Abbott

Let's Talk Troponin

What you need to know about high sensitivity troponin assays

Simon A. Mahler MD, MS, FACEP

CHEST PAIN MOUNTAIN

Disclosures

AHRQ, HRSA, EMF, Duke Endowment, NFEM

Roche Diagnostics

Abbott Laboratories

QuidelOrtho

Siemens

Polymedco

Genetesis

Beckman Coulter

Inflammatix

Radiometer

Brainbox

Repreive Cardiovascular

Genentech

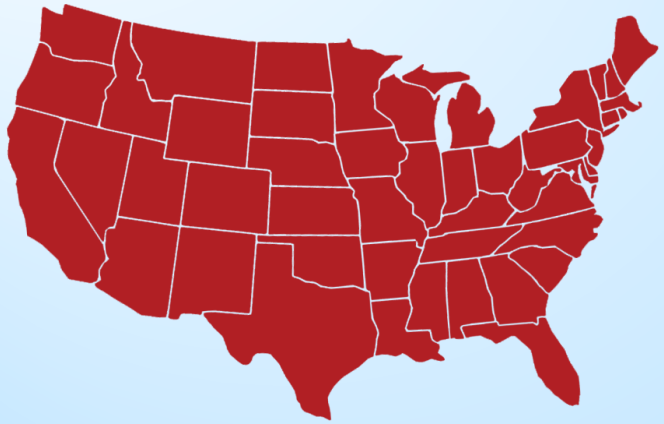
BlueJay Diagnostics

Impathiq Inc.

Learning Objectives

- Describe the benefits of high-sensitivity troponin versus contemporary troponin assays
- Examine the interpretation of hs-cTnI elevations in clinical context
- Identify the advantages and drawbacks of key hs-cTnI testing strategies
- Discuss key components of chest-pain pathways incorporating hs-cTnI assays

Chest Pain

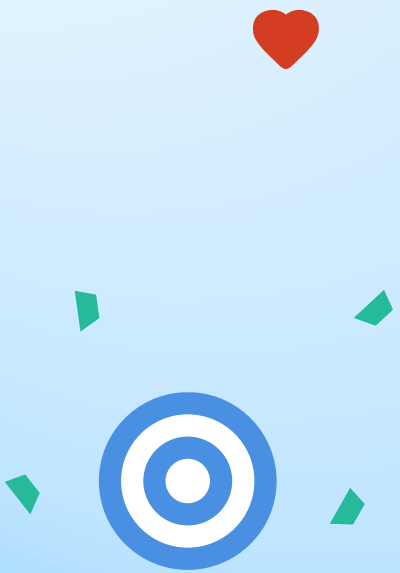


>7 Million Annual US ED Encounters for Acute Chest Pain

~1.4 Million have known CAD

~ $13 Billion spent on chest pain evaluations each year

Chest Pain



<10% Diagnosed with ACS

2 to 4 out of 100 Patients with ACS are initially missed

Inefficient Chest Pain Care
impact of over- and under- testing

Over-testing:

- Crowding
- Increased costs
- Radiation exposure
- False-positive/non-diagnostic tests
- Not patient-centered

Under-testing:

- Missed ACS
- Malpractice

ED Overcrowding

Significant and widespread problem

Decreases patient safety
- Mortality
- Treatment delays
- Elopements
- Ambulance diversions

Increased staff and provider burn-out

Loss of revenue

What do ED Providers WANT from a chest pain algorithm?

What do ED Providers WANT from a chest pain algorithm?

- Safe

What do ED Providers WANT from a chest pain algorithm?

- Safe
- Accurate

What do ED Providers WANT from a chest pain algorithm?

- Safe
- Accurate
- Fast

What do ED Providers WANT from a chest pain algorithm?

- Safe
- Accurate
- Fast
- Easy

What is the acceptable miss rate

Chest Pain Risk Stratification Toolbox

- Electrocardiogram
- Troponin
- Risk Scores
- Accelerated Diagnostic Pathways
- Cardiac Imaging
- *Artificial Intelligence?*

Case 1

A 60 yo woman with a history of heart failure presents to the ED with chest pain lasting 1.5 hours. Her ECG is non-diagnostic. Serial hs-cTnI were measured two hours apart and were 16 ng/L and 18 ng/L, respectively, just above the sex specific URL of 15 ng/L.

Can she be discharged?

Is this an MI?

Case adapted from Mahajan et. al, Circulation 2011

Case 2

A 64 yo man with a history of diabetes presents to the ED with chest pressure and diaphoresis lasting 1 hour. His ECG is Normal. Serial hs-cTnI were measured two hours apart and were 22 ng/L and 34 ng/L, respectively, above the sex specific URL of 20 ng/L.

Can he be discharged?

Is this an MI?

Case adapted from Mahajan et. al, Circulation 2011

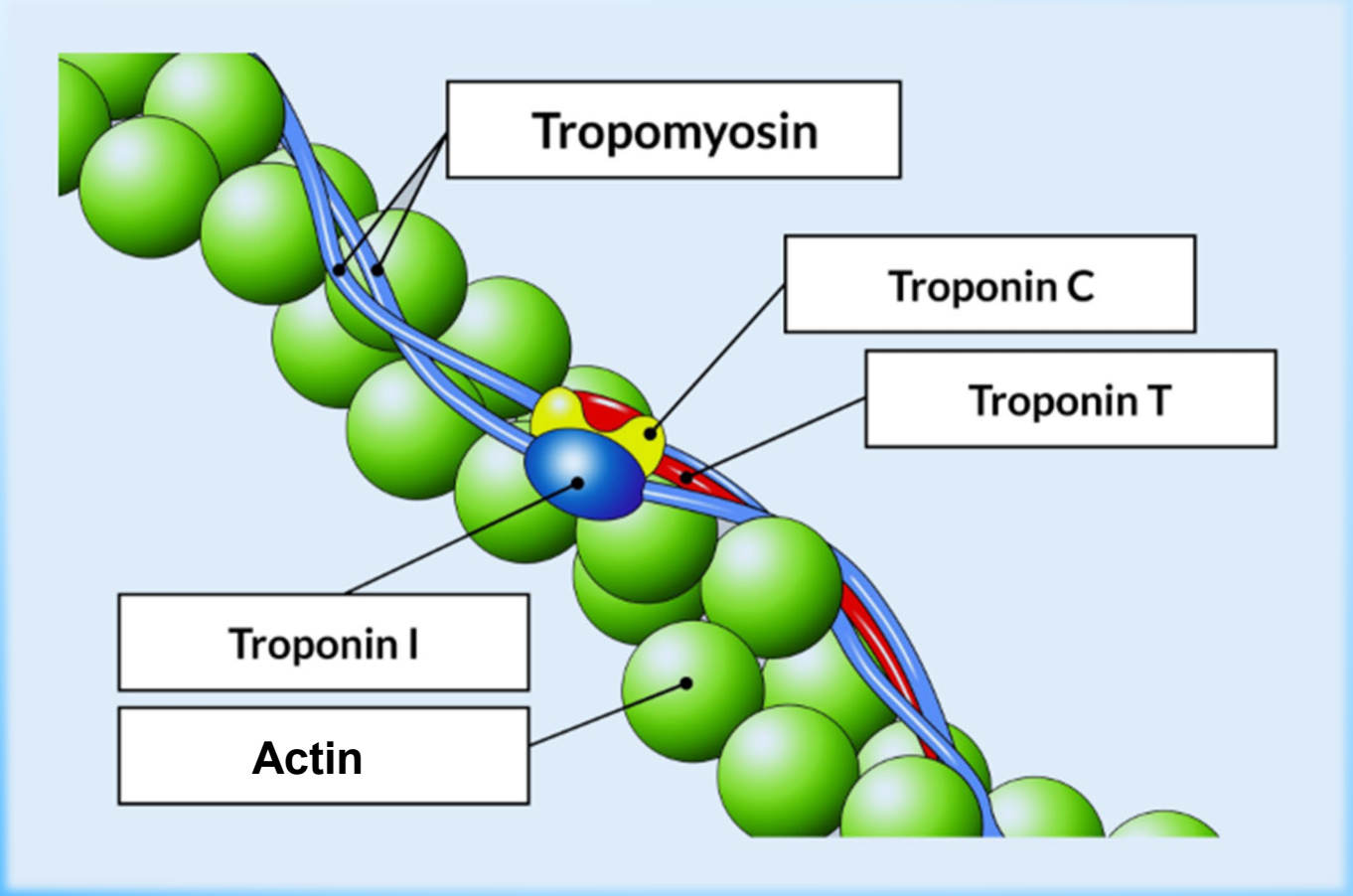
Case 3

A 73 yo woman with a history of hypertension and hyperlipidemia presents to the ED with chest pressure, diaphoresis, and radiation to both arms lasting 15 minutes and relieved by nitroglycerin. Her ECG shows new T-wave inversions. Serial hs-cTnI were measured two hours apart and were 7 ng/L and 9 ng/L, respectively, below the sex specific URL of 15 ng/L.

Can she be discharged?

Is this an MI?

Talking TROPONIN



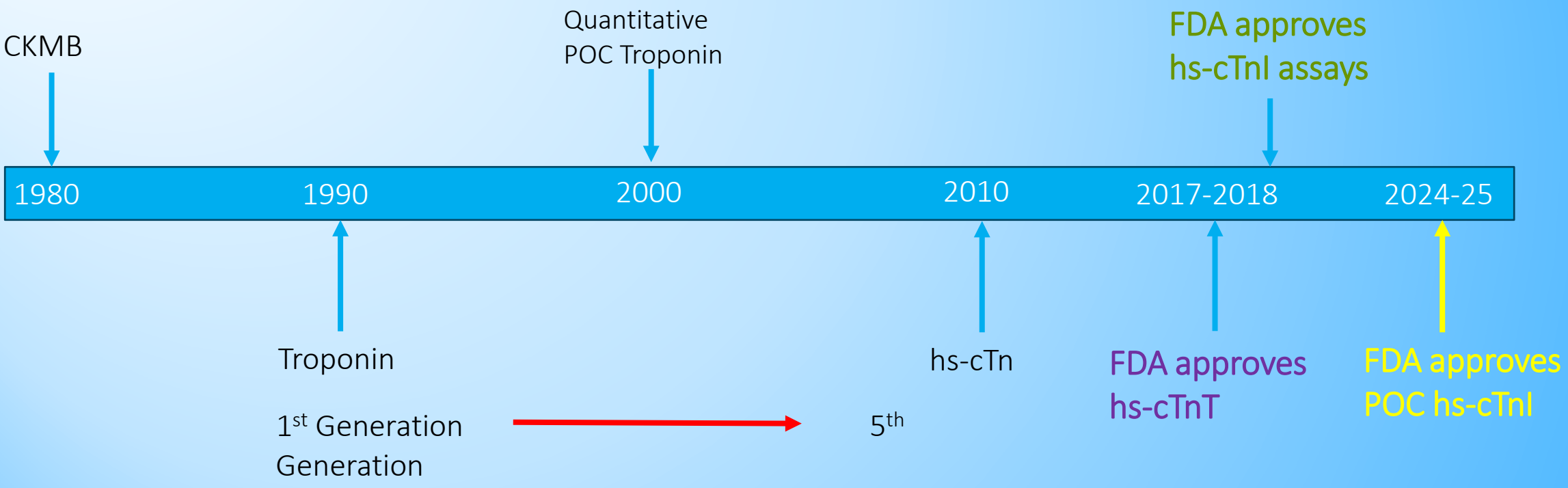
Gold Standard biochemical test for myocardial injury

Cardiac myocyte protein

Cardiac injury results in extracellular leak

Detectable in peripheral blood

Myocardial Injury Biomarker Timeline



hs-cTn = high sensitivity cardiac troponin

hs-cTn vs s-cTn (5th vs 4th generation troponin)

High Sensitivity Troponin Assays Defined

Measure same cardiac troponin protein

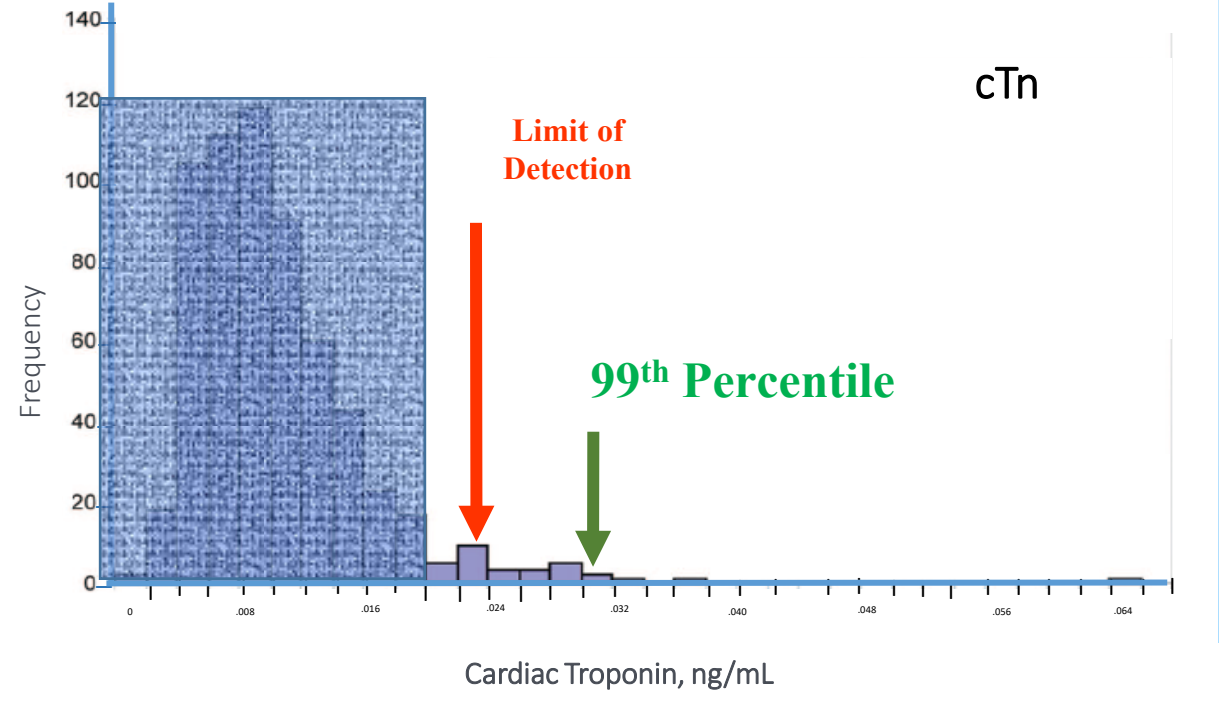
Are more precise, can detect lower levels; measurable levels in at least 50% of healthy patients

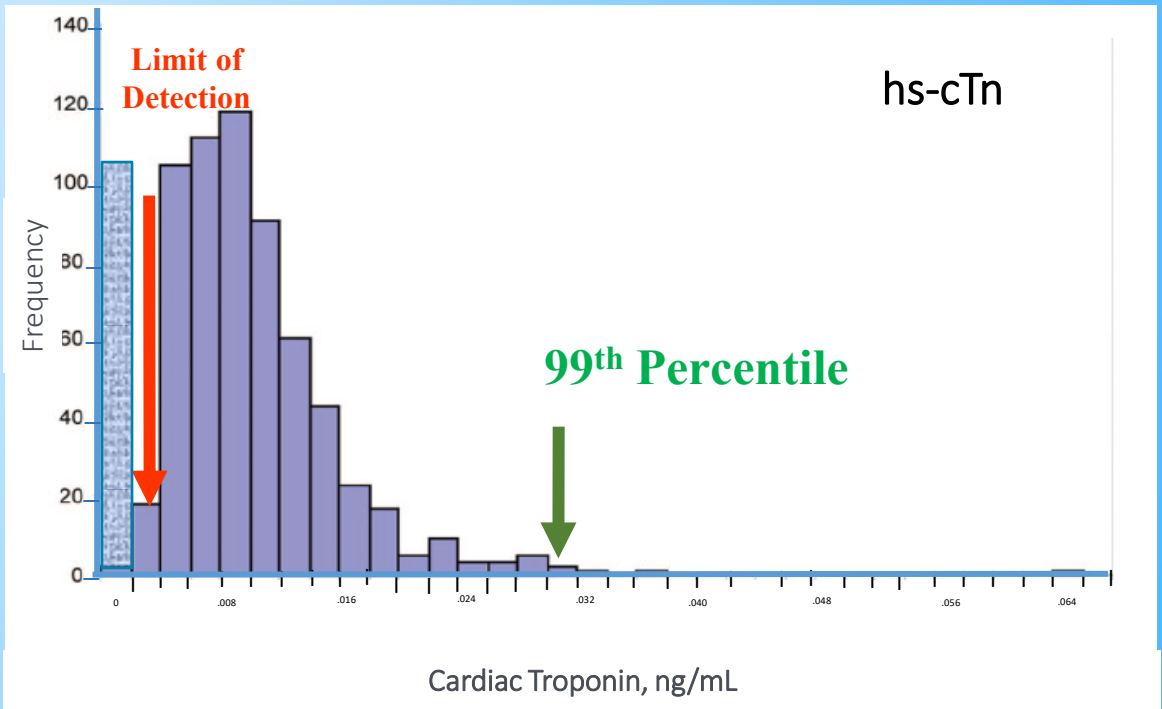
hs-cTn Units

Previously cTn measured in ng/ml
hs-cTn measured in ng/L--- REPORTED IN WHOLE NUMBERS

0.006 ng/ml → 6 pg/ml or ng/L
0.040 ng/ml → 40 pg/ml or ng/L

high Sensitivity Troponin Assays Measurable on Most Patients





Glossary

Limit of Blank (LOB)

value of water

Limit of Detection (LOD)

Lowest detectable level

Limit of Quantification (LOQ)

Lowest reliable measure

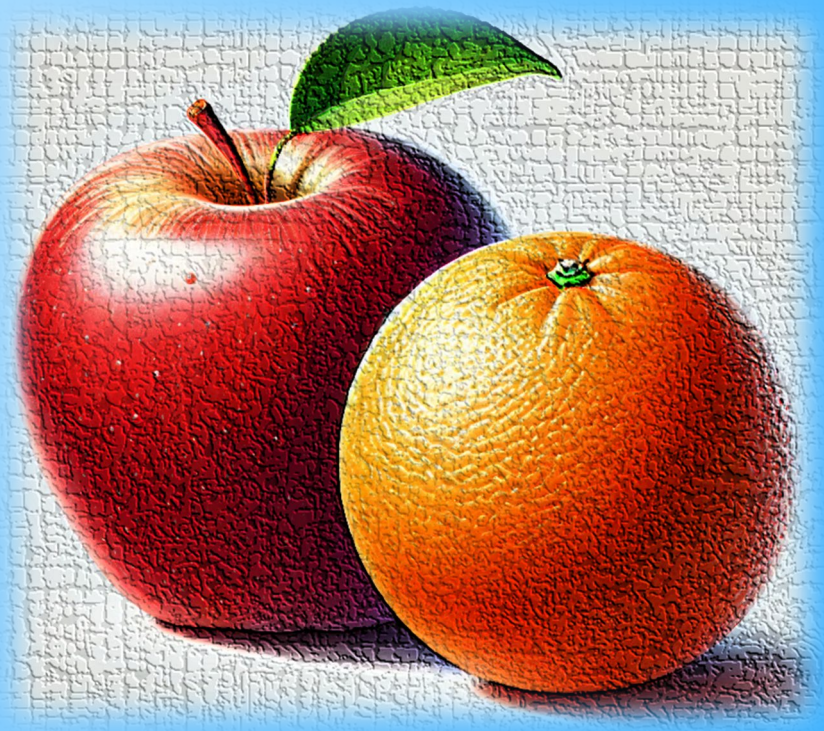
Upper Reference Limit (URL)

99^{th} percentile value

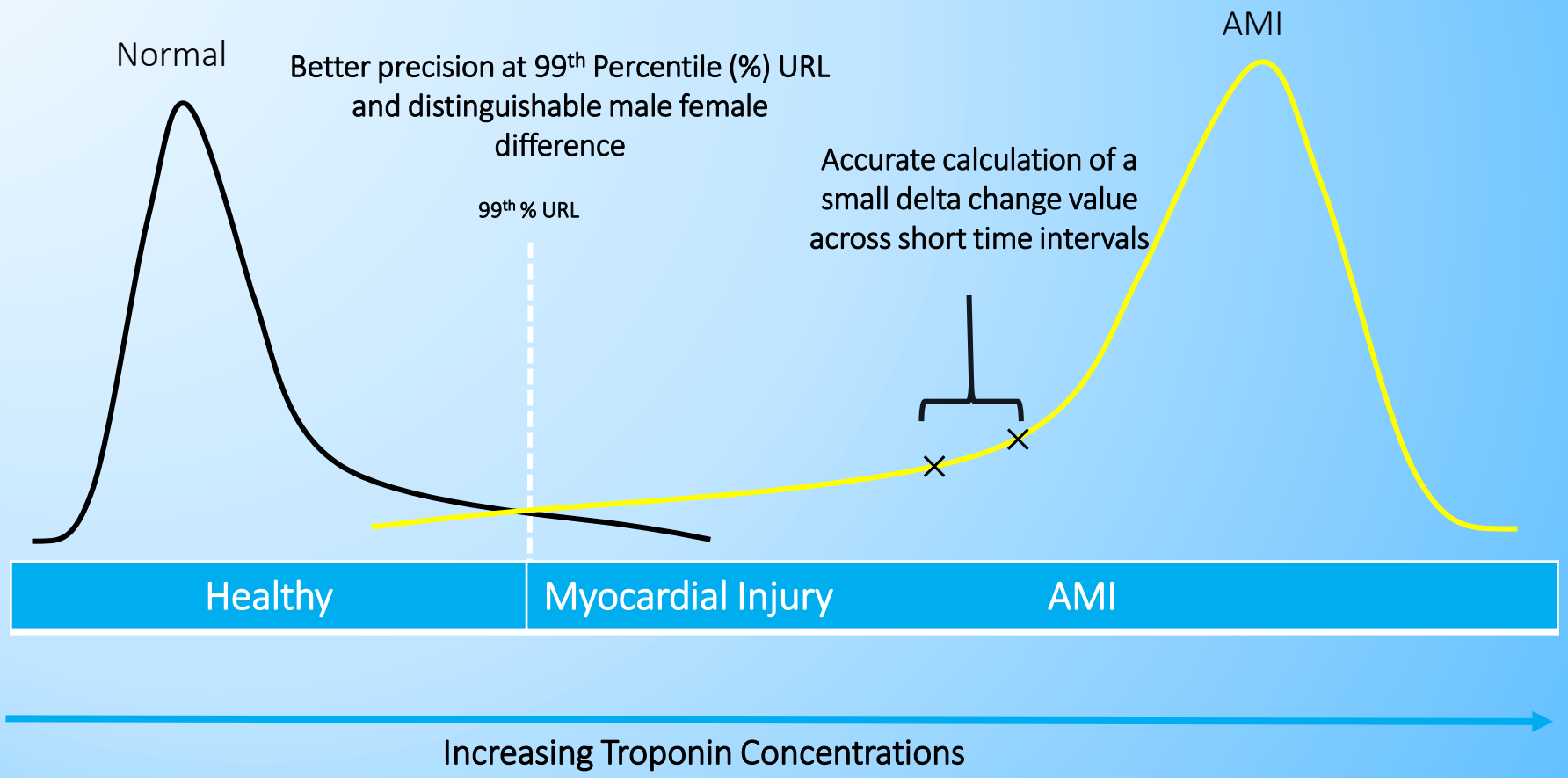
Comparing Different Assays

Each High Sensitivity Troponin Assay has a different LoD, LoQ, and URL

- Different assays are highly correlated
- There is no conversion factor



Analytical impact of hsTn assays



Adapted from Tan. 2017 Heart Asia.

Improved Precision

Earlier Generation Troponin

15% CV

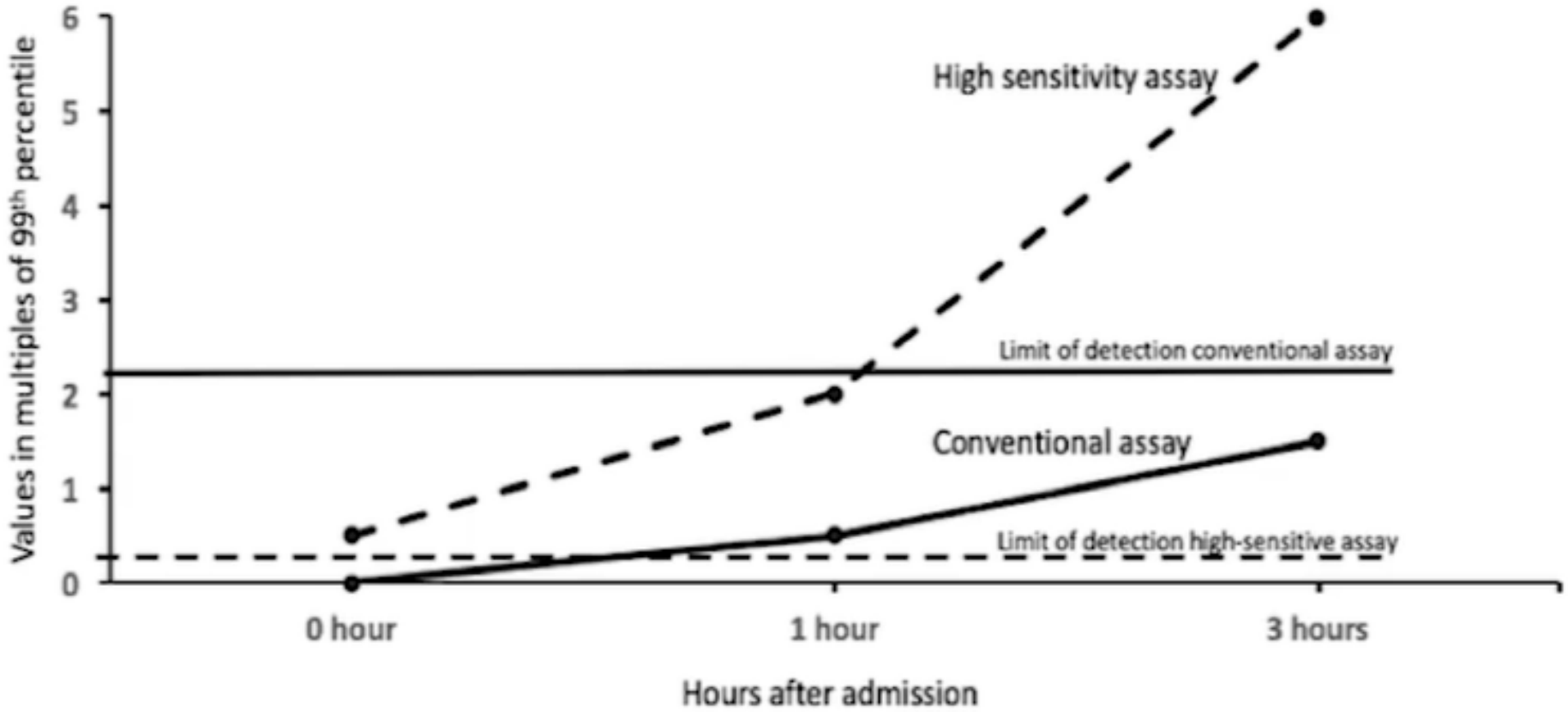
High Accuracy, Low Precision

High-Sensitivity Troponin

5% CV

High Accuracy & Precision

hs-cTn has earlier rise in patients with MI



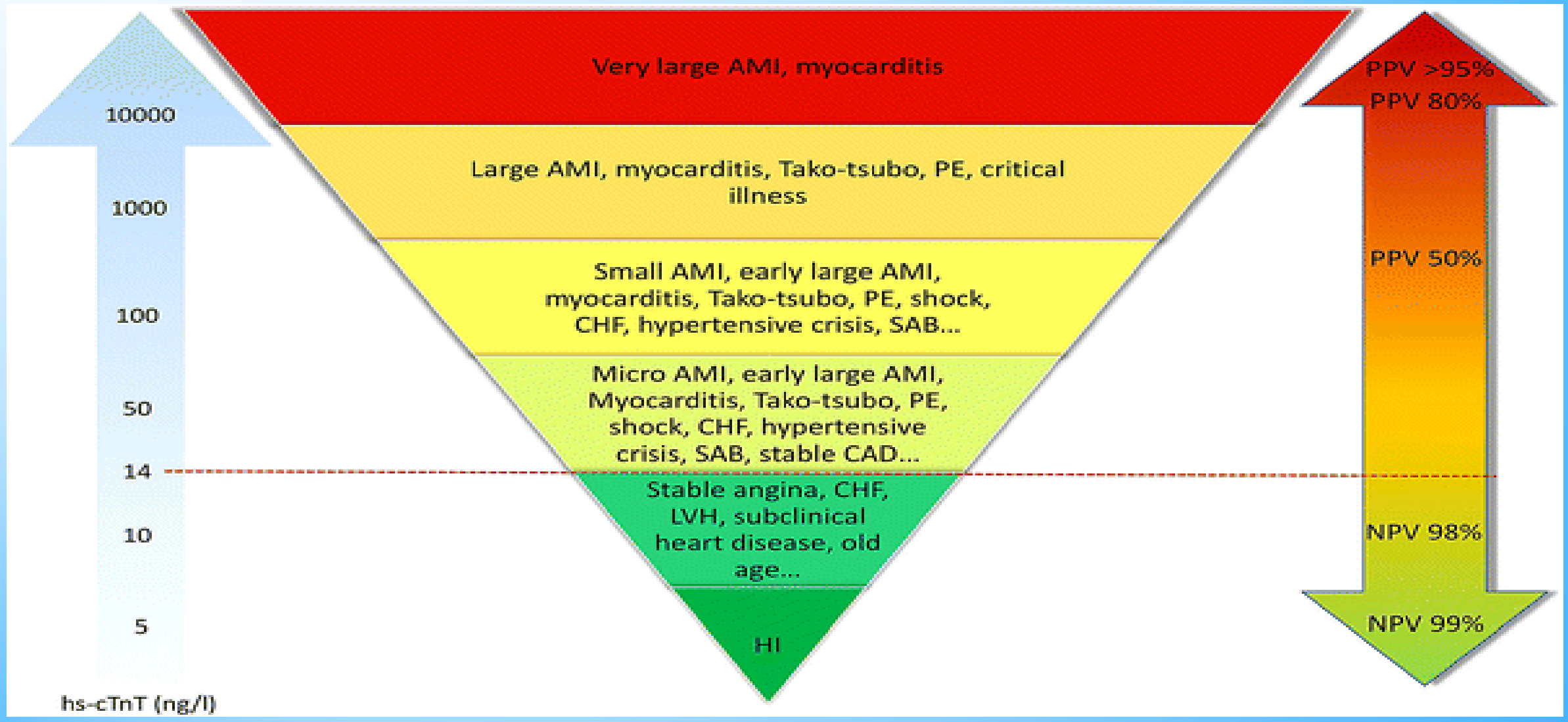
Elevation = Injury

Does not indicate the mechanism of injury

Conditions Associated with Elevated cTn Levels in the Absence of Ischemic Heart Disease

Cardiac contusion
Cardiac procedures (surgery, ablation, pacing, stenting)
Acute or chronic congestive heart failure
Aortic dissection
Aortic valve disease
Hypertrophic cardiomyopathy
Arrhythmias (tachy- or brady-)
Apical ballooning syndrome
Rhabdomyolysis with cardiac injury
Pulmonary hypertension
Pulmonary embolism
Acute neurologic disease (e.g., stroke, subarachnoid hemorrhage)
Myocardial infiltrative diseases (amyloid, sarcoid, hemochromatosis, scleroderma)
Inflammatory cardiac diseases (myocarditis, endocarditis, pericarditis)
Drug toxicity
Respiratory failure
Sepsis
Burns
Extreme exertion (e.g., endurance athletes)

Larger elevations increase likelihood of MI

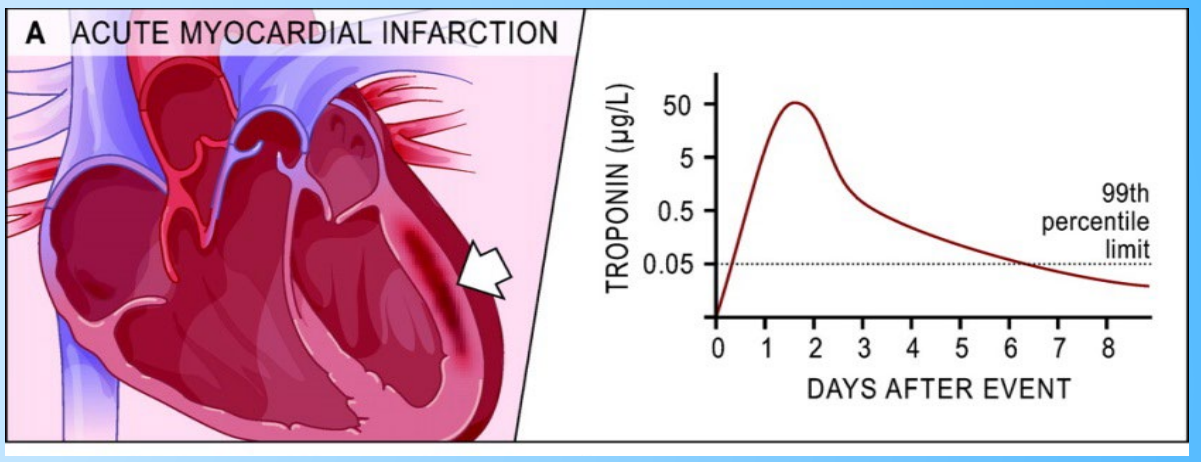


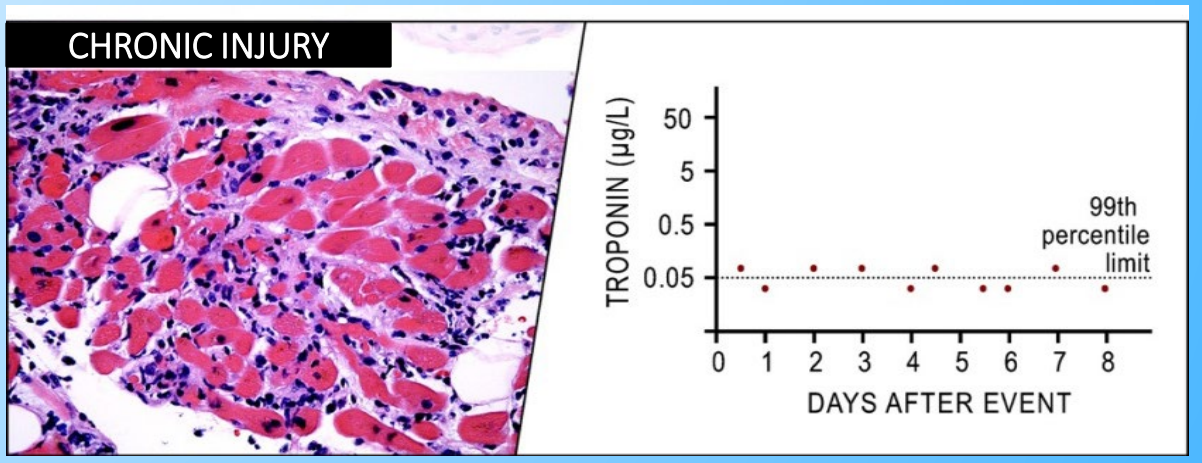
Pattern of Elevation

MI differentiated from non-ischemic cTn elevations based on:

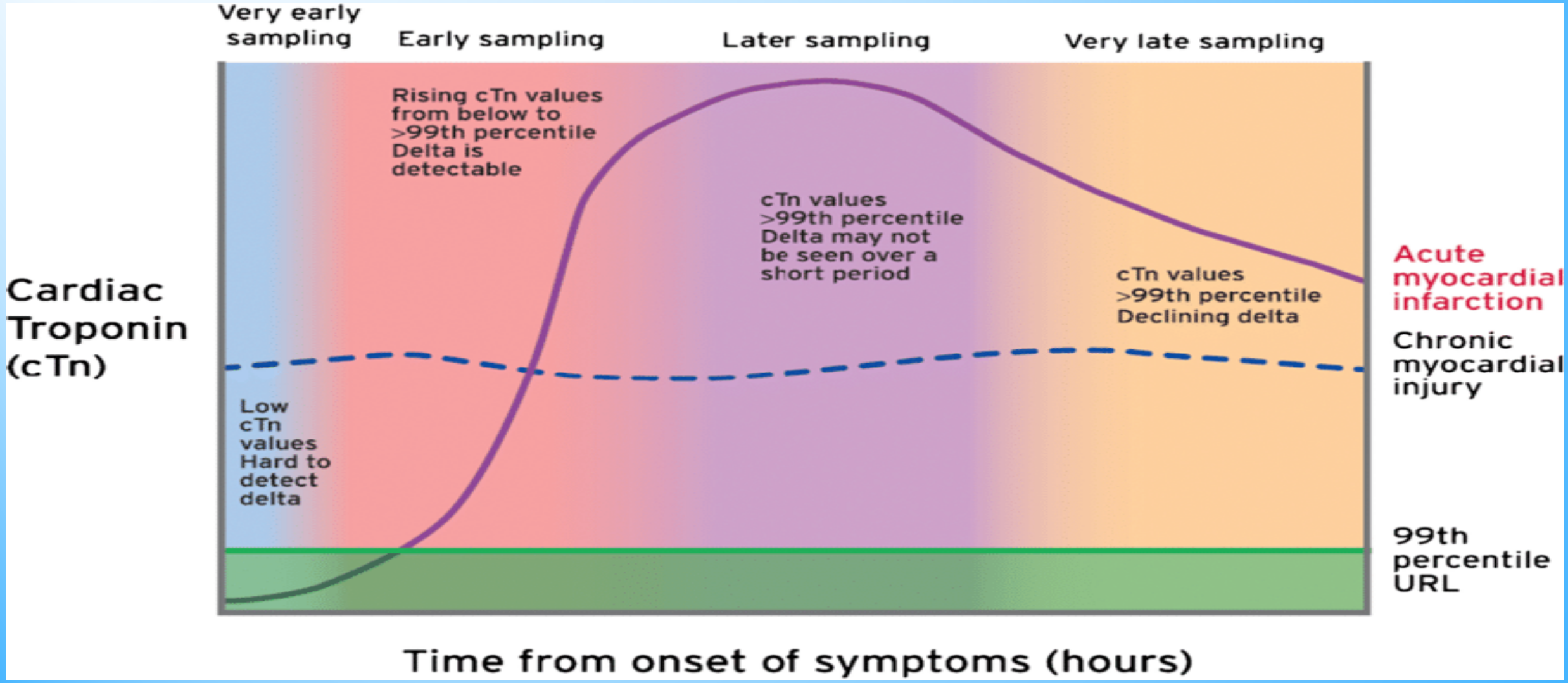
Pattern of elevation

Clinical context

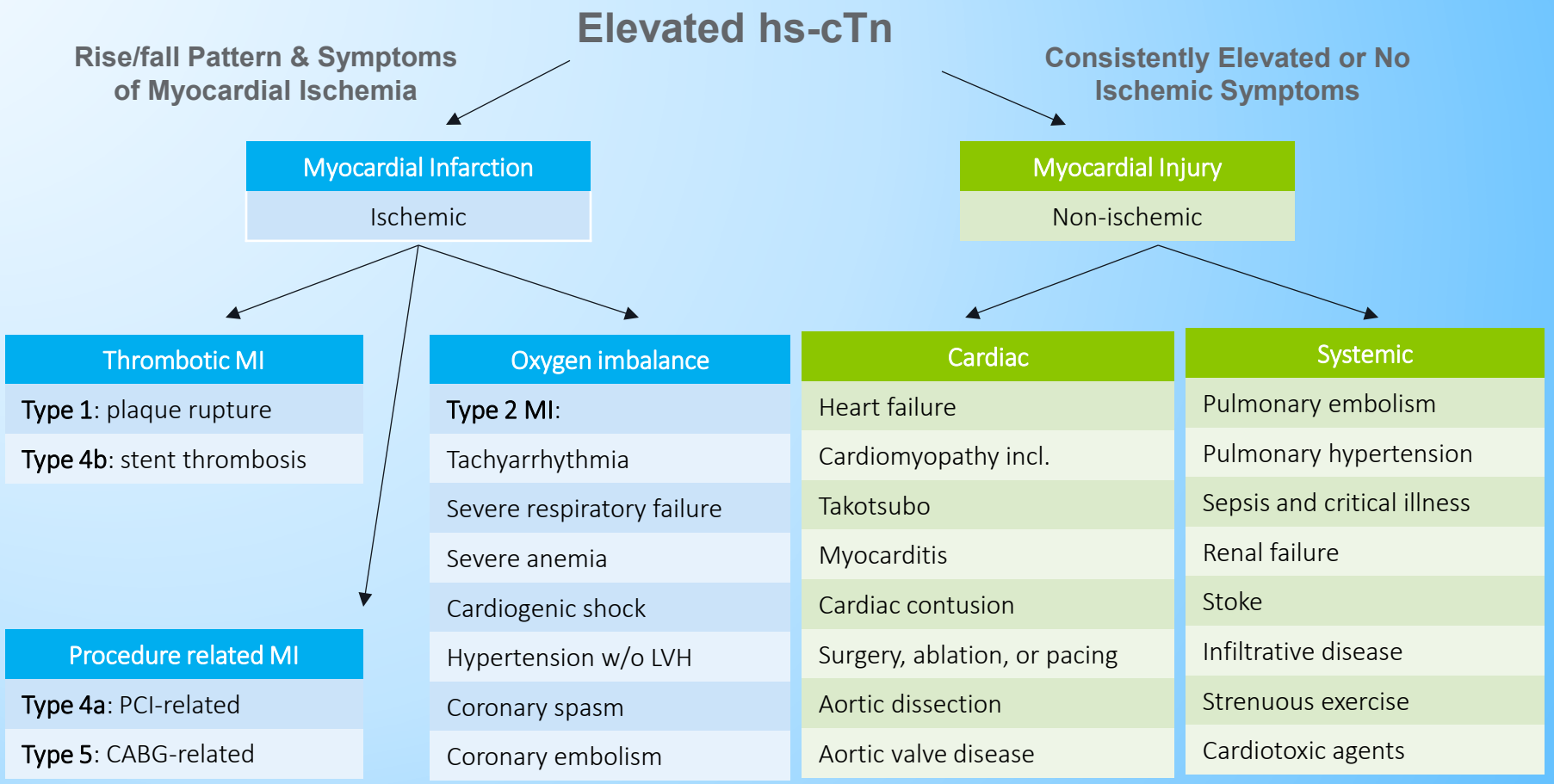




Timing of measurement matters



Interpretation of every hsTn elevation in clinical context



Mair. 2016 A.S. Maisel, A.S. Jaffe, *Cardiac Biomarkers*

Hs-cTn Strategies

One-&-Done to exclude MI

Onset of most recent chest pain ≥2-3 hours ago

Single very-low hs-cTn measure

One and Done Data

Meta-analysis

22,457 patients from 9 countries

Evaluated hs-cTnI <5 ng/L; Abbott Architect Assay

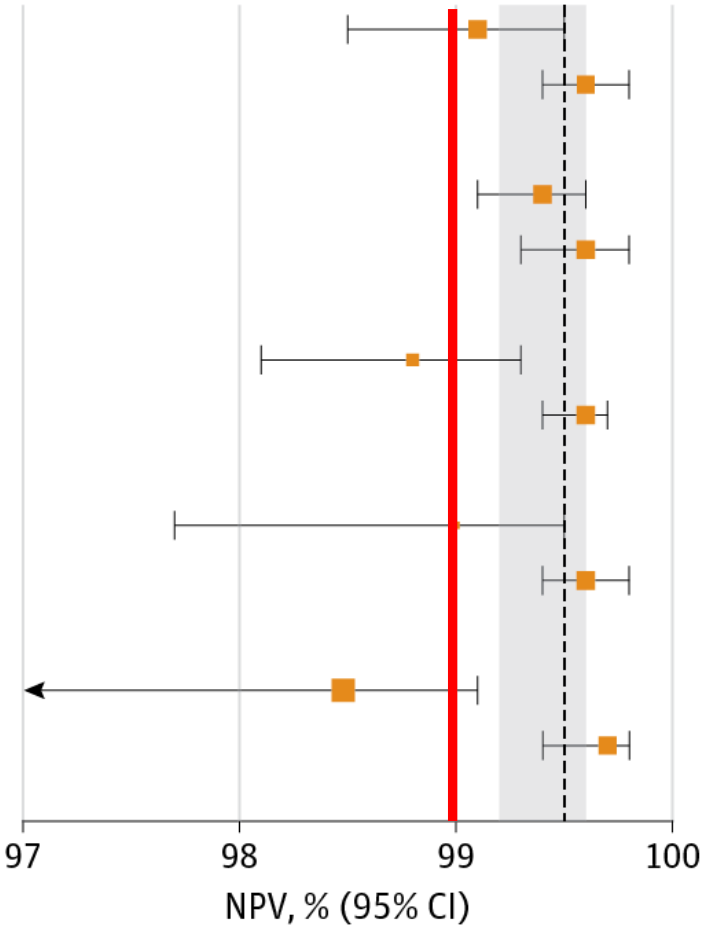
49% had hs-cTnI <5 ng/L

NPV 99.5% (95%CI: 99.3-99.6%) for type-1 MI

Chapman et al., JAMA, 2017

NPV of hs-cTnI <5 ng/L

Prespecified Subgroup	False Negatives, No.	True Negatives, No.	Total No. of Patients With Cardiac Troponin Concentrations ≤99th Percentile at Presentation	NPV, % (95% CI)	*P* Value
Age, y					
>65	26	2571	6818	99.1 (98.5-99.5)	.02
≤65	34	8381	11 430	99.6 (99.4-99.8)	
Sex					
Male	38	6043	10 920	99.4 (99.1-99.6)	.48
Female	22	4909	7328	99.6 (99.3-99.8)	
Ischemic heart disease					
Known[a]	22	1834	3990	98.8 (98.1-99.3)	.03
None known	31	7035	10 170	99.6 (99.4-99.7)	
Time from symptom onset to troponin sample collection, h					
≤2[b]	20	1540	2303	99 (97.7-99.5)	.003
>2	26	6851	11 101	99.6 (99.4-99.8)	
Myocardial ischemia on electrocardiogram					
Yes[c]	15	818	2178	98.2 (96.4-99.1)	<.001
No	39	8899	13 709	99.7 (99.4-99.8)	



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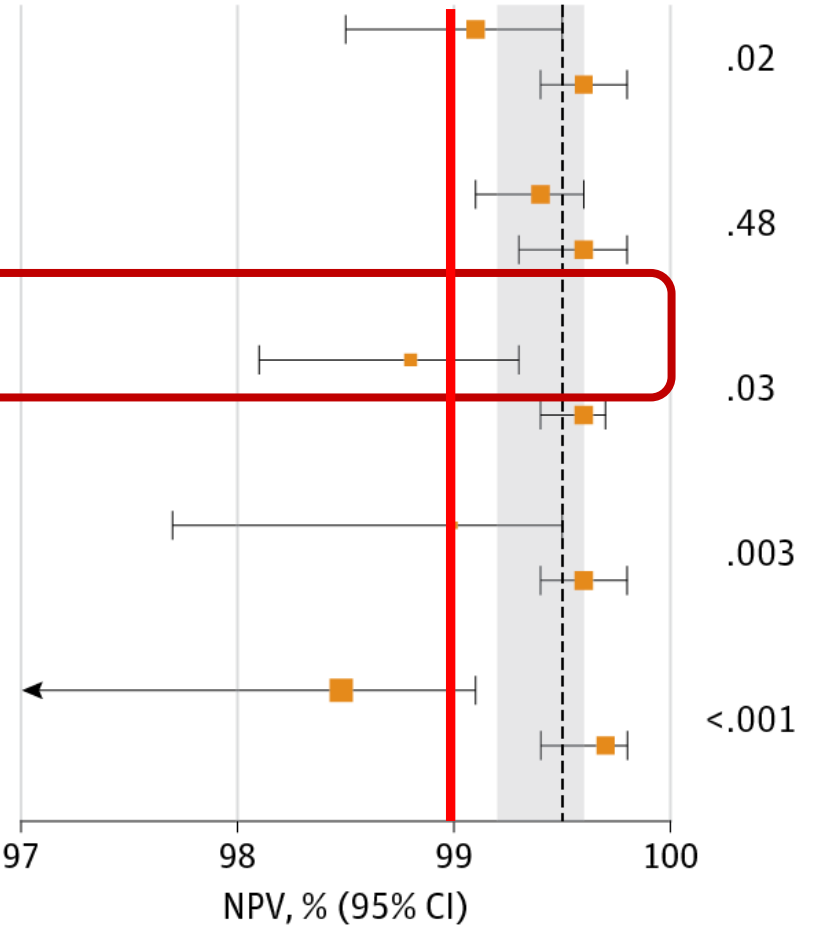

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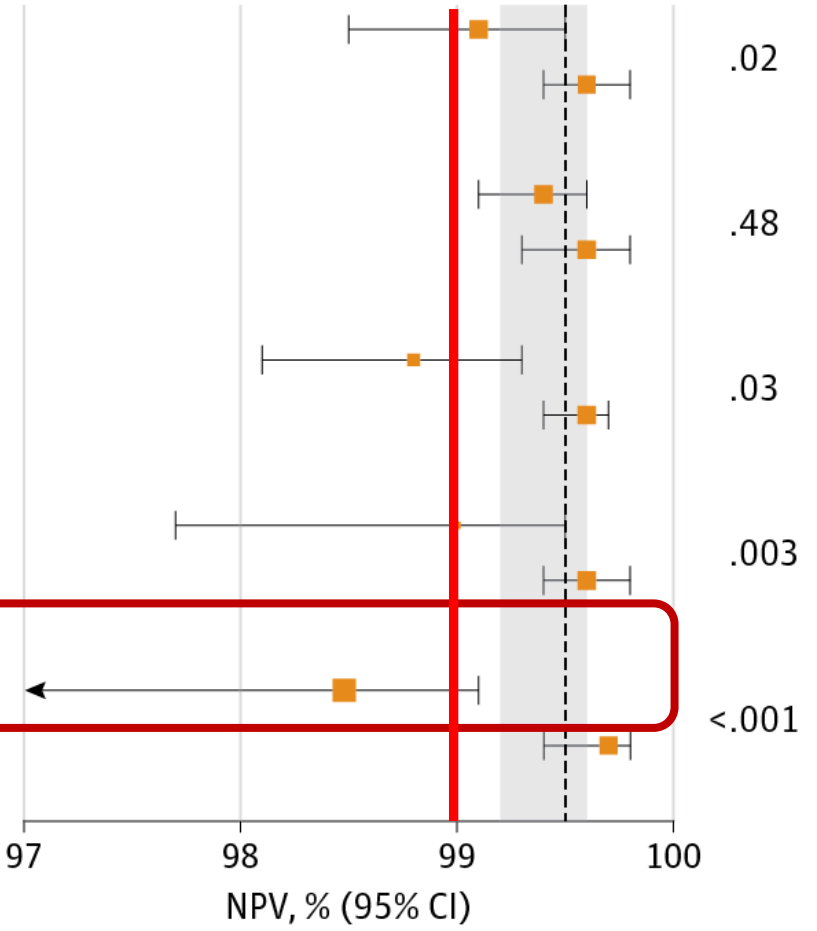

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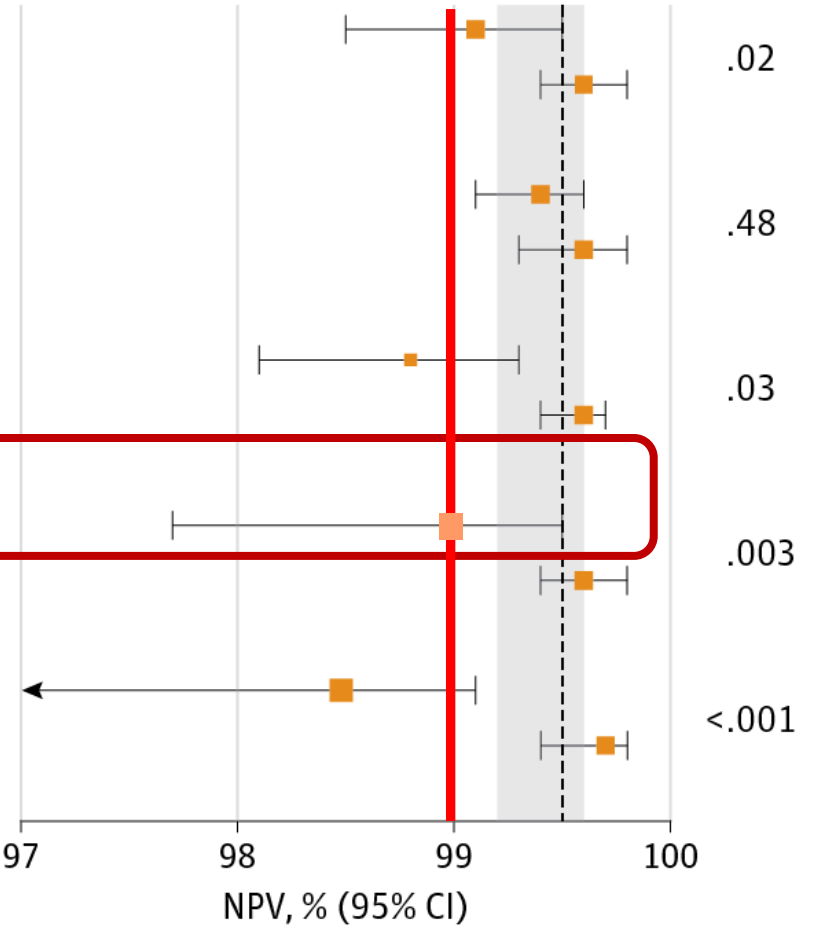


One-and-Done Data

1631 patients

UTROPIA cohort, USA

Abbott Architect hs-cTnI assay

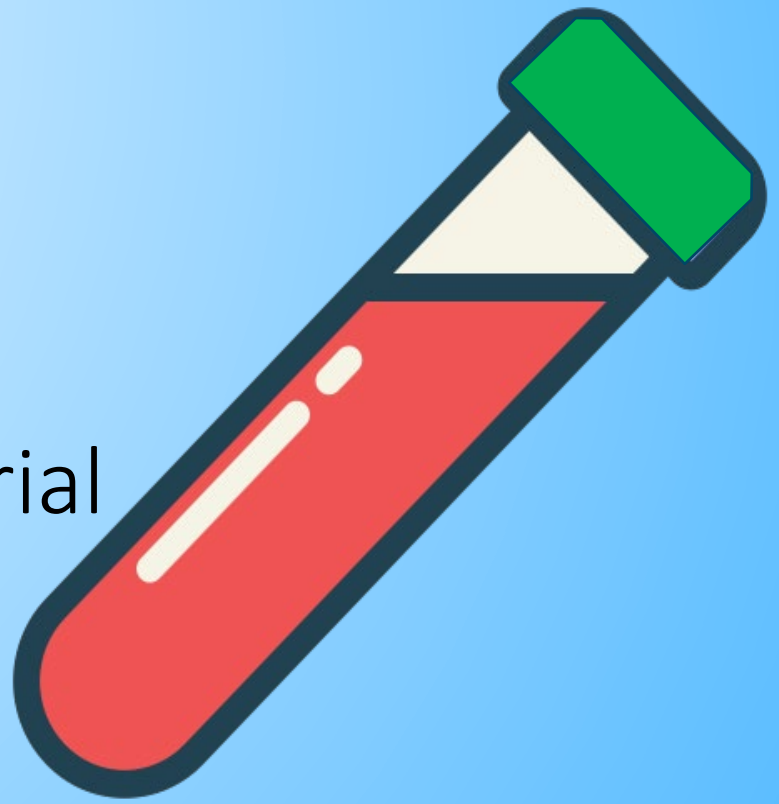
50% had hs-cTnI <5 ng/L
- NPV 98.9% for MI
- NPV 99.5% for MI when combined with a normal ECG

27% had hs-cTnI <2 ng/L (<LoD)
- NPV 98.8% for MI
- NPV 99.6% for MI when combined with a normal ECG

Sandoval et al., American J of Medicine, 2017

One and Done Pitfalls

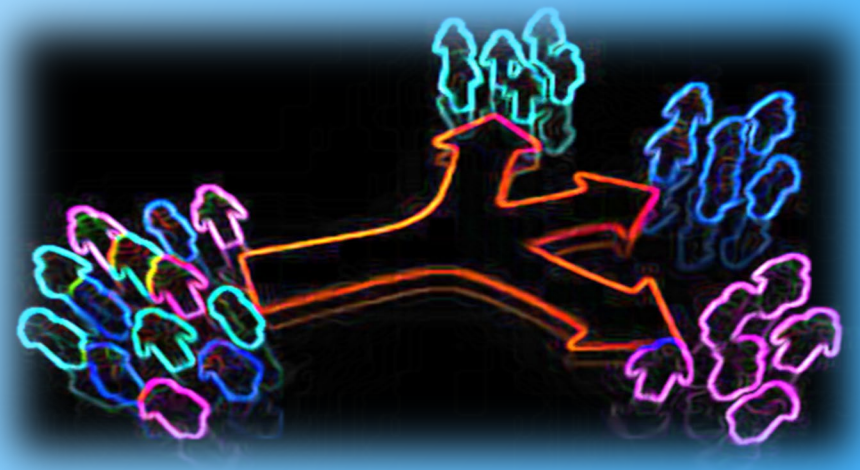
- Early presenters
  - Waxing and Waning Symptoms
- Patients with known CAD
- Patients with ischemic ECGs
- MI defined based on pattern of serial troponins



ADPs

hs-cTn Pathways that objectively combine data to risk stratify a patient into groups:

- rule-out
- observation
- rule-in

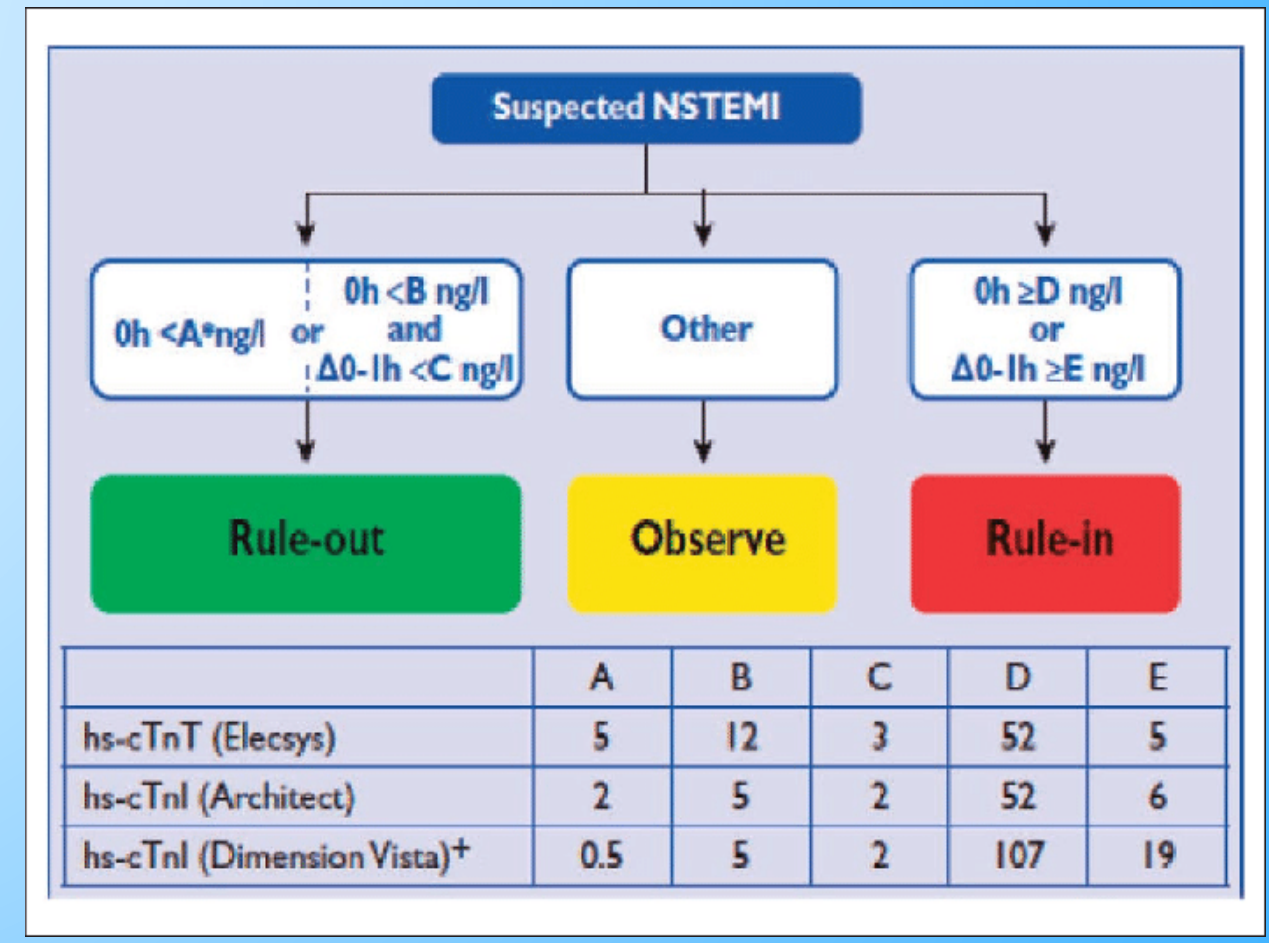


Troponin only ADPs

Serial hs-cTn Cut Points
0/1 – hour or 0/2-hour measures

Delta (change) Cut Points

ESC 0/1-h Algorithm



	A	B	C	D	E
hs-cTnT (Elecsys)	5	12	3	52	5
hs-cTnI (Architect)	2	5	2	52	6
hs-cTnI (Dimension Vista)+	0.5	5	2	107	19

Limitations of Troponin only ADPs

Do not formally include other clinical variables (EKG, history, etc)

Variability in clinical blood draw times for delta measure

Negative serial hs-cTn exclude acute myocardial injury

- *Does not fully predict or exclude an ACS event in the near future*

Unstable Angina

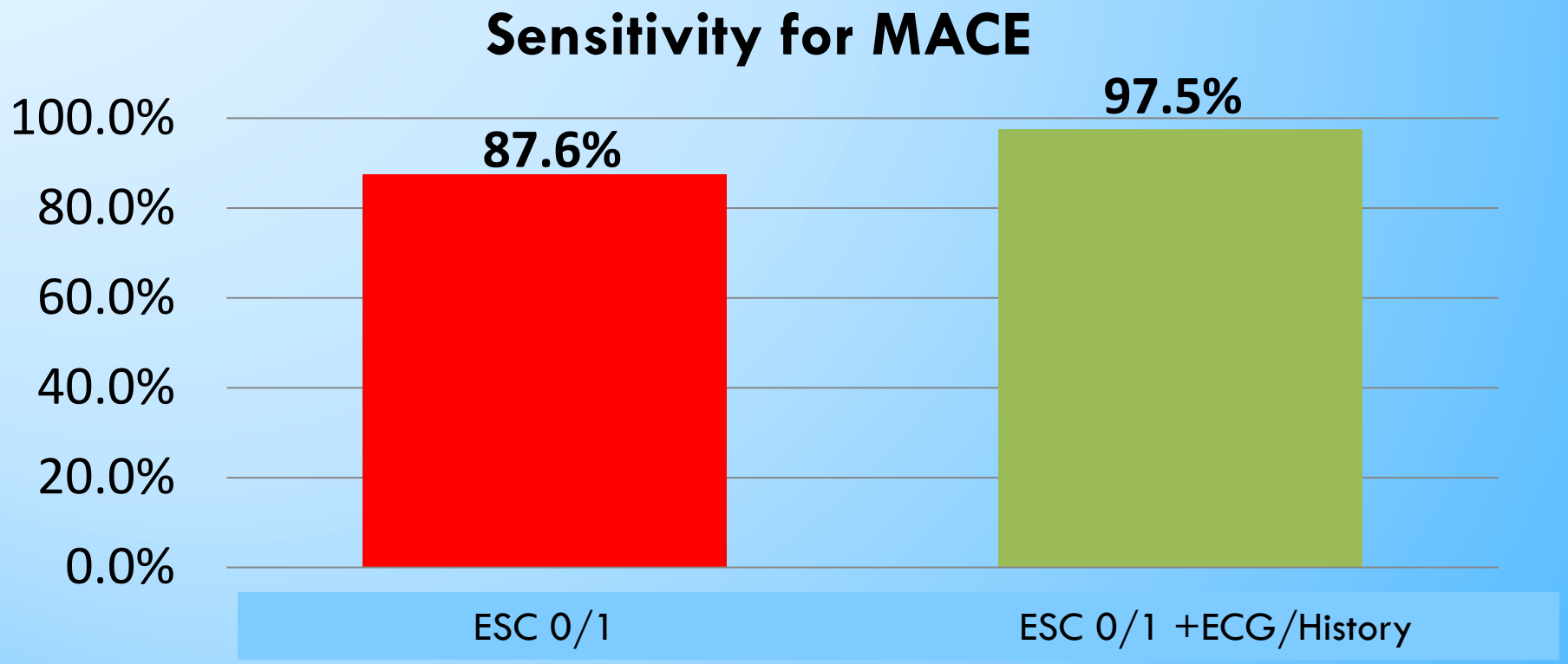
- Patients at high risk for MI
- Not a biomarker diagnosis

History and ECG

1038 patients with CP followed for 30-day events in Sweden

ESC 0/1-hr hs-cTnT algorithm vs

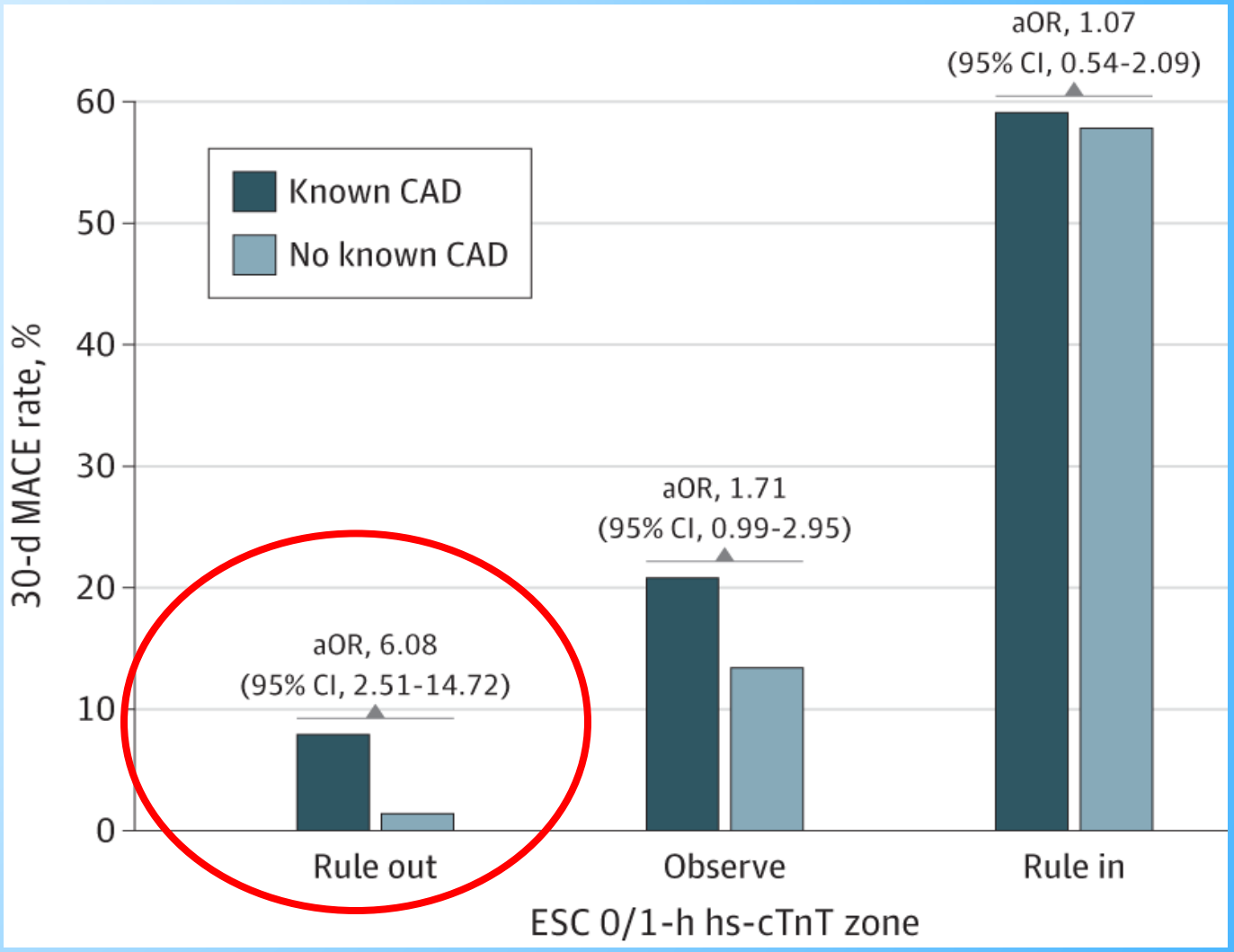
ESC 0/1-hr hs-cTnT algorithm + ECG + Physician History Assessment



Mokhtari et. al, JACC, 2016

ESC 0/1-h algorithm in patients with known CAD

- Multisite cohort study
- 1430 chest pain patients
  - 449 with known CAD
- 8 U.S .EDs
- Assessed diagnostic performance of ESC 0/1-h algorithm in
  - Known CAD
  - No Known CAD

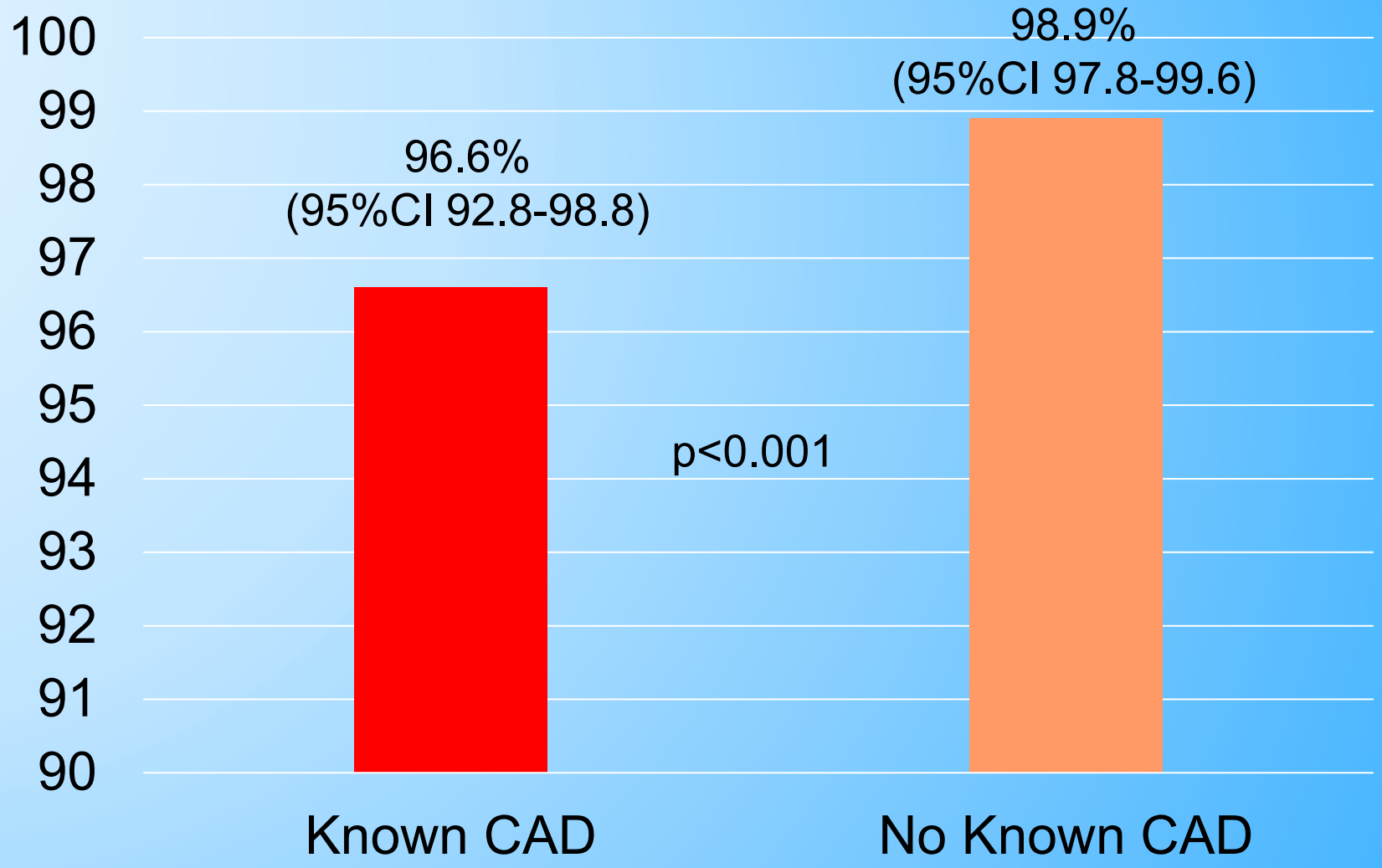


JAMA Network™ Ashburn et. al, JAMA Cardiol. 2023;8(4):347-356. doi:10.1001/jamacardio.2023.0031

NPV for 30-day Cardiac Death or MI

Patients with CAD:
39.6% (178/449)
Ruled-out

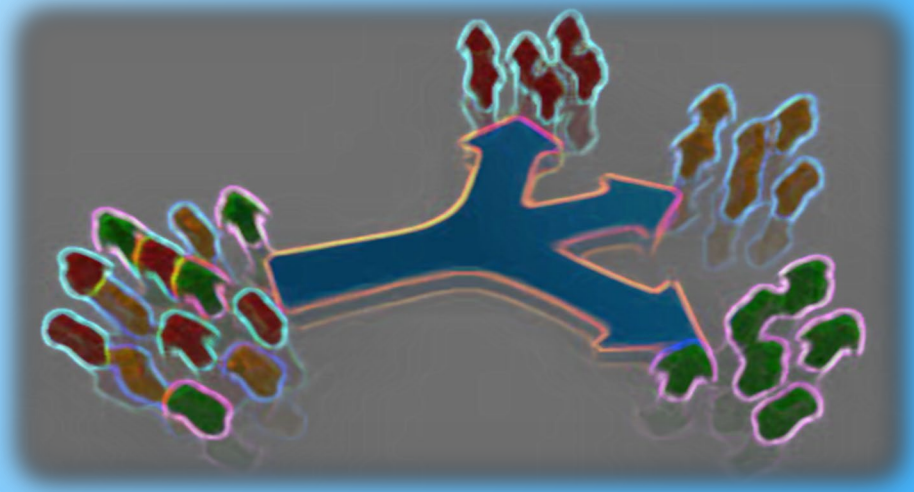
Cardiac death or MI occurred in 3.4% (6/178)



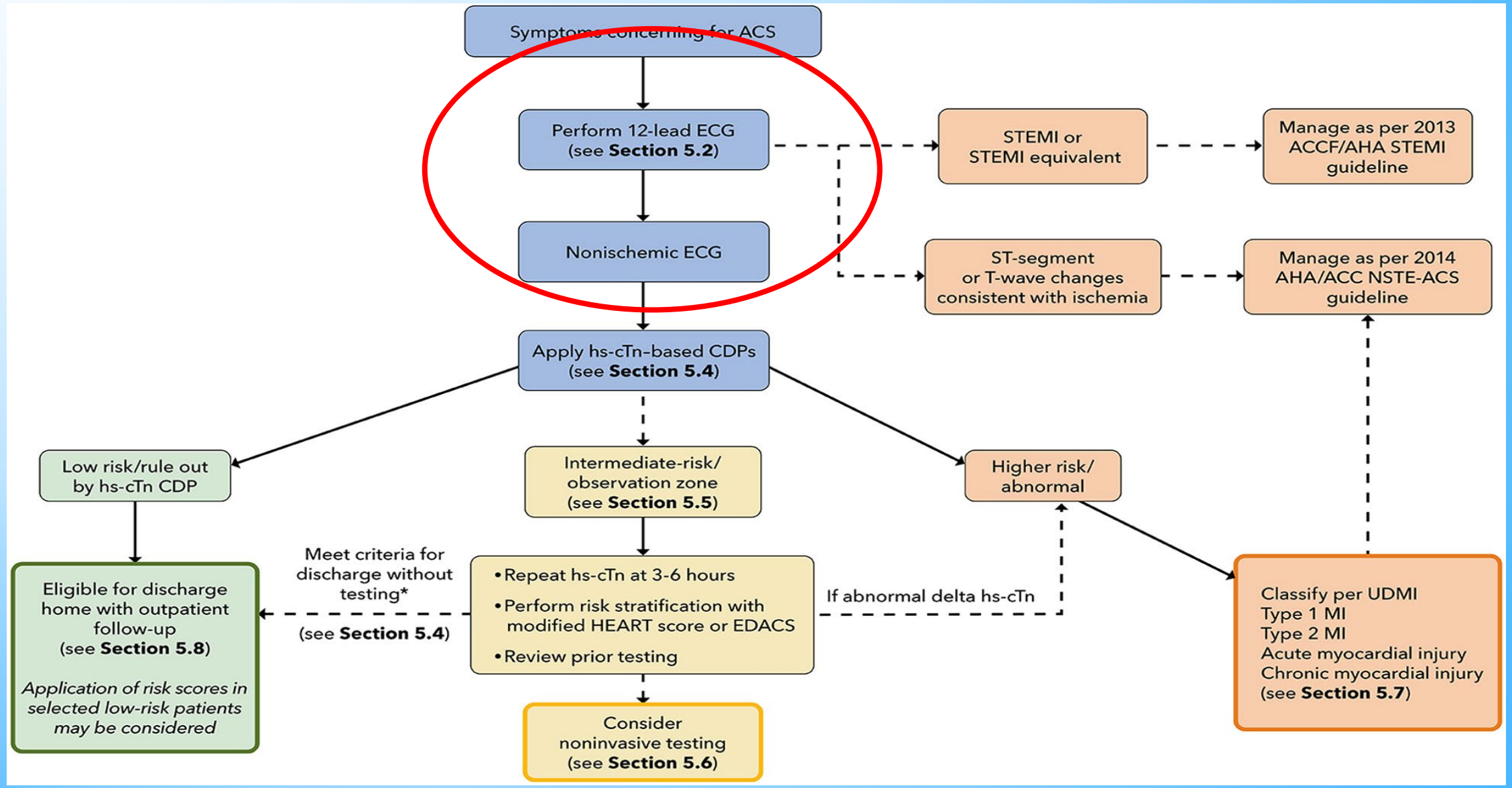
Multivariable ADPs

Combine clinical variables with hs-cTn measures

Serial hs-cTn 0/1 or 0/2 - hr cut points
Delta cut points
ECG
Risk score
Known CAD



ACC Expert Consensus Decision Pathway



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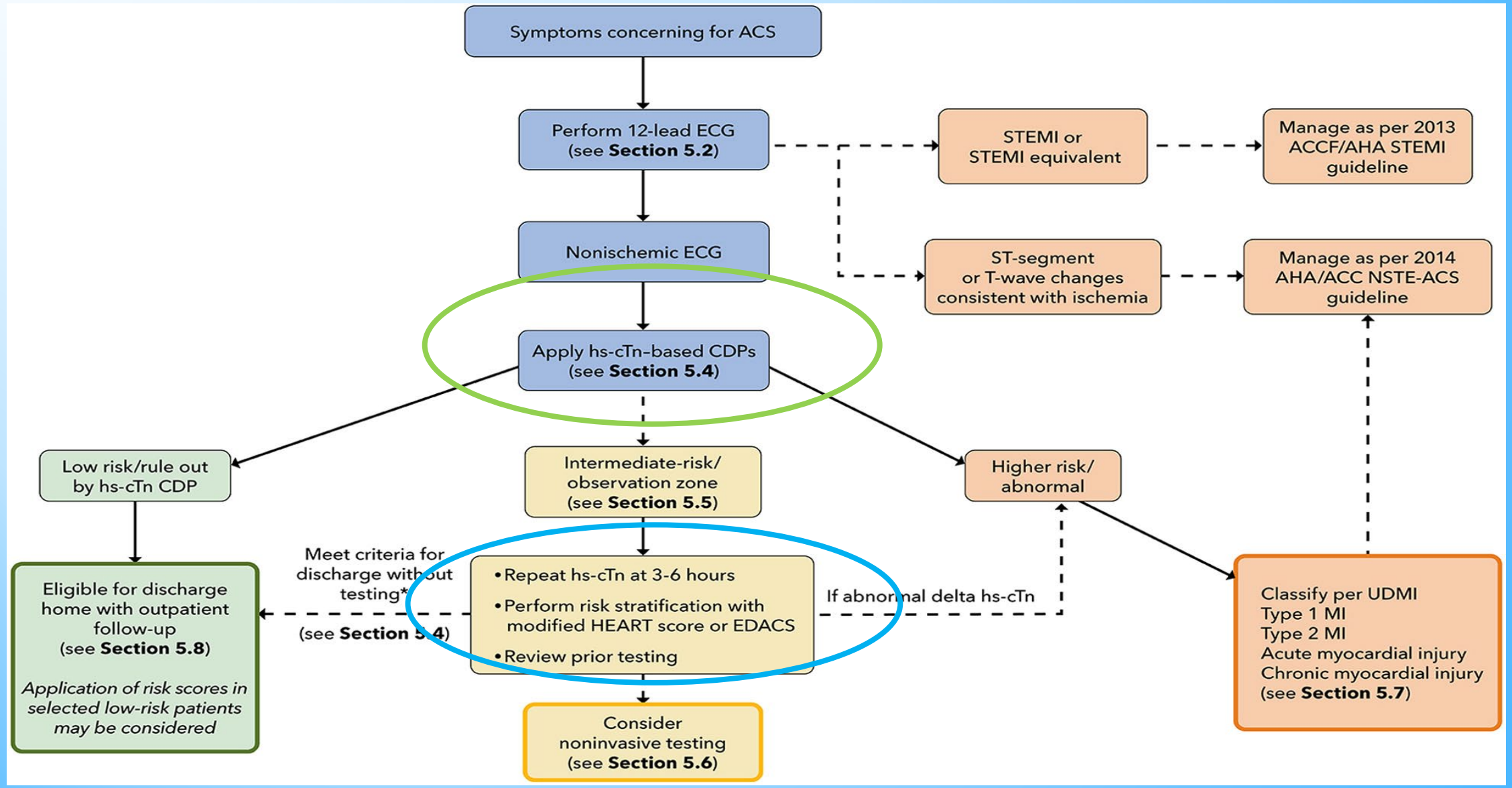
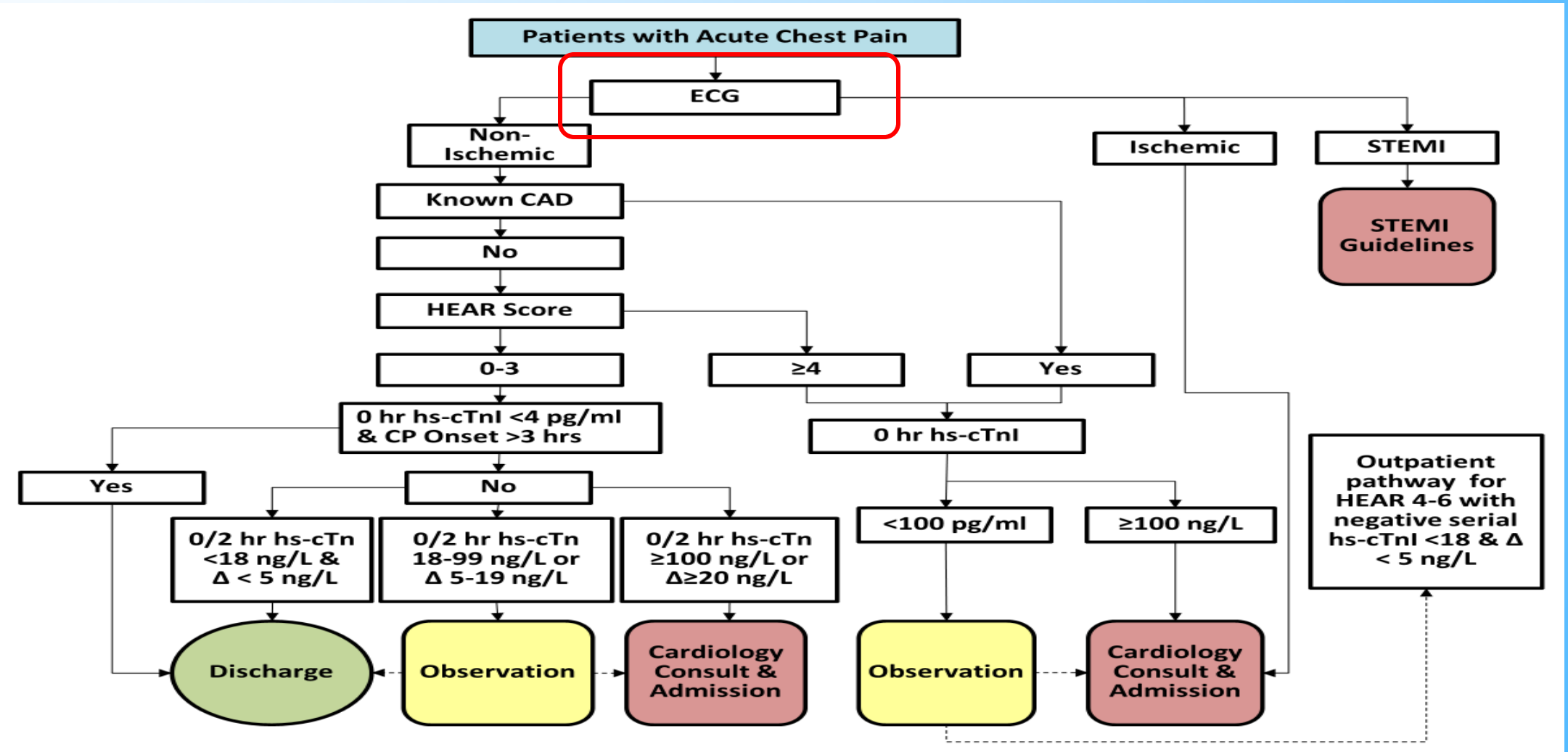
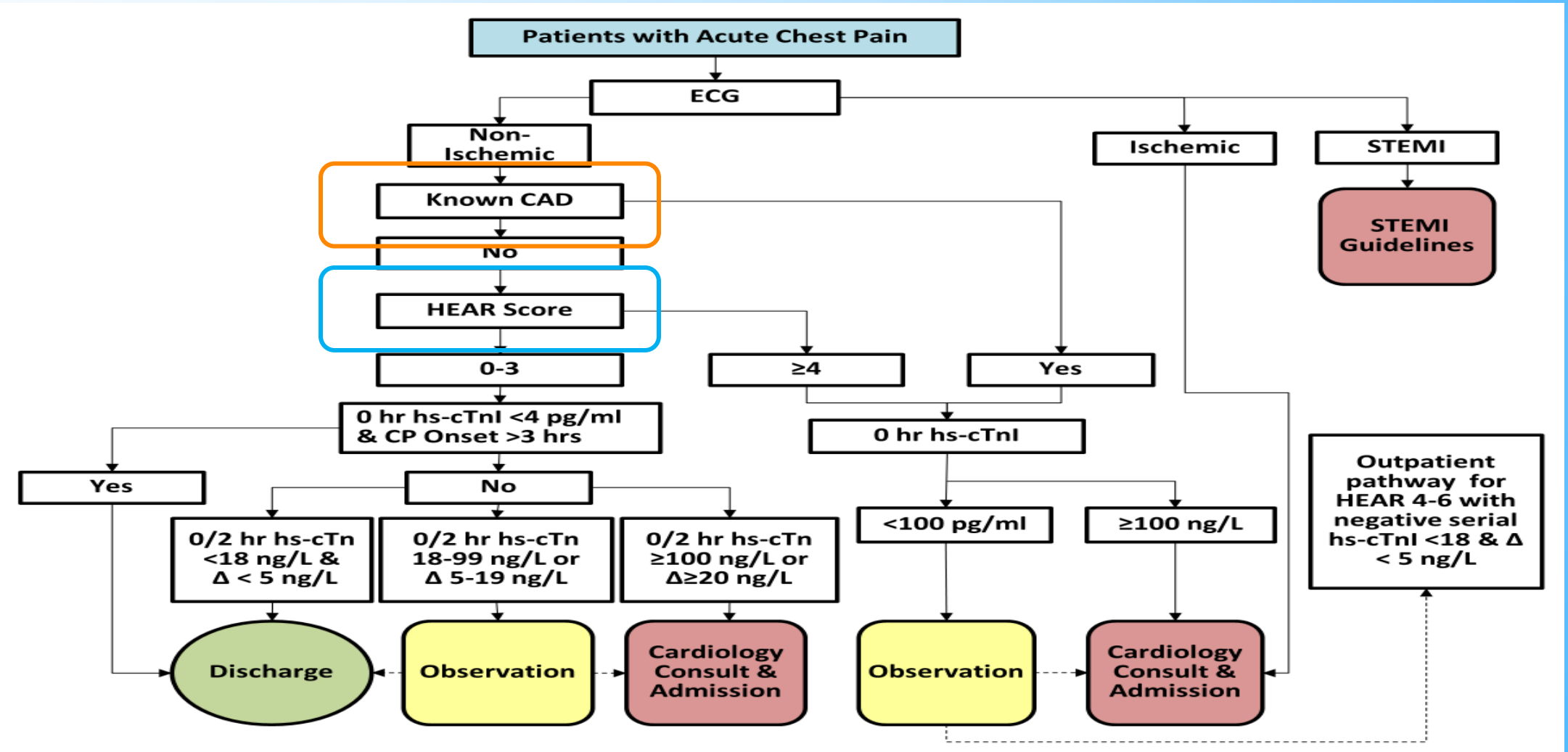


high-sensitivity HEART Pathway



Simon A. Mahler. Circulation: Cardiovascular Quality and Outcomes. Safety and Effectiveness of the High-Sensitivity Cardiac Troponin HEART Pathway in Patients With Possible Acute Coronary Syndrome, Volume: 17, Issue: 3, Pages: e010270, DOI: (10.1161/CIRCOUTCOMES.123.010270)

high-sensitivity HEART Pathway



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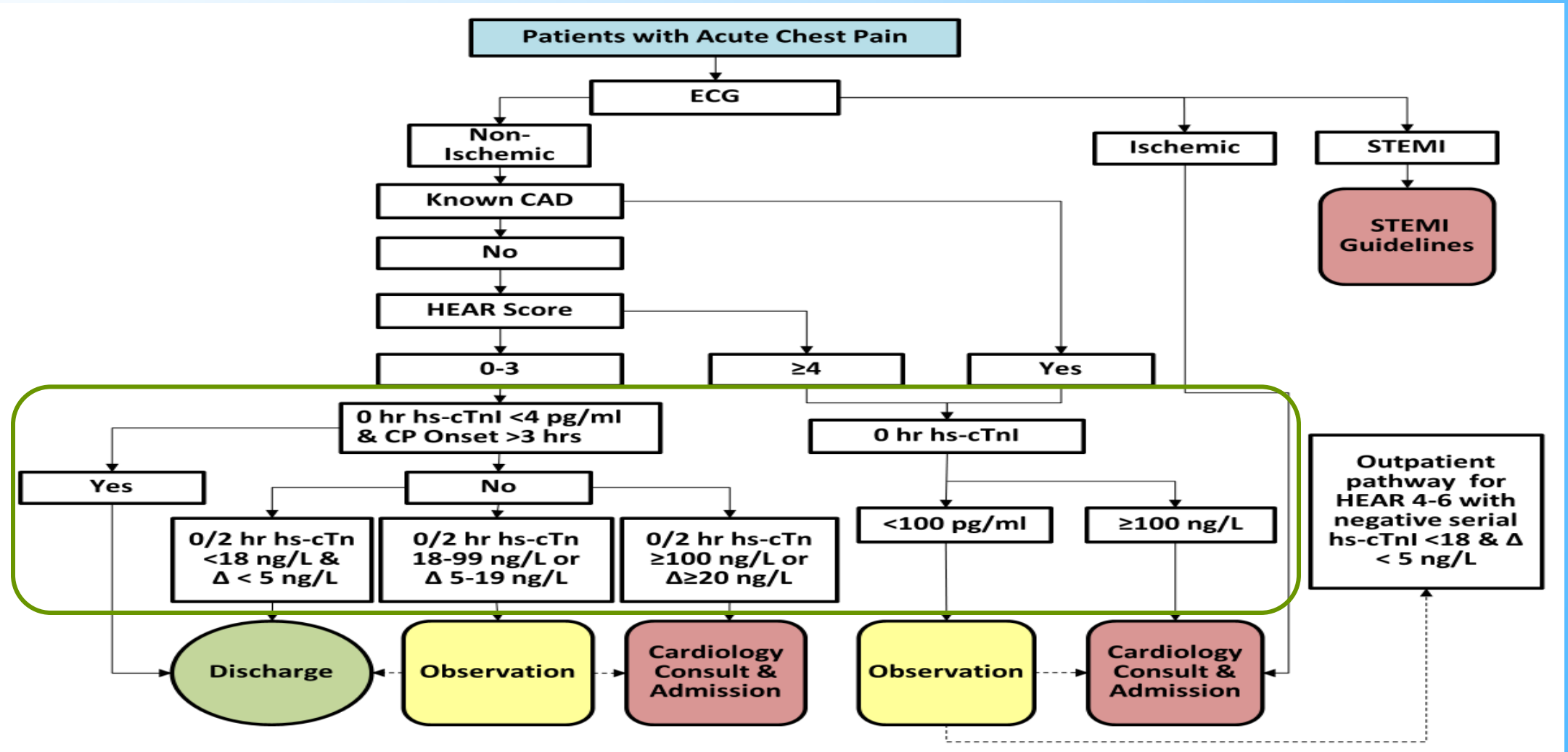

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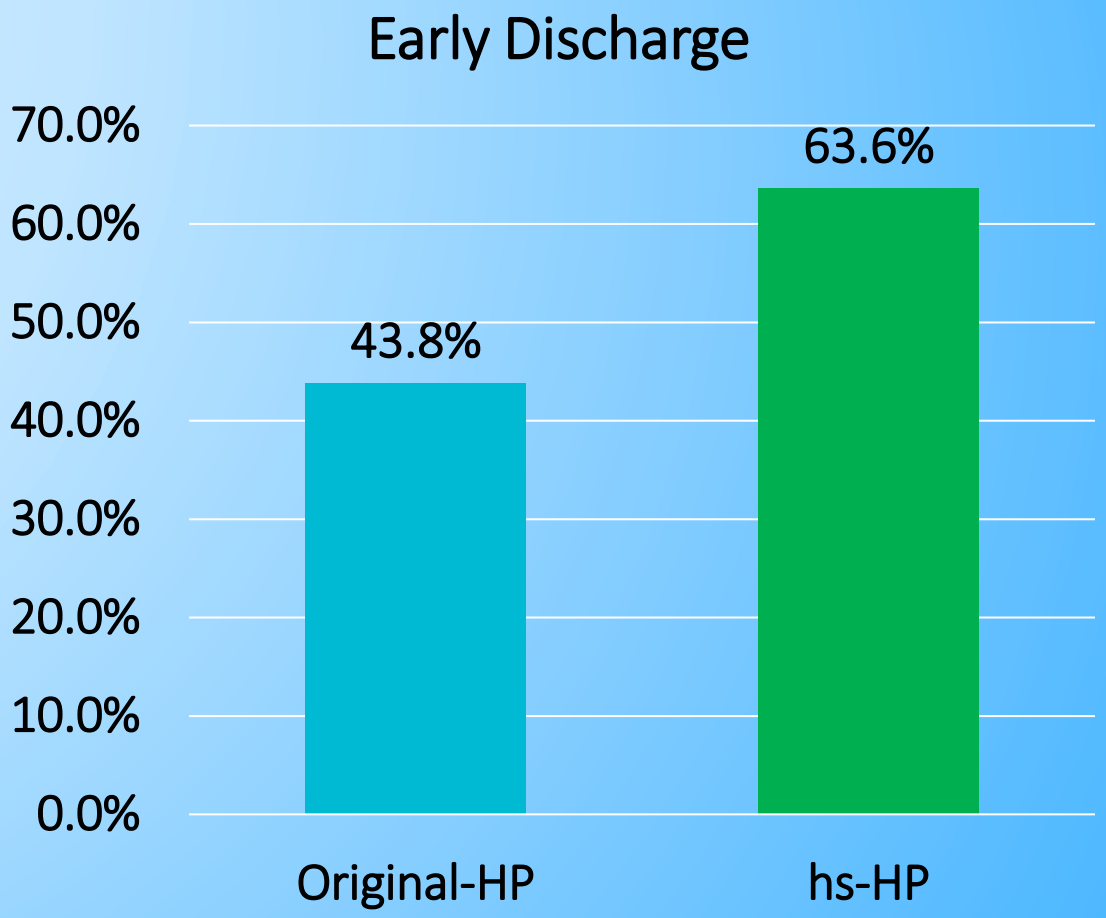
hs-HEART Pathway Implementation

hs-HEART Pathway **increased** the **early discharge** rate by

19.8% (p<0.0001)

- Reduced LOS
- Reduced stress testing
- 0.2% adverse event rate in low-risk patients



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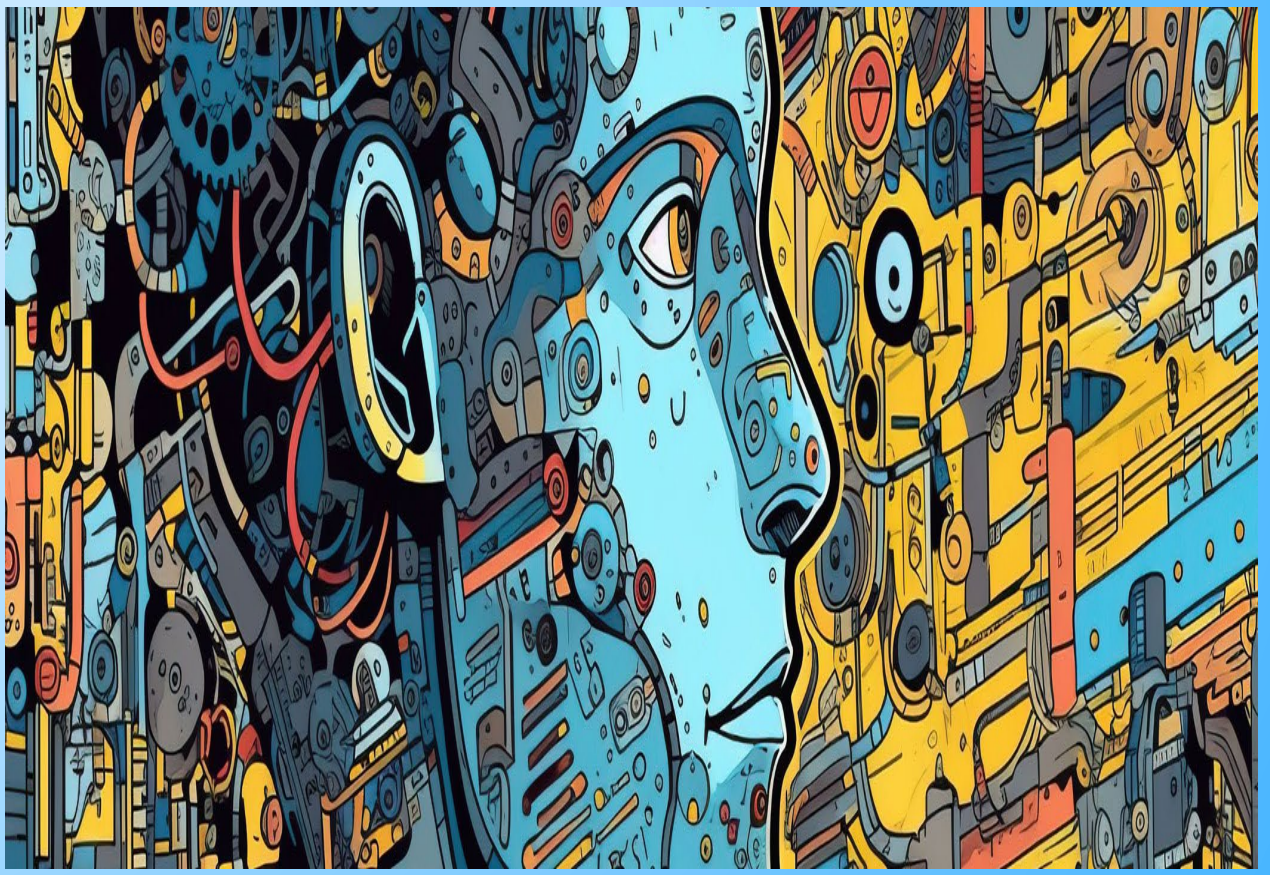
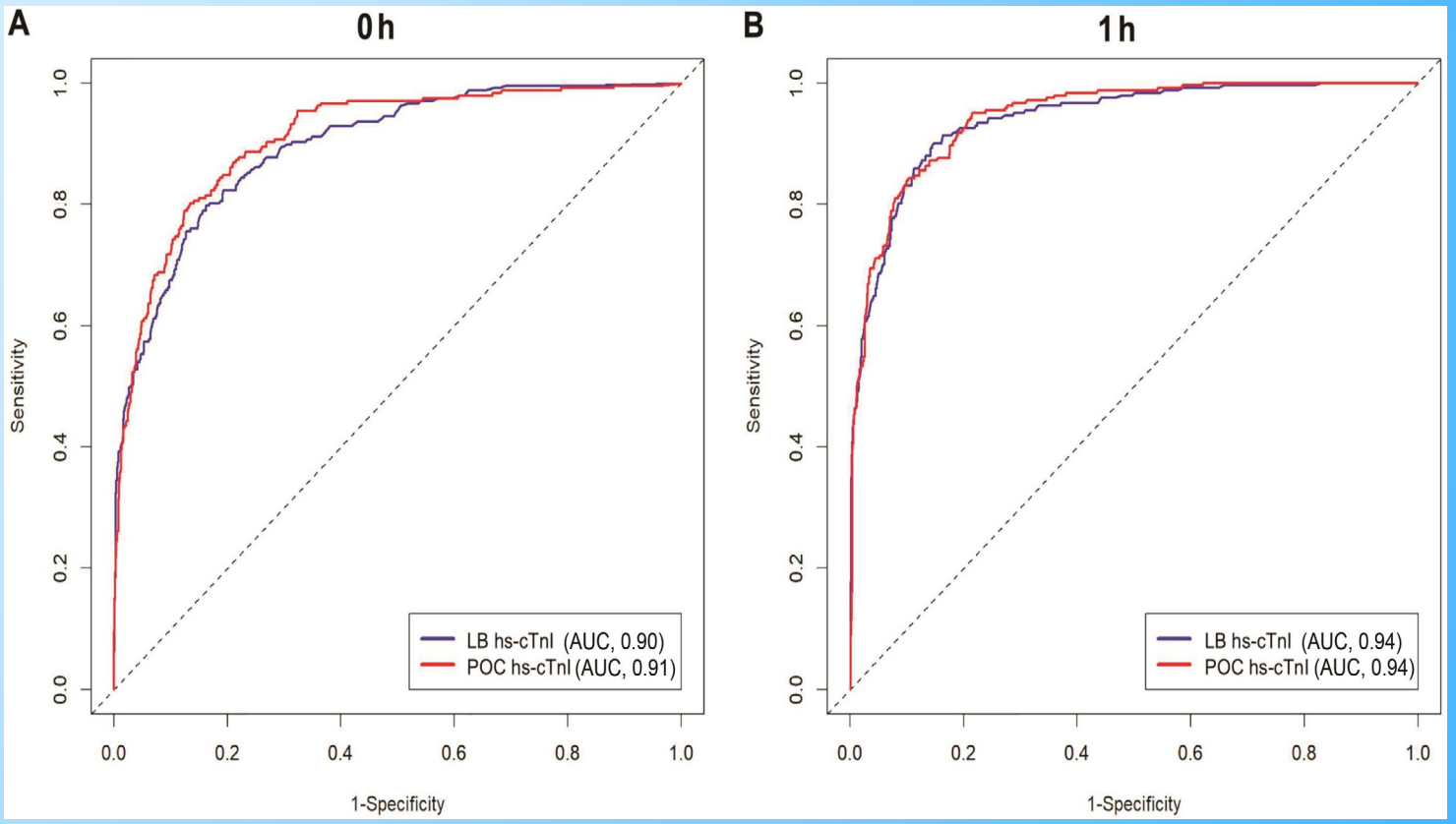
What’s Next?

- POC hs-cTn
- AI



POC hs-cTnI

- Faster turnaround time
- Similar analytical performance to central lab
- >1200 patients
- High correlation r=0.96
- AUC similar for NSTEMI



Clin Chem, Volume 65, Issue 12, 1 December 2019, Pages 1592–1601, https://doi.org/10.1373/clinchem.2019.307405

Promise of POC – hs-cTn

Recent RCT of Siemens POC 0/1-h algorithm vs 0/1-h central lab

1,494 patients in Norway

Among patients seen within 1 hour by a physician POC reduced the median ED length of stay by 15 minutes

Among patients with NSTEMI ED length of stay reduced by 43 minutes

Artificial Intelligence and Machine Learning

- MI^3
- CODE ACS
- ARTEMIS

Machine Learning to Predict the Likelihood of Acute Myocardial Infarction

Martin P. Than, John W. Pickering, Yader Sandoval, Anoop S.V. Shah, Athanasios Tsanas, Fred S. Apple, Stefan Blankenberg, Louise Cullen, Christian Mueller, Johannes T. Neumann, ... See all authors

Machine learning for diagnosis of myocardial infarction using cardiac troponin concentrations

Received: 4 October 2022

Accepted: 28 March 2023

Published online: 11 May 2023

Check for updates

Dimitrios Doudesis[1,2,32], Kuan Ken Lee[1,32], Jasper Boeddinghaus[1,3,32], Anda Bularga[1], Amy V. Ferry[1], Chris Tuck[1], Matthew T. H. Lowry[1], Pedro Lopez-Ayala[3], Thomas Nestelberger[3], Luca Koechlin[3,4], Miguel O. Bernabeu[2,5], Lis Neubeck[6], Atul Anand[1], Karen Schulz[7], Fred S. Apple[8], William Parsonage[9], Jaimi H. Greenslade[10,11,12], Louise Cullen[10,11,12], John W. Pickering[13,14], Martin P. Than[13], Alasdair Gray[15], Christian Mueller[3], Nicholas L. Mills[1,2] ✉ & CoDE-ACS Investigators*

AI/Machine Learning

- Each patient will have their own unique expected hs-cTn value
  - based on dozens/hundreds of variables
- Timing between hs-cTn draws accounted for
- Each patient's 30-day risk for cardiac death or MI reported automatically within the EHR

Case 1

A 60 yo woman with a history of heart failure presents to the ED with chest pain lasting 1.5 hours. Her ECG is non-diagnostic. Serial hs-cTnI were measured two hours apart and were 16 ng/L and 18 ng/L, respectively, just above the sex specific URL of 15 ng/L.

Can she be discharged?

Is this an MI?

Case adapted from Mahajan et. al, Circulation 2011

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Is this an MI?

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Her BNP was >5,000 pg/ml and she was diagnosed with acute on chronic heart failure

Case adapted from Mahajan et. al, Circulation 2011

Case 2

A 64 yo man with a history of diabetes presents to the ED with chest pressure and diaphoresis lasting 1 hour. His ECG is Normal. Serial hs-cTnI were measured two hours apart and were 22 ng/L and 34 ng/L, respectively, above the sex specific URL of 20 ng/L.

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Can he be discharged?

Is this an MI?

He was admitted and his next hs-cTnI was 200 ng/L.

Case adapted from Mahajan et. al, Circulation 2011

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A 64 yo man with a history of diabetes presents to the ED with chest pressure and diaphoresis lasting 1 hour. His ECG is Normal. Serial hs-cTnI were measured two hours apart and were 22 ng/L and 34 ng/L, respectively, above the sex specific URL of 20 ng/L.

Can he be discharged?

Is this an MI?

He was admitted and his next hs-cTnI was 200 ng/L.

An echo showed a focal wall motion abnormality and cardiac catheterization revealed a 90% LAD stenosis consistent with NSTEMI.

Case adapted from Mahajan et. al, Circulation 2011

Case 3

A 73 yo woman with a history of hypertension and hyperlipidemia presents to the ED with chest pressure, diaphoresis, and radiation to both arms lasting 15 minutes and relieved by nitroglycerin. Her ECG shows new T-wave inversions. Serial hs-cTnI were measured two hours apart and were 7 ng/L and 9 ng/L, respectively, below the sex specific URL of 15 ng/L.

Can she be discharged?

Is this an MI?

Case 3

A 73 yo woman with a history of hypertension and hyperlipidemia presents to the ED with chest pressure, diaphoresis, and radiation to both arms lasting 15 minutes and relieved by nitroglycerin. Her ECG shows new T-wave inversions. Serial hs-cTnI were measured two hours apart and were 7 ng/L and 9 ng/L, respectively, below the sex specific URL of 15 ng/L.

Can she be discharged?

Is this an MI?

She was discharged from the ED, but returns two days latter with similar pain unrelieved by nitroglycerin.

Case 3

A 73 yo woman with a history of hypertension and hyperlipidemia presents to the ED with chest pressure, diaphoresis, and radiation to both arms lasting 15 minutes and relieved by nitroglycerin. Her ECG shows new T-wave inversions. Serial hs-cTnI were measured two hours apart and were 7 ng/L and 9 ng/L, respectively, below the sex specific URL of 15 ng/L.

Can she be discharged?

Is this an MI?

She was discharged from the ED, but returns two days latter with similar pain unrelieved by nitroglycerin.

Her ECG on second visit to the ED is consistent with a STEMI.

hs-cTn Summary

- hs-cTn assays are superior to prior generations of cTn
- Should be obtained in all patients with suspected ACS
- Elevation = Injury
- Negative troponins alone do not exclude ACS
- Clinical context is key
- Best used as part of a risk stratification model/ADP
- POC & AI have potential to improve hs-cTn algorithms

CHEST PAIN MOUNTAIN