

What is the Preferred Marker of Cardiac Myocyte Injury or Death in 2021?

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Today's Presenter: Dr. William Winter, MD, FCAP

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 - Member of CAP Clinical Pathology Education Committee
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Agenda

- Cardiac Markers
- Clinical Use of Troponin in the Diagnosis of Acute Chest Pain
- Criteria for the Diagnosis of Myocardial Infarction
- Non-Myocardial Infarction Causes of Elevated Troponin
- Troponin Assays
- Q&A

Objectives

- Define and differentiate myocardial injury, acute myocardial injury, and myocardial infarction.
- List the five subtypes of myocardial infarction.
- Identify atherothrombosis as the most common cause of myocardial infarction.
- Choose the best plasma marker for the detection of cardiac myocyte injury and necrosis.
- Explain to laboratorians and clinicians the superiority of high sensitivity troponin measurements over traditional troponin measurements.

Cardiac Markers

What is a cardiac marker (a.k.a. - “cardiac biomarker”)?

Substances measured in **plasma** or **serum** . . .

... that are used in **diagnosis and risk stratification of patients with chest pain and suspected acute coronary syndrome (ACS).**

Suspected acute coronary syndrome:
a term applied to patients in whom there is a suspicion of acute myocardial ischemia or infarction

Which cardiac markers are currently clinically used?

Troponin (Tn) is the *only* cardiac marker that should be used clinically to assess possible ACS (& measure serially).

Tn can be used to diagnose re-infarction.

Cardiac markers *no longer in use*:

Comment:

CK

Lacks specificity

CK-MB

- MB isoenzyme of CK

Improved specificity BUT not as specific (nor sensitive) as Tn

Myoglobin

Lacks specificity

AST

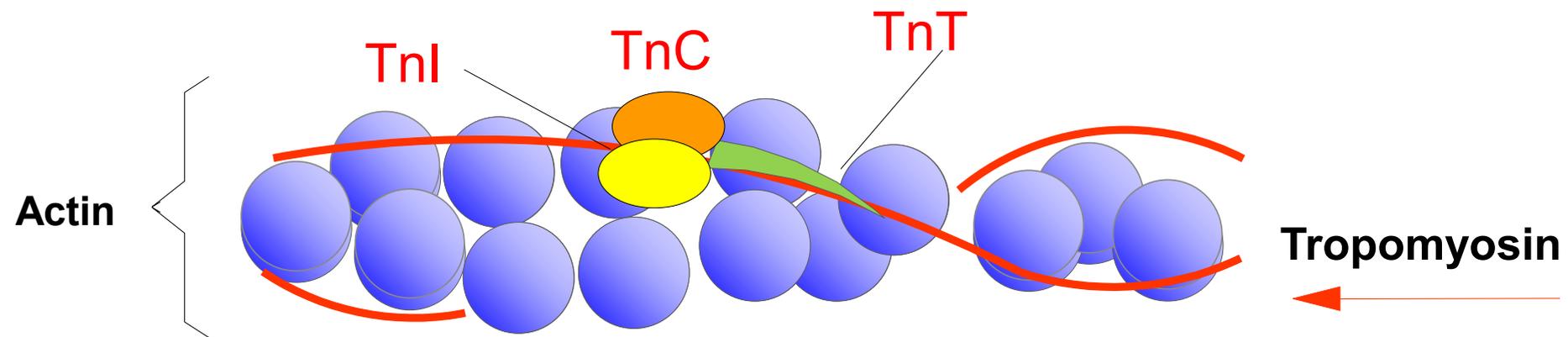
LD

Both lack specificity & are late markers

What is troponin?

Part of the contractile regulatory complex

There are: 3 forms of troponin



TnI ATPase **i**nhibitory

TnT Binds complex to **t**ropomyosin

TnC **C**a⁺⁺ binding

Are skeletal muscle and myocardial troponins different?

TnI	ATPase inhibitory	Yes 😊
TnT	Binds complex to tropomyosin	Yes 😊
TnC	Ca⁺⁺ binding	No! 😞

		<u>Specific for:</u>	<u>Abbreviations</u>
cTnI	– cardiac troponin I	myocardium	TnI
cTnT	– cardiac troponin T	myocardium	TnT
			Generic: Tn

Tn is released by cardiac myocyte injury or necrosis

Are cardiac troponins absolutely specific for cardiac muscle?

Well no... 😞

	Increased	
	cTnT (+)	cTnI (+)
Inherited & Acquired Myopathies	~70%	~4%

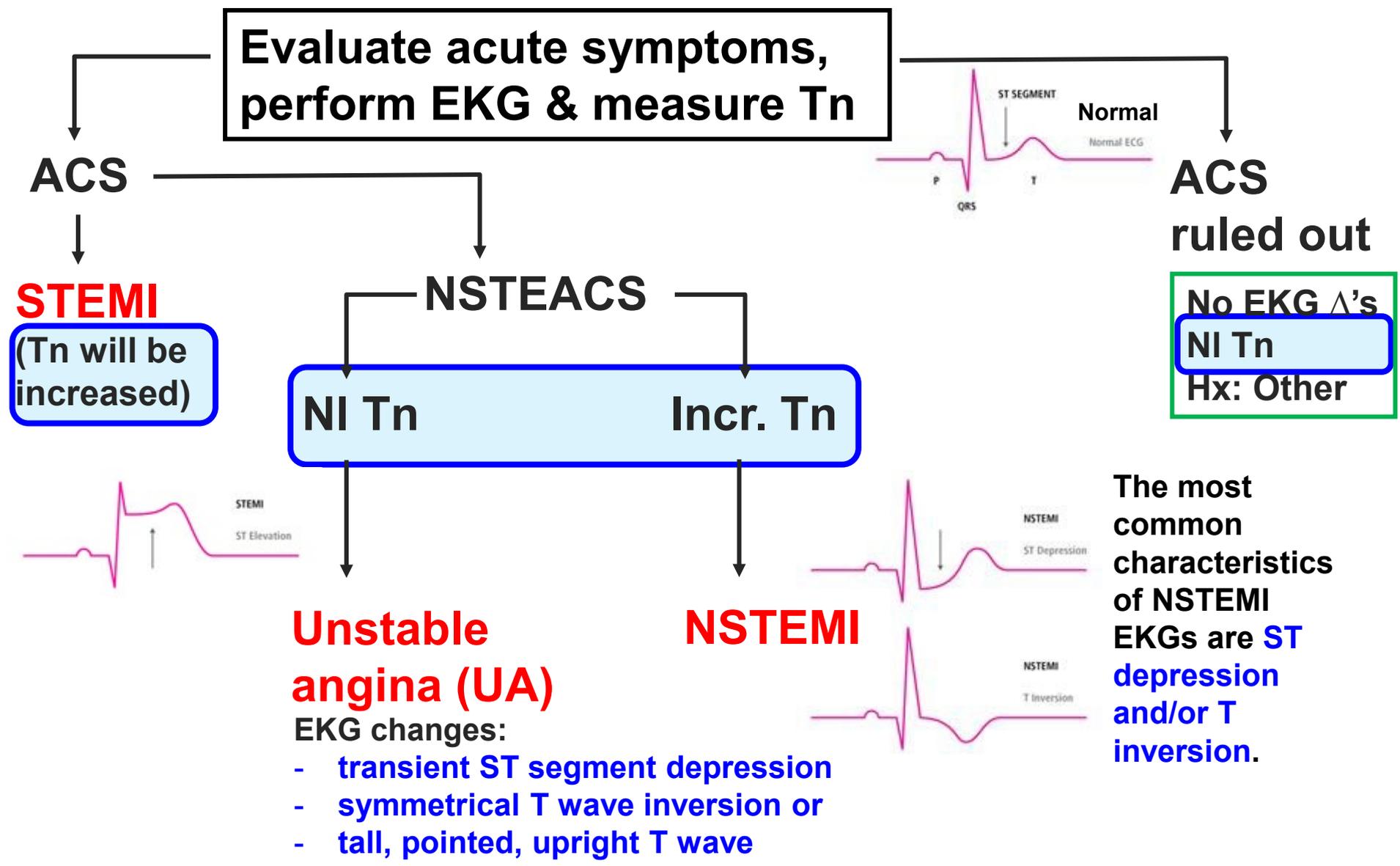
Examples: Dystrophic myopathy
Myotonic dystrophy
Nondystrophic myotonia
Inflammatory myopathy
Primarily neurogenic myopathy

Source: JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL . 71 , NO . 14 , 2018

Clinical Use of Troponin in the Diagnosis of Acute Chest Pain

How are troponin measurements predominantly used clinically?

Evaluation of suspected acute coronary syndrome (ACS)



What term is used to describe any Tn concentration >99th percentile?

Myocardial injury

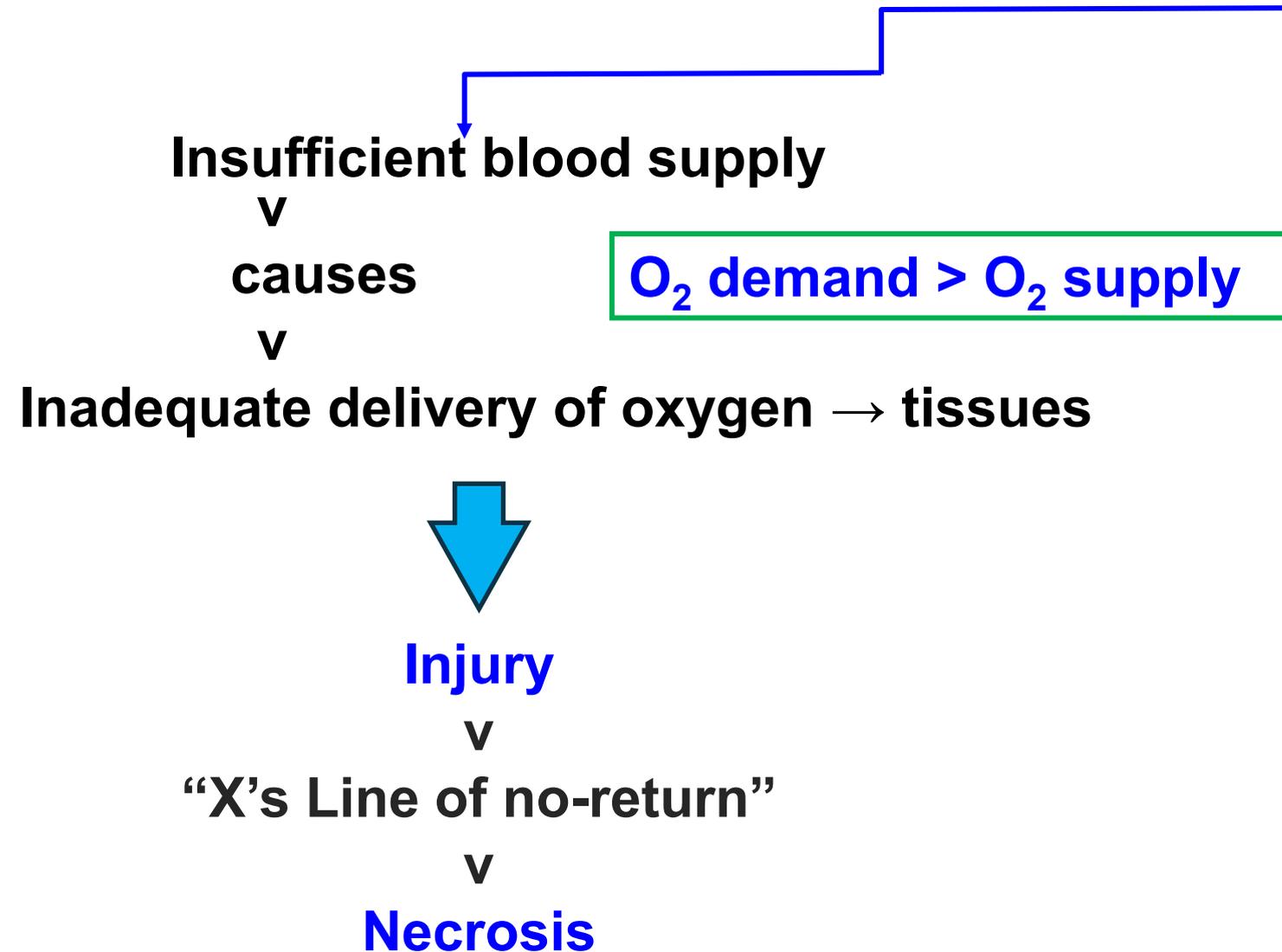
Defined solely on the basis of Tn testing

Dx of MI has specific criteria!

Criteria for the Diagnosis of Myocardial Infarction

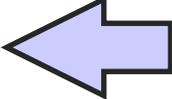
What is a “myocardial infarction?”

Coagulative necrosis of myocardium due to acute ischemia



How can the various causes of MI be classified?

Type

[1] Atherothrombosis 

Comment

Partial blockage: NSTEMI

Complete: STEMI

[2] Supply-demand imbalance

Fixed obstruction*: NSTEMI

[3] Acute death prior to pathologic changes & prior to increased Tn

Death by arrhythmia (most common)

[4] PCI, related to the PCI

Percutaneous coronary intervention

[5] Related to CABG

Coronary artery bypass graft

What are the current criteria for the diagnosis of a type 1 MI according to the Fourth Universal Definition (2018)?

The diagnosis of a type 1 MI requires:

[1] Acute myocardial injury*

(+) *Rise and/or fall in Tn, → 1 value >99th percentile

[2] Other supportive findings

Symptoms c/w ischemia

New ischemic EKG Δ 's and/or new Q waves

Abnormal imaging

Evidence of coronary thrombus

Non-Myocardial Infarction Causes of Elevated Troponin

What non-MI cardiac conditions can cause Tn concentrations to rise*? (1)

Severe ischemia

Coronary intervention

Cardiac surgery (eg, CABG)

Comments

If Tn >99^{percentile} + ↑ or ↓ = MI (types 1 or 2)

If ↑Tn, etc. = MI (type 4)

If ↑Tn, etc. = MI (type 5)

Other cardiac conditions

- **Heart failure**
- **Myocarditis**
- **Cardiomyopathy (any type)**
- **Takotsubo syndrome**
- **Non-revascularization cardiac surgery**
Can include: cardiopulmonary bypass

* Tn can increase yet the Dx of MI may not be achieved.

What non-MI cardiac conditions can cause Tn concentrations to rise*? (2)

Other cardiac conditions (continued)

- **Catheter ablation**
- **Defibrillator shocks**
- **Cardiac trauma (eg, blunt force trauma/contusion)**
- **Rejection of a transplanted heart**
- **Pericarditis**

* Tn can increase yet the Dx of MI may not be achieved.

What systemic conditions can cause Tn concentrations to rise?

Systemic conditions

- Sepsis, infectious disease
- Chronic kidney disease*
- Stroke, subarachnoid haemorrhage
- Pulmonary embolism, pulmonary hypertension
- Infiltrative diseases, eg, amyloidosis, sarcoidosis
- Chemotherapeutic agents
- Critically ill patients
- Strenuous exercise

Note: Tn can be elevated in patients on **renal dialysis**.

- elevation is usually mild (eg, low-level).
- predicts increased risk of subsequent death

Troponin Assays

Are all Tn assays created “equally?”



Graphic source: <http://clipart-library.com/clipart/gceo5kdbi.htm>

No!

Types of Tn immunoassays:

Abbreviations

Tn (“traditional”):

Little changed since 1990’s

Tn

High-sensitivity Tn:

Entering clinical use.

hsTn

What are the unique features of hsTn?

Improved analytical precision & accuracy

Extremely important @ 99th percentile (CV: ≤10%)

Reduced – lower limit of detection (LLD) (more sensitive)

hsTn detected in ≥50% of normal population

± Earlier dx of AMI; earlier r/o AMI

Sex-specific reference intervals:

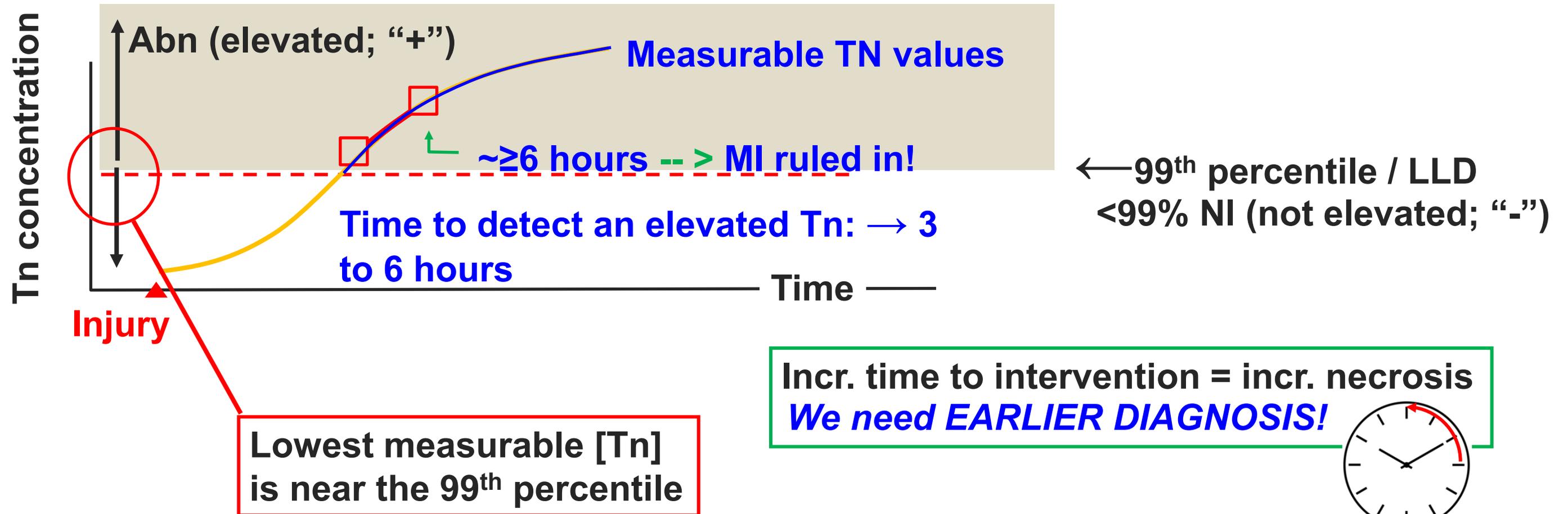
Upper limit of RI: Males > Females

Example: Beckman: 20 ng/L v. 15 ng/L

Reported in **WHOLE numbers** (ng/L; SI unit)

What is a major *limitation* of the traditional Tn assays (Tn)?

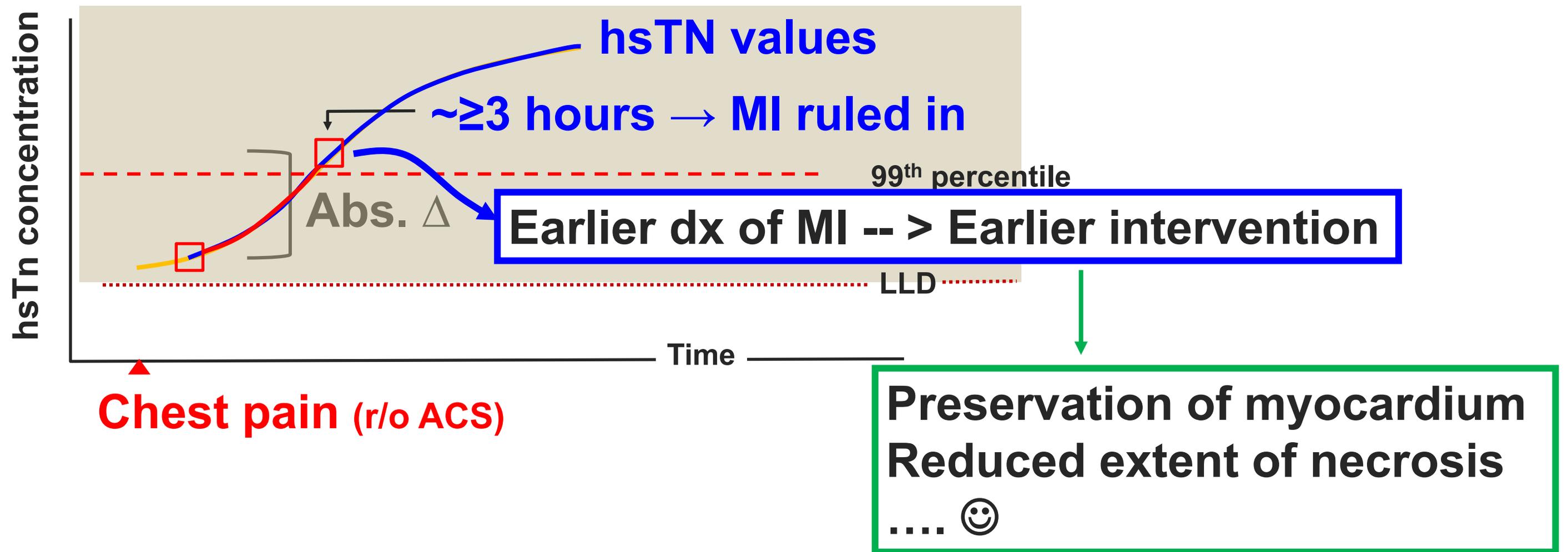
“Delayed” diagnosis of AMI



Graphic source: <https://icon-library.com/icon/clock-icon-white-23.html>

What is a major advantage of hsTn assays?

Potentially earlier diagnosis of MI



More rapid *r/o AMI*: zero \rightarrow 1 hour, \rightarrow 2 hours, \rightarrow 3 hours

Because it can still take several hours to diagnose MI, what can be done to “speed up” the diagnostic process?

Serial EKGs are a routine part of ACS evaluation.

If a ST segment elevation occurs, STEMI is diagnosed even if the Tn has not yet turned (+). ST segment elevation in STEMI can occur *very rapidly & within 1 hour.*

NOTE: T-wave inversion and ST segment depression do not make the diagnosis of NSTEMI → need a (+) Tn.

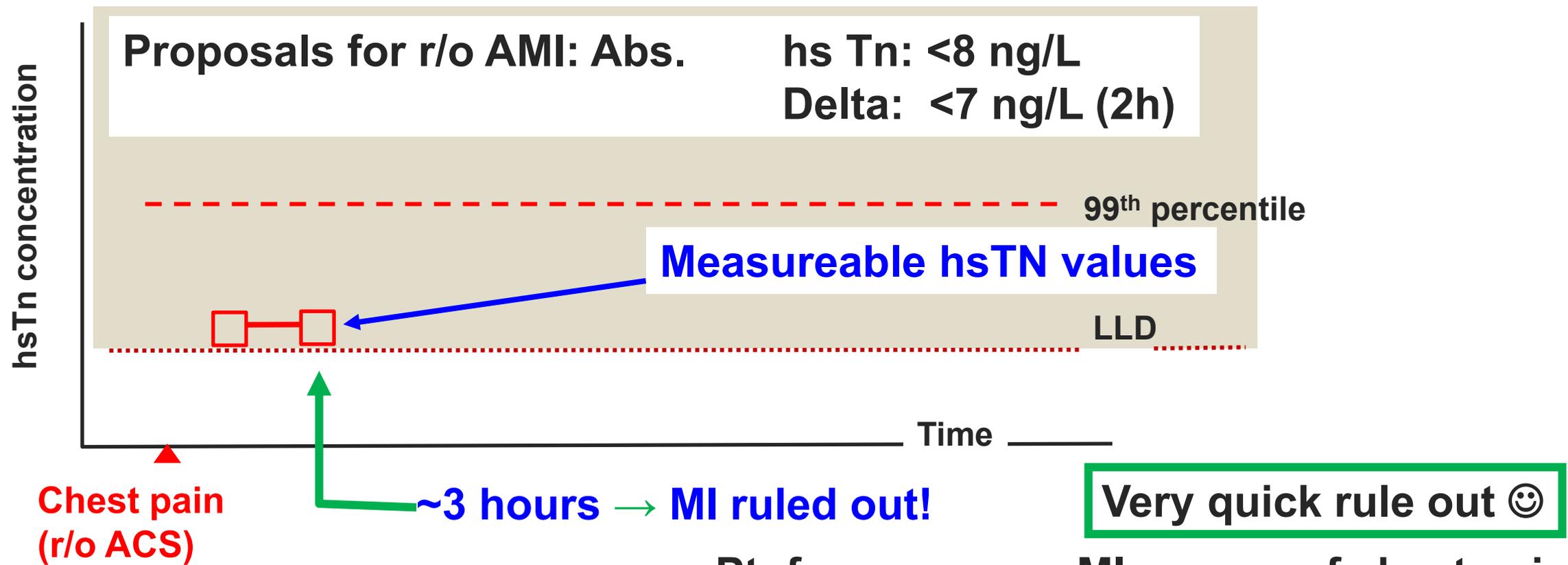
NOTE: EKG changes are similar in UA & NSTEMI → require Tn testing for their differentiation.

What is a major advantage of hsTn assays?

hsTn is measurable in $\geq 50\%$ of healthy individuals

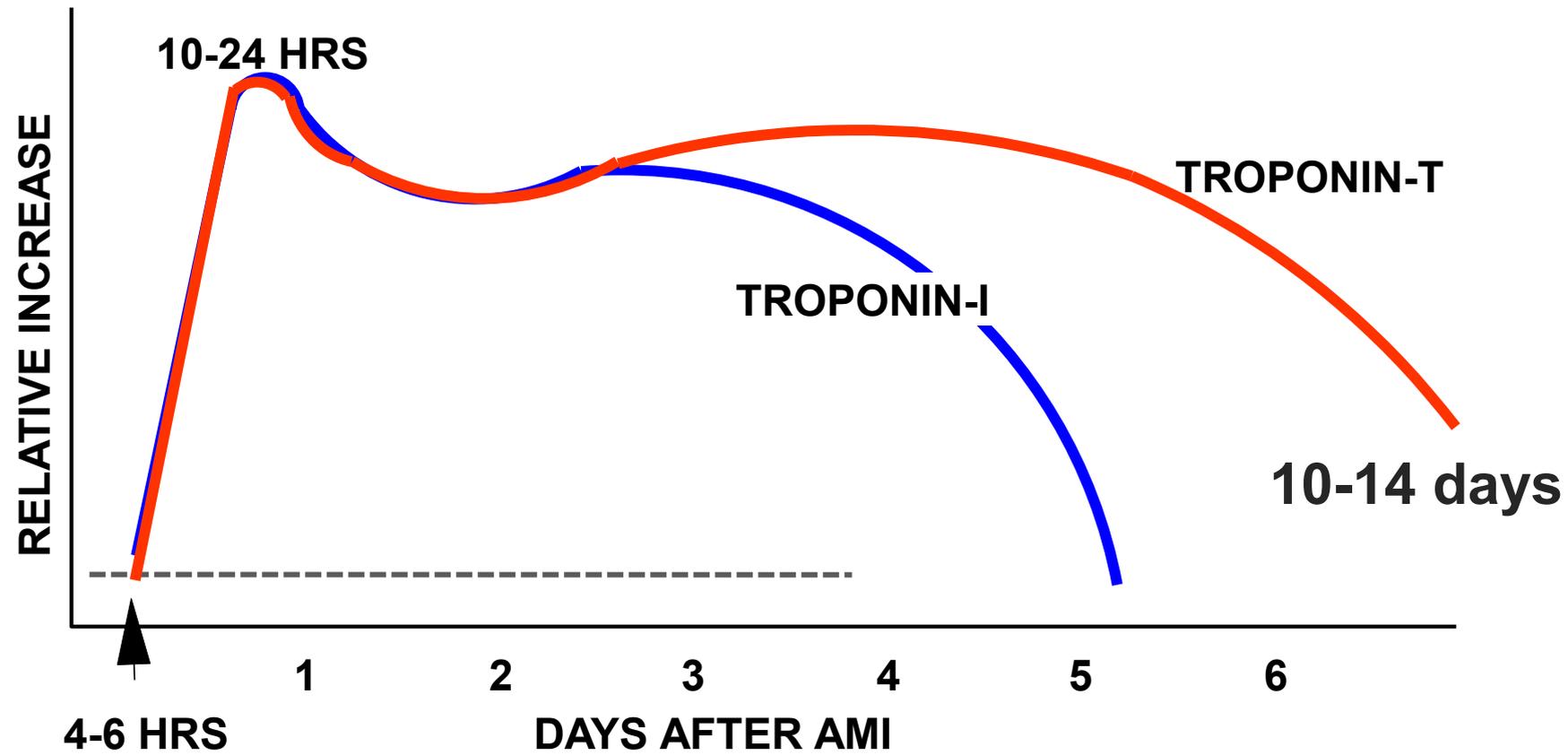
hsTn lower limit of detection (LLD) is far BELOW cut-point ($>99^{\text{th}}$ percentile)

Assume there is chest pain w/o MI \rightarrow



- Pt: focus on non-MI causes of chest pain
- Improved resource utilization

What are the kinetics of troponin elevation in MI?



Review

Tn – ~cardiac myocyte specific

Tn – used in evaluation of suspected ACS

MI = acute coagulative necrosis of myocytes

**Most common cause of MI: atherothrombosis
(type 1 MI)**

**Dx of MI: Incr. Tn + rise/fall (+) sx, EKG Δ 's, image/fn
 Δ 's, evidence coronary thrombosis**

Tn – ~organ specific, not specific to etiology

Review

Myocardial injury: Tn >99th percentile

Acute myocardial injury: Tn >99th percentile with rise/fall

Tn assays: hsTn assays are superior:

- **Rule out MI in ~ 3 hours**
- **More rapid rule in of MI**

CAP Proficiency Testing (PT) Programs

- Over 700 programs across 16 disciplines
 - Evaluate instrument and method performance
 - Indicators for laboratory quality
- **Three** high-sensitivity troponin programs
 - **HCRT** for high-sensitivity Troponin I and CK-MB (immunochemical) plus Myoglobin
 - **HCRTI** for high-sensitivity Troponin I and CK-MB (immunochemical), CK isoenzymes by electrophoresis, LD isoenzymes by electrophoresis, and Myoglobin
 - **HTNT** for high-sensitivity Troponin T assays

CAP Quality Cross Check (QCC) Programs

31 programs across six disciplines

- Monitor instrument performance
- Assess comparability across multiple instruments
- Identify potential issues before they affect patient results

CARDIAC MARKERS QUALITY CROSS CHECK - CRTQ

Analyte	Challenges per Shipment	Number of Shipments
CK-MB, immunochemical	3	Two shipments per year
Myoglobin	3	
Troponin I	3	

QCC is not a substitute for PT.



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