# Troponin I STAT

cobas®

**Troponin I (STAT "Short Turn Around Time")**

| REF | Σ | SYSTEM |
|---|---|---|
| **05094798** 190 | 100 | Elecsys 2010<br>**cobas e** 411<br>**cobas e** 601<br>**cobas e** 602 |

## English

### Intended use

Immunoassay for the in vitro quantitative determination of cardiac troponin I in human serum and plasma. This assay is intended to aid in the diagnosis and treatment of myocardial infarction and cardiac muscle damage. Cardiac troponin I determinations aid in the risk stratification of patients with unstable angina pectoris or non-ST-segment elevation acute coronary syndrome with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.

### Summary

Troponin I (TnI) is a key regulatory protein of the striated musculature. Although its function in the contractile apparatus is the same in all striated muscles, TnI originating from the myocardium (cardiac TnI, molecular weight 23.9 kD) clearly differs from skeletal muscle TnI. Due to this high tissue-specificity, cardiac troponin I (cTnI) is a highly sensitive marker for myocardial damage.[1,2,3,4,5] Cardiac TnI allows to differentiate between skeletal muscle lesions (e.g. rhabdomyolysis and polytraumatism) and myocardial injury.[6,7,8]

In cases of acute myocardial infarction (AMI), cTnI levels in serum rise about 3-6 hours after the onset of cardiac symptoms, peak at 12-16 hours, and can remain elevated for 4-9 days.[9,10] Elevated cTnI levels have also been reported in cases of unstable angina pectoris (UAP) and congestive heart failure (CHF).[11,12,13,14] Cardiac TnI is a well-established prognostic marker which can predict the near-, mid- and even long-term outcome of patients with acute coronary syndrome (ACS).[15,16,17,18]

Given that cTnI as well as cardiac troponin T are independent markers which best predict the outcome of patients with ACS, the joint committee of the European Society of Cardiology (ESC) and American College of Cardiology (ACC) redefined myocardial infarction (MI). According to this redefinition, MI is diagnosed when blood levels of cardiac troponin are above the 99$^{th}$ percentile of the reference limit (of a healthy population) in the clinical setting of acute ischemia. The imprecision (coefficient of variation) at the 99$^{th}$ percentile for troponin assays is required to be less than or equal to 10 %.[19,20,21]

Based on the redefinition of MI several recommendations have been published concerning the role of cardiac troponin testing in patients with ACS.[22,23,24]

In patients with UAP and those without evidence of ST segment elevation (NSTEMI) detectable levels of cardiac troponin correlate with higher incidence of mortality. Thus, the measurement of troponin can be useful in the risk stratification of these patients which is also part of the ACC/AHA (American Heart Association) guidelines for the management of patients with UAP and NSTEMI.[25,26]

In summary, elevated troponin levels point to myocardial injury, but are not necessarily indicative of an ischemic mechanism. The term MI should be used when there is evidence of cardiac damage, as detected by marker proteins in a clinical setting consistent with myocardial ischemia. If the clinical circumstance suggests that an ischemic mechanism is unlikely, other causes of cardiac injury should be considered.[22]

The Elecsys Troponin I assay employs two pairs of monoclonal antibodies specifically directed against human cardiac troponin I.

### Test principle

Sandwich principle. Total duration of assay: 9 minutes.

Elecsys 2010 and **cobas e** 411 analyzers:

- 1st incubation: 30 µL of sample, two biotinylated monoclonal anti-cardiac troponin I antibodies, and two monoclonal anti-cardiac troponin I antibodies labeled with a ruthenium complex[a)] react to form a sandwich complex.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.

**cobas e** 601 and **cobas e** 602 analyzers:

- During a 9 minute incubation, antigen in the sample (30 µL), two biotinylated monoclonal troponin I-specific antibodies, two monoclonal troponin I-specific antibodies labeled with a ruthenium complex and streptavidin-coated microparticles react to form a sandwich complex, which is bound to the solid phase.

All analyzers:

- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

a) Tris(2,2-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

### Reagents - working solutions

The reagent rackpack is labeled as TNISTAT.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-cardiac troponin I-Ab~biotin (gray cap), 1 bottle, 10 mL:
Two biotinylated monoclonal anti-cardiac troponin I-antibodies (mouse) 0.8 mg/L each; phosphate buffer 100 mmol/L, pH 7.4; preservative; inhibitors.

R2 Anti-cardiac troponin I-Ab~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 10 mL:
Two monoclonal anti-cardiac troponin I-antibodies (mouse) labeled with ruthenium complex 0.8 mg/L and 0.005 mg/L respectively; phosphate buffer 100 mmol/L, pH 7.4; preservative; inhibitors.

### Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

### Reagent handling

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.

All information required for correct operation is read in automatically from the respective reagent barcodes.

### Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the Elecsys reagent kit **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

| Stability: | |
|---|---|
| unopened at 2-8 °C | up to the stated expiration date |
| after opening at 2-8 °C | 4 weeks |
| on the analyzers | 14 days |

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### Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

$K_2$-EDTA, $K_3$-EDTA and Li-heparin plasma.

Plasma (EDTA, heparin) and serum samples should not be used interchangeably.

Criterion: Slope 0.8-1.2 + coefficient of correlation ≥ 0.95.

Stable for 2 hours at 20-25 °C, 12 months at -20 °C. Freeze only once.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

Do not use samples and controls stabilized with azide.

Ensure the samples, calibrators and controls are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples, calibrators and controls on the analyzers should be analyzed/measured within 2 hours.

### Materials provided

See "Reagents – working solutions" section for reagents.

### Materials required (but not provided)

- REF 05094801190, Troponin I STAT CalSet, for 4 x 1 mL
- REF 05095107190, PreciControl Troponin, for 2 x 2 mL each of PreciControl Troponin 1 and 2
- REF 03609987190, Diluent MultiAssay, 2 x 16 mL sample diluent
- General laboratory equipment
- Elecsys 2010 or **cobas e** analyzer

Accessories for Elecsys 2010 and **cobas e** 411 analyzers:

- REF 11662988122, ProCell, 6 x 380 mL system buffer
- REF 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- REF 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- REF 11933159001, Adapter for SysClean
- REF 11706802001, Elecsys 2010 AssayCup, 60 x 60 reaction vessels
- REF 11706799001, Elecsys 2010 AssayTip, 30 x 120 pipette tips

Accessories for **cobas e** 601 and **cobas e** 602 analyzers:

- REF 04880340190, ProCell M, 2 x 2 L system buffer
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- REF 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- REF 12102137001, AssayTip/AssayCup Combimagazine M, 48 magazines x 84 reaction vessels or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Accessories for all analyzers:

- REF 11298500316, Elecsys SysClean, 5 x 100 mL system cleaning solution

### Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Resuspension of the microparticles prior to use and the reading in of the test-specific parameters via the reagent barcode take place automatically. No manual input is necessary. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers.

Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

### Calibration

Traceability: This method has been standardized against a commercially available troponin I assay.

Every Elecsys reagent set has a barcoded label containing specific information for calibration of the particular reagent lot. The predefined master curve is adapted to the analyzer using the relevant CalSet.

*Calibration frequency:* Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer). Renewed calibration is recommended as follows:

- after 12 weeks when using the same reagent lot
- after 7 days (when using the same reagent kit on the analyzer)
- as required: e.g. quality control findings outside the defined limits

### Quality control

For quality control, use PreciControl Troponin.

In addition, other suitable control material can be used.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

### Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in µg/L or ng/mL).

### Limitations - interference

The assay is unaffected by icterus (bilirubin < 428 µmol/L or < 25 mg/dL), hemolysis (Hb < 0.247 mmol/L or < 0.400 g/dL), lipemia (Intralipid < 1500 mg/dL) and biotin (< 123 nmol/L or < 30 ng/mL).

Falsely depressed results are obtained when using samples with higher hemoglobin concentrations.

Criterion: Recovery within ± 15 % of initial value.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

No interference was observed from rheumatoid factors up to a concentration of 1500 IU/mL.

There is no high-dose hook effect at troponin I concentrations up to 1000 µg/L (ng/mL).

In vitro tests were performed on 52 commonly used pharmaceuticals. No interference with the assay was found.

In rare cases, interference due to extremely high titers of antibodies to immunological components, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

### Limits and ranges

#### Measuring range

0.16-25 µg/L or ng/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Blank are reported as < 0.1 µg/L or ng/mL. Values above the Limit of Blank but below the Limit of Detection will not be flagged by the instrument. Values above the measuring range are reported as > 25 µg/L or ng/mL (or up to 250 µg/L or ng/mL for 10-fold diluted samples).

#### Lower limits of measurement

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*Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ)*

Limit of Blank = 0.1 µg/L (ng/mL)

Limit of Detection = 0.16 µg/L (ng/mL)

Limit of Quantitation = 0.3 µg/L (ng/mL)

The Limit of Blank and Limit of Detection were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A requirements.

The Limit of Quantitation was determined using the result of functional sensitivity testing.

The Limit of Blank is the 95$^{th}$ percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation (functional sensitivity) is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 10 %.

**Dilution**

Samples with troponin I concentrations above the measuring range can be diluted with Diluent MultiAssay. The recommended dilution is 1:10 (either automatically by the Elecsys 2010 or **cobas e** analyzers or manually). The concentration of the diluted sample must be > 3 µg/L (ng/mL).

After manual dilution, multiply the result by the dilution factor.

After dilution by the analyzers, the Elecsys 2010 and **cobas e** software automatically takes the dilution into account when calculating the sample concentration.

**Expected values**

In studies performed with the Elecsys Troponin I assay involving 839 healthy volunteers in 4 US sites and 2 EU sites, the upper reference limit (99$^{th}$ percentile) for cTnI was 0.16 µg/L (ng/mL) (95 % confidence interval 0.12-0.60).

The lowest concentration with a CV less than or equal to 10 % with the Elecsys Troponin I assay was 0.30 µg/L (ng/mL).

Due to the release kinetics of cTnI, a result below the decision limit within the first hours of the onset of symptoms does not rule out myocardial infarction with certainty. If myocardial infarction is still suspected, repeat the test at appropriate intervals.

*Factors associated with elevated values*

Published clinical studies have shown elevations of cTnI in patients with myocardial injury, as seen in unstable angina pectoris, cardiac contusions, and heart transplants.

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

**Specific performance data**

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

**Precision**

Precision was determined using Elecsys reagents, pooled human sera and controls in a protocol (EP5-A) of the CLSI (Clinical and Laboratory Standards Institute): each sample was measured in 21 runs with 3 consecutive measurements on different days (n = 63).

The following results were obtained:

| Elecsys 2010 and **cobas e** 411 analyzers | | | | | |
|---|---|---|---|---|---|
| | | **Repeatability** | | **Intermediate precision** | |
| Sample | Mean µg/L (ng/mL) | SD µg/L (ng/mL) | CV % | SD µg/L (ng/mL) | CV % |
| Human serum 1 | 0.234 | 0.021 | 9.1 | 0.037 | 16.0 |
| Human serum 2 | 0.323 | 0.016 | 4.8 | 0.029 | 8.9 |
| Human serum 3 | 0.496 | 0.016 | 3.3 | 0.029 | 5.9 |
| Human serum 4 | 0.627 | 0.014 | 2.2 | 0.033 | 5.3 |
| Human serum 5 | 21.4 | 0.363 | 1.7 | 0.689 | 3.2 |
| PreciControl Tn1 | 0.439 | 0.018 | 4.2 | 0.030 | 6.7 |
| PreciControl Tn2 | 17.8 | 0.522 | 2.9 | 0.645 | 3.6 |

Precision was determined using Elecsys reagents, pooled human sera and controls in a protocol (EP5-A2) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplication each for 21 days (n = 84). The following results were obtained:

| **cobas e** 601 and **cobas e** 602 analyzers | | | | | |
|---|---|---|---|---|---|
| | | **Repeatability** | | **Intermediate precision** | |
| Sample | Mean µg/L (ng/mL) | SD µg/L (ng/mL) | CV % | SD µg/L (ng/mL) | CV % |
| Human serum 1 | 0.193 | 0.015 | 7.7 | 0.016 | 8.2 |
| Human serum 2 | 0.344 | 0.018 | 5.1 | 0.020 | 5.8 |
| Human serum 3 | 1.71 | 0.037 | 2.1 | 0.047 | 2.8 |
| Human serum 4 | 8.85 | 0.190 | 2.2 | 0.278 | 3.1 |
| Human serum 5 | 21.4 | 0.293 | 1.4 | 0.788 | 3.7 |
| PreciControl Tn1 | 0.335 | 0.013 | 3.9 | 0.014 | 4.2 |
| PreciControl Tn2 | 16.4 | 0.272 | 1.7 | 0.333 | 2.0 |

**Method comparison**

A comparison of the Elecsys Troponin I STAT assay (y) with a commercially available troponin I assay (x) using clinical samples gave the following correlations (µg/L or ng/mL):

Number of samples measured: 144

| Passing/Bablok[27] | Linear regression |
|---|---|
| y = 0.847x + 0.123 | y = 0.795x + 0.259 |
| τ = 0.825 | r = 0.957 |

The sample concentrations were between approximately 0.160 and 22.8 µg/L (ng/mL).

**Analytical specificity**

The Elecsys Troponin I STAT assay does not show any significant cross-reaction with the following substances (tested with troponin I concentrations of approximately 0.4 ng/mL and 3 ng/mL):

h-skeletal muscle troponin I 0.03 %, h-cardiac troponin T 0.05 %, h-skeletal muscle troponin T 0.0 % (not detectable) and human troponin C 0.0 % (not detectable).

**Diagnostic sensitivity and specificity**

One clinical center in Europe and one center in the US participated in prospective studies with patients presenting with chest pain in the emergency department. 358 patients were ruled in for calculation of sensitivity and specificity as selected by the following criteria: Onset of chest pain within 24 hours before admission, chest pain for > 20 minutes, assessment by ECG criteria, age > 20 years, no pregnancy, no previous MI within 3 weeks before admission and a minimum of two blood draws. Another criteria was the availability of a test result with a commercially available cardiac troponin I test measured in parallel. Patients with non-vascular cardiac disease were excluded from the calculations. The patients were diagnosed according to the current guideline for the assessment of

acute myocardial infarction with inclusion of results by the routine troponin tests.[15,16] 69 patients were diagnosed as STEMI or NSTEMI, 80 patients as unstable angina pectoris, and 209 patients had developed chest pain that was not caused by cardiac injury. A Receiver Operating Characteristic (ROC) curve was calculated from the peak troponin values. The ROC curve had an area under the curve (AUC) of 0.96 (95 % confidence intervall 0.91-0.98). The optimal cut-off in the assessment of acute myocardial infarction was calculated by ROC analysis at 0.30 µg/L (ng/mL) from peak troponin I values. Sensitivity and specificity were calculated for the ROC optimized cut-off (0.30 µg/L (ng/mL)) in the table below.

| Cut-off µg/L (ng/mL) | Sensitivity % | N | 95 % CI[b)] (%) | Specificity % | N | 95 % CI (%) |
|---|---|---|---|---|---|---|
| 0.30 | 84 | 58/69 | 74-91 | 94 | 272/289 | 91-96 |

b) CI = confidence interval

Calculation of the peak values of the commercially available cardiac troponin I test measured in parallel yielded the following results for the officially stated ROC optimized cut-off of 0.50 µg/L (ng/mL).

| Cut-off µg/L (ng/mL) | Sensitivity % | N | 95 % CI (%) | Specificity % | N | 95 % CI (%) |
|---|---|---|---|---|---|---|
| 0.50 | 61 | 42/69 | 49-72 | 100 | 289/289 | 99-100 |

The sensitivity and specificity was in addition calculated for different time intervals from admission to the hospital (Elecsys Troponin I test):

| Time periods from admission (hours) | Cut-off µg/L (ng/mL) | Sensitivity % | N | 95 % confidence interval (%) |
|---|---|---|---|---|
| 0 | 0.30 | 69 | 46/67 | 57-79 |
| 0-3 | 0.30 | 81 | 51/63 | 70-89 |
| 3-6 | 0.30 | 79 | 30/38 | 64-89 |
| > 6 | 0.30 | 69 | 20/29 | 51-83 |

| Time periods from admission (hours) | Cut-off µg/L (ng/mL) | Specificity % | N | 95 % confidence interval (%) |
|---|---|---|---|---|
| 0 | 0.30 | 99 | 276/280 | 96-99 |
| 0-3 | 0.30 | 96 | 269/280 | 93-98 |
| 3-6 | 0.30 | 96 | 197/205 | 93-98 |
| > 6 | 0.30 | 97 | 133/137 | 93-99 |

*Note:* In the event that an initial troponin value presents as negative and the subject presents clinical AMI signs and symptoms, a second sample should be taken after 6 hours and a follow-up measurement should be performed.

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For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information and the Method Sheets of all necessary components (if available in your country).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

**Symbols**

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard.

| | |
|---|---|
| CONTENT | Contents of kit |
| SYSTEM | Analyzers/Instruments on which reagents can be used |
| REAGENT | Reagent |
| CALIBRATOR | Calibrator |
| → | Volume after reconstitution or mixing |



CE

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com