High Sensitive Troponin

A Game Changer

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Nothing to Declare
Objectives

• Brief overview of Troponins

• Recent evidence about “RULE-OUT” ACS with hs-troponins
  • 219 studies in Medline

• Difference between
  • Undetectable troponin
  • Measurable but normal range troponin

• Implications for
  • ED Discharge
  • Follow up and future testing
“High-sensitive” Troponins

• Sensitivity of troponin tests
  • Ability to detect troponin molecules not sensitivity for myonecrosis

• Limit of Detection (LoD)
  • Old “standard” assays
    • 100 – 1000 ng/L (0.1 – 1.0 μg/L)
  • Sensitive
    • 30 – 50 ng/L (0.03 – 0.05 μg/L)
  • High sensitive
    • < 20ng/L – some as low as 0.5ng/L
      • Able to detect troponin in normal population

• Cardiac Specific – cTn
  • Specific for cardiac muscle damage, NOT ACS
“High-sensitive” Troponins

• New definition of abnormal
  • > 99th percentile of normal population (Upper Reference Limit: URL)

• Troponin results now fall into 3 bands
  • (< LoD) = Undetectable
  • (LoD – 99th percentile) = Normal range (≠ negative)
  • > 99th percentile = Abnormal

• Precision also increased at lower levels of detection
  • %CV – measure of scatter
  • Hs-Tn should have CV < 10% at 99th percentile or even near LoD
  • Makes “delta” meaningful
High Sensitive Troponins Assays

- **Siemens**
  - Vista Hs-Tropinin I (PathWest)
  - LoD 17ng/L; URL 50ng/L; 10% CV at 30ng/L
- **Roche**
  - Hs Troponin T
  - LoD 5ng/L; URL 14ng/L; 10% CV at 13ng/L
- **Abbott – various**
  - ARCHITECT Hs Troponin I
  - LoD: 9ng/L; URL 28ng/L; 10% CV at 32ng/L
- **Point of Care Troponins**
  - Typically LoD 50 – 80 ng/L (0.05 – 0.08 mcg/L)
  - “Positive” > 0.1mcg/L (100ng/L)
- **NB: Numbers across different analysers are not equivalent**
  - If looking at change over time – must be on the same analyser
# High Sensitive Troponins Change The Game

<table>
<thead>
<tr>
<th>“Old” Troponins</th>
<th>“New” hs-Troponins</th>
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</thead>
</table>
| **Good for cardiology**  
• Elevated Troponin meant ACS / AMI  
• Negative left for ED to worry about | **Good for ED**  
• Early Rule Out ACS – Short ED workup  
• Undetectable Troponin rules out ACS  
• No need for admission & testing |
| **Bad for ED**  
• Long ED Rule Out  
• Need for more testing  
• ? EST, Nuclear Scans, CTCA, ECHO | **Bad for Cardiology**  
• Normal people have detectable troponin  
• Elevated levels not always ACS  
• Uncertainty about best diagnostic strategy |
High Sensitivity = Low Specificity

- An elevated high sensitive troponin
  - Not necessarily ACS / Type I AMI (Plaque rupture)
- Type II “Stress” AMI – “Oxygen debt”
  - Increased demand (HR and Afterload)
  - Decreased supply (Critical illness)
- Other causes of myocyte damage

**It is a measure of badness**
- 31% mortality at 12 months, worse if “non-ACS” (Petrie et al 2014)
- Using change (delta) improves specificity
All Cause Mortality and Hs Troponin T in General Population

De Lemos et al 2010
Non-ACS Causes of Elevated Troponin

- Sepsis/systemic inflammatory response syndrome
- Hypotension
- Hypovolemia
- Supraventricular tachycardia
- Atrial fibrillation
- Left ventricular hypertrophy
- Coronary vasospasm
- Intracranial haemorrhage or stroke
- Ingestion of sympathomimetic agents
- Cardiac contusion

- Direct current cardioversion
- Cardiac infiltrative disorders
- Chemotherapy
- Myocarditis
- Pericarditis
- Cardiac transplantation
- Congestive heart failure
- **Pulmonary embolism**
- Pulmonary hypertension or emphysema
- Strenuous exercise
- Chronic renal insufficiency
Ruling Out ACS in ED

- History, Examination, ECG
  - Don’t forget the breathless
- Timing of the chest pain

- High Sensitive Troponin Timing
  - Single Trop on arrival (Time zero)
  - Second Trop – when?
- High Sensitive Troponin Level
  - Undetectable
  - Normal range
  - Delta
Single Undetectable Troponin (on arrival)

- Bandstein et al 2014
  - 14636 chest pain presentations
  - 8883 had initial hs-troponin T < 5ng/L
    - 39 had MI within 30 days
      - 24 had abnormal ECGs on presentation
      - 15 with normal ECG
        - 1 sent home immediately – STEMI at 18 days
        - 4 had ECG changes develop in ED
        - Remaining 10 had subsequent trop rise - none had a 2 hr troponin measured
          - 2 had normal coronary arteries
  - No deaths at 30 days
  - 38 (0.4%) deaths at 1 year (only 2 cardiac)
Undetectable hs-Troponin (<5ng/L) on Arrival

- Zhelev et al. 2015
  - Meta-analysis of 7 studies reporting undetectable hs-Tn
    - Excluded STEMI patients
  - Median prevalence of AMI 21% (Initial visit)
  - Single baseline value
  - Sensitivity 97.4% (94.9% – 98.7%)

- IS THIS GOOD ENOUGH TO RULE OUT AMI?
Single Undetectable Troponin T and Bayes

• From Zhelev
  • Sensitivity: 97.4%
  • Specificity: 42.4%
  • Negative LR: 0.06

<table>
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<tr>
<th>Pre-test Probability (%)</th>
<th>Post-test Probability (%)</th>
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<tbody>
<tr>
<td>25</td>
<td>1.6</td>
</tr>
<tr>
<td>20</td>
<td>1.2</td>
</tr>
<tr>
<td>15</td>
<td>0.9</td>
</tr>
<tr>
<td>10</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td>1</td>
<td>0.05</td>
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Single Undetectable Troponin I

- **Kelly et al 2015**
  - Siemens Ultra Troponin I
  - LoD 6ng/L
  - 1076 patients
    - Missed 4 AMIs – all had chest pain onset < 2 hours

- **Shah et al 2015**
  - Abbott Troponin I
  - LoD 1.2ng/l
  - <5ng/L on presentation
  - 2311 patients NPV = 99.6% for AMI on index visit
    - ~ missed 10 patients with AMI
    - 2160 patients had zero AMI or Death at 30 days

- **Carlton et al July 2016**
  - Troponin I (LoD 1.2ng/l)
  - 3155 patients
  - Sensitivity 99%, NPV 99.5% for death or MI at 30 days

- **Neuman et al July 2016**
  - Trop I <6ng/L at 1 hour
  - 1040 patients
  - NPV 99.8%
Second Undetectable hs-Troponin T
(<6ng/L)

• Reichlin 2009 & 2011
  • 1554 patients
  • 100% sensitivity for ACS / AMI at 2 hours

• Keller 2011
  • 1818 patients
  • 100% sensitivity for ACS / AMI at 0 & 3 hours

• Mueller 2016
  • 813 patients with Initial TnT <12ng/L and < 3ng/L rise at 1 hour
    • 7 subsequently had MI.
    • All at detectable TnT at 2 hours and/or ECG changes
Undetectable hs-Troponin rules out AMI*

- Possibly at presentation
  - If risk low
- Probably at 1 hour
- Definitely by 2 hours

* with non-ischaemic ECG
Troponins in the “Normal Range”
(LoD to 99\textsuperscript{th} Percentile)

- Multiple studies
- Variable sensitivities of troponin used
- Multiple timings of testing
- Variable risk cohorts
- Variable outcomes
  - Initial AMI versus later MACE
Troponins in the “Normal Range”
(LoD to 99th Percentile)

• Zhelev 2015
  • Meta-analysis 20 studies
  • **Single baseline** level > LOD & <99th Percentile (ie “normal range”)
  • Sensitivity 89.5% (86.3% - 92.1%)
  • Negative LR: 0.14 (0.1 – 0.18)

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<tr>
<td>5</td>
<td>0.8</td>
</tr>
<tr>
<td>1</td>
<td>0.2</td>
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Advantageous Predictors of ACS Evaluation (APACE) Studies

• APACE Studies (2015 – 2016)
  • Large Multi-centre studies
  • Hs-Trop T and I
  • 1 and 2 hour algorithms

• All Initial Troponin AND change (Delta) after 1 or 2 hours
  • 3 groups
    • ACS “Ruled Out”
    • Observe
    • ACS “Ruled In”
Reichlin et al 2015 (APACE)

One “missed” AMI had peak TropT 17ng/L

Rule-out acute MI

- Rule-out acute MI
- Baseline cTnT < 12 ng/L and absolute change within 1 h < 3 ng/L
- Rule-out acute MI
- n = 786 (59.5%)
- Acute MI n = 1
- Sensitivity: 99.6%
- Negative predictive value: 99.9%

Observational zone

- Observational zone
- n = 318 (24.1%)
- Acute MI n = 59
- Prevalence of acute MI: 18.6%

Rule-in acute MI

- Rule-in acute MI
- Baseline cTnT ≥ 52 ng/L or absolute change within 1 h ≥ 5 ng/L
- Rule-in acute MI
- n = 216 (16.4%)
- Acute MI n = 169
- Specificity: 95.7%
- Positive predictive value: 78.2%

hsTnT
LoD 5ng/L, URL 14ng/L
Advantageous Predictors of ACS Evaluation (APACE) Studies

• 7 Studies
• 12763 patients
• Rule in rate (AMI) 16 – 18%
• Ruled out by 1 or 2 hour algorithm:
  • 7150 patients
  • 28 (0.4%) subsequently had “AMI” (Tn > 99th percentile)
    • 27 had peak Troponin T < 60ng/L
    • 1 had peak Troponin I of 300ng/L (Known IHD and had no intervention)
Troponins in the “Normal Range” rule out AMI* 

X Not at presentation

❖ Almost certainly by 2 hours
  ✓ Delta small (< 5ng/L)
  ❖ Limited data on relative (%) change

* with non-ischaemic ECG
ACS “RULE OUT”

• Using high sensitive troponin
• Taken at presentation AND 2 hours LATER
• ACS RULED OUT IF:
  • EITHER
    • BOTH below level of detection
  • OR
    • Both below 99th percentile AND small delta
      • PathWest
      • 99th percentile: 50ng/L
      • Delta < 30%
FOLLOW UP TESTING
Can we identify those at risk?
"I'm stumped. We'll have to wait for the autopsy."
Cardiac Workup after ED “Rule Out”

• Consensus has been – “Non-invasive testing for all”
  • NHFA, NICE, AHA
  • Based on data from standard troponins studies (mostly last millennium)
    • 1 – 5% subsequent MACE after negative ECG and 10-12 hour troponin
    • “2% of AMIs are missed on initial visit”

• All studies look at the risk of not testing
  • Missing bad things
    • MACE

• Few look at the risk of testing
  • False positives
    • Bad events from unnecessary tests & treatments in healthy people
  • Radiation
  • Costs
Death after ED “Rule Out” – APACE Studies

Reichlin et al 2015
Gimenez et al 2015

A

- Rule-out
- Observational zone
- Rule-in

Mortality (%)

Time (days)

p<0.001

B

- Rule-out
- Observational zone
- Rule-in

Mortality (%)

Time (days)

p<0.001
Druey et al 2015

A

B

Days since presentation to the ED

Month since presentation to the ED

Mortality (%)

p-value < 0.001

Rule-out
Observational zone
Rule-in
Death after ED “Rule Out”

• At 30 days
  • Almost zero
  • APACE studies: 3 deaths at 30 days out of 7150 “Ruled Out” patients

• At 1 year
  • APACE studies ~ 1% mortality
30 day MACE after ED “Rule Out”

- Essential zero if
  - High sensitive troponin and non-ischaemic ECG
  - “Low Risk”
    - Clinical Decision Tool
    - Physician gestalt
    - Age <40
- Undetectable troponin
“When the music’s over, turn out the lights”
J. Morrison

You cannot get to zero risk
• Without perfect tests - Bayes
• Without infinitely large trials - Confidence intervals
• Without hurting the healthy - Clinical Trials

Concept of beyond reasonable doubt
NO testing strategy identifies those at risk of plaque rupture.
# Chest pain work up

History, examination and 0 & 2 hour ECG and hs-Troponin

<table>
<thead>
<tr>
<th>Both hsT undetectable Normal ECG History not c/w UA</th>
<th>Either hs-T measurable but below URL and non-significant delta</th>
<th>Either hs-T &gt; URL Measurable hs-T and significant delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge Manage risk factors</td>
<td>Consider alternate causes Assess risk factors and chest pain history – UA Cardiology referral if NOT “low risk”</td>
<td>Admit Consider alternate causes Manage as NSTEMI Manage risk factors</td>
</tr>
<tr>
<td>No non-invasive testing</td>
<td>Diagnostic strategy uncertain. Possible non-invasive testing</td>
<td>Cardiac workup</td>
</tr>
</tbody>
</table>

**URL:** Upper reference limit (99th percentile)

**UA:** Unstable angina

**Delta:** Difference between 0&2 hr troponin in EITHER direction

Lab defined or local agreement

Debate about relative or absolute difference
Summary

- **Know your troponin**
  - **Undetectable Hs-Troponin**
    - Rules out AMI early (2 hours)
    - Makes subsequent events highly unlikely
    - Further testing lacks utility
  - **Detectable Hs-Troponin in the normal range**
    - Needs a minimum 2 hours to rule out AMI
    - Delta helps identify ACS in this population
    - Measurable risk of subsequent events
    - Follow up testing based on history and risk factors