

A New Paradigm for Acute Coronary Syndrome: High Sensitive Troponin

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Key Messages

1. High sensitive troponin (hsTn) methods have excellent precision (10% CV concentration lower than the 99th percentile URL) and can detect more than 50% of a seemingly healthy population above the Limit of Detection (LoD).
2. ARCHITECT *STAT* High Sensitive Troponin-I (hsTnI) assay meets the expectations of a high sensitive (hs) method and is the first CE marked hsTnI assay to be commercially available.¹⁻⁴
3. Females have lower 99th percentile values than men. Gender-specific 99th percentile values are recommended for the ARCHITECT *STAT* High Sensitive Troponin-I (hsTnI) assay for improved discriminatory capability in women with suspected Acute Coronary Syndrome (ACS).
4. Delta algorithms in accordance to the site expectations for the diagnosis of Acute Coronary Syndrome (ACS) should be utilized to assess the clinical significance pertaining to the rise and fall of serial measurements.
5. The units for the hsTn assays should be reported in pg/mL (ng/L).
6. Any measurement of cardiac troponin, whether low or high, carries prognostic significance. Higher troponin concentrations are associated with higher risk for Major Adverse Cardiac Events (MACE) as well as All-Cause Mortality (ACM).
7. Troponin is specific to the heart, not the disease etiology. Therefore, interpretation of Troponin concentrations should always be performed within the clinical context of all supporting parameters, including the physical exam, symptoms, ECG, as well as patient and family history.

Abstract

We are entering a new era for cardiac troponin with the launch of high sensitivity troponin (hsTn) assays. Evidence supporting the use of hsTn assays for patients presenting to the emergency department (ED) with suspected acute coronary syndrome offers vast opportunities for improved overall management of these patients. Moreover, it is expected that high sensitive troponin (hsTn assays) will become the standard of care for cardiac biomarker testing in the acute setting, and potentially also in primary care.

Implementation of hsTn assays, however, should be met with tempered enthusiasm. Enthusiasm because the features of these new assays permit opportunities that were never before possible with the previous generation of assays. Tempered because successful implementation into routine use is far more complex than a mere appreciation for precision improvements relative to the contemporary or conventional methods that are still in use today.

This white paper will outline the attributes of high sensitivity assays, describe how the Abbott ARCHITECT *STAT* hsTnI differs clinically and analytically from the on-market contemporary assay and review important clinical considerations that are necessary to understand prior to routine use.

Definitions and Acronyms

ACM: All-Cause Mortality.

Acute Coronary Syndrome (ACS): The term Acute Coronary Syndrome (ACS) is applied to patients in whom there is a suspicion of myocardial ischemia. There are three types of ACS: ST Elevation MI (STEMI), Non-ST Elevation MI (NSTEMI), and Unstable Angina (UA). The first two are characterized by a typical rise and/or fall in biomarkers of myocyte injury.^{5, 6}

AMI: Acute Myocardial Infarction.

MACE: Major Adverse Cardiac Events.

TIMI for unstable angina: The TIMI (Thrombolysis in Myocardial Infarction) Risk Score is used to categorize the risk of death and ischemic events in patients experiencing unstable angina or a non-ST elevation myocardial infarction. It is used as a basis for therapeutic decision making.⁷

What is a “High Sensitive Troponin” Assay?

Part of the confusion of what is classified as a high sensitive (hs) assay is that there is no universal definition of the term. Making matters more complicated, adjectives have been used in product names (i.e., “ultra-sensitive”), suggesting performance advantages over contemporary methods, despite falling short of the evolving expectations that are now designated as high sensitivity.

The analytical attributes for the designation of a high sensitive assay by the International Federation of Clinical Chemistry (IFCC) Task Force on the Clinical Applications of Cardiac Biomarkers specify the following two criteria¹:

1. Total imprecision at the 99th percentile value should be less than or equal to 10% CV
2. An ability to detect at least 50% of seemingly healthy subjects with measureable values above the limit of detection (LoD)

The Abbott ARCHITECT *STAT* hsTnI assay achieves a 10% coefficient of variation (CV) at a concentration lower than the 99th percentile cutoff and can detect >50% of a seemingly healthy subjects with measureable values above its limit of detection. By meeting these criteria, the Abbott ARCHITECT *STAT* hsTnI assay is the first high sensitivity troponin-I assay to be commercially available^{1, 2, 3, 4}

What is the 99th percentile of the Abbott ARCHITECT STAT hsTnI assay?

There have been many studies that have evaluated the 99th percentile upper reference limit (URL) for the ARCHITECT STAT hsTnI assay.^{2, 8, 10} The study conducted by Abbott included over 1,500 subjects and involved matched specimen types to assess any potential performance differences between plasma (EDTA and Lithium Heparin) and serum. Biomarker exclusion criteria for natriuretic peptides, HbA1c and eGRF were used in accordance with expert opinion to rule out underlying disease confounders, such as left ventricular dysfunction, diabetes and renal disease.¹¹

Results summarized in Table 1 reveal overlapping confidence intervals among all three specimen types, demonstrating the ability to use common cutoffs regardless of specimen type. Results also demonstrate a clear gender relationship with females having lower troponin values than men. This trend has been consistent with other studies using this assay as well as other methods, suggesting improved discriminatory capability for high sensitive assays over contemporary methods which lack both the precision at low concentrations and the sensitivity to reliably appreciate comparable trending.^{2, 8-10}

Other variables, including age, more sophisticated coning strategies and sample size can have a significant role in the determination of the 99th percentile URL, and should therefore be taken into consideration when determining or verifying the 99th percentile URL for the population or institution.

Table 1: 99th Percentile Study By Specimen Type¹²

Specimen Type	Overall 99 th percentile (n, 90% CI)	Male 99 th percentile (n, 90% CI)	Female 99 th percentile (n, 90% CI)
Serum	22.3 pg/mL (ng/L) (1,529 / 18.5 - 25.9)	28.3 pg/mL (ng/L) (765 / 21.9, 34.5)	14.7 pg/mL (ng/L) (764 / 11.9 - 17.3)
EDTA	27.8 pg/mL (ng/L) (1,531 / 22.1 - 32.8)	35.1 pg/mL (ng/L) (766 / 26.5 - 44.4)	16.7 pg/mL (ng/L) (764 / 13.3 - 19.8)
LiHep	26.9 pg/mL (ng/L) (1,531 / 21.4 - 32.0)	34.5 pg/mL (ng/L) (766 / 25.7 - 43.3)	14.3 pg/mL (ng/L) (763 / 11.6 - 16.5)
Combined	26.6 pg/mL (ng/L) (4,593 / 23.3 - 29.7)	34.2 pg/mL (ng/L) (2,298 / 28.9 - 39.2)	15.6 pg/mL (ng/L) (2,292 / 13.8 - 17.5)

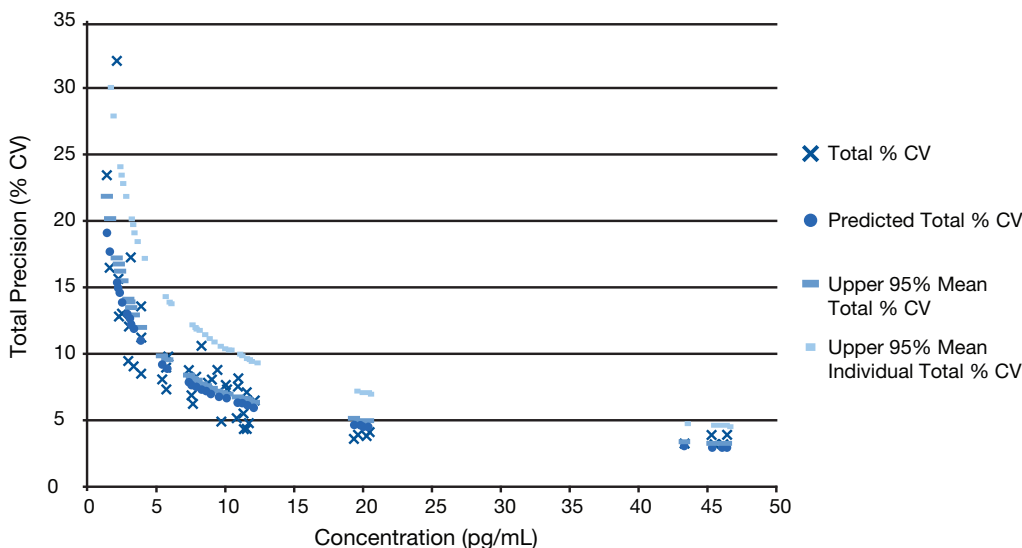
What is the 10% CV concentration of the Abbott ARCHITECT STAT hsTnI?

Calculations to determine a 10% CV concentration for any assay are not easy. This is because the relationship between the target concentrations and the reproducibility of the measurement (precision) is not linear and can be influenced by many variables (instrument, calibration, reagent lot to lot variability, etc.).

Nevertheless, the 10% CV concentration remains a critical parameter for the designation of high sensitivity and can offer confidence for users such that values above the estimated 10% CV concentration are accurate and precise.

The 10% CV concentration values for the ARCHITECT STAT hsTnI assay obtained in external evaluations have ranged from 3.9 to 6.0 pg/mL (ng/L).⁸⁻¹⁰ This data aligns well with the representative data from Abbott's internal testing depicted in Figure 1. The 10% CV concentration of ARCHITECT STAT hsTnI is 4.7 pg/mL (ng/L).¹¹

Figure 1: ARCHITECT STAT hsTnI Precision Profile¹²



Adapted from: Data on File at Abbott.

What percent of seemingly healthy subjects are identified by the ARCHITECT STAT hsTnI Assay above the LoD?

Not unlike the 99th percentile URL and 10% CV concentration values, there are many factors that impact the ability of an assay to measure high percentages of seemingly healthy subjects. For example, since females have lower troponin concentrations than men and younger people have lower troponin concentrations than the elderly, troponin assays are likely to detect fewer subjects in a seemingly healthy young female population than of elderly males. Nevertheless, an important distinction for the designation of a high sensitive assay, is the ability to detect more than 50% of a seemingly healthy population above the assay limit of detection (LoD).²

The LoD of an assay is an estimate of analytical noise. Thus, not unlike the 10% CV concentration, this value is subject to variation from many contributing variables. ARCHITECT STAT hsTnI Package Insert supports a range of 1.1 to 1.9 pg/mL (ng/L). This range has been supported with other external studies ranging from 1.0 to 1.2,^{9,10} although the highest LoD observed with this assay with an early R&D prototype was 3.4 ng/L (pg/mL).⁸

It is easy to appreciate that the LoD can have a substantial impact on the percent measured in a seemingly healthy population. However, in Table 2, all studies that have evaluated this metric irrespective of the corresponding LoD, support performance >50% with several studies suggesting discriminatory ability as high as 95-100%.

Table 2: Summary of Studies on Percent Normals Detected by Population

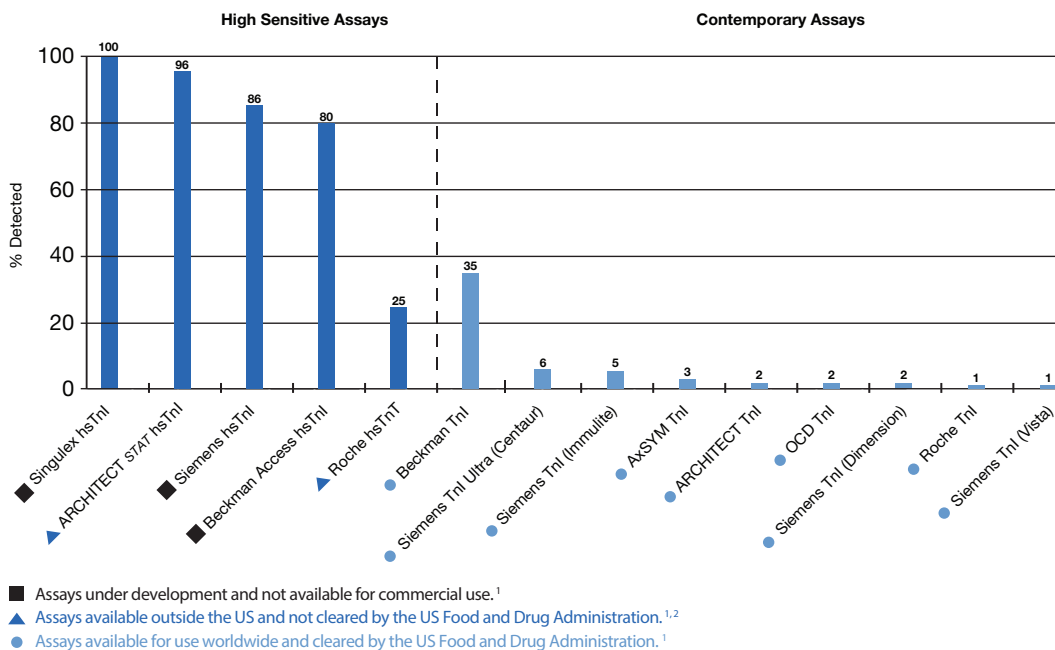
Population	% Normals Detected	Total n of Population	LoD
US ²	96%	524	1.2
Asia ⁹	92.3%	1,120	1.5
Australia ¹⁰	100%	497	1.0

How does the ARCHITECT STAT hsTnI assay compare against other Tn assays with respect to detection of cardio-healthy normals?

Since many factors contribute to an assay's ability to detect high percentages of a cardio-healthy population including the demographic characteristics of the cohort itself, the best method to compare assays would be using an identical cohort.

In a recent study (Figure 2) reporting 524 specimens across 19 different cardiac troponin assays (including both core laboratory and POC), the ARCHITECT STAT hsTnI assay detected 96% of normals – the highest among automated methods, second to only to a Singulex research assay.²

Figure 2: Percent of Normals Detected by Various Core Laboratory Troponin Vendors*



How does the ARCHITECT *STAT* hsTnI assay compare to the on-market ARCHITECT TnI assay?

Analytically, the ARCHITECT *STAT* hsTnI assay is superior to the contemporary ARCHITECT *STAT* Troponin-I (TnI) assay that is in use today. As demonstrated by the representative performance metrics outlined in Table 3, the high sensitive assay has a 7-fold improvement in overall precision at the 10% CV concentration as well as the ability to measure >50% of seemingly healthy subjects.

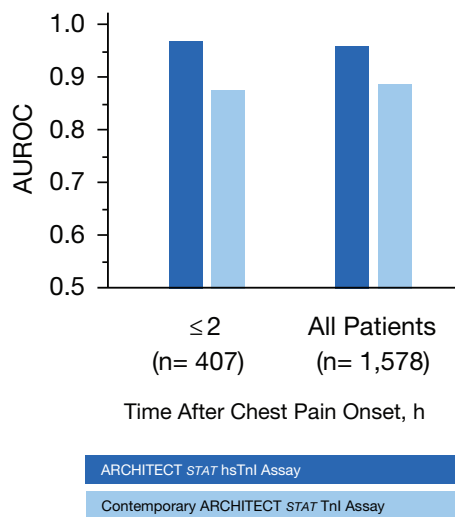
Table 3: Analytical Characteristics of ARCHITECT *STAT* TnI vs. ARCHITECT *STAT* hsTnI

	ARCHITECT <i>STAT</i> TnI (LN 2K41) ¹³		ARCHITECT <i>STAT</i> hsTnI (LN 3P25) ¹¹	
	ng/mL (µg/L)	pg/mL (ng/L)	ng/mL (µg/L)	pg/mL (ng/L)
Analytical Sensitivity* / LoD**	0.010*	10*	0.002**	1.9**
10% CV	0.032	32	0.005	4.7
99th percentile (overall)	0.028	28	0.026	26.2
99th percentile (males)	0.033	33	0.034	34.2
99th percentile (females)	0.013	13	0.016	15.6
Percent Detectable above LoD²	<50% of normals		>50% of normals	

Clinically and in the setting of suspected ACS, the ARCHITECT *STAT* hsTnI and contemporary ARCHITECT *STAT* TnI assay can appear comparable. This is because use of the 99th percentile cutoff with contemporary assays has already been an improvement to clinical care. However, additional advantages of high sensitivity methods become most evident for subjects that present within 1-3 hours of symptom onset.

As illustrated by this AUROC comparison (Figure 3), the AUROC for patients within 3 hours of statistical onset using the Abbott ARCHITECT *STAT* hsTnI assay was statistically significant when compared to the contemporary Abbott TnI assay under the same sample conditions. This data, coupled with data from other studies and assays, support guideline recommendations such that serial sampling using high sensitive methods can be reduced from 6-9 hours to 3 hours, allowing for the potential of substantial improvements in overall patient flow among busy emergency departments.¹⁴

Figure 3: Area Under the Receiver Operating Characteristic (AUROC) Curve on Admission According to Chest Pain Onset Time for both Troponin-I Assays⁸



Adapted from: Keller, T., et al. JAMA, 2011; 306(24): 2684-2693.

Do troponin values have prognostic significance?

Many studies using contemporary assays have shown that an elevated value of troponin carries prognostic risk for worse outcomes. This is true for patients with suspected ACS as well as other etiologies including heart failure, transplant rejection, syncope, post-operative monitoring following noncardiac surgery, etc.¹⁵⁻¹⁸

Recent data support comparable or even additive prognostic value using high sensitive methods, even in subjects that had previously undetected troponin concentrations using contemporary methods.¹⁹⁻²⁰ The data from Table 4 supports the prognostic value of baseline levels of hsTnI for subjects presenting to the emergency department with suspected ACS. Increased risk as represented by hazard ratio for a major adverse cardiac events as well as all-cause mortality at 30 and 90 days was associated with increased cardiac troponin measurements.¹¹

Table 4: 30-Day and 90-Day Hazard Ratios (Cox regression) for the gender-specific 99th percentile cutoffs (female, 15.6 pg/mL [ng/L]; male, 34.2 pg/mL [ng/L])¹¹

Tube Type	Follow-Up Time Point	n	Hazard Ratio	95% CI*	Likelihood Ratio P Value
K ₂ EDTA	30 Days	1,064	3.45	[1.79, 6.68]	0.0003
	90 Days	1,064	4.17	[2.52, 6.94]	<0.0001
Lithium Heparin Separator	30 Days	1,085	3.53	[1.83, 6.86]	0.0002
	90 Days	1,085	3.91	[2.39, 6.44]	<0.0001
Serum Separator	30 Days	1,027	3.28	[1.58, 6.73]	0.0018
	90 Days	1,027	3.98	[2.34, 6.79]	<0.0001

*CI= Confidence Interval

Are troponin concentrations below the 99th percentile clinically meaningful?

With assay improvements at the LoD and 10% CV concentration, analyzing results well below the respective 99th percentile may also have clinical meaning. This helps provide some insight into troponin levels that were not previously measurable with contemporary assays. The data from table 5 demonstrates that even in subjects suspect of ACS presenting to the emergency department with low troponin levels, a small proportion of MACE or ACM events still exist. This would support further investigation into the value of studies for asymptomatic cohorts where these low troponin concentrations can now be measured by hsTnI.

Table 5 demonstrates patients presenting with suspected ACS at risk for MACE and ACM within 30 and 90 days with cTnI values between the LoD and the 99th percentile medical decision points.

Table 5: ARCHITECT_{STAT} High Sensitive Troponin-I Clinical Study. Survival Analysis: Kaplan Meier Analysis, First Available Draw. Cutoff: 1.9 pg/mL, Female (>15.6 pg/mL) and Male (>34.2 pg/mL) Excluded¹²

Tube Type	Follow-Up Time Point	≤ Cutoff			> Cutoff			P Value
		MACE \ ACM ^a	No MACE \ ACM (Censored ^b)	Proportion	MACE \ ACM ^a	No MACE \ ACM (Censored ^b)	Proportion	
EDTA	30 Days	2	137	1.44%	16	665	2.35%	0.5046
	90 Days	3	136	2.16%	25	656	3.67%	0.3723
Lithium Heparin	30 Days	2	169	1.17%	15	633	2.31%	0.3508
	90 Days	3	168	1.75%	26	622	4.01%	0.1574
Serum	30 Days	2	126	1.56%	14	665	2.06%	0.7097
	90 Days	3	125	2.34%	24	655	3.53%	0.4941

^a ACM: All Cause Mortality.

^b Censored: Subject has not experienced MACE at the indicated follow-up point.

Lastly, elevated troponin levels, above or below the 99th percentile cutoff, have prognostic significance for worse outcomes in other etiologies as well. Examples include chronic patients with stable coronary artery disease as well as asymptomatic subjects who are seemingly free from cardiovascular risk.^{20, 21}

What additional considerations need to be understood before implementing an hsTn assay into routine practice?

The recommended units have changed. As a result of the sensitivity of the new methods, accuracy to several additional decimal places can now be achieved. The use of decimal places, particularly among results with several preceding zeroes, can cause confusion with clinically significant implications. Transcription errors have already occurred in published manuscripts, leading to a global endorsement for improved ease of use with pg/mL (ng/L) from ng/mL ($\mu\text{g/L}$).¹

The use of delta algorithms, albeit to assess percent change or absolute change, has increased importance using high sensitive methods. Published strategies have varied within and between different manufacturers and should therefore be understood prior to routine use to ensure the ideal serial timing and clinical algorithm for the respective institutions.

Lastly, detectable troponin levels will now occur in most individuals, and most of those individuals will not be suffering from an acute myocardial infarction. It is therefore critical to evaluate troponin concentrations within the clinical context of all supporting parameters, including the physical exam, symptoms, ECG, as well as patient and family history.

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