Elecsys Troponin T hs

cobas®

REF		Σ	SYSTEM
			cobas e 411
09315322190	09315322500	200	**cobas e** 601
			cobas e 602

English

System information

For **cobas e** 411 analyzer: test number 2590
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 576

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 (AMI), and as an aid for early discharge and outpatient management for patients suspected of acute coronary syndrome (ACS). 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 (cTnT).

In addition, this test can be used in the context of non-cardiac surgeries to predict pre-operatively the perioperative risk of major adverse cardiac events and in diagnosis of perioperative myocardial infarction (PMI) and myocardial injuries after non-cardiac surgeries (MINS).

The cTnT-hs values may also be used, in conjunction with clinical and diagnostics findings, to aid in stratifying the long-term risk of cardiovascular death, myocardial infarction, coronary revascularization, heart failure or ischemic stroke, and all-cause mortality in asymptomatic individuals.

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, 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 cTn 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 cardiac troponin (cTn) 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 and 2020 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 in conjunction with information from medical history and findings from clinical examination, ECG, additional laboratory and imaging information.[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 2020 TRAPID-AMI as well as in additional prospective trials. [13,14,15,16,17,18,19,20] Alternative approaches using cTnT-hs to rule-in or rule-out AMI within 2 hours with or without risk scores have been also developed.[9,21,22,23,24,25,26]

In contrast to ST elevation myocardial infarction (STEMI), the diagnosis of NSTEMI heavily relies on measured cTn results. According to the new Universal Definition of myocardial infarction (MI), is diagnosed when blood levels of cTn 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 cTn assay with an imprecision (coefficient of variation) at the 99th percentile less than or equal to 10 %.[27]

cTnT is an independent prognostic marker which can predict the near-, mid- and even long-term outcome of patients with ACS.[28,29,30,31]

In addition, 4 multicenter trials involving more than 7000 patients have shown that cTnT is also useful to identify patients that benefit from anti-thrombotic therapy (GPIIb/IIIa inhibitors, low molecular weight heparin).[32,33,34,35,36]

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.[37]

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)[9,38]

Cardiac 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.[27,39] 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.[27] Chronic elevations of cTn can be detected in clinically stable patients such as patients with ischemic or non-ischemic heart failure,[40,41,42] in patients with different forms of cardiomyopathy,[43] renal failure,[44,45,46,47,48,49] sepsis[50] and diabetes.[51,52]

Elevated levels of cTnT correlate with the severity of coronary artery disease and to poor outcome independent of natriuretic peptide (NT-proBNP or BNP) levels.[53,54]

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.[55,27]

Cardiac troponin T values are an independent predictor of cardiovascular events including occurrence and recurrence of atrial fibrillation (AF).[56]

Recently, cTnT-hs has also been included into the "ABC-bleeding risk 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.[57] 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.[58] 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).[58]

Myocardial cell injury leading to elevated cTnT concentrations in the blood can also occur in other clinical conditions such as myocarditis,[59] heart contusion,[60] pulmonary embolism,[61] kidney disease[62] and drug-induced cardiotoxicity.[63] In patients with COVID-19, cTnT levels above the 99th percentile upper reference limit were frequently reported on admission and during the course of the disease.[64,65,66,67] Elevated cTnT levels indicate myocardial injury and may predict the necessity of intensive care unit admission, invasive ventilation and the occurrence of mortality.[65,66,67,68,69]

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.[70,71,72,73,74,75,76]

Other diagnostic tests such as NT-proBNP or GDF-15 can complement the diagnostic and prognostic information of cTnT-hs in patients with heart failure and renal dysfunction.[77,78] 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.[78]

Measurements of cTnT-hs before non-cardiac surgery can be used to predict the peri-operative occurrence of major adverse cardiac events (MACE), such as cardiovascular death, MI[79] and for the peri-operative diagnosis of myocardial injury after non-cardiac surgery (MINS)[80] and for the peri-operative myocardial injury/infarction (PMI).[81] Cardiac troponin changes during surgery and cTn peak elevations within the first 3 days after surgery can be used to predict MACE, and to diagnose MINS, PMI or MI.[27,82,83,84]

The Elecsys Troponin T hs assay employs two monoclonal antibodies specifically directed against human cTnT.[85,86] The antibodies recognize two epitopes (amino acid position 125-131 and 136-147) located in the central part of the cTnT 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 cTnT 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.[87]

The International Federation of Clinical Chemistry (IFCC) has assigned the term "High-sensitivity (hs)" to cTn assays that have a CV of ≤ 10 % at the 99th percentile value and ≥ 50 % of the detectable values above the Limit of Detection in a healthy reference population of both genders.[88] Compliance to these 2 criteria have been externally confirmed.[89]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 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.
- 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 TNTHSX.

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, 14 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, 14 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.

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 09315365190, Troponin T hs 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 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.

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 assay (REF 08469717190/ 09315322190) 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

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Drug	Concentration tested mg/L
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
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)	1.58	2.53
Limit of Detection (ng/L = pg/mL)	2.54	3.16
Limit of Quantitation 10 % intermediate CV (ng/L = pg/mL)	7.45	3.94
20 % intermediate CV (ng/L = pg/mL)	4.01	1.72

Dilution

Samples with cTnT 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).[90] 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. Of these 533 volunteers, 306 (57.4 %) had a cTn value above 3 ng/L(pg/mL).[90] Several publications report that using cTnT-hs, sex-specific cutoffs do not add clinical value compared to one overall cutoff.[91,92,93,94,95,96,97]

Based on the WHO criteria for the definition of AMI[98] 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.[99,100]

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 cutoff value.[101]

Due to the release kinetics of cTnT, an initially test result < 99th percentile within the first hour of the onset of symptoms does not rule out MI in all patients. Therefore lower cutoffs 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 cTn values should always be used in conjunction with full clinical assessment (including chest pain characteristics and ECG).

ESC 0 h/1 h rule-in and rule-out diagnostic algorithm using cTnT-hs assay in patients presenting with suspected NSTEMI to the emergency department (ED).[9]

	cTnT-hs values in patients suspected of NSTEMI			
cTnT-hs concentration (ng/L or pg/mL)	0 h < 5 *	0 h < 12 and Δ 0-1 h < 3	other	0 h ≥ 52 or Δ 0-1 h ≥ 5
Orientation for the diagnosis of AMI	Rule-out	Rule-out	Observe	Rule-in

0 h and 1 h refer to the time since the first blood test.

* Only applicable if chest pain inset > 3 h.

Besides cTn, clinical evidence of myocardial ischemia is requested for the diagnosis of AMI and caution is advised when dealing with patient subsets such as elderly, critical ill individuals with sepsis or end-stage renal disease, those who present with atypical symptoms and those who present very early after the onset of symptoms.

As recommended in the ESC guidelines, 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 and other conditions is required.[9,27]

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 cTn.[9] If concentrations of cTn 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[27,59,102,103,104,105]

Published clinical studies have shown elevations of cTn 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 cTn 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.[9,27,38]

For peri-operative myocardial injury/infarction after non-cardiac surgeries (MINS/PMI)

According to Devereaux JP et al.[106,107] the diagnostic criteria of MINS are peak operative cTnT-hs values ≥ 20 ng/L with an absolute delta change between two measurements of ≥ 5 ng/L (pg/mL), or absolute values ≥ 65 ng/L (pg/mL) judged as resulting from myocardial ischemia (i.e. no evidence of a non-ischemic etiology) within 30 days after non-cardiac surgery and without the requirement of an ischemic feature (e.g. ischemic symptom, ischemic electrocardiography findings).[106]

The pathophysiology of MINS in surgical patients differs from that of MI in medical (non-surgical) patients.[108] According to Puelacher C et al. [81] diagnostic criteria for PMI are defined as an absolute increased in TnT-hs of ≥ 14 ng/L (pg/mL) between pre-operative and peak post-operative values (or between 2 post-operative values if the pre-operative value was missing) within 7 days of surgery.[81] Clinical guidelines recommend to consider peri-operative cTn testing before and 48-72 hours after major non-cardiac surgery of patients at high-risk for cardiovascular disease such as > 45 years old patients with a known history of cardiovascular disease and/or patients ≥ 65 years. [82,83] See result section for more details.

Expected values for asymptomatic individuals

According to the analysis of major publications, the following concentration range may be used to aid stratifying the long-term risk of cardiovascular disease in asymptomatic individuals.[72,74,109,110,111]

Proposed ranges/cutoff values for cardiovascular risk estimation in asymptomatic individuals

cTnT-hs range (ng/L or pg/mL)	< 5	5 - < 10	≥ 10
Risk category	Low	Intermediate	High

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	9.05	0.646	7.1	0.711	7.9
Human serum 2	12.9	0.594	4.6	0.634	4.9
Human serum 3	17.9	0.677	3.8	0.699	3.9
Human serum 4	156	3.18	2.0	4.65	3.0
Human serum 5	4558	43.2	0.9	69.1	1.5
Human serum 6	9378	151	1.6	190	2.0
PreciControl TN1	26.0	0.554	2.1	0.648	2.5
PreciControl TN2	1984	15.4	0.8	27.4	1.4

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	8.30	0.175	2.1	0.393	4.7
Human serum 2	15.0	0.385	2.6	0.576	3.8
Human serum 3	20.2	0.383	1.9	0.661	3.3
Human serum 4	162	2.26	1.4	2.86	1.8
Human serum 5	5164	103	2.0	126	2.4
Human serum 6	9916	138	1.4	333	3.4
PreciControl TN1	27.9	0.528	1.9	0.748	2.7
PreciControl TN2	2084	22.2	1.1	43.6	2.1

Method comparison

a) A comparison of the Elecsys Troponin T hs assay, REF 08469717190 / 09315322190 (**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[112]	Linear regression
y = 1.00x + 0.650	y = 0.998x + 2.23
τ = 0.971	r = 1.00

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

b) A comparison of the Elecsys Troponin T hs assay, REF 08469717190 / 09315322190 (**cobas e** 411 analyzer; y) with the Elecsys Troponin T hs assay, REF 08469717190 / 09315322190 (**cobas e** 601 analyzer; x), using clinical samples gave the following correlations (ng/L or pg/mL):

Number of samples measured: 157

Passing/Bablok[112]	Linear regression
y = 1.01x + 0.911	y = 1.02x - 2.91
τ = 0.967	r = 1.00

The sample concentrations were between 3 and 9300 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 0.052 %, h-cardiac troponin I 0.019 %, h-skeletal muscle troponin I 0.006 %, human troponin C 0.0002 %.

Elecsys Troponin T hs

cobas®

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[98] including ECG changes, symptoms characteristic for ACS and elevation of cTn, and
2. Criteria defined by the Joint ESC/ACCF/AHA/WHF task force.[113]

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

Patients with AMI were defined by routine cTn values above the 99th percentile/10 % CV criteria, and presence of chest pain or ECG changes. Sensitivity and specificity at peak cTnT-hs, 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 cTnT-hs levels.

cTnT-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 cTnT	Sensitivity %	N	95 % CI[d] (%)	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

d) confidence interval

Results using the cTnT-hs 0 h/1 h algorithm recommended by the ESC Guidelines for ACS patients presenting without persistent ST-elevation

Negative predictive value (NPV) values from prospective trials using cTnT-hs 0 h/1 h diagnostic algorithm recommended by the 2020 Guidelines for patients presenting to the ED with suspected NSTEMI are depicted in the table below for the assignment of patients to the rule-out zone discharged from the ED.[9,13,14,15,16,17,18,19]

Publications and trials	**Using cTnT-hs values for patient assignment to the rule-out zone: 0 h < 12 ng/L and Δ 1 h < 3 ng/L**	
	Negative predictive value (NPV)	All-cause mortality or MACE in Rule out
APACE[13]	100 %	30 days all-cause mortality: 0.2 % 2 years all-cause mortality: 1.9 %
APACE[14]	99.9 % (95 % CI: 99.3-100 %)	30 days all-cause mortality: 0 % 2 years all-cause mortality: 1.1 %
TRAPID-AMI[15]	99.1% (95 % CI: 98.2-99.7 %)	30 days all-cause mortality: 0.1 % 2 years all-cause mortality: 0.7 %
Mokhtari et al.[16]	NPV for 30 days MACE: 97.8 % (95 % CI: 98.6-99.9 %) using the extended algorithm (+non-ischaemic ECG + no high-risk history)	30 days MACE: 2.2 % 30 days MACE with the extended algorithm: 0.5 % (0 % when excluding unstable angina)
	Using cTnT-hs values for patient assignment to the rule-out zone: 0 h < 5 ng/L or 0 h < 12 ng/L and Δ 1 h < 3 ng/L	
APACE[19]	100 %	30 days and 1-year all-cause mortality: 0.2 %
RAPID-TnT[18]	99.6 % (95 % CI: 99.0-99.9 %) for 30 days death or MI	30 days all-cause death and MI:0.4 %
Shiozaki et al.[17]	100 % (95 % CI: 96.8-100 %)	30 days all-cause mortality: 0 %

Results from major trials using cTnT-hs to help for the diagnosis and predict MINS and PMI after non-cardiac surgeries

Data from the global, multicentric VISION study (Vascular Events in Noncardiac Surgery patients Cohort Evaluation)[106]

The VISION study was a global, prospective, multicentric cohort study enrolling 21848 patients aged ≥ 45 years undergoing inpatient non-cardiac surgery. Association between peri-operative (pre-, post- and absolute peri-operative changes) cTnT-hs levels and 30 days mortality as well as potential diagnostic criteria for MINS were determined. Descriptive statistics for specific peri-operative levels are depicted in the following tables.

Perioperative cTnT-hs levels (1 day before surgery in the majority of patients) with associated hazard ratios (HRs) for various adverse cardiovascular outcomes 30 days post-surgery.

	Unadjusted HR (95 % CI)				
cTnT-hs (ng/L or pg/mL)	MINS / vascular death	Death	MI	MI / death	N (%)
< 14	1 (reference population)				78.4
≥ 14 to < 28	5. 97 (5.34, 6.67)	2.46 (1.53, 3.95)	2.70 (2.13, 3.43)	2.74 (2.20, 3.40)	14.5
≥ 28	7.93 (6.96, 9.04)	7.49 (4.94, 11.36)	5.09 (3.98, 6.53)	5.49 (4.40, 6.84)	7.2

Additionally, cTnT-hs levels were measured 6-12 h post-operatively as well as on day 1, 2 and 3 after surgery to determine peak post-operative cTnT-hs levels which have been analyzed for estimation of the 30 days post-surgery mortality. Detection of an elevated cTnT-hs level in the post-operative period was found to be the strongest predictor of 30 day mortality.[106]

cTnT-hs (ng/L or pg/mL)	**Adjusted HR**	**95 % CI (%)**	**N (%)**
≥ 1000	227.01	87.35 - 589.92	0.2
≥ 65 to < 1000	70.34	30.60 - 161.71	5.1
≥ 20 to < 65	23.63	10.32 - 54.09	18.6
≥ 14 to < 20	9.11	3.76 - 22.09	11.6
≥ 5 to < 14	3.73	1.58 - 8.82	40.1
< 5	1 (reference)		24.4

Furthermore, absolute changes in cTnT-hs between various combination of pre- and post-operative measurements 6-12 h, 1 day, 2 days or 3 days after surgery were analyzed with respect to mortality at 30 days.[106]

	Adjusted HR (95 % CI)					
cTnT-hs (ng/L or pg/mL)	Pre vs post operative cTnT-hs (n = 7857)	N (%)	Between any two post-operative cTnT-hs (n = 18023)	N (%)	Between any two cTnT-hs measurements (n = 19373)	N (%)
< 5	1 (reference)	65.1	1 (reference)	64.0	1 (reference)	61.7
≥ 5	4.53 (2.77-7.39)	34.9	5.24 (3.92-7.01)	36.0	4.69 (3.52- 6.25)	38.3

In the BASEL-PMI study (single-centric, 2028 consecutive patients), Puelacher C. *et al* defined PMI as an absolute increase in cTnT-hs of ≥ 14 ng/L between pre-operative and peak post-operative values (or between 2 post-operative values if the pre-operative value is missing) within 7 days of surgery. According to these criteria, patients with PMI had an adjusted HR of 2,7 for 30 days mortality compared to patients without PMI.[81]

Results using cTnT-hs for long-term risk stratification in asymptomatic individuals

Results from the Atherosclerosis Risk community (ARIC) Study to predict coronary heart disease, fatal coronary heart disease and myocardial infarction, all-cause mortality, and heart failure hospitalization with increasing cTnT-hs values.[72]

	Adjusted HR (95% CI)				
Group	< 3 (ng/L or pg/mL)	3-5 (ng/L or pg/mL)	6-8 (ng/L or pg/mL)	9 -13 (ng/L or pg/mL)	≥ 14 (ng/L or pg/mL)
All CHD number of individuals	3258	2500	1971	1254	715
All CHD events	214	205	221	171	172
Model 1[e)]	1 (reference)	1.06 (0.88-1.29)	1.33 (1.09-1.62)	1.50 (1.21-1.86)	2.97 (2.38-3.71)
Model 2[f)]	1 (reference)	1.08 (0.89-1.31)	1.31 (1.07-1.59)	1.37 (1.10-1.71)	2.46 (1.96-3.08)
Model 3[g)]	1 (reference)	1.07 (0.88-1.30)	1.29 (1.06-1.58)	1.34 (1.07-1.67)	2.29 (1.81-2.89)
Hard CHD (fatal CHD + MI)	3258	2500	1971	1254	715
Hard CHF, events	118	104	107	81	117
Model 1	1 (reference)	1.02 (0.78-1.33)	1.22 (0.93-1.60)	1.34 (0.99-1.82)	3.74 (2.81-4.99)
Model 2	1 (reference)	1.06 (0.81-1.39)	1.26 (0.96-1.67)	1.31 (0.96-1.78)	3.28 (2.44-4.42)
Model 3	1 (reference)	1.05 (0.80-1.38)	1.23 (0.93-1.62)	1.23 (0.90-1.68)	2.84 (2.09-3.86)
All-cause mortality	3258	2500	1971	1254	715
All-cause mortality events	217	246	248	234	265
Model 1	1 (reference)	1.27 (1.05-1.52)	1.45 (1.20-1.76)	1.94 (1.59-2.37)	4.34 (3.55-5.29)
Model 2	1 (reference)	1.39 (1.15-1.67)	1.64 (1.35-1.98)	2.13 (1.74-2.60)	4.43 (3.61-5.44)
Model 3	1 (reference)	1.37 (1.14-1.65)	1.60 (1.32-1.94)	2.05 (1.68-2.51)	3.96 (3.21-4.88)
HF Hospitalization	3158	2413	1877	1188	640
HF Hospitalization events	105	124	147	130	159
	Adjusted HR (95% CI)				
Model 1	1 (reference)	1.45 (1.12-1.88)	2.21 (1.71-2.86)	3.07 (2.34-4.04)	8.61 (6.57-11.28)
Model 2	1 (reference)	1.51 (1.16-1.96)	2.24 (1.73-2.90)	2.84 (2.16-3.74)	7.00 (5.29-9.25)
Model 3	1 (reference)	1.46 (1.14-1.92)	2.17 (1.67-2.81)	2.68 (2.03-3.53)	5.95 (4.47-7.92)

e) Model 1: adjusted for age, sex, race.

f) Model 2: adjusted for model 1 + initial values for body mass index, smoking status and amount, diabetes mellitus, systolic blood pressure, antihypertensive medication use, high-density lipoprotein cholesterol, total cholesterol, lipid medication use, lipoprotein-associated phospholipase A_2 (Lp-PLA_2), prevalent atrial fibrillation, coronary heart disease, and heart failure.

g) Model 3: adusted the same as model 2 except incident atrial fibrillation, coronary heart disease, and heart failure were treated as time-dependent covariates.

Association of HR for stoke with increasing cTnT-hs values from the ARIC study.[74]

	cTnT-hs group (ng/L or pg/mL)					
Stroke model	< 3	3-5	6-8	9-13	≥ 14	P trend
No. for model 1	3492	2715	2214	1493	988	
No. for model 1 and 3	3317	2605	2105	1411	912	
Total stroke						
Rate/1000 person-year	2.79	3.18	3.20	4.93	7.71	
No. of strokes	109	106	95	103	94	
Model 1	1 (reference)	1.14 (0.97-1.50)	1.16 (0.87-1.54)	1.80 (1.34-2.40)	2.87 (2.11-3.91)	< 0.0001
Model 2	1 (reference)	1.25 (0.94-1.65)	1.13 (0.84-1.53)	1.60 (1.17-2.18)	2.04 (1.45-2.87)	< 0.0001
Model 3	1 (reference)	1.23 (0.93-1.63)	1.09 (0.81-1.48)	1.51 (1.11-2.06)	1.85 (1.31-2.61)	0.001

See previous table for model definition.

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

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

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

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