proBNP II
N-terminal pro B-type natriuretic peptide

English

Intended use

Immunoaassay 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. The test also aids in the assessment of heart failure severity in patients diagnosed with congestive heart failure. This assay is further indicated for the risk stratification of patients with left ventricular dysfunction. The test is also useful in assigning symptoms to cardiac or non-cardiac causes, and helps to identify subjects with left ventricular dysfunction. The European Society of Cardiology Task Force for the Diagnosis and Treatment of Chronic Heart Failure recommend in their guidelines that natriuretic peptides including NT-proBNP "may be most useful clinically as a rule out test due to consistent and very high negative predictive values". When used with the recommended cutoff values, the Elecsys proBNP assay yields negative predictive values ranging from 97% to 100% depending on age and gender. Changes in NT-proBNP concentration can be used to evaluate the success of treatment in patients with left ventricular dysfunction. In addition NT-proBNP is suitable for use in assessing vascular remodelling, and therefore contributes to the establishment of individualized rehabilitation procedures.

The significance of natriuretic peptides in the control of cardiovascular system function has been demonstrated. Studies reveal that natriuretic peptides can be used for diagnostic clinical problems associated with left ventricular dysfunction. The following natriuretic peptides have been described: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). 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. 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).

Studies indicate that NT-proBNP can be used in diagnostic and prognostic applications. The concentration of NT-proBNP in serum or plasma correlates with the prognosis of the left ventricular dysfunction. Fisher, et al. found that congestive heart failure patients with NT-proBNP values above median had a one year mortality rate of 53% compared to 11% in patients below median. In the GUSTO IV study which involved more than 6800 patients it was shown that NT-proBNP was the strongest independent predictor of one year mortality in patients with acute coronary syndrome.

In the ICON (International Collaborative of NT-proBNP) study which involved more than 1256 patients presenting acute shortness of breath at their admission in the emergency department, it was shown that evaluating NT-proBNP can increase the specificity and accuracy for diagnosing heart failure in patients presenting acute dyspnea in the emergent setting.

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 antibody labeled with a ruthenium complex form a sandwich complex. The reaction mixture is aspirated into the measuring cell where the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex is washed away with ProCell/ProCell M, which removes unbound substances.
- 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.

Reagents - working solutions

The reagent pack is labeled as PRO IBNP II.

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 mM/L, pH 5.8; preservative.

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: 04842464180 for the Elecsys proBNP II assay. The last 3 digits -190 have been replaced by -119 for logistic purposes.
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R2 Anti-NT-proBNP-Ab–Li2Ru(bpy)3 (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.
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.
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-to-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 °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:
<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>unopened at 2 °C</td>
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<tr>
<td></td>
<td>expiration date</td>
</tr>
<tr>
<td>after opening at 2 °C</td>
<td>12 weeks</td>
</tr>
<tr>
<td>on the analyzers</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

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.
LH2, LH3 (heparin), K2 (EDTA) and K3 (EDTA) plasma.
Criterion: Recovery within 90 ± 10 % of serum value or slope 0.9 ± 1 + intercept within < ± 2x analytical sensitivity (LLD) + coefficient of correlation > 0.95.
Stable for 3 days at 20–25 °C, 6 days at 2 °C, 24 months at 20 °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 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)
- 04842472190, proBNP II CatSet, for 4 x 1 mL
- 04917049190, PreciControl Cardiac II, for 2 x 2 mL each of PreciControl Cardiac II 1 and 2
- 11732277122, Diluent Universal, 2 x 16 mL sample diluent or 03183971122, Diluent Universal, 2 x 36 mL sample diluent
- General laboratory equipment
- Elecsys 2010, MODULAR ANALYTICS E170 or cobas e analyzer

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.
MODULAR ANALYTICS E170, cobas e 601 and cobas e 602 analyzers:
RePreclean 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 proBNP assay (03121640).
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). 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. Follow the applicable government regulations and local guidelines for quality control.
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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 assay is unaffected by icterus (bilirubin < 428 µmol/L or < 25 mg/dL), hemolysis (Hb < 0.621 mmol/L or < 1.0 g/dL), lipemia (Intralipid < 17.1 mmol/L or < 1500 mg/dL) and biotin (< 123 nmol/L or < 30 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 rheumatoid factors up to a concentration of 1500 IU/mL.

There is no high-dose hook effect at NT proBNP concentrations up to 33400 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 titer 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
5 pmol/L - 6.0 pg/mL and 0.6 pg/mL (defined by the lower detection limit and the maximum of the master curve). Values below the lower detection limit 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 (8277 pmol/L) for 2-fold diluted samples.

Lower limits of measurement
Lower detection limit of the test
Lower detection limit: 5 pg/mL (0.6 pmol/L)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying two standard deviations above that of the lowest standard (master calibrator, standard 1 + 2 SD, repeatability study, n = 21).

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 MODULAR ANALYTICS E170, Elecsys 2010 or cobas e 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 MODULAR ANALYTICS E170, Elecsys 2010 and cobas e 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
The following clinical data had been obtained using the Elecsys proBNP assay (first generation, REF 03121640122). All data sets established with the first test generation are marked with an index42.

Interpretation of NT proBNP values42
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.35,36

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).35

Cutoff values42
A number of studies support a decision threshold for NT proBNP of 125 pg/mL. 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.37,38 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).

Recommended cutoffs in patients with diagnosed stable chronic heart failure
Patients with stable heart failure (n = 721) were compared to the reference group (n = 2264).

ROC plot analysis at the cutoff value of 125 pg/mL showed a sensitivity of 88 %, a specificity of 92 %, a negative predictive value (NPV), and a positive predictive value (PPV) of 96.7 % and 80.6 %, respectively.

Expected values42
NT proBNP concentrations in the reference group are shown in the following tables. The most appropriate decision threshold apparent from these distributions is 125 pg/mL.

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

Reference group42
The circulating NT proBNP concentration was determined in samples from 1981 blood donors aged between 18 and 65 as well as 283 elderly patients aged between 50 and 90; both populations without known cardiac risks, symptoms or medical history.

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 (97.5th percentile).39

The descriptive statistics for NT proBNP concentrations (pg/mL) in the reference group are shown in the following table:

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>95th percentile</th>
<th>97.5th percentile</th>
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<tbody>
<tr>
<td>18-44</td>
<td>1323</td>
<td>35.6</td>
<td>30.2</td>
<td>20.4</td>
<td>97.3</td>
<td>115</td>
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<tr>
<td>45-54</td>
<td>408</td>
<td>49.3</td>
<td>63.3</td>
<td>30.7</td>
<td>121</td>
<td>172</td>
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<tr>
<td>55-64</td>
<td>398</td>
<td>72.6</td>
<td>84.4</td>
<td>47.3</td>
<td>198</td>
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<tr>
<td>65-74</td>
<td>102</td>
<td>107</td>
<td>85.9</td>
<td>85.1</td>
<td>285</td>
<td>349</td>
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<tr>
<td>≥ 75</td>
<td>33</td>
<td>211</td>
<td>152</td>
<td>174</td>
<td>526</td>
<td>738</td>
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<tr>
<td>Total</td>
<td>2264</td>
<td>50.3</td>
<td>62.4</td>
<td>27.9</td>
<td>149</td>
<td>196</td>
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Males

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<tr>
<th>Age (years)</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>95th percentile</th>
<th>97.5th percentile</th>
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<td>45-54</td>
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<td>21.6</td>
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<td>121</td>
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<td>55-64</td>
<td>259</td>
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<td>74.5</td>
<td>37.7</td>
<td>161</td>
<td>210</td>
</tr>
<tr>
<td>65-74</td>
<td>61</td>
<td>105</td>
<td>87.9</td>
<td>83.9</td>
<td>241</td>
<td>376</td>
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<td>≥ 75</td>
<td>13</td>
<td>163</td>
<td>116</td>
<td>151</td>
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<td>Total</td>
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<td>39.8</td>
<td>55.3</td>
<td>20.0</td>
<td>113</td>
<td>169</td>
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<table>
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<tr>
<th>Females</th>
<th>Age (years)</th>
<th>N</th>
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<th>Median</th>
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<td></td>
<td>18-44</td>
<td>508</td>
<td>48.2</td>
<td>32.8</td>
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<td>116</td>
<td>130</td>
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<td>≥ 75</td>
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<td>243</td>
<td>167</td>
<td>191</td>
<td>738</td>
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<td>69.3</td>
<td>47.8</td>
<td>177</td>
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Correlation of NT proBNP with NYHA classification in patients diagnosed with CHF

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<th>Median</th>
<th>95th percentile</th>
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<tr>
<td>Human serum 1</td>
<td>44.0</td>
<td>5.19</td>
<td>1.84</td>
<td>0.22</td>
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<tr>
<td>Human serum 2</td>
<td>126</td>
<td>14.9</td>
<td>3.06</td>
<td>0.36</td>
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</tr>
<tr>
<td>Human serum 3</td>
<td>2410</td>
<td>284</td>
<td>31.7</td>
<td>3.74</td>
<td>1.3</td>
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<tr>
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<td>3966</td>
<td>922</td>
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<td>2.7</td>
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<tr>
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<td>82.0</td>
<td>9.68</td>
<td>2.11</td>
<td>0.25</td>
<td>2.58</td>
</tr>
<tr>
<td>PC CARDII</td>
<td>2318</td>
<td>274</td>
<td>27.3</td>
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Intermediate precision

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Repeatability

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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 modified protocol (EPS I) of the CLSI (Clinical and Laboratory Standards Institute); 6 times daily for 10 days (n = 60); repeatability on MODULAR ANALYTICS E170 analyzer, n = 21. The following results were obtained:

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Method comparison
A comparison of the Elecsys proBNP II assay (y) with the Elecsys proBNP assay (x) using clinical samples gave the following correlations (pg/mL): Number of samples measured: 2133

y = 0.977x + 1.89

The sample concentrations were between approximately 5 and 30022 pg/mL (approximately 0.6 and 3543 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): 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 (3.1 µg/mL), Arg Vasopressin (1.0 ng/mL), BNP (3.5 µg/mL), CNP (2.2 µg/mL), endothelin (20 pg/mL) NT proANP (3.5 µg/mL), NT proANP (3.5 µg/mL), renin (50 ng/mL), urodilatin (3.5 µg/mL).
**proBNP II**

**N-terminal pro B-type natriuretic peptide**

**Functional sensitivity**

50 pg/mL (5.9 pmol/L)

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

**References**


proBNP II
N-terminal pro B-type natriuretic peptide

41 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
42. Data established with the Elecsys proBNP assay (first generation,
REF 03121640122).

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.

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