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 (¼picograms 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.6

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 guidelines1,9,10 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-sensitive’ assays. Most present cTn assays do not detect even in 50% of apparently disease-free individuals20 whereas high-sensitivity assays do and with some, detection may be as high as in 90%.21 – 23 In addition, reports for the hs-cTnl Singulex®, the hs-cTnT, and the Abbott® hs-cTnl 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-cTnl Beckman® research assay.20, 21

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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% range⁴⁻¹,² and although one report has values as high as 86%.⁴ Data on short- and long-term variation of hs-cTn baseline.⁴⁴,⁵¹ It appears that most of this difference is due to differences likely will need to be at least 50% to exceed the RCV. In contrast, it appears that changes in other diseases causing acute myocardial necrosis overlap substantially with those associated with AML.⁴⁵ 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.⁴⁹,⁵¹ 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 AML. 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.⁷ 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.¹ 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 AML.⁷,⁹,¹⁲ However, these studies used the older less-sensitive cTn assay values as the gold standard criteria. In studies using hs-cTnT for diagnosis of AML, it has been suggested that some patients will require at least 6 h for a definitive diagnosis.⁹ 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.⁷,⁴³ 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 AML.⁶⁰ 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-cTn 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...
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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References


High-sensitivity troponins - difficult friends in acute coronary syndromes

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Acute Coronary Syndromes

High-sensitivity Troponins—Difficult Friends in Acute Coronary Syndromes

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Abstract

The introduction of novel high-sensitivity cardiac troponin (hs-cTn) assays has made it possible to measure cardiac troponin levels that are up to 10-fold lower than those detectable by conventional cardiac troponin (cTn) assays. With such novel assays, an elevated risk of major adverse cardiovascular events was noted across the continuum of cTn levels, with an incremental risk of increasing levels even in healthy individuals, but also in patients with stable coronary artery disease, congestive heart failure or acute coronary syndrome (ACS). The rapid triage of patients presenting to the accident and emergency department with chest pain is critical to ensure optimal management, and the novel hs-cTn assays provide a valuable tool for a more rapid exclusion of acute myocardial infarction (AMI), with a higher sensitivity, negative predictive value and diagnostic accuracy compared with conventional cTn assays. The associated decrease in specificity and positive predictive value for the diagnosis of AMI can be overcome by serial measurements to assess the absolute and relative increases in cTn levels. This article provides a contemporary overview of the role of hs-cTn in the detection of individuals with subclinical disease, diagnosis of ACS, risk stratification and clinical management. Furthermore, aspects of uncertainty, such as cut-offs, and the role of hs-cTn for clinical decision-making are addressed.

Keywords
Cardiac troponins, acute coronary syndromes, diagnosis, risk stratification, clinical management

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Major reductions in death rates in acute coronary syndromes (ACS) were achieved with the implementation of percutaneous coronary intervention allowing rapid coronary reperfusion.1 Nonetheless, mortality and morbidity remain substantial during the ensuing five years after an acute coronary syndrome (ACS).2 Indeed, between 1987 and 2006, survival among 30-day survivors of ACS has not improved despite a marked reduction in early mortality and a substantial shift in the epidemiology of MI with the introduction of cardiac troponins in laboratory diagnostic tests.3 Thus, improvements in early diagnosis, risk stratification and clinical management of patients presenting with ACS are needed. ACS comprises the distinct entities of unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI), as defined by the current European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology (AHA/ACC) guidelines.4,5 Among the tools available for diagnosis, risk stratification, and clinical management of ACS, biomarkers figure prominently. Troponins as specific markers of myocardial necrosis constitute the main circulating biomarker for the differentiation between UA and NSTEMI4 and an early invasive strategy in high-risk patients identified by elevated troponin levels is associated with better short- and long-term outcomes.6

The development of novel high-sensitivity cardiac troponin (hs-cTn) assays for the quantification of cardiac troponins in the circulation at plasma concentrations at the 99th percentile or lower in a reference population with a coefficient of variance of ≤10 % made it possible to fulfill the quality criteria postulated by the Joint ESC/ACCF (American College of Cardiology Foundation)/AHA/WHF (World Heart Federation) Task Force for the Redefinition of Myocardial Infarction.7 In addition to determining the absolute plasma concentrations of cardiac troponins, the rise or fall of...
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Table 1: Thrombolysis in Myocardial Infarction Risk Score for Patients with Unstable Angina and Non-ST-elevation Myocardial Infarction – Predictor Variables

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Point Value of Variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>1</td>
<td>Risk factors:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Family history of CAD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypercholesterolemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Current smoker</td>
</tr>
<tr>
<td>≥3 risk factors for CAD</td>
<td>1</td>
<td>Risk factors:</td>
</tr>
<tr>
<td>Aspirin use in last 7 days</td>
<td>1</td>
<td>≥2 anginal events in last 24 hours</td>
</tr>
<tr>
<td>Recent, severe symptoms of angina</td>
<td>1</td>
<td>≥2 anginal events in last 24 hours</td>
</tr>
<tr>
<td>Elevated cardiac markers</td>
<td>1</td>
<td>CK-MB or cardiac-specific troponin level</td>
</tr>
<tr>
<td>ST deviation ≥0.5 mm</td>
<td>1</td>
<td>ST depression ≥0.5 mm is significant; transient ST elevation ≥0.5 mm for &lt;20 minutes is treated as ST-segment depression and is high risk; ST elevation &gt;1 mm for &gt;20 minutes places patients in the STEMI treatment category</td>
</tr>
<tr>
<td>Prior coronary artery stenosis &gt;50 %</td>
<td>1</td>
<td>Risk predictor remains valid even if this information is unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calculated TIMI Risk Score</th>
<th>Risk of ≥1 Primary Endpoint* in ≤14 days</th>
<th>Risk Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or 1</td>
<td>5 %</td>
<td>Low</td>
</tr>
<tr>
<td>2</td>
<td>8 %</td>
<td>Low</td>
</tr>
<tr>
<td>3</td>
<td>13 %</td>
<td>Intermediate</td>
</tr>
<tr>
<td>4</td>
<td>20 %</td>
<td>Intermediate</td>
</tr>
<tr>
<td>5</td>
<td>26 %</td>
<td>High</td>
</tr>
</tbody>
</table>

* Primary endpoints: death, new or recurrent MI or need for urgent revascularization

<table>
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These findings underline the futility of using an absolute threshold level alone and strongly call for additional parameters, such as the kinetics of troponin levels and/or additional biomarkers, for making the diagnosis of MI. Indeed, the former was addressed by a study showing that a doubling of the hs-cTnT concentration within three hours of the first time-point in conjunction with initially elevated hs-TnT levels allowed an increase in the positive predictive value for AMI to 100 %. Serial testing using hs-Tn assays at zero and six hours after hospitalization increases both sensitivity and specificity, and implementation of a delta criterion (% increase) further enhances specificity. Absolute changes of cTn levels determined two hours apart have a significantly higher diagnostic accuracy for AMI than relative changes (area under the ROC curve [AUC] for hs-TnT 0.95 versus 0.76, cardiac troponin I ultra 0.95 versus 0.72).

Three recent studies analysed the combination of copeptin (the arginine–vasopressin prohormone-derived peptide) in conjunction with hs-cTn for the rapid rule-out of MI. The use of pre-specified cut-offs for both markers was associated with an improvement in the rule-out of MI in patients admitted to the A&E department with a likely diagnosis of NSTEMI, whereas in patients presenting with acute chest pain, initial negative conventional cTnT levels and a non-diagnostic ECG, the rapid rule-out of MI using hs-TnT could not be further enhanced by adding copeptin (continuous) levels. For the identification of patients with MI presenting within three hours of onset of chest pain, a high-sensitivity cardiac troponin I (hs-cTnI) assay delivered an AUC of 0.96 alone, with a small but significant improvement to an AUC of 0.97 (p=0.00397) when copeptin was added. In all studies, the specificities remained low.

Risk Stratification of Patients with Acute Coronary Syndrome

The risk stratification of patients with ACS is of paramount clinical importance. Most, but not all, studies that simply compared conventional and sensitive troponin assays found that sensitive troponin assays improve risk prediction of event-free survival at both 30 days and one year. However, the predictive value of sensitive troponin assays must be regarded in conjunction with risk scores that combine the clinical parameters, ECG findings and basic laboratory parameters that have a well-documented clinical value and are recommended by current guidelines.

Commonly used is the Thrombolysis in Myocardial Infarction (TIMI) risk score based on the series of TIMI studies for patients with UA/NSTEMI (see Table 1) and STEMI, respectively. In turn, the Global Registry of Acute Coronary Event (GRACE) risk score (see Figure 3) is based on registry data and was developed to comprise all ACS entities. Clinical risk scores (all of which contain conventional troponin plasma concentration) provide the backbone against which novel biomarkers need to show incremental benefit as assessed by statistical methods using c-statistics, integrated discriminating index and net reclassification improvement (NRI). High-sensitivity troponin assays did not improve risk prediction in studies that included both STEMI and NSTEMI patients. In patients with acute chest pain, high-sensitivity troponin assays improved the prediction of death, but not of subsequent AMI, with an improved reclassification of patients (NRI 0.91) after adjustment for the TIMI risk score.

A recent multimarker analysis in the MERLIN-TIMI 36 trial of 4,352 patients with NSTEMI, identified a hs-cTn net improvement over the clinical TIMI risk score (excluding troponin) with c-index 0.784 > 0.805 (p=0.005) and NRI 0.389 (p=0.001) for cardiovascular death and similarly for MI, hospitalization for congestive heart failure and the composite endpoint of cardiovascular death and hospitalization for congestive heart failure. Furthermore, patients presenting with ACS and reclassified into NSTEMI from UA based on hs-Tn against cTn testing correlated with an increased
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risk of major adverse cardiovascular events and significantly improved risk stratification. In conclusion, if combined with clinical scores, sensitive troponin assays appear to improve risk prediction in NSTEMI–ACS patients but not, or less so, in STEMI patients.

Nonetheless, clinical judgement has become even more important for the correct interpretation of test results that integrate both laboratory parameters (absolute values of hs-Tn and the kinetics thereof) with clinical symptoms and ECG signs of myocardial ischemia to make the diagnosis of AMI. The increase in sensitivity of hs-cTnT tests at the expense of diminished specificity constitutes a challenge to make the diagnosis ("rule-in") of AMI. This important topic is currently addressed in two ways:

1. by analyzing the absolute/relative increase in hs-Tn concentration over the time necessary to make the diagnosis of AMI; and
2. by combining the hs-cTnT test with an ideally disease-specific complementary biomarker to enable the diagnosis of AMI at a single time-point.

Evidence is accumulating that hs-cTnT assays improve short- and long-term prediction, at least in NSTEMI patients, beyond clinical risk prediction rules, which include cTn levels measured by conventional assays. In addition, beyond risk estimation for elevated hs-cTnT concentration, the role of hs-cTnT testing in the choice of therapeutic intervention and its effects on clinical outcomes are being analysed.

Finally, the underlying mechanism for the stronger association of elevated troponin levels with structural heart disease events rather than with atherothrombotic events is of major interest.

**Clinical Management of Patients with Acute Coronary Syndromes**

As of now, only scarce data exist on the effect of introducing hs-tTN assays into clinical practice with respect to management and outcomes after therapeutic intervention. Interestingly, lowering the diagnostic threshold of cardiac troponin I (cTnI) from 0.20 ng/l to 0.05 ng/l by the introduction of a sensitive troponin assay (1,038 patients before and 1,054 after implementation) not only increased the rate of NSTEMI diagnosed in patients with suspected ACS, but also translated into major reductions in morbidity and mortality. Future trials will need to examine the benefit of an invasive therapy in AMI patients with elevated troponin, similar to those of the previous era with conventional cTnI. A prerequisite is the exploration of quantitative cut-offs for hs-cTn and changes over time (delta criteria) to serve as a guidance for therapeutic interventions.

**Summary and Conclusions**

The availability of hs-cTnT tests has improved the diagnostics of patients presenting to the A&E department with chest pain.