Primary care and use of high sensitivity troponins - here they come!

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disclosures

- Research: Abbott, Alere, Critical Dx. Novartis,
- Consulting: Critical Dx, Amgen, Trinity, Alere

CHEST PAIN?
Get to hospital fast.
Heart Foundation

Consequences……

What happens to an emergency doc who gets it wrong…..?

The single greatest award against emergency physicians:

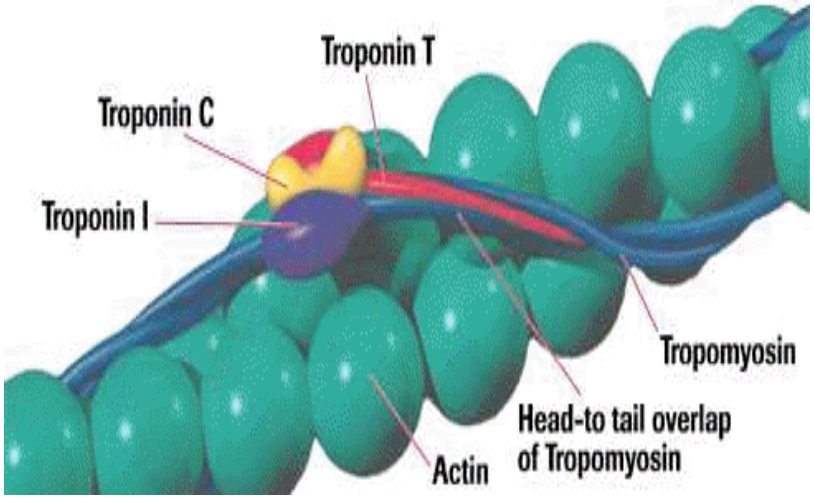
MISSED MYOCARDIAL INFARCTION

remember

- Early troponin assays were easy to use, providing simple "yes/no" answers because of their relative lack of sensitivity.
- They worked well, and troponins became an integral part of the universal definition of myocardial infarction

TROPONIN T

A regulatory protein released when cardiac cell necrosis occurs.



"Despite the pervasive measurement of cardiac troponin for the diagnosis of myocardial infarction, the continued evolution of assays and guidelines for their application has created uncertainty among many practitioners regarding the use of cutoff values for clinical interpretation. As such, many clinicians may not welcome more sensitive assays for troponin."

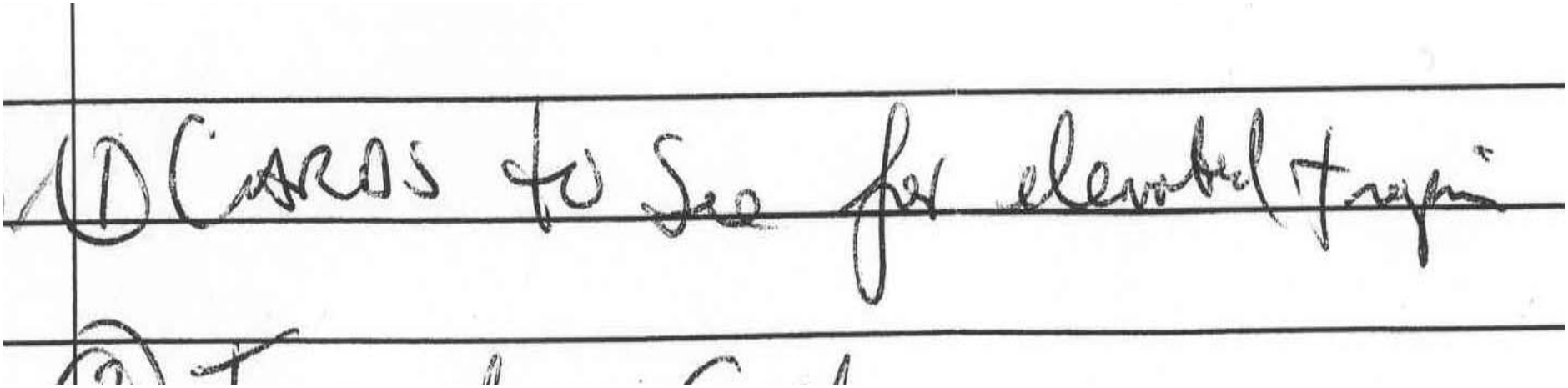
D Morrow, N Engl J Med 361:913, August 27, 2009

Quote -4-24-09 San Diego Biomarker Meeting R. Jesse MD

- “Troponin was great when it was a crappy assay.”
- “Now that it is a good assay, it sucks!”

Once a Troponin is “elevated”, the cat is out of the bag

“Cards to See for Elevated Troponin”



“Troponinemia” is NOT a diagnosis

- I have observed medical housestaff cast off the significance of elevated troponin levels in a patient by “troponinemia” and moving on, as if that were an explanation in and of itself

The fact is

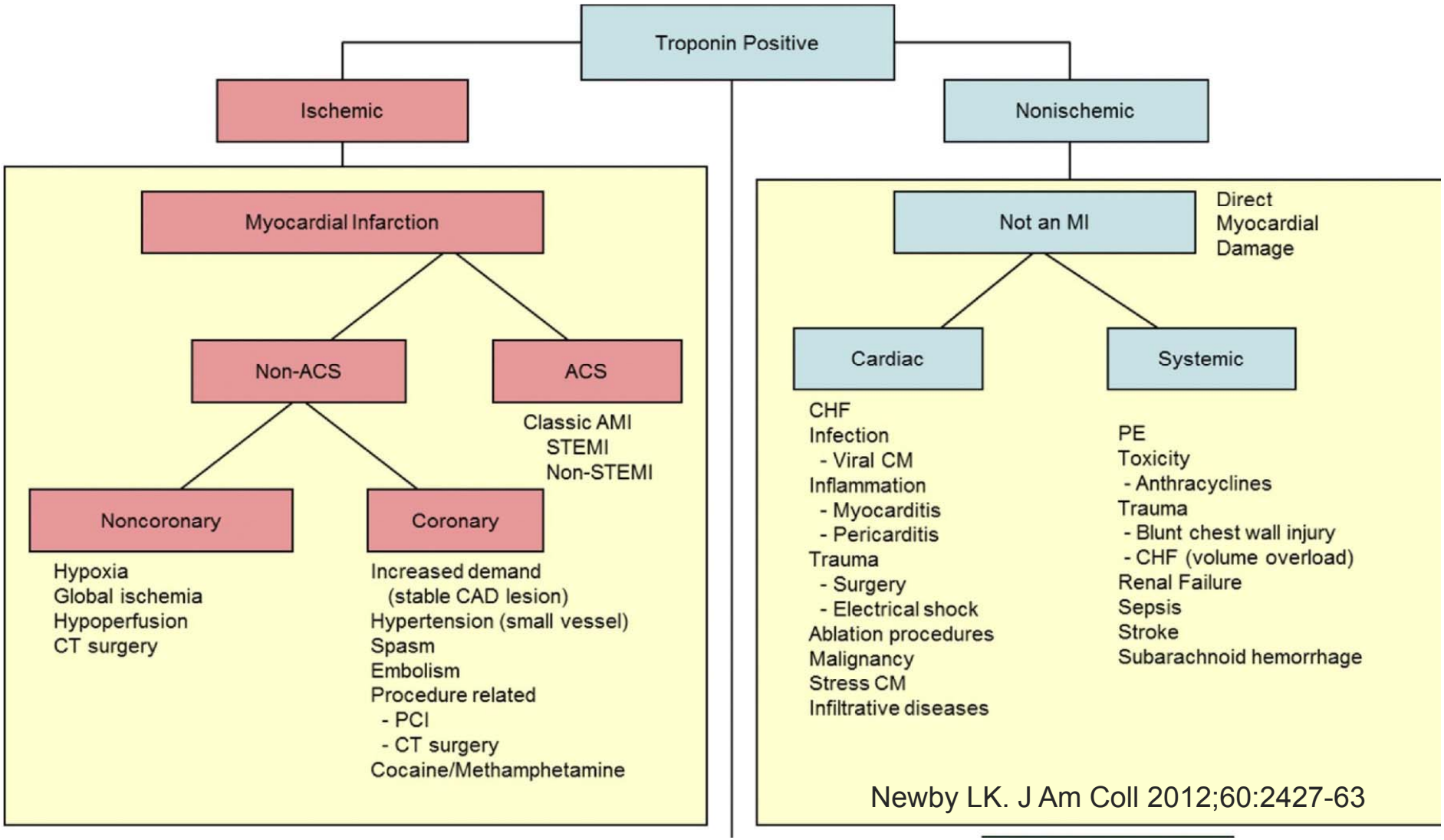
- Troponin assays are getting better- so much so, in fact, that we as clinicians need to similarly evolve in our understanding of how we can use them most effectively.

Most recently, “highly sensitive” troponin assays have emerged which can, by definition, detect troponin in over 50% of the general population. The most sensitive of these can detect troponin in almost everyone.

no longer simple binary “yes/no” but needs to be interpreted as continuous variables, and within a greater context of age, sex, and renal function

Evolution of clinical interpretation of cardiac troponin results

Not all elevations are acute myocardial infarction



Newby LK. J Am Coll 2012;60:2427-63

Background: High Sensitive (hs) Troponin (Tn) Assays

- All new troponin assays with improved sensitivity are not necessarily highly sensitive.
- High sensitive (hs) is an adjective that describes the assay method and not a different type of protein in the blood.
- While there is not an universally accepted definition for hsTn methods, experts have shared consensus opinion within recent literature.

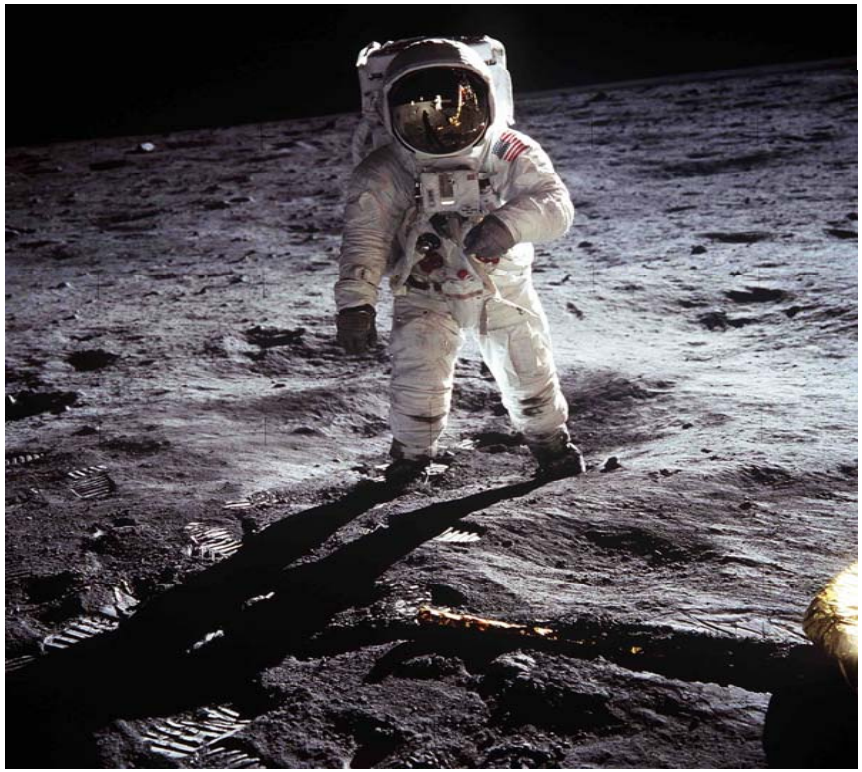
Assay designation	Measurable normal values below the 99th percentile, %
Level 4 (third generation, hs)	≥95
Level 3 (second generation, hs)	75 to <95
Level 2 (first generation, hs)	50 to <75
Level 1 (contemporary)	<50

Apple FS. A new season for cardiac troponin assays: it's time to keep a scorecard. Clin Chem 2009;55:1303–6.

First things first: Definition of elevation

- An *increased concentration of troponin* is defined as a level that exceeds the 99th percentile of a reference population – URL.

In 100 patients – 1 will be misclassified as false positive regardless of the assay used.



Alpert JS et al. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol. 2000 Sep;36(3):959-69*

Universal Definition of Myocardial Infarction

***Circulation.* 2007;116(22):2634-2653**

Criteria for acute myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
  - Symptoms of ischaemia;
  - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)];
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

And..

The Troponin assay should have

an imprecision of <10% coefficient of variation (CV)

at the 99th percentile (URL).

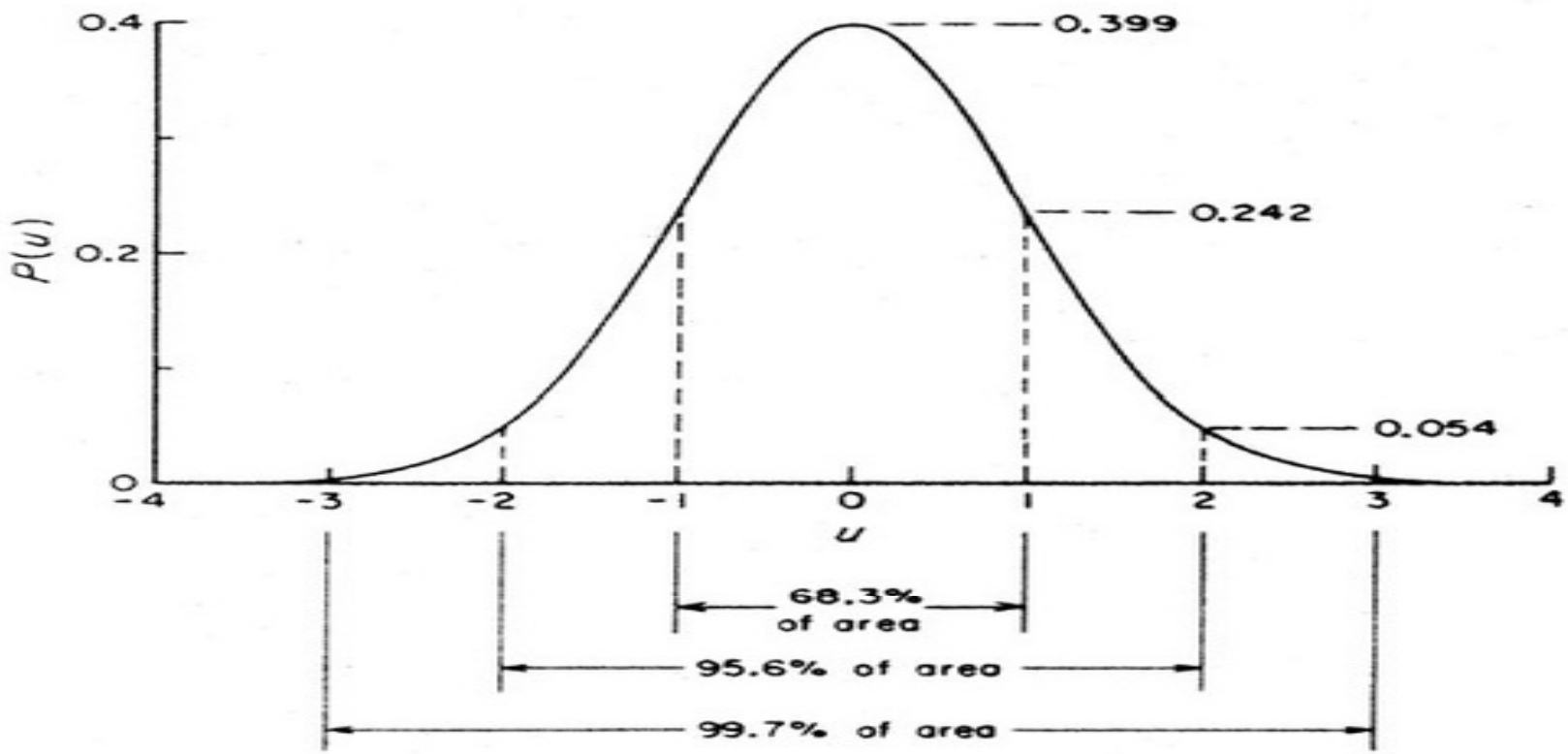
Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation. 2007 Nov 27;116(22):2634-53.*

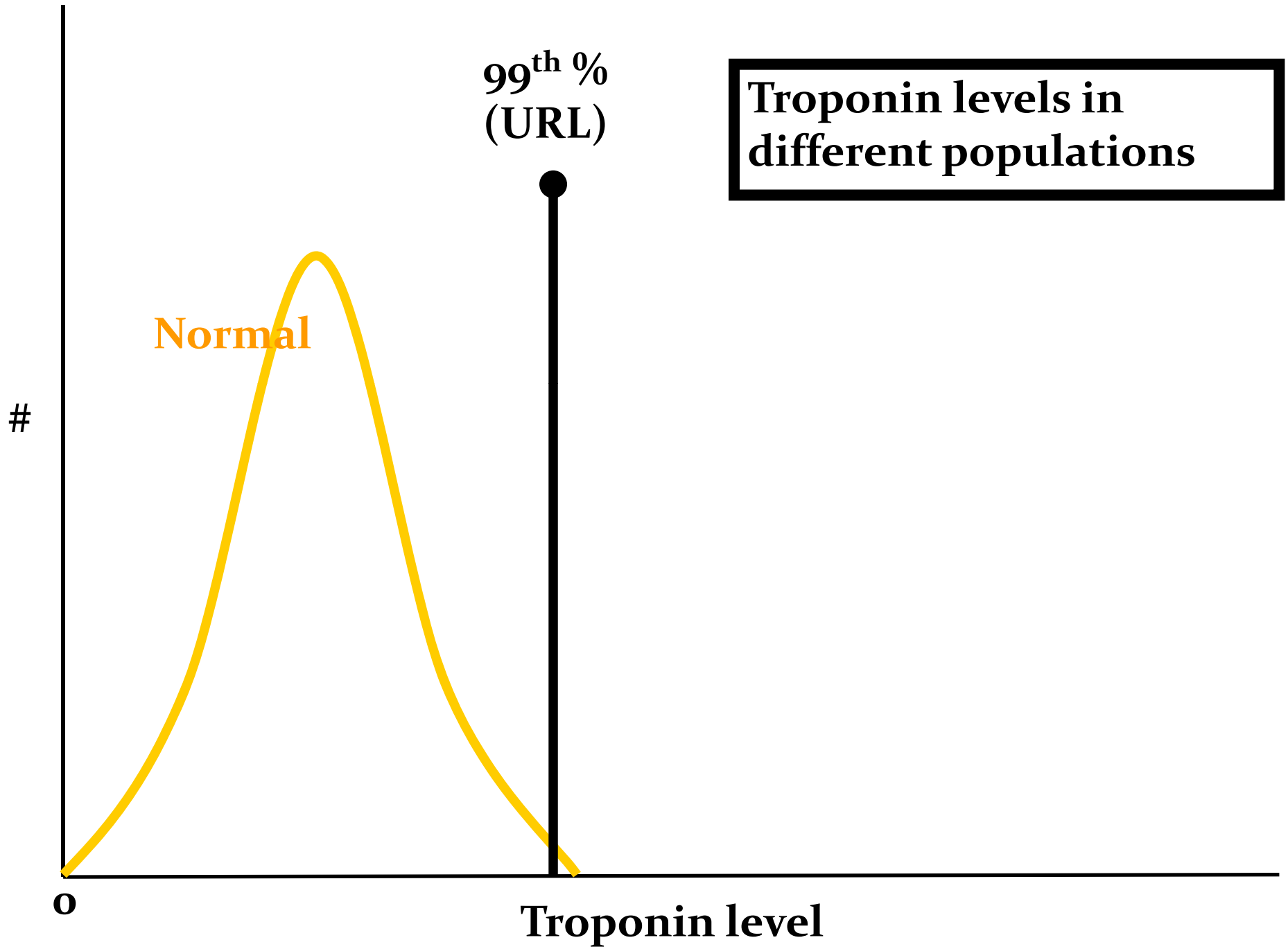
Critical values to know about troponin assays

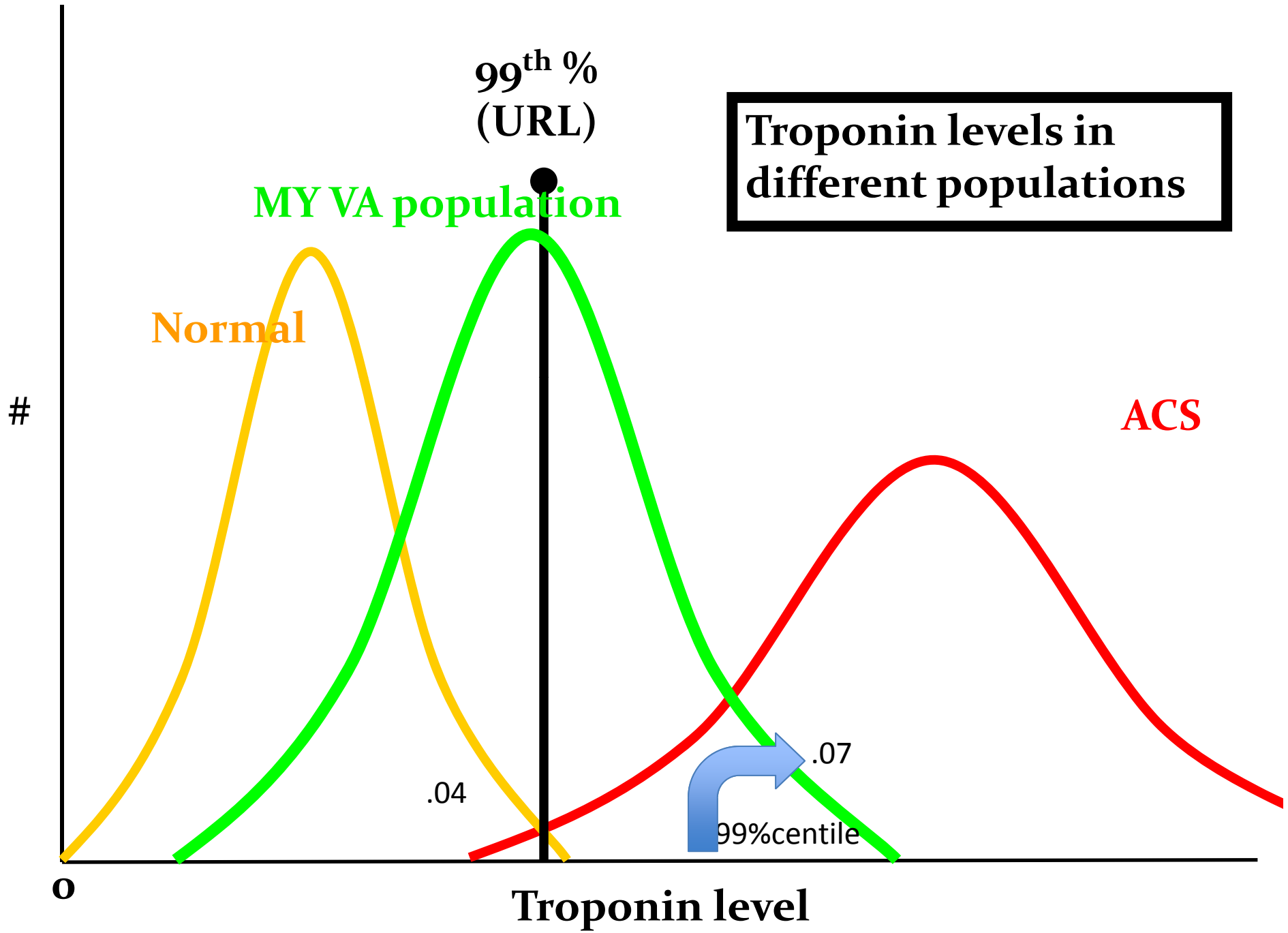
- URL – upper reference level
- CV – co-efficient of variation
- LoD – limit of detection

UPPER REFERENCE LEVEL (URL)

= 99th percentile of the URL of the normal population

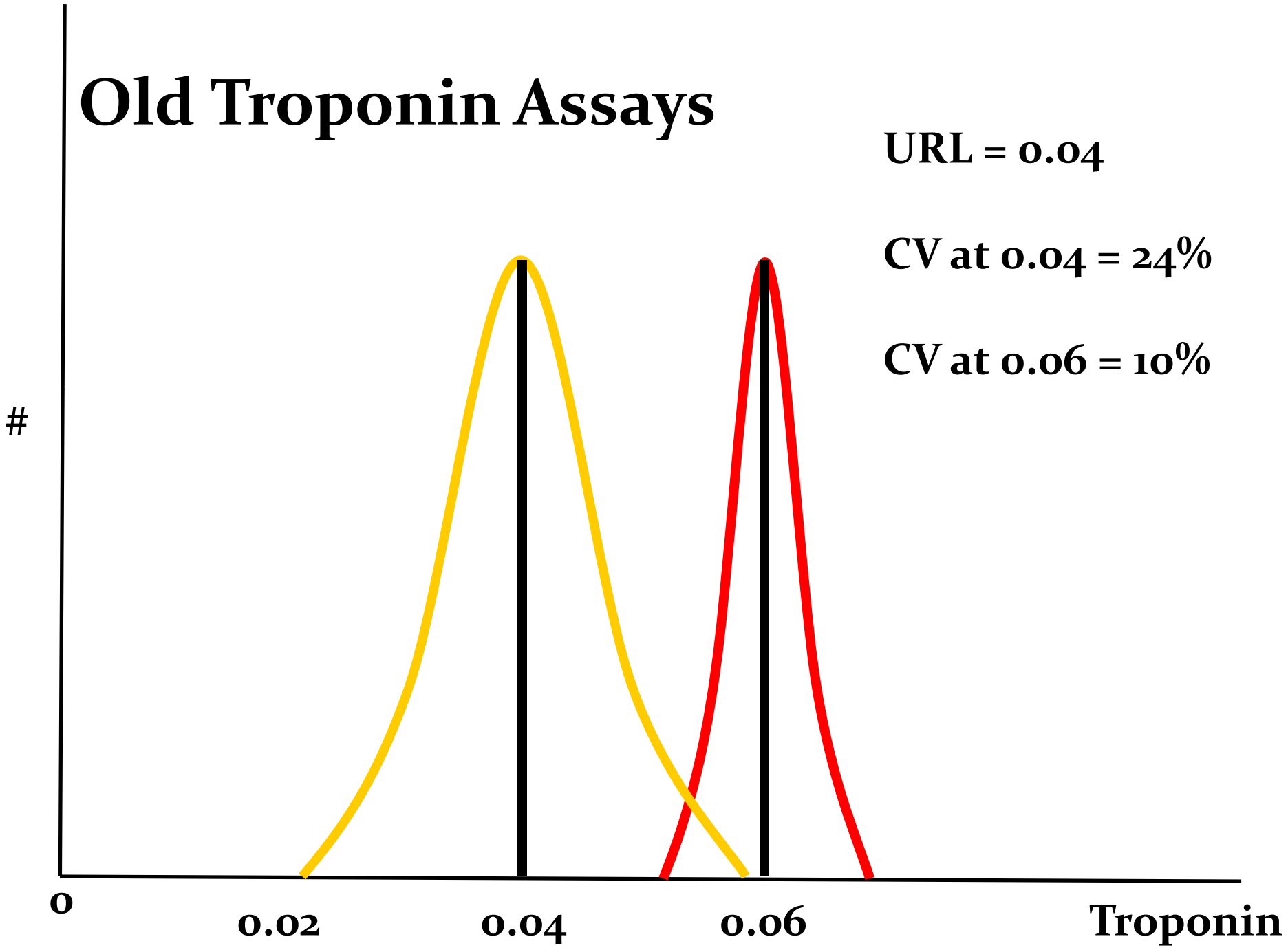



99th %
(URL)
Troponin levels in different populations
Normal
#
0
Troponin level

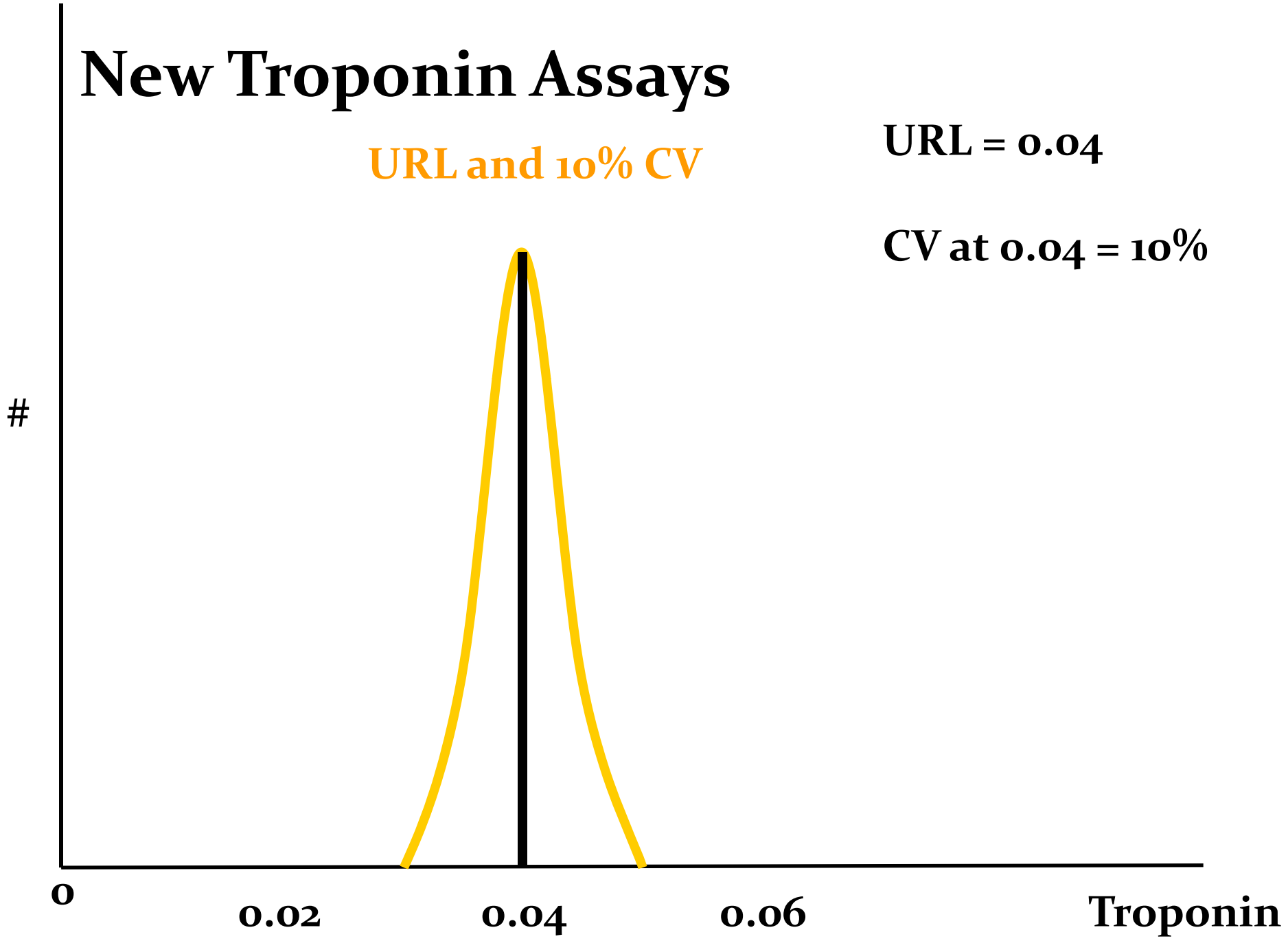

99th %
(URL)
Troponin levels in different populations
MY VA population
Normal
ACS
#
.04
.07
99%centile
0
Troponin level

Coefficient of variation (CV)

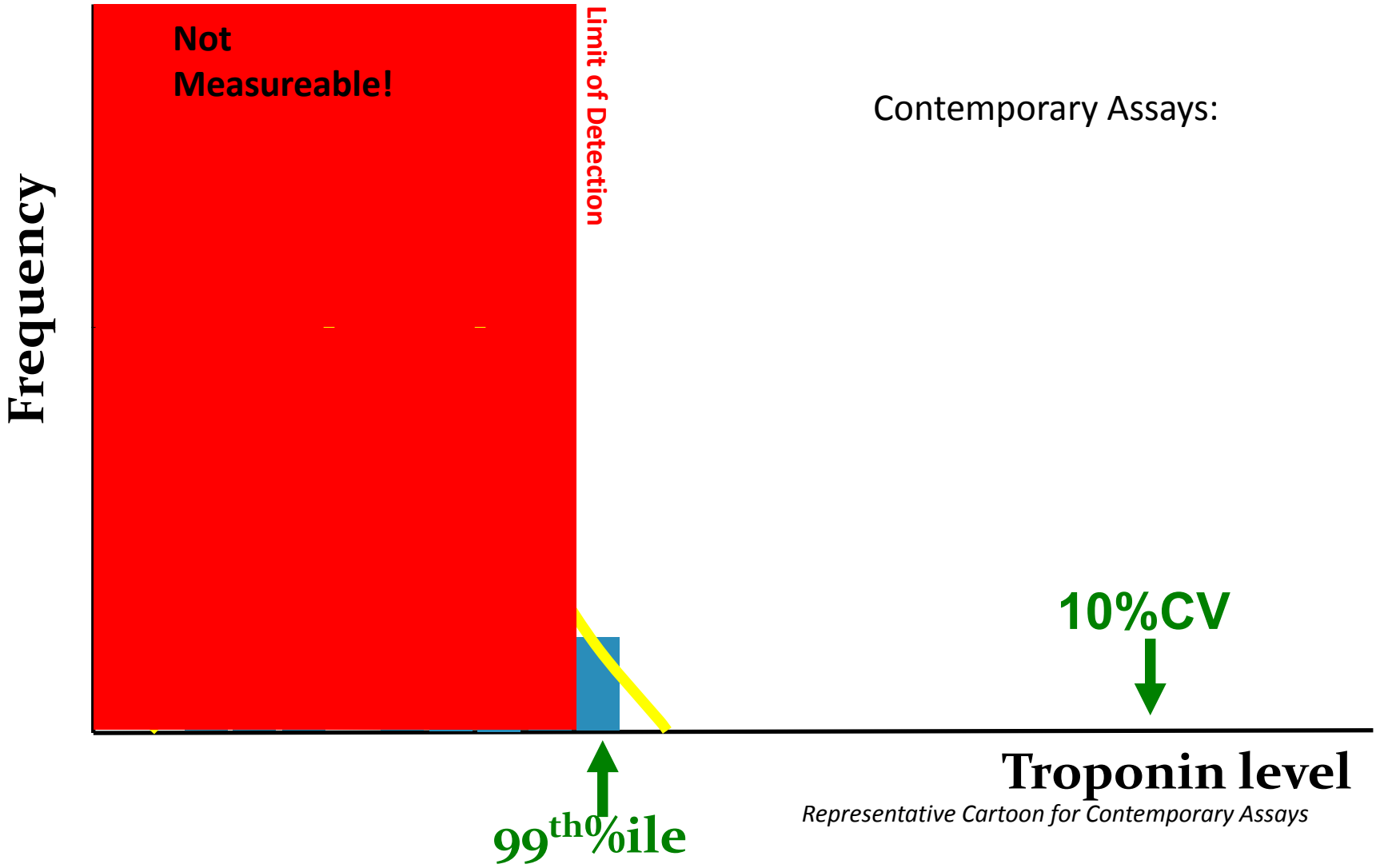
- A measure of how consistently an assay is able to produce the same result on the same sample.
- It is defined as the ratio of the standard deviation (σ) to the mean (μ): CV= σ/μ


Old Troponin Assays
URL = 0.04
CV at 0.04 = 24%
CV at 0.06 = 10%
#
0
0.02
0.04
0.06
Troponin

New Troponin Assays



What is meant by % Detection above the LoD?



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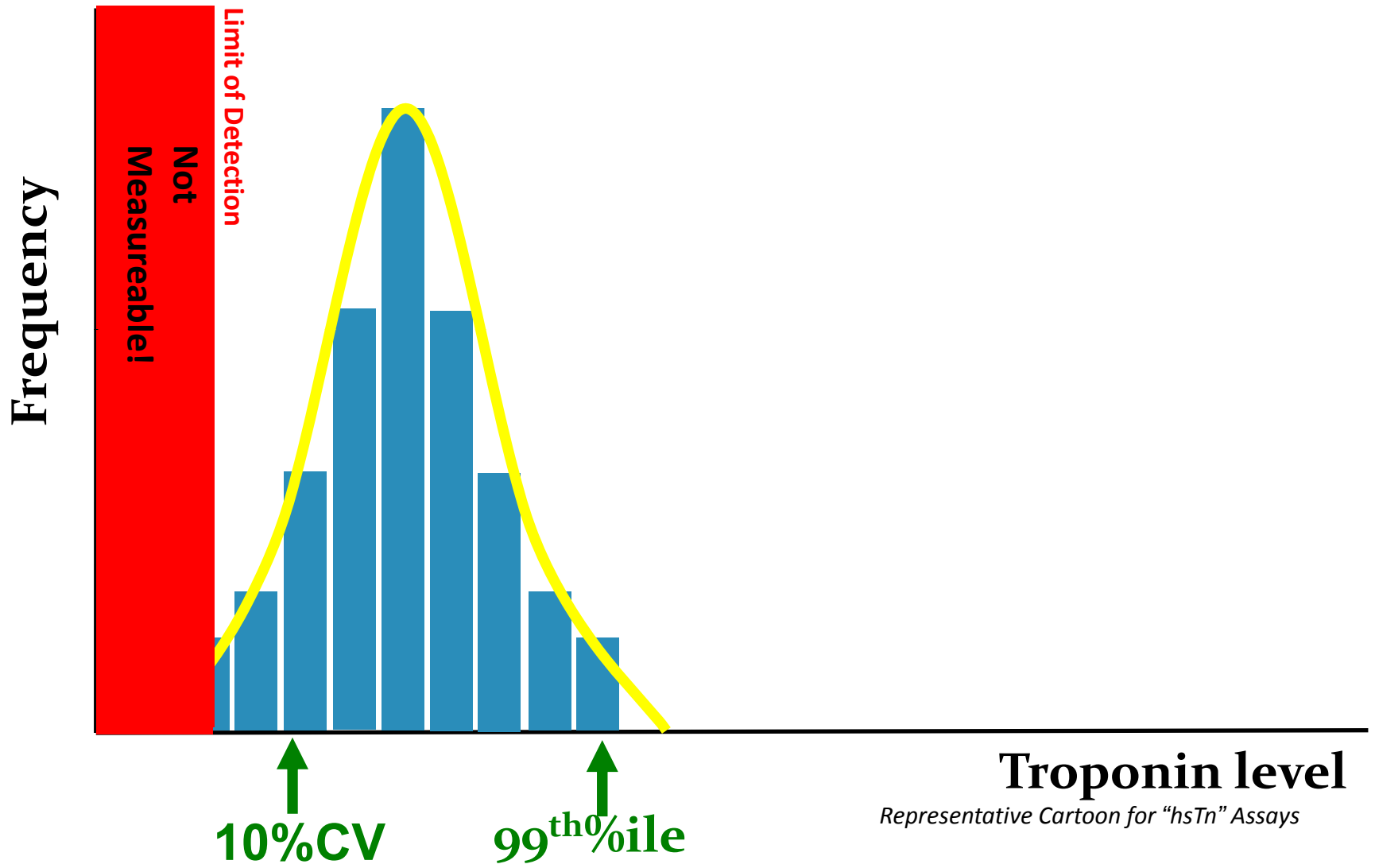

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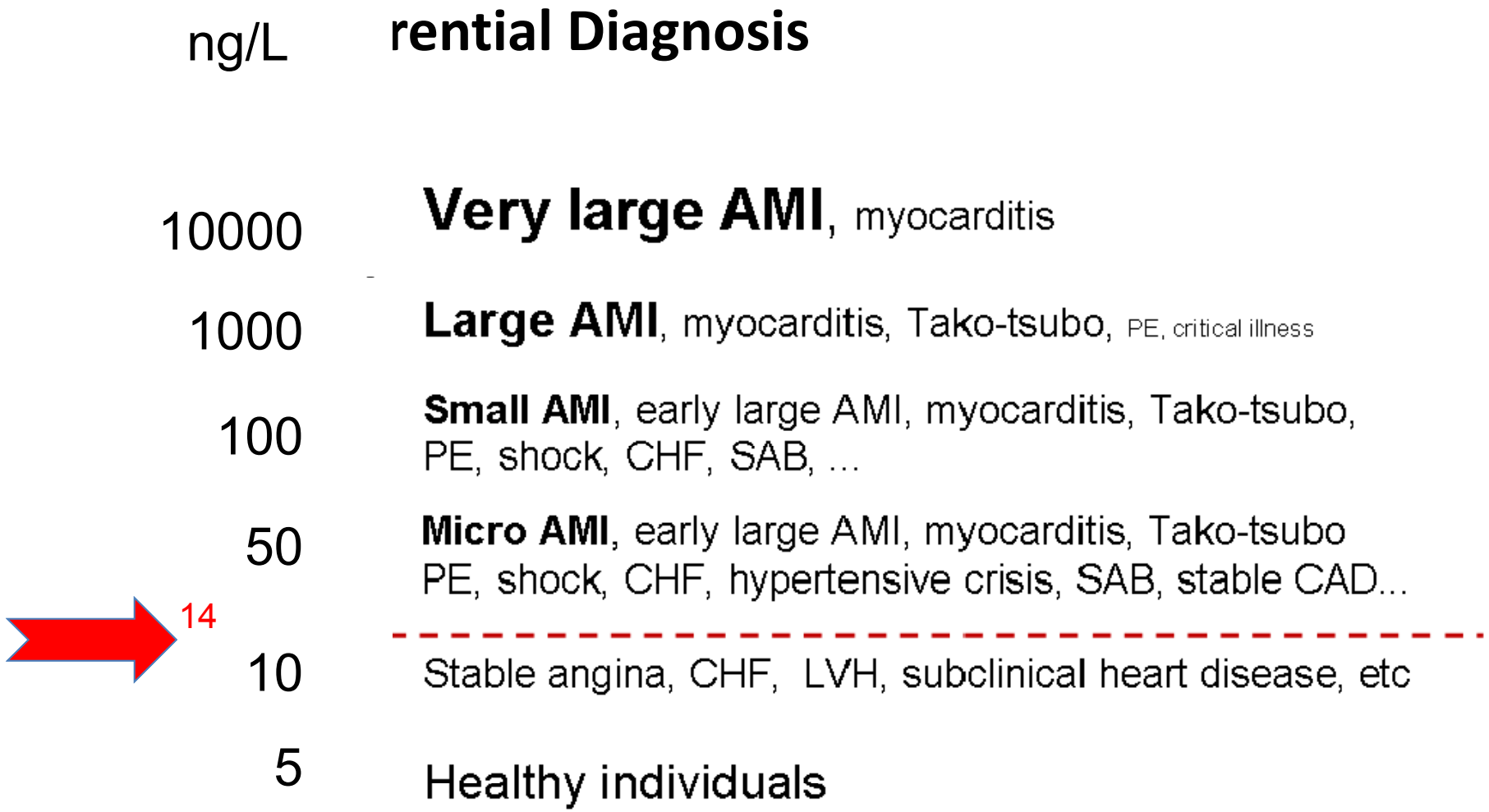
Comparison a Contemporary and hsTn Assay

	ARCHITECT TnI*		ARCHITECT hsTnI**	
	µg/L (ng/mL)	ng/L (pg/mL)	µg/L (ng/mL)	ng/L (pg/mL)
LoD	0.010	10	0.002	1.9
10%CV	0.032	32	0.005	4.5
99%ile	0.028	28	0.026	26.2
% Detectable above LoD	<50% of normals		>50% of normals	

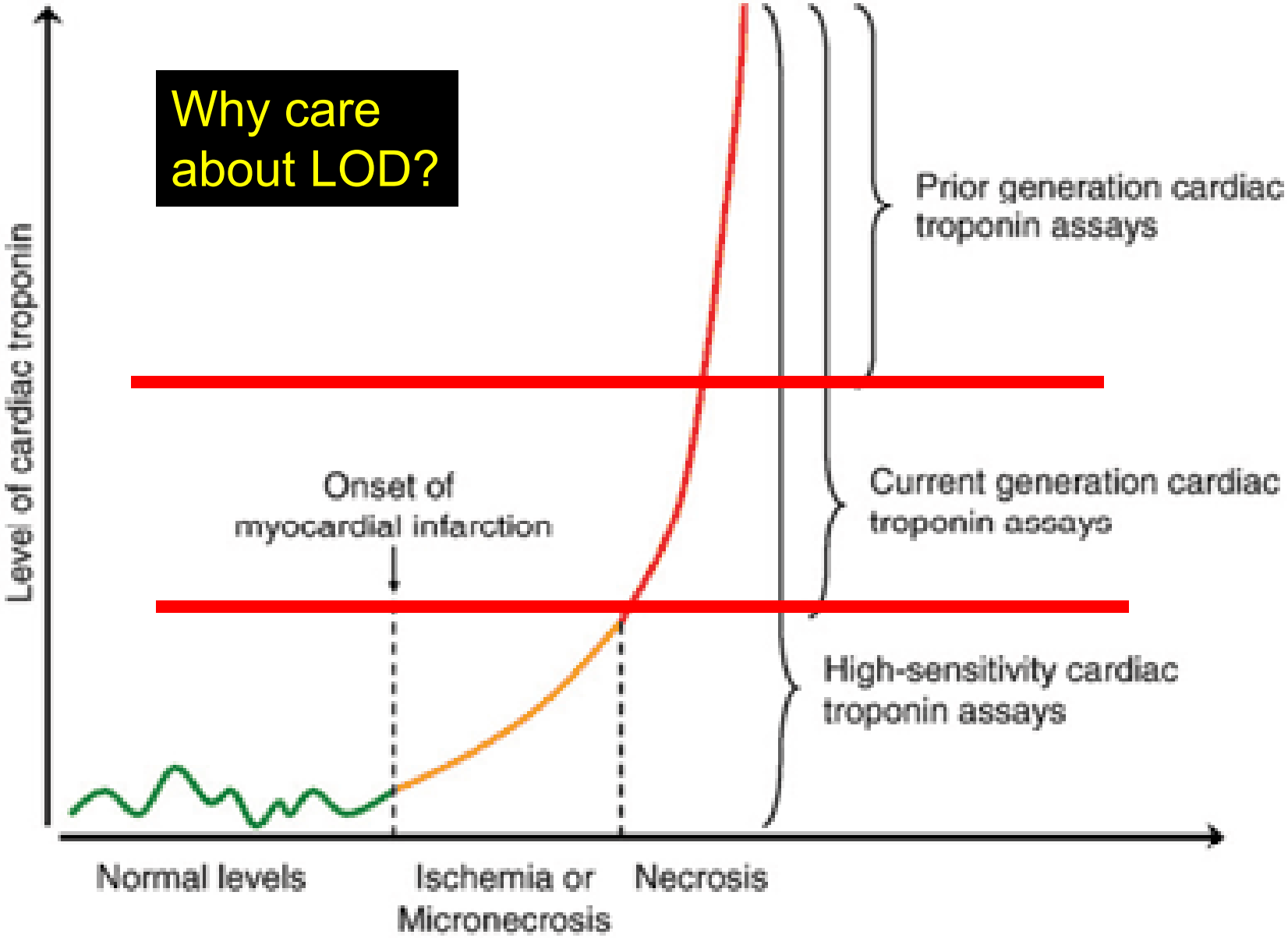
**Representative data from package insert **Internal R&D Final Verification Data*

- ~7x Improvement in precision without significant change to 99th%ile
- Increased percent detection rate of cardio-healthy or “normal” subjects

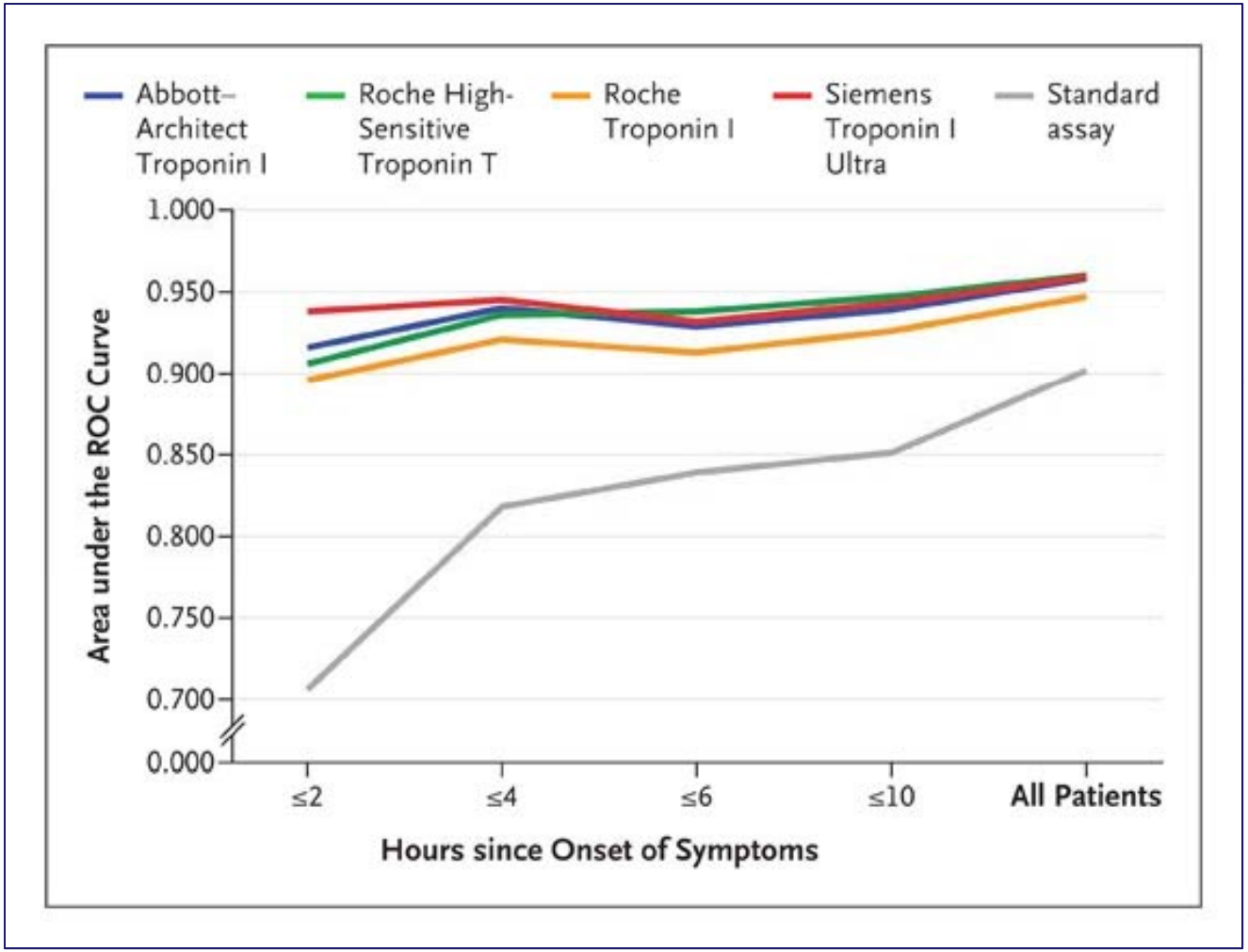
Hs-cTn: Quantitative marker of cardiomyocyte injury



Mueller C. Eur Heart J 2014


Why care about LOD?
Level of cardiac troponin
Prior generation cardiac troponin assays
Current generation cardiac troponin assays
High-sensitivity cardiac troponin assays
Onset of myocardial infarction
Normal levels
Ischemia or Micronecrosis
Necrosis

Diagnostic Accuracy of Cardiac Troponin Assays at Presentation According to Time since Onset of Chest Pain



718 consecutive patients with chest pain
17% with myocardial infarction

Reichlin T et al. N Engl J Med 2009;361:858-867

Algorithms for rule out MI in ED with hs Troponins

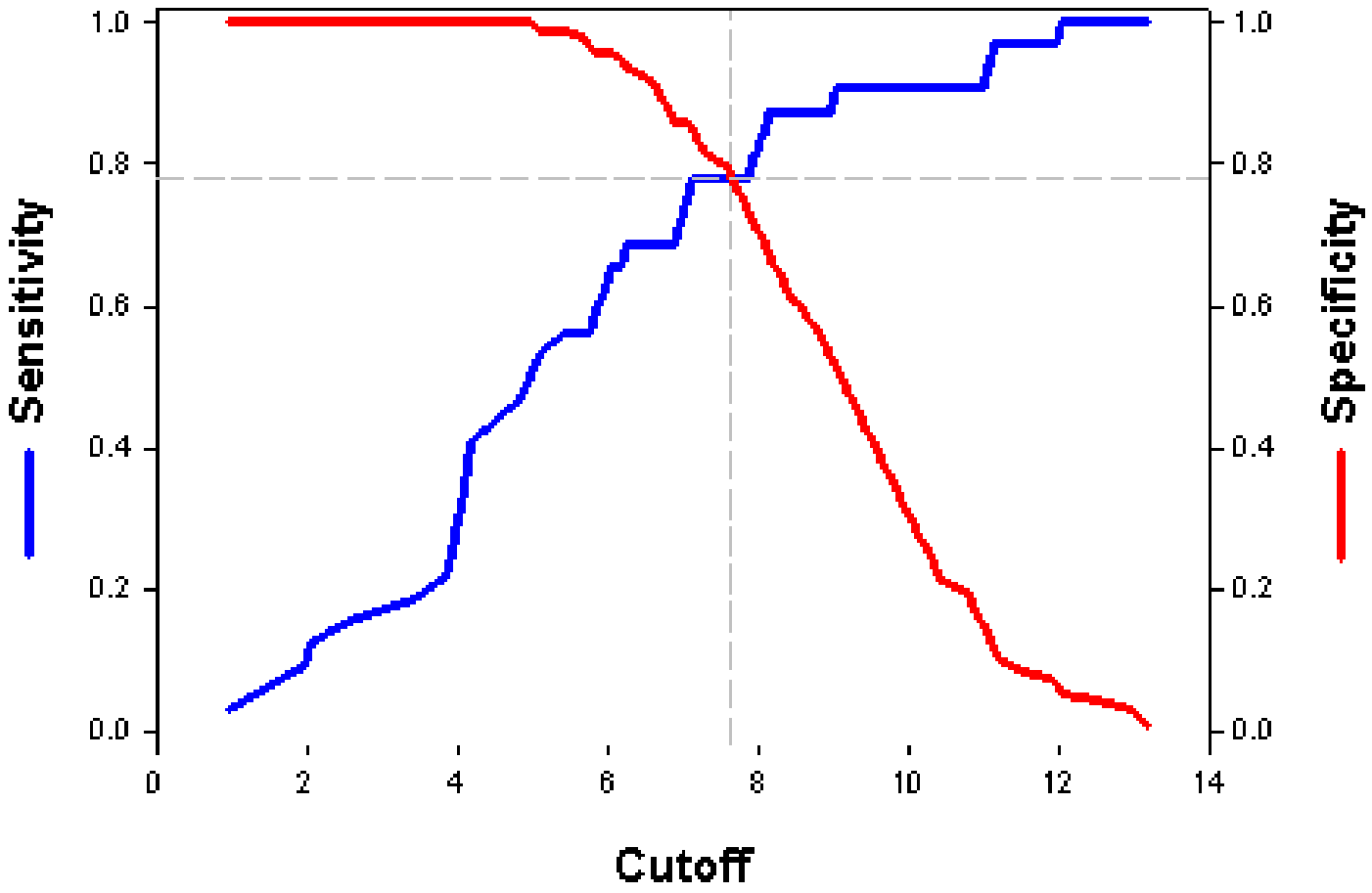
- One and done
  - Must have chest pain > 2 hours
  - Not a great story
  - No ecg changes
  - Low framingham risk score
  - (negative copeptin may be
  - Helpful)

Algorithms for rule out MI ir hs Troponins

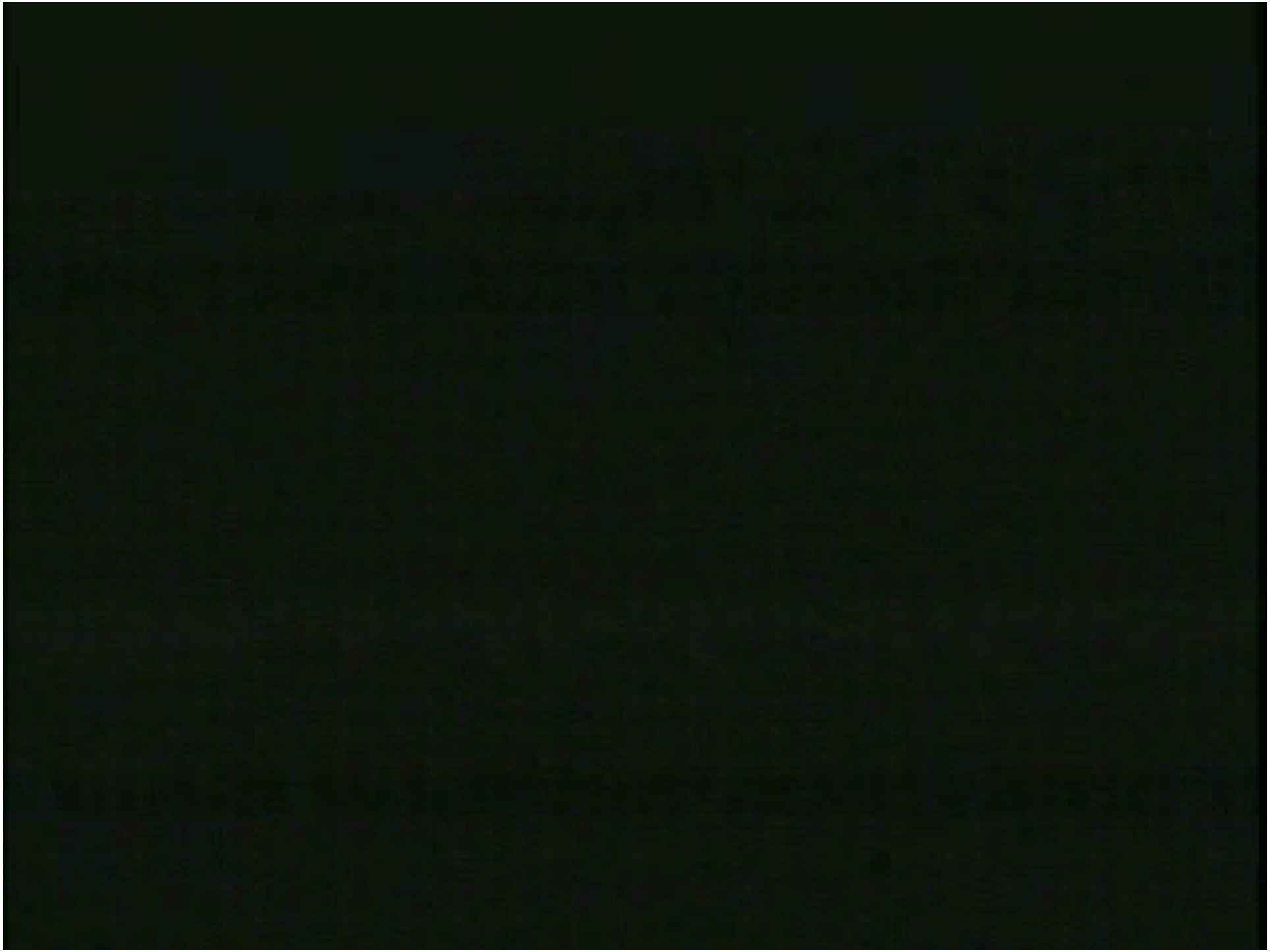
- Two negative troponins
  - Must have chest pain > 2 hours
  - Troponins should be 2-4 hours apart
  - No ecg changes.

  - Clinical story Trumps troponin- at least for
  - observation

You can't have it both ways...

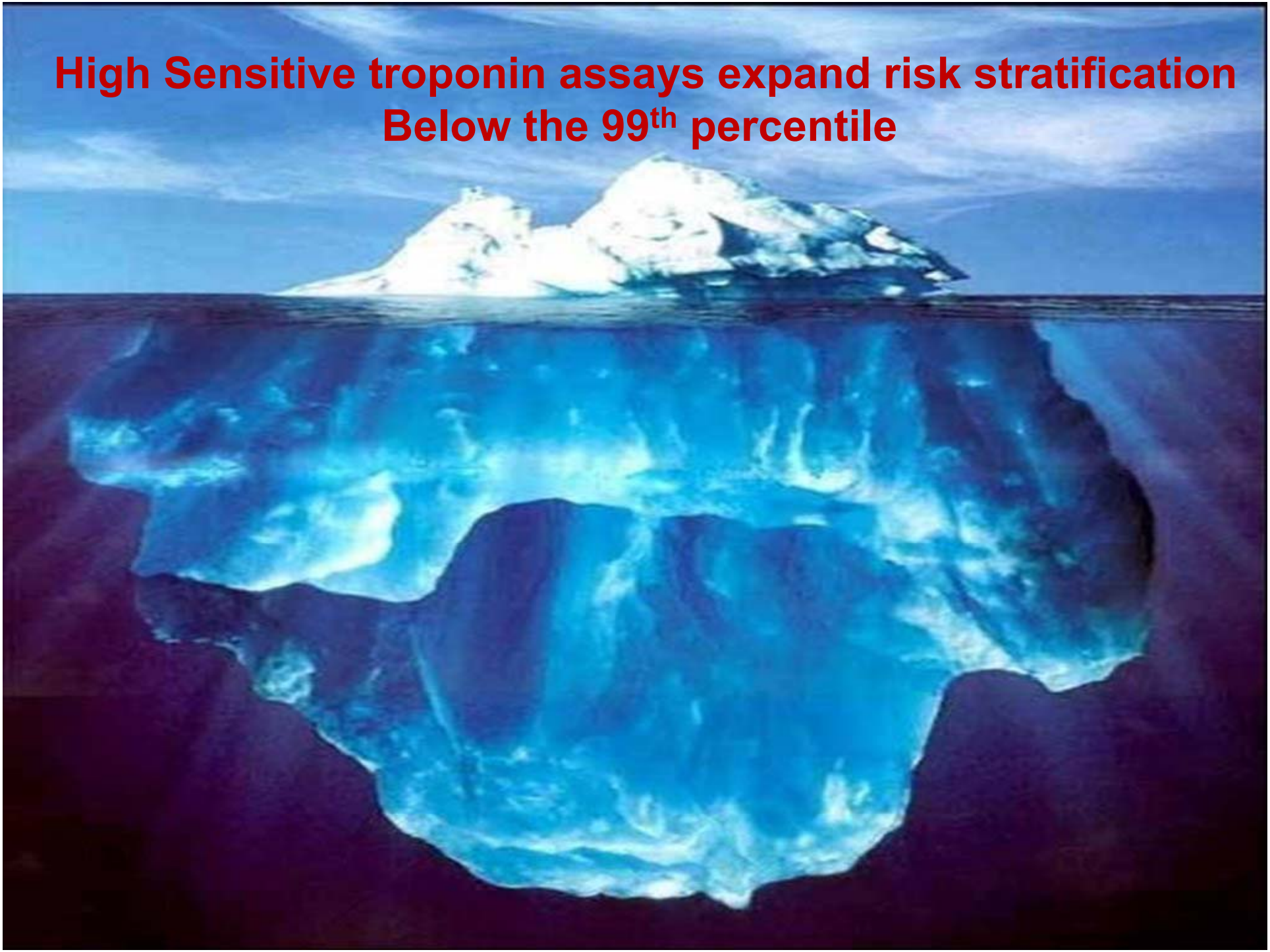


- The future is the home troponin test



“High sensitivity Troponin:

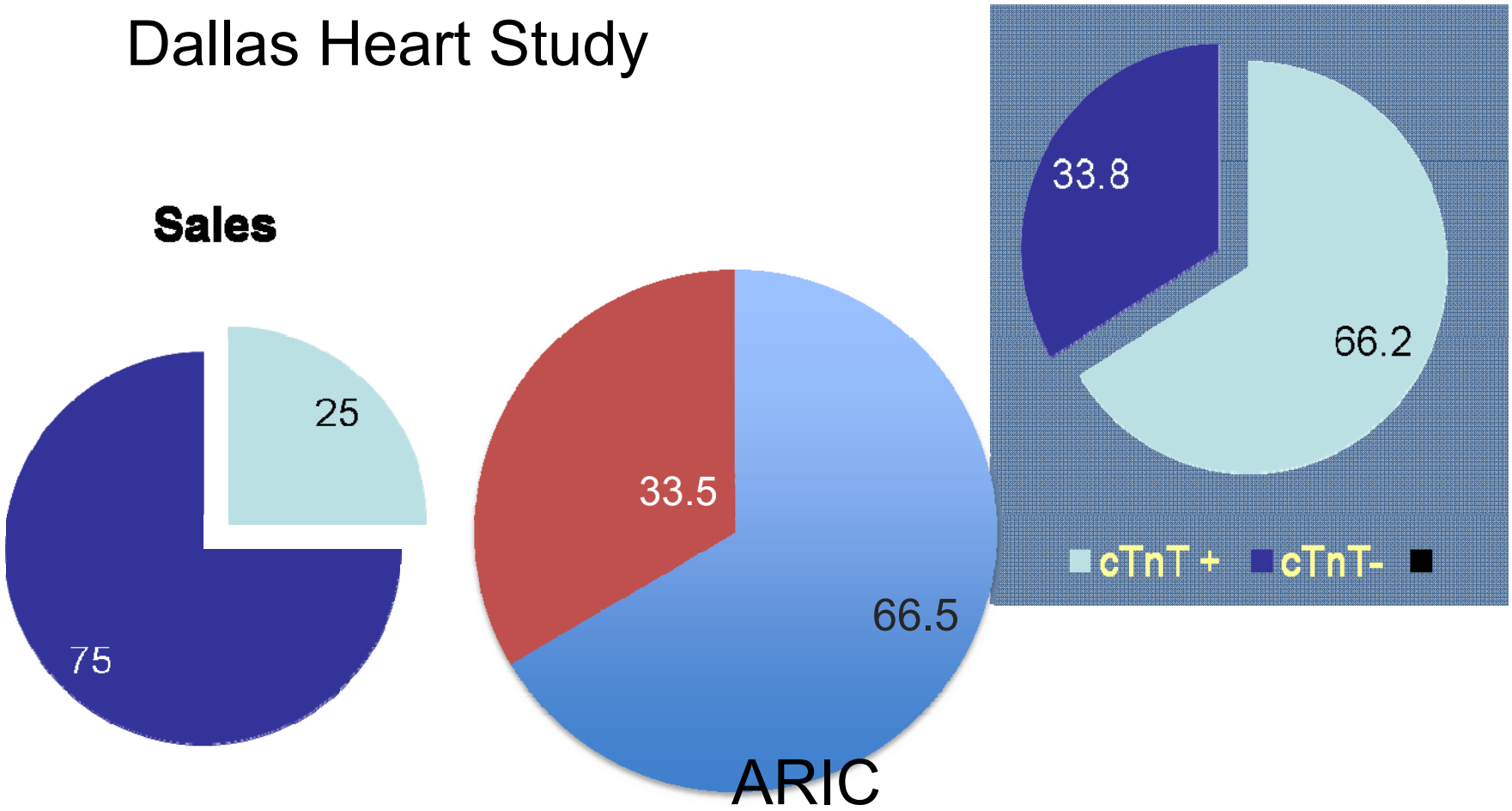
Uses beyond MI


High Sensitive troponin assays expand risk stratification
Below the 99th percentile

Proportion of Adults with Detectable cTnT (>3ng/L)

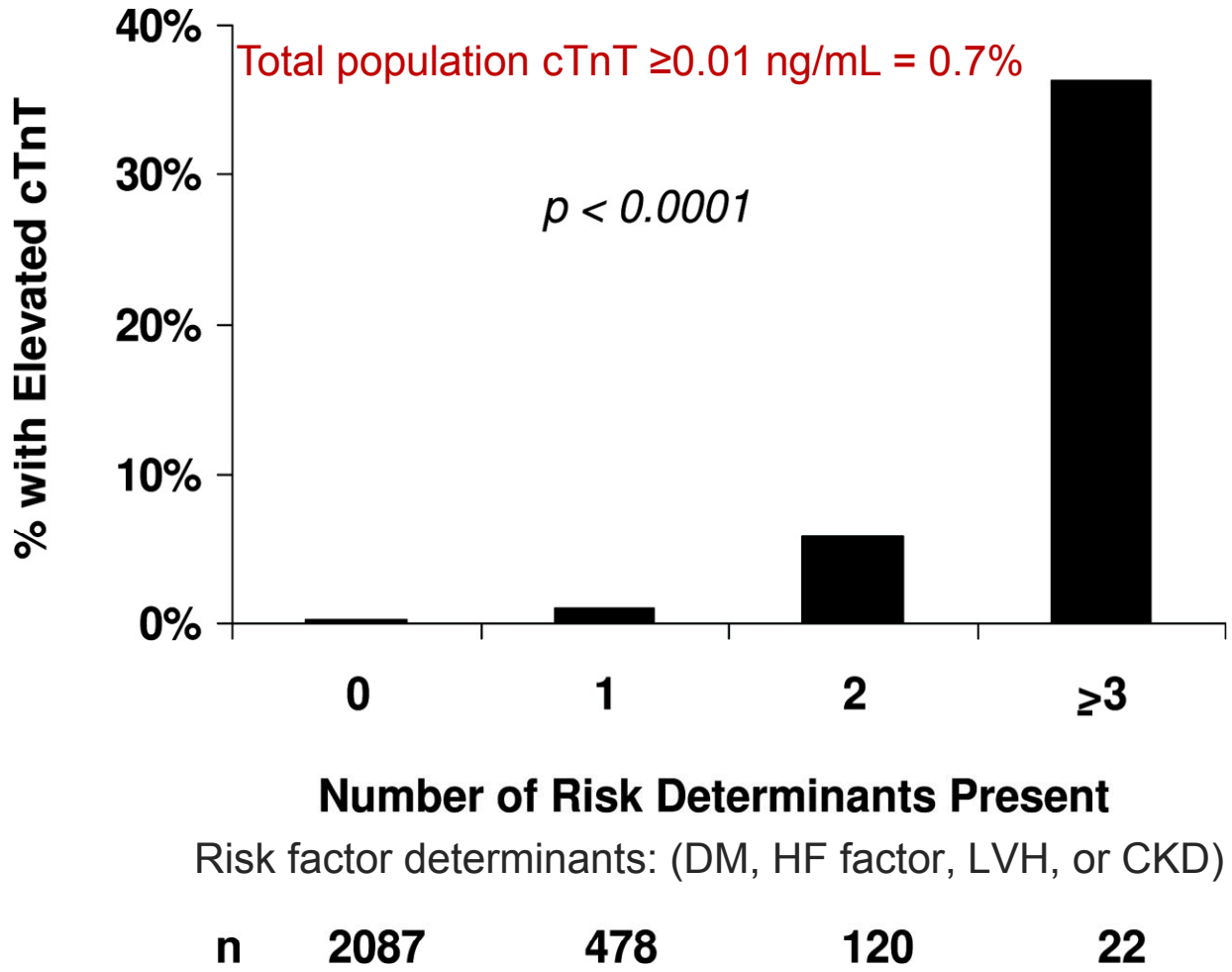
Cardiovascular Health Study

Dallas Heart Study



ARIC

Proportion of subjects with elevated contemporary cTnT levels in the general population



Wallace TW. Circulation 2006;113:1958-1965

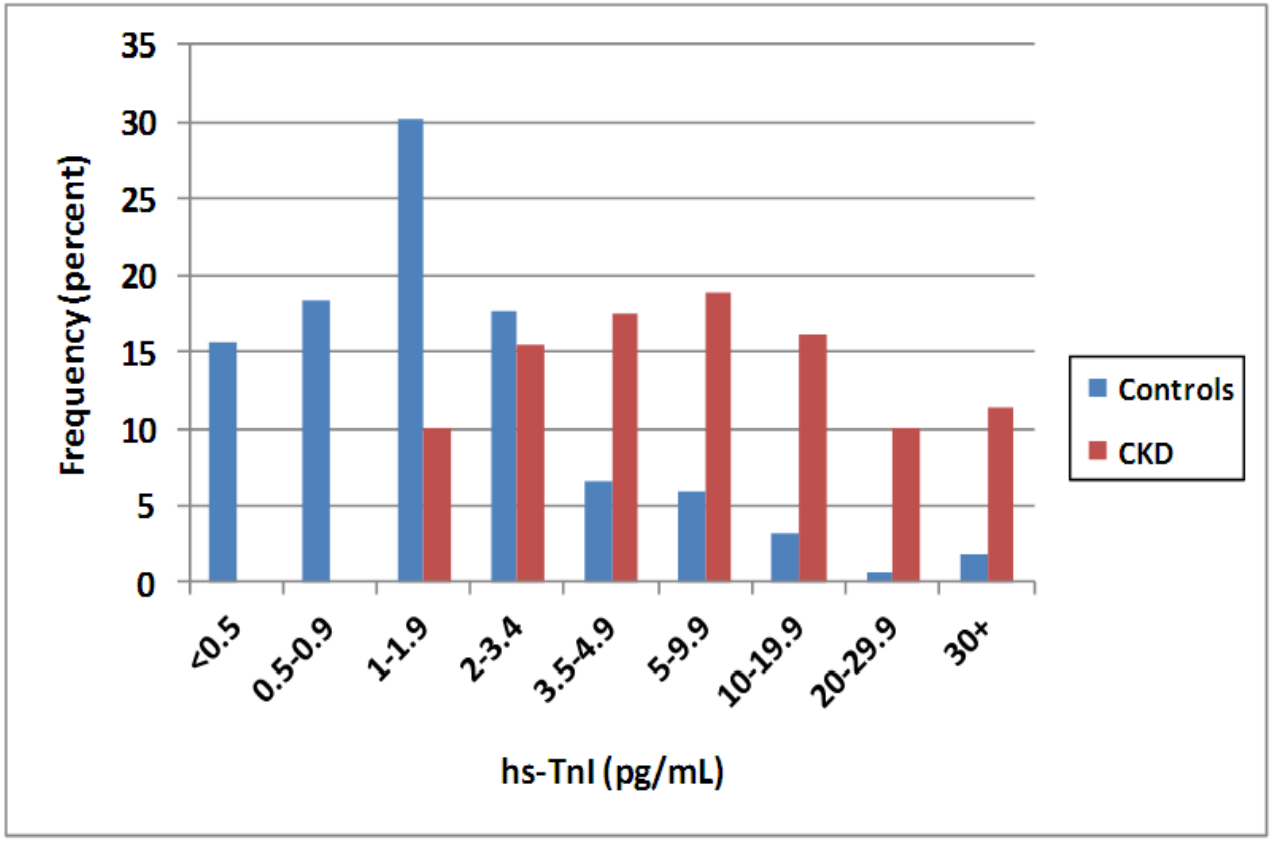
Multivariate Analysis of Risk Determinants for cTnT Elevation in the General Population

Risk factor	OR	95% CI
DM	4.6	1.8–11.6
LVH	5.4	2.0–14.6
CKD	**20.4**	**7.5–55.3**
CHF factor	5.3	1.9–14.8

CKD defined as eGFR < 60 mL/min/1.73m^2

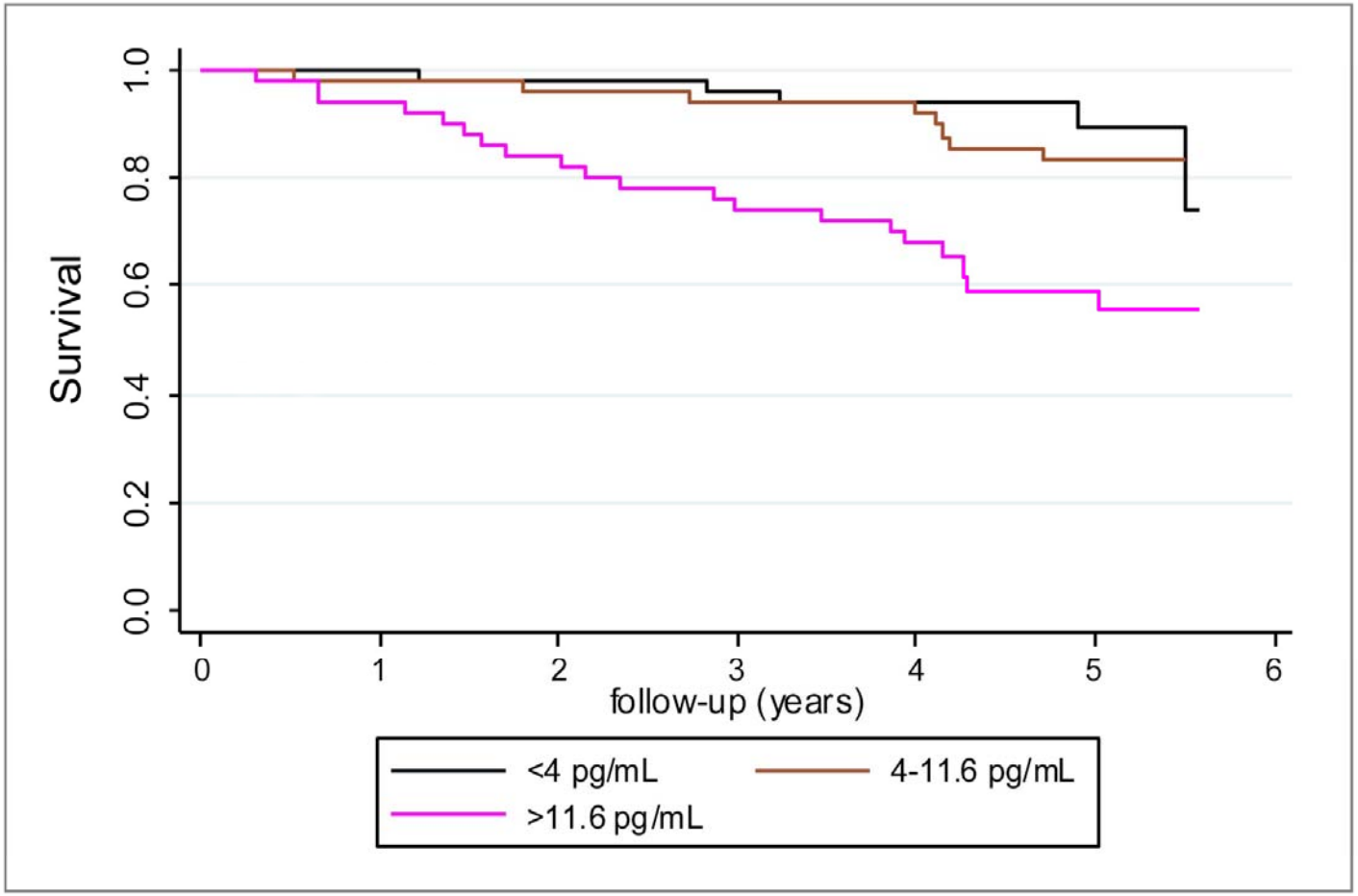
Wallace TW. Circulation 2006;113:1958-1965

Distribution of cTnI values measured by a Siemens hs assay in subjects with CKD (n=148) and a healthy control population (n=288).



deFilippi C. Clin Chem 2012;58:1342-51

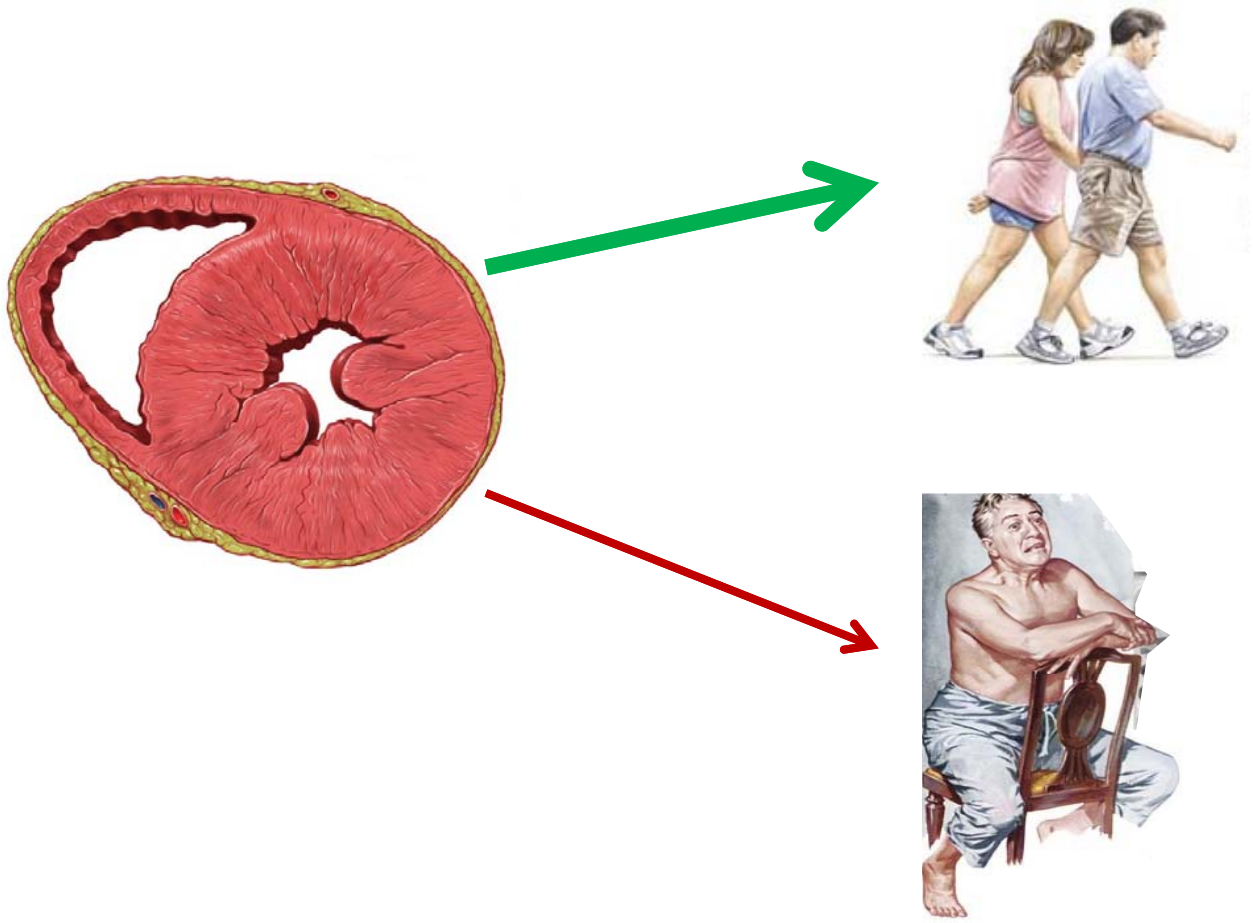
Survival based on hs cTnI values in ambulatory CKD subjects



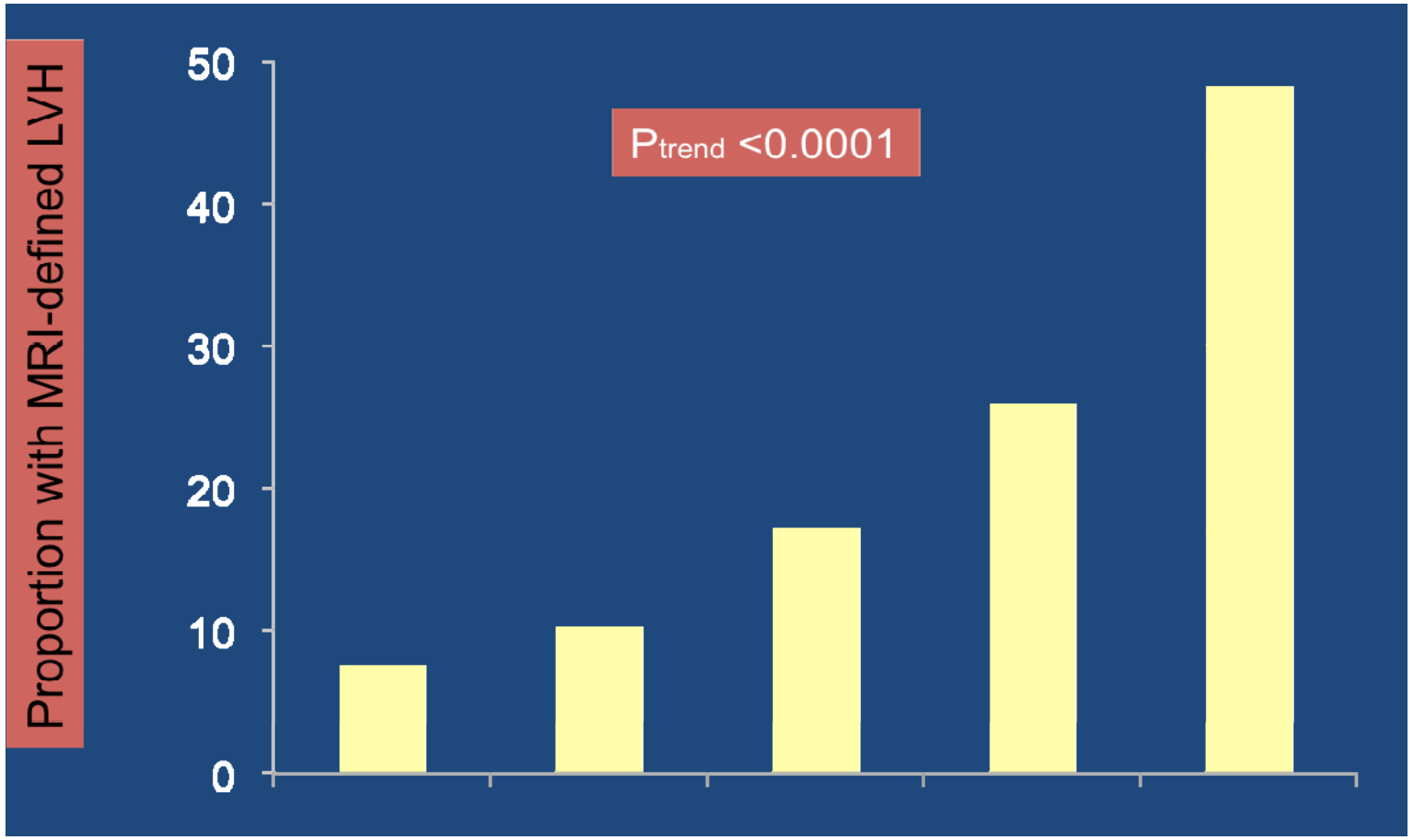
deFilippi C. Clin Chem 2012;58:1342-51

Left Ventricular Hypertrophy

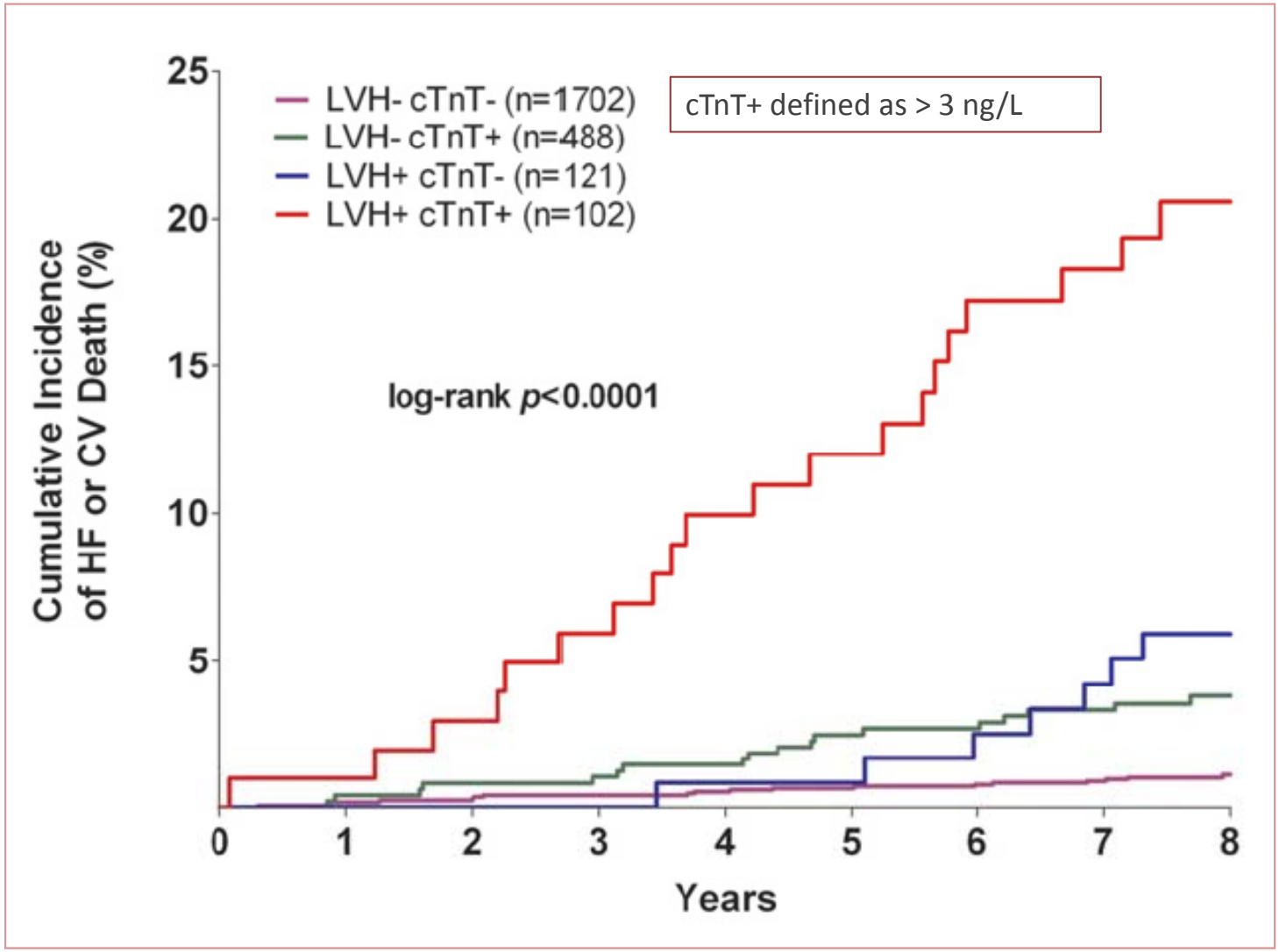
Heterogeneous Progression to Heart Failure



Dose-dependent Association with LVH



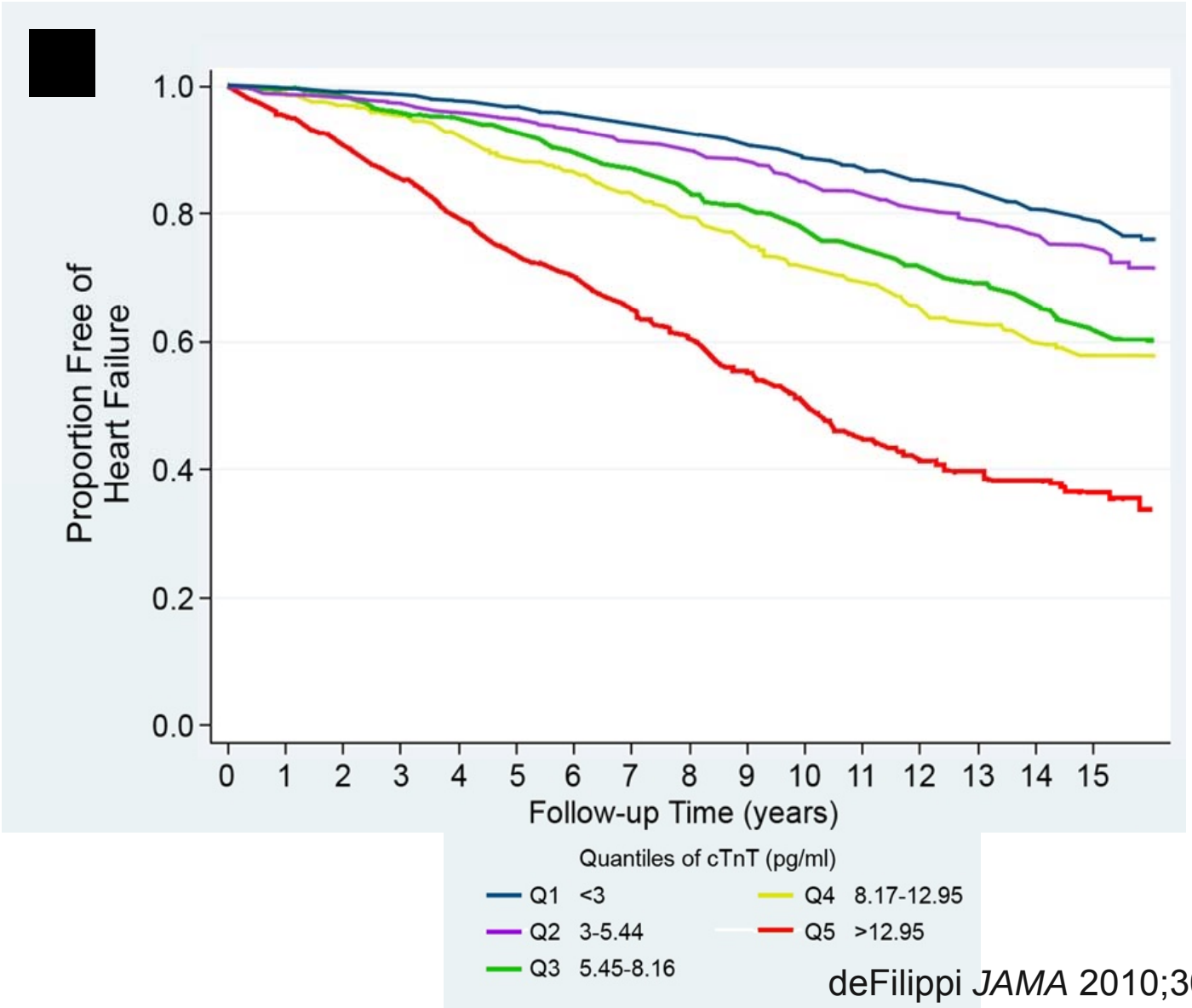
The “malignant” phenotype of LVH



Neeland I. J Am Coll Cardiol 2013;61:187–95

Risk of New Onset Heart Failure

Ambulatory Older Adults Stratified by cTnT level



deFilippi *JAMA* 2010;304:2494-2502

"Measuring hs-cTnI or hs-cTnT is (and should be until proved otherwise) the standard to test all other biomarkers in patients from a community population with or without known coronary artery disease. The use of hs cardiac troponin assays, I think, will assume a spot as a biomarker in primary prevention and will eventually become a risk factor alongside the conventional Framingham risk factors"

No more total cholesterol and CRP

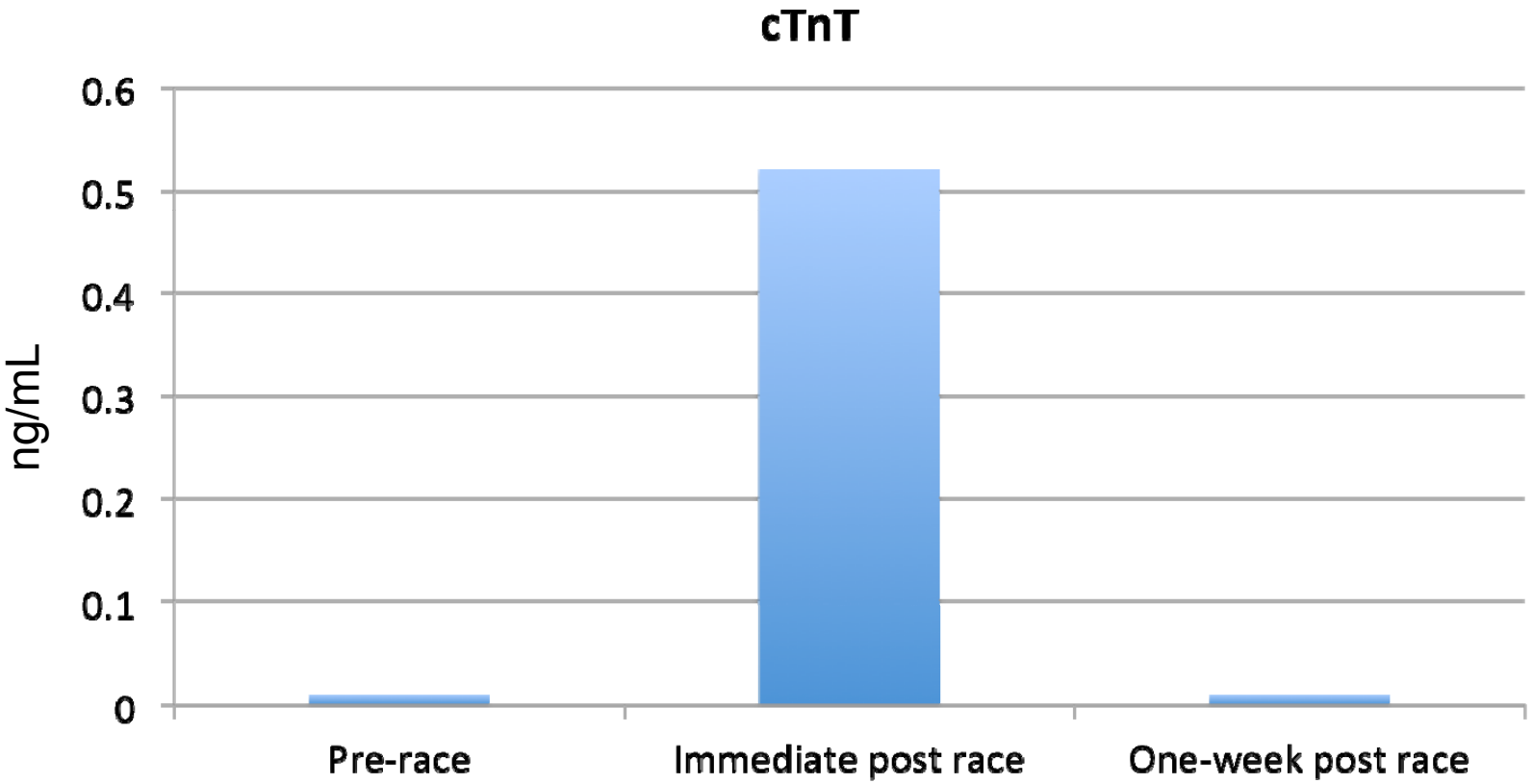
Now: NP, hsTrop, sST2

Apple F. Clin Chem 2011;57:537-9

Scotiabank Toronto Waterfront
MARATHON
+ Half-Marathon
Queen W
SUBWAY
50

Cardiac Troponin T levels

Pre and post marathon in 25 adults > 50 years



Karlstedt et al. Journal of Cardiovascular Magnetic Resonance 2012, 14:58

Cardiac MRI findings pre and within 24-hours post race

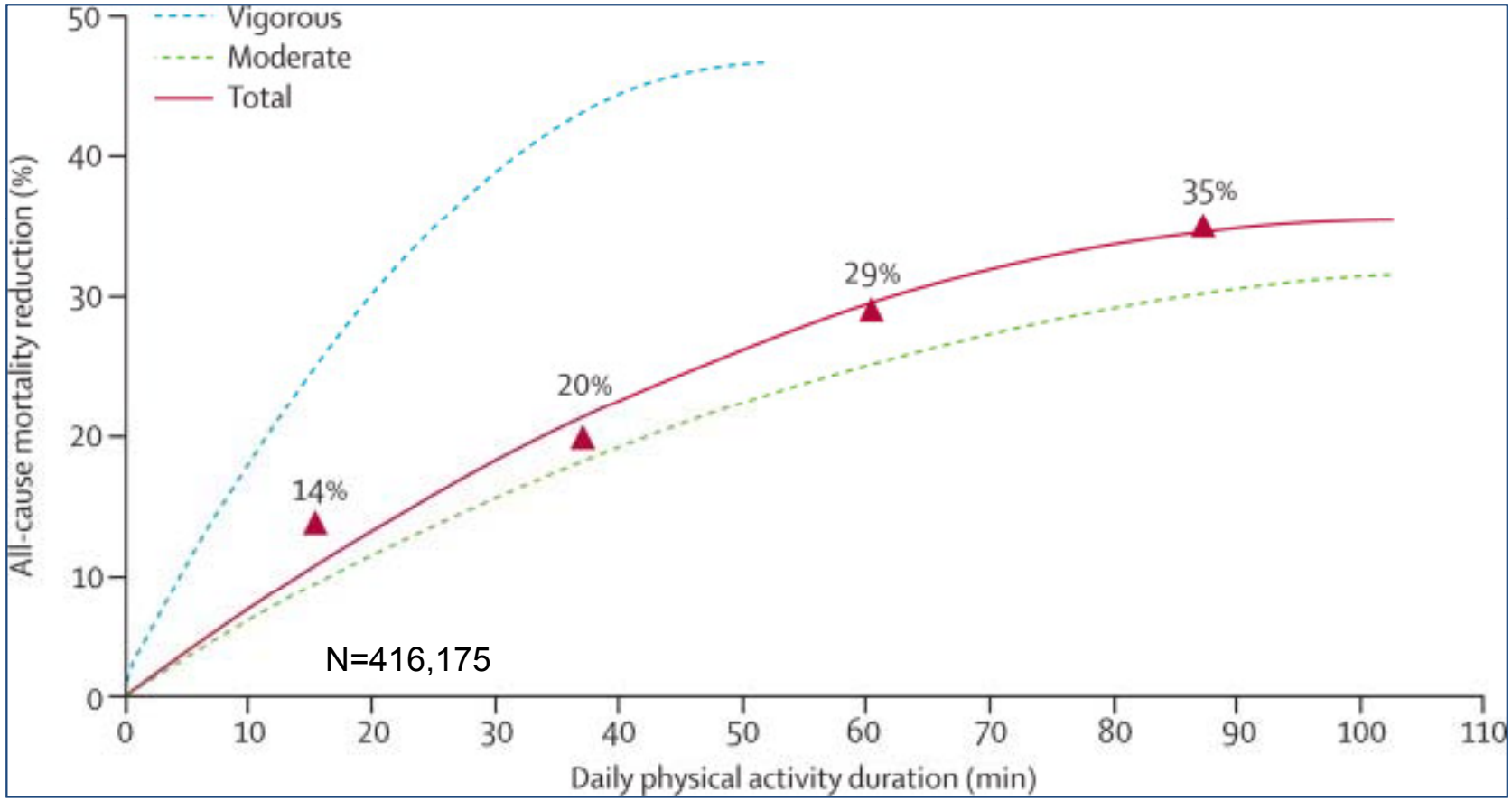
CMR parameters	Pre marathon	Post race
LV parameters		
LVEDD (mm)	52 ± 3	51 ± 4
LVESD (mm)	31 ± 4	30 ± 5
LVEF (%)	67 ± 4	69 ± 3
LV mass/ BSA (g/m^2)	126 ± 14	123 ± 9
RA and RV parameters		
RA volume (ml)	39 ± 8	57 ± 10*
RVEDD (cm)	33 ± 5	47 ± 4*
RVEDV (ml)	133 ± 19	190 ± 18*
RVEF (%)	65 ± 3	44 ± 6*
RV mass/BSA (g/m^2)	32 ± 4	34 ± 3

Karlstedt et al. Journal of Cardiovascular Magnetic Resonance 2012, 14:58

How much exercise is good?

Minimum amount of physical activity for reduced mortality

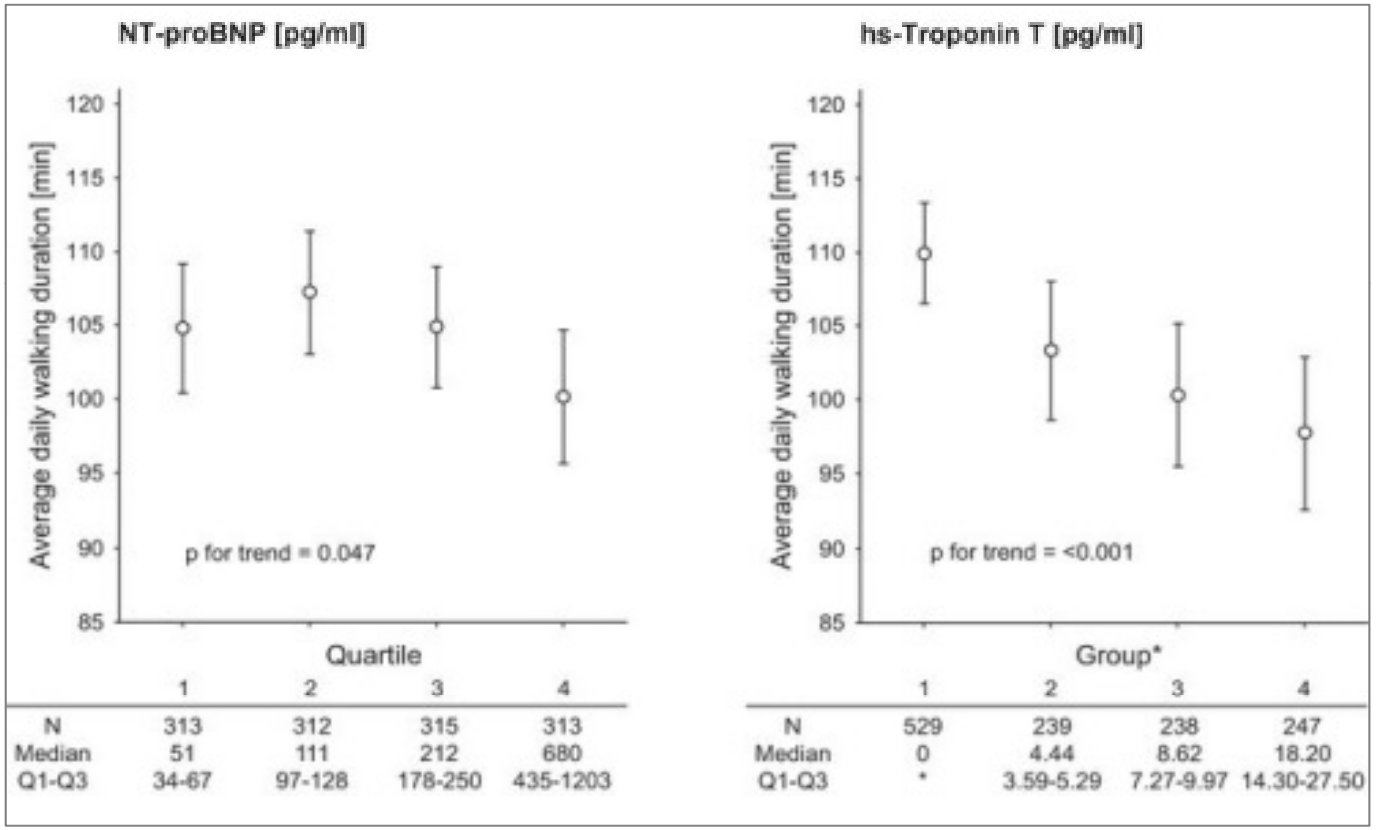
Daily physical activity duration



Wen C et al. The Lancet, 2011;378,:1244-53

Association of Physical Activity, NT-proBNP and hs cTnT level in older adults

The ActiFE Study

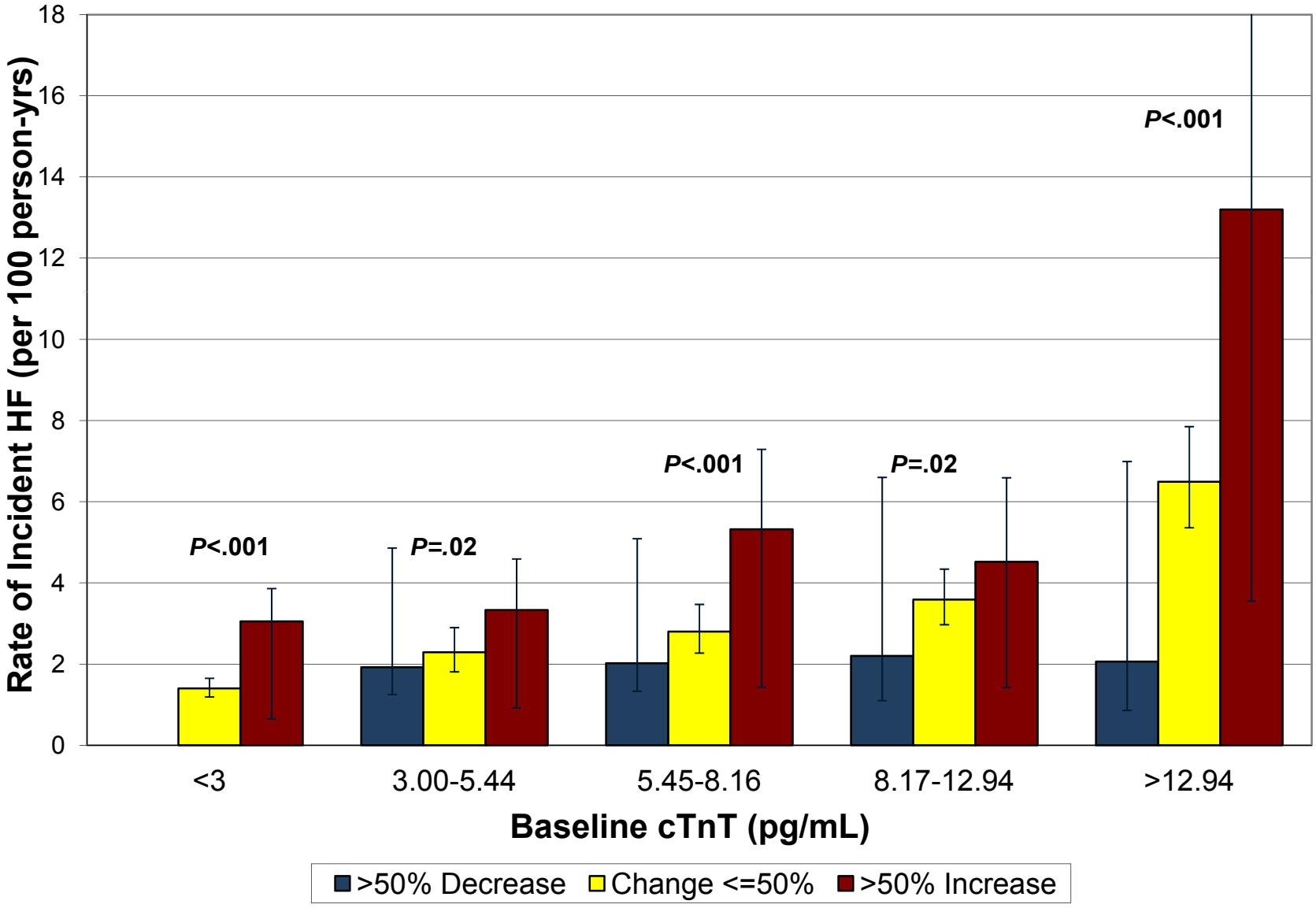


Duration of walking measured by accelerometer over 1 week

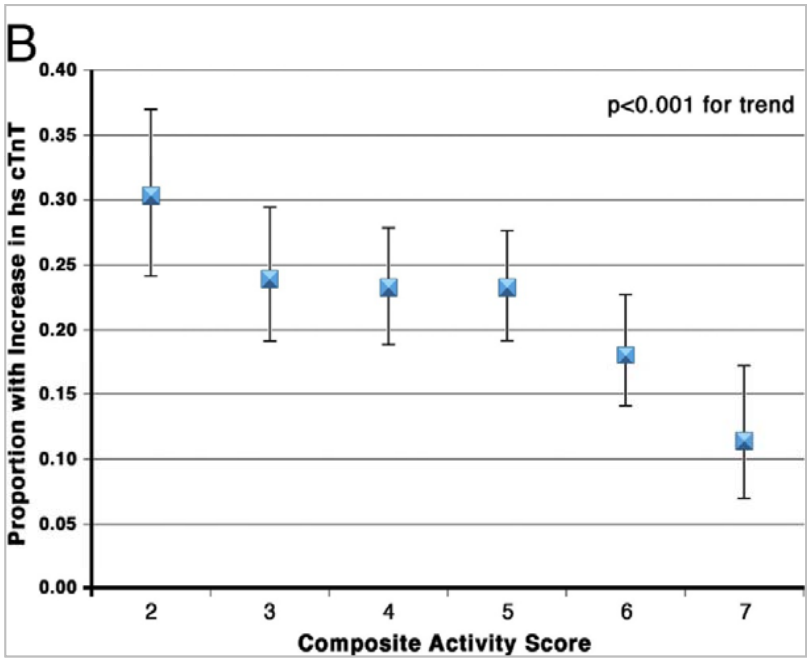
Klenk J. J Epidemiol Community Health 2013;67:194-197

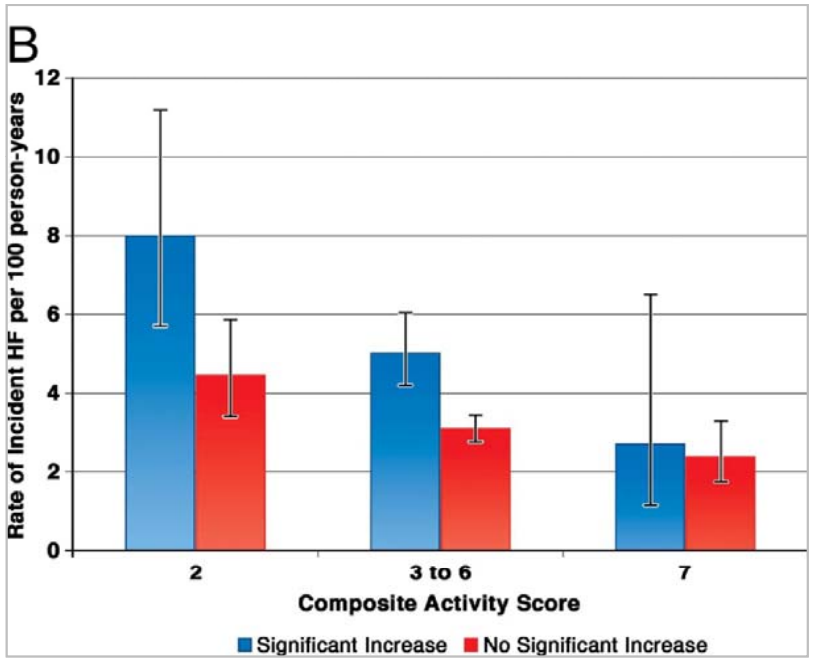
Change in cTnT level from baseline to follow-up

Association with new-onset heart failure



Association of moderate physical activity, rise in hs cTnT level and risk of new onset heart failure





Composite score is a sum of walking pace and duration of moderate to intense leisure activities A higher score is a faster pace and longer duration of activity. Significant increase in hs cTnT defined as > 50% rise from the baseline level.

deFilippi C. J Am Coll Cardiol 2012;60:2539-4

Initiation of physical activity reduces progression of cardiac injury in sedentary older adults

The Randomized LIFE Pilot Study

	Physical Activity N=156	**Successful Aging N=154**	**p-value**
Age (years)	76.3±4.1	77.0±4.3	0.1
Male	51 (32.7%)	48 (31.2%)	0.7
BMI (kg/m^2)	29.7 [26.5, 34.8]	28.9 [26.1, 32.9]	0.1
Activity (min/wk)	30 [0, 135]	60 [0, 210]	0.2
Activity (kcal/week)	180 [0, 809]	324 [0, 920]	0.3
Baseline hs cTnT (ng/L)	10.8 [7.5, 14.8]	10.5 [6.4, 16.3]	0.7

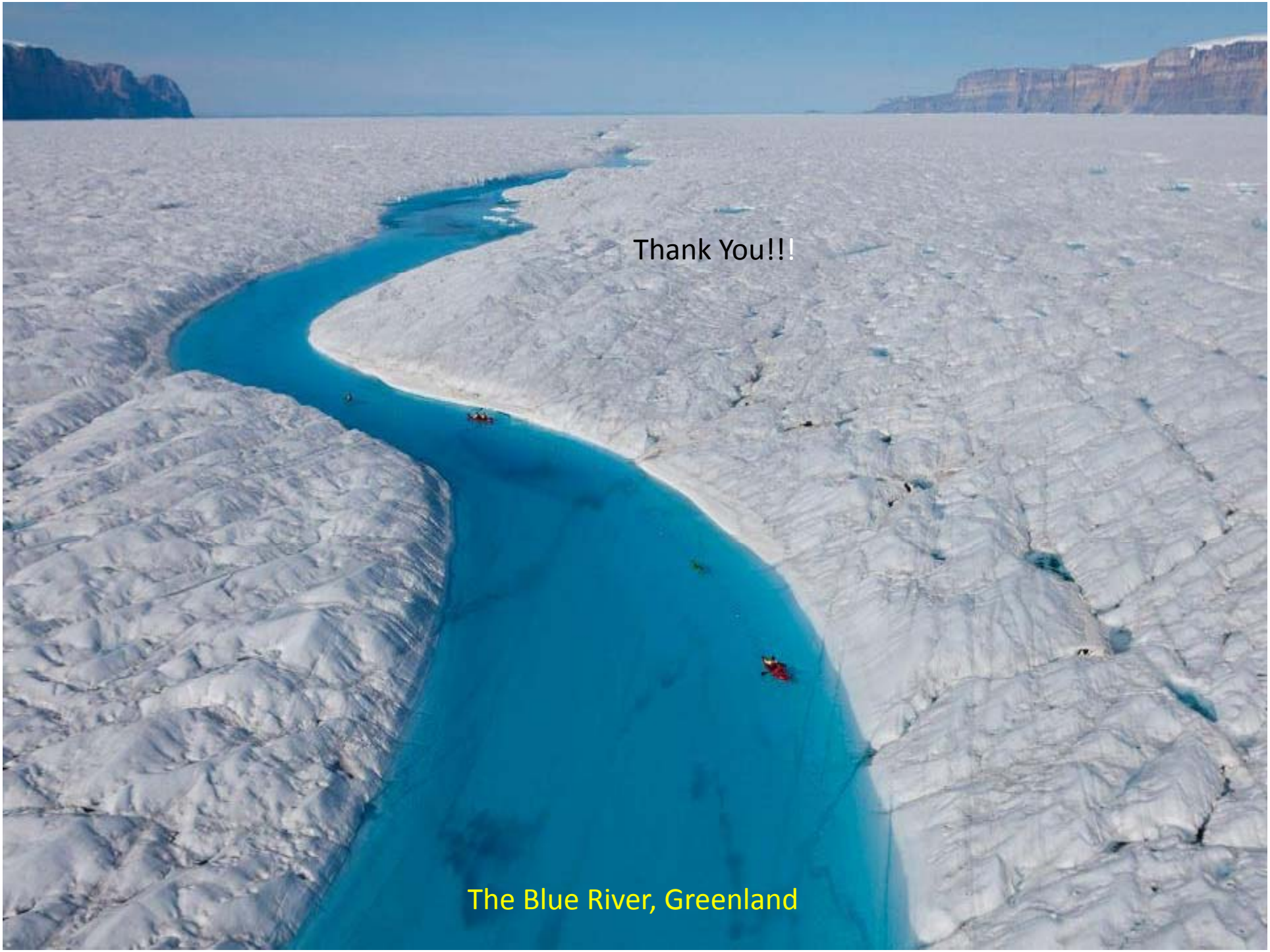
After one-year of study intervention

	Physical Activity N=156	**Successful Aging N=151**	**p-value**
Activity (min/wk)	135 [30, 330]	90 [0, 135]	<0.001
Activity (Kcal/week)	756 [165, 1625]	377 [0, 846]	<0.001
Δ hs cTnT (ng/L)	**0.19 [-1.1, 1.93]**	**0.73 [-0.64, 2.59]**	**0.02**
Δ hs cTnT (%)	**1.8 [-11.9, 20.0]**	**7.0 [-7.0, 24.7]**	**0.05**
Increase in hs cTnT level > 50% from baseline	8 (5.1%)	14 (9.3%)	0.16

deFilippi C. Circulation. 2013;128:A16937

Summary hs troponins

- The assays are here to stay.
- For ACS- you can use your old level (.04) – but they rise earlier so good for rule out
- For AHF- sometimes diagnostic, very prognostic, afford possible targeted therapy
- Will predict subclinical disease in primary care
- May be used to monitor exercise, aging, and other potential disease states


Thank You!!!
The Blue River, Greenland