High-sensitivity troponin in emergency room practice: pros and cons
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Introduction
Chest pain is the second most common reason for emergency room visits. These patients are frequently admitted to the emergency room to rule out an acute coronary syndrome (ACS). ACS is however diagnosed only in a minority (about 10–15%) and, as a consequence, a large number of patients is admitted to the hospital inappropriately. This practice produces an increase in costs and overcrowds the emergency rooms, with a negative impact on the patients’ and the healthcare system.

Troponin measurement is now a cornerstone in the diagnosis of ACS, complementing the clinical evaluation and the interpretation of the ECG.

The availability in Europe since 2011, but not yet in the United States, of the high-sensitivity troponin (hs-cTn) assay (which allows a reliable detection of biomarker concentrations even in healthy asymptomatic patients) has substantially changed the management of patients presenting with chest pain, both from a diagnostic and therapeutic perspective.

High-sensitivity troponin assays
Through the years the analytic precision of the troponin assays has been progressively improved, thus now allowing the reliable (i.e. with a variation coefficient of the measurement <10%) measurement of even minimal concentrations of the circulating biomarker.

As a reference, ‘normal’ concentrations of the marker are defined as those lower than the 99th percentile of the distribution of the values measured in a control population of healthy patients without cardiac disease.1 As stated before, hs-cTn assays have an elevated sensitivity and analytic precision even at minimal concentration of the biomarker, often significantly lower than the 99th percentile of the reference population and frequently approximating the limit of detection (LoD).

There is substantial agreement about the concept that the sensibility of the assay is indicated by the percentage of healthy patients with measurable levels of troponin. According to this assumption, it is possible to differentiate, among the ‘high-sensitivity’ assays available on the market, those which are more or less sensitive. The clinical impact of those differences in sensitivity is probably minimal.

In patients with suspected ACS, detectable levels lower than the 99th percentile could represent either the baseline level for that particular patient, or an increase still not exceeding the reference limit, mainly because of a limited time elapsed since the onset of cardiac injury.

The high analytic sensibility of new troponin assays allows also the assessment of the biological variability of circulating troponin levels in healthy patients1 and in patients with heart disease.2 Accordingly, it is possible to define the ‘reference change value’ (RCV), representing both the biological and analytic variability. For the majority of assays, the RCV varies between 40 and 60% but can reach 86%. This variability should be taken into account when interpreting the temporal variations of the levels in an attempt to identify acute myocardial damage. When detectable or elevated levels are present, it is still necessary to obtain a second sample at an appropriate time interval2 to make the diagnosis of myocardial injury and to define whether it is acute or chronic.

The exceptions to this rule are:

1. Significant high levels of the biomarker [more than five times over the 99th percentile according to European Society of Cardiology (ESC)1 Guidelines], which by itself are sufficient to rule in significant myocardial damage necessitating invasive evaluation by coronary angiography.

2. Undetectable levels in patients with chest pain more than 2 h, which could allow the rapid rule-out of acute myocardial infarction (MI) or, even better, the exclusion of the occurrence of major myocardial events during the following days or months (this issue is still not addressed by the guidelines).

Diagnostic algorithms
In patients with suspected ACS, the first diagnostic algorithm outlined in the ESC Guidelines recommends...
the measurement of cardiac troponin with a high-sensitivity assay upon emergency room admission and 3 h later. Significant temporal variation (rise or fall) from the baseline levels (according to the type of assay used) would indicate the need for an invasive approach, whether stable levels would suggest a conservative strategy. The algorithm provides two outstanding situations. The first covers patients presenting with more than 6 h since the onset of chest pain. In these patients when the initial serum levels are lower than the 99th percentile, the clinical risk is low (according to the risk score GRACE < 140), and symptoms do not recur, an early discharge is possible, followed by noninvasive testing for definitive ACS exclusion. The second is represented by patients with very high levels of troponin (more than five times over the higher reference limit), in whom if the clinical presentation is consistent with ACS, the second troponin measurement is not necessary to determine the ensuing therapeutic strategy.

In view of the diagnostic accuracy of most hs-cTn assays and of the results of recent studies confirming its sensitivity and specificity in the detection of type 1 MI, the ESC Guidelines suggest the use of an alternative algorithm based on the biomarker levels obtained at the time of admission and after 1 h interval. According to this algorithm, the diagnosis of type 1 MI could be reasonably ruled out when the initial troponin levels are very low and remain unchanged after 1 h. The cutoff levels confirming the diagnosis of type 1 MI vary according to the type of assay used (Fig. 1). The algorithm generates three classes of patients: patients for whom MI is ruled out and can safely be discharged home (rule-out class); patients for whom MI is confirmed and require invasive testing the timing of which is dictated by their clinical risk profile (rule-in class); patients requiring longer observation to clarify the diagnosis (observe class).

Supporting data are being collected for the rapid diagnosis algorithm. Recent investigations suggest that in patients with chest pain and serum levels of hs-cTn lower than LoD, type 1 MI as well as the risk of short-term cardiovascular events can be safely ruled out. The main study included 4870 patients admitted to the emergency room mainly for chest pain (82%) or other cardiovascular symptoms (18%) (syncope, dyspnoea or palpitations) with mean age of 64 years. Type 1 MI was diagnosed in 782 patients (16%). Thirty-two patients (1%) developed a recurrent MI and 75 (3.2%) died for cardiac causes during the first 30 days.

A troponin level less than 5 ng/l (Abbott hs-cTn I) was found in 2311 (61%) of the 3799 patients with serum levels less than the 99th percentile at admission. The negative predictive value of this concentration was 99.6% [95% confidence interval (CI); 99.3–99.8] and did not change after correction for clinical covariates such as sex, age, cardiovascular risk factors and history of cardiac disease.
Forty to 50% of the patients fall in the so-called grey zone; their follow-up mortality rate was 8.2%. The results of this study suggest that the 0–1-h algorithm based on a low and sensitive cut-off may be the safest and faster approach to patients presenting with chest pain in the emergency room.

Similar results have been documented when using hs-cTnT assay.\(^{12,13}\)

**Conclusion**

In patients presenting to the emergency room with suspected ACS, the hs-cTn assays allow:

1. To rule out acute MI when troponin T levels are not measurable or extremely low (troponin I Abbott). This assertion holds true for patients with more than 2 h onset of chest pain; it is however often necessary to repeat the measurement after 1 h in early-presenters. In these patients, the probability of ensuing adverse cardiovascular events is very low (<1%) in the short term.

2. When the probability of ACS is high, it is necessary to repeat the measurements after 3 h before considering type 1 MI definitively ruled out.

3. Patients with detectable levels at admission followed by significant increase after 1 or 3 h are at high risk of type 1 MI and require a rapid evaluation which, based on their clinical risk profile, includes the decision for urgent invasive procedures. Nonetheless, the critical increase of hs-cTn levels (the so-called delta change) to accurately confirm the diagnosis varies according to the hs-cTn assay used and, even for the most studied assays, has not yet been sufficiently validated.

4. Forty to 50% of the patients fall in the so-called grey zone and require prolonged observation. This group consists of some patients with type 1 MI undiagnosed with the diagnostic algorithm, many patients with type 2 MI and other acute cardiovascular conditions, and other patients with heart failure, renal insufficiency and so on. In this group of patients, further electrocardiographic and cardiac imaging tests are necessary to reach a correct diagnosis and to recommend the appropriate treatment.

**Acknowledgements**

**Conflicts of interest**

There are no conflicts of interest.

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**Table 1** 0–3-h and 0–1-h algorithms for rule-out/rule-in of type 1 myocardial infarction

<table>
<thead>
<tr>
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<th>0–3-h algorithm</th>
<th>0–1-h algorithm</th>
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<tbody>
<tr>
<td>Predictive negative value</td>
<td>98–100%</td>
<td>98–100%</td>
</tr>
<tr>
<td>Predictive positive value</td>
<td>Unknown, related to the delta value and assay method</td>
<td>75–80%</td>
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<tr>
<td>Clinical efficacy*</td>
<td>Undetermined</td>
<td>+++</td>
</tr>
<tr>
<td>Feasibility</td>
<td>+++ (GRACE Score is required)</td>
<td>+++</td>
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<tr>
<td>Problems</td>
<td>Variations in concentration (absolute or relative) are not determined and assay dependent</td>
<td>Cut-off levels are assay dependent and different from 99th percentile</td>
</tr>
<tr>
<td>Validation studies adequately powered</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>Other advantages</td>
<td>Already in clinical use</td>
<td>Shorter decision time</td>
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GRACE, Global Registry of Acute Coronary Events. *Clinical efficacy is defined as the percentage of patients with chest pain for whom the diagnosis of type 1 myocardial infarction is correctly ruled out or ruled in (not quantifiable for 0–3-h algorithm and 75% for 0–1-h algorithm). Modified with permission from.\(^{7}\)
References


