Chest Pain Wave I

Biomarker Testing in Chest Pain – Past, Present, and Future
Presenters

W. Franklin Peacock, MD, FACEP, FACC

Robert H. Christenson, Ph.D., DABCC, FACB, FACC
As a clinician, what makes an ideal chest pain biomarker?
Just your average Jane

- 19:00 Monday
- 42 yo ♀, began to vomit
- Ate some “bad sushi”
- Brought by daughter

- 8:00 pm, arrives in ER
• 8:30 pm
  – EKG completely normal
  – Dr orders lytes, CBC, TnI
  – Gets an IV
  – 4 mg odansetron
  – 1 liter normal saline
  – TnI

• 3.5 hours later (1am)
  – Feels better, wants to leave
  – Is discharged home

• Diagnosis: food poisoning
• At 6am Jane collapses
• Paramedics arrive within 4 minutes of call
• Found in VT, defibrillated
• 17 mins after arrest, returns to NSR

Prehospital ECG transmitted
Taken straight to cath lab
DTB 27 minutes

Jane never wakes up
Epidemiology of CHD in the US

• Single most frequent cause of death
  – 656,000 deaths in 2002, 1 of every 5 deaths

• Incidence each year
  – 1.2 million new or recurrent coronary event; >40% will die
  – 700,000 are 1st attacks; 500,000 are recurrences

• Prevalence
  – 13 million Americans have a history of CHD

• Legal consequences for emergency docs
  – #1 settlement cost
  – Most like to be sued in the 1st 5 years after residency

In 2018, it is estimated YOU will miss 423,600 AMIs

1/3 have no chest pain

8% of all ER visits are for chest pain

Canto JG et al. JAMA. 2000;283:3223-3229
What about Chest Pain in MI?

• In a study of 434,877 patients with confirmed MI from 1674 US hospitals
  
  – **More than one third** of all AMI patients present without chest pain
  
  – Of these, 63.7% were UA/NSTEMI patients

• Certain MI patients (women, elderly, HF) are more likely to present without chest pain

You don’t have to go home, but you can’t stay here....

- Semisonic
The ER docs challenge

Admit them all:
and let the insurance company sort them out…

Discharge them all
and let God sort them out…
Emergency Medicine Roulette

What % are discharged from the ED??
Consequences

- What happens to an emergency doc who gets it wrong.....?
The Ideal Biomarker for Suspect ACS (not CP)

• Veeeeeereee sensitive
  – Remember Tn in the “old days”
Hs Tn (STATISTICAL) Definition
You can’t have it both ways

**Sensitivity**

\[ \frac{TP}{TP+FN} \]

**Specificity**

\[ \frac{TN}{TN+FP} \]
The Ideal Biomarker for Suspect ACS (not CP)

- Veeeeeery statistically sensitive
- On a platform with EXCELLENT low level sensitivity
The Ideal Biomarker for Suspect ACS (not CP)

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The Ideal Biomarker for Suspect ACS (not CP)

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• Speed?
Speed?

- Rapid but insensitive?
- One and done?
  - If long symptoms?
    - Guidelines say yes
  - If really low level?
    - Data says no
Meta-analysis

- N=9241 pts in 11 studies
  - 2825 (30.6%) low risk
  - 14 (0.5%) AMI, no deaths
- AMI Sn = 98.7% (95% CI, 96.6% to 99.5%)
  - 87.5% to 100% in individual studies
- 30 day MACE Sn = 98.0% (CI, 94.7% to 99.3%)
  - 87.9% to 100%

Pickering JW
Ann Intern Med.
2017;166(10):715-724
The Ideal Biomarker for Suspect ACS (not CP)

- Veeeeeerey statistically sensitive
- On a platform with EXCELLENT low level sensitivity

- Speed
- Specificity?
Specificity:

Exactly how many ICU beds do you got?
Hospitalization MARKEDLY Increases HAC

Premier Database

- Definitions
  - Short LOS < 2 days
  - Adverse PE events (aPE) 2nd DVT, MB, or death
  - Hospital Acquired Conditions (HAC)

- 6,746 PE
  - 1,918 Low risk by sPESI
    - 688 (35.9%) LRPE had a short LOS
  - After PSM: 784 LRPE patients

No Difference in aPE btwn Short vs Long LOS (p>0.05)

887% increase in HAC
The Ideal Biomarker for Suspect ACS (not CP)

- Veeeeeeery statistically sensitive
- On a platform with EXCELLENT low level sensitivity

- Speed
- Specificity
- Costs?
Cost of hsTn vs conventional Tn

- Cost/LYG: €4945
- Cost/QALY: €7370

Vaidya A. BMC Cardiovascular Disorders 2014, 14:77

- Cost/QALY: £7,340 to £12,340

Thokala P. Heart 2012;98:1498e1503
The Ideal Biomarker for Suspect ACS (not CP)

- Veeeeeeery statistically sensitive
- On a platform with EXCELLENT low level sensitivity
- Speed
- Specificity
- Costs
- Prognosis?
As a laboratorian, what makes an ideal chest pain biomarker?
• In medicine, a **biomarker** is a measurable characteristic that reflects the severity or presence of some disease state. More generally a biomarker is anything that can be used as an indicator of a particular disease state or some other physiological state of an organism.

**Biochemical Marker**
When troponin is increased think heart

Cardiac isoforms in blood
Biomarker levels represent a summation of the influence of acute and chronic comorbidities.
Elevated Troponin in Patients without ACS 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**
  - Birth Complications in Infants
  - Extreme Low Birth Weight
  - Preterm Delivery
  - Acute Complications of
    - Inherited Disorders
    - Neurofibromatosis
    - Duchenne Muscular Dystrophy
    - Klippel-Feil syndrome
    - Environmental Exposure
    - Carbon Monoxide
    - Hydrogen Sulfide
    - Colchicine exposure

- **Other Medications**
  - **Myocardial Injury**
    - Blunt Chest Injury
    - Endurance athletes
    - Envenomation
    - Snake
    - Jellyfish
    - Spider
    - Centipede
    - Scorpion

- **Environmental Exposure**
  - Carbon Monoxide
  - Hydrogen Sulfide
  - Colchicine exposure
AMI Definition

Cardiac Troponin

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Marco Roffi* (Chairperson) (Switzerland), Carlo Patrono* (Co-Chairperson) (Italy), Jean-Philippe Collet (France), Christian Mueller* (Switzerland), Marco Valgimigli† (The Netherlands), Felicita Andrieutti (Italy), Jerosm J. Bar (The Netherlands), Michael A. Borger (Germany), Carlos Brotons (Spain), Derek P. Chew (Australia), Biris Gencer (Switzerland), Gerd Haenssens (Germany), Knud Kjeldsen (Denmark), Patrizio Lanciloti (Belgium), Ulf Lindgrens (Sweden), Juliana Mattioli (Germany), Debabrata Mukherjee (USA), Robert F. Stroke (UK), and Stephen Windisclaus (Switzerland)
Single Biomarker Test for MI

- All Patients
- Chest-Pain Onset < 3 Hr
- Chest-Pain Onset < 6 Hr
- Chest-Pain Onset < 12 Hr

Sensitivity vs. 1-Specificity graphs for different biomarkers:
- Troponin I
- Troponin T
- Myoglobin
- Creatine kinase MB
- Creatine kinase

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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</thead>
<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>
</tr>
<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>
</tr>
<tr>
<td>With contemporary troponin assays, CK-MB and myoglobin are not useful for diagnosis of ACS</td>
<td>III: No Benefit</td>
<td>A</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td></td>
<td></td>
</tr>
<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 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>


38% of SCPC accredited Medical Centers use Cardiac Troponin assay as the sole marker for diagnosis of ACS!
“Small heart attacks are so common; they are almost within normal range.”

Paul Dudley White, 1957
The Father of American Cardiology

Prophetic
Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin] with at least one value above the 99th percentile upper reference limit.

Consensus ‘Guidance’ Document
Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin] with at least one value above the 99th percentile upper reference limit …

• **Less than 50%** of institutions in the USA use the recommended *99th percentile cutpoint* for diagnosis of myocardial infarction.

• **Less that 50%** of the institutions in the developed world use the *99th percentile cutpoint* for diagnosis of myocardial infarction.
Implementation of a Sensitive Troponin I Assay and Risk of Recurrent Myocardial Infarction and Death in Patients With Suspected Acute Coronary Syndrome

Mills et al. JAMA. 2011;305(12):1210-1216
OK – so troponin is THE cardiac biomarker for now, and the foreseeable future...but, are all troponin tests the same and what does high-sensitivity mean?
Are All Cardiac Troponin Assays Created Equal?
Are All Cardiac Troponin Assays Created Equal?

NO
High Accuracy, Different Precision

High Sensitivity Cardiac Tn Assays are more precise

18% CV

5% CV
What is High-Sensitivity Cardiac Troponin?

• IFCC defines high-sensitivity cTn test as one that can measure ≥ 50 % of healthy subjects above the Limit of Detection.
• Also, high-sensitivity cTn assays perform at the highest level of day-to-day precision, i.e. CV ≤ 10%.

Clin Biochem 2015;48(4-5):201-203
The Next Generation

Current commercial TnI
Limit of detect ~ 0.005 ng/ml
10% CV = 0.02 - 0.04 ng/ml

Prior Gen commercial TnI
Limit of detect ~ 0.1 ng/ml
10% CV = 0.4 ng/ml

Next Gen Ultrasensitive
Limit of detect ~ 0.0001 ng/ml
10% CV <0.001 ng/ml

From: Contemporary Cardiology: Cardiovascular Biomarkers: Pathophysiology and Disease Management
Edited by: David A. Morrow © Humana Press Inc., Totowa, NJ
Troponin Normal Reference Interval

N=616; 20-70 years; 309 men (50.2%); 307 women 49.8%

LoD for 5th Gen TnT assay

99th %tile Healthy Normals

10% CV 4th Gen Cutoff

Women

Overall

Men

Clinical Chemistry 56:2
Cardiac Troponin Units of Measure

ng/mL, Contemporary versus ng/L, 5th Generation and High-sensitivity

- High-sensitivity: 19 ng/L
- Contemporary: 0.03 ng/mL
- High-sensitivity: 22 ng/L
- Contemporary: 0.003 ng/mL
- Contemporary: 0.006 ng/mL
- High-sensitivity: 14 ng/L
- High-sensitivity: 6 ng/L
5th Gen USA Package Insert

• Sex specific 99th percentile values
  – Women 14 ng/L
  – Men 22 ng/L
  – Overall 19 ng/mL
ROC Area and Time of Symptoms Onset

Early vs. Later Generation cTnI

% Positive

Recent generation cTnI

Earlier generation cTnI

Hours

Total Error in Temporal Samples
What does all this mean for patient care?
What is an ADP

- A series of activities to identify a patient as:
  1) Having an event
  2) Being at risk for having an event
  3) Having nothing
A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study

- 14 Asia-Pacific region EDs
- >18yo with >5 mins CP
- Risk stratification (blinded to care team)
  - TIMI<1, ECG non-dx,
  - Negative 0 & 2hr POC Tn, CKMB, myo
- Endpoint: 30 day MACE
TIMI Risk Score: 2 week MACE

- **Risk factors:**
  - Age ≥65 years
  - ≥3 risk factors for CAD
  - Prior coronary stenosis ≥50%
  - ST-segment deviation on ECG
  - ≥2 anginal events in last 24 hours
  - Use of ASA in last 7 days
  - Elevated serum cardiac markers CK-MB or troponin

Each risk factor is = 1 point, and total represents TIMI Risk Score

Event rates (all-cause mortality, MI, or UTVR) increase with each 1-point increase in score

• N=3582
  – 30 day MACE in 421 (11·8%)
  – Most often NSTEMI

• ADP identified 9·8% (352/3582) as low risk
  – 3 (0·9%) had 30 day MACE

## Impact of a Tn with higher low level sensitivity

### ASPECT (N=3582)

<table>
<thead>
<tr>
<th>TIMI</th>
<th>Low risk</th>
<th>30 d MACE</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>9.8% (352)</td>
<td>0.9% (3)</td>
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### ADAPT (N=1975)

<table>
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<th>TIMI</th>
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<th>30 d MACE</th>
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<tbody>
<tr>
<td>0</td>
<td>25.3% (392)</td>
<td>0.25% (1)</td>
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</table>

Than M. JACC 2012;59:2091–8)
Increased Troponin Sensitivity Leads to More Emergency Department Early Discharges

**ADAPT & APACE**

Low Risk:
Non-ischemic ECG, hs-TnI ≤26.2ng/L, and TIMI=0 or TIMI ≤1

<table>
<thead>
<tr>
<th>TIMI</th>
<th>ADAPT (N=1635)</th>
<th>APACHE (N= 909)</th>
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<tbody>
<tr>
<td></td>
<td>Low risk</td>
<td>30 d MACE</td>
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<tr>
<td>0</td>
<td>19.6% (320)</td>
<td>0% (0)</td>
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<tr>
<td>≤1</td>
<td>41.5% (678)</td>
<td>0.8% (2)</td>
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</tbody>
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Cullen L. JACC, 2013. 10.1016/j.jacc.2013.02.078
### ADAPT & APACE

#### 30 day MACE

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<thead>
<tr>
<th></th>
<th>ADAPT (N=1635)</th>
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<th>APACE (N= 909)</th>
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<td>Sn</td>
<td>NPV</td>
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<td>TIMI</td>
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<td>(98.5-100)</td>
<td>(98.8-100)</td>
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<tr>
<td>≤1</td>
<td>99.2%</td>
<td>99.7%</td>
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<td>99.4%</td>
<td>99.7%</td>
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<td>(97.1-99.8)</td>
<td>(98.9-99.9)</td>
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<td>(96.5-100)</td>
<td>(98.4-100)</td>
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Cullen L. JACC, 2013. 10.1016/j.jacc.2013.02.078
What does the future of biomarker-based chest pain care look like?
Necrosis Biomarkers Timeline

- 1950: LD & CK in MI
- 1960: AST in MI
- 1970: CK-MB isoenzymes in MI, Electrophoresis of CK and LD
- 1990: cTnI in MI, cTnI Mass, cTnT in MI, cTnT RIA
- 2000: cTnI/cTnT Risk Stratification
- 2010: Redefinition of MI
- 2020: Hs-cTnT Available non-U.S, Hs-cTnT Risk in Normals

Hs-cTnT Cleared by US FDA!
Why are updates needed?
Evolution of Temporal Serial Sampling

1. Rule-out
2. Rule-in

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<tbody>
<tr>
<td>0h</td>
<td></td>
<td>cTn</td>
<td>cTn</td>
<td>hs-cTn</td>
<td>cTn</td>
<td>cTn</td>
<td>hs-cTnT</td>
<td>hs-cTnT</td>
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<td>1h</td>
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1282 Patients with chest pain

- **0h < 12 ng/L AND Delta 1h < 3 ng/L**
  - Rule-out
    - 813 Patients (63.4%)
    - NPV: 99.1%
    - 95% CI 98.2-99.7%

- **0h ≥ 52 ng/L OR Delta 1h ≥ 5ng/L**
  - Rule-in
    - 184 Patients (14.4%)
    - PPV: 77.2%
    - 95% CI 70.4-83.0%

- **Others**
  - Observational Zone
    - 285 Patients (22.2%)
    - Prevalence of AMI 22.5%
NEED FOR SPEED!
Major Focus on Troponin

- Society of Cardiovascular Patient Care (SCPC): Requiring POCT 60 minutes or less TAT (90%) for accreditation
- CAP: Established Q-Monitor that measures TAT
- National Academy of Clinical Biochemistry and International Federation of Clinical Chemistry: Recommend 60 minutes or less TAT
- American College of Cardiology & American Heart Assoc. Recommends 60 minute TAT with preference at 30 minutes

- **Time is Critical (but Not Everything)**
So is it more about the marker or the pathway?
HEART Score for 6 week MACE

MACE = AMI, PCI, CABG, (+) cath, death

**Hx:** Hi =2, Mod =1, Slight =0

**ECG:** Sig ST dep =2, NS repol =1, Nl =0

**Age:** ≥65 =2, 45-65 =1, ≤ 45 =0

**Risks:** ≥3 =2, 1-2 =1, 0=0

**Tn:** ≥3x ULN =2
1-3 ULN =1
≤ ULN =0

RISKS
Hyperchole, HTN, DM, Tobbacco, (+) FH, Obesity

Low risk = 0-3; <2% MACE risk
**EDACS-ADP**
Emergency Department Assessment Chest Pain Score - Accelerated Diagnostic Procedure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Parameter</th>
<th>Points</th>
</tr>
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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>Age</td>
<td>18-45</td>
<td>+2</td>
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<tr>
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<td>46-50</td>
<td>+4</td>
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<td>51-55</td>
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<td>56-60</td>
<td>+8</td>
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<td>61-65</td>
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<td>66-70</td>
<td>+12</td>
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<td>76-80</td>
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<td>81-85</td>
<td>+18</td>
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<td></td>
<td>&gt;85</td>
<td>+20</td>
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</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>+6</td>
</tr>
<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>
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**Low Risk Criteria**
- EDACS Score <16
- No new ECG ischemia
- Negative 0 and 2h Tn
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
### Comparing Score Performance

<table>
<thead>
<tr>
<th>Standard cutpoint</th>
<th>Low risk (n) Definition</th>
<th>Missed AMI, %</th>
<th>Sensitivity set at 99%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td>Cutoff</td>
</tr>
<tr>
<td>Clinical</td>
<td>–</td>
<td>5.9 (3.0-11.2)</td>
<td>–</td>
</tr>
<tr>
<td>HEART-1</td>
<td>&lt;4</td>
<td>4.7 (2.1-9.9)</td>
<td>0</td>
</tr>
<tr>
<td>HEART-2</td>
<td>&lt;4</td>
<td>4.1 (1.9-8.7)</td>
<td>0-2</td>
</tr>
<tr>
<td>TIMI</td>
<td>0</td>
<td>0 (0-12.9)</td>
<td>0</td>
</tr>
<tr>
<td>EDACS</td>
<td>&lt;16</td>
<td>1.0 (0.2-4.1)</td>
<td>12</td>
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</tbody>
</table>
Suspected ACS?

- ECG
  - Positive?
    - Cath lab
    - Positive?
      - Cath lab
      - Negative?
        - Admit
          - BNP > 400
        - EDACS ≤ 12
          - Consider d/c and early f/u
        - EDACS > 12, TIMI ≤ 4
          - CTA/MPI unless recently tested
        - TIMI > 4
          - Consider admit, cards consult
Questions? Contact the E-QUAL team at equal@acep.org