Presenters

W. Franklin Peacock, MD, FACEP, FACC

Robert H. Christenson, Ph.D., DABCC, FACB, FACC
What does “high-sensitivity” really mean?
Cardiac Biomarkers Timeline

- AST in MI
- LD & CK in MI
- CK isoenzymes
- Electrophoresis CK and LD
- CK-MB RIA
- Myoglobin RIA
- WHO criteria MI
- CK-MB Mass
- cTnI in MI
- cTnT in MI
- cTnT Risk Stratification
- Redefinition of MI
- Standardsization
- Guidelines
- cTn Assays
- cTnT/cTn I Assays
- High-Sensitivity cTn I Assays
- FDA Clears cTnI Assays
- hscTnI Lab Instruments Clear FDA
- hscTnI Pathfast Thru FDA

Timeline:
- 1950
- 1960
- 1970
- 1980
- 1990
- 2000
- 2010
- 2018

- cTnI
- Mass
- cTnT
- RIA
Cardiac Troponin
2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
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<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
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</tr>
<tr>
<td>Measure cardiac-specific troponin (troponin I or T) at presentation and 3–6 h after symptom onset in all patients with suspected ACS to identify pattern of values</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Obtain additional troponin levels beyond 6 h in patients with initial normal serial troponins with electrocardiographic changes and/or intermediate/high risk clinical features</td>
<td>I</td>
<td>A</td>
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<tr>
<td>Consider time of presentation the time of onset with ambiguous symptom onset for assessing troponin values</td>
<td>I</td>
<td>A</td>
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<tr>
<td><strong>With contemporary troponin assays, CK-MB and myoglobin are not useful for diagnosis of ACS</strong></td>
<td>III: No Benefit</td>
<td>A</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td></td>
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<tr>
<td>Troponin elevations are useful for short- and long-term prognosis</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Remeasurement of troponin value once on d 3 or 4 in patients with MI may be reasonable as an index of infarct size and dynamics of necrosis</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>BNP may be reasonable for additional prognostic information</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

When troponin is increased think heart

Cardiac isoforms in blood
High Sensitivity Cardiac Troponin

Same Cardiac Troponin Analyte
Six commercial (Hytest) mAbs evaluated for use in a 1 x 1 “reference “immunoassay

Epitope 1

Epitope 2

mAb M18
mAb 3C7
mAb 19C7
mAb 560

mAb 267
mAb MF4

1  ADGSDAAREPRPAPIRRSSNYAYATEPHARKKSLFASRKLQLKT  50
51  LLLQIAXELEREAERRGEKRALSTRQODELAGLGAELQOLCRQHL  100
101 ARVDKVDEERYDIEAKVTKNITEIADLTQKIFDLRCFKEKPTLRRVISA  150
151 DAMMQALLGARAKESLDLRAHLKQVKKEDTEKENREVGDRKINIDALS  200
201 EGRKKKFES  209
What is High-sensitivity Cardiac Troponin?

AACC Academy and IFCC TFCACB defines a high-sensitivity cTn as:

1. An assay that can measure $\geq 50\%$ of healthy men and $50\%$ of healthy women (i.e. values above the limit of detection)
2. hs-cTn assays are precise (i.e. day-to-day Total CV $\leq 10\%$)

High-sensitivity cTn is not a different analyte!
Term refers to a more sensitive assay

Clinical Chemistry 64:4;645–655 (2018)
High Accuracy, Different Precision

Earlier Generation Troponin

High-sensitivity Troponin

15% CV

5% CV
Early Velocity (Delta) Change Apparent with hsTn assays

Cardiac Troponin, ng/L

- Earlier-gen cTn
- hs-Tn

95% CI
15% CV
5% CV

Presentation | 1 Hr | 3 Hr | 8 Hr
High-sensitivity Cardiac Troponin Assays

Definition is Analytical, Benefit is Clinical

- High-Sensitivity’ is an analytical term
- hsTn assays DO NOT measure a different analyte
Earlier vs. Later-generation cTnI

Early generation cTnI

High-sensitivity cTn

Contemporary cTnI

% Positive

0 2 4 6 8 10 12 14 16 18 20 22 24

Hours

How does a high-sensitivity assay help me at the bedside with decision-making?
High Sensitivity Troponin
Impact of hs-cTnT on clinical practice

- Within the APACE trial (prospective, international, multicenter, diagnostic study)
- Three hospitals (SUI 2, ESP 1) switching from conventional cTnT to hs-cTnT
- Investigate patients‘ management before/after hs-cTnT (n=2544 pts.)
  - N=1455 before hs-cTnT
  - N=1089 after hs-cTnT

Impact of hs-cTnT on use of coronary angiography


No increase in coronary angiographies
Impact of hs-cTnT on findings of coronary angiography

Impact of hs-cTnT on use of cardiac stress testing

34% reduction of subsequent cardiac stress testing

Impact of hs-cTnT on duration of stay in the ED


- 20% reduction of duration of stay in the ED
- Change in trend
- 15% more out-patients
Impact of hs-cTnT on total costs


- 20% reduction of total costs in out-patients
Findings from hospitals not switching to hs-cTn

**Time in ED**

- Phase A: \( y = 322 + 4.63 \times x \)
- Phase B: \( y = 287 + 2.5 \times x \)

**Change in slope: \( p = 0.259 \)**

**Costs**

- Phase A: \( y = 1510 + 1.77 \times x \)
- Phase B: \( y = 1444 + 11.7 \times x \)

**Change in slope: \( p = 0.558 \)**

*Twerenbold R, et al. EHJ 2016*
ED discharge vs Tn assay sensitivity

SAFE ED DISCHARGE RATE

INCREASING TROTONIN SENSITIVITY
100 patients

Crappy Tn

9.8%
DISCHARGE

100 patients

Sensitive Tn

387%
increase

KEEP 90 PATIENTS

KEEP 62 PATIENTS
(discharge 28 more)
Troponin cutpoints

99th %ile

95%ile, like every lab test in the world

AMI

Made up cutpoint

LOD

TRD

LOD
N = 1113
ED CP
5 yr F/U
MACE
MI
HF
CV dead

Abbott Architect i2000

Roche Cobas e411

HsTnI and CVD Outcomes

- N=8121, w/o baseline CVD
- Median F/U = 15 yrs
- HsTnI in quartiles
  - All associated with significant HR

Jia X. *Circulation*. 2019;139:00–00. DOI: 10.1161/CIRCULATIONAHA.118.038772Cric
SWEDEHEART registry

- cTn elevation
  - Associated with CV and non-CV comorbidities
  - Predicts MACE in acutely admitted patients, in whom no definite Dx was established

- The term Troponinemia:
  - Trivializing
  - Should be avoided.
  - Instead, a careful work-up is required

Eggers K. JACC 2019;73:1–9)
But Remember...

• A naked troponin is just a lab test
• The diagnosis of unstable angina is controversial
  – At least for the time being it is probably prudent to consider it is still with us

• So, what to do after 2 negative troponin’s?
Comparing Scores

- PEARL data set
  - 7 EDs
- Patient with suspected ACS
- Dr had to document risk of MI before Tn as:
  - Low
  - Moderate
  - High Risk
- N=458
EDACS-ADP
Emergency Department Assessment Chest Pain Score -
Accelerated Diagnostic Procedure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Parameter</th>
<th>Points</th>
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<tbody>
<tr>
<td>History</td>
<td>18-50 yo with CAD, or &gt;2 risk factors</td>
<td>+4</td>
</tr>
<tr>
<td></td>
<td>18-45</td>
<td>+2</td>
</tr>
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<td></td>
<td>46-50</td>
<td>+4</td>
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<td></td>
<td>51-55</td>
<td>+6</td>
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<td></td>
<td>56-60</td>
<td>+8</td>
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<td>61-65</td>
<td>+10</td>
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<td>66-70</td>
<td>+12</td>
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<td>71-75</td>
<td>+14</td>
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<td></td>
<td>76-80</td>
<td>+16</td>
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<td>81-85</td>
<td>+18</td>
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<td>&gt;85</td>
<td>+20</td>
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<td>+4</td>
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<td>51-55</td>
<td>+6</td>
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<td>&gt;85</td>
<td>+20</td>
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<tr>
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<th>Parameter</th>
<th>Points</th>
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<tbody>
<tr>
<td>Signs and Symptoms</td>
<td>Diaphoresis</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>Arm or shoulder radiation</td>
<td>+5</td>
</tr>
<tr>
<td></td>
<td>Pain occurred or worsened with inspiration</td>
<td>-4</td>
</tr>
<tr>
<td></td>
<td>Pain is reproduced with palpation</td>
<td>-6</td>
</tr>
</tbody>
</table>

Low Risk Criteria
- EDACS Score <16
- No new ECG ischemia
- Negative 0 and 2h Tn
Is the 99$^{\text{th}}$ percentile the same for all assays and all people?
99th percentile Upper Reference Limit
Different for different populations

Dr. Appel’s email signature line:
Some simple advice for all of us: "Eat less, eat right, move more"
99<sup>th</sup> percentile Cutoffs, Healthy Individuals

- Siemens hsTnI 99<sup>th</sup> percentile USA individuals ranging from 22–91 years.
- Lithium-heparin plasma from 2007 apparently healthy individuals.
- The 99 percentile values determined for lithium-heparin plasma (female, male, and combined). The 90% confidence intervals demonstrate that there is no statistical basis for using separate 99<sup>th</sup> percentile values based on sex.

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Gender</th>
<th>n</th>
<th>99th Percentile&lt;sup&gt;a&lt;/sup&gt; (pg/mL; ng/L)</th>
<th>90% CI&lt;sup&gt;b&lt;/sup&gt; (pg/mL; ng/L)</th>
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<tbody>
<tr>
<td>Lithium Heparin</td>
<td>Female</td>
<td>1007</td>
<td>34.11</td>
<td>27.36–66.23</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1000</td>
<td>53.48</td>
<td>38.73–80.22</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>2007</td>
<td>45.20</td>
<td>33.21–64.30</td>
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### Sex-Specific Cutoffs From Siemens HIGH-US Study For HTnl FDA Clearance

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<tr>
<th>Hours</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive PV</th>
<th>Negative PV</th>
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<tr>
<td>Female 99th percentile = 34.1 ng/L</td>
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<tr>
<td>0--&lt; 1.5</td>
<td>84.4 (71.2--92.3)</td>
<td>93.3 (90.4--95.3)</td>
<td>59.4 (47.1--70.5)</td>
<td>98.2 (96.3--99.1)</td>
</tr>
<tr>
<td>≥ 1.5--&lt; 2.5</td>
<td>89.9 (81.3--94.8)</td>
<td>91.7 (89.4--93.5)</td>
<td>54.6 (46.0--62.9)</td>
<td>98.8 (97.7--99.4)</td>
</tr>
<tr>
<td>≥ 2.5--&lt; 3.5</td>
<td>94.5 (86.7--97.8)</td>
<td>91.6 (89.2--93.6)</td>
<td>57.0 (48.1--65.5)</td>
<td>99.3 (98.2--99.7)</td>
</tr>
<tr>
<td>Male 99th percentile = 53.5 ng/L</td>
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<td></td>
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<tr>
<td>0--&lt; 1.5</td>
<td>75.0 (65.7--82.5)</td>
<td>91.5 (88.9--93.5)</td>
<td>61.0 (52.1--69.1)</td>
<td>95.4 (93.3--96.8)</td>
</tr>
<tr>
<td>≥ 1.5--&lt; 2.5</td>
<td>87.6 (81.6--91.8)</td>
<td>91.2 (89.1--92.8)</td>
<td>63.8 (57.3--69.9)</td>
<td>97.6 (96.4--98.5)</td>
</tr>
<tr>
<td>≥ 2.5--&lt; 3.5</td>
<td>89.8 (83.4--94.0)</td>
<td>90.0 (87.6--91.9)</td>
<td>60.5 (53.4--67.2)</td>
<td>98.1 (96.8--98.9)</td>
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<tr>
<td>Pooled 99th percentile = 45.2 ng/L</td>
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<tr>
<td>0--&lt; 1.5</td>
<td>77.2 (69.8--83.3)</td>
<td>91.8 (89.9--93.4)</td>
<td>58.9 (51.8--65.7)</td>
<td>96.4 (95.0--97.4)</td>
</tr>
<tr>
<td>≥ 1.5--&lt; 2.5</td>
<td>90.0 (85.6--93.2)</td>
<td>90.6 (89.1--91.9)</td>
<td>58.7 (53.6--63.6)</td>
<td>98.4 (97.6--98.9)</td>
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<tr>
<td>≥ 2.5--&lt; 3.5</td>
<td>92.0 (87.5--95.0)</td>
<td>90.6 (88.9--92.0)</td>
<td>58.9 (53.4--64.2)</td>
<td>98.7 (97.9--99.2)</td>
</tr>
</tbody>
</table>
What other issues and considerations do we need to know?
Cardiac Troponin Units of Measure

ng/mL, Contemporary versus ng/L, High-sensitivity

High-sensitivity • 19 ng/L
Contemporary • 0.03 ng/mL or 30 ng/L
High-sensitivity • 22 ng/L
Contemporary • 0.003 ng/mL or 3 ng/L
Contemporary • 0.30 ng/mL or 300 ng/L
High-sensitivity • 14 ng/L
High-sensitivity • 6 ng/L
How does all of this fit in with the 4th universal definition of MI?
Today’s fun fact:

All AMIs have increased hsTn. (95% at 3 hours)

**BUT**, not all hsTn increases are AMI. (50% at 3 hours)
Elevated Troponin in Patients without MI or Heart Failure

- **Acute Disease**
  - Cardiac and Vascular
  - Acute Aortic dissection
  - Cerebrovascular accident
  - Ischemic Stroke
  - Intracerebral Hemorrhage
  - Subarachnoid Hemorrhage
  - Medical ICU Patients

- **Chronic Disease**
  - ESRD
  - Cardiac infiltrative disorders
  - Amyloidosis
  - Sarcoidosis
  - Hemochromatosis
  - Scleroderma

- **Heart Specific Disease Specific**

- **Other Medications**
  - Birth Complications in Infants
  - Extreme Low Birth Weight
  - Preterm Delivery
  - Acute Complications of Myocardial Injury
  - Inherited Disorders
  - Neurofibromatosis
  - Duchenne Muscular Dystrophy
  - Klippel-Feil syndrome
  - Environmental Exposure
  - Carbon Monoxide
  - Hydrogen Sulfide
  - Colchicine exposure

- **Acute Disease**
  - Other Medications
  - Birth Complications in Infants
  - Extreme Low Birth Weight
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  - Environmental Exposure
  - Carbon Monoxide
  - Hydrogen Sulfide
  - Colchicine exposure
4th Universal Definition of Myocardial Infarction


- cTnI and cTnT are the preferred biomarkers for rule in and rule out myocardial injury, and thus to define MI and each specific subtype of MI.
- Detection of a rise and/or fall of cTn values is essential, and a key early component along with clinical evaluation to establish the diagnosis of acute MI.
How does this affect reporting from a lab perspective?
Factors Affecting the Interpretation of Troponin Assays

- Hemolysis
- Microclots
- Biotin (Vitamin B₁₂)

Cardiac Troponin Interferences

- cTn AutoAbs (usually to TIC complex)
- Heterophile Abs
- Skeletal muscle disease
- AutoAbs (usually to TIC complex)
High Sensitivity cTn Oriented for Rule-Out

SnOut:
- Sensitivity (TP/TP+FN) describes the ability of a test to identify true disease
  - A high sensitivity test has few **false negatives** and is effective at ruling conditions “out” (SnOut)

SpIn:
- Specificity (TN/TN+FP) describes the ability of an IVD test to correctly identify the absence of disease
  - A high specificity test has few **false positives** and is effective at ruling conditions “in” (SpIn).
<table>
<thead>
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<th>Sample Time</th>
<th>No.</th>
<th>Performance (95% CI)</th>
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<tr>
<td></td>
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<td>Sensitivity</td>
<td>Specificity</td>
<td>PPV</td>
<td>NPV</td>
</tr>
<tr>
<td>Overall URL (19 ng/L)</td>
<td></td>
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<tr>
<td>0 h</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1600</td>
<td>86.0 (79.7-90.9)</td>
<td>88.0 (86.2-89.6)</td>
<td>44.9 (39.3-50.6)</td>
<td>98.2 (97.3-98.9)</td>
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<tr>
<td>Male</td>
<td>829</td>
<td>88.1 (80.2-93.7)</td>
<td>84.1 (81.2-86.7)</td>
<td>43.4 (36.5-57.5)</td>
<td>98.1 (97.0-99.0)</td>
</tr>
<tr>
<td>Female</td>
<td>771</td>
<td>82.5 (70.9-90.9)</td>
<td>91.9 (89.7-93.8)</td>
<td>47.7 (38.1-57.5)</td>
<td>98.3 (97.0-99.2)</td>
</tr>
<tr>
<td>3 h</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1415</td>
<td>94.3 (89.1-97.5)</td>
<td>86.6 (84.6-88.4)</td>
<td>43.6 (37.9-49.4)</td>
<td>99.3 (98.6-99.7)</td>
</tr>
<tr>
<td>Male</td>
<td>733</td>
<td>95.6 (89.1-98.8)</td>
<td>83.0 (79.9-85.8)</td>
<td>44.4 (37.3-51.6)</td>
<td>99.3 (98.1-99.8)</td>
</tr>
<tr>
<td>Female</td>
<td>682</td>
<td>91.8 (80.4-97.7)</td>
<td>90.2 (87.6-92.4)</td>
<td>42.1 (32.6-52.0)</td>
<td>99.3 (98.2-99.8)</td>
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</table>
## hs Beckman Assay

### Preliminary Data

<table>
<thead>
<tr>
<th>g99 percentile URL cutoff, pg/mL (ng/L)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
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<td>% (n/N)</td>
<td>95% CI</td>
<td>% (n/N)</td>
<td>95% CI</td>
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<td><strong>Females: 14.9</strong></td>
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<td></td>
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<tr>
<td>Baseline</td>
<td>83 (25/30)</td>
<td>85 - 94</td>
<td>91 (234/256)</td>
<td>87 - 95</td>
</tr>
<tr>
<td>≥ 1-3 hour</td>
<td>93 (40/43)</td>
<td>81 - 99</td>
<td>92 (490/535)</td>
<td>89 - 94</td>
</tr>
<tr>
<td>≥ 3-6 hour</td>
<td>98 (49/50)</td>
<td>86 - 100</td>
<td>92 (509/556)</td>
<td>80 - 94</td>
</tr>
<tr>
<td>≥ 6-9 hour</td>
<td>100 (22/22)</td>
<td>86 - 100</td>
<td>88 (198/225)</td>
<td>83 - 92</td>
</tr>
<tr>
<td><strong>Males: 19.8</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>89 (63/71)</td>
<td>79 - 95</td>
<td>87 (271/311)</td>
<td>83 - 91</td>
</tr>
<tr>
<td>≥ 1-3 hour</td>
<td>98 (89/93)</td>
<td>89 - 99</td>
<td>88 (490/557)</td>
<td>86 - 91</td>
</tr>
<tr>
<td>≥ 3-6 hour</td>
<td>94 (98/102)</td>
<td>88 - 98</td>
<td>88 (536/607)</td>
<td>80 - 91</td>
</tr>
<tr>
<td>≥ 6-9 hour</td>
<td>98 (48/49)</td>
<td>89 - 100</td>
<td>81 (183/225)</td>
<td>76 - 96</td>
</tr>
</tbody>
</table>
Any closing thoughts?
UDMI

3rd UDMI
I: Plaque pathology causes a thrombus
II: Supply-demand imbalance
III: AMI causing death without a biomarker measured
IVa: AMI related to PCI
IVb: AMI related to stent thrombosis
V: AMI related to CABG

4th UDMI
II: Supply-demand imbalance unrelated to thrombus, AND with ischemia

Tn elevation in the absence of ischemia is defined as myocardial injury

Summary

• hsTn
  – Faster
  – Cheaper
  – Finds more patients with disease
  – CONSIDER PHYSIOLOGY!
    • Too early is dangerous

• Risk
  – Use a score, don’t be dumb
For More Information

- E-QUAL Website
  - www.acep.org/equal
  - equal@acep.org

- Contacts:
  - Nalani Tarrant: (Director)
    - ntarrant@acep.org
  - Dhruv Sharma: (Project Manager)
    - dsharma@acep.org