

ADVIA Centaur®
ADVIA Centaur® XP
ADVIA Centaur® XPT
 Immunoassay Systems

TnI-Ultra®

Current revision and date ^a	Rev. L, 2014-08	
Product Name	ADVIA Centaur® TnI-Ultra® assay (500 tests) ADVIA Centaur TnI-Ultra assay (100 tests)	REF 02790309 REF 02789602
Systems	ADVIA Centaur system ADVIA Centaur XP system ADVIA Centaur XPT system	
Materials Required but Not Provided	ADVIA Centaur Wash 1 (2 x 1500 mL) ADVIA Centaur Wash 1 (2 x 2500 mL)	REF 01137199 (112351) REF 03773025
Specimen Types	Serum, heparinized plasma, EDTA plasma	
Assay Range	0.006–50 ng/mL (µg/L)	
Reagent Storage	2–8°C	
Reagent On-System Stability	28 days	

^a In Rev. B or later, a vertical bar in the margin indicates a technical update to the previous version.

Intended Use

For *in vitro* diagnostic use in the quantitative determination of cardiac troponin I (cTnI) in serum, heparinized or EDTA plasma using the ADVIA Centaur®, ADVIA Centaur XP, and ADVIA Centaur XPT systems.

Cardiac troponin I determinations aid in the diagnosis of acute myocardial infarction and in the risk stratification of patients with non-ST segment elevation acute coronary syndromes with respect to relative risk of mortality, myocardial infarction (MI) or increased probability of ischemic events requiring urgent revascularization procedures.

Summary and Explanation

Troponin is a protein complex which regulates the contraction of striated muscle. It consists of three subunits which are located periodically along the thin filament of the myofibrils. Troponin C binds calcium, troponin T attaches to tropomyosin on the thin filament, and troponin I inhibits actomyosin ATPase.¹⁻³

Troponin I (TnI), an inhibitory protein of the troponin-tropomyosin complex, exists in three distinct isoforms: cardiac muscle, slow-twitch skeletal muscle, and fast-twitch skeletal muscle.⁴ Each isoform is encoded by a distinct gene, each with a unique amino acid sequence, leading to a 40% dissimilarity among isoforms.²⁻⁵ The cardiac form of troponin I is further unique having 31 additional amino acid residues on its N-terminal, not present in the skeletal forms, which allows for specific polyclonal and monoclonal antibody development.⁶ The cardiac specificity of this isoform improves the accuracy of diagnosis in patients with acute or chronic skeletal muscle injury and possible concomitant myocardial injury, and is the basis for its selection as a cardiac marker in the diagnosis of acute MI.^{1,7}

cTnI is the only troponin isotype present in the myocardium and is not expressed during any developmental stage in skeletal muscle.^{2,7,8} cTnI has a molecular weight of 24,000 daltons.⁶ Clinical studies have reported that cTnI is released into the bloodstream within hours of the onset of symptoms of MI or ischemic damage. It can be detected at 3 to 6 hours following onset of chest pain with peak concentrations at 12 to 16 hours, and remains elevated for 5 to 9 days,⁹⁻¹¹ providing more opportunity for detecting MI or excluding the diagnosis.

Always analyze cTnI results in the context of time elapsed since patient presentation to the hospital. Serial sampling is recommended to detect the temporal rise and fall of troponin levels characteristic of MI.^{12,13} In accord with published recommendations, serial testing of cTnI at intervals of 2 to 4 hours for up to 12 to 24 hours is suggested to corroborate a single cTnI result. An elevated troponin alone is not sufficient to make the diagnosis of MI. Other markers, such as CK-MB and myoglobin, can be used in conjunction with cTnI results in aiding the diagnosis of MI.

A positive troponin result is not always indicative of MI. Other conditions resulting in myocardial cell damage can contribute to elevated cardiac troponin I levels. These conditions include, but are not limited to, myocarditis, cardiac surgery, angina, unstable angina, congestive heart failure, and non-cardiac related causes, such as, renal failure and pulmonary embolism.¹⁴⁻¹⁶

Definition of Acute Myocardial Infarction

The World Health Organization (WHO) criteria for defining Acute Myocardial Infarction (AMI) are the presence of two of the following three elements:¹²

- continual chest pain for greater than 20 minutes
- ECG changes with ST-segment elevation
- elevated cardiac markers

Because of its high clinical specificity and sensitivity, the Joint European Society of Cardiology/American College of Cardiology Committee recognize troponin as the preferred biochemical marker for myocardial damage.¹⁷ The committee also suggests that any amount of myocardial necrosis caused by ischemia should be labeled as an infarct. Individuals previously diagnosed as having severe, stable or unstable angina pectoris might thus be diagnosed today as having had a small MI. The ESC/ACC committee additionally recommends an imprecision level (coefficient of variation, or CV) for Troponin assays of $\leq 10\%$ CV at the 99th percentile of normal. Based on imprecision and other performance criteria, the ADVIA Centaur TnI-Ultra assay is a high sensitivity cTnI method.

As with all *in vitro* diagnostic assays, each laboratory should establish its own diagnostic cutoff which reflects criteria for AMI diagnosis at their institution and is representative of specific populations.¹⁸

Risk Stratification Analysis of Acute Coronary Syndrome

Because of its cardiac specificity and sensitivity, cTnI has been used as a reliable marker in evaluating patients with unstable angina, a condition implying increased risk of MI and sudden death. Unstable angina patients with minimal values of cTnI are predicted to have a higher risk of short-term mortality. As the cTnI value progressively increases, the risk of mortality increases, presumably because the amount of myocardial damage also increases.^{19,20}

In a multicenter substudy of a clinical trial designed to assess the efficacy of low molecular weight heparin in the treatment of unstable angina and non Q-wave MI, blood specimens from 681 patients were analyzed for cTnI using the ACS:180® cTnI method. The 444 patients with levels of cTnI of at least 0.10 ng/mL (µg/L) had higher risk of morbidity and mortality than the 237 patients whose levels were less than 0.10 ng/mL (µg/L).²¹

cTnI results should always be analyzed in the context of time elapsed since patient presentation to the hospital. Serial sampling is recommended to detect the temporal rise and fall of troponin levels characteristic of MI.^{17,22} In accord with published recommendations, serial testing of cTnI at intervals of 2 to 4 hours for up to 12 to 24 hours is suggested in order to corroborate a single cTnI result. An elevated troponin alone is not sufficient to make the diagnosis of MI. Other markers such as CK-MB and myoglobin can be used in conjunction with cTnI results in aiding the diagnosis of MI.

Principles of the Procedure

The ADVIA Centaur TnI-Ultra assay is a three-site sandwich immunoassay using direct chemiluminometric technology. An ancillary reagent is included to reduce nonspecific binding. The Binary Lite reagent includes a polyclonal goat anti-troponin I antibody labeled with acridinium ester and 2 biotinylated mouse monoclonal anti-troponin I antibodies. The solid phase reagent is magnetic latex particles conjugated with streptavidin. All reagents are contained within the ReadyPack®.

The antibodies in the Binary Lite reagent bind to troponin I in the sample. The biotin contained in the immune complex then binds to the streptavidin-labeled magnetic particles.

Reagents

Reagent	Description	Storage	Reagent Stability
ADVIA Centaur TnI-Ultra ReadyPack primary reagent pack; Binary Lite Reagent	10.0 mL/reagent pack polyclonal goat anti-cTnI antibody (0.15 µg/mL) labeled with acridinium ester, 2 monoclonal mouse anti-cTnI antibodies labeled with biotin (2.0 µg/mL), in buffer with stabilizers and preservatives	2–8°C	Unopened: Stable until the expiration date on the carton On-system: 28 days
ADVIA Centaur TnI-Ultra ReadyPack primary reagent pack; Solid Phase Reagent	15.0 mL/reagent pack latex magnetic particles in buffer with stabilizers and preservatives	2–8°C	Unopened: Stable until the expiration date on the carton On-system: 28 days
ADVIA Centaur TnI-Ultra ReadyPack primary reagent pack; Ancillary Reagent	5.0 mL/reagent pack non-magnetic latex particles in buffer with sodium azide (< 0.1%)	2–8°C	Unopened: Stable until the expiration date on the carton On-system: 28 days
ADVIA Centaur UL Calibrator	2.0 mL/vial after reconstitution, low or high levels of bovine cTnI in goat serum with preservatives and stabilizers	2–8°C	Unopened: Stable until the expiration date on the vial Reconstituted: 1 day On-system: 4 hours
		≤ -20°C	Reconstituted: 30 days
ADVIA Centaur Wash 1 ^a WASH 1	1500 mL/pack phosphate-buffered saline with sodium azide (< 0.1%) and surfactant	2–25°C	Unopened: Stable until the expiration date on the pack On-system: 1 month
ADVIA Centaur Wash 1 ^a WASH 1	2500 mL/pack phosphate-buffered saline with sodium azide (< 0.1%) and surfactant	2–25°C	Unopened: Stable until the expiration date on the pack On-system: 1 month
ADVIA Centaur ReadyPack primary reagent pack; Probe Wash 4 ^b PW 4	25.0 mL/reagent pack 0.25 N sodium hydroxide	2–8°C	Unopened: Stable until the expiration date on the pack On-system: 1 month
ADVIA Centaur ReadyPack ancillary reagent pack; Multi-Diluent 11 ^b M-DIL 11	5.0 mL/pack tris buffer and goat serum with protein stabilizers and preservatives	2–8°C	Unopened: Stable until the expiration date on the pack On-system: 28 consecutive days after accessing the ancillary reagent pack
ADVIA Centaur Multi-Diluent 11 ^b M-DIL 11	10.0 mL/vial tris buffer and goat serum with protein stabilizers and preservatives	2–8°C	Unopened: Stable until the expiration date on the vial

^a See *Materials Required but Not Provided*

^b See *Optional Materials*

Warnings and Precautions

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



CAUTION

This device contains material of animal origin and should be handled as a potential carrier and transmitter of disease.

Contains sodium azide as a preservative. Sodium azide can react with copper or lead plumbing to form explosive metal azides. On disposal, flush reagents with a large volume of water to prevent buildup of azides. Disposal into drain systems must be in compliance with prevailing regulatory requirements.



H319, H315, H290 Warning!

P280, P264,

P305+P351+P338

Causes serious eye irritation. Causes skin irritation. May be corrosive to metals. Wear protective gloves/protective clothing/eye protection/face protection. Wash hands thoroughly after handling. IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
Contains: Sodium hydroxide; ADVIA Centaur Probe Wash 4

H412

P273, P501

Harmful to aquatic life with long lasting effects. Avoid release to the environment. Dispose of contents and container in accordance with all local, regional, and national regulations.
Contains: Microprotect; ADVIA Centaur UL Calibrator

Dispose of hazardous or biologically contaminated materials according to the practices of your institution. Discard all materials in a safe and acceptable manner and in compliance with prevailing regulatory requirements.

For *in vitro* diagnostic use.

Preparing Reagents

All reagents are liquid and ready to use.

Mix all primary reagent packs by hand before loading them onto the system. Visually inspect the bottom of the reagent pack to ensure that all particles are dispersed and resuspended. For detailed information about preparing the reagents for use, refer to the system operating instructions.

Note

- Discard the primary reagent packs at the end of the on-system stability interval.
- Do not use reagents beyond the expiration date.

Storing and Stability

Store the reagents upright at 2–8°C.

Protect reagent packs from all heat and light sources. Reagent packs loaded on the system are protected from light. Store unused reagent packs at 2–8°C away from heat and light sources.

All reagents are stable at 2–8°C until the expiration date on the packaging.

Specimen Collection and Handling

Serum, heparinized plasma, and EDTA plasma are the recommended sample types for this assay.

Evaluation of heparinized and EDTA plasma samples resulted in a mean 1% and 4% decrease in observed values, respectively, compared to serum. A comparison of values for pairs of serum and plasma specimens yielded the following Passing & Bablok equations:

heparinized plasma troponin I = 0.99 (serum troponin I) + 0.03 ng/mL (µg/L); n = 53

EDTA plasma troponin I = 0.96 (serum troponin I) + 0.02 ng/mL (µg/L); n = 31

It is not recommended that either plasma or serum samples from the same patient be used interchangeably with this test. Reference ranges should be established for the evaluation of serum samples, heparinized plasma, and EDTA plasma samples.

The following recommendations for handling and storing blood samples are furnished by the Clinical and Laboratory Standards Institute (CLSI):¹³





- Collect all blood samples observing universal precautions for venipuncture.
- Allow samples to clot adequately before centrifugation.
- Keep tubes stoppered and upright at all times.
- Do not use samples that have been stored at room temperature for longer than 4 hours.
- Tightly cap and refrigerate specimens at 2–8°C if the assay is not completed within 4 hours.
- Freeze samples at or below -20°C if the sample is not assayed within 24 hours.
- Freeze samples only once and mix thoroughly after thawing. Frozen specimens can remain frozen up to 1 month in non-frost free freezers.
- Frozen samples must be centrifuged at 2200 x g for 10 minutes before analysis.

The purpose of handling and storage information is to provide guidance to users. It is the responsibility of the individual laboratory to use all available references and/or its own studies when establishing alternate stability criteria to meet specific needs.

Procedure



Materials Provided

The following materials are provided:

REF	Contents	Number of Tests
02790309	5 ReadyPack primary reagent packs containing ADVIA Centaur TnI-Ultra Binary Lite Reagent, Solid Phase and ancillary reagent ADVIA Centaur TnI-Ultra Master Curve card 2 vials of lyophilized ADVIA Centaur low calibrator UL  2 vials of lyophilized ADVIA Centaur high calibrator UL  Barcode labels for the calibrators Calibrator UL Assigned Value Card	500
02789602	1 ReadyPack primary reagent pack containing ADVIA Centaur TnI-Ultra Binary Lite Reagent, Solid Phase and ancillary reagent ADVIA Centaur TnI-Ultra Master Curve card 1 vial of lyophilized ADVIA Centaur low calibrator UL  1 vial of lyophilized ADVIA Centaur high calibrator UL  Barcode labels for the calibrators Calibrator UL Assigned Value Card	100

Materials Required but Not Provided




The following materials are required to perform this assay, but are not provided:

Item	Description	
REF 01137199 (112351)	ADVIA Centaur Wash 1 	2 x 1500 mL/pack
REF 03773025	ADVIA Centaur Wash 1 ^a 	2 x 2500 mL/pack

^a for use with systems with 2500 mL capacity

Optional Materials

The following materials may be used to perform this assay, but are not provided:

Item	Description	
REF 05699280 (117228)	ADVIA Centaur Multi-Diluent 11 	2 ReadyPack ancillary reagent packs containing 5 mL/pack
REF 03479704 (111088)	ADVIA Centaur Multi-Diluent 11 	10 mL/vial
REF 02738323	ADVIA Centaur Tnl-Ultra Master Curve Material	5 x 1 mL
REF 04750940	ADVIA Centaur Probe Wash 4 	1 ReadyPack primary reagent pack containing 25.0 mL/pack

Assay Procedure

For detailed instructions on performing the procedure, refer to the system operating instructions.

The system automatically performs the following actions:

- Dispenses 100 µL of sample into a cuvette.
- Dispenses 100 µL of Binary Lite Reagent plus 50 µL of ancillary reagent and incubates for 2.75 minutes at 37°C.
- Dispenses 150 µL of Solid Phase Reagent and incubates for 5.0 minutes at 37°C.
- Separates, aspirates, and washes the cuvettes with Wash 1.
- Dispenses 300 µL each of Acid Reagent and Base Reagent to initiate the chemiluminescent reaction.
- Reports results according to the selected option, as described in the system operating instructions.

A direct relationship exists between the amount of troponin I present in the patient sample and the amount of relative light units (RLUs) detected by the system.

Preparing the System

Ensure that the system has sufficient primary and ancillary reagent packs. For detailed information about preparing the system, refer to the system operating instructions.

Load the ReadyPack reagent packs in the primary reagent area using the arrows as a placement guide. The system automatically mixes the primary reagent packs to maintain homogeneous suspension of the reagents. For detailed information about loading reagents, refer to the system operating instructions.

If automatic dilution of a sample is required, load ADVIA Centaur Multi-Diluent 11 in the ancillary reagent entry.

Preparing the Samples

This assay requires 100 µL of sample for a single determination. This volume does not include the unusable volume in the sample container or the additional volume required when performing duplicates or other tests on the same sample. For detailed information about determining the minimum required volume, refer to the system operating instructions.

Note The sample volume required to perform onboard dilution differs from the sample volume required to perform a single determination. For detailed information, refer to *Dilutions*.

Before placing samples on the system, ensure that samples have the following characteristics:

- Samples are free of fibrin or other particulate matter.
- Samples are free of bubbles.

On-System Stability

The ADVIA Centaur Tnl-Ultra assay reagents are stable unopened until the expiration date on the carton or onboard the system for 28 days.

Performing Calibration

For calibration of the ADVIA Centaur Tnl-Ultra assay, use the ADVIA Centaur Calibrator UL provided with each kit. The calibrators provided in this kit are matched to the ReadyPack primary reagent pack.

Note The Calibrator UL calibrators provided in this kit are matched to the Solid Phase and Binary Lite Reagent. Do not mix Calibrator UL lots with different lots of Solid Phase and Binary Lite Reagent.

Preparing Calibrators

Prepare calibrators using the following steps:

1. Add 2.0 mL of reagent water into each calibrator vial using a volumetric or precision pipet.

Note For information about reagent water, refer to the system operating instructions.

2. Let the calibrators stand undisturbed for 15–20 minutes at room temperature (20–30°C) to allow the lyophilized material to dissolve.
3. Gently swirl and invert the vials until homogeneous.

The calibrator can be aliquoted into sample cups that are sealed tightly. Freeze for up to 30 days and thaw only once. To ensure complete homogeneity, thawed calibrators must be gently mixed and inverted.

Using the Calibrator Assigned Value Card

Each lot of reagents contains a Calibrator Assigned Value card to facilitate entering the calibration values on the system. Enter the values using the barcode scanner or the keyboard. For detailed information about entering calibrator values, refer to the system operating instructions.

Scheduling the Calibrators

The calibration interval for the ADVIA Centaur Tnl-Ultra assay is 28 days.

1. Schedule the calibrators to the worklist:
 - a. Schedule Calibrator UL for the required tests.
 - b. Continue to schedule quality control and patient samples for the required tests.

2. Label the sample cups, one with a Low Calibrator barcode label and another with a High Calibrator barcode label.
Because calibrator barcode labels are lot number specific, use barcode labels that correspond to the lot number of the calibrator used.
3. Gently mix the Low and High Calibrators.
4. Dispense at least 1.0 mL of Low and High Calibrator into the labeled sample cups.
The sample cups are marked at 1.0 mL intervals to assist in filling.
The required calibrator volume depends on how many assays are being calibrated using these calibrators and the number of calibrator replicates.
5. Load the calibrator sample cups on the system.
The Low Calibrator cup position must precede the High Calibrator cup position.
Ensure that the appropriate reagents are loaded on the system.
6. Continue loading quality control and patient samples.
7. Start the system, if required.

Calibration Frequency

Calibrate the assay at the end of the 28-day calibration interval.

Additionally, the ADVIA Centaur TnI-Ultra assay requires a two-point calibration:

- When changing lot numbers of primary reagent packs.
- When replacing system components.
- When quality control results are repeatedly out of range.

Using Barcode Labels

Note Calibrator barcode labels are lot-number specific. Do not use barcode labels from one lot of calibrators with any other lot of calibrators.

Use the Calibrator UL barcode labels to label the Low and High Calibrator sample cups when performing the TnI-Ultra assay. Place the barcode label on the sample cup so that the readable characters on the side of the label are vertical on the sample cup.

Performing Master Curve Calibration

The ADVIA Centaur TnI-Ultra assay requires a Master Curve calibration when using a new lot number of Binary Lite Reagent and Solid Phase. For each new lot number of Binary Lite Reagent and Solid Phase, use the barcode reader or keyboard to enter the Master Curve values on the system. The Master Curve card contains the Master Curve values. For detailed information about entering calibration values, refer to the system operating instructions.

Performing Quality Control

Follow government regulations or accreditation requirements for quality control frequency.

For detailed information about entering quality control values, refer to the system operating instructions.

To monitor system performance and chart trends, as a minimum requirement, two levels of quality control material should be assayed on each day that samples are analyzed. Quality control samples should also be assayed when performing a two-point calibration. Treat all quality control samples the same as patient samples.

Siemens Healthcare Diagnostics recommends the use of commercially available quality control materials with at least 2 levels (low and high). A satisfactory level of performance is achieved when the analyte values obtained are within the Acceptable Control Range for the system or within your range, as determined by an appropriate internal laboratory quality control scheme.

Taking Corrective Action

If the quality control results do not fall within the Expected Values or within the laboratory's established values, do not report results. Take the following actions:

- Verify that the materials are not expired.
- Verify that required maintenance was performed.
- Verify that the assay was performed according to the instructions for use.
- Rerun the assay with fresh quality control samples.
- If necessary, contact your local technical support provider or distributor for assistance.

Results

Calculation of Results

For detailed information about how the system calculates results, refer to the system operating instructions.

The system reports serum troponin I results in ng/mL (common units) or µg/L (SI units), depending on the units defined when setting up the assay. The conversion formula is 1.0 ng/mL = 1.0 µg/L.

Dilutions

The sample volume required to perform onboard dilution differs from the sample volume required to perform a single determination. Refer to the following information for the sample volume required to perform onboard dilutions:

Dilution	Sample Volume (µL)
1:2	150
1:5	60
1:10	30

The following information pertains to dilutions:

- The assay range is 0.006 to 50 ng/mL (µg/L). Patient samples with troponin I levels greater than 50 ng/mL (µg/L) must be diluted and retested to obtain quantitative results.
- Patient samples can be automatically diluted by the system or prepared manually.
- For automatic dilutions, ensure that ADVIA Centaur Multi-Diluent 11 is loaded and set the system parameters as follows:

Dilution point: ≤ 50 ng/mL (µg/L)

Dilution factor: 2, 5, 10

For detailed information about automatic dilutions, refer to the system operating instructions.

- Manually dilute the patient samples when patient results exceed the linearity of the assay using automatic dilution, or when laboratory protocol requires manual dilution.
- Use Multi-Diluent 11 to manually dilute patient samples, and then load the diluted sample in the sample rack, replacing the undiluted sample.
- Ensure that results are mathematically corrected for dilution. If a dilution factor is entered when scheduling the test, the system automatically calculates the result.

Interpretation of Results

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

Limitations

The following information pertains to limitations of the assay:

- Do not pour the calibrators back into the vials after calibration because evaporation could occur, which may affect performance.
- Dispose of any calibrator remaining in the sample cups after 4 hours.
- Do not refill calibrator sample cups when the contents are depleted. If required, dispense fresh calibrators.
- Whenever Allergy Screen or sIgE reagents are used on the same ADVIA Centaur system as ADVIA Centaur TnI-Ultra reagents, ensure that sufficient Probe Wash 4 is available to eliminate any potential interference.
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays.²³ Patients routinely exposed to animals or to animal serum products can be prone to this interference and anomalous values may be observed. Additional information may be required for diagnosis.
- Samples from patients receiving preparations of mouse monoclonal antibodies for therapy or diagnosis may contain Human Anti-Mouse Antibodies (HAMA). Such samples may show either falsely elevated or falsely depressed values when tested with this method.²⁴

Expected Values

A reference range study was conducted using the ADVIA Centaur TnI-Ultra assay based on guidance from the Clinical and Laboratory Standards Institute (CLSI) Protocol C28-A2.²⁵ The study, which used 1845 fresh serum, lithium heparin plasma, and EDTA plasma samples from 648 apparently healthy individuals ranging from 17–91 years of age, demonstrated a 99th percentile of 0.04 ng/mL (µg/L). The potential range of results for the 99th percentile is 0.02 to 0.06 ng/mL (µg/L) for the ADVIA Centaur family of systems, dependent upon sample type, instrument, and reagent lot.

As with all *in vitro* diagnostic assays, each laboratory should establish its own diagnostic cutoff which reflects criteria for AMI diagnosis at their institution and is representative of specific populations.²⁵

The precision curve for the ADVIA Centaur TnI-Ultra assay demonstrates a total coefficient of variation of 10% at a level of 0.03 ng/mL (µg/L). This level of imprecision shows a CV of ≤ 10% at the 99th percentile of the reference population indicating that the TnI-Ultra assay meets the definition of a high sensitivity Troponin method as described by the ESC/ACC recommendations. Refer to *Precision*.

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. The Risk Stratification cutpoint was previously established with the ACS:180 cTnI assay at a level of 0.1 ng/mL (µg/L).

Performance Characteristics

Clinical Performance

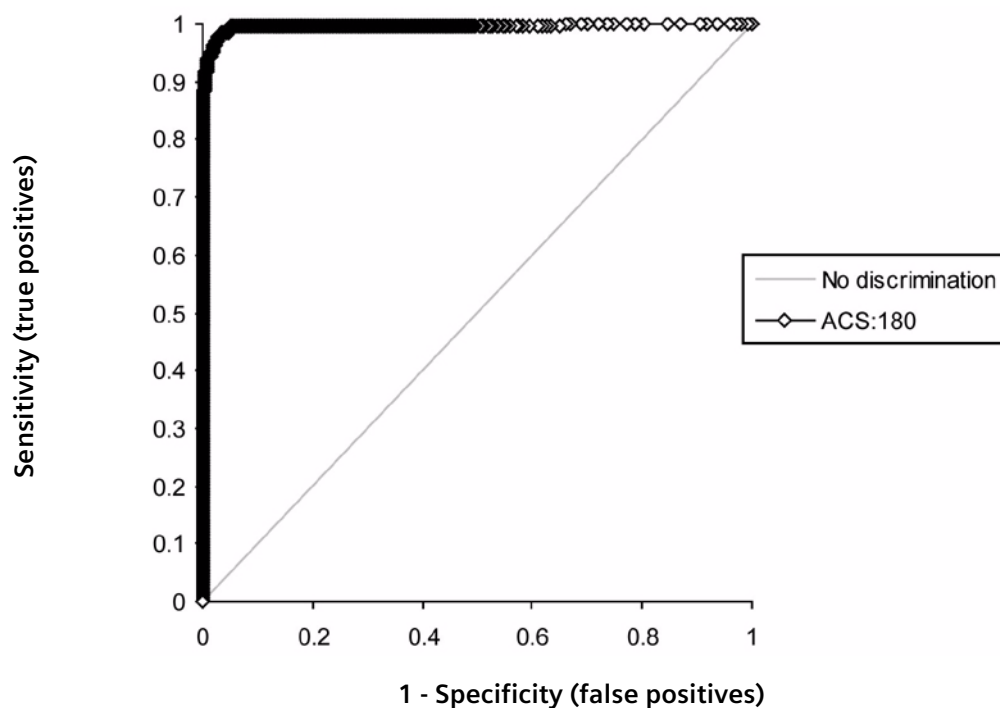
World Health Organization Definition for Diagnosis of MI

Utilizing the historical definition of MI as described by the World Health Organization (WHO), evaluation of a population consisting of patients from multiple clinical sites was previously performed using the ACS:180 cTnI assay. Clinical sensitivity and specificity were determined versus clinical diagnosis for 278 patients using serum samples. The patient population which included both males and females consisted of 112 individuals who ruled-in for AMI and 166 individuals who ruled-out for AMI. At least two of the following findings were present to establish clinical diagnosis:

- chest discomfort of ≥ 20 minutes
- abnormal ECG
- elevated cardiac markers

Results from clinical data were analyzed based on Receiver Operating Characteristics (ROC) plots using the guidelines presented in CLSI document GP10-A.²⁶ A 0.9 ng/mL ($\mu\text{g/L}$) diagnostic cutoff was determined for the ACS:180 cTnI assay.

The ROC analysis for the ACS:180 assay is presented in the following figure.



The following table summarizes the sensitivity and specificity of the ACS:180 results.

Method	% Sensitivity	% Specificity
ACS:180 cTnI	97.3	97.0
No. Patients (n)	112	166
95% Confidence Interval (CI)	92.4–99.4	93.1–99.0

The agreement between the ACS:180 cTnI assay and the ADVIA Centaur TnI-Ultra assay is shown in *Accuracy / Method Comparison*. Using the relationship between the two assays, the WHO-defined cutoff for the ADVIA Centaur TnI-Ultra method is 0.78 ng/mL (µg/L).

The cutoff and sensitivity/specificity information above should only be used as a guide when determining the appropriate cutoff for your institution. Since sensitivity and specificity are influenced by the cutoff, institutions should select a cutoff based on their specific sensitivity and specificity requirements. The WHO-defined cutoff reflects a higher level of myocardial damage than the information detailed in the ESC/ACC recommendation.

ESC/ACC Recommendation

A joint committee of the European Society of Cardiology and the American College of Cardiology has recommended a redefinition of MI. As part of this redefinition, the committee has suggested that an increased troponin level should be defined as a measurement exceeding the 99th percentile of the reference interval and that an acceptable imprecision (CV) for measurements at the 99th percentile is ≤ 10%.

The overall 99th percentile for the ADVIA Centaur TnI-Ultra assay is 0.04 ng/mL (µg/L).

The potential range of results for the 99th percentile is 0.02 to 0.06 ng/mL (µg/L) for the ADVIA Centaur family of systems, dependent upon sample type, instrument, and reagent lot. This was established utilizing 1845 fresh samples from 648 apparently healthy individuals.

Analytical Measuring Range

The ADVIA Centaur TnI-Ultra assay measures troponin I concentrations up to 50 ng/mL (µg/L) with a minimum detectable concentration (analytical sensitivity) of 0.006 ng/mL (µg/L). Analytical sensitivity is defined as the concentration of troponin I that corresponds to the RLUs that are two standard deviations greater than the mean RLUs of 20 replicate determinations of the TnI-Ultra zero standard.

Specificity

The ADVIA Centaur TnI-Ultra assay shows high specificity for cTnI. The following compounds were added at the concentration indicated to a sample with known cTnI concentration. ADVIA Centaur TnI-Ultra assay results from the spiked samples were compared with those of unspiked control samples. Percent cross-reactivity is calculated as:

$$\% \text{ cross-reactivity} = \frac{(\text{concentration of spiked sample} - \text{concentration of unspiked sample})}{\text{concentration of compound}} \times 100$$

Cross-reactant	Amount (ng/mL) (µg/L)	% Cross-reactivity
Cardiac Troponin T	1000	ND ^a
Skeletal Troponin I	1000	< 0.007
Tropomyosin	1000	ND
Actin	1000	< 0.005
Troponin C	1000	< 0.005
Myosin Light Chain	1000	ND
Myoglobin	1000	ND
CK-MB	1000	ND

a ND = Not Detectable

Interference testing was determined according to CLSI Document EP7-A2.²⁷

Sensitivity

The functional sensitivity is defined as the lowest cTnI concentration determined at a coefficient of variation of 20%. The ADVIA Centaur TnI-Ultra assay functional sensitivity was determined to be 0.017 ng/mL (µg/L). The total % CV profile in the assay range of 0.007 to 0.182 ng/mL (µg/L) is shown in *Precision*.

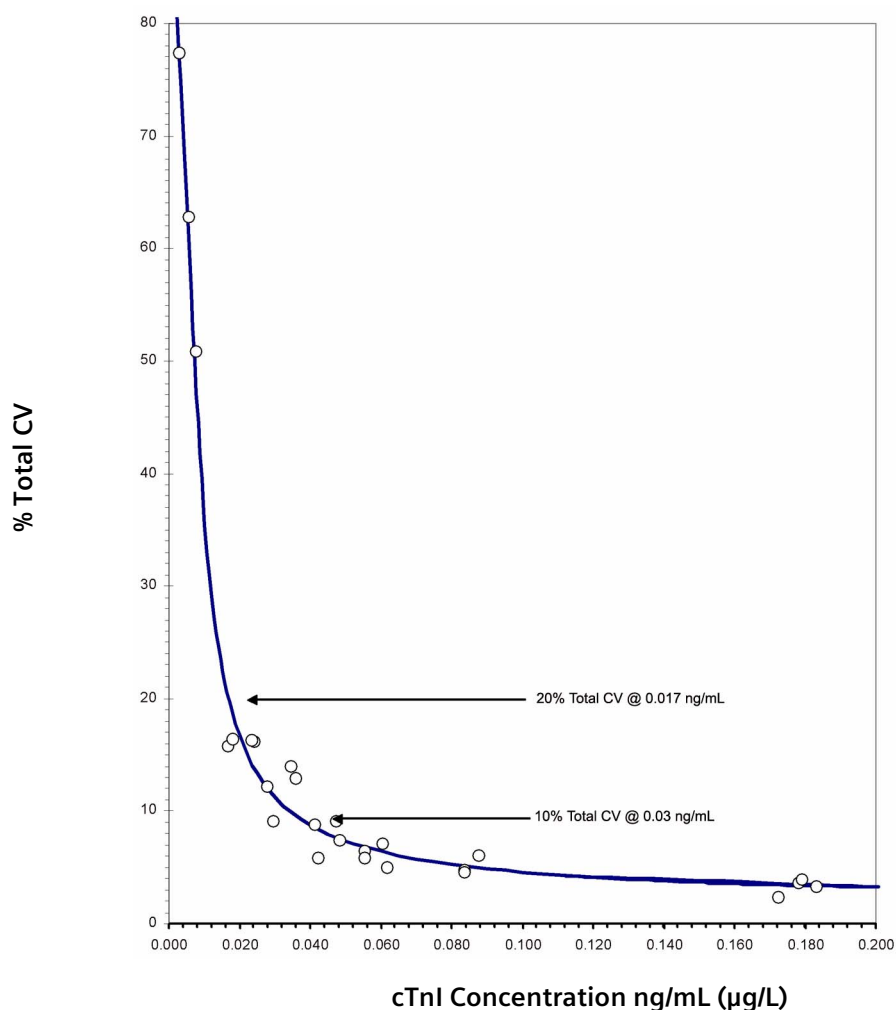
Precision

Six control products were assayed 2 times in each of 20 runs over a 20-day period on 2 systems. The following results were obtained:

Mean (ng/mL) (µg/L)	Within-run % CV	Total % CV
0.08	5.1	5.3
0.18	3.4	4.1
0.64	2.1	2.9
2.94	1.3	2.7
10.7	1.7	2.9
27.2	1.9	3.0

To assess low-end precision, controls and a low cTnI concentration serum panel were assayed in triplicate in each of 20 runs over a 20-day period. The following plot illustrates the mean TnI concentration versus total CV. These results yield a 10% Total CV at 0.03 ng/mL (µg/L).

Precision Curve



Accuracy / Method Comparison

The relationship between the ADVIA Centaur TnI-Ultra assay, the ACS:180 cTnI assay, the ADVIA Centaur cTnI assay, and the Beckman Coulter Access AccuTnI assay are described by using the Passing & Bablok method conversion:

ADVIA Centaur TnI-Ultra = 0.87 (ACS:180 cTnI) - 0.02 ng/mL (µg/L), $r = 0.97$;

334 serum samples from 0.1 to 30.9 ng/mL (µg/L)

ADVIA Centaur TnI-Ultra = 0.94 (ADVIA Centaur cTnI) + 0.01 ng/mL (µg/L), $r = 0.98$;

1039 lithium heparin samples from 0.1 to 46.0 ng/mL (µg/L)

ADVIA Centaur TnI-Ultra = 1.66 (Access AccuTnI) + 0.005 ng/mL (µg/L), $r = 0.98$;

542 lithium heparin samples from 0.0 to 37.4 ng/mL (µg/L)

Interferences

The following endogenous substances were added to human-based samples at the concentrations listed and evaluated for potential interference in the ADVIA Centaur TnI-Ultra assay. The results demonstrate a $\leq 10\%$ interference from each substance:

Specimens that have . . .	Demonstrate $\leq 10\%$ change in results up to . . .
hemolysis	500 mg/dL of hemoglobin
lipemia	1000 mg/dL of triglycerides
icterus	20 mg/dL of conjugated bilirubin
	20 mg/dL of unconjugated bilirubin
human IgG	12 g/dL of protein
biotin	10 ng/mL of biotin

The biotin level in a normal population is approximately 0.3 to 1.0 ng/mL (1.2 to 4.3 nmol/L).¹⁸ Biotin could be higher if a biotin supplement is used, particularly in dialysis patients taking multiple doses of vitamins. In samples with biotin levels greater than 10 ng/mL (41 nmol/L), the troponin-I assay may demonstrate a 10% decrease in results.

To assess clinical specificity, two groups of chronic renal failure patients were investigated before and after dialysis. Single specimens were evaluated from each patient.

Chronic Renal Failure	Pre-Dialysis Result	Post-Dialysis Result
No. of Patients	25	25
Range: ng/mL (μ g/L)	< 0.006–0.12	< 0.006–0.354
Median: ng/mL (μ g/L)	0.008	0.033

The following drugs were added to a human serum-based sample at the concentrations indicated and evaluated for potential interference in the ADVIA Centaur TnI-Ultra assay. The results demonstrated a $\leq 10\%$ interference from each drug.

Drug	Drug Concentration	Drug	Drug Concentration
Ampicillin	53 μ g/mL	Theophylline	40 μ g/mL
Quinidine	12 μ g/mL	Erythromycin	60 μ g/mL
Propanolol	10 ng/mL	Acetaminophen	250 ng/mL
Captopril	5 μ g/mL	Diclofenac	50 μ g/mL
Atenolol	10 μ g/mL	Aspirin	600 μ g/mL
Digoxin	200 ng/mL	Nitrofurantoin	4 μ g/mL
Allopurinol	400 μ g/mL	Cinnarizine	400 μ g/mL
Verapamil	2 μ g/mL	L-Ascorbic Acid	40 μ g/mL
Oxytetracycline	15 μ g/mL	Methyl DOPA	15 μ g/mL
Nifedipine	400 ng/mL	Nystatin	6.25 μ g/mL

Dilution Recovery

Ten human serum samples in the range of 9.55 to 45.02 ng/mL (µg/L) of cTnI were diluted 1:2, 1:5 and 1:10 with Multi-Diluent 11 and assayed for recovery and parallelism.

The recoveries ranged from 60% to 118% with a mean of 93%.

Sample	Dilution	Observed (ng/mL) (µg/L)	Expected (ng/mL) (µg/L)	Recovery %
1	—	9.55		
	1:2	4.67	4.77	98
	1:5	1.91	1.91	100
	1:10	0.89	0.95	93
	Mean			97
2	—	13.59		
	1:2	6.02	6.80	88
	1:5	2.25	2.72	83
	1:10	1.02	1.36	75
	Mean			82
3	—	13.19		
	1:2	6.00	6.60	91
	1:5	2.33	2.64	88
	1:10	0.79	1.32	60
	Mean			80
4	—	45.02		
	1:2	21.45	22.51	95
	1:5	8.02	9.00	89
	1:10	3.93	4.50	87
	Mean			90
5	—	27.43		
	1:2	13.54	13.71	99
	1:5	5.34	5.49	97
	1:10	2.58	2.74	94
	Mean			97
6	—	27.63		
	1:2	13.15	13.81	95
	1:5	5.12	5.53	93
	1:10	2.54	2.76	92
	Mean			93

Sample	Dilution	Observed (ng/mL) (µg/L)	Expected (ng/mL) (µg/L)	Recovery %
7	—	12.80		
	1:2	5.69	6.40	89
	1:5	2.21	2.56	86
	1:10	1.05	1.28	82
	Mean			86
8	—	35.88		
	1:2	19.40	17.94	108
	1:5	8.27	7.18	115
	1:10	4.24	3.59	118
	Mean			114
9	—	29.80		
	1:2	14.49	14.90	97
	1:5	5.91	5.96	99
	1:10	3.00	2.98	101
	Mean			99
10	—	19.29		
	1:2	9.16	9.65	95
	1:5	3.52	3.86	91
	1:10	1.71	1.93	89
	Mean			92
Mean				93

Linearity

Six human serum samples in the range of 2.05 to 27.80 ng/mL (µg/L) were diluted with negative serum, and assayed for recovery and linearity. The recoveries ranged from 92.5% to 105.5%.

Sample	% Sample	Observed (ng/mL) (µg/L)	Expected (ng/mL) (µg/L)	Recovery %
1	100	27.80		
	75	20.67	20.85	99.1
	50	13.21	13.90	95.0
	25	6.43	6.95	92.5
	Mean			95.5
2	100	5.13		
	75	3.87	3.85	100.5
	50	2.53	2.57	98.4
	25	1.35	1.28	105.5
	Mean			101.5
3	100	8.81		
	75	6.37	6.61	96.4
	50	4.26	4.40	96.8
	25	2.08	2.21	94.1
	Mean			95.8
4	100	4.49		
	75	3.25	3.37	96.4
	50	2.19	2.24	97.8
	25	1.09	1.12	97.3
	Mean			97.2
5	100	2.05		
	75	1.53	1.54	99.3
	50	1.05	1.03	101.2
	25	0.52	0.51	102.0
	Mean			100.8
6	100	7.78		
	75	5.71	5.84	97.8
	50	3.76	3.89	96.7
	25	1.91	1.94	98.5
	Mean			97.7
Mean				98.1

High-Dose Hook Effect

Patient samples with high troponin I levels can cause a paradoxical decrease in the RLUs (high-dose hook effect). In this assay, patient samples with troponin I levels as high as 1000 ng/mL (µg/L) will assay greater than 50 ng/mL (µg/L).

Standardization

The ADVIA Centaur TnI-Ultra assay is standardized to an internal standard manufactured using highly purified material. Assigned values for calibrators are traceable to this standardization. The ADVIA Centaur TnI-Ultra assay is traceable to NIST SRM 2921.

Technical Assistance

For customer support, please contact your local technical support provider or distributor.

www.siemens.com/diagnostics














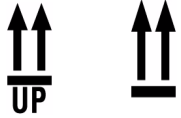










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Definition of Symbols

The following symbols may appear on the product labeling:

Symbol	Definition	Symbol	Definition
	<i>In vitro</i> diagnostic medical device	 REF	Catalog number
	Legal manufacturer		Authorized Representative in the European Community
	CE Mark		CE Mark with identification number of notified body
	Consult instructions for use		Biological risk
	Do not freeze (> 0°C)		Temperature limitation
	Lower limit of temperature		Upper limit of temperature
	Keep away from sunlight and heat		Up
	Use by		Contains sufficient for (n) tests
	Batch code		Shake the reagent pack vigorously. Refer to <i>Preparing Reagents</i> in the assay-specific ADVIA Centaur product instructions for detailed information.
YYYY-MM-DD	Date format (year-month-day)	Rev.	Revision
	Master Curve Definition		Variable hexadecimal number that ensures the Master Curve and Calibrator definition values entered are valid.
	Lot Details		Green dot
	Recycle		Printed with soy ink

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