08057966500V8.0

LDLC3

cobas®

LDL-Cholesterol Gen.3

Order information

REF	[i]	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
08057966190*	08057966500	LDL-Cholesterol Gen.3 (600 tests)	System-ID 2082 002	**cobas c** 303, **cobas c** 503, **cobas c** 703
08057966214*	08057966500	LDL-Cholesterol Gen.3 (600 tests)	System-ID 2082 002	**cobas c** 303, **cobas c** 503, **cobas c** 703

Materials required (but not provided):

12172623122	Calibrator f.a.s. Lipids (3 × 1 mL)	Code 20424	
05117003190	PreciControl ClinChem Multi 1 (20 × 5 mL)	Code 20391	
05947626190	PreciControl ClinChem Multi 1 (4 × 5 mL)	Code 20391	
05117216190	PreciControl ClinChem Multi 2 (20 × 5 mL)	Code 20392	
05947774190	PreciControl ClinChem Multi 2 (4 × 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

LDLC3: ACN 20820

Intended use

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

Summary

Measurements of LDL-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.

The Low Density Lipoproteins (LDLs) are derived from VLDLs (Very Low Density Lipoproteins) that are enriched 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) result in the destruction of the endothelial function and a higher LDL-cholesterol uptake in the monocyte/macrophage system as well as into smooth muscle cells in vessel walls. The majority of cholesterol stored in atherosclerotic plaques originates from LDL.

LDL particles play a key role in causing and influencing the progression of atherosclerotic cardiovascular diseases (ASCVDs), including coronary heart disease (CHD), ischemic stroke, peripheral artery disease, and aortic aneurysm.[1] Atherosclerosis is a condition when the arteries are hardened and narrowed by plaque formation, which is a deposition of fats, cholesterol and other substances in and on the artery walls. Over time, the plaques can remain asymptomatic or become obstructive (stable angina). Eventually, plaque rupture can occur, where the contact of blood with the exposed plaque content can lead to thrombus formation and subsequent myocardial infarction or stroke.[1] The LDL-cholesterol value is a measure of the cholesterol mass carried by LDL particles and is used as a clinical predictor for ASCVD.[2] As a result, measurements of LDL-cholesterol 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.[3,4] 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 and myocardial infarction.[3,4] Non-fasting sample results are slightly lower than fasting results.[5]

Various methods are available for the determination of LDL-cholesterol such as ultracentrifugation as the reference method, lipoprotein electrophoresis, high performance liquid chromatography (HPLC) and precipitation methods.[6,7] 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.[8] 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.[9]

The calculation of the LDL-cholesterol concentration according to Friedewald's formula is based on 2 cholesterol determinations (total cholesterol and HDL-cholesterol) and 1 triglyceride determination.[10]

Friedewald's formula for calculation of LDL-cholesterol 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-cholesterol using this assumption is only acceptable in samples with a triglyceride concentration < 2.0 mmol/L (177 mg/dL).[11,12] 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-cholesterol 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.

Comparable non-fasting results were observed with the beta quantification method.[13] This direct assay meets the 1995 NCEP goals of < 4 % total coefficient of variation (CV), bias ≤ 4 % versus reference method, and ≤ 12 % total analytical error.[14,15,16]

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

R3 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 R3 is in position C.

Precautions and warnings

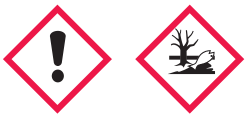
For in vitro diagnostic use for laboratory professionals. Exercise the normal precautions required for handling all laboratory reagents.

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:



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.

Hazardous components:

- reaction mass of 5-chloro-2-methyl-2H-isothiazol-3-one and 2-methyl-2H-isothiazol-3-one (3:1)

Product safety labeling follows EU GHS guidance.

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

Reagent handling

Ready for use

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:	26 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.[9]

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:[17,18]	7 days at 2-8 °C
	12 months at -20 °C (± 5 °C)
	12 months at -70 °C (± 5 °C)

Freeze only once.

It is reported that EDTA stabilizes lipoproteins.[16]

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_2O)
R1	82 µL	–
R3	27 µL	–

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*

Normal	1.1 µL	–	–
Decreased	5.5 µL	10 µL	90 µL
Increased	1.1 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: 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 beta quantification method as defined in the recommendations in the LDL Cholesterol Method Certification Protocol for Manufacturers.[19]

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 26 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 × 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:[20] 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:[20] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[20] 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.[21,22]

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.[23]

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[24]

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

0.10-14.2 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 95^{th} 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[25]

Levels in terms of risk for coronary heart disease.

mmol/L*

Adult levels:

Optimal	< 2.59 mmol/L
Near optimal/above optimal	2.59-3.34 mmol/L
Borderline high	3.37-4.12 mmol/L
High	4.14-4.89 mmol/L
Very high	≥ 4.92 mmol/L

* calculated by unit conversion factor

mg/dL

Adult levels:

Optimal	< 100 mg/dL
Near optimal/above optimal	100-129 mg/dL

Borderline high	130-159 mg/dL
High	160-189 mg/dL
Very high	≥ 190 mg/dL

Risk classification of patients and treatment therapies are described in international guidelines.[26]

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. 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 mmol/L*	*SD mmol/L*	*CV %*
PCCC1[d)]	1.43	0.00779	0.5
PCCC2[e)]	2.60	0.0129	0.5
Human serum 1	0.163	0.00288	1.8
Human serum 2	1.27	0.00627	0.5
Human serum 3	2.57	0.0131	0.5
Human serum 4	7.54	0.0358	0.5
Human serum 5	13.8	0.0627	0.5

Intermediate precision	*Mean mmol/L*	*SD mmol/L*	*CV %*
PCCC1[d)]	1.43	0.0147	1.0
PCCC2[e)]	2.60	0.0298	1.1
Human serum 1	0.163	0.00337	2.1
Human serum 2	1.27	0.00940	0.7
Human serum 3	2.57	0.0160	0.6
Human serum 4	7.54	0.0509	0.7
Human serum 5	13.8	0.0931	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

LDL-cholesterol values for human serum 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) = 86

Passing/Bablok[27]	Linear regression
y = 1.021x + 0.0546 mmol/L	y = 1.015x + 0.0745 mmol/L
τ = 0.984	r = 1.000

The sample concentrations were between 0.120 and 14.0 mmol/L.

LDL-cholesterol values for human serum 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) = 86

Passing/Bablok[27]	Linear regression
y = 1.005x + 0.0713 mmol/L	y = 1.008x + 0.0574 mmol/L
τ = 0.981	r = 1.000

The sample concentrations were between 0.130 and 13.8 mmol/L.

LDL-cholesterol values for human serum 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[27]	Linear regression
y = 0.973x - 0.0361 mmol/L	y = 0.981x - 0.0623 mmol/L
τ = 0.986	r = 1.000

The sample concentrations were between 0.208 and 13.9 mmol/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.

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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