Myocardial injury & Myocardial infarction
Where are we now?

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Co Investigator, Cardiac Biomarker Trials Laboratory, MMRF.

May 22nd, 2017

Objectives

1. Rationale
   a. Historical background

2. Disease process and outcomes
   a. Myocardial infarction: Focus Type 2 MI
   b. Myocardial injury

3. Clinical focus on diagnostics: Update
   a. High-sensitivity cardiac troponin assays
Why are we talking about this?

- **More than 8 million patients** present annually to the ED with acute chest pain.
- Cardiac biomarker testing occurs in **17%** of all ED visits.
- **29 million** out of 170 million ED visits in the United States (2009-2010).


Why are we talking about this?

LOW RISK  
RISK FOR MYOCARDIAL INFARCTION  
HIGH RISK

Arch Intern Med 2012; 172: 1211-1218
"I thought to myself that only sudden, progressively increasing disturbance of the nutrition of the heart...

"...can only be due to a thrombotic occlusion of at least one coronary artery"

"Thrombotic occlusion of one of the coronary arteries of the heart"
Coronary thrombosis

Acute myocardial infarction

Coronary thrombosis
Acute myocardial infarction not due to coronary artery occlusion

Friedberg CK, Horn CK. JAMA 1939; 112: 1675-9

"The myocardial changes seen... were indistinguishable from those ordinarily described as infarcts, and like infarcts, consisted of areas of necrosis due to ischemia caused by an inadequate coronary blood supply."
Acute myocardial infarction

1979
Nomenclature and Criteria for Diagnosis of Ischemic Heart Disease
Report of the Joint International Society and Federation of Cardiology
/ World Health Organization: Acute Myocardial Infarction


- History
- ECG
- Serum enzymes

Evolution of diagnostic modalities

ECG
Pathology
Imaging
Biochemistry

Myocardial infarction redefined: Consensus Document JACC 2000
Acute myocardial infarction

Universal Definition of Myocardial Infarction

- History
- ECG
- Serum enzymes

1979 Nomenclature and Criteria for Diagnosis of Ischemic Heart Disease Report of the Joint International Society and Federation of Cardiology / World Health Organization

1979 Nomenclature and Criteria for Diagnosis of Ischemic Heart Disease

2000 Myocardial Infarction Redefined – A Consensus Document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction (First Universal Definition of MI)

2007 ESC/ACCF/AHA/WHF Expert Consensus Document Universal Definition of Myocardial Infarction (Second Universal Definition of MI)

2012 ESC/ACCF/AHA/WHF Task Force Third Universal Definition of Myocardial Infarction

Type 1 Spontaneous MI
Type 2 MI secondary to an ischemic imbalance
Type 3 MI resulting in death when biomarker values are unavailable
Type 4 MI related to PCI
Type 4b MI related to stent thrombosis
Type 5 MI related to CABG

Universal Definition of Myocardial Infarction

Disease process

Mechanisms
Nomenclature
99th percentile
Rule-in Rule-out

Diagnostics
Universal Definition of Myocardial Infarction

Disease process

Nomenclature

99th percentile

Rule-in Rule-out

Myocardial injury with cell death marked by cardiac troponin elevation

Troponin leak
Troponinitis
Troponinemia
Myonecrosis
CELLULAR DEATH IN MYOCARDIAL INFARCTION

APOPTOSIS

NECROSIS

Myocardial injury with cell death marked by cardiac troponin elevation.

Myocardial injury with cell death marked by cardiac troponin elevation.

Clinical evidence of acute myocardial ischemia with rise and/or fall of cardiac troponin.

Myocardial infarction

Cardiac procedure
Non-cardiac major procedure
Tachy-/brady-arrhythmia
Heart failure
Renal failure
Myocardial injury with cell death marked by cardiac troponin elevation

Cardiac procedure
Non-cardiac major procedure
Tachy-/brady-arrhythmia
Heart failure
Renal failure

Myocardial infarction

Clinical evidence of acute myocardial ischemia with rise and/or fall of cardiac troponin

Differentiation between type 1 and 2 MI

Plaque rupture with thrombus
MI Type 1

Vasospasm or endothelial dysfunction
MI Type 2

Fixed atherosclerosis and supply-demand imbalance
MI Type 2

Supply-demand imbalance alone
MI Type 2
Mechanisms leading to myocardial ischemia in the absence of coronary plaque rupture.

Patients with cTn concentrations above the 99th percentile

Sandoval, Apple 2017
15% of cardiac troponin increases are due to type 1 myocardial infarction
Type 2 Myocardial Infarction: Incidence

Adjudication

Studied Population

Definition

cTn Assay and utilized cutoff value

T2MI Frequency
Type 2 Myocardial Infarction: Incidence

US Chest pain cohort

All-comers undergoing cTn measurements in United States emergency room

Sandoval et al. JACC 2014
**Type 2 Myocardial Infarction: Incidence**

- **Definition**
  - An approach in which adjudicators or clinicians evaluate all contributing variables affecting myocardial oxygen consumption and give a diagnosis of type 2 myocardial infarction without applying strict parameters.
  - Does require objective evidence or documentation of supply-demand mismatch.

- **Adjudication**
  - Studied Population

- **cTn Assay and utilized cutoff value**

- **T2MI Frequency**

**Type 2 Myocardial Infarction: Definition**

- **BROAD DIAGNOSTIC CRITERIA**
  - Sandoval et al. JACC 2014
Type 2 Myocardial Infarction: Definition

- Anemia: Hb <5.5 M, <5.0 F
- Shock: SBP <90 with organ dysfunction
- Bradyarrhythmia requiring treatment
- Coronary embolism
- Signs of acute respiratory failure for ≥20 minutes
- VT ≥20 minutes
- SVT ≥ 20 minutes, >150 BPM
- HTN pulmonary edema: >160 mmHg
- HTN: >160 mmHg and LVH

Type 2 Myocardial Infarction: Mechanisms

Saaby Am J Med 2013
Type 2 Myocardial Infarction: Mechanisms

- Anemia: 19%
- Respiratory failure: 10%
- Multi-factorial: 10%
- Pulmonary edema: 10%
- Shock: 5%
- Bradycardia: 5%
- Hypertension: 10%
- Coronary embolus: 15%
- Coronary spasm: 20%

Main trigger tachydysrhythmias: ~30%
Type 2 Myocardial Infarction: Mechanisms

Main trigger tachydysrhythmias: ~30%
US cohort (Sandoval/Apple 2015): 36%

Type 2 Myocardial Infarction: Prognosis

180 day all-cause mortality

Without myocardial cell death: 3.2%
Myocardial injury: 9.4%
Type 2 myocardial infarction: 11.4%

Type 2 Myocardial Infarction: Prognosis

180 day all-cause mortality

- Without myocardial cell death: 3.2%
- Myocardial injury: 9.4%
- Type 2 myocardial infarction: 11.4%

Adjusted HR 2.9 (1.4-5.9) p=0.004
Adjusted HR 2.5 (1.1-6.0) p=0.04


Catheter Sampled Blood Archive in Cardiovascular Disease (CASABLANCA)

Catheter Sampled Blood Archive in Cardiovascular Disease (CASABLANCA)

- Median follow-up ~3.3 years

CASABLANCA. Circulation 2017; 135: 116-17
Type 2 Myocardial Infarction: Prognosis

Catheter Sampled Blood Archive in Cardiovascular Disease (CASABLANCA)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse CV events</td>
<td>1.90</td>
<td>1.46-2.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause death</td>
<td>2.96</td>
<td>2.01-4.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2.16</td>
<td>1.36-3.43</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Incident diagnosis of type 2 myocardial infarction strongly predicted risk for subsequent MACE, all-cause death and CV death

Median follow-up ~3.3 years

CASABLANCA. Circulation 2017; 135: 116-17

Type 2 Myocardial Infarction: Management

- No guidelines exist addressing management.
- Absence of guidance results in variable management.
- Treat underlying etiology
- If underlying CAD contributing, consider ASA and statins, consider additional invasive or non-invasive imaging.

Sandoval JACC 2014
Sandoval Y, Thygesen K CCJ 2017
Type 2 Myocardial Infarction: Management

- No guidelines exist addressing management.
- Absence of guidance results in variable management.
- Treat underlying etiology
  - If underlying CAD contributing, consider ASA and statins, consider additional invasive or non-invasive imaging.

Type 2 Myocardial Infarction: CAD

Prevalence of CAD among pts. with T2MI undergoing angiography

- Baron 2016
- Javed 2009
- Saaby 2013
- Spatz 2015
MI with no obstructive coronary artery disease

MINOCA

n=3,533

~8% of all MIs undergoing angiography

Type 1 MINOCA

n=2,912 (82%)

Type 2 MINOCA

n=621 (18%)


Elevated troponin value(s) > 99th percentile URL

Myocardial cell death

Overt ischemia

Troponin rise/fall

Myocardial Infarction

Thrombosis

Type 1 MI
Atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus

Type 2 MI examples:
- Severe anemia
- Severe respiratory failure
- Tachyarrhythmia
- Cardiogenic or hypovolemic shock
- Severe hypertension
- Coronary embolism
- Coronary endothelial dysfunction or spasm

Oxygen imbalance

Cardiac

Examples:
- Heart failure
- Cardiomyopathy
- Myocarditis
- Cardiac confusion
- Cardiac surgery
- Defibrillator shocks
- Aortic dissection

Systemic

Examples:
- Sepsis / Infection
- Critically ill patients
- Renal failure
- Stroke
- Pulmonary embolism
- Toxic agents
- Rhabdomyolysis

Sandoval Y, Thygesen K CCJ 2017
Universal Definition of Myocardial Infarction

Disease process

Mechanisms

Nomenclature

99th percentile

Rule-in Rule-out

CARDIAC TROPONIN ASSAYS

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

High Sensitivity cTn Assay
- Measure cardiac troponin values above the LoD in ≥ 50% of a healthy cohort.
- CV<10% at the 99th URL

Apple FS, Sandoval Y, Jaffe AS, Ordonez-Llanos; for the IFCC TF CB. CCJ 2017
Impact of Analytical Variation on MI Diagnosis

Comparing Contemporary vs. hs-cTn Assays

<table>
<thead>
<tr>
<th>Manufacturer – assay</th>
<th>Measurable values &gt;LoD, %</th>
<th>CV% at the 99th percentile</th>
<th>Total Imprecision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott ARCHITECT – hs-cTnI</td>
<td>95%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Abbott ARCHITECT – cTnI</td>
<td>2%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Beckman Access 2 – hs-cTnI</td>
<td>80%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Beckman Access 2 – cTnI</td>
<td>35%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Siemens Dimension Vista – hs-cTnI</td>
<td>100%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Siemens Dimension Vista - cTnI</td>
<td>1%</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>

Selected examples.

Can we expedite the identification of patients at low risk in whom safe early discharge is feasible?
Rule-out Strategies

- Use of undetectable hs-cTn levels. (Below <LoD or <LoB)
- Hs-cTn in combination with a risk score (ADPs)
- Use of a single hs-cTn measurement in a concentration tailored to meet a clinical need
- Accelerated Serial hs-cTn sampling (0h and 1-3h)

Safety Outcome: 30-day AMI and Cardiac Death

<table>
<thead>
<tr>
<th>Study cohort</th>
<th>All</th>
<th>n = 1,631</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline hs-cTnI &lt;LoD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=444, 27%</td>
</tr>
<tr>
<td>NPV %</td>
<td>99.6</td>
<td>(98.9, 100)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity %</td>
<td>98.8</td>
<td>(97.2, 100)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proportion of missed MIs: 2 out of 171 (1.2%)


Rule-out Strategies

- Use of undetectable hs-cTn levels. (Below <LoD or <LoB)
- Hs-cTn in combination with a risk score (ADPs)
- Use of a single hs-cTn measurement in a concentration tailored to meet a clinical need
- Accelerated Serial hs-cTn sampling (0h and 1-3h)

### Rule-out strategies hs-cTn: Accelerated Diagnostic Protocols (ADPs)

<table>
<thead>
<tr>
<th>Author - Journal - Year</th>
<th>Total patients</th>
<th>cTn Assay</th>
<th>Protocol</th>
<th>% qualifying for strategy</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cullen L et al.</strong> JACC 2013</td>
<td>1635</td>
<td>Abbott hs-cTnI</td>
<td>ADAPT=0h and 2h TIMI ≤1, nL ECG, nL hs-cTnI (&lt;99th URL)</td>
<td>ADAPT=41.5%</td>
<td>NPV MACE*: 99.7%</td>
</tr>
<tr>
<td></td>
<td>909</td>
<td></td>
<td>APACE=38.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Carlton EW et al.</strong> Heart 2015</td>
<td>960</td>
<td>Roche hs-cTnT</td>
<td>TRUST ADP Low Risk: Goldman ≤1 Non-ischemic ECG Single hs-cTnT &lt; 99th URL (14 ng/L)</td>
<td>382 of 960 (39.8%)</td>
<td>99.7%</td>
</tr>
</tbody>
</table>

*Cullen et al. MACE (30-days): death (excluding clearly noncardiac, cardiac arrest, acute MI, emergency revascularization procedure, cardiogenic shock, ventricular arrhythmia requiring intervention and high-degree AV block requiring intervention.*

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### Rule-out Strategies

- **Use of undetectable hs-cTn levels.** (Below <LoD or <LoB)
- **Hs-cTn in combination with a risk score** (ADPs)
- **Use of a single hs-cTn measurement in a concentration tailored to meet a clinical need**
- **Accelerated Serial hs-cTn sampling** (0h and 1-3h)

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


Rule-out Strategies

- Use of undetectable hs-cTn levels. (Below <LoD or <LoB)
- Hs-cTn in combination with a risk score (ADPs)
- Use of a single hs-cTn measurement in a concentration tailored to meet a clinical need
- Accelerated Serial hs-cTn sampling (0h and 1-3h)

**Rule-out strategies with hs-cTn: Serial Sampling**

<table>
<thead>
<tr>
<th>Author - Journal - Year</th>
<th>Total patients</th>
<th>cTn Assay</th>
<th>Sampling algorithm</th>
<th>% qualifying for strategy</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reichlin T et al. CMAJ 2015</td>
<td>n=1320</td>
<td>Roche</td>
<td>hs-cTnT 0h and 1h</td>
<td>786 out of 1320</td>
<td>99.9%</td>
</tr>
<tr>
<td>Rubini Gimenez et al. AJM 2015</td>
<td>n=1811</td>
<td>Abbott</td>
<td>hs-cTnI 0h and 1h</td>
<td>50.5%</td>
<td>99.6%</td>
</tr>
<tr>
<td>Reichlin T et al. Arch Int Med 2012</td>
<td>DC=436</td>
<td>Roche</td>
<td>hs-cTnT 0h and 1h</td>
<td>259 out of 436</td>
<td>100%</td>
</tr>
<tr>
<td>Reichlin et al. AJM 2015</td>
<td>N=1665</td>
<td>Roche</td>
<td>hs-cTnT 0h and 2h</td>
<td>DC=60%</td>
<td>99.9%</td>
</tr>
<tr>
<td></td>
<td>VC=517</td>
<td>hs-cTnT</td>
<td>0h and 2h</td>
<td>VC=78%</td>
<td>99.5%</td>
</tr>
</tbody>
</table>

**2011 ESC Guidelines**

A rapid rule-out protocol (0h and 3h) recommended when **highly sensitive troponin tests** are available (Class I – LOE: B).

**2015 ESC Guidelines**

A rapid rule-out and rule-in protocol (0h and 1h) recommended with **high-sensitivity cardiac troponin** (Class I – LOE: B).

*** Concerns over performance particularly, early presenters

Eur Heart J 2011; 32: 2069-3054.
What will happen when **high-sensitivity troponin assays** are implemented in clinical practice?

### Contemporary cTnI

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

Across serial measurements
Over 7000 samples.

What will happen upon hs-assays implementation?

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

### High Sensitivity cTnI
- >99th: 27%
- LoD to 99th: 56%
- <LoD: 17%

Across serial measurements
Over 7000 samples.

- No increase in values above 99th URL
- Marked increase in measurable values (>LoD)

### MI Frequency: cTnI vs. hs-cTnI

<table>
<thead>
<tr>
<th>Adjudication Method by Assay – Total</th>
<th>99th percentile URL</th>
<th>MI n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIs adjudicated using contemporary assay</td>
<td>0.030 µg/L</td>
<td>43 (14%)</td>
</tr>
<tr>
<td>MIs adjudicated using a hs-cTnI assay</td>
<td>F:16 ng/L; M:34 ng/L</td>
<td>32 (10%)</td>
</tr>
</tbody>
</table>

**Transition to WHOLE NUMBERS**

**Use of GENDER-CUTOFFS**

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### Cardiac Troponin: A Paradigm Shift

**Cardiac Troponin Assays:** Guide to Understanding Analytical Characteristics and Their Impact on Clinical Care

Fred S. Apple,1,* Yader Sandoval,2 Allan S. Jaffe,3 and Jordi Ordonez-Llanos,4 for the IFCC Task Force on Clinical Applications of Cardiac Bio-Markers

**Present and Future of Cardiac Troponin in Clinical Practice: A Paradigm Shift to High-sensitivity Assays**

Yader Sandoval, MD,1,* Stephen W. Smith, MD,2 Fred S. Apple, PhD2

1Division of Cardiology, Department of Medicine, Hennepin County Medical Center, Minneapolis, Minn; 2Minneapolis Heart Institute, Abbot-Northeastern Hospital, Minn; 3Department of Emergency Medicine, Hennepin County Medical Center and University of Minnesota, Minneapolis; 4Department of Laboratory Medicine and Pathology, Hennepin County Medical Center and University of Minnesota, Minneapolis.
It is clear from the history and gross pathologic findings that Hammer’s case was not a case of atherosclerotic coronary artery disease.

An aortic valve vegetation with an attached thrombus had obstructed the coronary artery.

TAKE-HOME POINTS

1. Use the right nomenclature and avoid the use of terms that diminish the importance of these events.

2. Myocardial injury and type 2 myocardial infarction represent the majority of cTn increases in contemporary practice, ~ worse outcomes.

3. Implementing hs-assays will not necessarily equate to an epidemic of cardiac injury.

4. Hs-cTn assays will allow the rapid-rule out of AMI and provide a more precise test at low concentrations.