Elecsys Troponin T hs STAT

cobas®

REF		Σ	SYSTEM
			cobas e 411
08469814190	08469814500	100	**cobas e** 601
			cobas e 602

English

System information

For **cobas e** 411 analyzer: test number 090
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 107

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 **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "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 NSTE-ACS, also support the use of cTnT-hs testing to identify which NSTE-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] sepsis[45] 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 disease[57] 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]

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

Elecsys Troponin T hs STAT

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: 9 minutes.

cobas e 411 analyzer:

- 1st incubation: 50 µL of sample, 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.

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

- During a 9 minute incubation, antigen in the sample (50 µL), a biotinylated monoclonal anti-cardiac troponin T-specific antibody, a monoclonal anti-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.

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 or e-barcode.

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

Reagents - working solutions

The reagent rackpack is labeled as TNT-HSST.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL:

Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-troponin T-Ab~biotin (gray cap), 1 bottle, 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-troponin T-Ab~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 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.

H412 Harmful to aquatic life with long lasting effects.

Prevention:

P261 Avoid breathing dust/fume/gas/mist/vapours/spray.

P273 Avoid release to the environment.

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 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.

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	4 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 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.

Elecsys Troponin T hs STAT

cobas®

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 05092736190, Troponin T hs STAT CalSet, for 4 x 1.0 mL
- REF 05095107190, PreciControl Troponin, for 4 x 2.0 mL
- REF 03609987190, Diluent MultiAssay, 2 x 16 mL sample diluent
- General laboratory equipment
- **cobas e** analyzer

Additional materials for the **cobas e** 411 analyzer:

- 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, AssayCup, 60 x 60 reaction cups
- REF 11706799001, AssayTip, 30 x 120 pipette tips
- REF 11800507001, Clean-Liner

Additional materials 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 03004899190, PreClean M, 5 x 600 mL detection cleaning solution
- REF 12102137001, AssayTip/AssayCup, 48 magazines x 84 reaction cups or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Additional materials for all analyzers:

- 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 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

cobas e 601 and **cobas e** 602 analyzers: PreClean M solution is necessary.

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: The Elecsys Troponin T hs STAT assay (REF 08469814190) has been standardized against the Troponin T STAT assay (REF 04660307190. 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).

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 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.

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, µg/L (**cobas e** 601 and **cobas e** 602 analyzers) or in pg/mL, ng/mL, µg/L (**cobas e** 411 analyzer).

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

Elecsys Troponin T hs STAT

cobas®

Drug	Concentration tested mg/L
Lisinopril	10
Methylprednisolone (Urbason)	7.5
Metoprolol	150
Nifedipine	30
Phenprocoumon	3
Propafenone	300
Reteplase	33.3
Simvastatin	30
Spironolactone	75
Tolbutamide (Glibenclamide)	1500
Torasemide	15
Verapamil	240
Valsartan	206
Sacubitril	194
Dabigatran	300
Rivaroxaban	40

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 Blank and the maximum of the master curve). Values below the Limit of Blank 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 = 3 ng/L (pg/mL)

Limit of Detection = 5 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 ≥ 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:

	cobas e 411 analyzer	**cobas e** 601 and **cobas e** 602 analyzers
Limit of Blank (ng/L = pg/mL)	2.14	2.36
Limit of Detection (ng/L = pg/mL)	3.25	2.85
Limit of Quantitation 10 % intermediate CV (ng/L = pg/mL)	6.74	2.92
20 % intermediate CV (ng/L = pg/mL)	2.88	1.21

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 analyzers, 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 AMI[82] from the 1970's, the cutoff (clinical discriminator) value for troponin T is 0.1 µg/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]

Elecsys Troponin T hs STAT

cobas®

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 411 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/L (pg/mL)	SD ng/L (pg/mL)	CV %	SD ng/L (pg/mL)	CV %
Human serum 1	7.99	0.638	8.0	0.867	10.8
Human serum 2	13.6	0.542	4.0	0.745	5.5
Human serum 3	18.0	0.449	2.5	0.768	4.3
Human serum 4	144	3.36	2.3	4.17	2.9
Human serum 5	4709	93.2	2.0	125	2.7
Human serum 6	8824	199	2.3	258	2.9
PreciControl TN1	23.1	0.705	3.1	1.07	4.7
PreciControl TN2	1784	22.3	1.2	46.0	2.6

cobas e 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/L (pg/mL)	SD ng/L (pg/mL)	CV %	SD ng/L (pg/mL)	CV %
Human serum 1	9.18	0.187	2.0	0.338	3.7
Human serum 2	15.1	0.256	1.7	0.404	2.7
Human serum 3	20.4	0.381	1.9	0.560	2.7
Human serum 4	148	2.29	1.6	3.32	2.2
Human serum 5	4794	40.9	0.9	123	2.6
Human serum 6	8961	211	2.4	254	2.8
PreciControl TN1	25.9	0.348	1.3	0.641	2.5
PreciControl TN2	1883	13.8	0.7	27.7	1.5

Method comparison

A comparison of the Elecsys Troponin T hs STAT assay, REF 08469814190 (**cobas e** 601 analyzer; y) with the Elecsys Troponin T hs assay, REF 05092744190 (**cobas e** 601 analyzer; x), using clinical samples gave the following correlations (ng/L or pg/mL):

Number of samples measured: 156

Passing/Bablok[90]	Linear regression
y = 0.975x + 1.22	y = 0.978x + 5.56
τ = 0.966	r = 1.00

A comparison of the Elecsys Troponin T hs STAT assay, REF 08469814190 (**cobas e** 411 analyzer; y) with the Elecsys Troponin T hs STAT assay, REF 08469814190 (**cobas e** 601 analyzer; x), using clinical samples gave the following correlations (ng/L or pg/mL):

Number of samples measured: 158

Passing/Bablok[90]	Linear regression
y = 1.05x - 0.852	y = 1.06x - 5.65
τ = 0.956	r = 0.999

The sample concentrations were between 3 and 9300 ng/L (pg/mL).

Analytical specificity

The Elecsys Troponin T hs STAT 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 criteria[82] 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

Elecsys Troponin T hs STAT

cobas®

Time from admission (hours)	Test generation Troponin T	Sensitivity %	N	95 % confidence interval (%)	Specificity %	N	95 % confidence interval (%)
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

References

1 Katus HA, Remppis A, Looser S, et al. Enzyme linked immunoassay of cardiac troponin T for the detection of acute myocardial infarction in patients. Mol Cell Cardiol 1989;21(12):1349-1353.

2 Liebetrau C, Mollmann H, Nef H, et al. Release kinetics of biomarkers in patients undergoing transcoronary ablation of septal hypertr0pphy. Clin Chem 2012;58(6):1049-1054.

3 Katus HA, Scheffold T, Remppis A, et al. Proteins of the troponin complex. Laboratory Medicine 1992;23(5):311-317.

4 Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. NEJM 2009;361(9):858-867.

5 Giannitsis E, Becker M, Kurz K, et al. High sensitivity cardiac troponin T for early prediction of evolving non-ST segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin result on presentation. Clin Chem 2010;56(4):642-650.

6 Giannitsis E, Kurz K, Hallermayer K, et al. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56(2):254-261.

7 Hamm CW, Bassand JP, Agewall S, et al. ESC guidelines for the management of acute coronary syndrome in patients presenting without persistent ST-segment elevation. The Task Force for the management of acute coronary syndrome (ACS) in patient presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011;32(23):2999-3054.

8 NICE (2014) Myocardial infarction (acute): Early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays). NICE diagnostics guidance DG15. Available at www.nice.org.uk/dg15 [NICE guideline]

9 Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2016;37(3):267-315.

10 Bandstein N, Ljung R, Johansson M, et al. Undetectable high sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. J Am Coll Card 2014;63:2569-2578.

11 Body R, Burrows G, Carley S, et al. High-sensitivity cardiac troponin T concentrations below the limit of detection to exclude acute myocardial infarction: A prospective evaluation. Clin Chem 2015;61(7):983-989.

12 Rubini Gimenez M, Reichlin T, Zellweger C. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin. Int J Cardiol 2013;168(4):3896-3901.

13 Reichlin T, Schindler C, Drexler B, et al. One-hour rule-out and rule-in of acute myocardial Infarction using high-sensitivity cardiac troponin T. Arch Intern Med 2012;172(16):1211-1218.

14 Reichlin T, Twerenbold R, Wildi K, et al. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. CMAJ 2015;187(8):E243-252.

15 Mueller C, Giannitsis E, Christ M, et al. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac Troponin T. Ann Emerg Med 2016 Jul;68(1):76-87.

16 Parsonage W, Greenslade J, Hammett C, et al. Validation of an accelerated high-sensitivity troponin T assay protocol in an Australian cohort with chest pain. Med J Aust 2014;200:161-165.

17 Reichlin T, Cullen L, Parsonage WA, et al. Two hour algorithm for triage towards rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac Troponin T. Am J Med 2015;128:369-79.

18 Meller B, Cullen L, Parsonage WA, et al. Accelerated diagnostic protocol using high-sensitivity cardiac troponin T in acute chest pain patients. Int J Cardiol. 2015;184:208-15.

19 McRae AD, Innes G, Graham M, et al. Comparative Evaluation of 2-Hour Rapid Diagnostic Algorithms for Acute Myocardial Infarction Using High-Sensitivity Cardiac Troponin T. Can J Cardiol. 2017;33(8):1006-1012.

20 Wildi K, Cullen L, Twerenbold R, et al. Direct comparison of 2 rule-out strategies for acute myocardial infarction: 2-h accelerated diagnostic protocol vs 2-h algorithm. Clin Chem. 2017;63(7):1227-1236.

21 Than MP, Pickering JW, Dryden JM, et al. ICare-ACS (Improving Care processes for patients with suspected acute coronary syndrome): a study of cross-system implementation of a national clinical pathway. Circulation 2018;137(4):354-363.

22 Thygesen K, Alpert JS, Jaffe AS, et al. Fourth definition of myocardial infarction. J Am Coll Cardiol 2018;30:72(18):2231-2264.

23 Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. N Engl J Med 2002;346:2047-2052.

24 Lindahl B, Venge P, James S. The new high- sensitivity cardiac troponin T assay improves risk assessment in acute coronary syndromes. Am Heart J 2010;160:224-229.

25 Haaf P, Reichlin T, Twerenbold R, et al. Risk stratification in patients with acute chest pain using three high-sensitivity cardiac troponin assays. Eur Heart J 2014;35(6):365-375.

26 Bjurman C, Larsson M, Johanson P, et al. Small changes in troponin T levels are common in patients with Non-ST-elevation myocardial infarction and are linked to higher mortality. J Am Coll Cardiol 2014;62(14):1231-1238.

27 Lindahl B, Venge P, Wallentin L. Troponin T Identifies Patients With Unstable Coronary Artery Disease Who Benefit From Long-Term Antithrombotic Protection. J Am Coll Cardiol 1997;29(1):43-48.

28 Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. N Engl J Med 1999;340(21):1623-1629.

29 Heeschen C, Hamm CW, Goldmann BU, et al. for PRISM study investigators. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. Lancet 1999;354:1757-1762.

30 Lindahl B, Diderholm E, Lagerquist B, et al. Effects on mortality of long-term treatment with l.m.w. heparin in relation to troponin T level and ECG findings - a FRISC 2 substudy. Eur Heart J 2000;21(Suppl.):521.

31 Newby LK, Ohman EM, Christenson RH, et al. Benefit of Glycoprotein IIb/IIa Inhibition in Patients With Acute Coronary Syndromes and Troponin T-Positive Status: The PARAGON-B Troponin T Substudy. Circulation 2001;103:2891-2896.

32 Wallentin L, Lindholm D, Siegbahn A, et al. Biomarkers in relation to the effects of Ticagrelor compared with clopidogrel in non-ST-elevation acute coronary syndrome patients managed with or without in-hospital revascularization: a Substudy from the prospective randomized Platelet inhibition and Patient Outcomes (PLATO) Trial. Circulation 2014;129(3):293-303.

33 Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130(25):e344-426.

34 Reichlin T, Irfan A, Twerenbold R, et al. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. Circulation 2011;124(2):136-145.

35 Masson S, Anand I, Favero C, et al. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from two large randomized clinical trials. Circulation 2012;125(2):280-288.

36 Nambi V, Liu X, Chambless LE, et al. Troponin T and N-terminal pro-B–type natriuretic peptide: a biomarker approach to predict heart failure risk: the Atherosclerosis Risk in Communities Study. Clin Chem 2013;59(12):1802-1810.

37 Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128(16):e240-327.

38 Cramer G, Bakker J, Gommans F, et al. Relation of highly sensitive cardiac troponin T in hypertrophic cardiomyopathy to left ventricular mass and cardiovasscular risk. Am J Cardiol. 2014;113(7):1240-1245.

39 McGill D, Talaulikar G, Potter JM, et al. Over time, high-sensitivity TnT replaces NT-proBNP as the most powerful predictor of death in patients with dialysis-dependent chronic renal failure. Clin Chim Acta 2010;411(13-14):936-939.

40 K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45 (4 Suppl 3):S1-153.

41 Artunc F, Mueller C, Breidhardt T, et al. Sensitive troponins- which suits better for hemodialysis patients? Associated factors and prediction for mortality.PLoS One. 2012;7(10):e47610.

42 Wolley M, Steward R, Curry E, et al. Variation in and prosgnostic importance of troponin T measured using a high-sensitivity assay in clinically stable haemodialysis patients. Clin Kidney J. 2013;6(4):402-409.

43 Honneger Bloch S, Semple D, Sidhu K, et al. Prognostic value and long-term variation of high sensitivity troponin T in clinically stable haemodialysis patients. N Z Med J. 2014;127(1402):97-109.

44 Twerenbold R, Wildi K, Jeger C, et al. Optimal cutoff levels of more sensitive cardiac troponin assays for the early diagnosis of myocardial infarction in patients with renal dysfunction. Circulation 2015;131(23):2041-2050.

45 Landeberg G, Jaffe AS, Gilon D, et al. Troponin elevation in severe sepsis and septic shock: the role of left ventricular dysfunction and right ventricular dilatation. Crit Care Med 2014;42(4):790-800.

46 Hillis GS, Welsh P, Chalmers J, et al. The relative and combined ability of high sensitivity cardiac troponin T and N-terminal pro-BNP to predict cardiovascular events and death in patients with type 2 diabetes mellitus. Diabetes Care 2014;37(1):295-303.

47 Everett BM, Brooks MM, Vlachos HE, et al. Troponin and cardiac events in stable ischemic heart disease and diabetes. N Engl J Med. 2015;373(7):610-620.

48 Latini R, Masson S, Anand IS, et al. Prognostic Value of Very Low Plasma Concentrations of Troponin T in Patients with Stable Chronic Heart Failure. Circulation 2007;116:1242-1249.

49 Omland T, de Lemos JA, Sabatine MS, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med 2009;361:2538-2547.

50 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-2200.

51 Latini R, Masson S, Pirelli S, et al. On the behalf of the GISSI-AF Investigators. Circulating cardiovascular biomarkers in recurrent atrial fibrillation: data from the GISSI-Atrial fibrillation trial. J Intern Med 2011;269(2):160-171.

52 Hijazi Z, Oldgren J, Lindbäck J, et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. Lancet 2016; 387:2302-2311.

53 Berg DD, Ruff C, Jarolim P, et al. Performance of he ABC scores for assessing the risk of stroke or systemic embolism and bleeding in patients with atrial fibillation in ENGAGE AF-TIMI 48.,https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.118.038312.

54 Lewandrowski K. Special topics: cardiac markers in myocarditis. Cardiac transplant rejection and conditions other than acute coronary syndrome. Clin Lab Med 2014;34:129-135.

55 Swaanenburg JC, Klaase JM, DeJongste M, et al. Troponin I, troponin T, CK-MB-activity and CK-MB mass as markers for the detection of myocardial contusion in patients who experienced blunt trauma. Clin Chim Acta 1998;272:171-181.

56 Bajaj A, Saleeb M, Rathor P, et al. Prognostic value of troponins in acute noninvasive pulmonary embolism. A meta-analysis. Heart Lung 2105;44(4):327-334.

57 Dubin RF, Li Y, He J, et al. Predictors of high sensitivity cardiac troponin T in chronic kidney disease patients: a cross-sectional study in the chronic renal insufficiency cohort (CRIC). BMC Nephrol 2013;14(1):229.

58 Newby LK, Rodriguez I, Finkle J, et al. Troponin measurements during drug development-considerations for monitoring and management of potential cardiotoxicity. An educational collaboration among the Cardiac Safety Research Consortium, the Duke Clinical Research Institute, and the US Food and Drug Administration. Am Heart J 2011;162(1):64-73.

59 Willeit P, Welsh P, Evans JDW, et al., High-Sensitivity Cardiac Troponin Concentration and Risk of First-Ever Cardiovascular Outcomes in 154,052 Participants. J Am Coll Cardiol 2017;70(5):558-568.

60 deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010;304(22):2494-502.

61 Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011;123 (13):1367-1376.

62 Oluleye OW, Folsom AR, Nambi V, Lutsey PL, Ballantyne CM. Troponin T, B-type natriuretic peptide, C-reactive protein, and cause-specific mortality. Ann Epidemiol 2013;23 (2):66-73.

63 Folsom AR, Nambi V, Bell EJ, et al. Troponin T, N-terminal pro-B-type natriuretic peptide, and incidence of stroke: the Atherosclerosis Risk in Communities Study. Stroke 2013;44 (4):961-967.

64 Eggers KM, Al-Shakarchi J, Berglund L, et al. High-sensitive cardiac troponin T and its relations to cardiovascular risk factors, morbidity, and mortality in elderly men. Am Heart J 2013;166(3):541-548.

65 Willeit P, Kaptoge S, Welsh P, et al. Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis. Lancet Diabetes Endocrinol 2016;4(10):840-849.

66 Bosselmann H, Egstrup M, Rossing K, et al. Prognostic significance of cardiovascular biomarkers and renal dysfunction in outpatients with systolic heart failure: a long term follow-up study Int J Cardiol 2013;170(2):202-207.

67 Wallentin L, Lindhagen L, Ärnström E, et al. Early invasive versus noninvasive treatment in patients with non-ST-elevation acute coronary syndrome (FRISC-II): 15 year follow-up of a prospective, randomised, multicentre study. Lancet 2016;388(10054):1903-1911.

68 Duceppe E, Parlow J, MacDonald P, et al. Canadian cardiovascular society guidelines on perioperative cardiac risk assessment and management for patients undergoing noncardiac surgery. Canadian Journal of Cardiology Can J Cardiol. 2017;33(1):17-32.

69 Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative myocardial injury after noncardiac surgery: incidence, mortality, and characterization. Circulation. 2018; 137(12):1221-1232.

70 Writing Committee for the VISION Study Investigators., Devereaux PJ, Biccard BM, Sigamani A, et al. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. JAMA. 2017; 317(16):1642-1651.

71 Davis GK, Labugger R, Van Eyk JE, et al. Cardiac troponin T is not detected in western blots of diseased renal tissue. Clin Chem 2001;47(4):782-783.

Elecsys Troponin T hs STAT

cobas®

72 Ricchiuti V, Voss EM, Ney A, et al. Cardiac Troponin T isoforms expressed in renal diseased skeletal muscle will not cause false positive results by the second generation cTnT assay by Boehringer Mannheim; Clin Chem 1998;44(9):1919-1924.

73 Hallermayer K, Klenner D, Vogel R. Use of recombinant human cardiac troponin T for standardization of third generation troponin T methods. Scand J Clin Invest 1999;59(Suppl 230):128-131.

74 Saenger AK, Beyrau R, Braun S, et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. Clin Chim Acta 2011;412(9-10):748-754.

75 Rubini Giménez M, Twerenbold R, Boeddinghaus J, Nestelberger T et al. Clinical Effect of Sex-Specific Cutoff Values of High-Sensitivity Cardiac Troponin T in Suspected Myocardial Infarction. JAMA Cardiol. 2016;1(8):912-920.

76 Giannitsis E. Sex-specific troponin measures for diagnosis of acute coronary syndrome. Heart 2016; 102(2):91-92.

77 Mueller-Hennessen M, Lindahl B, Giannitsis E et al. Diagnostic and prognostic implications using age- and gender-specific cut-offs for high-sensitivity cardiac troponin T - Sub-analysis from the TRAPID-AMI study. Int J Cardiol. 2016;209:26-33.

78 Eggers KM, Jernberg T, Lindahl B. Prognostic importance of sex-specific cardiac troponin T 99(th) percentiles in suspected acute coronary syndrome. Am J Med 2016; 129 (8): 880.e1-880.e12.

79 Mueller-Hennessen M, Giannitsis E. Do we need to consider age and gender for accurate diagnosis of myocardial infarction?. Diagnosis (Berl.) 2016; 3(4):175-181.

80 Giannitsis E. Counterpoint: Potential Concerns Regarding the Use of Sex-Specific Cutpoints for High-Sensitivity Troponin Assays. Clin Chem. 2017; 63(1):264-266.

81 Twerenbold R, Boeddinghaus J, Nestelberger T, et al. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. J Am Coll Cardiol. 2017;70(8):996-1012.

82 World Health Organization. Report of the Joint International Society and Federation of Cardiology/World Health Organization Task Force on Standardization of Clinical Nomenclature. Nomenclature and criteria for diagnosis of ischemic heart disease. Circulation 1979;59:607-609.

83 Müller-Bardorff M, Hallermayer K, Schröder A, et al. Improved troponin T ELISA specific for cardiac troponin T isoform: assay development and analytical validation. Clin Chem 1997;43(3):458-466.

84 Klein G, Kampmann M, Baum H, et al. Clinical performance of the new cardiac markers troponin T and CK-MB on the Elecsys 2010. A multicenter evaluation. Wien Klin Wochenschr. 1998;110(Suppl3):40-51.

85 Mendis S, Thygesen K, Kuulasmaa K, et al. World Health Organization definition of myocardial infarction: 2008-09 revision. Int J Epidemiol 2011;40(1):139-146.

86 Ferjani M, Droc G, Dreux S, et al. Circulating cardiac troponin T in myocardial contusion. Chest 1997;111(2):427-433.

87 Erbel C, Taskin R, Doesch A, et al. High-sensitive troponin T measurements early after heart transplantation predict short- and long-term survival. Transpl Int 2013;26(3):267-272.

88 Li SF, Zapata J, Tillem E. The prevalence of false-positive cardiac troponin I in ED patients with rhabdomyolysis. Am J Emerg Med 2005;23(7):860-863.

89 Zhang L, Wang GC, Ma L, et al. Cardiac involvement in adult polymyositis or dermatomyositis: a systematic review Clin Cardiol 2012;35(11):686-691.

90 Bablok W, Passing H, Bender R, et al. A general regression procedure for method transformation. Application of linear regression procedures for method comparison studies in clinical chemistry, Part III. J Clin Chem Clin Biochem 1988 Nov;26(11):783-790.

91 The Task Force for the diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. Guidelines for the diagnosis and treatment of non-ST elevation acute coronary syndromes. European Heart Journal 2007;28:1598-1660.

For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets 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.

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 dialog.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number

CE 0123

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com
+800 5505 6606

Roche