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Optimizing Chest Pain Care: Implementing Rapid Point-of-Care Cardiovascular Diagnostic Testing into Your Workflow

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CHEST PAIN MOUNTAIN

Disclosures

- AHRQ, HRSA, EMF, Duke Endowment, NFEM
- Roche Diagnostics
- Abbott Laboratories
- Quidel
- Siemens
- Polymedco
- Genetesis
- Beckman Coulter
- Inflammatix
- Radiometer
- Brainbox
- Repreive Cardiovascular
- Genentech
- Impathiq Inc.

Learning Objectives

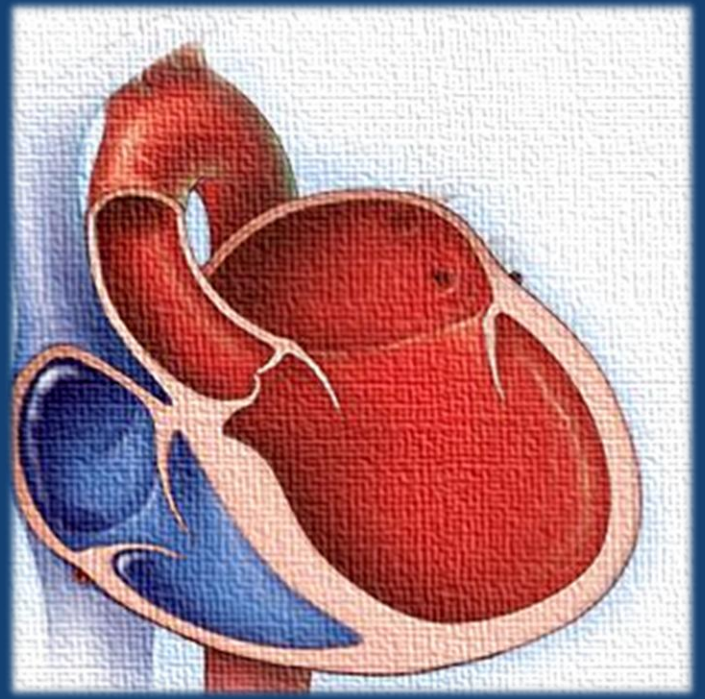
- Identify the current challenges and inefficiencies of emergency department chest pain risk stratification
- Discuss how cardiovascular point of care diagnostics can improve chest pain care
- Describe the advantages of point of care high sensitivity troponin and considerations for how best to implement them into emergency department workflow
- Analyze the utility of point of care D-dimer and natriuretic peptide testing

The Big Three

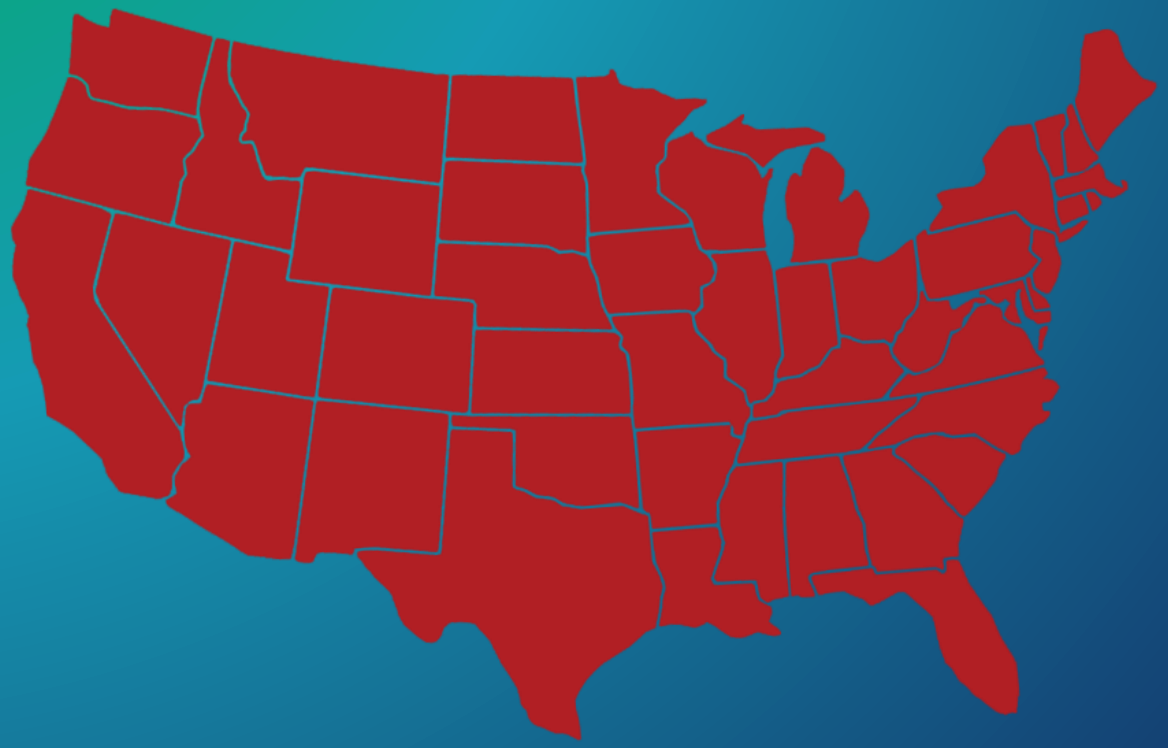
- Acute Coronary Syndrome (ACS)
- Pulmonary Embolism (PE)
- Aortic Dissection (AD)

CHF

- Can have overlap in symptoms with ACS or PE
  - Dyspnea
- ~1/3rd of patients presenting with chest pain have a history of CHF
- 20-30% of patients with CHF have chronic/recurrent chest pain
- Myocardial Ischemia is the most common cause of new CHF



Chest Pain



>7 Million Annual US ED Encounters for Acute Chest Pain

Chest Pain

~ $13 Billion spent on chest pain evaluations each year

Over-Testing

<10% Diagnosed with ACS

<5% Diagnosed with PE

<1% Diagnosed with AD

Under-Testing

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

10-15% of PE cases missed at initial ED visit

30-40% of AD missed or diagnosed late

Impact of Over- and Under-Testing

Over-testing:

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

Under-testing:

- Mortality
- Morbidity
- Malpractice

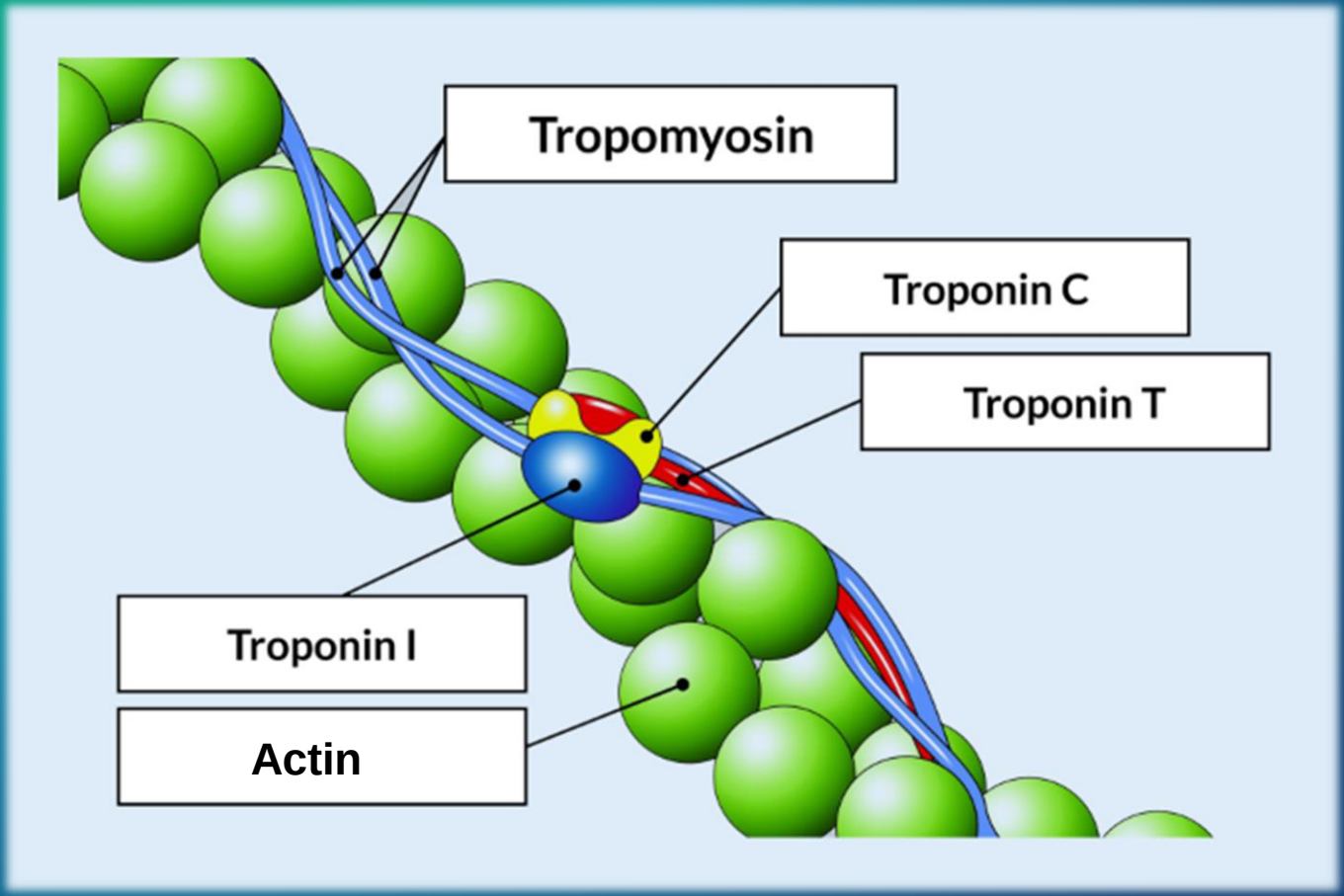
ED Overcrowding

- Significant and widespread problem
- Decreases patient safety
  - Mortality
  - Treatment delays
  - Elopements
  - Ambulance diversions
- Increased staff and provider burn-out
- Loss of revenue

Chest Pain Toolbox

- Electrocardiogram
- **Biomarkers**
- Risk Scores
- Accelerated Diagnostic Pathways
- Imaging

Let's Talk TROPONIN



- Gold Standard biochemical test for myocardial injury
- Recommended for ACS evaluations
- Cardiac myocyte protein
- Cardiac injury results in extracellular leak
  - Detectable in peripheral blood

Myocardial Injury Biomarker Timeline

CKMB

Quantitative
POC Troponin

FDA approves
hs-cTnI assays

1980 | 1990 | 2000 | 2010 | 2017-2018 | 2024

Troponin

1st Generation

hs-cTn

5th Generation

FDA approves
hs-cTnT

FDA approves
POC hs-cTnI

hs-cTn vs s-cTn (5^{th} vs 4^{th} 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

Improved Precision

Earlier Generation Troponin

15% CV

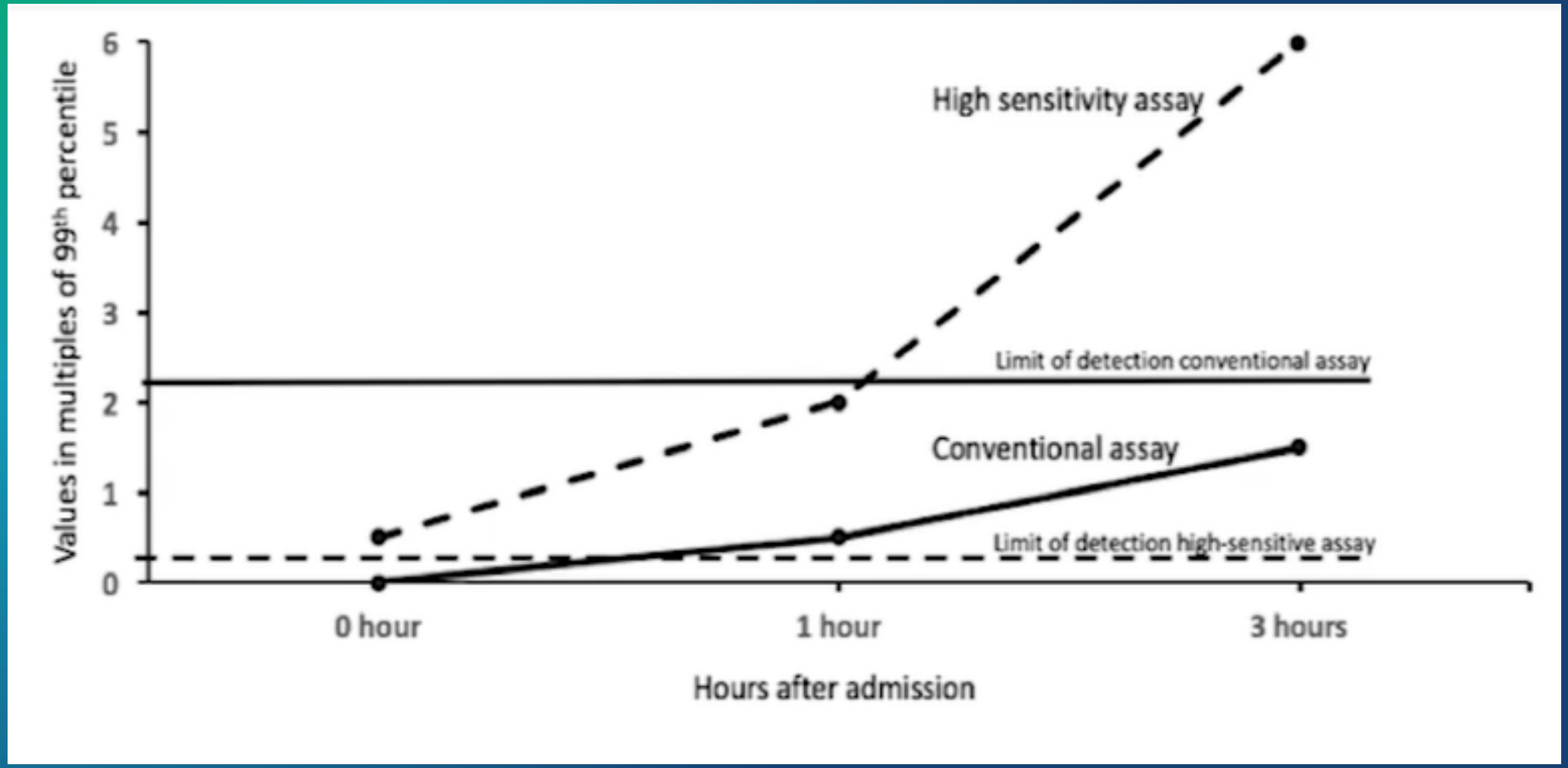
High Accuracy, Low Precision

High-Sensitivity Troponin

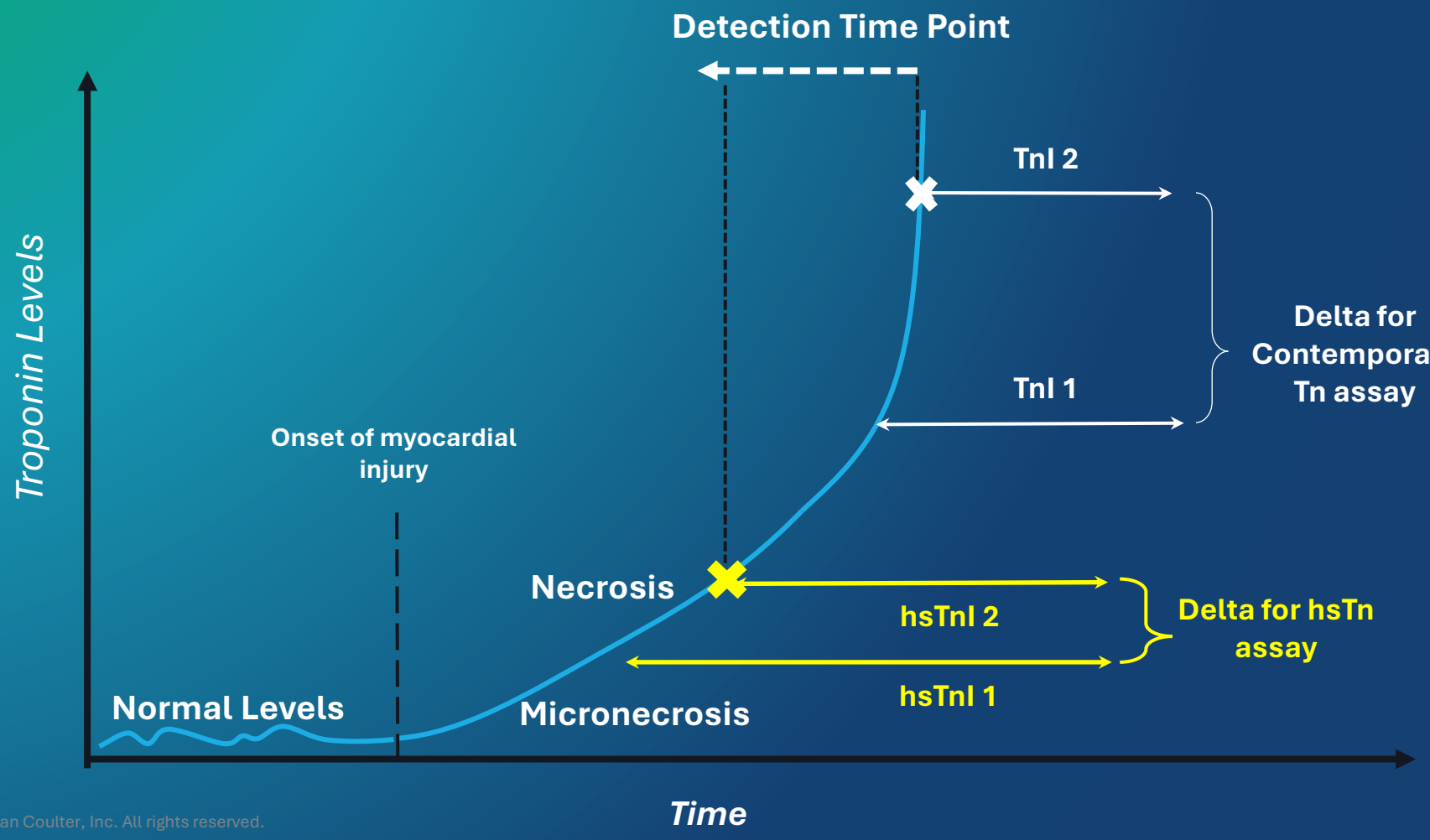
5% CV

High Accuracy & Precision

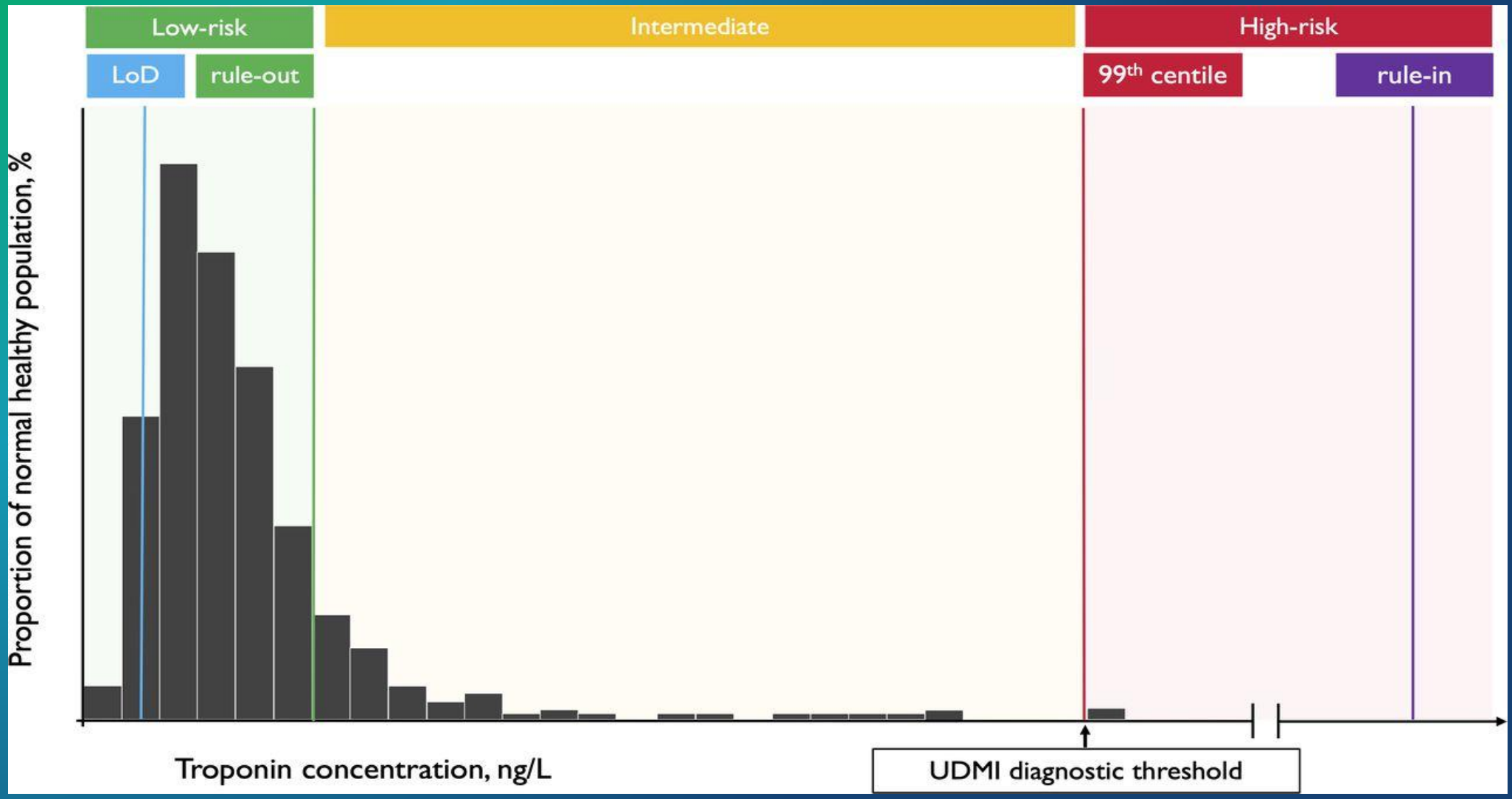
hs-cTn has earlier rise in patients with MI



hs-cTn allows measurement of absolute delta change and short time intervals 1-2 hours



hs-cTn measure interpretation



Lowry et al, BMJ 2021

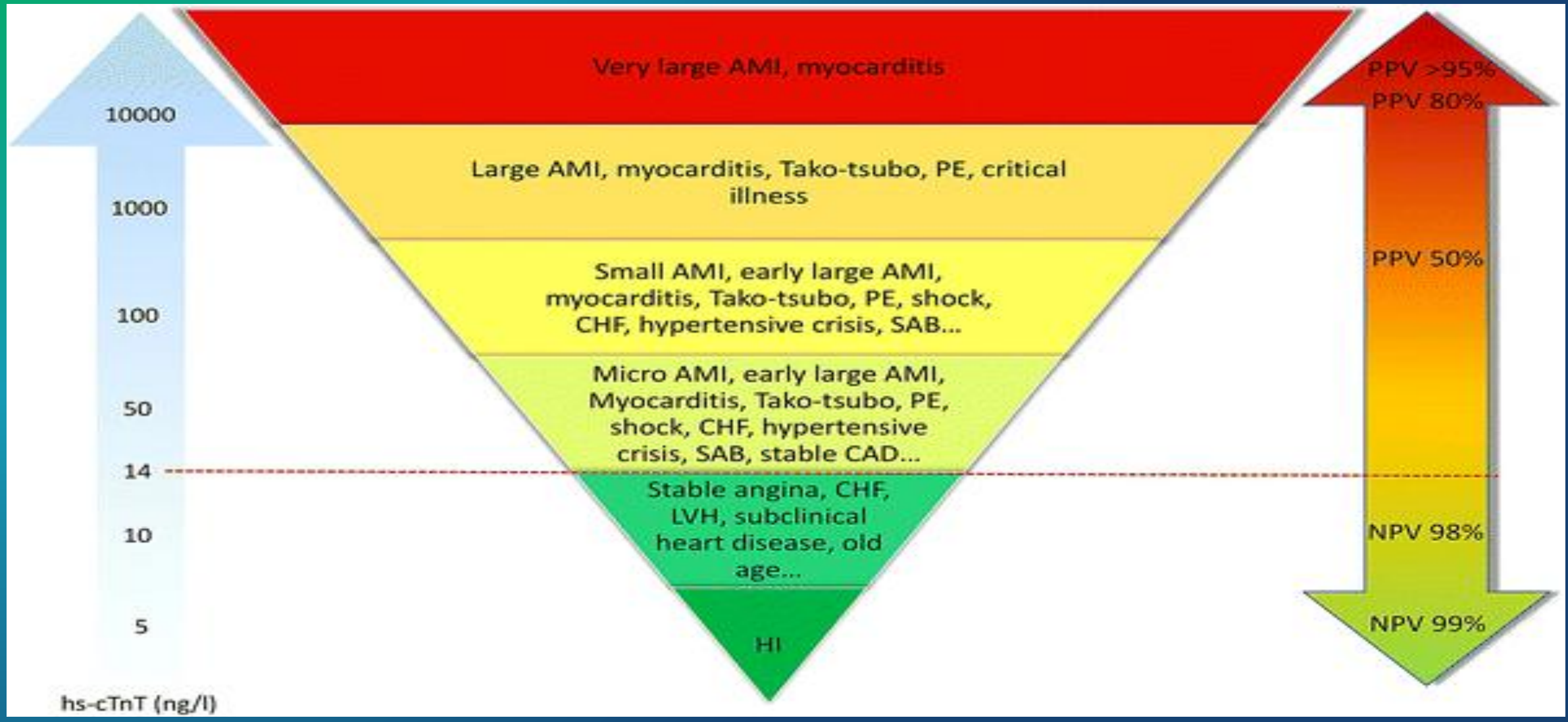
Elevation = Injury

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)

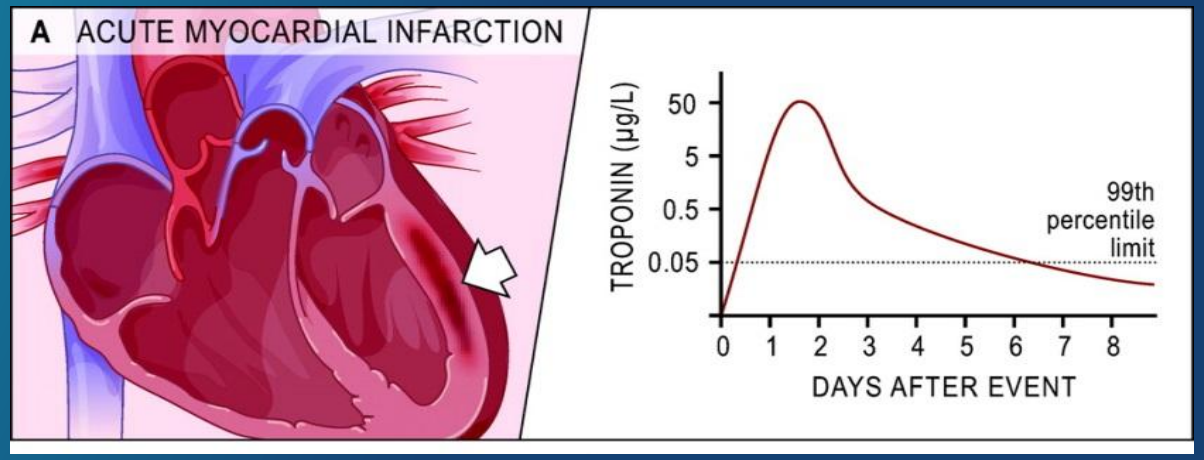
Larger elevations increase likelihood of MI

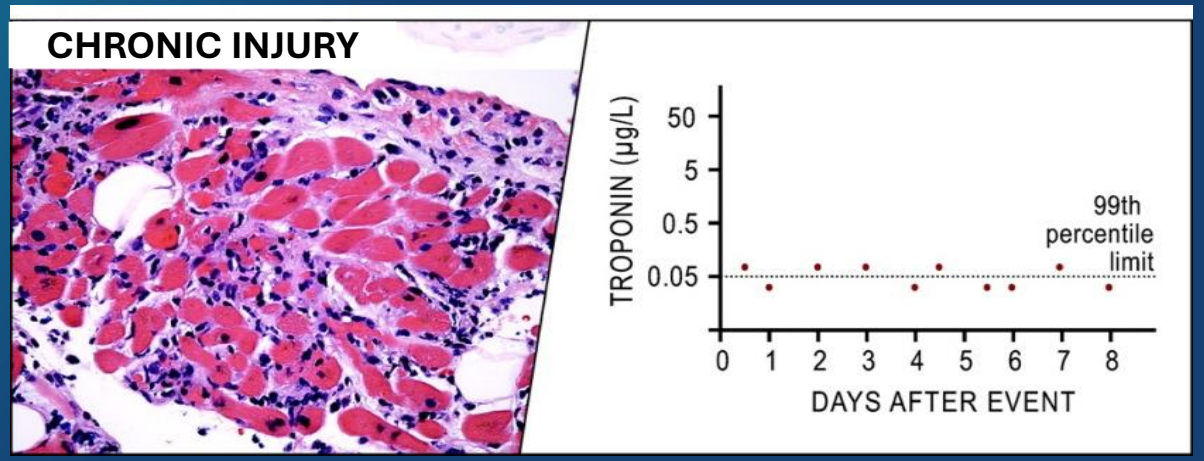


Pattern of Elevation

MI differentiated from non-ischemic cTn elevations based on:

- Pattern of elevation
- Clinical context





Hs-cTn Strategies

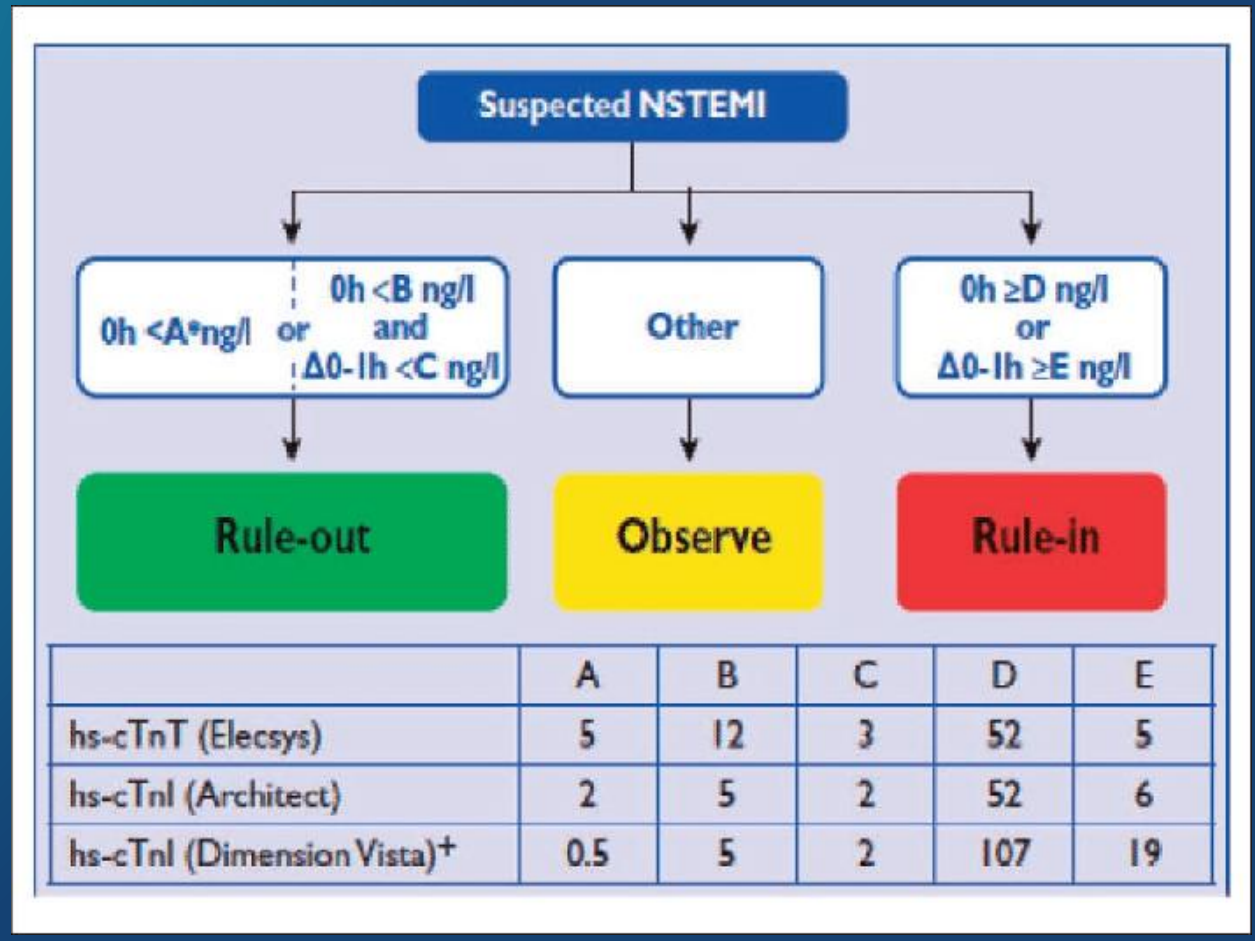
One-&-Done to exclude MI

- Onset of most recent chest pain ≥2-3 hours ago
- Single very-low hs-cTn measure

Hs-cTn Strategies

Troponin only ADPs

- Serial hs-cTn Cut Points
  - 0/1 – hour or 0/2-hour measures
- Delta (change) Cut Points

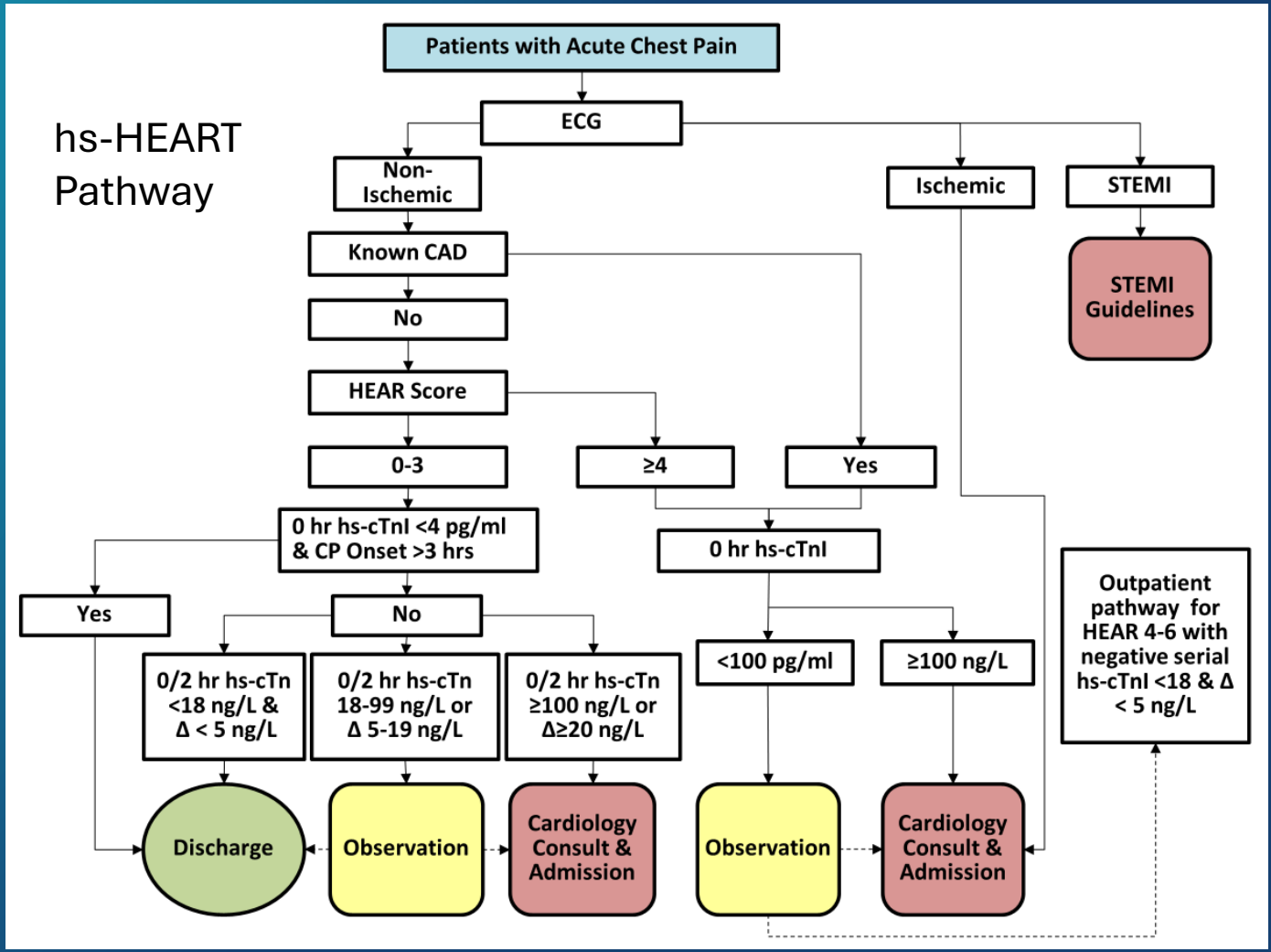


	A	B	C	D	E
hs-cTnT (Elecsys)	5	12	3	52	5
hs-cTnI (Architect)	2	5	2	52	6
hs-cTnI (Dimension Vista)+	0.5	5	2	107	19

Hs-cTn Strategies

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



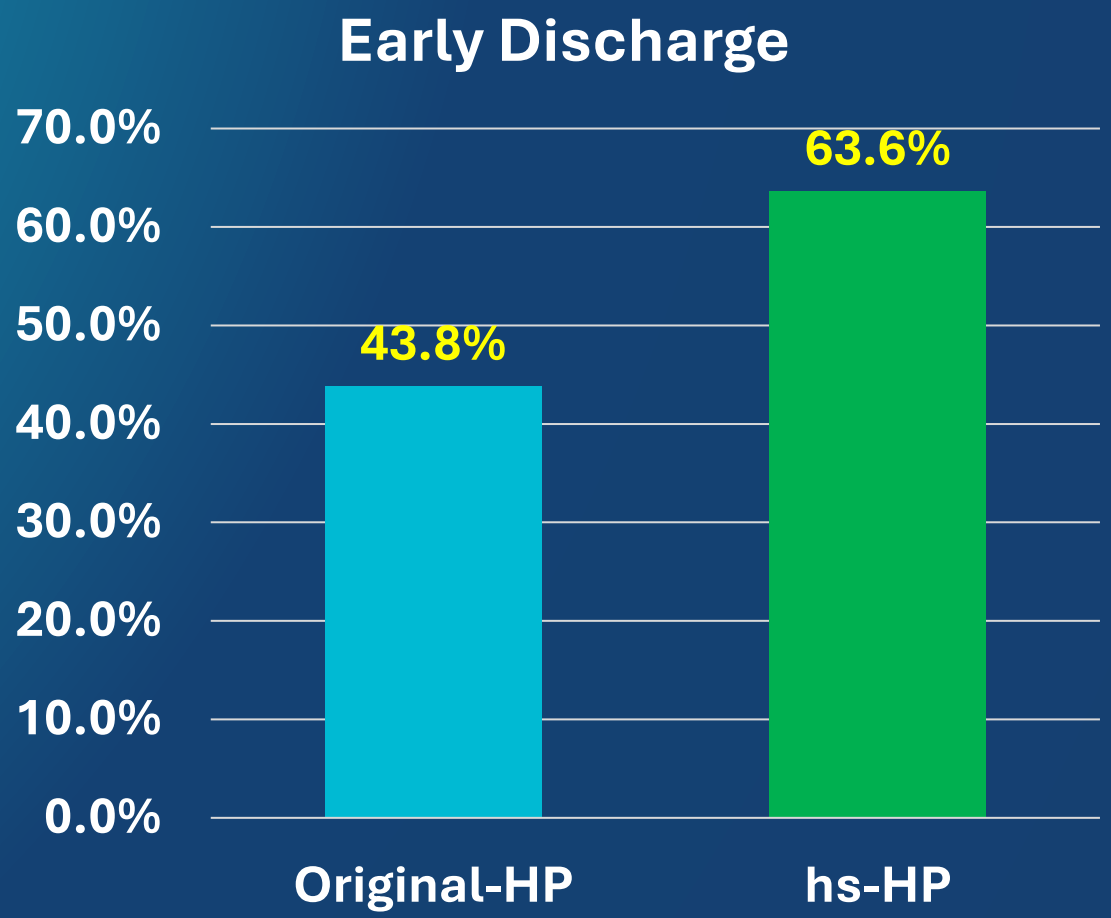
Simon A. Mahler. Circulation: Cardiovascular Quality and Outcomes. Safety and Effectiveness of the High-Sensitivity Cardiac Troponin HEART Pathway in Patients With Possible Acute Coronary Syndrome, Volume: 17, Issue: 3, Pages: e010270, DOI: (10.1161/CIRCOUTCOMES.123.010270)

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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Troponin in PE

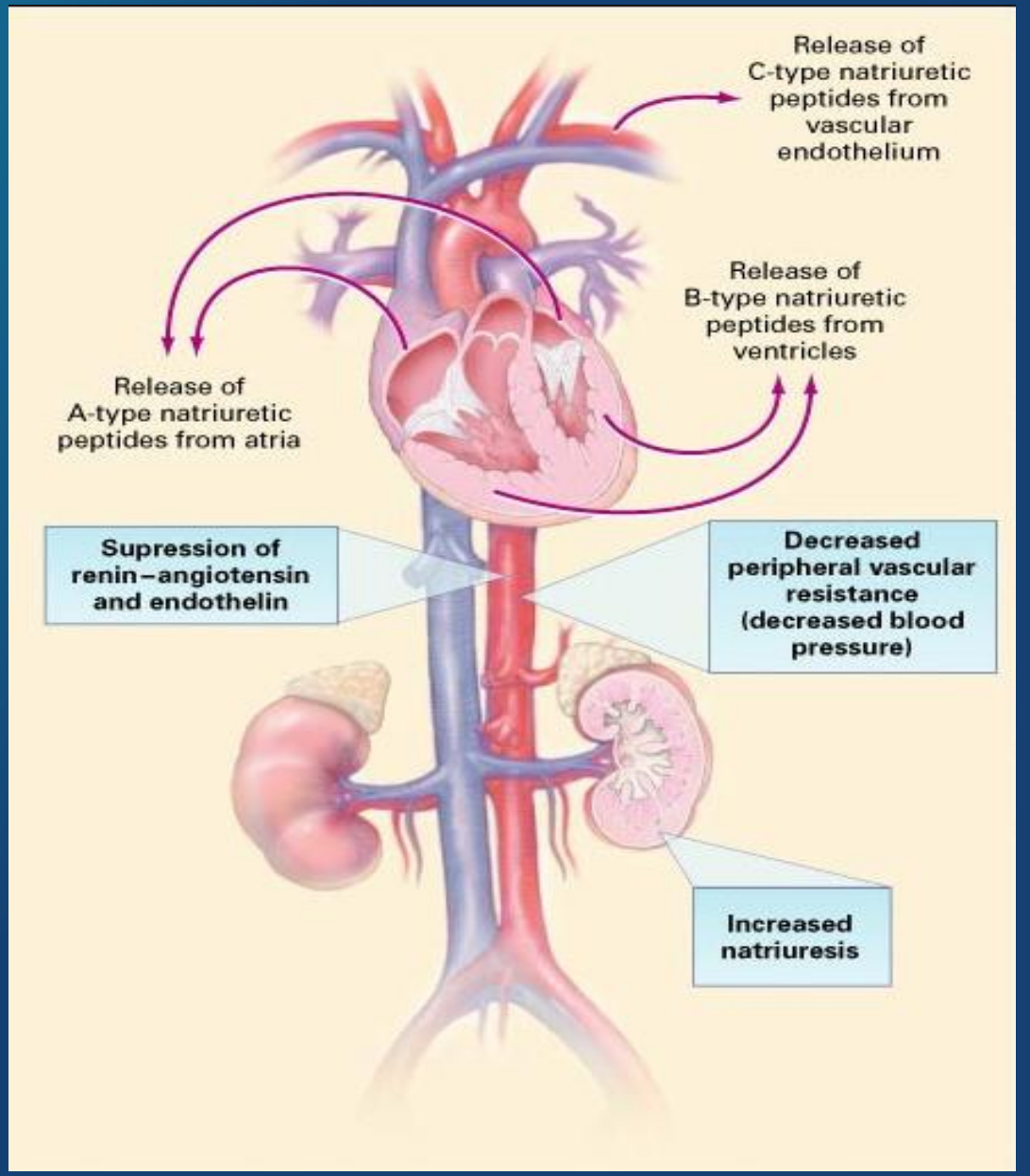
- 20-30% of PEs are associated with an elevated hs-cTn
  - Some studies up to 50% of PEs had elevated hs-cTn
- Can indicate myocardial injury from RV dysfunction
- But also seen in sub-massive PEs
- hs-cTn not currently recommended for routine assessment of PE
  - May overestimate PE severity
  - Its absence does not rule-out PE

Troponin in Aortic Dissection

- ~20% of ADs are associated with an elevated hs-cTn
  - Particularly Type-A
- Elevated hs-cTn is associated with increased in-hospital mortality
- May be useful to predict short-term risk

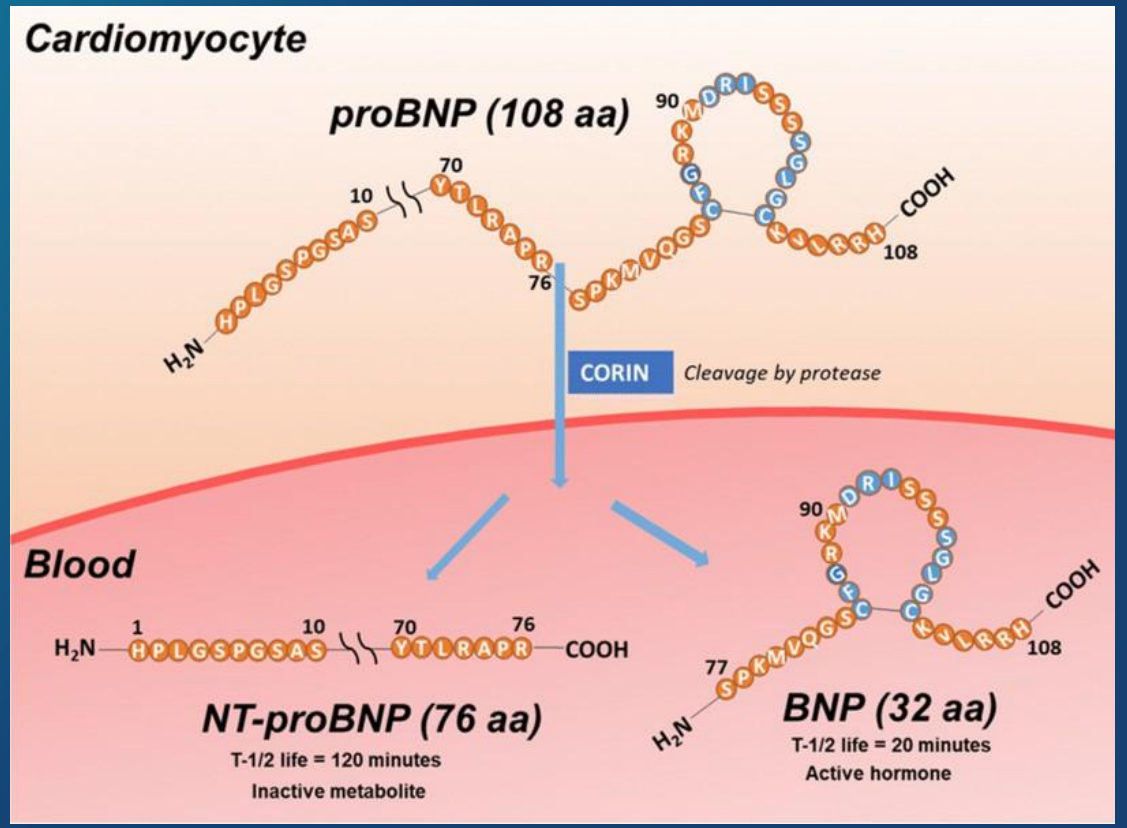
B-type Natriuretic Peptides

- Protein produced by ventricular myocardial stretch
  - Increased end-diastolic pressure and volume
- Used as a signal to reduce vascular resistance and blood volume
- The key biomarker for acute heart failure diagnosis



BNP and NT-ProBNP

- ProBNP is cleaved in into:
  - BNP
    - Active hormone
  - NT-proBNP
    - Inactive metabolite

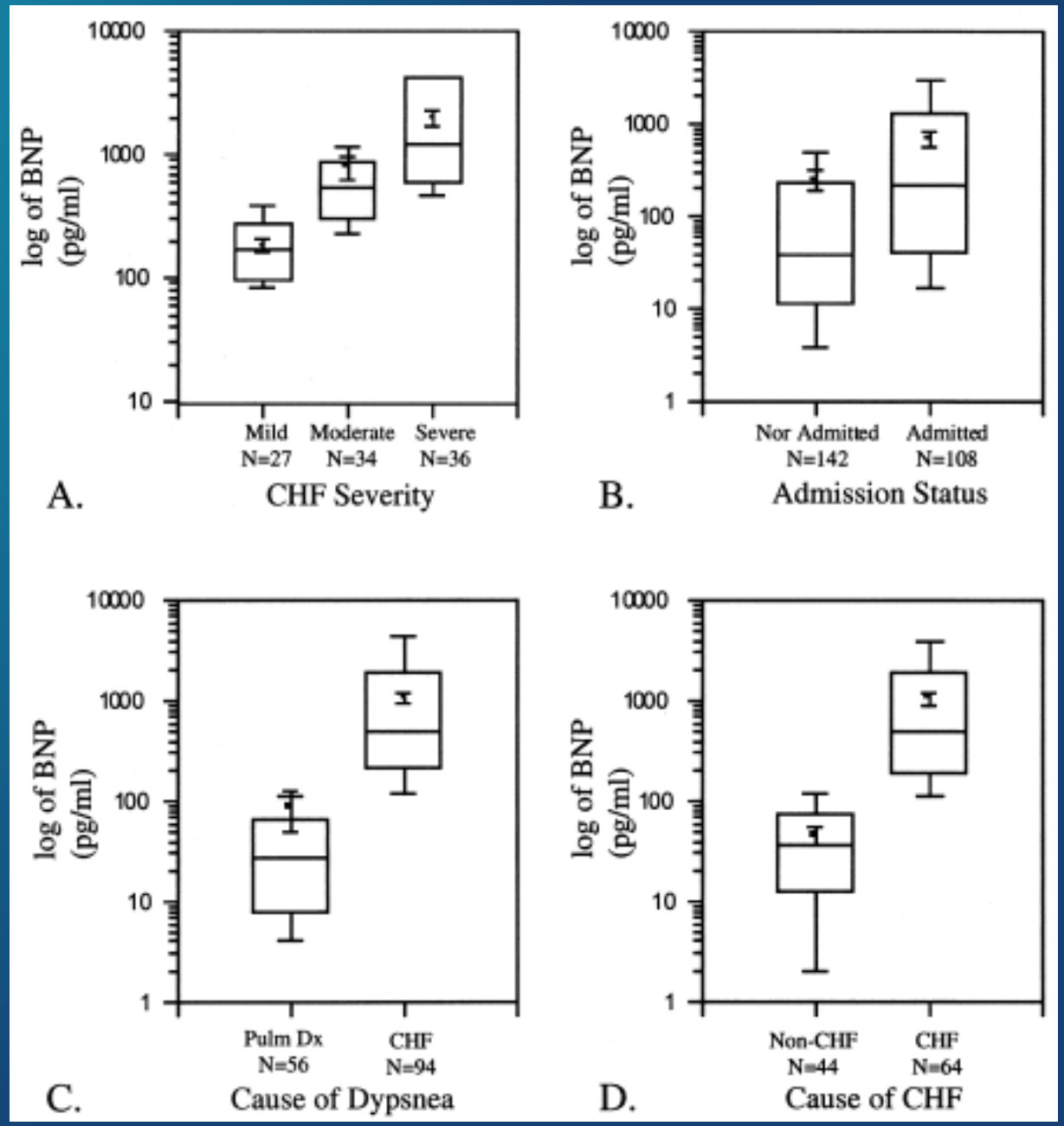


NP biological variability

- Body Mass
  - Obesity and high BMI is associated with lower BNP
  - Low BMI associated with higher BNP
- Sex
  - Women tend to have higher baseline BNP levels
- Age
  - Elderly patients have higher baseline BNP levels
- In Vitro Stability
  - NTproBNP more stable than BNP

The higher the BNP…

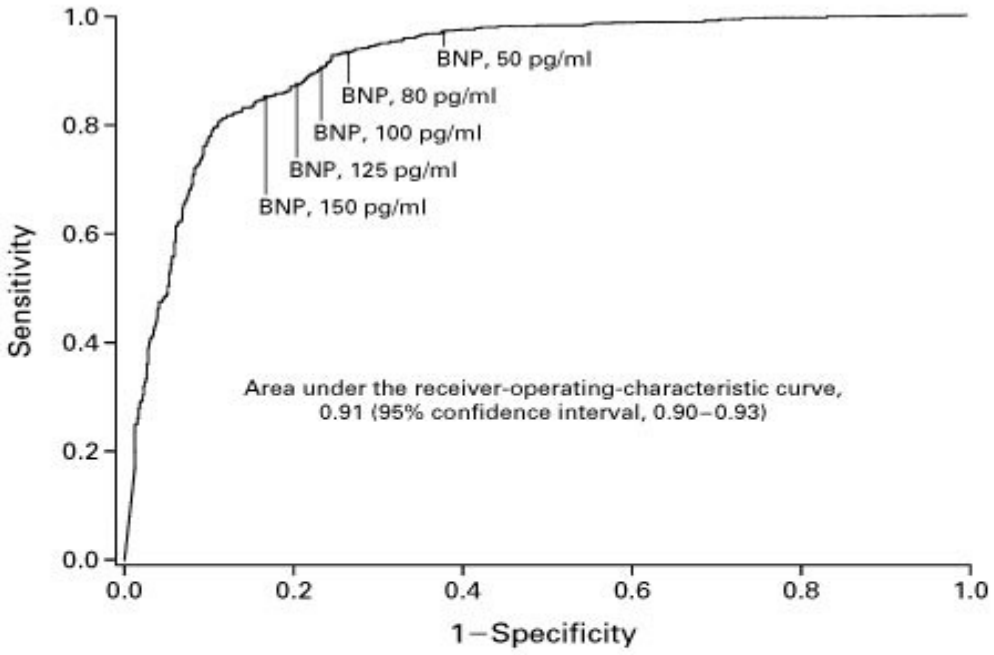
- More likely the patient has acute-HF
- Increased severity of HF
- Predicts Hospitalizations
- Prognostic of adverse events



Dao, et al., JACC, 2001

BNP Cut Points

- Established 100 pg/ml as cut point to maximize accuracy for CHF
- <100 pg/ml can be used to rule-out CHF
- >500 pg/ml has higher positive predictive value



BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
	(95 percent confidence interval)				
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–95)	74 (70–77)	77 (75–80)	92 (89–94)	83
100	90 (88–92)	76 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	85 (82–88)	83 (80–85)	83 (80–85)	85 (83–88)	84

Maisel et al, NEJM, 2002

Optimal NT-proBNP Cut-points

"Rule in"

Age strata	Optimal cut-point	Sensitivity	Specificity	PPV	NPV	Accuracy
All <50 years (n=183)	450 pg/ml	97%	93%	76%	99%	95%
All 50-75 years (n=554)	900 pg/ml	90%	82%	82%	88%	85%
All >75 years (n=519)	1800 pg/ml	85%	73%	92%	55%	83%
Overall average		92%	84%	88%	66%	93%

"Rule out"

	Optimal cut-point	Sensitivity	Specificity	PPV	NPV	Accuracy
Rule out	300 pg/ml	99%	62%	55%	99%	83%

A Maisel, et al EJHF 2014

PRIDE score

Predictor	Points
Elevated NT-Pro-BNP	4
Interstitial Edema on Chest X-Ray	2
Orthopnea	2
No Fever	2
Loop Diuretic Use	1
Age >75 Years	1
Rales	1
No Cough	1

A score of 0-5 has a low likelihood of acute heart failure

A score of 9-14 has a high likelihood of acute heart failure

Baggish et al, AHJ, 2006

NT-proBNP/BNP in ACS

- Often elevated in patients with acute MI
  - BNP level related to infarct size and ventricular dysfunction
  - BNP as a prognostic marker for patients with ACS
    - Mortality
    - Onset of HF
- BNP+hs-cTn vs hs-cTn alone
  - Small incremental improvement in diagnostic accuracy for ACS
  - Negative BNP + negative hs-cTn increases negative predictive value

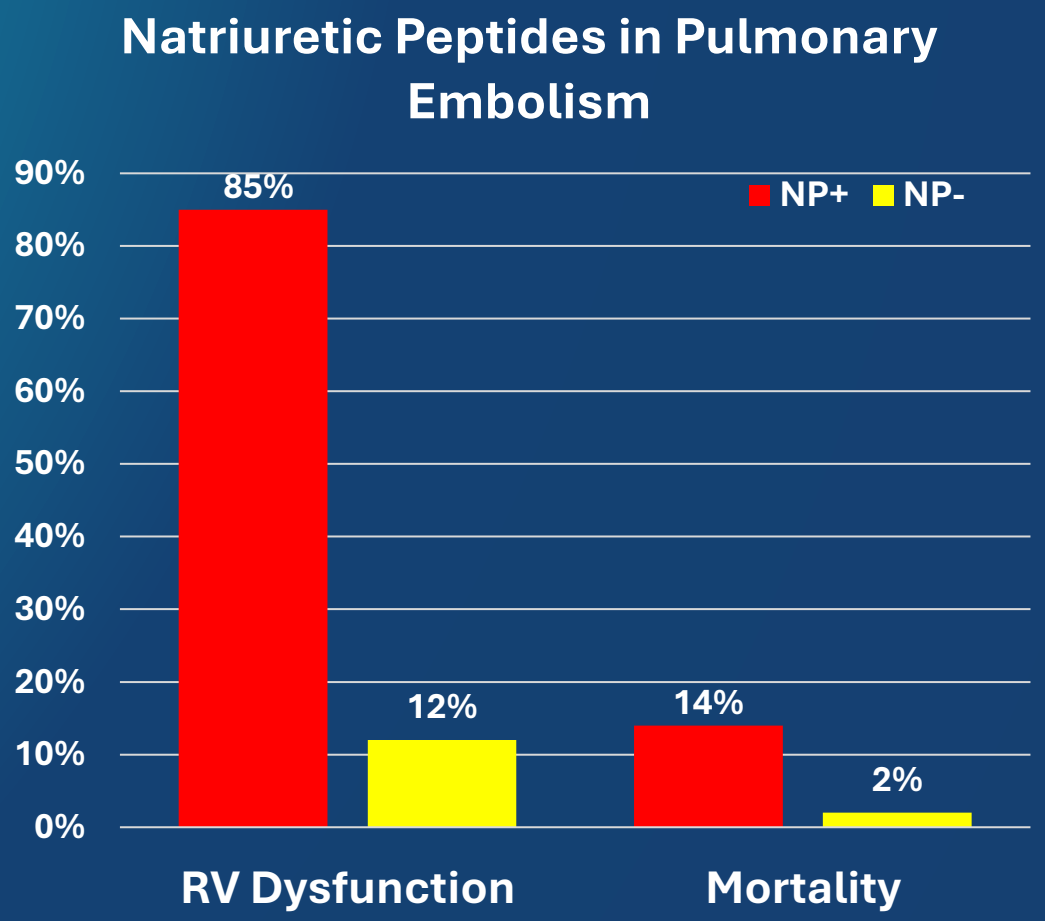
NTproBNP/BNP & Mild hs-cTn Elevations

- CHF is common cause of mild hs-cTn elevation
- BNP elevation increases likelihood of:
  - Chronic myocardial injury
  - Type 2 MI
- Patients with CHF and increased hs-cTn have increased mortality

Biomarker Utility	Troponin for ACS	Troponin for AHF
Sensitive or specific	+++	0
Reflects abnormal physiology	+++	+
Prognostic but clinically actionable?	+++	+
Used for ‘biomarker guided therapy’	+++	+
Bio-monitoring during therapy as surrogate of improvement	+++	0

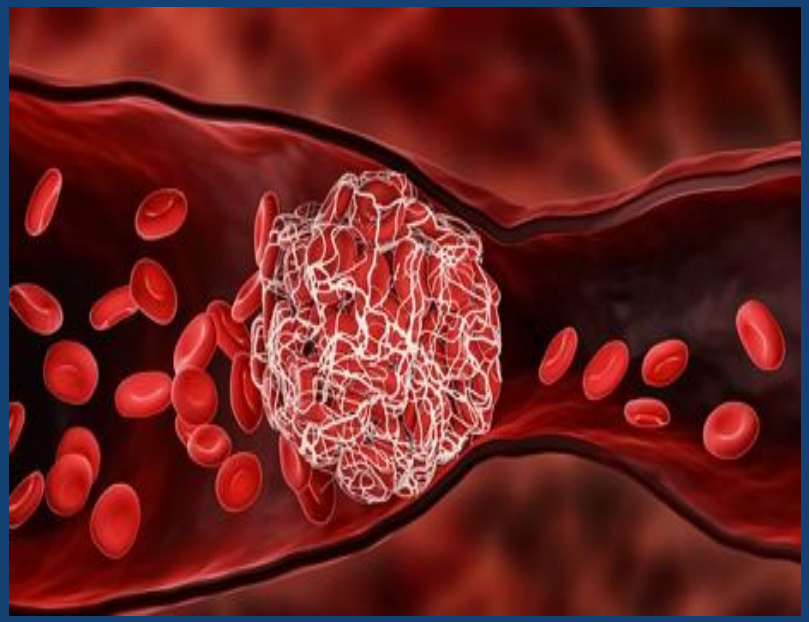
NTproBNP/BNP in PE

- Meta-analysis of 13 studies; 1,132 patients with PE
- 51% had elevated BNP or NT-proBNP
- Mortality 12% higher among patients with elevated NP
- RV dysfunction 73% higher in patients with elevated NP



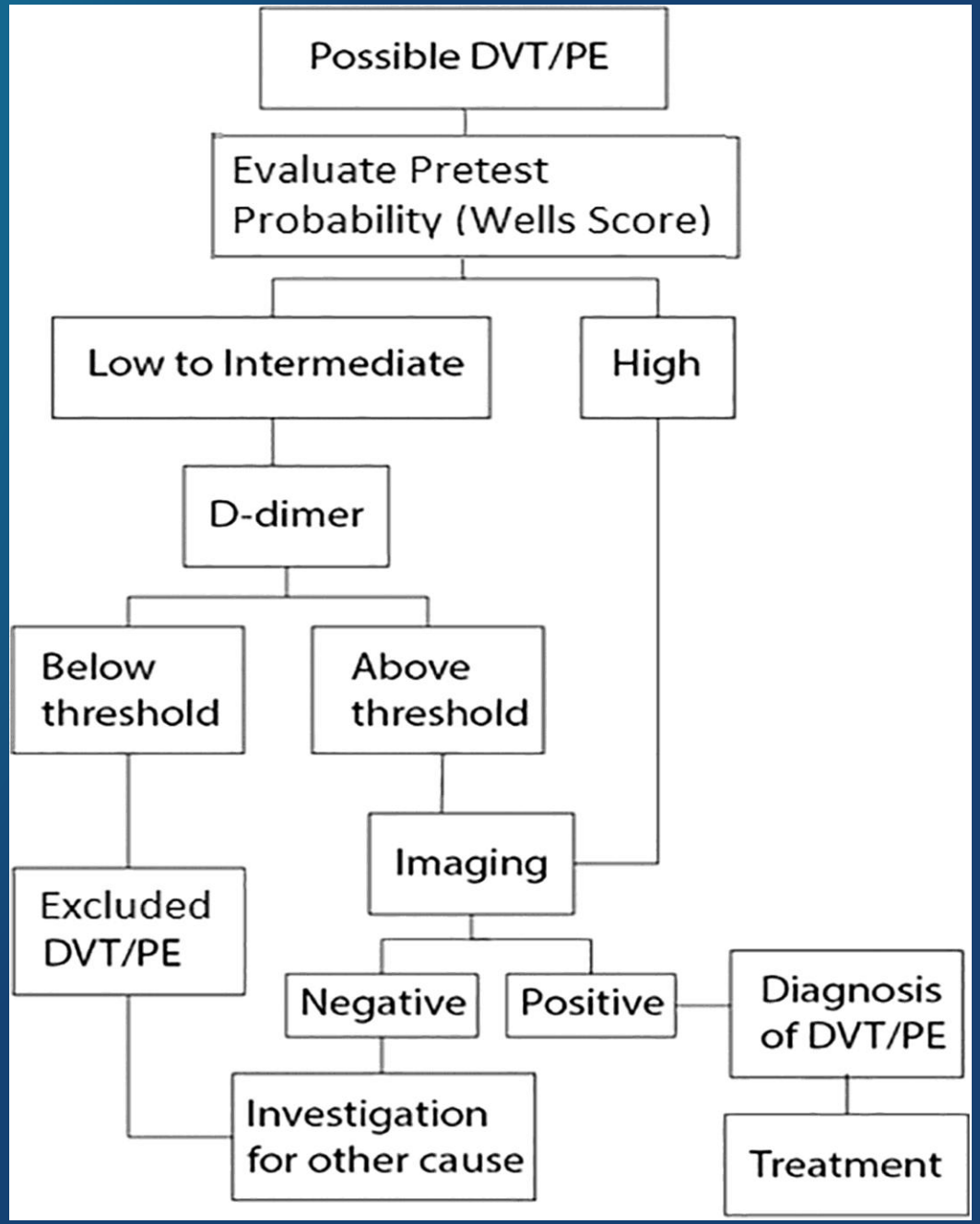
D-dimer

- Fibrin degradation product
- Clinical utility in PE and DVT Exclusion
- Acute Phase Reactant
  - Non-Specific



D-dimer for PE Exclusion

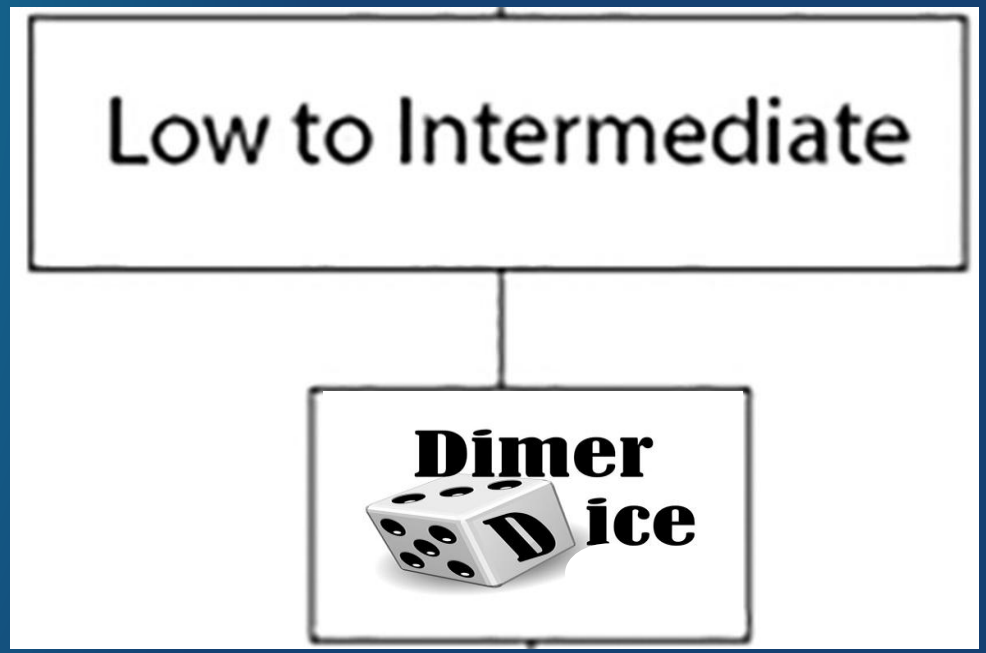
- Useful in patients with low to intermediate pre-test probability
  - <2% post-test probability of PE
- Unable to exclude PE in patients at high pre-test probability
- Positive D-Dimer does not rule-in PE



Non-Specific D-Dimer Elevations

- Age
- Inflammation
- Surgery
- Trauma
- Burns
- Aortic Dissection
- Malignancy
- Infection/Sepsis
- DIC
- Pregnancy
- Liver Disease
- Renal Disease
- Thrombolytic Therapy

Rolling the Dice



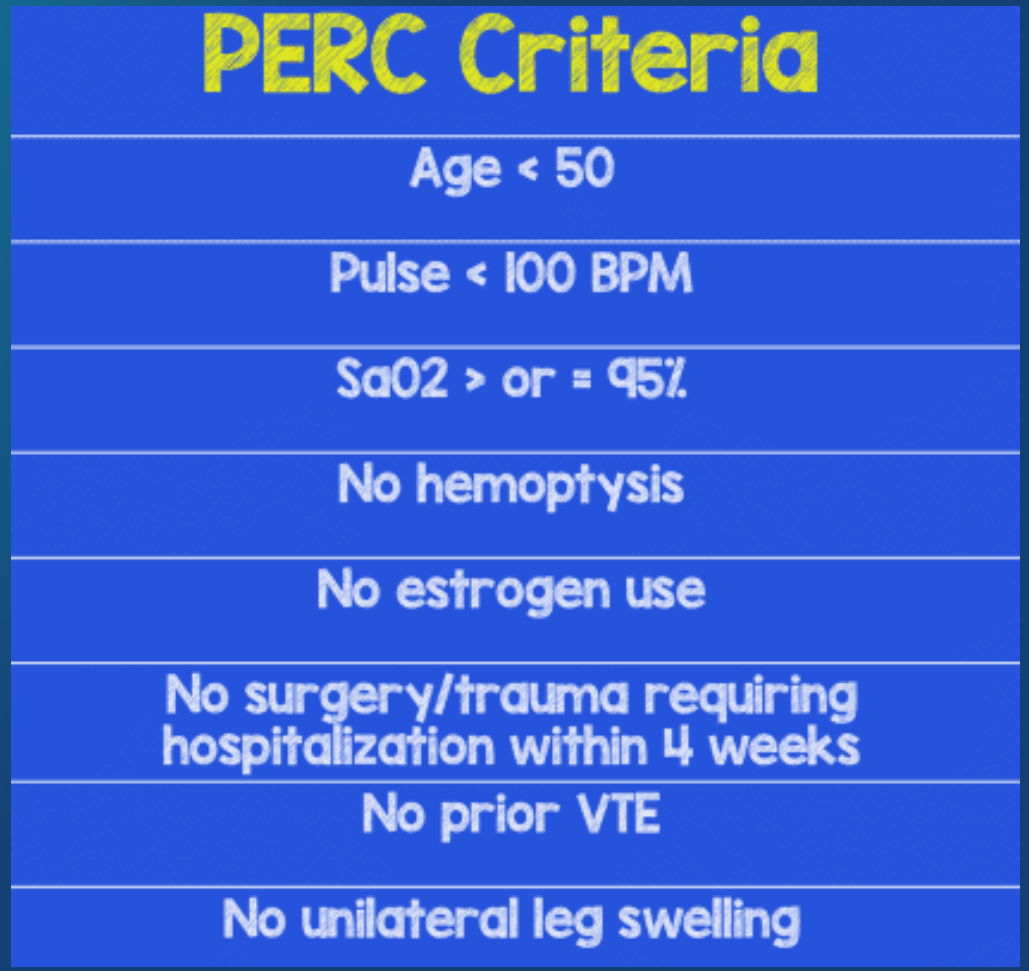
Negative D-Dimer → Exclude PE without CT imaging

Positive D-Dimer → Order CTA for PE

Pulmonary Embolism Rule Out Criteria (PERC)

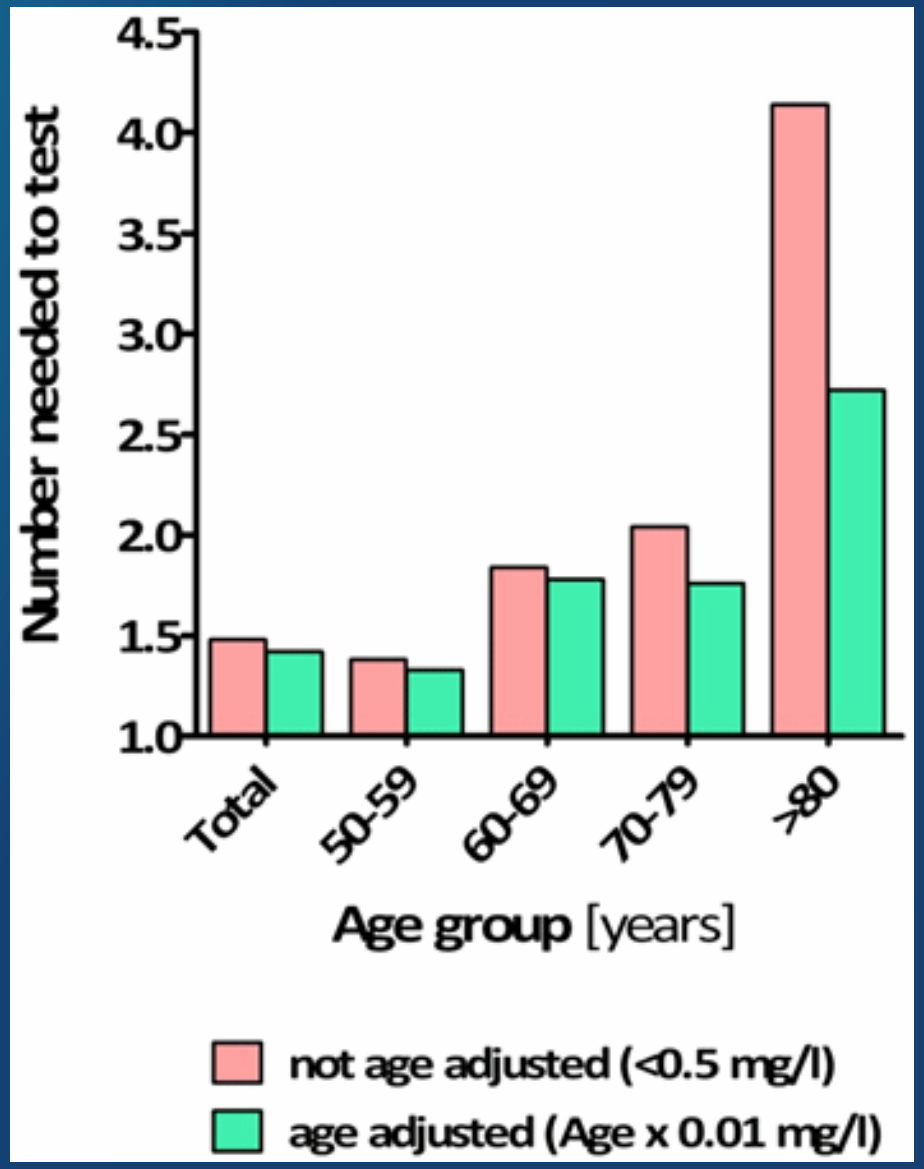
PROPER trial

- 1916 patients
- 0.1% prevalence of PE In PERC negative patients
- Can exclude PE in low probability patients without D-dimer testing
- Reduces CT imaging



Age Adjustment

- For Patients ≤50 y.o. the standard threshold is used
  - 500 ng/ml for most assays
- For Patients >50 the D-dimer threshold is the patient's age x 10
  - Example 650 ng/ml for a 65 y.o.

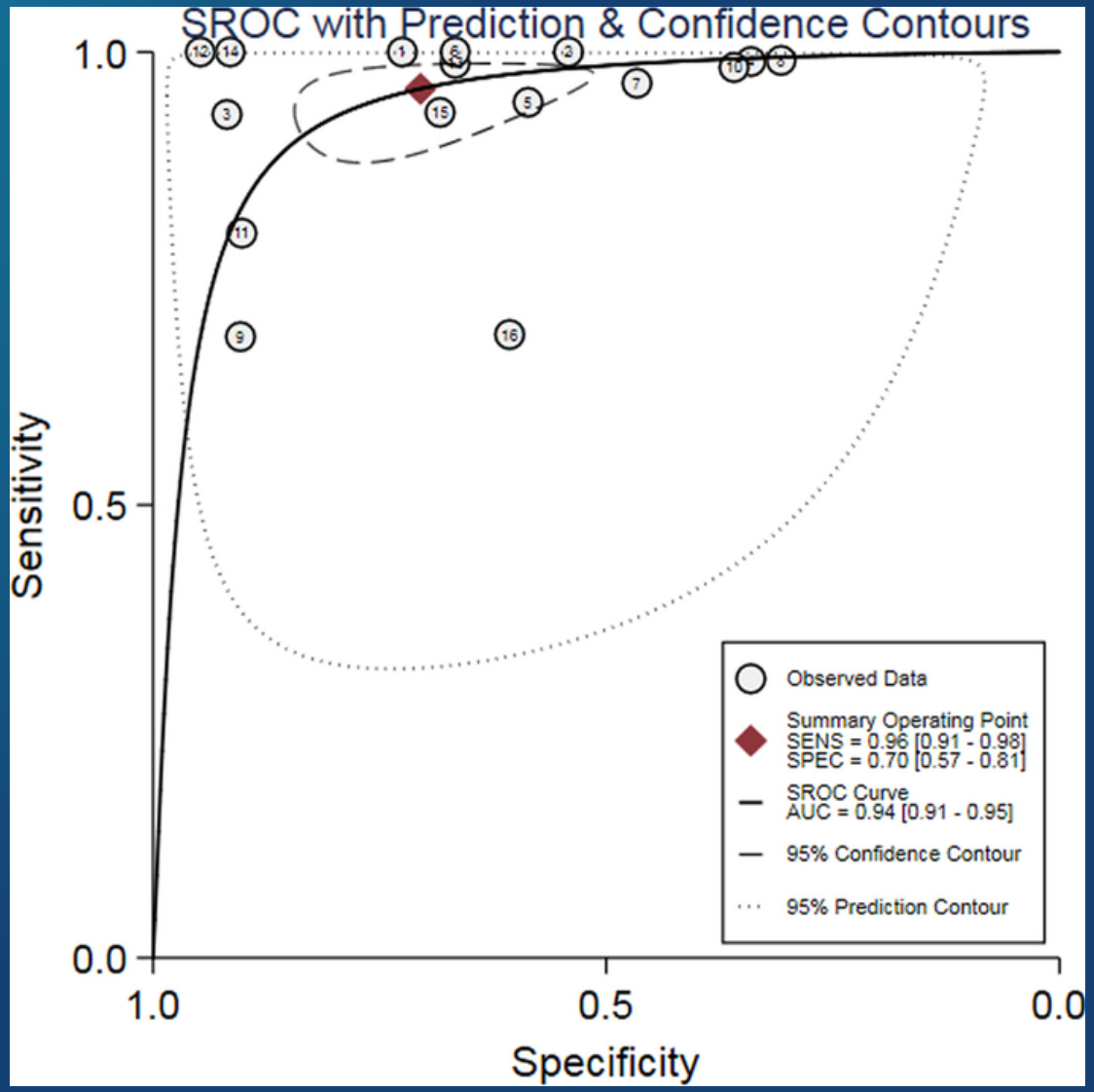


D-dimer in Aortic Dissection

- Most patients with AD have an elevated D-dimer
- May be helpful in excluding AD particularly in patients with low pretest probability
- A negative D-dimer does NOT definitively rule-out dissection
  - Small or early dissections
  - Dissections without significant clot formation

D-dimer in Aortic Dissection

- Meta-Analysis
- 16 Studies 1135 patients
- Pooled sensitivity of 96%
- -LR of 0.06
- AUC of 0.94



Guidelines: D-dimer in Aortic Dissection

- ACEP: “in patients with suspected nontraumatic aortic dissection, do not rely on D-dimer alone to exclude the diagnosis of aortic dissection”
- ACC/AHA: ‘in patients with low probability of acute aortic syndromes [AD and other life-threatening aortic wall disruptions] a non-elevated D-dimer (<500 ng/mL) makes the diagnosis unlikely.’

Aortic Dissection Detection Risk Score (ADDRS)

Nazerian et al.,

- Cohort study
- 6 Sites (Europe & Brazil)
- 1850 patients w/ concern for AD
- 7% had AD
- D-dimer had NPV of 99.2%
- D-dimer & ADDRS= 0 yielded an NPV of 99.7%

Predisposing Conditions	Pain Features	Physical Exam Findings
Marfan Syndrome	Abrupt Onset of Pain	Pulse Deficit or SBP Differential
Family History of Aortic Disease	Severe Pain Intensity	Focal Neurological Deficit + Pain
Known Aortic Valve Disease	Ripping or Tearing Pain	New Aortic Insufficiency Murmur + Pain
Recent Aortic Manipulation		Hypotension/Shock State
Known Thoracic Aortic Aneurysm		
If positive in any column, then add one point		

Point-of-Care

“laboratory testing conducted close to the site of patient care”

Handheld

Desktop

Point-of-Care vs Central Laboratory Cardiac Biomarkers

PROs

- Rapid Turnaround Time
- Ideal for Bedside or Stat-Lab Use
- Time to Disposition

CONs

- Analytical Sensitivity
- Cost

Point-of-Care vs Central Laboratory Cardiac Biomarkers

PROs

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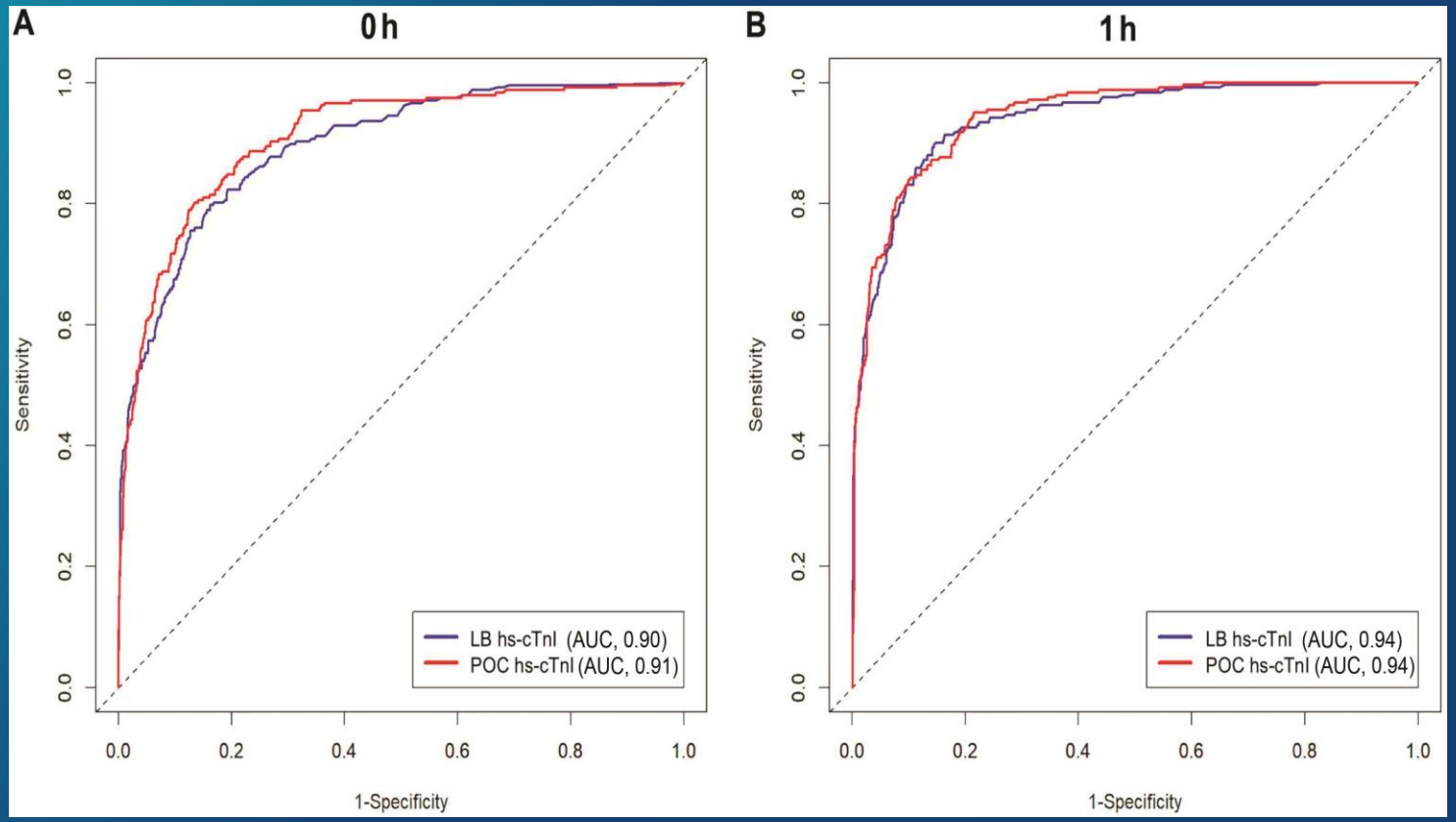
POC high sensitivity troponin

- Analytical Sensitivity Equivalent to Central Laboratory
  - Compatible with recommended hs-cTn strategies
- Polymedco Pathfast – first FDA approved
- Abbott i-Stat recently approved

Similar Analytical Performance to Central Lab hs-cTnI

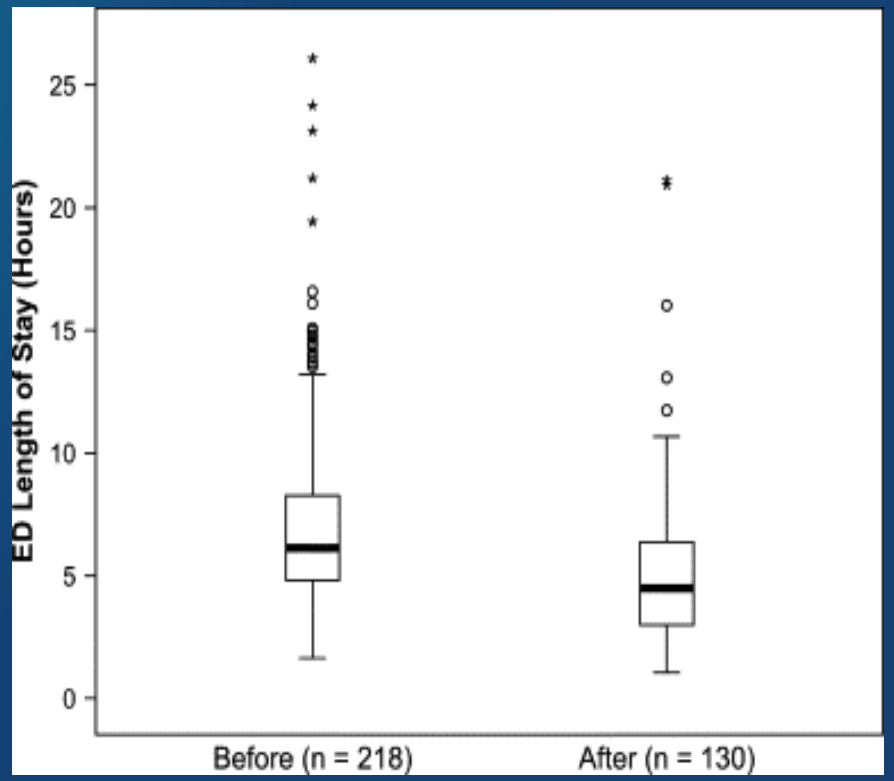
- Comparison of Pathfast hs-cTnI to central lab hs-cTn (Abbott)
- >1200 patients
- High correlation r=0.96
- AUC similar for NSTEMI



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

Reduced Length of Stay
The Promise of POC Troponin

- Pre-post study in suburban US ED with 75k annual volume
- 218 patients pre-implementation
- 130 patients post-implementation
- Mean reduction of 1.9 hours for ED length of stay
- Similar study of 369 ED patients in Boston - 41 minute mean ED LOS reduction



Singer et al., Annals of Emerg Med, 2005

Lee-Landrowski et al., Arch Pathol Lab Medicine, 2003

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

Potential Impact on Overcrowding

- 15-minute reduction in median LOS
- Extrapolated across the 14,000 annual chest pain ED visits
  - 3,500 open bed hours per year
  - Increases ED capacity by ~700 patients per year

Polymedco Pathfast

- hs-cTnI, NT-proBNP, & D-dimer tests
- Can run up to 6 samples simultaneously

hs-cTnI

- 6%CV at 99th percentile of 29 ng/L
- Reportable to 4 ng/L
- 66% of patients with detectable results
- 17-minute turnaround time

Abbott i-STAT

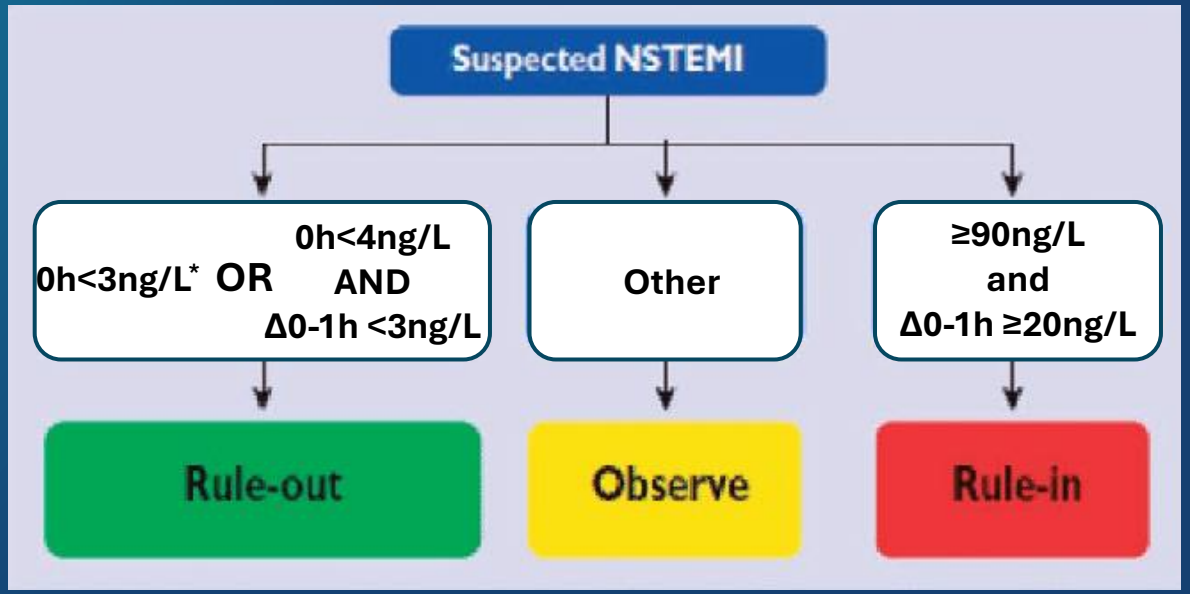
- Includes hs-cTnI and BNP
- Does not include D-dimer

hs-cTnI

- 10%CV at 7 ng/L
- 99th Percentile URL: 13 ng/L Female, 28 ng/L Male
- Reportable to 3 ng/L (LoQ)
- >50% of patients with detectable results
- 15-minute turnaround time
- Available for use with i-STAT 1

Implementation of POC hs-cTn: Algorithms

- 0/1-h algorithm for Pathfast hs-cTn
- Derived in 669 patients
- Validated in 610 patients
- Ruled-Out 48%
  - NPV of 99.7% for NSTEMI
- Ruled-in 14.6%
  - PPV of 86.5% for NSTEMI

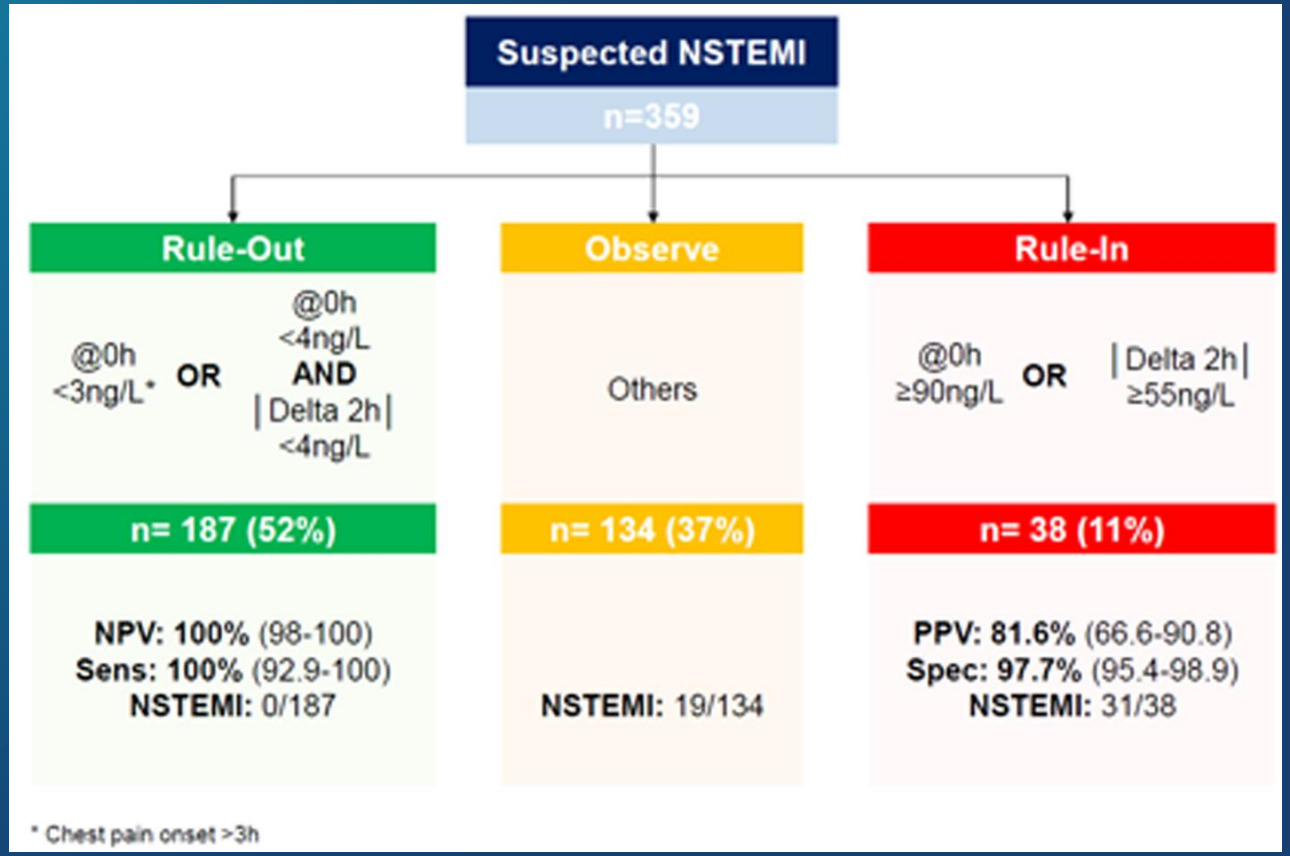


*chest pain >3 hours

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

Implementation of POC hs-cTn: Algorithms

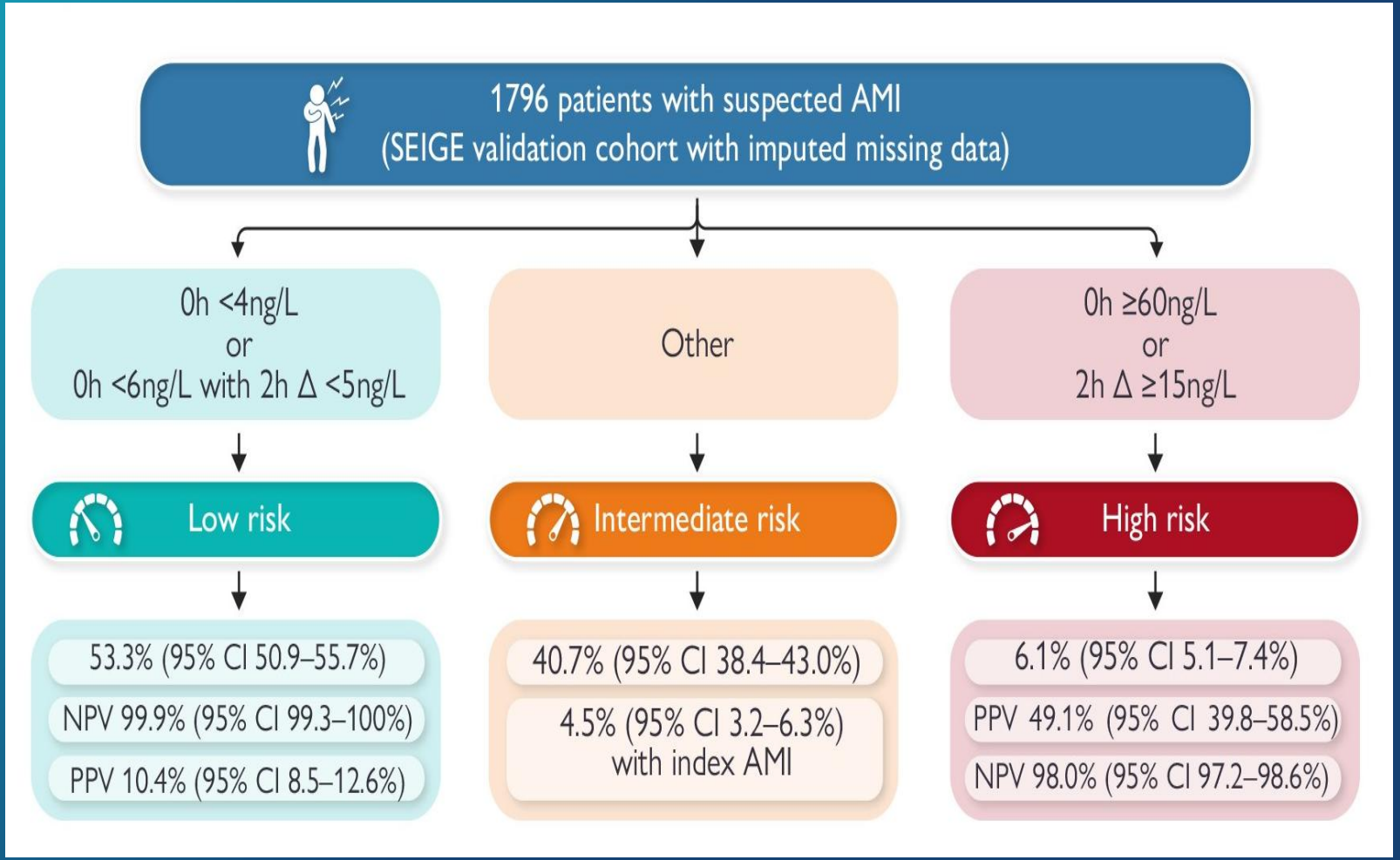
- 0/2-h algorithm for Pathfast hs-cTn
- Derived in 848 patients
- Validated in 359 patients
- Ruled-Out 52%
  - NPV of 100% for NSTEMI
- Ruled-in 11%
  - PPV of 81.6% for NSTEMI



Koechlin L, Boeddinghaus J, Lopez-Ayala P, et al. External validation of the 0/1h-algorithm and derivation of a 0/2h-algorithm using a new point-of-care Hs-cTnI assay. *Am Heart J.* 2024;268:104-113. doi:10.1016/j.ahj.2023.11.014

Other POC hs-cTnI Assay Algorithms

- 0/2-h algorithm for Siemens VTLI POC hs-cTn
- Derived in 1486 Australian patients
- Validated in 1756 USA patients



Eur Heart J, Volume 45, Issue 28, 21 July 2024, Pages 2508–2515, https://doi.org/10.1093/eurheartj/ehae343

Implementation of POC biomarkers: Logistics

Desktop Devices

- Ideal for Stat Laboratory testing
- Staffing
  - Trained Lab Technicians
  - Moderate Complexity CLIA
- Number of Devices
  - ED volume dependent

Handheld Devices

- Ideal for bedside testing
- Staffing
  - Nurses/paramedics
  - Dedicated staff?
  - Laboratory oversight for CLIA requirements
- Multiple Devices
  - ED volume dependent

Implementation of POC hs-cTn: Logistics

Multidisciplinary Implementation Committee

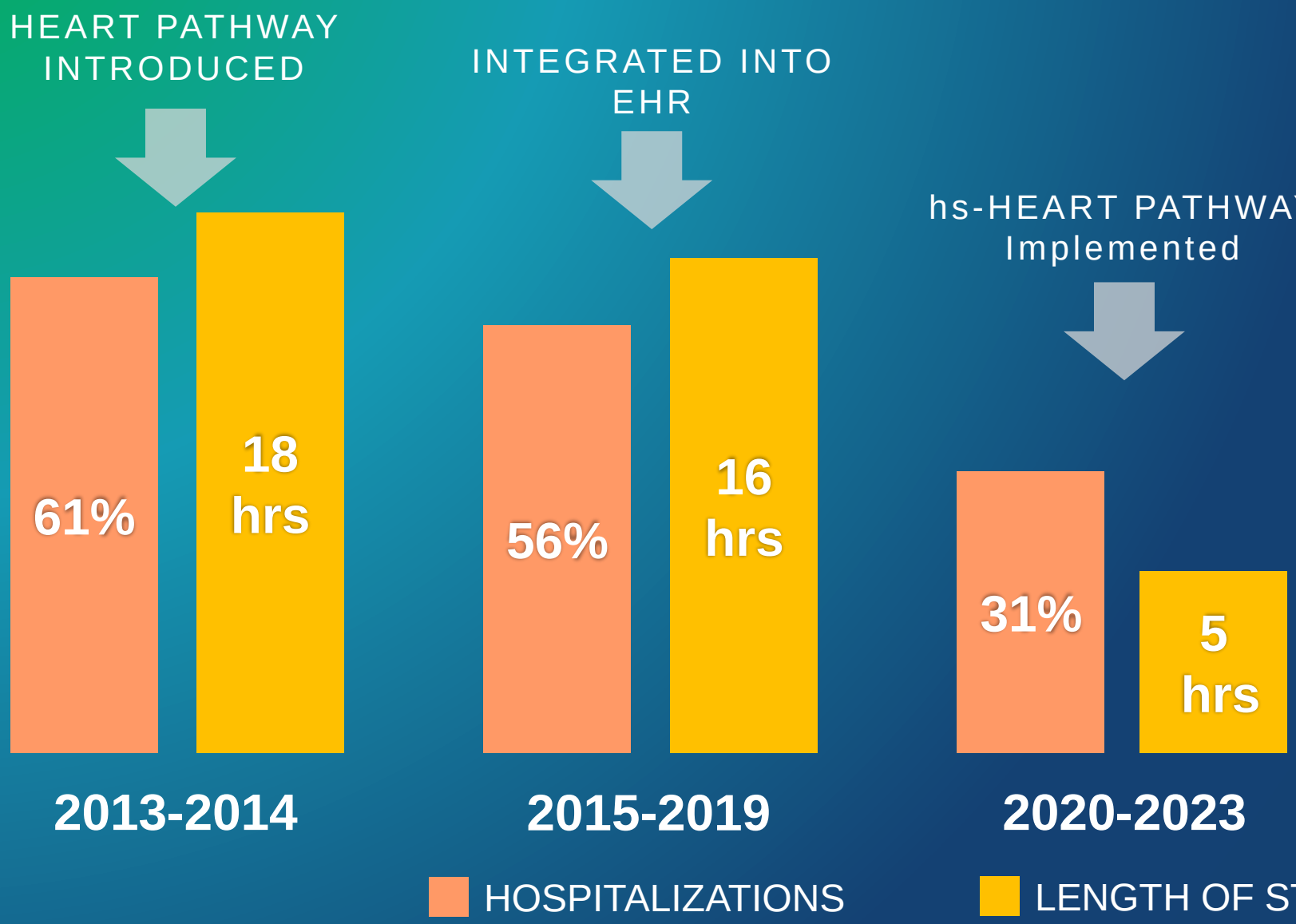
- Interdisciplinary
  - Emergency Medicine, Laboratory Medicine, Cardiology, Hospitalists, Primary Care
- Interprofessional
  - Physicians, Nurses, APCs

The Promise of

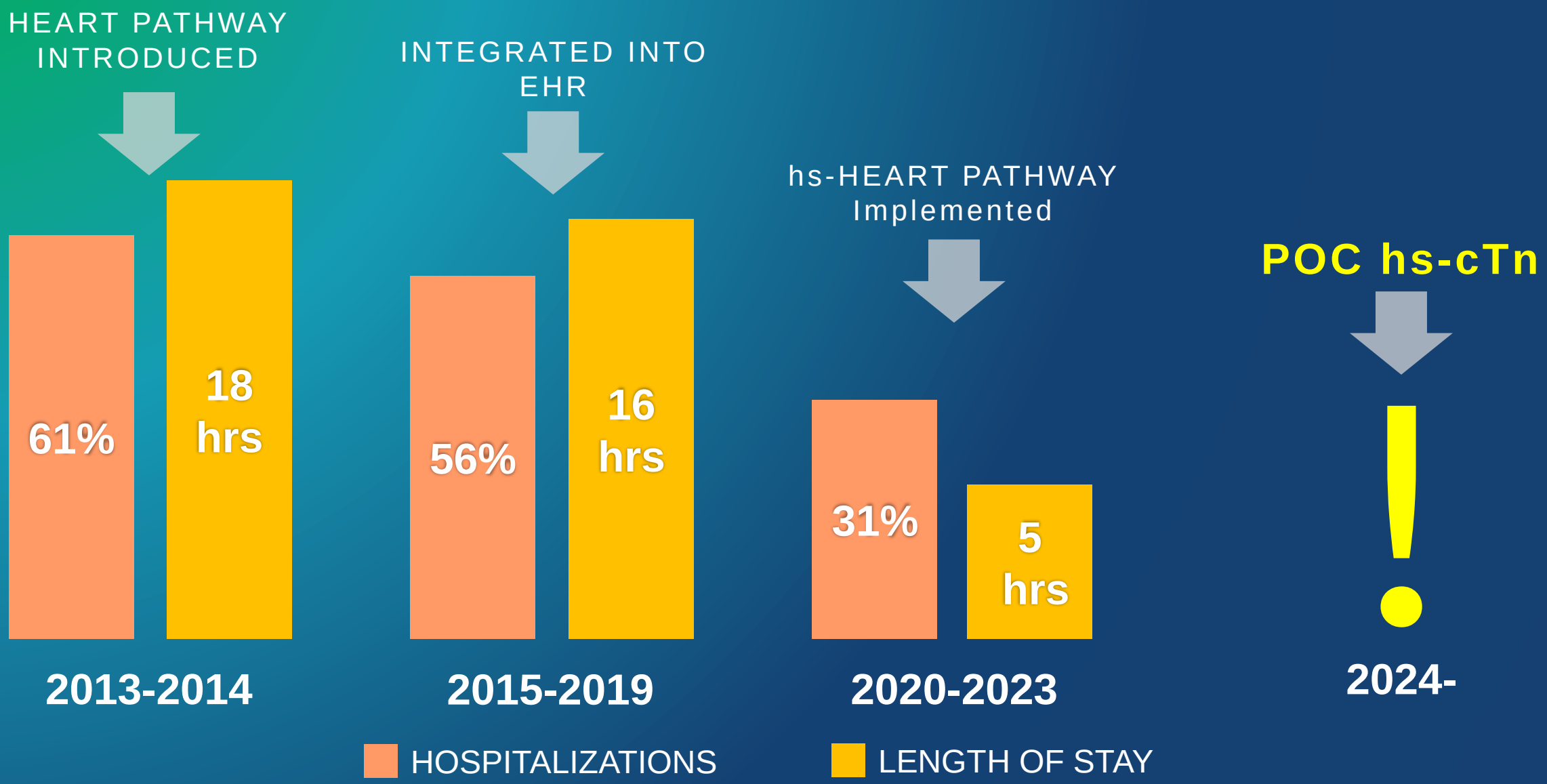
POC Cardiovascular biomarkers

- Safe ✓
- Accurate ✓
- Fast ✓
- Easy ✓

Improvements in Chest Pain Care



Improvements in Chest Pain Care



Summary

- Current chest pain care has over- and under-testing for the big 3
- Troponin is the primary biochemical test for ACS evaluation
- BNP is useful in HF diagnosis and the prognosis of ACS and PE
- D-dimer can exclude PE in low to intermediate risk patients

Summary

- POC cardiovascular biomarkers
  - As analytically sensitive as central laboratory assays
  - Can be used in rapid ADPs
  - Decreases time to results (turnround time)

- POC testing has the potential to safely reduce ED length of stay and reduce overcrowding