High-sensitivity cardiac troponins in everyday clinical practice

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Abstract

High-sensitivity cardiac troponin (hs-cTn) assays are increasingly being used in many countries worldwide, however, a generally accepted definition of high-sensitivity is still pending. These assays enable cTn measurement with a high degree of analytical sensitivity with a low analytical imprecision at the low measuring range. One of the most important advantages of these new assays is that they allow novel, more rapid approaches to rule in or rule out acute coronary syndromes (ACSs). The increase in early diagnostic sensitivity of hs-cTn assays for ACS comes at the cost of a reduced ACS specificity, because more patients with other causes of acute or chronic myocardial injury without overt myocardial ischemia are detected than with previous cTn assays.

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INTRODUCTION

Cardiac troponin I (cTnI) and cTnT are the biomarkers of choice for the diagnosis of myocardial damage, because they are the most sensitive and cardiac-specific biomarkers currently available. Recommendations for the use of cTn measurement in acute cardiac care and practical clinical considerations in the interpretation of cTn elevations have been published recently. Over the years the analytical sensitivity of cTn assays has been continuously improved, and more recently a new generation of cTn assays, i.e., the high-sensitivity (hs)-cTn assays, have been introduced into routine clinical practice. It is important to note, that these assays measure the same analyte as previous assay generations but with...
substantially improved analytical sensitivity and assay precision at the low measuring range\textsuperscript{[8,11,12,15]. It is also important to note due to discrepancies in routine use\textsuperscript{[7]}, that, regardless of how assays are named by manufacturers, hs-cTn assays should be only designated as hs-cTn assays, if the below listed analytical characteristics are met by an assay also in routine use together with publication of its hs analytical characteristics in peer-reviewed literature\textsuperscript{[7,8]}.}

From a clinical perspective it has been noted that the improved analytical performance of hs-cTn assays also increased their clinical ability to detect small amounts of myocardial damage and to precisely identify small differences in cTn concentrations in serial testing compared with previous cTn assay generations\textsuperscript{[9,10]}. It is expected that hs-cTn assays, if used appropriately, will improve both early diagnosis and short and long-term risk stratification. In this review recommendations for the clinical interpretation of hs-cTn test results are proposed based on the currently available clinical evidence, and it is also indicated where sufficient clinical data are still lacking.

ANALYTICAL CHARACTERISTICS OF HS-CTN ASSAYS

The analytical characteristics of hs-cTn assays are summarized in Table 1. The analytical lower limit of detection (LoD) is in the range of single digits of ng/L or even below\textsuperscript{[8,10,14]}. Therefore, it is recommended that hs-cTn assay results are reported as ng/L (\(\approx\) pg/mL), and cTn values below the LoD should not be reported as numbers\textsuperscript{[8]}. hs-cTn assays must have high precision in routine use at lower concentration ranges with total analytical coefficient of variation (CV) < 10\% at the 99\textsuperscript{th} percentile concentration of the reference population, which is the recommended upper reference limit (URL). Despite increased analytical sensitivity hs-cTn assay must maintain analytical specificity for the detection of cardiac troponin isoforms. There have been not reports of major analytical interferences with hs-cTn assays, but they are possible and thorough evaluations of possible analytical interferences is needed before approval for routine use\textsuperscript{[7,8]}. In contrast to conventional cTn assays, hs-cTn assays permit measurement of cTn concentrations in a significant proportion of apparently pathology-free individuals, which favours a precise calculation of the URL\textsuperscript{[8]}. There is still no consensus on a specific percentage of detectable cTn concentrations in the reference population which is required for the label hs as long as all the other criteria are fulfilled, but usually > 50\% are recommended\textsuperscript{[7]}. There are reports on sex-specific URLs which are higher for men than women for hs-cTn assays including the already commercially available hs-cTnI and hs-cTnT assays from Roche and Abbott Diagnostics\textsuperscript{[3,5,7-11]}, and it may turn out that sex-specific URLs should be used in routine as well. The underlying mechanisms for cTn release from normal hearts are still uncertain and remain to be established. Since analytical interferences can be ruled out\textsuperscript{[3,5,10]}, a constant limited turnover of cardiomyocytes appears to be present in normal hearts as well.

Table 1 Analytical characteristics of high-sensitivity cardiac troponin assays

| The analytical lower limit of detection is in the range of single digits of ng/L, and is markedly lower than the upper reference limit |
|---|---|
| Hs-cTn assays have high precision in routine use at lower concentration ranges with analytical CV < 10\% at the 99\textsuperscript{th} percentile concentration of the reference population |
| Hs-cTn assays enable detection of cTn in a significant proportion of the reference population, thereby allowing for a more accurate calculation of the 99\textsuperscript{th} percentile URL with its 95\% confidence interval |
| Hs-cTn assays must be highly specific for the detection of cardiac cTn isoforms |

Hs-cTn: High-sensitivity cardiac troponin; CV: Coefficient of variation; URL: Upper reference limit.

EARLY DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

Hs-cTn assays detect cTn release at an earlier time point than the previous generations of cTn assays leading to an improved early sensitivity for acute myocardial infarction (AMI) diagnosis within 3 h of presentation\textsuperscript{[12-15]}. Most but not all studies demonstrated a higher diagnostic accuracy of hs-cTn assays for early AMI diagnosis when compared to previous cTn assay generations on admission to the emergency department\textsuperscript{[10]}. However, scrutiny is needed when evaluating studies on this topic as differences between assays often have been overstated by use of different medical decision limits for the older and newer cTn assays, e.g., 10\% CV concentration limit vs 99\textsuperscript{th} percentile URL. This leads to apparent higher specificity and lesser sensitivity with non hs-cTn assays and magnifies the differences in early sensitivities at patient presentation observed with the hs-cTn assays\textsuperscript{[10]}. However, guidelines recommend the use of the URL as a medical decision limit even when it cannot be measured with a CV of < 10\%\textsuperscript{[3,11]}. Thus early sensitivities must be compared by using the 99\textsuperscript{th} percentile URL as a medical decision limit for standard and hs-cTn assays. In addition, some patients may not have AMI diagnosed because their standard cTn values do not increase above the cut-off value but do so with the hs-cTn assay. Thus, a significant number of patients with unstable angina may migrate from that designation to the AMI category if reclassified using the hs-cTn test results. Studies of the diagnostic performance of hs-cTn assays in more heterogeneous populations are also still needed because most present studies have been done in pre-selected emergency department populations presenting with cardiac symptoms or chest pain unit populations. Study design influences the sensitivity and the specificity of cTn, the optimal blood sampling regimens, and optimal decision limits for absolute or relative changes in serial testing. Statistical analyses are also heterogeneous. Most studies determine optimal decision limits according to receiver operating characteristic curve analysis which weighs sensitivity and specificity equally, while others have optimized cut-off values for specificity. The selection of criteria for change limits for AMI diagnosis will also differ depending on whether there is...
This algorithm for the rapid evaluation of clinically suspected acute myocardial infarction with high-sensitivity cardiac troponin testing. This algorithm is based on best current knowledge and may have to be modified with upcoming new data. This approach at least guarantees that the changes will be above the analytical and biological variation. It is important to note that hs-cTn changes over a 3 h period in patients presenting late after AMI onset may be less than 20%. For hs-cTnT some studies favor absolute changes over relative concentration changes. Evidence of acute myocardial ischemia by new ECG changes and/or new imaging corroborations. Hs-cTn: High-sensitivity cardiac troponin; URL: 99th percentile upper reference limit of healthy controls; ACS: Acute coronary syndrome; LoD: Lower limit of detection; AMI: Acute myocardial infarction; ECG: Electrocardiogram.

Figure 1 Algorithm for the rapid evaluation of clinically suspected acute myocardial infarction with high-sensitivity cardiac troponin testing.

Key to the use of hs-cTn assays is the need to evaluate cTn kinetics with serial testing in the clinical evaluation of chest pain patients. At least two measurements of hs-cTn test results to verify a kinetic pattern are required to comply with the Universal Definition of Myocardial Infarction. Even in patients with increased hs-cTn values a significant change must be documented by serial measurements.

Clinically relevant hs-cTn assay concentration changes in serial testing

Key to the use of hs-cTn assays is the need to evaluate cTn kinetics with serial testing in the clinical evaluation of chest pain patients. At least two measurements of hs-cTn test results to verify a kinetic pattern are required to comply with the Universal Definition of Myocardial Infarction. Even in patients with increased hs-cTn values a significant change must be documented by serial measurements.

In general, most AMI patients have substantial and obvious changes in hs-cTn values. It must be emphasized that dynamic changes are not specific for AMI but are rather indicative of acute myocardial damage. An algorithm for the use of hs-cTn serial measurements for the evaluation of AMI in patients presenting with symptoms suggestive for an acute coronary syndrome (ACS) based on the currently available clinical data is shown in Figure 1. Previous recommendations on change criteria just considered analytical variation and advocated based on a total CV < 10% any change in serial testing of > 20% to be significant. The precision necessary to implement this approach is not present within the reference range for hs-cTn assays either. In addition, biological variation needs to be considered. Changes of hs-cTn measurements near the 99th percentile URL must exceed joint analytical and biological variation to be of clinical significance. This is done by calculation of the so-called reference change values (RCV). 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 hs-cTn assay. For many assays, short-term RCVs are in the 40%-60% range, although one report has values as high as 86%. Data on short- and long-term variation of hs-cTn concentrations in clinically stable patients with chronic cardiac diseases are very limited, but the reported variation is in the range of healthy individuals. A recently published study evaluating serial changes using a pre-marketing version of the Abbott® 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 in patients with baseline values < URL and increases > 50% with modestly increased baseline values optimize specificity for the diagnosis of AMI. However, AMI diagnosis in this study was based on clinical criteria and an increase in a conventional local cTn assay > 99th percentile URL with a > 20% change over a 6 h period.

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. It has been described at hs-cTnT values below or close to the 99th percentile URL that an absolute increase of hs-cTnT values (e.g., > 7 ng/L over 2 h) is superior to a relative percentage changes from baseline. Other hs-cTn assays may require different metrics, because data on absolute changes in serial testing are assay specific. Undetectable hs-cTn ruled out ACS with a
negative predictive value > 99% on ED admission\textsuperscript{[15,16]}.

Timing of hs-cTn measurements in serial testing

According to the recent European guideline for the management of ACS, blood samples should be obtained at the time of presentation and 3 h after admission when using hs-cTn assays\textsuperscript{[19]}. There is recent evidence suggesting that many patients with an AMI can be reliably identified within 3 h after admission with close to 100\% sensitivity and negative predictive value using a hs-cTn assay, which indicates that observation time in the emergency department may be reduced for the rule out of AMI\textsuperscript{[15,18]}. However, most of these studies based the diagnosis of AMI on the prior less sensitive cTn assays and ignored AMI only detected with hs-cTn assays. Thus, if the clinical situation is ambiguous and the pre-test likelihood of disease is high, additional subsequent sampling (e.g., at 6 h and even beyond) is still necessary in individual patients.

Myocardial infarction after percutaneous coronary interventions or aortocoronary bypass grafting

There are still no data on hs-cTn decision limits in these clinical settings. In acute percutaneous coronary interventions (PCI) or nowadays rarely performed acute coronary artery bypass grafting (CABG) for evolving AMI acute myocardial damage is caused by AMI itself and the potential additional myocardial damage caused by PCI or CABG cannot be differentiated from cTn release caused by ongoing AMI. In elective PCI or CABG, by contrast, baseline cTn values are usually within the normal range and potential myocardial damage caused by these interventions can be reliably detected by hs-cTn measurements. However, in these elective patients hs-cTn decision limits for periprocedural AMI are also still not available. Thus, only the limits recommended by the universal definition of AMI can be currently used\textsuperscript{[20]}, i.e., increase > 5-times URL after PCI and > 10-times URL after CABG. However, these limits are still very controversially discussed in the communities of interventionists and cardiac surgeons, because it appears from the available data that periprocedural cTn increases in clinically uncomplicated patients must be substantially higher to be of prognostic significance\textsuperscript{[20]}.

DO WE NEED ADDITIONAL BIOMARKERS FOR AMI DIAGNOSIS WHEN HS-CTN ASSAYS ARE USED?

The most recently advertised markers for the early diagnosis of AMI are heart-type fatty acid binding protein (H-FABP) and copeptin. However, in the vast majority of studies these markers were compared only with previous, less sensitive cTn assays and comparative data with hs-cTn assays are still limited.

H-FABP

Despite its name this protein is not a cardiac-specific marker as it is also expressed, although in much lower amounts, in several other tissues. It is cleared by the kidneys and thereby increased in case of renal failure\textsuperscript{[30]}. H-FABP increases rapidly in ACS\textsuperscript{[13]}, but more recent data do not support a benefit when combined with hs-cTn\textsuperscript{[15,32]}.

Copeptin

Copeptin is the 39 amino acids long c-terminal part of pro-arginine-vasopressin and a stable surrogate marker of vasopressin secretion\textsuperscript{[31]}. It is a marker of stress\textsuperscript{[13]} and has been proposed for early AMI diagnosis on emergency department admission\textsuperscript{[34]}. More recent data do not support a benefit when combined with hs-cTn (Figure 2)\textsuperscript{[15,32]}.

In summary, when hs-cTn assays are used instead of standard cTn assays both H-FABP and copeptin do not add to the early diagnosis of AMI, particularly, if the LoD is used as an AMI rule-out limit for hs-cTn in chest pain patients. However, in case of point-of-care testing where the criteria for hs are very difficult to be fulfilled for cTn assays a combination with these markers may be useful.

DISEASES WITH POTENTIAL HS-CTN ELEVATIONS OTHER THAN AMI

Given the high frequency of detectable and slightly elevated hs-cTn values in the community\textsuperscript{[35-37]}, especially in patients with cardiovascular comorbidities, it is important to note that an increased hs-cTn concentration alone is not sufficient to make the diagnosis of AMI\textsuperscript{[54]}. hs-cTn increases must, therefore, be interpreted in relation to the clinical presentation (Table 2). Thus, a recent publication suggested that it may be advisable to use a higher cut-point (about 3-fold the 99\% percentile URL) as a decision criteria.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Diagnostic performances of high-sensitivity troponin T and copeptin for the diagnosis of acute myocardial infarction in chest pain patients. Own unpublished results, the area under receiver operator characteristic curves of the combination of copeptin with hs-cTnT (0.94) was not significantly different from the area under hs-cTnT curve (0.90). The worthless test is indicated as reference line. Hs-cTnT: High-sensitivity cardiac troponin T.}
\end{figure}
limit for AMI in > 70 year-old patients. However, it is likely that most of elevations in the elderly are caused by comorbidities. Thus, the use of higher cut-off values decreases early sensitivity for AMI in older patients without comorbidities. Regardless of the cut-off value used, the critical distinction that remains to be made is to determine whether there is a significant rising pattern of hs-cTn values in serial testing as an indicator of acute myocardial damage. Thus, clinical judgement still remains essential.

With hs-cTn assays, elevations above the 99\textsuperscript{th} percentile URL are common in patients with structural heart disease (Table 2), including patients with stable coronary artery disease. In patients with putative stable angina, a hs-cTnT value > 99\textsuperscript{th} percentile URL is found in 37\% of those with coronary plaques that are thought to be more labile or vulnerable. In stable heart failure patients, the median concentration for hs-cTnT is 12 ng/L, which is very close to the 99\textsuperscript{th} percentile URL of 14 ng/L for this assay. 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, heart failure, pulmonary embolism or chronic pulmonary arterial hypertension.

### Table 2 Elevations of high-sensitivity cardiac troponin in the absence of significant coronary artery disease

| Acute myocardial damage related to secondary myocardial ischemia (AMI type 2) | Tachycardia or bradycardia (e.g., rapid pacing during transcutaneous aortic valve replacement) | Aortic dissection with involvement of coronary ostia | Severe aortic valve stenosis | Hypertrophic cardiomyopathy |
| Acute myocardial damage not related to myocardial ischemia | Cardiac contusion | Cardiac incisions with surgery | Radiofrequency or cryoablation therapy for arrhythmias | Rhabdomyolysis with cardiac involvement |
| Indeterminate or multiform group | Apical ballooning syndrome | Cardiotoxic agents, e.g., anthracyclines, CO poisoning, severe burns affecting > 30\% of body surface |
| Analytical interferences | Rare, e.g., by high titres of auto- or hetero-phlic antibodies |

AMI: Acute myocardial infarction; CO: Carbone monoxide; CAD: Coronary artery disease.

Cardiac specificity of cTnT vs cTnI

A recent report again raised concerns regarding the cardiac-specificity of the current generation cTnT assay in patients with chronic skeletal muscle disorders due to potential reexpression of cTnT isoforms or expression of an immunoreactive protein in skeletal muscle myopathies. In patients without evidence of myocardial injury increases of creatine kinase MB (CKMB) iso-enzyme and cTnT without concomitant increases in cTnI were found. A potential release of cTnT from skeletal muscle with normal cTnI in patients with chronic skeletal muscle damage is also highlighted by an own case in whom we measured cTnT and cTnI with hs assays (Figure 3). The most cardiac-specific marker in this rare patient population with chronic skeletal muscle damage (e.g., muscular dystrophies) is cTn. Based on our experience patients with unexplained increased cTnT with normal cTnI should be also evaluated for possible, clinically still asymptomatic chronic skeletal muscular diseases.

RISK STRATIFICATION BY HS-CTN TESTING: IS THERE ADDITIONAL VALUE COMPARED WITH HIGH-SENSITIVITY C-REACTIVE PROTEIN OR NATRIURETIC PEPTIDE TESTING?

There are no studies to date evaluating hs-CRP or natriuretic peptides together with hs-cTn assays for risk stratification in non-ST-segment elevation myocardial infarctions. Patients in the community who have elevated values of hs-cTn have underlying cardiovascular disease and thus are in the long run at increased risk for ischemic events and heart failure, and hs-cTn was also described as an independent risk marker in the general population. However, despite robust statistical predictive value, hs-cTn is similar to hs-CRP and natriuretic peptide testing in the sense that when added to traditional risk factors, it only modestly improves risk stratification and reclassification. There are still insufficient data to as-
In case of borderline increased baseline values (>100%) increase together with an increase above the URL.

The 99th percentile concentration of the reference population should be used as the cTn URL and as the medical decision limit. In patients with clinically suspected AMI, the LoD of hs-cTn assays is a useful rule out decision limit with a negative predictive value >99% even on emergency department admission. The diagnosis of acute myocardial damage requires a significant change with serial hs-cTn testing. At low cTn baseline concentrations (≤99th percentile URL) the change in serial testing in order to be clinically significant requires to be a marked (>100%) increase together with an increase above the URL. In case of borderline increased baseline values (>URL and ≤3 times URL) only relative changes >50% should be considered as clinical significant. In the case of markedly elevated baseline values (>3 times URL), a minimum change >20% in follow-up testing is required. It may turn out that for some hs-cTn assays absolute hs-cTn concentration changes perform better than relative changes. Additional testing of other early markers of acute myocardial necrosis, such as myoglobin, CKMB isofoms, or H-FABP is no longer needed. Copeptin testing adds very little as well, particularly, if the LoD is used as an ACS rule out limit on emergency department admission for the hs-cTn assays. Blood sampling in patients with suspicion of AMI should be performed on admission and 3 h later at a minimum. Measurements of hs-cTn should be repeated at 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. According to the Universal Definition of Myocardial Infarction in chest pain patients presenting after 6 h subsequent blood sampling (e.g., after 12 h) is also needed to document a troponin rise or fall as a sign for acute myocardial damage. Blood sampling only at a single time point for troponin measurement is not recommended. cTn is a marker of myocardial necrosis but not a specific marker of AMI. AMI should only be diagnosed when there is a rise and/or fall of cTn together with characteristic symptoms, and/or electrocardiogram or imaging evidence of acute myocardial ischemia. Besides myocardial ischemia one should consider also other alternative causes of acute myocardial damage (e.g., acute heart failure, myocarditis, pulmonary embolism) whenever an elevated hs-cTn test result is obtained. Direct myocardial trauma (e.g., ablation therapy for arrhythmias, surgical incisions of the myocardium, myocardial contusion) also lead to troponin leakage from the myocardium. Stable or inconsistently variable troponin elevations without significant dynamic changes are likely markers of chronic structural heart disease, if analytical interferences (which are rare) have been ruled out.

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