A Change in Mindset: Highly Sensitive Cardiac Troponin I

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South Asia

Kuala Lumpur
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Agenda

• Historical diagnosis of ACS

• What’s in a Name of an Assay

• ARCHITECT STAT hsTnI Solution
  • Analytical Performance
  • Clinical Performance
    • Diagnosis
    • Prognosis

• Summary
Defining a High Sensitive Troponin Assay
Estimated 5-8 million patients present to the ED annually for chest pain

20-25% diagnosed with Acute Coronary Syndrome

~2,000,000

Low Risk/Observation Population: The other 6,000,000+ people
Nomenclature and Criteria for Diagnosis of Ischemic Heart Disease

World Health Organization defined myocardial infarction by a combination of 2/3 characteristics:

1. Typical symptoms (chest discomfort)
2. Unequivocal change in ECG pattern with the development of Q or QS waves
3. Unequivocal change in cardiac enzymes (CK, CK-MB)

Myoglobin and Troponin are NOT enzymes

Rapaport et al. (1979) Circ 59:607-609
Baseline Troponin I Levels Predict Risk of Mortality in ACS

Elevated cTnI was associated with increased risk of mortality even in patients whose CK-MB measurements are not considered abnormally elevated.

“[Our study]...emphasizes the use of a single measurement at presentation and describes the quantitative relation between measurements of cTnI and the risk of mortality.”

Baseline cTnI measurement in 1,404 subjects using Dade Stratus II fluorometric EIA (LoD 0.35ng/mL):
- 59% had undetectable cTnI
- 41% had detectable cTnI

Antman et al. (1996) NEJM 335:1342-9
Detection Ranges for Different Generations of Cardiac Troponin Assays

Early Release of Cardiac Biomarkers

Previous scientific evidence suggested myoglobin was the earliest cardiac biomarker released during cardiac injury.

Improvements in the sensitivity of assays demonstrated cardiac troponin T is the earliest marker released in cardiac injury.

Biomarker concentrations [median (IQR)] of all patients at baseline and throughout the study for (A) CK-MB, (B) myoglobin, (C) fourth generation (4th gen.) cTnT assay, and (D) hs-cTnT assay.

Defining a High Sensitive Troponin Assay

**International Federation of Clinical Chemistry (IFCC)**
Task Force Recommendation on Analytical Characteristics

Total imprecision at the 99th percentile value:

≤10% cv

Measurable concentrations below the 99th percentile should be attainable at a concentration value above the assay’s limit of detection for at least:

50% Of Healthy Individuals

**European Society of Cardiology (ESC)**
Clinical Guidelines

Recommended interval to repeat test after initial assessment with high sensitivity assay for rule out:

3-hours

References:
### Analytical characteristics of contemporary sensitive cardiac Troponin assays.

<table>
<thead>
<tr>
<th>Company/platform/assay</th>
<th>LoD, a µg/L</th>
<th>99th Percentile µg/L (CV)b</th>
<th>10% CV, µg/L</th>
<th>% of Normals Detected 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott AxSYM ADV</td>
<td>0.02</td>
<td>0.04 (14%)</td>
<td>0.16</td>
<td>3</td>
</tr>
<tr>
<td>Abbott ARCHITECT STATTnl</td>
<td>0.009</td>
<td>0.028 (14%)</td>
<td>0.32</td>
<td>2</td>
</tr>
<tr>
<td>Beckman Access AccuTnl</td>
<td>0.01</td>
<td>0.04 (14%)</td>
<td>0.06</td>
<td>35</td>
</tr>
<tr>
<td>OCD Vitros ECI ES</td>
<td>0.012</td>
<td>0.034 (10%)</td>
<td>0.034</td>
<td>2</td>
</tr>
<tr>
<td>Response RAMP</td>
<td>0.03</td>
<td>&lt;0.01 (18.5% at 0.05)</td>
<td>0.21</td>
<td>N/A</td>
</tr>
<tr>
<td>Roche Cobas h 232 cTnTcd</td>
<td>0.05</td>
<td>NA (%)</td>
<td>NA</td>
<td>N/A</td>
</tr>
<tr>
<td>Roche Elecsys TnT Gen 4</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>0.030</td>
<td>N/A</td>
</tr>
<tr>
<td>Siemens Centaur Ultra</td>
<td>0.016</td>
<td>0.16 (10%)</td>
<td>0.30</td>
<td>1</td>
</tr>
<tr>
<td>Siemens Dimension RxL</td>
<td>0.04</td>
<td>0.04 (8.8%)</td>
<td>0.03</td>
<td>6</td>
</tr>
<tr>
<td>Siemens Immulite 2500</td>
<td>0.1</td>
<td>0.2 (20%)</td>
<td>0.14</td>
<td>N/A</td>
</tr>
<tr>
<td>Siemens Vista</td>
<td>0.015</td>
<td>0.045 (10%)</td>
<td>0.04</td>
<td>1</td>
</tr>
<tr>
<td>Tosoh AIA</td>
<td>0.06</td>
<td>&lt;0.06 (NA)</td>
<td>0.09</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Analytical characteristics of point-of-care cardiac Troponin assays.

<table>
<thead>
<tr>
<th>Company/platform/assay</th>
<th>LoD, a µg/L</th>
<th>99th Percentile µg/L (CV)b</th>
<th>10% CV, µg/L</th>
<th>% of Normals Detected 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott i-STAT</td>
<td>0.02</td>
<td>0.08 (16.5%)</td>
<td>0.10</td>
<td>6</td>
</tr>
<tr>
<td>Alere Triage</td>
<td>0.05</td>
<td>&lt;0.05 (NA)</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Alere Triage Cardio</td>
<td>0.01</td>
<td>0.02 (17%)</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>BioMérieux Vidas Ultra</td>
<td>0.01</td>
<td>0.01 (27.7%)</td>
<td>0.11</td>
<td>1</td>
</tr>
<tr>
<td>Mitsubishi Pathfast</td>
<td>0.008</td>
<td>0.029 (5.0%)</td>
<td>0.014</td>
<td>N/A</td>
</tr>
<tr>
<td>Radiometer AQ790 xTnl</td>
<td>0.009</td>
<td>0.023 (17.7%)</td>
<td>0.039</td>
<td>N/A</td>
</tr>
<tr>
<td>Radiometer AQ790 xTnT e</td>
<td>0.008</td>
<td>0.017 (15.2%)</td>
<td>0.026</td>
<td>N/A</td>
</tr>
<tr>
<td>Roche Cardiac Reader cTnT e</td>
<td>0.03</td>
<td>NA</td>
<td>NA</td>
<td>N/A</td>
</tr>
<tr>
<td>Siemens Stratus CS</td>
<td>0.03</td>
<td>0.07 (10%)</td>
<td>0.06</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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a LoD, limit of detection; NA, not available; Gen 4, fourth-generation assay.  
b CV at 99th percentile.  
c Not cleared by the US Food and Drug Administration.  
d Standardized against hs-cTnT assay.  
e Standardized against Gen 4 cTnT assay.
What Troponin Assays Are High Sensitive?

### Analytical characteristics of hs cardiac Troponin assays.

<table>
<thead>
<tr>
<th>Company/Platform/Assay</th>
<th>Cardiac Troponin concentration at:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LoD, ng/L</td>
<td>99&lt;sup&gt;th&lt;/sup&gt; Percentile ng/L (CV)</td>
</tr>
<tr>
<td><strong>hs-cTnl</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbott ARCHITECT&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.2</td>
<td>16 (5.6%)</td>
</tr>
<tr>
<td>Beckman Access&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.3</td>
<td>8.6 (10%)</td>
</tr>
<tr>
<td>Nanosphere MTP&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.2</td>
<td>2.8 (9.5%)</td>
</tr>
<tr>
<td>Singulex Erenna&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.09</td>
<td>10.1 (9.0%)</td>
</tr>
<tr>
<td>Siemens Vista&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.5</td>
<td>9 (5.0%)</td>
</tr>
<tr>
<td><strong>hs-cTnT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roche Elecsys&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5.0</td>
<td><strong>14 (8%)</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup> LoD, limit of detection.
<sup>b</sup> CV at the 99<sup>th</sup> percentile.
<sup>c</sup> Under development and not available for commercial use.
<sup>d</sup> Available for use worldwide but not cleared by the US Food and Drug Administration for use in the US.

References:
**This value is based upon results using the Roche Cobas. The same reagent is used for both the Roche Elecsys and Cobas instruments and the performance is the same
Why is total imprecision <10% coefficient of variation at the 99th percentile important?

Why is detecting >50% of normals above the LoD important?
Improved Precision and Sensitivity

- An assay with poor precision at diagnostic cut-off cannot differentiate pre-analytical, analytical or clinical causes of troponin fluctuations, resulting in “false positives” or “false negatives” results.
Importance of CV ≤10% at 99th percentile

Poor imprecision leads to the potential risk of inaccurate rule-out/in

- Suspected ACS patients;
- Followed 500 days;
- Odds of death or recurrent MI in patients stratified by Tn concentration;
- CV at 99\textsuperscript{th} percentile is poor (contemporary assay);
- Potential risk of false positives and false negatives

BMJ 2012;344:e1533
Importance of CV ≤10% at 99th percentile

- 10% CV: 6.0 ng/L
  Aw, Clin Chim Acta, 2013;422:26-8

- 10% CV: 3.9 ng/L

- 10% CV: 5.4 ng/L
  Keller, JAMA, 2011;306(24):2684-93
ARCHITECT STAT hsTnI Assay
Analytical Performance
## What is Different From the Current Assay

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ARCHITECT STAT TnI (LN 2K41)</th>
<th>ARCHITECT STAT High Sensitive TnI (LN 3P25)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Volume</td>
<td>165 µL&lt;sup&gt;1&lt;/sup&gt;</td>
<td>210 µL&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Increased Signal</td>
</tr>
<tr>
<td></td>
<td>(includes 50 µL dead volume)</td>
<td>(includes 50 µL dead volume)</td>
<td></td>
</tr>
<tr>
<td>Antibody Selection</td>
<td>Epitopes: 24-40/87-91&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Epitope: 24-40&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Increased Signal</td>
</tr>
<tr>
<td>Capture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody Selection</td>
<td>Epitope: 41-49&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Epitope: 41-49&lt;sup&gt;4&lt;/sup&gt; Chimeric</td>
<td>Improved Specificity</td>
</tr>
<tr>
<td>Detection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference:
1. ARCHITECT STAT TnI Package 840653_R08
2. ARCHITECT STAT hsTnI Package Insert G45454/R03
**ARCHITECT cTnI & hsTnI**

<table>
<thead>
<tr>
<th></th>
<th>ARCHITECT STAT TnI (LN 2K41)</th>
<th>ARCHITECT STAT hsTnI (LN 3P25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>μg/L (ng/mL)</strong></td>
<td>0.010*</td>
<td>0.002**</td>
</tr>
<tr>
<td><strong>pg/mL (ng/L)</strong></td>
<td>10*</td>
<td>1.9**</td>
</tr>
<tr>
<td><strong>LoQ</strong></td>
<td>N/A</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>10% CV</strong></td>
<td>0.032</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>99th Percentile</strong></td>
<td>0.028</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>99th Percentile (males)</strong></td>
<td>0.033</td>
<td>0.034</td>
</tr>
<tr>
<td><strong>99th Percentile (females)</strong></td>
<td>0.013</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>% Detectable above LoD</strong></td>
<td>&lt;50% of normals</td>
<td>&gt;50% of normals</td>
</tr>
</tbody>
</table>

**Improved sensitivity with lower LoD**

~7x Improvement in the 10% CV concentration without significant change to 99th percentile

References:
1 ARCHITECT STAT TnI Package Insert 840653_R08.
2 ARCHITECT STAT hs Troponin-I Package Insert G45454/R03
A Change in Mindset
High Sensitive Tn Presentation

Put science on your side.

Architect STAT High Sensitive Troponin-I

Frequency

Not Measureable!

High Sensitive LoD

Contemporary LoD

Tnl Level

10% CV

Not Measureable!

10% CV

4.7 pg/mL

Female 99th %ile

15.6 pg/mL

Male

34.2 pg/mL

5.3% CV 4.0% CV 3.5% CV

Precision

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Female

Overall

Male

26.2 pg/mL

10% CV

Cartoon for ARCHITECT STAT hsTnl

ARCHITECT STAT hs Troponin-I Package Insert G45454/R03

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ADD-00002344_v1

A Change in Mindset
High Sensitive Tn Presentation
Distribution of Men and Women According to Type of ACS

Note: Distribution of men and women according to the type of ACS

## Mortality Rate in Women Versus Men

Patients presenting with acute myocardial infarctions from different countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Study Design</th>
<th>Women/Men</th>
<th>Reperfusion (Women vs Men)</th>
<th>Mortality (Women vs Men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>2005</td>
<td>Retrospective</td>
<td>14,552/21,323</td>
<td>PCI: 31% vs 40%</td>
<td>6% vs 4%</td>
</tr>
<tr>
<td>Italy</td>
<td>2002</td>
<td>Retrospective</td>
<td>225/653</td>
<td>Th: 19% vs 41% (p &lt;0.001)</td>
<td>24% vs 13% (p &lt;0.0001)</td>
</tr>
<tr>
<td>Germany</td>
<td>2006</td>
<td>Prospective</td>
<td>2,033/4,033</td>
<td>Th: 41% vs 51% (p &lt;0.02); PCI: 6% vs 9% (p &lt;0.04)</td>
<td>21% vs 12% (p &lt;0.06)</td>
</tr>
<tr>
<td>Thailand</td>
<td>2007</td>
<td>Prospective</td>
<td>1,223/2,613</td>
<td>Th: 28% vs 31% (p &lt;0.03); PCI: 39% vs 49% (p &lt;0.001)</td>
<td>24% vs 14% (p &lt;0.001)</td>
</tr>
<tr>
<td>Israel</td>
<td>2000</td>
<td>Prospective</td>
<td>742/2,175</td>
<td>Th: 42% vs 48% (p = 0.03); PCI: 11% vs 15% (p = 0.007)</td>
<td>18% vs 10% (p &lt;0.0001)</td>
</tr>
<tr>
<td>Lebanon</td>
<td>1999</td>
<td>Prospective</td>
<td>99/334</td>
<td>NA</td>
<td>16% vs 8% (p &lt;0.03)</td>
</tr>
<tr>
<td>Kuwait</td>
<td>2001</td>
<td>Retrospective</td>
<td>89/267</td>
<td>Th: 40% vs 62% (p = 0.001)</td>
<td>21% vs 11% (p = 0.02)</td>
</tr>
<tr>
<td>Qatar</td>
<td>2004</td>
<td>Retrospective</td>
<td>451/1,147</td>
<td>Th: 19.5% vs 28.4% (p = 0.08)</td>
<td>24% vs 14% (p = 0.02)</td>
</tr>
<tr>
<td>Present study</td>
<td>2009</td>
<td>Prospective</td>
<td>1,983/6,183</td>
<td>Th: 80% vs 84% (p = 0.17); PCI: 5% vs 8% (p = 0.07)</td>
<td>14% vs 5% (p &lt;0.001)</td>
</tr>
</tbody>
</table>

NA = not available; Th = thrombolysis; PCI = percutaneous coronary intervention

### Gender Differences Among 19 Different Assays Do Exist

#### 99th Percentile values in a presumably healthy population measured by high-sensitivity, sensitive-contemporary, cTnl and cTnT assays.

<table>
<thead>
<tr>
<th>Manufacturer/Analyzer/Assay</th>
<th>LoD ng/L</th>
<th>Measureable Values &gt; LoD, %</th>
<th>99th percentile of all study participants (90% CI), ng/L</th>
<th>Male 99th percentile ng/L</th>
<th>Female 99th percentile ng/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbott • ARCHITECT i2000&lt;sub&gt;SR&lt;/sub&gt; STAT • hs-cTnl&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.2</td>
<td>96</td>
<td>23 (16-63)</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td>Beckman • Access 2 • hsTnl&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2.5</td>
<td>80</td>
<td>32 (22-69)</td>
<td>52</td>
<td>23</td>
</tr>
<tr>
<td>Roche • Cobas e601 • hs-cTnT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5</td>
<td>25</td>
<td>15 (13-28)</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Siemens • Dimension Vista • hsTnl&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.5</td>
<td>86</td>
<td>58 (34-125)</td>
<td>81</td>
<td>42</td>
</tr>
<tr>
<td>Singulex • Erenna • hsTnI&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.09</td>
<td>100</td>
<td>40 (25-215)</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td><strong>Sensitive contemporary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbott • ARCHITECT i2000&lt;sub&gt;SR&lt;/sub&gt; STAT • cTnl</td>
<td>9</td>
<td>2</td>
<td>13 (&lt;9-23)</td>
<td>20</td>
<td>&lt;9</td>
</tr>
<tr>
<td>Abbott AxSYM ADV Troponin-I</td>
<td>20</td>
<td>3</td>
<td>34 (22-39)</td>
<td>38</td>
<td>29</td>
</tr>
<tr>
<td>Beckman • Access 2 • modified-sensitive cTnl</td>
<td>2.5</td>
<td>35</td>
<td>56 (27-100)</td>
<td>48</td>
<td>85</td>
</tr>
<tr>
<td>OCD • Vitros 3600 • cTnl ES</td>
<td>12</td>
<td>2</td>
<td>19 (12-22)</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Roche • Cobas e 601 • cTnl</td>
<td>160</td>
<td>1</td>
<td>184 (&lt;160-706)</td>
<td>300</td>
<td>60</td>
</tr>
<tr>
<td>Siemens • Centaur • Tnl Ultra</td>
<td>6</td>
<td>6</td>
<td>12 (10-16)</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Siemens • Dimension EXL 200 • cTnl</td>
<td>17</td>
<td>2</td>
<td>34 (17-44)</td>
<td>39</td>
<td>22</td>
</tr>
<tr>
<td>Siemens • Dimension Vista • cTnl</td>
<td>15</td>
<td>1</td>
<td>21 (&lt;15-39)</td>
<td>30</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Siemens • Immulite 2000 XPi • cTnl</td>
<td>100</td>
<td>5</td>
<td>392 (190-520)</td>
<td>394</td>
<td>451</td>
</tr>
</tbody>
</table>

<sup>a</sup> Available for use worldwide but not cleared by the US Food and Drug Administration for use in the US.

<sup>*</sup> In development


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**Put science on your side.**  
A Change in Mindset  
High Sensitive Tn Presenceation  
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# Global Representation of the 99th Percentile Data

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Study Type</th>
<th>Specimen Type</th>
<th>&quot;Definition of Normal&quot;</th>
<th>n</th>
<th>Overall (ng/L or pg/mL)</th>
<th>Male (ng/L or pg/mL)</th>
<th>Female (ng/L or pg/mL)</th>
<th>Age (Overall Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott¹</td>
<td>US</td>
<td>All</td>
<td>BNP, HbA1c, eGFR</td>
<td>4593</td>
<td><strong>26.2</strong></td>
<td><strong>34.2</strong></td>
<td><strong>15.6</strong></td>
<td>≥18 ≤75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EDTA</td>
<td>BNP, HbA1c, eGFR</td>
<td>1531</td>
<td>27.8</td>
<td>35.1</td>
<td>16.7</td>
<td>≥18 ≤75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum</td>
<td>BNP, HbA1c, eGFR</td>
<td>1529</td>
<td>22.3</td>
<td>32.1</td>
<td>14.7</td>
<td>≥18 ≤75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LiHep</td>
<td>BNP, HbA1c, eGFR</td>
<td>1531</td>
<td>26.9</td>
<td>34.5</td>
<td>14.3</td>
<td>≥18 ≤75</td>
</tr>
<tr>
<td>Aw²</td>
<td>Normal Range</td>
<td>Serum</td>
<td>BNP, HbA1c, eGFR</td>
<td>1120</td>
<td>25.6</td>
<td>32.7</td>
<td>17.9</td>
<td>≥35 ≤65</td>
</tr>
<tr>
<td>Apple³</td>
<td>US DNR Study</td>
<td>Li Hep</td>
<td>Blood Donors &amp; Questionnaire</td>
<td>524</td>
<td>23</td>
<td>36</td>
<td>15</td>
<td>≥18 ≤64</td>
</tr>
<tr>
<td>Koerbin⁴</td>
<td>Aussie Normal</td>
<td>Serum</td>
<td>BNP, eGFR</td>
<td>497</td>
<td>13.9</td>
<td>14.6</td>
<td>11.3</td>
<td>≥20 ≤84</td>
</tr>
</tbody>
</table>

The 99th percentile values that were generated in the ARCHITECT STAT hsTnI Package Insert has been verified through different studies globally utilizing different protocols, study populations, and different samples.

Reference:
1. ARCHITECT STAT hs Troponin-I Package Insert G45454/R03
Under-Diagnosis of AMI in Women

High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study

Anoop SV Shah,1 Megan Griffiths,1 Kuan Ken Lee,1 David A McAllister,2 Amanda L Hunter,1 Amy V Ferry,1 Anne Cruikshank,3 Alan Reid,3 Mary Stoddart,4 Fiona Strachan,1 Simon Walker,4 Paul O Collinson,5 Fred S Apple,6 Alasdair J Gray,7 Keith A A Fox,1 David E Newby,1 Nicholas L Mills,1

Prospective Cohort Study
• n = 1126 (46% female)
• Mean age = 66

Serial draws:
1. Admission
2. 6h
3. 12h

Diagnosis:
• Type I MI
• Type II MI
• Myocardial injury
• UA

• ARCHITECT cTnI
  – Single cut-off = 50 ng/L (10% CV)

• ARCHITECT hsTnI:
  – Total cut-off = 26 ng/L
  – Male cut-off = 34 ng/L
  – Female cut-off = 16 ng/L

Under-Diagnosis of AMI in Women

Initial adjudication of NSTEMI using cTnI serial draws

Reclassification using hsTnI single cut-off
- Males: 19% > 23%
- Females: 11% > 16%

Reclassification using hsTnI gender cut-offs
- Males: 19% > 21%
- Females: 11% > 22%

ARCHITECT STAT hsTnI Assay
Clinical Performance—Diagnosis
### Alternative Diagnosis to Cardiac Ischemia for Patients with Chest Pain

#### Non-ischemic cardiovascular
- Aortic dissection*
- Myocarditis
- Pericarditis

#### Chest wall
- Cervical disc disease
- Costochondritis
- Fibrositis
- Herpes zoster (before the rash)
- Neuropathic pain
- Rib fracture
- Sternoclavicular arthritis

#### Pulmonary
- Pleuritis
- Pneumonia
- Pulmonary embolus*
- Tension pneumothorax*

#### Psychiatric
- Affective disorders (eg., depression)
- Anxiety disorders
  - Hyperventilation
  - Panic disorder
  - Primary anxiety
- Somatiform disorders
  - Thought disorders (eg., fixed delusions )

#### Gastrointestinal
- Biliary
  - Cholangitis
  - Cholecystitis
  - Choledocholithiasis
  - Colic
- Esophageal
  - Esophagitis
  - Spasm
  - Reflux
  - Rupture*
- Pancreatitis
- Peptic ulcer disease
  - Nonperforating
  - Perforating*

* Potentially life-threatening conditions.

Adapted from [http://www.uptodate.com/contents/image?imageKey=CARD%2F53227&search=acute com; accessed on 11/18/2013](http://www.uptodate.com/contents/image?imageKey=CARD%2F53227&search=acute com; accessed on 11/18/2013)
What keeps clinicians up at night?

- Among patients with ACS, a common misdiagnosis is gastroesophageal reflux disease.
- Patients with ACS commonly describe their pain as burning.
- Four populations that are more likely to be discharged from the emergency department with ACS include:
  - Women <55 years old
  - nonwhite patients
  - dyspnea as the primary complaint
  - patients with a normal ECG

1. Biomarkers of myocardial necrosis should be measured in all patients who present with symptoms consistent with ACS.

2. The patient’s clinical presentation (history, physical exam) and ECG should be used in conjunction with biomarkers in the diagnostic evaluation of suspected MI.

3. Cardiac troponin is the preferred marker for the diagnosis of MI.

## Other causes of troponin elevation

<table>
<thead>
<tr>
<th>Injury related to primary myocardial ischaemia</th>
<th>Injury not related to myocardial ischaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque rupture</td>
<td>Cardiac contusion, surgery, ablation, pacing, or defibrillator shocks</td>
</tr>
<tr>
<td>Intraluminal coronary artery thrombus formation</td>
<td>Rhabdomyolysis with cardiac involvement</td>
</tr>
<tr>
<td></td>
<td>Cardiotoxic agents e.g. anthracyclines, herceptin</td>
</tr>
<tr>
<td>Injury related to supply/demand of myocardial ischaemia</td>
<td>Multifactorial or indeterminate myocardial injury</td>
</tr>
<tr>
<td>Tachy/brady arrhythmias</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Aortic dissection or severe value disease</td>
<td>Stress (Takotsubo) cardiomyopathy</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Severe pulmonary embolism or pulmonary hypertension</td>
</tr>
<tr>
<td>Severe respiratory failure</td>
<td>Sepsis and critically ill patients</td>
</tr>
<tr>
<td>Severe anaemia</td>
<td>Renal Failure</td>
</tr>
<tr>
<td>Hypertension with our without LVH</td>
<td>Severe acute neurological diseases e.g. stroke subarachoid</td>
</tr>
<tr>
<td>Coronary spasm</td>
<td>Haemorrhage</td>
</tr>
<tr>
<td>Coronary embolism or vasculitis</td>
<td>Infiltrative diseases eg. amloidosis, sarcoidosis</td>
</tr>
<tr>
<td>Coronary endothelial dysfunction without significant CAD</td>
<td>Strenuous exercise</td>
</tr>
</tbody>
</table>

Source: adapted from Thygesen et al. Eur Heart J. 2012;33:2551-67
Myocardial Infarction Diagnosis with Troponin

• The preferred biomarker for myocardial necrosis is cardiac troponin.
• In patients with MI, an initial rise in troponins occurs within 4 hours after symptom onset.
• Troponins may remain elevated for up to 2 weeks.
• There is no fundamental difference between troponin T and troponin I.
• Currently, an “increased value” is defined as a Tn measurement:
  • exceeding the 99th percentile of a normal reference population
  • (URL) previously defined*
  • with an assay that have total imprecision <10%
  • optimal imprecision [coefficient of variation (CV)] at the 99th percentile
    URL for each assay should be defined as ≤10%.

* The percentile must be determined for each specific assay with normal reference population
  (URL = upper reference limit)

Thygesen et al., European Heart Journal, 2012. 33: 2551-2567
Historical use of two cTn cut-offs

A. Myoglobin/CK-MB isoforms after AMI
B. cTn after AMI
C. CK-MB after AMI
D. cTn after unstable angina

AMI DL based upon ROC analysis
URL = 97.5%ile

In 1999 the IFCC suggested the need for two cTn cut-off concentrations:

- A low abnormal value to suggest presence of myocardial damage (97.5%ile healthy population)
- Higher value to suggest diagnosis of AMI (as determined by ROC curve)

Alpert et al. (2000) JACC 36:959-969
Commenting on the ever-increasing sensitivity and decreasing specificity of cTn assays:

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

- Dr Robert Jesse

The early imprecise Troponin assays provided binary results (positive or negative) for diagnosing AMI – could only detect high levels of cTn.
Abbott Proposed Algorithm hsTnI Result Interpretation

Acute Chest Pain NSTE-ACS

Baseline hsTnI Test

<Limit of Detection pg/mL (ng/L)\textsuperscript{3,5,7}

Male ≤34.2 pg/mL (ng/L) \textsuperscript{6,7}
Female ≤ 15.6 pg/mL (ng/L)\textsuperscript{6,7}

Male ≥34.2 pg/mL (ng/L) \textsuperscript{6,7}
Female ≥ 15.6 pg/mL (ng/L)\textsuperscript{6,7}

Highly Abnormal Result (10x 99\textsuperscript{th} Percentile) + Clinical Presentation\textsuperscript{1,8}

Pain >6 Hours\textsuperscript{1}

Pain < 6 Hours\textsuperscript{1}

Retest hsTnI 3 Hours\textsuperscript{1,3,7}

hsTnI No Significant Change

\(\Delta\) change 50\%\textsuperscript{3,7} and / or > gender specific 99\textsuperscript{th} %tile

hsTnI No Significant Change

Pain free, GRACE <140 or TIMI ≤1, differential diagnosis excluded\textsuperscript{1,4}

Discharge/Stress Testing\textsuperscript{1}

Invasive Management\textsuperscript{1}

Work-up Differential Diagnosis\textsuperscript{1}

Invasive Management\textsuperscript{1}

References located on slide 52

*Each institution must determine the appropriate delta for their patients, while this may be a good starting point for evaluation purposes

hsTnI= Abbott STAT high sensitive troponin I, GRACE=global registry of acute coronary events, TIMI=thrombolysis UA/NSTEMI, NSTE-ACS = Non ST Elevation Acute Coronary Syndrome
Detection Ranges for Different Generations of Cardiac Troponin Assays

## Diagnostic Performance for Identification of Acute Myocardial Infarction by Use of Serial hsTnI Determination.

<table>
<thead>
<tr>
<th></th>
<th>hsTnI, % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On Admission</td>
</tr>
<tr>
<td></td>
<td>LoD</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
</tr>
<tr>
<td>LoD</td>
<td>100.0 (98.0-100.0)</td>
</tr>
<tr>
<td>99th Percentile</td>
<td>82.3 (77.3-86.5)</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
</tr>
<tr>
<td>LoD</td>
<td>35.3 (32.3-38.4)</td>
</tr>
<tr>
<td>99th Percentile</td>
<td>92.1 (90.3-93.7)</td>
</tr>
<tr>
<td>Positive predictive Value (PPV)</td>
<td></td>
</tr>
<tr>
<td>LoD</td>
<td>30.8 (27.8-33.9)</td>
</tr>
<tr>
<td>99th Percentile</td>
<td>75.1 (69.9-79.8)</td>
</tr>
<tr>
<td>Negative predictive value (NPV)</td>
<td></td>
</tr>
<tr>
<td>LoD</td>
<td>100.0 (98.4-100.0)</td>
</tr>
<tr>
<td>99th Percentile</td>
<td>94.7 (93.1-96.1)</td>
</tr>
<tr>
<td>No. positive/total</td>
<td></td>
</tr>
<tr>
<td></td>
<td>915/1260</td>
</tr>
<tr>
<td></td>
<td>1241/1260</td>
</tr>
</tbody>
</table>

Abbreviations: cTnI, contemporary sensitive Troponin-I; hsTnI, highly sensitive Troponin-I; LoD, level of detection.

*Number of patients with positive test criteria/number of patients with available data on criteria.

Reference: Adapted from Keller, T., et al., JAMA, 2011; 306 (24): 2684-2693
Ruling Out with LoD

Rubini Giménez, et al., Int J Cardiol, 2013;168:3896-3901
Detection Ranges for Different Generations of Cardiac Troponin Assays

## Dynamic Change Recommendation

### Delta Change

<table>
<thead>
<tr>
<th>High Sensitive Troponin I</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>99th percentile at 30 pg/mL</td>
<td>On admission &gt; 99th percentile</td>
<td>82.3 (77.3-86.5)</td>
<td>92.1 (90.3-93.7)</td>
<td>75.1 (69.9-79.8)</td>
</tr>
<tr>
<td></td>
<td>After 3 hours &gt; 99th percentile</td>
<td>98.2 (95.9-99.4)</td>
<td>90.4 (88.4-92.2)</td>
<td>74.7 (69.9-79.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>On admission or after 3 hours &gt; 99th percentile AND hsTnI Change 0 to 3 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change ≥20%</td>
</tr>
<tr>
<td>Change ≥30%</td>
</tr>
<tr>
<td>Change ≥50%</td>
</tr>
<tr>
<td>Change ≥75%</td>
</tr>
<tr>
<td>Change ≥100%</td>
</tr>
<tr>
<td>Change ≥150%</td>
</tr>
<tr>
<td>Change ≥200%</td>
</tr>
<tr>
<td>Change ≥250%</td>
</tr>
</tbody>
</table>

**hsTnI Clinical Performance**

- Accurate rule out with 99\textsuperscript{th} percentile cutoff
- NPV greater than 99%
- Improved specificity for rule in with relative change and 99\textsuperscript{th} percentile cutoff at 3hr post admission

In the full cohort (Figure, n=1578):
- **AUC for hsTnI**: 0.962
- **AUC for cTnI**: 0.921

With Early Presenters:
- **Chest Pain <2 hours** (n=407):
  - **AUC for hsTnI**: 0.970
  - **AUC for cTnI**: 0.888

ARCHITECT STAT hsTnI Assay
Clinical Performance—Prognosis
Improved Precision and Sensitivity

Why is total imprecision <10% coefficient of variation at the 99th percentile important?

Why is detecting >50% of normals above the LoD important?
Up to 23% of adjudicated MI patients present with levels below the 99th %
Hoeller et. al. heartjnl-2013-303643
Prognostic Performance of hsTnI Assay in Patients NST ACS

Copyright with permission from Bhoula May, et al., *Clin Chem* 2014; 60(1): 158-164.
Prognostic Performance of hsTnI Assay in Patients NST ACS

Graded relationship between hs-cTnI and cardiovascular death or MI at 30 days. Testing for a trend across all categories of hs-cTnI was significant (P-trend < 0.001).

Copyright with permission from Bhoula May, et al., Clin Chem 2014; 60(1): 158-164.
Where else is there hsTnI value

European Heart Journal Advance Access published October 8, 2013

European Heart Journal
do:10.1093/eurheartj/eht406

High population prevalence of cardiac troponin I measured by a high-sensitivity assay and cardiovascular risk estimation: the MORGAM Biomarker Project Scottish Cohort

Tanja Zeller¹, Hugh Tunstall-Pedoe²✉, Olli Saarela³,⁴, Francisco Ojeda¹, Renate B. Schnabel¹, Tarja Tuovinen⁴, Mark Woodward²,⁵,⁶, Allan Struthers⁷, Maria Hughes⁸, Frank Kee⁸, Veikko Salomaa⁴, Kari Kuulasmaa⁴, and Stefan Blankenberg¹✉, for the MORGAM Investigators
General Population Cohorts

Summary

• Abbott ARCHITECT hsTnI meets all the requirements of a hsTnI assay
• Analytical performance is robust
• Excellent detection of “normals”
• Clinical performance
  • Gender specific opportunity
• Low end accuracy for non-acute applications
Thank You