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Troponin T

cobas®

Troponin T, CARDIAC T

REF	Σ	SYSTEM
		Elecsys 2010
		MODULAR ANALYTICS E170
04491815 190	200	**cobas e** 411
		cobas e 601
		cobas e 602

English

Intended use

Immunoassay for the in vitro quantitative determination of troponin T in human serum and plasma. This assay can be used as an aid in the differential diagnosis of acute coronary syndrome to identify necrosis, e.g. acute myocardial infarction. The test is further indicated for the risk stratification of patients presenting with acute coronary syndrome and for cardiac risk in patients with chronic renal failure. The test may also be useful for the selection of more intensive therapy and intervention in patients with elevated levels of cardiac troponin T.

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 T (TnT) is a component of the contractile apparatus of the striated musculature. Although the function of TnT is the same in all striated muscles, TnT originating exclusively from the myocardium (cardiac TnT, molecular weight 39.7 kD) clearly differs from skeletal muscle TnT. As a result of its high tissue-specificity, cardiac troponin T (cTnT) is a cardiospecific, highly sensitive marker for myocardial damage. In cases of acute myocardial infarction (AMI), troponin T levels in serum rise about 3-4 hours after the occurrence of cardiac symptoms and can remain elevated for up to 14 days.[1,2]

Troponin T is an independent prognostic marker which can predict the near-, mid- and even long-term outcome of patients with acute coronary syndrome (ACS).[3,4,5,6,7]

In addition, four multicenter trials involving more than 7000 patients have shown that troponin T is also useful to identify patients that benefit from anti-thrombotic therapy (GPIIb/IIIa inhibitors, low molecular weight heparin).[8,9,10,11,12]

Because it has been proven that cardiac troponin is an independent marker which best predicts the outcome of patients with ACS and is a useful tool in guiding anti-thrombotic therapy, the joint committee of the European Society of Cardiology (ESC) and American College of Cardiology (ACC) redefined myocardial infarction (MI). According to this new definition, MI is diagnosed when blood levels of cardiac troponin are above the 99th percentile of reference limit (of a healthy population) in the clinical setting of acute ischemia. The imprecision (coefficient of variation) at the 99th percentile for each troponin assay should be defined as less than or equal to 10 %.[13]

Thus, patients with ACS and elevated cardiac troponin and/or CK-MB are considered to have experienced a non-ST-elevation MI (NSTEMI); whereas the diagnosis of unstable angina is established if cardiac troponin and CK-MB are within the reference range. This redefinition of MI is now also part of the new ACC/AHA guidelines for the management of patients with unstable angina and NSTEMI.[14]

Based on the redefinition of myocardial infarction several recommendations have been published concerning the role of cardiac troponin testing in patients with ACS.[15,16]

Myocardial cell injury leading to elevated troponin T concentrations in the blood can also occur in other clinical settings like congestive heart failure,[17] cardiomyopathy,[18] myocarditis,[19] heart contusion,[20] renal failure,[21] lung embolism,[22] stroke,[23] left ventricular dysfunction in septic shock,[24] and interventional therapy like cardiac surgery,[25] non-cardiac surgery,[26] PTCA,[27] and drug-induced cardiotoxicity.[28] In many of these cases – in particular in patients with renal failure – increased levels of cardiac troponin T identify patients with poorer prognosis.[29,30,31,32,33,34]

In summary, elevated troponin levels are indicative of myocardial injury, but elevations are not synonymous with an ischemic mechanism of injury. 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 pursued.[15]

The Elecsys Troponin T assay employs two monoclonal antibodies specifically directed against human cardiac troponin T.[35,36] The antibodies recognize two epitopes (amino acid position 125-131 and 136-147) located in the central part of the cardiac troponin T protein, which consists of 288 amino acids. Elecsys Troponin T assay detects free troponin T as well as binary and ternary complexes of troponin.[37]

Troponin T CalSet contain recombinant human cardiac troponin T (rec. hcTnT). The rec. hcTnT is isolated from cell culture of E. coli BL21 containing a pET vector with human cardiac troponin T isoform 3 gene. After fermentation, the cells are disrupted by sonication and rec. hcTnT is purified by ion exchange chromatography. Purified rec. hcTnT is further characterized by SDS PAGE, Western blotting, immunological activity, and protein content.[38]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 15 µL of sample, a biotinylated monoclonal troponin T-specific antibody, and a monoclonal troponin T-specific antibody 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.
- 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 TN-T.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 12 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-troponin T-Ab~biotin (gray cap), 1 bottle, 18 mL:
Biotinylated monoclonal anti-troponin T-antibody (mouse) 1.5 mg/L; phosphate buffer 100 mmol/L, pH 6.0; preservative; inhibitors.

R2 Anti-troponin T-Ab~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 17 mL:
Monoclonal anti-troponin T-antibody (mouse) labeled with ruthenium complex 1.2 mg/L; phosphate buffer 100 mmol/L, pH 6.0; preservative.

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 from the respective reagent barcodes.

Troponin T

Troponin T, CARDIAC T

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	12 weeks
on the analyzers	8 weeks

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, Li-heparin and sodium citrate plasma.

Criterion: Recovery within 90-110 % of serum value or slope 0.9-1.1 + intercept within < ± 2x analytical sensitivity (LDL) + coefficient of correlation > 0.95.

Do not use oxalate/fluoride plasma samples for this assay.

Stable for 24 hours at 2-8 °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 04856627190, Troponin T CalSet, for 4 x 1 mL
- REF 03530469190, PreciControl Troponin T, for 2 x 2 mL each of PreciControl Troponin T 1 and 2
- REF 11732277122, Diluent Universal, 2 x 16 mL sample diluent or REF 03183971122, Diluent Universal, 2 x 36 mL sample diluent
- General laboratory equipment
- Elecsys 2010, MODULAR ANALYTICS E170 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 MODULAR ANALYTICS E170, **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
- REF 11298500160, Elecsys SysClean, 5 x 100 mL system cleaning solution (for USA)

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 takes place automatically prior to use. Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers.

Bring the cooled reagents to approx. 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: The Troponin T assay (4th generation, REF 04491815) has been standardized against the Troponin T STAT assay (4th generation, REF 04660307). This in turn was originally standardized against the Enzymun-Test Troponin T (CARDIAC T) method.

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 1 month (28 days) 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 T.

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 < 462 µmol/L or < 27 mg/dL), hemolysis (Hb < 0.062 mmol/L or < 0.1 g/dL; samples showing visible signs of hemolysis may cause interference.), lipemia (Intralipid < 1500 mg/dL) and biotin (< 205 nmol/L or < 50 ng/mL).

Falsely depressed results are obtained when using samples with hemoglobin concentrations > 0.1 g/dL.

Criterion: Recovery within ± 20 % of initial value at troponin T concentrations < 0.1 µg/L or ng/mL (± 10 % at troponin T concentrations ≥ 0.1 µg/L or ng/mL).

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.

Troponin T

Troponin T, CARDIAC T

No interference was observed from rheumatoid factors up to a concentration of 2000 IU/mL.

There is no high-dose hook effect at troponin T concentrations up to 400 µg/L (ng/mL).

In vitro tests were performed on 50 commonly used pharmaceuticals. No interference with the assay was found.

Plasma samples collected using tubes containing oxalate/fluoride, revealed sample-dependent low troponin T values when compared to results obtained on serum samples. Therefore, do not use oxalate/fluoride plasma samples for the assay.

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, 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

0.010-25.0 µg/L or ng/mL (defined by the lower detection limit and the maximum of the master curve). Values below the lower detection limit are reported as < 0.010 µg/L (ng/mL). Values above the measuring range are reported as > 25.0 µg/L or ng/mL (or up to 250 µg/L or ng/mL for 10-fold diluted samples).

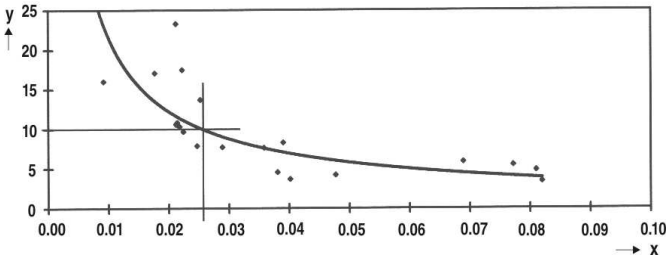
Lower limits of measurement

Lower detection limit of the test

Lower detection limit: 0.010 µg/L (ng/mL)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying three standard deviations above that of the lowest standard (master calibrator, standard 1 + 3 SD, repeatability study, n = 21).

≥ 0.030 µg/L (ng/mL) is the troponin T concentration, which is read off from the trendline, that can be reproducibly measured with the intermediate precision coefficient of variation of 10 %.



x: Concentration (ng/mL)

y: CV (%)

When taking lot to lot variability into consideration, at 0.030 ng/mL a CV of 18 % is achieved and at 0.060 ng/mL a CV of 10 % is achieved.

Dilution

Samples with troponin T concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:10 (either automatically by the MODULAR ANALYTICS E170, Elecsys 2010 and **cobas e** analyzers or manually). The concentration of the diluted sample must be > 1.00 µg/L (ng/mL).

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

After dilution by the analyzers, the MODULAR ANALYTICS E170, 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 T assay involving 1951 healthy volunteers, the upper reference limit (99th percentile) for troponin T was < 0.010 µg/L (ng/mL). [b)]

The lowest concentration with a CV less than or equal to 10 % with the Elecsys Troponin T assay was 0.030 µg/L (ng/mL) (intermediate within lot precision) or 0.060 µg/L (ng/mL) (intermediate lot to lot precision).

Based on the WHO criteria for the definition of AMI from the 1970's, the cutoff (clinical discriminator) value for troponin T is 0.100 µg/L (ng/mL) according to ROC analysis.[39,40]

Due to the release kinetics of troponin T, a negative result 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 [41,42,43,44,45,46,47]

Published clinical studies have shown elevations of troponin T in patients with myocardial injury, as seen in unstable angina pectoris, cardiac contusions, and heart transplants. Elevations have also been seen in patients with rhabdomyolysis and polymyositis.

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

b) Data (status July 1999) combined from: Multicenter evaluation of troponin T (3rd generation), April 1999, and International Elecsys 1010 study, Cardiac markers, March 1999.

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 modified protocol (EP5-A) of the CLSI (Clinical and Laboratory Standards Institute): 6 times daily for 10 days (n = 60); repeatability on MODULAR ANALYTICS E170 analyzer, n = 21. 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	0.040	0.001	3.4	0.002	5.6
Human serum 2	0.647	0.010	1.6	0.018	2.8
Human serum 3	6.04	0.088	1.5	0.159	2.6
PreciControl TNT1	0.134	0.002	1.6	0.003	2.3
PreciControl TNT2	2.96	0.033	1.1	0.051	1.7

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers						
	Repeatability			**Intermediate precision**		
Sample	Mean µg/L (ng/mL)	SD µg/L (ng/mL)	CV %	Mean µg/L (ng/mL)	SD µg/L (ng/mL)	CV %
Human serum 1	0.045	0.001	2.4	0.038	0.002	5.0
Human serum 2	0.624	0.006	0.9	0.600	0.014	2.3
Human serum 3	5.96	0.068	1.2	5.68	0.131	2.3
PreciControl TNT1	0.141	0.002	1.2	0.133	0.002	1.7
PreciControl TNT2	3.00	0.023	0.8	2.93	0.058	2.0

Method comparison

A comparison of the Elecsys Troponin T assay (y) with the Elecsys Troponin T STAT assay (x) using clinical samples gave the following correlations:

Number of samples measured: 60

Passing/Bablok[48]	Linear regression
y = 0.98x + 0.01	y = 0.99x - 0.01
τ = 0.974	r = 0.999

The sample concentrations were between approx. 0.06 and 19 µg/L (ng/mL).

Analytical specificity

For the monoclonal antibodies used, the following cross-reactivities were found:

h-skeletal muscle troponin T 0.001 %, h-cardiac troponin I 0.002 %, h-skeletal muscle tropomyosin 0.001 %, h-cardiac tropomyosin 0.1 %, and h-cardiac myosin light chain 1 0.003 %.

Diagnostic sensitivity and specificity

Data are based on blood samples taken from 294 patients with chest pain and suspected myocardial infarction admitted to the emergency department during a 10 week period.[40]

154 patients (171 samples) were not hospitalized because AMI or other serious diseases (e.g. pulmonary embolism) were ruled out. 58 patients (576 samples) with acute myocardial infarction (AMI) classified acc. to WHO standards, 50 patients (396 samples) with unstable angina pectoris (UAP) and 32 patients (212 samples) without acute ischemic syndromes were admitted to the hospital.

These samples were taken at 0, 3, 6, 12, 24, 48, 72, and 96 hours after admission or until discharge and measured by the following test methods:

- Elecsys Troponin T 2nd gen.
- Enzymun-Test Troponin T
- Elecsys CK-MB mass
- Stratus CK-MB mass
- Total CK activity via CHEM 1 analyzer

Analysis of clinical sensitivity and specificity for the detection of myocardial infarction on admission and the following samples showed comparable results between Elecsys measurements and the respective reference methods - see table below. Three hours after admission, most AMI patients underwent effective reperfusion therapies which partly accounts for high sensitivities in follow up blood samples.

The results of apparently low specificity for troponin T in AMI, compared to CK-MB, are largely due to the detection of minor myocardial damage (MMD) in patients with unstable angina pectoris: excluding these patients from analysis leads to specificities of almost 100 % for troponin T for the detection of AMI. For example, at 6 hours after admission specificity for the Elecsys Troponin T assay would be 97.5 %, at 24 hours 100 %. Specificity for CK-MB mass at 6 hours after admission would be 92.9 %, at 24 hours, 91.7 % if UAP were excluded for the calculation of the specificity for AMI detection.

Hours after admission	0	3	6	12	24	48	72	96
Elecsys Troponin T assay, 2nd gen.								
Sensitivity†	60.7	96.0	98.0	100.0	100.0	97.7	95.7	97.7
Specificity†	96.5	86.6	82.5	83.3	83.9	86.9	82.7	87.8
Enzymun-Test Troponin T method								
Sensitivity†	60.7	96.0	98.0	100.0	100.0	97.3	95.7	97.7
Specificity†	95.8	84.4	80.3	82.4	85.3	88.2	82.8	88.9
Elecsys CK-MB assay								
Sensitivity†	69.6	98.0	100.0	95.7	89.4	75.0	34.8	18.6
Specificity†	94.1	86.7	84.5	85.3	89.7	94.1	100.0	100.0
Stratus CK-MB								
Sensitivity†	63.0	98.0	100.0	95.7	87.2	77.3	37.0	11.6
Specificity†	94.4	87.5	85.7	84.9	90.6	95.5	100.0	100.0
Total CK activity								
Sensitivity†	56.9	86.1	93.3	92.9	83.7	69.2	58.5	31.6
Specificity†	86.6	84.2	84.9	86.7	88.1	93.4	98.1	97.9
Total number of patients	294	140	121	115	115	112	104	97

† For calculation of the sensitivity and specificity the group of UAP patients is included in the control group.

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