

REF



SYSTEM

08836752119

08836752500

300

cobas e 801

## English

### System information

Short name	ACN (application code number)	Application
PBNP	10199	18 minutes
PBNPST	10200	9 minutes (STAT = Short Turn Around Time)

### 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.<sup>1,2,3,4,5,6,7,8</sup>

The test also aids in the assessment of heart failure severity in patients diagnosed with congestive heart failure.<sup>9,10</sup>

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

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

Note: Please note that the catalogue number appearing on the package insert retains only the first 8 digits of the licensed 11-digit Catalogue Number: 08836752190 for the Elecsys proBNP II assay. The last 3 digits -190 have been replaced by -119 for logistic purposes.

### 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.<sup>1,2,3</sup> Left ventricular dysfunction can be one of the functional precursors of heart failure.<sup>1,2</sup>

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.<sup>1,2</sup>

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  $\geq 50\%$ ; 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).<sup>1,2,3</sup> Clinical information and imaging procedures are used to confirm the diagnosis of heart failure.<sup>1,2,3</sup>

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).<sup>21,22</sup>

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.<sup>23,24,25</sup> 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).<sup>22,23</sup>

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.<sup>1,2</sup>

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.<sup>9,10</sup>

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.<sup>1,2</sup>

The European Society of Cardiology Heart Failure Guidelines recommends natriuretic peptides, including NT-proBNP, as an initial diagnostic test.<sup>1</sup> 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.<sup>1</sup>

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

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.<sup>15</sup>

In patients hospitalized for acute decompensated heart failure, pre-discharge measurement of natriuretic peptides is useful to categorize patient's risk at discharge.<sup>1,16</sup> Changes in NT-proBNP levels during hospitalization demonstrated to be a strong predictor of outcomes.<sup>16,26,27,28,29</sup> A decrease in NT-proBNP values of  $\geq 30\%$  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.<sup>16</sup>

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.<sup>1,2,17,18,20,30,31</sup>

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.<sup>1,2,17,32</sup>

When NT-proBNP levels change during treatment of chronic heart failure, decrease over the course of the disease correlates with improved clinical outcomes.<sup>1,2,18,20</sup> This interpretation of NT-proBNP results remains unchanged when using the new drug class Angiotensin receptor-neprilysin inhibitor<sup>1,2</sup> (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.<sup>19,33,34</sup> In patients treated with sacubitril-valsartan, rapid and sustained reduction of NT-proBNP levels has been observed, reflecting reduced wall stress<sup>33</sup> and benefits of the drug correlating with a lower rate of cardiovascular death and heart failure hospitalization.<sup>20</sup>

NT-proBNP can be used before non-cardiac surgery to evaluate patients' perioperative cardiac risk.<sup>35</sup>

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<sup>1,36,37</sup> or interventions causing fluid retention or volume overload (e.g. COX-2 inhibitors, nonsteroidal anti-inflammatory drugs).<sup>38,39,40,41,42,43,44,45</sup>

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.<sup>46</sup>

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

The Elecsys proBNP II assay was adapted to the Elecsys proBNP assay (first generation, REF 03121640122) with respect to analytical sensitivity, measuring range, standardization and recovery of proBNP in human samples.<sup>59</sup>

### Test principle

Sandwich principle.

Total duration of assay: 18 minutes.

- 1st incubation: Antigen in the sample (9  $\mu$ L), a biotinylated monoclonal NT-proBNP-specific antibody, and a monoclonal NT-proBNP-specific antibody labeled with a ruthenium complex<sup>9</sup> form a sandwich complex.

- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.

Total duration of assay: 9 minutes.

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

For both assay applications:

- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the **cobas** link.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex (Ru(bpy)<sub>3</sub><sup>2+</sup>)

### Reagents - working solutions

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

- M Streptavidin-coated microparticles, 1 bottle, 12.4 mL:  
Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 Anti-NT-proBNP-Ab~biotin, 1 bottle, 21.0 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)<sub>3</sub><sup>2+</sup>, 1 bottle, 19.7 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.

Exercise the normal precautions required for handling all laboratory reagents.

Disposal of all waste material should be in accordance with local guidelines. 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:

2-methyl-2H-isothiazol-3-one hydrochloride

EUH 208 May produce an allergic reaction.

Product safety labeling follows EU GHS guidance.

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

### Reagent handling

The Elecsys proBNP II assay can be used for both the 9-minute application and the 18-minute application.

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

All information required for correct operation is available via the **cobas** link.

### Storage and stability

Store at 2-8 °C.

Do not freeze.

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

Stability:	
unopened at 2-8 °C	up to the stated expiration date
on the <b>cobas e</b> 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<sub>2</sub>-EDTA and K<sub>3</sub>-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 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] 08884277190, CalSet proBNP II, for 4 x 1.0 mL
  - [REF] 04917049190, PreciControl Cardiac II, for 2 x 2.0 mL
  - [REF] 07299001190, Diluent Universal, 45.2 mL sample diluent
  - 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 the Elecsys proBNP assay ([REF] 03121640122). This in turn is traceable to pure synthetic NT-proBNP (1-76) by weight.

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 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 **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 pmol/L or pg/mL).

Conversion factors:  $\text{pmol/L} \times 8.457 = \text{pg/mL}$   
 $\text{pg/mL} \times 0.118 = \text{pmol/L}$

### 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).

#### Pharmaceutical substances

In vitro tests were performed on 16 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	75.0
Digoxin	0.25
Epinephrine (Adrenaline)	0.50
Insulin	1.60
Lidocaine	80.0

Drug	Concentration tested mg/L
Lisinopril	10.0
Methylprednisolone	7.50
Metoprolol	150
Nifedipine	30.0
Phenprocoumon (Marcumar)	3.00
Propafenone	300
Reteplase	33.3
Simvastatin	30.0
Spironolactone	75.0
Tolbutamide	1500
Torsemide	15.0
Verapamil	240

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 < Limit of Detection) 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

5-35000 pg/mL or 0.6-4130 pmol/L (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 5 pg/mL (< 0.6 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 = 3 pg/mL (0.4 pmol/L)

Limit of Detection = 5 pg/mL (0.6 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 Blank is the 95<sup>th</sup> percentile value from  $n \geq 60$  measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation 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. The recommended dilution is 1:2 (either automatically by the analyzer 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 analyzer, 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

Some of the following clinical data was obtained using the Elecsys proBNP assay (first generation, REF 03121640122). All data sets established with the first test generation are marked with an index <sup>59</sup>.

### 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.<sup>47,48</sup> 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.<sup>49</sup> 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	95 <sup>th</sup> percentile	97.5 <sup>th</sup> percentile	99 <sup>th</sup> percentile	Median	95 <sup>th</sup> percentile	97.5 <sup>th</sup> percentile	99 <sup>th</sup> 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.<sup>50</sup> 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	25 <sup>th</sup> percentile	75 <sup>th</sup> percentile	N	Median	25 <sup>th</sup> percentile	75 <sup>th</sup> 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

Furthermore, NT-proBNP concentration was also determined in the pediatric population aged between 1 and 18 with values ranging between 112 and 370 ng/L (97.5<sup>th</sup> percentile).<sup>51,59</sup>

## Recommended cutoffs in patients for diagnosis of chronic heart failure in non-acute onset<sup>59</sup>

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.<sup>1,3,52,53,54,55,56</sup> 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 %.<sup>1</sup>

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<sup>59</sup>

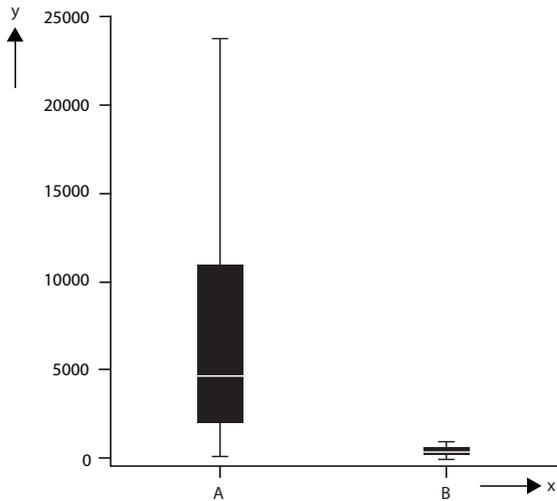
NT-proBNP values (pg/mL) for patients with reduced left ventricular ejection fraction (majority under therapy):

	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
5 <sup>th</sup> percentile	32.9	103	126	148
95 <sup>th</sup> 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<sup>10,59</sup>

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:<sup>10</sup>



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 %
<i>Rule in cut-point</i>						
< 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
<i>Rule out cut-point</i>						
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<sup>57</sup>

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 [25-75<sup>th</sup> 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<sup>10</sup> are shown in the table below for both populations:

Category	Optimal cut-point pg/mL	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
<i>Rule in cut-point</i>						
< 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
<i>Rule out cut-point</i>						
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 analyzer is 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 801 analyzer (18-minute application)					
Sample	Repeatability				
	Mean		SD		CV %
	pg/mL	pmol/L	pg/mL	pmol/L	
Human serum 1	20.2	2.38	1.87	0.221	9.2
Human serum 2	67.7	7.99	1.86	0.219	2.8
Human serum 3	145	17.1	2.84	0.335	2.0
Human serum 4	462	54.5	9.87	1.16	2.1
Human serum 5	1014	120	17.2	2.03	1.7
Human serum 6	2088	246	42.8	5.05	2.0
Human serum 7	16399	1935	274	32.3	1.7
Human serum 8	33786	3987	731	86.3	2.2

cobas e 801 analyzer (18-minute application)					
Sample	Repeatability				
	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
PC CARDII <sup>b)</sup> 1	140	16.5	2.11	0.249	1.5
PC CARDII2	4846	572	89.3	10.5	1.8

b) PC CARDII = PreciControl Cardiac II

cobas e 801 analyzer (18-minute application)					
Sample	Intermediate precision				
	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
Human serum 1	20.2	2.38	2.52	0.297	12.5
Human serum 2	67.7	7.99	2.69	0.317	4.0
Human serum 3	145	17.1	4.86	0.573	3.4
Human serum 4	462	54.5	14.8	1.75	3.2
Human serum 5	1014	120	30.9	3.65	3.0
Human serum 6	2088	246	73.2	8.64	3.5
Human serum 7	16399	1935	553	65.3	3.4
Human serum 8	33786	3987	1153	136	3.4
PC CARDII1	140	16.5	4.07	0.480	2.9
PC CARDII2	4846	572	141	16.6	2.9

cobas e 801 analyzer (9-minute application)					
Sample	Repeatability				
	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
Human serum 1	20.8	2.45	0.677	0.080	3.3
Human serum 2	65.1	7.68	1.51	0.178	2.3
Human serum 3	138	16.3	2.36	0.278	1.7
Human serum 4	443	52.3	8.74	1.03	2.0
Human serum 5	970	114	17.0	2.01	1.7
Human serum 6	2012	237	33.4	3.94	1.7
Human serum 7	17514	2067	261	30.8	1.5
Human serum 8	33353	3936	679	80.1	2.0
PC CARDII1	148	17.5	2.20	0.260	1.5
PC CARDII2	5229	617	85.4	10.1	1.6

cobas e 801 analyzer (9-minute application)					
Sample	Intermediate precision				
	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
Human serum 1	20.8	2.45	0.961	0.113	4.6
Human serum 2	65.1	7.68	2.09	0.247	3.2
Human serum 3	138	16.3	4.27	0.504	3.1
Human serum 4	443	52.3	13.0	1.53	2.9
Human serum 5	970	114	25.0	2.95	2.6
Human serum 6	2012	237	54.6	6.44	2.7
Human serum 7	17514	2067	565	66.7	3.2
Human serum 8	33353	3936	939	111	2.8
PC CARDII1	148	17.5	3.89	0.459	2.6

cobas e 801 analyzer (9-minute application)					
Sample	Intermediate precision				
	Mean		SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%
PC CARDII2	5229	617	137	16.2	2.6

### Method comparison

a) A comparison of the Elecsys proBNP II assay (18-minute application; y), [REF] 08836752190 with the Elecsys proBNP II assay (18-minute application; x), [REF] 07027664190 on the **cobas e 801** analyzer gave the following correlations (pg/mL):

Number of samples measured: 163

Passing/Bablok <sup>58</sup>	Linear regression
$y = 1.02x + 1.66$	$y = 1.02x - 3.92$
$\tau = 0.991$	$r = 1.00$

The sample concentrations were between 16.8 and 34019 pg/mL (1.98 and 4014 pmol/L).

b) A comparison of the Elecsys proBNP II assay (9-minute application; y), [REF] 08836752190 with the Elecsys proBNP II assay (9-minute application; x), [REF] 07027664190 on the **cobas e 801** analyzer gave the following correlations (pg/mL):

Number of samples measured: 162

Passing/Bablok <sup>58</sup>	Linear regression
$y = 1.02x - 7.82$	$y = 1.01x + 64.1$
$\tau = 0.990$	$r = 1.00$

The sample concentrations were between 16.5 and 34207 pg/mL (1.95 and 4036 pmol/L).

c) A comparison of the Elecsys proBNP II assay (18-minute application), [REF] 08836752190 (**cobas e 801** analyzer; y), with the Elecsys proBNP II assay, [REF] 08836736190 (**cobas e 601** analyzer; x), gave the following correlations (pg/mL):

Number of samples measured: 162

Passing/Bablok <sup>58</sup>	Linear regression
$y = 1.03x - 3.43$	$y = 1.04x - 16.3$
$\tau = 0.985$	$r = 0.999$

The sample concentrations were between 16.8 and 34019 pg/mL (1.98 and 4014 pmol/L).

d) A comparison of the Elecsys proBNP II assay (9-minute application; y), [REF] 08836752190 with the Elecsys proBNP II assay (18-minute application; x), [REF] 08836752190 on the **cobas e 801** analyzer gave the following correlations (pg/mL):

Number of samples measured: 161

Passing/Bablok <sup>58</sup>	Linear regression
$y = 0.973x + 1.02$	$y = 0.960x + 56.2$
$\tau = 0.991$	$r = 0.999$

The sample concentrations were between 16.5 and 33783 pg/mL (1.95 and 3986 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 100 pg/mL and 2500 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

Cross-reactant	Concentration tested
ANP <sub>28</sub>	3.1 µg/mL
Arg-vasopressin	1.0 ng/mL
BNP <sub>32</sub>	3.5 µg/mL
CNP <sub>22</sub>	2.2 µg/mL
Endothelin	20 pg/mL
NT-proANP <sub>1-30</sub> (preproANP <sub>26-55</sub> )	3.5 µg/mL
NT-proANP <sub>31-67</sub> (preproANP <sub>56-92</sub> )	1.0 ng/mL
NT-proANP <sub>79-98</sub> (preproANP <sub>104-123</sub> )	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.

### 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):

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

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