers involved in the ACS setting for short-term (72 h) serious cardiac outcomes for a population with early onset of chest pain.

During a 1-month period in 2003, we enrolled patients in the study if they were ≥18 years of age, had possible cardiac ischemic symptoms within 6 h before presentation, and had a cardiac troponin test ordered by an ED physician (10). Patients were excluded from the study if they refused to participate, were referred directly to trauma or surgery, or had an outcome before the results of their first cardiac troponin test were known. We followed up patients (n = 186) directly at 72 h after presentation to determine if they experienced any of the study outcomes: MI, heart failure, serious arrhythmia, refractory ischemic cardiac pain, or death.

3 Nonstandard abbreviations: ED, emergency department; MI, myocardial infarction; ACS, acute coronary syndrome; cTnI, cardiac troponin I; CK, creatine kinase; CK-MB, CK isoenzyme MB; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hs-cTnT, high-sensitivity cardiac troponin T; IL-6, interleukin-6; hs-cTnI, high-sensitivity cTnI; AUC, area under the ROC curve.
A cardiologist and an emergency physician independently adjudicated these serious cardiac outcomes while blinded to the biomarker data, except for cardiac troponin I (cTnI) (Abbott AxSym), which was used clinically (10). See outcome definitions in Table 1 in the Data Supplement that accompanies the online version of this Brief Communication at http://www.clinchem.org/content/vol58/issue1. Additional demographic and study entry information may also be found in the original report on this study population (10). This study received research ethics board approval.

After enrollment, all blood samples for analysis were transported immediately to the laboratory, where the serum was separated after clotting and either tested for biomarkers or stored in liquid nitrogen (10). The biomarkers measured (and platforms) in 2003 in this population were creatine kinase (CK) (Roche Modular P instruments), CK isoenzyme MB (CK-MB), cTnI (Abbott AxSym), and ischemia-modified albumin (Ischemia Technologies) (10). In 2011, a serum aliquot was thawed (first thaw) and analyzed for the following biomarkers (and platforms): N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) (Roche Elecsys 2010); interleukin-6 (IL-6), enhanced AccuTnI (Beckman Coulter), and high-sensitivity cardiac troponin I (hs-cTnI) (Beckman Coulter Access II). The CVs for the assays over the testing period were <3% for NT-proBNP and <6% for IL-6 with manufacturer control material. For the cardiac troponin assays and a low-concentration patient pool material, the CVs were 23% at 0.015 µg/L for the enhanced AccuTnI assay (n = 16), 9.6% at 13.7 ng/L for the hs-cTnI assay (n = 17), and 14% at 12.5 ng/L for the hs-cTnT assay (n = 19). The stability of these biomarkers in long-term storage below −70 °C has previously been demonstrated (12, 13).

Percentages for samples from individuals exceeding the various cutoffs, diagnostic sensitivity, diagnostic specificity, positive predictive value, and negative predictive value (with 95% CIs) were calculated for the combined serious outcome (death, MI, heart failure, serious arrhythmia, refractory ischemic cardiac pain). We analyzed ROC curves for the serious outcome and MI alone with the biomarkers by evaluating the area under the ROC curve (AUC) by nonparametric means and determining the 95% CI with the DeLong variance estimate. The Delong–Clarke-Pearson method was used to compare ROC curves. Finally, descriptive statistics and differences between groups were evaluated by nonparametric methods and were analyzed with StatsDirect (StatsDirect Ltd.), Analyse-it (Analyse-it Software), and SAS (SAS Institute) software. A P value <0.05 was considered statistically significant.

With an outcome at 72 h, 24 individuals from the cohort (12.9%; 95% CI, 8.4%–18.6%) had at least one serious cardiac outcome (14 outcomes of MI, 5 of heart failure, 3 of serious arrhythmia, and 9 of refractory ischemic cardiac pain). There were no differences between those with and those without an outcome with respect to age, total CK concentration, ischemia-modified albumin concentration, and IL-6 concentration at presentation (Table 1). ROC curve analyses of the 9 biomarkers revealed 3 clusters with different AUCs (Fig. 1). One cluster had nonsignificant AUCs (CK, ischemia-modified albumin, and IL-6 with AUCs...

### Table 1. Associations between cardiac biomarkers and serious outcomes in an ED population with potential ACS (N = 186).

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Serious 72-h cardiac outcome (n = 24)</th>
<th>No serious 72-h cardiac outcome (n = 162)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (n = 186: 24 + 162)</td>
<td>65 (56–73)</td>
<td>59 (49–73)</td>
<td>0.24</td>
</tr>
<tr>
<td>hs-cTnI, ng/L (n = 159: 20 + 139)</td>
<td>39 (19–367)</td>
<td>6.8 (4.7–12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>hs-cTnT, ng/L (n = 178: 22 + 156)</td>
<td>43 (14–94)</td>
<td>4.6 (2.9–12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Enhanced AccuTnI, µg/L (n = 172: 20 + 152)</td>
<td>0.05 (0.016–0.55)</td>
<td>0.005 (0.002–0.12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-6, ng/L (n = 163: 20 + 143)</td>
<td>3.4 (2.9–4.1)</td>
<td>3.7 (1.9–7.3)</td>
<td>0.70</td>
</tr>
<tr>
<td>NT-proBNP, ng/L (n = 172: 21 + 151)</td>
<td>506 (139–3137)</td>
<td>123 (38–419)</td>
<td>0.004</td>
</tr>
<tr>
<td>Abbott AxSym cTnI, µg/L (n = 185: 24 + 161)</td>
<td>0.30 (0.30–2.3)</td>
<td>0.30 (0.30–0.30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CK-MB, µg/L (n = 171: 23 + 148)</td>
<td>4.0 (1.0–8.0)</td>
<td>2.0 (1.0–3.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>IMA&lt;sup&gt;c&lt;/sup&gt;, U/L (n = 173: 23 + 150)</td>
<td>84 (80–98)</td>
<td>89 (81–94)</td>
<td>0.78</td>
</tr>
<tr>
<td>Total CK, U/L (n = 186: 24 + 162)</td>
<td>103 (74–160)</td>
<td>102 (63–155)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

* Data are presented as the median (interquartile range).
* Wilcoxon Mann–Whitney test.
* IMA, ischemia-modified albumin.
Another cluster consisted of AUCs ranging from 0.69 to 0.71 for CK-MB, NT-proBNP, and an older version of a CTnI assay (Abbott AxSym). The last cluster consisted of the sensitive and high-sensitivity cardiac troponin assays, all of which yielded significantly higher AUCs (ranging from 0.82 to 0.86) compared with the AUCs for CK-MB, NT-proBNP, and the less sensitive CTnI assay ($P < 0.05$; see Table 2 in the online Data Supplement).

Application of the published 99th percentiles for the AccuTnI assay ($\geq 0.04 \mu g/L$), the hs-cTnI assay ($\geq 10 ng/L$), and the hs-cTnT assay ($\geq 14 ng/L$) (14, 15) yielded the following proportions of positive cases in the cohort: 13.4% (95% CI, 8.7%–19.4%), 39.0% (95% CI, 31.4%–47.0%), and 30.3% (95% CI, 23.7%–37.7%), respectively. The diagnostic sensitivity and diagnostic specificity for predicting a serious outcome with the 99th percentiles were: 60.0% (95% CI, 36.1%–80.9%) and 92.8% (95% CI, 87.4%–96.3%), respectively, for the AccuTnI assay, 80.0% (95% CI, 56.3%–94.3%) and 66.9% (95% CI, 58.4%–74.6%) for the hs-cTnI assay, and 77.3% (95% CI, 54.6%–92.2%) and 76.9% (95% CI, 69.5%–83.3%) for the hs-cTnT assay. The ROC curve–optimized cutoffs were 0.018 $\mu g/L$, 19 ng/L, and 32 ng/L for the AccuTnI, hs-cTnI, and hs-cTnT assays, respectively. Applying these cutoffs produced the following diagnostic sensitivities and diagnostic specificities: AccuTnI assay, 75% (95% CI, 51%–91%) and 86% (95% CI, 79%–91%), respectively; hs-cTnI assay, 80% (95% CI, 56%–94%) and 88% (95% CI, 81%–93%); hs-cTnT assay, 68% (95% CI, 45%–86%) and 92% (95% CI, 87%–96%) (Fig. 1). Using either the 99th percentile or the optimized cutoffs yielded negative predictive values $\geq 95\%$ (see Table 3 in the online Data Supplement).

ROC curve analyses for MI alone for the sensitive and high-sensitivity cardiac troponin assays yielded the following AUCs (optimal cutoffs): 0.96 (95% CI, 0.91–1.00) for the AccuTnI assay (optimal cutoff, $\geq 0.05 \mu g/L$), 0.95 (95% CI, 0.88–1.00) for the hs-cTnI assay (optimal cutoff, $\geq 38 ng/L$), and 0.94 (95% CI, 0.89–0.99) for the hs-cTnT assay (optimal cutoff, $\geq 35 ng/L$).

Our data further describe the clinical performance of high-sensitivity cardiac troponin assays for patients who present early after possible ACS symptoms. Importantly, the data demonstrate that concentrations higher than the published 99th percentiles (derived from healthy, younger populations) are perhaps more suitable for early risk stratification (i.e., 72 h) in a low-risk population. This conclusion is in line with a previous report that investigated the use of a prototype hs-cTnI assay with an unselected high-risk ED population, which also indicated that concentrations higher than the 99th percentile (e.g., $> 40 ng/L$) might be of more prognostic importance for outcomes at 30 days (16).
For the sensitive AccuTnI assay, however, the optimal cutoff for predicting MI was equivalent to the 99th percentile for this assay (>0.04 μg/L), with lower concentrations (0.02 μg/L) being useful for identifying serious outcomes. This result is in line with other studies that assessed long-term outcomes with the AccuTnI assay, which also indicated that concentrations >0.02 μg/L are important for cardiovascular outcomes (17, 18). This divergence between sensitive and high-sensitivity assays may be more heavily attributed to the analytical sensitivity and imprecision at very low concentrations, where the CV of the enhanced AccuTnI assay is higher than the CV of the hs-cTnI assay. Unlike the hs-cTnT assay, in which concentrations (<50 ng/L) (15) measured with the hs-cTnT assay are higher than the fourth-generation cTnT assay, there is correlation between the AccuTnI and hs-cTnI assays for detectable concentrations (16). This finding may be the reason for the similar cutoffs for the enhanced AccuTnI assay and the hs-cTnI assay (0.018 μg/L, or 18 ng/L, for the AccuTnI assay vs 19 ng/L for the hs-cTnI assay, for predicting a serious outcome).

Our data also lend further support for using sensitive and high-sensitivity cardiac troponin assays for early risk stratification in the ED setting, given that the other assays were either not informative or less prognostic, findings consistent with those of previous reports that assessed early markers (2, 19). Our finding of the optimal cutoff for the hs-cTnI assay for an early serious cardiac outcome is the same concentration (i.e., 19 ng/L) as the 99th percentile for an older population (>60 years) (20). Thus, in addition to obtaining cutoffs based on outcomes, future studies assessing high-sensitivity cardiac troponin assays may also wish to explore age- and sex-specific cutoffs, as have already been identified for the hs-cTnT assay (15).

There are limitations to our study. First, the study population was small and selected and was from a single center. Second, the limited number of outcomes preceded a definitive concentration cutoff for predicting a serious cardiac outcome with these assays. A larger study assessing hard end points (e.g., cardiovascular death) might be preferred to using outcomes in which the cardiac troponin value is part of the diagnosis (e.g., MI). Third, we assessed only the presentation sample; later samples might provide more diagnostic and prognostic information with respect to outcomes. Despite these shortcomings, a strength of our study was the exclusion of patients for whom a diagnosis had been made before the first cardiac troponin result became available, because patients with obvious disease may impart a bias when biomarkers are evaluated. In summary, our findings further solidify the role of sensitive and high-sensitivity cardiac troponin assays for risk stratification of patients presenting early to the ED with potential ACS symptoms.

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References


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