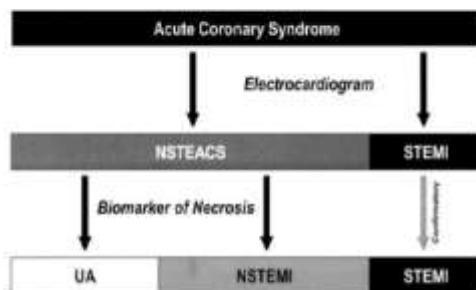


Troponin Grey Zone

What the Guidelines Say

Yasser Baghdady, MD
 Prof. of Cardiology
 Cairo University

Definitions--



"U.S. spends an estimated \$8 billion to \$13 billion per year in managing chest pain patients in the ED. "And approximately up to 80 percent of these patients don't have ACS."

Dr. Luis LeSaliva CAP Today Feb. 2009

2 Types of Myocardial Infarction

STEMI (EKG Diagnosed)

400k Cases Annually in the United States

EKG Diagnosed
50% Sensitivity?



NSTEMI (Biomarker Confirmed)

1.4m Cases Annually in the United States

Biomarker Diagnosed
Sensitivity and Specificity Variable



Photos courtesy of Boehringer Ingelheim International GmbH, by Lennart Nilsson.

3 Types of Troponin

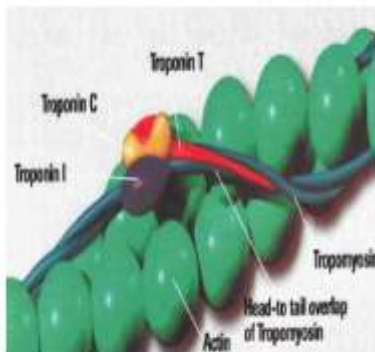


Illustration: Chaikhouni A, M.D.; Al-Zaim H, M.D.;
Department of Cardiothoracic Surgery, Al-Salam
Hospital, Aleppo, Syria.

Cardiac Implications

- Troponin C
- Troponin I
- Troponin T

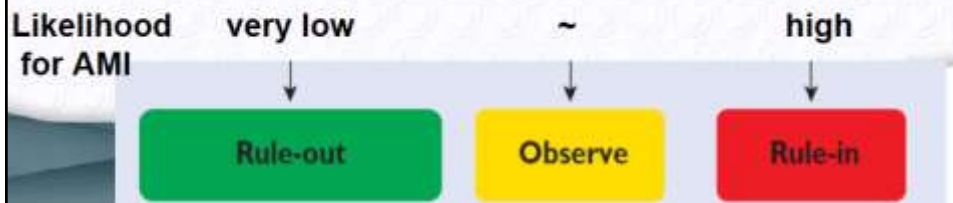
Presently the belief is that Troponin I & T reside only in myocardial cells=great cardiac specificity

- Troponin C is found in other muscle fibers in addition to the heart.

Present cardiac guidelines state that either Troponin I (cTnI) or Troponin T (cTnT) will yield clinically similar information.

Background

- cTns are structural proteins unique to the heart.
- cTn, measured in blood, is a quantitative marker of cardiomyocyte injury
- Cardiomyocyte injury is an obligatory feature of AMI, but multiple causes other than AMI also lead to cardiomyocyte injury
- Accordingly cTn \neq pregnancy test!



Troponin Assays

- Can be measured using immunoassays
- Most use 2 or 3 antibodies
- Because of differences in antibodies and reagents used in the assay, numbers cannot be compared between different kits.
- cTnT and cTnI have equal utility

Troponin Assays

- Older assays are less sensitive than newer assays
- Thus, rise of conventional (sensitive) and highly sensitive assays.
- Guidelines now recommend use of hs-cTn.
- These assays can detect troponin in > 80% of normal individuals.

Current Utilization for Troponin Testing



Diagnostic Utilization

1. Detect elevations caused by impaired blood flow to the myocardium:
 - Acute Coronary Syndromes
 - NSTEMI
 - STEMI
2. Risk Stratification
 - To assess the probability that the patient's symptoms are related to acute coronary ischemia;
 - To assess the patient's risk of recurrent cardiac events, including death and recurrent ischemia.

Prognostic Utilization

- Predicting morbidity and mortality
- Predicting future ACS events
- Prognosis in Heart Failure outcomes...to name a few

"These abnormal concentrations have been significant predictors of an adverse short and/or long-term prognosis in nearly every available study."

AHA/ACC/NACB Guidelines; Circulation 2007

Sources of Confusion

Clinical Confounders

- Diagnostic Dilemmas
- Prognostic Dilemmas
- Clinical vs. Analytical Variables



Guideline Perspectives

- Numerous organizations with differing standards
- Constantly evolving criteria for best demonstrated practices.

Laboratory Confounders

- Assay Performance Variables
- Analyzer Performance Variable

Industry Confounders

- Continuous enhancement of assay performance
- Next generation assays and expanded clinical utility?
- New analyzer platforms with decreased Turn Around Time (TAT)

Clinical Confusion, *why after all these years?*

"It's almost being drawn for all emergency patients and people are using the assay in a way that wasn't intended. The confusion about how to use and interpret cTn results is so significant that the assay is being misused.

Kristin Newby, MD, MHS, Duke University Medical Center

There are a lot of places where doctors admit every single person with troponin elevations, and the admitting physicians are reflexively consulting cardiologists.

- When the cardiologists see these patients, they ask, 'why am I being consulted'? because this patient clearly doesn't have cardiac ischemia"

Francis Esmer, MD, FACEP, director of the department of emergency medicine, University of Tennessee-Chattanooga

A cardinal misuse of the assay is that it is ordered often in patients with an extremely low pre-test likelihood of ACS. "If the doctor thinks the patient has extremely low odds of having ACS, then he/she shouldn't order the test. That's what gets you in trouble, particularly in terms of false positive results,".

Robert Christenson, PhD, professor of pathology University of Maryland School of Medicine in Baltimore



cTn „grey zone“ varies according to setting

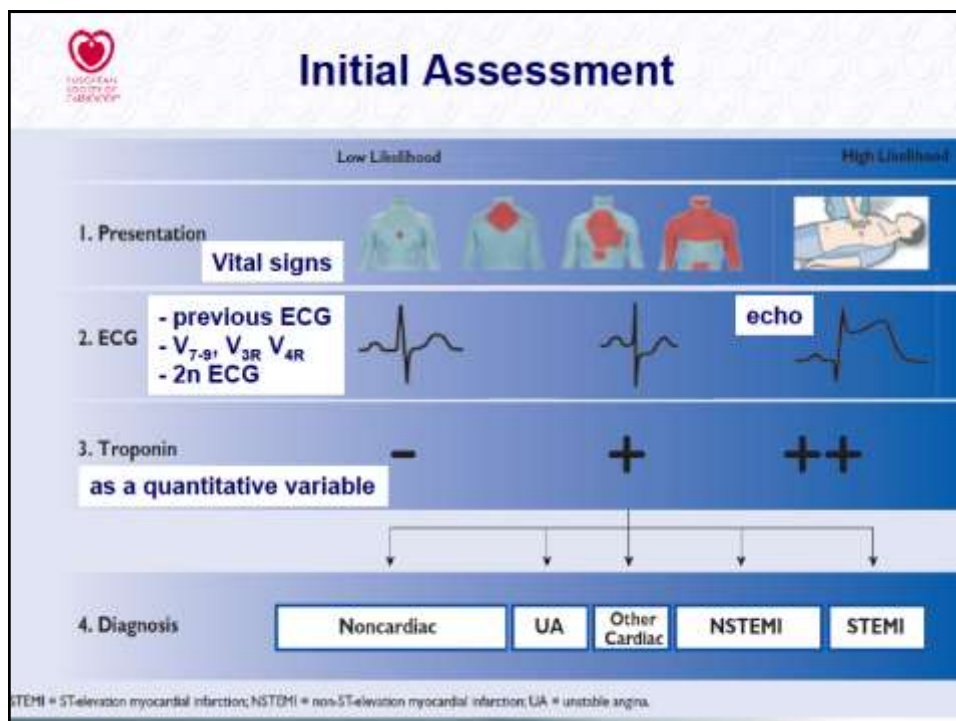
- **ED/CPU**
 - Chest pain and/or suspected AMI
 - AHF
- ICU
- Post cardiac surgery
- Post non-cardiac surgery
- Screening
- Risk stratification in PE

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)

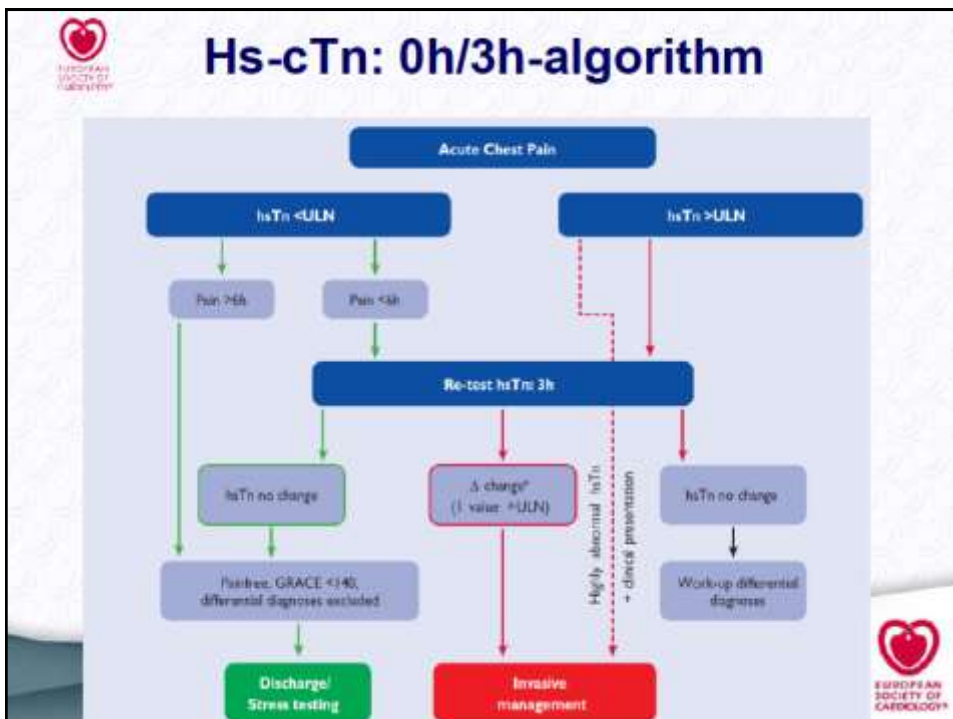
Authors/Task Force Members: Marco Roffi^{*} (Chairperson) (Switzerland), Carlo Patrono^{*} (Co-Chairperson) (Italy), Jean-Philippe Collet[†] (France), Christian Mueller[‡] (Switzerland), Marco Valgimigli[‡] (The Netherlands), Felicita Andreotti (Italy), Jeroen J. Bax (The Netherlands), Michael A. Borger (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)

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Hs-cTn: Quantitative marker of cardiomyocyte injury

PPV for AMI		Differential Diagnosis	
	$\mu\text{g/L}$	ng/L	
	100	2000	Very large AMI , myocarditis
PPV >95%	10	1000	Large AMI , myocarditis, Tako-tsubo, PE, critical illness
PPV 80%	1	100	Small AMI , early large AMI, myocarditis, Tako-tsubo, PE, shock, CHF, SAB, ...
PPV 50%	0.1	30	Micro AMI , early large AMI, myocarditis, Tako-tsubo, PE, shock, CHF, hypertensive crisis, SAB, stable CAD...
NPV 95%	0.01	10	Stable angina, CHF, LVH, subclinical heart disease, etc
NPV 99%	0.001	5	Healthy individuals



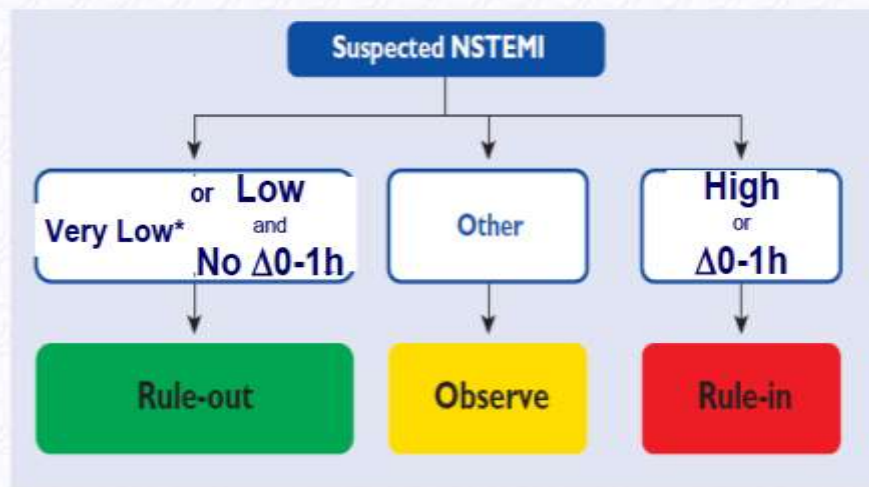
Levels of high-sensitivity cardiac troponin should be interpreted as quantitative markers of cardiomyocyte damage (i.e. the higher the level, the greater the likelihood of MI):

- Elevations beyond 5-fold the upper reference limit have high (>90%) positive predictive value for acute type I MI.
- Elevations up to 3-fold the upper reference limit have only limited (50–60%) positive predictive value for acute MI and may be associated with a broad spectrum of conditions.
- It is common to detect circulating levels of cardiac troponin in healthy individuals.

Rising and/or falling cardiac troponin levels differentiate acute from chronic cardiomyocyte damage (the more pronounced the change, the higher the likelihood of acute MI).



Hs-cTn: 0h/1h-algorithm



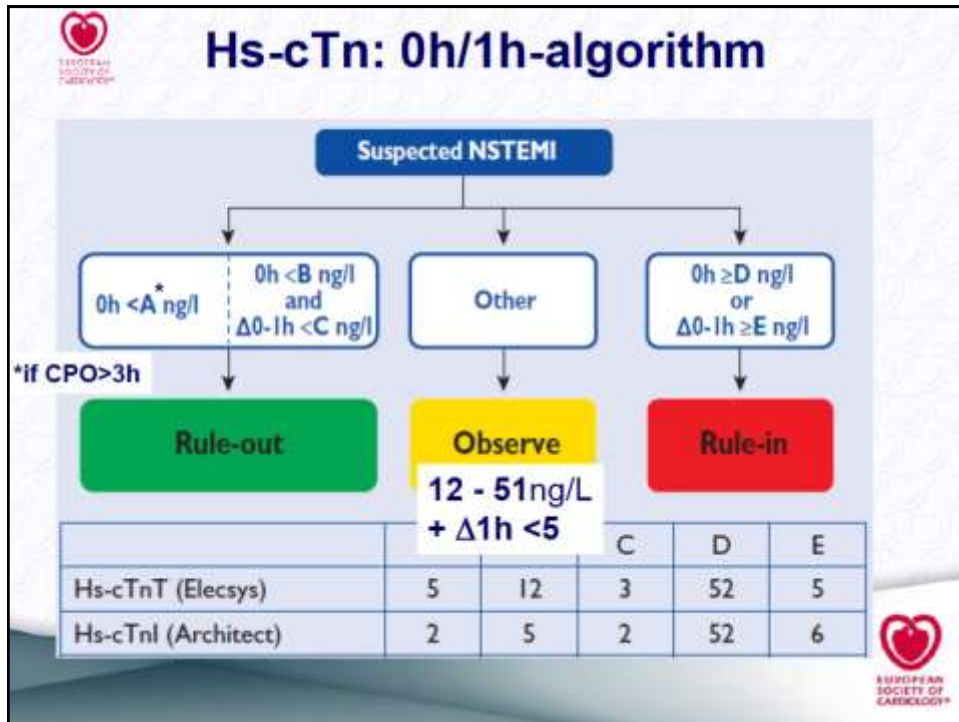


Table 4 Conditions other than acute myocardial infarction type 1 associated with cardiac troponin elevation

Tachyarrhythmias
Heart failure
Hypertensive emergencies
Critical illness (e.g. shock/ sepsis/ burns)
Myocarditis*
Tako-Tsubo cardiomyopathy
Structural heart disease (e.g. aortic stenosis)
Aortic dissection
Pulmonary embolism, pulmonary hypertension
Renal dysfunction and associated cardiac disease
Coronary spasm
Acute neurological event (e.g. stroke or subarachnoid haemorrhage)
Cardiac contusion or cardiac procedures (CABG, PCI, ablation, pacing, cardioversion, or endomyocardial biopsy)
Hypo- and hyperthyroidism
Infiltrative diseases (e.g. amyloidosis, haemochromatosis, sarcoidosis, scleroderma)
Myocardial drug toxicity or poisoning (e.g. doxorubicin, 5-fluorouracil, herceptin, snake venoms)
Extreme endurance efforts
Rhabdomyolysis

Grey zone: Mild cTn \uparrow ($<3 \times \text{ULN}$)

1. **What is the pre-test probability for AMI based on chest pain onset, signs and ECG findings?**
E.g. typical pain, CPO 2h, ST-segment \downarrow ... PPV $\approx 90\%$
2. **Does my patient have a readily identifiable non-AMI cause for the low level cTn elevations?** E.g. Age, heart failure, aortic stenosis, PE. The more plausible the alternative cause for low level cTn elevations, the less likely that any immediate further diagnostic work-up for AMI is justified and/or necessary.
3. **What other diagnostic test is useful?**
1h/3h hs-cTn, echo, stress-echo, CMR



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GUIDELINES CLINICAL QUERIES

Questions and answers on diagnosis and risk assessment: a companion document of the 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation[†]

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If the patient is assigned to the observe zone, what next?

- 20-30% lie in the observe zone
- The majority will require repeat troponin after 3 hrs
- Coronary Angio should be considered in those with a high likelihood of ACS
- Low/intermediate risk: non-invasive test (CT angio, MPI, stress echo, MRI etc)

