

Incorporating high-sensitivity cardiac troponin assays into clinical practice: these assays are your friend

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Abstract

The objective of this review is to provide an overview of the current analytical, clinical, and risk assessment status of cardiac troponin (cTn) high-sensitivity (hs) assays and on how to better understand their use in clinical practice. The introduction of hs-cTnI and hs-cTnT assays into clinical practice has enabled improved diagnostic accuracy using serial changes. However, there remains substantial investigative work to be done before coherent evidence-based guidelines can be established for the full spectrum of available assays. Not all cTn assays, I or T, are alike, whether contemporary sensitive or high-sensitivity. Each assay and each platform on which cTn is measured requires development of its own evidence-based delta criteria in order to support optimal use for patients presenting with symptoms suggestive of ischemia. The growth in utilization of hs-cTn assays will both improve diagnostics for early rule in and early rule out of patients presenting with symptoms suggestive of acute coronary syndrome (ACS). As for patients with non-ACS presentation and for primary and or secondary prevention for risk assessment, future therapeutic studies will best define the power of hs-cTn assays and their role in clinical practice. However, what we do know is that an increased cTn concentration indicates a poor outcome and need for increased clinical vigilance. ■ *Heart Metab.* 2015;67:9-14

Keywords: biomarkers; cardiac troponin; diagnostic accuracy; high-sensitivity assays; myocardial infarction; outcomes

The objective of this review is to provide an overview of the current analytical, clinical, and risk assessment outcomes status of high-sensitivity cardiac troponin (hs-cTn) assays from our review of the literature and on how to better understand their use in clinical practice.

Analytical performance

According to the 2012 Third Universal Definition of Myocardial Infarction, the preferred biomarker for detection of myocardial infarction (MI) is cardiac troponin (cTn).¹ Any discussion of the clinical utility of cTn must begin with a brief discussion of the analytical

Abbreviations

ACS: acute coronary syndrome; **cTn:** cardiac troponin; **cTnl:** cardiac troponin I; **cTnT:** cardiac troponin T; **hs-cTn:** high-sensitivity cardiac troponin; **hs-cTnl:** high-sensitivity cardiac troponin I; **hs-cTnT:** high-sensitivity cardiac troponin T; **LOD:** limit of detection; **MI:** myocardial infarction; **URL:** upper reference limit

aspects of contemporary and hs-cTn assays, which are not standardized. This means that no two assays should be expected to provide equivalent concentration measurements from the same sample. This also means that laboratories should not interchange assays in clinical practice, as this will lead to clinical confusion. Readers interested in a more in-depth de-

scription of cTn biochemistry are directed to a detailed review by the International Federation of Clinical Chemistry (IFCC) Task Force on Clinical Applications of Cardiac Biomarkers.² Based on the biochemistry of cTn, there is considerable complexity regarding standardization of cTn assays, arising from the many forms of circulating cTn in blood released from injured myocardial tissue, the heterogeneity of antibodies used in assays to detect different circulating cTn epitopes (*Table 1*), as well as the lack of an acceptable primary reference material to uniformly calibrate all assays.²⁻⁴ Current recommendations endorse the use of two criteria for assay precision that earn the designation of “high sensitivity”: (i) a coefficient of variation (%CV) $\leq 10\%$ at the 99th percentile upper reference limit (URL); and (ii) the ability to measure cTn in $\geq 50\%$

Company/platform/assay	LOD, $\mu\text{g/L}$	99th Percentile, $\mu\text{g/L}$	10% CV, $\mu\text{g/L}$	Epitopes recognized by capture (C) and detection (D) antibodies
Abbott AxSYM ADV	0.02	0.04	0.16	C: 87-91, 41-49; D: 24-40
Abbott ARCHITECT	0.009	0.028	0.032	C: 87-91, 24-40; D: 41-49
Abbott i-STAT	0.02	0.08	0.10	C: 41-49, 88-91; D: 28-39, 62-78
Alere Triage	0.05	<0.05	NA	C: NA; D: 27-40
Alere Triage Cardio3*	0.01	0.02	NA	C: 27-39; D: 83-93, 190-196
Beckman Access AccuTnl	0.01	0.04	0.06	C: 41-49; D: 24-40
bioMerieux Vidas Ultra	0.01	0.01	NA	NA
Mitsubishi Pathfast	0.008	0.029	NA	C: 41-49; D: 71-116, 163-209
Ortho Vitros ECi ES	0.012	0.034	0.034	C: 24-40, 41-49; D: 87-91
Radiometer AQT90 cTnl	0.009	0.023	0.039	C: 41-49, 190-196; D: 137-149
Radiometer AQT90 cTnT	0.01	<0.01	0.03	C: 125-131; D: 136-147
Response RAMP	0.03	<0.01	0.21	C: 85-92; D: 26-38
Roche E170/Elecsys 2010	0.01	<0.01	0.03	C: 125-131; D: 136-147
Siemens Centaur Ultra	0.006	0.04	0.03	C: 41-49, 87-91; D: 27-40
Siemens Dimension RxL	0.04	0.07	0.14	C: 27-32; D: 41-56
Siemens Immunlite 2500	0.1	0.2	0.42	C: 87-91; D: 27-40
Siemens Stratus CS	0.03	0.07	0.06	C: 27-32; D: 41-56
Siemens VISTA	0.015	0.045	0.04	C: 27-32; D: 41-56
Tosoh AIA II	0.06	<0.06	0.09	C: 41-49; D: 87-91
Trinity Meritas	0.012	0.019	0.024	C: 24-40, 88-90; D: 137-147, 190-196
hs-cTnl†		ng/L	ng/L	
Abbott ARCHITECT*	1.2	16 (5.6%)	3.0	C: 24-40; D: 41-49
Beckman Access	2-3	8.6 (10%)	8.6	C: 41-49; D: 24-40
Singulex Errena	0.09	10.1 (9.0%)	0.88	C: 41-49; D: 27-41
Siemens VISTA	0.5	9 (5.0%)	3.0	C: 30-35; D: 41-56, 171-190
hs-cTnT†				
Roche E170/Elecsys*	1.0	13 (8%)	12.0	C: 125-131; D: 136-147

Table 1 Analytical characteristics of contemporary sensitive, point-of-care, and high-sensitivity cardiac troponin assays. *Available for use outside the USA as it is not cleared by the Food and Drug Administration; †In parentheses, the % of coefficient of variation at the 99th percentile upper reference limit.

Abbreviations: CV, coefficient of variation; hs-cTnl, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; LOD, limit of detection; MTP, microtiter plate assay; NA, not available.

Modified from reference 2: Apple FS, Collinson PO. Clin Chem. 2011;58:54-61. © 2015 American Association for Clinical Chemistry.

of healthy reference subjects above an assay's limit of detection (LOD).² This allows high-sensitivity cardiac troponin I (hs-cTnI) and T (hs-cTnT) assays to measure biological variation within a healthy population, allowing reference change values to be calculated (approximately 50%), and providing the ability to distinguish real cTn changes from analytical noise within the reference range.

Reviewing the literature will uncover substantial discrepancies in assay analytical features between claimed assay performance in manufacturers' package inserts and peer-reviewed findings (*Table 1*).^{2,4-6} One example of the heterogeneous nature of cTn assays comes from a reference range study from Apple.³ They found distinctively different 99th percentile URLs for the majority of 19 contemporary, point of care, and high-sensitivity cTnI and cTnT assays while examining a common set of reference samples, even for multiple assays from the same manufacturer. Furthermore, gender and age influence the distribution of troponin concentrations for both the hs-cTnI^{3,6,7} and hs-cTnT^{3,8-10} assays.

As a biomarker of myocardial injury, with irreversible myocyte damage releasing cTn, increased cTn levels do not indicate the etiology of damage, which makes clinical context key to their use and interpretation. The lack of diagnostic specificity becomes more complicated with the use of cTn measurements in clinical evaluations that are not related to acute coronary syndrome (ACS).^{11,12} Current guidelines for the diagnosis of ACS recommend serial measurement of cTn, including the use of hs-cTn assays.^{1,5} Serial cTnI measurements (*Figure 1*) at presentation and over the following 2 to 3 hours for high-specificity assays or 6 hours for contemporary assays determines whether a rising or falling pattern above the URL is present,

which distinguishes acute from chronic sources of myocardial necrosis or structural disease. Split sample replicates, run on both contemporary and hs-cTnI assays, have shown that hs-cTnI assays lead to fewer single cTn concentrations above the URL by virtue of the decreased analytical noise of these assays.¹¹ Few false positive cTn values are observed with hs-cTn assays. However, hemolysis may falsely increase cTn measured with hs-cTn assays.¹³

To better understand the implications of each hs-cTn assay used in routine clinical practice, the following general points will assist clinicians. First, cTn results are not interchangeable, even for assays from a single manufacturer. Second, know what the 99th percentile URL is for the hs-cTn assay in use in your practice. At present, there is one hs-cTnI assay (Abbott Diagnostics) and one hs-cTnT assay (Roche Diagnostics) in clinical practice that meet the criteria outlined above.² Third, follow at least 2 serial measurements over time. Look for an increasing or falling pattern, with at least one value above the 99th percentile URL to determine myocardial injury. Fourth, as high-sensitivity assays detect a larger number of non-ACS pathologies with concomitant myocardial injury, a single cTn value measured by a high-sensitivity assay will have a clinical specificity for MI as low as 65% to 75%. These are truly positive results, just not an indicator of MI. A delta value, the absolute concentration difference between two serial hs-cTn values, will assist in improving diagnostic specificity for MI to >90% with high-sensitivity assays.^{10,14,15} Fifth, hs-cTn assays have concentration units expressed in whole numbers, ie, 10 ng/L, compared with contemporary assays that use $\mu\text{g/L}$, ie, 0.010 $\mu\text{g/L}$.²

Clinical diagnostics

Reaching a diagnosis of acute MI is facilitated by the use of cTn assays with optimal precision that are able to reliably detect changing values over time.^{1,5,10} Herein lies the clinical value of hs-cTn assays, which are characterized by guideline-acceptable precision.^{2,16} hs-cTn assays are appealing due to their ability to rule in or rule out acute MI more rapidly, shifting testing from a 6-hour window for contemporary assays to a 2- to 3-hour window for high-sensitivity assays.^{14,15,17} *Figure 1* displays the serial concentration differences found between contemporary and hs-cTn assays during the early course of an acute MI. Using a hs-

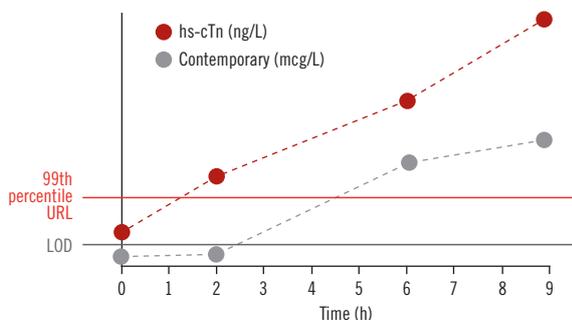


Fig. 1 Serial concentration differences found between contemporary and high-sensitivity cardiac troponin (hs-cTn) assays during the early course of an acute myocardial infarction.

Abbreviations: h, hour; LOD, limit of detection; URL, upper reference limit.

cTnI assay, Keller demonstrated in a European study that by combining the 99th percentile URL at admission with the serial change in hs-cTnI concentrations within 3 hours, the positive predictive value (rule in MI) increased from 75.1% at admission to 95.8% after 3 hours.¹⁴ By applying the 99th percentile to a second hs-cTnI measurement, ruling out MI at 3 hours was shown to have a negative predictive value of 99.4%. Similarly using the hs-cTnT assay, Reichlin demonstrated the clinical utility of absolute and relative hs-cTnT changes in the early diagnosis of acute MI.¹⁷ They showed that the sensitivity obtained by absolute changes in hs-cTnT according to baseline levels (≥ 14 ng/L) at 2 hours was 90%, whereas the positive and negative predictive value were 76% (at 0 h [baseline]) and 95% (at 2 h) respectively.

The role of hs-cTn assays in reducing unnecessary hospital admissions and potentially reducing costs by excluding acute MI has been studied (utilizing values below the 99th percentile). Using a cutoff of 3 ng/L limit of blank for a hs-cTnT assay, Body et al demonstrated a sensitivity and negative predictive value of 100%, including those with a symptom onset of less than 3 hours.¹⁸ Bandstein further reported a negative predictive value for MI within 30 days of 99.8% among patients with hs-cTnT assay values < 5 ng/L (LOD) and nonischemic electrocardiograms.¹⁹

From a diagnostic perspective, the conceivable advantages of using hs-cTn assays over contemporary cTn assays rely primarily on the possibility of improving our ability to rule in MI sooner; improved analytical precision at lower cTn concentrations allows clinicians to reliably follow serial concentration changes over time. *Figure 2* demonstrates how the improved precision at the 99th percentile using a hs-cTnI assay can decrease false positive MI diagnoses that occur with the use of the less precise contemporary cTn assays.¹¹ Cullen, using a protocol combining the TIMI (Thrombolysis In Myocardial Infarction) risk score, electrocardiography, and 0- and 2-hour hs-cTnI measurements, has also demonstrated the potential to decrease observation periods and admissions for approximately 40% of patients with suspected ACS.²⁰

However, there are several challenges that clinicians may encounter with the implementation of hs-cTn assays. First, hs-cTn assays identify a higher number of results above the 99th percentile URL. Reichlin compared contemporary and hs-cTnT assays at presentation and demonstrated 22% versus

36% had increased concentrations above the 99th percentiles, respectively.²¹ Second, using the hs-cTnT assay resulted in an increased incidence of acute MI (from 198 with contemporary assay to 242 with hs-cTnT assay); due to 44 additional non-ST elevation MIs (35 type 1 MIs, 9 type 2 MIs). These findings coincided with a decrease in the incidence of unstable angina; from 151 to 122 cases, respectively. Third, the higher frequency of cTn increases encountered using hs-cTn assays identifies a larger subset of patients having myocardial injury. Myocardial injury may be: (i) primary myocardial ischemia (eg, plaque rupture); (ii) a supply/demand imbalance of myocardial ischemia (eg, arrhythmia); (iii) unrelated to myocardial ischemia (eg, cardiac contusion, myocarditis, etc); or (iv) linked to multifactorial/indeterminate causes (eg, renal failure, sepsis in critically ill patients, heart failure, etc).¹ Consequently, clinicians will be frequently faced with the challenge of deciding whether increased values are due to acute or chronic conditions, and if acute, whether increases are due to type 1 MI, type 2 MI, or an alternate non-MI condition that has increased hs-cTn (*Table II*).^{1,22,23} Discerning these conditions is a challenge in itself and is of major importance due to the distinct therapeutic approaches required, particularly in type 1 MI.

Fourth, the challenge of how to assess and incorporate serial hs-cTn changes, or deltas, into clinical practice will be important to differentiate acute from chronic/static myocardial injury. Gaps exist as to how studies should be carried out to define delta changes to diagnose or exclude acute MI. Deltas will need to be individualized by hs-cTn assay because of their

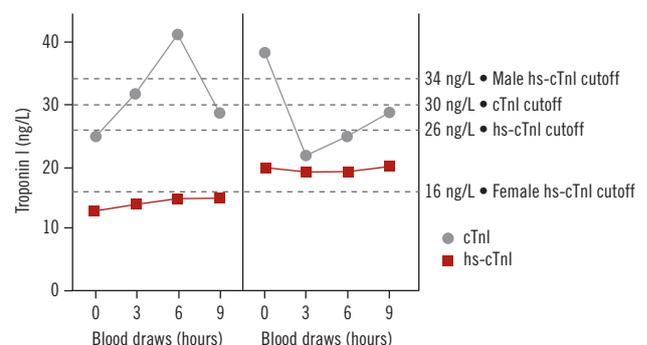


Fig. 2 Improved precision of a high-sensitivity cardiac troponin I (hs-cTnI) assay decreases false positive diagnoses of myocardial infarction compared with a less precise contemporary cardiac troponin I (cTnI) assay.

From reference 11: Sandoval Y et al. Clin Chem. 2015;61:657-663. Reproduced with permission from the American Association for Clinical Chemistry.

unique analytical and biological characteristics due to the lack of assay standardization. Early evidence points toward establishing an absolute concentration delta over a 2-hour period after presentation. It is important to acknowledge that each individual cTn assay will require a specific delta determination for both absolute and percent delta changes. A convenient approach to the delta value, such as the 20% relative change proposed by the National Academy of Clinical Collaboration (NACB) laboratory medicine practice guidelines in 2007, should be abandoned, as it does not perform as well as a delta optimized for the individual assay.²⁴ The primary aim of using a delta criterion has been to provide improved clinical specificity compared with a single determination using the 99th percentile URL, not to improve sensitivity.

Risk stratification and outcomes assessment

Both hs-cTnI and hs-cTnT assays have been shown to: (i) risk-stratify symptomatic and stable ACS pa-

tients in both the short term (admission) and the long term (over 6 months), for major adverse cardiac events; (ii) identify nonischemic (non-ACS) pathologies that cause myocardial injury (*Table II*) and demonstrate that patients with them are at higher risk of adverse outcomes compared with ACS patients; and (iii) predict cardiovascular mortality in the ambulatory community or multiethnic populations with or without known coronary artery disease, in whom increased hs-cTn values are associated with structural heart disease and chronic kidney disease.²⁵⁻³⁰ What distinguishes hs-cTn assays from contemporary assays is their ability to precisely measure very low cTnI and cTnT concentrations (1-20 ng/L), which is below the LOD of contemporary assays used in clinical practice today.² This added analytical sensitivity allows hs-cTn assays to reliably measure concentrations in almost 100% of healthy individuals, compared with contemporary assays that measure values in only <20% of healthy individuals. Future studies will be necessary to define the role of hs-cTn assays in screening apparently healthy individuals to estimate their risk of future events, and how potential interventions may influence their outcomes.

<p>Injury related to primary myocardial ischemia Atherosclerotic plaque rupture Intraluminal coronary artery thrombus formation</p>
<p>Injury related to supply/demand imbalance of myocardial ischemia Tachy- or bradyarrhythmias Aortic dissection or severe aortic valve disease Hypertrophic cardiomyopathy Cardiogenic, hypovolemic, or septic shock Severe respiratory failure Severe anemia Hypertension with or without LVH Coronary spasm Coronary embolism or vasculitis Coronary endothelial dysfunction without significant CAD</p>
<p>Injury not related to myocardial ischemia Cardiac contusion, surgery, ablation, pacing, or defibrillator shocks Rhabdomyolysis with cardiac involvement Myocarditis Cardiotoxic agents, eg, anthracyclines, herceptin</p>
<p>Multifactorial or indeterminate myocardial injury Heart failure Stress (takotsubo) cardiomyopathy Severe pulmonary embolism or pulmonary hypertension Sepsis and critically ill patients Renal failure Severe acute neurological diseases, eg, stroke, subarachnoid hemorrhage Infiltrative diseases, eg, amyloidosis, sarcoidosis Strenuous exercise</p>

Table II Pathological etiologies that cause cardiac troponin to increase above the 99th percentile upper reference limit.

From reference 1: Thygesen K et al. Eur Heart J. 2012;20:2551-2567. © 2012, The European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, Inc, and the World Heart Federation.

Abbreviations: CAD, coronary artery disease; LVH, left ventricular hypertrophy.

Conclusion

The introduction of hs-cTnI and hs-cTnT assays into clinical practice has enabled improved diagnostic accuracy using serial changes. However, there remains substantial investigative work to be done before coherent evidence-based guidelines can be established for the full spectrum of available assays.³¹ Not all cTn assays, T or I, are alike, whether conventional or high-sensitivity. Each assay and each platform on which cTn is measured requires development of its own evidence-based delta criteria in order to support optimal use for patients presenting with symptoms suggestive of ischemia.^{1,32} The growth in utilization of hs-cTn assays will improve diagnostics for early rule in and early rule out of patients presenting with symptoms suggestive of ACS. As for patients with non-ACS presentation and for primary and/or secondary prevention for risk assessment, future therapeutic studies will best define the power of hs-cTn assays and their role in clinical practice. However, what we do know is that an increased cTn concentration points toward a poor outcome and need for appropriate management. ■

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