Cardiac Troponin: Impact of Assay Sensitivity on Patient Management

Linda C. Rogers, PhD, DABCC, FACB
Take Home Messages

✓ Troponin assays differ numerically due to:
  ✓ Standardization
  ✓ Detection antibodies (assays detect different fragments)

✓ Numerical values DO NOT correlate with the sensitivity of the assay

✓ Improved sensitivity of troponin assays translates to:
  #1  smaller areas of necrosis are detectable
  #2  earlier detection following injury
  #3  shorter serial testing protocols
Increasing Sensitivity of cTn Assays Enables Detection of Smaller Areas of Necrosis

Assay sensitivity impacts time to detection

0 and 3-6 hr?

or

0 and 6-12 hr?

“When troponin was a lousy assay it was a great test, but now that it’s a great assay it’s a lousy test.”

“…cardiac troponin is an organ specific biomarker, not a disease specific marker. Thus improved sensitivity has proved to be a two-edged sword…”

Robert Jesse, MD
Third universal definition of MI (2012):
Biochemical criteria for acute MI (AMI)

1. Evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia.

2. Detection of a rise or fall of cardiac biomarker values, preferably cTn, with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

   - Symptoms of Ischemia
   - New or presumed new significant ST-segment-T wave changes or new left bundle branch block (LBBB)
   - Development of pathological Q waves in the ECG
   - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
   - Identification of an intracoronary thrombus by angiography or autopsy.
3rd Universal Definition of MI (2012)

- Cardiac Troponin (cTn) critical to the identification of NSTEMI
- A changing cTn pattern aids differentiation of AMI from other causes of chronic cTn elevation
- As cTn is not standardized, the 99th percentile of the assay URL is used
- 5 different types of MI are defined

Each of the 5 types defines a value for \( \text{cTn} \) for a diagnosis
Type 1 MI: Plaque rupture, ulceration, fissuring, erosion or dissection with resulting thrombus

Ischemia produces cardiac damage

cTn>99th percentile and showing a changing pattern

**Type 2 MI: Ischemic imbalance**

- Vasospasm or endothelium dysfunction
- Fixed atherosclerosis and supply-demand imbalance

**Thygesen et al. Eur Heart J. 2012;33;2251-67.**

- cTn > 99\textsuperscript{th} percentile and showing a changing pattern

© Siemens Healthcare Diagnostics Inc. 2015 All rights reserved.

Page 8 2015-03-16 A91DX-CAI-141249-GC1-4A00
LETTER TO THE EDITOR

Angiographic Correlates in Type 1 and 2 MI by the Universal Definition

A total of 224 patients were identified and studied: 193 with type 1 and 31 with type 2 MI

Conclusions:

- Nearly all type 1 STEMI patients (95%) had an identifiable culprit lesion
- In type 1 NSTEMI patients, an identifiable culprit lesion was found in 56%
- Of the 31 type 2 MI patients, only 1 had an identifiable culprit vessel

Ambrose et al, JACC, 5(4) 2012.
AMI and the 99th Percentile of a Normal Healthy Reference Population

CV of ≤10% at the 99th percentile

Theoretically: 100% of AMI's detected and a 1% error rate

Healthy reference population w/detectable cTn
Analytic Performance Varies Among cTn Assays (2009)

Opinions

A New Season for Cardiac Troponin Assays:  
It's Time to Keep a Scorecard

Fred S. Appel*

**Table 1. Scorecard designations of cTn assays.**

<table>
<thead>
<tr>
<th>Acceptance designation</th>
<th>Total imprecision at the 99th percentile, CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline acceptable</td>
<td>≤10</td>
</tr>
<tr>
<td>Clinically usable</td>
<td>&gt;10 to ≤20</td>
</tr>
<tr>
<td>Not acceptable</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

© Siemens Healthcare Diagnostics Inc. 2015 All rights reserved.

Page 11    2015-03-16  A91DX-CAI-141249-GC1-4A00  K. Soreng, K. Wilson, R. Levy / Global Marketing
<table>
<thead>
<tr>
<th>Type</th>
<th>Company</th>
<th>Platform</th>
<th>99th percentile µg/L</th>
<th>CV% at 99th percentile</th>
<th>CV 10% µg/L</th>
<th>Ratio CV 10%/99th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central lab</td>
<td>Siemens</td>
<td>ADVIA Centaur®</td>
<td>0.040</td>
<td>8.8%</td>
<td>0.030</td>
<td>0.75</td>
</tr>
<tr>
<td>POC</td>
<td>Siemens</td>
<td>Stratus® CS</td>
<td>0.070</td>
<td>8.2% (0.067)</td>
<td>0.060</td>
<td>0.86</td>
</tr>
<tr>
<td>Central lab</td>
<td>Siemens</td>
<td>Dimension Vista®</td>
<td>0.045</td>
<td>&lt;10%</td>
<td>0.040</td>
<td>0.89</td>
</tr>
<tr>
<td>Central lab</td>
<td>Siemens</td>
<td>Dimension® EXL™</td>
<td>0.056</td>
<td>&lt;10%</td>
<td>0.050</td>
<td>0.89</td>
</tr>
<tr>
<td>Central lab</td>
<td>Ortho</td>
<td>VITROS ECi ES</td>
<td>0.034</td>
<td>10%</td>
<td>0.034</td>
<td>1.00</td>
</tr>
<tr>
<td>Central lab</td>
<td>Abbott</td>
<td>ARCHITECT</td>
<td>0.028</td>
<td>14%</td>
<td>0.032</td>
<td>1.14</td>
</tr>
<tr>
<td>POC</td>
<td>Abbott</td>
<td>i-STAT</td>
<td>0.080</td>
<td>17%</td>
<td>0.100</td>
<td>1.25</td>
</tr>
<tr>
<td>Central lab</td>
<td>Roche</td>
<td>Elecsys (TnI)</td>
<td>0.160</td>
<td>NA</td>
<td>0.300</td>
<td>1.88</td>
</tr>
<tr>
<td>Central lab</td>
<td>Siemens</td>
<td>Dimension® RxL</td>
<td>0.070</td>
<td>20%</td>
<td>0.140</td>
<td>2.00</td>
</tr>
<tr>
<td>Central lab</td>
<td>Beckman</td>
<td>Access AccuTnI /+3</td>
<td>0.02</td>
<td>20%</td>
<td>0.04</td>
<td>2.00</td>
</tr>
<tr>
<td>Central lab</td>
<td>Roche</td>
<td>Elecsys (TnT gen 4)</td>
<td>0.010</td>
<td>NA</td>
<td>0.030</td>
<td>3.00</td>
</tr>
<tr>
<td>POC</td>
<td>Alere</td>
<td>Triage Cardiac</td>
<td>&lt;0.050</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Guideline Acceptable
Clinically Usable
The 99th Percentile Is Assay-specific Assays Available in the U.S.

Adapted from Apple et al Clin Chem 2012;58:1574-1581
Serial cTn should be obtained at presentation and at 3-6 hours. Assess change value in cTn (rising or falling pattern) using the 99th percentile and >20% change.

Additional cTn testing beyond 6 hours if time of symptom onset is unclear or if clinical suspicion for MI remains.

“Clinicians should be aware of the sensitivity of the tests used for troponin evaluation in their hospitals and cut-point concentrations for clinical decisions.”

“Depending on the assay, values may not become abnormal for up to 12 hours.”
A guideline acceptable troponin assay could potentially show a significant change at 3 hrs as opposed to 6 hrs for a clinically useable assay thereby expediting the diagnosis of myocardial infarction.

An early diagnosis of myocardial infarction facilitates rapid decision making and treatment and therefore improves the outcome in patients presenting with symptoms of chest pain.
Impact of Age on Diagnostic Cut-points

Early Diagnosis of Acute Myocardial Infarction in the Elderly Using More Sensitive Cardiac Troponin Assays

Compared 4 troponin assays at presentation. (Serial sampling after 1, 2, 3, and 6 h to ascertain diagnosis)
1098 patients presenting with chest pain; 406 of patients >70 years of age

- Siemens TnI-Ultra (sensitive)
- Abbott cTnI (sensitive)
- Roche cTnT-hs (5th gen)
- 4th gen cTnT (standard)

- Diagnostic accuracy was significantly greater for the s-cTn assays compared with the standard 4th gen Roche cTnT assay.
Impact of Age on Diagnostic Cut-points

Early Diagnosis of Acute Myocardial Infarction in the Elderly Using More Sensitive Cardiac Troponin Assays

Cardiac marker level (% of peak)

Time since admission, h

Patients > 70 years

Patients ≤ 70 years

- Abbott Troponin I
- Siemens TnI-Ultra
- Standard assay, 4th gen cTnT
- Roche cTnT-hs
Earlier rule-out with sensitive, guideline-compliant assays?

“Although the achieved NPV’s of 99% for 1 h and 2 h algorithms (either very high), it is important to highlight that they should only be obsersted clinically “in conjunction with full clinical assessment including patient history and exam, and the 12-lead ECG.”

“30-day mortality was 0.2% for patients assigned to the rule-out zone, further documenting the safety of this approach and the suitability of many of these patients for early discharge.”
Earlier rule-out with sensitive, guideline-compliant assays?

“When used in conjunction with other clinical information including the ECG, a simple algorithm incorporating s-cTnI* values at presentation and after 1 h (or 2 h) will allow safe-rule-out and accurate rule-in of AMI in the majority of patients.”

Note: 41.5% (n=901) were defined as “early presenters” (chest pain onset <3 h) and 58.5% (n=1272) had chest pain onset >3 h

*s-cTnI assay used was the Siemens TnI-Ultra
Summary from publications

- Published data supports clinically superior performance of sensitive cTnI compared to clinically usable assays such as the 4\textsuperscript{th} gen cTnT
  - Superior performance for more sensitive detection (less time between testing needed)
  - Superior performance in early presenters

- The ACC/AHA recommends a 0 and 3-6 hour testing algorithm if using a sensitive assay
  - Published data do not support the performance in a 0 and 3 hour protocol if using clinically usable assays such as the 4\textsuperscript{th} gen cTnT
  - Published data suggest performance of the Siemens sensitive assays in a 0 and 3 hour protocol (as well as shorter testing algorithms)
  - Published data suggest moving to a 0 and 3-6 hour protocol, which could significantly reduce LOS
Sensitive and High Sensitive cTn for an AMI Diagnosis: Summary

Both sensitive and high sensitive assays support rapid identification of an AMI

Less sensitive assays can miss MI’s

Increased sensitivity can reduce specificity

Increased sensitivity can identify myocardial necrosis earlier and reduce serial sampling times

Use the same assay to assess change as troponin assays differ and produce numerically different results

“Know your troponin”
Linda C Rogers, PhD, DABCC, FACB
Clinical Consultant
Scientific & Clinical Affairs
Siemens Healthcare
Phone: +1 (949) 421-9101
E-mail: rogers.linda@siemens.com

Siemens Healthcare Diagnostics, a global leader in clinical diagnostics, provides healthcare professionals in hospital, reference, and physician office laboratories and point-of-care settings with the vital information required to accurately diagnose, treat, and monitor patients. Our innovative portfolio of performance-driven solutions and personalized customer care combine to streamline workflow, enhance operational efficiency, and support improved patient outcomes.

Product availability may vary from country to country and is subject to varying regulatory requirements.

Answers for life.