0107005717190c501V5.0

LDLC3

cobas®

LDL-Cholesterol Gen.3

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
07005717 190	LDL-Cholesterol Gen.3 (200 tests)	System-ID 07 7565 7	Roche/Hitachi **cobas c** 311, **cobas c** 501/502

Materials required (but not provided):

12172623 122	Calibrator f.a.s. Lipids (3 × 1 mL)	Code 424	
05117003 190	PreciControl ClinChem Multi 1 (20 × 5 mL)	Code 391	
05947626 190	PreciControl ClinChem Multi 1 (4 × 5 mL)	Code 391	
05117216 190	PreciControl ClinChem Multi 2 (20 × 5 mL)	Code 392	
05947774 190	PreciControl ClinChem Multi 2 (4 × 5 mL)	Code 392	
04489357 190	Diluent NaCl 9 % (50 mL)	System-ID 07 6869 3	

English

System information

For **cobas c** 311/501 analyzers:

LDLC3: ACN 552

For **cobas c** 502 analyzer:

LDLC3: ACN 8552

Intended use

In vitro test for the quantitative determination of LDL-cholesterol in human serum and plasma on Roche/Hitachi **cobas c** systems.

Summary

Low Density Lipoproteins (LDL) play a key role in causing and influencing the progression of atherosclerosis and, in particular, coronary sclerosis.[1,2] The LDLs are derived from VLDLs (Very Low Density Lipoproteins) rich in triglycerides by the action of various lipolytic enzymes and are synthesized in the liver. The elimination of LDL from plasma takes place mainly by liver parenchymal cells via specific LDL receptors. Elevated LDL concentrations in blood and an increase in their residence time coupled with an increase in the biological modification rate results in the destruction of the endothelial function and a higher LDL-cholesterol uptake in the monocyte/macrophage system as well as by smooth muscle cells in vessel walls. The majority of cholesterol stored in atherosclerotic plaques originates from LDL. The LDL-cholesterol value is the most powerful clinical predictor among all of the single parameters with respect to coronary atherosclerosis. Therefore, therapies focusing on lipid reduction primarily target the reduction of LDL-cholesterol which is then expressed in an improvement of the endothelial function, prevention of atherosclerosis and reducing its progression as well as preventing plaque rupture.

Various methods are available for the determination of LDL-cholesterol such as ultracentrifugation as the reference method, lipoprotein electrophoresis, HPLC and precipitation methods.[3,4] In the precipitation methods apolipoprotein B-containing LDL-cholesterol is, for example, precipitated using either polyvinyl sulfate, dextran sulfate or polycyclic anions. The LDL-cholesterol content is usually calculated from the difference between total cholesterol and cholesterol in the remainder (VLDL and HDL-cholesterol) in the supernate after precipitation with polyvinyl sulfate and dextran sulfate.[5] Lipid Research Clinics recommend a combination of ultracentrifugation and precipitation methods using polyanions in the presence of divalent cations. The precipitation methods are, however, time-consuming, cannot be automated and are susceptible to interference by hyperlipidemic serum, particularly at high concentrations of free fatty acids. A more recent method is based on the determination of LDL-cholesterol after the sample is subjected to immunoadsorption and centrifugation.[6]

The calculation of the LDL-cholesterol concentration according to Friedewald's formula is based on two cholesterol determinations (total cholesterol and HDL-cholesterol) and one triglyceride determination.[7]

Friedewald's formula for calculation of LDL-C presumes that a direct relationship exists between VLDL-cholesterol and triglycerides in fasting blood samples (VLDL-cholesterol = Trigl./5 mg/dL, VLDL-cholesterol = Trigl./2.2 mmol/L). The bias in calculating LDL-C using this assumption is only acceptable in samples with a triglyceride concentration < 2.0 mmol/L (177 mg/dL).[8,9] Even in the presence of small amounts of chylomicrons or abnormal lipoproteins, the formula gives rise to artificially low LDL-cholesterol values. Non-fasting samples cannot be used for the calculation of LDL-C because they contain a high concentration of chylomicrons and in many cases the limit of acceptable triglyceride concentration is exceeded.

For these reasons, a simple and reliable method for routine measurement of LDL-cholesterol without any preparatory steps was developed. This automated method for the direct determination of LDL-cholesterol takes advantage of the selective micellary solubilization of LDL-cholesterol by a nonionic detergent and the interaction of a sugar compound and lipoproteins (VLDL and chylomicrons). When a detergent is included in the enzymatic method for cholesterol determination (cholesterol esterase - cholesterol oxidase coupling reaction), the relative reactivities of cholesterol in the lipoprotein fractions increase in this order:
HDL < chylomicrons < VLDL < LDL.

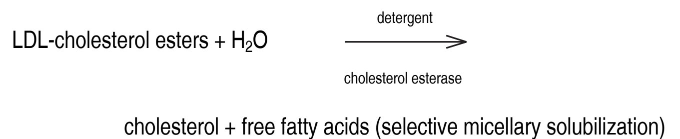
The combination of a sugar compound with detergent enables the selective determination of LDL-cholesterol in serum and plasma samples.

Non-fasting sample results are slightly lower than fasting results. Comparable non-fasting results were observed with the beta quantification method.[10] This direct assay meets the 1995 NCEP goals of < 4 % total CV, bias ≤ 4 % versus reference method, and ≤ 12 % total analytical error.[11,12,13]

Test principle

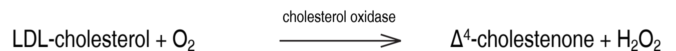
Homogeneous enzymatic colorimetric assay

Cholesterol esters and free cholesterol in LDL are measured on the basis of a cholesterol enzymatic method using cholesterol esterase and cholesterol oxidase in the presence of surfactants which selectively solubilize only LDL. The enzyme reactions to the lipoproteins other than LDL are inhibited by surfactants and a sugar compound. Cholesterol in HDL, VLDL and chylomicron is not determined.



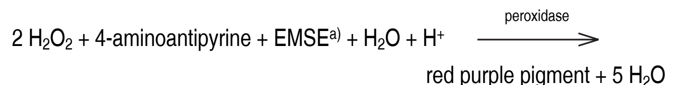
$$\text{LDL-cholesterol esters} + H_2O \xrightarrow[\text{cholesterol esterase}]{\text{detergent}} \text{cholesterol} + \text{free fatty acids (selective micellary solubilization)}$$

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



$$\text{LDL-cholesterol} + O_2 \xrightarrow{\text{cholesterol oxidase}} \Delta^4\text{-cholestenone} + H_2O_2$$

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



$$2\ H_2O_2 + \text{4-aminoantipyrine} + \text{EMSE}^{a)} + H_2O + H^+ \xrightarrow{\text{peroxidase}} \text{red purple pigment} + 5\ H_2O$$

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

In the presence of peroxidase, the hydrogen peroxide generated reacts with 4-aminoantipyrine and EMSE to form a red purple dye. The color intensity of this dye is directly proportional to the cholesterol concentration and is measured photometrically.

Reagents - working solutions

R1 Bis-tris[b)] buffer: 20.1 mmol/L, pH 7.0; 4-aminoantipyrine: 0.98 mmol/L; ascorbate oxidase (AOD, Acremonium spec.): ≥ 66.7 µkat/L; peroxidase (recombinant from Basidiomycetes): ≥ 166.7 µkat/L; BSA: 4.0 g/L; preservative

R2 MOPS[c] buffer: 20.1 mmol/L, pH 7.0; EMSE: 2.16 mmol/L; cholesterol esterase (Pseudomonas spec.): ≥ 33.3 µkat/L; cholesterol oxidase (recombinant from E. coli): ≥ 31.7 µkat/L; peroxidase (recombinant from Basidiomycetes): ≥ 333.3 µkat/L; BSA: 4.0 g/L; detergents; preservative

b) bis(2-hydroxyethyl)-amino-tris-(hydroxymethyl)-methane

c) 3-morpholinopropane-1-sulfonic acid

R1 is in position B and R2 is in position C.

Precautions and warnings

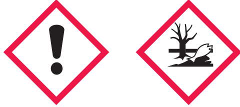
For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

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.

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



Warning

H317	May cause an allergic skin reaction.
H319	Causes serious eye irritation.
H411	Toxic to aquatic life with long lasting effects.

Prevention:

P261	Avoid breathing mist or vapours.
P273	Avoid release to the environment.
P280	Wear protective gloves/ eye protection/ face protection.

Response:

P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P337 + P313	If eye irritation persists: Get medical advice/attention.
P391	Collect spillage.

Product safety labeling follows EU GHS guidance.

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

Reagent handling

Ready for use

Storage and stability

LDLC3

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

Diluent NaCl 9 %

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, K_2- and K_3-EDTA plasma.

Fasting and non-fasting samples can be used.[6]

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:[14,15]	7 days at 2-8 °C
	12 months at -20 °C
	12 months at -70 °C

It is reported that EDTA stabilizes lipoproteins.[13]

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

cobas c 311 test definition

Assay type	2-Point End
Reaction time / Assay points	10 / 6-31
Wavelength (sub/main)	700/600 nm
Reaction direction	Increase
Units	mmol/L (mg/dL, g/L)

Reagent pipetting		Diluent (H_2O)
R1	150 µL	–
R2	50 µL	–

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2 µL	–	–
Decreased	10 µL	15 µL	135 µL
Increased	2 µL	–	–

cobas c 501 test definition

Assay type	2-Point End
Reaction time / Assay points	10 / 10-47
Wavelength (sub/main)	700/600 nm
Reaction direction	Increase
Units	mmol/L (mg/dL, g/L)

Reagent pipetting		Diluent (H_2O)
R1	150 µL	–
R2	50 µL	–

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2 µL	–	–
Decreased	10 µL	15 µL	135 µL
Increased	2 µL	–	–

cobas c 502 **test definition**

Assay type	2-Point End
Reaction time / Assay points	10 / 10-47
Wavelength (sub/main)	700/600 nm
Reaction direction	Increase
Units	mmol/L (mg/dL, g/L)

Reagent pipetting		Diluent (H_2O)
R1	150 µL	–
R2	50 µL	–

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2 µL	–	–
Decreased	10 µL	15 µL	135 µL
Increased	4 µL	–	–

Calibration

Calibrators	S1: H_2O
	S2: C.f.a.s. Lipids
Calibration mode	Linear
Calibration frequency	2-point 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 beta quantification method as defined in the recommendations in the LDL Cholesterol Method Certification Protocol for Manufacturers.[16]

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

Roche/Hitachi **cobas c** systems automatically calculate the analyte concentration of each sample.

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

Limitations – interference

Criterion: Recovery within ± 0.40 mmol/L of initial values of samples ≤ 4.0 mmol/L and within ± 10 % for samples > 4.0 mmol/L.

Icterus:[17] 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:[17] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[17] No significant interference up to an L index of 1000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

No significant interference from HDL-C (≤ 3.03 mmol/L or ≤ 117 mg/dL), VLDL-C (≤ 3.63 mmol/L or ≤ 140 mg/dL), or chylomicrons (≤ 22.6 mmol/L or ≤ 2000 mg/dL triglycerides).

Drugs: No interference was found at therapeutic concentrations using common drug panels.[18,19]

Nicotinic acid (Niacin), statins (Simvastatin) and fibrates (Clofibrate) tested at therapeutic concentration ranges did not interfere.

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 LDL-C results. 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.

Ascorbic acid: No significant interference from ascorbic acid up to a concentration of 28.4 mmol/L (500 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 LDL-cholesterol result is significantly negatively biased versus beta quantification results.

EDTA plasma may cause decreased values compared to serum.[20]

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[21]

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 Roche/Hitachi **cobas c** systems. The latest version of the carry-over evasion list can be found with the NaOHD-SMS-SmpCln1+2-SCCS Method Sheets. For further instructions refer to the operator's manual. **cobas c** 502 analyzer: All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is required in certain cases.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

0.10-14.2 mmol/L (3.87-549 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	= 0.10 mmol/L (3.87 mg/dL)
Limit of Detection	= 0.10 mmol/L (3.87 mg/dL)
Limit of Quantitation	= 0.10 mmol/L (3.87 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 ≥ 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 for LDL-C is 0.10 mmol/L determined in accordance with the guidelines in CLSI document EP17-A2, based on a minimum of 48 determinations, and a total error goal of 10 % calculated using RMS error model.

Expected values[22]

Levels in terms of risk for coronary heart disease.

Adult levels:

Optimal	< 2.59 mmol/L (< 100 mg/dL)
Near optimal/above optimal	2.59-3.34 mmol/L (100-129 mg/dL)
Borderline high	3.37-4.12 mmol/L (130-159 mg/dL)
High	4.14-4.89 mmol/L (160-189 mg/dL)
Very high	≥ 4.92 mmol/L (≥ 190 mg/dL)

Risk classification of patients and treatment therapies are described in international guidelines.[23]

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 analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Repeatability and intermediate precision were determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP5 requirements (4 aliquots per run, 1 run per day, 21 days). The following results were obtained:

Repeatability	*Mean mmol/L (mg/dL)*	SD mmol/L (mg/dL)	CV %
Precinorm L	2.69 (104)	0.02 (1)	0.7
Precipath HDL/LDL-C	4.93 (191)	0.03 (1)	0.7
Human serum 1	0.302 (11.7)	0.004 (0.2)	1.2
Human serum 2	2.93 (113)	0.02 (1)	0.7
Human serum 3	7.83 (303)	0.06 (2)	0.7
Human serum 4	3.67 (142)	0.03 (1)	0.7
Human serum 5	13.6 (526)	0.1 (4)	0.8

Intermediate precision	*Mean mmol/L (mg/dL)*	SD mmol/L (mg/dL)	CV %
Precinorm L	2.69 (104)	0.06 (2)	2.3
Precipath HDL/LDL-C	5.02 (194)	0.11 (4)	2.1
Human serum 1	0.316 (12.2)	0.008 (0.3)	2.5
Human serum 2	3.03 (117)	0.06 (2)	2.1
Human serum 3	8.14 (315)	0.16 (6)	1.9
Human serum 4	3.71 (143)	0.08 (3)	2.1
Human serum 5	13.7 (530)	0.3 (12)	2.0

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

Method comparison

LDL cholesterol values for human serum samples obtained on a Roche/Hitachi **cobas c** 501 analyzer (y) were compared to those determined using the previous reagent (LDL_C) on the same analyzer (x).

Sample size (n) = 100

Passing/Bablok[24]	Linear regression
y = 0.984x - 0.019 mmol/L	y = 0.971x + 0.043 mmol/L
τ = 0.919	r = 0.999

The sample concentrations were between 0.129 and 13.8 mmol/L (4.99 and 534 mg/dL).

LDL cholesterol values for human serum samples obtained on a Roche/Hitachi **cobas c** 501 analyzer (y) were compared to those determined using the corresponding reagent on a Roche/Hitachi **cobas c** 701 analyzer (x).

Sample size (n) = 167

Passing/Bablok[24]	Linear regression
y = 0.988x + 0.021 mmol/L	y = 0.982x + 0.047 mmol/L
τ = 0.937	r = 0.999

The sample concentrations were between 0.180 and 14.2 mmol/L (6.926 and 549 mg/dL).

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

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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 (for USA: see dialog.roche.com for definition of symbols used):

Symbol	Meaning
CONTENT	Contents of kit
⟶	Volume after reconstitution or mixing
GTIN	Global Trade Item Number

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

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