Elecsys proBNP II

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REF		Σ	SYSTEM
			cobas e 411
09315268190	09315268500	100	**cobas e** 601
			cobas e 602

English

System information

For **cobas e** 411 analyzer: test number 2570
cobas e 601 and **cobas e** 602 analyzers: Application Code Number 574

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 test can help in the cardiovascular risk assessment of patients with type 2 diabetes mellitus.[21,22,23,24,25,26,27,28,29] The test is further indicated to aid in the identification of patients at risk with type 2 diabetes mellitus, without known history of cardiovascular disease, to optimize cardioprotective treatment.[30]

This test can be used to identify elderly individuals at high-risk for atrial fibrillation.[31]

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

Biology of natriuretic peptides

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).[32,33]

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.[34,35,36]

Definition of heart failure

Heart failure (HF) 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 HF.[1,2]

HF 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 HF.[1,2,3]

Based on the symptoms, the severity of HF is classified in stages (New York Heart Association classification [NYHA] I-IV).[1,2]

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

Clinical relevance of NT-proBNP in HF

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).[33,34]

Several studies have demonstrated the significant role of natriuretic peptide testing, including NT-proBNP, in HF 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.[1,2,3]

NT-proBNP in the diagnosis of HF

The European Society of Cardiology HF 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]

When patients are grouped according to their NYHA classification, NT-proBNP levels increase with increasing NYHA class and reflect the severity of cardiac impairment.[10]

The test is also useful in the early stages of HF, 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 in the management of HF in hospital setting

In patients hospitalized for acute decompensated HF, 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.[16,37,38,39,40] 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]

NT-proBNP in the management of HF in outpatient setting

In chronic heart failure (CHF), serial measurement of NT-proBNP concentration can be used to monitor the disease progression, to predict outcomes and evaluate the success of treatment.[1,2,17,18,20,41,42]

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.[1,2,17,43] When NT-proBNP levels change during treatment of chronic HF, 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.[19,44,45] In patients treated with sacubitril-valsartan, rapid and sustained reduction of NT-proBNP levels has been observed, reflecting reduced wall stress[34] and benefits of the drug correlating with a lower rate of cardiovascular death and HF hospitalization.[20]

NT-proBNP in patients with type 2 diabetes mellitus

Several clinical studies have consistently shown a graded relationship between circulating NT-proBNP concentration and cardiovascular risk: both single measurements and changes over time predict the occurrence of subsequent cardiovascular events.[21,22,23,24,25,26,27,28,29,46,47]

In the PONTIAC study,[30] high-risk patients with type 2 diabetes mellitus but without known history of cardiovascular disease were identified by levels of NT-proBNP > 125 pg/mL. Those patients received an intensified cardiac therapeutic strategy with up-titration of renin-angiotensin system antagonists and beta-blockers to the maximum tolerated dosages. Over 2 years of follow-up, this strategy led to a reduction of the rate of hospitalization or death due to cardiac disease by 65 %.

NT-proBNP in patients with atrial fibrillation

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NT-proBNP values are an independent predictor of cardiovascular events including occurrence and recurrence of atrial fibrillation (AF).[48]

NT-proBNP levels are highly associated with prevalent atrial fibrillation in the population aged 65 and more.[49,50]

In the STROKESTOP II study,[31] all 75/76-year-old individuals residing in Stockholm region (n = 28712) were randomized in a 1:1 design to either be invited to a screening program for atrial fibrillation or to serve as a control group. Among the 6868 individuals who accepted the screening invitation, an index-ECG (30-s ECG) was recorded using a handheld one-lead device and NT-proBNP was analyzed in the 6315 participants without known atrial fibrillation. Participants were stratified into a low-risk group with NT-proBNP < 125 pg/mL and a high-risk group with NT-proBNP ≥ 125 pg/mL. Participants in the high-risk group (n = 3766) with an index-ECG showing sinus rhythm were offered an extended ECG screening (2 week intermittent ambulatory handheld ECG recordings, four times daily). This stepwise mass-screening allowed to identify 4.4 % of the high-risk participants with unknown atrial fibrillation.

In addition, NT-proBNP has been included into the "ABC stroke risk score" taking into account age, biomarkers (cTnT hs and NT-proBNP) and history of prior stroke / transient ischemic attack. The ABC stroke risk score was shown to significantly improve the prediction of stroke in AF patients compared to the widely used CHA2DS2-VASc score.[51] Results of the ENGAGE AF TIMI 48 trial evaluating the ABC stroke and the ABC bleeding risk scores (taking into account age, biomarkers GDF-15, cTnT-hs, and hemoglobin, and history of bleeding) confirmed that these scores may help to identify AF patients most likely to benefit from treatment with non-vitamin K antagonist oral anticoagulants (NOACs).[52]

NT-proBNP in other populations at risk of CVD/HF

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]

NT-proBNP can be used to identify patients at higher cardiovascular risk receiving non-cardiovascular treatments. It may be helpful in monitoring the use and dosing of cancer drugs[53] or interventions causing fluid retention or volume overload (e.g. COX-2 inhibitors, nonsteroidal anti inflammatory drugs).[54,55,56,57,58] NT-proBNP can be used before non-cardiac surgery to evaluate patients' perioperative cardiac risk.[59]

In meta-analysis including 95617 patients without history of cardiovascular disease, NT-proBNP concentration strongly predicted first-onset HF and augmented chronic heart disease and stroke prediction, suggesting that NT-proBNP could serve as a biomarker in new therapeutic approaches that integrate HF into cardiovascular disease primary prevention.[60]

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.
- 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 PBNPX.

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

Response:

P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.

Disposal:

P501	Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

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

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

Reagent handling

The 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

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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 09315292190, 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
- 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.

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 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.[61,62] 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; they reflect NT-proBNP levels in individuals without known cardiovascular disease and should not be used for the differential diagnosis of HF.

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.[63] 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.[64] 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:[65]

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

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Age (years)	N	NT-proBNP (ng/L)	
		75th percentile	97.5th percentile
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 HF.[1,3,66,67,68,69,70] NT-proBNP values < 125 pg/mL exclude cardiac dysfunction with a high level of certainty in patients with symptoms suggestive of HF 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, HF, 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 HF (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

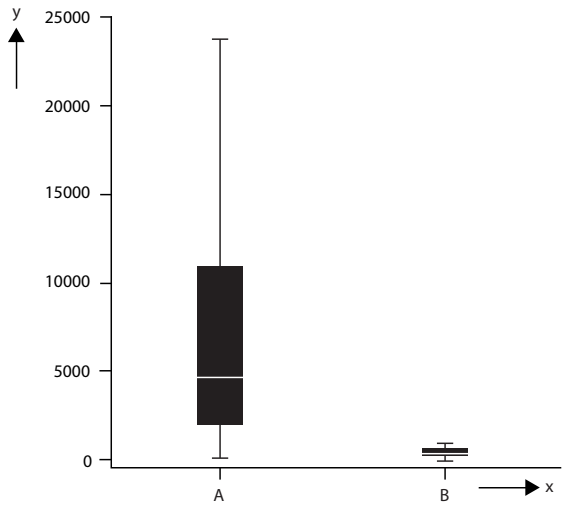
NT-proBNP values (pg/mL) for patients with reduced left ventricular ejection fraction (majority under therapy):

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
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, HF, or pulmonary disease. 720 subjects were found to be suffering from acute exacerbation of HF, 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 HF (n = 720); B: Not acute HF (n = 536)

Y --> NT-proBNP (pg/mL)

Diagnostic category	Median (IQR) NT-proBNP, pg/mL
Acute HF	4639 (1882-10818)
Not Acute HF	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 HF 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[71]

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, HF, 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

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

cobas e 411 analyzer					
	Repeatability				
Sample	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
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
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

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cobas e 601 and **cobas e** 602 analyzers					
	Intermediate precision				
Sample	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
PC CARDII2	4721	557	156	18.4	3.3

Method comparison

A comparison of the Elecsys proBNP II assay, REF 08836736190 / 09315268190 (**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[72]	Linear regression
y = 0.974x + 0.121	y = 0.956x + 90.2
τ = 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-reactivity with the following substances, tested with NT-proBNP concentrations of approximately 230 pg/mL and 2300 pg/mL (maximum 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 and the Method Sheets of all necessary components (if available in your country).

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

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

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

Symbols

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

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

CE 0123

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