Chest Pain Wave I

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

Presenters

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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

Jane's Course

- 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 caall
- Found in VT, defibrillated
- 17 mins after arrest, returns to NSR
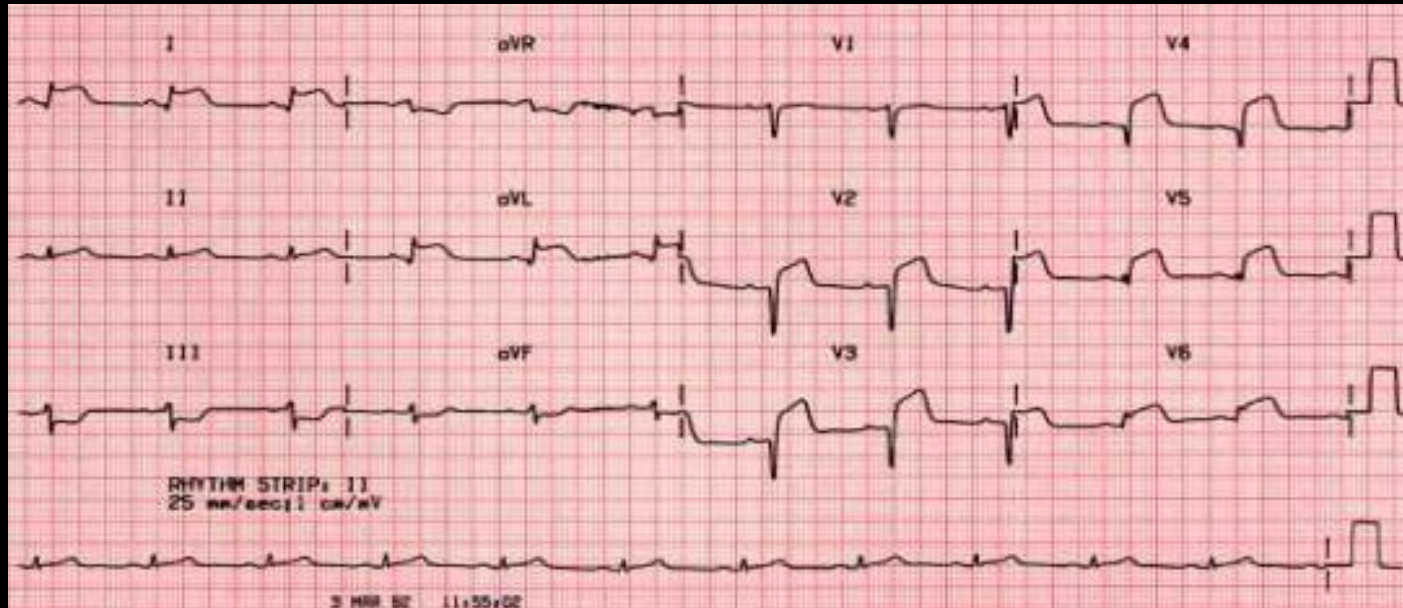
Prehospital ECG transmitted
Taken straight to cath lab
DTB 27 minutes

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

If you think this is the way they look...

In 2018, it is estimated <u>YOU will miss 423,600</u> 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

Canto JG et al. *JAMA*. 2000;283:3223-3229.

Closing Time

- 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…*

Acute CHEST PAIN.
ECG is NONDIAGNOSTIC.
Low RISK for MI.
Moderate risk for UNSTABLE ANGINA.

SHOULD YOU SEND HIM HOME?

Nuclear imaging can help you improve the management of patients with acute chest pain.¹ With nuclear imaging in its chest pain protocol, an emergency department in Virginia reduced admissions by 20% and length of stay by 50-83%.¹

NUCLEAR IMAGING.
THE CONFIDENCE OF KNOWING.

Fujisawa Healthcare, Inc.
COMMITTED TO CARDIOLOGY
www.fujisawa.com

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)

- Veeeeeeery sensitive
  - Remember Tn in the "old days"

Hs Tn (STATISTICAL) Definition
You can't have it both ways

Sensitivity

$$TP/(TP+FN)$$

American College of Emergency Physicians®

Specificity

$$TN/(TN+FP)$$

AMERICAN COLLEGE OF CARDIOLOGY

The Ideal Biomarker for Suspect ACS (not CP)

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

The Ideal Biomarker for Suspect ACS (not CP)

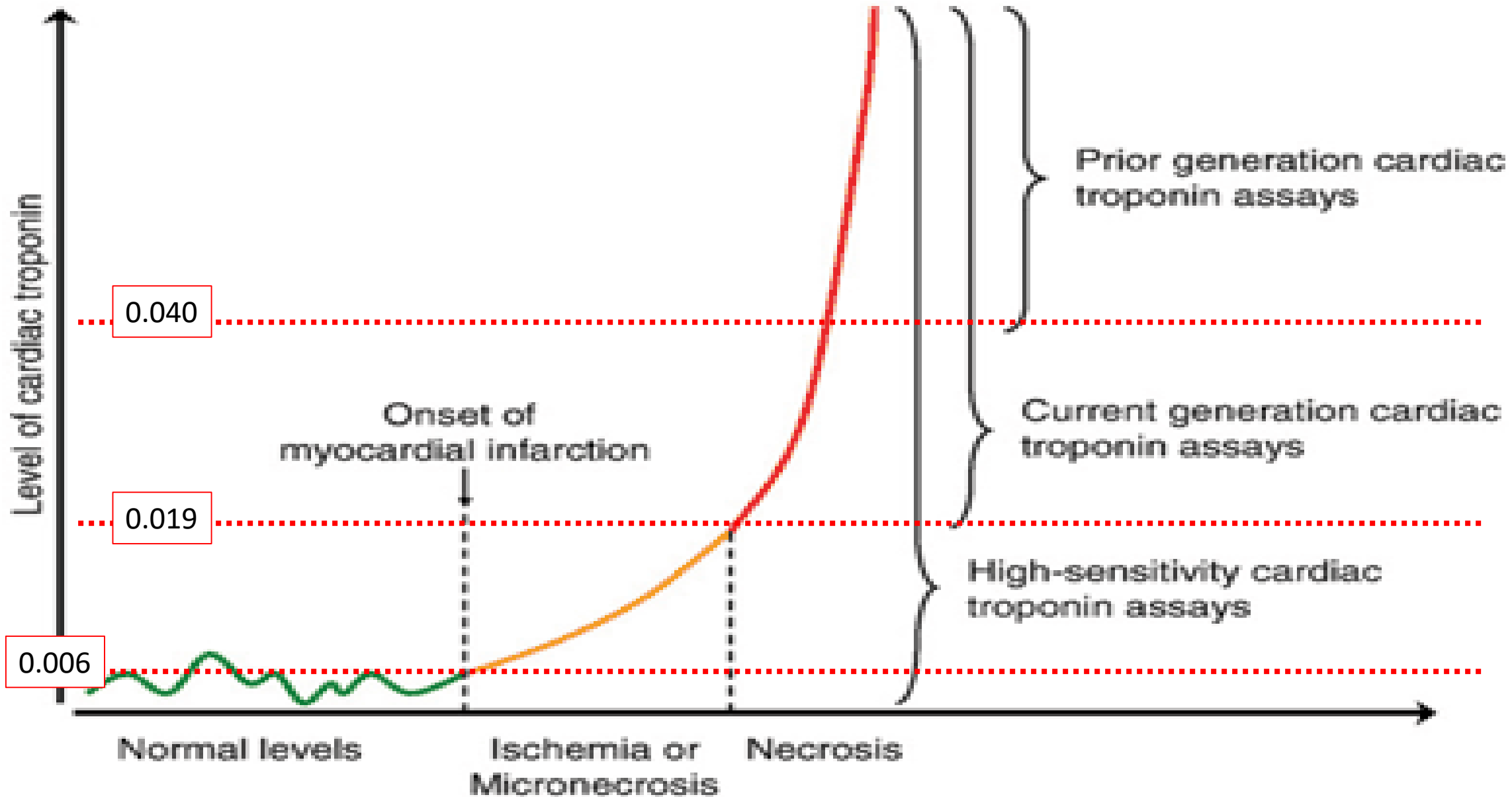- Veeeeeeery statistically sensitive
- On a platform with EXCELLENT low level sensitivity

The Ideal Biomarker for Suspect ACS (not CP)

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

- 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%

The Ideal Biomarker for Suspect ACS (not CP)

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

- Speed
- Specificity?

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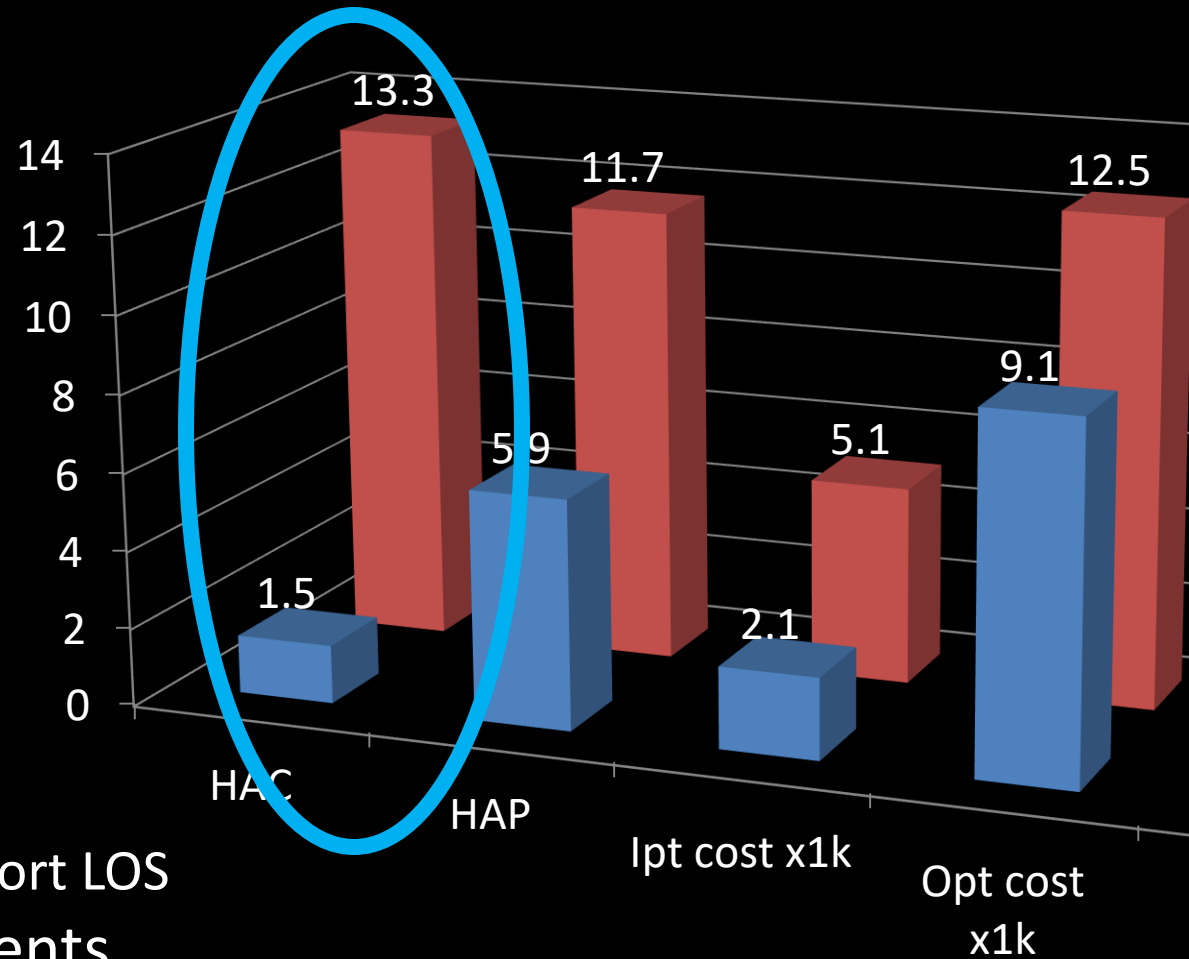
Hospitalization MARKEDLY Increases HAC

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

Chart values:
- HAC: 1.5, 13.3
- HAP: 5.9, 11.7
- Ipt cost x1k: 2.1, 5.1
- Opt cost x1k: 9.1, 12.5

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.
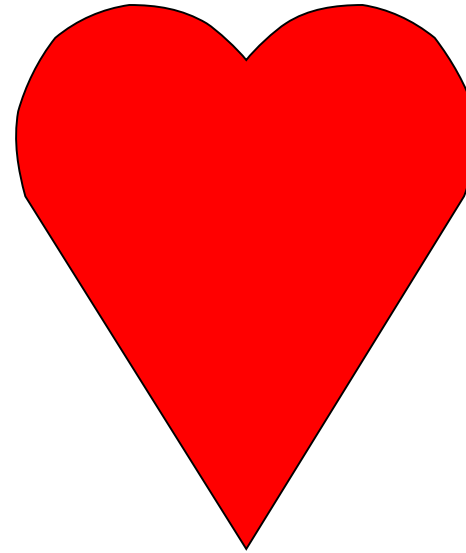
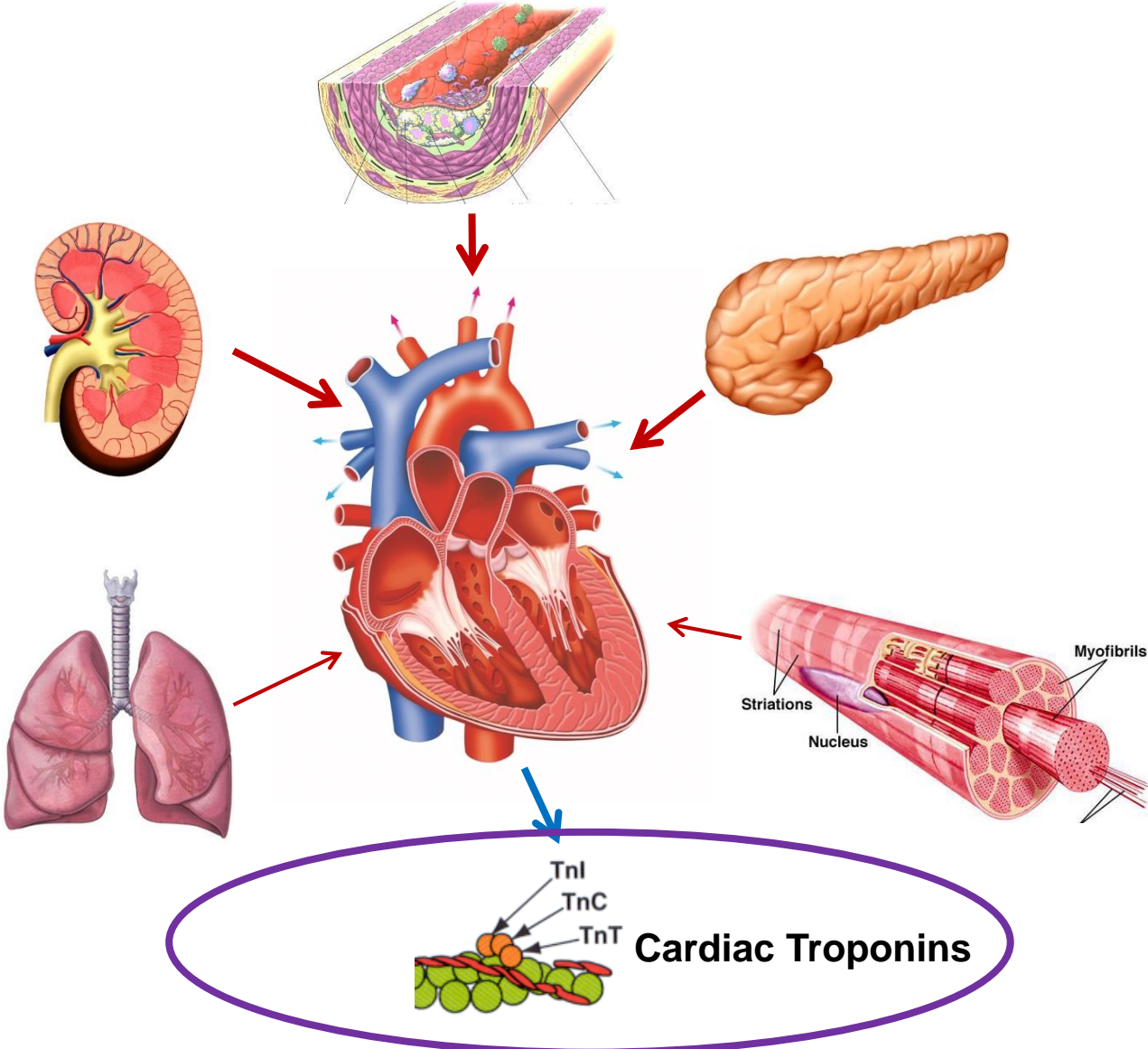 **Biochemical Marker**

When troponin is increased think heart

Cardiac isoforms in blood
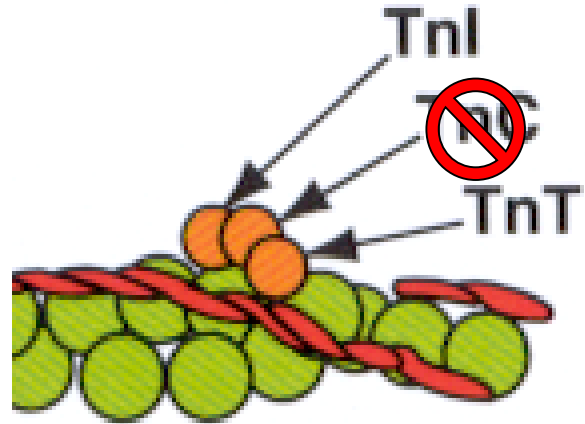
Biomarker levels represent a summation of the influence of acute and chronic comorbidities

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

2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes: Executive Summary
A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons

Endorsed by the American Association for Clinical Chemistry

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BIOMARKERS OF ACUTE CORONARY SYNDROMES AND HEART FAILURE

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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 Andreotti (Italy), Jeroen J. Bax (The Netherlands), Michael A. Borger (Germany), Carlos Brotons (Spain), Derek P. Chew (Australia), Baris Gencer (Switzerland), Gerd Hasenfuss (Germany), Keld Kjeldsen (Denmark), Patrizio Lancellotti (Belgium), Ulf Landmesser (Germany), Julinda Mehilli (Germany), Debabrata Mukherjee (USA), Robert F. Storey (UK), and Stephan Windecker (Switzerland)

Third universal definition of myocardial infarction

Kristian Thygesen, Joseph S. Alpert, Allan S. Jaffe, Maarten L. Simoons, Bernard R. Chaitman and Harvey D. White: the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction

Authors/Task Force Members Chairpersons: Kristian Thygesen (Denmark)*, Joseph S. Alpert, (USA)*, Harvey D. White, (New Zealand)*, Biomarker Subcommittee: Allan S. Jaffe (USA), Hugo A. Katus (Germany), Fred S. Apple (USA), Bertil Lindahl (Sweden), David A. Morrow (USA), ECG Subcommittee: Bernard R. Chaitman (USA), Peter M. Clemmensen (Denmark), Per Johanson (Sweden), Hanoch Hod (Israel), Imaging Subcommittee: Richard Underwood (UK), Jeroen J. Bax (The Netherlands), Robert O. Bonow (USA), Fausto Pinto (Portugal), Raymond J. Gibbons (USA), Classification Subcommittee: Keith A. Fox (UK), Dan Atar (Norway), L. Kristin Newby (USA), Marcello Galvani (Italy), Christian W. Hamm (Germany), Intervention Subcommittee: Barry F. Uretsky (USA), Ph. Gabriel Steg (France), William Wijns (Belgium), Jean-Pierre Bassand (France), Phillippe Menasché (France), Jan Ravkilde (Denmark), Trials & Registries Subcommittee: E. Magnus Ohman (USA), Elliott M. Antman (USA), Lars C. Wallentin (Sweden), Paul W. Armstrong (Canada), Maarten L. Simoons (The Netherlands), Heart Failure Subcommittee: James L. Januzzi (USA), Markku S. Nieminen (Finland), Mihai Gheorghiade (USA), Gerasimos Filippatos (Greece), Epidemiology Subcommittee: Russell V. Luepker (USA), Stephen P. Fortmann (USA), Wayne D. Rosamond (USA), Dan Levy (USA), David Wood (UK), Global Perspective Subcommittee: Sidney C. Smith (USA), Dayi Hu (China), José-Luis Lopez-Sendon (Spain), Rose Marie Robertson (USA), Douglas Weaver (USA), Michal Tendera (Poland), Alfred A. Bove (USA), Alexander N. Parkhomenko (Ukraine), Elena J. Vasilieva (Russia), Shanti Mendis (Switzerland).

Single Biomarker Test for MI
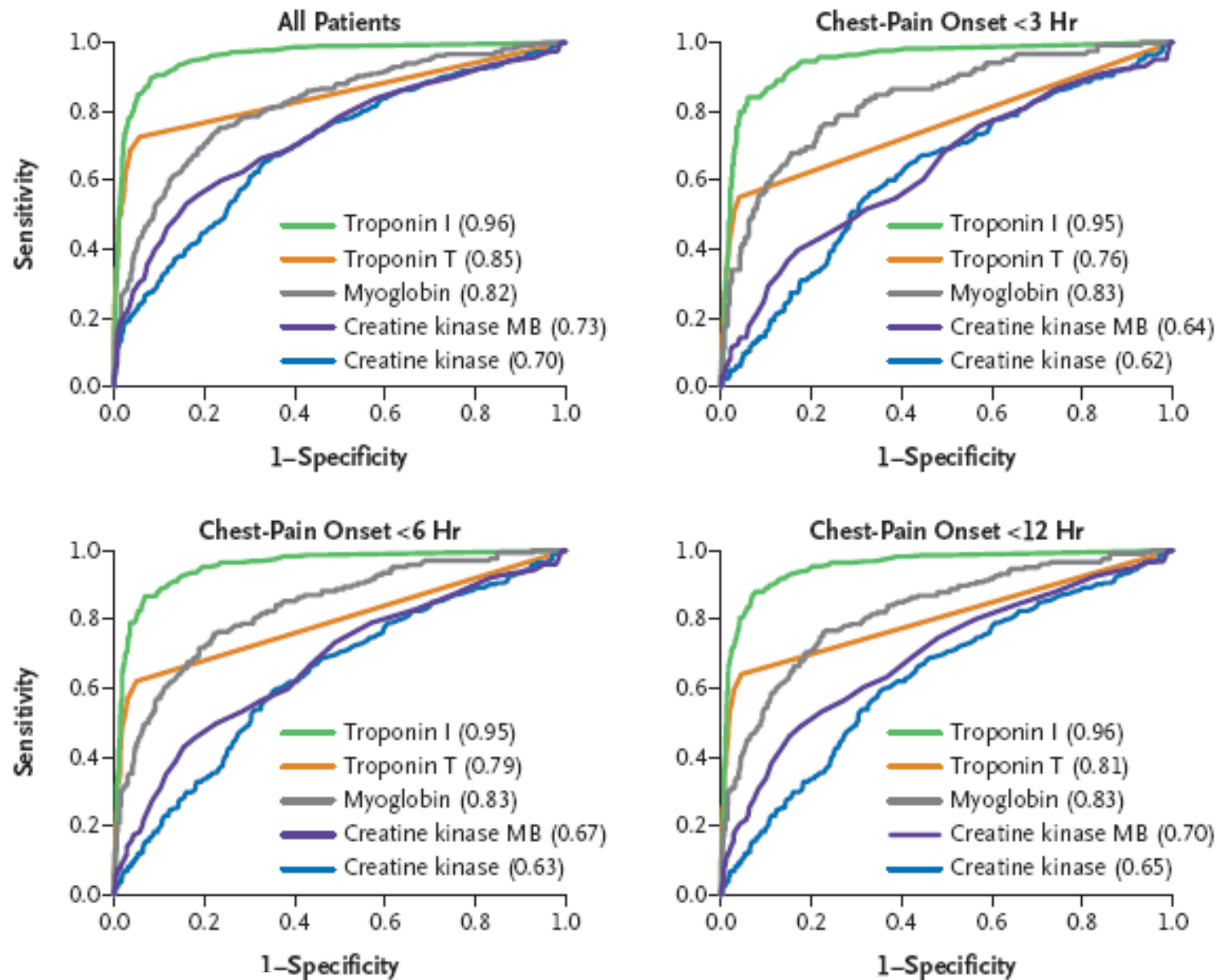
2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

Recommendations	COR	LOE
Diagnosis		
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	I	A
Obtain additional troponin levels beyond 6 h in patients with initial normal serial troponins with electrocardiographic changes and/or intermediate/high risk clinical features	I	A
Consider time of presentation the time of onset with ambiguous symptom onset for assessing troponin values	I	A
With contemporary troponin assays, CK-MB and myoglobin are not useful for diagnosis of ACS	III: No Benefit	A
Prognosis		
Troponin elevations are useful for short- and long-term prognosis	I	B
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	IIb	B
BNP may be reasonable for additional prognostic information	IIb	B

Circulation. 2014 Dec 23;130(25):e344-426.

38% of SCPC accreditedMedical Centers use Cardiac Troponin assay as the sole marker for diagnosis of ACS!

Definition of Myocardial Infarction

"Small heart attacks are so common; they are almost within normal range."

Paul Dudley White, 1957
The Father of American Cardiology

Prophetic

Third Universal Definition of Myocardial Infarction

published online August 24, 2012; Circulation.

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
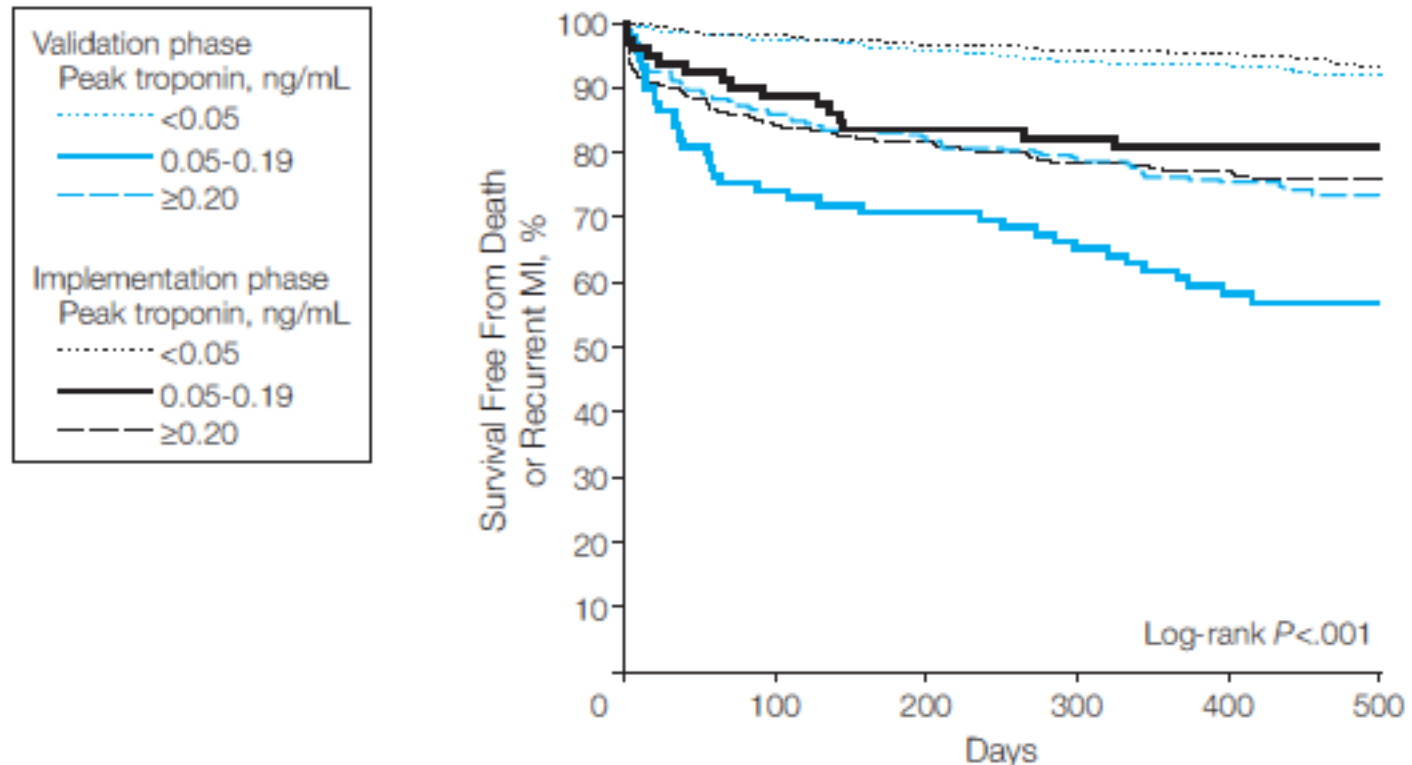
Mills et al. JAMA. 2011;305(12):1210-1216

OK – so troponin is THE cardiac biomaker 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^{1000}

High Accuracy, Different Precision

high accuracy
low precision

18% CV

high accuracy
high precision

5% CV
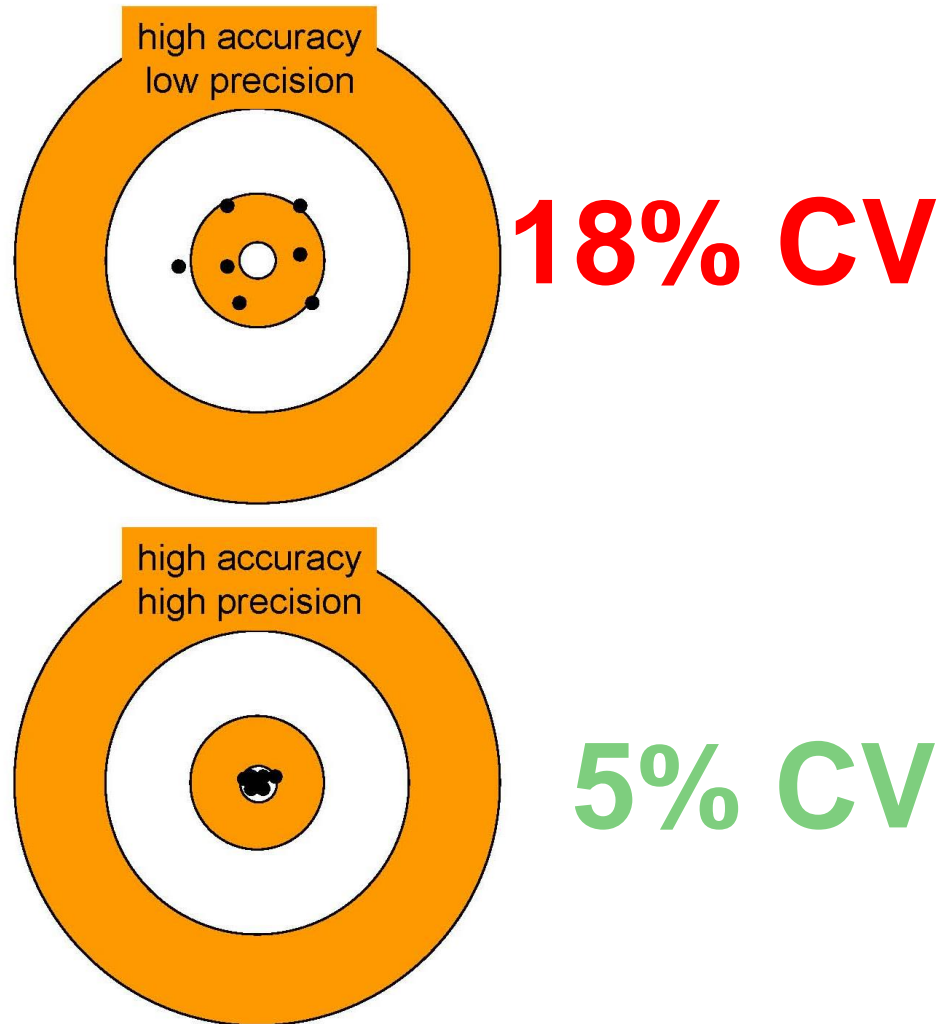
High Sensitivity Cardiac Tn Assays are more precise

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%.

The Next Generation

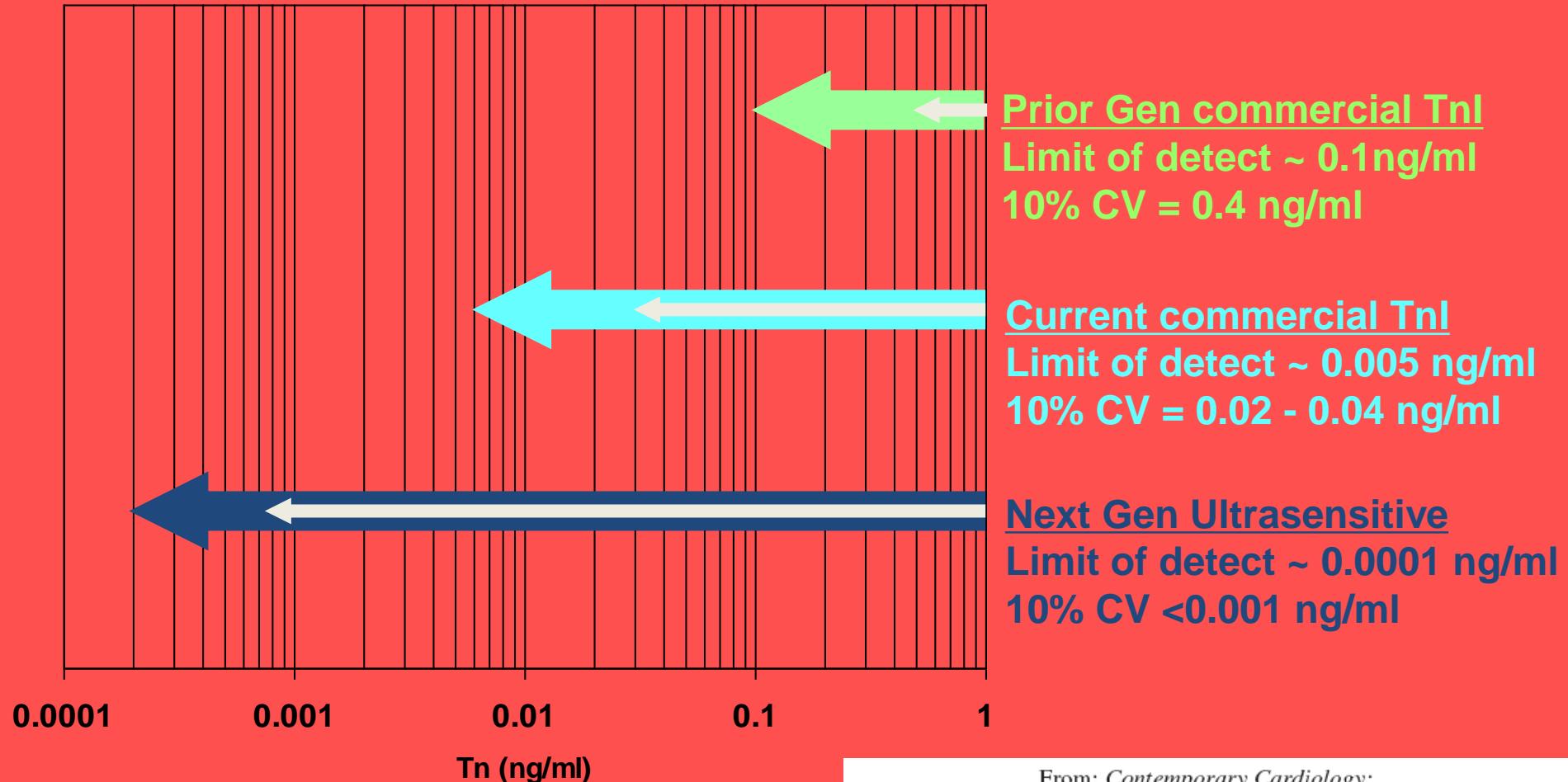
Prior Gen commercial TnI
Limit of detect ~ 0.1ng/ml
10% CV = 0.4 ng/ml

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

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

0.0001   0.001   0.01   0.1   1
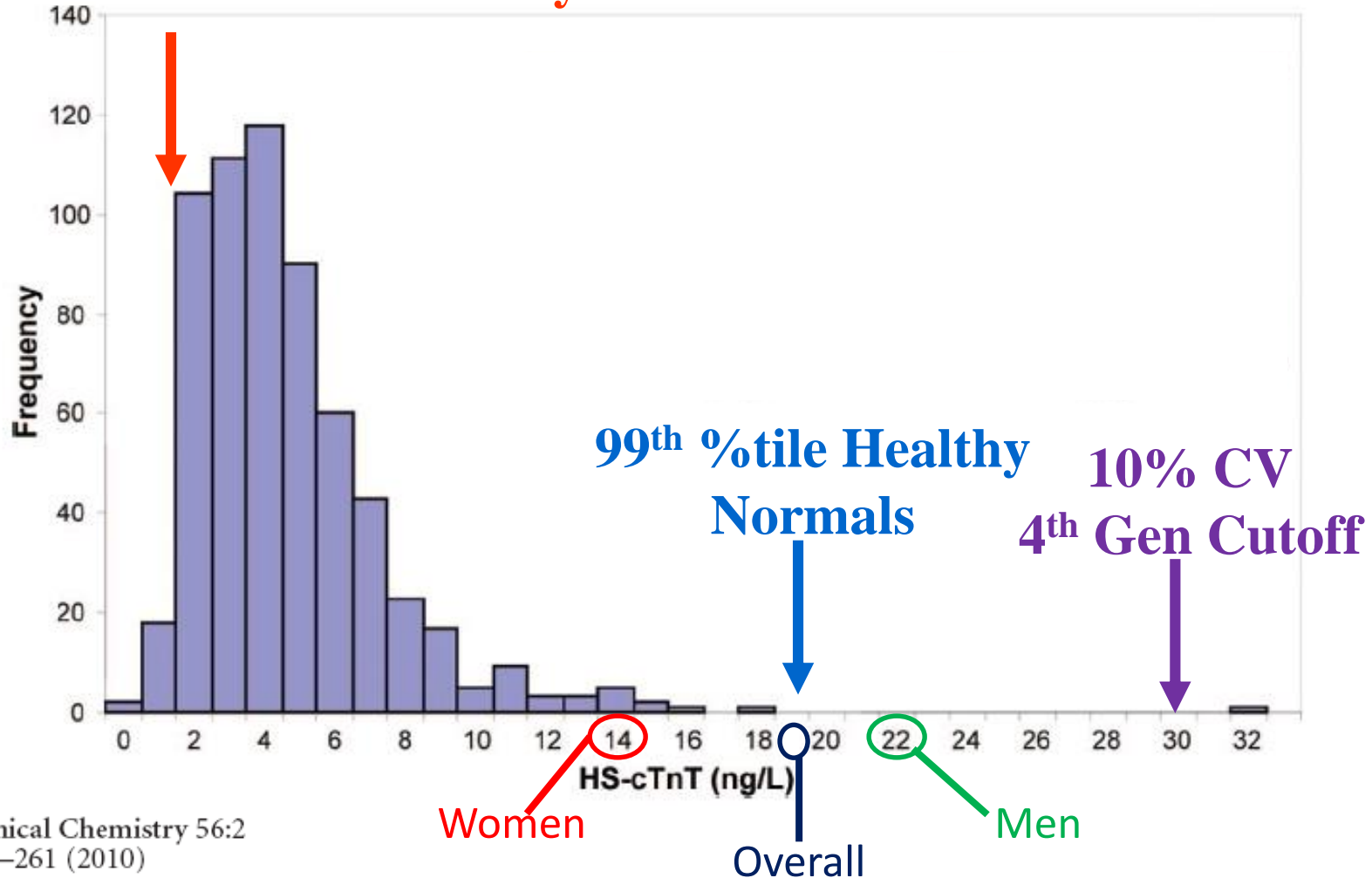
Tn (ng/ml)

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

45

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

46

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

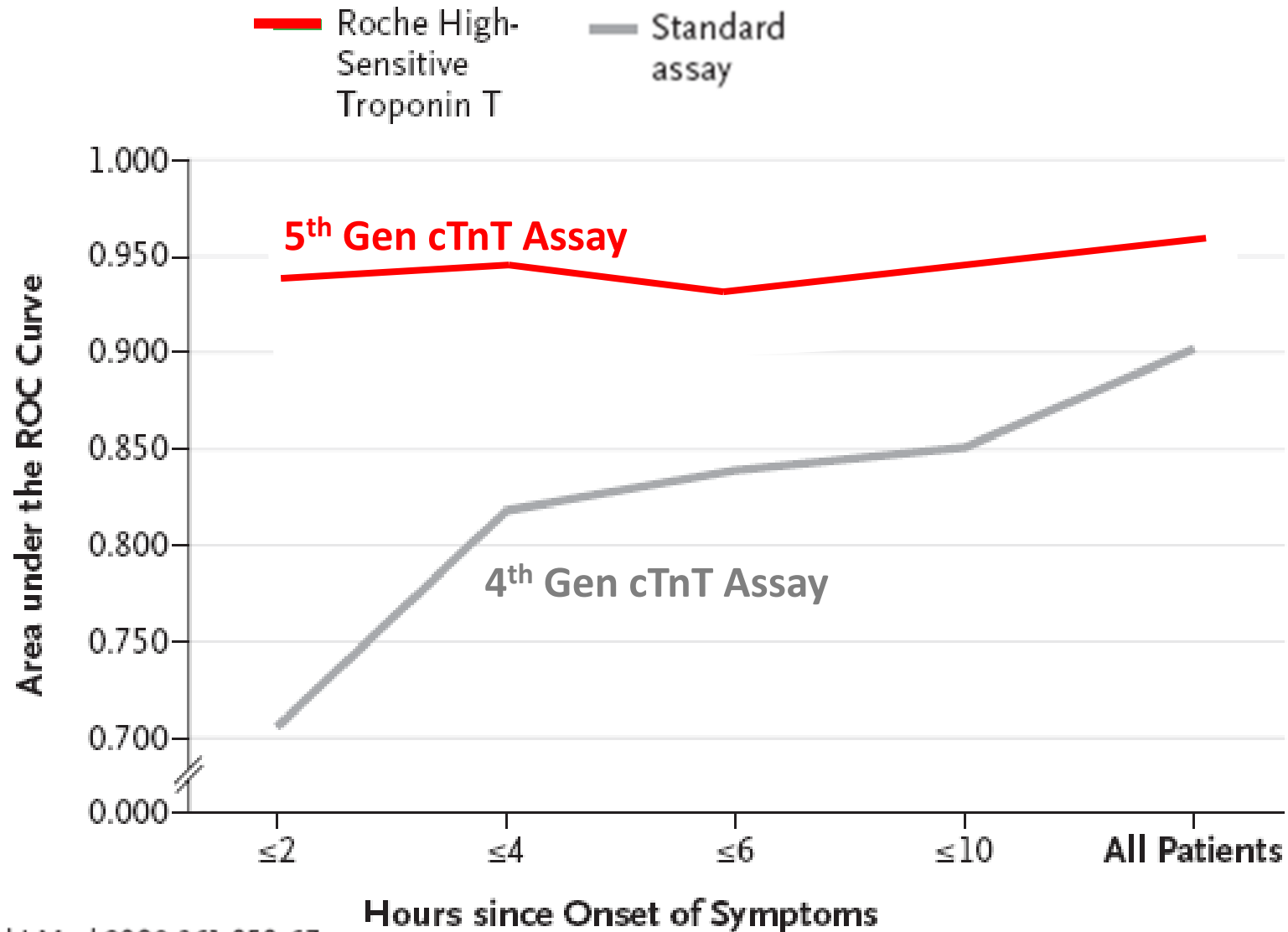High-sensitivity • 14 ng/L

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

5th Gen cTnT Assay

4th Gen cTnT Assay

Legend: Roche High-Sensitive Troponin T | Standard assay

Y-axis: Area under the ROC Curve (0.000, 0.700, 0.750, 0.800, 0.850, 0.900, 0.950, 1.000)

X-axis: Hours since Onset of Symptoms (≤2, ≤4, ≤6, ≤10, All Patients)

N Engl J Med 2009;361:858-67.

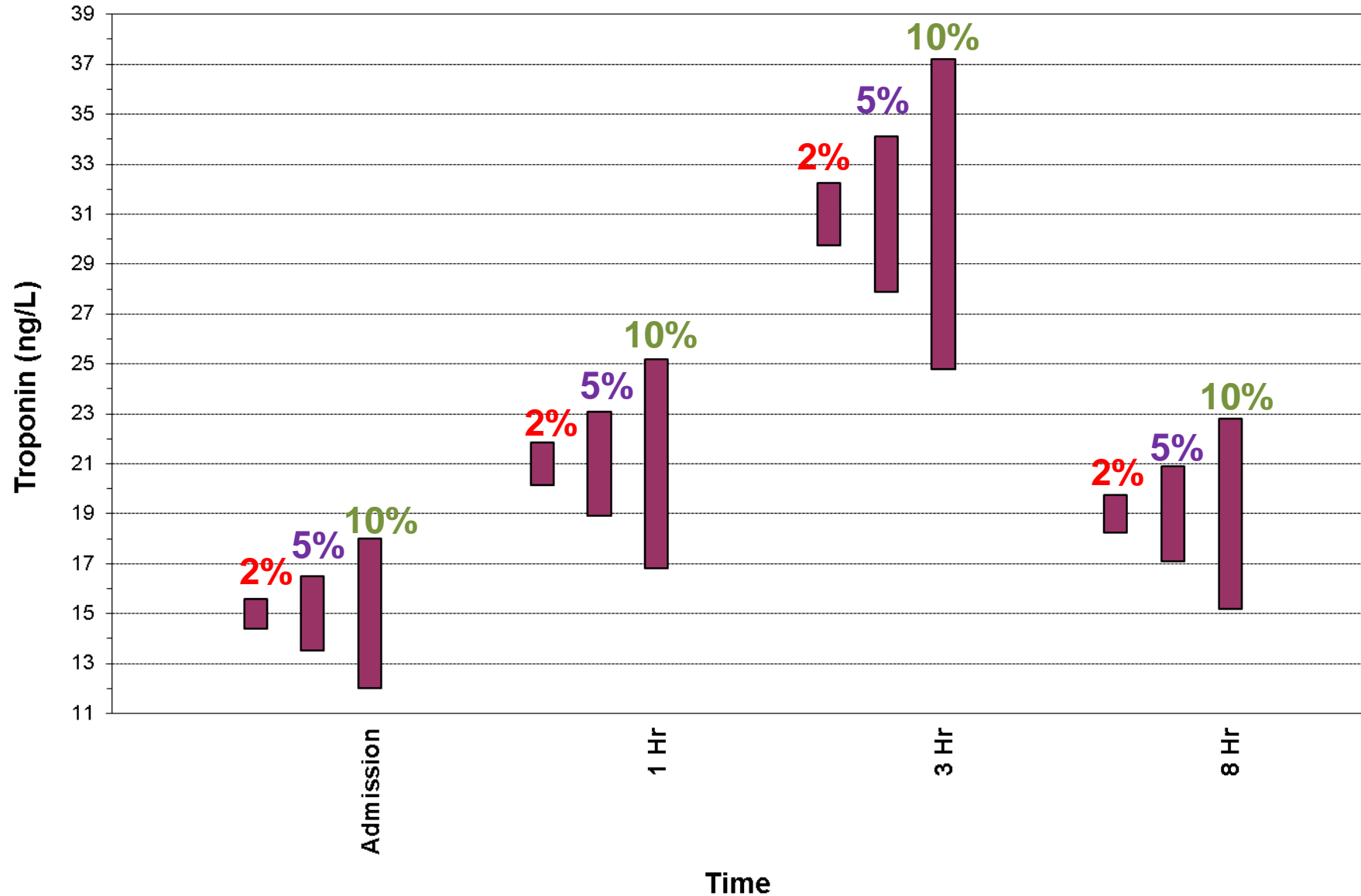# Early vs. Later Generation cTnI
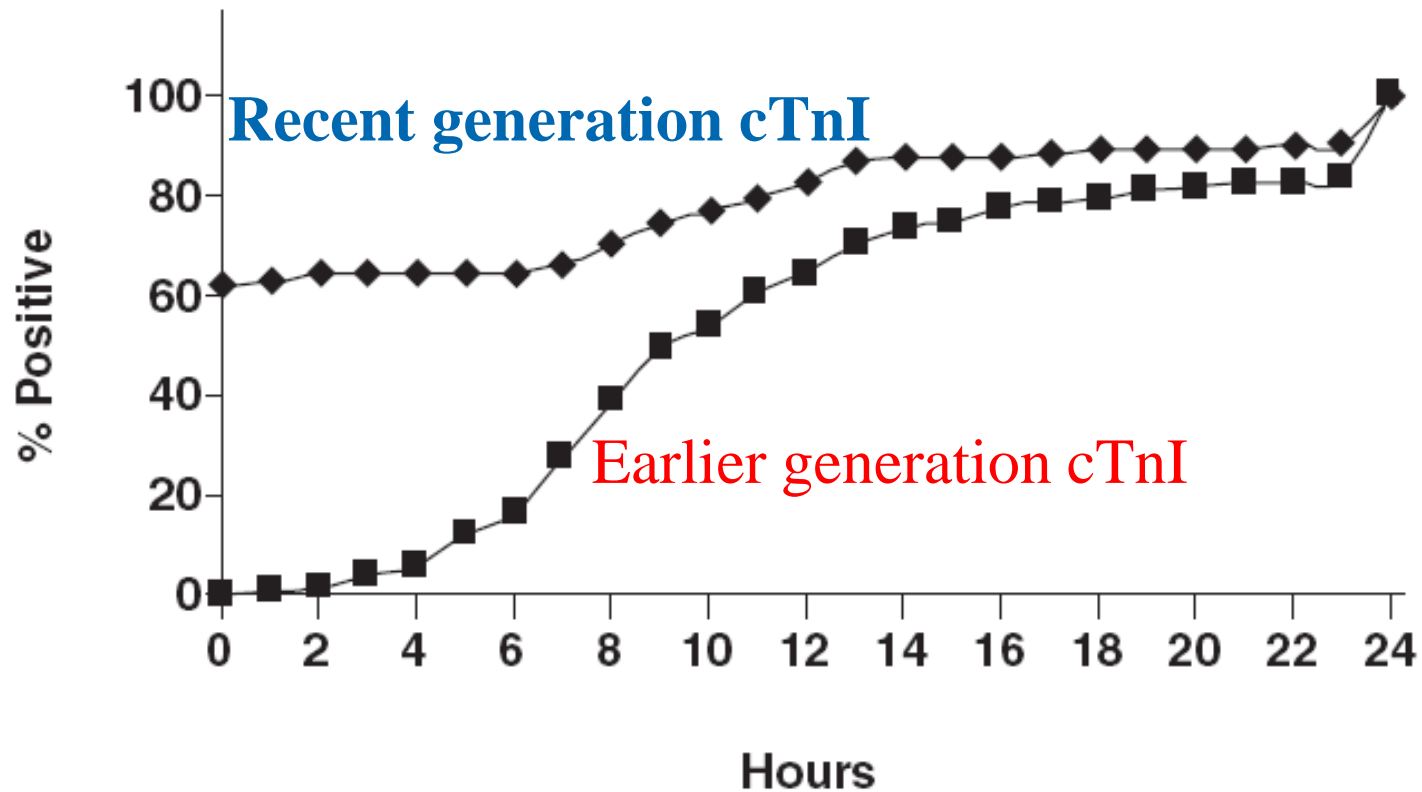
Total Error in Temporal Samples

What does all this mean for patient care?

What is an ADP

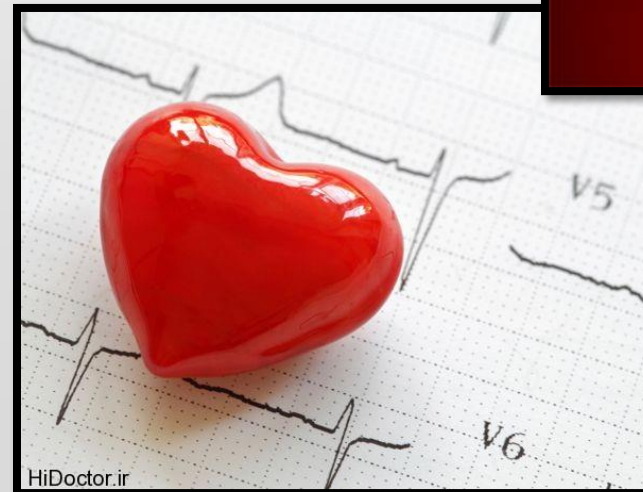▪ A series of activities to identify a patient as:

1) Having an event

2) Being at risk for having an event

   Do you admit crackheads?

   For being old?

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
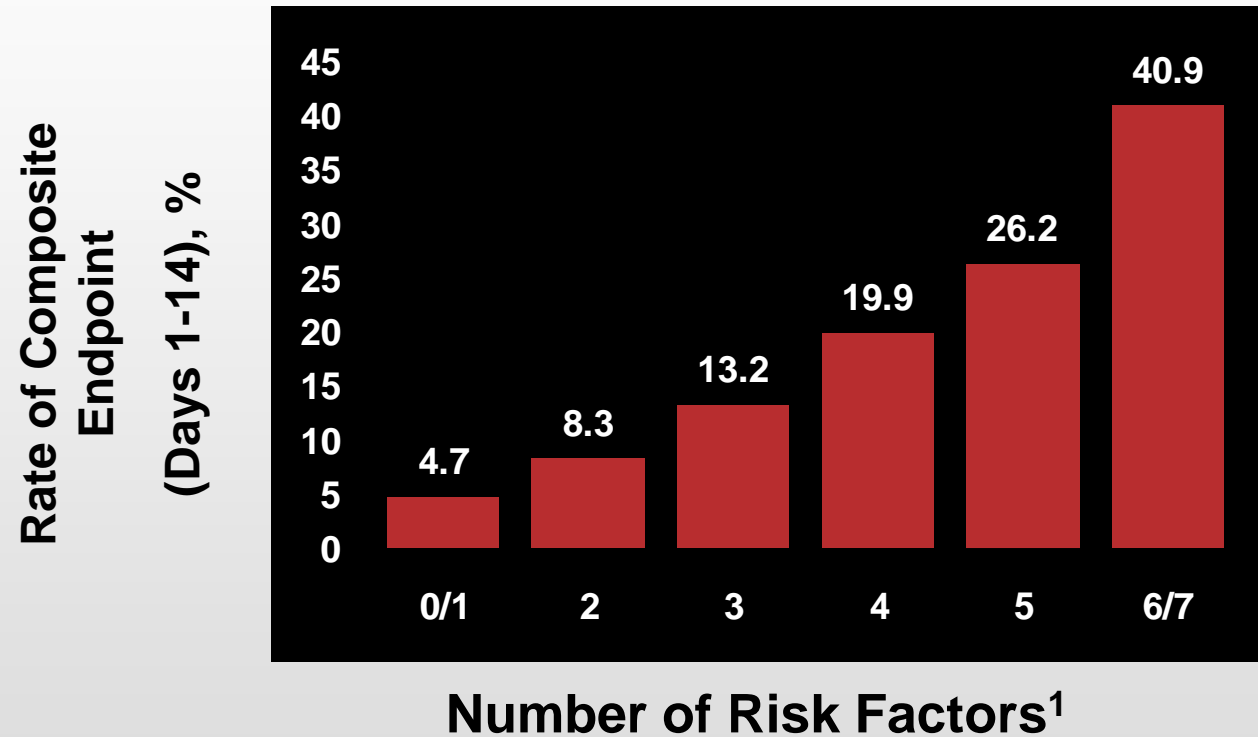
Martin Than, Louise Cullen, Christopher M Reid, Swee Han Lim, Sally Aldous, Michael W Ardagh, W Frank Peacock, William A Parsonage, Hiu Fai Ho,

- 14 Asia-Pacific region EDs
- >18yo with >5 mins CP
- Risk stratification (blinded to care team)   **LOW RISK**
  - 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

Rate of Composite Endpoint (Days 1-14), %

Number of Risk Factors[1]	Rate
0/1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6/7	40.9

Number of Risk Factors[1]

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

Antman EM et al. *JAMA*. 2000;284:835-842.

ASPECT

- **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

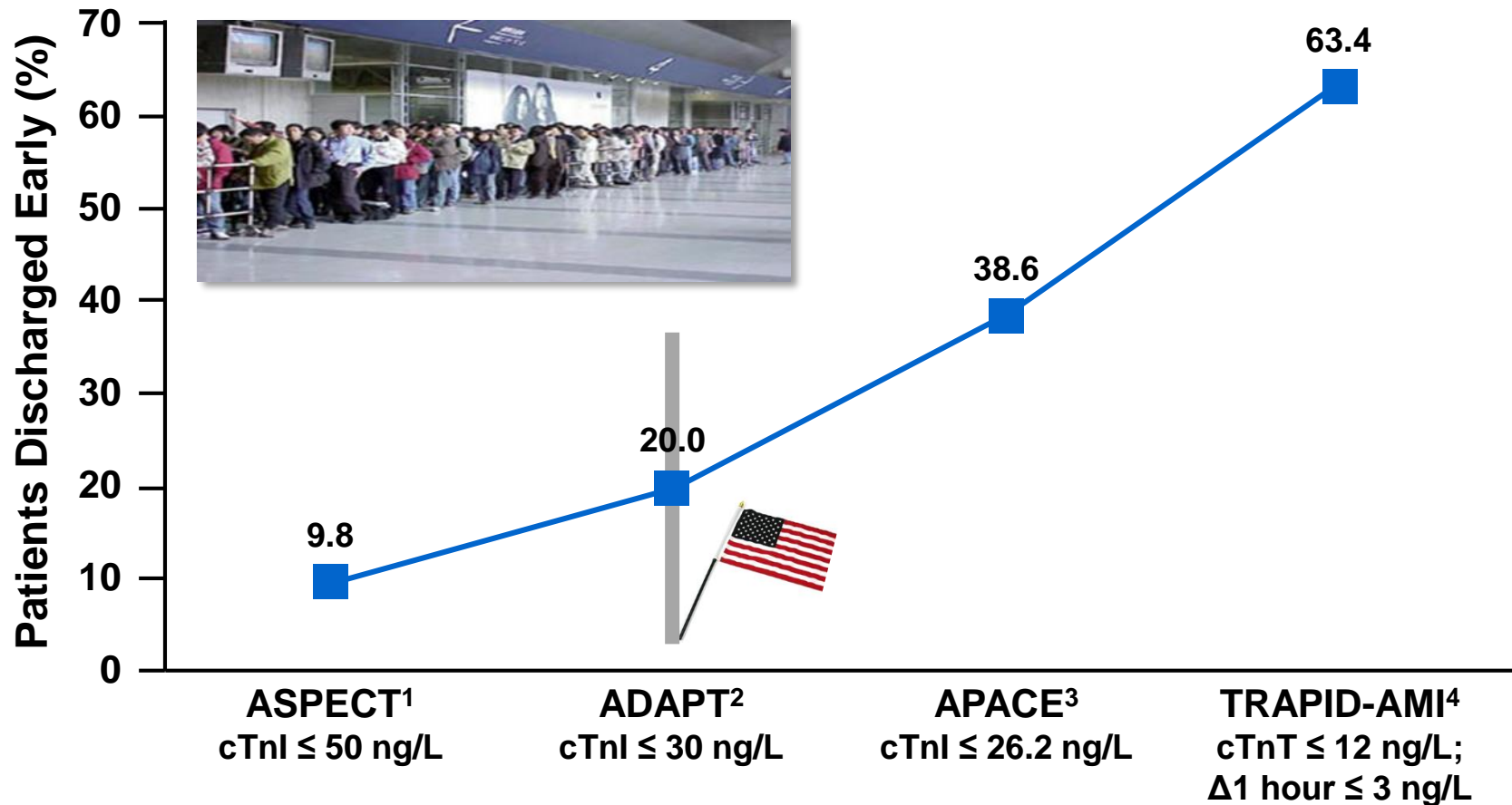# Impact of a Tn with higher low level sensitivity

ASPECT (N=3582)		
TIMI	Low risk	30 d MACE
0	9.8% (352)	0.9% (3)

ADAPT (N=1975)		
TIMI	Low risk	30 d MACE
0	25.3% (392)	0.25% (1)

Increased Troponin Sensitivity Leads to More Emergency Department Early Discharges

Patients Discharged Early (%)

- 9.8
- 20.0
- 38.6
- 63.4

ASPECT[1]	ADAPT[2]	APACE[3]	TRAPID-AMI[4]
cTnI ≤ 50 ng/L	cTnI ≤ 30 ng/L	cTnI ≤ 26.2 ng/L	cTnT ≤ 12 ng/L; Δ1 hour ≤ 3 ng/L

1. Than M, Cullen L, Reid C, et al. *Lancet*. 2011;377:1077-84.
2. Than M, Cullen L, Aldous S, et al. *J Am Coll Cardiol*. 2012;59(23):2091-8.
3. Cullen L, Mueller C, Parsonage WA, et al. *J am Coll Cardiol*. 2013;62(14):1242-9.
4. Mueller C, Giannitsis E, Christ M, et al. *Ann Emerg Med*. 2016;68(1):76-87.

ADAPT & APACE

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

TIMI	ADAPT (N=1635)		APACE (N= 909)	
	Low risk	30 d MACE	Low risk	30 d MACE
0	19.6% (320)	0% (0)	25.3% (230)	0% (0)
≤1	41.5% (678)	0.8% (2)	38.6% (351)	0.8% (1)

STRIVE

ADAPT & APACE
30 day MACE

TIMI	ADAPT (N=1635)		APACE (N= 909)	
	Sn	NPV	Sn	NPV
0	100% (98.5-100)	100% (98.8-100)		
≤1	99.2% (97.1-99.8)	99.7% (98.9-99.9)	99.4% (96.5-100)	99.7% (98.4-100)

STRIVE

What does the future of biomarker based chest pain care look like?
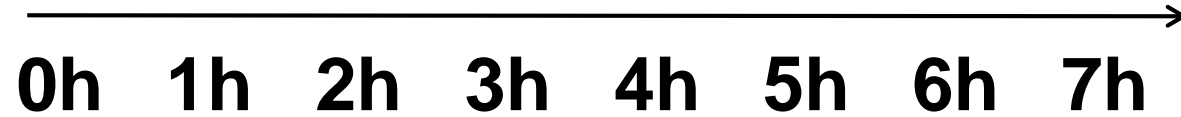
Necrosis Biomarkers Timeline
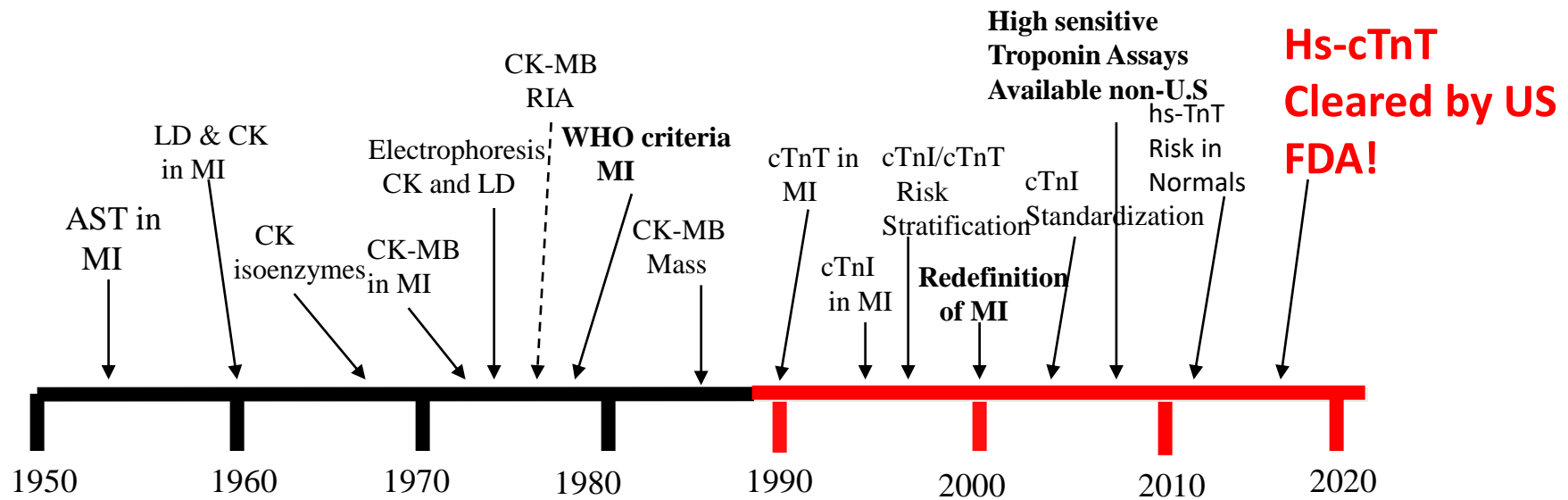
Why are updates needed?
Evolution of Temporal Serial Sampling

1. Rule-out

2. Rule-in

0h 1h 2h 3h 4h 5h 6h 7h

ECG

NACB 2007
cTn →

cTn

2nd Universal 2007
cTn →

cTn

ESC 2011
hs-cTn   hs-cTn

3nd Universal 2012
cTn   ← cTn →

ACC/AHA 2014
cTn   ← cTn →

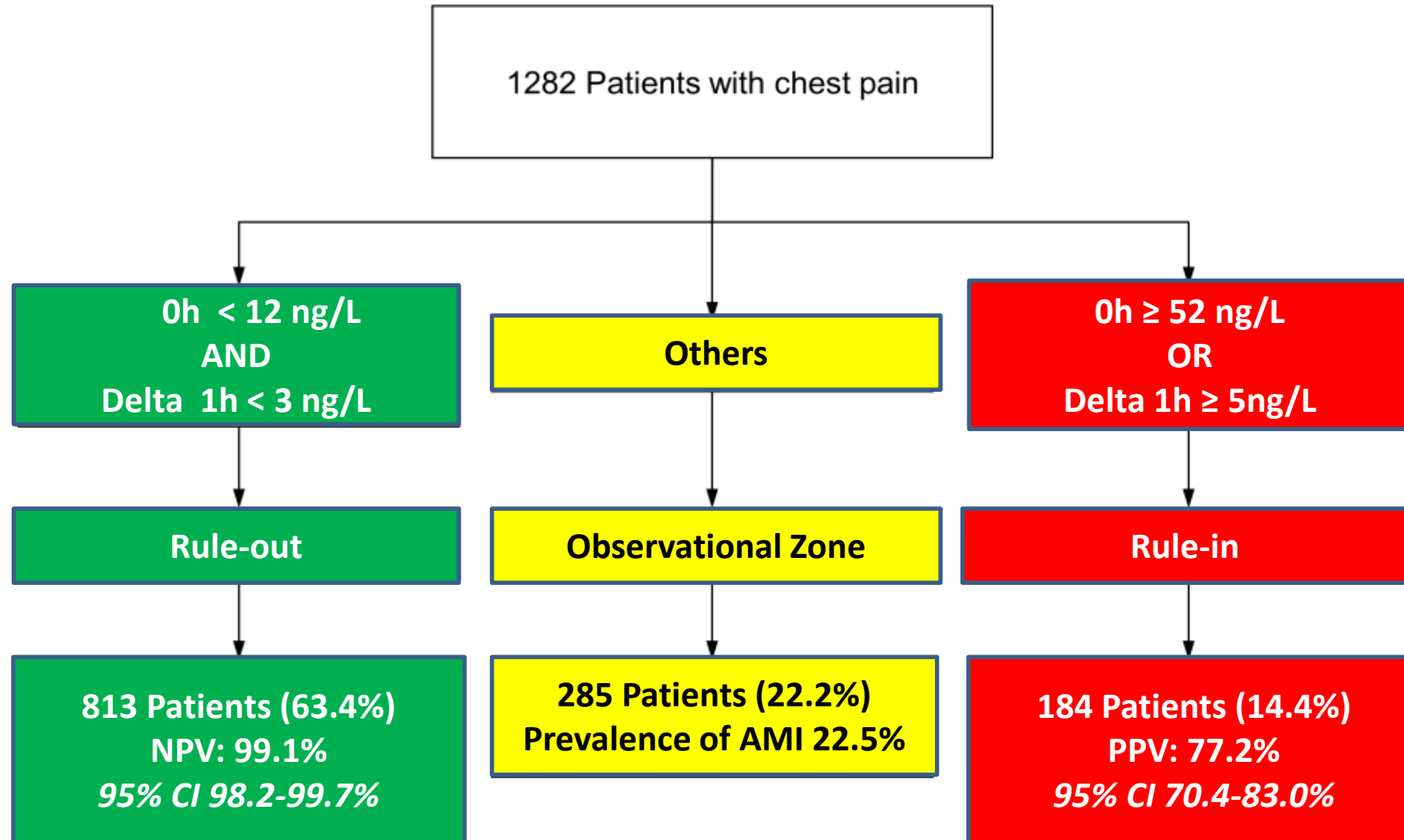**5th Gen Roche label**
hs-cTnT   hs-cTnT

TRAPID-AMI
hs-cTnT hs-cTnT

TRAPID-AMI

Acad Emerg Med. 2016 Sep;23(9):1004-13

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 Internatio... Federation of Clinical Chemistry: Recommend 60 minute... 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, NI =0

Age: ≥65 =2, 45-65 =1, ≤ 45 =0

Risks: ≥3 =2, 1-2 =1, 0=0

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

Tn: ≥3x ULN =2
1-3 ULN =1
≤ ULN =0

Low risk = 0-3;
<2% MACE risk

EDACS-ADP
Emergency Department Assessment Chest Pain Score - Accelerated Diagnostic Procedure

| Characteristic	Parameter	Points
History	18-50 yo with CAD, or >2 risk factors	+4
Age	18-45	+2
	46-50	+4
	51-55	+6
	56-60	+8
	61-65	+10
	66-70	+12
	71-75	+14
	76-80	+16
	81-85	+18
	>85	+20

Characteristic	Parameter	Points
Sex	Male	+6
Signs and Symptoms	Diaphoresis	+3
	Arm or shoulder radiation	+5
	Pain occurred or worsened with inspiration	-4
	Pain is reproduced with palpation	-6

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
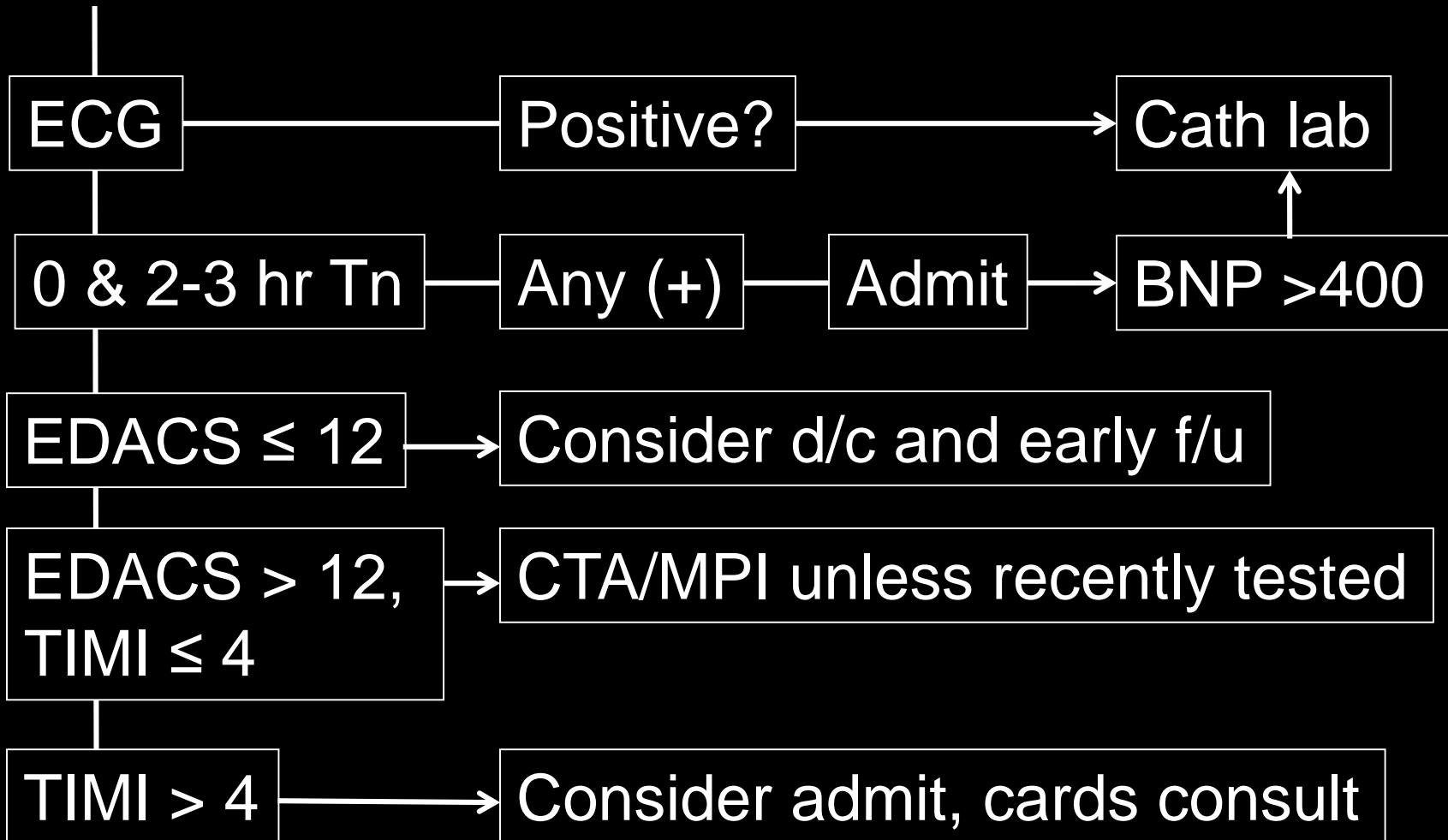 risk of MI before Tn as:
  Low
  Moderate
  High Risk

- N=458
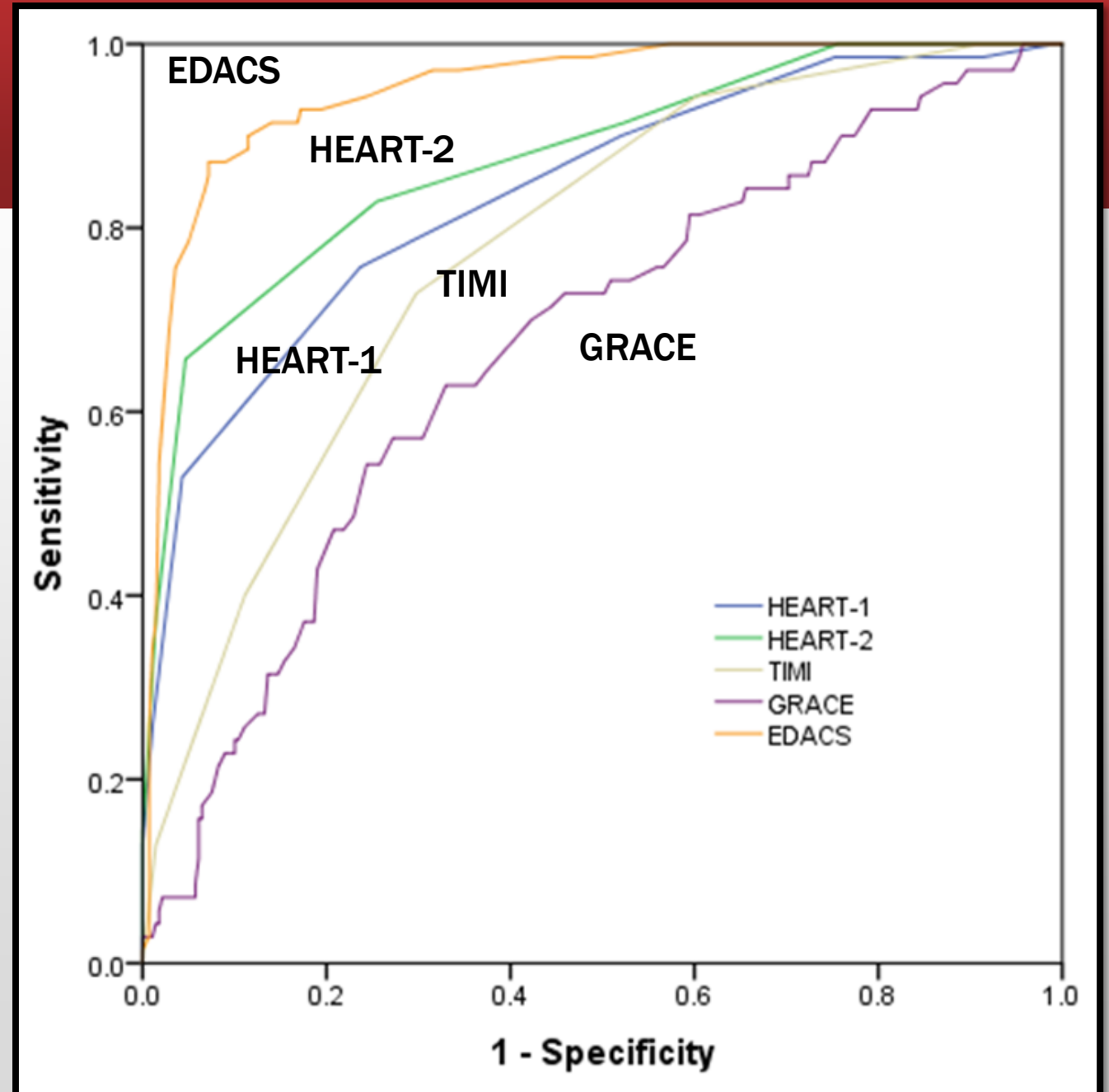
Comparing Score Performance

	Standard cutpoint		Sensitivity set at 99%	
% Low	Low risk (n) Definition	Missed AMI, %	Cutoff	% Low Risk
Clinical	–	5.9 (3.0-11.2)	–	–
HEART-1	<4	4.7 (2.1-9.9)	0	1
HEART-2	<4	4.1 (1.9-8.7)	0-2	18.9
TIMI	0	0 (0-12.9)	0	7
EDACS	<16	1.0 (0.2-4.1)	12	34.3

Questions? Contact the E-QUAL team at equal@acep.org