Waiting for High-Sensitivity POCT Cardiac Troponin Assays: Clinical and Analytical Needs
“I Have a Pain in My Chest That Hurts Very Bad”

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http://mmrf.org/about-us/research-programs/cardiac-biomarkers/

Copenhagen Denmark September 24, 2016
AACC CPOCT 26th International Symposium
Apple Disclosures - Biomarkers

- Consultation:
  - Metanomics Healthcare,
  - Philips Healthcare Incubator

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  - Abbott, Beckman, Alere, Roche, OCD, Siemens, Singulex, BD, IL, Trinity, bioMerieux, Nanomix, Davita, Amgen

- Honorarium
  - Abbott POC, Instrumentation Laboratory

- Board of Directors
  - HyTest
Neils Bohr University of Copenhagen
Nobel Prize in Physics 1922
Philosopher, Promotor of Research, Humanitarian
heart attack. or heart attack,

Park Nicollet Heart Center at Methodist Hospital

POCT cTn Assay

High Sensitivity cTn Assay

Minneapolis MN 2005
‘efforts to make sure the right patients get the right treatment…’

Institute of Medicine
I Need A Show of Hands

- Do any labs still use CKMB?
- Do any labs use myoglobin or FABP?
- Who does not use a high sensitivity cTn assay?
- Who uses hs-cTnT assay?
- Who uses hs-cTnI assay?
- Who uses POC testing assays?
- Which labs do not use the 99th percentile URL?
High-Cardiac Troponin on Presentation to Rule Out Acute Myocardial Infarction

Derivation cohort: NPV is 99.6% (95% CI 99.3 to 99.8) at troponin concentrations <5 ng/L

Validation cohorts: NPV is 99.4% (95% CI 99. to 99.8) at troponin concentrations <5 ng/L
### hs-cTnI Myocardial Injury Safety Outcomes: 30-day AMI and Cardiac Death

<table>
<thead>
<tr>
<th>Study cohort</th>
<th>Baseline</th>
<th>Baseline hs-cTnI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hs-cTnI &lt;LoD</td>
<td>&lt;LoD and non-ischemic ECG</td>
</tr>
<tr>
<td>n=448, 27%</td>
<td>99.6 (98.4-100)</td>
<td>99.6 (98.1-100)</td>
</tr>
<tr>
<td>n=283, 17%</td>
<td>98.8 (95.8-99.9)</td>
<td>99.4 (96.8-100)</td>
</tr>
</tbody>
</table>

2 had an AMI, with no cardiac deaths. Miss rate of 0.45% (2/448).
How POC cTn Testing Is, or Could Be, Integrated Into the ACS Management Pathway Depends Primarily on the Setting of Care

1. Most EDs in large urban centers have access to central laboratories 24 hours a day, seven days a week. POC cTn testing may have a role in shortening test result turnaround time, which could help decrease time to discharge if MI is not diagnosed.

2. In settings where central laboratories are open only for defined working hours, POC cTn may help to avoid unnecessary patient transfers to a percutaneous coronary intervention (PCI) facility for those with a negative first test awaiting serial testing when a central lab reopens.

3. In settings with no access to a central laboratory, the role of POC cTn is most likely to avoid patient transfers to PCI facilities for people ultimately diagnosed with UA.

CADTH Optimal Use Report: Canada 2015
Do I Need POCT for Cardiac Troponin or Is Central Laboratory Testing Adequate

Why

• Better lab TAT likely results in more efficient patient triage in ER
• Results in hands of providers faster
• For rural medical centers/hospitals with limited 24/7 staffing
• Field research

Why Not

• Poor analytical sensitivity
• Poor analytical imprecision
• Inability to measure normals
• Poor diagnostic sensitivity for early rule in MI
• Poor diagnostic NPV for early rule out MI
• Added costs
Why Talk About POC cTn Testing?

- Cardiac biomarker testing (cTnI or cTnT and/or CKMB) occurs in 16.9% of all ED visits.
- Roughly 6000 to 8000 cTnI analyzed in HCMC ED lab each year.
- Additional 22,000 to 26,000 performed in central lab.
- Estimated that at minimum 50% inappropriate orders with ‘zero’ clinical utility.
there are no ‘high sensitivity’ POC cTnI or cTnT assays
HCMC Emergency Department Lab

350 sq ft embedded in ER; median time to presentation 3.5h

cTnI order set: 0, 3, 6, 9h

Staffing: 2 FTEs day, evening shifts
1 FTE late night shift

cTnI testing since 1996 transitioned from:
Dade Stratus CS quantitative
Dade Stratus CS qualitative pos/neg
Abbott Architect i1000 (same results as central lab, 20 minutes slower)
Based on cTn Assay TAT
Decreased ER LOS
40 Min Optimal

POC Assay Drive

2.77 hrs

2.17 hrs
Case: Year 2016

- An out of town 63-year old male (tourist/clinical chemist) with no known past medical history presents with accelerating chest discomfort to the local hospital.
- During his preparations leading up to an International presentation, the patient describes having 2 weeks of nearly daily central pain/discomfort that occurred on exertion and relieved with rest.
- On the morning of admission the patient has a recurrent episode of severe substernal central chest pain, this time radiating to his jaw, with shortness of breath and mild nausea.
- In the ER the pain remitted with nitroglycerin.

<table>
<thead>
<tr>
<th>Time</th>
<th>POC cTnI, 99th: 0.030 µg/L</th>
<th>hs-cTnI, 99th: 34 ng/L (Male)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 h</td>
<td>&lt; LoD</td>
<td>9 (measureable)</td>
</tr>
<tr>
<td>3h</td>
<td>0.020</td>
<td>42*</td>
</tr>
<tr>
<td>6h</td>
<td>0.051*</td>
<td>86*</td>
</tr>
</tbody>
</table>

* increased
### POC Assays

**Manufacturer Claims – Assays Never Will be Standardized**

<table>
<thead>
<tr>
<th>Company/platform/assay</th>
<th>LoD µg/L</th>
<th>99th Percentile µg/L</th>
<th>10% CV µg/L</th>
<th>Risk Claim</th>
<th>Epitopes recognized by antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott i-STAT</td>
<td>0.020</td>
<td>0.080 (16.5%)</td>
<td>0.100</td>
<td>Yes</td>
<td>C: 41-49, 88-91; D: 28-39,62-78</td>
</tr>
<tr>
<td>Alere Triage</td>
<td>0.050</td>
<td>&lt;0.050 (NA)</td>
<td>NA</td>
<td>No</td>
<td>C: NA; D: 27-40</td>
</tr>
<tr>
<td>Alere Triage</td>
<td>0.010</td>
<td>0.020 (17%)</td>
<td>NA</td>
<td>NA</td>
<td>C: 27-39; D: 83-93, 190-196</td>
</tr>
<tr>
<td>Medisense Pathfast</td>
<td>0.008</td>
<td>0.029 (5.0%)</td>
<td>0.014</td>
<td>No</td>
<td>C: 41-49; D: 71-116, 163-209</td>
</tr>
<tr>
<td>Radiometer AQT cTnI (CE)</td>
<td>0.009</td>
<td>0.023 (17.7%)</td>
<td>0.039</td>
<td>NA</td>
<td>C: 41-49, 190-196; D: 137-149</td>
</tr>
<tr>
<td>Radiometer AQT cTnI (CE)</td>
<td>0.008</td>
<td>0.017 (15.2%)</td>
<td>0.026</td>
<td>NA</td>
<td>C: 125-131, D: 136-147</td>
</tr>
<tr>
<td>Response RAMP</td>
<td>0.030</td>
<td>&lt;0.010 (18.5% @ 0.050)</td>
<td>0.210</td>
<td>No</td>
<td>C: 85-92; D: 26-38</td>
</tr>
<tr>
<td>Roche Cardiac Reader cTnT</td>
<td>0.030</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>C: 125-131; D: 136-147</td>
</tr>
<tr>
<td>Siemens Stratus CS</td>
<td>0.030</td>
<td>0.070 (10%)</td>
<td>0.060</td>
<td>Yes</td>
<td>C: 27-32; D: 41-56</td>
</tr>
<tr>
<td>Trinity Meritas (CE)</td>
<td>0.030</td>
<td>0.036 (20%)</td>
<td>0.036</td>
<td>No</td>
<td>C:41-49,86-90;D:24-40,137-148,190-6</td>
</tr>
</tbody>
</table>
Know Your POC Assay and Its Limitations

26/200 patients (13%) were negative by POC i-STAT vs positive by central lab Architect cTnI at ER Presentation.
POC cTnl Assay Serial Kinetics & Diagnostics
Clinical Diagnostics Based on 99th Percentile

Subject

Prevalence of AMI in population 19/169 = 11.2%

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>iSTAT</th>
<th>PATHFAST</th>
<th>AQT90</th>
<th>Vitros</th>
</tr>
</thead>
<tbody>
<tr>
<td>0h</td>
<td>32%</td>
<td>53%</td>
<td>26%</td>
<td>68%</td>
<td></td>
</tr>
</tbody>
</table>

Palamalai Clin Biochem  2013
What is a High-Sensitivity cTn Assay?

Contemporary cTn Assay
- Measure cardiac troponin values above the LoD in LESS than 50% of a reference population.

High Sensitivity cTn Assay
- Measure cardiac troponin values above the LoD in ≥ 50% of a reference population.
- CV <10% at the 99th URL
- Whole number reporting, in ng/L, no decimal place
Two Assays: hs-cTnI vs. POC

Eliminating the Noise

SUBJECT A

SUBJECT B

Troponin I (ng/L)

Blood Draws (hours)

34 ng/L • Male hs-cTnI cutoff
26 ng/L • hs-cTnI cutoff
16 ng/L • Female hs-cTnI cutoff

0.030 µg/L

Clin Chem 2015
Providing Rapid Out of Hospital Acute Cardiovascular Treatment 4 (PROACT-4)

Justin A. Ezekowitz, MBCh, MSc; Robert C. Welsh, MD; Dale Weiss; Michael Chan, MD; William Keeble, BMBS, DM; Fadi Khadour, MD; Sanjay Sharma, MD; Wayne Tyynchak, MD; Sunil Sookram, MD; Neil Brass, MD; Darren Knapp, EMT-A; Thomas L. Koshy, PhD; Yinggan Zheng, MA, MEd; Paul W. Armstrong, MD

Background—Whether prehospital point-of-care (POC) troponin further accelerates the time to diagnosis in patients with chest pain (CP) is unknown. We conducted a randomized trial of POC-Troponin testing in the ambulance.

Methods and Results—Patients with chest pain presenting by ambulance were randomized to usual care (UC) or POC-Troponin; ST-elevation myocardial infarction patients or those with noncardiovascular symptoms were excluded. Pre-hospital high-sensitivity troponin was analyzed on a POC device and available to the paramedic and emergency department (ED) staff. The final diagnosis was centrally adjudicated. The primary endpoint was time from first medical contact to discharge from ED or admission to hospital. We randomized 601 patients in 19 months; 296 to UC and 305 to POC-Troponin. After ambulance arrival, the first troponin was available in 38 minutes in POC-Troponin and 139 minutes in UC. In POC-Troponin, the troponin was >0.01 ng/mL in 17.4% and >0.03 ng/mL in 9.8%. Patients spent a median of 9.0 hours from first medical contact to final disposition, and 165 (27.4%) were admitted to the hospital. The primary endpoint was shorter in patients randomized to POC-Troponin (median 8.8 hours [6.2–10.8] compared to UC (median 9.1 hours [6.7–11.2]; P=0.05). There was no difference in the secondary endpoint of repeat ED visits, hospitalizations, or death in the next 30 days.

Conclusions—In this broad population of patients with CP, ambulance POC-Troponin accelerated the time to final disposition. Enhanced and more cost-effective early ED discharge of the majority of patients with CP calling 911 is an unrealized opportunity.


Key Words: acute coronary syndromes • ambulance • chest pain • clinical trial • troponin

Alere POC Triage Cardio 2 Assay:
LoD 0.01 µg/L, 99th percentile 0.02 µg/L (no %CV given)
Positive test result 0.03 µg/L; Sensitivity: 44%, NPV 87.2%
Patient Charges • PrePOC vs. PostPOC
(at a time when central lab TAT was 165 min)

Mean Patient Charges

- Total Charges
  - PrePOC: $4281/patient admission
  - PostPOC: -25%
- Boarding
  - PrePOC: -21%
- Other Depts
  - PrePOC: -58%
- Pharmacy
  - PrePOC: -28%
- Labs
  - PrePOC: -22%
- Non-Cardiac Proc
  - PrePOC: -26%
- Cardiac Proc
  - PrePOC: -14%
- Emergency Dept
  - PrePOC: +2%

Apple 2006 Clin Chim Acta
Percentage of Patients (n=1069) Who Died Within 35 Months With Concentrations > 99th Percentile Admitted Through the ER

The percentage of patients who died within 35 months (all-cause death or CVD death) who had levels above the 99th percentile cutoffs of the 4 cTnI assays, respectively. The statistics indicate significant differences between the laboratory and the 2 POC assays.
Trinity Biotech Announces European Approval of Guideline Compliant, Point-of-Care, High Sensitivity Troponin I Product

January 29, 2014 08:27 ET | Source: Trinity Biotech plc

DUBLIN, Jan 29, 2014 (GLOBE NEWSWIRE) -- Trinity Biotech plc. (Nasdaq TBBI) today announced it has obtained the CE mark (i.e. European approval) for its Meritas, high sensitivity Troponin I (hsTnI) product. With its unrivalled precision, it is now the only point-of-care product capable of meeting all of the guidelines stipulated by the world's leading cardiac organisations for detection of heart attacks.

Troponin market

Troponin is the leading marker used in the detection of heart attacks or myocardial infarctions (MI). The worldwide market for Cardiac Troponin testing is estimated to be $1.2bn, growing at a rate of 12% per annum. Of this market, approximately $350m represents point-of-care testing carried out in the Emergency Room (ER) with the remainder being laboratory based testing. Historically, laboratory based testing has demonstrated significantly greater accuracy, albeit in a much slower timeframe. Typically, laboratory testing takes approximately 90 minutes versus the 15 minutes which can be achieved in the point-of-care environment. Speed is a crucial factor in the diagnosis and treatment of heart attack patients.

In 2007, a task force consisting of the ESC (European Society of Cardiology), ACCF (American College of Cardiology Foundation), AHA (American Heart Association) and WHF (World Heart Foundation) was convened to define MI and its diagnosis. Based on the recommendations of this task force, Troponin has been identified as the preferred biomarker to identify suspected heart attacks. A heart attack is diagnosed when Troponin levels in the blood exceed the 99th percentile reference limit of a normal healthy population whilst accompanied by one other clinical symptom. The task force further stipulated that high sensitivity Troponin assays should also demonstrate excellent precision at very low concentrations of Troponin, namely 10% or less variation at the 99th percentile value of the normal population. The current point-of-care market for Troponin is dominated by three participants, none of whose products come to near to meeting this guideline.

Since 2012, following its acquisition of Fiorn Diagnostics, Trinity has been developing a high sensitivity Troponin test capable of delivering laboratory based quality in the Emergency Room environment. The objective was to develop a test capable of meeting the 2007 guideline with a testing time of no more than 15
Common Presumably Healthy Population

252 females, 273 males

Troponin 99th percentile (ng/L)

% Measureable

Apple Clin Chem 2012
**Male Caucasian 60 y.o.**

Normal ?

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnI Vitros ES OCD</td>
<td>13 ng/L</td>
</tr>
<tr>
<td>hs-cTnI Architect Abbott</td>
<td>5 ng/L</td>
</tr>
<tr>
<td>hs-cTnT Elecsys 2010 Roche</td>
<td>3 ng/L</td>
</tr>
<tr>
<td>cTnI POC i-STAT Abbott</td>
<td>&lt; 6ng/L</td>
</tr>
<tr>
<td>cTnI AQT90 POC Radiometer</td>
<td>&lt; 9 ng/L</td>
</tr>
</tbody>
</table>

Substantial Difference Between Assays…

With POC assays not detecting cTn
hs-cTnT (Roche) values above the limit of detection (LoD)

- Mueller (n=402): 11%
- Chenevix (n=177): 20%
- Ungerer (n=204): 21%
- Apple (n=524): 25%
- Saenger (n=533): 32%
- Franzini (n=872): 38%
- Koertin (n=104): 42%
- Kimenai (n=1540): 43%
- Mean (total=6,158): 29%
What Happens Upon hs-Assay Implementation

Contemporary/POC cTnI

- >99th: 28%
- <LoD: 43%
- LoD to 99th: 29%

High Sensitivity cTnI

- >99th: 27%
- <LoD: 17%
- LoD to 99th: 56%

Across serial measurements
Over 7000 samples.

- No increase in values above 99th URL
- Marked increase in measurable values (>LoD)
Using hs-cTnI assay and gender cutoffs additional MIs: women 56, men 14
Scotland, suspected ACS n = 1126 total subjects.

BMJ Shah 2015
2015 ESC Guidelines

A rapid rule-out and rule-in protocol (0h and 1h) is recommended if a high-sensitivity cardiac troponin test with a validated 0h/1/h algorithm is available. (Class I – LOE: B).

European Heart Journal Advance Access published August 29, 2015

2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation
Utility of Absolute and Relative Changes in Cardiac Troponin Concentrations in the Early Diagnosis of Acute Myocardial Infarction

![Graph showing ROC curves for different troponin changes](image)

- hs-cTnT 1h absolute change (Δ), AUC 0.93
- cTnI Ultra 1h absolute change (Δ), AUC 0.94
- hs-cTnT 1h relative change (Δ%), AUC 0.66
- cTnI Ultra 1h relative change (Δ%), AUC 0.64

Reichlin T et al. Circulation 2011
POC Conclusions

• Quality analytics critical in defining POC assays
  – Imprecision and ability to measure normal subjects
  – Imprecision influences MI adjudication and rule out

• Normality needs to be defined by gender
  – Age and ethnicity/race in future likely
  – Influences MI diagnostics

• TAT/thruput important to meet clinical needs

• Clinical use setting dependent
  – Providers need to understand pros/cons

• Collaborative interdisciplinary efforts regarding ordering processes and utilization important
What Should Be Happening With High-Sensitivity Troponin Assays In Clinical Use

To quote ‘Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care (EHJ 2010)’

“If the first blood sample for cTn is not elevated, a second should be obtained after 6-9h, and sometimes a third sample after 12-24h. This changes with high sensitivity assays.”

Contemporary/POC assays: 0, 3, 6 / 9-24h

High Sensitivity Assays (POC or Central Lab): 0, 1.5, 3 / 6-12h
Biomarker Protocols and Troponin Cut-points

Year

Proportion (%)

- 99th Percentile
- Troponin Only
- Troponin (I/T) & CKMB
- Troponin (I/T), CKMB & Myoglobin

From: TRENDS IN CARDIAC BIOMARKER PROTOCOLS AND TROPONIN CUT-POINTS
Implantable Magnetic Relaxation Sensors Measure Cumulative Exposure to Biomarkers

Ling, Apple Nature Biotech 2011
Questions ?