Introduction

Cardiovascular disease is the leading cause of mortality for both sexes worldwide. Approximately 1 in 10 people visiting the Emergency Department (ED) present with signs and symptoms suggestive of Acute Myocardial Infarction (AMI). The majority of patients will be negative for AMI or have other conditions. Those diagnosed with AMI need immediate treatment, and thus it is important that patients be triaged expeditiously upon arrival to the ED. Cardiac biomarkers are central for the early diagnosis of AMI, along with ECG and clinical assessment. Cardiac troponins (cTn: cTnI and cTnT) are released from the heart soon after AMI and are the preferred biomarkers for this use. Over the past 20 years the analytical sensitivity and precision of cTn assays have improved for very low cTn concentrations. The most analytically sensitive assays are termed “high-sensitivity cardiac troponin” (hs-cTn) and are defined in universal expert consensus documents. The advantages of hs-cTn assays include aiding clinicians with the diagnosis and risk stratification in patients presenting to the ED with suspected AMI; this has led to potential opportunities for decreased congestion and length of time spent in the ED and healthcare cost savings.

High-sensitivity cardiac troponin I assays are not harmonized or standardized; values from one assay cannot be directly compared with those from another assay, and cutoff values must be determined for each assay. For the management of non-ST-elevation-acute coronary syndrome (NST-ACS) patients, the 2020 European Society of Cardiology (ESC) recommends the use of rapid 0/1 hour (h) and 0/2h well-validated algorithms over 0/3h algorithms for rule-in and rule-out of AMI along with clinical evidence of acute myocardial ischemia. For rule-out of AMI, the ESC optimal thresholds are very low values at presentation, or low values coupled with absence of notable change after 1h or 2h. For AMI rule-in, the ESC thresholds are high values at presentation, or a significant change on serial sampling. Those who do not fall into either category are triaged for continued observation. Alternatively, the 2018 Fourth Universal Definition of Myocardial Infarction (4th UDMI) document defined AMI as clinical evidence of acute myocardial ischemia accompanied by a rise and/or fall in cTn values (>50% change in initial value if initial value <99th percentile upper reference limit (URL), and >20% change in initial value if initial value >99th percentile URL) with at least one value above the 99th percentile URL—along with other hallmarks of AMI. Good precision is imperative for rule-out strategies (based on very low and low cutoff values), for determining significant changing patterns, and for rule-in strategies based on the 99th percentile URL. Myocardial injury (cell necrosis/death) conditions other than AMI are also characterized by elevated levels of cTn (above the 99th percentile URL) and require careful clinical assessment. Acute myocardial injury conditions other than AMI may also demonstrate a significant rising/falling pattern, but elevated concentrations in chronic myocardial injury conditions remain fairly stable compared to the significant rising and/or falling pattern seen in acute myocardial injury patients.

High-Sensitivity Cardiac Troponin Literature Compendium (Part 2)

In Part 2 of this compendium, the first article consolidates prior expert guidance on the use of hs-cTnI assays (mainly for the U.S.) with respect to assay type (POC vs. central lab), sex-specific cutoffs, serial testing, single-test rule-out, and reporting units. The remaining six articles describe studies using the Siemens Healthineers assays to determine the following: biological variation (Atellica® IM High-Sensitivity Troponin I Assay); clinical validation of the 0/1h algorithm in a Japanese population (ADVIA Centaur® High-Sensitivity Troponin I Assay); value of risk scores in combination with a hs-cTnI result (Atellica IM High-Sensitivity Troponin I Assay); efficacy of a single-test rule-out at presentation (ADVIA Centaur High-Sensitivity Troponin I Assay); association of carotid intima-media thickness with hs-cTnI levels (ADVIA Centaur High-Sensitivity Troponin I Assay); and 99th percentile URL values according to methods used for identifying outliers (ADVIA Centaur High-Sensitivity Troponin I Assay).
List of Articles in Compendium

Implementation of High-sensitivity Cardiac Troponin into Clinical Practice
Wu AHB, Lynch KL. MLO: Medical Laboratory Observer. 2020 Feb 8–12.

The European Biological Variation Study (EuBIVAS): Weekly Biological Variation of Cardiac Troponin I Estimated by the Use of Two Different High-sensitivity Cardiac Troponin I Assays (Atellica IM High-Sensitivity Troponin I Assay)

Prospective Validation of 0-hour/1-hour Algorithm Using High-sensitivity Cardiac Troponin I in Japanese Patients Presenting to Emergency Department (ADVIA Centaur High-Sensitivity Troponin I Assay)

The Utility of Risk Scores When Evaluating for Acute Myocardial Infarction Using High-sensitivity Cardiac Troponin I (Atellica IM High-Sensitivity Troponin I Assay)

Single Test Rule-out of Acute Myocardial Infarction Using the Limit of Detection of a New High-sensitivity Cardiac Troponin I Assay (ADVIA Centaur High-Sensitivity Troponin I Assay)

Carotid Intima-Media Thickness is a Predictor of Subclinical Myocardial Damage in Men with Type 2 Diabetes Mellitus (ADVIA Centaur High-Sensitivity Troponin I Assay)

Establishing the 99th Percentile of a Novel Assay for High-sensitivity Troponin I in a Healthy Blood Donor Population (ADVIA Centaur High-Sensitivity Troponin I Assay)

Increases in High-Sensitivity Cardiac Troponin I in Athletes during a Long-Term Period of Routine Training Out of Competition (Atellica IM High-Sensitivity Troponin I Assay)

Outpatient Versus Observation/Inpatient Management of Emergency Department Patients Rapidly Ruled-out for Acute Myocardial Infarction: Findings from the HIGH-US Study

No Increase in the Incidence of Cardiac Troponin I Concentration above the 99th Percentile by Siemens ADVIA Centaur High-sensitivity Troponin I Compared to the Contemporary Assay. (ADVIA Centaur)

Glossary of Terms

ACS:  Acute coronary syndrome
AMI:  Acute myocardial infarction
APACE: Advantageous Predictors of Acute Coronary Syndrome Evaluation
AUC:  Area under the curve
d:  Day(s)
ECG:  Electrocardiography
ED:  Emergency department
h:  Hour(s)
High-STEACS:  High-Sensitivity Troponin in the Evaluation of Patients with Acute Coronary Syndrome
hs-cTn:  High-sensitivity cardiac troponin
LoB:  Limit of blank
LoD:  Limit of detection
LoQ:  Limit of quantitation
URL:  99th percentile upper reference limit
NIST:  National Institute of Standards and Technology
NPV:  Negative predictive value
NSTEMI:  Non-ST-elevation myocardial infarction
PPV:  Positive predictive value
QC:  Quality control
ROC:  Receiver operator curves
SRM:  Standard reference material
STEMI:  ST-elevation myocardial infarction
Tn:  Cardiac troponin
U.S.  United States Federal Food and Drug Administration
Implementation of High-sensitivity Cardiac Troponin into Clinical Practice
Wu AHB, Lynch KL. MLO: Medical Laboratory Observer. 2020 Feb 8-12.

Objective
Summarize steps for successful launch of hs-cTn assays.

<table>
<thead>
<tr>
<th>1st-gen cTn Assays</th>
<th>2nd-gen cTn Assays</th>
<th>hs-cTn</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>History</td>
<td>History</td>
</tr>
<tr>
<td>Approved for many years outside the U.S. (Conformite Europeene (CE). U.S. FDA approvals:</td>
<td>• 2011 Mitsubishi PATHFAST POC benchtop hs-cTnI</td>
<td>• 2017 Roche Diagnostics 5th-gen hs-cTnT</td>
</tr>
<tr>
<td>• 2018 Beckman hs-cTnI</td>
<td>• 2018 Siemens Healthineers hs-cTnI</td>
<td>• 2019 Abbott Laboratories hs-cTnI</td>
</tr>
<tr>
<td>History</td>
<td>History</td>
<td>History</td>
</tr>
<tr>
<td>Cutoffs</td>
<td>Cutoffs</td>
<td>Cutoffs</td>
</tr>
<tr>
<td>• ROC derived for AMI vs. non-AMI.</td>
<td>• ROC derived for AMI vs. non-AMI.</td>
<td>• ROC derived for AMI vs. non-AMI.</td>
</tr>
<tr>
<td>• Tn undetected in healthy subjects.</td>
<td>• Able to stratify short-term risk of mild increases in cTn.</td>
<td>• 99th percentile URL cutoff for myocardial injury and AMI.</td>
</tr>
<tr>
<td>• Specificity reduced for AMI.</td>
<td>• Assay must detect cTn in &gt;50% of each sex above the LoD or LoQ (20% CV).</td>
<td></td>
</tr>
<tr>
<td>Sex-specific cutoffs</td>
<td>Sex-specific cutoffs</td>
<td>Sex-specific cutoffs</td>
</tr>
<tr>
<td>• None</td>
<td>• None</td>
<td>• None</td>
</tr>
<tr>
<td>• FDA requires hs-cTn assays to have separate sex and combined cutoffs.</td>
<td>• Debate as to whether female cutoff will suffice.</td>
<td>• Institution must decide if using separate sex-specific cutoffs.</td>
</tr>
<tr>
<td>Reporting units</td>
<td>Reporting units</td>
<td>Reporting units</td>
</tr>
<tr>
<td>• ng/mL</td>
<td>• ng/mL</td>
<td>• ng/L whole numbers (hs-cTn assays have 10-fold lower values; ng/L conforms to SI units).</td>
</tr>
<tr>
<td>Quality control materials</td>
<td>Quality control materials</td>
<td>Quality control materials</td>
</tr>
<tr>
<td>• NA</td>
<td>• NA</td>
<td>• AACC recommends three QC levels to satisfy both rule-in and rule-out:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. &gt;LoQ and lowest sex-specific 99th percentile URL cutoff</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Close to the highest sex-specific 99th percentile URL cutoff</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. High, near upper reportable range</td>
</tr>
<tr>
<td>Serial testing</td>
<td>Serial testing</td>
<td>Serial testing</td>
</tr>
<tr>
<td>• At 0, 6, 12 hours</td>
<td>• At 0, 3, 6 hours</td>
<td>• At 0 and 1h (rule-out NPV 99.7%; 18% rule-in; 50% safe discharge)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• At 0 and 2h (rule-out NPV 99.7%; 18% rule-in; 50% safe discharge)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• At 0 and 3h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Used low value—significant serial change after 1, 2, or 3h, or very low presentation (0h) value alone.</td>
</tr>
<tr>
<td>Single cTn for rule-out</td>
<td>Single cTn for rule-out</td>
<td>Single cTn for rule-out</td>
</tr>
<tr>
<td>• No</td>
<td>• No</td>
<td>• Lower cutoff at LoD will allow &gt;99% NPV, but LoD not allowed by FDA in U.S.</td>
</tr>
<tr>
<td>Point-of-care device status</td>
<td>Point-of-care device status</td>
<td>Point-of-care device status</td>
</tr>
<tr>
<td>• Not sensitive or high-sensitivity</td>
<td>• Not sensitive or high-sensitivity</td>
<td>• No handheld devices are FDA-approved yet.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Issues and opportunities are listed.</td>
</tr>
</tbody>
</table>

Authors’ Conclusions
• “Understand that diseases besides AMI will produce abnormal results.”
• “Prior to implementation, it is essential that members of the ED, cardiologists and clinical laboratory meet to discuss the ramifications of hs-cTn assays” such as “change of units and...sex-specific cutoff limits.”
• Aim of “hs-cTn assays is to reduce the time for AMI rule-out and improve accuracy of AMI diagnosis and risk stratification for future adverse cardiac events.”

Significance
• Analytical sensitivity and precision of hs-cTn assays are much improved at low clinical decision cutoffs, allowing earlier rule-out.
• Values are to be reported in ng/mL and in whole numbers.
• Use of sex-specific cutoffs are recommended when using the 99th percentile URLs.
• Many myocardial injury conditions in addition to AMI are now detected above the 99th percentile URL with hs-cTn assays. A significant rising/falling serial change can differentiate acute myocardial injury from stable myocardial disease but is not totally specific for AMI. Thus, diagnosis must be made in conjunction with clinical assessment and electrocardiogram.
• Need to educate staff.
Objective
Determine the within- and between-subject weekly biological variation (BV) or cTnI using hs-cTnI assays on the Singulex Clarity System (no longer on market) and Atellica® IM Analyzer.

Methods
Weekly fasting blood draws from about 90 subjects over 10 weeks.

Results

<table>
<thead>
<tr>
<th></th>
<th>Atellica IM Analyzer</th>
<th>Singulex Clarity System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample type</td>
<td>Serum</td>
<td>EDTA plasma</td>
</tr>
<tr>
<td>Number of subjects detectable (%) male and female</td>
<td>74.3</td>
<td>99.4</td>
</tr>
<tr>
<td>Within-subject BV (CV1) (%) for same subjects</td>
<td>13.9</td>
<td>15.6</td>
</tr>
<tr>
<td>Between-subject BV (CVG) (%) for same subjects Men: 59.5 Women: 36.3</td>
<td>Men: 65.5 Women: 42.3</td>
<td></td>
</tr>
<tr>
<td>Analytical variation (CV A) (%)</td>
<td>10.7</td>
<td>10.8</td>
</tr>
<tr>
<td>Analytical performance specification (APS) for precision (CV APS) (%)</td>
<td>6.9</td>
<td>8.3</td>
</tr>
<tr>
<td>Analytical performance specification (APS) for bias (BAPS) (%)</td>
<td>9.7</td>
<td>10.9</td>
</tr>
<tr>
<td>Relative change value (RCV) (%); decrease/increase</td>
<td>–33.4/50.1</td>
<td>–37.4/59.7</td>
</tr>
<tr>
<td>Index of individuality Men: 0.40 Women: 0.40</td>
<td>Men: 0.33 Women: 0.44</td>
<td></td>
</tr>
</tbody>
</table>

\[ CV_{APS} = 0.5CV_1 \]
\[ B_{APS} = 0.25(CV_1^2 + CV_G^2)^{0.5} \]

- hs-cTnI detectable % (male and female): Atellica IM Analyzer: 74.3%; Singulex: 99.4%; higher in men.
- For Atellica IM Analyzer, 60% of women had values above the LoD, consistent with previous reports.
- Within-subject BV (CV1) same for men and women.
- Analytical performance specifications and reference change values were similar for both assays.

Authors’ Conclusions
- “First study able to estimate cTnI biological variation for such a large cohort...deriving objective analytical performance specifications and relative change values for detecting significant variations in cTnI serial measurements, even within the 99th percentile.”
- “BV estimates based on weekly sampling...results thus cannot be directly applied to AMI diagnosis.”

Significance
- The Atellica IM High-Sensitivity Troponin I Assay provides estimates for BV parameters in healthy subjects outside of an ED setting.
- The number of measurable samples above the LoD was consistent with manufacturers’ specifications.
- The lower values found in women versus men are in line with published reports.
- The relative change values confirm estimates by other reports when <99th percentile URL.
Prospective Validation of 0-hour/1-hour Algorithm Using High-sensitivity Cardiac Troponin I in Japanese Patients Presenting to Emergency Department


Objective
Validate the 0/1h algorithm (established in a derivation study with the European Advantageous Predictors of Acute Coronary Syndrome Evaluation [APACE] cohort) in a Japanese population using the ADVIA Centaur High-Sensitivity Troponin I assay.

Methods
• Included over 700 Japanese patients presenting to the ED with suspicious NSTEMI.
• The cTnI concentration was determined using the ADVIA Centaur High-Sensitivity Troponin I assay at presentation and after 1h.
• Patients were placed in three groups according to the algorithm (established with the APACE Cohort): – Rule-out: <3 ng/L if chest pain onset >3h, or <6 ng/L + delta 1h <3 ng/L. Safety was measured by negative predictive value (NPV) for NSTEMI. – Rule-in: ≥120 ng/L, or delta 1h ≥12 ng/L. Accuracy was measured by positive predictive value (PPV). – Observe: all remaining patients.
• Efficacy of algorithm was determined by proportion of patients triaged as rule-out or rule-in within 1h.

Results
• Prevalence of NSTEMI was 7.4%.
• Rule-out: NPV was 100% and sensitivity 100%, similar to previous reports.\textsuperscript{17-20}
• Rule-in: PPV was 37.1% and specificity was 79.6%.

Authors’ Conclusions
“The 0-hour/1-hour algorithm using hs-TnI is very safe and effective in triaging Japanese patients with suspected NSTEMI.”

Significance
In an Asian population, results for the 0/1h algorithm support previously published reports for the ADVIA Centaur High-Sensitivity Troponin I assay in European (APACE)\textsuperscript{17} and High-Sensitivity Cardiac Troponin I Assays in the United States (HIGH-US)\textsuperscript{19} cohorts, and for the Atellica IM High-Sensitivity Troponin I Assay in European High-Sensitivity Troponin in the Evaluation of Patients with Acute Coronary Syndrome (HIGH-STEACS)\textsuperscript{20} and HIGH-US\textsuperscript{19} cohorts.
The Utility of Risk Scores when Evaluating for Acute Myocardial Infarction Using High-sensitivity Cardiac Troponin I


Objective
Compare the prognostic utility of three cardiac risk stratification scores (TIMI, HEART, sEDACS), each in combination with an hs-cTnI assay result.

Methods
• Secondary analysis of HIGH-US study.
• Over 2000 patients with suspicious AMI; 29 hospitals in the U.S.
• Samples tested using the Atellica IM High-Sensitivity Troponin I Assay.
• Low-risk scores included cTnI <45 ng/L (99th percentile URL) and one of the following at 0 and 2–3h.
  – The Thrombolysis in Myocardial Infarction (TIMI) score = 0
  – History, Electrocardiogram, Age, Risk Factors, and Troponin (HEART) score ≤3
  – Simplified Emergency Department Assessment of Chest Pain Score (sEDACS) ≤15
• Some elements of the HEART score and the sEDACS were modified.
• 30 d MACE for AMI, mortality, and revascularization was determined.

Results
• At 30 d, 12.1% were diagnosed with AMI; 1% deaths; 9.1% revascularizations.
• Elevated hs-cTnI was found in 86.6% of those that died or with AMI.
• The rate for death or AMI at 30 d was 0–0.83%, within the <1% accepted missed MACE rate.
• HEART and sEDACS identified about three times more subjects at low risk vs. TIMI score.

Authors’ Conclusions
• “The HEART score and sEDACS identified more low-risk patients compared with the TIMI score.”
• “With the advent of hs-TnI assays, the incremental value of existing risk scores appears to be reduced, with most prognostic power tied to presenting hs-TnI levels.”

Significance
Low-risk patients identified by the HEART and sEDACS scores combined with hs-cTnI could be considered for discharge from the ED.
**Single Test Rule-out of Acute Myocardial Infarction Using the Limit of Detection of a New High-sensitivity Troponin I Assay**


**Objective**
Determine the diagnostic accuracy of the ADVIA Centaur High-Sensitivity Troponin I assay for AMI in patients presenting to the ED with suspicious acute coronary syndromes.

**Methods**
- Bedside Evaluation of Sensitive Troponin (BEST) study in United Kingdom.
- About 1000 patients; 14 centers; presentation <12h of symptom onset.
- Serial testing at 0h and after 3–6h.
- Primary outcome: adjudicated AMI diagnosis.
- Incidence of major adverse cardiac events (MACE) after 30 d.
- LoD, LoB determinations according to CLSI Document EP17-A.
- Analysis stratified by <3h or >3h from symptom onset (54% of patients <3h).

**Results**
- 13% were diagnosed with AMI.
- Using LoQ <3 ng/L cutoff (in fact they did not use the LoD 1.6 but the LoQ 2.5 [rounded to 3.0 ng/L]): sensitivity 100%; NPV 99.7%; rule out about 27% of patients; MACE in 0.7% patients. No difference in the absence of ECG ischemia.
- Using higher 5 ng/L cutoff: sensitivity 99.2%; NPV 99.8%; rule out about 50% of patients; MACE in 1.4% patients.
- A single hs-cTnl of ≥120 ng/L in the ED could rule in AMI with PPV of 88.4% (8.6% of patients).
- LoB and LoD estimates were in accordance with the manufacturer’s package insert, and imprecision values at 10% and 20% CV exceeded the manufacturer’s minimum specifications.
- Diagnostic accuracy was not altered by time (< or >3h) from symptom onset.

**Authors’ Conclusions**
- “The Siemens ADVIA Centaur hs-cTnI assay has high sensitivity and NPV when used to rule out the diagnosis of AMI with a single test in the ED, using a cut-off set at the LoQ of the assay (<3ng/L).”
- “A single hs-cTnl concentration of ≥120 ng/L in the ED could be used to rule in AMI without serial sampling.”
- “This may help to rapidly triage patients...unburdening crowded EDs.”

**Significance**
- The ADVIA Centaur High-Sensitivity Troponin I assay was able to rule out AMI with a single test in the ED using the LoQ cutoff (<3 ng/L) in patients presenting within <12h of symptom onset. At this cutoff, 28.6% of patients were eligible for discharge.
- A single measurement of ≥120 ng/L in the ED was able to rule in AMI with PPV almost 90%. The 99th percentile URL was not invoked.
**Carotid Intima-media Thickness is a Predictor of Subclinical Myocardial Damage in Men with Type 2 Diabetes Mellitus**


**Objective**
Examine the association of hs-cTnI with cardiovascular risk factors and carotid intima-media thickness (cIMT) as a marker of atherosclerosis in patients with type 2 diabetes mellitus (T2DM).

**Methods**
- Over 200 adults with T2DM with 10-y median time of disease.
- Troponin concentrations were measured with the ADVIA Centaur XPT High-Sensitivity Troponin I assay.
- cIMT was evaluated by high-resolution ultrasound.

**Results**
- 93% of T2DM patients had hs-cTnI concentrations below the sex-specific 99th percentile URL (median concentration was 4.0 ng/L).
- hs-cTnI was significantly associated with sex, renal function, and C-reactive protein.
- In men, cIMT and renal function were significantly associated with hs-cTnI.
- In women, only age was significantly associated with hs-cTnI.

**Authors’ Conclusions**
“In a real-world clinical setting in patients with T2DM, cIMT is a predictor of subclinical myocardial damage in men, but not in women.”

**Significance**
- The majority of patients with T2DM had measurable hs-cTnI concentrations using the ADVIA Centaur High-Sensitivity Troponin I assay. Coupled with previous studies showing higher cTn concentrations in T2DM vs. non-diabetics, this study supports obtaining hs-cTn measurements in the risk stratification of patients with T2DM to identify those at increased risk for cardiovascular events.
- Sex-specific associations of cIMT with hs-cTnI were found; therefore, sex-specific risk stratification in T2DM should be performed.
- Only age was associated with hs-cTnI in T2DM women, consistent with age as the major risk factor for cardiovascular death in women.
- Men had higher hs-cTn concentrations than women, consistent with several studies.
Establishing the 99th Percentile of a Novel Assay for High-sensitivity Troponin I in a Healthy Blood Donor Population


Objective
Determine the 99th percentile URL in healthy blood donors using the ADVIA Centaur High-Sensitivity Troponin I assay.

Methods
• Fresh lithium heparin plasma samples were obtained from 100 apparently healthy blood donors.
• The ADVIA Centaur High-Sensitivity Troponin I assay and Roche hs-cTnT, creatinine, NT-proBNP, and glycated hemoglobin (HBA1c) (the latter in EDTA-blood) were measured.
• The 99th percentile URL was determined for males and females separately and combined using nonparametric methods according to CLSI Document C28-A3c.

Results
• The male, female, and combined 99th percentile URLs were much higher than those reported by the manufacturer; however, after different statistical treatment of outliers using Tukey’s test, the values resembled those of the manufacturer.
• Results for Roche cTnT did not differ from the manufacturer using the same methods and analyses as for the ADVIA Centaur High-Sensitivity Troponin I assay.

Authors’ Conclusions
“There is a need for further specifications regarding how subjects used for estimating the 99th percentile of cTns in healthy populations should be recruited and how outlier values should be identified, as this can highly influence the diagnostic cut-off applied for AMI.”

Significance
• The manufacturer’s 99th percentile URL values were confirmed in this study using an alternative test (Tukey’s) to that used by the manufacturer (Reed’s) to remove outliers.
• The estimate of the 99th percentile URL diagnostic cutoff depends on how healthy patients are recruited and how cutoff and outlier values are determined. Initially, 99th percentile URL values for the ADVIA Centaur High-Sensitivity Troponin I assay were much higher than the manufacturer’s, but after exclusion of outliers using Tukey’s test, results agreed with those in the manufacturer’s package insert.
• All subjects reported working out before sample collection, and this was speculated to possibly have caused the higher values for the ADVIA Centaur High-Sensitivity Troponin I assay.
Increases in High-sensitivity Cardiac Troponin I in Athletes During a Long-term Period of Routine Training Out of Competition

DOI: 10.1093/clinchem/hvaa129.

Objective
Examine cTnI concentrations during stable (no high-endurance) athletic training; if cTnI increased, duration of increase, effect of high-intensity training, and time since the latest training were assessed.

Methods
• Atellica IM High-Sensitivity Troponin I Assay: LoD 1.3 ng/L (Note: IFU LoD is 1.6 ng/L). Total of 292 blood samples.
• Used sex-specific 99th percentiles: male: 54 ng/L; female: 39 ng/L.
• 30 healthy athletes (15 male) from triathlon clubs exercising >13h per week.
• High endurance was defined as heart rate >82% of maximum heart rate.
• Samples were collected each month for 11 months (no high-endurance exercise allowed for 24h before sample draw; low, medium exercise allowed during 24h before sample draw).

Results
• For those with and without exercise during the previous 24h, 18% of female samples (from four females) and 22% of male samples (from seven males) had at least one value >99th percentile URL.
• For those with exercise during the prior 24h, 29% of samples (from five males and three females) were >99th percentile URL vs. 9% of samples (from three males and three females) with no exercise during the previous 24h.
• Hs-cTnI concentration was significantly different for those exercising during 24h before sample draw vs. those who rested.
• Negative correlation was obtained between hs-cTnI and hours since the last exercise.

Authors’ Conclusions
“hs-cTnI values above the 99th percentile were observed in athletes under stable training conditions. The performance of moderate exercise in the time frame of 24h before sampling was directly related to hs-cTnI concentration, and hs-cTnI concentrations were also inversely related to the elapsed time since the last exercise session.”

Significance
Clinicians should be aware of variations in cTnI concentrations when using hs-cTnI assays in athletes visiting the emergency room.
Outpatient Versus Observation/Inpatient Management of Emergency Department Patients Rapidly Ruled-out for Acute Myocardial Infarction: Findings from the HIGH-US Study


Objectives
• To describe clinical characteristics of the AMI ruled-out patients placed in observation/inpatient beds (OBS/ADM) vs. those with an ED discharge (EDD) using the HIGH-US 0/1h study algorithm.
• To describe the cardiac testing and interventions that were completed in the AMI ruled-out group placed in OBS/ADM.

Methods
• Adults (2113) presenting with suspicious AMI were enrolled (2015-2016) in 29 US medical centers. There were no exclusion criteria. The study included a final count of 2022 adults.
• Baseline and 1-hour plasma samples were analyzed using the Siemens Atellica IM High-Sensitivity Troponin I Assay (99th percentile URL: 45.2 ng/L). AMI diagnosis was independently adjudicated by a combination of cardiologists and ED physicians using local contemporary cTn assays and clinical data.
• All cardiac stress test (CST), coronary angiogram (CA) and coronary revascularization (CR) reports for the OBS/ADM patients were analyzed.

Results
• 1020 (50.4%) individuals were ruled out for AMI at 1 hour (of which 584 [57.3%] were EDD and 436 [42.7%] were placed in OBS/ADM) by contemporary clinical assessment; none had an AMI/death while in hospital. At 30 days, one AMI and one death (2 or 0.5%) had occurred. Cardiac testing was not performed in 176 (40.4%) individuals.
• The cardiac testing and/or interventions completed in some remaining patients were:
  - 175 (40.1%) had a CST with most results 143 (81.7%) normal, and 32 (18.3%) abnormal.
  - Coronary angiography was done in 11 (34.4%) with abnormal and in 13 (9.1%) with normal CST. About 50% patients in each group with a CST had abnormal CA results.
  - Of the 85 (19.5%) patients receiving a CA without prior CST, 47 (55.3%) were abnormal.
  - Of AMI ruled out OBS/ADM patients, 26 (6.0%) had a CR procedure (one coronary artery bypass surgery and 25 percutaneous coronary interventions). Also, the mean length of stay was longer in the OBS/ADM group compared to those discharged from the ED (2.0 vs. 0.6 days, p <0.001).

• The 30-day and one-year AMI/death rates in these two groups were low and not significantly different—0.2% for 30-day and <3% for one-year.
• The HIGH-US 0/1h study algorithm—rule-out: 50.4%, NPV: 99.7%, and sensitivity: 98.7%.

Authors’ Conclusions
• “Patients in rapid hs-cTn rule-out AMI zones have very low 30-day adverse outcomes.”
• “In the HIGH-US study 43% of these patients were not ED discharged by the clinicians.”
• “They had more risk factors for AMI and 26 (6%) received coronary revascularization.”
• “One-year AMI/all cause death rates were very low, suggesting all could be discharged.”
• “Recent reports suggest these patients with new/prior CAD can be medically managed.”

Significance
For patients at very low risk for AMI/death within 30 days, those with a history of coronary artery disease (CAD), stroke, hypertension, or having an abnormal ECG, or a family history of CAD were more likely placed in OBS/ADM than EDD. Decisions to place these patients in OBS/ADM could be reduced based on the excellent prognosis for these patients and the 0/1h rapid algorithm. This would lead to shorter lengths of hospital stay and fewer patients receiving CSTs, CAs, and CR procedures.
**No Increase in the Incidence of Cardiac Troponin I Concentration above the 99th Percentile by Siemens ADVIA Centaur High-Sensitivity Troponin I Assay Compared to the Contemporary [ADVIA Centaur] Assay.**


**Objective**

To compare the Siemens Healthineers ADVIA Centaur TnI-Ultra (contemporary) and High-Sensitivity Troponin I (hs-cTnI) assays for the number of subjects with cTnI concentrations >LoQ, and the sex-specific 99th percentile URL.

**Methods**

- 1056 patients presenting to NY hospital. Paired samples were analyzed and simultaneously tested using the hs-cTnI assay.
- Contemporary assay equivalent values for LoD=6 ng/L; LoQ=30 ng/L; 99th percentile URL=40 ng/L.
- Hs-cTnI values for LoQ=2.5 ng/L; 99th percentile URL (male=57 ng/L; female=37 ng/L).
- Analytical performance for each instrument was monitored three times per day using biomarker controls (BioRad).
- Validation was performed at a separate institution on about 500 patients.

**Results**

- ED samples >99th percentile URL (>700 samples)
  - Contemporary vs. hs-cTnI
    - Male 21.5% vs. 16.6% (not significant)
    - Female 21.1% vs. 19.6 (not significant)
- ED samples >LoQ
  - Contemporary vs. hs-cTnI
    - 27% vs. 86%
- All samples number >99th percentile URL (>1000 patients)
  - Contemporary vs. hs-cTnI:
    - Male 38.7% vs. 31.4% (significant)
    - Female 30.2% vs. 27.4% (not significant)
- All samples number >LoQ
  - Contemporary: Male=43.9%; female=36.1%
  - Hs-cTnI: Male=93.8%; female=85.7%.

**Authors’ Conclusions**

“Concentration above the sex-specific 99th percentile URLs is not expected to increase after switching from contemporary cTnI to the hs-cTnI assay. Our findings, confirmed in an independent patient cohort from another academic institute, have important implications to other hospitals which will transition to the hs-cTnI assay.”

**Significance**

The hs-cTnI assay on the ADVIA Centaur System did not increase the proportion of patients with elevated cTnI above the sex-specific 99th percentile when compared to the contemporary ADVIA Centaur TnI-Ultra assay. In fact, the same is true for another hs-cTnI assay (Abbott). This should reassure and encourage physicians who are fearful to transition on this basis.
References:


At Siemens Healthineers, our purpose is to enable healthcare providers to increase value by empowering them on their journey toward expanding precision medicine, transforming care delivery, and improving patient experience, all made possible by digitalizing healthcare.

An estimated 5 million patients globally benefit every day from our innovative technologies and services in the areas of diagnostic and therapeutic imaging, laboratory diagnostics, and molecular medicine, as well as digital health and enterprise services.

We are a leading medical technology company with over 120 years of experience and 18,000 patents globally. Through the dedication of more than 50,000 colleagues in 75 countries, we will continue to innovate and shape the future of healthcare.

ADVIA Centaur, Atellica, and all associated marks are trademarks of Siemens Healthcare Diagnostics Inc., or its affiliates. All other trademarks and brands are the property of their respective owners.

Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.