High Sensitivity Troponins. IT'S TIME TO SAVE LIVES. Updates from the ESC 2015 Guidelines

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Dr. Marcel El Achkar

Chairperson of Laboratory department

Nini Hospital

Lecturer FHS Balamand University

Disclosure

Dr ACHKAR reports no conflict of interest in this lecture.

Introduction

CVD epidemiology

History of cardiac biomarkers for MI diagnosis.

What are Troponins.

Third universal definition for MI.

Definition of hs-Troponins by the IFCC task force.

Older generation Troponin vs hs-Troponins.

Technical characteristics of the most used assays in Lebanon. Roche hs Trop T vs Abbott hs Trop I.

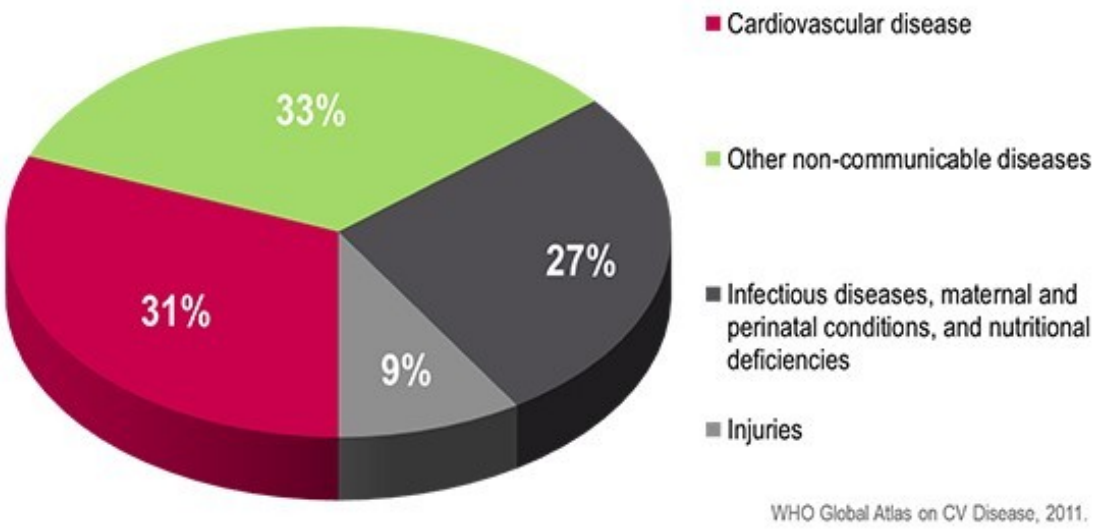
Clinical outcome Roche hs Trop T vs Abbott hs Trop I.

Take home message.

CVD epidemiology

- Cardiovascular disease is the single largest cause of death worldwide and is commonly associated with myocardial infarction.1
- According to the WHO, 17.3 million deaths in 2008 were attributable to cardiovascular disease, with 7.3 million (42% of all cardiovascular deaths) being due the result of a myocardial infarction.1
- In 2009, approximately 1 in 6 people in the United States died of coronary heart disease.2
- Major causes of death including cardiovascular disease

CVD epidemiology



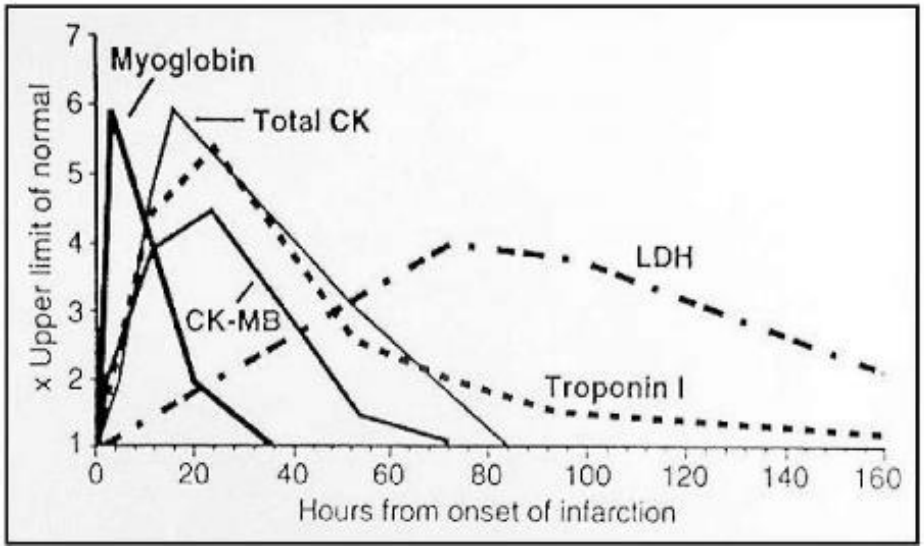
WHO Global Atlas on CV Disease, 2011.

HISTORY OF CARDIAC BIOMARKERS FOR MI DIAGNOSIS

History of use of biochemical markers of myocardial injury.

Time	Marker
Late 1950s	Aspartate aminotransferase (AST, SGOT)
1960s	Creatine kinase (CK, CPKa)
1970s	Creatine kinase isoenzyme (CK-MB activity)
1970s	Lactate dehydrogenase isoenzymes (ratio of LD1 to LD2)
Late 1980s	CK-MB mass concentration
Mid-1990s	cTnI, cTnT

HISTORY OF CARDIAC BIOMARKERS FOR MI NOSIS



Biomarker	Time to Initial Elevation	Time to Peak Elevation	Time to Return to Normal
Myoglobin	1-2 hours	8-10 hours	24 hours
CK-MB isoforms	4-6 hours	18 hours	2-4 days
cTnI	4-6 hours	12 hours	3-10 days
cTnT	4-6 hours	12-48 hours	7-10 days
LD-I	10-12 hours	48-72 hours	7-10 days

CK-MB, MB isoenzyme of creatine kinase; LD-I, lactate dehydrogenase isoenzyme; cTnI, cardiac troponin I; cTnT, cardiac troponin T

What are troponins?

Troponins are protein molecules that are part of cardiac and skeletal muscle. Smooth muscle cells do not contain troponins.

Three types of troponins exist—troponin I, troponin T, and troponin C. Each subunit has a unique function:

Troponin T binds to tropomyosin and helps position it on actin, and with the rest of the troponin complex modulates contraction of striated muscle.

Troponin I inhibits the interaction of myosin with actin.

Troponin C contains the binding sites for Ca^{2+} that helps initiate contraction

What are troponins?

Calcium binds to troponin and exposes myosin binding sites on actin

A ‘regulatory muscle protein released into the circulation following acute cardiac injury’ Shah 2013

Part of the criteria for the universal definition of MI – ESC, AHA, ACC, WHF

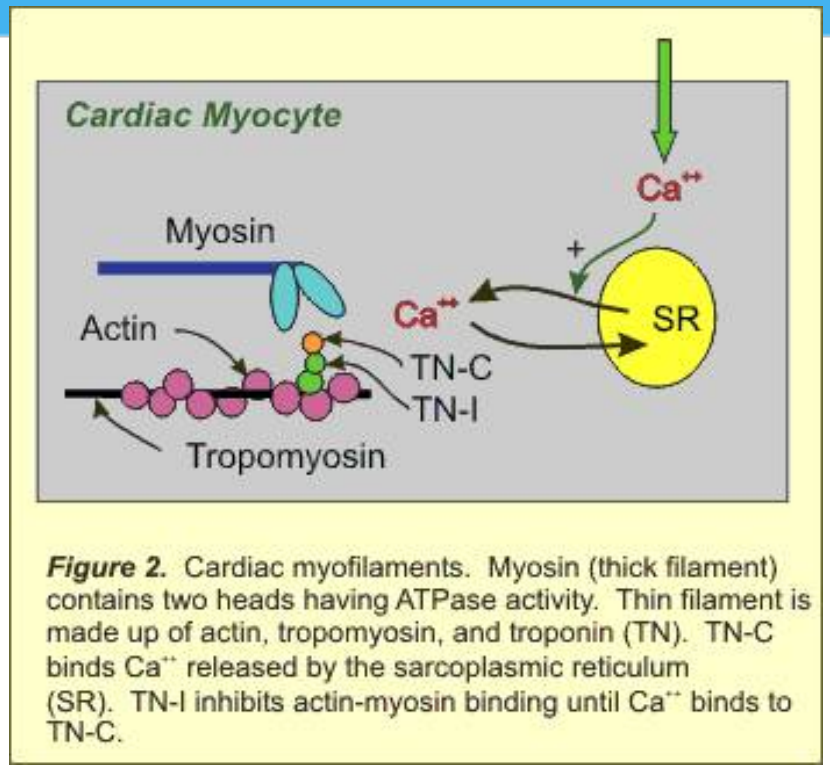


Figure 2. Cardiac myofilaments. Myosin (thick filament) contains two heads having ATPase activity. Thin filament is made up of actin, tropomyosin, and troponin (TN). TN-C binds Ca^{++} released by the sarcoplasmic reticulum (SR). TN-I inhibits actin-myosin binding until Ca^{++} binds to TN-C.

What are troponins?

it is known that gender, age, race, renal function, heart failure, and structural heart disease, including increased left ventricular (LV) mass are associated with increased cTn concentrations. *

*Collinson PO, Heung YM, Gaze D, et al. Influence of population selection on the 99th percentile reference value for cardiac troponin assays. Clin Chem 2012;58:219 –25.

THIRD UNIVERSAL DEFINITION OF MI

In 2000, the First Global MI Task Force presented a new definition of MI, which implied that any necrosis in the setting of myocardial ischaemia should be labelled as MI

These principles were further refined by the Second Global MI Task Force, leading to the Universal Definition of Myocardial Infarction Consensus Document in 2007, which emphasized the different conditions which might lead to an MI.

THIRD UNIVERSAL DEFINITION OF MI

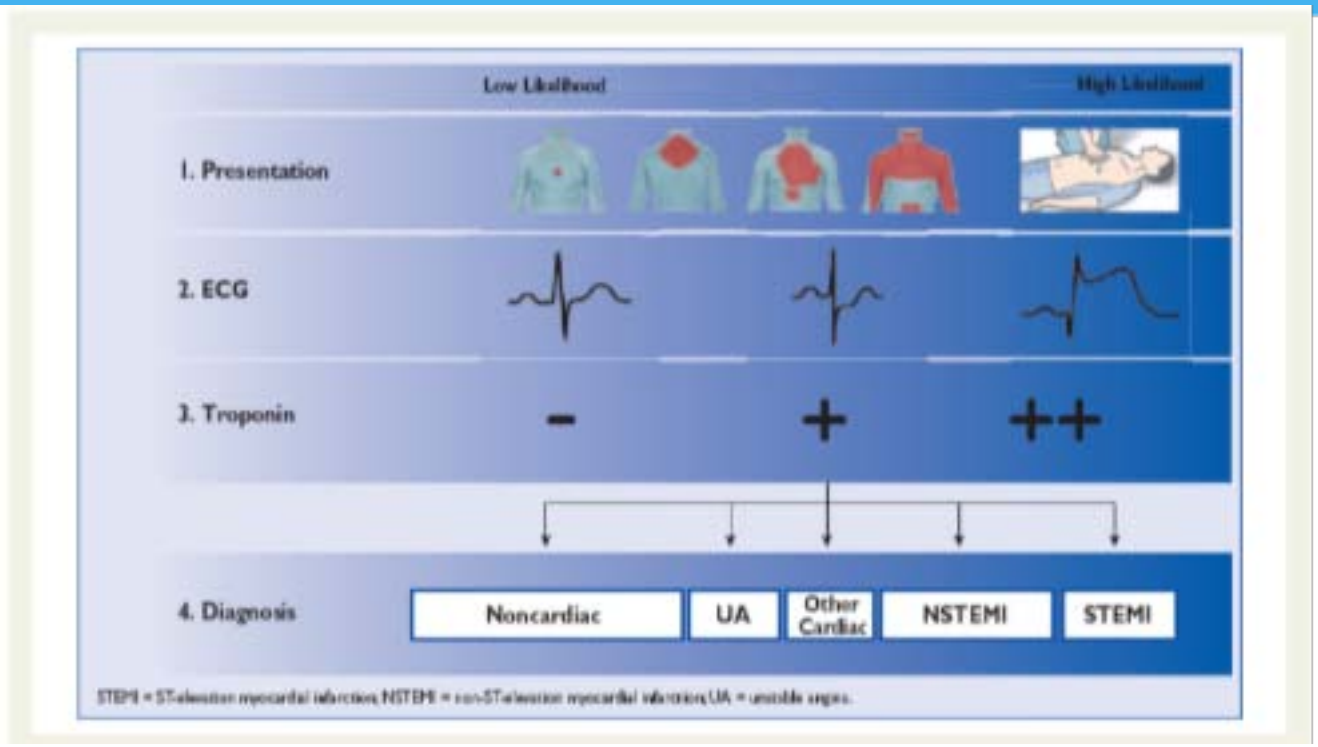
Acute myocardial infarction (MI) defines cardiomyocyte necrosis in a clinical setting consistent with acute myocardial ischaemia. A combination of criteria is required to meet the diagnosis of acute MI, namely the detection of an increase and/or decrease of a cardiac biomarker, preferably high-sensitivity cardiac troponin, with at least one value above the 99th percentile of the upper reference limit and at least one of the following:

(1) Symptoms of ischaemia.

(2) New or presumed new significant ST-T wave changes or left bundle branch block on 12-lead ECG.

(3) Development of pathological Q waves on ECG.

THIRD UNIVERSAL DEFINITION OF MI



Definition of hs-Troponins by the IFCC task force

A **percentile** is a measure that tells us what percent of the total frequency scored below that measure.

So the 99th percentile of Troponin in a given population correspond to the upper reference limit (URL) where 99% of measurements falls under this reference.

Definition of hs-Troponins by the IFCC task force

Limit of Detection (LoD) : is the lowest analyte concentration that can be measured.

The Limit of Quantitation (LoQ) (functional sensitivity) is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 10 %.

Definition of hs-Troponins by the IFCC task force

High-sensitivity assays, by expert consensus, should have a coefficient of variance (CV) of <10% at the 99th percentile value in the population of interest.

To be classified as high-sensitivity assays, concentrations below the 99th percentile should be detectable above the assay's limit of detection for >50% of healthy individuals in the population of interest.

Definition of hs-Troponins by the IFCC task force

The IFCC task force on Clinical Applications of Cardiac Bio-Markers document now provides definitive guidance: the 99th percentile should be powered for each sex and use a minimum of 300 males and 300 females. Because men have higher values than women, it is very important to determine sex-specific cutoffs.

Older generation Troponin vs hs-Troponins

Older units for troponin first & second generations use to be µg/l.

Hs- Troponin assays units are ng/l = pg/ml

1 µg/l: 1000 ng/l

Old cut-offs for the rule out of MI was < 0.4 µg/l : 400 ng/l.

Older generation Troponin vs hs-Troponins

Table 2 Classification of High-Sensitivity Cardiac Troponin Assays

Category	Description
First Generation	Able to measure cTn in 50%–75% of a reference population
Second Generation	Able to measure cTn in 75%–95% of a reference population
Third Generation	Able to measure cTn in more than 95% of a reference population.

Adapted from Apple and Collinson (3).

Older generation Troponin vs hs-Troponins

Measurement of lower Troponin concentration improved the sensitivity of hs-cTn for the diagnosis of acute cardiac injury. However, it does so at the cost of specificty.

Older generation Troponin vs hs-Troponins

The sensitivity and specificity at the 99th percentile (Elecsys Troponin T hs assay)/10 % CV (Elecsys Troponin T assay, 4th gen.; 0.03 ng/mL) criteria were in addition calculated for different time intervals from admission to the hospital:

Time from admission (hours)	Test generation Troponin T	Sensitivity %	N	95 % confidence interval (%)	Specificity %	N	95 % confidence interval (%)
0	4th gen.	71	40/56	58-83	99	142/143	96-100
	Troponin T hs	93	52/56	83-98	76	109/143	68-83
0-3	4th gen.	81	75/93	71-88	99	356/359	98-100
	Troponin T hs	98	91/93	93-100	79	282/359	74-83
3-6	4th gen.	83	53/64	71-91	100	300/301	98-100
	Troponin T hs	100	64/64	94-100	77	232/301	72-82
6-9	4th gen.	86	42/49	73-94	99	201/203	97-100
	Troponin T hs	98	48/49	89-100	76	155/203	70-82
9-12	4th gen.	83	15/18	59-96	100	43/43	92-100
	Troponin T hs	94	17/18	73-100	72	31/43	56-85
> 12	4th gen.	83	25/30	65-94	98	56/57	91-100
	Troponin T hs	100	30/30	88-100	60	34/57	46-72

Hs Trop T Sensitivity and specificity calculated with AMI defined according to the ESC/ACCF/AHA/WHF guidelines

Older generation Troponin vs hs-Troponins

Using the fourth generation cTnT assay, approximately 0.7% of patients in the general population have modest elevations 99th percentile URL. In the same population, this number was 2% with the hs-cTnT assay.*

Higher deltas improve specificity more and lower ones improve sensitivity and it is not clear that all physicians want the same tradeoffs in this regard. ED physicians often prefer high-sensitivity so that their miss rate is low (1%)*

* Korley and Jaffe. Preparing the U.S. for High-Sensitivity Troponin, JACC Vol. 61, No. 17, 2013 April 30, 2013:1753–8

Older generation Troponin vs hs-Troponins

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[a]
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

Bold = most frequent conditions; CABG = coronary artery bypass surgery; PCI = percutaneous coronary intervention.
[a]Includes myocardial extension of endocarditis or pericarditis.

Older generation Troponin vs hs-Troponins

Due to the higher sensitivity and diagnostic accuracy for the detection of acute MI at presentation, the time interval to the second cardiac troponin assessment can be shortened with the use of high-sensitivity assays. This may reduce substantially the delay to diagnosis, translating into shorter stays in the emergency department and lower costs.

Technical charcteristics Roche hs Trop T vs Abbott hs Trop I

PARAMETER	ROCHE hs Trop T	Abbott hs Trop I
LoD LoQ	5 ng/L 13 /ng/L	1.1-1.9 ng/L 4.0-10 ng/L
99th percentile (CV%)	14 ng/L	Female: 15.6 ng/L Male: 34.2 ng/L
TAT	For STAT hs TROP T: **9 min** For hs Trop T: 18 min	For STAT hs TROP I: **16 min**
Specimens	Serum collected using standard sampling tubes or tubes containing separating gel. K2-EDTA, K3-EDTA, Li-heparin and Na-heparin plasma	Serum collected using standard sampling tubes or tubes containing separating gel. K2-EDTA, K3-EDTA, Li-heparin.
Stability on the analysers	4 weeks	30 Days
Measuring range	3-10000 ng/L	4-50000 ng/L

Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction

To assess whether cardiac troponin (cTn) I or cTnT is the preferred biomarker in the early diagnosis of acute myocardial infarction without ST segment elevation (NSTEMI).*

*European Heart Journal (2014) 35, 2303–2311

Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction

A prospective multicentre study, we measured cTnI and cTnT using clinically available high-sensitivity assays (hs-cTnI Abbott and hs-cTnT Roche) and compared their diagnostic and prognostic accuracies in consecutive patients presenting to the emergency department with acute chest pain*

*European Heart Journal (2014) 35, 2303–2311

Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction

The mean follow-up was 24 months.

Blood samples for determination of hs-cTnI (Abbott) and hs-cTnT (Roche) were collected at presentation to the ED. Additional samples were collected at 1, 2, 3, and 6 h.

Among 2226 consecutive patients, 18% had an adjudicated final diagnosis of NSTEMI*

*European Heart Journal (2014) 35, 2303–2311

Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction

Diagnostic accuracy at presentation as quantified by the area under the receiver-operating-characteristics curve

(AUC) for NSTEMI was very high and similar for hs-cTnI [AUC: 0.93, 95% confidence interval (CI) 0.92–0.94] and hs-cTnT (0.94, 95% CI: 0.92–0.94) P = 0.62*

*European Heart Journal (2014) 35, 2303–2311

Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction

In early presenters (< 3 h since chest pain onset) hs-cTnI showed a higher diagnostic accuracy (AUC: 0.92, 95% CI: 0.89–0.94) when compared with hs-cTnT AUC

(0.89, 95% CI: 0.86–0.91) (P = 0.019)*

*European Heart Journal (2014) 35, 2303–2311

Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction

hs-cTnT was superior in late presenters [AUC hs-cTnT 0.96 (95% CI: 0.94–0.96) vs. hs-cTnI 0.94 (95% CI: 0.93–0.95); P = 0.007].

The prognostic accuracy for all-cause mortality,

quantified by AUC, was significantly higher for hs-cTnT (AUC: 0.80; 95% CI: 0.78–0.82) when compared with hs-cTnI (AUC: 0.75; 95% CI: 0.73–0.77); P = 0.001)

*European Heart Journal (2014) 35, 2303–2311

Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction

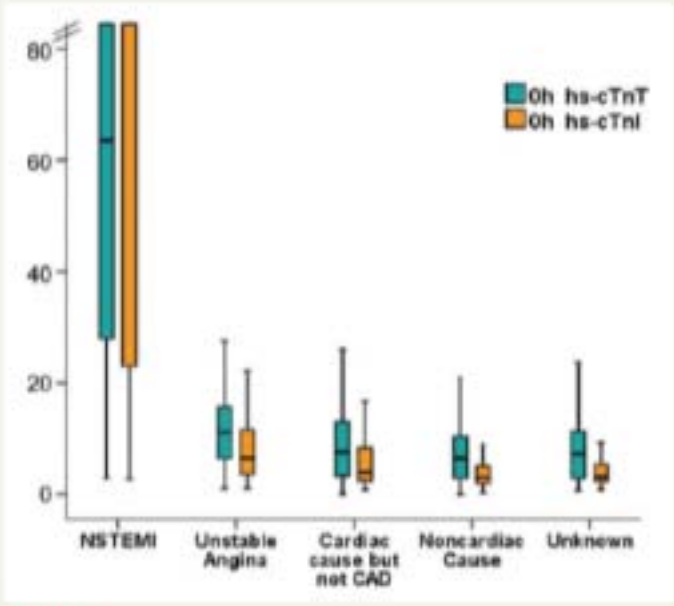


Figure 1 Levels of high-sensitivity cardiac troponin according to final diagnoses. Troponins levels at the time of patients' presentation to the emergency department. The boxes represent median and inter-quartile ranges. hs-cTn, high-sensitivity cardiac troponin; AMI, acute myocardial infarction; CAD, coronary artery disease.

*European Heart Journal (2014) 35, 2303–2311

Take home messages

- Troponin is standard biomarker for assessing chest pain (Thygesen *EHJ* 2012).
- hs-Troponin are able to measure 10-fold lower concentrations with high precision (a CV 10% at the 99th percentile of the URL).
- Does not exclude unstable angina

Take home messages

Table 3 **Clinical implications of high-sensitivity cardiac troponin assays**

Compared with standard cardiac troponin assays, high-sensitivity assays:
• Have higher negative predictive value for acute MI.
• Reduce the "troponin-blind" interval leading to earlier detection of acute MI.
• Result in a ~4% absolute and ~20% relative increase in the detection of type 1 MI and a corresponding decrease in the diagnosis of unstable angina.
• Are associated with a 2-fold increase in the detection of type 2 MI.
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 1 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).

MI = myocardial infarction.

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It is recommended to use the 0 h/3 h algorithm

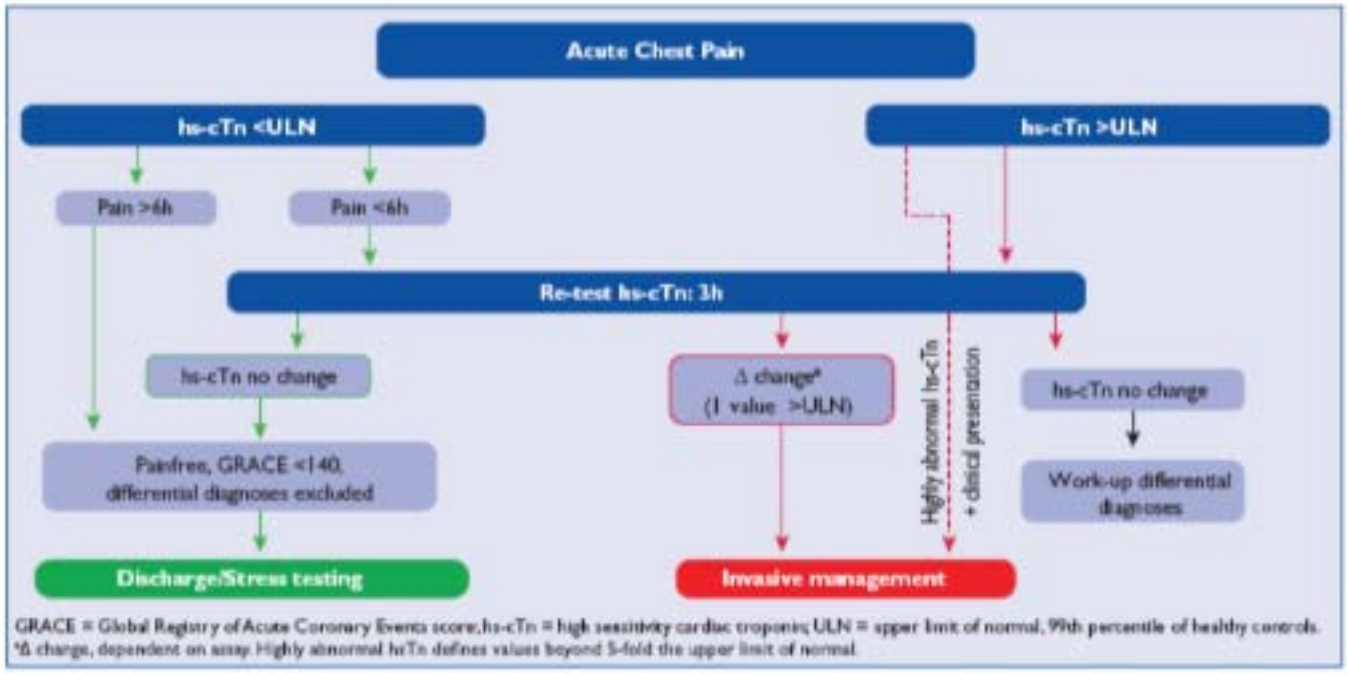
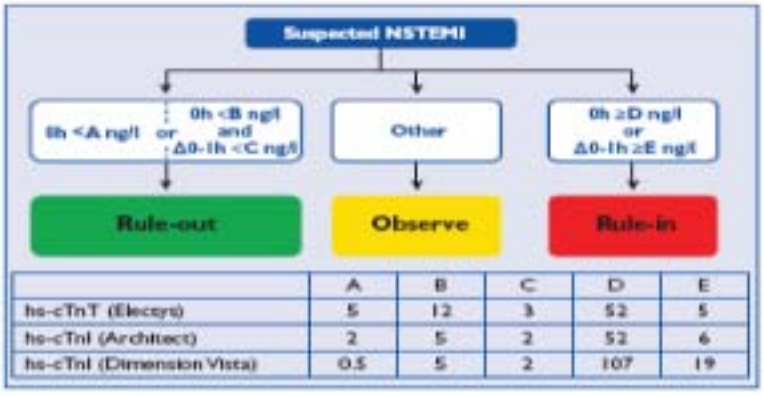


Figure 2 0 h/3 h rule-out algorithm of non-ST-elevation acute coronary syndromes using high-sensitivity cardiac troponin assays.

0 h/1 h assessments



	A	B	C	D	E
hs-cTnT (Elecsys)	5	12	3	52	5
hs-cTnI (Architect)	2	5	2	52	6
hs-cTnI (Dimension Vista)	0.5	5	2	107	19

Figure 3 0 h/1 h rule-in and rule-out algorithms using high-sensitivity cardiac troponins (hs-cTn) assays in patients presenting with suspected non-ST-elevation myocardial infarction (NSTEMI) to the emergency department. 0 h and 1 h refer to the time from first blood test. NSTEMI can be ruled-out already at presentation, if the hs-cTn concentration is very low. NSTEMI can also be ruled-out by the combination of low baseline levels and the lack of a relevant increase within 1 h. Patients have a high likelihood for NSTEMI if the hs-cTn concentration at presentation is at least moderately elevated or hs-cTn concentrations show a clear rise within the first hour. Cut-off levels are assay-specific. Cut-off levels for other hs-cTn assays are in development.

As an alternative, 0 h/1 h assessments are recommended when high-sensitivity cardiac troponin assays with a validated algorithm are available

0 h/1 h assessments

- The negative predictive value for MI in patients assigned ‘rule-out’ exceeded 98% in several large validation cohorts.
- Used in conjunction with clinical and ECG findings, the 0 h/1 h algorithm may allow the identification of candidates for early discharge and outpatient management

0 h/1 h assessments

The positive predictive value for MI in those patients meeting the ‘rule-in’ criteria was 75– 80%.

Most of the ‘rule-in’ patients with diagnoses other than MI did have conditions that usually require inpatient coronary angiography for accurate diagnosis, including Tako–Tsubo cardiomyopathy

and myocarditis.

0 h/1 h assessments

Patients who do not qualify for ‘rule-out’ or ‘rule-in’ represent a heterogeneous group that may require further investigations if no alternative explanation for the cardiac troponin elevation is identified.

Ex: hs Trop at 3h or Coronary angiography or computed tomography (CT) coronary angiography.

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