Intended Use: The CTNI method is an *in vitro* diagnostic test for the quantitative measurement of cardiac troponin I in human serum and plasma on the Dimension Vista® System. Measurements of cardiac troponin I are used to aid in the diagnosis of acute myocardial infarction (AMI) and in the risk stratification of patients with acute coronary syndromes with respect to their relative risk of mortality.

Summary: Troponin is the contractile regulatory protein complex of striated muscle. It is found periodically along the thin filament of the myofibrils, in conjunction with the protein tropomyosin. The troponin complex consists of three distinct polypeptide components: troponin-C (the calcium binding element), troponin-I (the actinomyosin ATPase inhibitory element), and troponin-T (the tropomyosin binding element). The complex serves to regulate the calcium dependent interaction of myosin and actin and thus plays an integral role in muscle contraction.[1] Troponin-I exists in three distinct molecular forms which correspond to specific isotypes found in fast-twitch skeletal muscle, slow-twitch skeletal muscle, and heart, respectively. The skeletal isotypes are similar in molecular size approximately 20000 daltons, but exhibit an amino acid sequence heterogeneity of approximately 40%. The cardiac isotype also exhibits about a 40% sequence heterogeneity with respect to the skeletal isotypes, but also has an additional 31 residues at the amino terminus, resulting in a molecular weight of about 24000 daltons.[2,3]

Several reports in the literature have indicated that cardiac troponin-I is released into blood within hours of the onset of symptoms of myocardial infarction and that it remains elevated for several days post-infarction. The cumulative data from these reports indicate that troponin-I levels become abnormal 4–8 hours following onset of chest pain, peak at 12–16 hours, and remain elevated for 5–9 days following an infarction.[2,3,4] Based upon these studies it appears that troponin-I is elevated over a time period which covers the diagnostic window of both CKMB and LD.[5] Clinical studies also suggest an improved cardiac specificity for troponin-I compared to CKMB for detection of myocardial injury in the presence of skeletal muscle injury.[6,7]

Measurement of cardiac troponin-I levels provide sensitive and specific determination of myocardial injury over a wide diagnostic window. Elevations in cardiac troponin-I levels have been observed across a spectrum of acute coronary syndromes including Q-wave MI, non-Q-wave MI and unstable angina. A significantly higher incidence of mortality has been observed in patients with non-Q-wave MI and unstable angina who have detectable levels of cardiac troponin-I. This suggests that cardiac troponin-I provides a means for risk stratification of these individuals.[8]

Given troponin's high myocardial specificity and sensitivity, the Joint European Society of Cardiology/American College of Cardiology Committee recognizes troponin as the preferred biochemical marker for myocardial damage. The committee also recommends an imprecision level (coefficient of variation or CV) for Troponin assays of <10% at the 99th percentile of normal.[9] Based on imprecision and other performance characteristics, the Dimension Vista® System CTNI method is a high sensitivity troponin I method.

Principles of Procedure: The CTNI method is a homogeneous, sandwich chemiluminescent immunoassay based on LOCI® technology. The LOCI® reagents include two synthetic bead reagents and a biotinylated anti-cardiac troponin I monoclonal antibody fragment. The first bead reagent (Sensibeads) is coated with streptavidin and contains photosensitizer dye. The second bead reagent (Chemibeads) is coated with a second anti-cardiac troponin I monoclonal antibody and contains chemiluminescent dye. Sample is incubated with Chemibeads and biotinylated antibody to form bead-cardiac troponin I-biotinylated antibody sandwiches. Sensibeads are added and bind to the biotin to form bead-pair immunocomplexes. Illumination of the complex at 680 nm generates singlet oxygen from Sensibeads which diffuses into the Chemibeads, triggering a chemiluminescent reaction. The resulting signal is measured at 612 nm and is a direct function of the cardiac troponin I concentration in the sample.[10.11,12]

Reagents

Wells[a]	Form	Ingredient	Concentration[b]	Source
1–2	Liquid	Biotinylated Antibody[c]	8 µg/mL	Mouse monoclonal
3–4	Liquid	Troponin I Chemibeads[c]	190 µg/mL	Mouse monoclonal
7–8	Liquid	Streptavidin Sensibead[c]	1500 µg/mL	Recombinant *E. coli*
9–12	Liquid	Assay Buffer		

a. Wells are numbered consecutively from the wide end of the cartridge.
b. Nominal value per well in a cartridge.
c. Antibody titer and reagent activity may vary lot to lot.

Risk and Safety

H317

P280, P272, P302 + P352, P333 + P313, P501

Warning!

May cause an allergic skin reaction.

Wear protective gloves/protective clothing/eye protection/face protection. Contaminated work clothing should not be allowed out of the workplace. IF ON SKIN: Wash with plenty of soap and water. If skin irritation or rash occurs: Get medical advice/attention. Dispose of contents and container in accordance with all local, regional, and national regulations.

Contains: 5-chloro-2-methyl-3(2h)-isothiazolone mixture with 2-methyl-3(2h)-isothiazolone.

Safety data sheets (MSDS/SDS) available on www.siemens.com/diagnostics

Precautions: Used LOCI® reaction vessels contain human body fluids; handle with appropriate care to avoid skin contact or ingestion.

For *in vitro* diagnostic use.

Reagent Preparation: All reagents are liquid and ready to use.

Store at: 2–8 °C

Expiration: Refer to carton for expiration date of individual unopened reagent cartridges. Sealed wells on the instrument are stable for 30 days.

Open Well Stability: 7 days for wells 1–12

Specimen Collection and Handling: Recommended specimen types: serum or plasma (sodium or lithium heparin).

Samples and controls stabilized with azide cannot be used.

Serum or plasma samples can be collected using recommended procedures for collection of diagnostic blood specimens by venipuncture.[13]

Follow the manufacturer's instructions for their specimen collection device for use and processing.[15]

Comparative testing of 63 contemporaneous draws of serum and lithium heparinized plasma produced the following regression line: lithium heparin plasma = 1.02 serum + 0.031. The serum CTNI concentration varied from 0.026 – 22.9 ng/mL [µg/L]. A similar study was conducted between lithium and sodium heparin which produced the following regression line: sodium heparin plasma = 0.99 lithium heparin plasma + -0.05. The lithium heparin CTNI concentration varied from 0.09 – 39.85 ng/mL [µg/L] for 50 samples.

Complete clot formation should take place before centrifugation. Serum should be physically separated from cells as soon as possible with a maximum limit of two hours from the time of collection.[14, 15] Specimens should be free of particulate matter.

Samples are stable for at least 2 days when stored at 2–8 °C or for at least 8 weeks when frozen at -20 °C or below.[16] Repetitive freezing and thawing of specimens should be avoided.

The purpose of specimen storage information is to provide guidance to users; however, users may validate their own procedures for storing patient samples.

Procedure

Materials Provided

CTNI Flex® reagent cartridge, Cat. No. K6421

Materials Required But Not Provided

CTNI CAL, Cat. No. KC678

CTNI SDIL, Cat. No. KD692

Quality Control Materials

Test Steps

Sampling, reagent delivery, mixing, and processing are automatically performed by the Dimension Vista® System. For details of this processing, refer to your Dimension Vista® Operator's Guide.

Test Conditions

Sample Volume (delivered to the reaction vessel)	20 µL
Chemibead Reagent Volume	20 µL
Biotinylated Antibody Reagent Volume	20 µL

Sensibead Reagent Volume	13 µL
Assay Buffer Volume	100 µL
Temperature	37.0 °C
Reaction Time	10 minutes
Wavelength	680 and 612 nm
Type of Measurement	Chemiluminescence

Calibration

Calibration Material	CTNI Calibrator, Cat. No. KC678
Calibration Scheme	6 levels, n=3
Units	ng/mL [µg/L] [d] (ng/mL x 1) = [µg/L]
Typical Calibration Levels	Level 1 (Calibrator A): 0 ng/mL [µg/L] Level 2 (Calibrator B): 0.5 ng/mL [µg/L] Level 3 (Calibrator C): 4.0 ng/mL [µg/L] Level 4 (Calibrator D): 8.0 ng/mL [µg/L] Level 5 (Calibrator E): 20.0 ng/mL [µg/L] Level 6 (Calibrator F): 41.0 ng/mL [µg/L]
Calibration Frequency	Every 30 days for any one lot Calibration interval may be extended based on acceptable verification of calibration.
A new calibration is required:	• For each new lot of Flex® reagent cartridges • After major maintenance or service, if indicated by quality control results • As indicated in laboratory quality control procedures • When required by government regulations

d. Système International d'Unités [SI units] are in brackets.

Quality Control

Follow government regulations or accreditation requirements for quality control frequency. At least once each day of use, analyze two levels of a Quality Control (QC) material with known cardiac troponin I concentrations. Follow your laboratory internal QC procedures if the results obtained are outside acceptable limits.

Results: The instrument calculates the concentration of cardiac troponin I in ng/mL [µg/L] using the calculation scheme described in your Dimension Vista® Operator's Guide.

Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation and other findings.

Analytical Measurement Range (AMR): 0.015–40 ng/mL [µg/L]

This is the range of analyte values that can be measured directly from the specimen without any dilution or pretreatment that is not part of the usual analytical process and is equivalent to the assay range.

- Samples with results in excess of 40 ng/mL [µg/L] should be repeated on dilution.

  Manual Dilution: Dilute with CTNI Sample Diluent (Cat. No. KD692) to obtain results within reportable range. Enter dilution factor on the instrument, but no greater than 1:5. Reassay. Resulting readout is corrected for dilution.

  Autodilution (AD): Autodilution requires onboard CTNI SDIL (Cat. No. KD692). The autodilute sample volume is 20 µL (dilution factor = 5) for serum/plasma to obtain results within the analytical measurement range.
- Samples with results less than 0.015 ng/mL [µg/L] will be reported as "less than 0.015 ng/mL [µg/L]" by the instrument.

Limitations of Procedure

Patient samples may contain heterophilic antibodies that could react in immunoassays to give falsely elevated or depressed results. This assay has been designed to minimize interference from heterophilic antibodies.Nevertheless, complete elimination of this interference from all patient specimens cannot be guaranteed. A test result that is inconsistent with the clinical picture and patient history should be interpreted with caution. [17,26]

The instrument reporting system contains flags and comments to provide the user with information regarding instrument processing errors, instrument status information and potential errors in cardiac troponin I results. Refer to your Dimension Vista® Operator's Guide for the meaning of report flags and comments. Any report containing flags and/or comments should be addressed according to your laboratory's procedure manual and not reported.

Expected Results: In a study of 199 serum samples from apparently healthy individuals, the reference interval encompassing the 99th percentile for the Dimension Vista® CTNI method was as follows:

N	Range encompassing the 99th Percentile
199	**0.00–0.045 ng/mL [µg/L]**

Each laboratory should establish its own expected values for CTNI as performed on the Dimension Vista® System.

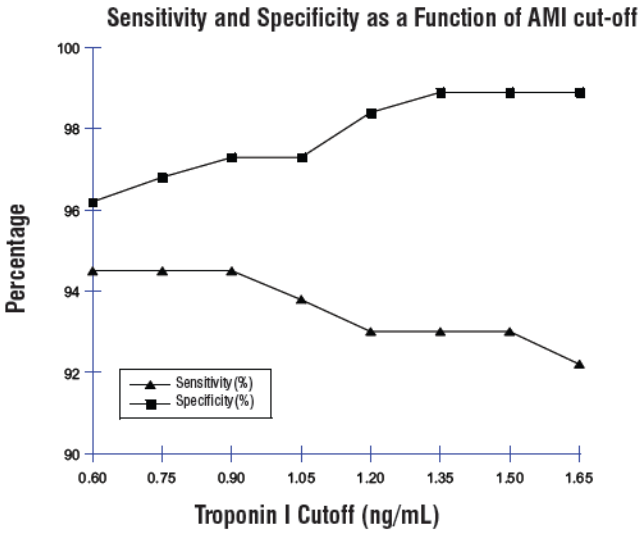
Interpretation of Results

The temporal evaluation of cardiac troponin-I concentration is a useful tool in the diagnosis of myocardial infarction. Serial samples from a patient with a myocardial infarction will result in the classic rise and fall in cardiac troponin I concentration observed with other markers of myocardial infarction such as CK-MB. Unlike CK-MB, cardiac troponin-I values generally remain elevated above the reference range for several (5–9) days.[2,3,4] The National Academy of Clinical Biochemistry (NACB) recommends serial sampling at admission, 2–4 hours, 6–9 hours, and 12–24 hours (optional).[19] Clinical studies indicate that elevated levels of cardiac troponin I are a useful indicator of myocardial injury for a range of acute coronary syndromes including unstable angina, non Q-Wave and Q-wave myocardial infarction.[4,5,6,7,8] Each institution should establish its own reference interval and cutoffs to ensure proper representation of specific populations, taking into account current practice and criteria for diagnosing AMI at its institution. Other conditions which can lead to myocardial injury, such as cardiac contusion and myocarditis, have the potential to cause elevations in the circulating concentrations of proteins found in the myocardium, including cardiac troponin I. Factors such as these should be considered when interpreting results.[20]

Risk Stratification: Statistically significant increases in mortality have been observed as a function of increasing levels of cardiac troponin-I. In patients with acute coronary syndromes such as unstable angina or non-Q-wave myocardial infarction, cardiac troponin-I levels provide useful prognostic information and aid in early detection of such patients with an increased risk of death.[8] A joint committee from the American College of Cardiology (ACC) and the American Heart Association (AHA) has defined the short-term risk of death or non-fatal MI in association with troponin levels as high risk with elevated (>0.1 ng/mL) levels, intermediate risk with slightly elevated (<0.1 ng/mL) levels, and low risk for normal levels.[20]

ESC/ACC Recommended Definition of AMI: A joint committee from the European Society of Cardiologists (ESC) and the American College of Cardiology (ACC) has recommended a redefinition of myocardial infarction (MI). The committee defines MI as the typical rise and gradual fall of troponin or more rapid raise and fall of CK-MB in conjunction with ischemic symptoms, pathologic ECG Q waves, ECG ST segment elevation/depression, and/or coronary artery intervention. The committee further recommends that an increased troponin level should be defined as a measurement exceeding the 99th percentile of the reference interval and that an acceptable imprecision (coefficient of variation) for measurements at the 99th percentile is <10%.[9] The 99th percentile of the reference interval for the Dimension Vista® CTNI method was determined to be 0.045 ng/mL [µg/L] and the 10% CV limit was estimated to be <0.04 ng/mL [µg/L].

W.H.O. Definition of AMI: The definition of AMI as described by the World Health Organization (WHO) requires satisfying two of the following criteria for confirmation of acute myocardial infarction: electrocardiogram changes consistent with infarction, temporal changes in cardiac marker levels, chest discomfort of significant duration (≥ 20 minutes).[21] In a study[22] performed with the Stratus® II cardiac Troponin-I assay, Troponin-I cutoffs in the range 0.6–1.5 ng/mL were found to be consistent with the WHO criteria for AMI. This was a multi-center study which included 314 patients presenting with chest pain, 128 of whom ruled-in for AMI. Satisfying the biomarker criteria for AMI in this study required a CKMB value which exceeded 5.6 ng/mL along with a temporal change of at least 3 ng/mL. Both clinical sensitivity and clinical specificity were found to be greater than 90% across this range of cutoff values when serial sampling of patients with chest pain was performed (see figure below). This study is provided for reference based on comparability of results between the Stratus® II cardiac Troponin-I method and the Dimension® RxL cardiac Troponin-I assay (Dimension® RxL = 1.10 Stratus® II–0.075; r = 0.992; n = 111; range = 0–47.9 ng/mL) and comparability of results between the Dimension® RxL cardiac Troponin-I assay and the Dimension Vista® cardiac Troponin-I assay (data provided in this product insert under Method Comparison). It is important to note that Troponin-I cutoffs in the range of 0.6–1.5 ng/mL represent a higher level of myocardial damage than the 99th percentile cutoff recommended by the European Society of Cardiology and American College of Cardiology (ESC/ACC). The ranges reported above should be used only as a guide.



Maximum Observed Repeatability

The expected maximum observed standard deviations for repeatability (within-run precision) using n = 5 replicates at the following cardiac troponin I concentrations are:

CTNI concentration	Acceptable SD Maximum
0.5 ng/mL [µg/L]	0.063 ng/mL [µg/L]
8.0 ng/mL [µg/L]	0.939 ng/mL [µg/L]

A system malfunction may exist if the acceptable SD maximum is exceeded.

Specific Performance Characteristics

The following data represent typical performance for the Dimension Vista® System.

Precision[23, e]

Material	Mean ng/mL[µg/L]	Standard Deviation (% CV) Repeatability		Within-Lab	
Serum Pool	0.123	0.005	(4.2)	0.007	(5.8)
Serum Pool	0.55	0.012	(2.3)	0.016	(2.9)
Serum Pool	31.4	0.95	(3.0)	1.18	(3.8)
Liquichek™ Cardiac Markers Control LT					
Level 2	0.28	0.016	(5.8)	0.019	(6.6)
Level 3	1.41	0.021	(1.5)	0.049	(3.4)

e. CLSI/NCCLS EP5-A2 was used. During each day of testing, two separate runs with two test samples for each test material were analyzed for 20 days.
Liquichek™ Cardiac Markers Control LT is a trademark of Bio-Rad Laboratories, Irvine, CA 92618.

Method Comparison[24]

Regression Statistics[f]

Comparative Method	Slope	Intercept ng/mL [µg/L]	Correlation Coefficient	n
Dimension® RxL system	1.0150	-0.003	0.993	197[g]

f. CLSI/NCCLS EP9-A2 was used. The method used to fit the linear regression line was ordinary least squares.

g. The range of 197 values in the correlation study was 0.0–35.72 ng/mL [µg/L].

Specificity

Hemolysis, Icterus, Lipemia (HIL) Interference

The CTNI method was evaluated for interference according to CLSI/NCCLS EP7-A2.[25] Bias is the difference in the results between the control sample (without the interferent) and the test sample (contains the interferent) expressed in percent. Bias exceeding 10% is considered interference.

Substance Tested	Substance Concentration	CTNI ng/mL [µg/L]	Bias* %
Hemoglobin (hemolysate)	Hemoglobin (monomer) 500 mg/dL [0.31 mmol/L]	0.945	<10
Bilirubin (unconjugated)	40 mg/dL [684 µmol/L]	0.907	<10
Bilirubin (conjugated)	40 mg/dL [684 µmol/L]	0.879	<10
Lipemia (Intralipid®)	3000 mg/dL [33.9 mmol/L]	0.970	<10
Lipemia cholesterol	500 mg/dL [5.7 mmol/L]	0.941	<10

Intralipid® is a registered trademark of Fresenius Kabi AG, Bad Homburg, Germany.

*** Analyte results should not be corrected based on this bias.**

Non Interfering Substances

The following substances have no significant effect (less than 10%) on the CTNI method when added to a 1.5 ng/mL [µg/L] serum pool at the concentrations indicated:

Compound	Concentration	SI Units
Acetaminophen	20 mg/dL	1323 µmol/L
Allopurinol	2.5 mg/dL	184 µmol/L
Amikacin	15 mg/dL	256 µmol/L
Ampicillin	5 mg/dL	143 µmol/L
Ascorbic acid	3 mg/dL	170 µmol/L
Atenolol	1.0 mg/dL	37.6 µmol/L
Caffeine	10 mg/dL	515 µmol/L
Carbamazepine	12 mg/dL	508 µmol/L
Captopril	5.0 mg/dL	230 µmol/L
Cholesterol	500 mg/dL	12.9 mmol/L
Chloramphenicol	25 mg/dL	774 µmol/L
Chlordiazepoxide	2 mg/dL	67 µmol/L
Chlorpromazine	5 mg/dL	157 µmol/L
Cimetidine	10 mg/dL	396 µmol/L
Cinnarizine	3.0 mg/dL	81.4 µmol/L
Creatinine	30 mg/dL	2652 µmol/L
Cyclosporine A	4000 ng/mL	3.3 µmol/L
Dextran 75	2500 mg/dL	333 µmol/L
Diazepam	2 mg/dL	70 µmol/L
Digoxin	5 ng/mL	6.4 nmol/L
Dopamine	65 mg/dL	3.4 mmol/L
Erythromycin	20 mg/dL	272 µmol/L
Ethanol	350 mg/dL	76 mmol/L
Ethosuximide	30 mg/dL	2125 µmol/L
Furosemide	2 mg/dL	61 µmol/L
Gentamicin	12 mg/dL	251 µmol/L
Sodium heparin	8 U/mL	8000 IU/L
Ibuprofen	40 mg/dL	1939 µmol/L
Isosorbide dinitrate	6.0 mg/dL	254 µmol/L
Lidocaine	6 mg/dL	256 µmol/L
Lipemia (triglyceride)	3000 mg/dL	33.9 mmol/L
Lithium chloride	3.5 mg/dL	5.07 mmol/L
L-thyroxine	60 µg/dL	0.77 µmol/L
Methyldopa	2.5 mg/dL	118 µmol/L
Nicotine	2 mg/dL	123 µmol/
Nifedipine	6.0 mg/dL	173 µmol/L
Penicillin G	25 U/mL	25000 U/L

Compound	Concentration	SI Units
Pentobarbital	10 mg/dL	442 µmol/L
Phenobarbital	15 mg/dL	646 µmol/L
Phenytoin	10 mg/dL	396 µmol/L
Primidone	10 mg/dL	458 µmol/L
Propoxyphene	0.4 mg/dL	12 µmol/L
Propranolol	0.15 mg/dL	5.1 µmol/L
Protein, human albumin	6 g/dL	60 g/L
Protein, human IgG	3.5 g/dL	35 g/L
Salicylic acid	50 mg/dL	3.6 mmol/L
Theophylline	25 mg/dL	1388 µmol/L
Urea	500 mg/dL	83.3 mmol/L
Uric acid	20 mg/dL	1.2 mmol/L
Valproic acid	50 mg/dL	3467 µmol/L
Verapamil	16 mg/dL	0.33 µmol/L

Hook Effect

One step sandwich immunoassays are susceptible to a high-dose "hook effect", where an excess of antigen prevents simultaneous binding of the capture and detection antibodies to a single analyte molecule.[18] The CTNI method shows no hook effect up to 1000 ng/mL [µg/L].

Cross-reactivity

CTNI method is specific for cardiac troponin I. Cardiac troponin I was evaluated for cross-reactivity in the presence of other myofibrillar proteins found in human muscle. The percent cross-reactivity was calculated as follows:

$$\% \text{ cross reactivity} = \frac{\text{measured analyte} - \text{control analyte (ng/mL[µg/L])}}{\text{metabolite added}} \times 100$$

Crossreactant	Concentration	SI Units	Percent Crossreactivity
Troponin-C (cardiac)	1000 ng/mL	1000 µg/L	None
Troponin-T (cardiac human)	1000 ng/mL	1000 µg/L	0.06
Troponin-I (skeletal human)	1000 ng/mL	1000 µg/L	0.12
Troponin-I (skeletal human)	280 ng/mL	280 µg/L	0.13

Recovery:

Serum samples containing elevated and low levels of CTNI were tested using different mixing volumes. The observed values were then compared to the expected values for each mixture.

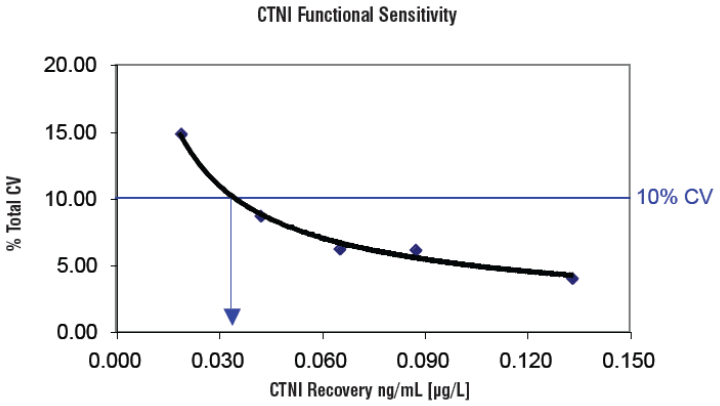
Sample Mixture	CTNI Serum Sample 1	CTNI Serum Sample 2	1:1 Mixture Expected	1:1 Mixture Obtained	CTNI Percent Recovery
A	16.03	0.001	8.02	7.95	99.2
B	11.275	0.845	6.1	6.00	99.1

Analytical Sensitivity: 0.015 ng/mL [µg/L]

This sensitivity is defined as the concentration that corresponds to the mean value (n=20) plus two standard deviations of the Low level A (0 ng/mL [µg/L]) CTNI Calibrator (or sample devoid of CTNI).

Limit of Quantitation (Functional Sensitivity): Evaluation of the 10% CV limit

Functional sensitivity was evaluated by determining total imprecision of natural TnI serum samples. Total imprecision was measured by a two replicate per day, twenty day ANOVA study. The limit of quantitation (functional sensitivity /imprecision profile) for the Dimension Vista® troponin method corresponds to a coefficient of variation (CV) of 10% at a troponin I concentration of <0.04 ng/mL [µg/L]. Imprecision as demonstrated in the Imprecision Study graph is indicative of a high sensitivity method.



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