# Lipoprotein (a) [Lp(a)]

**En**

**Reference Number: LN080**
**Reference Number: LN081**

**Diagnostic reagent for determination of Lipoprotein (a) [Lp(a)] concentration.**
Liquid. Dual Reagents (Ratio: R1/R2: 4/1). Store at +2/+8°C. For in Vitro Diagnostic Use (IVD). Do not freeze.
The products with LN080/LN081 reference numbers provided are compatible for use with Abbott Alinity biochemistry autoanalyzer series.

*Changes made in the instructions for use are marked as grey.*

## INTENDED USE [1]

This test is for in vitro diagnostic use in the quantitative determination of lipoprotein (a) [Lp(a)] concentration in human serum or plasma by automated methods of biochemistry analyzers. It aids in the assessment of ers such as LDL cholesterol, remnant cholesterol, apoB, and related cardiovascular risk markers. It also supports clinical decision-making in identifying individuals who may have an increased inherited or particle-related cardiovascular risk, especially in cases where elevated Lp(a) levels may contribute to disease risk independently of other lipid abnormalities.

## GENERAL INFORMATION [1]

The variation in apo(a) molecular size gives rise to structural diversity among Lp(a) particles, and this diversity is a major consideration for the reliable determination of Lp(a) in human plasma.[2] Because repeated antigenic sites occur in differing numbers among Lp(a) particles, antibody binding to these repeated epitopes may depend on the size of apo(a). Therefore, immunoassays that use polyclonal antibodies, or monoclonal antibodies directed specifically against kringle 4 type 2 epitopes, may produce biased results. In samples containing smaller apo(a) isoforms than those used in the assay calibrator, apo(a) concentration may be underestimated, whereas samples containing larger apo(a) isoforms may yield overestimated values. The influence of apo(a) size variability on Lp(a) measurement has been examined in detail.[3,4] Assays based on monoclonal antibodies offer a theoretical benefit, since these antibodies can be immunochemically defined and selected according to their reactivity with individual epitopes, including epitopes outside the kringle 4 type 2 region.

Lp(a) can be measured by several analytical formats, including turbidimetric, nephelometric, radiometric, and enzymatic methods. With the exception of enzyme immunoassays such as ELISA, most of these methods rely on polyclonal antibodies obtained from different animal species. Commercial direct-binding sandwich ELISA systems generally use combinations of monoclonal and polyclonal antibodies. One assay design makes use of the fact that Lp(a) particles contain both apo(a) and apoB. In this format, Lp(a) particles are captured by a monoclonal or polyclonal antibody directed against apo(a), and an enzyme-labeled anti-apoB antibody is used for detection. An ELISA based on this principle has been described and is available commercially.[5] In an alternative design, both the capture and detection antibodies are directed against apo(a). At present, it remains uncertain which assay approach is superior for estimating the risk of coronary heart disease or stroke, because the underlying pathogenic mechanisms have not been fully clarified. It is therefore unclear whether the risk is mainly related to an increased number of circulating Lp(a) particles, as reflected by assays using anti-apoB detection antibodies, or whether it is also associated with apo(a) isoforms of particular sizes, which may be more readily identified by assays using anti-apo(a) detection antibodies. It is likely that both particle number and apo(a) size contribute to risk.

Traditionally, Lp(a) results have been expressed either as total Lp(a) particle mass or as Lp(a) protein concentration. When the objective is to obtain Lp(a) measurements that are not influenced by apo(a) size, it is recommended that assays use antibodies directed against apo(a) regions other than kringle 4 type 2, or against the apoB component of Lp(a). This approach allows results to be reported in nanomoles per liter (nmol/L). If specific apo(a) polyform sizes are considered relevant to risk, mixtures of pan-monoclonal antibodies against kringle 4 type 2 may be more appropriate.[2]

Currently, Lp(a) testing is not fully standardized, and most assays have not been systematically assessed for sensitivity to apo(a) size. Consequently, Lp(a) values reported in clinical studies are not always directly comparable. Nevertheless, a total Lp(a) particle mass of approximately 30 mg/dL has historically been used as a threshold above which increased Lp(a) concentrations are associated with a higher risk of coronary heart disease. Lp(a) may also be reported in terms of particle number, apo(a) mass, apoB mass, or Lp(a)-associated cholesterol. In routine use, however, total Lp(a) mass remains the most common form of reporting.

Because reference methods and standardization

procedures for Lp(a) are still limited, it is difficult to establish precise decision limits for clinical interpretation. One practical, although imperfect, approach is to define a reference interval for each assay and report patient results as percentile values within that interval. In white populations, Lp(a) concentrations above the 80th percentile may be interpreted as indicating an increased risk of coronary atherosclerosis. However, since Lp(a) concentrations differ among ethnic groups, reference values should be established on a population-specific basis, and decision limits may also need to account for race. For example, African Americans generally have substantially higher Lp(a) concentrations than whites, but this does not necessarily correspond to a higher observed incidence of coronary heart disease. Using a strategy similar to that applied by the apoA-I and apoB committee, an IFCC committee developed reference materials suitable for use with commercially available Lp(a) methods. As expected, the use of a shared calibrator improved agreement among Lp(a) results, although it did not achieve complete standardization. True standardization can only be achieved when appropriate antibodies are used.

Nearly all retrospective case-control studies, large prospective population-based investigations, and large genetic studies conducted in white populations have demonstrated a strong relationship between elevated Lp(a) concentrations and increased risk of coronary heart disease, aortic valve stenosis, and all-cause mortality.[6-9] For this reason, increased Lp(a) is regarded as a causal risk factor for ASCVD, similar to elevated LDL cholesterol and remnant cholesterol.

Several studies have indicated that apo(a) isoform size may be associated with a higher prevalence of coronary heart disease. The method providing the highest resolution and analytical sensitivity for apo(a) phenotype determination involves separation of apo(a) by agarose gel electrophoresis, followed by immunoblotting with a specific antibody and detection using radiolabeled protein A. This technique enables identification of at least 34 different apo(a) polymorphs. It also allows apo(a) size to be reported according to kringle number and is in agreement with findings on apo(a) gene size variability obtained by pulsed-field gel electrophoresis and genomic blotting.[10] In addition, DNA-based approaches, such as real-time polymerase chain reaction (PCR), can be used to determine the combined number of kringle 4 type 2 repeats present on the two alleles.[11]

## TEST PRINCIPLE

**Immunoturbidimetric Method**

When the serum sample is combined with anti-human Lp(a) antiserum, Lp(a) present in the sample reacts specifically with the antibody and forms antigen-antibody complexes. The formation of these complexes produces turbidity in the reaction mixture. The change in turbidity is measured photometrically at 340 nm and 700 nm, and the Lp(a) concentration in the sample is calculated quantitatively.

## REAGENT COMPONENTS

**R1:**
Glycine-buffer (pH:8.0-8.5): < 1.5%
Sodium azide : < 0.1%

**R2:**
Glycine-buffer (pH:8.0-8.5): < 1.5%
Latex particles coated with anti-human lipoprotein (a) antibody (rabbit)
Sodium azide : < 0.1%

## REAGENT PREPARATION

Reagent is ready for use.

## REAGENT STABILITY AND STORAGE

Reagents are stable at +2/+8˚C till the expiration date stated on the label which is only for closed vials.

Once opened vials are stable for 30 days at +2/+8°C in optimum conditions. On board stability is strongly related to auto analyzers' cooling specification and carry-over values.

Reagent stability and storage data have been verified by using Clinical and Laboratory Standards Institute (CLSI) EP25-A protocol.[12]

## SAMPLE REQUIREMENTS

Serum, heparin plasma or EDTA plasma can be used and are collected according to the standard procedures. Multiple sample freezing and thawing should be avoided. The sample should be homogenized before testing.

**Lp(a) activity stability in serum and plasma:**
8 days at +2/+8ºC

**Unit Conversion:**[23]
mg/dL = (nmol/L + 3.83) × 0.4587

## CALIBRATION AND QUALITY CONTROL

**Calibration:** The assay requires the use of a Lipoprotein (a) Calibrator.

Calibration stability depends on the application characteristics and cooling capacity of the autoanalyzer used. Calibration stability is 4 weeks.

**Control:** Commercially available control material with established values determined by this method can be used.

At least two level controls must be run once in every 24 hours. Each laboratory should determine its own quality control scheme and procedures. If quality control results are not within acceptable limits, calibration is required.

## REFERENCE INTERVALS / MEDICAL DECISION LEVELS

Not elevated: < 30 mg/dL (< 75 nmol/L)
Borderline: 30-50 mg/dL (75-125 nmol/L)
Elevated: > 50 mg/dL (> 125 nmol/L) [24]

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

Reference interval has been verified by using CLSI EP28-A3c protocol.[13]

## PERFORMANCE CHARACTERISTICS

### Measuring Interval

According to CLSI EP34-ED1:2018, "Measuring Interval" refers to the interval where the analyte concentration is measured with intended accuracy in terms of medical and laboratory requirements without dilution, concentrating or any kind of pre-treatment that is between the analyte's lower limit of quantitation (LLoQ) and upper limit of quantitation (ULoQ).[14]

The determined analytic measuring interval for Lp(a) is 5.0 – 85.0 mg/dL

### Detection Capability

**Limit of Detection (LoD):** 2.9 mg/dL

**Limit of Quantitation (LoQ):** 5.0 mg/dL

**Note:** LoQ values are based on Coefficient of Variation Percentage (CV) ≤ 20%.

LoD and LoQ values have been verified by using CLSI EP17-A2:2012 protocol.[15]

### Linearity

This method shows measurement linearity in the activities up to 85 mg/dL.

Autoanaylzer's auto-dilution system can be used if the concentrations have higher values. See device manual for further information.

For manual dilution procedure, dilute the sample 10-fold using 0.90% isotonic. After the dilution, multiply the result of rerun sample by the dilution factor. Do not report the sample result after dilution if it is marked as lower than the linear lower limit. Rerun with a suitable dilution.

Linearity Studies data have been verified by using CLSI EP06-A:2003 protocol.[16]

### Precision

Running system has been developed according to 20x2x2 "The Single Site" protocol. Repeatability and Within-Laboratory Precision/Within-Device values have been obtained according to the running results.

According to the protocol in use, 2 separate runs per day have been made for 20 days (no obligation for being consecutive days). This protocol has been applied to each low and high samples separately and 80 results have been obtained for each one. Statistically, the results have been obtained using 2-factor Nested-ANOVA model.[17]

Repeatability (Within Run) and Repeatability (Day to Day) SD (standard deviation) and CV% values of Lp(a) have been given in the table 1 and 2 respectively.

**Table 1. Lp(a) Repeatability (Within Run) results obtained from samples in two different concentrations**

| Mean Concentration | SD | CV% | n |
|---|---|---|---|
| 26.2 mg/dL | 0.81 | 3.1 | 40 |
| 40.1 mg/dL | 0.88 | 2.2 | 40 |

**Note:** This working system has been named "Within-Run Precision" in the previous CLSI - EP05-A2 manual.[18]

**Table 2. Lp(a) Repeatability (Day to Day) results obtained from samples in two different concentrations**

| Mean Concentration | SD | CV% | n |
|---|---|---|---|
| 26.2 mg/dL | 1.10 | 4.2 | 84 |
| 40.1 mg/dL | 1.16 | 2.9 | 84 |

**Note:** This working system has been named "Total Precision" in the previous CLSI - EP05-A2 manual.[18]

### Method Comparison

As a result of the statistical evaluation of the method comparison data:

Passing-Bablock equation:[19]
y= -2.66 + 0.99x
r=0.98

### Interference

Endogenous interferant and analyte concentrations that have been used in the Lp(a) scanning tests has been determined according to "CLSI EP37-ED1:2018" and "CLSI EP07-ED3:2018" manuals.[20,21]

The total acceptable error rate, which is going to be used to detect whether the observed differential value obtained from Lp(a) interference scanning test is appropriate, is determined as ±25%.[22]

In Lp(a) test results, no significant interaction has been observed in the determined endogenous interferant and analyte concentrations or between interferants and analyte.

Hemoglobin : 1000 mg/dL
Bilirubin : 40 mg/dL
Triglycerides : 500 mg/dL

It should be noted that endogenous interferants, as well as various medicines and metabolites, anticoagulants (e.g. Heparin, EDTA, citrate, oxalate) and preservatives (e.g. sodium floride, iodoacetate, hydrochloride acide) such as additives, materials that may contact with samples during collection and processing (serum separator devices, sample collection containers and contents, catheters, catheter wash solutions, skin disinfectants, hand cleaners and lotions, glass washing detergents, powder gloves), dietary substances known to affect some specific tests (caffeine, beta-carotene, poppy seeds, etc.), or some substances present in a sample that cause foreign proteins (heterophilic antibodies, etc.), autoimmune response (autoantibodies, etc.), or due to malignancy (for example, interference by paraproteins with phosphate testing and indirect ion selective electrode methods) may show some negative effects that will cause various attempts and some misjudgements.[21]

These performance characteristics have been obtained using an autoanalyzer. Results may vary slightly when using different equipment or manual procedures.

## WARNINGS AND PRECAUTIONS

IVD: For in Vitro Diagnostic use only.
Do not use expired reagents.
Reagents with two different lot numbers should not be interchanged.
For professional use.
Follow Good Laboratory Practice (GLP) guidelines.
Contains sodium azide.

CAUTION: Human source samples are processed with this product. All human source samples must be treated as potentially infectious materials and must be handled in accordance with OSHA (Occupational Safety and Health Administration) standards.

**Danger**

| | |
|---|---|
| EUH032 | :Releases a very toxic gas if contacts with acid. |
| H317 | :May cause allergic skin reaction. |

**Precaution**

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| P280 | :Use protective gloves / clothes / glasses / mask. |
| P264 | :Wash your hands properly after using. |
| P272 | :Contaminated work clothes should not be allowed to be used outside of the workplace. |

**Intervention**

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|---|---|
| P302+P352 | :Wash with plenty of water and soap if it contacts with skin. |
| P333+P313 | :Seek medical help if it irritates your skin or develops rash. |
| P362+P364 | :Remove contaminated clothes and wash properly before using. |

**Disposal**

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| P501 | :Dispose the vials and contents according to the local regulations. |

## REFERENCES


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## SYMBOLS

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|---|---|
| IVD | In Vitro Diagnostic Medical Device |
| LOT | Lot Number |
| R1 | Reagent 1 |
| R2 | Reagent 2 |
| GTIN | Global Trade Item Number |
| REF | Reference Number |
| GLP | Good Laboratory Practices |
| FOR USE WITH | Identifies Products to Be Used Together |
| PRODUCT OF TURKEY | Product of Turkey |
|  | Manufacturer |
|  | Expiration Date |
|  | Temperature Limits |
|  | Consult Instructions for Use |
|  | Caution |
|  | Number of Tests |




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