EVOLVING USE OF CARDIAC TROPONINS IN THE EMERGENCY DEPARTMENT

North Hollywood, California
March 14, 2019

Thomas K. Bane, PhD, PPM
Director, Medical & Scientific Affairs
LEARNING OBJECTIVES

› Understand the challenges facing the Emergency Department in rapid diagnosis of chest pain patients
› Understand recent research and updates to guidelines surrounding use of cardiac troponins
› Understand the clinical benefits of high sensitivity troponin
EVOLUTION OF THE TROPONIN ASSAY

- Evolution of analytical sensitivity has led to improved clinical sensitivity

- Detection Time
- Onset of myocardial injury
- Normal Levels
- Ischemia or Micronecrosis
- Necrosis
- LoD
- Prior generation troponin assays
- Contemporary troponin assays
- High-sensitivity troponin assays

Wu, 2014 EJIFCC.
CONTENT

History and Practice Guidelines

What is current practice?

Emerging clinical utility

Who benefits?

Making the transition to high sensitivity
CONTENT

History and Practice Guidelines

What is current practice?

Emerging clinical utility

Who benefits?

Making the transition to high sensitivity
THE HEART IS THE STRONGEST MUSCLE

› Works all day, every day
› Life is 100% dependent on its activity
› Provides nutrients to every organ, muscle, nerve and tissue
› Over a lifetime, will beat an average of three billion times and pump one million gallons of blood
› When cardiac injury occurs, time matters
CARDIOVASCULAR DISEASE (CVD) AND ACUTE MYOCARDIAL INFARCTION (AMI) STATISTICS

› Three million STEMI, four million NSTEMI worldwide each year
› More than 2,150 Americans die of CVD each day, an average of 1 death every 40 seconds
› Coronary heart disease alone causes ~ 1 of every 7 deaths in the U.S. in 2011
› In 2011, CVD still accounted for 31.3% (786,641) of all 2,515,458 deaths or ~ 1 of every 3 deaths in the U.S.

Source: Heart Disease and Stroke Statistics-2015 Update
A Report From the American Heart Association
HEART DISEASE: THE LEADING CAUSE OF DEATH

National Vital Statistics System, United States, 2015
MMWR April 21, 2017/66(15);413.
COST OF ED CARE AND CHEST PAIN

- High volume diagnosis + high treatment intensity = high cost
- Driving malpractice litigation: AMI patients inadvertently released home have an 11% to 25% risk of dying from their MI
- Implementing the right protocols and best practice tools can help increase quality of care while controlling costs

Sources:
American College of Emergency Physicians – ‘Chest Pain Units in Emergency Departments’:
https://www.acep.org/Clinical---Practice-Management/Chest-Pain-Units-in-Emergency-Departments/
Data compiled by Dr. J. Slutzman, presented to the American College of Emergency Physicians:
ED VISITS – UNITED STATES

130 million annually

10.4 million (8%) chest pain high volume

6.3 million (63%) suspected or actual cardiac

3.1 million (50%) non-cardiac

2.1 million (20%) AMI

1.5 million (24%) unstable angina (UA)

374,000 (6%) sudden death

4.1 million sent home as non-cardiac

50,000 myocardial infarction (MI’s) high liability

Source: Frank Peacock, MD Baylor College of Medicine
WHAT IS A HEART ATTACK?

Source: 3rd Universal Definition of MI, ESC Guidelines 2012: ESC/ACCF/AHA/WHF
2018: 4TH UNIVERSAL DEFINITION OF MI

Acute Myocardial Injury ≠ Acute Myocardial Infarction

Acute Myocardial Injury + Troponin Rise or Fall + Doctor = AMI

ECG change
Pathologic IQ Waves
Imaging Evidence
Angiography

Thygesen. 2018. EHJ
Myocardial Infarction Type 1

Plaque rupture/erosion with occlusive thrombus

Plaque rupture/erosion with non-occlusive thrombus
Myocardial Infarction Type 2

- Atherosclerosis and oxygen supply/demand imbalance
- Vasospasm or coronary microvascular dysfunction
- Non-atherosclerotic coronary dissection
- Oxygen supply/demand imbalance alone
INTERPRETATION OF EVERY hsTn ELEVATION IN THE CONTEXT OF CLINICAL SITUATION

Elevated hsTn

Rise/fall Pattern

Myocardial Infarction

- Elevated
- Consistently Elevated

Myocardial Injury

- Consistently Elevated

Thrombotic MI

Type 1: plaque rupture
Type 4b: stent thrombosis

Procedure related MI

Type 4a: PCI-related
Type 5: CABG-related

Oxygen imbalance

Type 2 MI:
- Heart failure
- Cardiomyopathy incl.
- Takotsubo
- Cardiac contusion
- Surgery, ablation, or pacing
- Aortic dissection
- Aortic valve disease

Type 2 MI:
- Tachyarrhythmia
- Severe respiratory failure
- Severe anemia
- Cardiogenic shock
- Hypertension w/o LVH
- Coronary spasm
- Coronary embolism

Cardiac

Systemic

Cardiac

- Heart failure
- Cardiomyopathy incl.
- Takotsubo
- Myocarditis
- Cardiac contusion
- Surgery, ablation, or pacing
- Aortic dissection
- Aortic valve disease

Systemic

- Pulmonary embolism
- Pulmonary hypertension
- Sepsis and critical illness
- Renal failure
- Stoke
- Infiltrative disease
- Strenuous exercise
- Cardiotoxic agents

Mair. 2016 A.S. Maisel, A.S. Jaffe, Cardiac Biomarkers
RECOMMENDED MODEL FOR INTERPRETING MYOCARDIAL INJURY — 4TH UNIVERSAL DEFINITION OF MI

Elevated Cardiac Troponin Value(s) >99th percentile URL

Troponin rise and/or fall

- With acute ischaemia
  - Acute myocardial infarction
    - Atherosclerosis + thrombosis
      - Type 1 MI: triggers
        - Plaque rupture
        - Plaque erosion
      - Type 2 MI: examples
        - Severe hypertension
        - Sustained tachyarrhythmia
  - Oxygen supply and demand imbalance
    - Examples
      - Acute heart failure
      - Myocarditis

- Without acute ischaemia
  - Acute myocardial injury

Troponin level stable

- Chronic myocardial injury
  - Examples
    - Structural heart disease
    - Chronic kidney disease

Thygesen. 2018. EHJ
ELEVATED TROPONIN: NOT JUST MYOCARDIAL INFARCTION

Emergency room evaluations for chest pain. n = 1,023

- Acute myocardial Infarction: 17%
- Unstable angina: 11%
- Stable angina: 3%
- Heart failure: 18%
- Heart failure and renal failure: 6%
- Miscellaneous: 29%
- Pulmonary embolism: 2%
- Tachycardia: 2%
- Atrial fibrillation: 5%
- Myocarditis: 1%
- Cardiomyopathy: 3%
- Renal failure: 3%
- Myocarditis: 1%
- Atrial fibrillation: 5%
- Pulmonary embolism: 2%
- Tachycardia: 2%
- Miscellaneous: 29%

Acute coronary syndrome (ACS) is characterized by rising/falling pattern in cardiac biomarkers.

Other myocardial injuries may have steady elevated levels.

TROPONINS

Regulatory proteins of the thin filament

Cardiac muscle cell

Generally, size and intracellular location determine rate of release into circulation

CONTENT

History and Practice Guidelines

What is current practice?

Emerging clinical utility

Who benefits?

Making the transition to high sensitivity
NORMALIZING TERMINOLOGY

- **Critical Value**
- **Positive/Elevated**
- **Negative/Non-Elevated**

- **Troponin Levels**
- **Time**

- **PPV**
- **NPV**

- **Normal Levels**
- **Ischemia or Micronecrosis**
- **Necrosis**
- **Clinical Myocardial Infarction**

- **99% URL**
Cardiac Troponin Medical Cutoffs/Medical Decision Points

Rule In
- PPV – Critical Value

Trend
- Serial – Trend

Rule Out
- Sgl – NPV
- Serial – Trend?

AMI
- 95% Confidence Limit

Gray Zone
- 99% Cutoff

Normal
- LOD - cutoff
ABSOLUTE VS. RELATIVE DELTA


Fig. 2. ROC curves for individual cTnl values, absolute and relative changes in cTnl.
WHAT TOOLS ARE AVAILABLE?
ECG/EKG: STEMI VS. NSTEMI

STEMI
- ST Segment Elevation
- J-Point

NSTEMI
- ST Segment Depression
- T Inversion
For your consideration:
› Does time savings apply to all clinical situations?
› Sensitive enough?
   • Rule-in, rule-out, serial draws/deltas?
› Precise enough?
   • CV”s at cutoff?
› What is the impact of a high-sensitivity on this time line?
COMPARISON: POC VS. CENTRAL LAB

Findings:
1. POC showed an increase in patients with <8 hour stay in the ER.
2. POC was inferior to the central lab at predicting AMI.
3. Central lab delivered greater sensitivity & diagnostic accuracy.
4. No evidence of cost effectiveness for POC vs. central lab.

Takeaway:

POC testing will yield results more rapidly than lab-based assays but:
- Has value only if caregivers take action on the result.
- Is limited to percentage of customers with immediate rule-in values.
- Overall POC use is at the cost of accuracy and thus, overall patient care.

Blomkalns. www.emcreg.org/publications/monographs/acep
CURRENT CLINICAL PROTOCOL

![Diagram showing cTn (ng/L) over time with 99th Percentile URL]

- Presentation Time
- Time

© 2017 Beckman Coulter. All rights reserved.
CONTENT

History and Practice Guidelines

What is current practice?

Emerging clinical utility

Who benefits?

Making the transition to high sensitivity
Evolution of analytical sensitivity has led to improved clinical sensitivity

Evolution of the Troponin Assay

- Normal Levels
- Ischemia or Micronecrosis
- Necrosis
- Clinical Myocardial Infarction

Detection Time

Onset of myocardial injury

LoD

Prior generation troponin assays

Contemporary troponin assays

High-sensitivity troponin assays

Wu. 2014 EJIFCC.
DEPTH PERCEPTION
IFCC DEFINITION OF A HIGH-SENSITIVITY TROPONIN (hsTn) ASSAY IS CONSIDERED TO BE THE STANDARD CRITERIA

1. Coefficient of variation (CV) ≤10% at the 99th percentile of the reference population

2. At least 50% measurable concentrations below the 99th percentile and above the assay’s limit of detection (LoD)

NEW – Measures at least 50% of healthy individuals above LoD in men and women separately

CLARIFICATION ON NAMING/APPLICATION/USAGE

“I think the “high sensitivity” troponin test suffers greatly from its name.”

_Carter Wahl_
Pathologist
_Sharpe Healthcare_
_San Diego, California_

High Sensitivity refers only to one of these terms: _Analytical Sensitivity_, i.e., the ability of a test to detect low levels of a substance. _Diagnostic Sensitivity_, i.e., the ability to correctly classify patients as positive for AMI.

Sum:
High Sensitivity **does not** inherently indicate more positives, more consults.

The test detects low levels of troponin and has high analytic sensitivity.

Cutoffs can be adjusted for unique population and practice needs, setting the diagnostic sensitivity to fit your specific needs.
HIGH-SENSITIVITY TROPONIN MEASURES WITH A GREATER DEGREE OF ANALYTICAL SENSITIVITY

95% CI, 100pg/ml – Rule in

0.040 ng/ml or 40 pg/ml

12 or 20 pg/ml

4.1 or 5.6 pg/ml

10% CV

4% CV

10% CV

Accu TnI +3

hsTnI

Wu, 2014 EJIFCC.
STANDARD VS. HIGH SENSITIVITY TROPONIN

Better defined 99th Percentile URL means distinguishable male/female cutoffs
WHAT IS HIGH SENSITIVITY TRO PonIN

› Same molecule that is specific to cardiac muscle cell
  • Acute coronary syndrome (ACS) is characterized by rising/falling pattern in cardiac biomarkers
  • Other myocardial injuries may have steady elevated levels
› Improved analytical sensitivity
  • Better precision at clinical decision points
  • Lower limits of detection enabling quantification of troponin levels that were undetectable with current assay

Enhances ability to rapidly diagnose patients
A broader differential diagnosis associated with lower-range elevations of hs-cTn begins to narrow as concentrations are higher. HF = heart failure; LVH = left ventricular hypertrophy; MI = myocardial infarction; PE = pulmonary embolism. Modified with permission from Mueller (21).
UNIT CHANGE

First a word about units:

– IFCC guidelines now recommend whole-number reporting for troponin
  • Whole-number reporting provides clarity, less chance for mistakes
  • To convert from ng/mL to pg/mL, multiply by 1,000

– Example: 0.03 ng/mL = 30 pg/mL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AccuTnl +3*</th>
<th>Access hsTnl UniCel Dxi</th>
</tr>
</thead>
<tbody>
<tr>
<td>LoD (pg/mL)</td>
<td>10</td>
<td>2.3</td>
</tr>
<tr>
<td>10% CV (pg/mL)</td>
<td>40</td>
<td>5.6</td>
</tr>
<tr>
<td>20% CV (pg/mL)</td>
<td>30</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*DXI
Cardiac Troponin Medical Cutoffs/Medical Decision Points

Rule In
- PPV – Critical Value

Trend
- Serial – Trend

Rule Out
- Sgl – NPV
- Serial – Trend?

AMI

95% Confidence Limit

Gray Zone

99% Cutoff

Normal

LOD - cutoff
CONTEMPORARY ASSAY CLINICAL PROTOCOL

![Graph showing cTn (ng/L) over time with presentation time and 99th percentile URL highlighted.](Image)

© 2017 Beckman Coulter. All rights reserved.
POTENTIAL CLINICAL PROTOCOL

![Graph showing cTn (ng/L) over time with presentation times and 99th Percentile URL]
CLINICAL TRIAL – RESULTS

› Identifies ≥94% of true AMI patients in as little as one hour post presentation
› 99% NPV in as little as one hour after ED admission
› Specificity
  • Increases with change from 30ng/L (AccuTnI+3) to 18ng/L (hsTnI).
  • For sex-specific cutoffs
    – Sensitivity & Specificity remain the same as unisex
    – Slight improvement for female-specific cutoff
  • PPV is as expected.
    • Not all elevated cTn values are an infarction
    • Improves with use of deltas

<table>
<thead>
<tr>
<th>99th %URL cutoff, ng/L</th>
<th>Hours After Admission to ED</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td>88</td>
<td>89</td>
<td>58</td>
<td>98</td>
</tr>
<tr>
<td>≥1-3 hour</td>
<td></td>
<td>94</td>
<td>90</td>
<td>54</td>
<td>99</td>
</tr>
<tr>
<td>≥3-6 hour</td>
<td></td>
<td>94</td>
<td>90</td>
<td>55</td>
<td>99</td>
</tr>
<tr>
<td>≥6-9 hour</td>
<td></td>
<td>99</td>
<td>85</td>
<td>51</td>
<td>100</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>83</td>
<td>91</td>
<td>53</td>
<td>98</td>
</tr>
<tr>
<td>≥1-3 hour</td>
<td></td>
<td>93</td>
<td>92</td>
<td>47</td>
<td>99</td>
</tr>
<tr>
<td>≥3-6 hour</td>
<td></td>
<td>96</td>
<td>92</td>
<td>51</td>
<td>100</td>
</tr>
<tr>
<td>≥6-9 hour</td>
<td></td>
<td>100</td>
<td>88</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>89</td>
<td>87</td>
<td>61</td>
<td>97</td>
</tr>
<tr>
<td>≥1-3 hour</td>
<td></td>
<td>96</td>
<td>88</td>
<td>57</td>
<td>99</td>
</tr>
<tr>
<td>≥3-6 hour</td>
<td></td>
<td>94</td>
<td>88</td>
<td>58</td>
<td>99</td>
</tr>
<tr>
<td>≥6-9 hour</td>
<td></td>
<td>98</td>
<td>81</td>
<td>53</td>
<td>100</td>
</tr>
</tbody>
</table>

DxI using plasma
Re-design elements

AccuTnI+3

- New solid phase particle has a more uniform surface, which reduces susceptibility to non-specific binding
- New antibody pair reduces interferences from known heterophiles

Access hsTnI
### EXAMPLES OF IMPROVED PERFORMANCE

<table>
<thead>
<tr>
<th>Scenario #1: Non Repeatable False Positive</th>
<th>Cause: Pre-analytical variability, such as poorly mixed tube at time of collection creating inadequate sample clotting</th>
<th>Initial Replicate</th>
<th>New Assay: hsTnI (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>870</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scenario #2: Repeatable False Positive</th>
<th>Cause: Presence of circulating interfering human anti-mouse antibodies, binds to mouse antibody pair in reagent</th>
<th>Initial Replicate</th>
<th>New Assay: hsTnI (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1242</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1287</td>
<td>12</td>
</tr>
</tbody>
</table>
Case Study

Contemporary Practice:
- 42 year old female presents to ED with nausea, vomiting, trouble breathing
- Normal sinus rhythm, left ventricle hypertrophy. 2nd ECG noted ST elevation
- Final Diagnosis:
  - Acute MI – STEMI
- Patient received IV tissue plasminogen activator

<table>
<thead>
<tr>
<th>Time</th>
<th>Current assay (ng/mL)</th>
<th>Current assay (pg/mL)</th>
<th>hsTnI (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>&lt;0.03</td>
<td>&lt;30</td>
<td>14</td>
</tr>
<tr>
<td>3 hr.</td>
<td>&lt;0.03</td>
<td>&lt;30</td>
<td>36</td>
</tr>
<tr>
<td>6 hr.</td>
<td>0.63</td>
<td>630</td>
<td>562</td>
</tr>
<tr>
<td>12 hr.</td>
<td>26.43</td>
<td>26430</td>
<td>18762</td>
</tr>
</tbody>
</table>

Emergent Practice:
- Baseline hsTnI level is above 99th percentile for females >12pg/mL
- 3hr troponin level also abnormal, including significant change as compared to baseline.
- This pattern is seen with early presenters.
# HIGH-SENSITIVITY TROPONIN MARKET PLACE

## High Sensitivity Cardiac Troponin Assays

<table>
<thead>
<tr>
<th>Product</th>
<th>IFCC/FDA Approval</th>
<th>Available in US</th>
<th>Platform Availability</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beckman hsTnI</td>
<td>Yes - Aug 2018</td>
<td>Yes</td>
<td>All</td>
<td>None</td>
</tr>
<tr>
<td>Siemens hsTnI</td>
<td>Yes - Sept 2018</td>
<td>Yes</td>
<td>Advia XP/XPT</td>
<td>Biotin, Hemolysis</td>
</tr>
<tr>
<td>Abbott hsTnI</td>
<td>Yes - Sept 2019</td>
<td>Yes</td>
<td>Architect i2000sr, not Alinity i</td>
<td>EDTA only</td>
</tr>
<tr>
<td>Roche TnT (5th)</td>
<td>No</td>
<td>NA</td>
<td>Cobas</td>
<td>Sensitivity, Biotin, Hemolysis</td>
</tr>
<tr>
<td>POC</td>
<td>No</td>
<td>NA</td>
<td>Several Standalone Platforms</td>
<td>Sensitivity, Accuracy, Versatility, Matrix Effects, Cost, User-dependent</td>
</tr>
</tbody>
</table>
What is Different: Deltas

Accurate calculation of a small delta change value across short time intervals earlier.

<table>
<thead>
<tr>
<th>Healthy</th>
<th>Myocardial Injury</th>
<th>AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increasing Troponin Concentrations

- LoD (10) 20% CV
- LoD (2.0) 10% CV (4.1) 4% CV
- 10% CV (40)
- Contemporary Troponin Assays*
- High Sensitivity Troponin Assays*
SUMMARY: ACCESS HIGH SENSITIVITY TROPONIN

Provide clinicians with greater confidence in making a diagnosis of myocardial infarction in patients who have only small elevations in troponin

› Meets the current cardiac guidelines for high sensitivity troponin
› Offers best in class analytical sensitivity
› Supports rapid rule-in and rule-out of MI

The key advantages include:
› Ability to measure troponin in the normal population
› Ability to differentiate AMI in Men & Women
› Confidence in interpreting small levels or small changes in troponin results
› Less susceptibility to artifact interference

Accuracy + precision = confidence
hsTN IMPLEMENTATION IN THE CLINIC

Notify  Educate  Logistics

Audit, assess, communicate, repeat
CONTENT

History and Practice Guidelines

What is current practice?

Emerging clinical utility

Who benefits?

Making the transition to high sensitivity
WHO BENEFITS?

Cardiovascular Disease Mortality Trends

Women’s rates are not declining in line with men’s

Deaths in thousands

Year

© 2017 Beckman Coulter. All rights reserved.
IMPLEMENTING ACCESS hsTNI AT GWH

An early rule in/out protocol was introduced using gender specific cut-off points.

Access Accu TnI+3
- 0 & 6 hr protocol
- Combined M&F 99% URL

Access hsTnI
- 0 & 3 hr protocol
- Gender specific 99% URL
REDUCED PATIENT WAITING TIMES IN A&E

52% fewer patients presenting to A&E with chest pain are waiting longer than 4 hours following implementation of Access hsTnI in Q1 2018/19

An average of 52% fewer patients with CP wait >4hrs in A&E since the introduction of Access hsTnI

March 2018: 46% patients with CP waited >4hrs

Access hsTnI introduced April 2018

April – August 2018: Following introduction of Access hsTnI an average of 22% patients with CP waited >4hrs
High-sensitivity cardiac troponin I immunoassay reduces the chance of patient misclassification in the emergency department

Giuseppe Lippi¹, Fabian Sanchis-Gomar²,³,⁴, Rosalia Aloe⁵, Laura Bonfanti⁶, Gian Luca Salvagno¹, Gianfranco Cervellin⁶

Figure 3 Chance of misclassification of patients admitted to the emergency department with suspected acute myocardial infarction using a contemporary-sensitive (CS) or a high-sensitive (HS) cardiac troponin I (cTnI) immunoassay.
Additional Values at Low End are Relevant

Approx 20% of AMI patients had initial Troponin BELOW 99th Percentile

Hs-cTnI concentration at presentation vs. final diagnoses

Boeddinghaus, Clin Chem 2019  65:7
Same Decisions – Better Information Quicker

Presentation: Late
CP onset >3 hrs

Presentation: Early
CP Onset <3 hrs

ADP: 0-1-3 hrs

99% Cutoff

Critical

Critical Value

Onset of myocardial injury

PPV

NPV

99% URL

Time

0 1 2 3
2 HOUR RISK STRATIFICATION

Diagnostic Accuracy of a New High-Sensitivity Troponin I Assay and Five Accelerated Diagnostic Pathways for Ruling Out Acute Myocardial Infarction and Acute Coronary Syndrome

Jaimi H. Greenslade, PhD*; Edward W. Carlton, PhD; Christopher Van Hise, BA; Elizabeth Cho, MS; Tracey Hawkins, BN; William A. Parsonage, MD; Jillian Tate, MSc, BSc(Hons); Jacobus Ungerer, MBChB; Louise Cullen, PhD

Conclusion: In this cohort with a low prevalence of acute myocardial infarction and acute coronary syndrome, using the Beckman’s Access high-sensitivity troponin I assay with the new Vancouver Chest Pain Rule or No Objective Testing Rule enabled approximately one third of patients to be safely discharged after 2-hour risk stratification with no further testing.

RAPID DIAGNOSTIC PROTOCOLS – 2 HOUR PATHWAYS

- Including Access hsTnI within accelerated diagnostic pathways help early rule-in/-out low risk patients within 2 hours
CONTENT

History and Practice Guidelines

What is current practice?

Emerging clinical utility

Who benefits?

Making the transition to high sensitivity
Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine

LAB RECOMMENDATIONS FOR hsTnI IMPLEMENTATION

› For hs-cTn assays, labs should measure at minimum three QC concentrations daily
  • (1) between LoQ and lowest sex-specific 99th percentile
  • (2) within 20% highest sex-specific 99th percentile
  • (3) concentration that challenges the analytical measurement range of reportable cTn results
› During initiation of hs-cTn testing and annually thereafter, validate the LoB, LoD outside USA, or LoQ as applicable per FDA regulations in USA
› hs-cTn to be reported in whole numbers, using pg/mL or ng/L without decimal points. For reporting QC values, we recommend one decimal point
  • For contemporary cTn assays, units are reported in ng/mL to two significant figures. (three sig figs for QC)
› A defined reference population to be used to report 99th percentile concentrations according to sex-specific hs-cTn cutoffs
  • This recommendation is not relevant for contemporary cTn assays
› The lab should educate clinicians on the importance of specific metrics by which true clinical changes in cTn concentrations can be distinguished from analytical and biological variability
Key points for a successful implementation:

• Investigate what other institutions have done successfully
• Convene a small group of empowered and knowledgeable decision makers
• Communicate the change
• Make the change
• Anticipate uncertainty
• Assess outcomes
Cardiac Troponin Medical Cutoffs/Medical Decision Points

- Rule In
  - PPV – Critical Value

- Gray Zone
  - Trend
    - Serial – Trend

- Normal
  - LOD - cutoff
  - Rule Out
    - Sgl – NPV
    - Serial – Trend?
Potential early rule-out strategies at admission to be investigated further
DELTA VALUES INCREASE THE DIAGNOSTIC SPECIFICITY TO RULE IN TRUE MI PATIENTS

<table>
<thead>
<tr>
<th>Delta change value (≥)</th>
<th>Time</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 ng/L</td>
<td>Baseline vs. 1–3 hours</td>
<td>76</td>
<td>95</td>
<td>66</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Baseline vs. 3–6 hours</td>
<td>87</td>
<td>92</td>
<td>62</td>
<td>98</td>
</tr>
<tr>
<td>5 ng/L</td>
<td>Baseline vs. 1–3 hours</td>
<td>71</td>
<td>97</td>
<td>76</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Baseline vs. 3–6 hours</td>
<td>78</td>
<td>95</td>
<td>72</td>
<td>97</td>
</tr>
<tr>
<td>11 ng/L</td>
<td>Baseline vs. 1–3 hours</td>
<td>61</td>
<td>99</td>
<td>83</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Baseline vs. 3–6 hours</td>
<td>60</td>
<td>98</td>
<td>78</td>
<td>94</td>
</tr>
<tr>
<td>22 ng/L</td>
<td>Baseline vs. 1–3 hours</td>
<td>50</td>
<td>99</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Baseline vs. 3–6 hours</td>
<td>54</td>
<td>99</td>
<td>88</td>
<td>93</td>
</tr>
</tbody>
</table>

Delta values were also assessed in conjunction with the sex-specific 99th percentiles, evaluating males and females separately; there appeared to be no significant impact to diagnostic accuracy.

Note: Access hsTnI 10% CV @5.6 ng/L, 20% CV @2.3 ng/L
Setting the numbers

<table>
<thead>
<tr>
<th>Current Adoption Protocols</th>
<th>Contemporary Assay</th>
<th>High Sensitivity Troponin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutoff</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unisex</td>
<td>~0.04 ng/ml</td>
<td>18 pg/ml</td>
</tr>
<tr>
<td>Male</td>
<td>na</td>
<td>20 pg/ml</td>
</tr>
<tr>
<td>Female</td>
<td>na</td>
<td>12 pg/ml</td>
</tr>
<tr>
<td><strong>Rule Out</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at T=0</td>
<td>&lt;0.01 ng/ml</td>
<td>&lt;4-6 pg/ml</td>
</tr>
<tr>
<td>~No Change (Relative %)</td>
<td></td>
<td>~5 pg/ml Delta</td>
</tr>
<tr>
<td><strong>Serial Draw Protocol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rule In</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical Value at T=0</td>
<td>~&gt;0.1 ng/ml</td>
<td>~90 pg/ml</td>
</tr>
<tr>
<td>Unisex</td>
<td>na</td>
<td>100 pg/ml</td>
</tr>
<tr>
<td>Male</td>
<td>na</td>
<td>~75 pg/ml</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serial Draw Protocol</td>
<td>Rising/Falling Value (one over cutoff)</td>
<td>13-15 pg/ml Delta</td>
</tr>
<tr>
<td></td>
<td>0-2, 0-3, 0-6, 0-12 hours</td>
<td>0-1-3, 0-2</td>
</tr>
</tbody>
</table>
hsTnI Decision Making w/ the HEART Score

0 Hour

- **≤5.0 pg/ml**
  - Not needed

- **>2.3 and ≤99th URL**
  - Female: 14.9 pg/ml
  - Male: 19.8 pg/ml
  - Move to Rule-out

- **>14.9 – 75 pg/ml**
  - >19.8 – 99 pg/ml
  - Potential Early Presenters

- **>75 pg/ml**
  - >99 pg/ml
  - Critical Result

- **>2.3 – 99% URL**
  - Female: 14.9 pg/ml
  - Male: 19.8 pg/ml
  - Move to Rule-out

2 Hour

- **Δ ≤5 pg/ml**
  - Above URL or ≥15 pg/ml
  - Move to Rule-in

- **Δ >15 pg/ml**
  - Move to Rule-in

**Potential Early Presenters**

- **>14.9 – 75 pg/ml**
  - >19.8 – 99 pg/ml

**Observational Testing**

**Additional Testing**

**Rule-out or ADP**

**ADP* to distinguish injury/AMI**

**Move to Rule-In**

**Critical Result**

**Move to Rule-In**

**Myocardial Injury**

**Move to Rule-In**

© 2020 Beckman Coulter, Inc. All rights reserved.
© 2017 Beckman Coulter. All rights reserved.

Move healthcare forward.
hsTnI Decision Making w/ the HEART Score

0 Hour
- ≤5.0 pg/ml
- ≥2.3 and ≤99th URL
  - ♀ 14.9 pg/ml
  - ♂ 19.8 pg/ml
- >14.9 – 75 pg/ml
- >19.8 – 99 pg/ml
- >75 pg/ml
- >99 pg/ml

Potential Early Presenters
- Elevated result-Intermediate Result

Critical Result

Move to Rule-out
- Rule out
- Or
- ADP
- ADP* to distinguish injury/AMI

Move to Rule-in

1 Hour
- >2.3 – 99% URL
  - ♀ 14.9 pg/ml
  - ♂ 19.8 pg/ml
- >14.9 – 75 pg/ml
- >19.8 – 99 pg/ml

Δ ≤5 pg/ml
- Above URL or
  - ≥12 pg/ml

Late Presenter
- Δ ≥12 pg/ml

Move to Rule-out*
- Move to Rule-in
- AMI

Move to Rule-in - AMI

Myocardial Injury

HEART Score 2 or 3
Observational Testing
Additional Testing
SharpHealth Care Decision Making

### High Sensitivity Troponin I – Result Algorithm

Clinical judgement supersedes the algorithm especially in high risk patients or patients with unusual symptoms or an unstable/concerning ECG.

<table>
<thead>
<tr>
<th>Draw Times</th>
<th>Move to Rule-Out AMI</th>
<th>Move to Rule-In AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0 hour</strong></td>
<td>≤5.0 pg/mL</td>
<td>&gt;99.0 pg/mL Males</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;75.0 pg/mL Females</td>
</tr>
<tr>
<td><strong>0 - 2 hours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.0 pg/mL and</td>
<td>Δ &lt;5.0 pg/mL*</td>
<td>Δ &gt;15.0 pg/mL</td>
</tr>
<tr>
<td>Below the Cutoff</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male – 19.8 pg/mL Female – 14.9 pg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant HEART score/clinical presentation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **0 - 2 hours** |                 |                    |
| Above the Cutoff |               |                     |
| Male – 19.8 pg/mL Female – 14.9 pg/mL |               |                     |
| Δ <5.0 pg/mL* |               | Δ >15.0 pg/mL       |

* Δ between 5-15 pg/mL need to be interpreted with clinical context

Possible Non-Ischemic causes of elevated troponins: Tachyarrhythmias, congestive heart failure, critically ill patients (sepsis, respiratory failure, inflammatory diseases, burns), pulmonary embolism or severe pulmonary hypertension, severe hypertension or hypotension, apical ballooning cardiomyopathy (Takotsubo Syndrome), stroke or subarachnoid hemorrhage, renal failure, myocarditis, myopericarditis, cardioversion or ablations, aortic stenosis, chest trauma, hypertrophic cardiomyopathy, coronary spasm, hypothyroidism, infiltrative cardiomyopathy, extreme exertion, drug toxicity (some chemotherapies).

**Reference:** Clinical Use of High-Sensitivity Cardiac Troponin in Patients with Suspected Myocardial Infarction

hsTN IMPLEMENTATION IN THE CLINIC

Notify
Educate
Logistics

Audit, assess, communicate, repeat
EMPOWERMENT IN A TEAM SPORT

› The diagnosis of a myocardial infarction is a complex medical decision requiring the **cooperative collaboration and timely flow of accurate procedures and information** between several key hospital personnel from nurses and phlebotomists to the laboratorian and back to the medical specialists **in order to ensure optimal patient outcomes.**
Troponin Testing for Clinicians

› Professional Societies Weigh In
  • Januzzi – Transition, JACC 2019
  • Ljung – ED Impact, Cardiology 2019
  • Neumann – Outcomes, NEJM 2019
  • Jia – Comorbidities, 2019 Circulation
  • Baugh – ED Implementation, 2019

› Cardiology Concerns
  • Brush - JACC 2016, 68(21):2365-75
    - Analytical Performance
    - Clinical Sensitivity/Specificity
    - Clinical Reasoning for Ordering
    - Clinical Context of Interpretation

  - Increase in Elevated Values
    • >Cutoff<Critical Value
      • Delta
      • Risk Stratification Protocols
      • Clinical Context
CONVERSION SUMMARY

› The diagnosis of MI is a complex issue.
  • Diagnosis involves:
    • Troponin + imaging + presentation/history + doctor = MI
  • Effective treatment of patients requires:
    • The active cooperation, planning, and the establishment of Standards of Practice of several partners, i.e., ER MDs, Nurses, Cardiologists, Lab Directors, laboratorians and other essential personnel.

› Best practices in diagnosis of MI is constantly evolving
  • hsTnI is here to stay. It is not new or experimental
  • Education is key
  • Protocol driven

› It’s a team sport. Good luck!!