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 electrochemiluminescence immunoassay "ECLIA" is intended for use on cobas e immunoassay analyzers.

Summary

Troponin T (TnT) is a component of the contractile apparatus of the striated musculature. Although the function of TnT is the same in all striated muscles, TnT originating exclusively from the myocardium (cardiac TnT, molecular weight 39.7 kDa) clearly differs from skeletal muscle TnT. As a result of its high tissue-specificity, cardiac troponin T (cTnT) is a cardio-specific, highly sensitive marker for myocardial damage. Cardiac troponin T increases rapidly after acute myocardial infarction (AMI) and may persist up to 2 weeks thereafter.[1,2,3] Early detectability of the troponin increase in blood depends on the analytical sensitivity of the specific troponin test used; cardiac troponin T-high sensitive (cTnT-hs) helped to reduce the observational time from 6 to 3 hours when compared to conventional troponin tests as suggested by several studies[4,5,6] and recommended by the 2011 ESC and the 2014 NICE guidelines on non-ST elevation myocardial infarction (NSTEMI).[7,8] The 2015 ESC guidelines on NSTEMI propose to further shorten the observation time to 0 h/1 h. This accelerated approach to rule-in or rule-out AMI within 0 h/1 h has to be used with high-sensitive cardiac Troponin (hs-cTn) tests and using an algorithm validated for the specific hs-cTn assay.[9,10,11,12] The specific algorithm values for cTnT-hs were recommended in these guidelines and have been validated in 3 studies, APACE, APACE-2015 and TRAPID-AMI.[13,14,15] Alternative approaches using cTnT-hs to rule-in or rule-out AMI within 2 hours with or without risk scores have been also developed.[16,17,18,19,20,21]

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

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

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

The results of a sub-study of the PLATO trial, involving 9946 patients hospitalized for 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 recognize two epitopes (amino acid position 125-131 and 136-147) located

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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.

Do not use samples and controls stabilized with azide.

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

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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 04680307190. 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
Lisinopril	10
Methylprednisolone (Urbason)	7.5

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Drug	Concentration tested mg/L
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)	6.60	2.97
20 % intermediate CV (ng/L = pg/mL)	2.84	1.25

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]

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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	0.700	8.8	0.868	10.9
Human serum 2	13.6	0.540	4.0	0.746	5.5
Human serum 3	18.0	0.502	2.8	0.764	4.2
Human serum 4	144	3.43	2.4	4.20	2.9
Human serum 5	4709	97.9	2.1	125	2.7
Human serum 6	8824	195	2.2	254	2.9
PreciControl TN1	23.1	0.726	3.1	1.07	4.7
PreciControl TN2	1784	27.0	1.5	45.9	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	0.233	2.5	0.338	3.7
Human serum 2	15.1	0.249	1.6	0.400	2.6
Human serum 3	20.4	0.381	1.9	0.555	2.7
Human serum 4	148	3.02	2.0	3.28	2.2
Human serum 5	4794	40.9	0.9	123	2.6
Human serum 6	8961	212	2.4	254	2.8
PreciControl TN1	25.9	0.311	1.2	0.617	2.4
PreciControl TN2	1883	18.8	1.0	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
r = 0.986	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
r = 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[92] 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

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Time from admission (hours)	Test generation Troponin T	Sensitivity %	N	95 % confidence interval (%)	Specificity %	N	95 % confidence interval (%)
0-12	4th gen.	83	15/18	59-96	100	43/43	92-100
	Troponin T hs	94	17/18	73-100	72	31/43	56-85
> 12	4th gen.	83	25/30	65-94	98	56/57	91-100
	Troponin T hs	100	30/30	88-100	60	34/57	46-72

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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).

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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.

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CALIBRATOR	Calibrator
→	Volume after reconstitution or mixing
GTIN	Global Trade Item Number

CE 0123

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System information

For cobas e 411 analyzer: test number 2270
cobas e 601 and cobas e 602 analyzers: Application Code Number 117

Intended use

Immunoassay for the in vitro quantitative determination of N-terminal pro B-type natriuretic peptide in human serum and plasma. This assay is indicated as an aid in the diagnosis of individuals suspected of having congestive heart failure and detection of mild forms of cardiac dysfunction.[1,2,3,4,5,6,7,8]

The test also aids in the assessment of heart failure severity in patients diagnosed with congestive heart failure.[9,10]

This assay is further indicated for the risk stratification of patients with acute coronary syndrome[11,12,13,14,15] and congestive heart failure, and it can also be used for monitoring the treatment in patients with left ventricular dysfunction.[1,2,16,17,18,19,20]

The electrochemiluminescence immunoassay "ECLIA" is intended for use on cobas e immunoassay analyzers.

Summary

Heart failure is a clinical syndrome characterized by systemic perfusion inadequate to meet the body's metabolic demands as a result of a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress.[1,2,3] Left ventricular dysfunction can be one of the functional precursors of heart failure.[1,2]

Heart failure is a progressive disease where in both hospitalized and ambulatory patients, most deaths are due to cardiovascular causes, mainly sudden death and worsening HF.[1,2]

The typical terminology used to describe HF is based on measurement of the Left Ventricular Ejection Fraction (LVEF). According to latest ESC guidelines, HF comprises a wide range of patients, from those with normal LVEF [typically considered as ≥ 50 %; HF with preserved EF (HFpEF)] to those with reduced LVEF [typically considered as < 40 %; HF with reduced EF (HFrEF)]. Patients with an LVEF in the range of 40-49 % represent a 'grey area', which is now defined as HF with midrange EF (HFmrEF).[1,2,3] Clinical information and imaging procedures are used to confirm the diagnosis of heart failure.[1,2,3]

The significance of natriuretic peptides in the control of cardiovascular system function has been demonstrated. The following natriuretic peptides have been described: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP).[21,22]

ANP and BNP, as antagonists of the renin-angiotensin-aldosterone system, influence by means of their natriuretic and diuretic properties, the electrolyte and fluid balance in an organism.[23,24,25] In subjects with left ventricular dysfunction, serum and plasma concentrations of BNP increase, as does the concentration of the putatively inactive amino-terminal fragment, NT-proBNP. ProBNP, comprising 108 amino acids, is secreted mainly by the ventricle and, in this process, is cleaved into physiologically active BNP (77-108) and the N-terminal fragment NT-proBNP (1-76).[22,23]

Several studies have demonstrated the significant role of natriuretic peptide testing, including NT-proBNP, in heart failure management from diagnosis to monitoring, leading to the recommendation to use them in clinical practice by major international guidelines with often highest level of evidence and recommendation.[1,2]

Based on the symptoms, the severity of heart failure is classified in stages (New York Heart Association classification [NYHA] I-IV). When patients are grouped according to their NYHA classification, NT-proBNP levels increase with increasing class numbers and reflect the severity of cardiac impairment.[9,10]

Heart failure symptoms are often non-specific and do not help to discriminate between heart failure and other conditions, such as (non-cardiogenic) pulmonary edema, chronic obstructive pulmonary disease (COPD), pneumonia or sepsis.[1,2]

The European Society of Cardiology Heart Failure Guidelines recommends natriuretic peptides, including NT-proBNP, as an initial diagnostic test.[1] Patients with NT-proBNP below the recommended NT-proBNP cutoffs for non-acute and acute onsets are unlikely to have HF, and therefore do not require echocardiography and elevated NT-proBNP levels help to identify patients who require further cardiac investigation.[1]

The test is also useful in the early stages of heart failure, where symptoms may be transient rather than present all the time.[3] The high sensitivity of NT-proBNP allows also the detection of mild forms of cardiac dysfunction in asymptomatic patients with structural heart disease.[4,5,6,7,8]

NT-proBNP can also be used for prognostic applications in patients with acute coronary syndrome. The GUSTO IV study, with more than 6800 patients, showed that NT-proBNP was the strongest independent predictor of one year mortality in patients with acute coronary syndrome.[15]

In patients hospitalized for acute decompensated heart failure, pre-discharge measurement of natriuretic peptides is useful to categorize patient's risk at discharge.[1,16] Changes in NT-proBNP levels during hospitalization demonstrated to be a strong predictor of outcomes.[16,26,27,28,29] A decrease in NT-proBNP values of ≥ 30 % has shown to be correlated with favorable outcome, while an increase in NT-proBNP values > 30 % was correlated with 6.6 times higher risk of rehospitalization or death in 6 months.[16]

In chronic heart failure, serial measurement of NT-proBNP concentration can be used to monitor the disease progression, to predict outcomes and evaluate the success of treatment.[1,2,17,18,20,30,31]

Elevated NT-proBNP values are strongly predictive of adverse outcomes and rising values identify a risk, while significant lowering of NT-proBNP denotes improved outcomes and better prognosis.[1,2,17,32]

When NT-proBNP levels change during treatment of chronic heart failure, decrease over the course of the disease correlates with improved clinical outcomes.[1,2,18,20] This interpretation of NT-proBNP results remains unchanged when using the new drug class Angiotensin receptor–neprilysin inhibitor[1,2] (ARNI, e.g. sacubitril-valsartan): In contrast to BNP, NT-proBNP degradation is not inhibited by the drug so that NT-proBNP results are not increased by the mode of action of the drug.[19,33,34] In patients treated with sacubitril-valsartan, rapid and sustained reduction of NT-proBNP levels has been observed, reflecting reduced wall stress[33] and benefits of the drug correlating with a lower rate of cardiovascular death and heart failure hospitalization.[20]

NT-proBNP can be used before non-cardiac surgery to evaluate patients' perioperative cardiac risk.[35]

In addition NT-proBNP can be used to identify patients at higher risk of cardiotoxicity which can lead to heart failure and may be helpful in monitoring the use and dosing of cardiotoxic tumor drugs[1,36,37] or interventions causing fluid retention or volume overload (e.g. COX-2 inhibitors, nonsteroidal anti-inflammatory drugs).[38,39,40,41,42,43,44,45]

In meta-analysis including 95617 patients without history of cardiovascular disease, NT-proBNP concentration strongly predicted first-onset heart failure and augmented chronic heart disease and stroke prediction, suggesting that NT-proBNP could serve as a biomarker in new therapeutic approaches that integrate heart failure into cardiovascular disease primary prevention.[46]

The Elecsys proBNP II assay contains two monoclonal antibodies which recognize epitopes located in the N-terminal part (1-76) of proBNP (1-108).

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: Antigen in the sample (15 µL), a biotinylated monoclonal NT-proBNP-specific antibody, and a monoclonal NT-proBNP-specific antibody labeled with a ruthenium complex[a)] 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.

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- 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 PBNP.

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

R1 Anti-NT-proBNP-Ab~biotin (gray cap), 1 bottle, 9 mL:
Biotinylated monoclonal anti-NT-proBNP antibody (mouse) 1.1 µg/mL; phosphate buffer 40 mmol/L, pH 5.8; preservative.

R2 Anti-NT-proBNP-Ab~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 9 mL:
Monoclonal anti-NT-proBNP antibody (sheep) labeled with ruthenium complex 1.1 µg/mL; phosphate buffer 40 mmol/L, pH 5.8; preservative.

Precautions and warnings

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

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

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

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

Warning

H317	May cause an allergic skin reaction.
Prevention:	
P261	Avoid breathing dust/fume/gas/mist/vapours/spray.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves.
Response:	
P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.
Disposal:	
P501	Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

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

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

Reagent handling

The 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	8 weeks

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

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

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

Plasma tubes containing separating gel can be used.

Criterion: Slope 0.9-1.1 + intercept within ≤ ± 10 pg/mL + coefficient of correlation ≥ 0.95.

Stable for 3 days at 20-25 °C, 6 days at 2-8 °C, 24 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 08884234190, proBNP II CalSet, for 4 x 1.0 mL
- REF 04917049190, PreciControl Cardiac II, for 4 x 2.0 mL
- REF 05192943190, Diluent Universal 2, 2 x 36 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

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- 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: This method has been standardized against the Elecsys proBNP assay (REF 03121640122). This in turn is traceable to pure synthetic NT-proBNP (1-76) by weight.

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 Cardiac II.

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 pmol/L or pg/mL).

Conversion factors: pmol/L x 8.457 = pg/mL

pg/mL x 0.118 = pmol/L

Limitations - interference

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

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 428 µmol/L or ≤ 25 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 14326 nmol/L or ≤ 3500 ng/mL
Rheumatoid factors	≤ 1500 IU/mL
IgG	≤ 6.0 g/dL
IgA	≤ 1.6 g/dL
IgM	≤ 1.0 g/dL

Criterion: Recovery of ± 10 pg/mL of initial value ≤ 100 pg/mL and ± 10 % of initial value > 100 pg/mL.

There is no high-dose hook effect at NT-proBNP concentrations up to 35400 pmol/L (300000 pg/mL).

In vitro tests were performed on 51 commonly used pharmaceuticals. No interference with the assay was found.

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.

In extremely rare cases (global incidence: < 1 in 10 million), patients may show discrepant results when tested with the assay kit (values < lower detection limit) due to a NT-proBNP genetic variant.

cobas e 601 and cobas e 602 modules:

Note: Only required if the Elecsys proBNP II assay runs on the same analyzer module as the Elecsys Troponin I/ Troponin I STAT assay.

Make sure that in the Special Wash List (Screen → Utility → Special Wash → Immune) the Elecsys proBNP II assay is combined with all assays performed on the analyzer.

From test	Step	To test	Step 0	Step 1	Step 2
Elecsys proBNP II	1	all items	X	X	X

The described additions to the Special Wash List have to be entered manually. Please refer to the operator's manual.

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

10-35000 pg/mL or 1.18-4130 pmol/L (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 10 pg/mL (< 1.18 pmol/L). Values above the measuring range are reported as > 35000 pg/mL (> 4130 pmol/L) or up to 70000 pg/mL (8260 pmol/L) for 2-fold diluted samples.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 8 pg/mL (0.944 pmol/L)

Limit of Detection = 10 pg/mL (1.18 pmol/L)

Limit of Quantitation = 50 pg/mL (5.9 pmol/L)

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 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 Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank

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corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

Dilution

Samples with NT-proBNP concentrations above the measuring range can be diluted with Diluent Universal 2. The recommended dilution is 1:2 (either automatically by the analyzers or manually). The concentration of the diluted sample must be > 1770 pmol/L or > 15000 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.

Dilutions of up to 1:10 may entail maximum deviations of 25 % from the theoretical value.

Clinical data

Interpretation of NT-proBNP values

With increasing age atherosclerosis and aging processes of the heart (e.g. fibrosis) result in cardiac dysfunction. Development of cardiac dysfunction is individually different and clinically asymptomatic in its early stages.[47,48] NT-proBNP levels reflect cardiac function or dysfunction respectively. With increasing age elevated levels of NT-proBNP are more frequently found in apparently healthy individuals, thus reflecting the increasing frequency of cardiac dysfunction.

NT-proBNP values need to be interpreted in conjunction with the medical history, clinical findings and other information (e.g. imaging, laboratory findings, accompanying disorders, treatment effects).

Expected values

NT-proBNP concentrations in the reference group are shown in the following tables.

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

Reference group

The circulating NT-proBNP concentration was determined in samples from 4266 subjects aged between 35 and 74 years, enrolled into the Gutenberg Health Study in Germany. [49] These individuals had no prevalent cardiovascular diseases such as former history of stroke, myocardial infarction, coronary artery disease, peripheral artery disease, chronic heart failure or atrial fibrillation. The descriptive statistics for NT-proBNP (pg/mL) in the reference group are shown in the following table:

Age (years)	Men				Women			
	Median	95th percentile	97.5th percentile	99th percentile	Median	95th percentile	97.5th percentile	99th percentile
35-44	18.9	90.8	115	137	59.9	202	237	311
45-54	23.5	121	173	273	63.8	226	284	395
55-64	47.4	262	386	920	81.8	284	352	417
65-74	89.3	486	879	2346	133	470	623	784
All	35.6	238	344	703	78.6	304	389	509

The circulating NT-proBNP concentration was also determined in samples from 2812 subjects aged between 20 and above 70 years, enrolled in a cardiovascular health screening program at a tertiary medical center in Taipei, Taiwan.[50] These individuals had no known cardiovascular or systemic co-morbidities, and no structural heart diseases. The descriptive statistics for NT-proBNP (pg/mL) in the reference group are shown in the following table:

Age (years)	Men (N = 1836)				Women (N = 976)			
	N	Median	25th percentile	75th percentile	N	Median	25th percentile	75th percentile
20-29	48	9	5.0	19.7	33	30.1	10.3	41.9
30-39	369	13.5	5.0	29.7	153	34.9	20.8	60.4
40-49	708	17	7.8	32.4	346	40.1	18.9	62.5
50-59	558	22.8	11.6	42.6	310	44.4	27.3	64.7
60-69	130	31.5	16.6	59.1	112	61.7	30.8	85.2
≥ 70	23	66.1	34.2	106.6	22	77.5	46.3	123.0

In the pediatric population aged between 1 and 18 the following NT-proBNP values were obtained using the Elecsys proBNP assay. REF 03121640122:[51]

Age (years)	N	NT-proBNP (ng/L)	
		75th percentile	97.5th percentile
1-3	13	231	320
4-6	21	113	190
7-9	32	94	145
10	11	73	112
11	69	93	317
12	21	95	186
13	23	114	370
14	18	68	363
15	24	74	217
16	24	85	206
17	24	71	135
18	12	53	115

Recommended cutoffs in patients for diagnosis of chronic heart failure in non-acute onset

A number of studies and ESC guidelines support a decision threshold for NT-proBNP of 125 pg/mL in non-acute onset for the diagnosis of heart failure.[1,3,52,53,54,55,56] NT-proBNP values < 125 pg/mL exclude cardiac dysfunction with a high level of certainty in patients with symptoms suggestive of heart failure e.g. dyspnea. NT-proBNP values > 125 pg/mL may indicate cardiac dysfunction and are associated with an increased risk of cardiac complications (myocardial infarction, heart failure, death). At the cut-off value, ESC Guidelines state that natriuretic peptides have a very high negative predictive value (NPV) comprised between 94 % and 98 % and a positive predictive value (PPV) comprised between 44 % and 57 %.[1]

Patients with stable heart failure (n = 721) including patients with asymptomatic left ventricular dysfunction (n = 176) and patients with congestive heart failure (n = 545) were compared to a reference group (n = 2264).

ROC plot analysis at the cutoff value of 125 pg/mL showed a sensitivity of 90 % and a specificity of 93 %.

Correlation of NT-proBNP with NYHA classification in patients diagnosed with chronic heart failure

NT-proBNP values (pg/mL) for patients with reduced left ventricular ejection fraction (majority under therapy):

	NYHA functional class			
	NYHA I	NYHA II	NYHA III	NYHA IV
N	182	250	234	35
Mean	1016	1666	3029	3465
SD	1951	2035	4600	4453
Median	342	951	1571	1707

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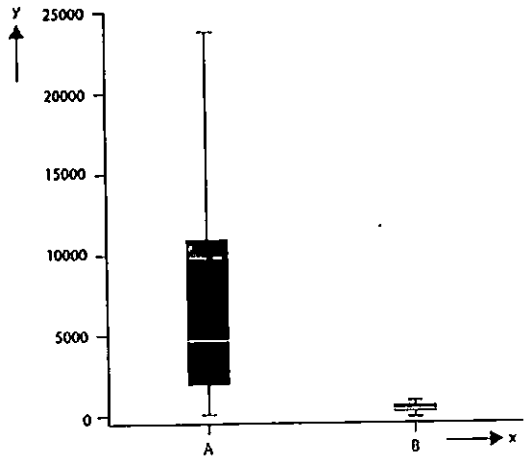
	NYHA functional class			
	NYHA I	NYHA II	NYHA III	NYHA IV
5th percentile	32.9	103	126	148
95th percentile	3410	6567	10449	12188
% > 125 pg/mL	78.6	94.0	95.3	97.1

Recommended cutoffs in patients for diagnosis of chronic heart failure in acute onset

ICON (International Collaborative of NT-proBNP) study[10]

NT-proBNP concentrations were determined in samples from 1256 patients presenting with acute shortness of breath to emergency departments at four hospitals. This population included patients with a prior history of hypertension, coronary artery disease, myocardial infarction, heart failure, or pulmonary disease. 720 subjects were found to be suffering from acute exacerbation of heart failure, while the remainder were determined to present dyspnea due to other causes. The descriptive statistics for NT-proBNP concentrations (pg/mL) for both groups are shown in the following figure adapted from the ICON study:[10]



X --> A: Acute CHF (n = 720); B: Not acute CHF (n = 536)
Y --> NT-proBNP (pg/mL)

Diagnostic category	Median (IQR) NT-proBNP, pg/mL
Acute CHF	4639 (1882-10818)
Not Acute CHF	108 (37-381)

By using the optimal cutoffs established by the ICON study group and shown in the table below, physicians can increase the specificity and accuracy for diagnosing heart failure in patients presenting acute dyspnea in the emergent setting.

Category	Optimal cut-point pg/mL	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Rule in cut-point						
< 50 years (n = 184)	450	97	93	76	99	94
50-75 years (n = 537)	900	90	82	83	88	85
> 75 years (n = 535)	1800	85	73	92	55	83
Rule out cut-point						
All patients (n = 1256)	300	99	60	77	98	83

Performance of NT-proBNP for diagnosis of acute heart failure in an Asian compared with a Western setting[57]

NT-proBNP concentrations were determined in samples from patients presenting with acute shortness of breath to emergency departments in Singapore (n = 606) and in New Zealand (n = 500). This population included patients with a prior history of hypertension, hyperlipidemia, coronary artery disease, myocardial infarction, heart failure, or pulmonary disease. NT-proBNP concentration in patients with final adjudicated diagnosis of acute heart failure was 4234 [2008-9799] pg/mL in Singapore (median [25-75th percentile], n = 148) and 4429 [2123-9479] pg/mL in New Zealand (n = 180).

The diagnostic performances of NT-proBNP at the cutoffs established in the ICON Study[10] are shown in the table below for both populations:

Category	Optimal cut-point pg/mL	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Rule in cut-point						
< 50 years						
Singapore (n = 196)	450	100	91	58	100	92
New Zealand (n = 41)		86	76	43	96	78
50-75 years						
Singapore (n = 350)	900	88	83	68	95	85
New Zealand (n = 236)		91	75	58	96	80
>75 years						
Singapore (n = 60)	1800	79	81	73	85	80
New Zealand (n = 223)		87	63	69	84	75
Rule out cut-point						
All patients						
Singapore (n = 606)	300	97	73	54	99	79
New Zealand (n = 500)		97	42	49	96	62

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Specific performance data

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

Precision

Precision was determined using Elecsys reagents, pooled human sera and controls in a protocol (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				
Sample	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
Human serum 1	12.3	1.45	1.70	0.201	13.9
Human serum 2	55.9	6.60	2.62	0.309	4.7
Human serum 3	129	15.2	3.07	0.362	2.4
Human serum 4	423	49.9	8.91	1.05	2.1
Human serum 5	925	109	23.0	2.71	2.5
Human serum 6	1924	227	43.8	5.17	2.3
Human serum 7	15620	1843	248	29.3	1.6
Human serum 8	33526	3956	778	91.8	2.3
PC CARDII[b]1	132	15.6	3.29	0.388	2.5
PC CARDII2	4477	528	135	15.9	3.0

b) PC CARDII = PreciControl Cardiac II

cobas e 411 analyzer					
	Intermediate precision				
Sample	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
Human serum 1	12.3	1.45	2.95	0.348	24.0
Human serum 2	55.9	6.60	4.35	0.513	7.8
Human serum 3	129	15.2	7.40	0.873	5.7
Human serum 4	423	49.9	18.0	2.12	4.3
Human serum 5	925	109	44.3	5.23	4.8
Human serum 6	1924	227	88.8	10.5	4.6
Human serum 7	15620	1843	662	78.1	4.2
Human serum 8	33526	3956	1591	188	4.7
PC CARDII1	132	15.6	5.97	0.704	4.5
PC CARDII2	4477	528	216	25.5	4.8

cobas e 601 and cobas e 602 analyzers					
	Repeatability				
Sample	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
Human serum 1	21.6	2.55	1.63	0.192	7.6
Human serum 2	68.3	8.06	1.96	0.231	2.9
Human serum 3	145	17.1	3.24	0.382	2.2
Human serum 4	467	55.1	12.8	1.51	2.7
Human serum 5	1004	118	20.0	2.36	2.0
Human serum 6	2075	245	38.9	4.59	1.9
Human serum 7	15985	1886	371	43.8	2.3
Human serum 8	34624	4086	609	71.9	1.8
PC CARDII1	140	16.5	2.48	0.293	1.8

cobas e 601 and cobas e 602 analyzers					
	Repeatability				
Sample	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
PC CARDII2	4721	557	70.2	8.3	1.5

cobas e 601 and cobas e 602 analyzers					
	Intermediate precision				
Sample	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
Human serum 1	21.6	2.55	2.40	0.283	11.2
Human serum 2	68.3	8.06	3.26	0.385	4.8
Human serum 3	145	17.1	5.95	0.702	4.1
Human serum 4	467	55.1	17.6	2.08	3.8
Human serum 5	1004	118	34.6	4.08	3.5
Human serum 6	2075	245	68.6	8.09	3.3
Human serum 7	15985	1886	579	68.3	3.6
Human serum 8	34624	4086	1367	161	3.9
PC CARDII1	140	16.5	4.94	0.583	3.5
PC CARDII2	4721	557	156	18.4	3.3

Method comparison

a) A comparison of the Elecsys proBNP II assay, REF 08836736190 (cobas e 411 analyzer; y), with the Elecsys proBNP II assay, REF 04842464190 (cobas e 411 analyzer; x), gave the following correlations (pg/mL):

Number of samples measured: 161

Passing/Bablok[58]	Linear regression
y = 0.974x + 0.121	y = 0.956x + 90.2
r = 0.992	r = 1.00

The sample concentrations were between 26.6 and 32852 pg/mL (3.14 and 3877 pmol/L).

Analytical specificity

The Elecsys proBNP II assay does not show any significant cross reactions with the following substances, tested with NT-proBNP concentrations of approximately 230 pg/mL and 2300 pg/mL (max. tested concentration):

Cross-reactant	Concentration tested
Adrenomedullin	1.0 ng/mL
Aldosterone	0.6 ng/mL
Angiotensin I	0.6 ng/mL
Angiotensin II	0.6 ng/mL
Angiotensin III	1.0 ng/mL
ANP_{28}	3.1 µg/mL
Arg-vasopressin	1.0 ng/mL
BNP_{32}	3.5 µg/mL
CNP_{22}	2.2 µg/mL
Endothelin	20 pg/mL
NT-proANP$_{1-30}$ (preproANP$_{26-55}$)	3.5 µg/mL
NT-proANP$_{31-67}$ (preproANP$_{56-92}$)	1.0 ng/mL
NT-proANP$_{79-98}$ (preproANP$_{104-123}$)	1.0 ng/mL
Renin	50 ng/mL
Urodilatin	3.5 µg/mL

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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 after reconstitution or mixing
GTIN	Global Trade Item Number

CE 0123

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

Roche

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05957648500V9.0

Elecsys CK-MB STAT

cobas®

REF		Σ	SYSTEM
			cobas e 411
05957648190	05957648500	100	cobas e 601
			cobas e 602

English

System information

For cobas e 411 analyzer: test number 211
For cobas e 601 and cobas e 602 analyzers: Application Code Number 118

Intended use

Immunoassay for the in vitro quantitative determination of the MB isoenzyme of creatine kinase in human serum and plasma.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers.

Summary

Creatine kinase (CK) is a dimeric enzyme which occurs in 4 different forms: a mitochondrial isoenzyme and the cytosolic isoenzymes CK-MM (muscle type), CK-BB (brain type) and CK-MB (muscle-brain type).[1,2]

CK-MB is an important biomarker of acute myocardial infarction and other causes of myocardial injury, such as heart failure and myocarditis.[3] CK-MB is detectable in the blood about 3-8 hours after the onset of cardiac symptoms and can remain detectable over a lengthy period of time, depending on the course of the condition.[1]

CK-MB may also appear in other clinical conditions, e.g. in rhabdomyolysis and stroke.[1,4] Within the scope of laboratory diagnostics, the determination of total CK, troponin T and/or myoglobin can contribute to the differentiation of these clinical pictures. Because of their higher sensitivity and specificity, cardiac troponins, measured by high-sensitivity assays, are the preferred biomarkers to define myocardial infarction,[3] and if a troponin assay is not available, the best alternative is CK-MB measured by a mass assay.[3]

The sensitivity of a CK-MB determination is dependent upon the time at which a sample was taken. Follow-up assays are therefore meaningful.[1,5]

The Elecsys CK-MB assay employs two different monoclonal antibodies directed against human CK-MB.

Test principle

Sandwich principle. Total duration of assay: 9 minutes.

cobas e 411 analyzer:

- 1st incubation: 15 µL of sample, a biotinylated monoclonal anti-CK-MB antibody, and a monoclonal CK-MB-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 (15 µL), a biotinylated monoclonal anti-CK-MB antibody, a monoclonal CK-MB-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 CKMBSTAT.

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

R1 Anti-CK-MB-Ab-biotin (gray cap), 1 bottle, 9 mL:
Biotinylated monoclonal anti-CK-MB antibody (mouse) 1.2 mg/L; phosphate buffer 100 mmol/L, pH 7.0; preservative.

R2 Anti-CK-MB-Ab-$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 9 mL:
Monoclonal anti-CK-MB antibody (mouse) labeled with ruthenium complex 1.2 mg/L; phosphate buffer 100 mmol/L, pH 7.0; preservative.

Precautions and warnings

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

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

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

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

Warning

H317	May cause an allergic skin reaction.
Prevention:	
P261	Avoid breathing dust/fume/gas/mist/vapours/spray.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves.
Response:	
P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.
Disposal:	
P501	Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

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

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

Reagent handling

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

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

Storage and stability

Store at 2-8 °C.

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Elecsys CK-MB STAT

cobas®

Do not freeze.

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

Stability:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	12 weeks
on the analyzers	8 weeks

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

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

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

Plasma tubes containing separating gel can be used.

Criterion: Recovery within 80-120 % of value from single serum/plasma pairs or slope 0.9-1.1 + intercept within ≤ ± 0.5 x Limit of Detection + coefficient of correlation ≥ 0.95.

Stable for 5 hours at 20-25 °C, 12 hours at 2-8 °C, 3 months at -20 °C (± 5 °C). Freeze only once.

CK-MB stability is extremely temperature-dependent. A CK-MB decrease of > 10 % can occur after the sample has stood for 1 hour at 32 °C.

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 heat-inactivated samples.

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 05957656190, CK-MB STAT CalSet, for 4 x 1.0 mL
- REF 04917049190, PreciControl Cardiac II, 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 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

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 CK-MB STAT assay is traceable to the Abbott IMx CK-MB assay and linearized using human recombinant CK-MB[6] from Seradyn.

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 Cardiac II.

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 ng/mL or µg/L).

Limitations - interference

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

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 581 µmol/L or ≤ 34 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 1500 mg/dL
Albumin	≤ 20 g/dL

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Elecsys CK-MB STAT

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Compound	Concentration tested
Biotin	≤ 123 nmol/L or ≤ 30 ng/mL
Rheumatoid factors	≤ 1500 IU/mL
IgG	≤ 7.0 g/dL
IgA	≤ 1.6 g/dL
IgM	≤ 1.0 g/dL

Criterion: Recovery with a standard deviation ≤ 0.4 ng/mL of initial value at concentrations between 0.3-5 ng/mL; recovery within ± 20 % of initial value at concentrations > 5 ng/mL.

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

No interference was observed from samples from dialysis patients.

There is no high-dose hook effect at CK-MB concentrations up to 5000 ng/mL.

In vitro tests were performed on 51 commonly used pharmaceuticals. No interference with the assay was found.

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

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

Limits and ranges

Measuring range

0.3-300 ng/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.3 ng/mL. Values above the measuring range are reported as > 300 ng/mL (or up to 600 ng/mL for 2-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.1 ng/mL

Limit of Detection = 0.3 ng/mL

Limit of Quantitation = 1 ng/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-A 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 is defined as the lowest amount of analyte in a sample that can be accurately quantitated with a total allowable error of ≤ 20 %.

Dilution

Samples with CK-MB concentrations above the measuring range can be diluted with Diluent MultiAssay. The recommended dilution is 1:2 (either automatically by the analyzers, or manually). The concentration of the diluted sample must be > 50 ng/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

The values below were obtained in two studies (Kiel I and Kiel II) using the Elecsys CK-MB assay (4th generation). The calculation is based on samples from 879 apparently healthy volunteers (463 women, 416 men).

	N	Median ng/mL	97.5th percentile ng/mL	99th percentile ng/mL
Women	463	1.39	3.61	4.88
Men	416	1.72	4.87	6.22

When myocardial infarction is suspected the diagnostic strategy proposals in the consensus document of European and American cardiologists should in general be followed.[7]

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 (EP5-A2) 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/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	0.621	0.018	2.9	0.035	5.7
Human serum 2	5.46	0.066	1.2	0.135	2.5
Human serum 3	29.5	0.397	1.3	1.24	4.2
Human serum 4	93.5	1.25	1.3	3.86	4.1
Human serum 5	301	4.46	1.5	10.0	3.3
PC[b] CARDII1	4.44	0.059	1.3	0.115	2.6
PC CARDII2	57.9	0.828	1.4	1.76	3.0

b) PC = PreciControl

cobas e 601 and cobas e 602 analyzers					
		Repeatability		Intermediate precision	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	0.644	0.018	2.8	0.020	3.1
Human serum 2	5.34	0.061	1.1	0.075	1.4
Human serum 3	27.3	0.289	1.1	0.885	3.2
Human serum 4	89.2	0.946	1.1	2.25	2.5
Human serum 5	283	2.19	0.8	6.09	2.2
PC CARDII1	4.27	0.050	1.2	0.059	1.4
PC CARDII2	54.3	0.503	0.9	0.723	1.3

Method comparison

A comparison of the Elecsys CK-MB STAT assay (y) with the Elecsys CK-MB STAT assay - previous version (x) using clinical samples gave the following correlations:

Number of samples measured: 196

Passing/Bablok[8]	Linear regression
y = 1.048x - 0.326	y = 1.085x - 0.915
r = 0.975	r = 0.999

The sample concentrations were between 0.3 and 300 ng/mL.

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Analytical specificity

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

CK-MM none, CK-BB 0.1 %.

References

1 Rozenman Y, Gotsman MS. The earliest diagnosis of acute myocardial infarction. Annu Rev Med 1994;45:31-44.

2 Adams JE, Abendschein DR, Jaffe AS. Biochemical markers of myocardial injury: Is MB creatine kinase the choice for the 1990s? Circulation 1993;88:750-763.

3 Thygesen K, Alpert JS, Jaffe AS, et al. Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infaction. Fourth Universal Definition of Myocardial Infarction. Glob Heart 2018;13(4):305-338.

4 Ay H, Arsava EM, Saribas O. Creatine Kinase-MB Elevation After Stroke is not cardiac in origin. Stroke 2002;(33)286-289.

5 Apple FS. Diagnostic markers for detection of acute myocardial infarction and reperfusion. Laboratory Medicine 1992;23(5):297-322.

6 Christenson RH, Valdya H, Landt Y, et al. Standardization of Creatine Kinase-MB (CK-MB) Mass Assays: The Use of Recombinant CK-MB as a Reference Material. Clin Chem 1999;45(9):1414-1423.

7 Thygesen K, Alpert JS, Jaffe AS, et al. Third Universal Definition of Myocardial Infarction. J Am Coll Cardiol 2012;60:1581-1598.

8 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.

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 after reconstitution or mixing
GTIN	Global Trade Item Number

CE 0123

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

Roche

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07026960500V5.0

Elecsys β-CrossLaps/serum

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REF		Σ	SYSTEM
07026960190	07026960500	100	cobas e 801

English

System information

Short name	ACN (application code number)
CROSSL	10062

Intended use

Immunoassay for the in vitro quantitative determination of degradation products of type I collagen in human serum and plasma as an aid in assessing bone resorption. The test may be used as an aid in monitoring antiresorptive therapies in osteoporotic patients.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on the cobas e 801 immunoassay analyzer.

Summary

Type I collagen is an important component of the bone matrix and its degradation products are the most commonly used bone resorption markers.[1]

During normal bone metabolism, mature type I collagen is degraded and small fragments pass into the circulation and are excreted via the kidneys.

In physiologically or pathologically elevated bone resorption (e.g. in old age or as a result of osteoporosis), type I collagen is degraded to an increased extent, and there is a commensurate rise in the level of collagen fragments in the blood.

Especially relevant fragments are the β-isomerized C (carboxy)-terminal cross-linking telopeptides (β-CTx), produced by osteoclastic hydrolysis of type I collagen.[1,2,3]

Elevated serum levels of isomerized C-terminal telopeptides of type I collagen have been reported for patients with increased bone resorption. The serum levels return to normal during anti-resorptive therapy.[4,5,6,7]

Determination of the C-terminal telopeptides in serum is recommended for monitoring the efficacy of antiresorptive therapy (e.g. bisphosphonates or hormone replacement therapy - HRT) in osteoporosis or other bone diseases. By these means, therapy-induced changes can be demonstrated after just a few months.[8,9]

Serum CTx has been selected by the IOF-IFCC Bone Marker Standards Working Group as marker for bone resorption, mainly based on the following criteria:

- It has been evaluated both for fracture prediction and monitoring osteoporosis therapies.
- The assay is widely available, for serum or plasma samples, with well documented requirements for sample handling and stability.
- The analyte is well characterized and allows the development of clearly defined reference standard.[1]

The Elecsys β-CrossLaps/serum assay is specific for crosslinked β-isomerized type I collagen fragments, independent of the nature of the crosslink (e.g. pyrrole, pyridinolines, etc.).[10] The assay specificity is guaranteed through the use of two monoclonal antibodies each recognizing linear β-8AA octapeptides (EKAHD-β-GGR). The Elecsys β-CrossLaps/serum assay therefore quantifies all type I collagen degradation fragments that contain the isomerized octapeptide β-8AA twice (β-CTx).[5,7]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 30 µL of sample and a biotinylated monoclonal anti-β-CrossLaps antibody are incubated together; the antigen in the sample is liberated from the serum components.
- 2nd incubation: Following addition of streptavidin-coated microparticles and a monoclonal β-CrossLaps-specific antibody labeled with a ruthenium complex[a], a sandwich complex is formed which 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 II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the cobas link.

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

Reagents - working solutions

The cobas e pack is labeled as CROSSL.

M Streptavidin-coated microparticles, 1 bottle, 5.8 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-β-CrossLaps-Ab~biotin, 1 bottle, 7.6 mL:
Biotinylated monoclonal anti-β-CrossLaps antibody (mouse) 2.5 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

R2 Anti-β-CrossLaps-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 6.8 mL:
Monoclonal anti-β-CrossLaps antibody (mouse) labeled with ruthenium complex 2.4 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

Precautions and warnings

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

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

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

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

Warning

H317	May cause an allergic skin reaction.
Prevention:	
P261	Avoid breathing dust/fume/gas/mist/vapours/spray.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves.
Response:	
P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.
Disposal:	
P501	Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

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

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

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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 available via the cobas link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the cobas e pack upright in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability:	
unopened at 2-8 °C	up to the stated expiration date
on the cobas e 801 analyzer	16 weeks

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

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

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

Li-heparin plasma tubes containing separating gel can be used.

Criterion: Slope 0.9-1.1 + intercept within ≤ ± 0.02 ng/mL + coefficient of correlation ≥ 0.95.

It is recommended to draw blood as fasting, morning samples. For long-term investigations, the samples should always be taken under same conditions as the baseline sample, as the serum β-CTx concentration is to some extent subject to a circadian rhythm.

Preference should be given to K_2- or K_3-EDTA plasma, as it is stable longer than serum.

Stability of serum: 6 hours at 20-25 °C, 8 hours at 2-8 °C.

Stability of Li-heparin plasma: 4 hours at 20-25 °C, 8 hours at 2-8 °C.

Stability of K_2- and K_3-EDTA plasma: 24 hours at 20-25 °C, 8 days at 2-8 °C.

Serum, heparinized and EDTA plasma are stable for 3 months at -20 °C (± 5 °C). For longer periods, store at -80 °C (± 10 °C). Freeze only once.

Hemolyzed samples (Hb > 0.5 g/dL) elicit a decrease in the β-CTx concentration.

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 heat-inactivated samples.

Do not use samples and controls stabilized with azide.

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

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

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- REF 11972316122, β-CrossLaps CalSet, 4 x 1.0 mL
- REF 05618860190, PreciControl Varia, for 4 x 3.0 mL
- General laboratory equipment
- cobas e 801 analyzer

Additional materials for the cobas e 801 analyzer:

- REF 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- REF 06908853190, PreClean II M, 2 x 2 L wash solution
- REF 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- REF 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- REF 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

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

Resuspension of the microparticles takes place automatically prior to use.

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

Calibration

Traceability: This method has been standardized against reference standards precisely defined by weighing out synthetic peptide.

The predefined master curve is adapted to the analyzer using the relevant CalSet.

Calibration frequency: Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the cobas e pack was registered on the analyzer).

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

Renewed calibration is recommended as follows:

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

Quality control

For quality control, use PreciControl Varia.

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 cobas e pack, and following each calibration.

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

If necessary, repeat the measurement of the samples concerned.

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

Calculation

The analyzer automatically calculates the analyte concentration of each sample either in ng/mL or pg/mL.

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	≤ 1112 µmol/L or ≤ 65 mg/dL
Hemoglobin	≤ 0.3 mmol/L or ≤ 500 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 123 nmol/L or ≤ 30 ng/mL
Rheumatoid factors	≤ 1000 IU/mL

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Criterion: For concentrations ≤ 0.50 ng/mL the deviation is ≤ 0.05 ng/mL. For concentrations > 0.50 ng/mL the deviation is ≤ ± 10 %.

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

There is no high-dose hook effect at β-CTx concentrations up to 150 ng/mL (150000 pg/mL).

Pharmaceutical substances
In vitro tests were performed on 16 commonly used pharmaceuticals. No interference with the assay was found.

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

Special drugs

Drug	Concentration tested mg/L
Ibandronate	6
Actonel (Risedronate)	150
Vitamin D3	0.075
Calcium Carbonate	2500
Vitamin D (25-OH)	1
17-β-Estradiol	2.5
β-Estradiol-17-valerate	2.5
β-Estradiol-3-sulfate	2.5

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.

Results may be confounded by clinical conditions known to affect bone resorption, e.g. hyperparathyroidism or hyperthyroidism.

Caution should be exercised when measuring serum β-CTx levels in patients with reduced renal function as this may lead to reduced excretion of serum β-CTx and a consequent increase in the apparent serum β-CTx levels is seen.[11]

There is evidence that β-CTx can predict loss of bone density.[12] However, a correlation with increased fracture risk has not yet been demonstrated. The properties of β-CTx in case of hyperparathyroidism or hyperthyroidism have not yet been unequivocally described, either.

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

They should not be used as a sole determinant for deciding on or modifying an existing treatment regimen.

Limits and ranges

Measuring range

0.01-6.00 ng/mL or 10-6000 pg/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.010 ng/mL (< 10 pg/mL). Values above the measuring range are reported as > 6.00 ng/mL (> 6000 pg/mL).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.008 ng/mL

Limit of Detection = 0.01 ng/mL

Limit of Quantitation = 0.05 ng/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 is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

Dilution

Not necessary due to the broad measuring range.

Expected values

The following 95 % reference intervals (RI) for serum βCTx in 1039 healthy men, and in 1029 healthy premenopausal and postmenopausal women (age range 24-76 years) were obtained from a Danish study with the Elecsys β-CrossLaps/serum assay. Subjects included were characterized by their history of osteoporosis and lifestyle, and women by their menopausal state and by taking no anti-osteoporotic medication. Based on the patterns in the sex-, age-, and menopause-stratified 95 % RIs, subjects were grouped into age intervals for each gender, and into pre-menopausal and postmenopausal.[13] Other studies have demonstrated, that ranges can differ between ethnicities and geographical locations.[14,15] Thus, measurements should be compared to reference intervals established on material from similar geographical regions and should reflect the same gender, age, and pre-/post-menopausal status.

The table shows the geometric means and 95% reference intervals of healthy male and female subjects after stratification for age, and for menopause of female subjects from a Danish study.[13]

1. Healthy subjects

Age range (years)	Men			Women		
	N	GM (pg/mL)	95 % RI (pg/mL)	N	GM (pg/mL)	95 % RI (pg/mL)
< 29.9	39	492	238-1019	58	378	148-967
30-39.9	80	459	225-936	111	308	150-635
40-49.9	234	382	182-801	257	296	131-670
50-59.9	248	345	161-737	281	440	183-1060
60-69.9	303	316	132-752	234	408	171-970
>70	135	302	118-776	88	362	152-858
Pre-menopause	-	-	-	449	306	136-689
Post-menopause	-	-	-	578	424	177-1015

Intra-individual variance and least significant change (LSC)

The intra-individual variance of βCTx was determined in a subset of 18 healthy postmenopausal women (mean βCTx at baseline 0.516 ± 0.217 ng/mL) at 5 time points over 3 months. The median intra-individual variability as expressed by the mean CVi (intra-individual coefficient of variation) for serum βCTx values was 9.4 % (range, 4.1-27 %). On the basis of this CVi, the least significant change (LSC) was determined to be 27 %, meaning that an individual should display a ≥ 27 % decrease of serum βCTx concentrations when receiving antiresorptive therapy to have a < 5 % chance ($p < 0.05$) of the decrease being the result of random variation in marker concentration.[16]

Monitoring during antiresorptive therapy

Detecting changes of serum βCTx concentrations is valuable in the monitoring of antiresorptive therapies with bisphosphonates and in the assessment of therapy adherence of patients.[17] Bisphosphonates including alendronate, risedronate, ibandronate and zoledronic acid are commonly used medications to treat osteoporosis. They reduce bone resorption by inhibiting osteoclasts and thereby increasing bone mineral density (BMD). BMD is widely used to monitor response to treatment; however, treatment-induced increments in BMD are modest (typically 2 % per year). Taking a repeat error of 1-2 % into account true changes in BMD are observed only several years after starting treatment. Treatment-induced changes in bone turnover markers are much more rapid and occur at 3-6 months[18] or earlier.

a. Ibandronate therapy

The DIVA (Dosing IntraVenous Administration) study enrolled 1395 women aged 55-80 years, who were > 5 years menopausal, with osteoporosis diagnosed by lumbar spine [L2-L4] bone mineral density T score less than -2.5. Participants received a daily calcium dose of 500 mg and 400 IU vitamin D. A dosing scheme of oral 2.5 mg ibandronate daily, which has

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proven antifracture efficacy was compared with an i.v. 3 mg every 3 months dosing scheme and investigated for non-inferiority.

The table shows the median (%) change from baseline in serum βCTx levels after 2, 3, 4, 6 and 12 months[9] and after 24 months.[19]

The following values have been obtained from studies with the Elecsys β-CrossLaps/serum assay in healthy test subjects:

	Oral ibandronate 2.5mg/daily		I.v. ibandronate 3 mg every 3 months	
Month	N	Median (95 % CI)	N	Median (95 % CI)
2	181	-45.0 (-48.7, -40.5)	-	-
3	192	-54.1 (-57.8, -48.7)	356	-43.2 (-45.9, -40.8)
4	180	-57.6 (-66.7, -50.0)	-	-
6	372	-62.5 (-65.3, -60.0)	353	-58.4 (-61.5, -55.2)
12	368	-62.6 (-66,0, -58.9)	352	-58.6 (-61.5, -55.4)
24	310	-59.9 (no CI available)	298	-53.4 (no CI available)

b. Other anti-osteoporotic medications

Studies with different anti-osteoporotic medications (alendronate, risedronate, zoledronic acid and other drugs) at licensed doses revealed that βCTx reductions from baseline varied between the treatments, but serum βCTx was clinically useful in monitoring all anti-resorptive therapies. In a placebo-controlled clinical study with healthy postmenopausal women comparing the changes of different bone turnover markers, serum βCTx levels showed the highest decrease with 63.7 % in the alendronate group (N = 75) and 21.6 % in the placebo group (N = 73) after 12 months. Serum βCTx showed the highest correlation (r = 0.60, p < 0.0001) with changes in lumbar spine bone mineral density after 12 months.[20] In a clinical study performed in 54 study centers worldwide, the effectiveness of 5 mg i.v. zoledronic acid on the increase of lumbar spine bone mineral density was compared with 5 mg oral risedronate and monitored with bone turnover markers, e.g. serum βCTx.[21] The strong decrease of βCTx levels occurring within 9-11 days after onset of both treatments was maintained during the 12 months of the study. The reduction of βCTx levels after 6 and 12 months reflected the efficacy of both medications, i.e. the changes in lumbar bone mineral density.

Comparison of the least significant change (LSC) with the observed change in serum βCTx is a commonly proposed approach to determine its physiological relevance. A reduction in serum βCTx of smaller than the LSC of 27 % in a treated patient after 3 months from treatment initiation can thus be used as indicator of poor adherence or poor response of the patient to the anti-osteoporotic therapy.[17]

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 analyzer is 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 801 analyzer					
		Repeatability		Intermediate precision	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	0.074	0.003	4.5	0.004	5.8
Human serum 2	0.444	0.013	3.5	0.020	5.5
Human serum 3	0.630	0.013	2.5	0.015	2.8
Human serum 4	3.28	0.054	2.0	0.074	2.7
Human serum 5	5.59	0.081	1.8	0.100	2.1

cobas e 801 analyzer					
		Repeatability		Intermediate precision	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
PC[b] Varia1	0.295	0.007	3.1	0.009	3.4
PC Varia2	0.814	0.018	2.7	0.021	2.9

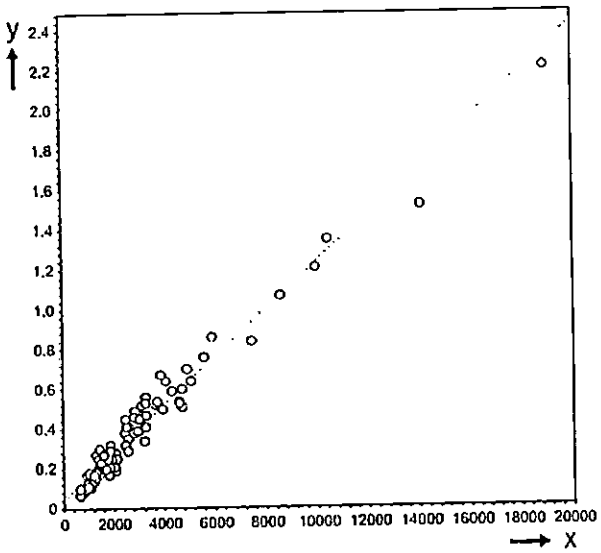
b) PC = PreciControl

Method comparison

A comparison of the Elecsys β-CrossLaps/serum assay (y) - ng/mL - with the Serum CrossLaps[TM] One Step ELISA test from Osteometer Bio Tech A/S (x) - pmol/L - using human serum is shown in the diagram below (linear regression):

Number of samples measured: 96

The sample concentrations were between approximately 0.07 and 2.2 ng/mL for the Elecsys β-CrossLaps/serum assay and between approximately 620 and 18900 pmol/L for the comparison test.



x: β-CrossLaps comparison β-CTx (pmol/L)

y: Elecsys β-CrossLaps/serum assay (ng/mL)

y = 0.0001x + 0.048

r = 0.983

The differing magnitudes of the concentrations is mainly due to the different forms of standardization used. Recalculation of the units is not possible.

A comparison of the Elecsys β-CrossLaps/serum assay, REF 07026960190 (cobas e 801 analyzer; y) with the β-CrossLaps/serum assay, REF 11972308122 (cobas e 601 analyzer; x) gave the following correlations (ng/mL):

Number of samples measured: 146

Passing/Bablok[22]	Linear regression
y = 0.913x - 0.002	y = 0.894x + 0.026
r = 0.968	r = 0.996

The sample concentrations were between 0.048 and 5.69 ng/mL.

Analytical specificity

The monoclonal antibodies used in the Elecsys β-CrossLaps/serum assay recognize all fragments of type I collagen containing the β-8AA octapeptide twice. No cross-reactivity detectable with osteocalcin, parathyroid hormone (PTH) or bone Alkaline phosphatase (ALP).

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Elecsys β-CrossLaps/serum

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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.

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 after reconstitution or mixing
GTIN	Global Trade Item Number

CE 0123

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