Impact of Troponin Performance on Patient Care

Linda C, Rogers PhD, DABCC, FACB
Agenda

- Introduction
- Diagnosis of MI
  - Guidelines
- Troponin
  - Assay differences
  - Classification of troponin assays
- Guideline acceptable vs clinically usable assays
  - Importance in testing protocols
  - Recent studies and comparison
- Definition of high sensitive troponin assays
  - Guideline acceptable vs high sensitive assays
  - Recent studies and comparison
Global Burden of Cardiovascular Disease

2012
31%
of all deaths globally are from cardiovascular disease

2030
23.3 Million CVD deaths globally

80%
occur in low and middle income countries

Number One
cause of death in the industrialized world

http://www.who.int/mediacentre/factsheets/fs317/en/
U.S. Hospitals Are Facing Increased Pressures

Financial Pressure
Healthcare Reform and Quality Metrics
Patient Outcomes
ED Chest Pain Evaluation

Is the patient having an MI?
Acute-care Diagnostic Tests for AMI

Signs and Symptoms

Electrocardiogram

Cardiac Biomarkers

Imaging

Clinical history, risk factors, and physical exam

Amsterdam EA, et al. Circulation 2014;130:e344-426
Chest Pain due to myocardial reasons:

- ACS or AMI or other cardiac damage
- Pulmonary embolism
- Aortic dissection
- Aortic aneurysm
- Pneumonia
- Sickle cell Anemia
- Musculoskeletal injury
- Vascular
- Orthopedic/infectious

Chest Pain due to myocardial reasons:

- ACS or AMI or other cardiac damage
Cardiac Damage Is Often Not ACS-related

Acute Coronary Syndromes

https://www.clinicalkey.com/topics/gerontology/acute-myocardial-infarction.html
A typical situation:
- acute chest pain
- electrocardiogram is non-diagnostic
- low risk for myocardial infarction
- moderate risk for unstable angina

The most critical questions:
- Should the patient be sent home?
- Should the patient be admitted to the cath lab?
Biomarkers Are Critical for Diagnosing the Majority of Patients

Creatine kinase
CK-MB

Cardiac troponin (cTn)
Two types: cTnI and cTnT

Myoglobin

2000: cTn is the preferred biomarker. Values >99th percentile with an assay that has <10%CV at the 99th percentile recommended.

- Integrates new knowledge.
- Small myocardial injury can be detected using sensitive assay or imaging.
- **Rising or falling kinetics** helps discriminate acute from chronic illness.

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.

Five different types of MI are defined.

Each of the five types defines a value for cTn for a diagnosis.

Guideline Acceptable: The 99th Percentile Is Determined Using an Apparently Healthy Reference Population

A CV of ≤10% at the 99th percentile improves the ability to assess change.

99% correct (no pathology)
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

Supply-demand imbalance

Demand

Supply

cTn >99th percentile and showing a changing pattern

AMI Diagnostic Algorithm

Admission → Chest Pain

Working Diagnosis → Acute Coronary Syndrome

ECG → Persistent ST Elevation

Biochemistry → STEMI (12%)

Diagnosis → ST/T Abnormalities

Troponin Rise/Fall → NSTEMI (18%)

Normal or Undetermined ECG → Troponin Normal → Unstable Angina (70%)

Troponin Controls Myofibril Contraction

- cTnC
- Troponin
- cTnI
- cTnT
- Myofibril
- Actin
- Tropomyosin
Release of Cardiac TnI and TnT Have the Same Profile


- cTnI: Primarily I:C complex and complete T:I:C complex
- cTnT: Primarily free TnT, T:I:C trimeric complex, and some smaller immunoreactive fragments

Majority of cTnT is associated with the intact filament
Why do troponin assays differ numerically?

- Standardization
  - No universal standard is currently available
  - Manufacturers use their own standards

- Capture antibodies differ among manufacturers

- Detection antibodies differ among manufacturers

- Troponin is degraded into multiple fragments
  - A troponin assay may or may not detect different fragments

- Numeric values have no relationship to sensitivity of the assay
Troponin I Molecule

Immunoassays use antibodies to bind and capture the troponin molecule. Troponin is degraded in the circulation, therefore the best assay design is to target the stable region.
# Examples of Assay Antibody detection for Troponin I

<table>
<thead>
<tr>
<th>Assay Antibody regions</th>
<th>Cardiac Specific Region</th>
<th>Most Stable Region</th>
<th>Region of proteolytic degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Phosphorylation**
- Ser23, Ser24

**Oxidation**
- Cys80, Cys97

**Heparin Interference**

**Auto-antibody Interference**

**Access (Beckman Coulter)**
- Antibody regions: 24-40, 41-49

**AxSYM and Architect (Abbott)**
- Antibody regions: 20-39, 41-49

**Centaur (Siemens)**
- Antibody regions: 27-40, 41-49

**Liaison (Byk-Sangtec Diagnostica)**
- Antibody regions: 27-39, 41-49

**Vista (Siemens)**
- Antibody regions: 27-32, 41-56

**polyclonal antibody**

**monoclonal antibody**
The 99th Percentile Is Assay-specific Assays Available in the U.S.

Adapted from Apple et al Clin Chem 2012;58:1574-1581
Analytic Performance Varies among cTn Assays (2009)

"A New Season for Cardiac Troponin Assays: It’s Time to Keep a Scorecard"
Clin Chem, 2009

<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>&lt;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>

### Definition of various cardiac troponin assays

<table>
<thead>
<tr>
<th>Classification</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional (clinically not usable)</td>
<td>No 99&lt;sup&gt;th&lt;/sup&gt; percentile or &gt;20% CV at the 99&lt;sup&gt;th&lt;/sup&gt; percentile</td>
</tr>
<tr>
<td>Contemporary-sensitive</td>
<td>Guideline acceptable (&lt;10% CV at the 99&lt;sup&gt;th&lt;/sup&gt; percentile)</td>
</tr>
<tr>
<td>High-sensitive</td>
<td>Guideline compliant (&lt;10% CV at 99&lt;sup&gt;th&lt;/sup&gt; percentile) AND detects &gt;50% of a healthy reference population using LoD.</td>
</tr>
<tr>
<td>All assays</td>
<td>Clinically usable (10-20% CV at the 99&lt;sup&gt;th&lt;/sup&gt; percentile)</td>
</tr>
</tbody>
</table>

## Analytical Characteristics of Troponin Assays

<table>
<thead>
<tr>
<th>Type</th>
<th>Company</th>
<th>Platform</th>
<th>Low End Assay Range µg/L</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>0.0060*</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 System</td>
<td>0.0300*</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® System</td>
<td>0.0150*</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™ System</td>
<td>0.0170†</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>0.012†</td>
<td>0.034</td>
<td>10%</td>
<td>0.034</td>
<td>1.00</td>
</tr>
<tr>
<td>POC</td>
<td>Mitsubishi</td>
<td>PATHFAST cTnl-II</td>
<td>0.007*</td>
<td>0.029</td>
<td>5%</td>
<td>0.014</td>
<td>0.48</td>
</tr>
<tr>
<td>Central Lab</td>
<td>Abbott</td>
<td>ARCHITECT</td>
<td>0.009*</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>0.020*</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>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>0.050*</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>UniCel Dxl AccuTnl +3</td>
<td>0.010†</td>
<td>0.03</td>
<td>20%</td>
<td>0.04</td>
<td>1.33</td>
</tr>
<tr>
<td>Central Lab</td>
<td>Beckman</td>
<td>Access AccuTnl +3</td>
<td>0.010†</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>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>0.050*</td>
<td>&lt;0.050</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Analytical sensitivity †Limit of detection (LoD)

Adapted from Apple. Clinical Chemistry. 2012;58:1; updated 2014

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Impact of Assay Type on Patient Care

What data suggests clinical inequality?

Guideline-compliant sensitive cTn

Less-sensitive cTn

AMI Diagnosis

AHA/ACC Guidelines for Management of NSTEMI


Circ, 2014

• 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.”

Why Serial Testing?

Serial testing can aid differentiation of an elevated cTnI resulting from an AMI from other causes of chronic cTnI elevation.

This is especially important when using sensitive/high-sensitive cTn assays.
Impact of Troponin Precision on Significant Change

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.
Accelerated risk stratification of patients with ACS symptoms may occur at **2 h** post-presentation using troponin results measured by a sensitive* assay.”

“Incorporation of such strategy could support improvements in patient flow within emergency departments.”

*Similar results were found using a longer **0 and 6 hour** testing strategy with the Beckman Accu TnI assay

*Sensitive cTn assay used was Siemens Dimension EXL LOCI cTnI.

“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.

Earlier Rule-out with Sensitive, Guideline Acceptable Assays?

“The 1 h/2 h algorithms assigned 70% of patients a definite process (either rule-out or rule-in), with 30% of patients remaining in the observational zone.”

“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.”

“Although the achieved NPVs for the 1 h and 2 h algorithms were very high, it is important to highlight that they should only be used clinically in conjunction with full clinical assessment including patient history and exam, and the 12-lead ECG.”

Important Aspects of Cardiac Troponin Testing

Sensitivity varies tremendously among commercially available cTn assays.

**Sensitivity** of the tests used for troponin evaluation in their hospitals and cut-point concentrations for clinical decisions differ.

Depending on the assay or time of presentation, values may **not** become abnormal for **up to 12 hours**.

Late presenters may not demonstrate a significant serial change if near the peak, or if troponin levels have declined.

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
Impact of Assay Type on Patient Care

Sensitive cTn

High-Sensitive cTn

AMI Diagnosis
2014: IFCC Task Force on How to Define High Sensitivity

Guideline Acceptable (Sensitive) Assay:

99th percentile cutoff universally endorsed:

- Determined in a healthy population.
- Derived from peer-reviewed literature or manufacturer.
- Analytical precision should be ≤10% CV.

High-sensitive Assay Should be Guideline Acceptable AND:

- High-sensitivity assays (hs assays) should measure cTn >limit of detection (LoD) in ≥50% of the healthy subjects used to determine the 99th percentile.
- Results reported in ng/L or pg/mL instead of µg/L (gives whole-number values instead of decimals for easier interpretation).

“Sensitive’ and ‘high-sensitive’ are terms often used by manufacturers to describe their assays for marketing purposes.”

Don’t Rely on the Name of an Assay

“How a ‘high-sensitivity’ assay is defined has yet to be universally accepted.”

“It is important not to be influenced by the marketed name of the assay but instead rely on the performance characteristics of the assay.”

HS assays detect 50% or more of healthy people >LoD

CV of ≤10% at the 99th percentile

AMI and the 99th Percentile of a Normal Healthy Reference Population

% Population Distribution

LoD

LoB

50th percentile

Healthy

AMI or Other Pathology

cTn Level

100%
The Problem: How Do You Define a Normal “Healthy” Reference Population?

Screening method for “healthy”?
- Questionnaire?
- Clinical testing?

Age range?

Gender?

Ethnicity?

No uniform guidelines.

Each manufacturer and study uses a different reference population.

Increasing Sensitivity of cTn Assays Enables Detection of Smaller Areas of Necrosis

Troponin sensitivity: Does analytically more sensitive always mean an improvement clinically?
Current “Sensitive” cTn Assays

Conclusion

“The diagnostic performance of sensitive cardiac troponin assays is excellent, and these assays can substantially improve the early diagnosis of acute myocardial infarction, particularly in patients with a recent onset of chest pain.”

Most Sensitive and High Sensitive Assays Have Comparable Diagnostic Accuracy


<table>
<thead>
<tr>
<th>Assay</th>
<th>99th percentile cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siemens TnI-Ultra</td>
<td>40 ng/L</td>
</tr>
<tr>
<td>Abbott Architect cTnI</td>
<td>28 ng/L</td>
</tr>
<tr>
<td>Roche hs-cTnT</td>
<td>14 ng/L</td>
</tr>
<tr>
<td>Roche cTnI</td>
<td>160 ng/L</td>
</tr>
<tr>
<td>Roche 4th gen cTnT</td>
<td>35 ng/L (10% CV)</td>
</tr>
</tbody>
</table>

Sensitive vs. High-Sensitive cTn in AMI Diagnosis

“The Clinical and Diagnostic Performance Characteristics of the High-Sensitivity Abbott Cardiac Troponin I Assay”
Clin Biochem, 2015

Compared:
- Abbott hs-cTnI
- Roche hs-cTnT
- Siemens TnI-Ultra
- Siemens Stratus cTnl
- Beckman Accu Tni+3

Samples tested at 0 and 90 minutes post-admission.

Note: In this study, they refer to Siemens and Beckman assays as “contemporary.”

Admission and peak samples for Abbott’s hs-cTnI assay were statistically indistinguishable from the other troponin assays (AUC 0.90–0.94). Use of gender-specific cut points reduced the sensitivity for males but increased the sensitivity for females.
Study of cTnI Sensitivity from Harvard Medical School

“Evaluation of the Diagnostic Performance of Current and Next-Generation Assays for Cardiac Troponin I in the BWH-TIMI ED Chest Pain Study”
Eur Heart J: Acute CV Care, 2013

Compared a current sensitive assay (Siemens TnI-Ultra) to an investigational hs-cTnI assay (Singulex) and a less-sensitive (“local”) cTnI (previous-generation Siemens cTnI).

“A contemporary sensitive assay delivered similar overall accuracy to the investigational test, suggesting that we have reached a point of maximum diagnostic return with increasing analytical sensitivity.”

**Study of cTnl Sensitivity from Harvard Medical School**

"Evaluation of the Diagnostic Performance of Current and Next-Generation Assays for Cardiac Troponin I in the BWH-TIMI ED Chest Pain Study"

_Eur Heart J: Acute CV Care, 2013_

### Table 2. Diagnostic performance for MI of baseline and peak cTnl by assay.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Myocardial infarction (n=381)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline cTnl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>78 (69–86)</td>
<td>97 (95–99)</td>
<td>90 (82–96)</td>
</tr>
<tr>
<td>Tnl-Ultra</td>
<td>94 (87–98)</td>
<td>92 (88–95)</td>
<td>80 (71–87)</td>
</tr>
<tr>
<td>S-Tnl</td>
<td>97 (91–99)</td>
<td>81 (76–85)</td>
<td>63 (55–71)</td>
</tr>
<tr>
<td><strong>Peak cTnl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>97 (91–99)</td>
<td>91 (87–94)</td>
<td>78 (69–85)</td>
</tr>
<tr>
<td>Tnl-Ultra</td>
<td>95 (88–98)</td>
<td>84 (80–89)</td>
<td>67 (59–75)</td>
</tr>
<tr>
<td>S-Tnl</td>
<td>98 (93–100)</td>
<td>74 (69–79)</td>
<td>56 (48–64)</td>
</tr>
</tbody>
</table>

Values are % (95% CI).
cTnl, cardiac troponin I; NPV, negative predictive value; PPV, positive predictive value; S-Tnl, Erenna hS-Tnl, Singulex; Tnl-Ultra, Siemens Healthcare Diagnostics.

High Sensitivity Impacts Specificity

“Do We Really Need High-Sensitivity Troponin Immunoassays in the Emergency Department? Maybe Not”

“It is undeniable that the leading drawback of HS immunoassays is represented by the lower specificity for diagnosing ACS. With awareness of this limitation, the use of serial sampling is virtually irrenunciable for increasing the positive-predictive value of HS methods.”

“Although sensitive cTn assays do present an advantage compared to higher cut point conventional assays, the benefit of higher sensitivity assays compared to sensitive assays in the context of an MI diagnosis is unclear.”

“Highly sensitive assays may, however, cause a diagnostic dilemma as to what to do with newly detectable elevations that do not exceed the 99% MI cutoff.”

Preparing for the Implementation of hs-Assays*

1. Educate lab and clinical staff on relevant literature pertaining to the new assay

2. Understand that the concentration of troponin will change and will not involve a conversion factor

3. Establish a URL at the 99th percentile

4. Change from a single sex to a sex-specific 99th percentile

5. Report only whole numbers in ng/L

6. Define a QC material at the 99th percentile to monitor %CV

Preparing for the Implementation of hs-Assays*

7. Consider using troponin values <LoD of the hs-assay as a potential rule-out characteristic

8. Provide serial testing protocols that consider earlier measurements, such as baseline, 1.5, and 3 hours for diagnostic determinations

9. Educate clinicians that although an increased troponin is reflective of cardiac damage but not for ischemic damage

10. Assure good preanalytical sampling as the hs-assays are so sensitive that poor sample quality can be a problem

Summary: Sensitive and High Sensitive cTn for an AMI Diagnosis

- Both sensitive (guideline acceptable) and high-sensitive assays support rapid identification of an AMI.
- Less-sensitive assays can miss MIs.
- Use the same assay to assess change.
- Improved sensitivity of troponin assays translates to:
  - Detection of smaller areas of necrosis
  - Earlier detection following injury
  - Shorter serial testing protocols

- High sensitive troponin assays are under development but are not yet available in the US
  - Preparation and education of labs and clinicians will be needed prior to implementation
  - New protocols may be needed.
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