

# hs-cardiac troponin and other biomarkers

Ahmed Adel Elamragy, MD  
Faculty of Medicine  
Cairo University

## Introduction

- Cardiac biomarkers have been used for the diagnosis of acute MI since the 1950s.
- Improvements with CK-MB then cardiac troponin.
- What is hs-cTn?
- Hs-cTn assay detects very low plasma levels of cTn I 6ng/L and T 5 ng/L.
- Between 1995 and 2007, the limit of detection: 500 ng/L → 6 ng/L.
- Detection of cTns in healthy individuals → must define what is a +ve cTn result.

## Criteria for Acute Myocardial Infarction

- **Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99<sup>th</sup> percentile upper reference limit (URL) and with at least one of the following:**
  - Ischaemic symptoms;
  - ECG changes of new ischaemia (new ST-T changes or new LBBB);
  - Development of pathologic Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
  - Identification of an intracoronary thrombus by angiography or autopsy.

## Biomarkers for Detection of Myocardial Infarction



- **Preferably**
  - Detection of rise and/or fall of cardiac Troponin (I or T) with at least one value above the 99<sup>th</sup> percentile of the upper reference limit measured with a coefficient of variation  $\leq 10\%$ .
- **When cardiac Troponin is not available**
  - Detection of rise and/or fall of CKMB mass with at least one value above the 99<sup>th</sup> percentile of the upper reference limit measured with a coefficient of variation  $\leq 10\%$ .

## Definitions

### Box 2

#### Key definitions relating to analytical performance of cardiac troponin T assays

##### 99th percentile

Refers to the 99th percentile of cTn concentrations in a sample of apparently healthy individuals.

By convention, this is used to define the upper reference limit of cTn assays

##### Limit of blank (LoB)

When analyzing a sample containing no cTn, assays will not always return a result of zero

The LoB is derived by repeatedly testing a sample that is known to contain no cTn and is equal to the mean plus 1.645 multiplied by the standard deviation of the results obtained

##### Limit of detection (LoD)

The lowest concentration of analyte that can be distinguished from the LoB; the LoD will, therefore, be higher than the LoB

##### Coefficient of variation (CV)

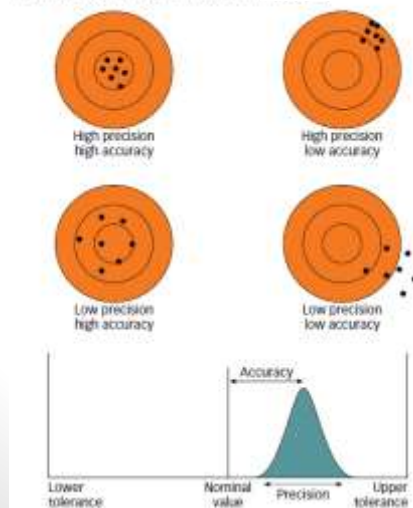
Measures the precision of an assay and expressed as a percentage

Equal to the standard deviation divided by the mean of repeated measurements on any given sample

Data from Armbruster D, Pry T. Limit of blank, limit of detection and limit of quantitation. Clin Biochem Rev 2008;29(Supplement 1):549-52.

## Precision of the assay (vs accuracy)

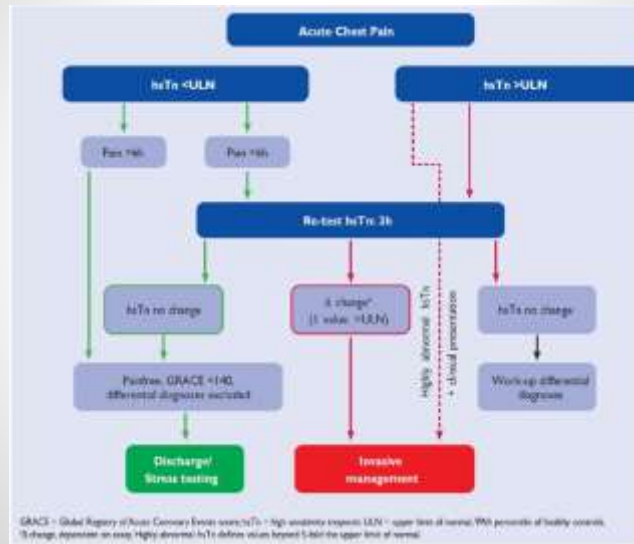
### Accuracy vs. precision



How to interpret hs-cTn?

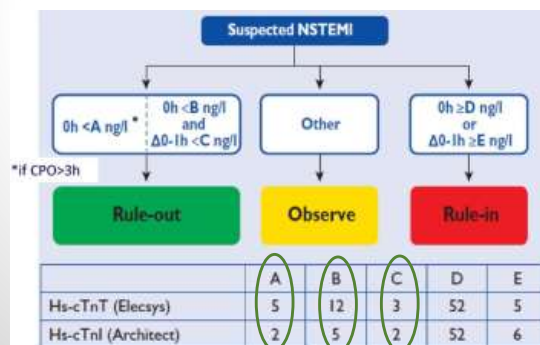
Early rule out strategy

## 1) 0- and 3- hr algorithm



## 3) 0- and 1- hr algorithm

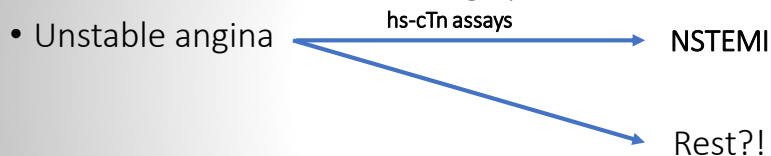
- Absolute change of hs-cTn conc over 1 hr (with both values normal).
- Very effective and rapid.
- No need for risk scores.
- Sensitivity of 96.7% and a NPV of 99.1% within 6 hr of symptom onset.



# Discharge the patient?!

## The concept of risk scores

- Troponin-based strategies: cannot necessarily be used alone to guide decisions to admit or discharge patients.



- Incidence of MACE in patients with ruled out AMI by troponin-based strategies: **not low**
- 1-hour hs-cTnT algorithm: 30 day MACE sensitivity of 87.5% only!
- Additional risk stratification is needed before decision of discharge and stop further investigation.

## Risk scores

Troponin Timing		Details of Risk Score		Summary of Evidence Base	
HEART score	On arrival	0-2 points for each of the		Derivation	
ADAPT ADP	0 and 2 h	TIMI risk score criteria: 1 point		Derivation	
ED-ACS score	On arrival	Score calculated using the		Derivation <sup>41</sup>	
Troponin-only Manchester Acute Coronary Syndromes (MACS) decision aid	On arrival	Computer algorithm, accounting for		Derivation <sup>37</sup>	Sensitivity 99.0%
	HEART pathway	On arrival and 3 h later	As for the HEART score but requires a second troponin test after 3 h	n = 703, derived by logistic Derivation (retrospective) <sup>42</sup>	1070 subjects with nondiagnostic ECG incidence of MACE in subjects with (original) HEART score <3 was 0.6% but sensitivity for MACE only 58% (95% CI 32%-81%). Adding a second troponin at 4-6 h gave 100% sensitivity (95% CI 72%-100%) External validation <sup>43</sup> Secondary analysis from prospective cohort, n = 1050. 20% subjects identified as low-risk Sensitivity 99% (95% CI 57%-100%) for MACE Intervention trial 282 subjects randomized to HEART pathway or standard care (serial biomarkers plus subsequent objective cardiac testing) More subjects discharged without objective cardiac testing in the HEART pathway arm (39.7% vs 18.3%, <i>P</i> <.001) with no MACEs at 30 d

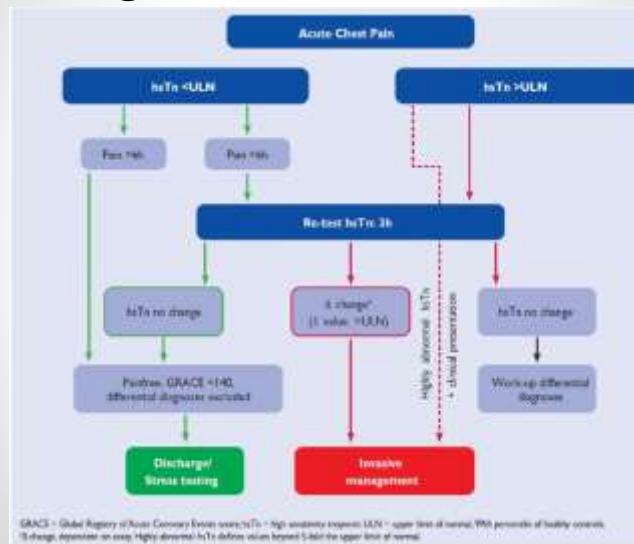
## Ruling IN AMI?



## Rule-in MI

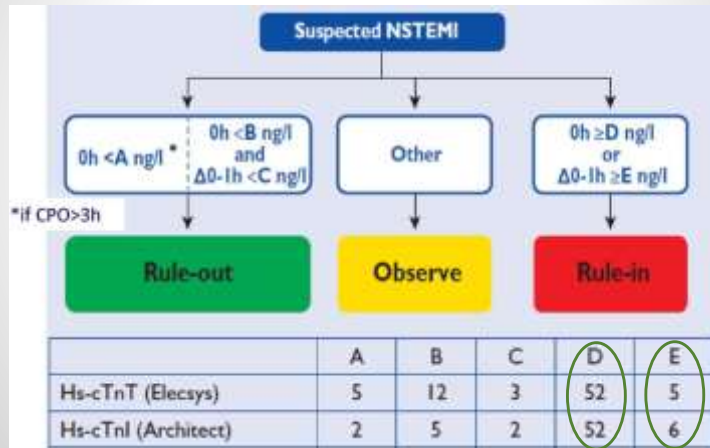
- Early rule-out of AMI: important to unburden crowded hospitals and ERs
- Early rule-in: facilitate rapid treatment of patients !
- Meta-analysis:
  - early intervention ↓ recurrent ischemia, hospital stay & trend ↓ major bleeding.
- In T-MACS trial: early invasive strategy in high-risk patients → 28% ↓ in death, myocardial injury, stroke, or refractory ischemia.

## 0- and 3- hr algorithm





## 0- and 1- hr algorithm



## Rule-in MI (caveats)

- Prevalence of +ve cTn increased with increasingly sensitive assays
- Small AMI!!!
- cTn is highly cardiac-specific.
- ↑conc = myocardial injury (DD)

## Differential diagnosis

**Table. Causes of Elevated Plasma Cardiac Troponin Other Than Acute Coronary Syndromes**

Cardiac Causes	Noncardiac Causes
Cardiac contusion resulting from trauma	Pulmonary embolism
Cardiac surgery	Severe pulmonary hypertension
Cardioversion	Renal failure
Endomyocardial biopsy	Stroke, subarachnoid hemorrhage
Acute and chronic heart failure	Infiltrative diseases, eg, amyloidosis
Aortic dissection	Cardiotoxic drugs
Aortic valve disease	Critical illness
Hypertrophic cardiomyopathy	Sepsis
Tachyarrhythmia	Extensive burns
Bradyarrhythmia, heart block	Extreme exertion
Apical ballooning syndrome	
Post-percutaneous coronary intervention	
Rhabdomyolysis with myocyte necrosis	
Myocarditis or endocarditis/pericarditis	

Adapted from Jaffe et al<sup>7</sup> with permission of the publisher. Copyright © 2006, Elsevier.

## A) Clinical context

- The most crucial step in determining the cause of myocardial injury.

### Criteria for Acute Myocardial Infarction

- **Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99<sup>th</sup> percentile upper reference limit (URL) and with at least one of the following:**
  - Ischaemic symptoms;
  - ECG changes of new ischaemia (new ST-T changes or new LBBB);
  - Development of pathologic Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
  - Identification of an intracoronary thrombus by angiography or autopsy.

## B) Rise /fall in troponin

- Many patients have chronic elevation of cTn at baseline.
- Serial sampling: no significant change over time (avoid overDx & overttt)!
- Acute myocardial injury: increase and/or decrease in cTn conc over time.
- Serial sampling: required to rule in the diagnosis of AMI.
- Improved precision of cTn assays: detect smaller changes in cTn conc.
- Absolute changes in conc: better diagnostic accuracy than relative changes.

## Biomarkers for Detection of Myocardial Infarction



- **Preferably**

- Detection of rise and/or fall of cTn (I, II, or T) with at least one value above the 99<sup>th</sup> percentile of the upper reference limit measured with a coefficient of variation  $\leq 10\%$ .

- **When cardiac Troponin is not available**

- Detection of rise and/or fall of CKMB mass with at least one value above the 99<sup>th</sup> percentile of the upper reference limit measured with a coefficient of variation  $\leq 10\%$ .

Exceptions:  
Thrombus on angio  
Very high levels (>80 ng/L)

## Cases

- 48 y male
- Chest discomfort 2hr
- Flu like symptoms 3 days
- ECG: diffuse ST changes

- Steady slow  $\uparrow$  cTnI
- Peak 9 ng/L
- Echo: LV dysfunction

- 60 y female
- History of HF
- Chest pain for 1.5 hr
- ECG: non diagnostic

- Mild  $\uparrow$  cTnI  
(5-9 ng/L)

- 54 y male
- History of DM
- Chest pain for 1 hr
- ECG: normal

- $\uparrow$  cTnI: 6.3  $\rightarrow$  53 ng/L
- Chest pain for 1 hr
- ECG: normal

## Cases

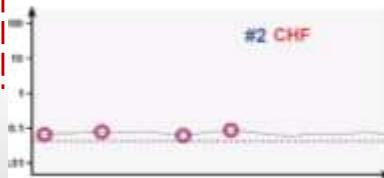
- 48 y male
- Chest discomfort 2hr
- Flu like symptoms 3 days
- ECG: diffuse ST changes

- Steady slow  $\uparrow$  cTnI



- 60 y female
- History of HF
- Chest pain for 1.5 hr
- ECG: non diagnostic

- Mild  $\uparrow$  cTnI  
(5-9 ng/L)



- 54 y male
- History of DM
- Chest pain for 1 hr
- ECG: normal

- $\uparrow$  cTnI: 6.3  $\rightarrow$  53 ng/L



## Other biomarkers

- There is interest in identifying additional ACS biomarkers (especially for early presenters).
- Unfortunately, none could add value to sensitive cTn assays.

## Copeptin

- Vasopressin prohormone.
- Increases very early in AMI.
- Two meta-analyses: copeptin + cTn → greater diagnostic accuracy than cTn.
- Contemporary cTn assay + copeptin sensitivity: suboptimal for rule-out (95%).
- hs-cTnT + copeptin → higher pooled sensitivity (98%;95% CI 96%–100%).
- RCT of 902 subjects: copeptin reduced LOS (7 vs 4 hrs,  $p<0.001$ ) and yields non-inferior clinical outcomes (similar MACE).
- Added value of copeptin to hs-cTn-based rule-out strategies remains to be proven.

## Heart-type fatty acid-binding protein (H-FABP)

- Small highly cardiac-specific protein.
- Increases early in AMI.
- Provides diagnostic and prognostic information independent of cTn and ECG abnormalities.
- Systematic review: sensitivity and NPV may be suboptimal for early rule-out.
- More evidence is still required for routine use of this promising biomarker.

## Conclusion

- Cardiac biomarkers are central to the diagnosis of AMI.
- cTn *is* the reference standard biomarker.
- AMI could be ruled out in 2/3 of patients with 2 samples hs-cTn, 1 hour apart.
- Validated risk scores may help increase the safety of early discharge.
- Although highly cardiac-specific, remember that hs-cTn is a *marker of myocardial injury!*
- Clinicians must interpret cTn conc *in conjunction with clinical context.*
- Except for very high initial cTn, *serial sampling* is necessary to differentiate chronic elevations from acute myocardial injury.
- New biomarkers need more evidence to implement them in clinical practice.



**THANK YOU**