REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Present and Future of Cardiac Troponin in Clinical Practice: A Paradigm Shift to High-Sensitivity Assays

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ABSTRACT

Despite its wide utilization and central role in the evaluation of patients with potential ischemic symptoms, misconceptions and confusion about cardiac troponin (cTn) prevail. The implementation of high-sensitivity (hs) cTn assays in clinical practice has multiple potential advantages provided there is an education process tied to the introduction of these assays that emphasizes the appropriate utilization of the test. Several diagnostic strategies have been explored with hs-cTn assays, including the use of undetectable values, accelerated serial hs-cTn sampling, hs-cTn measurements in combination with a clinical-risk score, and the use of a single hs-cTn measurement with a concentration threshold tailored to meet a clinical need. In this document we discuss basic concepts that should facilitate the integration of hs-cTn assays into clinical care in years to come.

 • *The American Journal of Medicine (2016) 129, 354-365*

KEYWORDS: Acute myocardial infarction; High-sensitivity cardiac troponin; Troponin

Cardiac troponin (cTn) plays a central role in the evaluation of patients with potential ischemic symptoms.[1] In the US, contemporary cTn assays that measure normal values below the 99th percentile in <50% of a reference population are predominately used in clinical practice.[2] Contemporary cTn assays require prolonged serial sampling to achieve optimal diagnostic accuracy to rule in and rule out acute myocardial infarction, contributing to overcrowding in the emergency department, unnecessary admissions, and cost.[3-5] Most contemporary cTn assays don't have optimal imprecision at clinical-practice guideline cut points (ie, coefficient of variation [CV] ≤10% at the 99th percentile) for the diagnosis of acute myocardial infarction.[6] This is clinically relevant as better imprecision facilitates detection of changing values, particularly at low cTn concentrations.[1,6]

These limitations have led to the development and validation of high-sensitivity cTn (hs-cTn) assays, which have been used for several years in most developed countries.[6-8] The 2015 European Society of Cardiology (ESC) guidelines provide a class I recommendation for both a 0-h/1-h rapid-rule out and rule-in protocol and a 0-h/3-h rapid rule-out sampling protocol.[8] Conversely, the US Food and Drug Administration (FDA) has not yet cleared hs-cTn assays for clinical use (hopefully in 2016).[9] Despite numerous studies describing and validating the use of high-sensitivity assays and being clinically used worldwide outside the US, misconceptions prevail. What specifically constitutes an hs-cTn assay and its potential advantages and disadvantages still confuses clinicians. Pending approval in the US, it is

Funding: None.

Conflict of Interest: YS: nonsalaried Advisor, Roche Clinical Diagnostics; nonfinancial support for Roche scientific meeting. SWS: Consultant: Alere; Advisor: Roche Clinical Diagnostics. FSA: Consultant, Phillips Health Incubator; Honorarium, Abbott Diagnostics and Beckman (Speaker at national meeting); Research through Minneapolis Medical Research Foundation (MMRF), not salaried: Abbott Diagnostics, Roche Diagnostics, Siemens Healthcare, Alere, Ortho-Clinical Diagnostics, Trinity, Nanomix, Becton Dickinson. Other: Associate Editor, *Clinical Chemistry*.

Authorship: All of the authors have contributed to the conception, design, analysis, interpretation, writing, critical revision, and final approval of this manuscript.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2015.12.005

very important for clinicians to better understand the available evidence regarding high-sensitivity assays. This document addresses basic concepts that should facilitate the integration of hs-cTn assays into clinical care.

UNDERSTANDING CARDIAC TROPONIN ASSAYS: ANALYTICAL CHARACTERISTICS

As with any diagnostic test that is frequently used in clinical decision-making, one should be familiar with its basic characteristics. For practical purposes, clinicians should be familiar with the following characteristics.

Limit of Blank and Limit of Detection

Limit of blank (LoB) and limit of detection (LoD) are analytical parameters used to describe the smallest concentrations of cTn that can be reliably measured.[10] Understanding these terms is related to the emerging clinical evidence suggesting that at "undetectable levels" (concentrations less than either LoB or LoD), clinicians can potentially safely rule out acute myocardial infarction earlier, using a single cTn, based on a very high negative predictive value (NPV).[11] The LoB is the highest apparent cTn concentration measurement expected when replicates of a sample containing no cTn is tested (often not clinically reportable).[10] LoD, a concentration greater than the LoB, is the lowest detectable cTn concentration reliably distinguished from the LoB in a sample containing a low cTn concentration.[10] Clinicians at minimum need to be acquainted with these terms. In the US, laboratories do not report values at these concentrations because currently available contemporary cTn assays have poor imprecision, and the FDA does not allow manufacturers to report cTn assay results at concentrations less than the lowest concentration that has a %CV of >20% (defined as the limit of quantitation).

The 99th Percentile Value of Cardiac Troponin

The 99th percentile upper-reference limit (URL) corresponds to the clinical-practice guideline cut point for the diagnosis of acute myocardial infarction.[1,8,12] This URL is derived from apparently normal individuals enrolled in studies by manufacturers or investigators.[13] For hs-cTn assays, the International Federation of Clinical Chemistry Task Force on Clinical Applications of Cardiac Biomarkers has proposed recommendations for determining 99th percentiles.[14]

Sex is an important factor influencing the 99th percentile, and sex-specific 99th percentiles will need to be reported for clinical use when using high sensitivity assays.[13] The use of a single diagnostic cTn threshold contributes to the underdiagnosis of acute myocardial infarction in women, whereas with sex-specific cutoffs, the proportion of men and women with the diagnosis of acute myocardial infarction is similar.[15] For high-sensitivity assays, cTn results will also be reported in whole numbers in nanograms per liter (ng/L) to distinguish them from contemporary assays.[6,13]

While globally endorsed, the 99th percentile URL is still not uniformly employed. For example, in the ISCHEMIA trial, only one-third of their laboratories used this cut point,[16] potentially compromising the diagnosis of acute myocardial infarction in clinical practice, as well as the adjudication of acute myocardial infarction endpoints in clinical trials.

CLINICAL SIGNIFICANCE

- Understanding analytical cardiac troponin (cTn) concepts is critical to interpreting emerging diagnostic strategies using high-sensitivity assays.
- High-sensitivity (hs)-cTn assays measure cTn above the limit of detection in ≥50% of normal individuals, with ≤10% coefficient of variation at the 99th percentile.
- cTn assays have unique 99th percentiles and deltas.
- Improved imprecision allows use of rapid rule-out/in protocols based on 0-hour and 1—3-hour intervals.
- Low hs-cTn concentrations may expedite the exclusion of acute myocardial infarction.

Total Imprecision—coefficient of Variation (%CV) at the 99th Percentile

The imprecision of cTn assays is defined by the %CV at the 99th percentile, and should ideally be ≤10%.[1] Each laboratory result is associated with analytical variation, which can be calculated by repeatedly measuring one sample and calculating the analytical %CV from the mean and standard deviation.[17] cTn assays have been deemed "guideline acceptable" if they have a %CV of ≤10% at the 99th percentile; "clinically usable" if the %CV is >10% to ≤20%; and "not acceptable" if the %CV is >20%.[1,2] High-sensitivity assays have less analytical noise and meet clinical-practice guideline precision recommendations (% CV ≤10% at the 99th percentile), whereas most contemporary cTn assays have a %CV between 10% and 20%.[6] Using hs-cTn assays decreases analytical noise, allowing reporting of real cTn increases above the 99th percentile indicative of myocardial injury, rather than increased cTn results due to analytical variation, hence improving diagnostic accuracy.[18]

WHAT IS A HIGH-SENSITIVITY CARDIAC TROPONIN ASSAY?

An assay is denoted as high-sensitivity if it measures cTn above the LoD in ≥50% of a reference population and has a %CV of ≤10% at the 99th percentile[6,14] (**Table 1**). In