i-STAT hs-TnI Cartridge

NAME

i-STAT hs-TnI Cartridge (REF 09P81-25)

INTENDED USE

The i-STAT hs-TnI cartridge with the i-STAT System is intended for use in the *in vitro* quantification of cardiac troponin I (cTnI) in whole blood or plasma samples in point of care or clinical laboratory settings.

The i-STAT hs-TnI cartridge with the i-STAT System is intended to be used as an aid in the diagnosis of myocardial infarction (MI).

SUMMARY AND EXPLANATION / CLINICAL SIGNIFICANCE

TEST PRINCIPLE

The i-STAT High Sensitivity Troponin-I (i-STAT hs-TnI) test is an immunoassay test for cardiac troponin I. The i-STAT hs-TnI test uses an enzyme-linked immunosorbent assay (ELISA) method with electrochemical detection of the resulting enzyme signal. The test reports a quantitative measurement of the sample concentration of cTnI in units of ng/L.

The i-STAT hs-TnI immunoassay test method uses anti-cTnI antibodies for labeling and capture. The capture antibodies are coated on para-magnetic microparticles. Both label and capture antibodies are contained within the cartridge on a biosensor chip. The ELISA is initiated when the test cartridge is inserted into the analyzer. The sample is positioned over the biosensor chip to dissolve the reagents. This forms the ELISA sandwich (detection antibody-label/antigen/capture antibody). The sample and excess antibody-conjugate are then washed off the sensors. An enzyme within the ELISA sandwich generates an electrochemically detectable product. The biosensor chip measures the enzyme product which is proportional to the concentration of cTnI within the sample.

The i-STAT hs-TnI cartridge is a single use test cartridge. The cartridge contains a biosensor chip and all reagents required to execute the test cycle. All fluid movements within the cartridge (test sample or reagent) are automatically controlled by the i-STAT System by electro-mechanical interaction with the cartridge. No additional reagents or steps are required to run the cartridge.

CLINICAL SIGNIFICANCE

Biochemical cardiac markers, including cTnI, are useful for the diagnosis of myocardial infarction that can help guide the choice of therapeutic options. For optimal diagnostic usefulness, a cardiac marker should be specific for cardiac tissue, should be rapidly released into the bloodstream with a direct proportional relationship between the extent of myocardial injury and the measured level of the marker, and should persist in blood for a sufficient length of time to provide a convenient diagnostic time window.[1] Cardiac troponin is the preferred biomarker for the detection of myocardial infarction based on improved sensitivity and superior tissue-specificity compared to other available biomarkers of necrosis, including CK-MB, myoglobin, lactate dehydrogenase, and others.[2-4]

High sensitivity troponin assays have been defined as those which can achieve less than or equal to 10%CV at the 99th percentile of a healthy population and are capable of detecting troponin in greater than 50% of both men and women individually.[5,6]

Per the fourth universal definition of MI[7], the term myocardial injury should be used when there is evidence of elevated cardiac troponin (cTn) values with at least 1 value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values. The term acute myocardial infarction is defined as acute myocardial injury with clinical evidence of acute myocardial ischemia and with at least one of the following: new ischemic ECG changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology or identification of a coronary thrombus by angiography.[7]

The high tissue specificity of cTnI measurements should not be confused with specificity of the mechanism of the injury. When an increased value is encountered (e.g. exceeding the 99th URL) in the absence of myocardial ischemia, other etiologies of cardiac damage should be considered.[2] Elevated troponin levels may be indicative of myocardial injury associated with heart failure, renal failure, chronic renal disease, myocarditis, arrhythmias, pulmonary embolism, or other clinical conditions.[8,9]

Where there are inconsistencies in the clinical information or where diagnostic criteria are not fully satisfied, the possibility of erroneous (i.e. biased) results should be recognized – see Test Limitations.

REAGENTS

Contents

Each i-STAT hs-TnI cartridge provides a sample inlet, sensors to detect the cTnI as described above, and all the necessary reagents needed to perform the test. The cartridge contains a buffer and preservatives. A list of reactive ingredients is indicated below:

Reactive Ingredient	Biological Source	Minimum Quantity
Antibody / Alkaline Phosphatase Conjugate	Murine IgG:Caprine IgG / Bovine Intestine	0.004 µg
IgG	Caprine IgG	11.2 µg
IgG	Murine IgG	17.3 µg
Sodium Aminophenyl Phosphate	N/A	2.8 mg
IgM	Murine IgM	2.7 µg
Heparin	Porcine intestine	0.3 IU

Warnings and Precautions

- For *in vitro* diagnostic use.
- DO NOT REUSE—cartridges are intended for single-use only.
- Although the sample is contained within the cartridge, cartridges should be disposed of as biohazardous waste according to local, state, and national regulatory guidelines.
- The i-STAT System automatically runs a comprehensive set of quality checks of both the analyzer and cartridge performance each time a sample is tested. This internal quality system will suppress results by generating a Quality Check Code (QCC)/Quality Check Failure (QCF) if the analyzer, cartridge or sample does not meet certain internal specifications. To minimize the probability of delivering a result with medically significant error, the internal specifications are very stringent. It is typical for the system to suppress a very small percentage of results in normal operation given the stringency of these specifications. If, however, the analyzer or cartridges have been compromised, results may be persistently suppressed, and one or the other must be replaced to restore normal operating conditions. Where unavailability of results while awaiting replacement of analyzers or cartridges is unacceptable, Abbott Point of Care Inc. recommends maintaining both a backup *i-STAT System* and cartridges from an alternate lot number.

For additional warnings and precautions about the i-STAT System refer to the i-STAT 1 System Manual and i-STAT Alinity System Operations Manual located at www.globalpointofcare.abbott.

Storage Conditions

Note: For optimal performance, cartridge storage at 2 to 8 °C (35 to 46 °F) is recommended.

- The expiration date, expressed as YYYY-MM-DD on the packaging, indicates the last day the product may be used.
- Refrigeration at 2 to 8 °C (35 to 46 °F) until expiration date.
- Room Temperature at 18 to 30 °C (64 to 86 °F) for up to 14 days.

INSTRUMENTS

The i-STAT hs-TnI cartridge is intended for use with the i-STAT System which includes the i-STAT 1 analyzer and the i-STAT Alinity instrument.

For a detailed description of the analyzer and system procedures, refer to the i-STAT 1 System Manual or i-STAT Alinity System Operations Manual located at www.globalpointofcare.abbott.

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Specimen Types

Whole blood or plasma

Sample Volume: Approximately 22 µL

Blood Collection Options and Test Timing (time from collection to cartridge fill)

Assay	Syringes	Test Timing	Evacuated Tubes	Test Timing
hs-TnI	Blood without anticoagulant.	3 minutes	Blood without anticoagulant.	3 minutes
	Blood or plasma with lithium heparin anticoagulant. Syringe must be filled to labeled capacity.* • Remix whole blood thoroughly before filling cartridge.	4 hours	Blood or plasma with lithium heparin anticoagulant (with or without plasma separator). Tubes must be filled to labeled capacity.* • Remix whole blood thoroughly before filling cartridge.	4 hours

* Underfilling will cause higher heparin to blood ratios which may affect results.

PROCEDURE FOR CARTRIDGE TESTING

The i-STAT System should be used by healthcare professionals trained and certified to use the system and should be used according to the facility's policies and procedures.

The i-STAT System incorporates a comprehensive group of components needed to perform blood analysis at the point of care or in clinical laboratory settings. A portable analyzer, a cartridge with required tests, and whole blood or plasma will allow the caregiver to view quantitative results.

Each cartridge is sealed in a portion pack (individual cartridge package) for protection during storage—do not use if the portion pack has been damaged or punctured.

- A cartridge should not be removed from its protective portion pack until it is at room temperature (18-30 °C or 64-86 °F). For best results, the cartridge and analyzer should be at room temperature.
- Since condensation on a cold cartridge may prevent proper contact with the analyzer, allow refrigerated cartridges to equilibrate at room temperature for 5 minutes for a single cartridge and 1 hour for an entire box before use.
- Use a cartridge immediately after removing it from its protective portion pack; prolonged exposure may cause a cartridge to fail a Quality Check.
- Do not return unopened, previously refrigerated cartridges to the refrigerator.
- Cartridges may be stored at room temperature for the time frame indicated on the cartridge box.

Filling and Sealing the Cartridge (after cartridge has been equilibrated and blood sample has been collected).

Whole Blood:

1. Remove the cartridge from the portion pack and place the cartridge on a flat surface.
2. Follow the blood collection options provided above.
3. Invert a lithium heparin blood collection tube at least 10 times. If sample was collected into a syringe, invert syringe for 5 seconds, then roll the syringe between the palms (hands parallel to the ground) for 5 seconds, flip and roll for an additional 5 seconds. The blood in the hub of the syringe will not mix, therefore expelling 2 drops before filling a cartridge is desired. Note that it may be difficult to properly mix a sample in a 1.0 mL syringe.
4. Fill the cartridge immediately after mixing. Direct the hub of syringe or tip of the transfer device (pipette or dispensing tip) into the sample well of the cartridge.
5. Slowly dispense sample into the sample well until the sample reaches the fill mark indicated on the cartridge. Cartridge is properly filled when the sample reaches the 'fill to' mark and a small amount of sample is in the sample well. The sample should be continuous, no bubbles or breaks (see i-STAT 1 System Manual and i-STAT Alinity System Operations Manual for details).
6. Slide the closure clip of the cartridge over the sample well.

Plasma:

1. Remove the cartridge from the portion pack and place the cartridge on a flat surface.
2. Follow the blood collection options for evacuated tubes provided above and obtain the plasma sample.
3. Using a transfer device without anticoagulant, remove a small plasma sample from the lithium heparin tube that has been spun down being careful not to disturb the lipid layer between the plasma and red blood cells.
4. Fill the cartridge by directing the tip of the transfer device into the sample well of the cartridge.
5. Slowly dispense sample until the sample reaches the 'fill to' mark indicated on the cartridge. Cartridge is properly filled when the sample reaches the 'fill to' mark and a small amount of sample is in the sample well. The sample should be continuous, no bubbles or breaks (see i-STAT 1 System Manual and i-STAT Alinity System Operations Manual for details).
6. Slide the closure clip of the cartridge over the sample well.

Performing Patient Analysis

i-STAT 1 analyzer

1. Press the power button to turn on the analyzer.
2. Press 2 for *i-STAT Cartridge*.
3. Follow the analyzer prompts.
4. Scan the lot number on the cartridge portion pack.
5. Continue normal procedures for preparing the sample, and filling and sealing the cartridge.
6. Insert the sealed cartridge into the cartridge port until it clicks into place.
7. Wait for the test to complete. When the test is complete, the results are displayed.
8. Review the results.

i-STAT Alinity instrument

1. Press the power button to turn on the instrument.
2. From the Home screen, touch *Perform Patient Test.* This initiates the patient testing pathway.
3. Follow instructions on the screen to "Scan or Enter OPERATOR ID".
4. Follow instructions on the screen to "Scan or Enter PATIENT ID".
5. Continue to follow prompts on the screen to proceed with patient testing. "Scan CARTRIDGE POUCH Barcode". Scanning of cartridge portion pack is required. Information cannot be entered manually.
6. Follow instructions on the screen to "Close and Insert Filled Cartridge". The action buttons at the bottom of the screen allow forward, backward and pause functionality.
7. Wait for the test to complete. When the test is complete, the results are displayed.
8. Review the results.

For additional information for cartridge testing, refer to the i-STAT 1 System Manual and i-STAT Alinity System Operations Manual located at www.globalpointofcare.abbott.

Analysis Time

Approximately 15 minutes.

Results

The i-STAT hs-TnI test is a quantitative assay. The test reports a quantitative measurement of the sample concentration of cTnI in units of ng/L.

Interpretation of results

As with all analyte determinations, the cTnI value should be used in conjunction with information available from clinical evaluation and other diagnostic procedures.

Troponin results should always be used in conjunction with the patient's clinical data, signs, and symptoms in accordance with the fourth universal definition of MI[7] requiring acute myocardial injury with clinical evidence of acute myocardial ischemia, detection of a rise and/or fall of cTn values, at least one value above the 99th percentile URL, and at least one of the following: symptoms of myocardial ischemia, new ischemic ECG changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, identification of a coronary thrombus by angiography.

For additional information refer to the i-STAT 1 System Manual and i-STAT Alinity System Operations Manual located at www.globalpointofcare.abbott.

REPORTABLE RANGE

Based on representative data for the limit of quantitation (LoQ), the range over which results can be reported is provided below according to the definition from Clinical and Laboratory standards Institute (CLSI) EP17-A2, 2nd ed.[10]

Units*	Lower Limit of Reportable Range	Upper Limit of Reportable Range
ng/L or pg/mL	2.9	1000.0

*The i-STAT System can be configured with the preferred units. For additional information, refer to the i-STAT 1 System Manual and i-STAT Alinity System Operations Manual located at www.globalpointofcare.abbott.

Results may be preceded by the symbols for greater than (>) or less than (<) if the result is outside of the reportable range.

PROCEDURE FOR QUALITY CONTROL TESTING

Quality Control

The i-STAT quality control regimen comprises four aspects, with a system design that reduces the opportunity for error, including:

1. A series of automated, on-line quality measurements that monitors the sensors, fluidics, and instrumentation each time a test is performed.
2. A series of automated, on-line procedural checks that monitors the user each time a test is performed.
3. Liquid materials that are used to verify the performance of a batch of cartridges when they are first received or when storage conditions are in question. The performance of this procedure is not a Manufacturer's Quality System Instruction (MQSI).
4. Traditional quality control measurements that verify the instrumentation using an independent device, which simulates the characteristics of the electrochemical sensors in a way that stresses the performance characteristics of the instrumentation.

For additional information on Quality Control, refer to the i-STAT 1 System Manual and i-STAT Alinity System Operations Manual located at www.globalpointofcare.abbott. For information on performing liquid quality control testing, refer to the i-STAT hs-TnI Controls Levels 1-3 instructions for use located at www.globalpointofcare.abbott. Each laboratory should follow local, state and national regulations regarding quality control testing.

Calibration Verification

Calibration Verification procedure is intended to verify the accuracy of results over the entire measurement range of a test as may be required by regulatory or accreditation bodies. The performance of this procedure is not a Manufacturer's Quality System Instruction (MQSI). The Calibration Verification Set contains three levels spanning the hs-TnI reportable range.

For information on performing calibration verification testing, refer to the i-STAT hs-TnI Calibration Verification Levels 1-3 instructions for use located at www.globalpointofcare.abbott.

EXPECTED VALUES

A reference range study was conducted with a United States (US)-based general population. Venous whole blood specimens were collected with lithium heparin anticoagulant from 895 apparently healthy subjects between the ages of 18 and 87 years at point-of-care settings in eight (8) clinical sites. Subjects included met the following biomarker criteria: N-terminal pro-B-type natriuretic peptide (NT-proBNP)

<125 pg/mL (for subjects younger than 75 years) or < 450 pg/mL (for subjects 75 years or older), glomerular filtration rate (eGFR) values ≥ 60 mL/min, and Hemoglobin A1c (HbA1c) ≤ 6.5%.

Subjects were excluded based on the following criteria: BMI < 16.0 or > 35.0 kg/m^2, Type 1 or Type 2 diabetes, hospitalization within the previous 3 months, personal history of heart disease or vascular conditions (e.g. high blood pressure requiring medication, heart attack (acute myocardial infarction), angina), stent procedure or percutaneous cardiac intervention, angioplasty or balloon angioplasty, coronary artery bypass graft, surgery for a circulation problem (e.g., leg), statin use within the last 6 months, or known pregnancy or within 6 weeks postpartum.

The venous whole blood and plasma specimens were tested with the i-STAT hs-TnI cartridge with the i-STAT System to determine the 99th percentile URL for cardiac troponin I and associated 90% confidence intervals for the female, male, and overall population. Based on the test results from venous whole blood specimen testing, the 99th percentile upper reference limit (URL) of an apparently healthy population for the i-STAT hs-TnI test was determined to be as follows:

Sex	N	99th Percentile (ng/L, pg/mL)	90% CI (ng/L, pg/mL)
Female	490	13	(10, 17)
Male	404	28	(19, 58)
Overall	895	21	(14, 30)

Note: The overall and female 99th percentile URL values were determined using all data. The male 99th percentile URL value was determined using data with one outlier excluded.

The i-STAT hs-TnI test meets the definition of a high-sensitivity troponin assay per the fourth universal definition of MI.[7]

1. Total imprecision (CV) at the 99th percentile URL value should be at or below 10%.
   - The 10 %CV concentration was determined to be 6.88 ng/L for whole blood and 3.70 ng/L for plasma based on a representative study.
2. Measurable concentrations should be attainable at concentrations above the limit of detection (LoD) in at least 50% of healthy subjects.
   - Greater than 50% of the healthy patient population used to determine the 99th percentile URL produced a value above the LoD.

Sex specific cut-off values are recommended for high sensitivity assays.[7] Representative data are provided in this section. Results obtained in individual laboratories may vary.

METROLOGICAL TRACEABILITY

The i-STAT System test for cardiac troponin-I (cTnI) measures cardiac troponin I amount-of-substance concentration in plasma or the plasma fraction of whole blood for *in vitro* diagnostic use. Cardiac troponin-I values assigned to i-STAT controls and calibration verification materials are traceable to i-STAT's working calibrator prepared from human cardiac troponin-ITC complex (NIST SRM2921).

i-STAT System controls and calibration verification materials are validated for use only with the i-STAT System and assigned values may not be commutable with other methods.

Additional information regarding metrological traceability is available from Abbott Point of Care Inc. To obtain additional information and technical support, refer to the company website at www.globalpointofcare.abbott.

PERFORMANCE CHARACTERISTICS

The typical performance of the i-STAT hs-TnI assay with the i-STAT hs-TnI cartridge using the i-STAT System are summarized below.

Precision

A study was conducted based on CLSI EP05-A3 3rd ed.[11] with three (3) lots of i-STAT hs-TnI cartridges over 20 days, two (2) runs per day, by at least two (2) operators. The precision of the assay was evaluated using frozen plasma samples with concentrations across the hs-TnI reportable range.
Representative data is shown below.

Sample Level	N	Mean (ng/L)	Repeatability		Between-Run		Between-Day		Within-Laboratory[a]	
			SD (ng/L)	CV (%)	SD (ng/L)	CV (%)	SD (ng/L)	CV (%)	SD (ng/L)	CV (%)
1	239 [b]	11.59	0.755	6.52	0.129	1.11	0.026	0.22	0.767	6.61
2	240	15.62	0.619	3.97	0.262	1.68	0.224	1.44	0.709	4.54
3	240	33.94	1.184	3.49	0.333	0.98	0.211	0.62	1.248	3.68
4	240	84.25	2.750	3.26	0.163	0.19	0.403	0.48	2.784	3.30
5	240	511.95	19.298	3.77	4.825	0.94	3.189	0.62	20.146	3.94
6	240	786.65	35.636	4.53	9.337	1.19	6.291	0.80	37.372	4.75

[a] Includes repeatability, between-run and between-day variability.

[b] One outlier excluded

Whole blood and plasma precision were evaluated using venous whole blood and plasma specimens prospectively collected with lithium heparin in point of care settings at three (3) clinical sites. At each site, whole blood and plasma specimens were tested using i-STAT hs-TnI cartridges across three (3) runs (1 replicate/analyzer/run) for a total of 24 replicates per specimen. The repeatability analysis was conducted using the data collected across multiple point of care sites.

Whole Blood:

Site	Level	N	Mean (ng/L)	Repeatability		Within-Laboratory	
				SD (ng/L)	CV (%)	SD (ng/L)	CV (%)
1	1	24	5.16	0.457	8.86	0.513	9.93
	2	24	19.13	0.681	3.56	0.735	3.84
	3	23	29.03	1.056	3.64	1.056	3.64
	4	24	244.50	13.525	5.53	13.525	5.53
	5	24	638.50	31.329	4.91	31.329	4.91
	5	23	744.37	26.291	3.53	32.323	4.34
	6	22	934.77	22.925	2.45	30.986	3.31
2	1	24	7.39	0.523	7.08	0.683	9.25
	2	23	20.32	1.034	5.09	1.034	5.09
	3	23	44.22	1.376	3.11	1.548	3.50
	3	23	39.97	1.408	3.52	1.408	3.52
	4	24	71.44	3.114	4.36	3.114	4.36
	4	23	478.95	18.569	3.88	21.192	4.42
	5	24	606.65	27.684	4.56	29.946	4.94

Site	Level	N	Mean (ng/L)	Repeatability		Within-Laboratory	
				SD (ng/L)	CV (%)	SD (ng/L)	CV (%)
	6	24	795.93	33.125	4.16	36.436	4.58
	6	22	881.15	29.334	3.33	33.437	3.79
3	1	24	12.49	0.609	4.87	0.645	5.16
	2	24	17.39	0.772	4.44	0.772	4.44
	3	24	26.57	0.757	2.85	0.941	3.54
	3	24	47.28	2.161	4.57	2.161	4.57
	4	23	336.58	13.989	4.16	14.166	4.21
	5	23	681.89	30.929	4.54	30.929	4.54
	5	24	742.43	36.996	4.98	43.869	5.91
	6 [a]	24	869.70	26.891	3.09	26.891	3.09

[a] Specimen from one (1) subject was spiked with ≤ 5% v/v recombinant cardiac troponin I antigen.

Plasma:

Site	Level	N	Mean (ng/L)	Repeatability		Within-Laboratory	
				SD (ng/L)	CV (%)	SD (ng/L)	CV (%)
1	1	23	6.08	0.763	12.55	0.778	12.80
	2	23	20.58	0.999	4.86	0.999	4.86
	3	23	30.83	0.818	2.65	0.932	3.02
	4	24	243.97	10.688	4.38	10.750	4.41
	5	24	602.70	32.572	5.40	32.572	5.40
	6	23	764.50	51.255	6.70	51.823	6.78
2	1	24	8.03	0.306	3.81	0.320	3.98
	2	24	22.59	0.889	3.94	0.900	3.99
	3	24	44.19	1.572	3.56	2.007	4.54
	4	24	76.81	1.977	2.57	1.977	2.57
		24	499.76	16.575	3.32	19.219	3.85
	5	24	712.17	52.591	7.38	56.223	7.89
		24	680.01	40.429	5.95	40.429	5.95
	6	21	945.62	23.419	2.48	35.201	3.72
3	1	23 [b]	12.77	0.378	2.96	0.400	3.13
	2	23 [b]	24.48	0.930	3.80	0.930	3.80
	2	24	18.80	0.798	4.24	0.798	4.24
	3	24	47.00	1.705	3.63	1.807	3.84
	4	24	338.27	10.893	3.22	14.165	4.19
	5	24	672.29	24.813	3.69	24.813	3.69
	5	24	743.01	33.451	4.50	34.114	4.59
	6 [a]	24	847.93	34.701	4.09	34.701	4.09

[a] Specimen from one (1) subject was spiked with ≤ 5% v/v recombinant cardiac troponin I antigen.
[b] With outlier excluded.

A within-laboratory precision study was conducted with five (5) levels of i-STAT hs-TnI controls and calibration verification materials at a single site based on CLSI guidance EP15-A3[12]. The study was conducted using one (1) lot of i-STAT hs-TnI cartridges and each of five (5) unique levels of frozen i-STAT

hs-TnI control materials tested in five (5) replicates over five (5) consecutive days. The precision of the i-STAT hs-TnI test was evaluated using one (1) lot each of i-STAT hs-TnI Controls Levels 1 and 2 (L1 and L2) and one (1) lot each of i-STAT hs-TnI Calibration Verification Levels 1, 2, and 3 (CV1, CV2, and CV3). The statistics for Mean, Standard Deviation (SD) and Coefficient of Variation (CV) are represented below. This is representative data. Results in individual laboratories may vary.

Fluid Level*	N	Mean (ng/L)	Repeatability		Between-Day		Within-Laboratory	
			SD (ng/L)	CV (%)	SD (ng/L)	CV (%)	SD (ng/L)	CV (%)
CV1	25	2.85	0.202	7.07	0.066	2.33	0.212	7.45
L1	25	20.43	0.640	3.13	0.178	0.87	0.664	3.25
L2	25	98.46	3.108	3.16	0.924	0.94	3.242	3.29
CV2 / L3	25	592.85	28.288	4.77	12.617	2.13	30.974	5.22
CV3	25	1174.29	55.117	4.69	15.296	1.30	57.200	4.87

* i-STAT hs-TnI Calibration Verification Level 2 (CV2) and i-STAT hs-TnI Control Level 3 (L3) share the same target.

Lower Limits of Measurement

The limit of blank (LoB) is defined as the highest measurement result that is likely to be observed for a blank sample.

The limit of detection (LoD) is defined as the lowest concentration at which the analyte can be detected with 95% probability.

The limit of quantitation (LoQ) is defined as the lowest amount of a measurand in a sample that can be measured with a maximum precision of 20%CV.

A study was performed based on guidance from CLSI EP17-A2 2nd ed[10]. LoB and LoQ were established using four (4) i-STAT hs-TnI cartridge lots and using the highest value determined by lot. LoD was established using three (3) i-STAT cartridge lots and using the highest value determined by lot.

The lower limit of the reportable range was set to be the greater of the LoQ values for whole blood and plasma.

Sample Type	LoB (ng/L)	LoD (ng/L)	LoQ (ng/L)
Whole Blood	0.78	1.61	2.90
Plasma	0.57	1.05	1.18

The 10 %CV concentration was determined to be 6.88 ng/L for whole blood and 3.70 ng/L for plasma based on a representative study.

Linearity

Linearity studies were performed based on guidance from CLSI EP06 2nd ed.[13] The results using lithium heparinized whole blood and plasma samples demonstrated linearity across the reportable range of 2.9 to 1000.0 ng/L.

Sample Type Comparison

Comparison studies were performed based on CLSI EP35 1st ed[14] using fresh lithium heparinized whole blood and plasma samples with the i-STAT hs-TnI cartridge. The relationship between the two methods

is summarized below using a Passing-Bablok regression.

Sample Type Comparison	Slope	Intercept	r
Whole Blood vs. Plasma	1.01	0.603	0.99

High Dose Hook Effect

The i-STAT hs-TnI cartridge was evaluated for high dose hook effect. The testing was conducted using whole blood and plasma samples spiked to high levels cardiac troponin I (up to 500,000 ng/L). No hook effect was detected in samples up to 500,000 ng/L.

Clinical Performance

The i-STAT High Sensitivity Troponin-I (i-STAT hs-TnI) test should be used in conjunction with other diagnostic information such as ECG, clinical observations and patient symptoms to aid in the diagnosis of MI.

A pivotal study using prospectively collected venous whole blood and plasma specimens was conducted at 28 sites to assess diagnostic accuracy of the i-STAT hs-TnI test in the i-STAT hs-TnI cartridge with the i-STAT System. The facilities used and the study staff that performed the testing, were representative of point of care end-users.

Venous whole blood specimens collected into lithium heparin tubes from 3399 subjects presenting to the Emergency Department (ED) with chest discomfort or equivalent ischemic symptoms consistent with Acute Coronary Syndrome (ACS) were included in the clinical performance evaluation.

The study sites represented geographically diverse EDs associated acute care hospitals, medical centers, tertiary care facilities, and primary care clinics with patient populations representing regional, urban, and rural areas of the United States. Subjects were adjudicated by board-certified cardiologists and/or emergency medicine physicians based on the fourth universal definition of MI.[7] The observed MI prevalence in this study was 7.1% for females and 11.9% for males.

Sex	MIs	Non-MIs	Total Subjects	% MI Prevalence
Female subjects	154	2010	2164	7.1
Male subjects	147	1088	1235	11.9

An analysis for both females and males was performed using the overall (21 ng/L) and sex-specific (female 13 ng/L, male 28 ng/L) 99th percentile URL to demonstrate the clinical performance (clinical sensitivity, clinical specificity, positive predictive value (PPV) and negative predictive value (NPV)) of the i-STAT hs-TnI test in the i-STAT hs-TnI cartridge with the i-STAT System to aid in the diagnosis of MI. The results are summarized in the tables below.

The study design followed the standard of care at each site where few specimens would be obtained at later time points because most patients would not typically require further serial cTnI testing after 6 hours. Therefore, the lower specificity at the > 6 hour time point was the result of the disproportionate number of elevated and non-elevated specimens carried over from previous time points. The i-STAT hs-TnI result should be used in conjunction with information available from clinical evaluation and other diagnostic procedures.

Of the specimens collected at greater than or equal to 6 hours (>6 in tables below), specimens were collected within 9 hours from presentation to the ED, except for 6 specimens from 3 female subjects collected within 10 hours from presentation to the ED, and 4 specimens from a male subject collected within 23 and 25 hours.

Whole Blood:

The clinical performance for the i-STAT hs-TnI cartridge in whole blood using the overall 99th percentile URL (21 ng/L) is as follows:

Sex	Time Point (hours)	N	MI	Non- MI	Sensitivity (%)		Specificity(%)		PPV(%)		NPV(%)	
					Estimate	Lower Limit of One Sided 97.5% CI	Estimate	Lower Limit of One Sided 97.5% CI	Estimate	Lower Limit of One Sided 97.5% CI	Estimate	Lower Limit of One Sided 97.5% CI
Female	0 to 1	1766	127	1639	86.61	79.61	89.02	87.41	37.93	32.54	98.85	98.16
	>1 to 3	1745	117	1628	92.31	86.02	89.43	87.85	38.57	33.06	99.39	98.84
	>3 to 6	709	70	639	95.71	88.14	85.76	82.84	42.41	34.97	99.46	98.41
	>6	60	16	44	93.75	71.67	65.91	51.14	50.00	33.15	96.67	83.33
Male	0 to 1	1046	128	918	83.59	76.22	78.21	75.43	34.85	29.74	97.16	95.69
	>1 to 3	1006	117	889	92.31	86.02	77.50	74.64	35.06	29.95	98.71	97.57
	>3 to 6	432	68	364	95.59	87.81	74.45	69.73	41.14	33.77	98.91	96.83
	>6	47	12	35	91.67	64.61	54.29	38.19	40.74	24.51	95.00	76.39

The clinical performance for the i-STAT hs-TnI cartridge in whole blood using the sex-specific 99th percentile URL (female 13 ng/L, male 28 ng/L) is as follows:

Sex	Time Point (hours)	N	MI	Non-MI	Sensitivity (%)		Specificity(%)		PPV(%)		NPV(%)	
					Estimate	Lower Limit of One Sided 97.5% CI	Estimate	Lower Limit of One Sided 97.5% CI	Estimate	Lower Limit of One Sided 97.5% CI	Estimate	Lower Limit of One Sided 97.5% CI
Female	0 to 1	1766	127	1639	91.34	85.15	82.61	80.70	28.93	24.71	99.19	98.56
	>1 to 3	1745	117	1628	96.58	91.54	81.88	79.93	27.70	23.58	99.70	99.23
	>3 to 6	709	70	639	97.14	90.17	77.62	74.23	32.23	26.29	99.60	98.55
	>6	60	16	44	100.00	80.64	54.55	40.07	44.44	29.54	100.00	86.20
Male	0 to 1	1046	128	918	79.69	71.90	84.10	81.59	41.13	35.19	96.74	95.27
	>1 to 3	1006	117	889	90.60	83.95	83.58	81.00	42.06	36.13	98.54	97.41
	>3 to 6	432	68	364	94.12	85.83	82.97	78.77	50.79	42.17	98.69	96.69
	>6	47	12	35	91.67	64.61	57.14	40.86	42.31	25.54	95.24	77.33

* All time points are relative to ED presentation.

Troponin results should always be used in conjunction with clinical data, signs, and symptoms.

Plasma:

The clinical performance for the i-STAT hs-TnI cartridge in plasma using the overall 99th percentile URL (21 ng/L) is as follows:

Sex	Time Point (hours)	N	MI	Non-MI	Sensitivity (%)		Specificity(%)		PPV(%)		NPV(%)	
					Estimate	Lower Limit of One Sided 97.5% CI	Estimate	Lower Limit of One Sided 97.5% CI	Estimate	Lower Limit of One Sided 97.5% CI	Estimate	Lower Limit of One Sided 97.5% CI
Female	0 to 1	1761	126	1635	87.30	80.37	88.87	87.25	37.67	32.31	98.91	98.24
	>1 to 3	1745	116	1629	92.24	85.91	89.38	87.79	38.21	32.72	99.39	98.84
	>3 to 6	709	70	639	94.29	86.21	85.76	82.84	42.04	34.60	99.28	98.15
	>6	60	16	44	93.75	71.67	68.18	53.44	51.72	34.43	96.77	83.81
Male	0 to 1	1048	128	920	83.59	76.22	78.04	75.25	34.63	29.54	97.16	95.69
	>1 to 3	1002	116	886	92.24	85.91	76.64	73.74	34.08	29.05	98.69	97.53
	>3 to 6	432	68	364	95.59	87.81	73.35	68.58	40.12	32.89	98.89	96.78
	>6	47	12	35	91.67	64.61	54.29	38.19	40.74	24.51	95.00	76.39

The clinical performance for the i-STAT hs-TnI cartridge in plasma using the sex-specific 99th percentile URL (female 13 ng/L, male 28 ng/L) is as follows:

Sex	Time Point (hours)	N	MI	Non-MI	Sensitivity (%)		Specificity(%)		PPV(%)		NPV(%)	
					Estimate	Lower Limit of One Sided 97.5% CI	Estimate	Lower Limit of One Sided 97.5% CI	Estimate	Lower Limit of One Sided 97.5% CI	Estimate	Lower Limit of One Sided 97.5% CI
Female	0 to 1	1761	126	1635	92.06	86.01	81.59	79.64	27.82	23.73	99.26	98.64
	>1 to 3	1745	116	1629	96.55	91.47	81.40	79.44	26.99	22.94	99.70	99.23
	>3 to 6	709	70	639	97.14	90.17	77.15	73.74	31.78	25.91	99.60	98.54
	>6	60	16	44	100.00	80.64	54.55	40.07	44.44	29.54	100.00	86.20
Male	0 to 1	1048	128	920	79.69	71.90	83.15	80.60	39.69	33.90	96.71	95.23
	>1 to 3	1002	116	886	90.52	83.81	82.39	79.75	40.23	34.46	98.52	97.36
	>3 to 6	432	68	364	94.12	85.83	80.22	75.82	47.06	38.87	98.65	96.58
	>6	47	12	35	91.67	64.61	54.29	38.19	40.74	24.51	95.00	76.39

* All time points are relative to ED presentation.

Troponin results should always be used in conjunction with clinical data, signs, and symptoms.

Due to the release kinetics of cardiac troponin I, an initial test result may not be definitive in diagnosing MI. Serial cardiac troponin measurements are suggested. The patient's clinical presentation (history, risk factors, physical exam, and ECG findings), a rise/fall pattern in results, and noninvasive modalities should be considered in conjunction with troponin in the diagnostic evaluation of suspected myocardial infarction in accordance with the fourth universal definition of MI to help guide the choice of therapeutic options.[7,15]

LIMITATIONS OF THE PROCEDURE

The analyte results should be assessed in conjunction with the patient's medical history, clinical examination, and other findings. If results appear inconsistent with the clinical assessment, the patient sample should be retested using another cartridge.

- The frequency of suppressed results is affected by atmospheric pressure. Suppressed result rates may increase with higher elevations (decreased barometric pressure) and may become persistent if testing is performed at more than 7500 feet (2286 meters) above sea level. Where unavailability of results is unacceptable, Abbott Point of Care recommends having an alternate method.

- Samples from patients who have been exposed to animals or who have received therapeutic or diagnostic procedures employing immunoglobulins or reagents derived from immunoglobulins may contain antibodies, e.g., HAMA or other heterophile antibodies, which may interfere with

immunoassays and produce erroneous results.[16-22] The generation of potentially interfering antibodies in response to bacterial infections has been reported.[18] While this product contains reagents that minimize the effect of these interferents and QC algorithms designed to detect their effects, the possibility of interference causing erroneous results should be evaluated carefully in cases where there are inconsistencies in the clinical information.

- Troponin autoantibodies have been reported to be present in approximately 10% to 20% of patients presenting to the emergency department (ED) and may lead to falsely low troponin assay results.[23,24]

- When an increased cardiac troponin I value is encountered (e.g. exceeding the 99th percentile URL) in the absence of myocardial ischemia, other etiologies of cardiac damage should be considered[2]. Elevated troponin levels may be indicative of myocardial injury associated with heart failure, acute renal failure, chronic kidney disease, sepsis, myocarditis, arrhythmias, pulmonary embolism, or other clinical conditions[8,9]. Additionally, as documented in literature, in certain samples, a high molecular weight complex comprised of immunoglobulin and cTnI (macrotroponin) can be present[25,26] and may result in elevated cTnI measurements. The patient's clinical presentation (history, risk factors, physical exam, and ECG findings), a rise/fall pattern in results, and noninvasive modalities should be considered in conjunction with troponin in the diagnostic evaluation of suspected myocardial infarction to help guide the choice of therapeutic options[7,15].

- The analyzer must remain on a flat surface with the display facing up during testing. Movement of the analyzer during testing may increase the frequency of suppressed results or quality check codes. A level surface includes running the analyzer in the downloader/recharger.

- The test results should be assessed in conjunction with the patient's symptoms, clinical examination, and other findings.

- The results of different troponin assays are not generally comparable: cTnI and cTnT are distinct molecules and results are not interchangeable, nor comparable. In addition, significant variation in absolute troponin values may be observed for a given patient specimen with different analytic methods.[27]

- Cardiac troponin may not appear in circulation for 4-6 hours following the onset of symptoms of MI.[28] Consequently, a single negative result may not be sufficient to rule out MI. Per the fourth universal definition of MI[7], myocardial injury is considered acute when there is evidence of elevated cardiac troponin (cTn) values with at least 1 value above the 99th percentile upper reference limit (URL) and there is a rise and/or fall of cTn values.

Factors Affecting Results

Factor	Effect
Altitude	The i-STAT hs-TnI test has not been evaluated at altitudes >10,000 feet. No impact on performance was found up to 10,000 feet of altitude.
Hematocrit Sensitivity	The i-STAT hs-TnI test was characterized between 15–60 %PCV. Increased imprecision was observed for whole blood samples ≥ 55 %PCV.
Hemolysis	Grossly hemolyzed samples can cause a decreased alkaline phosphatase activity, increased assay backgrounds, and/or quality check failures.
Tilt	The i-STAT hs-TnI test was characterized for tilt angle between -20° (display angled down) and +30° (display angled up) versus a level surface. Increased bias was observed for a tilt angle more than -15° (display angled down).

Interference Testing

Interference studies were based on CLSI guideline EP07 3rd ed.[29] The substances listed were evaluated in lithium heparin whole blood and plasma. For those identified as an interferant the interference is described. Substances identified below as having no interference had no significant effect (less than 10%) on the i-STAT hs-TnI test.

	Test Concentration		Interfering (Yes/No)			Comment
Substance*	µmol/L	mg/dL, unless specified	Whole Blood	Plasma	Overall	
Acetaminophen	1030	15.6	No	No	No	
Acetylsalicylic Acid	167	3.01	No	No	No	
Alkaline Phosphatase	3060 (U/L)		No	No	No	
Allopurinol	441	6.00	No	No	No	
Ambroxol[a]	965	40	No	No	No	
Ampicillin	215	7.51	No	No	No	
Ascorbic Acid	298	5.25	No	No	No	
Atenolol	33.8	0.900	No	No	No	
Bilirubin (Conjugated)	475	40.0	No	Yes	Yes	Decreased results > 23.7 µmol/L (2 mg/dL). The reference range per CLSI EP37 for Bilirubin (Conjugated) is 0.0-2.4 µmol/L (0.0-0.2 mg/dL).
Bilirubin (Unconjugated)	684	40.0	Yes	Yes	Yes	Decreased results > 85.5 µmol/L (5 mg/dL). The reference range per CLSI EP37 for Bilirubin (Unconjugated) is 0-34 µmol/L (0.0-2.0 mg/dL). Elevated levels of unconjugated bilirubin may be observed in patients with hemolytic disorders (i.e. hemolytic anemia), cholestatis, and disorders of impaired bilirubin conjugation and secretion, such as Gilbert's syndrome, Crigler-Najjar syndrome, chronic viral hepatitis or chronic alcohol cirrhosis.
Biotin	14.3	0.349	No	No	No	
Bivalirudin[a]	18.3	3.99	No	No	No	
Caffeine	556	10.8	No	No	No	
Carvedilol[a]	370	15	No	No	No	
Cefoxitin	15500	697	No	Yes	Yes	Decreased results > 6564 µmol/L (295 mg/dL)

Substance*	Test Concentration µmol/L	Test Concentration mg/dL, unless specified	Interfering (Yes/No) Whole Blood	Interfering (Yes/No) Plasma	Interfering (Yes/No) Overall	Comment
Cholesterol	10300	398	No	No	No	
Clopidogrel[a]	180	7.5	No	No	No	
Cocaine[a]	11.406	0.346	No	No	No	
Cyclosporine	1.50	0.180	No	No	No	
Diclofenac	81.0	2.58	No	No	No	
Digoxin	0.0499	0.00390	No	No	No	
Dopamine	4.06	0.0770	No	No	No	
Doxycycline	40.5	2.08	No	No	No	
Enalaprilat	2.35	0.0903	No	No	No	
Enoxaparin[a]	500 IU/dL	5	No	No	No	
Epinephrine[a]	1.7	0.037	No	No	No	
Eptifibatide[a]	11	0.90	No	No	No	
Erythromycin	188	13.8	No	No	No	
Ethanol	130000	599	No	No	No	
Fibrinogen[a]	N/A	1 g/dL	No	Yes	Yes	Decreased results > 0.4 g/dL. The reference range per literature for Fibrinogen is 0.2-0.4 g/dL[30]
Fondaparinux[a]	2.3	0.40	No	No	No	
Furosemide	48.1	1.59	No	No	No	
Hemoglobin	N/A	1000	No	No	No	
Human Anti-Mouse Antibody (HAMA)[a]	3000 (ng/mL)		No	No	No	
Ibuprofen	1060	21.9	No	No	No	
Intralipid (Intralipid 20%)[a]	N/A	3144	No	No	No	
Isosorbide Dinitrate	25.1	0.593	No	No	No	
Levodopa	38.0	0.749	No	No	No	
Lithium Heparin[a]	~3160 IU/dL		No	No	No	
Methyldopa	107	2.55	No	Yes	Yes	Increased results > 84 µmol/L (2.00 mg/dL)
Methylprednisolone	20.9	0.783	No	No	No	
Metronidazole	719	12.3	No	No	No	
Nicotine	5.97	0.0969	No	No	No	
Nifedipine	1.70	0.0589	No	No	No	
Nitrofurantoin	8.94	0.213	No	No	No	
Nystatin[a]	181.4	16.80	No	No	No	
Oxytetracycline[a]	24	1.2	No	No	No	
Phenobarbital	2970	69.0	No	No	No	
Phenylbutazone	1040	32.1	No	No	No	
Phenytoin	238	6.00	No	No	No	

Substance*	Test Concentration µmol/L	Test Concentration mg/dL, unless specified	Interfering (Yes/No) Whole Blood	Interfering (Yes/No) Plasma	Interfering (Yes/No) Overall	Comment
Pravastatin	0.488	0.0218	No	No	No	
Primidone	261	5.70	No	No	No	
Rheumatoid Factor (RF)[a]	500 IU/mL		Yes	Yes	Yes	Decreased results >300 IU/mL
Rifampicin	58.3	4.80	No	No	No	
Salicylic Acid	207	3.31	No	No	No	
Simvastatin	0.199	0.00833	No	No	No	
Sodium Heparin	330 IU/dL		No	No	No	
Theophylline	333	6.00	No	No	No	
Tissue Plasminogen Activator (TPA)[a]	N/A	0.23	No	No	No	
Total Protein (Human Serum Albumin)	N/A	15 g/dL	No	Yes	Yes	Decreased results ≳ 8.5 g/dL. The reference range per CLSI EP37 for Total Protein is 6.4-8.3 g/dL.
Triglyceride	16940	1500	No	No	No	
Trimethoprim	145	4.21	No	No	No	
Verapamil	3.51	0.172	No	No	No	
Warfarin	243	7.49	No	No	No	

[a] The test concentration for this substance is not included in CLSI guideline EP37 1st ed.[31]

* The compound tested to evaluate the interfering substance is presented in parenthesis.

As per the CLSI guideline EP07 3rd ed.[29], the interference testing was performed at two levels of cardiac troponin I, approximately 20 ng/L and 600 ng/L.

This is representative data and results may vary from study to study due to matrix effects. Viscosity, surface tension, turbidity, ionic strength and pH are common causes of matrix effects. It is possible that interfering substances other than those tested may be encountered. The degree of interference at concentrations other than those listed might not be predictable.

Analytical Specificity

Cross Reactivity

The i-STAT hs-TnI cartridge is specific to the measurement of cardiac troponin I (cTnI). A study was performed to evaluate the i-STAT hs-TnI cartridge in the presence of potentially cross-reactive endogenous substances using whole blood and plasma samples based on guidance from CLSI EP07 3rd ed.[29]. The endogenous substances in the table below were tested at a concentration of 1,000,000 ng/L and none were found to have significant impact on the i-STAT hs-TnI test.

Substance	Substance Test Concentration (ng/L)	Cross-reactivity (Yes/No)
Actin	1,000,000	No
Human Cardiac Troponin T (cTnT)	1,000,000	No
Human Creatine Kinase Myocardial Band (CK-MB)	1,000,000	No
Human Myoglobin	1,000,000	No
Human Myosin LC (Light Chain)	1,000,000	No
Human Skeletal Troponin I (sTnI)	1,000,000	No
Human Skeletal Troponin T (sTnT)	1,000,000	No
Human Troponin C (TnC)	1,000,000	No
Tropomyosin	1,000,000	No

KEY TO SYMBOLS

Symbol	Definition/Use
	14 days room temperature storage at 18–30 °C
	Use by or expiration date. An expiration date expressed as YYYY-MM-DD means the last day the product can be used.
	The Manufacturer lot number/batch will appear adjacent to this symbol.
	Contains sufficient for <n> tests
	Temperature limitations. The upper and lower limits for storage are adjacent to upper and lower arms.
	Catalog number, list number, or reference.
	Do not re-use
	Manufacturer
	Consult instructions for use or see System Manual for instructions.
	*In vitro* diagnostic medical device
	Device for near-patient testing
	U.K. Conformity Assessed (UKCA) marking in accordance with the UK Medical Device Regulations 2002.
	For prescription use only.

Additional Information: to obtain additional product information and technical support, refer to the Abbott company website at www.globalpointofcare.abbott.

Product issues and adverse events should be reported to Abbott through your Abbott Point of Care support service.

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Abbott Point of Care Inc.
400 College Road East
Princeton, NJ 08540 USA

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