ARCHITECT

# STAT High Sensitive Troponin-I

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STAT High Sensitive Troponin-I
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Package insert instructions must be carefully followed. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

## NAME

ARCHITECT STAT High Sensitive Troponin-I

## INTENDED USE

The ARCHITECT STAT High Sensitive Troponin-I assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of cardiac troponin I (cTnI) in human plasma and serum on the ARCHITECT iSystem with STAT protocol capability.

The cTnI values are used as an aid in the diagnosis of myocardial infarction (MI) and to aid in the assessment of 30-day and 90-day prognosis relative to all-cause mortality and major adverse cardiac events (MACE) consisting of myocardial infarction, revascularization, and cardiac death in patients who present with symptoms suggestive of acute coronary syndrome (ACS).

The cTnI values may also be used, in conjunction with clinical and diagnostic findings, to aid in stratifying the risk of cardiovascular disease, including cardiovascular death, MI, coronary revascularization, heart failure, or ischemic stroke in asymptomatic individuals.

## SUMMARY AND EXPLANATION OF THE TEST

Cardiac troponin I is a regulatory subunit of the troponin complex associated with the actin thin filament within cardiac muscle cells.[1] Troponin I, in conjunction with troponin C and troponin T, plays an integral role in the regulation of muscle contraction. Three distinct tissue-specific isoforms of troponin I have been identified from skeletal and cardiac muscles. The cardiac isoform exhibits only 60% similarity with the skeletal muscle isoform and contains additional amino acids at the N-terminus; cTnI has a molecular weight of approximately 24,000 daltons.[2, 3]

Clinical studies have demonstrated the release of cTnI into the blood stream within hours following myocardial infarction (MI) or ischemic injury. High sensitivity assays can detect elevated levels of cTnI (above the 99th percentile of an apparently healthy reference population) within 3 hours after the onset of chest pain. Cardiac troponin I reaches peak concentrations in approximately 8 to 28 hours and remains elevated for 3 to 10 days following MI.[2, 4] Cardiac troponin is the preferred biomarker for the detection of myocardial injury based on improved sensitivity and superior tissue-specificity compared to other available biomarkers of necrosis, including CK-MB, myoglobin, lactate dehydrogenase, and others.[5, 6] The high tissue specificity of cTnI measurements is beneficial for identifying cardiac injury in clinical conditions involving skeletal muscle injury resulting from surgery, trauma, extensive exercise, or muscular disease.[7-9] High tissue specificity of cTnI, however, should not be confused with the specificity for the mechanism of injury (e.g., MI versus myocarditis). When an increased value for cTnI is encountered (e.g., exceeding the 99th percentile of a reference control population) in the absence of evidence of myocardial ischemia, a careful search of other possible etiologies for cardiac damage should be taken.[5] 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.[10, 11]

In 2012, the Global Task Force with joint leadership among the European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and World Heart Federation (WHF) refined past criteria with the third universal definition of MI that also supports use of cTnI as a preferred biomarker for myocardial injury. Their universal definition of MI is a typical rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following: ischemic symptoms, pathological Q waves on electrocardiogram (ECG), ischemic ECG changes, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or identification of an intracoronary thrombus by angiography or autopsy.[10] The recommended criteria are based on the principle that any reliable detectable amount of myocardial necrosis, if caused by myocardial ischemia, constitutes an MI.[5] A gender difference in 99th percentile has been reported, indicating the benefit of using gender specific 99th percentile cutoff values.[12]

A single, elevated cTnI value may not be sufficient to make the diagnosis of myocardial infarction. Serial sampling to detect the temporal rise and fall of cTnI levels is recommended for the differentiation of acute cardiac events from chronic cardiac disease.[6, 10] The use of delta values (difference of cTnI levels between two test points) may have the potential to improve the clinical specificity for ACS.[13, 14]

Several major studies have shown that cTnI is also useful as a predictor of cardiac risk in patients with unstable angina.[15, 16] Additional studies have shown that during a 30-day follow-up, patients with acute coronary syndromes (including unstable angina) were at greater risk of progressing to MI if cTnI was elevated.[17, 18] Results from the PRISM trial showed that elevated cTnI levels could help to identify patients with unstable angina who had additional cardiac risk (especially within the first 72 hours after onset of symptoms) and who could benefit from treatment with a glycoprotein IIb/IIIa receptor antagonist.[17] Thus, cTnI can play an important role in identifying patients with acute coronary syndromes who are at greater risk for cardiac events. The ESC, ACCF, AHA, and National Academy of Clinical Biochemistry (NACB) also recommend using cTnI results when making treatment decisions regarding unstable angina and non-ST segment elevation MI (NSTEMI).[6, 19]

Studies employing sensitive troponin assays, capable of measuring troponin levels in the general population or in patients with stable cardiovascular disease, have shown that elevated troponin levels are associated with structural heart disease, risk of future cardiovascular events, and mortality.[20-23] Other research has shown that elevated troponin is indicative of future risk in patients undergoing chemotherapy, following non-cardiac surgery, or with heart failure.[24-26]

Also, studies have demonstrated that troponin values generated using the ARCHITECT STAT High Sensitive Troponin-I (3P25) assay can be incorporated into cardiovascular risk prediction models and risk scores to stratify the risk (low/moderate/elevated) of future cardiac events in asymptomatic individuals.[44-52]

## BIOLOGICAL PRINCIPLES OF THE PROCEDURE

The ARCHITECT STAT High Sensitive Troponin-I assay is a two-step immunoassay to determine the presence of cTnI in human plasma and serum using CMIA technology with flexible assay protocols, referred to as Chemiflex.

1. Sample and anti-troponin I antibody-coated paramagnetic microparticles are combined. The cardiac troponin I present in the sample binds to the anti-troponin I coated microparticles.
2. After incubation and washing, anti-troponin I acridinium-labeled conjugate is added to create a reaction mixture.
3. Following another incubation and wash cycle, Pre-Trigger and Trigger solutions are added to the reaction mixture.
4. The resulting chemiluminescent reaction is measured as relative light units (RLUs). There is a direct relationship between the amount of cTnI in the sample and the RLUs detected by the ARCHITECT iSystem optics.

   The concentration of cTnI is read relative to a standard curve established with calibrators of known cTnI concentrations.

For additional information on system and assay technology, refer to the ARCHITECT System Operations Manual, Section 3.

## REAGENTS

**Kit Contents**

ARCHITECT STAT High Sensitive Troponin-I 3P25

**NOTE:** Some kit sizes are not available in all countries or for use on all ARCHITECT iSystems. Please contact your local distributor.

| REF | 3P25-27 | 3P25-37 |
|---|---|---|
| Σ | 100 | 500 |
| MICROPARTICLES | 1 x 6.6 mL | 1 x 29.0 mL |
| CONJUGATE | 1 x 5.9 mL | 1 x 28.5 mL |

MICROPARTICLES Anti-troponin I (mouse, monoclonal) coated microparticles in TRIS buffer with protein (bovine) stabilizer. Minimum concentration: 0.035% solids. Preservative: ProClin 300.

CONJUGATE Anti-troponin I (mouse-human chimeric, monoclonal) acridinium-labeled conjugate in MES buffer with protein (bovine) stabilizer and human IgG. Minimum concentration: 0.1 mg/L. Preservative: ProClin 300.

**Other Reagents**

MULTI-ASSAY MANUAL DILUENT 1 x 100 mL ARCHITECT Multi-Assay Manual Diluent, REF 7D82-50, containing phosphate buffered saline solution. Preservative: antimicrobial agent.

PRE-TRIGGER SOLUTION ARCHITECT Pre-Trigger Solution containing 1.32% (w/v) hydrogen peroxide.

TRIGGER SOLUTION ARCHITECT Trigger Solution containing 0.35 N sodium hydroxide.

WASH BUFFER ARCHITECT Wash Buffer containing phosphate buffered saline solution. Preservatives: antimicrobial agents.

**Warnings and Precautions**

- IVD
- For *In Vitro* Diagnostic Use

**Safety Precautions**

⚠ **CAUTION:** This product contains human-sourced and/or potentially infectious components. Refer to the **REAGENTS** section of this package insert. No known test method can offer complete assurance that products derived from human sources or inactivated microorganisms will not transmit infection. Therefore, all human-sourced materials should be considered potentially infectious. It is recommended that these reagents and human specimens be handled in accordance with the OSHA Standard on Bloodborne Pathogens. Biosafety Level 2 or other appropriate biosafety practices should be used for materials that contain or are suspected of containing infectious agents.[27-30]

The human sourced material used in the conjugate is nonreactive for HBsAg, HIV-1/HIV-2 and HCV.

The following warnings and precautions apply to:

**MICROPARTICLES**

| | |
|---|---|
| **WARNING** | Contains methylisothiazolones. |
| H317 | May cause an allergic skin reaction. |
| **Prevention** | |
| P261 | Avoid breathing mist / vapors / spray. |
| P272 | Contaminated work clothing should not be allowed out of the workplace. |
| P280 | Wear protective gloves / protective clothing / eye protection. |
| **Response** | |
| P302+P352 | IF ON SKIN: Wash with plenty of water. |
| P333+P313 | If skin irritation or rash occurs: Get medical advice / attention. |
| P362+P364 | Take off contaminated clothing and wash it before reuse. |
| **Disposal** | |
| P501 | Dispose of contents / container in accordance with local regulations. |

The following warnings and precautions apply to:

**CONJUGATE**

| | |
|---|---|
| **WARNING** | Contains methylisothiazolones and polyethylene glycol octylphenyl ether. |
| H317 | May cause an allergic skin reaction. |
| H319 | Causes serious eye irritation. |
| H316* | Causes mild skin irritation. |
| **Prevention** | |
| P261 | Avoid breathing mist / vapors / spray. |
| P264 | Wash hands thoroughly after handling. |
| P272 | Contaminated work clothing should not be allowed out of the workplace. |
| P280 | Wear protective gloves / protective clothing / eye protection. |
| **Response** | |
| P305+P351 +P338 | IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. |
| P337+P313 | If eye irritation persists: Get medical advice / attention. |
| P302+P352 | IF ON SKIN: Wash with plenty of water. |
| P333+P313 | If skin irritation or rash occurs: Get medical advice / attention. |
| P362+P364 | Take off contaminated clothing and wash it before reuse. |
| **Disposal** | |
| P501 | Dispose of contents / container in accordance with local regulations. |

*Not applicable where regulation EU 1272/2008 (CLP) or OSHA Hazard Communication 29CFR 1910.1200 (HCS) 2012 have been implemented.

Safety Data Sheets are available at www.abbottdiagnostics.com or contact your local representative.

For a detailed discussion of safety precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 8.

**Reagent Handling**

- Do not use reagent kits beyond the expiration date.
- **Do not pool reagents within a kit or between kits.**
- Before loading the reagent kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that may have settled during shipment. For microparticle mixing instructions, refer to the **PROCEDURE, Assay Procedure** section of this package insert.
- **Septums MUST be used to prevent reagent evaporation and contamination and to ensure reagent integrity. Reliability of assay results cannot be guaranteed if septums are not used according to the instructions in this package insert.**
  - To avoid contamination, wear clean gloves when placing a septum on an uncapped reagent bottle.
  - Once a septum has been placed on an open reagent bottle, **do not invert the bottle** as this will result in reagent leakage and may compromise assay results.
  - Over time, residual liquids may dry on the septum surface. These are typically dried salts and have no effect on assay efficacy.

For a detailed discussion of handling precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 7.

**Reagent Storage**

When stored and handled as directed, reagents are stable until the expiration date.

| | Storage Temperature | Maximum Storage Time | Additional Storage Instructions |
|---|---|---|---|
| **Unopened/ Opened*** | 2-8°C | Until expiration date | May be used immediately after removal from 2-8°C storage.<br>Store in upright position. |
| **On board** | System temperature | 30 days | Discard after 30 days.<br>For information on tracking onboard time, refer to the ARCHITECT System Operations Manual, Section 5. |

* Reagents may be stored on or off the ARCHITECT iSystem. If reagents are removed from the system, store them at 2-8°C (with septums and replacement caps) in an upright position. For reagents stored off the system, it is recommended that they be stored in their original trays and boxes to ensure they remain upright. **If the microparticle bottle does not remain upright (with a septum installed) while in refrigerated storage off the system, the reagent kit must be discarded.** For information on unloading reagents, refer to the ARCHITECT System Operations Manual, Section 5.

**Indications of Reagent Deterioration**

When a control value is out of the specified range, it may indicate deterioration of the reagents or errors in technique. Associated test results are invalid, and samples must be retested. Assay recalibration may be necessary. For troubleshooting information, refer to the ARCHITECT System Operations Manual, Section 10.

## INSTRUMENT PROCEDURE

The ARCHITECT STAT High Sensitive Troponin-I assay is designed for use with the ARCHITECT iSystem with STAT protocol capability.

The ARCHITECT STAT High Sensitive Troponin-I assay file must be installed on the ARCHITECT iSystem with STAT protocol capability from an ARCHITECT iSystem Assay CD-ROM prior to performing the assay.

ARCHITECT iSystem software version 8.10 or higher must be installed on the ARCHITECT iSystem with STAT protocol capability.

For detailed information on assay file installation and viewing and editing assay parameters, refer to the ARCHITECT System Operations Manual, Section 2.

For information on printing assay parameters, refer to the ARCHITECT System Operations Manual, Section 5.

For a detailed description of system procedures, refer to the ARCHITECT System Operations Manual.

**Alternate Result Units**

Edit assay parameter "Result concentration units" to select an alternate unit.

Conversion formula:

(Concentration in Default result unit) x (Conversion factor) = (Concentration in Alternate result unit)

| Default result unit | Conversion factor | Alternate result unit |
|---|---|---|
| pg/mL | 0.001 | ng/mL |
| | 0.001 | µg/L |
| | 1.0 | ng/L |

## SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

**Specimen Types**

The specimen collection tubes listed below can be used with the ARCHITECT STAT High Sensitive Troponin-I assay.

- Lithium heparin with and without separator
- $K_2$ EDTA, $K_3$ EDTA
- Serum with and without separator
- Serum with thrombin-based clot activator

Note: For limitations, refer to the Limitations bullets under the **Preparation for Analysis** and **Specimen Storage** subsections of the **SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS** section.

- Performance has not been established for the use of cadaveric specimens or body fluids other than human serum or plasma.
- When serial specimens are being evaluated, use the same specimen type throughout the evaluation.
- Liquid anticoagulants may have a dilution effect resulting in lower concentrations for individual patient specimens.
- The instrument does not provide the capability to verify specimen type. It is the responsibility of the operator to verify that the correct specimen types are used in the assay.

**Specimen Conditions**

- Performance has not been established for the use of the following specimen types:
  - heat-inactivated
  - pooled
  - obvious microbial contamination
- **For accurate results, serum and plasma specimens should be free of fibrin, red blood cells, and other particulate matter, including cryoprecipitate.**
  - Ensure that complete clot formation in serum specimens has taken place prior to centrifugation.

- Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting time. If the specimen is centrifuged before a complete clot forms, the presence of fibrin may cause erroneous results.

- To prevent cross contamination, use of disposable pipettes or pipette tips is recommended.

**Preparation for Analysis**

- Follow the tube manufacturer's processing instructions for collection tubes. Gravity separation is not sufficient for specimen preparation.
- Limitations
  - For serum collection tubes, allow for proper clotting prior to analysis.

    **Note: Serum specimens from individuals on anticoagulant therapy may show inconsistent results due to incomplete clotting. Abbott recommends the use of plasma for rapid turnaround of results.**
  - Serum with thrombin-based clot activator showed acceptable results when centrifuged 30 minutes after blood draw. Other clotting times were not evaluated.
- If the specimens
  - contain fibrin, red blood cells, or other particulate matter, including cryoprecipitate, or
  - have been stored at 2-8°C for more than 24 hours, centrifuge at a Relative Centrifugal Force (RCF) of 3,000 to 3,500 x g for 30 minutes before testing to ensure consistency in results.
- Transfer clarified specimen to a sample cup or secondary tube for testing. For centrifuged specimens with a lipid layer, transfer only the clarified specimen and not the lipemic material.
- Frozen serum and plasma specimens:
  - Mix thawed specimens thoroughly by gentle inversion or low-speed vortexing. Visually inspect the specimens. If layering or stratification is observed, continue mixing until specimens are visibly homogeneous. If samples are not homogeneous, inconsistent results may be obtained.
  - Process specimens as follows before testing:
    - Serum specimens:
      - centrifuge at an RCF of 3,000 to 3,500 x g for 30 minutes.
    - Plasma specimens:
      - centrifuge at an RCF of 13,000 to 13,500 x g for 30 minutes.

      OR
      - centrifuge at an RCF of 3,000 to 3,500 x g for 10 minutes,
      - transfer the supernatant into a new centrifuge tube, taking care to avoid transfer of any pellet, and
      - spin again at an RCF of 3,000 to 3,500 x g for an additional 10 minutes.
- Transfer the supernatant to a sample cup or secondary tube for testing. Care must be taken to avoid transfer of any pellet or lipid layer, if present.
- Inspect all specimens for bubbles. Remove bubbles with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.

**Specimen Storage**

| Specimen Type | Storage Temperature | Maximum Storage Time |
|---|---|---|
| Serum/Plasma | Room temperature | ≤ 8 hours |
| | 2-8°C | ≤ 24 hours |

Specimens may be stored on or off the clot, red blood cells, or separator gel.

If testing will be delayed more than 72 hours, plasma or serum should be removed from the red blood cells, clot, or separator gel and stored at -10°C or colder.

Freeze specimens only once.

Limitations

- If testing is delayed by more than 2 hours from specimen collection, studies demonstrated a mean difference of ≤ 10% (within the range of 10 to 50,000 pg/mL) and +/- 1 pg/mL (within the range of 3.2 to 10 pg/mL) under the following conditions:
  - On or Off the clot, red blood cells, or separator gel at room temperature for up to 8 hours
  - On or Off the clot, red blood cells, or separator gel at 2-8°C for up to 24 hours.
- If testing is delayed by more than 2 hours from specimen collection for refrigerated or frozen specimens, studies demonstrated a mean difference of < 20% in concentration under the following conditions:
  - On or Off the clot, red blood cells, or separator gel at 2-8°C for 24 to 72 hours.
  - Off the clot, red blood cells, or separator gel frozen at -10°C or colder for up to 31 days.
- Serum with thrombin-based clot activator: after 24 hours at 2-8°C, serum should be stored at -10°C or colder.
- Plasma specimens stored at -70°C or colder were reported to be stable for up to 5 years.[31]

**Specimen Shipping**

- Package and label specimens in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances.
- Do not exceed the storage limitations listed above.

## PROCEDURE

**Materials Provided**

3P25 ARCHITECT STAT High Sensitive Troponin-I Reagent Kit

**Materials Required but not Provided**

- ARCHITECT STAT High Sensitive Troponin-I Assay file obtained from the ARCHITECT iSystem e-Assay CD-ROM found on www.abbottdiagnostics.com.
- 3P25-01 ARCHITECT STAT High Sensitive Troponin-I Calibrators
- 3P25-02 ARCHITECT STAT High Sensitive Troponin-I Calibrators
- 3P25-10 ARCHITECT STAT High Sensitive Troponin-I Controls or other commercial controls
- 3P25-11 ARCHITECT STAT High Sensitive Troponin-I Controls or other commercial controls
- 7D82-50 ARCHITECT Multi-Assay Manual Diluent
- ARCHITECT Pre-Trigger Solution
- ARCHITECT Trigger Solution
- ARCHITECT Wash Buffer
- ARCHITECT Reaction Vessels
- ARCHITECT Sample Cups
- ARCHITECT Septum
- ARCHITECT Replacement Caps
- Pipettes or pipette tips (optional) to deliver the volumes specified on the patient or control order screen.

For information on materials required for maintenance procedures, refer to the ARCHITECT System Operations Manual, Section 9.

**Assay Procedure**

- Before loading the reagent kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that may have settled during shipment. After the first time the microparticles have been loaded, no further mixing is required.
  - **Invert the microparticle bottle 30 times.**
  - Visually inspect the bottle to ensure microparticles are resuspended. If microparticles are still adhered to the bottle, continue to invert the bottle until the microparticles have been completely resuspended.
  - **If the microparticles do not resuspend, DO NOT USE. Contact your local Abbott representative.**
  - Once the microparticles have been resuspended, place a septum on the bottle. For instructions about placing septums on bottles, refer to the **Reagent Handling** section of this package insert.
- Load the reagent kit on the ARCHITECT iSystem with STAT protocol capability.
  - Verify that all necessary reagents are present.
  - Ensure that septums are present on all reagent bottles.
- Order calibration, if necessary.
  - For information on ordering calibrations, refer to the ARCHITECT System Operations Manual, Section 6.
- Order tests.
  - For information on ordering patient specimens and controls and for general operating procedures, refer to the ARCHITECT System Operations Manual, Section 5.
- Minimum sample cup volume is calculated by the system and printed on the Orderlist report. To minimize the effects of evaporation, verify adequate sample cup volume is present prior to running the test.

  Maximum number of replicates sampled from the same sample cup: 8
  - Priority:

    Sample volume for first test: 210 µL

    Sample volume for each additional test from same sample cup: 160 µL
  - ≤ 3 hours on board:

    Sample volume for first test: 210 µL

    Sample volume for each additional test from same sample cup: 160 µL
  - > 3 hours on board: Replace with a fresh sample (patient specimens, controls, and calibrators.)
  - If using primary or aliquot tubes, use the sample gauge to ensure sufficient patient specimen is present.
- Prepare ARCHITECT STAT High Sensitive Troponin-I Calibrators and Controls.
  - ARCHITECT STAT High Sensitive Troponin-I Calibrator and Control preparation instructions vary depending on the storage condition. **Refer to the package inserts specific to the ARCHITECT STAT High Sensitive Troponin-I Calibrator and Control in use in your laboratory.**
  - Hold bottles **vertically** and dispense recommended volumes into each respective sample cup.
  - Recommended volumes:

    for each calibrator: 15 drops

    for each control: 10 drops
- Load samples.
  - For information on loading samples, refer to the ARCHITECT System Operations Manual, Section 5.
- Press RUN.
  - For additional information on principles of operation, refer to the ARCHITECT System Operations Manual, Section 3.
  - For optimal performance, it is important to perform routine maintenance as described in the ARCHITECT System Operations Manual, Section 9. Perform maintenance more frequently when required by laboratory procedures.

**Specimen Dilution Procedures**

Specimens with a troponin I value exceeding 50,000.0 pg/mL are flagged with the code "> 50,000.0 pg/mL" and may be diluted using the Automated Dilution Protocol or the Manual Dilution Procedure.

**Automated Dilution Protocol**

The system performs a 1:10 dilution of the specimen and automatically calculates the concentration of the specimen before dilution and reports the result.

**Manual Dilution Procedure**

Suggested dilution: 1:10

1. Add 25 µL of the patient specimen to 225 µL of ARCHITECT Multi-Assay Manual Diluent.
2. The operator must enter the dilution factor in the Patient or Control order screen. The system will use this dilution factor to automatically calculate the concentration of the sample before dilution and report the result. The result should be > 10.0 pg/mL (concentration) before the dilution factor is applied.

For detailed information on ordering dilutions, refer to the ARCHITECT System Operations Manual, Section 5.

**Calibration**

- Test Calibrators A, B, C, D, E, and F in duplicate. The calibrators should be priority loaded.

  A single sample of each control level must be tested to evaluate the assay calibration. Ensure that assay control values are within the ranges specified in the respective control package insert.
- Calibration Range: 0.0 – 50,000.0 pg/mL.
- Once an ARCHITECT STAT High Sensitive Troponin-I calibration is accepted and stored, all subsequent samples may be tested without further calibration unless:
  - A reagent kit with a new lot number is used or
  - Controls are out of range.
- For detailed information on how to perform an assay calibration, refer to the ARCHITECT System Operations Manual, Section 6.

**Quality Control Procedures**

The recommended control requirement for the ARCHITECT STAT High Sensitive Troponin-I assay is that a single replicate of each control level be tested once every 24 hours each day of use. If the quality control procedures in your laboratory require more frequent use of controls to verify test results, follow your laboratory-specific procedures.

Additional controls may be tested in accordance with local, state, and/or federal regulations or accreditation requirements and your laboratory's quality control policy.

Each laboratory should establish control ranges to monitor the acceptable performance of the assay. If a control is out of its specified range, the associated sample results are invalid and the samples must be retested. Recalibration may be indicated.

**Verification of Assay Claims**

For protocols to verify package insert claims, refer to the ARCHITECT System Operations Manual, Appendix B.

The ARCHITECT STAT High Sensitive Troponin-I assay belongs to method group 1.

## RESULTS

**Calculation**

The ARCHITECT STAT High Sensitive Troponin-I assay utilizes a 4 Parameter Logistic Curve fit data reduction method (4PLC, Y-weighted) to generate a calibration curve.

**Flags**
Some results may contain information in the Flags field. For a description of the flags that may appear in this field, refer to the ARCHITECT System Operations Manual, Section 5.

**Measuring Interval**
Measuring interval is defined as the range of values in pg/mL which meets the limits of acceptable performance for both imprecision and bias for an undiluted sample.[32]

From the verification studies described in this package insert, the range is 3.2 pg/mL (Limit of Quantitation - LoQ) to 50,000 pg/mL.

## LIMITATIONS OF THE PROCEDURE

- Any condition resulting in myocardial injury can potentially increase cardiac troponin I levels.[10, 11] For MI diagnostic purposes, the ARCHITECT STAT High Sensitive Troponin-I results should be used in conjunction with other information such as ECG, clinical observations, and symptoms, etc.
- A single cTnI result may not be sufficient to evaluate MI. Serial blood draws are recommended for evaluation of acute coronary syndrome (ACS) patients.[5, 6, 10]
- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits such as ARCHITECT STAT High Sensitive Troponin-I that employ mouse monoclonal antibodies. Additional information may be required for diagnosis.[33, 34]
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays. 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.[35]
- Rheumatoid factor (RF) in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays.[35]
- Although the ARCHITECT STAT High Sensitive Troponin-I assay is specifically designed to minimize the effects of HAMA, heterophilic antibodies, and RF, assay results that are not consistent with other clinical observations may require additional information for diagnosis.
- Specimens from individuals with pathologically high total protein may demonstrate anomalous values. Additional information may be required for diagnosis.
- The ARCHITECT STAT High Sensitive Troponin-I assay cannot be used on the ARCHITECT i2000 System.
- Refer to the **SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS** section in this package insert for specimen limitations.

## EXPECTED VALUES

Data in the **EXPECTED VALUES** section were generated using the ARCHITECT i2000SR System.

Assay results obtained in individual laboratories may vary from data presented.

Any condition resulting in myocardial injury can potentially increase cardiac troponin I levels.[10, 11]

A reference range study was conducted based on guidance from Clinical and Laboratory Standards Institute (CLSI) document C28-A3c.[36] Specimens were collected in 3 tube types (serum separator, lithium heparin separator, $K_2$ EDTA) from 1,531 apparently healthy individuals in a US population with normal levels of BNP, HbA1c, and estimated GFR values. Each specimen was frozen, thawed, and evaluated in replicates of one using the ARCHITECT STAT High Sensitive Troponin-I assay. The 4,593 results were used to establish the 99th percentiles below. The observed 99th percentiles described below for this population were determined using the robust statistical method described in CLSI document C28-A3c.

**Apparently Healthy Population**

| Population | N | Age Range (years) | 99th Percentile (pg/mL) | 90% CI* (pg/mL) |
|---|---|---|---|---|
| Female | 764** | 21 - 75 | 15.6 | [13.8, 17.5] |
| Male | 766 | 21 - 73 | 34.2 | [28.9, 39.2] |
| Overall | 1531 | 21 - 75 | 26.2 | [23.3, 29.7] |

* CI = Confidence Interval

** During the gender-specific analysis, the 3 tube type results from one female subject were identified as outliers using the Dixon method. The subject and results were excluded from the gender-specific analysis, the subject and results were included in the overall analysis.

It is recommended that each laboratory verify that the 99th percentile is transferable to its own population or establish its own 99th percentile.

## RISK STRATIFICATION

Gender-specific risk stratification cut-offs were derived from selected peer-reviewed published data[44-51] and validated in a prospective study.

The following cut-off points may be used to aid in stratifying the risk of cardiovascular disease in asymptomatic individuals.

| | Troponin Level | |
|---|---|---|
| Risk | Male (pg/mL) | Female (pg/mL) |
| Low | $< 6$ | $< 4$ |
| Moderate | $\geq 6 - \leq 12$ | $\geq 4 - \leq 10$ |
| Elevated | $> 12$ | $> 10$ |

Asymptomatic individuals with elevated troponin levels are associated with a higher risk of developing cardiovascular related diseases in the future. Refer to the **Clinical Results, Risk Stratification Data** section of this package insert for further details.

## SPECIFIC PERFORMANCE CHARACTERISTICS

Data in the **SPECIFIC PERFORMANCE CHARACTERISTICS** section were generated using the ARCHITECT i2000SR System. Assay results obtained in individual laboratories may vary from data presented.

**Precision**
The ARCHITECT STAT High Sensitive Troponin-I assay is designed to have within-laboratory (total) imprecision of ≤ 10% CV with controls or panels across the range of 10 to 50,000 pg/mL.

A study was performed for the ARCHITECT STAT High Sensitive Troponin-I assay with guidance from the National Committee for Clinical Laboratory Standards (NCCLS/CLSI) document EP5-A2.[37]

The ARCHITECT STAT High Sensitive Troponin-I Controls and 6 panels were assayed in replicates of 2 at 2 separate times per day for 20 days on 2 instruments using 3 reagent lots and 2 calibrator lots. Each reagent lot used a single calibration curve throughout the study. Results from this study are summarized in the following table.

| Sample Level | Instrument | Reagent Lot | N | Mean (pg/mL) | Within Run SD | Within Run %CV | Within-Laboratory (Total) SD | Within-Laboratory (Total) %CV |
|---|---|---|---|---|---|---|---|---|
| Low Control | 1 | A | 80 | 19.3 | 0.61 | 3.2 | 0.72 | 3.7 |
| | | B | 80 | 20.3 | 0.61 | 3.0 | 0.78 | 3.9 |
| | | C | 80 | 19.7 | 0.64 | 3.3 | 0.78 | 3.9 |
| | 2 | A | 80 | 20.4 | 0.84 | 4.1 | 0.85 | 4.1 |
| | | B | 80 | 20.2 | 0.64 | 3.2 | 0.83 | 4.1 |
| | | C | 80 | 20.0 | 0.66 | 3.3 | 0.87 | 4.3 |

| Sample Level | Instrument | Reagent Lot | N | Mean (pg/mL) | Within Run SD | Within Run %CV | Within-Laboratory (Total) SD | Within-Laboratory (Total) %CV |
|---|---|---|---|---|---|---|---|---|
| Medium Control | 1 | A | 80 | 190.7 | 4.21 | 2.2 | 5.54 | 2.9 |
| | | B | 80 | 195.0 | 3.57 | 1.8 | 4.13 | 2.1 |
| | | C | 80 | 191.2 | 4.27 | 2.2 | 4.49 | 2.3 |
| | 2 | A | 80 | 197.8 | 5.26 | 2.7 | 5.76 | 2.9 |
| | | B | 80 | 196.8 | 4.65 | 2.4 | 5.36 | 2.7 |
| | | C | 80 | 194.3 | 4.43 | 2.3 | 5.95 | 3.1 |
| High Control | 1 | A | 80 | 14891.8 | 268.17 | 1.8 | 376.40 | 2.5 |
| | | B | 80 | 15126.3 | 360.09 | 2.4 | 380.69 | 2.5 |
| | | C | 80 | 15159.9 | 336.55 | 2.2 | 364.08 | 2.4 |
| | 2 | A | 80 | 15332.3 | 337.76 | 2.2 | 414.90 | 2.7 |
| | | B | 80 | 15184.3 | 286.64 | 1.9 | 342.34 | 2.3 |
| | | C | 80 | 15033.8 | 300.33 | 2.0 | 370.72 | 2.5 |
| Panel 1 (Native cTnI) | 1 | A | 80 | 10.8 | 0.45 | 4.2 | 0.57 | 5.3 |
| | | B | 80 | 11.6 | 0.45 | 3.9 | 0.54 | 4.6 |
| | | C | 80 | 11.5 | 0.49 | 4.3 | 0.51 | 4.4 |
| | 2 | A | 80 | 11.7 | 0.51 | 4.4 | 0.56 | 4.8 |
| | | B | 80 | 11.3 | 0.47 | 4.1 | 0.50 | 4.4 |
| | | C | 80 | 11.7 | 0.58 | 4.9 | 0.61 | 5.2 |
| Panel 2 (Bio-Rad Level Low) | 1 | A | 80 | 43.3 | 1.27 | 2.9 | 1.46 | 3.4 |
| | | B | 80 | 46.1 | 1.48 | 3.2 | 1.57 | 3.4 |
| | | C | 80 | 45.4 | 1.27 | 2.8 | 1.51 | 3.3 |
| | 2 | A | 80 | 45.2 | 1.36 | 3.0 | 1.82 | 4.0 |
| | | B | 80 | 46.4 | 1.80 | 3.9 | 1.84 | 4.0 |
| | | C | 80 | 46.0 | 1.40 | 3.0 | 1.48 | 3.2 |
| Panel 3 (Native cTnI) | 1 | A | 80 | 195.4 | 4.73 | 2.4 | 6.52 | 3.3 |
| | | B | 80 | 197.3 | 4.46 | 2.3 | 5.21 | 2.6 |
| | | C | 80 | 196.8 | 5.12 | 2.6 | 5.76 | 2.9 |
| | 2 | A | 80 | 203.4 | 6.01 | 3.0 | 7.67 | 3.8 |
| | | B | 80 | 199.1 | 4.93 | 2.5 | 7.77 | 3.9 |
| | | C | 80 | 199.2 | 5.42 | 2.7 | 7.43 | 3.7 |
| Panel 4 (Bio-Rad Level 2) | 1 | A | 80 | 1198.0 | 31.13 | 2.6 | 33.80 | 2.8 |
| | | B | 80 | 1281.3 | 33.38 | 2.6 | 40.95 | 3.2 |
| | | C | 80 | 1267.1 | 27.57 | 2.2 | 31.72 | 2.5 |
| | 2 | A | 80 | 1260.1 | 38.34 | 3.0 | 42.33 | 3.4 |
| | | B | 80 | 1309.1 | 28.25 | 2.2 | 42.68 | 3.3 |
| | | C | 80 | 1309.6 | 35.68 | 2.7 | 43.81 | 3.3 |
| Panel 5 (Bio-Rad Level 3) | 1 | A | 80 | 2812.3 | 64.56 | 2.3 | 80.50 | 2.9 |
| | | B | 80 | 3023.0 | 83.52 | 2.8 | 93.82 | 3.1 |
| | | C | 80 | 3015.3 | 94.13 | 3.1 | 95.14 | 3.2 |
| | 2 | A | 80 | 2978.3 | 80.34 | 2.7 | 102.42 | 3.4 |
| | | B | 80 | 3103.9 | 83.93 | 2.7 | 96.25 | 3.1 |
| | | C | 80 | 3138.2 | 55.49 | 1.8 | 84.50 | 2.7 |
| Panel 6 (Recombinant cTnI) | 1 | A | 80 | 43831.7 | 605.31 | 1.4 | 937.33 | 2.1 |
| | | B | 80 | 44451.6 | 677.99 | 1.5 | 824.60 | 1.9 |
| | | C | 80 | 44043.5 | 674.69 | 1.5 | 699.10 | 1.6 |
| | 2 | A | 80 | 45736.7 | 785.00 | 1.7 | 1265.55 | 2.8 |
| | | B | 80 | 45699.5 | 1046.06 | 2.3 | 1181.84 | 2.6 |
| | | C | 80 | 44607.4 | 1039.92 | 2.3 | 1319.32 | 3.0 |

**Precision Profile**

Data from the 20-day precision and limit of quantitation (LoQ) studies were evaluated together to estimate the following parameters:

| Precision Below LoQ |
|---|
| 10% CV = 4.7 pg/mL |
| 20% CV = 1.3 pg/mL* |

| Precision at 99th Percentiles | |
|---|---|
| Female | 15.6 pg/mL = 5.3% CV |
| Male | 34.2 pg/mL = 3.5% CV |
| Overall | 26.2 pg/mL = 4.0% CV |

* Concentration is within the observed range of the Limit of Detection (LoD): 1.1 to 1.9 pg/mL

**Linearity**

The ARCHITECT STAT High Sensitive Troponin-I assay is designed to have a deviation from linearity of ± 1.0 pg/mL for samples ≤ 10 pg/mL and ± 10% for samples between 10 and 50,000 pg/mL.

A linearity study based on guidance from NCCLS/CLSI document EP6-A[38] was performed for the ARCHITECT STAT High Sensitive Troponin-I assay. Dilution sets with cTnI concentrations ranging from ≤ 3.2 to > 50,000 pg/mL were evaluated. The observed deviation from linearity was ≤ 8.4% for samples ≥ 10 pg/mL and 0.2 pg/mL for samples < 10 pg/mL.

**Automated Dilution Procedure Verification**

A study was performed to evaluate 36 samples prepared by spiking recombinant cTnI stock solution into human serum samples at concentrations between 40,000 and 500,000 pg/mL. Each specimen was tested with the automated dilution protocol and manual dilution procedure (dilution factor: 1:10). The mean difference in concentration (% Diff) was calculated for each level.*

The mean difference in measured concentration was 1.6% for samples > 50,000 pg/mL and 1.1% for samples ≤ 50,000 pg/mL.

$$* \text{ \% Diff} = 100 \times \frac{\text{Auto Dilution Mean Concentration} - (\text{Manual Mean Concentration} \times \text{DF})}{(\text{Manual Mean Concentration} \times \text{DF})}$$

**Sensitivity (Detection Limits)**

A study to determine Limit of Quantitation (LoQ), Limit of Blank (LoB), and Limit of Detection (LoD) was performed based on guidance from the NCCLS/CLSI document EP17-A.[39] Testing was performed using 2 instruments and 2 reagent lots. The LoQ, LoB, and LoD were determined for each of the 4 reagent lot and instrument combinations.

Limit of Quantitation

The ARCHITECT STAT High Sensitive Troponin-I assay is designed to have an LoQ of ≤ 3.2 pg/mL. The LoQ is defined as the lowest amount of analyte in a sample that can be accurately quantitated with imprecision ≤ 20% CV.

The observed LoQ for the ARCHITECT STAT High Sensitive Troponin-I assay ranged from 1.5 to 2.9 pg/mL across the 4 reagent lot/instrument combinations.

Limit of Blank, Limit of Detection

The observed LoB ranged from 0.7 to 1.3 pg/mL, and the observed LoD ranged from 1.1 to 1.9 pg/mL across the 4 reagent lot/instrument combinations.

**Analytical Specificity**

The ARCHITECT STAT High Sensitive Troponin-I assay is designed to have analytical specificity of ≤ 0.1% cross-reactivity with skeletal troponin I and ≤ 1% cross-reactivity with cardiac troponin T and troponin C.

A study was performed for the ARCHITECT STAT High Sensitive Troponin-I assay. Specificity was determined by studying the cross-reactivity of 1000 ng/mL skeletal troponin I, 1000 ng/mL cardiac troponin T, and 1000 ng/mL troponin C in samples prepared with cTnI across the range of ≤ 3.2 to 45,000 pg/mL. The observed percent cross-reactivity for each potential cross-reactant at each cTnI concentration was ≤ 0.1%.

## Interference

### Evaluation of Potentially Interfering Drugs

In the ARCHITECT STAT High Sensitive Troponin-I assay, potential interference from various drugs is ≤ 10% at the levels tested.

A study based on guidance from the CLSI document EP7-A2[40] was performed for the ARCHITECT STAT High Sensitive Troponin-I assay. The potentially interfering drugs listed below were tested in samples with cTnI concentrations of 15 pg/mL and 500 pg/mL.

Each cTnI level was tested with potentially interfering drugs at therapeutic and high concentrations. The observed percent differences ranged from -3.1% to 4.3% at the therapeutic concentrations and -5.5% to 4.1% at the high concentrations.

| Potentially Interfering Drug | Therapeutic Conc. | High Conc. | Potentially Interfering Drug | Therapeutic Conc. | High Conc. |
|---|---|---|---|---|---|
| Abciximab | 4 µg/mL | 20 µg/mL | Low MW Heparin | 1.8 U/mL | 5 U/mL |
| Acetamino-phen | 20 µg/mL | 250 µg/mL | Levodopa | 1.8 µg/mL | 20 µg/mL |
| Acetylsalicylic Acid | 260 µg/mL | 1000 µg/mL | Methyldopa | 4 µg/mL | 25 µg/mL |
| Adrenaline | 60 ng/mL | 0.37 µg/mL | Methyl-prednisolone | 8 µg/mL | 80 µg/mL |
| Allopurinol | 12 µg/mL | 400 µg/mL | Metronidazole | 23 µg/mL | 200 µg/mL |
| Ambroxol | 0.1 µg/mL | 400 µg/mL | Nicotine | 37 ng/mL | 2 mg/dL |
| Ampicillin | 10 µg/mL | 1000 µg/mL | Nifedipine | 125 ng/mL | 60 µg/mL |
| Ascorbic Acid | 12 µg/mL | 300 µg/mL | Nitrofurantoin | 2.0 µg/mL | 64 µg/mL |
| Atenolol | 1 µg/mL | 10 µg/mL | Nystatin | 2 µg/mL | 7.5 µg/mL |
| Bivalirudin | 11 µg/mL | 42 µg/mL | Oxytetra-cycline | 2 µg/mL | 5 µg/mL |
| Caffeine | 12 µg/mL | 100 µg/mL | Phenobarbital | 25 µg/mL | 15 mg/dL |
| Captopril | 1.0 µg/mL | 50 µg/mL | Phenytoin | 12 µg/mL | 100 µg/mL |
| Carvedilol | 5 µg/mL | 150 µg/mL | Phenyl-butazone | 30 µg/mL | 400 µg/mL |
| Cefoxitin | 120 µg/mL | 2500 µg/mL | Propranolol | 1 µg/mL | 5 µg/mL |
| Cinnarizine | 4 µg/mL | 400 µg/mL | Primidone | 10 µg/mL | 10 mg/dL |
| Clopidogrel | 15 µg/mL | 75 µg/mL | Quinidine | 4 µg/mL | 20 µg/mL |
| Cocaine | 0.1 µg/mL | 10 µg/mL | Rifampicin | 7 µg/mL | 60 µg/mL |
| Cyclosporine | 0.8 µg/mL | 5 µg/mL | Salicylic Acid | 199 µg/mL | 600 µg/mL |
| Diclofenac | 2.5 µg/mL | 50 µg/mL | Simvastatin | 4 µg/mL | 20 µg/mL |
| Digoxin | 1 ng/mL | 7.5 µg/mL | Sodium Heparin | 2 U/mL | 8 U/mL |
| Dopamine | 0.3 µg/mL | 900 µg/mL | Streptokinase | 4 U/mL | 31.3 U/mL |
| Doxycycline | 10 µg/mL | 50 µg/mL | Theophylline | 12 µg/mL | 75 µg/mL |
| Eptifibatide | 2 µg/mL | 7 µg/mL | TPA | 0.52 µg/mL | 2.3 µg/mL |
| Erythromycin | 11 µg/mL | 200 µg/mL | Trimethoprim | 12 µg/mL | 75 µg/mL |
| Fondaparinux | 1.2 µg/mL | 4 µg/mL | Verapamil | 325 ng/mL | 160 µg/mL |
| Furosemide | 20 µg/mL | 400 µg/mL | Warfarin | 2 µg/mL | 30 µg/mL |
| Ibuprofen | 40 µg/mL | 500 µg/mL | | | |

Conc. = Concentration

TPA = Tissue plasminogen activator

Note: As the ARCHITECT STAT High Sensitive Troponin-I (3P25) assay does not utilize a biotinylated antibody complex, there is no risk of potential interference to Troponin-I values reported by the assay when analyzing samples containing Biotin.

### Evaluation of Potentially Interfering Endogenous Substances

In the ARCHITECT STAT High Sensitive Troponin-I assay, potential interference from endogenous substances is ≤ 10% at the levels tested.

A study based on guidance from the CLSI document EP7-A2[40] was performed for the ARCHITECT STAT High Sensitive Troponin-I assay. Potentially interfering endogenous substances were evaluated to determine the impact on cTnI results. Samples with cTnI concentrations of 15 pg/mL and 500 pg/mL demonstrated interference within ± 10% for the potentially interfering substances listed below.

| Potentially Interfering Substance | Potentially Interfering Substance Concentration |
|---|---|
| Unconjugated Bilirubin | ≤ 20.0 mg/dL |
| Conjugated Bilirubin | ≤ 20.0 mg/dL |
| Hemoglobin | ≤ 500.0 mg/dL |
| Triglycerides | ≤ 3000 mg/dL |

Total protein was evaluated using human serum albumin (HSA) and concentrated normal specimens. Samples supplemented with HSA to total protein ≤ 12 g/dL demonstrated interference within ± 10%.

Specimens were concentrated to produce elevated total protein concentrations. The concentrated specimens were supplemented with cTnI to target concentrations of 15 and 500 pg/mL. The results are presented in the following table.

| 15 pg/mL cTnI | | 500 pg/mL cTnI | |
|---|---|---|---|
| Total Protein Concentration | Observed Interference | Total Protein Concentration | Observed Interference |
| 9.9 g/dL | -7.3% | 9.6 g/dL | -8.5% |
| 12.6 g/dL | -7.5% | 12.2 g/dL | -16.6% |

### Evaluation of Potentially Interfering Clinical Conditions

The ARCHITECT STAT High Sensitive Troponin-I assay was evaluated using specimens with human anti-mouse antibodies (HAMA) and rheumatoid factor (RF) to assess the clinical specificity.

Twenty-two specimens positive for HAMA and 22 specimens positive for RF were evaluated. The results are summarized in the following table.

| Clinical Condition | Mean (Range) % Interference | Native cTnI Concentration Range (pg/mL) |
|---|---|---|
| HAMA | -2.8% (-11.7% to 3.3%) | 10.1 to 370.3 |
| RF | -3.4% (-21.2% to 9.5%) | 11.9 to 386.0 |

## Clinical Results

### Diagnosis

**Serial sampling to detect the temporal rise and fall of cTnI levels is recommended for the differentiation of acute cardiac events from chronic cardiac disease.**[6, 10]

A prospective study was performed to assess diagnostic accuracy of the ARCHITECT STAT High Sensitive Troponin-I assay. Specimens were collected at 11 emergency departments from 1,101 subjects presenting to the emergency department with symptoms consistent with acute coronary syndrome (ACS). All subject diagnoses were adjudicated by three board certified cardiologists according to current standard of care.[41] The observed MI prevalence in this study was 11.81%.

- 748 specimens with serial sampling from 130 MI subjects
- 7,488 specimens with serial sampling from 971 non-MI subjects

The specimens were collected in three tube types (lithium heparin separator, $K_2$ EDTA, serum separator) and frozen. The specimens were thawed and evaluated using the ARCHITECT STAT High Sensitive Troponin-I assay.

The Area Under the Curve (AUC) results[42] are summarized in the following table.

| Tube Type | Time Point | N | AUC | 95% CI* |
|---|---|---|---|---|
| K2 EDTA | Baseline | 931 | 0.9326 | [0.9048, 0.9604] |
| | 2 - 4 Hours | 942 | 0.9431 | [0.9081, 0.9782] |
| | 4 - 9 Hours | 862 | 0.9503 | [0.9149, 0.9857] |
| Lithium | Baseline | 951 | 0.9197 | [0.8914, 0.9480] |
| Heparin | 2 - 4 Hours | 958 | 0.9349 | [0.8986, 0.9712] |
| Separator | 4 - 9 Hours | 903 | 0.9498 | [0.9190, 0.9805] |
| Serum | Baseline | 884 | 0.9412 | [0.9102, 0.9722] |
| Separator | 2 - 4 Hours | 942 | 0.9419 | [0.9041, 0.9796] |
| | 4 - 9 Hours | 863 | 0.9449 | [0.9046, 0.9852] |

* CI = Confidence Interval

The results were further analyzed using the serial sampling time points collected during the emergency department visit. The results using the gender-specific 99th percentile cutoffs (female 15.6 pg/mL; male 34.2 pg/mL) are summarized in the table below.

| Tube Type | Time Point | N | Sensitivity[a] (%) [95% CI*] | Specificity[b] (%) [95% CI*] | Positive Predictive Value[c] (%) [95% CI*] | Negative Predictive Value[d] (%) [95% CI*] |
|---|---|---|---|---|---|---|
| K2 EDTA | Baseline | 931 | 84.44 [75.28, 91.23] | 85.49 [82.93, 87.81] | 38.38 [31.58, 45.54] | 98.09 [96.82, 98.95] |
| | 2 - 4 Hours | 942 | 90.91 [82.16, 96.27] | 84.74 [82.17, 87.07] | 34.65 [28.11, 41.65] | 99.05 [98.06, 99.62] |
| | 4 - 9 Hours | 862 | 93.90 [86.34, 97.99] | 83.33 [80.53, 85.88] | 37.20 [30.60, 44.17] | 99.24 [98.23, 99.75] |
| Lithium Heparin Separator | Baseline | 951 | 81.05 [71.72, 88.37] | 83.18 [80.50, 85.62] | 34.84 [28.58, 41.52] | 97.53 [96.13, 98.53] |
| | 2 - 4 Hours | 958 | 90.70 [82.49, 95.90] | 83.03 [80.37, 85.46] | 34.51 [28.33, 41.10] | 98.91 [97.86, 99.53] |
| | 4 - 9 Hours | 903 | 93.94 [87.27, 97.74] | 79.98 [77.04, 82.69] | 36.61 [30.68, 42.86] | 99.08 [98.00, 99.66] |
| Serum Separator | Baseline | 884 | 87.32 [77.30, 94.04] | 85.85 [83.27, 88.18] | 35.03 [28.02, 42.54] | 98.73 [97.60, 99.42] |
| | 2 - 4 Hours | 942 | 90.67 [81.71, 96.16] | 84.54 [81.96, 86.89] | 33.66 [27.18, 40.63] | 99.05 [98.06, 99.62] |
| | 4 - 9 Hours | 863 | 93.15 [84.74, 97.74] | 82.03 [79.17, 84.64] | 32.38 [26.10, 39.16] | 99.23 [98.22, 99.75] |

* CI = Confidence Interval

The results using the overall 99th percentile cutoff (26.2 pg/mL) are summarized in the table below.

| Tube Type | Time Point | N | Sensitivity[a] (%) [95% CI*] | Specificity[b] (%) [95% CI*] | Positive Predictive Value[c] (%) [95% CI*] | Negative Predictive Value[d] (%) [95% CI*] |
|---|---|---|---|---|---|---|
| $K_2$ EDTA | Baseline | 931 | 84.44 [75.28, 91.23] | 85.73 [83.18, 88.03] | 38.78 [31.92, 45.98] | 98.10 [96.82, 98.95] |
| | 2 - 4 Hours | 942 | 92.21 [83.81, 97.09] | 85.20 [82.66, 87.50] | 35.68 [29.03, 42.76] | 99.19 [98.25, 99.70] |
| | 4 - 9 Hours | 862 | 93.90 [86.34, 97.99] | 82.82 [79.99, 85.40] | 36.49 [29.99, 43.38] | 99.23 [98.22, 99.75] |
| Lithium Heparin Separator | Baseline | 951 | 85.26 [76.51, 91.70] | 83.76 [81.12, 86.17] | 36.82 [30.43, 43.56] | 98.08 [96.81, 98.95] |
| | 2 - 4 Hours | 958 | 91.86 [83.95, 96.66] | 83.72 [81.09, 86.11] | 35.75 [29.43, 42.45] | 99.05 [98.05, 99.62] |
| | 4 - 9 Hours | 903 | 94.95 [88.61, 98.34] | 80.72 [77.82, 83.39] | 37.75 [31.71, 44.09] | 99.24 [98.22, 99.75] |
| Serum Separator | Baseline | 884 | 87.32 [77.30, 94.04] | 86.35 [83.79, 88.63] | 35.84 [28.70, 43.47] | 98.73 [97.61, 99.42] |
| | 2 - 4 Hours | 942 | 92.00 [83.40, 97.01] | 85.81 [83.31, 88.07] | 35.94 [29.16, 43.16] | 99.20 [98.27, 99.71] |
| | 4 - 9 Hours | 863 | 93.15 [84.74, 97.74] | 84.05 [81.31, 86.54] | 35.05 [28.36, 42.21] | 99.25 [98.26, 99.76] |

* CI = Confidence Interval

[a] Sensitivity = $100 \times \frac{A}{A + C}$

[b] Specificity = $100 \times \frac{D}{B + D}$

[c] Positive Predictive Value = $100 \times \frac{A}{A + B}$

[d] Negative Predictive Value = $100 \times \frac{D}{C + D}$

| ARCHITECT STAT High Sensitive Troponin-I | Diagnosis | |
|---|---|---|
| | MI | Non-MI |
| cTnI Value > cutpoint | A | B |
| cTnI Value ≤ cutpoint | C | D |

The use of delta values (difference of cTnI levels between two test points) may have the potential to improve the clinical specificity for acute coronary syndrome (ACS). An analysis of delta values was performed based on analyses described in the literature.[13, 43] The absolute percent difference (delta value) was calculated between each of the three time points (Baseline, 2-4 Hours, 4-9 Hours) for each subject. The following two groups of subjects were compared:

- Subjects who had an absolute percent difference greater than the given cutoff and at least one value greater than the 99th percentile
- Subjects who had an absolute percent difference less than or equal to the given cutoff or did not have any value greater than the 99th percentile

The sensitivity, specificity, positive predictive value, and negative predictive value were calculated for the given cutoffs for each tube type. The absolute percent change for lithium heparin separator tubes using the gender-specific 99th percentile cutoffs (female 15.6 pg/mL; male 34.2 pg/mL) are summarized in the table below. The $K_2$ EDTA and serum separator results were comparable.

| Cutoff (Absolute Percent Change) | Time Point | N | Sensitivity[a] (%) | Specificity[b] (%) | Positive Predictive Value[c] (%) | Negative Predictive Value[d] (%) |
|---|---|---|---|---|---|---|
| 20% | Baseline vs. 2 - 4 Hours | 836 | 70.77 | 93.26 | 46.94 | 97.43 |
| | Baseline vs. 4 - 9 Hours | 772 | 79.17 | 90.57 | 46.34 | 97.69 |
| | 2 - 4 Hours vs. 4 - 9 Hours | 819 | 63.24 | 94.81 | 52.44 | 96.61 |
| 50% | Baseline vs. 2 - 4 Hours | 836 | 56.92 | 95.20 | 50.00 | 96.33 |
| | Baseline vs. 4 - 9 Hours | 772 | 73.61 | 93.29 | 53.00 | 97.17 |
| | 2 - 4 Hours vs. 4 - 9 Hours | 819 | 50.00 | 97.34 | 62.96 | 95.56 |

| Cutoff (Absolute Percent Change) | Time Point | N | Sensitivity[a] (%) | Specificity[b] (%) | Positive Predictive Value[c] (%) | Negative Predictive Value[d] (%) |
|---|---|---|---|---|---|---|
| 100% | Baseline vs. 2 - 4 Hours | 836 | 36.92 | 97.80 | 58.54 | 94.84 |
| | Baseline vs. 4 - 9 Hours | 772 | 61.11 | 95.00 | 55.70 | 95.96 |
| | 2 - 4 Hours vs. 4 - 9 Hours | 819 | 42.65 | 98.40 | 70.73 | 94.99 |
| 250% | Baseline vs. 2 - 4 Hours | 836 | 29.23 | 98.83 | 67.86 | 94.31 |
| | Baseline vs. 4 - 9 Hours | 772 | 55.56 | 96.86 | 64.52 | 95.49 |
| | 2 - 4 Hours vs. 4 - 9 Hours | 819 | 19.12 | 98.80 | 59.09 | 93.10 |

The absolute percent change for the lithium heparin separator tubes using the overall 99th percentile cutoff (26.2 pg/mL) are summarized in the table below. The $K_2$ EDTA and serum separator results were comparable.

| Cutoff (Absolute Percent Change) | Time Point | N | Sensitivity[a] (%) | Specificity[b] (%) | Positive Predictive Value[c] (%) | Negative Predictive Value[d] (%) |
|---|---|---|---|---|---|---|
| 20% | Baseline vs. 2 - 4 Hours | 836 | 70.77 | 93.51 | 47.92 | 97.43 |
| | Baseline vs. 4 - 9 Hours | 772 | 79.17 | 90.71 | 46.72 | 97.69 |
| | 2 - 4 Hours vs. 4 - 9 Hours | 819 | 63.24 | 94.67 | 51.81 | 96.60 |
| 50% | Baseline vs. 2 - 4 Hours | 836 | 56.92 | 95.46 | 51.39 | 96.34 |
| | Baseline vs. 4 - 9 Hours | 772 | 73.61 | 93.71 | 54.64 | 97.19 |
| | 2 - 4 Hours vs. 4 - 9 Hours | 819 | 50.00 | 97.20 | 61.82 | 95.55 |
| 100% | Baseline vs. 2 - 4 Hours | 836 | 36.92 | 97.80 | 58.54 | 94.84 |
| | Baseline vs. 4 - 9 Hours | 772 | 61.11 | 95.14 | 56.41 | 95.97 |
| | 2 - 4 Hours vs. 4 - 9 Hours | 819 | 42.65 | 98.40 | 70.73 | 94.99 |
| 250% | Baseline vs. 2 - 4 Hours | 836 | 29.23 | 98.83 | 67.86 | 94.31 |
| | Baseline vs. 4 - 9 Hours | 772 | 55.56 | 96.86 | 64.52 | 95.49 |
| | 2 - 4 Hours vs. 4 - 9 Hours | 819 | 19.12 | 98.80 | 59.09 | 93.10 |

[a] Sensitivity = $100 \times \frac{A}{A + C}$

[b] Specificity = $100 \times \frac{D}{B + D}$

[c] Positive Predictive Value = $100 \times \frac{A}{A + B}$

[d] Negative Predictive Value = $100 \times \frac{D}{C + D}$

| | Diagnosis | |
|---|---|---|
| ARCHITECT STAT High Sensitive Troponin-I | MI | Non-MI |
| cTnI Value > cutpoint | A | B |
| cTnI Value ≤ cutpoint | C | D |

**Risk Stratification Data**

To demonstrate the ability of the ARCHITECT STAT High Sensitive Troponin-I assay for risk stratification of asymptomatic individuals into risk categories for cardiovascular disease including cardiovascular death, MI, coronary revascularization, heart failure, or ischemic stroke, specimen testing was performed with prospectively collected clinical specimens from two cohorts. The purpose of the studies was to investigate determinants of heart disease in relation to traditional cardiovascular risk factors.

Subjects from the study above were followed-up for subsequent events by medical record review and follow-up visits to assess for correlation between cardiovascular outcome and troponin values in prospectively collected samples. The hazard ratios for the gender-specific Risk Stratification cutoffs (female < 4, ≥ 4 - ≤ 10 and > 10 pg/mL; male < 6, ≥ 6 - ≤ 12 and > 12 pg/mL) are summarized in the tables below. In addition, the prospectively collected samples were evaluated against ARCHITECT CRP Vario (6K26) and using the Framingham model.

Published studies also show that cTnI elevations above the risk categories stated are associated with increased risk of MI, heart failure or cardiovascular death. cTnI values determined using ARCHITECT STAT High Sensitive Troponin-I provide superior predictive information to cCRP (cardiac CRP High Sensitive) values determined using ARCHITECT CRP Vario. Study results suggest that cTnI measurement is a better risk stratification tool than cCRP to identify individuals at high CVD (cardiovascular disease) risk and may represent the preferred biomarker for targeted prevention.[52]

Published studies also show that a change in cTnI is associated with a modification in risk for CVD.[44] Additionally, studies show that statin therapy use where cTnI concentrations were above 6 pg/mL had the most benefit or risk reduction for CVD.[45, 46]

**Baseline characteristics for the cohorts used to validate ARCHITECT STAT High Sensitive Troponin-I for risk stratification of CVD**

| | Summary |
|---|---|
| Age | 59.0 [18.0 to 75.0] |
| Gender (Female) | 6632 / 11529 (57.5%) |
| **Race/ethnicity** | |
| Black | 3431 / 11529 (29.8%) |
| Non-black | 8098 / 11529 (70.2%) |
| Hypertension Treatment | 3787 / 11429 (33.1%) |
| Diabetes | 1600 / 11490 (13.9%) |
| Current Smoker | 2155 / 11487 (18.8%) |
| **Blood Pressure** | |
| Systolic | 124.0 [113.0 to 137.0] |
| Diastolic | 73.0 [66.0 to 80.0] |
| **Cholesterol (mg/dL)** | |
| Total Cholesterol | 194.0 [170.0 to 219.0] |
| HDL | 48.0 [39.0 to 59.0] |
| Body Mass Index | 28.2 [24.9 to 32.2] |
| **Family History of CHD** | |
| Mother Side | 1237 / 7711 (16.0%) |
| Father Side | 2375 / 7380 (32.2%) |

Continuous variables except for age are presented as median [25-75% Inter Quartile Range]. Age is reported as median [min-max]

Categorical variables are presented as number / total (percent)

### Unadjusted Cox Proportional Hazards Model, ARCHITECT STAT High Sensitive Troponin-I

| Population | Cohort | N | ARCHITECT STAT High Sensitive Troponin-I category (pg/mL) | Estimate | Standard Error | Hazard Ratio | 95% CI | P value |
|---|---|---|---|---|---|---|---|---|
| Overall | Pooled Cohort | 11,035 | Moderate Risk: Male 6 - 12 pg/mL, Female 4 - 10 pg/mL | 0.67 | 0.062 | 1.95 | [1.72, 2.19] | < 0.0001 |
| | | | Elevated Risk: Male > 12 pg/mL, Female > 10 pg/mL | 0.43 | 0.070 | 1.54 | [1.34, 1.77] | < 0.0001 |
| Female | Pooled Cohort | 6,386 | Moderate Risk: 4 - 10 pg/mL | 0.86 | 0.084 | 2.37 | [2.00, 2.78] | < 0.0001 |
| | | | Elevated Risk: > 10 pg/mL | 0.51 | 0.104 | 1.67 | [1.35, 2.04] | < 0.0001 |
| Male | Pooled Cohort | 4,649 | Moderate Risk: 6 - 12 pg/mL | 0.52 | 0.092 | 1.68 | [1.40, 2.01] | < 0.0001 |
| | | | Elevated Risk: > 12 pg/mL | 0.36 | 0.095 | 1.43 | [1.18, 1.72] | 0.0002 |

### Unadjusted Cox Proportional Hazards Model, ARCHITECT CRP Vario

| Population | Cohort | N | ARCHITECT CRP Vario category (mg/L) | Estimate | Standard Error | Hazard Ratio | 95% CI | P value |
|---|---|---|---|---|---|---|---|---|
| Overall | Pooled Cohort | 10,725 | Average Risk: 1.0 - 3.0 mg/L | 0.12 | 0.066 | 1.13 | [0.99, 1.28] | 0.0683 |
| | | | High Risk: > 3.0 mg/L | 0.09 | 0.060 | 1.09 | [0.97, 1.23] | 0.1375 |

### Event Summary by ARCHITECT STAT High Sensitive Troponin-I Risk Category for Pooled Cohort Data

| Female | Total | Low Risk: < 4 pg/mL (%) | Moderate Risk: 4 - 10 pg/mL (%) | Elevated Risk: > 10 pg/mL (%) | P value for Trend |
|---|---|---|---|---|---|
| Global CVD | 984 / 6387 (15.4%) | 697 / 5238 (13.3%) | 181 / 635 (28.5%) | 106 / 514 (20.6%) | < 0.0001 |
| All Death | 501 / 6387 (7.8%) | 352 / 5238 (6.7%) | 94 / 635 (14.8%) | 55 / 514 (10.7%) | < 0.0001 |
| CHF | 360 / 6387 (5.6%) | 213 / 5238 (4.1%) | 91 / 635 (14.3%) | 56 / 514 (10.9%) | < 0.0001 |
| MI | 180 / 6387 (2.8%) | 119 / 5238 (2.3%) | 29 / 635 (4.6%) | 32 / 514 (6.2%) | < 0.0001 |
| Stroke | 141 / 6387 (2.2%) | 92 / 5238 (1.8%) | 30 / 635 (4.7%) | 19 / 514 (3.7%) | < 0.0001 |
| Revascularization | 205 / 6387 (3.2%) | 170 / 5238 (3.2%) | 22 / 635 (3.5%) | 13 / 514 (2.5%) | 0.3323 |
| Cardiac Death | 59 / 6387 (0.9%) | 33 / 5238 (0.6%) | 10 / 635 (1.6%) | 16 / 514 (3.1%) | < 0.0001 |
| **Male** | **Total** | **Low Risk: < 6 pg/mL (%)** | **Moderate Risk: 6 - 12 pg/mL (%)** | **Elevated Risk: > 12 pg/mL (%)** | **P value for Trend** |
| Global CVD | 1171 / 4651 (25.2%) | 908 / 3865 (23.5%) | 136 / 379 (35.9%) | 127 / 407 (31.2%) | < 0.0001 |
| All Death | 591 / 4651 (12.7%) | 446 / 3865 (11.5%) | 73 / 379 (19.3%) | 72 / 407 (17.7%) | < 0.0001 |
| CHF | 281 / 4651 (6.0%) | 172 / 3865 (4.5%) | 57 / 379 (15.0%) | 52 / 407 (12.8%) | < 0.0001 |
| MI | 236 / 4651 (5.1%) | 175 / 3865 (4.5%) | 29 / 379 (7.7%) | 32 / 407 (7.9%) | < 0.0001 |
| Stroke | 114 / 4651 (2.5%) | 84 / 3865 (2.2%) | 13 / 379 (3.4%) | 17 / 407 (4.2%) | 0.0028 |
| Revascularization | 419 / 4651 (9.0%) | 336 / 3865 (8.7%) | 47 / 379 (12.4%) | 36 / 407 (8.8%) | 0.0670 |
| Cardiac Death | 84 / 4651 (1.8%) | 51 / 3865 (1.3%) | 9 / 379 (2.4%) | 24 / 407 (5.9%) | < 0.0001 |

### Event Summary by Framingham Risk Score Group for Pooled Cohort Data

| Female | Total | Low Risk: < 10% | Medium Risk: 10% - 20% | High Risk: > 20% | P value for Trend |
|---|---|---|---|---|---|
| Global CVD | 976 / 6301 (15.5%) | 820 / 5856 (14.0%) | 140 / 406 (34.5%) | 16 / 39 (41.0%) | < 0.0001 |
| All Death | 497 / 6301 (7.9%) | 415 / 5856 (7.1%) | 71 / 406 (17.5%) | 11 / 39 (28.2%) | < 0.0001 |
| CHF | 356 / 6301 (5.6%) | 289 / 5856 (4.9%) | 60 / 406 (14.8%) | 7 / 39 (17.9%) | < 0.0001 |
| MI | 177 / 6301 (2.8%) | 147 / 5856 (2.5%) | 25 / 406 (6.2%) | 5 / 39 (12.8%) | < 0.0001 |
| Stroke | 139 / 6301 (2.2%) | 105 / 5856 (1.8%) | 31 / 406 (7.6%) | 3 / 39 (7.7%) | < 0.0001 |
| Revascularization | 204 / 6301 (3.2%) | 166 / 5856 (2.8%) | 35 / 406 (8.6%) | 3 / 39 (7.7%) | < 0.0001 |
| Cardiac Death | 59 / 6301 (0.9%) | 39 / 5856 (0.7%) | 16 / 406 (3.9%) | 4 / 39 (10.3%) | < 0.0001 |
| **Male** | **Total** | **Low Risk: < 10%** | **Medium Risk: 10% - 20%** | **High Risk: > 20%** | **P value for Trend** |
| Global CVD | 1157 / 4594 (25.2%) | 166 / 1571 (10.6%) | 832 / 2686 (31.0%) | 159 / 337 (47.2%) | < 0.0001 |
| All Death | 580 / 4594 (12.6%) | 96 / 1571 (6.1%) | 407 / 2686 (15.2%) | 77 / 337 (22.8%) | < 0.0001 |
| CHF | 280 / 4594 (6.1%) | 33 / 1571 (2.1%) | 190 / 2686 (7.1%) | 57 / 337 (16.9%) | < 0.0001 |
| MI | 232 / 4594 (5.1%) | 23 / 1571 (1.5%) | 167 / 2686 (6.2%) | 42 / 337 (12.5%) | < 0.0001 |
| Stroke | 113 / 4594 (2.5%) | 11 / 1571 (0.7%) | 81 / 2686 (3.0%) | 21 / 337 (6.2%) | < 0.0001 |
| Revascularization | 418 / 4594 (9.1%) | 35 / 1571 (2.2%) | 315 / 2686 (11.7%) | 68 / 337 (20.2%) | < 0.0001 |
| Cardiac Death | 79 / 4594 (1.7%) | 17 / 1571 (1.1%) | 52 / 2686 (1.9%) | 10 / 337 (3.0%) | 0.0033 |

**Event Summary by cTnI Additive Values to Framingham Risk Score Group for Pooled Cohort Data**

| Overall | Elevated Risk: Male cTnI > 12 pg/mL Female cTnI > 10 pg/mL (%) | High Risk: Framingham > 20% (%) | High Risk: Male cTnI > 12 pg/mL Female cTnI > 10 pg/mL or Framingham > 20% (%) | P value for Trend[a] |
|---|---|---|---|---|
| Global CVD | 233 / 921 (25.3%) | 175 / 376 (46.5%) | 369 / 1233 (29.9%) | < 0.0001 |
| All Death | 127 / 921 (13.8%) | 88 / 376 (23.4%) | 189 / 1233 (15.3%) | < 0.0001 |
| CHF | 108 / 921 (11.7%) | 64 / 376 (17.0%) | 155 / 1233 (12.6%) | < 0.0001 |
| MI | 64 / 921 (6.9%) | 47 / 376 (12.5%) | 102 / 1233 (8.3%) | < 0.0001 |
| Stroke | 36 / 921 (3.9%) | 24 / 376 (6.4%) | 50 / 1233 (4.1%) | < 0.0001 |
| Revascularization | 49 / 921 (5.3%) | 71 / 376 (18.9%) | 109 / 1233 (8.8%) | < 0.0001 |
| Cardiac Death | 40 / 921 (4.3%) | 14 / 376 (3.7%) | 46 / 1233 (3.7%) | < 0.0001 |

| Female | Elevated Risk: cTnI > 10 pg/mL (%) | High Risk: Framingham > 20% (%) | High Risk: cTnI > 10 pg/mL or Framingham > 20% (%) | P value for Trend[a] |
|---|---|---|---|---|
| Global CVD | 106 / 514 (20.6%) | 16 / 39 (41.0%) | 115 / 532 (21.6%) | < 0.0001 |
| All Death | 55 / 514 (10.7%) | 11 / 39 (28.2%) | 60 / 532 (11.3%) | < 0.0001 |
| CHF | 56 / 514 (10.9%) | 7 / 39 (17.9%) | 58 / 532 (10.9%) | < 0.0001 |
| MI | 32 / 514 (6.2%) | 5 / 39 (12.8%) | 35 / 532 (6.6%) | < 0.0001 |
| Stroke | 19 / 514 (3.7%) | 3 / 39 (7.7%) | 19 / 532 (3.6%) | < 0.0001 |
| Revascularization | 13 / 514 (2.5%) | 3 / 39 (7.7%) | 16 / 532 (3.0%) | 0.0034 |
| Cardiac Death | 16 / 514 (3.1%) | 4 / 39 (10.3%) | 18 / 532 (3.4%) | < 0.0001 |

| Male | Elevated Risk: cTnI > 12 pg/mL (%) | High Risk: Framingham > 20% (%) | High Risk: cTnI > 12 pg/mL or Framingham > 20% (%) | P value for Trend[a] |
|---|---|---|---|---|
| Global CVD | 127 / 407 (31.2%) | 159 / 337 (47.2%) | 254 / 701 (36.2%) | < 0.0001 |
| All Death | 72 / 407 (17.7%) | 77 / 337 (22.8%) | 129 / 701 (18.4%) | < 0.0001 |
| CHF | 52 / 407 (12.8%) | 57 / 337 (16.9%) | 97 / 701 (13.8%) | < 0.0001 |
| MI | 32 / 407 (7.9%) | 42 / 337 (12.5%) | 67 / 701 (9.6%) | < 0.0001 |
| Stroke | 17 / 407 (4.2%) | 21 / 337 (6.2%) | 31 / 701 (4.4%) | < 0.0001 |
| Revascularization | 36 / 407 (8.8%) | 68 / 337 (20.2%) | 93 / 701 (13.3%) | < 0.0001 |
| Cardiac Death | 24 / 407 (5.9%) | 10 / 337 (3.0%) | 28 / 701 (4.0%) | < 0.0001 |

[a] Trend test p-value for cTnI and Framingham Risk Score combined

**Prognosis**

The ARCHITECT STAT High Sensitive Troponin-I assay was evaluated for use as an aid in the assessment of 30-day and 90-day prognosis relative to all-cause mortality (ACM) and major adverse cardiac events (MACE) consisting of myocardial infarction, urgent revascularization, and cardiac death in subjects who present with symptoms suggestive of acute coronary syndrome (ACS).

Subjects from the diagnostic study above were followed-up for subsequent events by medical record review and/or subject/caregiver contact.

The 30-day and 90-day prognosis (Kaplan-Meier analysis) and hazard ratios (Cox regression) for the gender-specific 99th percentiles (female, 15.6 pg/mL; male, 34.2 pg/mL) are summarized in the tables below.

**30-Day and 90-Day Prognosis Results**

| | | ≤ Cutoff | | | > Cutoff | | | |
|---|---|---|---|---|---|---|---|---|
| Tube Type | Follow-Up Time Point | MACE/ ACM* | No MACE/ ACM* (Censored ‡) | Proportion | MACE/ ACM* | No MACE/ ACM* (Censored ‡) | Proportion | Log-Rank P Value |
| $K_2$ EDTA | 30 Days | 18 | 802 | 2.20% | 18 | 226 | 7.38% | < 0.0001 |
| | 90 Days | 28 | 792 | 3.41% | 33 | 211 | 13.52% | < 0.0001 |
| Lithium Heparin Separator | 30 Days | 17 | 802 | 2.08% | 19 | 247 | 7.14% | < 0.0001 |
| | 90 Days | 29 | 790 | 3.54% | 35 | 231 | 13.16% | < 0.0001 |
| Serum Separator | 30 Days | 16 | 791 | 1.98% | 14 | 206 | 6.36% | 0.0006 |
| | 90 Days | 27 | 780 | 3.35% | 28 | 192 | 12.73% | < 0.0001 |

* ACM = all cause mortality

‡ Censored = subject has not experienced MACE at the indicated follow-up time point.

### 30-Day and 90-Day Hazard Ratios

| Tube Type | Follow-Up Time Point | N | Hazard Ratio [95% CI*] | Likelihood Ratio P Value |
|---|---|---|---|---|
| $K_2$ EDTA | 30 Days | 1064 | 3.45 [1.79, 6.68] | 0.0003 |
| | 90 Days | 1064 | 4.17 [2.52, 6.94] | < 0.0001 |
| Lithium Heparin Separator | 30 Days | 1085 | 3.53 [1.83, 6.86] | 0.0002 |
| | 90 Days | 1085 | 3.91 [2.39, 6.44] | < 0.0001 |
| Serum Separator | 30 Days | 1027 | 3.28 [1.58, 6.73] | 0.0018 |
| | 90 Days | 1027 | 3.98 [2.34, 6.79] | < 0.0001 |

* CI = Confidence Interval

The 30-day and 90-day prognosis (Kaplan-Meier analysis) and hazard ratios (Cox regression) for the overall 99th percentile cutoff (26.2 pg/mL) are summarized in the tables below.

### 30-Day and 90-Day Prognosis Results

| | | ≤ Cutoff | | | > Cutoff | | | |
|---|---|---|---|---|---|---|---|---|
| Tube Type | Follow-Up Time Point | MACE/ ACM* | No MACE/ ACM* (Censored ‡) | Proportion | MACE/ ACM* | No MACE/ ACM* (Censored ‡) | Proportion | Log-Rank P Value |
| $K_2$ EDTA | 30 Days | 19 | 802 | 2.31% | 17 | 226 | 7.00% | 0.0004 |
| | 90 Days | 30 | 791 | 3.65% | 31 | 212 | 12.76% | < 0.0001 |
| Lithium Heparin Separator | 30 Days | 17 | 803 | 2.07% | 19 | 246 | 7.17% | < 0.0001 |
| | 90 Days | 30 | 790 | 3.66% | 34 | 231 | 12.83% | < 0.0001 |
| Serum Separator | 30 Days | 17 | 796 | 2.09% | 13 | 201 | 6.07% | 0.0020 |
| | 90 Days | 29 | 784 | 3.57% | 26 | 188 | 12.15% | < 0.0001 |

* ACM = all cause mortality

‡ Censored = subject has not experienced MACE at the indicated follow-up time point.

### 30-Day and 90-Day Hazard Ratios

| Tube Type | Follow-Up Time Point | N | Hazard Ratio [95% CI*] | Likelihood Ratio P Value |
|---|---|---|---|---|
| $K_2$ EDTA | 30 Days | 1064 | 3.09 [1.59, 5.95] | 0.0011 |
| | 90 Days | 1064 | 3.65 [2.21, 6.05] | < 0.0001 |
| Lithium Heparin Separator | 30 Days | 1085 | 3.54 [1.84, 6.87] | 0.0002 |
| | 90 Days | 1085 | 3.68 [2.25, 6.05] | < 0.0001 |
| Serum Separator | 30 Days | 1027 | 2.95 [1.41, 6.05] | 0.0050 |
| | 90 Days | 1027 | 3.55 [2.08, 6.03] | < 0.0001 |

* CI = Confidence Interval

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## Key to Symbols

| | |
|---|---|
|  | Caution |
|  | Consult instructions for use |
|  | Manufacturer |
|  | Sufficient for |
|  | Temperature limitation |
|  | Use by/Expiration date |
| CONJUGATE | Conjugate |
| CONTROL NO. | Control Number |
| IVD | *In Vitro* Diagnostic Medical Device |
| LOT | Lot Number |
| MICROPARTICLES | Microparticles |
| MULTI-ASSAY MANUAL DILUENT | Multi-Assay Manual Diluent |
| PRE-TRIGGER SOLUTION | Pre-Trigger Solution |
| PRODUCT OF IRELAND | Product of Ireland |
| REACTION VESSELS | Reaction Vessels |
| REAGENT LOT | Reagent Lot |
| REF | List Number |
| REPLACEMENT CAPS | Replacement Caps |
| SAMPLE CUPS | Sample Cups |
| SEPTUM | Septum |
| SN | Serial number |
| TRIGGER SOLUTION | Trigger Solution |
| WARNING: EYE IRRITANT | Warning: Causes serious eye irritation. |
| WARNING: SENSITIZER | Warning: May cause an allergic reaction. |
| WASH BUFFER | Wash Buffer |



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