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CURRENT OPINION

How to use high-sensitivity cardiac troponins in acute cardiac care†

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Introduction

Recommendations for the use of cardiac troponin (cTn) measurement in acute cardiac care have recently been published.[1] Subsequently, a high-sensitivity (hs) cTn T assay was introduced into routine clinical practice.[2] This assay, as others, called highly sensitive, permits measurement of cTn concentrations in significant numbers of apparently illness-free individuals. These assays can measure cTn in the single digit range of nanograms per litre (=picograms per millilitre) and some research assays even allow detection of concentrations <1 ng/L.[2–4] Thus, they provide a more precise calculation of the 99th percentile of cTn concentration in reference subjects (the recommended upper reference limit [URL]). These assays measure the URL with a coefficient of variation (CV) <10%.[2–4] The high precision of hs-cTn assays increases their ability to determine small differences in cTn over time. Many assays currently in use have a CV >10% at the 99th percentile URL limiting that ability.[5–7] However, the less precise cTn assays do not cause clinically relevant false-positive diagnosis of acute myocardial infarction (AMI) and a CV <20% at the 99th percentile URL is still considered acceptable.[8]

We believe that hs-cTn assays, if used appropriately, will improve clinical care. We propose criteria for the clinical interpretation of test results based on the limited evidence available at this time.

Comparison between assays of cardiac troponin and high-sensitivity cardiac troponin

'Sensitive' and 'high-sensitive' are terms often used by manufacturers to describe their assays for marketing purposes. In some cases, it reflects higher sensitivity than former assays developed by the same company, and in other situations it reflects a higher sensitivity than most assays on the market. Although there is still no consensus regarding when the terms 'sensitive' and 'high-sensitive' should be applied, we advocate that cTn assays should be labelled 'high-sensitive' only if they fulfil the analytical criteria suggested by guidelines[1,9,10] not only in the research laboratories of the manufacturers but also in routine clinical laboratories.[11–19] Often manufacturers' claims for assay precision cannot be achieved in clinical laboratories (see *Table 1*). It is also important to note that there may be substantial differences between 'high-sensitivity' assays. Most present cTn assays do not detect even in 50% of apparently disease-free individuals[20] whereas high-sensitivity assays do and with some, detection may be as high as in 90%.[4,20,21] In addition, reports for the hs-cTnI Singulex®, the hs-cTnT, and the Abbott® hs-cTnI assays suggest a need for different 99th percentile values in men and women, although that does not seem to be the case with the hs-cTnI Beckman® research assay.[2,21–24]

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Table 1 Peer-reviewed analytical evaluation data on cardiac troponin assays approved for routine diagnostics

Company/platform/ assay	Analyte	Characteristics provided by manufacturer				Peer-reviewed published data		References
		LoB	LoD	99th Percentile (ng/L)	CV at 99th percentile	99th Percentile (ng/L)	CV at 99th percentile	
Mitsubishi Chemical PATHFAST[a]	cTnI	8	NA	29	5%	13	29%	11
Ortho VITROS Troponin I ES	cTnI	7	12	34	10%	13,34	52%, 20%	7,12
Roche cobas/ E170 hs-cTnT[b]	cTnT	3	5	14	9%	14, 16.9, 13.5, 16	<10%, <10%, 9%	2,13,22,23
Siemens Centaur Ultra	cTnI	6	NA	40	9%	13, 21, 39, 60, 87	23%, 20%, 13%, <10%, <10%	5,7,15,16
Siemens Dimension EXL	cTnI	17	NA	45	10%	NA	NA	NA
Siemens Stratus CS[a]	cTnI	30	NA	70	10%	30, 70	32%, 10%	16,17
Siemens VISTA	cTnI	15	NA	45	10%	22	14%	18
Tosoh ST AIA-PACK	cTnI	60	NA	60	9%	40	35%	19
Abbott Architect STAT high sensitive[c]	cTnI	1.2	3.4	16	5.6%	30, 24	NA	40

In addition, hs-cTnI assays fulfilling the analytical criteria of guidelines have been developed by Beckman®, Nanosphere®, Singulex®, and Siemens®, which are still in the pre-marketing phase but may also become available for routine use subsequently. None of the currently commercially available cTn assays except for the hs-cTnT and the yet to be approved hs-cTnI assay from Abbott Diagnostics meets the proposed criteria for a high-sensitivity assay in routine use.
It is important to differentiate between the LoB and the LoD, because these terms are frequently not correctly used in the cTn literature. The LoB is the highest signal in a test which can be expected from a sample without the analyte, in contrast the LoD is the lowest concentration of an analyte in a sample which reliably can be differentiated from a sample without the analyte. The LoD is always higher than the LoB.
NA, not available; LoB, lower limit of blank; LoD, lower limit of detection.
[a]Bench-top systems suitable for point-of-care (POC) analysis but no hand-held POC devices.
[b]Not approved by the US Food and Drug Administration so far.
[c]May be approved for routine use in Europe in 2012.

The key differentiating feature of hs-cTn assays when compared with the former cTn assays is increased sensitivity, which is only apparent at values near the 99th percentile URL. The clinical interpretation of hs-cTn concentrations in this range is challenging, but this is responsible for the increased sensitivity. Some, but not all, studies demonstrate a higher diagnostic accuracy of hs-cTn assays for the early diagnosis of AMI when compared with former cTn assays on admission to the emergency department.[25–27] However, scrutiny is needed when evaluating such studies as differences between assays often have been overstated by use of different medical decision limits for the old and new cTn assays, e.g. 10% CV limit vs. 99th percentile URL. This view, in part, reflects a reluctance of clinicians to use sensitive decision limits and perhaps the thought that the higher 10% CV cut-off value must be used as a decision limit if the 99th percentile URL cannot be measured with a CV of 10% or less. However, this approach is not guideline driven and for this reason the Joint ESC/ACCF/AHA/WHF task force for the universal definition of myocardial infarction has attempted to clarify this misconception.[8]

Nevertheless, it appears that hs-cTn assays detect cTn release at an earlier time point than the older cTn tests leading to an improved early sensitivity for AMI diagnosis.[25–27] Given the high frequency of detectable and slightly elevated hs-cTn values in the community[28] and especially in patients with cardiovascular co-morbidities,[28–30] it is important to note that an increased hs-cTn concentration alone is not sufficient to make the diagnosis of AMI.[9] In addition, the potential for analytical interferences with hs-cTn assays because of their high sensitivity is greater than with conventional assays. These include reductions specifically in hs-cTnT concentrations due to haemolysis or increases due to heterophilic antibodies or decreases due to autoantibodies in hs-cTnI assays.[2,31]

Critical clinical concepts regarding analytical characteristics of high-sensitivity cardiac troponin assays

(1) Test results should be reported as nanograms per litre (=picograms per millilitre), the analytical detection limit of hs-cTn assays is in the range of single digits or below.
(2) Cardiac troponin values below the lower limit of detection should not be reported as numbers.
(3) High-sensitivity cardiac troponin assays have high precision at lower concentration ranges with analytical CV <10% at the 99th percentile concentration of the reference population (URL).
(4) High-sensitivity cardiac troponin assays enable detection of cTn in a significant proportion of the reference population,

thereby allowing for a more accurate calculation of the 99th percentile URL with its 99% confidence interval.

(5) There is concern about analytical interference with hs-cTn assays. More thorough evaluation of these potential problems is needed.

Conditions with potential high-sensitivity cardiac troponin elevations other than acute myocardial infarction

With hs-cTn assays, elevations above the 99th percentile URL are common in patients with structural heart disease, including patients with stable coronary artery disease (CAD).[32] In stable heart failure patients, the median concentration of hs-cTnT is 12 ng/L, which is very close to the 99th percentile URL of 14 ng/L for this assay.[33] In patients with putative stable angina, a hs-cTnT value >99th percentile URL is found in 37% of those with coronary plaques that are thought to be more labile or vulnerable.[32,34] Up to 2% of the general population have been shown to have elevations of hs-cTnT above the 99th percentile URL in population studies.[28,35,36] These individuals usually have either stable CAD, heart failure, renal failure, left ventricular hypertrophy, or these co-morbidities in combination, reflecting other mechanisms including ischaemia causing cTn release.[37] Therefore, hs-cTn elevations, indicating myocardial injury with necrosis must be interpreted in relation to the clinical presentation. However, regardless of the cause, elevations of hs-cTn values are associated with an adverse clinical outcome in most clinical conditions as in patients with AMI, stable CAD,[32,34] chronic heart failure,[29,33] acute pulmonary embolism, or chronic pulmonary arterial hypertension.[38,39]

Rule-in of acute myocardial infarction with high-sensitivity cardiac troponin assays

Various considerations related to the criteria used have confounded the interpretation of the literature in this area. One problem relates to the fact that in many studies the diagnosis of AMI has been based on assays less sensitive than the hs-cTn assay being evaluated and at times, the cut-off values used have been higher than those recommended by guidelines (see above).[27,40] This leads to apparent higher specificity with non-hs-cTn assays and lesser sensitivity and magnifies the differences in early sensitivities observed with the hs-cTn assays.

Some patients may not have AMI diagnosed because their cTn values do not increase above the cut-off value of the less sensitive assay but do so with the hs-cTn assay. If so, a substantial number of patients with unstable angina may migrate from that designation to the AMI category. In addition, patients with CAD and an elevated hs-cTn are likely to be diagnosed as having AMI even if the values are not significantly changing. Such a group may comprise up to 14% of the patients diagnosed with AMI.[41] As it is known that patients with stable angina may have elevations in hs-cTn,[32] we may, by using an elevated hs-cTn value in isolation, include patients who have stable disease in the AMI category. All of these situations need to be considered in defining the minimum time course necessary to rule in AMI.

Studies of the diagnostic performance of hs-cTn in a more heterogeneous populations are needed because most present studies have been done in pre-selected emergency department populations presenting with cardiac symptoms. Thus, the study design influences the sensitivity or the specificity of cTn, the optimal blood sampling regimens and optimal decision limits for absolute or relative changes in serial testing. The statistical analyses are also heterogeneous. Most studies determine optimal decision limits according to receiver operating characteristic analysis which weighs sensitivity and specificity equally; others have optimized cut-off values for specificity. The selection of criteria for change limits for AMI diagnosis will differ depending on whether there is a need for high specificity at the cost of lower sensitivity or increased sensitivity at the cost of lower specificity. Clinicians must be aware of this trade-off in evaluating individual patients. For these reasons, the pooling of study data from the literature is problematic.

Clinically relevant high-sensitivity cardiac troponin changes in serial testing

Key to the use of hs assays is the need to evaluate hs-cTn kinetics with serial testing in the clinical evaluation of chest pain patients.[42,43] It should be recognized, however, that the application of any change criteria so far has been associated with an increase in specificity for AMI but at the price of a decrease in sensitivity.[27,44] It should be clear that dynamic changes are not specific for AMI but are rather indicative of active myocardial injury with necrosis.

Analytical variation

Both the Joint ESC/ACCF/AHA/WHF task force for the universal definition of myocardial infarction and the National Academy of Clinical Biochemistry recommend a 20% change from an elevated cTn value as indicative of additional myocardial necrosis.[9,43] This 20% change represents a significant (>3 standard deviations of the variation associated with an elevated baseline concentration) change in cTn on the basis of a 5–7% analytical total CV.[43] This is the only metric that can be developed with conventional cTn assays. Assumptions of low imprecision are not valid when applied to cTn concentrations in the reference interval or around the 99th percentile URL with conventional cTn assays. Depending on the assay's CV at the baseline and follow-up sample concentration, changes may need to be much higher (up to 100–200%) to be outside of analytical variation, if baseline values are in the normal range or only slightly increased, i.e. above the 99th percentile URL but below the 10% CV value of the cTn assay. Changes of hs-cTn measurements near the 99th percentile URL also must exceed conjoint analytical and biological variation to be of clinical significance.

Reference change values of high-sensitivity cardiac troponin

With hs-cTn assays, one can now measure combined biological and analytical variation. This allows the calculation of the so-called reference change values (RCV) based on biological short-term (hourly) and intermediate-term (weekly) variation. Such values can be calculated only for reference individuals, but the theory of biological variation postulates the same process in patients with disease. These calculated RCV values are assay- and analyte-specific and must be obtained separately for each commercially available cTnT or cTnI assay. For many assays, short-term RCVs are in the 40–60% range[45–47] although one report has values as high as 86%.[48] Data on short- and long-term variation of hs-cTn concentrations in clinically stable patients with chronic cardiac diseases are very limited,[49] but the reported variation is in the range of healthy individuals. Whether this RCV should be applied in patients with acute disease is a matter of debate. However, it should be appreciated that using change criteria below the reported RCV is likely to include some patients whose change could be explained by biological and analytical variation alone. This is of particular concern at concentration ranges around the URL, because, in general, most patients with definite acute cardiac events have substantial and obvious changes in hs-cTn values which are often considerably greater than the RCV.[27,50,51] In contrast, it appears that changes in other diseases causing acute myocardial necrosis overlap substantially with those associated with AMI.[41] It is very likely that with minimal changes (e.g. only 20% or less from a value in the normal range) an acute event can be ruled out. But if the clinical situation is ambiguous and the pre-test likelihood of disease is high, additional subsequent sampling is necessary (see *Figure 1*).

Use of absolute or relative percentage changes of high-sensitivity cardiac troponin values in serial testing

Whether the diagnostic performances of percentage change differ from an absolute change of cTn concentrations, has been tested with the hs-cTnT assay in recent clinical studies.[44,51] They suggest that an absolute increase of hs-cTnT values (e.g. >7 ng/L over 2 h) is superior to a relative percentage changes from the baseline.[44,51] It appears that most of this difference is due to patients who present late after the onset of symptoms and have higher values at baseline.[51]

Figure 1 provides a template for the use of hs-cTn in the early diagnosis of AMI. It is based on a consensus derived from the literature,[52] which mainly has investigated hs-cTnT. The provided approach at least guarantees that the changes will be above the analytic variation. It is important to note that hs-cTn changes over a 3–6 h period in patients presenting with subacute AMI may be <20%. This area is complex and with the increasing number of publications on this topic the proposed change criteria in *Figure 1* may have to be adjusted. It is clear, however, that these critical change values will need to be estimated separately for each hs-cTn assay, but the principle involved will be similar although the actual numbers are likely to differ significantly.

General concepts regarding the use of high-sensitivity cardiac troponin assays

Timing of high-sensitivity cardiac troponin measurements in serial testing

At least two measurements of hs-cTn to verify a kinetic pattern are required to comply with the universal definition of myocardial infarction.[9] According to the recent guideline for the management of acute coronary syndromes, blood samples should be obtained at the time of presentation and 3 h after admission when using hs-cTn assays.[42] There is recent evidence suggesting that patients with an AMI can be reliably identified within 3 h after admission with up to 100% sensitivity and up to 100% negative predictive value using a hs-cTn assay indicating that observation time may be reduced for the rule-out of AMI.[39,51,53] However, these studies used the older less-sensitive cTn assay values as the gold standard criteria. In studies using hs-cTnT for diagnosis of AMI, it has been suggested that some patients will require at least 6 h for a definitive diagnosis.[41] Given the paucity of data, we still recommend additional blood sampling in patients strongly suspected of having an AMI but no significant hs-cTn increase after 3 h (see *Figure 1*). Moreover, in patients with increased hs-cTn values a significant change must be documented which may require supplementary measurements.

Assessment of a changing pattern of high-sensitivity cardiac troponin concentrations

A 20% increase in values when baseline levels are markedly elevated is probably adequate based on analytical variation.[9,43]

For hs-cTnT at values below or close to the 99th percentile URL, increases above the URL with relative increases of at least >50% or absolute increases for hs-cTnT of >7 ng/L within 2 h suggest a rising pattern and optimize the overall accuracy of AMI diagnosis.[44,51]

For hs-cTnI, a recently published study evaluating serial changes using the Abbott® research hs-cTnI assay in pre-selected chest pain unit patients, suggested that increases above the 99th percentile URL with relative increases of >250% over a 3 h period optimize specificity for the diagnosis of AMI.[40] However, the diagnosis in that study was based on clinical criteria and an increase in a standard cTn assay >99th percentile URL with a >20% change over a 6 h period. Higher sensitivities were found at lower percentage changes.

Other hs-cTnI assays may require different metrics. On the basis of the available data on short-term biological variation,[10] these changes likely will need to be at least >50% to exceed the RCV.

Diagnosing acute myocardial infarction using high-sensitivity cardiac troponin

The 99th percentile hs-cTn URL value should be used as the decision limit for the diagnosis of AMI in an appropriate clinical context. Documentation of a significant rise with serial testing is

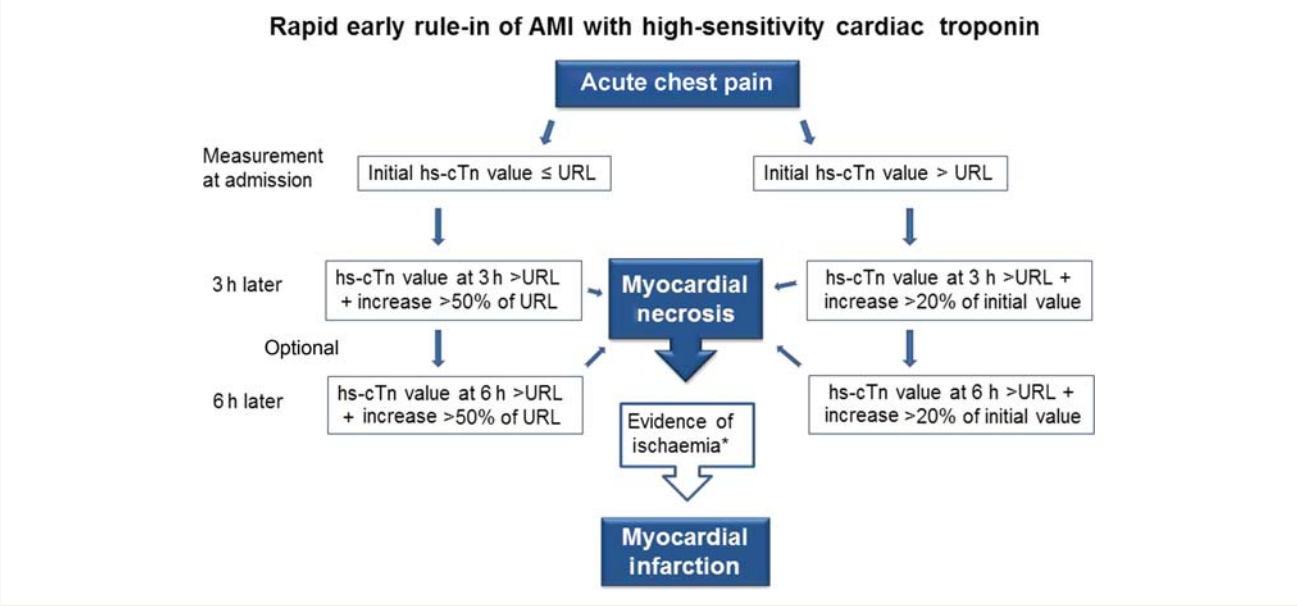

Figure 1 Template for rapid early rule-in of acute myocardial infarction with high-sensitivity cardiac troponin displaying an algorithm for clinical use of high-sensitivity cardiac troponin testing based on current knowledge. It should be noted that the stated algorithm may vary according to the troponin assay evaluated. This approach optimizes sensitivity for acute myocardial infarction diagnosis, but clinicians may also wish to choose more stringent metrics to improve specificity (see text).
AMI, acute myocardial infarction; hs-cTn, high-sensitivity cardiac troponin; URL, 99th percentile upper reference limit.
*Evidence of ischaemia by symptoms and/or new electrocardiogram changes and/or new imaging corroboration.

required. There is a need to use different cut-points for men and women in the future depending on the assay used.[2,22–24]

Groups with subclinical ischaemic heart disease and slightly increased high-sensitivity cardiac troponin baseline values

With higher-sensitivity assays, some groups, such as elderly individuals and diabetic patients, may have increased baseline cTn concentrations,[35,36,53] because structural heart disease is so common in these patient groups. A recent publication suggested that it may be advisable to use a higher cut-point (about three-fold the 99th percentile URL) as a decision limit for AMI in >70-year-old patients.[51] However, regardless of the cut-off value used, the critical distinction that must be made is to determine whether there is a significant rising and/or falling pattern of hs-cTn values as an indicator of acute myocardial necrosis.

Summary regarding use of high-sensitivity cardiac troponin in clinical routine

(1) Use the 99th percentile concentration of the reference population as the cTn URL.
(2) The diagnosis of acute myocardial necrosis requires a significant change with serial testing. At low cTn baseline concentrations (around the 99th percentile), the change in serial testing in order to be clinically significant requires to be marked, in case of markedly elevated baseline, a minimum change of >20% in follow-up testing is required (see *Figure 1*).
(3) Additional testing of other early markers of acute myocardial necrosis, such as myoglobin or creatine kinase MB is no longer needed.
(4) Blood sampling in patients with suspicion of AMI should be performed on admission and 3 h later. Measurement of hs-cTn should be repeated 6 h after admission in patients of whom the 3 h values are unchanged but in whom the clinical suspicion of AMI is still high.
(5) Cardiac troponin is a marker of myocardial necrosis and not a specific marker of AMI. The latter may be only diagnosed with a rise and/or fall of cTn together with characteristic symptoms, and/or electrocardiogram changes indicative of ischaemia and/or imaging evidence of acute myocardial ischaemia. Consider also other causes of myocardial necrosis (e.g. acute heart failure or myocarditis) when an elevated hs-cTn test result is obtained.
(6) Stable or inconsistently variable cTn values without significant dynamic changes are likely markers of chronic structural heart disease.

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