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Lipoprotein(a) : Lp(a)

Proven to be the best methodology on the market

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Background

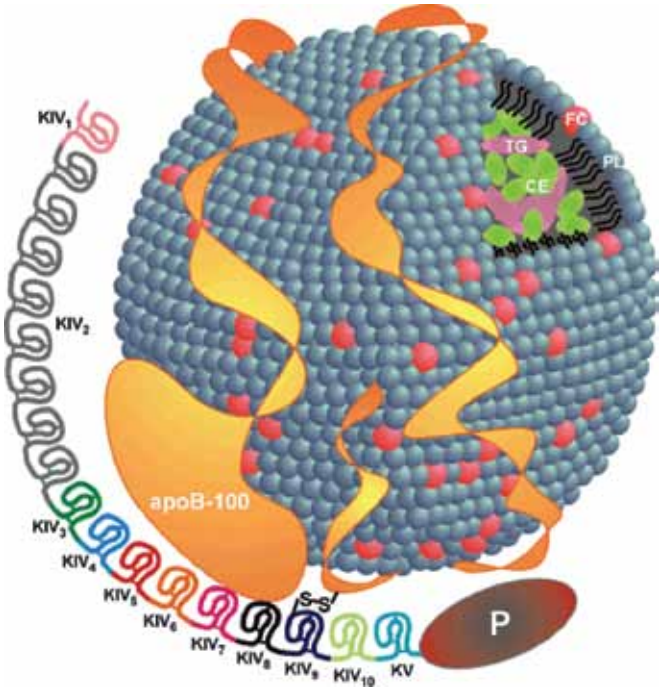
Cardiovascular disease (CVD) and more specifically, Myocardial Infarction (MI) remains a leading cause of morbidity and mortality, despite the targeting of LDL cholesterol via statin therapy.

There is a need for additional causal risk factors, beyond the traditional LDL measurement[1].

Large scale studies and international guidelines published between 2009 and 2010, have proven that Lp(a) is a major independent genetic risk factor for premature CVD and should be screened in all patients at moderate to high risk.

What is Lipoprotein(a) : Lp(a)?

- Lp(a) is a major independent genetic risk factor for cardiovascular disease[2]
- Lp(a) particles are similar to LDL consisting of a cholesterol-rich core, with an apoB-100 protein attached[3]
- However, Lp(a) uniquely differs to LDL in that it also has an apo(a) protein attached via a disulfide bond (see diagram)
- The apo(a) is comprised of a series of kringle structures
- There are 10 types of kringle IV and only one copy of each type except for type 2. Kringle IV, type 2 (KIV_2) is particularly susceptible to being manufactured repeatedly, depending on an individual's genetics (2-40 repeats)
- The number of KIV_2 repeats generates different isoforms and a major affect on the size of the apo(a) protein which affects the level of Lp(a)
- Apo(a) is synthesised in the liver and binds to newly synthesised apoB-100
- The size of the apo(a) protein is genetically determined and varies widely[1] hence, levels of Lp(a) can vary up to 1000-fold between individuals[1]
- Plasma levels rise shortly after birth up to a consistent level within several months, typical plasma levels of Lp(a) are similar in men and women: one in five (20%) have levels above 50 mg/dL.



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2010 Guidelines on Lp(a)[4]

Recent years have seen major scientific advances in the understanding of Lp(a) and its causal role in premature CVD.

Elevated Lp(a) levels associate robustly and specifically with increased CVD risk. This association is continuous and does not depend on high levels of LDL or non-HDL cholesterol, or the presence of other CVD risk factors. Lp(a) levels, like elevated LDL, is causally related to premature development of atherosclerosis and CVD.

Table 1 Comparison of evidence supporting the contention that elevated LDL cholesterol and elevated Lp(a) each cause cardiovascular disease[4]

Assay details	Elevated LDL cholesterol	Elevated Lp(a)
Human epidemiology	Direct association in numerous studies	Direct association in numerous studies
Human genetic studies	Direct association in numerous studies, e.g. familial hypercholesterolaemia	Direct association in numerous studies, e.g. for kringle IV type 2 polymorphism
Mechanistic studies	Mechanism clearly demonstrated: LDL accumulates in intima and causes atherosclerosis	Mechanism similar to that for LDL cholesterol and/or prothrombotic/anti-fibrinolync effects
Animal models	Proatherogenic effect in numerous studies	Proatherogenic effect in numerous studies
Human intervention trials	Statin trials gave final proof of causality	Niacin trials are favourable

Whom to screen?[4]

The European Atherosclerotic Society suggest that Lp(a) should be measured once in all subjects at intermediate or high risk of CVD/CHD who present with:

i. Premature CVD
ii. Family hypercholesterolaemia
iii. A family history of premature CVD and/or elevated Lp(a)
iv. Recurrent CVD despite statin treatment
v. ≥ 3% 10-year risk of fatal CVD according to the European guidelines
vi. ≥ 10% 10-year risk of fatal and/or non-fatal CHD according to the US guidelines

Repeat measurement is only necessary if treatment for high Lp(a) levels is initiated in order to evaluate therapeutic response.

The evidence clearly supports Lp(a) as a priority for **reducing cardiovascular risk**, beyond that associated with LDL cholesterol. Clinicians should consider screening statin-treated patients with **recurrent heart disease**, in addition to those considered at moderate to high risk of heart disease - ***EAS Consensus Panel***[5]

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Desirable Levels[4]

Table 2 Desirable levels for low-density Lipoprotein cholesterol and lipoprotein(a) levels in the fasting or non-fasting state[4]

	Patients with CVD and/or diabetes	Other patients and individuals	Highest level of evidence for treatment
LDL cholesterol	< 2 mmol/L[a] (<77 mg/dL)	< 3 mmol/L[a] (116 mg/dL)	Ia: meta-analysis of randomised, controlled trials of statin treatment
Lp(a)	< 80th percentile (<~50 mg/dL[b])	< 80th percentile (<~50 mg/dL[b])	Ia: meta-analysis of randomised, controlled trials of niacin treatment

[a] According to the 2007 European guidelines
[b] The 80th percentile roughly corresponds to 50 mg/dL in Caucasians.

How to treat elevated Lp(a)?

- Patients with moderate or high risk of CVD should be screened for Lp(a)[1]
- Reducing Lp(a) to below cut-off should be a treatment priority, along with the lowering of LDL cholesterol[1]
- Lp(a) levels are generally not strongly affected by lifestyle changes[1]
- In general, serial measurement of Lp(a) is not required and only needs to be repeated if evaluating therapeutic response
- If Lp(a) is above cut-off the primary focus of treatment should be on reducing the patient's risk.[1] In addition, niacin therapy can be considered, particularly in high risk patients, as this has been shown to reduce Lp(a) by 30-40%.[1] Niacin-based therapies have been shown to improve patients' atherogenic lipid profile (increases HDL-C, decreases LDL-C, decreases Lp(a) and decreases triglycerides)
- LDL apheresis which removes Lp(a) efficaciously[8] should be considered in young or middle-aged patients with evidence of progressive coronary disease and markedly elevated plasma Lp(a)[4]

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Choosing your Lp(a) assay

Lp(a) levels are heavily influenced by the size of the attached apo(a) protein[7].

The size variation of apo(a) represents a serious challenge in the immunochemical measurement of Lp(a) for the following reasons[7]:

i. The antibodies should have isoform-insensitive immunoreactivity to apo(a)
ii. The choice of apo(a) size in the assay calibrator tends to be random and is not representative of all possible apo(a) size variations found in the general population
iii. Depending on the size of apo(a) used in the calibrator, many commercially available assays either underestimate or overestimate the concentrations of Lp(a) in plasma – hence they are strongly affected by "apo(a) size-related bias"

Utilisation of an inadequate methodology for Lp(a) is highly likely to lead to increased numbers of both false negatives and false positives[7] .This will lead to the potential misclassification of a significant number of both high and low risk patients.[7]

Randox Lp(a) Assay Details

Proven to be the best methodology on the market

- The Randox assay contains a very high density of isoform-insensitive antibodies and detection reagent – ensuring more Lp(a) bound antibodies are detected and more accurate measurement

- Randox produces a 5-point calibrator which takes into account the heterogeneity of the Lp(a) molecule for each of the levels, resulting in excellent commutability of the calibrator with patient samples

- Liquid ready-to-use IT assay
- Excellent stability (open vial stability 30 days on board)
- No sample preparation required
- Fully automated applications available for a wide range of analysers

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Randox Lp(a) Assay Details

High Performance Reagents

Assay Range - 2.1-90 mg/dl.

Sensitivity - 2.1 mg/dl.

Precision - The following coefficients of variation were obtained on a Hitachi™ 717 analyser.

	Lipoprotein (a) Mean (mg/dl)	Mean % CV	n
Intra-assay precision	21.0	1.63	20
	51.5	1.53	20
	83.05	2.40	20
Inter-assay precision	24.19	3.11	20
	32.58	3.52	20
	50.48	2.83	20

Product Description	Size	Cat. No.
Lp(a) Kit	1x10 ml, 1x6 ml 1x30 ml, 1x15ml	LP3403 LP2757
Lp(a) Kit for Dimension®	4x40 T	LP2878
Lp(a) Calibrator	5x1 ml	LP3404
Lp(a) Control (Level 3)	3x1 ml	LP3406
Lipid Control (Level 1)	5x3 ml or 5x1 ml	LE2661 or LE2668
Lipid Control (Level 2)	5x3 ml or 5x1 ml	LE2662 or LE2669
Lipid Control (Level 3)	5x3 ml or 5x1 ml	LE2663 or LE2670

Instrument Applications Available for Randox Lp(a)

Instruments

Abbott Aeroset/Architect
ABX Pentra 400
BS 120/200/300/400
BT 2000/BT3000/ILAB 300/Targa
CL 7200, ILab 1800, ILab 900
Express 550
Humalyzer 850, Humalyzer 900S
ILAB 600
ILAB 900/ILAB1800/Shimadzu CL 7200
Kone Progress, Kone Specific
Konelab 20i/30i/60i
Lisa 200-500/Mascott Plus/Clinline
Manual
Menarini Alcyon 300/Alcyon Falcor
Olympus AU400/AU600/AU2700
Olympus AU560
Olympus AU800/AU1000
Ortho Vitros Fusion
Prestige 24i/Saphire
RA 1000, RA Opera, RA XT
Randox RX daytona, RX imola
Roche Cobas 4000
Roche Cobas 6000 (c501)
Roche Cobas FARA
Roche Cobas Integra 400
Roche Hitachi 704
Roche Hitachi 717
Roche Hitachi 747/Modular P
Roche Hitachi 902
Roche Hitachi 904/911/912
Roche Hitachi 917/P Module
Siemens Dimension
Synchron CX 4/5/7/9/LX20
Unicel 600/800
Technicron RA1000/RAXT/Opera
Vitalab Flexor/Selectra E/Selectra II

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RX imola

Designed for medium to high throughout laboratories, the RX imola is a random access bench top clinical analyser with a maximum throughput of 560 tests per hour including ISEs.

RX daytona

Convenient bench top system, the RX daytona clinical analyser has a throughput of 450 tests per hour including ISEs via the optional ISE unit.

RX suzuka

The latest addition to the RX family of analysers, the RX suzuka is a fully automated, discrete random access clinical analyser with a throughput of 1200 tests per hour including ISEs.

RX daytona plus

A bench-top, fully automated, random access clinical analyser capable of performing routine and emergency STAT sampling with a throughput of 270 photometric tests per hour and 450 tests per hour including ISEs.

RANDOX

International Headquarters

Randox Laboratories Limited, 55 Diamond Road, Crumlin, County Antrim, United Kingdom, BT29 4QY

T +44 (0) 28 9442 2413 **F** +44 (0) 28 9445 2912 **E** marketing@randox.com **I** www.randox.com

Australia
Randox (Australia) Pty Ltd.
Tel: +61 (0) 2 9615 4640

Brazil
Randox Brasil Ltda.
Tel: +55 11 5181-2024

China
Randox Laboratories Ltd.
Tel: +86 021 6288 6240

Czech Republic
Randox Laboratories S.R.O.
Tel: +420 2 1115 1661

France
Laboratoires Randox
Tel: +33 (0) 130 18 96 80

Germany
Randox Laboratories GmbH
Tel: +49 (0) 2151/93 706-11

Hong Kong
Randox Laboratories Hong Kong Limited
Tel: +852 3595 0515

Italy
Randox Laboratories Ltd.
Tel: +39 06 9896 8954

India
Randox Laboratories India Pvt Ltd.
Tel: +91 22 6714 0600

Poland
Randox Laboratories Polska Sp. z o.o.
Tel: +48 22 862 1080

Portugal
Irlandox Laboratorios Quimica Analitica Ltda
Tel: +351 22 589 8320

Puerto Rico
Clinical Diagnostics of Puerto Rico, LLC
Tel: +1 787 701 7000

Republic of Ireland
Randox Teoranta
Tel: +353 7495 22600

Slovakia
Randox S.R.O.
Tel: +421 2 6381 3324

South Africa
Randox Laboratories SA (Pty) Ltd.
Tel: +27 (0) 11 312 3590

South Korea
Randox Korea
Tel: +82 (0) 31 478 3121

Spain
Laboratorios Randox S.L.
Tel: +34 93 475 09 64

Switzerland
Randox Laboratories Ltd. (Switzerland)
Tel: +41 41 810 48 89

USA
Randox Laboratories-US, Ltd.
Tel: +1 304 728 2890

Vietnam
Randox Laboratories Ltd. Vietnam
Tel: +84-8-39 11 09 04

RANDOX

Randox Laboratories Limited, 55 Diamond Road, Crumlin, County Antrim, BT29 4QY, United Kingdom
T +44 (0) 28 9442 2413 **F** +44 (0) 28 9445 2912 **E** marketing@randox.com **I** www.randox.com

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