What About Lipoprotein(a)?

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Disclosures

• None
Lipoprotein(a)
Lipoprotein(a) is a Modified LDL Particle

Tsimikas, S. A Test in Context: Lipoprotein(a). JACC 2017
Lipoprotein(a) Elevation is a Common, Causal CVD Risk Factor

- ~30% of people have Lp(a) > 25-30 mg/dL
- Lp(a)-associated risk: > 50 mg/dL (> 125 nmol/L)
- As Lp(a) levels increase, risk increases linearly
Lipoprotein(a) Elevation is a Common, Causal CVD Risk Factor

Emdin, C.A. et al. Phenotypic characterization of genetically lowered human lipoprotein(a) levels. JACC 2016
Lipoprotein(a) is Reported as Mass or Particle Number

<table>
<thead>
<tr>
<th>Lp(a) mass</th>
<th>Lp(a) particle number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units: mg/dL</td>
<td>Units: nmol/L</td>
</tr>
<tr>
<td>Includes all Lp(a) components:</td>
<td>Measures apo(a)</td>
</tr>
<tr>
<td>• apo(a)</td>
<td></td>
</tr>
<tr>
<td>• apoB100</td>
<td></td>
</tr>
<tr>
<td>• cholesteryl esters</td>
<td></td>
</tr>
<tr>
<td>• phospholipids</td>
<td></td>
</tr>
<tr>
<td>• triglycerides</td>
<td></td>
</tr>
</tbody>
</table>

**Example:** 50 mg/dL

**Note:** Mass assays are isoform independent

**Example:** 125 nmol/L

**“Corrected LDL-C”:**

- 30-45% of Lp(a) mass is Lp(a)-C
- LDL-C includes Lp(a)-C
- \( \text{LDL-C}_{\text{corrected}} = \text{LDL-C}_{\text{measured}} - (30\% \times \text{Lp(a) mass (mg/dL)}) \)
  - **Example:**
    - LDL-C 70 mg/dL, Lp(a) 90 mg/dL
    - \( \text{LDL-C}_{\text{corrected}} = 70 - (30\% \times 90) \approx 40 \text{ mg/dL} \)

Tsimikas, S. A Test in Context: Lipoprotein(a). JACC 2017


Who Should Have Lipoprotein(a) Measured?
Guidelines

ACC/AHA

- Relative indications:
  - Family history of premature ASCVD
  - Personal history of ASCVD not explained by major risk factors

ESC/EAS

- “Measurement of Lp(a) levels should be considered at least once in each person’s lifetime, if available, to identify people who have inherited an extremely elevated level of Lp(a) ≥ 180 mg/dL (≥ 430 nmol/L) and therefore have a very high lifetime risk of ASCVD that is approximately equivalent to the risk associated with HeFH”

Mach, F. et al 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk, European Heart Journal 2019
Guidelines

**CCS**

- “We suggest that Lp(a) might aid risk assessment in subjects with intermediate FRS or with a family history of premature coronary artery disease”

- “Particular attention should be given to individuals with Lp(a) > 30 mg/dL for whom CVD risk is increased by ~twofold”

- “…repeat measures are not indicated”

**NLA**

- “…a case could be made to measure Lp(a) in all individuals, at least once in a lifetime…”

- ”However, there is no current evidence to substantiate the benefit of such an approach…”

- “…although some panel members supported it, a recommendation for universal testing of Lp(a) was not made at this time.”

*Wilson, D.P., et al. Use of Lipoprotein(a) in clinical practice: a biomarker whose time has come. 2019 J Clinical Lipidology*
What Affects Lipoprotein(a) Levels?
### Lipoprotein(a) Levels are Genetically Determined and Generally Stable

- > 90% of Lp(a) levels are **genetically determined** *(LPA)*\(^1\)

<table>
<thead>
<tr>
<th>Increase Lp(a)</th>
<th>Decrease Lp(a)</th>
<th>No effect on Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins (+ 10-20%)(^5)</td>
<td>Niacin (- 20-30%)(^2)</td>
<td>Exercise</td>
</tr>
<tr>
<td>Chronic kidney disease(^2)</td>
<td>PCSK9 inhibitors (- 15-30%)(^3,4)</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Low fat diet</td>
<td>Mipomersen (- 20-30%)(^2,1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CETP inhibitors (- 20-30%)(^2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estrogen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apheresis (- 30-35% (time-averaged))(^1)</td>
<td></td>
</tr>
</tbody>
</table>

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\(^1\) Tsimikas, S. A Test in Context: Lipoprotein(a). JACC 2017
\(^2\) Mach, F. et al 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk, Eur Heart J 2019
\(^3\) Warden, B.A. Impact of PCSK9 Inhibitors on plasma lipoprotein(a) concentrations with or without a background of niacin therapy. J Clinical Lipidology 2019
\(^5\) Tsimikas, S. Statin therapy increases lipoprotein(a) levels. Eur Heart J 2019.
Future Directions
Targeted Therapies to Potently Lower Lipoprotein(a)

Anti-sense oligonucleotide (ASO)

- AKCEA-APO(a)-LRx
  - GalNac ligand enhances uptake in hepatocytes

Phase 2 trial

Inclusion: ASCVD & Lp(a) ≥ 60 mg/dL

Primary end-point: Mean percent change in Lp(a) from baseline vs placebo at week 25-27.

AE: Well-tolerated, no effects on platelets, liver or renal function. Most frequent AE was injection site erythema.
Targeted Therapies to Potently Lower Lipoprotein(a)

Anti-sense oligonucleotide (ASO)

- Lp(a) HORIZON
- Phase 3 CV End-Points Trial
  - Monthly TQJ230 80mg subQ injection vs placebo
  - Key inclusion criteria:
    - Lp(a) ≥ 70 mg/dL
    - Optimal LDL-C lowering treatment
    - History of MI, ischemic stroke, or symptomatic PAD

Small interfering RNA (siRNA)

- AMG 890 (directed at apo(a) mRNA) vs placebo
- Phase 1, single ascending doses
- Inclusion: baseline Lp(a) elevation
- Results in 2020

https://clinicaltrials.gov/ct2/show/NCT04023552?term=lipoprotein(a)+HORIZON&rank=1
https://clinicaltrials.gov/ct2/show/NCT03626662?term=AMG+890&rank=1
Conclusions

- Lp(a) is a causal, genetically determined risk factor for CVD
- Risk from Lp(a) begins at levels > 50 mg/dL
- Lp(a) is measured as mass (mg/dL) or particle number (nmol/L)
- Lp(a) should be measured at least once in (just about) everyone
- More data are required to know whether reducing Lp(a) with pharmacotherapy reduces CVD risk
- Ongoing trials of potent, Lp(a) targeted therapies are poised to address the “Lp(a) hypothesis”
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