

Proposal for the use in emergency departments of cardiac troponins measured with the latest generation methods in patients with suspected acute coronary syndrome without persistent ST-segment elevation

Ivo Casagrande,¹ Mario Cavazza,² Aldo Clerico,³ Marcello Galvani,⁴ Filippo Ottani,² Martina Zaninotto,⁵ Luigi M. Biasucci,⁶ Gianfranco Cervellin,⁷ Tiziano Lenzi,⁸ Giuseppe Lippi,⁹ Mario Plebani,¹⁰ Marco Tubaro¹¹

¹Emergency Department, Santi Antonio e Biagio e Cesare Arrigo Hospital, Alessandria; ²Emergency Department, S. Orsola-Malpighi Hospital, Bologna; ³Life Science Institution, S. Anna School, Pisa; ⁴Emergency Department, Morgagni-Pierantoni Hospital, Forlì; ⁵Department of Laboratory Medicine, University of Padua; ⁶Department of Cardiovascular Medicine, Sacro Cuore Catholic University, Rome; ⁷Emergency Department, University Hospital of Parma; ⁸Emergency Department, Santa Maria della Scaletta Civil Hospital, Imola; ⁹Laboratory of Clinical Chemistry and Hematology, University Hospital of Parma; ¹⁰Department of Laboratory Medicine, Padua University Hospital; ¹¹Cardiovascular Department, San Filippo Neri Hospital, Rome, Italy

Abstract

The purpose of this document is to develop recommendations on the use of the latest generation of cardiac troponins in emergency room settings for the diagnosis of myocardial infarction in patients with suspected acute coronary syndrome without persistent ST-segment elevation (NSTE-ACS). The main points which have been addressed reaching a consensus are: i) suitability and appropriateness of the terminology; ii) appropriateness of the request; iii) confirmation of the diagnosis of myocardial infarction (rule-in); iv) exclusion of the diagnosis of myocardial infarction (rule-out). Each point has been analyzed by taking into account the evidence presented in medical publications. Recommendations were developed using the criteria adopted by the European Society of Cardiology and the

American Heart Association/American College of Cardiology. Each point of the recommendation was submitted for validation to an external audit by a Group of Experts (named above).

Suitability and appropriateness of the terminology

Definition of high sensitivity cardiac troponin assay

At the beginning of the new century, an international consensus document^{1,2} pointed out the prominent role of cardiac troponins I (cTnI) or T (cTnT) for the diagnosis of acute myocardial infarction (AMI). These suggestions have further developed in the subsequent decade,^{2,3} reaching the strength of a *Universal Definition of Myocardial Infarction*.

According to these recommendations, the diagnosis of AMI is based on detecting the variation of cardiac troponin values with a typical rise and falling pattern in patients with clinical suspicion of myocardial ischemia.^{2,3} This approach is also confirmed in the latest *Universal Definition of Myocardial Infarction*,² which recommends, as a decision level for the diagnosis of AMI, that cTnI and cTnT elevations are defined as concentrations greater than the 99th percentile of distribution values measured in a reference population consisting of apparently healthy individuals free from heart disease. The same guidelines recommend that such a decision level must be measured with imprecision less than or equal to 10% [coefficient of variation (CV)]. These quality specifications for the determination of cardiac troponins were initially confirmed by a task force from the National Academy of Clinical Biochemistry (NACB) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) committee for standardization of markers of cardiac damage laboratory medicine, and more recently by an interdisciplinary study group organized by the European Society of Cardiology (ESC).^{3,4}

At the time of publication of the first consensus document,¹ the recommended quality specifications were not satisfied by commercially available methods for the measurement of cTnI and cTnT.^{5,6} Only recently, in fact, some methods for cardiac troponin assay, characterized by an improved analytical sensitivity (*i.e.* high-sensitivity assay), entered the marketplace.⁶ It is noteworthy that *only* those immunometric techniques which are able to measure the 99th percentile of the distribution of proteins cTnI and cTnT in the reference population with an error (expressed as CV) equal to or lower than 10% – as currently required by international guidelines – are defined as

Correspondence: Ivo Casagrande, Emergency Department, Santi Antonio e Biagio e Cesare Arrigo Hospital, via Venezia 16, 15100 Alessandria, Italy. Tel/Fax: +39.0131.206224. E-mail: casagrande@libero.it

Key words: acute coronary syndrome, cardiac troponin, emergency department, high-sensitivity assays, non-ST-segment elevation.

Note: this paper is also published in *Clin Chem Lab Med* 2013;51:1727-1737. DOI 10.1515/cclm-2013-0423 with permission of Walter de Gruyter Publication.

Contributions: the authors contributed equally.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 1 March 2013.
Accepted for publication: 8 March 2013.

This work is licensed under a Creative Commons Attribution 3.0 License (by-nc 3.0).

©Copyright I. Casagrande et al., 2013
Licensee PAGEPress, Italy
Emergency Care Journal 2013; 9:e14
doi:10.4081/ecj.2013.e14

newer high-sensitivity methods for measuring cardiac troponins cTnI and cTnT.¹⁻⁴ These assays should also be able to measure the levels of cTnI and cTnT in most (*i.e.* no less than 75%) adult subjects in apparent good health. In accordance with a recent article by Apple,⁷ one should classify the sensitivity of the latest generation methods into four levels, depending on the proportion of apparently healthy subjects in which it is possible to measure the analyte concentrations (Table 1). As such, only methods that measure cTnI and cTnT concentrations in most (*i.e.* >75%) healthy subjects should be defined as high-sensitivity. The denomination of ultra-sensitive methods should therefore be abandoned, because there is no reliable analytical basis to support the use of this term.

The study group of the ESC⁴ has recently concluded that the reference population on which to calculate the 99th percentile of the distribution of cTnI and cTnT values should consist of at least 300 apparently healthy subjects of both genders and distributed according to a broad age distribution. In addition, these subjects should result negative in a stress test and possess cardiac function within normal limits, as assessed by means of cardiac imaging.

Unfortunately, these recommendations are difficult to implement at the local level by individual laboratories, principally because of the difficulty in recruiting a carefully selected wide target population. Individual laboratories may

adopt as reference values those suggested by manufacturers or reported by recent scientific papers with the same technique, and which have been determined on a suitable number of healthy adults.⁶⁻¹⁴ However, it is well known that the concentrations of cTnI and cTnT are higher in males than in women of the same age, and tend to increase progressively over 60 years.⁶⁻¹⁴ It follows that the calculated value of the 99th percentile varies considerably depending on the demographic characteristics of the reference population considered.⁶ It is also noteworthy that the average age of the reference population on which the 99th percentile was calculated ranged from 37 to 59 years, according to some studies.^{12,14} By contrast, the average age of patients presenting to the emergency department with chest pain and suspected acute coronary syndrome can vary from 52 to 62 years, depending on the studies,¹⁵⁻¹⁷ and in clinical practice, it may be even higher. A Canadian study investigated the age of 54,134 patients who presented to the emergency department with chest pain and/or suspicion of acute coronary syndrome between 1998 and 2001. The study reported that patients with unstable angina or AMI had a higher average age of some 10-15 years compared to those without acute ischemic cardiac complications.¹⁸

Importantly, cTnI is measured by various methods, distributed by different manufacturers, and therefore the measured levels vary considerably (even more than 20 times) from method to method, as well as the reference values.⁵ By contrast, cTnT is currently being measured by the same analytical procedure, and thereby presents practically the same values and the same reference limits, even using different automated platforms. Table 2 shows some analytical characteristics and 99th percentile values of the reference population of some cTnI and cTnT methods. Unfortunately, there are conflicting results in the literature concerning the analytical characteristics of cTnI methods.⁸⁻¹⁰ These differences are due both to different experimental protocols used for the calculation of the limit of detection (LOD) and limit of quantitation (LOQ) values, and to different versions of evaluated methods (for example prototype instead of commercially available version).^{5,6,8-10,19} In Table 2, only the analytical characteristics of cTnI methods currently most diffuse and commercially available in Italy are reported. Since cTnT and cTnI are different molecules, results are not interchangeable, nor directly comparable.²⁰

The high degree of analytical sensitivity of newer methods also allows the evaluation of the biological variation of circulating levels of cTnI and cTnT in healthy subjects²¹ or patients with cardiomyopathy.²² As a result, it is possible to calculate the reference change value (RCV), which is related to both biological vari-

ation and analytical imprecision. For many analytical methods, the RCV values vary in a range from 40-60% up to 86%. It is very likely that in presence of minor variations of cTnI and cTnT (e.g. 20% at concentration below the reference range), it is possible to rule out an acute event. In cases of strong clinical suspicion or high pre-test probability it is recommended, under these conditions that the test should be repeated after a few hours (typically between 3 and 4 h).⁴

Recommendations

One should define as latest generation methods for determining troponins cTnI and cTnT only those immunometric assays that measure the 99th percentile of the distribution of proteins cTnI and cTnT in the reference population with an error (expressed as CV) equal to or lower than 10%, as required by international guidelines.¹⁻⁴ Latest generation methods showing an intermediate imprecision (10-20%) should be considered clinically usable.

One should define as latest generation methods of high sensitivity only those methods that measure the levels of cTnI and cTnT in the majority of apparently healthy adults who compose the population of normal reference range.

The reference population on which the 99th percentile of the distribution of the values of cTnI and cTnT is calculated should consist of at least 300 apparently healthy subjects of both genders, and be based on a broad age distribution.⁴ This reference population should also have demographic characteristics as similar as possible to patients who present to the emergency department with chest pain and suspected acute coronary syndrome.

Appropriateness of the troponin test request

The advent of biomarkers assessment in the

Table 1. Classification of methods with high sensitivity for the detection of cardiac troponins I and T.

Level score	Measurable normal values below the 99 th percentile (%)
1 (Contemporary)	<50
2 (First generation, hs)	50 to <75
3 (Second generation, hs)	75 to <95
4 (Third generation, hs)	≥95

hs, high-sensitivity (according to Apple*).

Table 2. Limit of detection, limit of quantitation at 10% coefficient of variation, and 99th percentile of widely diffuse cardiac troponins I and T methods commercially available in Italy.

Methods	LoD (ng/L)	LoQ (ng/L)	99 th Percentile (ng/L)	Reference values
cTnI				
Access AccuTnI Beckman (Beckman Coulter, Brea, CA, USA)	10	60	40	9
ADVIA TnI Ultra Siemens 6 (Siemens, Munich, Germany)	57	72	8	
AIA-PACK 3rd Gen Tosoh (Tosoh Corp., Tokyo, Japan)	8	100	33	10
ARCHITECT Abbott (Abbott Laboratories, Abbott Park, IL, USA)	9	32	28	9
Dimension RxL Siemens (Siemens)	40	140	70	9
Pathfast Mitsubishi (Mitsubishi Chemical Medience Corp., Tokyo, Japan)	8	14	29	9
Stratus CS Siemens (Siemens)	30	60	70	9
Vidas Ultra bioMérieux (bioMérieux SA, Marcy l'Etoile, France)	10	110	20	9
Dimension Vista Siemens (Siemens)	15	40	45	9
cTnT				
Roche Elecsys TnT hs (Roche Diagnostics, Basel, Switzerland)	5	13	14	9

LoD, limit of detection; LoQ, limit of quantitation (functional sensitivity) at 10% CV level; CV, coefficient of variation; cTnI, cardiac troponins I; cTnT, cardiac troponins T; hs, high-sensitivity.

context of diagnosis of chest pain has provided emergency physicians with an important tool to quickly identify patients with suspected acute coronary syndrome. The recent introduction of new methods for assessment of biomarkers of myocardial necrosis, in particular the latest generation of cardiac troponins, has allowed the identification of increasingly large areas of *biochemistry positivity*, that is not always securely attributable to the context of myocardial ischemia. The increased sensitivity of the test, in fact, inevitably causes a lower specificity for ischemic damage.

Therefore, it is increasingly common to detect a value exceeding the upper reference limit (99th percentile) of the latest generation troponins that is not necessarily ischemic in origin. These troponins have, in fact, a high specificity for *myocardial injury* but not for AMI (low positive predictive value). For this reason, it is essential that the emergency physician has broad awareness about the diagnostic maze of chest pain, using the markers appropriately.

The diagnosis of AMI in patients with normal or non-diagnostic electrocardiogram (ECG) [generally referred to as non-ST elevation myocardial infarction (NSTEMI)], should be based on the correct interpretation of the values of cTn, in particular its release kinetics, distinguishing myocardial damage caused by myocardial ischemia from myocardial injury caused by other factors. Evidence to support this possibility is still somewhat preliminary so far.²³

The evaluation of chest pain patients with a non-diagnostic ECG in the emergency department is a dynamic and articulate process, where the use of marker should be targeted and *guided* especially as to the probability (*i.e.* likelihood) of disease.²⁴ To avoid excessive use of this biomarker, it should be measured only in patients with chest pain who have a pre-test probability, even low, of suffering from myocardial infarction.²⁵ It is necessary to systematically correlate symptoms, clinical presentation and likelihood of disease.²⁵⁻²⁷ In particular, it is suggested to investigate all those patients with at least one risk factor of coronary artery disease (CAD), even when associated with atypical chest pain and those patients with no risk factors for CAD but with typical chest pain.

Many patients, however, present with symptoms other than chest pain (atypical presentation), such as isolated dyspnea, transient palpitations, sudden fatigue, nausea/vomiting, diaphoresis, an acute confused state and syncope.²⁸⁻³² In the study by Canto *et al.*,³³ the variables associated with a presentation characterized by the absence of chest pain were: history of heart failure or stroke, older age (>75 years), diabetes mellitus, female gender and race other than white. In this study, only 17% of AMI patients without these risk factors had

no chest pain at presentation; however, patients with at least three risk factors had a 50% or greater chance of not having chest pain at presentation. Patients with AMI and atypical presentation – with the exception of those with diaphoresis – are at high risk of death. The isolated dyspnea, particularly in diabetic patients and in the elderly, may be the only presenting symptom in the course of an acute coronary syndrome which is worsened by its high mortality rate.^{33,34} The appearance of palpitations, in particular from ventricular arrhythmia, has been linked by some authors with a manifestation of myocardial ischemia in the elderly population.³⁵ Sudden fatigue can be a symptom that precedes or accompanies AMI in the absence of chest pain, particularly in diabetic patients.³⁶⁻³⁸ A syncope onset without prodromes should be considered suspect inasmuch as the cause may be the onset of ventricular arrhythmia following acute coronary ischemia.³⁹ Due to the aforementioned reasons, a call to standardize symptom presentation in acute coronary syndromes has recently been advocated. As such, rather than accepting descriptions as typical or atypical symptoms, it is now considered imperative to elucidate the entire ACS symptom complex.⁴⁰ It is therefore appropriate to test troponin in patients presenting in the emergency department for ongoing or previous chest pain (regardless of the *a priori* probability of coronary heart disease), but also in those who report atypical symptoms in the presence of the high-risk conditions already mentioned (associated or not with electrocardiographic abnormalities). These patients are at high risk in cases where the diagnosis of myocardial infarction is confirmed. It is inevitable that this approach emphasizes the sensitivity of the diagnosis with respect to the specificity, with possible implications of increased workload and operating costs.

Recommendations

The measurement of cardiac troponins should be requested in patients presenting to the emergency department with ongoing or previous chest pain.

The measurement of troponins should be considered in patients without chest pain, but who have one of the following symptoms considered equivalent to angina: sudden onset isolated dyspnoea, diaphoresis, palpitations, nausea/vomiting, sudden fatigue, an acute confused state or syncope. These symptoms arise the suspicion of acute coronary syndrome.

In case of the symptoms just listed, the measurement of troponins should be requested in patients with at least one of the following conditions: previous stroke, previous heart failure, advanced age (>75 years) diabetes mellitus, female gender.

The assessment of troponins measured with the latest generation assay (characterized by improved diagnostic sensitivity) makes it inappropriate and virtually useless the contextual request of additional biochemical markers of myocardial ischemia and/or injury [*e.g.* myoglobin, creatine kinase MB (CK-MB), and others].⁴¹

Biochemical confirmation of the diagnosis of myocardial infarction (rule-in)

The introduction in the market of new methods, with improved analytical sensitivity⁴¹ requires the redefinition of the diagnostic approach of suspected NSTEMI-ACS in terms of application of the biochemical algorithms used so far. Currently, we know that an increase above the cut-off in patients without typical ECG-changes, implies the same prognosis as overt STEMI. On the other hand, the optimal timing of coronary intervention for NSTEMI is still under debate. However, NSTEMI will change considerably with these new troponin assays and further interventions studies should be performed.

The most discussed aspects in the application of these improved analytical methods in clinical practice mainly concern: i) the time of blood sampling; ii) the cut-off concentrations used for the diagnosis of AMI; iii) the amount of changes of troponin concentrations *found* in consecutive samples necessary to make the diagnosis of AMI.

In this regard, some observations are needed.

First, the improved analytical sensitivity allows accurate measurement of protein concentrations nearly 5 to 20 times lower than those measured using previous generation methods. Accordingly, the concentrations measured upon admission may already be suggestive of myocardial infarction in a significantly larger percentage of patients. In addition, it can be expected that troponin concentrations change very rapidly within shorter time intervals.^{41,42}

Second, the availability of methods able to measure the protein concentrations in a population of healthy subjects implies a decision making level (cut-off) corresponding to the 99th percentile.

Third, there are several, not necessarily ischemic, clinical conditions (Table 3),⁴³ associated with increased troponin concentrations, and which make it necessary a differential clinical and biochemical diagnosis, based on the evaluation of the kinetics of release and/or extent of increase.

Recommendations

Based on analytical considerations and troponin concentration on admission (baseline sampling T0) in the clinical context of chest pain, the following diagnostic algorithms may be recommended^{44,45} (Figures 1 and 2).

First, troponin on admission (T0) at or above the 99th percentile: serial sampling at intervals of 3 h (T1, high-sensitivity methods) or 6 h (T1, latest generation methods). The blood sample at the 6th h may be optionally considered for *high sensitivity* methods. Interpretation: the kinetics are suggestive of acute myocardial necrosis if the increase of concentration in the blood samples after 3/6 h (T1) is greater than or equal to 50% of the baseline value (T0).

Second, troponin on admission (T0) at or below the 99th percentile: serial sampling at intervals of 3 h (T1, high-sensitivity methods) or 6 h (T1, latest generation methods). The blood sample at the 6th h may be optionally considered for *high sensitivity* methods. Interpretation: the kinetics are suggestive of acute myocardial necrosis if the concentration in the blood sample after 3/6 h (T1) is greater than or equal to 99th percentile and the extent of the increase is greater than or equal to 50% of the baseline value (T0). Acute myocardial infarction should be diagnosed in patients showing concentration changes as described above, when associated with clinical context of myocardial ischemia (based on the symptoms and/or ECG changes and/or the finding of imaging techniques). The percentage of increase recommended above takes into account current analytical performance of

most methods commercially available, which measure the concentration at the 99th percentile with an imprecision of about 20%.

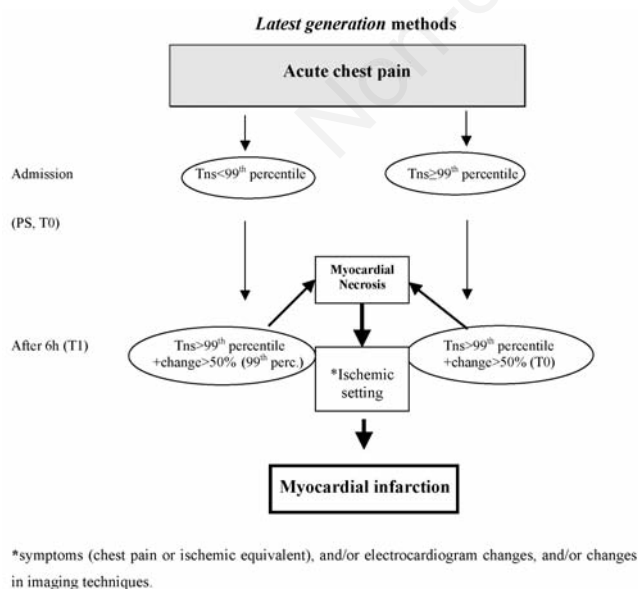
The use of the RCV calculated from studies of biological variability, needs further confirmation, because the published data are conflicted and only available for some meth-

ods.^{21,46,47} It has been proposed that the significance of the percentage increase may vary according to the baseline concentration: 20% for values equal or above the 99th percentile, 50% for baseline values below 99th percentile, and 10% for values *significantly* increased at the presentation.^{42,48-50} The choice of the 50%

Table 3. Clinical conditions associated with increased troponin concentrations (adapted from: Thygesen *et al.*⁴³).

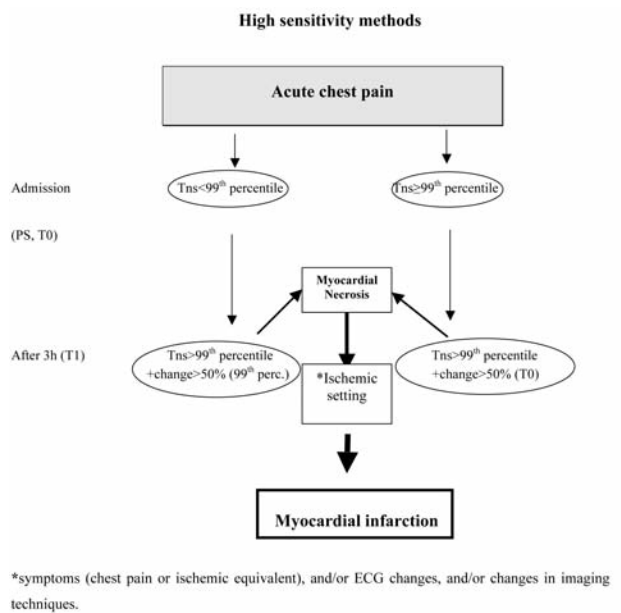
Injury related to primary myocardial ischemia
Plaque rupture
Intraluminal coronary artery thrombus formation
Injury related to supply/demand imbalance of myocardial ischemia
Tachy-/brady-arrhythmias
Aortic dissection or severe aortic valve disease
Hypertrophic cardiomyopathy
Cardiogenic, hypovolemic, or septic shock
Severe respiratory failure
Severe anemia
Hypertension with or without LVH
Coronary spasm
Coronary embolism or vasculitis
Coronary endothelial dysfunction without significant CAD
Injury not related to myocardial ischemia
Cardiac contusion, surgery, ablation, pacing, or defibrillator shocks
Rhabdomyolysis with cardiac involvement
Myocarditis
Cardiotonic agents, <i>e.g.</i> anthracyclines, herceptin
Multifactorial or indeterminate myocardial injury
Heart failure
Stress (Takotsubo) cardiomyopathy
Severe pulmonary embolism or pulmonary hypertension
Sepsis and critically ill patients
Renal failure
Severe acute neurological diseases, <i>e.g.</i> stroke, subarachnoid
Hemorrhage
Infiltrative diseases, <i>e.g.</i> amyloidosis, sarcoidosis
Strenuous exercise

LVH, left ventricular hypertrophy; CAD, coronary artery disease.



*symptoms (chest pain or ischemic equivalent), and/or electrocardiogram changes, and/or changes in imaging techniques.

Figure 1. Latest generation methods diagnosing myocardial infarction.



*symptoms (chest pain or ischemic equivalent), and/or ECG changes, and/or changes in imaging techniques.

Figure 2. High sensitivity methods diagnosing myocardial infarction.

variation compared to basal value (recommendations of the first two sections; Figures 1 and 2) should be considered to be the best compromise taking into account both the biological variation of troponins and the imprecision of the major part of the methods at present time commercially available in Italy. Of course, the use of 50% variation increases test specificity, but also decreases test sensitivity in respect to the use of a lower percent variation (such as 20%).⁴² As a result, in some specific clinical setting, the choice of a lower percent variation may be preferable.

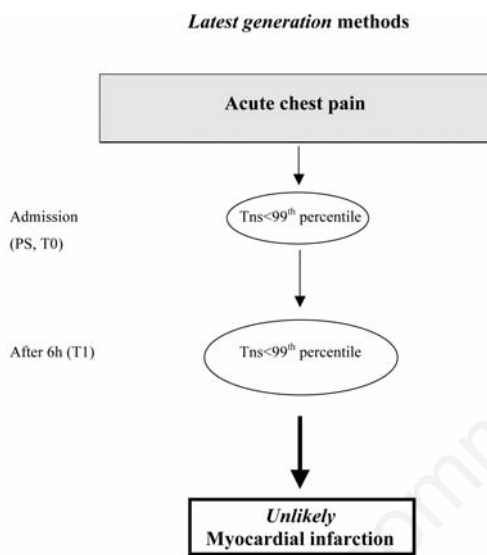
Recent studies⁵¹⁻⁵⁶ have shown that the variation in absolute value of the concentration of troponin, allows a more accurate diagnosis than the percentage change, especially for values close to the 99th percentile. Nevertheless,

since this variation is method-dependent, it is not possible to provide a concentration value applicable to all methods available on the market and the former approach is thereby preferable also for purposes of harmonization.

Biochemical exclusion of myocardial infarction (rule-out)

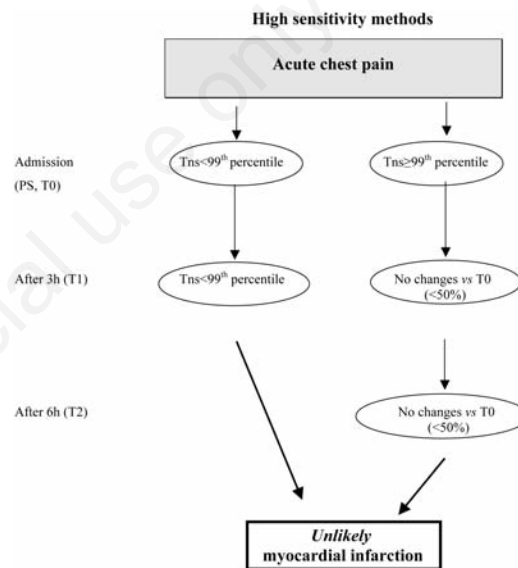
It is essential for the emergency physician to rapidly rule out AMI and to discharge the patient with reasonable safety, particularly in those cases where he/she may have presented with chest pain and normal or non-diagnostic ECG. As for the rule-in, it is essential to estab-

lish the timing of assessment of serum troponin value. In cases where the value of troponin is normal in the established time intervals, the patient may be discharged with reasonable confidence if the probability of acute coronary syndrome – at the end of the observation period – is sufficiently low (Table 4).⁵⁷ In case of troponin elevation and in the presence of conditions associated with persistently increased values (*e.g.* renal failure), it is necessary to establish the percentage increment below which it is reasonable to conclude that myocardial damage is caused by a chronic rather than an acute condition and, possibly, that the variation is not attributable to myocardial necrosis secondary to an acute ischemic event. We suggest an observational period of no less than 6 h before discharging patients



The ischemic setting is represented by symptoms (chest pain or ischemic equivalent), and/or ECG changes, and/or changes in imaging.

Figure 3. Latest generation methods diagnosing unlikely myocardial infarction.



The ischemic setting is represented by symptoms (chest pain or ischemic equivalent), and/or ECG changes, and/or changes in imaging.

Figure 4. High sensitivity methods diagnosing unlikely myocardial infarction.

Table 4. Probability of acute coronary syndrome secondary to coronary artery disease based on signs and symptoms at presentation (adapted from: Braunwald *et al.*⁵⁷).

	History	Examination	ECG	Cardiac markers
Likelihood				
Low	Probable ischemic symptoms without any medium likelihood characteristics; recent drug use	Chest discomfort	T-wave flattening or inversion in leads with dominant R waves	Normal
Medium	Main symptom: chest or left arm pain or discomfort; old age; male sex; diabetes mellitus	Extracardiac vascular disease	Fixed Q waves; abnormal ST segments or T waves not documented as new	Normal
High	Main symptom: chest or left arm pain or discomfort reproducing previously documented angina; previously documented coronary artery disease, including myocardial infarction	Transient mitral regurgitation, hypotension, diaphoresis, pulmonary edema, rales	New transient ST-segment deviation or T-wave inversion with symptoms	Elevated cardiac TnI, TnT, or CK-MB

ECG, electrocardiogram; TnI, troponins I; TnT, troponins T; CK-MB, creatine kinase MB.

safely, considering the first assessment (T0) at the admission to the emergency department.⁴¹ Discharge can be considered only for patients with low or intermediate probability of ACS (Table 4).⁵⁷ For troponins measured by using the latest generation methods – not high sensitivity – in patients admitted to the emergency department, the following schedule can be proposed (Figure 3): i) the first determination is the time of arrival in the emergency department (considered as T0); ii) the second determination is obtained after 6 h.

In case of patients with low or intermediate probability/risk of disease, if after 6 h the concentration of serum troponin does not exceed the 99th percentile or does not show a significant kinetic increment (<50%), the diagnosis of AMI is highly unlikely and the patient is at low risk of adverse events in short-term; persistently negative troponin concentrations during observation identify a low-risk population for which it is possible to assume a fairly safe rule-out of AMI if non-coronary acute cardiac conditions can be excluded. These patients may be discharged with an outpatient indication stress test within the shortest time.

If troponins are measured using high sensitivity methods, the following schedule of blood samples can be recommended⁵⁸ (Figure 4): i) the first determination is the time of arrival in the emergency department (considered as T0); ii) the second determination after 3 h.

If after 3 h the concentration of hs-Tn does not exceed the 99th percentile, the diagnosis of AMI is unlikely^{41,48,58} and it is highly unlikely if the concentration of high-sensitivity troponins (hs-Tns) remains constantly below the limits of analytical sensitivity (4.5). In cases where the increase of the concentration is less than the percentage increment considered significant ($\geq 50\%$ variation from baseline) for myocardial infarction and concentrations do not exceed the 99th percentile, a second blood sample is indicated at the sixth hour.^{45,48,59,60} If at this time point the value does not exceed the 99th percentile, patients can be classified as at low risk of adverse events and may be discharged with an outpatient indication stress test within a short time.

Recommendations

To rule out AMI, the assessment of troponin measured by the latest generation methods should be performed at time 0 (arrival in the emergency department) and after 6 h, if all the values observed are $\leq 99^{\text{th}}$ percentile or the variation concentration is <50% (below the 99th percentile), the patient can be discharged.

When using high sensitivity methods, it is recommended to assess troponin values at time 0 and after 3 h. When both values are below the limit of analytical sensitivity, the patient may be discharged. When both values are <99th percentile and the patient is at low or

intermediate probability of ACS, the patient can be discharged if different acute cardiac conditions can be ruled out. Patients with recurrent symptoms and high probability of coronary heart disease should be kept under observation over 3-6 h, or until a final diagnosis has been reached.

References

- Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined: a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959-69.
- Thygesen K, Alpert JSA, Jaffe AS, et al. The writing group on behalf of the joint ESC/ACCF/AHA/WHF task force for the universal definition of myocardial infarction. *Circulation* 2012;126:2020-35.
- Apple FS, Jesse RL, Newby LK, et al. National academy of clinical biochemistry and IFCC committee for standardization of markers of cardiac damage laboratory medicine practice guidelines: analytical issues for biochemical markers of acute coronary syndromes. *Clin Chem* 2007;53:547-51.
- Thygesen K, Mair J, Katus H, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J* 2010;31:2197-206.
- Panteghini M, Pagani F, Yeo KT, et al. Committee on standardization of markers of cardiac damage of the IFCC. Evaluation of imprecision for cardiac troponin assays at low-range concentrations. *Clin Chem* 2004;50:327-32.
- Clerico A, Giannoni A, Prontera T, Giovannini S. High-sensitivity troponin: a new tool for pathophysiological investigation and clinical practice. *Adv Clin Chem* 2009;49:1-30.
- Apple FS. A new season for cardiac troponin assays: it's time to keep a scorecard. *Clin Chem* 2009;55:1303-6.
- Prontera C, Fortunato A, Storti S, et al. Evaluation of analytical performance of the Siemens ADVIA TnI Ultra immunoassay. *Clin Chem* 2007;53:1722-3.
- Apple FS, Collinson PO. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem* 2012;58:54-61.
- Franzini M, Prontera C, Masotti S, et al. Evaluation of analytical performance of a novel immunoenzymometric assay for cTnI. *Clin Chim Acta* 2013;416:48-9.
- Clerico A, Fortunato A, Prontera C, et al. Distribution of plasma cardiac troponin-I values in healthy subjects: pathophysiological considerations. *Clin Chem Lab Med* 2008;46:804-8.
- Venge P, Johnston N, Lindahl B, James S. Normal plasma levels of cardiac troponin I misurate by the high-sensitivity cardiac troponin I access prototype assay and the impact on the diagnosis of myocardial ischemia. *J Am Coll Cardiol* 2009;54:1165-72.
- Giannitsis E, Kurz K, K Hallermayer, et al. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem* 2010;56:254-61.
- Saenger AK, Beyrau R, Braun S, et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. *Clin Chim Acta* 2011;412:748-54.
- Chang AM, Mumma B, Sease KL, et al. Gender bias in cardiovascular testing persists after adjustment for presenting characteristics and cardiac risk. *Acad Emerg Med* 2007;14:599-605.
- Chandra A, Lindsell CJ, Limkakeng A, et al. Emergency physician high pretest probability for acute coronary syndrome correlates with adverse cardiovascular outcomes. *Acad Emerg Med* 2009;16:740-8.
- Yates RB, Hestand BC. Effects of age, race, and sex on door-to-electrocardiogram time in emergency department non-ST elevation acute coronary syndrome patients. *J Emerg Med* 2011;40:123-7.
- Kaul P, Chang WC, Westerhout CM, et al. Differences in admission rates and outcomes between men and women presenting to emergency departments with coronary syndromes. *CMAJ* 2007;177:1193-9.
- Panteghini M. Assay-related issues in the measurement of cardiac troponins. *Clin Chim Acta* 2009;402:88-93.
- Lippi G, Cervellini G, Aloe R, et al. Non-commutability of results of highly sensitive troponin I and T immunoassays. *Biochem Med (Zagreb)* 2012;22:127-9.
- Wu AHB, Lu QA, Todd J, et al. Short- and long-term biological variation in cardiac troponin I measured with high-sensitivity assay: implications for clinical practice. *Clin Chem* 2009;55:52-8.
- Frankenstein L, Remppis A, Giannitsis E, et al. Biological variation of high sensitive troponin T in stable heart failure patients with ischemic or dilated cardiomyopathy. *Clin Res Cardiol* 2011;100:633-40.
- Newby LK, Jesse RL, Babb JD, et al. ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of Cardiology Foundation task force on clinical expert consensus documents. *J Am Coll Cardiol* 2012;60:2427-63.
- Haaf P, Drexler B, Reichlin T, et al. High-sensitivity cardiac troponin in the distinct-

- tion of acute myocardial infarction from acute cardiac noncoronary artery disease. *Circulation* 2012;126:31-4.
25. Grimes DA, Schulz KF. Refining clinical diagnosis with likelihood ratios. *Lancet* 2005;365:1500-5.
 26. Ottani F, Binetti N, Casagrande I, et al. Percorso di valutazione del dolore toracico. Valutazione dei requisiti di base per l'implementazione negli ospedali italiani. *G Ital Cardiol* 2009;10:46-63.
 27. Diamond GA, Forrester JS. Analysis of probability as an aid to the clinical diagnosis of coronary artery disease. *New Engl J Med* 1979;300:1350-8.
 28. Braunwald E. Unstable angina. A classification. *Circulation* 1989;80:410-4.
 29. Diamond GA, Kaul Sanjay. How would reverend Bayes interpret high-sensitivity troponin? *Circulation* 2010;121:1172-5.
 30. Stern S. Symptoms other than chest pain may be important in the diagnosis of "silent ischemia," or "the sound of silence." *Circulation* 2005;111:e435-e437.
 31. Briger D, Kim A, Goodman S, et al. Acute coronary syndrome without chest pain, an underdiagnosed and undertreated high-risk group. *Chest* 2004;126:461-9.
 32. Sinclair D. Myocardial infarction. Consideration for geriatric patients. *Can Fam Physicians* 1994; 40:1172-7.
 33. Canto JG, Shlipak MG, Rogers WJ, et al. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. *JAMA-J Am Med Assoc* 2000;283:3223-9.
 34. Hammaad A, Lip GYH, MacFachyen RJ. Acute coronary syndromes presenting solely with heart failure symptoms: are they under recognized? *Eur J Heart Fail* 2004;6:683-6.
 35. Stern S, Behar S, Leor J, et al. Presenting symptoms, admission electrocardiogram, management and prognosis in acute coronary syndromes: differences by age. *Am J Geriatr Cardiol* 2004;13:188-96.
 36. Tresch DD, Arrow WS. Clinical manifestations and diagnosis of coronary artery disease. *Clin Geriatr Med* 1966;12:89-100.
 37. Braunwald E. Examination of the patient: the history. In: Braunwald E, Zipes DP, Libby P, eds. *Heart disease: a textbook of cardiovascular medicine*. Philadelphia, PA: WB Saunders; 2001. pp 27-44.
 38. American Diabetes Association. Consensus development conference on the diagnosis of coronary heart disease in people with diabetes. *Diabetes Care* 1998;21:1551-9.
 39. Moya A, Sutton R, Ammirati F, et al. The task force for the diagnosis and management of syncope of the European Society of Cardiology. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J* 2009;30:2631-71.
 40. Canto GJ, Goldberg RJ, Sopko G. A call to standardize symptom presentation in acute coronary syndromes. *Am Heart J* 2012;164:801-6.
 41. Hamm CW, Bassand JP, Agewall S, et al. The task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2011;32:2999-3054.
 42. Thygesen K, Mair J, Giannitsis E, et al. Study group on biomarkers in cardiology of the ESC working group on acute cardiac care. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J* 2012;33:2252-7.
 43. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012;60:1-18.
 44. Giannitsis E, Becker M, Kurz K, et al. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with acute coronary syndrome Suspected and negative troponin results on admission. *Clin Chem* 2010;56:642-50.
 45. White DH. Higher sensitivity troponin levels in the community: what do they mean and how will the diagnosis of myocardial infarction be made? *Am Heart J* 2010; 159:934-6.
 46. Frankenstein L, Wu AHB, Hallermayer K, et al. Biological variation and reference change value of high-sensitivity troponin T in healthy individual during short and intermediate follow-up periods. *Clin Chem* 2011;57:1068-71.
 47. Vasile VC, Saenger AK, Kroning JM, et al. Biological variation of a novel cardiac troponin I assay. *Clin Chem* 2011;55:1395-405.
 48. Keller T, Zeller T, Ojeda F, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. *JAMA-J Am Med Assoc* 2011;306:2684-93.
 49. Aldous SJ, Richards AM, Cullen L, Than MP. Early dynamic change in high-sensitivity cardiac troponin T in the investigation of acute myocardial infarction. *Clin Chem* 2011;57:1154-60.
 50. Apple FS, Perace LA, SW Smith, et al. Role of monitoring changes in sensitive cardiac troponin assay results for early diagnosis of myocardial infarction and prediction of risk of adverse events. *Clin Chem* 2009;55:930-7.
 51. Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation* 2011;124:136-45.
 52. Mueller M, Biener M, Vafaei M, et al. Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased At troponin in the absence of acute coronary syndrome. *Clin Chem* 2012;58:209-18.
 53. Kavsk PA, Allen LC, Apple FS, et al. Cardiac troponin testing in the acute care setting: ordering, reporting, and high sensitivity assays-an update from the Canadian Society of Clinical Chemists. *Clin Biochem* 2011;44:1273-7.
 54. Pretorius CJ, Wilgen U, Ungerer JP. Serial cardiac troponin differences commensurate on four contemporary analyzers: relative differences, actual differences and reference change values compared. *Clin Chim Acta* 2012;413:1786-91.
 55. Schreiber DH, Agbo C, Wu AH. Short-term (90 min) diagnostic performance for acute ST segment elevation non-myocardial infarction and 30-day prognostic evaluation of a novel third-generation high sensitivity troponin I assay. *Clin Biochem* 2012;45:1295-301.
 56. Apple FS, Smith SW, Pearce LA, Murakami MM. Delta changes for optimizing clinical specificity and 60-day risk of adverse events in patients presenting with symptoms suggestive of acute coronary syndrome utilizing the ADVIA Centaur TnI-Ultra assay. *Clin Biochem* 2012;45:711-3.
 57. Braunwald E, Mark DB, Jones RH, et al. Unstable angina: diagnosis and management. Rockville, MD, USA: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, US Public Health Service, US Department of Health and Human Services Publ.; 1994.
 58. Braunwald E. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-elevation myocardial infarction. *J Am Coll Cardiol* 2000;36:970-1062.
 59. Body R, Carley S, McDowell G, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using high-sensitivity assay. *J Am Coll Cardiol* 2011;58:1332-9.
 60. Aldous S, Pemberton C, Richards AM, et al. High-sensitivity troponin T for early rule-out of myocardial infarction in recent onset chest pain. *Emerg Med J* 2012;29: 805-10.