DIRECTIVES / GUIDELINES

USE OF THE HIGH-SENSITIVITY TROPONIN ASSAYS IN THE EVALUATION OF PATIENTS WITH CHEST PAIN

A Consensus Document from the Working Group on Troponin of the Lebanese Society of Cardiology

http://www.lebanesemedicaljoumal.org/articles/68-3/guidelines1.pdf

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ABSTRACT • Chest pain is a common clinical presentation, especially in the emergency department. Both rapid identification of patients with myocardial infarction, as well as those with non-cardiac chest pain, are important in order to start therapy in the former and avoid unnecessary investigations and delay in discharge in the latter. Beside EKG, cardiac biomarkers are a key element in decision making. Conventional creatinine kinase and troponin assays are not sensitive enough and have to be repeated at least 6 to 12 hours after initial evaluation. New high-sensitivity troponin tests are currently available and if used appropriately can substantially improve management of these patients. Because the analytical characteristics and protocol of use of these high-sensitivity assays may not be well understood by the medical community, the Lebanese Society of Cardiology created a working group charged with the mission of writing a concise and easy to read document addressing this important topic. This manuscript reviews the most important characteristics of hs-sensitivity troponin assays and the algorithms in which they should be used in patients with chest pain. The objective is to provide to Lebanese physicians evidence-based recommendations to rapidly rule-in or rule-out myocardial infarction in patients with chest pain.

Keywords : biomarkers; troponin; acute coronary syndrome; chest pain

EVALUATION OF CHEST PAIN

Chest pain is one of the most common complaints evaluated in.the emergency department. The objective of the treating physician is to rapidly diagnose myocardial ischemia. Several tools have been proposed. While EKG (electrocardiogram) is the cornerstone of the diagnostic evaluation, it is frequently normal or exhibits minor nonspecific abnormalities [1]. Cardiac enzymes, such as CK-MB and standard troponin tests are not sensitive enough and their levels are frequently undetectable on first evaluation. They have to be repeated after at least 6 hours in order to detect a significant rise [2]. As a result, many patients are kept several hours in the emergency department for observation or are admitted to the cardiac floor or intensive care unit to rule-in or rule-out myocardial infarction (MI). This approach results in a large number of patients being unnecessary admitted as well as in discharge of few patients who would experience a MI outside the hospital [3].

Several biomarkers other than cardiac troponin or CK-MB were tested in the evaluation of chest pain patients, such as myoglobin and fatty-acid binding protein, but they failed to increase the positive and negative predictive values of the classical markers [4-5], Similarly, other diagnostic approaches were proposed, such as acute rest myocardial perfusion imaging with sestamibi, echocardiography, or cardiac computed tomographic angiography [6-7]. These techniques, however, are expensive and not routinely available.

More recently the continuous improvement in troponin tests led to the development of high-sensitive assays capable of detecting very low levels of cardiac troponin, such as those present in healthy individuals [8-10]. These tests were introduced in clinical practice about 10 years ago and became the standard assays for ruling in and ruling out MI [2]. However, these high-sensitive troponin (hs-trop) assays created a lot of confusion among physicians who were used to "negative" or "positive" troponin values.

The fact that troponin levels are now detectable in almost everyone, combined with the fear of missing a MI, led to an explosion in unnecessary cardiology consults, described as the "troponinitis" syndrome.

Aware of this problem, the Lebanese Society of Cardiology created in early 2019 a working group with the mission to write a concise and easy-to-read document related to evaluation of patients with chest pain using hs-trop tests.

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Standard and high-sensitivity troponin

The contractile system of the cardiac myocyte contains three troponins: C, I and T. Troponins T and I are specific for the heart, while the two isoforms of cardiac and skeletal muscle troponin C are undistinguishable. Troponins are released in the circulation whenever cardiac myocyte damage occurs, whether caused by ischemia or by other conditions.

The old generation serum troponin assays had higher detection level than current high-sensitive ones [8-10]. For example, the minimal detection level of the fourth-generation troponin T assay released in 2005 was 0.01 ng/mL. The majority of "healthy" patients had a troponin T level below that value (reported as undetectable or negative). In a setting of myocardial ischemia, troponin level would rise rapidly in a degree proportional to the amount of infarction but it takes several hours for the level to go above the detectable concentration of 0.01 ng/mL. This is why the prior guidelines of the European Society of Cardiology and the American College of Cardiology recommended waiting 6-12 hours before ordering the second sample of troponin in order to rule-in or rule-out MI in patients presenting with chest pain.

The new hs-trop assays have several features that differentiate them from the old ones [8-10]. First, as their name implies, they can detect a much lower serum concentration of troponin. For example, the new hs-trop T minimal detection level is 0.005 ng/mL, which is twice lower than the standard troponin T test of 2005. Second, these tests can measure the level of troponin in the majority of healthy individuals. Because of this, the "normal" upper cut-off value of hs-trop was defined by the 99th percentile, which is the value that is higher than 99% of that in healthy individuals. Third, because of the precision of their measurement, the coefficient of variation of hs-trop test is < 10% when the troponin level is below the 99th percentile. This practically means that if the test is repeated in similar conditions (without ongoing ischemia or necrosis), the value of the new measurement should be within 10% of the first one. Fourth, because of all the above characteristics, these high-sensitivity tests can rapidly detect any minor myocardial damage, which would be reflected by an elevation in troponin level. Figure 1 displays the difference in sensitivities of old and newer assays.

As shown, level of troponin is frequently undetectable with the old tests at the time of evaluation. To the contrary, with high sensitivity tests the level is already elevated at the time of presentation and continues to increase with time, allowing detection of "minor" changes in concentration and subsequently rapid diagnosis of MI. As a result, there is a reduction in the "troponin-blind" interval leading to earlier detection of acute MI [2].

Given their low values in healthy populations, it is currently recommended to report hs-trop in ng/L rather than ng/mL in order to avoid decimal numbers that can lead to errors. For example, the lower cut-off value of hs-trop T is reported as 5 ng/L rather than 0.005 ng/mL and the 99th percentile is reported as 14 ng/L.

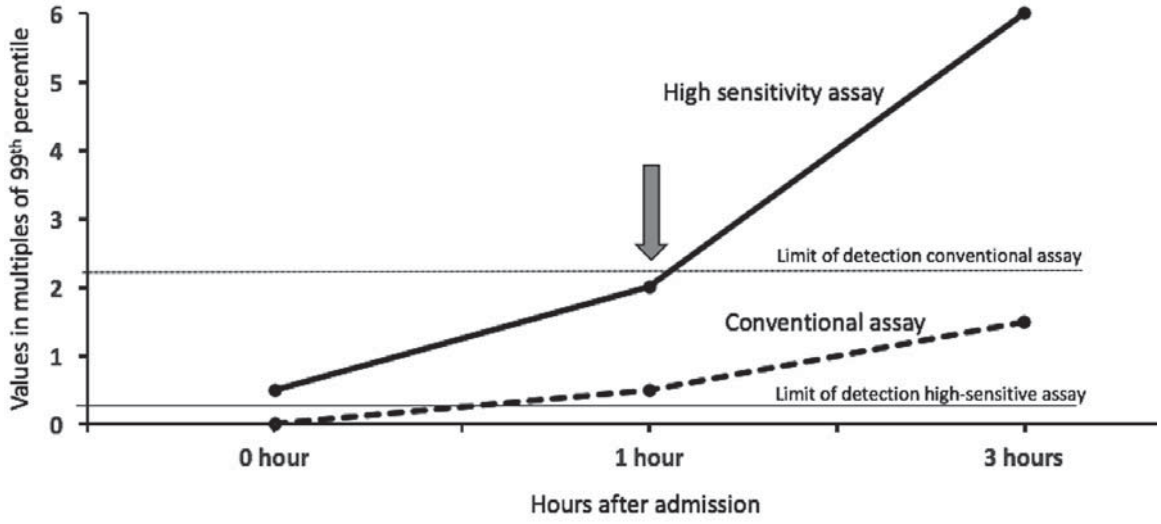


Figure 1. Comparison of high-sensitivity and conventional troponin assays.

With conventional assay, levels of troponin are below the lower detection limit during the first 3 hours after onset of myocardial infarction. Measurements should be repeated 6-12 hours later in order to detect a significant rise. With the high sensitive assays very low levels can be measured at time of admission and any minor change can be detected after one hour. This allows a much earlier diagnosis of myocardial infarction.

Hs-troponin T *vs.* Hs-troponin I

Both troponin T and I are very sensitive and specific for myocardial damage. There is however no head to head comparison in a randomized clinical trial evaluating patients with chest pain. Below are the main points to consider when comparing the two biomarkers.

First, only one company manufactures hs-trop T (Roche), while several manufacture hs-trop I. As a result, hs-trop T assay is standardized, while the assays of hs-trop I are not. Table I summarizes different hs-troponin I assays available. Depending on the assay, the 99th percentile of hs-trop I varies from 3 to 9 ng/L for women and 11 to 55 ng/L for men [9-10]. Second, hs- trop I values are gender specific. To the contrary, gender differences are less important for hs-trop T and the same cut-off values can be used for rule-in or rule-out MI in men and women [9-15]. Third, hs-trop T is the most studied troponin, especially in the setting of chest pain [11-14]. The only hs-trop I assay evaluated in a large study of chest pain patients is the Abbot Architect's assay [15]. Fourth, only 4 hs-trop assays are currently approved by the FDA. Those are the Roche Elecsys hs-trop T (first one to get approval), Beckman Access hs-trop I, Abbot Architect hs-trop I and Siemens Vista hs-trop I assays. Fifth, both hs-trop T and hs-trop I levels are commonly above the 99th percentile in patients with acute and chronic kidney disease [16]. In that setting, the kinetic (delta change over time) of hs-trop is more important than the baseline value. Both hs-trop T and hs-trop I have similar performance in patients with renal failure and either of them can be used [2,16].

TABLE I

ANALYTICAL CHARACTERISTICS OF CURRENT HIGH SENSITIVITY CARDIAC TROPONIN I ASSAYS

Company / Assay	Limit of detection (ng/L)	99th percentile (ng/L)	10% CV*
Abbot / Architect	1.2	F: 16 M: 34	3
Beckman/Access	2.1	F: 9 M: 11	8.6
Ortho-clinical diagnostics / Vitros	1	F: 16 M: 19	6.5
Singulex / Erenna MTP	0.1	F: 15 M: 27	0.9
Siemens / Vista	0.8	F: 33 M: 55	3

*CV = coefficient of variation at the 99th percentile

Causes of elevation of hs-troponin

Several causes other than ischemia and infarction can increase hs-troponin level [2]. These conditions are summarized in Table II. In the majority of cases, the elevation is minor (such as in renal failure, hypertension, congestive heart failure, etc.), but in some conditions affecting a large area of the myocardium, such as severe myocarditis and Tako-Tsubu cardiomyopathy, the elevation may be important. In general, levels above five times the 99th percentile should raise the possibility of acute MI until proven otherwise. The kinetic of hs-troponin is as important as the level. In acute MI, there is a quick rise followed by a fall while in the majority of other conditions, the kinetic of the biomarker is flat over time.

TABLE II

POSSIBLE NON-ACUTE CORONARY SYNDROME CAUSES FOR HS-TROPONIN ELEVATION

- Severe congestive heart failure: acute and chronic
- Chronic or acute renal dysfunction
- Hypertensive crisis
- Tachy- or bradyarrhythmias
- Pulmonary embolism, severe pulmonary hypertension
- Inflammatory disease, e.g. myocarditis
- Acute neurologic disease, including stroke or subarachnoid haemorrhage
- Aortic dissection, aortic valve disease or hypertrophic cardiomyopathy
- Cardiac contusion, ablation, pacing, cardioversion or endomyocardial biopsy
- Hypothyroidism
- Apical ballooning syndrome (Tako-Tsubo cardiomyopathy)
- Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, sclerodermia
- Drug toxicity, e.g. Adriamycin, 5-fluorouracil, Herceptin, snake venoms
- Burns, if affecting > 30% of body surface area
- Rhabdomyolysis
- Critically ill patients, especially with respiratory failure or sepsis

TABLE III MAJOR TRIALS EVALUATING HS-TROP IN CHEST PAIN PATIENTS

Study Year publication [reference]	Number of patients	Rule-out	Observation	Rule-in
		Hs-Troponin T (Roche Elecsys)		
APACE 2012 [11]	436	60% of patients NPV: 100%	23% of patients	17% of patients PPV: 84%
APACE 2015 [12]	1,320	60% of patients NPV: 99.6%	24% of patients	16% of patients PPV: 78.2%
TRAPID-AMI 2016 [13]	1,282	63.4% of patients NPV: 96.7%	22.2% of patients	14.4% of patients PPV: 77.2%
REAL WORLD STUDY 2019 [14]	2,296	62% of patients*	25% of patients	13% of patients*
		Hs-Troponin I (Abbot Architect)		
APACE 2015 [15]	905	50.5% of patients NPV: 99.6%	30.5% of patients	19% of patients PPV: 75.6%

APACE: advantageous predictors of acute coronary syndrome evaluation NPV: negative predictive value PPV: positive predictive value
TRAPID-AMI: the high sensitivity cardiac troponin T assay for rapid rule-out of acute myocardial infarction
*Negative & positive predictive values not reported

Given that several conditions other than MI are associated with high levels of hs-troponin, the universal definition of MI requires all the following:

1) A hs-troponin level above the 99th percentile for the assay being used;
2) A rise and/or fall of hs-troponin level &
3) One of the following conditions: symptoms suggestive of ischemia, or ST-segment elevation on EKG, or a new left bundle branch block on EKG, or development of new Q waves on EKG, or images of new loss of viable myocardium, or new regional wall motion abnormality, or identification of an intracoronary clot on angiography or autopsy [2].

Use of hs-troponin for rapid rule-in or rule-out MI

Because of its high sensitivity and specificity, high accuracy and ease of dosage, hs-trop is currently the marker of choice for rapid decision making in patients with chest pain.

Three major trials [11-13] performed on 1,848 patients have tested the new 0-hour/l-hour hs-trop T algorithm to rule in or rule out MI in patients with chest pain (Table III).

This algorithm is based on obtaining a 12-lead EKG, history, physical exam and a measurement of a baseline level of hs-trop T, called hs-trop T 0-hour sample. In the absence of ST segment elevation on the EKG, the measurement of hs-trop T is repeated 1 hour later (Figure 2). If the hs-trop T at 0-hour is < 12 ng/L and the change after 1 hour is < 3, the patient can be safely discharged. To the contrary, if baseline hs-trop T is > 52 ng/L or the change is > 5, the patient is admitted with a high likelihood of MI. For values in-between, the patient is kept for observation and can be reevaluated with a third hs-trop T measured at 3-hour.

In those three trials, the algorithm allowed to reach a decision in 1 hour in almost 75% of patients, with 60-63% being ruled out and 14-17% being ruled in for MI. The negative predictive value for adverse cardiovascular outcome at 30-day ranged from 99.1 to 100% but the positive predictive value for MI was lower and varied from 77 to 84%. This imperfect positive predictive value is due to the fact that several other conditions may increase hs-trop level (as discussed above). Many of these conditions however, require admission and appropriate management.

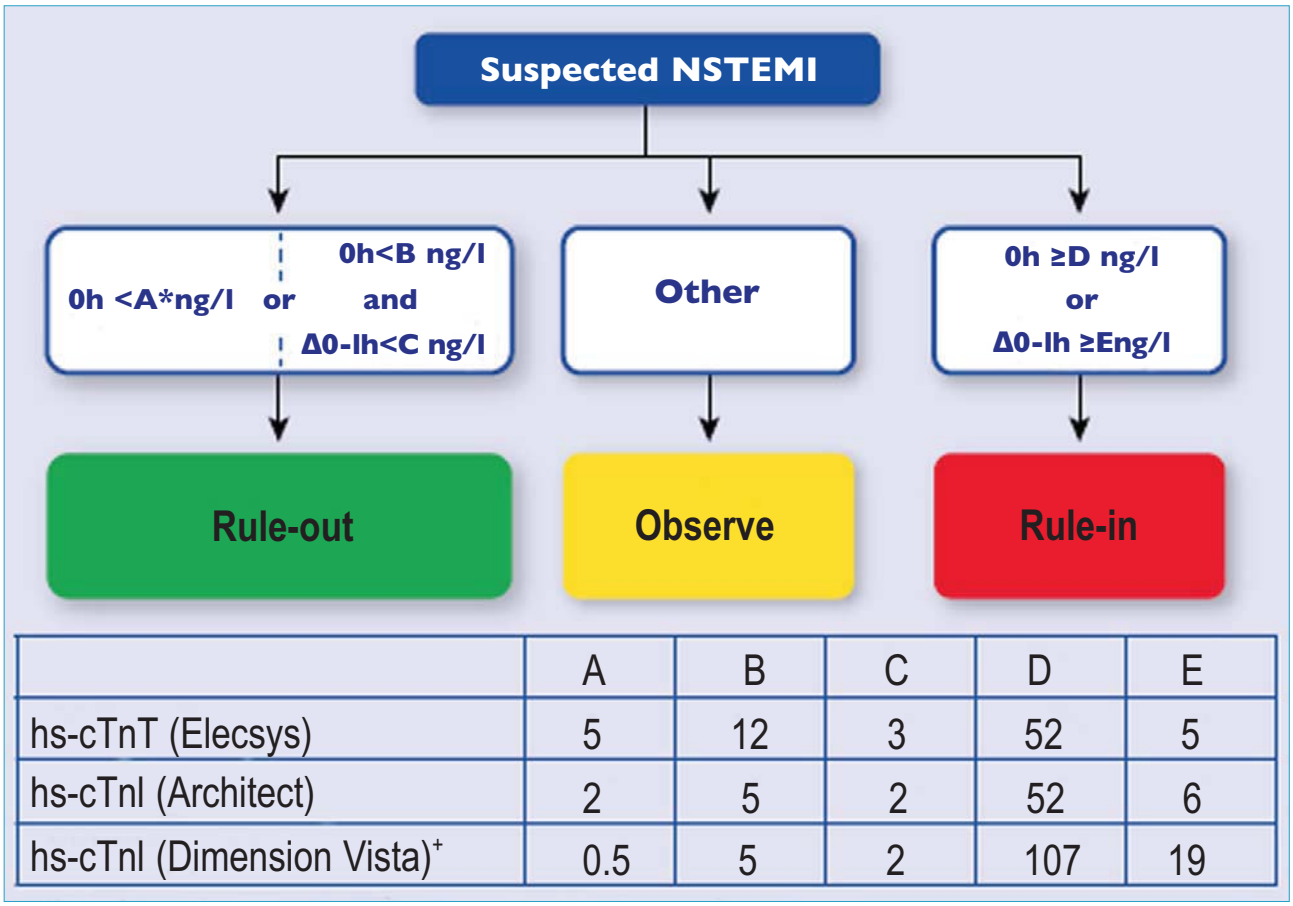
These three studies were recently confirmed in a large real world international trial that enrolled 2,296 patients. Of utmost importance, the event rate in the 1,619 patients discharged home was 0.1% at 30-day follow-up [14].

Similar to hs-trop T, hs-trop I was also evaluated in the 0 hour/1 hour algorithm [15]. The negative predictive and the the positive predictive values for MI were 99.6% and 75.6%, respectively. The hs-trop I assay used was the Abbot Architect assay.

Guidelines of the European Society of Cardiology for the use of hs-troponin in chest pain patients

The guidelines of the European Society of Cardiology recommend the use of the 0 hour/1 hour algorithm to investigate patients with chest pain when hs-trop tests are available [2].

This algorithm is a class I recommendation and is preferred over the 0 hour/3 hour algorithm because it was validated in larger multicenter studies, has excellent neg-



	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 2. European Society of Cardiology 0 hour/1 hour rule-out or rule-in algorithm in patients with chest pain.
*Applicable only if chest pain onset > 3 hours prior to evaluation + Not commercially available

ative and positive predictive values, is easier to perform and shortens time to decision [2]. The algorithm is summarized in Figure 2 and can be used when one of the three hs-troponin assays are available: hs-trop T (Roche Elecsys 5th generation), hs-trop I (Abbot, Architect) and hs-trop I (Siemens, Dimension Vista). Values at baseline and the delta change at 1 hour are specific for each assay and should be used to rule-in or rule-out MI as described in the algorithm. Several important points need to be emphasized:

1) Non ST elevation MI can be ruled out at presentation (time 0) if hs-trop is very low (< 5 ng/mL for hs-trop T) provided the onset of chest pain is > 3 hours;
2) Non ST elevation MI can be diagnosed at time 0 if initial hs-trop level is significantly high but the positive predictive value is < 83% for the reasons discussed above;
3) For very early presenters (chest pain onset < 1 hour prior evaluation), this algorithm is not recommended. The second hs-trop level should be obtained at 3 h due to the time dependency of troponin release (0 hour/3 hour algorithm);
4) Patients who do not fit in the rule-out or rule-in zones should be kept for observation. They can be evaluated according to the 0 hour/3 hour algorithm where a 3rd measurement is performed at 3 hours. If initial hs-trop level is > 99th percentile, a rise or fall of more than 20% in the level compared to 0 hour sample is very suspicious and requires admission, but if the initial hs-trop level is < 99th percentile, the change in hs-trop should be > 50% of the upper reference limit of the assay being used, to be considered significant. Absence of a significant change makes the diagnosis of MI very unlikely and mandates a work-up for a differential diagnosis [2,8]. The 0 hour/3 hour algorithm is summarized in Figure 3.
5) Algorithms should always be used in combination with clinical information and EKG. When the clinical suspicion of ischemia is high, or if there is recurrence of chest pain, admission and further testing with a hs-trop several hours later is preferred, as in about 1% of cases, the rise in hs-trop may be delayed [2].

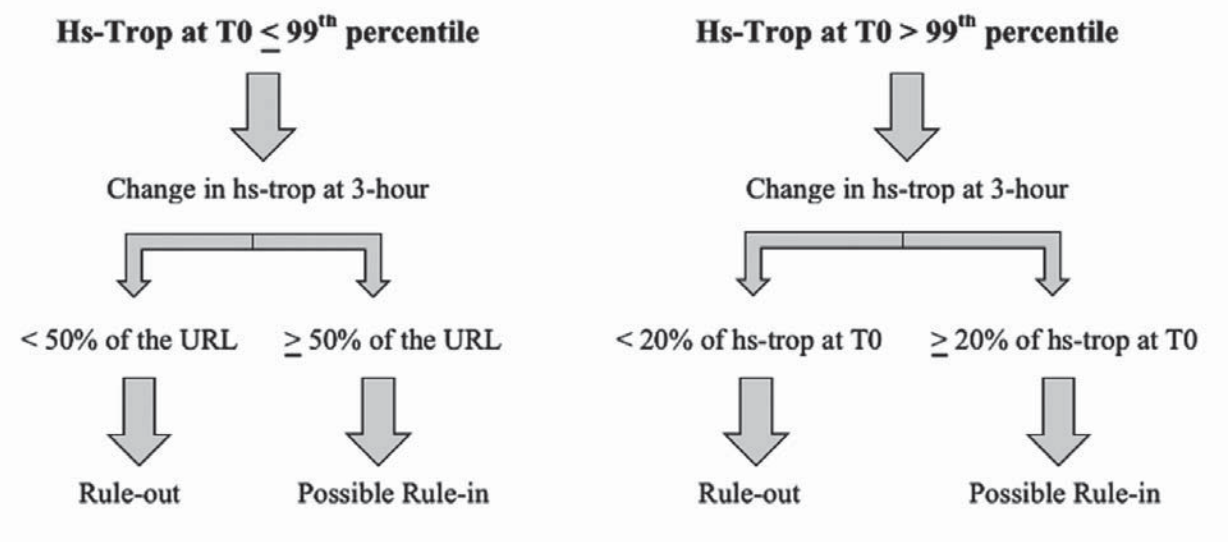


Figure 3. 0 hour / 3 hour algorithm

This algorithm is to be performed when the 0 hour/1 hour algorithm is not applicable: i.e. patients who present before the first hour after onset of chest pain and patients who fall in the observational zone.

If hs-trop is ≤ 99th percentile at 0 hour, the change is considered significant if it is ≥ 50% of the upper reference value of the assay used (i.e. ≥ 7 ng/L in the case of hs-trop T). But if hs-trop at 0 hour is > 99th percentile, a relative change of more than 20% compared to baseline, is considered significant.

Patients who rule-out can be discharged if they are pain free, if the GRACE score is < 140 and if other serious diagnoses that can increase hs-trop are excluded. Patients who rule-in should be admitted for further evaluation and management. Diagnosis of MI requires an additional clinical or EKG or imaging criterion as mentioned in the manuscript.

T0 = time 0 hour URL = upper reference limit

Patients who are discharged should be evaluated with a non-invasive exam, while patients who rule-in or who have a high index of suspicion for ischemia should undergo coronary angiography.

CONCLUSION

The 10 Recommendations of the Working Group of the Lebanese Society of Cardiology

Given all the above, the authors of this manuscript recommend the following:

1) High-sensitivity assays of troponin T or troponin I, rather than conventional ones, should be used in the evaluation of patients with chest pain. Point-of-care troponin tests in particular, have poor analytical and clinical sensitivity and are not appropriate for rapid triage;
2) Hs-trop assay values should be reported in ng/L (or pg/mL) in order to avoid errors related to the presence of several decimals;
3) Given their elevation in several conditions other than MI, the kinetic of hs-trop is as important as its initial value. As a result, it is recommended to repeat a hs-trop level whenever there is doubt of ongoing ischemia;
4) The two hs-Trop assays that have been validated for the 0 hour/1 hour algorithm are the Roche Elecsys hs-trop T and the Abbot Architect hs-trop I; other assays cannot be used in this algorithm;
5) The 0 hour/1 hour algorithm is preferred over the 0 hour/3 hour algorithm because it is supported by evidence from larger and more robust studies [2]l. Emergency departments and cardiac floors should have copies of that algorithm placed in strategic locations where it can be accessed by physicians. Alternatively, an electronic version of the algorithm can be downloaded on portable phones and used to assist in decision making;
6) The 0 hour/3 hour algorithm should be used for very early presenters (chest pain onset < 1 hour prior to evaluation) and for patients who fall in the observational zone of the 0 hour/1 hour algorithm. Copies of that algorithm should also be displayed in the emergency department and cardiology floor;
7) The diagnosis of MI requires in addition to hs-trop, another criteria such as chest pain or documentation of ischemia/infarction by history, ECG, imaging, or coronary angiography;
8) In patients with renal failure, either hs-trop T or hs-trop I can be used. In that setting, initial value may be above the 99th percentile. The kinetic at 1- or 3-hour will allow rapid stratification into high-

or low-risk according to the algorithm;

9) Combining hs-trop T and hs-trop I is not recommended because it increases cost without improving the diagnostic accuracy [17];
10) All algorithms are not a substitute for clinical judgment and should be integrated with a detailed clinical assessment.

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