Lipoprotein(a) : Lp(a)

Proven to be the best methodology on the market
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 (KIV2) is particularly susceptible to being manufactured repeatedly, depending on an individual’s genetics (2-40 repeats)

- The number of KIV2 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.
2010 Guidelines on Lp(a)\textsuperscript{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>
<thead>
<tr>
<th>Assay details</th>
<th>Elevated LDL cholesterol</th>
<th>Elevated Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human epidemiology</td>
<td>Direct association in numerous studies</td>
<td>Direct association in numerous studies</td>
</tr>
<tr>
<td>Human genetic studies</td>
<td>Direct association in numerous studies, e.g. familial hypercholesterolaemia</td>
<td>Direct association in numerous studies, e.g. for kringle IV type 2 polymorphism</td>
</tr>
<tr>
<td>Mechanistic studies</td>
<td>Mechanism clearly demonstrated: LDL accumulates in intima and causes atherosclerosis</td>
<td>Mechanism similar to that for LDL cholesterol and/or prothrombotic/anti-fibrinolytic effects</td>
</tr>
<tr>
<td>Animal models</td>
<td>Proatherogenic effect in numerous studies</td>
<td>Proatherogenic effect in numerous studies</td>
</tr>
<tr>
<td>Human intervention trials</td>
<td>Statin trials gave final proof of causality</td>
<td>Niacin trials are favourable</td>
</tr>
</tbody>
</table>

**Whom to screen?**\textsuperscript{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*\textsuperscript{5}.
Desirable Levels

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

<table>
<thead>
<tr>
<th></th>
<th>Patients with CVD and/or diabetes</th>
<th>Other patients and individuals</th>
<th>Highest level of evidence for treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>&lt; 2 mmol/L (&lt;77 mg/dL)</td>
<td>&lt; 3 mmol/L (116 mg/dL)</td>
<td>la: meta-analysis of randomised, controlled trials of statin treatment</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>&lt; 80th percentile (&lt;~50 mg/dL)</td>
<td>&lt; 80th percentile (&lt;~50 mg/dL)</td>
<td>la: meta-analysis of randomised, controlled trials of niacin treatment</td>
</tr>
</tbody>
</table>

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).
- Reducing Lp(a) to below cut-off should be a treatment priority, along with the lowering of LDL cholesterol.
- Lp(a) levels are generally not strongly affected by lifestyle changes.
- 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. In addition, niacin therapy can be considered, particularly in high risk patients, as this has been shown to reduce Lp(a) by 30-40%. 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 should be considered in young or middle-aged patients with evidence of progressive coronary disease and markedly elevated plasma Lp(a).
Choosing your Lp(a) assay

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

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

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. This will lead to the potential misclassification of a significant number of both high and low risk patients.

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
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:

<table>
<thead>
<tr>
<th>Lipoprotein (a)</th>
<th>Mean (mg/dl)</th>
<th>Mean % CV</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intra-assay precision</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.0</td>
<td>1.63</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>51.5</td>
<td>1.53</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>83.05</td>
<td>2.40</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>Inter-assay precision</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24.19</td>
<td>3.11</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>32.58</td>
<td>3.52</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>50.48</td>
<td>2.83</td>
<td>20</td>
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<table>
<thead>
<tr>
<th>Product Description</th>
<th>Size</th>
<th>Cat. No.</th>
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<tbody>
<tr>
<td>Lp(a) Kit</td>
<td>1x10 ml, 1x6 ml, 1x30 ml, 1x15ml</td>
<td>LP3403, LP2757</td>
</tr>
<tr>
<td>Lp(a) Kit for Dimension®</td>
<td>4x10 T</td>
<td>LP2878</td>
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<tr>
<td>Lp(a) Calibrator</td>
<td>5x1 ml</td>
<td>LP3404</td>
</tr>
<tr>
<td>Lp(a) Control (Level 3)</td>
<td>3x1 ml</td>
<td>LP3406</td>
</tr>
<tr>
<td>Lipid Control (Level 1)</td>
<td>5x3 ml or 5x1 ml</td>
<td>LE2661 or LE2668</td>
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<tr>
<td>Lipid Control (Level 2)</td>
<td>5x3 ml or 5x1 ml</td>
<td>LE2662 or LE2669</td>
</tr>
<tr>
<td>Lipid Control (Level 3)</td>
<td>5x3 ml or 5x1 ml</td>
<td>LE2663 or LE2670</td>
</tr>
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</table>

Instrument Applications Available for Randox Lp(a)

**Instruments**

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

1. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA 2009;301:2331-2339.


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