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# Roche CARDIAC proBNP+

**cobas**<sup>®</sup>

N-terminal pro B-type natriuretic peptide

REF



SYSTEM

05533643190

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cobas h 232

05533643191

## English

### Intended use

The Roche CARDIAC proBNP+ is an in vitro diagnostic test for the quantitative determination of NT-proBNP in heparinised venous blood for use with the **cobas h 232** instrument. The Roche CARDIAC proBNP+ test serves as an aid in the diagnosis of patients with suspected heart failure, in the monitoring of patients with compensated left ventricular dysfunction and in the risk stratification of patients with acute coronary syndromes.

The test is intended for near-patient testing.

Not for self-testing.

### Summary

NT-proBNP is a physiologically inactive fragment which is released when the active hormone BNP is cleaved from its precursor protein proBNP. Synthesis of the precursor protein in the cardiomyocytes is controlled by mechanical factors (dilatation of the ventricular wall) and neurohormonal factors (noradrenalin and angiotensin II). The secretion of NT-proBNP into the blood as a result of cleavage correlates directly with an increase in ventricular volume and ventricular pressure in heart failure. Consequently, when the concentration of NT-proBNP in the blood is low, cardiac dysfunction can be ruled out with high probability. Although the normal range for NT-proBNP is subject to gender and age-specific variability, a clinical cut-off of 125 pg/mL allows sufficient diagnostic accuracy.

Nevertheless, NT-proBNP values should always be interpreted in conjunction with the medical history, clinical findings and other diagnostic information (imaging methods and laboratory results).

The Roche CARDIAC proBNP+ test is intended to be used in professional non-critical care and critical care environments such as general practitioner's offices, hospital wards, and intensive care units.

### Test principle

The test contains 1 monoclonal and 1 polyclonal antibody against epitopes of the NT-proBNP molecule of which one is gold-labelled and the other biotinylated. The antibodies form a sandwich complex with the NT-proBNP in the blood. Following removal of erythrocytes from the sample, plasma passes through the detection zone in which the gold-labelled NT-proBNP sandwich complexes accumulate and the positive signal is displayed as a reddish line (the signal line). Excess gold-labelled antibodies accumulate along the control line, signalling that the test was valid. The intensity of the signal line increases in proportion to the NT-proBNP concentration.

The optical system of the instrument detects the 2 lines and measures the intensity of the signal line. The integrated software converts the signal intensity to a quantitative result and shows it in the display.

### Reagents

1 test contains:

- Biotinylated polyclonal anti-NT-proBNP antibodies > 0.4 µg
- Gold-labelled monoclonal anti-NT-proBNP antibodies > 0.1 µg
- Buffer and non-reactive components > 2.0 mg

### 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.

### Storage and stability

Until the printed expiration date at 2-8 °C.

Up to 1 week at room temperature (15-25 °C).

The test can be used immediately after removal from the refrigerator.

The test must be used within 15 minutes once the pouch has been opened.

**Sample stability:** 8 hours at room temperature. Do not refrigerate or freeze sample.

### Specimen collection and preparation

Use **heparinized venous whole blood** only.

Do not use other anticoagulants, capillary blood, serum or plasma, blood collection tubes containing EDTA, citrate, sodium fluoride or other additives.

The following heparin blood collection tubes have been tested: Sarstedt Monovette, Becton Dickinson Vacutainer, Becton Dickinson Vacutainer PST II, Greiner Vacuette. In the case of Sarstedt Monovettes, only tubes without separating gel are suitable.

No data is available for blood collection tubes supplied by other manufacturers. An influence on the test result in individual cases cannot be ruled out.

**Sample volume:** 150 µL

### Materials provided

- REF 05533643190, REF 05533643191 Roche CARDIAC proBNP+ test
- 1 code chip

### Materials required (but not provided)

- REF 11622889190, Roche CARDIAC Pipettes, 20 disposable syringes, 150 µL (or other suitable pipettes with pipetting volume of 150 µL)
- REF 04890493190, Roche CARDIAC Control proBNP (2 x 1 mL)
- REF 04880668190, Roche CARDIAC IQC
- REF 04901126190, **cobas h 232** instrument (software version ≥ 01.04.01)
- REF 04901142190, **cobas h 232** instrument with scanner (software version ≥ 01.04.01)

General laboratory equipment

### Calibration

Each test strip lot of the Roche CARDIAC proBNP+ test is calibrated against the Elecsys proBNP test.

The instrument automatically reads in the lot-specific calibration data from the code chip, eliminating the need for calibration by the user.

Calibration has been performed so that the results obtained are comparable to those obtained using the Elecsys proBNP reference method with heparin plasma as the sample material.

### Lot code

Every kit contains a lot-specific code chip. The instrument display prompts the user to insert the chip. To ensure that the code chip and test strip lot match, compare the lot number in the display with the number on the code chip. The code chip provides the instrument with all required lot-specific information. An error message is displayed if the wrong code chip is inserted for a test strip lot.

### Quality control

For quality control, use Roche CARDIAC Control proBNP.

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.

### Display of results

At the end of the reaction time, the **cobas h 232** instrument shows the result in the display. The reaction time for the Roche CARDIAC proBNP+ test to display a quantitative result is 12 minutes. In addition, approximately 2 minutes are required for sample detection. Depending on the measured concentration, the result may be displayed in different ways.

| NT-proBNP concentration         | Result displayed                |
|---------------------------------|---------------------------------|
| less than 60 pg/mL              | proBNP < 60 pg/mL               |
| between 60 pg/mL and 9000 pg/mL | for example "proBNP 2000 pg/mL" |
| greater than 9000 pg/mL         | proBNP > 9000 pg/mL             |



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When the measured concentration is significantly higher than 9000 pg/mL, the instrument displays "proBNP > 9000 pg/mL" after 5 minutes.

## Limitations - interference

The assay is unaffected by icterus (bilirubin  $\leq$  30 mg/dL), hemolysis (Hb  $\leq$  178 mg/dL), lipemia (triglycerides  $\leq$  300 mg/dL), haematocrit values in the range of 30-50 %, and biotin  $\leq$  200 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 300 IU/mL.

High concentrations of lipoic acid (e. g. in pharmaceuticals or as food additive) can lead to lower measurement values.

There is no high-dose hook effect at analyte concentrations up to 30000 pg/mL. Very high concentrations of NT-proBNP (approx. > 25000 pg/mL) may cause the control line to fail to appear and the instrument may display an error message. In this case, determination must be carried out using another method, like the Elecsys proBNP test.

Patient samples may contain heterophilic antibodies which could react in immunoassays to give falsely elevated or decreased results. Reasons for the presence of heterophilic antibodies might be for example elevated levels of rheumatoid factors or the treatment of patients with monoclonal mouse antibodies for therapeutic or diagnostic purposes.

The Roche CARDIAC proBNP+ test contains ingredients that minimise interference from heterophilic antibodies. However, complete elimination of interference from all samples cannot be guaranteed. Interferences caused by pharmaceuticals at therapeutic concentrations are not known.

No interferences of the following special cardiac drugs have been observed up to the specified concentrations:

Amlodipine (0.075 mg/L), Evolocumab (300 mg/L), Atorvastatin (0.15 mg/L), Canagliflozin (60 mg/L), Carvedilol (50 mg/L), Clopidogrel (75 mg/L), Dabigatran (525 mg/L), Digoxin (0.5 mg/L), Epinephrine (Adrenaline) (0.5 mg/L), Insulin (1.6 mg/L), Isosorbide mononitrate (2.21 mg/L), Lidocaine (20 mg/L), Liraglutide (0.168 mg/L), Lisinopril (8 mg/L), Methylprednisolone (80 mg/L), Metoprolol (150 mg/L), Phenprocoumon (Marcumar) (15 mg/L), Propafenone (180 mg/L), Reteplase (6.66 mg/L), Rivaroxaban (8 mg/L), Sacubitril (194.4 mg/L), Spironolactone (400 mg/L), Tolbutamide (300 mg/L), Torasemide (200 mg/L), Valsartan (205.6 mg/L), Verapamil (240 mg/L).

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

## Measuring range

60–9000 pg/mL.

## Expected values

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>1</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 for men and women:

| 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                         |

*Recommended cutoffs 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 settings for the diagnosis of heart failure.<sup>2,3,4,5,6,7,8</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  $\geq$  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>2</sup>

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

ICON (International Collaborative of NT-proBNP) study<sup>9</sup> NT-proBNP concentrations were determined in samples from 1256 patients presenting with acute shortness of breath to emergency departments at 4 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. 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 (years)          | Optimal cut-point pg/mL | Sensitivity % | Specificity % | PPV % | NPV % | Accuracy % |
|---------------------------|-------------------------|---------------|---------------|-------|-------|------------|
| <i>Rule in cut-point</i>  |                         |               |               |       |       |            |
| < 50 (n = 184)            | 450                     | 97            | 93            | 76    | 99    | 94         |
| 50-75 (n = 537)           | 900                     | 90            | 82            | 83    | 88    | 85         |
| > 75 (n = 535)            | 1800                    | 85            | 73            | 92    | 55    | 83         |
| <i>Rule out cut-point</i> |                         |               |               |       |       |            |
| All patients (n = 1256)   | 300                     | 99            | 60            | 77    | 98    | 83         |

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

## Specific performance data

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

## Precision

Repeatability was measured with 3 lots in 6 hospitals. Pooled coefficient of variation resulting from 10-fold serial testing with patient heparin blood samples were 9.2 % in the low medically relevant concentration range (60 to 225 pg/mL), 6.9 % in the medium concentration range (226 to 1200 pg/mL) and 9.2 % in the high concentration range (1201 to 9000 pg/mL) of the assay. The upper one-sided 95 % confidence limit of the pooled coefficient of variation was below 9.0 % over the entire measurement range.

Intermediate precision was measured with control level 1 and control level 2 in 6 hospitals. The upper one-sided 95 % confidence limit of the pooled coefficient of variation was 11.6 % with level 1 and 12.0 % with level 2.

## Method comparison

Representative comparison of 3 lots of the Roche CARDIAC proBNP+ test with the Elecsys proBNP II test in a clinical patient population showed slopes between 1.03 and 1.16. The correlation coefficient Pearson r in these method comparisons were  $\geq$  0.95.<sup>10</sup>

## References

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CE 0123



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For further information, please refer to the appropriate Operators Manual for the analyzer concerned, and the Method Sheets of all necessary components.

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 [navifyportal.roche.com](http://navifyportal.roche.com) for definition of symbols used):



Device for near-patient testing



Device not for self-testing.

SYSTEM

Analyzers/Instruments on which reagents can be used

GTIN

Global Trade Item Number

UDI

Unique Device Identifier

PZN

Pharmazentralnummer (for Germany only)

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