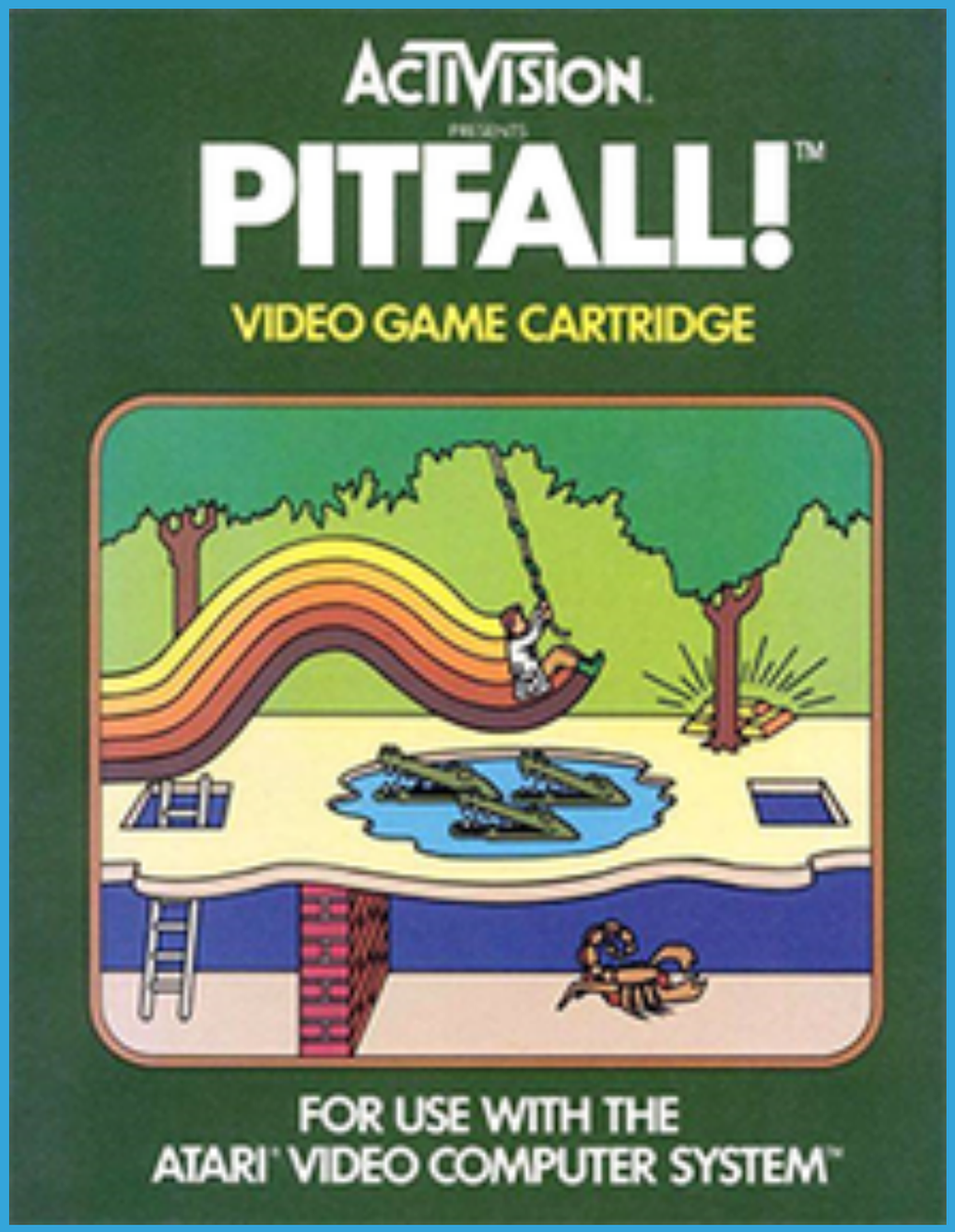
A SISYPHEAN PURSUIT OF ZERO PERCENT MISS RATE FOR ACS

HIGH SENSITIVITY (LOW SPECIFICITY) TROPONIN

OBJECTIVES

- Discuss analytic characteristics of high sensitivity troponin assays
- Apply Bayesian Principles when interpreting these diagnostic tests
- Predict the 30 day probability of MACE for ED patients with acute chest pain
- Incorporate high sensitivity troponin assays into clinical decision making and implement safe and efficient accelerated diagnostic protocols



IMPORTANCE

Enthusiasm exists among cardiologists to start using these assays to rule out AMI and discharge patients directly from the ED

SO WHAT'S THE ISSUE?

The "Imminent Plague of Troponinitis" that is doomed to afflict ED's in the United States

INDISCRIMINATE USE WILL LEAD TO FURTHER INVASIVE TESTING, UNNECESSARY ADMISSIONS, INCREASED ED LENGTH OF STAYS, AND PATIENT MORBIDITY

EP's should only order testing if clinically concerned

WHAT IS THE DEFINITION OF "HIGH SENSITIVITY TROPONIN?"

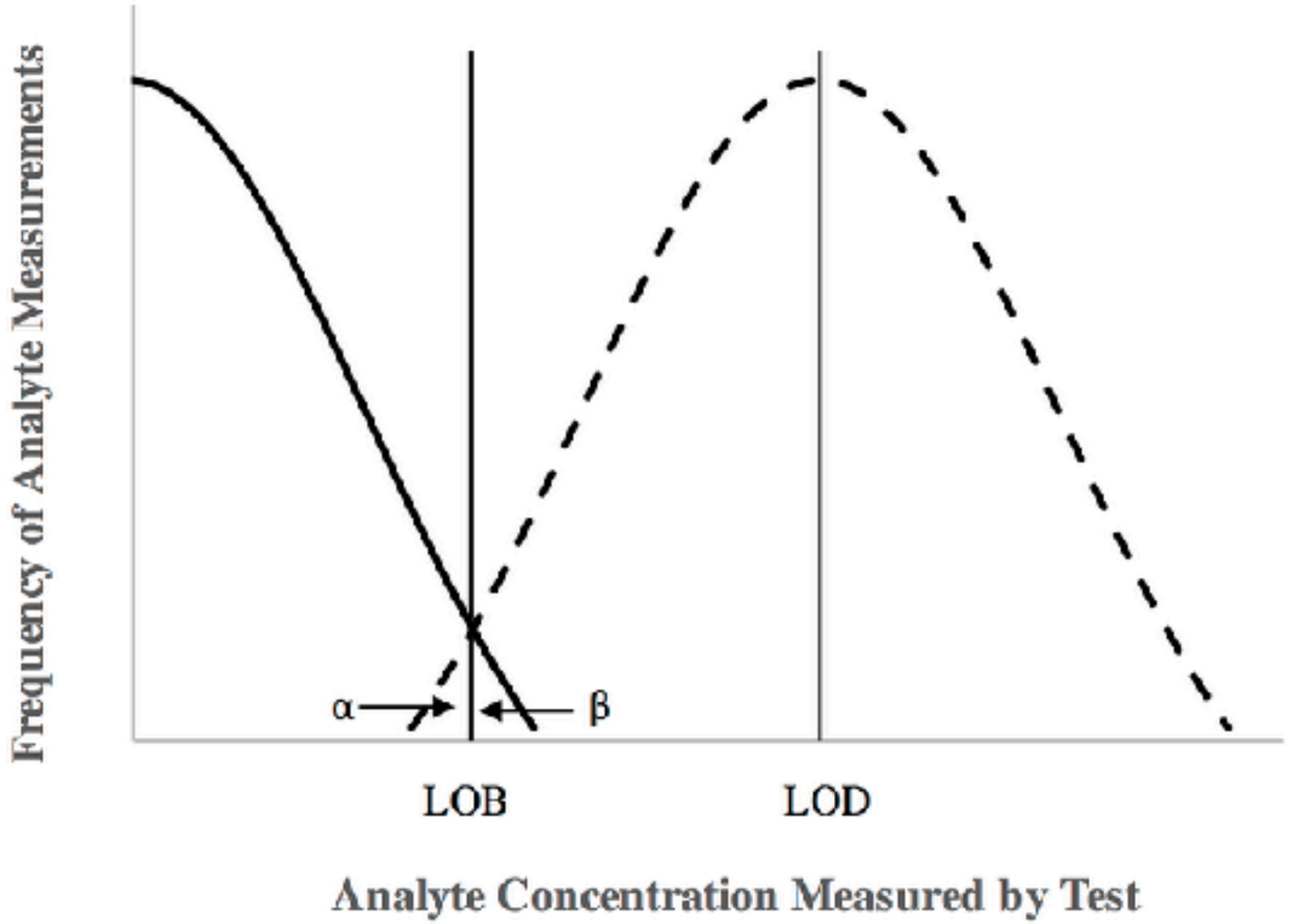
The assay can detect the presence of circulating cardiac biomarkers in 50% of **healthy** individuals

ANALYTIC CHARACTERISTICS 101 FOR EMERGENCY PHYSICIANS

- Sorry…we must talk about these to understand how to interpret the results of the assay
  - Limit of Blank (LOB)
  - Limit of Detection (LOD)
  - 99th percentile upper reference limit (URL)
  - Coefficient of variation (precision)

LIMIT OF BLANK

Theoretically, a sample with zero troponin in it

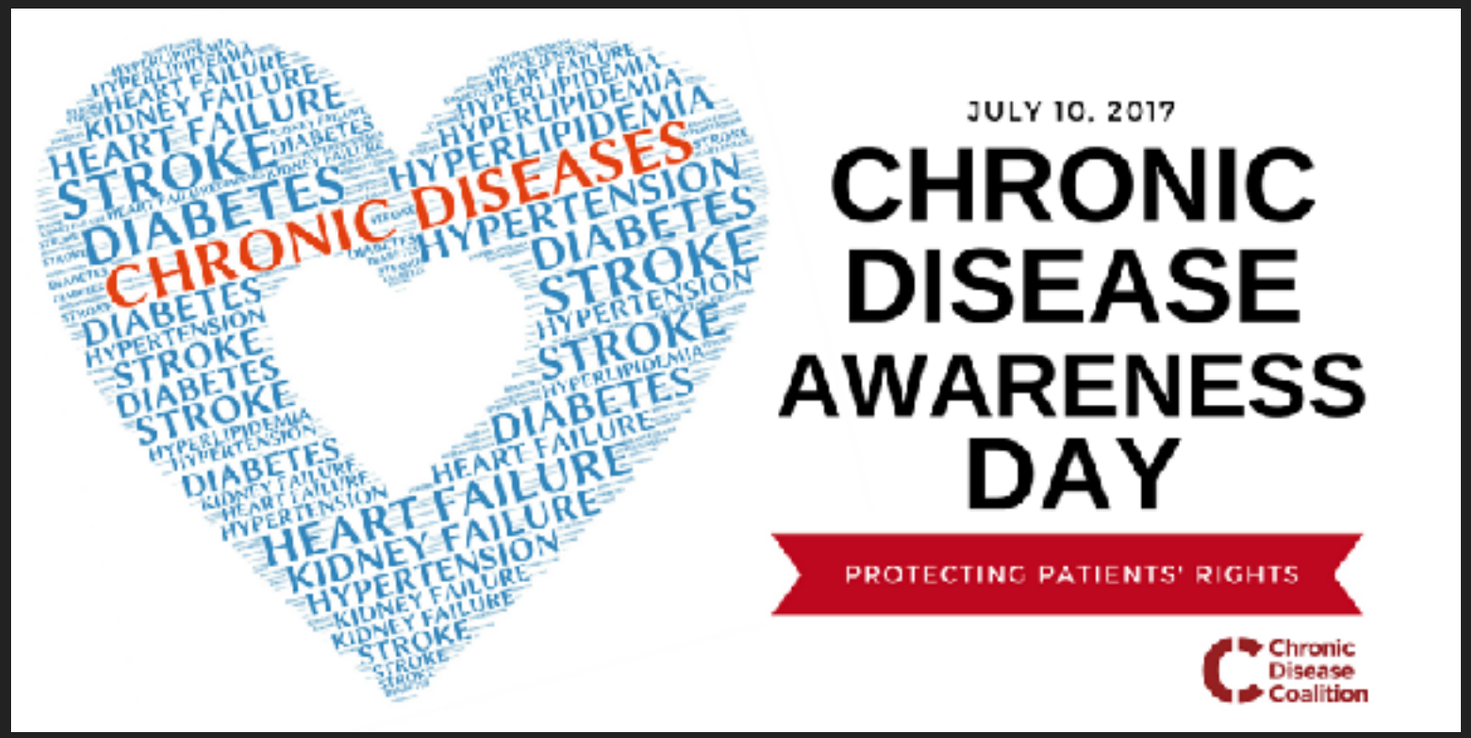


LIMIT OF DETECTION

The value that defines "positivity" but DOES NOT necessarily define abnormal

UPPER REFERENCE LIMIT

The value that is greater than the 99th percentile of a healthy population (abnormal value)



THE 99TH PERCENTILE URL

VARIES WITH THE REFERENCE POPULATION

ROCHE HIGH SENSITIVITY TROPONIN T ANALYTIC CHARACTERISTICS

- LOB 3 ng/L, LOD 5 ng/L, URL 14 ng/L (derived from European population)
- 1,312 young, healthy US patients from 15 ED's in the US with no chronic disease found URL 19 ng/L
- So…what's abnormal in Europe is normal in the US

Roche Diagnostics

EMERGENCY PHYSICIANS MUST KNOW THE ANALYTIC CHARACTERISTICS OF THE ASSAY IN USE AT THEIR INSTITUTION

Because patients from one study may be different from YOUR patients

TYPICAL DIAGNOSTIC ACCURACY STUDY

- Purely observational
- Study setting outside US
- Included patients with non-ischemic EKG
- Excluded chronic kidney disease
- Blood samples frozen and analyzed after standard care
- They only report the NPV for AMI!

LIMITATIONS OF EXISTING DIAGNOSTIC ACCURACY STUDIES

- Clinicians didn't make decisions based upon high sensitivity troponin testing
- Patients often admitted and stress tested
- Variability regarding timing of delta troponin testing
- Generalizability of results to United States
- Primary outcome AMI (not 30 day MACE)

HIGH SENSITIVITY TROPONIN I (ABBOTT)

	AMI	No AMI
HsTnI > 5 ng/L	585	6,651
HsTnI < 5 ng/L	60	10,952

*Note: the URL for hsTnI is 26 ng/L as reported by the manufacturer!

TEST CHARACTERISTICS

SENS 91%

SPEC 62%

FOR ACS, THIS TEST IS INADEQUATELY SENSITIVE USING THE URL CUTOFF AND PROBABLY NOT GOOD ENOUGH AT THE LOD EITHER

As shown by these large systematic reviews

PICKERING, ET AL. ANN INT MED, 2017

META-ANALYSIS OF HIGH SENSITIVITY TROPONIN T

- 11 cohorts across 5 European countries (n = 9,241)
- Pooled sensitivity for hsTnT < LOD at presentation was 98.7%, *however…*
- Estimate of heterogeneity was astronomical (I^2 = 90%)
- THE AUTHORS DON'T REPORT THE NUMBER OF FALSE POSITIVES!

HIGH SENSITIVITY TROPONIN T (ROCHE)

	AMI	No AMI
HsTnT > 5 ng/L	1,409	5,007
HsTnT < 5 ng/L	14	2,811

TEST CHARACTERISTICS

SENS 98.7%

SPEC 36%

USING CUTOFFS BELOW THE LOD WILL MAXIMIZE SENSITIVITY AT THE EXPENSE OF SPECIFICITY

Classifying less patients as suitable for discharge

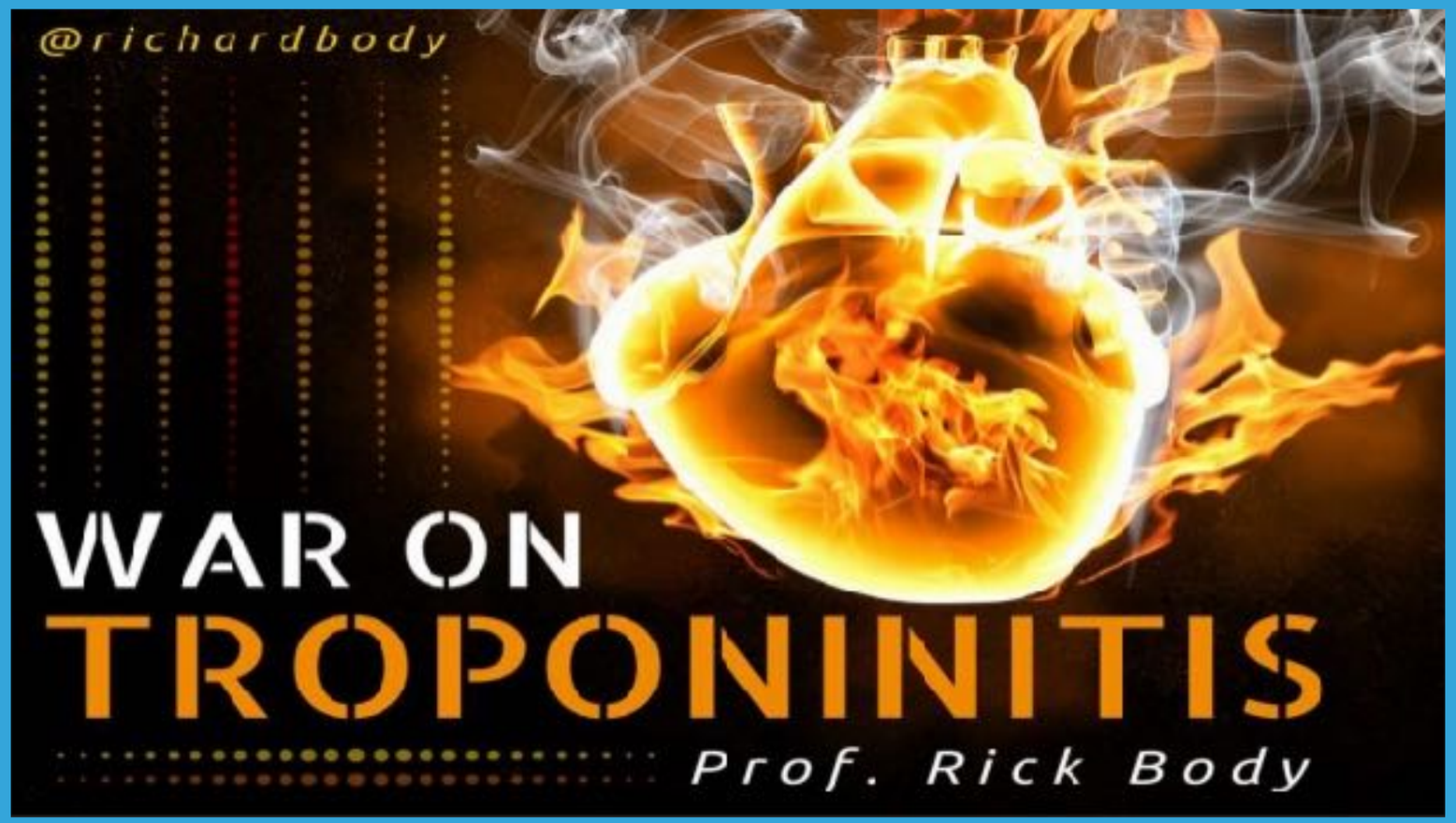
IS IT AT LEAST USEFUL AS AN EARLIER RULE-IN TEST FOR AMI ?

Maybe . . .

Using cutoffs of hsTnT > 52 ng/L or 1 hour delta > 5 ng/L: Specificity 94.6%

THIRD UNIVERSAL DEFINITION OF AMI

- Troponin > 99th percentile AND one of the following:
  - Ischemic CP
  - Echo evidence
  - Ischemic EKG
  - Angiographic evidence



THE ISSUE

High Sensitivity Troponin > 99th percentile no longer necessarily = AMI, even if applied in the correct clinical context

EMERGENCY PHYSICIANS SHOULD INTERPRET HIGH SENSITIVITY ASSAYS AS QUANTITATIVE TESTS NOT QUALITATIVE ONES

WHAT'S A "POSITIVE" TROPONIN IS UP FOR DEBATE

CHAPMAN, ET AL. JAMA 2017.

META-ANALYSIS OF HIGH SENSITIVITY TROPONIN I

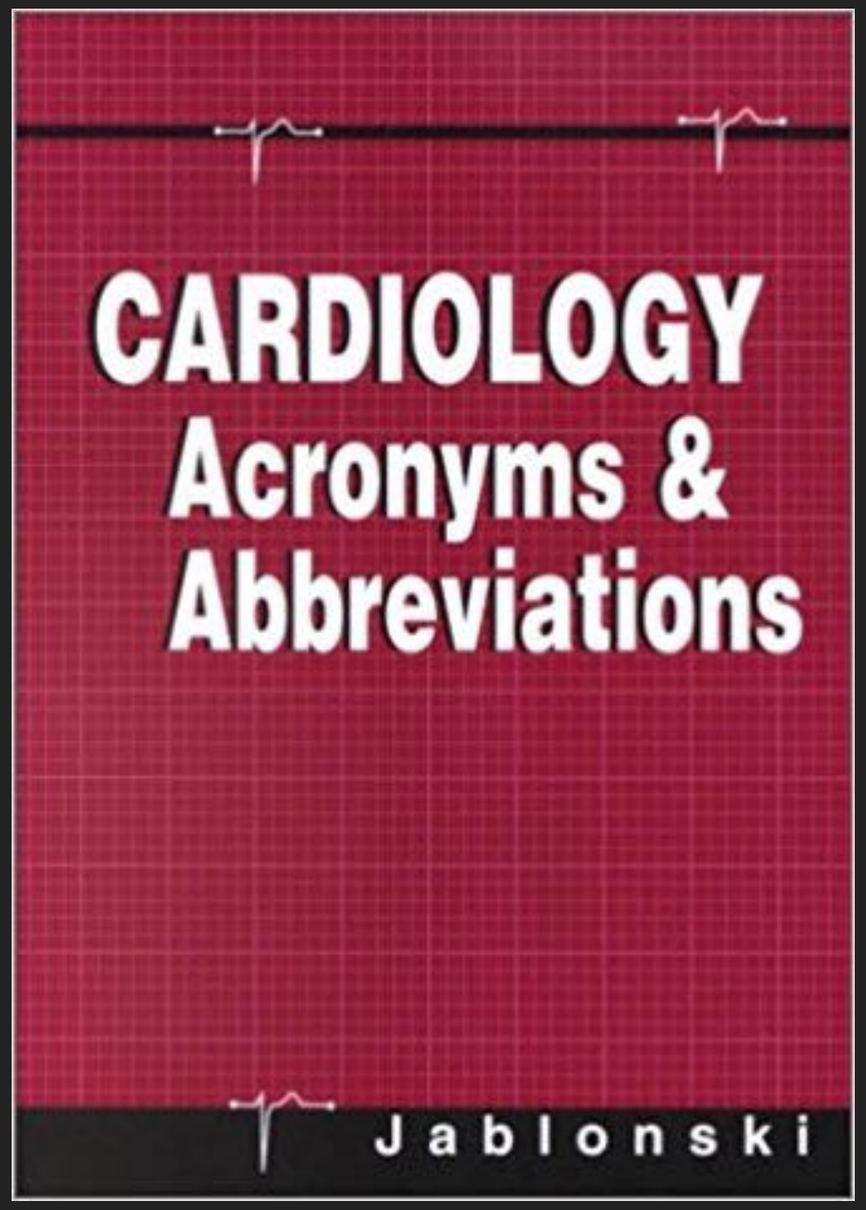
- Pooled data from 19 cohorts across 9 countries
- 22,497 patients, excluded 4,209 with concentrations above the URL at presentation
- NPV 99.5% for AMI if hsTnI < 5 ng/L at presentation
- Pretty good, right?

TO RULE IN AMI, CUTOFFS MARKEDLY HIGHER THAN THE URL OR A SIGNIFICANT RISE WITH DELTA TESTING IS REQUIRED

When HsTn becomes useful as rule-in test, it simultaneously becomes ineffective as a rule-out test

ACCELERATED DIAGNOSTIC PROTOCOLS

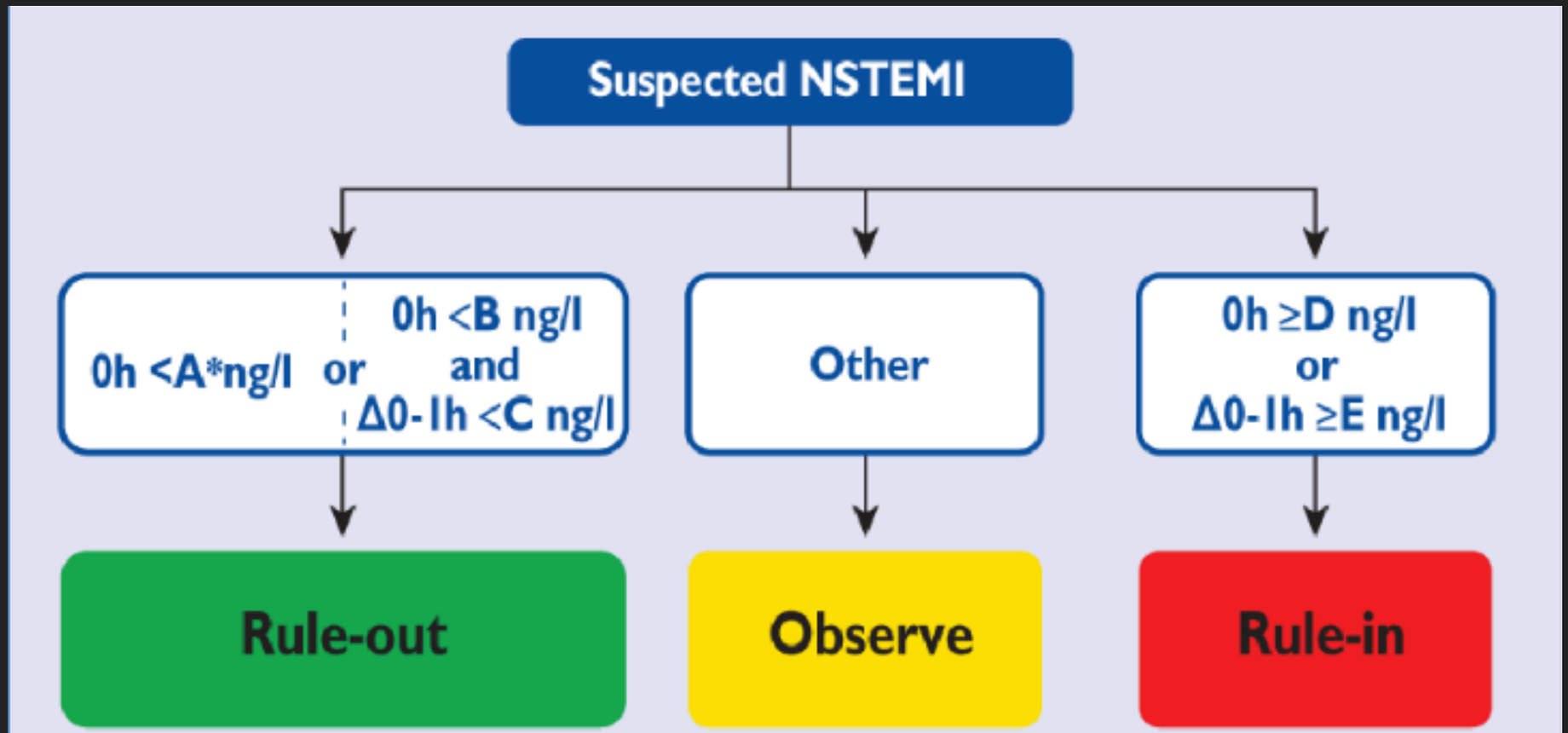
- European Society of Cardiology (ESC) Guidelines
- High Sensitivity Troponin in Evaluation of ACS (High STEACS) Protocol
- National Institute of Health and Care Excellence (NICE) Guidelines
- EDACS, GRACE, ADAPT, TMACS, TIMI, APACE, HEART, seriously?



ESC 0/3 HOUR RULE OUT ALGORITHM

- Rule out criteria:
  - CP > 6 hours and hsTnT < URL (14 ng/L)
  - CP < 6 hours, hsTnT < URL, *and* 3 hour delta < 50%
- 1,218 patients with suspected ACS in whom clinician ordered standard troponin testing
- Results: Sensitivity 89.3%

ESC GUIDELINES 1 HOUR RULE-OUT OPTION



	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

LOD

LOB

>2 to 3 times the URL!

ESC 0/1 HOUR RULE OUT OPTION

- 2,222 patient with possible ACS and non-ischemic EKG
- Rule out criteria:
  - CP > 3 hours and hsTnT < 5 ng/L (LOD)
  - CP < 3 hours, hsTn < 12 ng/L *and* 1 hour delta < 3 ng/L
- Results: sensitivity 97.1% for AMI, specificity 62%

LOWER CUTOFFS (LOD) MAXIMIZE SENSITIVITY BUT IDENTIFY FEWER PATIENTS FOR EARLY DISCHARGE

because by definition 50% of healthy people have detectable troponin

HIGH STEACS PATHWAY

- Rule out criteria:
  - CP > 2 hours and hsTnI < 5 ng/L
  - CP < 2 hours, 3 hour hsTnI < URL *and* delta < 3 ng/L
- Sensitivity 97.7%, specificity 87.6%

NICE PATHWAY

- Rule out criteria:
  - HsTnT < 3 ng/L (LOB) *or*
  - 2 hour hsTnT < 14 ng/L (URL) *and* < 20% change
- 3,374 patients with possible ACS in whom clinician ordered standard troponin testing
- Sensitivity 97.7%, specificity 87.6%
- 30 day MACE rate for those ruled out = 8.5%!

SINCE HIGH SENSITIVITY TROPONIN IS NOT ADEQUATELY SENSITIVE BY ITSELF…

WHAT IF WE COMBINE TESTING WITH A CLINICAL RISK SCORE?

COMBINE WITH TIMI RISK SCORE?

- 3,159 patients with acute CP and non-ischemic EKG
- TIMI = 0 and hsTnT < 5 ng/L (LOD) was 99.5% sensitive and 20% specific for 30 day MACE
- TIMI ≤ 1 and hsTnT < LOD was 98.4% sensitive and 39.4% specific
- But…out of 5,316 patients, 2,157 were excluded for missing hsTnT results

TIMI
Age≥65 y
≥3 risk factors* for coronary artery disease
Use of aspirin in last 7 days
Significant coronary stenosis (>50%)†
Recent severe angina (≥2 angina events in preceding 24h)

I DON'T KNOW ABOUT YOU, BUT NOBODY HAS A TIMI RISK SCORE OF ZERO IN MY ED EXCEPT PRIVATE SNUFFY

History:
Highly suspicious: 2
Moderately suspicious: 1
Slightly suspicious: 0

ECG:
Significant ST depression[‡]: 2
Non-specific repolarisation disturbance: 1
Normal: 0

Age:
≥65 years: 2
45-65 years: 1
<45 years: 0

Risk Factors:
≥3 Risk factors* for coronary artery disease: 2
1 or 2 risk factors: 1
No risk factors: 0

Troponin:
hs-cTnT:
≥30ng/L[§]: 2
>14ng/L to <30ng/L[§]: 1
≤14ng/L: 0

WHAT ABOUT THE HEART SCORE?

SCORE ≤ 3 =

SENSITIVITY 93.7%

SPECIFICITY 33.9%

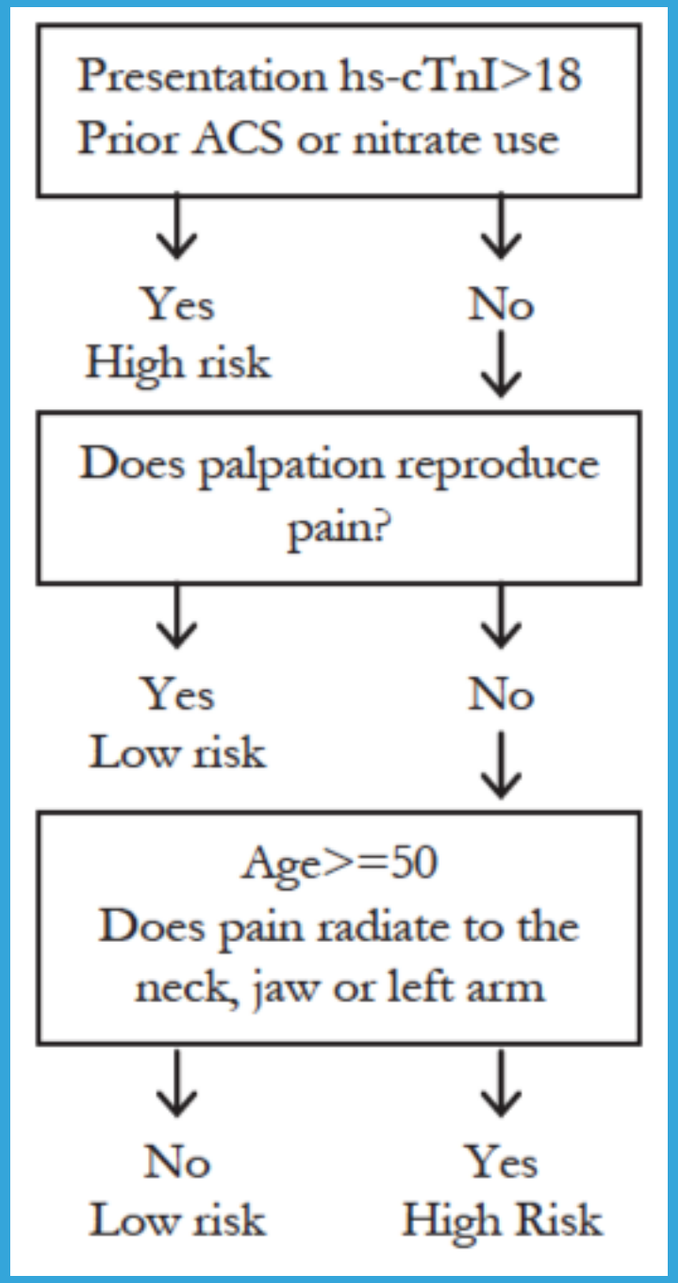
FOR 30 DAY MACE

1 point for each of:
Age ≥50 y
≥3 risk factors
(hypertension, dyslipidemia, family history of CAD, diabetes, or current smoking)
Previous MI or CAD

THE NO OBJECTIVE TESTING (NOT) RULE

NOT SCORE = 0 + HIGH SENSITIVITY TROPONIN I < 18 NG/L AT 0 AND 2 HOURS

SENSITIVITY 99.3%
SPECIFICITY 37.3%
FOR 30 DAY MACE

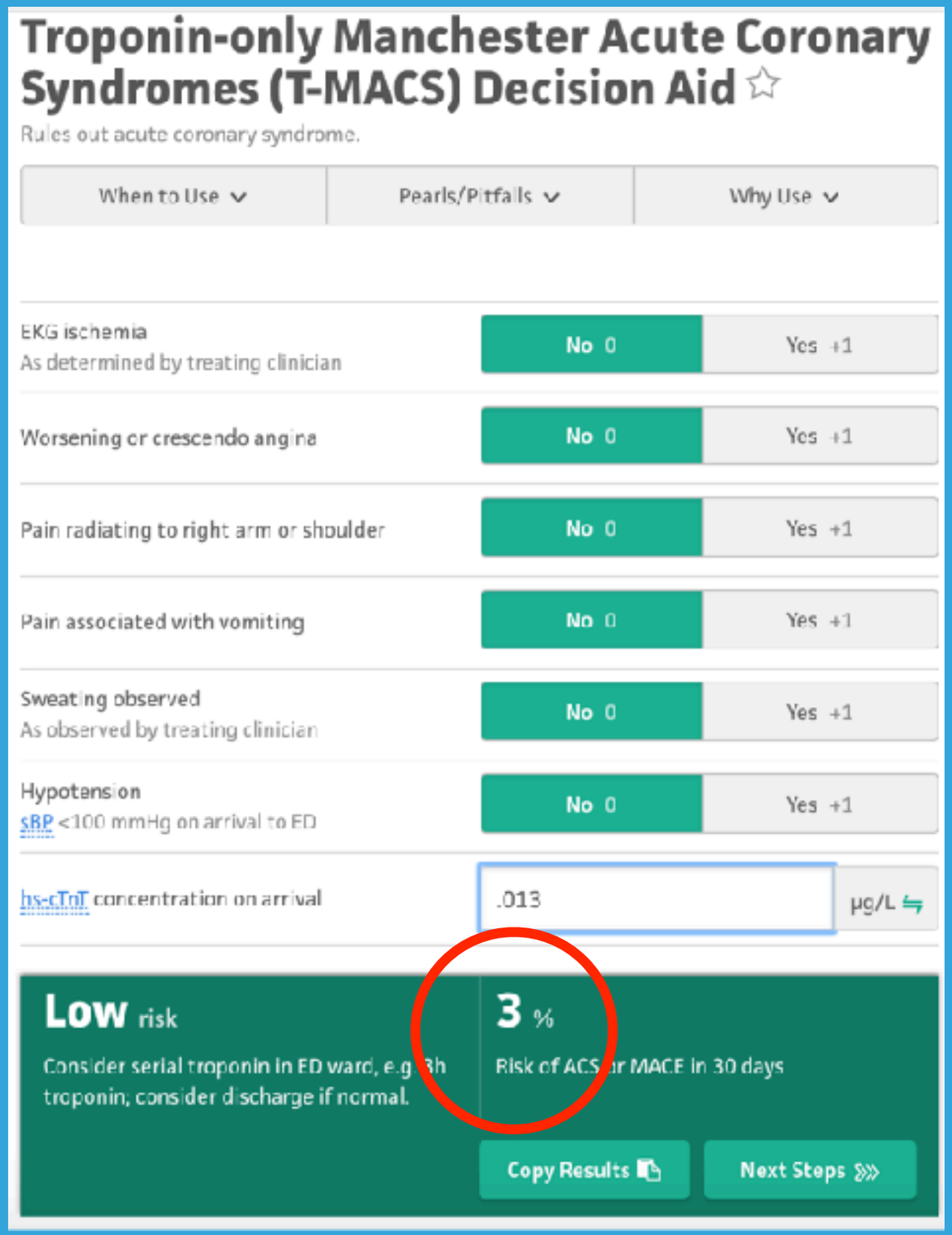


VANCOUVER CHEST PAIN RULE

SENSITIVITY 98.6%

SPECIFICITY 30.4%

FOR 30 DAY MACE



"T-MACS" DECISION AID

A computer-derived model with sensitivity of 97% for "low risk" patients

(47% specific for those classified as HIGH risk)

BOTTOM LINE

HIGH SENSITIVITY TROPONIN IS NOT A:

Panacea

Greek Goddess of
Universal Remedy

Solution to all
problems; **Cure-all**

WHEN COMBINED WITH LOW CLINICAL RISK ASSESSMENT, HIGH SENSITIVITY TROPONIN MAY BE USEFUL TO IDENTIFY A SMALL COHORT OF PATIENTS AT LOW RISK FOR 30 DAY MACE

but standard troponin can probably do this too

DO HIGH SENSITIVITY ASSAYS HAVE ADDED DIAGNOSTIC VALUE OVER STANDARD TROPONIN?

Maybe, but not likely in patients with CP > 6 hours

ESC 0/3 HOUR ALGORITHM

- In 2,727 consecutive ED patients with acute CP and low risk GRACE score:
- Assays were comparable in patients with CP > 6 hours
- High sensitivity troponin: correctly ruled out 1,088 of 1,094 (99.5%)
- Standard troponin: correctly ruled out 1,186 of 1,193 (99.4%)

KORLEY, ACADEMIC EMERGENCY MEDICINE, 2016

ARE HIGH SENSITIVITY TROPONINS SUPERIOR TO STANDARD TROPONIN?

- 808 patients with possible ACS and non-diagnostic EKG
- 65 patients had negative standard troponin but “positive” hsTn > URL
- Of these patients, 3 were eventually diagnosed with ACS
- Authors conclusions: “these troponin elevations are likely to be associated with more chronic than acute cardiac conditions.”

IT IS ESTIMATED THAT WE WOULD HAVE TO TEST 270 PATIENTS WITH HIGH SENSITIVITY TROPONIN TO DETECT ONE EXTRA CASE OF ACS, AND A FALSE POSITIVE RESULT IS 21 TIMES MORE LIKELY

Key Point # 3

ARE THESE ASSAYS COST EFFECTIVE?

One study estimated cost of $108,552 for every adverse outcome avoided. Increased costs were driven by increased length of stays.

THE STUDY I WANT TO SEE COMPLETED

- International, pragmatic RCT
- ED patients with acute chest pain and either non specific or normal EKG
- Randomized to strategy of 0/3 hour standard troponin testing versus 0/1 hsTn testing
- The accelerated diagnostic protocol should include a clinical risk assessment (score)
- Primary outcome of 30 day MACE along with a cost-effective analysis

SUMMARY

- A zero percent miss rate is a truly Sisyphean task
- In exchange for modest improvement in sensitivity, hsTn assays come at the expense of a significant decrease in specificity
- Potential impacts of false positive testing include increased length of stays, increased costs, and unnecessary interventions
- Without pragmatic trials in actual clinical practice, it is unclear if these assays will actually help or hinder the EP