

## Tina-quant Lipoprotein (a) Gen.2

REF		CONTENT		Analyzer(s) on which cobas c pack(s) can be used
08106126190	08106126500	Tina-quant Lipoprotein (a) Gen.2 (150 tests)	System-ID 2086 001	<b>cobas c 303, cobas c 503</b>

Materials required (but not provided):

05852641190	Preciset Lp(a) Gen.2 (5 × 1 mL)	Codes 20962-20966	
05852650190	PreciControl Lp(a) Gen.2 Level Low (2 × 1 mL) Level High (2 × 1 mL)	Code 20137 Code 20138	
08063494190	Diluent NaCl 9 % (123 mL)	System-ID 2906 001	

## English

## System information

LPA2: ACN 20860

## Intended use

In vitro test for the quantitative determination of lipoprotein (a) in human serum and plasma on **cobas c** systems.

## Summary

Lipoprotein (a) [Lp(a)] measurements, performed with this assay in human serum and plasma are used as an aid in evaluating lipid metabolism disorders and assessing atherosclerotic cardiovascular disease, when used in conjunction with clinical evaluation and other lipoprotein tests.

Lp(a) is a class of lipoprotein particles with structural properties similar to low density lipoprotein (LDL).<sup>1,2</sup> Compared to LDL, Lp(a) contains the Lp(a)-specific glycoprotein apolipoprotein(a) [apo(a)]. Apo(a) is a carbohydrate-rich protein and is bound to apoB-100 through a single disulfide bridge.<sup>3</sup> It is highly homologous to plasminogen and contains multiple Kringle domains, which are loop-like structures.<sup>3,4</sup> Kringle IV (KIV) exhibits 10 different types in apo(a), with type 1 and 3 to 10 present as a single copy and type 2 present in a number of variable copies in different individuals. The number of KIV type 2 (KIV-2) are genetically determined by the apo(a) gene LPA on chromosome 6 and may range from 1 to > 40 copies, resulting in multiple different isoforms and thus in a large size heterogeneity of apo(a) size ranging from 250 kDa to > 800 kDa.<sup>5,6</sup> There is a pronounced inverse correlation between the number of KIV 2 repeats and the serum/plasma concentration of Lp(a).<sup>7</sup> Individuals expressing a low number of repeats resulting in small apo(a) isoforms have on average markedly higher serum Lp(a) concentrations, compared with individuals carrying only large apo(a) isoforms.<sup>8</sup>

Lp(a) levels are predominantly genetically determined by the apo (a) gene and are not influenced by age or diet.<sup>9,10</sup> Concentrations may vary among individuals and among populations of different ancestries.<sup>11</sup>

The variable number of identical KIV-2 repeats may interfere with the accurate measurement of Lp(a) in serum and plasma: Lp(a) with a lower number of KIV repeats might be underestimated and Lp(a) with a larger number of KIV repeats might be overestimated by KIV-2 dependent methods.<sup>2,3</sup> Due to this pronounced size heterogeneity, accurate quantification of the mass of Lp(a) is problematic because the size of the molecule in the samples may be greatly different than the size in the assay calibrators. For this reason, the scientific community recommends the use of Lp(a) assays not affected or minimally affected by apo(a) size variation and calibrated in nmol/L.<sup>12,13,14</sup> In addition, the value of the present WHO/IFCC reference material for Lp(a) and that of the new reference material being prepared by the current IFCC Standardization group, are expressed in nmol/L.<sup>3,12</sup>

Assays that provide measurements in nmol/L require standardization against an apo(a) size independent method. For this assay, the standardization process is performed by comparison to an ELISA method based on a monoclonal antibody that detects a single epitope per Lp(a) molecule located at the Kringle IV type 9, allowing for the reporting of measurements in nmol/L.<sup>2,3</sup> The comparability of the Roche assay against this apo(a) size independent ELISA reference method is constantly assessed through a certification process repeated for every master calibrator.

There is strong evidence that a statistically significant, independent relationship exists between increased Lp(a) concentrations and an increased risk of atherosclerotic cardiovascular disease.<sup>15,16,17</sup> High Lp(a) concentrations in serum correlate with premature manifestation of atherosclerosis and strokes.<sup>15</sup> Lp(a) is also a risk for aortic valve stenosis.<sup>15</sup>

A high Lp(a) concentration should be interpreted in the context of other risk factors and absolute global cardiovascular risk.<sup>15</sup>

Multiple national and international societies have incorporated recommendations for Lp(a) testing into their guidelines.<sup>15,18,19,20,21,22, 23,24</sup> The Canadian Cardiovascular Society and the European Atherosclerosis Society (EAS) recommend all adults be tested for elevated Lp(a) at least once in their lifetime.<sup>21,23</sup> According to the EAS, Lp(a) measurements should also be considered in selected cases with a family history of premature cardiovascular disease.<sup>21</sup> The ACC/AHA considers Lp(a) an ASCVD risk enhancer and recommends screening in selected individuals with borderline or intermediate risk.<sup>20</sup>

## Test principle

Particle enhanced immunoturbidimetric assay.<sup>25</sup>

Human lipoprotein (a) agglutinates with latex particles coated with anti-Lp(a) antibodies. The precipitate is determined turbidimetrically.

## Reagents - working solutions

- R1** Glycine buffer: 170 mmol/L, pH 7.0; stabilizers; BSA; rabbit serum 0.1 %, preservative
- R3** Latex particles coated with polyclonal anti-human lipoprotein(a) antibodies (rabbit); glycine buffer: 170 mmol/L, pH 7.3, BSA; preservative

R1 is in position B and R3 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.

## Reagent handling

Ready for use

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

## 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 or K<sub>2</sub>-EDTA and K<sub>3</sub>-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.

With K<sub>3</sub>-EDTA tubes pay particular attention that the tubes are adequately filled.

Centrifuge samples containing precipitates before performing the assay.

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

Stability:

If samples are not assayed within 8 hours, samples should be stored at 2-8 °C.<sup>26</sup>

If samples are not assayed within 48 h,<sup>26</sup> samples should be stored frozen at -70 °C (± 10 °C) or below.<sup>27,28</sup> Frozen samples should be thawed only once. Analyte deterioration may occur in samples that are repeatedly frozen and thawed.

#### 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)	800/660 nm		
Reagent pipetting		Diluent (H <sub>2</sub> O)	
R1	100 µL	–	
R3	25 µL	–	
<i>Sample volumes</i>	<i>Sample</i>	<i>Sample dilution</i>	
		<i>Sample</i>	<i>Diluent (NaCl)</i>
Normal	1.5 µL	–	–
Decreased	6.0 µL	8 µL	88 µL
Increased	1.5 µL	–	–

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

#### Calibration

Calibrators	S1: H <sub>2</sub> O S2-S6: Preciset Lp(a) Gen.2
Calibration mode	Non-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 IFCC reference material SRM2B for nmol/L.<sup>29</sup>

#### 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 nmol/L (mg/dL).

Conversion factor:<sup>30</sup> mg/dL = (nmol/L + 3.83) × 0.4587

#### Limitations – interference

Criterion: Recovery within ± 6 nmol/L of initial values of samples ≤ 60 nmol/L and within ± 10 % for samples > 60 nmol/L.

Icterus:<sup>31</sup> 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:<sup>31</sup> No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):<sup>31</sup> No significant interference up to an L index of 2000. 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 1200 IU/mL.

Plasminogen: No significant cross-reactivity in the tested concentration range (up to 150 mg/dL).

Apolipoprotein B: No significant cross-reactivity in the tested concentration range (up to 200 mg/dL).

Drugs: No interference was found at therapeutic concentrations using common drug panels.<sup>32, 33</sup>

High dose hook-effect: No false result occurs up to a lipoprotein (a) concentration of 450 nmol/L.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.<sup>34</sup>

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

Measuring range: 7-240 nmol/L

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:3 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 3.

##### Lower limits of measurement

*Limit of Blank, Limit of Detection and Limit of Quantitation*

Limit of Blank = 6 nmol/L

Limit of Detection = 7 nmol/L

Limit of Quantitation = 7 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 95<sup>th</sup> 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.

## Tina-quant Lipoprotein (a) Gen.2

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 lipoprotein (a) samples.

## Expected values

A Lp(a) concentration of 30 mg/dL corresponding to the 75th percentile in a male Caucasian reference population is widely used as cut-off point or threshold value.<sup>35,36</sup>

The European Atherosclerosis Society recommends screening for elevated Lp(a) in those at intermediate or high CVD/CHD risk and defines a desirable Lp(a) level  $\leq 50$  mg/dL.<sup>37</sup>

However the NHLBI recommends to stop using data for total Lp(a) mass, and to use nmol/L units instead, which consider the number of particles. Additionally they recommend to use assays independent from apo(a) size and standardized according to the IFCC reference material SRM2B.<sup>38</sup>

Based on the evaluation of Framingham data values above 75 nmol/L are regarded as a cut-off value for the presence of an increased risk.<sup>38</sup>

Elevated Lp(a) levels can be found in most racial/ethnicity groups, with the prevalence being lowest in whites and Asians. The median Lp(a) levels in black subjects and in Asian Indians from southern locations are 2- to 4-fold higher compared with whites, and up to 68 % of blacks have Lp(a) levels  $> 75$  nmol/L, whereas levels above this threshold are present in around 25 % of whites.<sup>39</sup>

Therefore reference ranges have not been established for this assay for different ethnic populations or disease states. Since Lp(a) levels are largely influenced by hereditary factors and vary with ethnic populations it is recommended that each laboratory establish own expected values.

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 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 nmol/L	SD nmol/L	CV %
Lp (a) Control Level Low	35.2	0.412	1.2
Lp (a) Control Level High	97.7	0.435	0.4
Human serum 1	19.7	0.414	2.1
Human serum 2	49.3	0.516	1.0
Human serum 3	80.5	0.434	0.5
Human serum 4	120	0.546	0.5
Human serum 5	203	0.794	0.4
Intermediate precision	Mean nmol/L	SD nmol/L	CV %
Lp (a) Control Level Low	35.1	0.562	1.6
Lp (a) Control Level High	99.0	1.14	1.2
Human serum 1	19.7	0.508	2.6
Human serum 2	49.3	0.676	1.4
Human serum 3	80.5	0.831	1.0
Human serum 4	119	1.14	1.0

Human serum 5	203	1.33	0.7
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The data obtained on **cobas c** 503 analyzer(s) are representative for **cobas c** 303 analyzer(s).

## Method comparison

Lipoprotein (a) 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 ( $n$ ) = 99

Passing/Bablok <sup>40</sup>	Linear regression
$y = 1.019x + 0.878$ nmol/L	$y = 1.010x + 1.34$ nmol/L
$\tau = 0.988$	$r = 1.000$

The sample concentrations were between 7.34 and 235 nmol/L.

Lipoprotein (a) 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 ( $n$ ) = 72

Passing/Bablok <sup>40</sup>	Linear regression
$y = 0.984x + 2.00$ nmol/L	$y = 0.988x + 1.70$ nmol/L
$\tau = 0.990$	$r = 1.000$

The sample concentrations were between 7.07 and 222 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.

### 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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