

HDLC4

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| REF | | CONTENT | | Analyzer(s) on which cobas c pack(s) can be used |
|--------------|-------------|-------------------------------------|--------------------|--|
| 08057877190 | 08057877500 | HDLC4-Cholesterol Gen.4 (700 tests) | System-ID 2071 002 | cobas c 303, cobas c 503, cobas c 703 |
| 08057877214* | 08057877500 | HDLC4-Cholesterol Gen.4 (700 tests) | System-ID 2071 002 | cobas c 303, cobas c 503, cobas c 703 |

Materials required (but not provided):

| | | | |
|-------------|---|--------------------|--|
| 12172623122 | Calibrator f.a.s. Lipids (3 x 1 mL) | Code 20424 | |
| 05117003190 | PreciControl ClinChem Multi 1 (20 x 5 mL) | Code 20391 | |
| 05947626190 | PreciControl ClinChem Multi 1 (4 x 5 mL) | Code 20391 | |
| 05117216190 | PreciControl ClinChem Multi 2 (20 x 5 mL) | Code 20392 | |
| 05947774190 | PreciControl ClinChem Multi 2 (4 x 5 mL) | Code 20392 | |
| 08063494190 | Diluent NaCl 9 % (123 mL) | System-ID 2906 001 | |

* Some kits shown may not be available in all countries.

English

System information

HDLC4: ACN 20710

Intended use

In vitro diagnostic test for the quantitative determination of the HDL-cholesterol concentration in human serum and plasma on **cobas c** systems.

Summary

Measurements of HDL-cholesterol, performed with this assay in human serum or plasma, are used for screening, aid in diagnosis and monitoring of dyslipidaemias as well as for assessment of cardiovascular risk such as in ASCVD and CHD.

High density lipoproteins (HDL) are responsible for the reverse transport of cholesterol from the peripheral cells to the liver. In the liver, cholesterol is transformed to bile acids which are then excreted into the intestine via the biliary tract.

Monitoring of HDL-cholesterol in serum or plasma is of clinical relevance as the HDL-cholesterol concentration is important in the assessment of atherosclerotic cardiovascular risk (ASCVD).¹ Elevated HDL-cholesterol concentrations protect against coronary heart disease (CHD), whereas reduced HDL-cholesterol concentrations, particularly in conjunction with elevated triglycerides, increase cardiovascular risk.¹

Two cholesterol related variables that are predictive of cardiovascular disease (CVD) have emerged. These are non-HDL-cholesterol^{2,3,4} (= total cholesterol - HDL-cholesterol) and the rate of cholesterol transfer from the macrophages to HDL, also described as cholesterol efflux capacity.⁵ Whereas both cholesterol and HDL-cholesterol can be readily determined with high accuracy, currently, non-HDL-cholesterol appears to be best suited for patient management.^{2,3,4}

A variety of methods are available to determine HDL-cholesterol, including ultracentrifugation (reference method in combination with cholesterol measurement by the Abell-Kendall method), electrophoresis, high performance liquid chromatography (HPLC), precipitation, and direct methods.^{6,7} Of these, the direct methods are used routinely. Roche HDLC4 is also a direct method. The automated HDLC4 assay uses detergents, cholesterol esterase (CHER), cholesterol oxidase (CHOD) and peroxidase to form a colored pigment that is measured optically.^{8,9}

The HDLC4 assay meets the 1998 National Institutes of Health (NIH) / National Cholesterol Education Program (NCEP) goals for precision and accuracy.^{10,11}

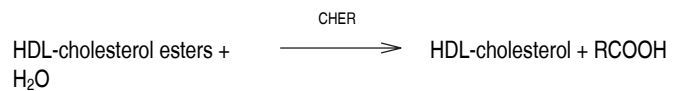
Test principle^{8,9}

Homogeneous enzymatic colorimetric test.

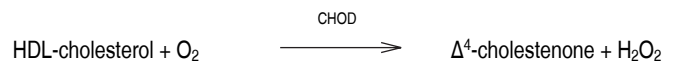
Non-HDL lipoproteins such as LDL, VLDL and chylomicrons are combined with polyanions and a detergent forming a water-soluble complex. In this complex the enzymatic reaction of CHER and CHOD towards non-HDL lipoproteins is blocked.

Finally only HDL-particles can react with CHER and CHOD. The concentration of HDL-cholesterol is determined enzymatically by CHER and CHOD.

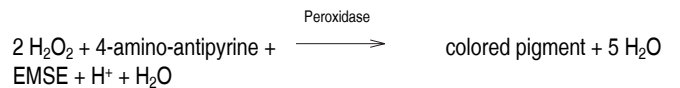
Cholesterol esters are broken down quantitatively into free cholesterol and fatty acids by CHER.



In the presence of oxygen, cholesterol is oxidized by cholesterol oxidase to Δ^4 -cholestenone and hydrogen peroxide.



In the presence of peroxidase, the hydrogen peroxide generated reacts with 4-amino-antipyrene and EMSE^{a)} to form a dye. The color intensity of this dye is directly proportional to the cholesterol concentration and is measured photometrically.



a) N-ethyl-N-(3-methylphenyl)-N'-succinylethylenediamine

Reagents - working solutions

R1 TAPSO^{b)} buffer: 62.1 mmol/L, pH 7.77; polyanion: 1.25 g/L; EMSE: 1.08 mmol/L; ascorbate oxidase (cucurbita): $\geq 50 \mu\text{kat/L}$; peroxidase (horseradish): $\geq 166.7 \mu\text{kat/L}$; detergent; BSA: 2.0 g/L; preservative

R3 Bis-Tris^{c)} buffer: 20.1 mmol/L, pH 6.70; cholesterol esterase (microorganism): $\geq 7.5 \mu\text{kat/L}$; cholesterol oxidase (recombinant E. coli): $\geq 7.17 \mu\text{kat/L}$; cholesterol oxidase (microorganism): $\geq 76.7 \mu\text{kat/L}$; peroxidase (horseradish): $\geq 333 \mu\text{kat/L}$; 4-amino-antipyrene: 1.48 mmol/L; BSA: 3.0 g/L; detergents; preservative

b) 2-Hydroxy-N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid

c) Bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane

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.

Reagent handling

Ready for use

The intrinsic color of the reagent does not interfere with the test.

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cobas[®]**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: 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, K₂- and K₃-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.

Collect blood by using an evacuated tube or syringe. Specimens should preferably be analyzed on the day of collection.

Fasting and non-fasting samples can be used.^{12,13}

Stability in serum: 72 hours at 15-25 °C¹³
7 days at 2-8 °C¹³
12 months at -20 °C (± 5 °C)¹⁴
24 months at -70 °C (± 5 °C)¹⁵

Freeze only once.

Stability in Li-heparin, K₂- and K₃-EDTA plasma: 72 hours at 15-25 °C¹³
7 days at 2-8 °C¹³
3 months at -20 °C (± 5 °C) °C¹³
18 months at -70 °C (± 5 °C)¹³
18 months at -80 °C (± 5 °C)¹⁶

Freeze only once.

It is reported that EDTA stabilizes lipoproteins.¹⁷

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

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) | 700/600 nm | |
| Reagent pipetting | | Diluent (H ₂ O) |
| R1 | 80 µL | – |
| R3 | 27 µL | – |
| <i>Sample volumes</i> | <i>Sample</i> | <i>Sample dilution</i> |

| | | <i>Sample</i> | <i>Diluent (NaCl)</i> |
|-----------|--------|---------------|-----------------------|
| Normal | 1.6 µL | – | – |
| Decreased | 8.0 µL | 10 µL | 90 µL |
| Increased | 1.6 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 ₂ O S2: C.f.a.s. Lipids |
| Calibration mode | Linear |
| Calibration frequency | Automatic full calibration - after reagent lot change Full calibration - 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 designated CDC reference method (ultracentrifugation method).¹⁰ The standardization meets the requirements of the "HDL Cholesterol Method Evaluation Protocol for Manufacturers" of the US National Reference System for Cholesterol, CRMLN (Cholesterol Reference Method Laboratory Network), November 1994.

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. It is recommended to perform quality control always after lot calibration and subsequently at least every 12 weeks.

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 mmol/L (mg/dL, g/L).

Conversion factors: mmol/L x 38.66 = mg/dL
mmol/L x 0.3866 = g/L

Limitations - interference¹⁸

Criterion: Recovery within ±0.1 mmol/L of initial values of samples ≤ 1 mmol/L (38.7 mg/dL) and within ±10 % for samples > 1 mmol/L.

Icterus:¹⁹ No significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL).

Hemolysis:¹⁹ No significant interference up to an H index of 1200 (approximate hemoglobin concentration: 745 µmol/L or 1200 mg/dL).

Lipemia (Intralipid):¹⁹ No significant interference up to an L index of 2000. No significant interference from native triglycerides up to 13.7 mmol/L or 1200 mg/dL. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Other: Elevated concentrations of free fatty acids and denatured proteins may cause falsely elevated HDL-cholesterol results.

Ascorbic acid: No significant interference from ascorbic acid up to a concentration of 2.84 mmol/L (50 mg/dL).

Abnormal liver function affects lipid metabolism; consequently, HDL and LDL results are of limited diagnostic value. In some patients with abnormal liver function, the HDL-cholesterol result may significantly differ from the DCM (designated comparison method) result due to the presence of lipoproteins with abnormal lipid distribution.²⁰

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Drugs: No interference was found at therapeutic concentrations using common drug panels.^{21,22}

Statins (Simvastatin) and fibrates (Bezafibrate) tested at therapeutic concentration ranges did not interfere.

N-acetylcysteine: No significant interference from N-acetylcysteine up to a concentration of 2.76 mmol/L (450 mg/L).

Acetaminophen intoxications are frequently treated with N-acetylcysteine. N-acetylcysteine at the therapeutic concentration when used as an antidote and the acetaminophen metabolite N-acetyl-p-benzoquinone imine (NAPQI) independently may cause falsely low HDL-cholesterol results.

Metamizole: Venipuncture should be performed prior to the administration of metamizole. Venipuncture immediately after or during the administration of metamizole may lead to falsely low results.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.²³

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

0.08-3.88 mmol/L (3.09-150 mg/dL)

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 = 0.08 mmol/L (3.09 mg/dL)

Limit of Detection = 0.08 mmol/L (3.09 mg/dL)

Limit of Quantitation = 0.08 mmol/L (3.09 mg/dL)

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 $n \geq 60$ 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 precision of ≤ 30 % CV. It has been determined using low concentration HDL-cholesterol samples.

Expected values

mmol/L

| | No risk | Moderate risk | High risk |
|----------------------------|---------------|------------------|---------------|
| Females ^{7,24,25} | > 1.68 mmol/L | 1.15-1.68 mmol/L | < 1.15 mmol/L |
| Males ^{7,24,25} | > 1.45 mmol/L | 0.90-1.45 mmol/L | < 0.90 mmol/L |

mg/dL

| | No risk | Moderate risk | High risk |
|----------------------------|------------|---------------|------------|
| Females ^{7,24,25} | > 65 mg/dL | 45-65 mg/dL | < 45 mg/dL |
| Males ^{7,24,25} | > 55 mg/dL | 35-55 mg/dL | < 35 mg/dL |

National Cholesterol Education Program (NCEP) guidelines:²⁶

< 40 mg/dL: Low HDL-cholesterol (major risk factor for CHD)

≥ 60 mg/dL: High HDL-cholesterol ("negative" risk factor for CHD)

HDL-cholesterol is affected by a number of factors, e.g. smoking, exercise, hormones, sex and age.

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

National Cholesterol Education Program (NCEP) guidelines are based on serum values. When classifying patients, serum or serum equivalent values should be used. Therefore the NCEP recommends using a factor of 1.03 to convert EDTA plasma values to serum values. A later study found EDTA plasma concentrations to be 4.7 % lower than those in serum.²⁷ To comply with the 1998 NCEP goal of a bias < 5 % it is recommended that each laboratory validates this conversion factor and enters it into the test parameters for HDL-cholesterol.²⁸

Treatment goals for non-HDL-cholesterol have been proposed:²

| | NCEP ATP III | ADA/AHA Guidelines for patients with increased cardiometabolic risk |
|--|--------------------------------|---|
| Optional goal for very-high/highest risk patients (known CVD, diabetes with elevated risk) | < 3.37 mmol/L (< 130 mg/dL) | < 2.59 mmol/L (< 100 mg/dL) |
| Optional goal for those with established cardiovascular disease and multiple major risk factors | < 2.59 mmol/L (< 100 mg/dL) | |
| Optional goal for high-risk patients, CHD-risk-equivalent (Framingham 10-year risk score > 20 %/10 years, diabetes without other major risk factors) | < 3.37 mmol/L (< 130 mg/dL) | < 3.37 mmol/L (< 130 mg/dL) |
| Optional goal for moderately-high/intermediate risk patients (≥ 2 major CVD risk factors, Framingham 10-year risk score from 10-20 %) | < 4.14 mmol/L (< 160 mg/dL) | < 3.37 mmol/L (< 130 mg/dL) |
| Optional goal for high-risk patients, CHD-risk-equivalent (Framingham 10-year risk score > 20 %/10 years, diabetes without other major risk factors) | < 3.37 mmol/L (< 130 mg/dL) | |

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 heterogenous 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 |
|----------------------|--------|---------|-----|
| | mmol/L | mmol/L | % |
| PCCC ^{1 d)} | 0.764 | 0.00290 | 0.4 |
| PCCC ^{2 e)} | 1.45 | 0.00690 | 0.5 |

| | | | |
|---------------|-------|---------|-----|
| Human serum 1 | 0.148 | 0.00177 | 1.2 |
| Human serum 2 | 1.07 | 0.00512 | 0.5 |
| Human serum 3 | 1.49 | 0.00673 | 0.5 |
| Human serum 4 | 1.92 | 0.00715 | 0.4 |
| Human serum 5 | 3.53 | 0.0152 | 0.4 |

Intermediate precision

| | Mean | SD | CV |
|--|--------|--------|----|
| | mmol/L | mmol/L | % |

| | | | |
|---------------------|-------|---------|-----|
| PCCC1 ^{d)} | 0.760 | 0.00630 | 0.8 |
| PCCC2 ^{e)} | 1.44 | 0.00974 | 0.7 |
| Human serum 1 | 0.148 | 0.00229 | 1.5 |
| Human serum 2 | 1.07 | 0.00708 | 0.7 |
| Human serum 3 | 1.49 | 0.0105 | 0.7 |
| Human serum 4 | 1.92 | 0.0145 | 0.8 |
| Human serum 5 | 3.54 | 0.0249 | 0.7 |

d) PreciControl ClinChem Multi 1

e) PreciControl ClinChem Multi 2

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

HDL-cholesterol values for human serum and plasma samples obtained on a **cobas c 503** analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c 501** analyzer (x).

Sample size (n) = 70

| Passing/Bablok ²⁹ | Linear regression |
|--------------------------------------|--------------------------------------|
| $y = 1.001x - 0.0175 \text{ mmol/L}$ | $y = 1.012x - 0.0274 \text{ mmol/L}$ |
| $\tau = 0.976$ | $r = 1.000$ |

The sample concentrations were between 0.110 and 3.57 mmol/L.

HDL-cholesterol values for human serum and plasma samples obtained on a **cobas c 303** analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c 501** analyzer (x).

Sample size (n) = 70

| Passing/Bablok ²⁹ | Linear regression |
|--------------------------------------|--------------------------------------|
| $y = 1.011x - 0.0242 \text{ mmol/L}$ | $y = 1.028x - 0.0389 \text{ mmol/L}$ |
| $\tau = 0.977$ | $r = 1.000$ |

The sample concentrations were between 0.110 and 3.57 mmol/L.

HDL-cholesterol 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) = 75

| Passing/Bablok ²⁹ | Linear regression |
|--------------------------------------|--------------------------------------|
| $y = 1.000x - 0.0200 \text{ mmol/L}$ | $y = 1.000x - 0.0159 \text{ mmol/L}$ |
| $\tau = 0.994$ | $r = 1.000$ |

The sample concentrations were between 0.115 and 3.67 mmol/L.

References

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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.

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. |

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