09213031001V2.0

Roche CARDIAC POC NT-proBNP cobas®

N-terminal pro B-type natriuretic peptide

REF	Σ	SYSTEM
09213074190 09213074191	10	**cobas h** 232

English

Intended use

The Roche CARDIAC POC NT-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 POC NT-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 can help in the cardiovascular risk assessment of patients with type 2 diabetes mellitus. The test is further indicated to aid in the identification of patients at cardiovascular risk with type 2 diabetes mellitus without known history of cardiovascular disease to optimize cardioprotective treatment. The test can be used to identify elderly individuals at high-risk for atrial fibrillation.

The test is intended for near-patient testing.
Not for self-testing.

Summary

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]

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
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]

NT-proBNP in the management of HF in hospital setting
In patients hospitalized for acute decompensated HF, changes in NT-proBNP levels during hospitalization demonstrated to be a strong predictor of outcomes.[4,5,6,7] 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.[4]

NT-proBNP in the management of HF in outpatient setting
In chronic HF, serial measurement of NT-proBNP concentration can be used to monitor the disease progression. 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.[1,2,8,9]
When NT-proBNP levels change during treatment of chronic HF, decrease over the course of the disease correlates with improved clinical outcomes.[1,2,10,11] 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 patients treated with sacubitril-valsartan, rapid and sustained reduction of NT-proBNP levels has been observed, reflecting reduced wall stress and benefits of the drug correlating with a lower rate of cardiovascular death and HF hospitalization.[11]

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 predicted the occurrence of subsequent cardiovascular events.[12,13,14,15,16,17,18,19,20]

In the PONTIAC study[21], high-risk patients with type 2 diabetes mellitus but without known history of cardiac 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
NT-proBNP levels are highly associated with prevalent atrial fibrillation in the population aged 65 and more.[22,23] In the STROKESTOP II study[24] performed with 75/76-year-old individuals, participants at high risk for atrial fibrillation (NT-proBNP ≥ 125 ng/L) were offered an extended ECG-screening, allowing to identify 4.4 % of the high-risk participants with unknown atrial fibrillation.

NT-proBNP in other populations at risk of CVD/HF
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[25] or interventions causing fluid retention or volume overload (e.g. COX-2 inhibitors, nonsteroidal anti-inflammatory drugs).[26,27,28,29,30]
NT-proBNP can be used before non-cardiac surgery to evaluate patients' perioperative cardiac risk.[31]

The Roche CARDIAC POC NT-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.

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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 09213074190, REF 09213074191 Roche CARDIAC POC NT-proBNP
- 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 09302344190, Roche CARDIAC POC NT-proBNP Control (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 POC NT-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 POC NT-proBNP Control.

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 POC NT-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

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 ≤ 30 mg/dL), hemolysis (Hb ≤ 178 mg/dL), lipemia (triglycerides ≤ 300 mg/dL), haematocrit values in the range of 30-50 %, and biotin ≤ 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.

Roche CARDIAC POC NT-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.

Clinical data

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

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.[32] 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

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Age (years)	Men				Women			
	Median	95th percentile	97.5th percentile	99th percentile	Median	95th percentile	97.5th percentile	99th percentile
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.[1,3,33,34,35,36,37]

NT-proBNP values < 125 pg/mL exclude cardiac dysfunction with a high level of certainty in patients with symptoms suggestive of heart failure e.g. dyspnea. NT-proBNP values ≥ 125 pg/mL may indicate cardiac dysfunction and are associated with an increased risk of cardiac complications (myocardial infarction, heart failure, death). At the cut-off value, ESC Guidelines state that natriuretic peptides have a very high negative predictive value (NPV) comprised between 94 % and 98 % and a positive predictive value (PPV) comprised between 44 % and 57 %.[1]

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

ICON (International Collaborative of NT-proBNP) study[38] 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 %**
Rule in cut-point						
< 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
Rule out cut-point						
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

Equivalence of Roche CARDIAC POC NT-proBNP and Roche CARDIAC proBNP+ was shown. Data presented here were obtained with the Roche CARDIAC proBNP+ and are representative for both tests.

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 test strip lots 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 ≥ 0.95.[39]

References

1 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.Eur J Heart Fail 2016;18(8):891-975.

2 Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology. Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013 15;128(16):1810-1852.

3 Taylor CJ, Rutten FH, Brouwer JR, Hobbs FR.Practical guidance on heart failure diagnosis and management in primary care: recent EPCCS recommendations. Br J Gen Pract. 2017;67(660):326-327.

4 Bettencourt, P., Azevedo A, Pimenta J, et al. N-Terminal-Pro-Brain Natriuretic Peptide Predicts Outcome After Hospital Discharge in (2004). Circulation;110(15):2168-74.

5 Salah K, Kok WE, Eurlings LW, et al. A novel discharge risk model for patients hospitalised for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels: a European coLlaboration on Acute decompeNsated Heart Failure: ELAN-HF Score. Heart. 2014 Jan;100(2):115-25.

6 Stienen S, Salah K, Dickhoff C, et al. N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) Measurements Until a 30% Reduction Is Attained During Acute Decompensated Heart Failure Admissions and Comparison With Discharge NT-proBNP Levels: Implications for In-Hospital Guidance of Treatment. J Card Fail. 2015 Nov;21(11):930-4.

7 Stienen S, Salah K, Eurlings LW, et al. Challenging the two concepts in determining the appropriate pre-discharge N-terminal pro-brain natriuretic peptide treatment target in acute decompensated heart failure patients: absolute or relative discharge levels? Eur J Heart Fail. 2015 Sep;17(9):936-44.

8 Masson S,Latini R, Anand IS, et al. Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). J Am Coll Cardiol. 2008 Sep 16;52(12):997-1003.

9 Masson S, Latini R, Anand IS, et al. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. Clin Chem. 2006;52:1528–1538.

10 Januzzi JL, Throughton R. Are Serial BNP Measurements Useful in Heart Failure Management? Serial Natriuretic Peptide Measurements Are Useful in Heart Failure Management. Circulation. 2013;127:500-508.

11 Zile MR, Claggett BL, Prescott MF et al. Prognostic Implications of changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure. J Am Coll Cardiol. 2016;68:2425-36.

12 Scirica BM, Braunwald E, Raz I, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation. 2014;130:1579-88.

13 Bergmark BA, Morrow DA, Bhatt DL, et al. Natriuretic peptides versus a clinical history of heart failure for risk prediction in patients with diabetes. J Am Coll Cardiol. 2019; 73(19):681.

14 Bidadkosh A, Lambooy SPH, Heerspink HJ, et al. Predictive Properties of Biomarkers GDF-15, NTproBNP, and hs-TnT for Morbidity and Mortality in Patients With Type 2 Diabetes With Nephropathy. Diabetes Care. 2017;40(6):784-792.

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15 Hamano K, Nakadaira I, Suzuki J, et al. N-terminal fragment of probrain natriuretic peptide is associated with diabetes microvascular complications in type 2 diabetes. Vasc Health Risk Manag. 2014;10:585-9.

16 Hillis GS, Welsh P, Chalmers J, et al. The relative and combined ability of high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide to predict cardiovascular events and death in patients with type 2 diabetes. Diabetes Care. 2014;37(1):295-303.

17 Bruno G, Landi A, Barutta F, et al. N-terminal probrain natriuretic peptide is a stronger predictor of cardiovascular mortality than C-reactive protein and albumin excretion rate in elderly patients with type 2 diabetes: the Casale Monferrato population-based study. Diabetes Care. 2013;36(9):2677-82.

18 Neuhold S, Resl M, Huelsmann M, et al. Repeat measurements of glycated haemoglobin A(1c) and N-terminal pro-B-type natriuretic peptide: divergent behaviour in diabetes mellitus. Eur J Clin Invest. 2011;41(12):1292-8.

19 Wolsk E, Claggett B, Diaz R, et al. Increases in Natriuretic Peptides Precede Heart Failure Hospitalization in Patients With a Recent Coronary Event and Type 2 Diabetes Mellitus. Circulation. 2017;136(16):1560-1562.

20 Jarolim P, White WB, Cannon CP, et al. Serial measurement of natriuretic peptides and cardiovascular outcomes in patients with type 2 diabetes in the EXAMINE trial. Diabetes Care. 2018; 41(7): 1510-1515.

21 Huelsmann M, Neuhold S, Resl M, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. J Am Coll Cardiol. 2013;62(15):1365-72.

22 Patton KK, Ellinor PT, Heckbert SR, et al. N-terminal pro-B-type natriuretic peptide is a major predictor of the development of atrial fibrillation: The Cardiovascular Health Study. Circulation 2009;120:1768-1774.

23 Seegers J, Zabel M, Gruter T, et al. Natriuretic peptides for the detection of paroxysmal atrial fibrillation. Open Heart 2015;2:e000182.

24 Kemp Gudmundsdottir K, Fredriksson T, Svennberg E, et al. Stepwise mass screening for atrial fibrillation using N-terminal B-type natriuretic peptide: the STROKESTOP II study. EP Europace 2019.

25 Zamorano JL, Lancellotti P, Rodriguez Muñoz D et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(36):2768-2801.

26 Brune K, Katus HA, Moecks J, et al. N-terminal pro-B-type natriuretic peptide concentrations predict the risk of cardiovascular adverse events from antiinflammatory drugs: apilot trial. Clin Chem 2008;54(7):1149-1157.

27 Bojunga J, Sarrazin C, Hess G, et al. Elevated plasma levels of Nterminal pro-brain natriuretic peptide in patients with chronic hepatitis C during interferon-based antiviral therapy. World J Gastroenterol 2006;12(36):5875-5877.

28 Slordal L, Spigset O. Heart failure induced by non-cardiac drugs. Drug safety 2006;29(7):567-586.

29 Giannitsis E. Rationale for testing the cardiovascular risk for patients with COX-2 inhibitors on the basis of biomarker NT-proBNP. Clin Lab 2005;51(1-2):63-83.

30 Häupl T, Burmester GR, Giannitsis E, et al. N-terminal prohormone brain natriuretic peptide: a biomarker for detecting cardiovascular risks in patients with rheumatoid arthritis or osteoarthritis? Ann Rheum Dis 2007;66(6):838-839.

31 Duceppe E, Parlow J, MacDonald P, et al. Canadian cardiovascular society guidelines on perioperative cardiac risk assessment and management for patients undergoing noncardiac surgery. Can J Cardiol. 2017;33(1):17-32.

32 Tzikas S, Keller T, Wild PS, et al. Midregional pro-atrial natriuretic peptide in the general population/insights from the Gutenberg Health Study. Clin Chem Lab Med. 2013;51(5):1125-33.

33 Al-Barjas M, Nair D, Morris R, et al. How can the role of N terminal pro B Natriuretic Peptide (NT-proBNP) be optimised in heart failure screening? A prospective observational comparative study. Eur J Heart Fail 2004;3:51 Supplement 1.

34 Gustafsson F, Badskjær J, Hansen F, et al. Value of N-Terminal proBNP in the Diagnosis of Left Ventricular Systolic Dysfunction in Primary Care Patients Referred for Echocardiography. Heart Drug 2003,3:141-146.

35 Zaphiriou A, et al. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. Eur J Heart Fail. 2005;7(4):537-41.

36 Gustafsson F, et al. Diagnostic and prognostic performance of N-terminal ProBNP in primary care patients with suspected heart failure. J Card Fail. 2005;11(5 Suppl):S15-20.

37 Taylor CJ, et al. Primary care REFerral for EchocaRdiogram (REFER) in heart failure: a diagnostic accuracy study. Br J Gen Pract. 2017;67(655):e94-e102.

38 Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients The International Collaborative of NT-proBNP Study Euro Heart Journ 2006;27(3):330-337.

39 Jørgensen B, Bertsch T, Bröker H-J, et.al. Multicentre Evaluation of a Second Generation Point-of-Care Assay with an Extended Range for the Determination of N-Terminal Pro-Brain Natriuretic Peptide. Clin. Lab. 2012;58:515-525.

For further information, please refer to the appropriate Operators Manual for the instrument 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 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)

CE 0123

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