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Making Sense of High-Sensitivity Troponin Elevations

TCPi | Transforming Clinical Practices Initiative

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Presenters

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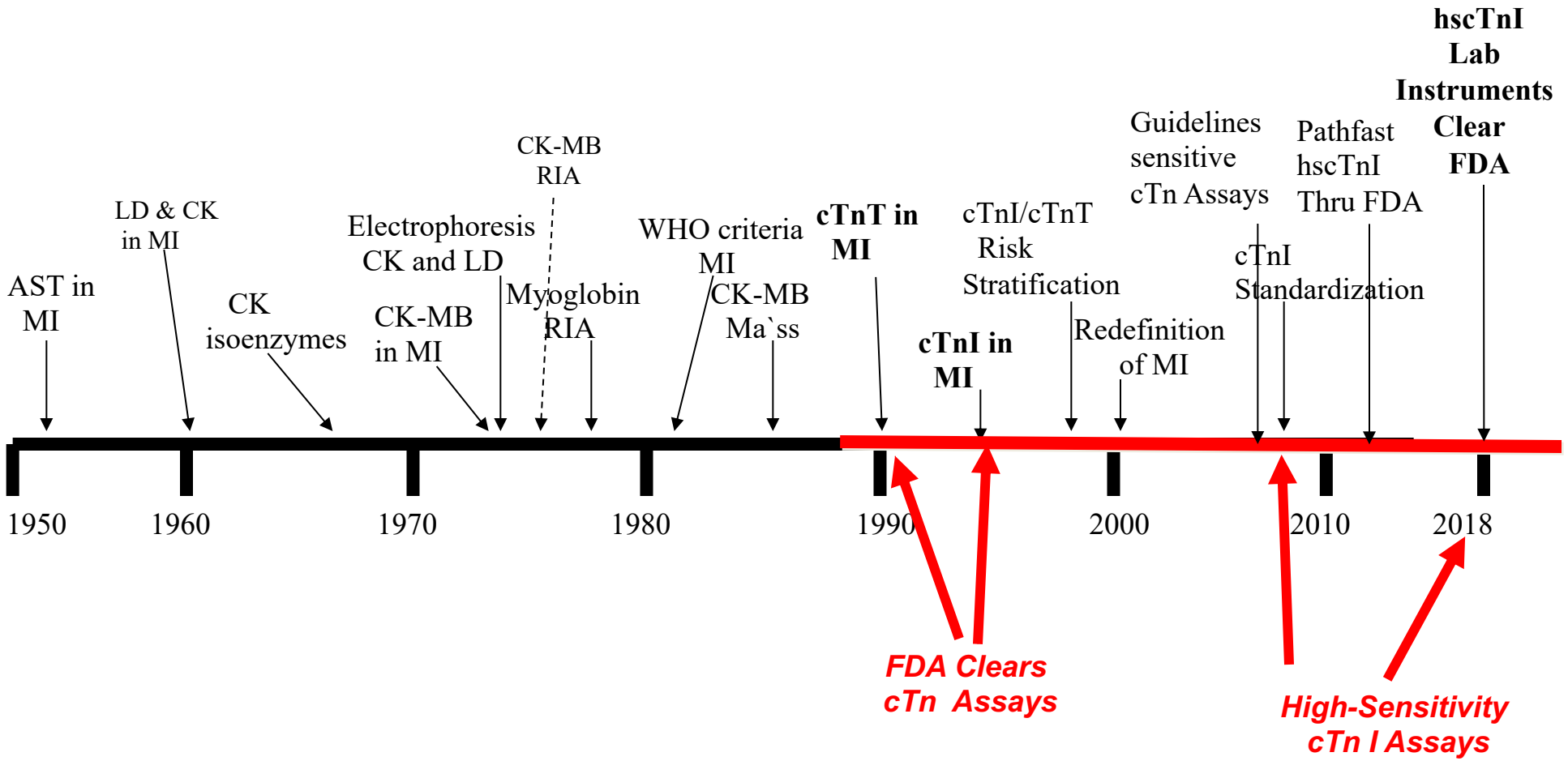
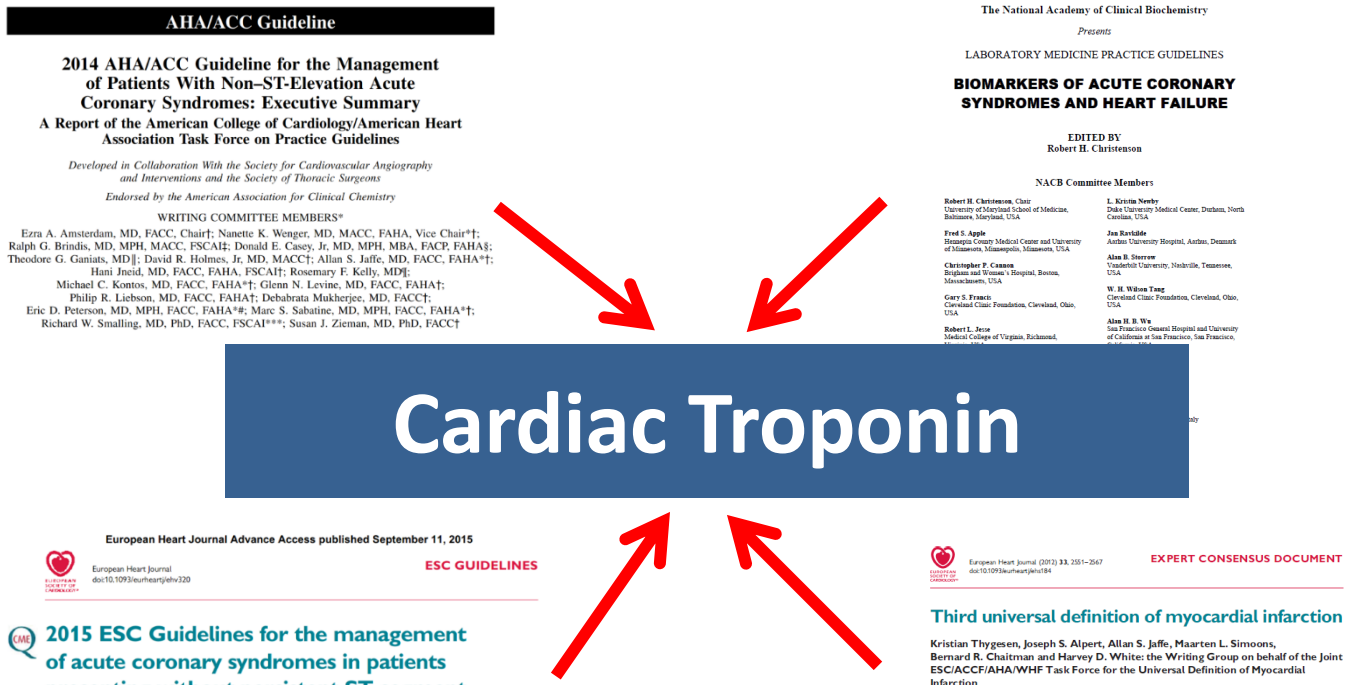
What does ”high-sensitivity” really mean?

Cardiac Biomarkers Timeline




AHA/ACC Guideline
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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The National Academy of Clinical Biochemistry
Presents
LABORATORY MEDICINE PRACTICE GUIDELINES
BIOMARKERS OF ACUTE CORONARY SYNDROMES AND HEART FAILURE
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Cardiac Troponin
European Heart Journal Advance Access published September 11, 2015
European Heart Journal
doi:10.1093/eurheartj/ehv320
ESC GUIDELINES
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)
European Heart Journal (2012) 33, 2551–2567
doi:10.1093/eurheartj/ehs184
EXPERT CONSENSUS DOCUMENT
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).

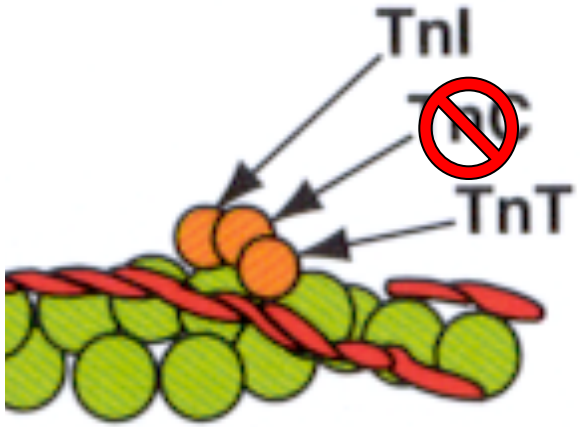
2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

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.

When troponin is increased think heart

Cardiac isoforms in blood



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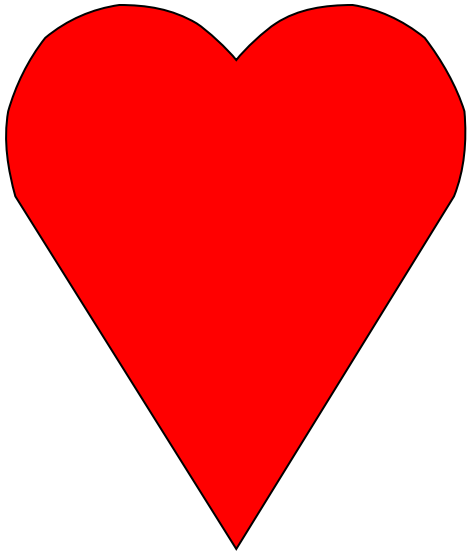
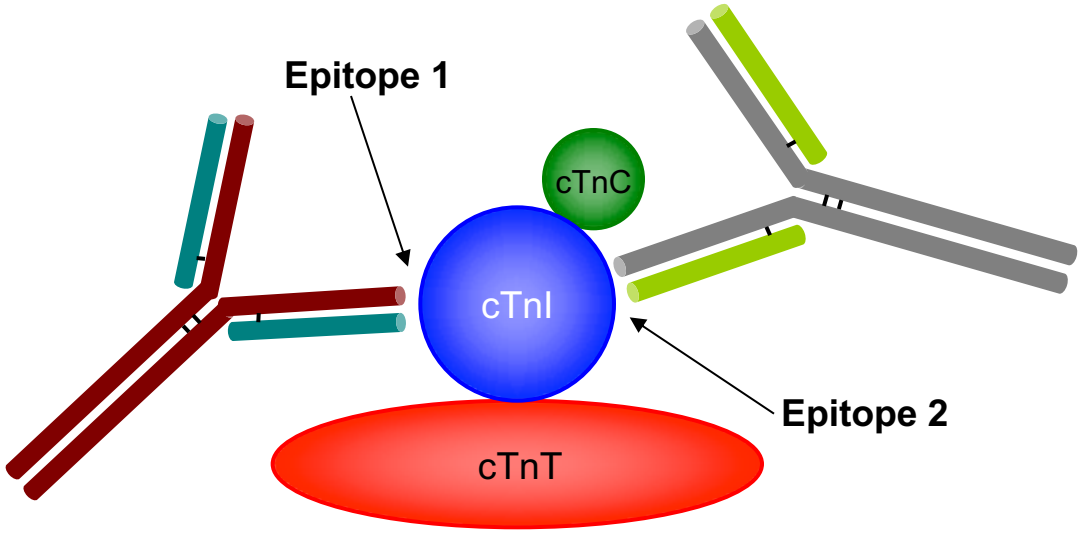


High Sensitivity Cardiac Troponin

Same Cardiac Troponin Analyte

Six commercial (Hytest) mAbs evaluated for use in a 1 x 1 “reference “immunoassay



What is High-sensitivity Cardiac Troponin?

AACC Academy and IFCC TFCACB defines a high-sensitivity cTn as:

1. An assay that can measure ≥50% of healthy men and 50% of healthy women (i.e. values above the limit of detection)
2. hs-cTn assays are precise (i.e. day-to-day Total CV ≤10%)

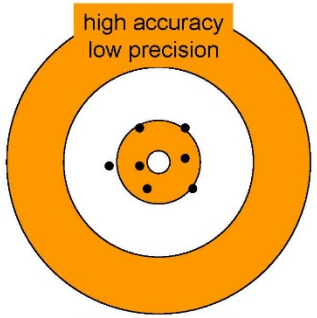
High-sensitivity cTn is not a different analyte!

Term refers to a more sensitive assay

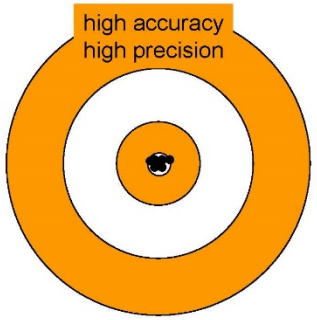
Clinical Chemistry 64:4;645–655 (2018)

High Accuracy, Different Precision

Earlier Generation Troponin



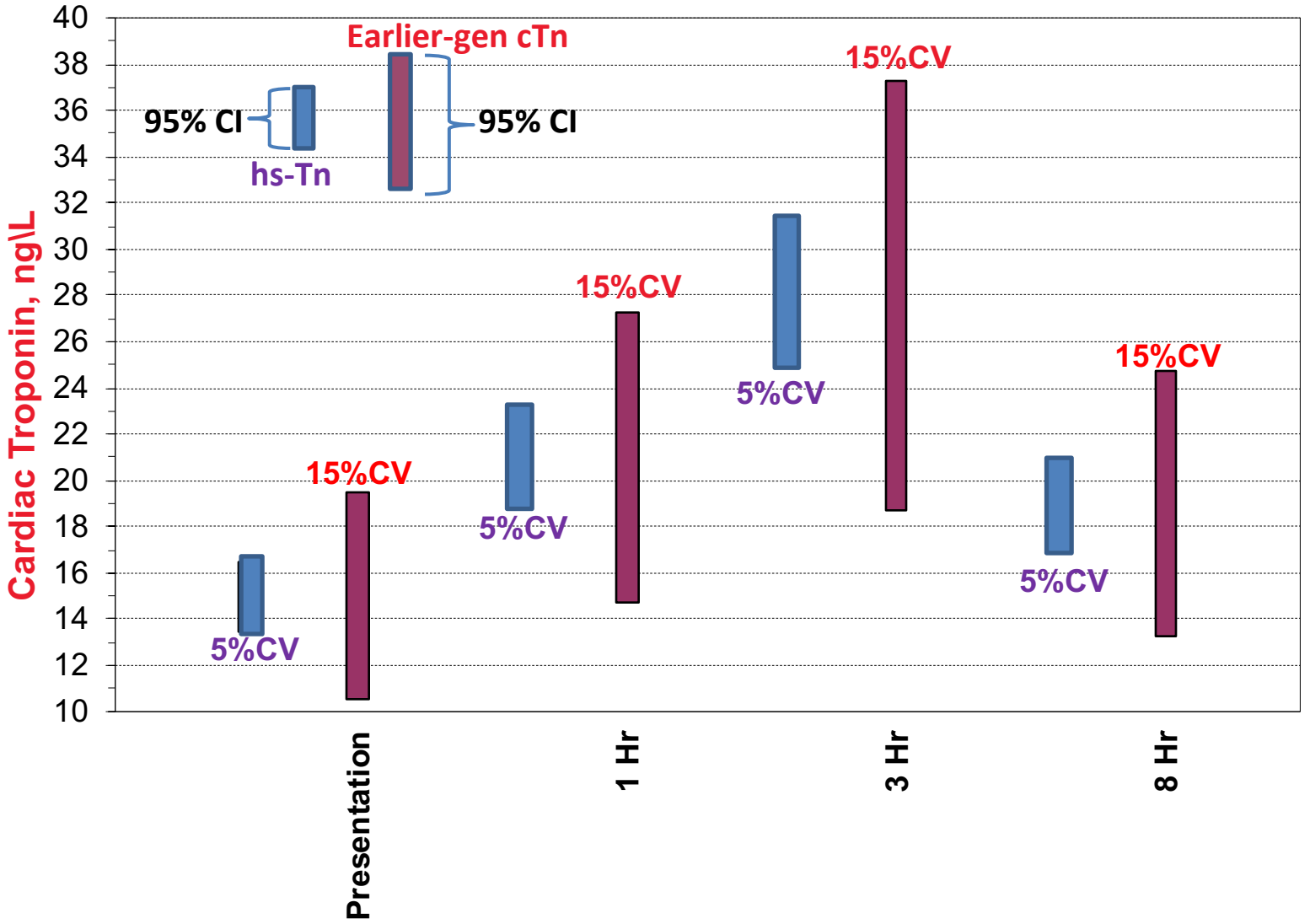
15% CV



5% CV

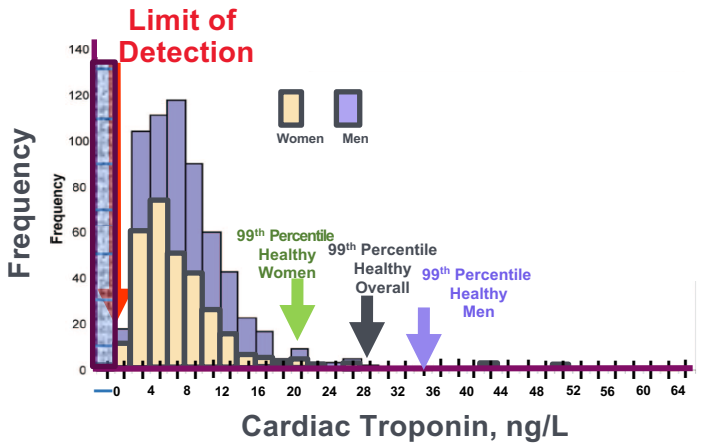
High-sensitivity Troponin

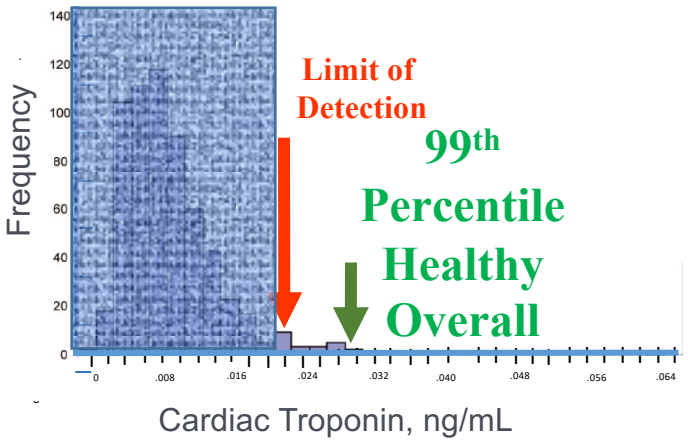
Early Velocity (Delta) Change Apparent with hsTn assays



High-sensitivity Cardiac Troponin Assays

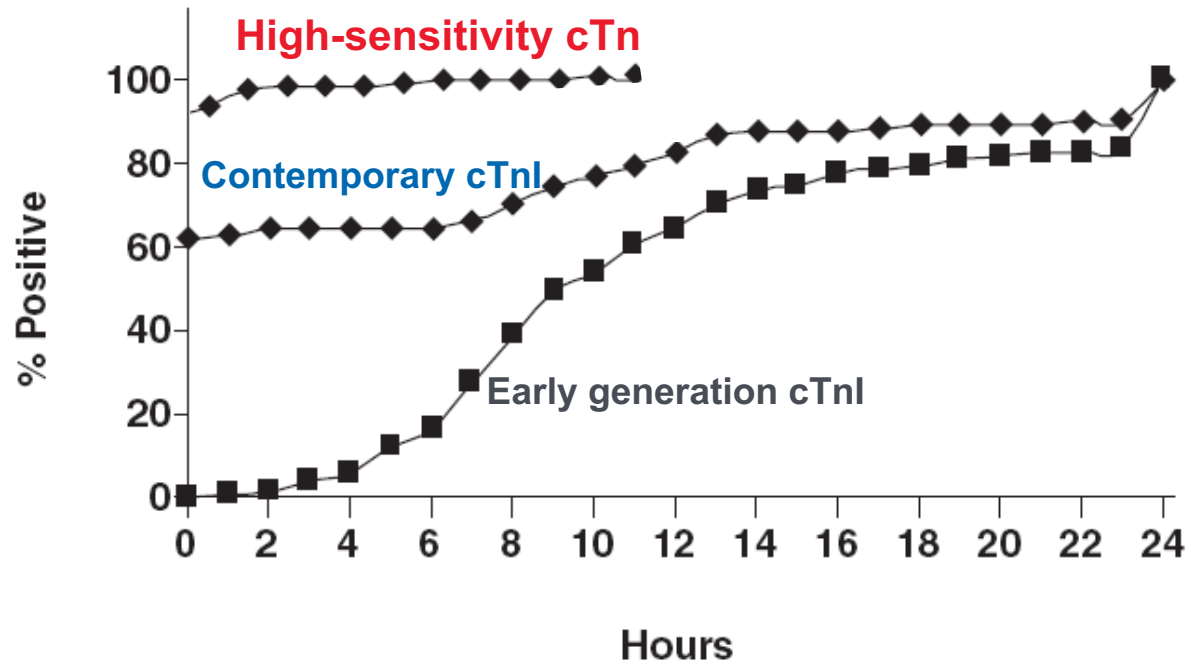
Definition is Analytical, Benefit is Clinical





- **High-Sensitivity' is an analytical term**
- **hsTn assays DO NOT measure a different analyte**

Earlier vs. Later-generation cTnI



Am J Clin Pathol 2007;128:282-286

How does a high-sensitivity assay help me at the bedside with decision-making?

High Sensitivity Troponin

Impact of hs-cTnT on clinical practice

European Heart Journal
doi:10.1093/eurheartj/ehw232

CLINICAL RESEARCH
Acute coronary syndromes

Impact of high-sensitivity cardiac troponin on use of coronary angiography, cardiac stress testing, and time to discharge in suspected acute myocardial infarction

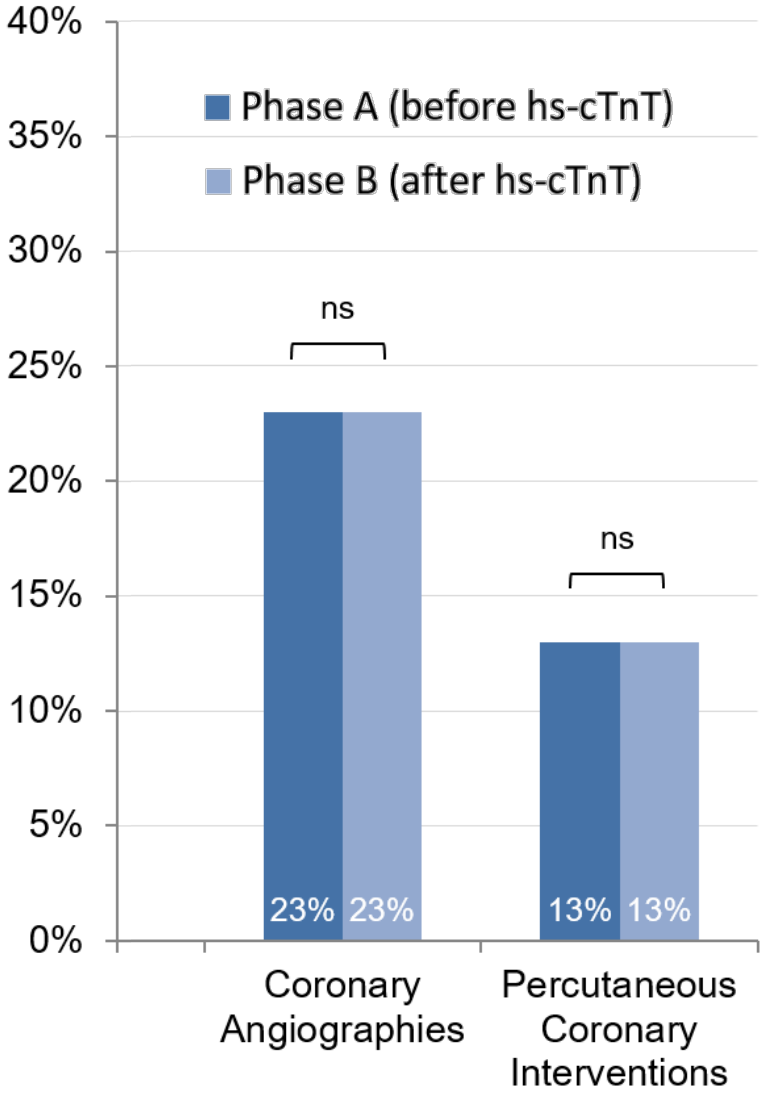
Raphael Twerenbold[1,2], Cedric Jaeger[1,2], Maria Rubini Gimenez[1,2], Karin Wildi[1,2], Tobias Reichlin[1,2], Thomas Nestelberger[1,2], Jasper Boeddinghaus[1,2], Karin Grimm[1,2], Christian Puelacher[1,2], Berit Moehring[1,2], Gil Pretre[1,2], Nicolas Schaerli[1,2], Isabel Campodarve[3], Katharina Rentsch[4], Stephan Steuer[5], Stefan Osswald[1,2], and Christian Mueller[1,2]*

APACE
acute chest pain

- Within the APACE trial (prospective, international, multicenter, diagnostic study)
- Three hospitals (SUI 2, ESP 1) switching from conventional cTnT to hs-cTnT
- Investigate patients‘ management before/after hs-cTnT (n=2544 pts.)
  - N=1455 before hs-cTnT
  - N=1089 after hs-cTnT

Twerenbold R, et al. EHJ 2016

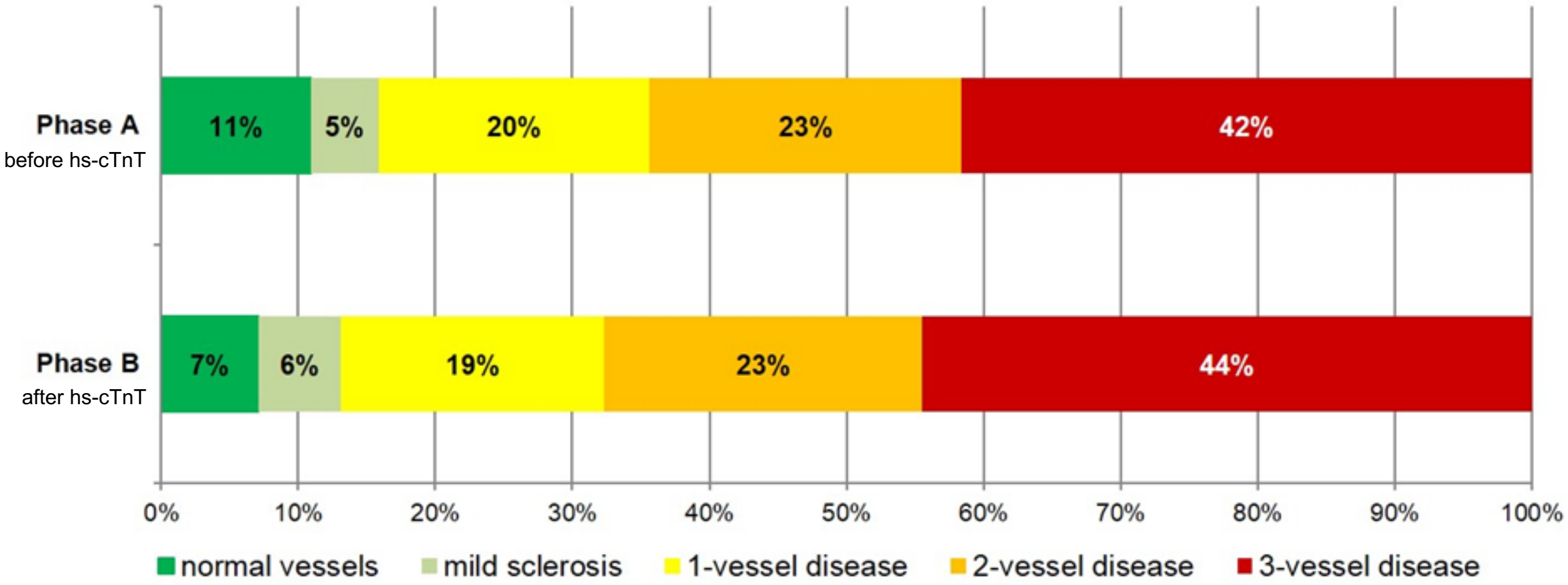
Impact of hs-cTnT on use of coronary angiography



No increase in coronary angiographies

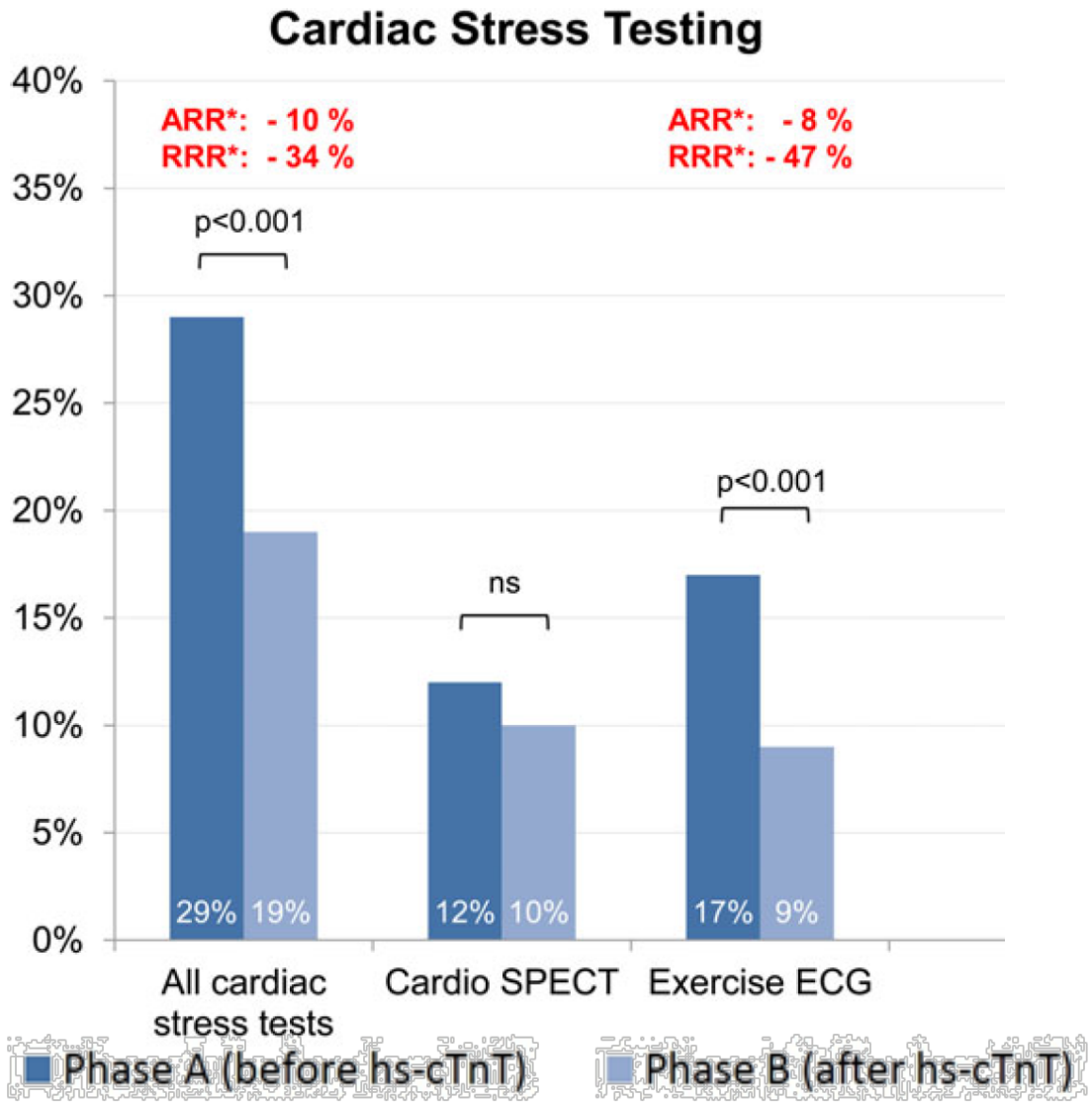
Twerenbold R, et al. EHJ 2016

Impact of hs-cTnT on findings of coronary angiography



Twerenbold R, et al. EHJ 2016

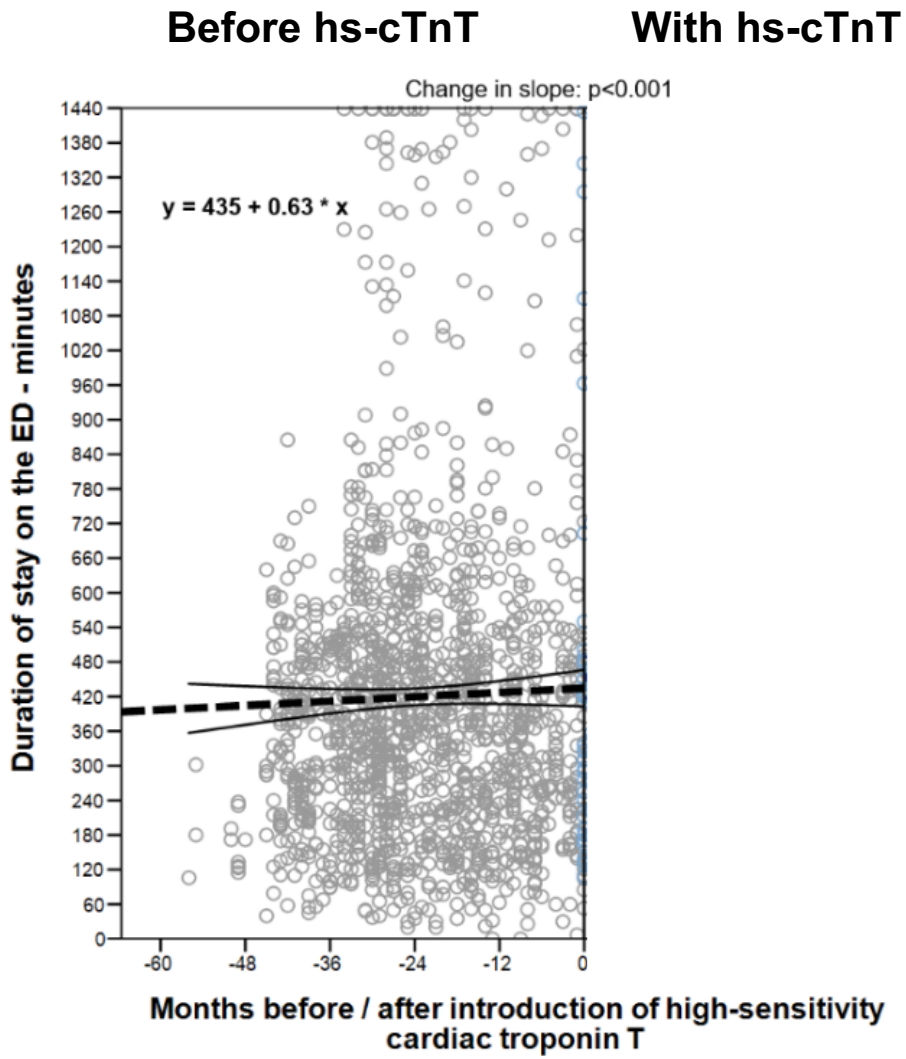
Impact of hs-cTnT on use of cardiac stress testing



34% reduction of subsequent cardiac stress testing

Twerenbold R, et al. EHJ 2016

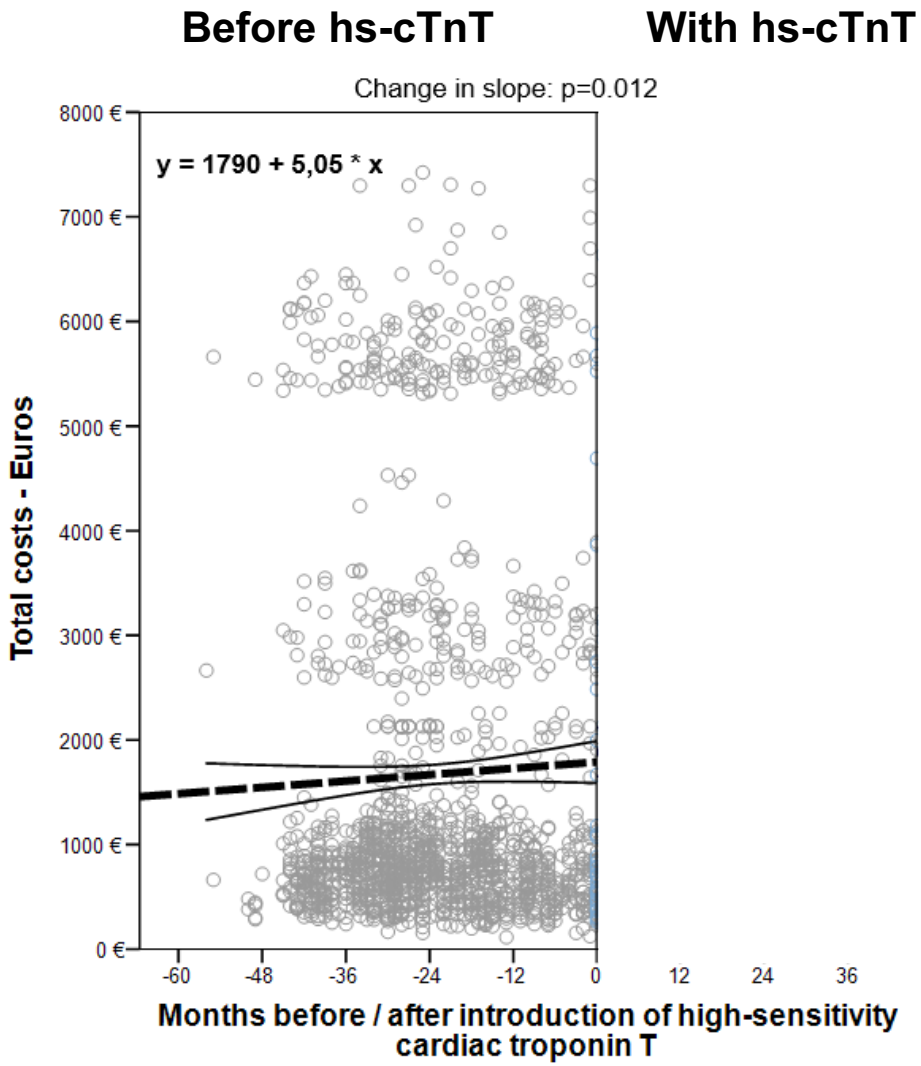
Impact of hs-cTnT on duration of stay in the ED



- 20% reduction of duration of stay in the ED
- Change in trend
- 15% more out-patients

Twerenbold R, et al. EHJ 2016

Impact of hs-cTnT on total costs

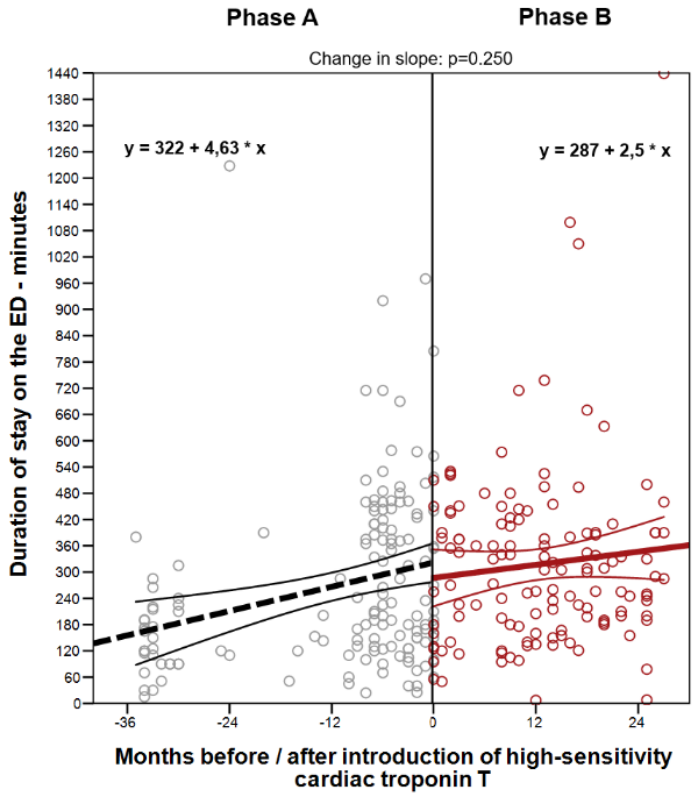


- 20% reduction of total costs in out-patients

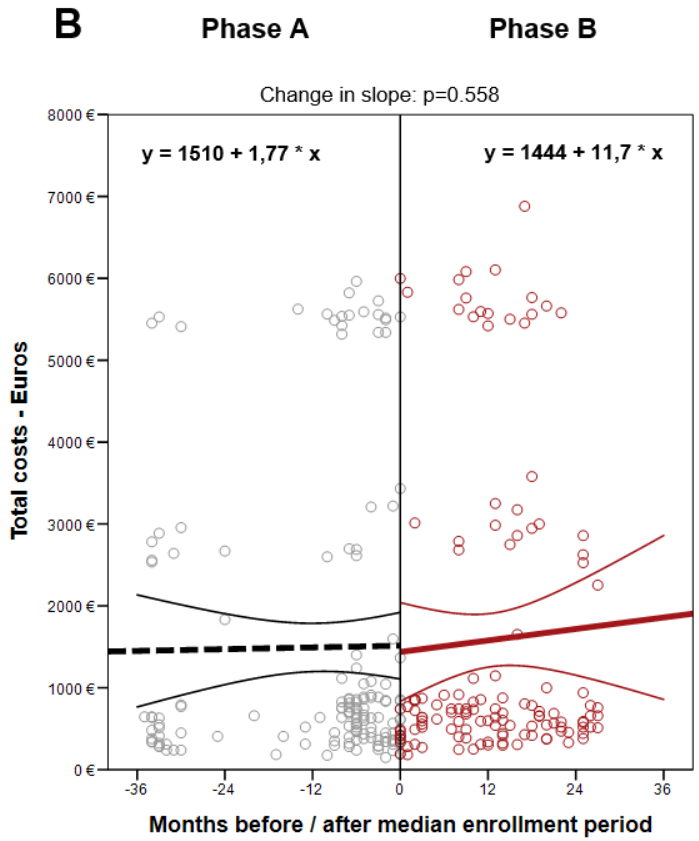
Twerenbold R, et al. EHJ 2016

Findings from hospitals not switching to hs-cTn

Time in ED



Costs



Twerenbold R, et al. EHJ 2016

University Hospital Basel

ED discharge vs Tn assay sensitivity

SAFE ED DISCHARGE RATE

INCREASING TROPONIN SENSITIVITY

9.8%
DISCHARGE

KEEP 90 PATIENTS

Crappy Tn

100 patients

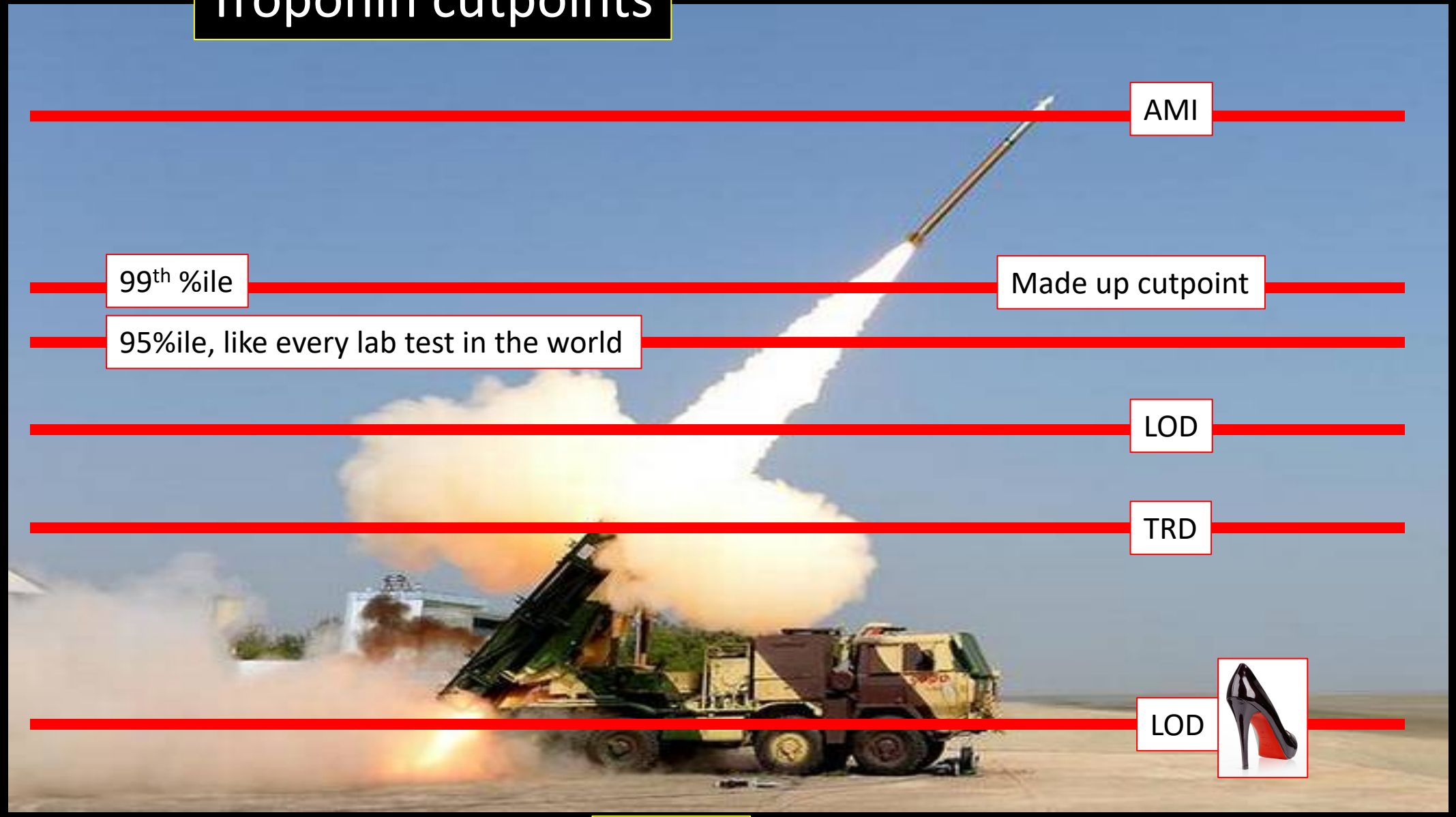
387% increase

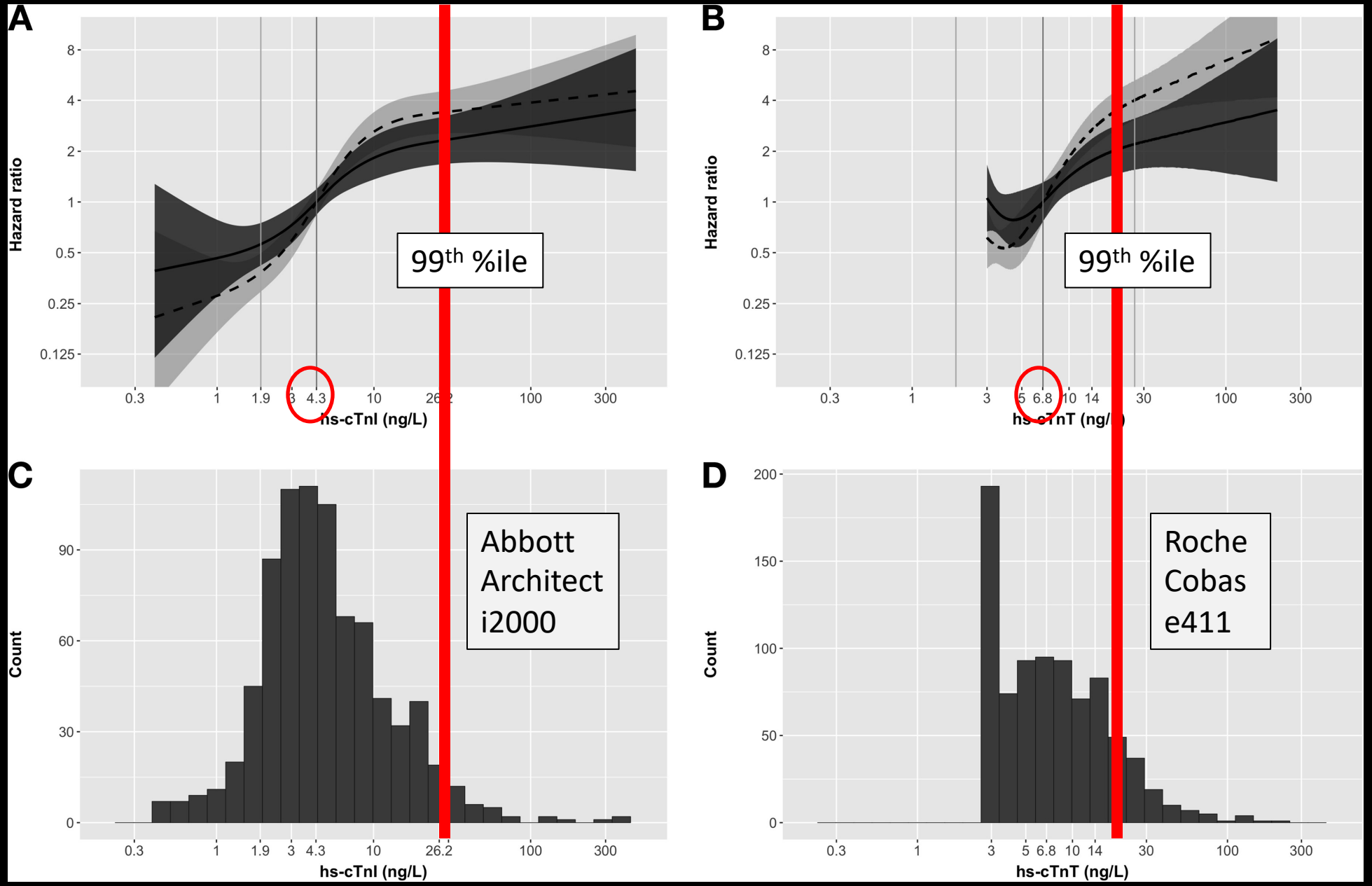
Sensitive Tn

38%
DISCHARGE

KEEP 62 PATIENTS
(discharge 28 more)

Troponin cutpoints

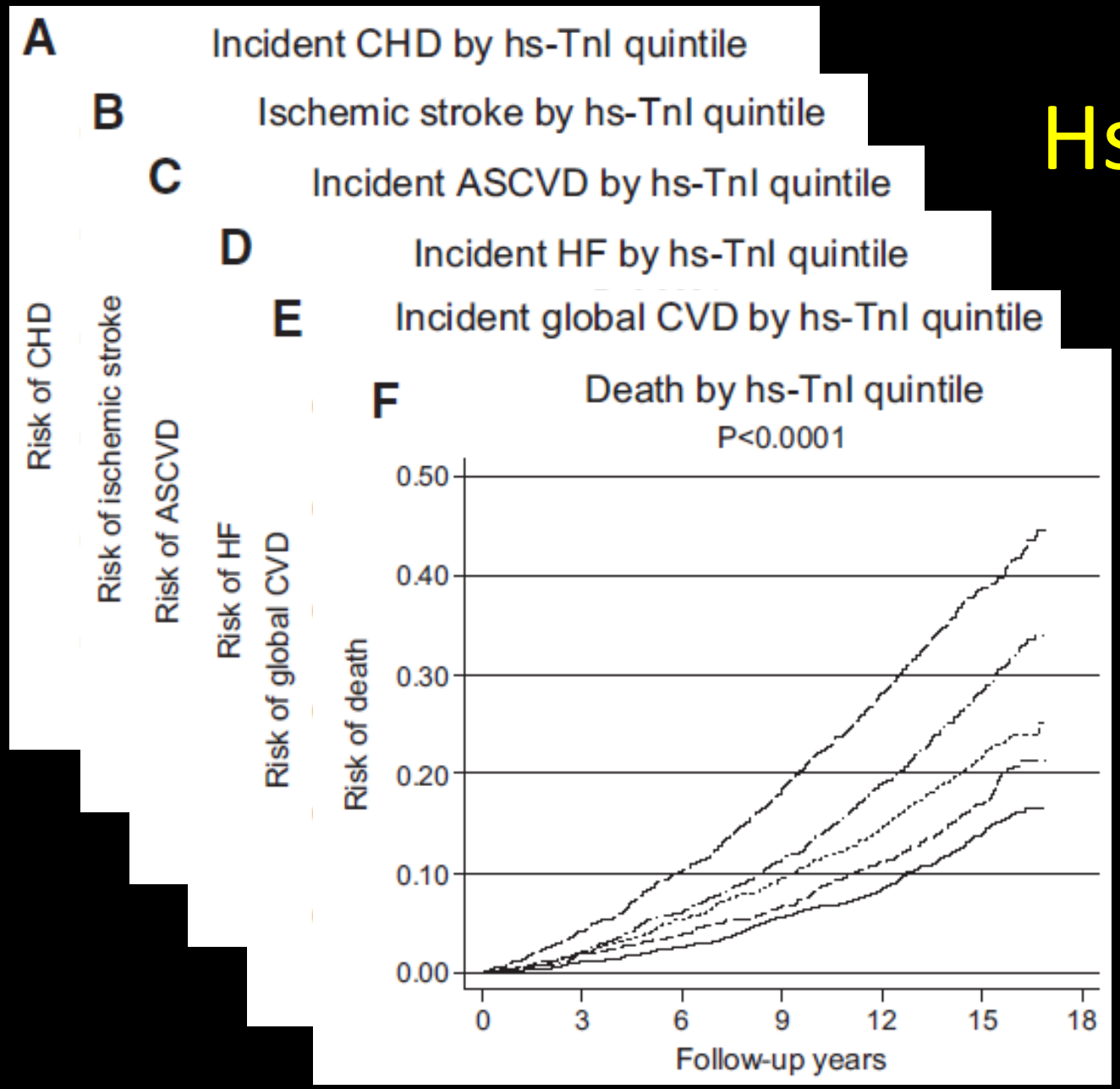




- N= 1113
- ED CP
- 5 yr F/U
- MACE
  - MI
  - HF
  - CV dead

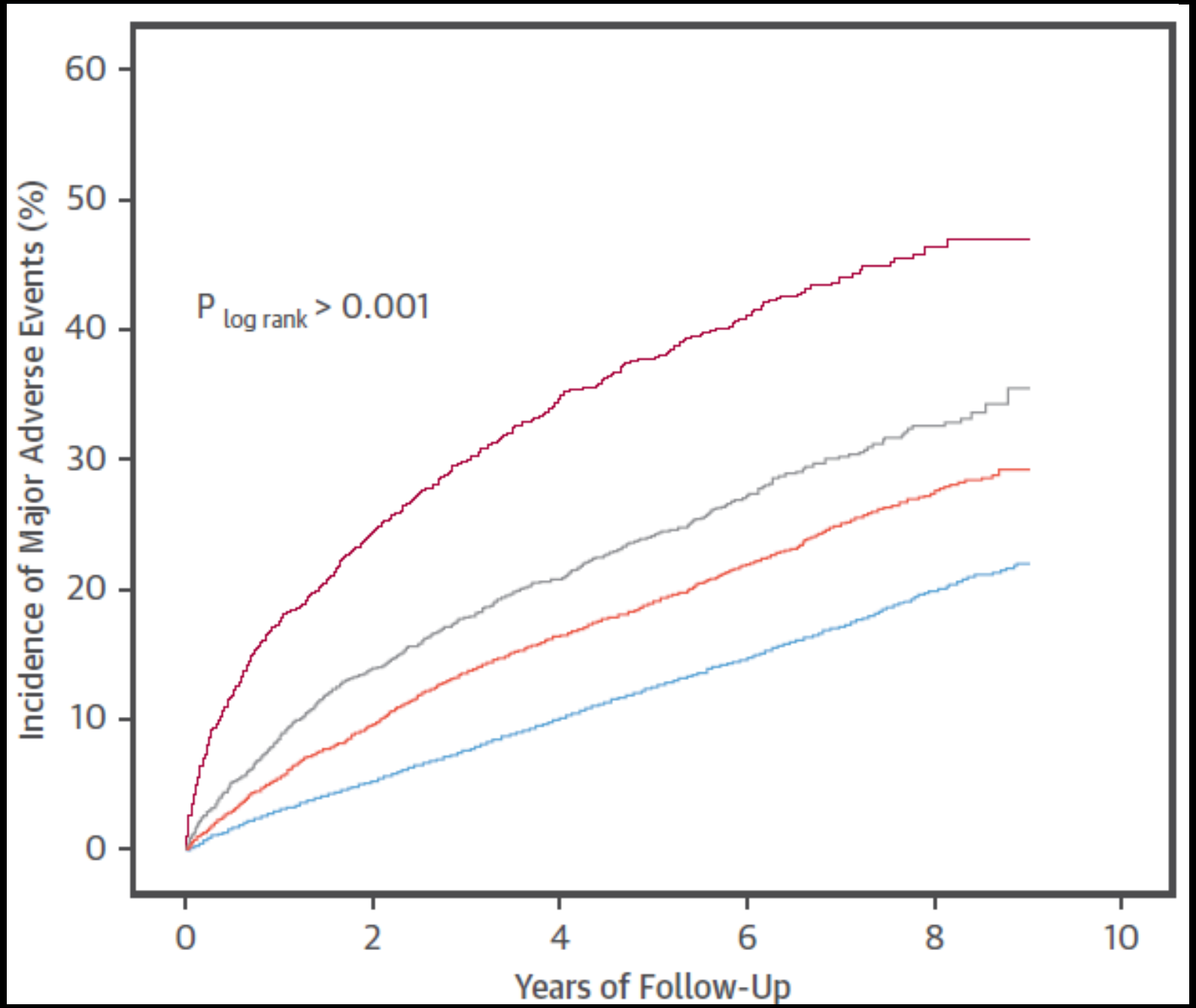
Than MP. Clin Chem 64:7, 1044–1053 (2018)

HsTnI and CVD Otucomes



- N=8121, w/o baseline CVD
- Median F/U = 15 yrs
- HsTnI in quartiles
  - All associated with significant HR

Jia X. *Circulation.* 2019;139:00–00. DOI: 10.1161/CIRCULATIONAHA.118.038772Cric



SWEDEHEART registry

- cTn elevation
  - Associated with CV and non-CV comorbidities
  - Predicts MACE in acutely admitted patients, in whom no definite Dx was established

- The term Troponinemia:
  - Trivializing
  - Should be avoided.
  - Instead, a careful work-up is required

Eggers K. JACC 2019;73:1–9)

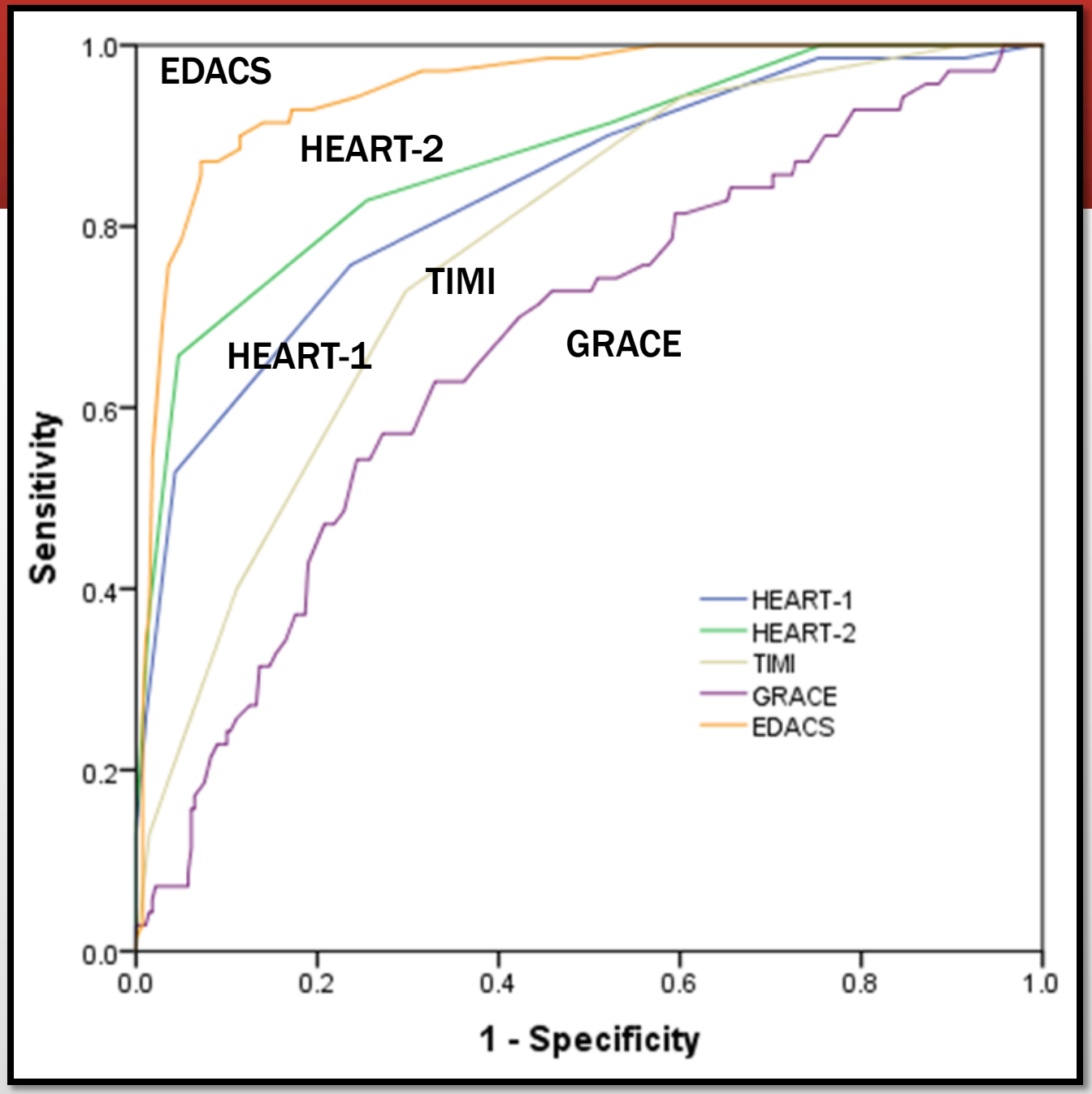
But Remember...

- A naked troponin is just a lab test
- The diagnosis of unstable angina is controversial
  - At least for the time being it is probably prudent to consider it is still with us

- So, what to do after 2 negative troponin's?

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



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

Is the 99th percentile the same for all assays and all people?

99th percentile Upper Reference Limit
Different for different populations

vs

Dr. Appel's email signature line:
Some simple advice for all of us: "Eat less, eat right, move more"

99th percentile Cutoffs, Healthy Individuals

- Siemens hsTnI 99th percentile USA individuals ranging from 22–91 years.
- Lithium-heparin plasma from 2007 apparently healthy individuals
- The 99th percentile sex specific values determined using the non-parametric statistical method described in CLSI Document EP28-A3c.23 determination.
- The 99th percentile values determined for lithium-heparin plasma (female, male, and combined). The 90% confidence intervals demonstrate that there is no statistical basis for using separate 99th percentile values based on sex.

Sample Type	Gender	n	99th Percentile[a] (pg/mL; ng/L)	90% CI[b] (pg/mL; ng/L)
Lithium Heparin	Female	1007	34.11	27.36–66.23
	Male	1000	53.48	38.73–80.22
	Combined	2007	45.20	33.21–64.30

Sex-Specific Cutoffs From

Siemens HIGH-US Study For HTnI FDA Clearance

Hours	Sensitivity	Specificity	Positive PV	Negative PV
	Female 99th percentile = 34.1 ng/L			
0–< 1.5	84.4 (71.2–92.3)	93.3 (90.4–95.3)	59.4 (47.1–70.5)	98.2 (96.3–99.1)
≥ 1.5–< 2.5	89.9 (81.3–94.8)	91.7 (89.4–93.5)	54.6 (46.0–62.9)	98.8 (97.7–99.4)
≥ 2.5–< 3.5	94.5 (86.7–97.8)	91.6 (89.2–93.6)	57.0 (48.1–65.5)	99.3 (98.2–99.7)
	Male 99th percentile = 53.5 ng/L			
0–< 1.5	75.0 (65.7–82.5}	91.5 (88.9–93.5)	61.0 (52.1–69.1)	95.4 (93.3–96.8)
≥ 1.5–< 2.5	87.6 (81.6–91.8)	91.2 (89.1–92.8)	63.8 (57.3–69.9)	97.6 (96.4–98.5)
≥ 2.5–< 3.5	89.8 (83.4–94.0)	90.0 (87.6–91.9)	60.5 (53.4–67.2)	98.1 (96.8–98.9)
	Pooled 99th percentile = 45.2 ng/L			
0–< 1.5	77.2 (69.8–83.3)	91.8 (89.9–93.4)	58.9 (51.8–65.7)	96.4 (95.0–97.4)
≥ 1.5–< 2.5	90.0 (85.6–93.2)	90.6 (89.1–91.9)	58.7 (53.6–63.6)	98.4 (97.6–98.9)
≥ 2.5–< 3.5	92.0 (87.5–95.0)	90.6 (88.9–92.0)	58.9 (53.4–64.2)	98.7 (97.9–99.2)

What other issues and considerations do we need to know?

Cardiac Troponin Units of Measure

ng/mL, Contemporary versus ng/L, High-sensitivity

- High-sensitivity • 19 ng/L
- Contemporary • 0.03 **ng/mL** **or 30 ng/L**
- High-sensitivity • 22**ng/L**
- Contemporary • 0.003**ng/mL** **or 3 ng/L**
- Contemporary • 0.30 **ng/mL** **or 300 ng/L**
- High-sensitivity • 14**ng/L**
- High-sensitivity • 6 **ng/L**

How does all of this fit in with the 4th universal definition of MI?

Today's fun fact:

All AMIs have increased hsTn. (95% at 3 hours)

BUT, not all hsTn increases are AMI. (50% at 3 hours)

Elevated Troponin in Patients without MI or Heart Failure

Kelley et al. Clin. Chem. 2009 Dec;55(12):2098-112

- **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

- 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

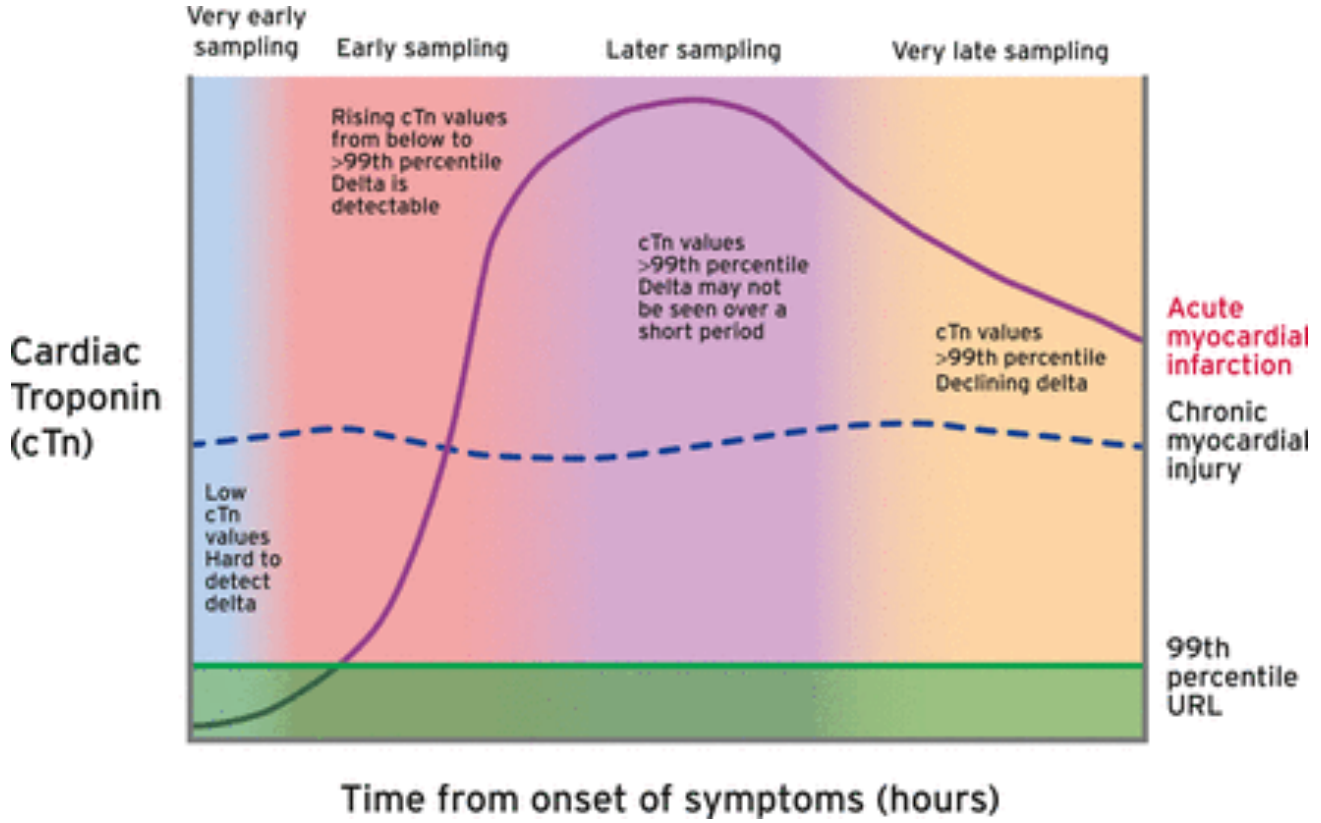
- Other Medications

- **Myocardial Injury**
- Blunt Chest Injury
- Endurance athletes
- Envenomation
- Snake
- Jellyfish
- Spider
- Centipede
- Scorpion

4th Universal Definition of Myocardial Infarction

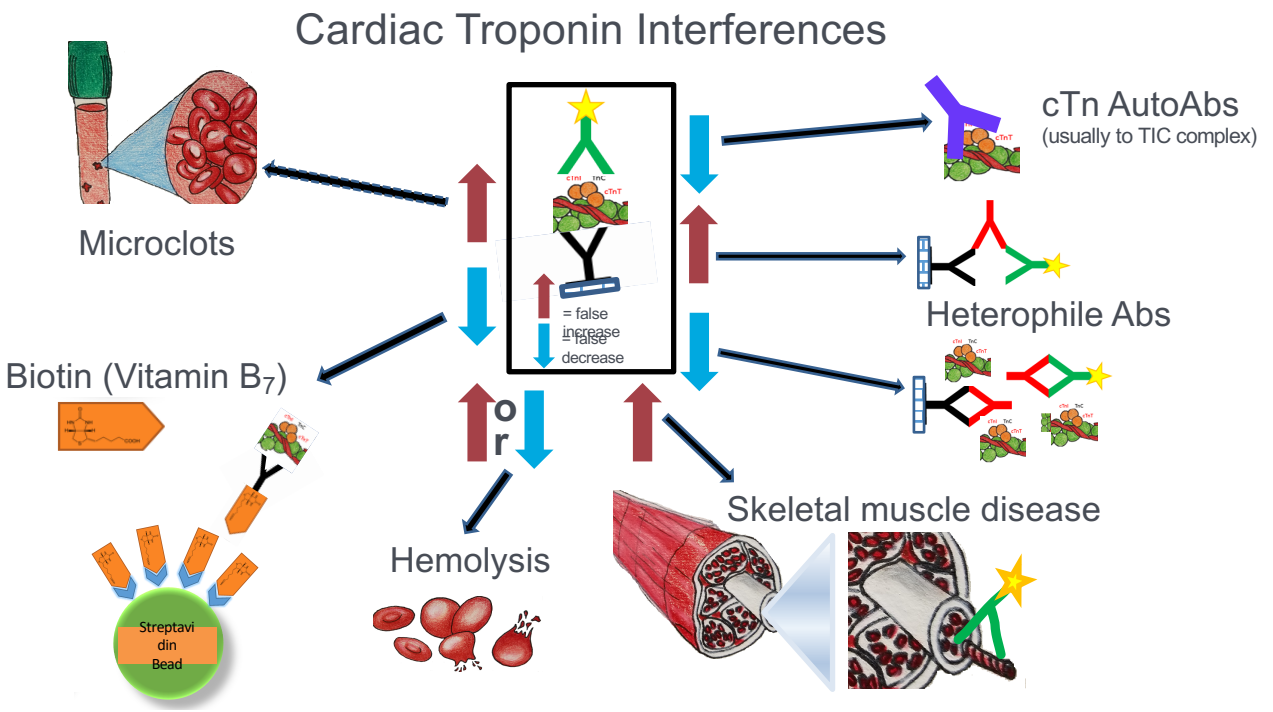
Eur Heart J. **2019** Jan 14;40(3):237-269.

- cTnI and cTnT are the preferred biomarkers for rule in and rule out myocardial injury, and thus to define MI and each specific subtype of MI.
- Detection of a rise and/or fall of cTn values is essential, and a key early component along with clinical evaluation to establish the diagnosis of acute MI



How does this affect reporting from a lab perspective?

Factors Affecting the Interpretation of Troponin Assays



High Sensitivity cTn Oriented for Rule-Out

<u>SnOut:</u>

- Sensitivity (TP/TP+FN) describes the ability of a test to identify true disease
  - A high *sensitivity* test has few **false negatives** and is effective at ruling conditions “out” (SnOut)

<u>SpIn:</u>

- Specificity (TN/TN+FP) describes the ability of an IVD test to correctly identify the absence of disease
  - A high *specificity* test has few **false positives** and is effective at ruling conditions “in” (SpIn).

JAMA Cardiol. 2018;3(2):104-111

Peacock et al.

Sample Time	No.	Performance (95% CI)			
		Sensitivity	Specificity	PPV	NPV
Overall URL (19 ng/L)					
0 h					
All	1600	86.0 (79.7-90.9)	88.0 (86.2-89.6)	44.9 (39.3-50.6)	98.2 (97.3-98.9)
Male	829	88.1 (80.2-93.7)	84.1 (81.2-86.7)	43.4 (36.5-57.5)	98.1 (97.0-99.0)
Female	771	82.5 (70.9-90.9)	91.9 (89.7-93.8)	47.7 (38.1-57.5)	98.3 (97.0-99.2)
3 h					
All	1415	94.3 (89.1-97.5)	86.6 (84.6-88.4)	43.6 (37.9-49.4)	99.3 (98.6-99.7)
Male	733	95.6 (89.1-98.8)	83.0 (79.9-85.8)	44.4 (37.3-51.6)	99.3 (98.1-99.8)
Female	682	91.8 (80.4-97.7)	90.2 (87.6-92.4)	42.1 (32.6-52.0)	99.3 (98.2-99.8)

hs Beckman Assay

Preliminary Data

99th percentile URL cutoff, pg/mL (ng/L)	Hours After Admission to ED	Sensitivity		Specificity		PPV		NPV	
		% (n/N)	95% CI	% (n/N)	95% CI	% (n/N)	95% CI	% (n/N)	95% CI
Females: 14.9	Baseline	83 (25/30)	65 - 94	91 (234/256)	87 - 95	53 (25/47)	38 - 68	98 (234/239)	95 - 99
	≥ 1-3 hour	93 (40/43)	81 - 99	92 (490/535)	89 - 94	47 (40/85)	36 - 58	99 (490/493)	98 - 100
	≥ 3-6 hour	96 (48/50)	86 - 100	92 (509/556)	89 - 94	51 (48/95)	40 - 61	100 (509/511)	99 - 100
	≥ 6-9 hour	100 (22/22)	85 - 100	88 (198/225)	83 - 92	45 (22/49)	31 - 60	100 (198/198)	98 - 100
Males: 19.8	Baseline	89 (63/71)	79 - 95	87 (271/311)	83 - 91	61 (63/103)	51 - 71	97 (271/279)	94 - 99
	≥ 1-3 hour	96 (89/93)	89 - 99	88 (490/557)	85 - 91	57 (89/156)	49 - 65	99 (490/494)	98 - 100
	≥ 3-6 hour	94 (96/102)	88 - 98	88 (536/607)	86 - 91	58 (96/167)	50 - 65	99 (536/542)	98 - 100
	≥ 6-9 hour	98 (48/49)	89 - 100	81 (183/225)	76 - 86	53 (48/90)	43 - 64	100 (183/184)	97 - 100

Any closing thoughts?

UDMI

3rd UDMI	4th UDMI
I: Plaque pathology causes a thrombus II: Supply-demand imbalance III: AMI causing death without a biomarker measured IVa: AMI related to PCI IVb: AMI related to stent thrombosis V: AMI related to CABG	II: Supply-demand imbalance unrelated to thrombus, AND with ischemia Tn elevation in the absence of ischemia is defined as myocardial injury

Thygesen K. European Heart Journal (2012) 33, 2551–2567 doi:10.1093/eurheartj/ehs184
Thygesen K. European Heart Journal (2018) 00, 1–33 doi:10.1093/eurheartj/ehy462

Summary

- hsTn
  - Faster
  - Cheaper
  - Finds more patients with disease
  - CONSIDER PHYSIOLOGY!
    - Too early is dangerous
- Risk
  - Use a score, don’t be dumb

For More Information

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