CRPHS

cobas®

Cardiac C-Reactive Protein (Latex) High Sensitive

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
04628918 190	Cardiac C-Reactive Protein (Latex) High Sensitive (300 tests)	System-ID 07 6866 9	COBAS INTEGRA 400 plus COBAS INTEGRA 800

Materials required (but not provided):

11355279 216	Calibrator f.a.s. Proteins (5 × 1 mL)	System-ID 07 6557 0	
11355279 160	Calibrator f.a.s. Proteins (5 × 1 mL, for USA)	System-ID 07 6557 0	
20766321 322	CRP T Control N (5 × 0.5 mL)	System-ID 07 6632 1	
10557897 122	Precinorm Protein (3 × 1 mL)	System-ID 07 9105 9	
10557897 160	Precinorm Protein (3 × 1 mL, for USA)	System-ID 07 9105 9	
05117003 190	PreciControl ClinChem Multi 1 (20 × 5 mL)	System-ID 07 7469 3	
05947626 190	PreciControl ClinChem Multi 1 (4 × 5 mL)	System-ID 07 7469 3	
05947626 160	PreciControl ClinChem Multi 1 (4 × 5 mL, for USA)	System-ID 07 7469 3	
20756350 322	NaCl Diluent 9 % (6 × 22 mL)	System-ID 07 5635 0	

English

System information

COBAS INTEGRA Cardiac C-Reactive Protein (Latex) High Sensitive (CRPHS)

Test CRPHS, test ID 0-033

Intended use

In vitro test for the quantitative determination of C-reactive protein (CRP) in human serum and plasma on COBAS INTEGRA systems. Measurement of CRP is of use for the detection and evaluation of inflammatory disorders and associated diseases, infection and tissue injury. Highly sensitive measurement of CRP may also be used as an aid in the assessment of the risk of future coronary heart disease. When used as an adjunct to other laboratory evaluation methods of acute coronary syndromes, it may also be an additional independent indicator of recurrent event prognosis in patients with stable coronary disease or acute coronary syndrome.

Summary[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21]

C-reactive protein is the classic acute phase protein to inflammatory reactions. It is synthesized by the liver and consists of five identical polypeptide chains that form a five-member ring having a molecular weight of 105000 Daltons. CRP is the most sensitive of the acute phase reactants and its concentration increases rapidly during inflammatory processes. Complexed CRP activates the complement system beginning with C1q. CRP then initiates opsonization and phagocytosis of invading cells, but its main function is to bind and detoxify endogenous toxic substances produced as a result of tissue damage. CRP assays are used to detect systemic inflammatory processes (apart from certain types of inflammation such as SLE and Colitis ulcerosa); to assess treatment of bacterial infections with antibiotics; to detect intrauterine infections with concomitant premature amniorrhexis; to differentiate between active and inactive forms of disease with concurrent infection, e.g. in patients suffering from SLE or Colitis ulcerosa; to therapeutically monitor rheumatic disease and assess anti-inflammatory therapy; to determine the presence of post-operative complications at an early stage, such as infected wounds, thrombosis and pneumonia and to distinguish between infection and bone marrow transplant rejection.

Sensitive CRP measurements have been used and discussed for early detection of infection in pediatrics and risk assessment of coronary heart disease. Several studies came to the conclusion that the highly sensitive measurement of CRP could be used as a marker to predict the risk of coronary heart disease in apparently healthy persons and as an indicator of recurrent event prognosis. Increases in CRP values are non-specific and should not be interpreted without a complete clinical history. The American Heart Association and the Centers for Disease Control and Prevention have made several recommendations concerning the use of high sensitivity C-Reactive Protein (hsCRP) in cardiovascular risk assessment.[21]

Testing for any risk assessment should not be performed while there is an indication of infection, systemic inflammation or trauma. Patients with persistently unexplained hsCRP levels above 10 mg/L (95.2 nmol/L) should be evaluated for non-cardiovascular etiologies. When using hsCRP to assess the risk of coronary heart disease, measurements should be made on metabolically stable patients and compared to previous values. Optimally, the average of hsCRP results repeated two weeks apart should be used for risk assessment. Screening the entire adult population for hsCRP is not recommended, and hsCRP is not a substitute for traditional cardiovascular risk factors. Acute coronary syndrome management should not depend solely on hsCRP measurements. Similarly, application of secondary prevention measures should be based on global risk assessment and not solely on hsCRP measurements. Serial measurements of hsCRP should not be used to monitor treatment. Various assay methods are available for CRP determination, such as nephelometry and turbidimetry. The Roche CRP assay is based on the principle of particle-enhanced immunological agglutination.

Test principle[22,23]

Particle enhanced turbidimetric assay

Human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The precipitate is determined turbidimetrically at 552 nm.

Reagents - working solutions

R1 TRIS buffer with bovine serum albumin and immunoglobulins (mouse); preservative; stabilizers.

SR Latex particles coated with anti-CRP (mouse) in glycine buffer; preservative; stabilizers.

R1 is in position B and SR is in position C.

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.

For USA: For prescription use only.

Reagent handling

COBAS INTEGRA 400 plus analyzers

All new (not punctured) **cobas c** packs must be mixed for 1 minute using the Cassette Mixer before placing on-board the instrument.

COBAS INTEGRA 800 analyzers

The reagent is automatically mixed for 1 minute after **cobas c** pack puncture.

Storage and stability

Shelf life at 2-8 °C	See expiration date on **cobas c** pack label
COBAS INTEGRA 400 plus system	
On-board in use at 10-15 °C	12 weeks
COBAS INTEGRA 800 system	

On-board in use at 8 °C	12 weeks

Specimen collection and preparation

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Serum
Plasma: Li-heparin, K_2-EDTA plasma

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.

Stability:[24]	11 days at 15-25 °C
	2 months at 2-8 °C
	3 years at (-15)-(-25) °C

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

NaCl Diluent 9 %, Cat. No. 20756350 322, system-ID 07 5635 0 for automatic postdilution and standard serial dilutions. NaCl Diluent 9 % is placed in its predefined rack position and is stable for 4 weeks on-board COBAS INTEGRA 400 plus/800 analyzers.

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.

Application for serum and plasma
COBAS INTEGRA 400 plus test definition

Measuring mode	Absorbance
Abs. calculation mode	Kinetic
Reaction mode	R1-S-SR
Reaction direction	Increase
Wavelength A	552 nm
Calc. first/last	35/63
Typical prozone effect	> 40 mg/L (> 380 nmol/L)
Antigen excess check	Yes[a)]
Unit	mg/L

Pipetting parameters

		Diluent (H_2O)
R1	82 µL	48 µL
Sample	6 µL	
SR	28 µL	14 µL
Total volume	178 µL	

COBAS INTEGRA 800 test definition

Measuring mode	Absorbance
Abs. calculation mode	Kinetic
Reaction mode	R1-S-SR
Reaction direction	Increase
Wavelength A	552 nm
Calc. first/last	46/96
Typical prozone effect	> 40 mg/L (> 380 nmol/L)
Antigen excess check	Yes[a)]
Unit	mg/L

Pipetting parameters

		Diluent (H_2O)
R1	82 µL	48 µL
Sample	6 µL	
SR	28 µL	14 µL
Total volume	178 µL	

a) Samples with concentrations > 40 mg/L are flagged either >TEST RNG or "HIGH ACT". Rerun the sample with postdilution or, if the sample has already been postdiluted, rerun the sample with a higher postdilution factor.

Calibration

Calibrator	Calibrator f.a.s. Proteins
Calibration dilution ratio	**COBAS INTEGRA 400 plus analyzers:** 1:5, 1:10, 1:20, 1:40, 1:80 and 0 mg/L performed automatically by the instrument. **COBAS INTEGRA 800 analyzers:** 1:5, 1:10, 1:20, 1:40, 1:80 and 0 mg/L performed automatically by the instrument.
Calibration mode	Linear interpolation
Calibration replicate	Duplicate recommended
Calibration interval	Each lot and as required following quality control procedures

Enter the assigned lot-specific CRP value for the Calibrator f.a.s. Proteins.

Traceability: This method has been standardized by method comparison to the Tina-Quant CRPLX high sensitive assay. The Tina-Quant CRPLX high sensitive assay has been standardized with regard to the IFCC/BCR/CAP reference preparation CRM 470 (RPPHS 91/0619) for 14 serum proteins.

Quality control

Reference range	CRP T Control N
Pathological range	Precinorm Protein or PreciControl ClinChem Multi 1
Control interval	24 hours recommended
Control sequence	User defined
Control after calibration	Recommended

For quality control, use control materials as listed in the "Order information" section. In addition, other suitable control material can be used.

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.

Calculation

COBAS INTEGRA analyzers automatically calculate the analyte concentration of each sample. For more details, please refer to Data Analysis in the Online Help (COBAS INTEGRA 400 plus/800 analyzers).

Conversion factors:	mg/L × 9.52 = nmol/L
	mg/L × 0.1 = mg/dL
	nmol/L × 0.001 = µmol/L

Limitations - interference

Criterion: Recovery within ± 10 % of initial value.

Serum, plasma

Icterus:[25] No significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 60 mg/dL or 1026 µmol/L).

Hemolysis:[25] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 1000 mg/dL or 621 µmol/L).

Lipemia (Intralipid):[25] No significant interference up to an L index of 500 (at 2 mg/L or 19 nmol/L CRP). There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

High-dose hook effect: Does not occur at CRP concentrations below 40 mg/L or 380 nmol/L. Samples with concentrations > 40 mg/L are flagged either >TEST RNG or "HIGH ACT".

Rheumatoid factors: No interference up to 1200 IU/mL.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[26,27]
Exception: Significantly decreased CRP values may be obtained from samples taken from patients who have been treated with carboxypenicillins.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[28]

HAMA: Although measures were taken to minimize interference caused by human anti-mouse antibodies, erroneous findings may be obtained from samples taken from patients who have been treated with monoclonal mouse antibodies or have received them for diagnostic purposes.

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

ACTION REQUIRED
Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on COBAS INTEGRA analyzers. Refer to the CLEAN Method Sheet for further instructions and for the latest version of the Extra wash cycle list.
Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

0.1-20 mg/L (0.952-190 nmol/L) (typical measuring range)

The upper and lower limits of the measuring range depend on the actual calibrator value.

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:15 dilution. Results from samples diluted by the rerun function are automatically multiplied by a factor of 15.

Lower limits of measurement

Lower detection limit of the test

0.1 mg/L (0.952 nmol/L)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of a zero sample (zero sample + 3 SD, repeatability, n = 21).

Expected values

Consensus reference interval for adults:[29,30]

IFCC/CRM 470

mg/dL	mg/L	nmol/L
< 0.5	< 5.0	< 47.6

The CDC/AHA recommended the following hsCRP cut-off points (tertiles) for CVD risk assessment:[21,31]

hsCRP level (mg/L)	hsCRP level (nmol/L)	Relative risk
< 1.0	< 9.52	low
1.0-3.0	9.52-28.6	average
> 3.0	> 28.6	high

Patients with higher hsCRP concentrations are more likely to develop myocardial infarction and severe peripheral vascular disease.

5-95 % reference intervals of neonates and children:[32]

Neonates (0-3 weeks): 0.1-4.1 mg/L (0.95-39.0 nmol/L)

Children (2 months-15 years): 0.1-2.8 mg/L (0.95-26.7 nmol/L)

Roche has not evaluated reference ranges in a pediatric population.

It is important to monitor the CRP concentration during the acute phase of the illness.

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

Increases in CRP values are non-specific and should not be interpreted without a complete clinical history.

When using hsCRP to assess the risk of coronary heart disease, measurements should be made on metabolically stable patients and compared to previous values. Optimally, the average of hsCRP results repeated 2 weeks apart should be used for risk assessment. Measurements should be compared to previous values. When the results are being used for risk assessment, patients with persistently unexplained hsCRP levels of above 10 mg/L (95.2 nmol/L) should be evaluated for non-cardiovascular origins. Testing for any risk assessment should not be performed while there is indication of infection, systemic inflammation or trauma.[21]

Specific performance data

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

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 21 days). The following results were obtained:

	Repeatability		Intermediate precision	
Sample	Mean	CV	Mean	CV
	mg/L (nmol/L)	%	mg/L (nmol/L)	%
Control Level 1	3.3 (31.4)	0.9	3.3 (31.4)	3.5
Control Level 2	8.0 (76.2)	0.7	8.0 (76.2)	2.2
Human pool 1	1.6 (15.2)	1.3	1.5 (14.3)	3.1
Human pool 2	11.4 (109)	0.6	11.4 (109)	2.3

Functional sensitivity (limit of quantitation)

0.3 mg/L (2.96 nmol/L)

The functional sensitivity (limit of quantitation) is the lowest CRP concentration that can be reproducibly measured with an inter-assay coefficient of variation of < 10 %.

Method comparison

CRP values for human serum and plasma samples obtained on a COBAS INTEGRA 700 analyzer using the COBAS INTEGRA Cardiac C-Reactive Protein (Latex) High Sensitive reagent (y) were compared to two commercially available alternative automated systems (x). Sample size (n) represents all replicates.

System 1

Sample size (n) = 58

Passing/Bablok[33]	Linear regression
y = 1.0548x + 0.0414	y = 0.9877x + 0.1264
τ = 0.956	r = 0.996

The sample concentrations were between 0.2 and 16.3 mg/L (1.9 and 15.5 nmol/L).

System 2

Sample size (n) = 54

Passing/Bablok[33]	Linear regression
y = 0.9715x + 0.0211	y = 0.9941x + 0.0295
τ = 0.935	r = 0.998

The sample concentrations were between 0.1 and 9.0 mg/L (1.0 and 8.6 nmol/L).

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

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

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

Symbols

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

CONTENT	Contents of kit
→	Volume after reconstitution or mixing
GTIN	Global Trade Item Number

FOR US CUSTOMERS ONLY: LIMITED WARRANTY

Roche Diagnostics warrants that this product will meet the specifications stated in the labeling when used in accordance with such labeling and will be free from defects in material and workmanship until the expiration date printed on the label. THIS LIMITED WARRANTY IS IN LIEU OF ANY OTHER WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR PARTICULAR PURPOSE. IN NO EVENT SHALL ROCHE DIAGNOSTICS BE LIABLE FOR INCIDENTAL, INDIRECT, SPECIAL OR CONSEQUENTIAL DAMAGES.

Additions, deletions or changes are indicated by a change bar in the margin.

CRPHS

Cardiac C-Reactive Protein (Latex) High Sensitive

CE 0123

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