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HIGH SENSITIVITY TROPONOINS AND DIAGNOSIS OF MYOCARDIAL INFARCTION

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ABSTRACT

Early diagnosis of acute myocardial infarction (AMI) in patients presenting with acute chest pain improves clinical outcome. Moreover, rapid exclusion of AMI is important to triage patients in view of limited resources in the emergency department. 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 of cTn assays (coefficient of variation of < 10% at the 99th percentile upper reference limit). Measurement of cardiac troponin levels, as a marker of myocyte necrosis, is essential for diagnosing, AMI.1 Compared with sensitive troponin assays, high-sensitivity troponin assays enhance the accuracy and speed of the diagnosis, 1- 4 improve outcome, and are cost-effective. 5 Recent studies suggest that AMI can be diagnosed earlier than 3 hours, when values below the 99th percentile are used as cutoff values. This concept was incorporated into the 2015 European Society of Cardiology guidelines for NSTEMI as an alternative to the standard approach.8 we aimed to develop an algorithm for accurate and rapid exclusion and diagnosis of AMI after 1 hour using a cutoff below the 99th percentile and compare it with the recommended 3-hour approach. 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) than with previous cTn assay generations which are still more commonly used in practice worldwide. hs-cTn is also more sensitive for the detection of myocardial damage unrelated to acute myocardial ischemia. Therefore, 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. As hs-cTn assays are increasingly being adopted in clinical practice and more hs-cTn assays are being developed, this review attempts to synthesize the available clinical data to make recommendations for their everyday clinical routine use.

INTRODUCTION

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 of cTn assays (coefficient of variation of < 10% at the 99th percentile upper reference limit). 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) than with previous cTn assay generations which are still more commonly used in practice worldwide. hs-cTn is also more sensitive for the detection of myocardial damage unrelated to acute myocardial ischemia. Therefore, 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. As hs-cTn assays are increasingly being adopted in clinical practice and more hs-cTn assays are being developed, this review attempts to synthesize the available clinical data to make recommendations for their everyday clinical routine use. 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 [1,2]. Recommendations for the use of cTn measurement in acute cardiac care[1] and practical clinical considerations in the interpretation of cTn elevations[2] 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, has been introduced into routine clinical practice [3]. 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 [3-6]. It is also important to

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note because of discrepancies in routine use[7,8], 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[7].

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 [8]. 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. 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[1,2]. Recommendations for the use of cTn measurement in acute cardiac care[1] and practical clinical considerations in the interpretation of cTn elevations[2] 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, has been introduced into routine clinical practice [3]. 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 [3-6]. It is also important to note because of discrepancies in routine use[7,8], 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[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 [8]. 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.

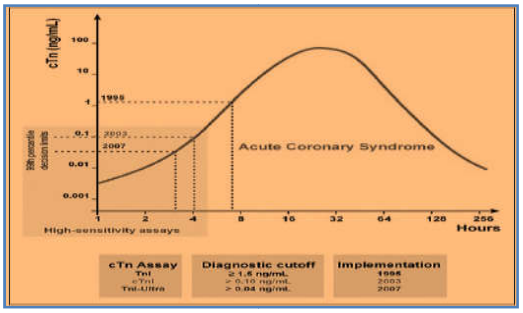
METHODS

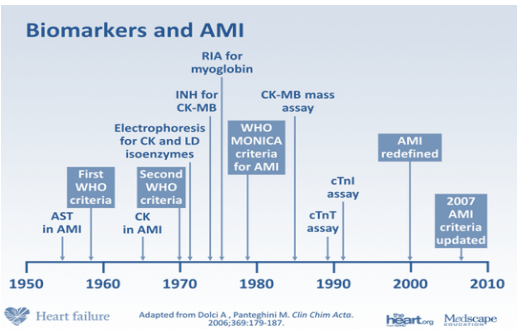
Study Overview

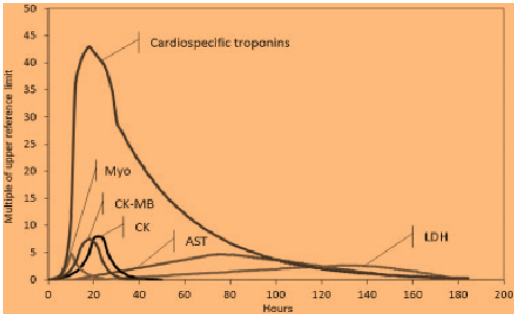
The present study investigates the application of a high-sensitivity troponin I assay in 3 cohorts of patients with acute chest pain. We aimed to identify an optimal cutoff using troponin I levels for diagnosing NSTEMI in a cohort of 1040 patients with acute chest pain suggestive of AMI (the Biomarkers in Acute Cardiac Care [BACC] cohort).[9] With this cutoff, we identified or excluded AMI in patients with acute chest pain. We tested a 1-hour vs. a 3-hour algorithm and compared the diagnostic accuracy of the calculated lower cutoff vs. the 99th percentile and evaluated follow-up mortality. We then validated this lower troponin cutoff level in an independent 2-Hour study. Accelerated Diagnostic Protocol to assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker trial (ADAPT)[10] and Advantageous Predictors of Acute Coronary Syndrome Evaluation Study (APACE)[11] with 1748 and 2261 patients, respectively. The current analysis was prespecified in the BACC study protocol. The study complied with the Declaration of Helsinki,[12] and the ethics committee of the University Medical Center Hamburg-Eppendorf approved the study protocol. All patients provided written informed consent.

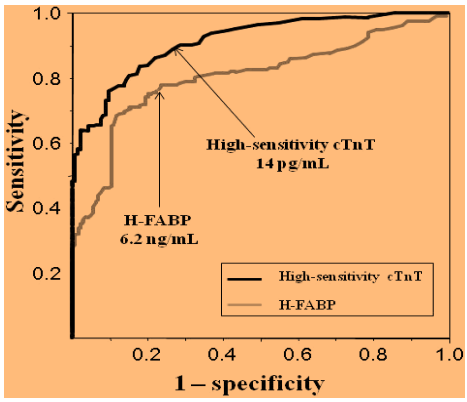
Early Diagnosis of Mi

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 [3,5]. 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 [6]. 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.** 99th 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 [1, 6]. However, guidelines recommend the use of the URL as a medical decision limit even when it cannot be measured with a CV of < 10% [1, 7]. Thus early sensitivities must be compared by using the 99th percentile URL as a medical decision limit for standard

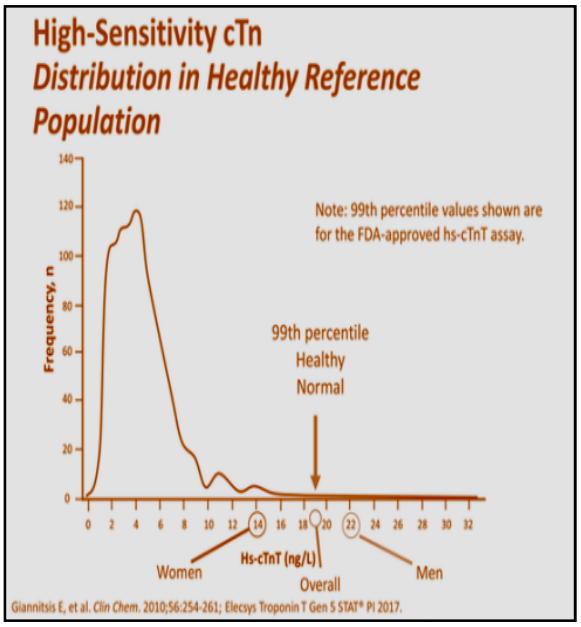


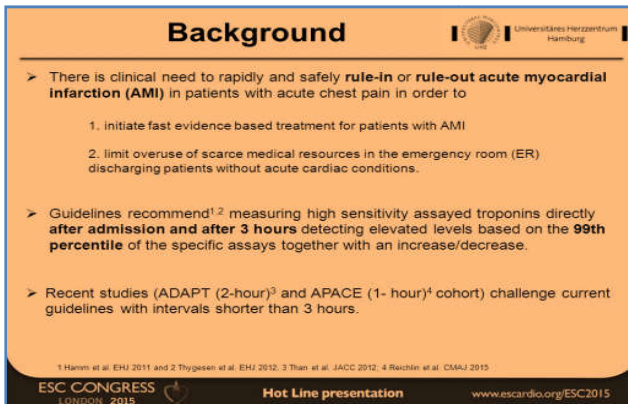






High Sensitivity Assay





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 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 all these reasons, the pooling of study data from the literature is currently problematic.

Timing of hs-cTn measurements in serial testing

According to the recent 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 [1, 9]. 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 [2, 5]. 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.

Role of cardiac biomarkers in patients with nondiagnostic ECGs

Cardiac biomarkers are crucial to establish the diagnosis of ACS, especially in patients with nondiagnostic findings on ECG.[12] Cardiac biomarkers used include creatinine kinase, myoglobin, cardiac troponin (cTn), brain natriuretic peptide, lactate dehydrogenase, aspartate aminotransferases, and heart fatty acid binding protein.[13] Cardiac troponin: Cardiac troponins T and I (cTnT and cTnI) are the most sensitive and cardiac specific biomarkers currently available to diagnose non-STACS,[10,11] owing to the tissue-specific expression of cTnT and cTnI in the myocardium.[14] However, in patients with chronic renal failure, cTnI has greater specificity for myocardial injury than cTnT[5]. A diagnosis of AMI is based on the detection of a rise and/or fall of cTn along with the presence of characteristic symptoms, and/or ECG or imaging evidence of acute myocardial ischemia.[13,6] The cut-off value of cTn to diagnose MI is defined as a concentration exceeding the 99th percentile of a normal reference population (i.e. upper reference limit [URL]) using an assay with an imprecision (coefficient of variation, CV) ≤10% at the URL.[11] However, the contemporary cTn assays cannot measure cTn levels at low concentrations corresponding to the 99th percentile value of a normal reference population.[1,7] Thus, they lack the precision criteria to diagnose AMI. Consequently, the high-sensitivity cardiac troponin (hs-cTn) assays were developed to meet the requirements of analytical precision and overcome the shortcomings associated with contemporary cTn assays.[1, 8]

Entry of high-sensitive cardiac troponin has changed the landscape of NSTEMI

According to the International Federation of Clinical Chemistry (IFCC) Task Force Recommendation on Analytical Characteristics, an assay is considered high sensitive if the total imprecision (i.e. CV) at the 99th percentile value is ≤10%, and measurable concentrations below the 99th percentile can be attained at a concentration value above the

assay's limit of detection (LOD) in at least 50% (and ideally >95%) of healthy individuals.[9] The hs-cTn assays are capable of measuring cTn in single digit ranges of nanograms per liter; some research assays facilitate detection of cTn at concentrations even lower than 1 ng/L. Thus, with the use of hs-cTn assays, the 99th percentile of cTn levels can be calculated more precisely in the reference population, which is the recommended URL. Additionally, the hs-cTn assays measure the URL with a CV of <10%. Small differences in cTn levels over time can be detected more easily due to the high precision of hs-cTn assays.[2]

In a recent publication by Love *et al*. the two high-sensitivity assays are discussed, one by Abbott Diagnostics and the other by Roche Diagnostics, an overview of which is presented in Table 1.[21] The hs-cTn assays are advantageous when compared with contemporary cTn assays in that they are associated with increased sensitivity, higher diagnostic accuracy for early diagnosis. Several hs-cTn assays with different values for the 99th percentile URL as defined by the manufacturer are currently available in the market.[22] According to the manufacturer's specifications, the Abbott ARCHITECT STAT hs-cTnI assay can detect troponin I in 96% of the reference population and has a turnaround time (TAT) of 16 min.[3] The Roche Elecsys high-sensitive troponin T assay can detect troponin T in 25% of the reference population and has an estimated TAT of 18 min.[2, 3] It is also available as a STAT version, which has a short TAT of 9 min. Since the 99th percentile value and the rate of detection of cardiac troponin in reference population differ for each assay, the name of the test kit or the assay instrument used should be mentioned as assay references.

A single high-sensitivity cardiac troponin

T (hs-cTnT) test with findings below the level of detection, teamed with a nonischemic electrocardiogram (ECG), can identify patients with chest pain in the emergency department (ED) who are at sufficiently low risk for acute myocardial infarction (AMI) to be safely released to outpatient care, a new study has found. John W. Pickering, PhD, from the University of Otago in Christchurch, New Zealand, and colleagues, report the findings of their meta-analysis online April 17 in Annals of Internal Medicine.

A second repeat after 2 to 3 hours

The researchers and an independent commentator caution that after symptom onset a second test becomes imparative. "Because troponin may not be detectable in the circulation immediately after myocardial injury, some patients with AMI who present very early after onset of pain may not have detectable troponin," the researchers explain.

"For this reason, guidelines recommend a second sample approximately 3 hours after symptom onset in these patients. We observed that 50% of patients with false-negative results had blood sampling within 3 hours of symptom onset and therefore recommend a cautious approach to implementation to exclude patients presenting soon after symptom onset. Data are currently insufficient to establish a minimum safe duration below 3 hours," the authors write. A previous study of the use of hs-cTnT to rule out AMI concluded that only 0.2% of 14,636 patients sustain an AMI within 30 days of discharge after a determination of low risk with hs-cTnT and ECG. However, the data were collected from just one urban university hospital. Other studies have considered patients from EDs that use different cutoffs and sometimes measured troponin I as well as troponin T. To re-evaluate the relationship between use of hs-cTnT and ECG to identify ED patients at low risk for AMI within 30 days, the new meta-analysis included 11 geographically diverse cohorts (from France, England, Germany, the Netherlands, Spain, Italy, Switzerland, New Zealand, and Australia) that used a level of detection less than 0.005 µg/L on the Roche Diagnostics hs-cTnT assay. The researchers searched MEDLINE and EMBASE for prospective studies published in peer-reviewed journals from 2008 to 2016 that followed evaluation of acute coronary syndrome in the ED using ECG and hs-cTnT. The two tests establish the primary endpoint of biochemical evidence of myocardial damage (hs-cTnT) and clinical evidence of ischemia (ECG). Secondary endpoints were death and major adverse cardiac events (cardiac arrest, AMI, cardiogenic shock, emergency revascularization procedure, ventricular arrhythmia, or high-degree atrioventricular block requiring intervention) within 30 days. The 11 studies included 9241 patients, ranging from 166 to 2831 at individual institutions. Of the patients, 15.4% actually had an AMI. Use of the two tests showed that on average 30.6% of patients were at low risk for AMI, although this figure ranged from 3.8% to 73.5%.

The pooled estimate of sensitivity was 98.7% (95% confidence interval [CI], 96.6% - 99.5%), and sensitivities of the cohorts ranged from 87.5% to 100% (**P** < .001).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 [1, 8]. 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 [2]. 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 [2]. The precision necessary to implement this approach is not present within the reference range for hs-cTn assays either [11]. In addition, biological variation needs to be considered. Changes of hs-cTn measurements near the 99th percentile URL must exceed conjoint 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 [11], although one report has values as high as 86% [2, 5]. Data on short- and long-term variation of hs-cTn concentrations in clinically stable patients with chronic cardiac diseases are very limited [2, 6], 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 [5]. However, AMI diagnosis in this study was based on clinical criteria and an increase in a conventional local cTnI assay > 99th percentile URL with a > 20% change over a 6 h period. As expected, higher cTnI sensitivities were found at lower percentage changes.

CONCLUSION

The application of a 1-hour algorithm with a troponin I cutoff level of 6 ng/L in patients with suspected AMI allows for accurate and rapid exclusion and identification of AMI. The 1- and 3-hour approaches yielded results that was not statistically different, whereas the 1-hour approach would allow faster diagnosis or discharge. A low cutoff performed significantly better than the 99th percentile as cutoff in view of follow-up mortality

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