HSCRP

cobas®

Tina-quant Cardiac high sensitivity CRP III

Order information

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
09188231190	09188231500	Tina-quant Cardiac high sensitivity CRP III (500 tests)	System-ID 2150 001	**cobas c** 303, **cobas c** 503, **cobas c** 703

Materials required (but not provided):

11355279216	Calibrator f.a.s. Proteins (5 x 1 mL)	Code 20656	
20766321322	CRP T Control N (5 x 0.5 mL)	Code 20235	
05117003190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 20391	
05947626190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 20391	
08063494190	Diluent NaCl 9 % (123 mL)	System-ID 2906 001	

English

System information

HSCRP: ACN 21500

Intended use

In vitro test for the quantitative determination of C-reactive protein (CRP) in human serum and plasma on **cobas c** systems. CRP measurements, performed with this assay, in human serum or plasma, are used as aid in diagnosis, monitoring, prognosis, and management of suspected inflammatory disorders and associated diseases, acute infections 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

C-reactive protein is the classic acute phase protein in inflammatory reactions.[1] 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.[1,2,3,4] CRP is the most sensitive of the acute phase reactants and its concentration increases rapidly during inflammatory processes.[2,3] Complexed CRP activates the classical complement pathway. The CRP response frequently precedes clinical symptoms, including fever.[1,3] After onset of an acute phase response the serum CRP concentration rises rapidly and extensively.[2,3,4] The increase begins within 6 to 12 hours and the peak value is reached within 24 to 48 hours.[1,3,5] CRP response may be less pronounced in patients suffering from liver disease.[6]

CRP assays are used to detect systemic inflammatory processes (apart from certain types of inflammation such as systemic lupus erythematosus (SLE) and Colitis ulcerosa);[1,3,4,6] to assess treatment of bacterial infections with antibiotics;[1,4,6,7] to detect intrauterine infections with concomitant premature amniorrhexis;[4,6] to differentiate between active and inactive forms of disease with concurrent infection, e.g. in patients suffering from SLE or Colitis ulcerosa;[3,4,6] to therapeutically monitor rheumatic disease and assess anti-inflammatory therapy;[1,4,6] 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.[1,4,6]

Sensitive CRP measurements have been used and discussed for early detection of infection in pediatrics and risk assessment of coronary heart disease.[8,9,10,11] 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.[10,12,13,14,15,16] Increases in CRP values are non-specific and should not be interpreted without a complete clinical history.[17] 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.[17,18] Measurement of hsCRP may also be used as an aid in the assessment of the risk of future coronary heart disease and as a risk-enhancing factor in patients with borderline- or intermediate-risk for atherosclerotic cardiovascular disease.[19] 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.[17,20]

Testing for any risk assessment should not be performed while there is an indication of infection, systemic inflammation or trauma.[11,17,21] Patients with persistently unexplained hsCRP levels above 10 mg/L (95.2 nmol/L) should be evaluated for non-cardiovascular etiologies.[13,17] When using hsCRP to assess the risk of coronary heart disease, measurements should be made on metabolically stable patients and compared to previous values.[17] Optimally, the average of hsCRP results repeated two weeks apart should be used for risk assessment.[17] Screening the entire adult population for hsCRP is not recommended, and hsCRP is not a substitute for traditional cardiovascular risk factors.[17] Acute coronary syndrome management should not depend solely on hsCRP measurements.[14,17] Serial measurements of hsCRP should not be used to monitor treatment.[17]

Studies indicate an influence of gestational age on the kinetics of CRP in preterm infants, which may materialize as a blunted response to infection when comparing preterm and term newborns.[22,23,24] This phenomenon, most likely due to immature liver function, may result in a lower sensitivity of CRP in the diagnosis of neonatal sepsis in preterm compared to term newborns.[25] In adult patients with advanced liver dysfunction, CRP levels are reduced in response to acute infection, however production is nevertheless maintained.[26] Although the liver is considered the main source of CRP, serum levels are not significantly lower in patients with cirrhosis than in other patients, and the predictive performance for infection is similar for patients with and without cirrhosis.[27]

Various assay methods are available for CRP determination, such as nephelometry and turbidimetry.[28,29] The Roche CRP assay is based on the principle of particle-enhanced immunological agglutination.

Test principle[28,29]

Particle enhanced immunoturbidimetric assay.

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

Reagents - working solutions

R1 TRIS[a)] buffer with bovine serum albumin; preservative

R3 Latex particles coated with anti-CRP (mouse) in glycine buffer; immunoglobulins (mouse); preservative

a) TRIS = Tris(hydroxymethyl)-aminomethane

R1 is in position B and R3 is in position C.

Precautions and warnings

For in vitro diagnostic use for laboratory 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.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

HSCRP

Tina-quant Cardiac high sensitivity CRP III

Warning

H317	May cause an allergic skin reaction.

Prevention:

P261	Avoid breathing mist or vapours.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves.

Response:

P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.

Disposal:

P501	Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

Reagent handling

Ready for use

Carefully invert reagent container several times prior to use to ensure that the reagent components are mixed. Avoid the formation of foam.

Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	24 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 and 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.

See the limitations and interferences section for details about possible sample interferences.

Stability in serum and Li-heparin plasma:	14 days at 15-25 °C
	28 days at 2-8 °C
	12 months at -20 °C (±5 °C)
Stability in K_2-EDTA plasma:	2 days at 15-25 °C
	28 days at 2-8 °C
	12 months at -20 °C (±5 °C)

Specimens can be repeatedly frozen and thawed up to 4 times.

Materials provided

See “Reagents – working solutions” section for reagents.

Materials required (but not provided)

See “Order information” section

General laboratory equipment

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.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

Test definition

Reporting time	10 min		
Wavelength (sub/main)	800/570 nm		
Reagent pipetting		Diluent (H_2O)	
R1	98 µL	–	
R3	31 µL	16 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2.6 µL	–	–
Decreased	5.2 µL	20 µL	60 µL
Increased	2.6 µL	–	–

For further information about the assay test definitions refer to the application parameters setting screen of the corresponding analyzer and assay.

Calibration

Calibrators	S1: H_2O
	S2-S6: C.f.a.s. Proteins
Calibration mode	Non-linear
Calibration frequency	Full calibration - after reagent lot change - as required following quality control procedures

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: This method has been standardized against the certified reference material in human serum of the IRMM (Institute for Reference Materials and Measurements) ERM-DA474/IFCC.[30]

Quality control

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 c systems automatically calculate the analyte concentration of each sample in the unit mg/L (nmol/L, mg/dL).

Conversion factors:	mg/L x 9.52 = nmol/L
	mg/L x 0.1 = mg/dL

Limitations - interference

Criterion: Recovery within ± 0.100 mg/L of initial values of samples ≤ 1.00 mg/L and within ± 10.0 % for samples > 1.00 mg/L.

Icterus:[31] No significant interference up to an I index of 60 for conjugated bilirubin and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 60 mg/dL or 1026 µmol/L).

Hemolysis:[31] No significant interference up to an H index of 700 (approximate hemoglobin concentration: 435 µmol/L or 700 mg/dL).

Lipemia (Intralipid):[31] No significant interference up to an L index of 1000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Rheumatoid factors: No significant interference from rheumatoid factors up to a concentration of 500 IU/mL.

High dose hook-effect: No false result occurs up to a CRP concentration of 100 mg/L.

In vitro tests were performed on commonly used pharmaceuticals. In addition, special pharmaceuticals were tested. Among them, the following substance caused interference:

Substance	No significant interference up to
Ticarcilin	540 mg/L

Drug interferences are measured based on recommendations given in CLSI guidelines EP07 and EP37 and other published literature. Effects of concentrations exceeding these recommendations have not been characterized.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[32]

In patients with reduced liver function such as patients with liver cirrhosis or preterm neonates, CRP levels in response to acute infections may be blunted. This may lead to lower sensitivity of CRP in the diagnosis of neonatal sepsis, while predictive performance for infection in patients with cirrhosis seems to be maintained.

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 c** systems. All special wash programming necessary for avoiding carry-over is available via the **cobas** link. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/SCCS Method Sheet. For further instructions, refer to the operator's manual.

Limits and ranges

Measuring range

0.150-10.0 mg/L (1.43-95.2 nmol/L)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:2 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 2.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank	= 0.100 mg/L (0.952 nmol/L)
Limit of Detection	= 0.150 mg/L (1.43 nmol/L)
Limit of Quantitation	= 0.150 mg/L (1.43 nmol/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 95th percentile value from n ≥ 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 a total error of 20 %. It has been determined using low concentration C-reactive protein samples.

Expected values

A statement of the CDC/AHA from 2003 recommended the following hsCRP cut-off points (tertiles) for CVD risk assessment for adults:[17,33]

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

Patients with higher hsCRP concentrations are more likely to develop myocardial infarction and severe peripheral vascular disease.[17,33]

In addition, the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease recommended an hsCRP cut-off of ≥ 2 mg/L as risk-enhancing factor for individual risk assessment.[18]

A reference range study for hsCRP recommends the following 5-95 % reference intervals in neonates and children:[34]

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

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

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

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

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 two 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 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.[18]

Specific performance data

Representative performance data on the analyzers are given below. These data represent the performance of the analytical procedure itself.

Results obtained in individual laboratories may differ due to heterogeneous sample materials, aging of analyzer components and mixture of reagents running on the analyzer.

Precision

Precision was determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP05-A3 requirements with repeatability (n = 84) and intermediate precision (2 aliquots per run, 2 runs per day, 21 days). Results for repeatability and intermediate precision were obtained on the **cobas c** 503 analyzer.

Repeatability	*Mean*	*SD*	*CV*
	mg/L	*mg/L*	*%*
CRPTN[a)]	4.14	0.0158	0.4
PCCC1[b)]	6.40	0.0222	0.3
Human serum 1	0.429	0.00795	1.9
Human serum 2	1.09	0.0184	1.7
Human serum 3	2.93	0.0159	0.5
Human serum 4	6.46	0.0340	0.5
Human serum 5	9.86	0.0432	0.4

Intermediate precision	*Mean*	*SD*	*CV*
	mg/L	*mg/L*	*%*
CRPTN[a)]	4.14	0.0216	0.5
PCCC1[b)]	6.44	0.0643	1.0
Human serum 1	0.429	0.00826	1.9
Human serum 2	1.09	0.0221	2.0
Human serum 3	2.93	0.0225	0.8
Human serum 4	6.46	0.0517	0.8

Human serum 5	9.86	0.0636	0.6

a) CRP T Control N

b) PreciControl ClinChem Multi 1

The data obtained on **cobas c** 503 analyzer(s) are representative for **cobas c** 303 analyzer(s) and **cobas c** 703 analyzer(s).

Method comparison

HSCRP values for human serum and plasma samples obtained on a **cobas c** 503 analyzer (y) were compared to those determined using the Cardiac C-Reactive Protein (Latex) High Sensitive on a **cobas c** 501 analyzer (x).

Sample size (n) = 159

Passing/Bablok[35]

y = 1.057x + 0.0388 mg/L

τ = 0.967

r = 0.997

The sample concentrations were between 0.160 and 9.75 mg/L .

HSCRP values for human serum and plasma samples obtained on a **cobas c** 303 analyzer (y) were compared to those determined using the corresponding reagent on a **cobas c** 503 analyzer (x).

Sample size (n) = 213

Passing/Bablok[35]

y = 1.015x - 0.0621 mg/L

τ = 0.993

r = 1.000

The sample concentrations were between 0.189 and 9.79 mg/L.

HSCRP values for human serum and plasma samples obtained on a **cobas c** 703 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 503 analyzer (x).

Sample size (n) = 68

Passing/Bablok[35]

y = 1.012x + 0.100 mg/L

y = 1.034x + 0.00681 mg/L

τ = 0.990

r = 0.999

The sample concentrations were between 0.266 and 9.55 mg/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:

CONTENT	Contents of kit
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

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