



Elecsys Troponin T hs

cobas®

REF			SYSTEM
08469873190	08469873500	300	cobas e 402 cobas e 801

English

System information

Short name	ACN (application code number)	Application
TNTHS	10011	18 minutes
TNTHSST	10012	9 minutes (STAT = Short Turn Around Time)

Intended use

Immunoassay for the in vitro quantitative determination of cardiac 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 electrochemiluminescence immunoassay "ECLIA" is intended for use on **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 kDa) clearly differs from skeletal muscle TnT. As a result of its high tissue-specificity, cardiac troponin T (cTnT) is a cardio-specific, highly sensitive marker for myocardial damage. Cardiac troponin T increases rapidly after acute myocardial infarction (AMI) and may persist up to 2 weeks thereafter.^{1,2,3} Early detectability of the troponin increase in blood depends on the analytical sensitivity of the specific troponin test used; cardiac troponin T-high sensitive (cTnT-hs) helped to reduce the observational time from 6 to 3 hours when compared to conventional troponin tests as suggested by several studies^{4,5,6} and recommended by the 2011 ESC and the 2014 NICE guidelines on non-ST elevation myocardial infarction (NSTEMI).^{7,8} The 2015 ESC guidelines on NSTEMI propose to further shorten the observation time to 0 h/1 h. This accelerated approach to rule-in or rule-out AMI within 0 h/1 h has to be used with high-sensitive cardiac Troponin (hs-cTn) tests and using an algorithm validated for the specific hs-cTn assay.^{9,10,11,12} The specific algorithm values for cTnT-hs were recommended in these guidelines and have been validated in 3 studies, APACE, APACE-2015 and TRAPID-AMI.^{13,14,15} Alternative approaches using cTnT-hs to rule-in or rule-out AMI within 2 hours with or without risk scores have been also developed.^{16,17,18,19,20,21}

In contrast to ST elevation myocardial infarction (STEMI), the diagnosis of NSTEMI heavily relies on measured cardiac troponin results. According to the new Universal Definition of myocardial infarction, MI is diagnosed when blood levels of cardiac troponin are above the 99th percentile of the reference limit (of a healthy population) together with evidence of myocardial ischemia (symptoms, electrocardiogram (ECG) changes or imaging results). The definition requires a troponin assay with an imprecision (coefficient of variation) at the 99th percentile less than or equal to 10 %.²²

Cardiac troponin T (cTnT) is an independent prognostic marker which can predict the near-, mid- and even long-term outcome of patients with acute coronary syndrome (ACS).^{23,24,25,26}

In addition, 4 multicenter trials involving more than 7000 patients have shown that cardiac troponin T is also useful to identify patients that benefit from anti-thrombotic therapy (GPIIb/IIIa inhibitors, low molecular weight heparin).^{27,28,29,30,31}

The results of a sub-study of the PLATO trial, involving 9946 patients hospitalized for NSTEMI-ACS, also support the use of cTnT-hs testing to identify which NSTEMI-ACS patients will benefit most from an aggressive anti-platelet treatment strategy.³²

Cardiac troponin has been reconfirmed as the preferred marker of myocardial injury in the new guidelines for the diagnosis and treatment of non-ST elevation myocardial infarction (NSTEMI).^{9,33}

Troponins are released during the process of myocyte necrosis. While they are cardiac specific, they are not specific of MI only. To distinguish between acute and chronic cTn elevations, the Universal Definition of AMI requires the need for serial sampling to observe a rise and/or fall of cTn with at least one value above the 99th percentile upper reference limit. Absolute changes in cTn appear to have a higher diagnostic accuracy for AMI compared to relative changes.^{22,34} Results interpretation have to be analyzed integrating the clinical assessment, including ischemic symptoms and electrocardiographic changes.

The Universal Definition of AMI recognizes that the improved analytical sensitivity of cTn assays used over the last years have allowed for detection of myocardial injury associated with other etiologies.²² Chronic elevations of cTn can be detected in clinically stable patients such as patients with ischemic or non-ischemic heart failure,^{35,36,37} in patients with different forms of cardiomyopathy,³⁸ renal failure,^{39,40,41,42,43,44} sepsis⁴⁵ and diabetes.^{46,47}

Elevated levels of troponin T correlate with the severity of coronary artery disease and to poor outcome independent of natriuretic peptide (NT-proBNP or BNP) levels.^{48,49}

The 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure and the fourth definition of Acute Myocardial Infarction recognize the role of cTn in risk stratification and decision-making in patients with Acute Heart Failure (AHF). These guidelines recommend in addition to B-type natriuretic peptides the measurement of cTn upon presentation, in all patients with acute dyspnea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnea or to exclude myocardial injury or type 1 AMI.^{50,22}

Troponin T values are an independent predictor of cardiovascular events including occurrence and recurrence of atrial fibrillation (AF).⁵¹

Recently, troponin T has also been included into the "ABC-bleeding score" taking into account age, biomarkers (GDF-15, cTnT-hs, and hemoglobin) and history of bleeding, and into the "ABC-stroke risk score" taking into account age, NT-proBNP, cTnT-hs, and prior stroke/transient ischemic attack. The ABC-bleeding risk score was shown to significantly improve the prediction of bleeding events of AF patients.⁵² The ABC-bleeding risk score could therefore be a valuable decision support tool regarding indications for and selection of treatment with oral anticoagulants in patients with AF.⁵³ Results of the ENGAGE AF-TIMI 48 trial evaluating the ABC-stroke and the ABC-bleeding risk scores confirmed that these scores may help to identify AF patients most likely to benefit from treatment with non-vitamin K antagonist oral anticoagulants (NOACs).⁵³

Myocardial cell injury leading to elevated cTnT concentrations in the blood can also occur in other clinical conditions such as myocarditis,⁵⁴ heart contusion,⁵⁵ pulmonary embolism,⁵⁶ kidney disease⁵⁷ and drug-induced cardiotoxicity.⁵⁸

Several studies in the general population have shown that cTnT-hs elevations below the 99th percentile upper reference limit (URL) can have prognostic value for increased risk of cardiovascular disease. This association was strongest for fatal CVD and applies to both Coronary Heart Disease (CHD) and stroke, and persisted after adjustment for conventional risk factors.^{59,60,61,62,63,64,65}

Other diagnostic tests such as NT-proBNP or GDF-15 can complement the diagnostic and prognostic information of troponin T in patients with heart failure and renal dysfunction.^{66,67} The results of the FRISC-II study suggest that in patients with non-ST elevation ACS, prioritisation for early invasive procedures might be facilitated by use of biomarkers such as cTnT-hs and GDF-15.⁶⁷

In addition, cTnT-hs measurements can be used in patients who undergo major non-cardiac surgery to predict patients' peri and postoperative cardiac events.^{22,68,69} In a prospective multicenter, international cohort study (VISION) including 21842 patients who underwent noncardiac surgery, peak level of cTnT-hs during the first 3 days after surgery was significantly associated with 30-day mortality and helped to identify MINS (myocardial injury after non-cardiac surgery).⁷⁰

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The Elecsys Troponin T hs assay employs two monoclonal antibodies specifically directed against human cardiac troponin T.^{71,72} 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.

The Troponin T hs calibrators (Troponin T hs 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.⁷³

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: Antigen in the sample (30 µL), a biotinylated monoclonal cardiac troponin T-specific antibody, and a monoclonal cardiac 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.

Total duration of assay: 9 minutes.

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

For both assay applications:

- 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 II 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 **cobas** link.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex (Ru(bpy)₃²⁺)

Reagents - working solutions

The **cobas e** pack is labeled as TNTHS.

- M Streptavidin-coated microparticles, 1 bottle, 12.4 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 Anti-cardiac troponin T-Ab~biotin, 1 bottle, 15.8 mL:
Biotinylated monoclonal anti-cardiac troponin T-antibody (mouse) 2.5 mg/L; phosphate buffer 100 mmol/L, pH 6.0; preservative; inhibitors.
- R2 Anti-cardiac troponin T-Ab~Ru(bpy)₃²⁺, 1 bottle, 15.8 mL:
Monoclonal anti-cardiac troponin T-antibody (mouse) labeled with ruthenium complex 2.5 mg/L; phosphate buffer 100 mmol/L, pH 6.0; preservative.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:

Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:

Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:



Warning

- H317 May cause an allergic skin reaction.

Prevention:

- P261 Avoid breathing mist or vapours.
- P272 Contaminated work clothing should not be allowed out of the workplace.
- P280 Wear protective gloves.

Response:

- 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 to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

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

Reagent handling

The Elecsys Troponin T hs assay can be used for both the 9-minute application and the 18-minute application.

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 available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **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
on the analyzers	16 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.

K₂-EDTA, K₃-EDTA, Li-heparin and Na-heparin plasma.

Plasma tubes containing separating gel can be used.

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

Criterion: Slope 0.90-1.10 + coefficient of correlation ≥ 0.95.

Stable for 24 hours at 2-8 °C, 12 months at -20 °C (± 5 °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.

Re-centrifuge K2/K3-EDTA plasma samples in a secondary tube for 5 minutes at 3000 x g or 30 seconds at 10000 x g prior to measurement.

Do not use samples and controls stabilized with azide.

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

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Due to possible evaporation effects, samples and calibrators 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] 07401671190, CalSet Troponin T hs, for 4 x 1.0 mL
- [REF] 05095107190, PreciControl Troponin, for 4 x 2.0 mL
- [REF] 07299010190, Diluent MultiAssay, 36 mL sample diluent
- General laboratory equipment
- **cobas e** analyzer

Additional materials for **cobas e** 402 and **cobas e** 801 analyzers:

- [REF] 06908799190, ProCell II M, 2 x 2 L system solution
- [REF] 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- [REF] 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- [REF] 06908853190, PreClean II M, 2 x 2 L wash solution
- [REF] 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- [REF] 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- [REF] 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- [REF] 11298500316, ISE Cleaning Solution/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 takes place automatically prior to use.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

Calibration

Traceability: The Elecsys Troponin T hs assay ([REF] 08469873190) has been standardized against the Elecsys Troponin T STAT assay ([REF] 04660307190). This in turn was originally standardized against the Enzymun-Test Troponin T (CARDIAC T) method.

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 **cobas e** pack was registered on the analyzer).

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration is recommended as follows:

- after 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

Use PreciControl Troponin or other suitable controls for routine quality control procedures.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per **cobas e** pack, 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.

If necessary, repeat the measurement of the samples concerned.

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

Calculation

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

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 428 µmol/L or ≤ 25 mg/dL
Hemoglobin	≤ 0.062 mmol/L or ≤ 100 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 4.92 µmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1200 IU/mL
Albumin	≤ 7 g/dL

Criterion: Recovery of ± 2.8 pg/mL of initial value < 14 pg/mL, ± 20 % of initial value 14-100 pg/mL and ± 10 % of initial value > 100 pg/mL.

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

There is no high-dose hook effect at troponin T concentrations up to 100000 ng/L (pg/mL).

Pharmaceutical substances

In vitro tests were performed on 17 commonly used pharmaceuticals. No interference with the assay was found.

In addition, the following special cardiac drugs were tested. No interference with the assay was found.

Special cardiac drugs

Drug	Concentration tested mg/L
Carvedilol	37.5
Clopidogrel	75
Digoxin	0.25
Epinephrine	0.5
Insulin aspart	1.6
Lidocaine	80
Lisinopril	10
Methylprednisolone (Urbason)	7.5
Metoprolol	150
Nifedipine	30
Phenprocoumon	3
Propafenone	300
Reteplase	33.3
Simvastatin	30
Spironolactone	75
Tolbutamide (Glibenclamide)	1500
Torsemide	15
Verapamil	240
Valsartan	206
Sacubitril	194
Dabigatran	300
Rivaroxaban	40

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Drug interferences are measured based on recommendations given in CLSI guidelines EP07 and EP37 and other published literature. Effects of concentrations exceeding these recommendations have not been characterized.

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

3-10000 ng/L or pg/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 3 ng/L or pg/mL. Values above the measuring range are reported as > 10000 ng/L or pg/mL (or up to 100000 ng/L or pg/mL for 10-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 2.5 ng/L (pg/mL)

Limit of Detection = 3 ng/L (pg/mL)

Limit of Quantitation = 13 ng/L (pg/mL)

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from $n \geq 60$ 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 %.

An internal study was performed based on guidance from the CLSI protocol EP17-A2. Limit of Blank, Limit of Detection and Limit of Quantitation were determined to be the following-see table below. In addition for analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 % the following results were obtained:

	18-min application	9-min application
Limit of Blank (ng/L = pg/mL)	2.21	1.91
Limit of Detection (ng/L = pg/mL)	2.97	2.72
Limit of Quantitation 10 % intermediate CV (ng/L = pg/mL)	5.40	3.22
20 % intermediate CV (ng/L = pg/mL)	2.30	1.00

Dilution

Samples with cardiac troponin T concentrations above the measuring range can be diluted with Diluent MultiAssay. The recommended dilution is 1:10 (either automatically by the analyzer or manually). The concentration of the diluted sample must be ≥ 1000 ng/L (pg/mL).

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

After dilution by the analyzers, the software automatically takes the dilution into account when calculating the sample concentration.

Expected values

In studies performed with the Elecsys Troponin T hs assay involving 533 healthy volunteers (age range: 20-71 years), the upper reference limit (URL) (99th percentile) for troponin T was determined at 14 ng/L (pg/mL), 95 % confidence interval 12.7-24.9 ng/L (pg/mL).⁷⁴ This study also defines

the 99th percentile URL at 9.0 ng/L (pg/mL) for females ($n = 265$) and 16.8 ng/L (pg/mL) for males ($n = 268$) using a non-parametric approach. Several publications report that using cTnT-hs, sex-specific cut-offs do not add clinical value compared to one overall cut-off.^{75,76,77,78,79,80,81}

Based on the WHO criteria for the definition of AMI⁸² from the 1970's, the cutoff (clinical discriminator) value for troponin T is 0.1 $\mu\text{g/L}$ (ng/mL) or 100 ng/L (pg/mL) as determined from ROC analysis in results with an earlier test generation of the Elecsys Troponin T assay.^{83,84}

The WHO definition of AMI has been recently updated and takes into consideration the ESC/ACCF/AHA/WHF definition recommending the detection of a rise and/or fall of cardiac troponin in the clinical setting of myocardial ischemia using the 99th percentile troponin cut-off value.⁸⁵

Due to the release kinetics of cardiac troponin T, an initially test result < 99th percentile within the first hour of the onset of symptoms does not rule out myocardial infarction in all patients. Therefore lower cut-offs have been proposed for immediate rule-out and also specific delta changes for 0 h/1 h algorithms.⁹ Additional testing at appropriate time intervals is indicated if the first measurements are not conclusive and the clinical condition is still suggestive of ACS.⁹ The troponin values should always be used in conjunction with full clinical assessment (including chest pain characteristics and ECG).

It is important to obtain a careful history and a precise description of the symptoms. A physical examination with particular attention to the possible presence of cardiac contusion, acute and chronic heart failure, aortic dissection, aortic valve disease, hypertrophic cardiomyopathy, tachy- or bradyarrhythmias, apical ballooning syndrome, rhabdomyolysis with cardiac injury, pulmonary embolism, severe pulmonary hypertension, acute neurological disease, infiltrative diseases, drug toxicity, respiratory failure, sepsis, burns is required.^{9,22}

An ECG is recorded for allowing differentiation of patients with or without ST-segment changes.

Laboratory assessment of patients with suspicion of ACS should include markers of myocardial damage, preferably cardiac troponin.⁹ If concentrations of troponin or cardiac enzymes rise, irreversible myocyte cell damage will have occurred and these patients must be regarded as having had myocardial damage.

Factors associated with elevated values^{22,54,86,87,88,89}

Published clinical studies have shown elevations of cardiac troponin 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.

The ESC and AHA/ACC guidelines and the Universal Definition of MI recommend serial sampling with a rise or fall in troponin to distinguish between acute and chronic cTn elevations. Results should be interpreted in conjunction with clinical presentation including medical history, signs and symptoms, ECG data and biomarker concentrations.^{9,22,33}

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, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days ($n = 84$). The following results were obtained:

cobas e 402 and cobas e 801 analyzers (18-minutes application)					
Sample	Mean ng/L (pg/mL)	Repeatability		Intermediate precision	
		SD ng/L (pg/mL)	CV %	SD ng/L (pg/mL)	CV %
Human serum 1	9.73	0.449	4.6	0.649	6.7
Human serum 2	12.5	0.522	4.2	0.631	5.0
Human serum 3	21.4	0.506	2.4	0.781	3.6

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cobas e 402 and cobas e 801 analyzers (18-minutes application)					
		Repeatability		Intermediate precision	
Sample	Mean ng/L (pg/mL)	SD ng/L (pg/mL)	CV %	SD ng/L (pg/mL)	CV %
Human serum 4	166	3.62	2.2	5.65	3.4
Human serum 5	5557	139	2.5	224	4.0
Human serum 6	9984	209	2.1	459	4.6
PreciControl TN1	28.3	0.575	2.0	0.977	3.5
PreciControl TN2	2136	24.9	1.2	61.2	2.9

cobas e 402 and cobas e 801 analyzers (9-minutes application)					
		Repeatability		Intermediate precision	
Sample	Mean ng/L (pg/mL)	SD ng/L (pg/mL)	CV %	SD ng/L (pg/mL)	CV %
Human serum 1	9.87	0.266	2.7	0.537	5.4
Human serum 2	12.2	0.311	2.5	0.528	4.3
Human serum 3	21.6	0.351	1.6	0.777	3.6
Human serum 4	156	3.24	2.1	6.01	3.9
Human serum 5	4740	38.8	0.8	144	3.0
Human serum 6	9172	79.0	0.9	314	3.4
PreciControl TN1	26.5	0.399	1.5	0.864	3.3
PreciControl TN2	1964	24.1	1.2	55.6	2.8

Method comparison

A comparison of the Elecsys Troponin T hs assay, [REF] 08469873190 (cobas e 801 analyzer; 18-min. application; y) with the Elecsys Troponin T hs assay, [REF] 07028075190 (cobas e 801 analyzer; 18-min. application; x), using clinical samples gave the following correlations (ng/L or pg/mL):

Number of samples measured: 155

Passing/Bablok⁹⁰ Linear regression
 $y = 0.999x + 1.04$ $y = 0.990x + 6.27$
 $r = 0.951$ $r = 1.00$

A comparison of the Elecsys Troponin T hs assay, [REF] 08469873190 (cobas e 801 analyzer; 9-min. application; y) with the Elecsys Troponin T hs assay, [REF] 08469873190 (cobas e 801 analyzer; 18-min. application; x), using clinical samples gave the following correlations (ng/L or pg/mL):

Number of samples measured: 158

Passing/Bablok⁹⁰ Linear regression
 $y = 1.00x + 0.132$ $y = 1.02x - 0.235$
 $r = 0.966$ $r = 1.00$

The sample concentrations were between 3 and 9700 ng/L (pg/mL).

A comparison of the Elecsys Troponin T hs assay, [REF] 08469873190 (cobas e 402 analyzer; 18-min. application; y) with the Elecsys Troponin T hs assay, [REF] 08469873190 (cobas e 801 analyzer; 18-min. application; x) gave the following correlations (ng/L or pg/mL):

Number of samples measured: 158

Passing/Bablok⁹⁰ Linear regression
 $y = 1.04x - 0.945$ $y = 1.01x + 8.37$
 $r = 0.966$ $r = 0.999$

The sample concentrations were between 4.67 and 9682 ng/L (pg/mL).

Analytical specificity

The Elecsys Troponin T hs assay does not show any significant cross-reaction with the following substances (tested with TnT concentrations of approximately 18 ng/L (pg/mL); concentration of cross-reacting substances 500 ng/mL):

h-skeletal muscle troponin T 0.066 %, h-cardiac troponin I 0.017 %, h-skeletal muscle troponin I 0.006 %, human troponin C 0.0003 %.

Diagnostic sensitivity and specificity

One clinical center in Germany, one center in India, one center in Switzerland, and two centers in the US participated in prospective studies in patients presenting with chest pain in the emergency department.

507 patients were ruled in for calculation of sensitivity and specificity as selected by the following criteria: Chest pain for > 20 minutes, assessment by 12-lead ECG, age > 20 years, no pregnancy, no previous MI within 3 weeks before admission and a minimum of two blood draws. The patients were diagnosed for acute MI by application of:

1. WHO criteria⁹² including ECG changes, symptoms characteristic for ACS and elevation of cardiac troponin, and
2. Criteria defined by the Joint ESC/ACCF/AHA/WHF task force.⁹¹

Sensitivity and specificity calculated with AMI defined according to the ESC/ACCF/AHA/WHF guidelines

Patients with AMI were defined by routine cardiac troponin values above the 99th percentile/10 % CV criteria, and presence of chest pain or ECG changes. Sensitivity and specificity at peak troponin T, high sensitive values were calculated at the 99th percentile of 14 ng/L (pg/mL).

Sensitivity %	N	95 % confidence interval (%)	Specificity %	N	95 % confidence interval (%)
100	112/112	97-100	75	297/395	71-79

Sensitivity and specificity of the Elecsys Troponin T hs assay were calculated at different troponin T levels.

Troponin T hs pg/mL	Sensitivity %	LCI ^{b)} %	UCI ^{c)} %	Specificity %	LCI %	UCI %
30	98	93.7	99.5	93	90.0	95.1
50	95	88.8	97.5	98	96.1	99.0
70	84	76.0	89.6	99	98.2	99.9
100	75	66.2	82.1	99	98.2	99.9

b) LCI = lower confidence interval

c) UCI = upper confidence interval

The sensitivity and specificity at the 99th percentile (Elecsys Troponin T hs assay)/10 % CV (Elecsys Troponin T assay, 4th gen.; 0.03 ng/mL) criteria were in addition calculated for different time intervals from admission to the hospital:

Time from admission (hours)	Test generation Troponin T	Sensitivity %	N	95 % confidence interval (%)	Specificity %	N	95 % confidence interval (%)
0	4th gen.	71	40/56	58-83	99	142/143	96-100
	Troponin T hs	93	52/56	83-98	76	109/143	68-83
0-3	4th gen.	81	75/93	71-88	99	356/359	98-100
	Troponin T hs	98	91/93	93-100	79	282/359	74-83
3-6	4th gen.	83	53/64	71-91	100	300/301	98-100
	Troponin T hs	100	64/64	94-100	77	232/301	72-82
6-9	4th gen.	86	42/49	73-94	99	201/203	97-100
	Troponin T hs	98	48/49	89-100	76	155/203	70-82
9-12	4th gen.	83	15/18	59-96	100	43/43	92-100
	Troponin T hs	94	17/18	73-100	72	31/43	56-85
> 12	4th gen.	83	25/30	65-94	98	56/57	91-100
	Troponin T hs	100	30/30	88-100	60	34/57	46-72

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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.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: <https://ec.europa.eu/tools/eudamed>

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.roche.com for definition of symbols used):

	Contents of kit
	Analyzers/Instruments on which reagents can be used
	Reagent
	Calibrator
	Volume for reconstitution
	Global Trade Item Number

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