Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis -
A European Atherosclerosis Society Consensus Statement

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https://doi.org/10.1093/eurheartj/ehac361
Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement

Why a new Lp(a) consensus paper?

- Since 2010 consensus paper lots of new evidence
- **Novel epidemiological & genetic studies (e.g. on causality for CVD)**
- Novel findings on outcomes: aortic valve stenosis, diabetes mellitus
- Points became revisited: thromboembolic events, niacin, ...
- **Novel recommendations how to incorporate Lp(a) in clinical practice**
- Specific, potent Lp(a)-lowering therapies in phase 1-3 trials
Overview

1. Epidemiological and genetic findings
2. Lp(a) testing and measurement issues
3. How to incorporate Lp(a) in risk estimation?
4. Managing high Lp(a) concentrations
The association between Lp(a) and major CVD* outcomes is **continuous independent of ethnicity** → Lp(a) measurement is relevant globally

* defined as the composite of the first occurrence of fatal or non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, or coronary revascularization [percutaneous coronary intervention or coronary artery bypass graft surgery]

Data are provided by Prof. Brian Ference using data from the UK Biobank

https://doi.org/10.1093/eurheartj/ehac361
Lifetime risk for major cardiovascular events with increasingly higher Lp(a)

Data are provided by Brian Ference et al. using data from the UK Biobank

https://doi.org/10.1093/eurheartj/ehac361
Risk of Lp(a) concentrations with various CVD outcomes: *stronger association for Lp(a) with MI and aortic valve stenosis*

Data provided by Prof. Børge G. Nordestgaard and Dr. Anne Langsted
Genetics provide a strong support for a causal association of Lp(a) concentrations with outcomes

modified from Coassin & Kronenberg: Atherosclerosis 349:17-35, 2022
Mendelian randomization studies: Life-long genetic exposure to high or low Lp(a) concentrations

Lp(a)-increasing genetic variants
(e.g. small apo(a) isoforms, rs10455872, rs3798220)

- strong association

High Lp(a) → Increased CVD risk

Causal disease association

Lp(a)-decreasing genetic variants
(e.g. large apo(a) isoforms, 4733G>A, 4925G>A, rs41267813, ...)

- strong association

Low Lp(a) → Decreased CVD risk

Causally protected against disease

https://doi.org/10.1093/eurheartj/ehac361
Genetic variants associated with increased Lp(a) concentrations are associated with increased CVD risk

Data are provided by Ference, Catapano et al. using data from the UK Biobank

- rs10455872 and rs37982220
- Introduced by R. Clarke et al.
- Not functionally active
Genetic variants associated with increased Lp(a) concentrations are not associated with thromboembolic events

Data are provided by Ference, Catapano et al. using data from the UK Biobank

### Effect of Lp(a) on risk of venous thromboembolic events

<table>
<thead>
<tr>
<th>LPA genetic score</th>
<th>No. Events</th>
<th>No. Participants</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of 100 nmol/L higher Lp(a)</td>
<td>15,789</td>
<td>440,368</td>
<td>0.99 [0.96, 1.03]</td>
</tr>
</tbody>
</table>

### Number of Lp(a) increasing variants [measured Lp(a)]

<table>
<thead>
<tr>
<th>Number of Lp(a) increasing variants</th>
<th>[median Lp(a)]</th>
<th>No. Events</th>
<th>No. Participants</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13.6 nmol/L; 5.9 mg/dL</td>
<td>12,872</td>
<td>358,464</td>
<td>1.00 [reference]</td>
</tr>
<tr>
<td>1</td>
<td>146.3 nmol/L; 63.6 mg/dL</td>
<td>2,764</td>
<td>77,655</td>
<td>0.99 [0.96, 1.04]</td>
</tr>
<tr>
<td>2</td>
<td>261.9 nmol/L; 113.9 mg/dL</td>
<td>153</td>
<td>4,249</td>
<td>1.00 [0.85, 1.19]</td>
</tr>
</tbody>
</table>
**Very low** Lp(a) concentrations may associate with diabetes mellitus:

Random effects meta-analysis of studies examining baseline very low Lp(a) concentrations with incident diabetes (N=165,813; No of cases=10,503).

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>RR</th>
<th>[95% CI] bottom vs top quintile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mora (2010)</td>
<td>1.28</td>
<td>[1.10; 1.49]</td>
</tr>
<tr>
<td>Tolbus (2017)</td>
<td>1.33</td>
<td>[1.12; 1.58]</td>
</tr>
<tr>
<td>Kamstrup (2013)</td>
<td>1.26</td>
<td>[1.09; 1.45]</td>
</tr>
<tr>
<td>Langsted (2021)</td>
<td>1.42</td>
<td>[1.28; 1.58]</td>
</tr>
<tr>
<td>Ye (2014)</td>
<td>1.59</td>
<td>[1.23; 2.05]</td>
</tr>
<tr>
<td>Kaya (2017)</td>
<td>2.03</td>
<td>[1.00; 4.10]</td>
</tr>
<tr>
<td>Paige (2017)</td>
<td>1.37</td>
<td>[0.74; 2.53]</td>
</tr>
<tr>
<td>Gudbjartsson (2019)</td>
<td>1.79</td>
<td>[1.36; 2.36]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1.38</td>
<td>[1.29; 1.48]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 8.74$ ($P = .27$), $I^2 = 20\%$

Clinical impact for Lp(a) lowering interventions in patients with very high Lp(a): to be determined

Meta-analysis provided by Prof. Samia Mora, Dr. Olga Demler and Dr. Yanyan Liu
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Consensus panel recommendations for Lp(a) testing

- Lp(a) should be measured at least once in all adults to identify those with high cardiovascular risk

- Screening recommended in youth with a history of stroke or family history of high Lp(a), or premature ASCVD without other identifiable risk factors

- Family cascade screening for high Lp(a) recommended in the settings of FH, family history of (very) high Lp(a), and family history of ASCVD
Consensus panel recommendations for Lp(a) measurement

- Laboratories should use an Lp(a) assay insensitive to apo(a) isoform and traceable to official reference materials.

- Measurement of Lp(a) should be in molar units if available. If not, units in which the assay is calibrated should be used for reporting.

- Rather than absolute values, clinical guidelines should consider using risk thresholds with ‘grey’ zones.

![Diagram showing Lp(a) concentration and CHD risk](https://doi.org/10.1093/eurheartj/ehac361)
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Incremental increase in absolute risk caused by increasing Lp(a) categories

Estimated baseline absolute lifetime risk

Additional risk above the estimated baseline risk caused by the respective Lp(a) concentration category

Baseline risk categories based on traditional risk factors

Baseline estimated lifetime risk calculated using the Joint British Societies (JBS3) Lifetime Risk Estimating algorithm

Data provided by Ference, Catapano et al. using data from the UK Biobank
Incremental increase in absolute risk caused by a 50 mg/dL Lp(a) level

Baseline estimated lifetime risk calculated using the Joint British Societies (JBS3) Lifetime Risk Estimating algorithm

Baseline risk of ASCVD events (%) → Risk of ASCVD events (%)
5 → 7%
15 → 20.9%
25 → 34.9%
50 mg/dL

Lp(a) plasma concentrations
- 150 mg/dL (350 nmol/L)
- 100 mg/dL (230 nmol/L)
- 75 mg/dL (175 nmol/L)
- 50 mg/dL (115 nmol/L)
- 30 mg/dL (70 nmol/L)
- 7 mg/dL (16 nmol/L)

≈1.4-fold risk increase

Data provided by Ference, Catapano et al. using data from the UK Biobank

https://doi.org/10.1093/eurheartj/ehac361
Incremental increase in absolute risk caused by a 150 mg/dL Lp(a) level

Baseline estimated lifetime risk calculated using the Joint British Societies (JBS3) Lifetime Risk Estimating algorithm

If Lp(a) level is not considered, absolute risk might be underestimated substantially

Data provided by Ference, Catapano et al. using data from the UK Biobank

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Consensus panel recommendations for managing high Lp(a) concentrations

- In absence of specific Lp(a)-lowering therapies, early ‘traditional’ risk factor management is recommended for individuals with elevated Lp(a), taking into account their absolute cardiovascular risk and Lp(a) level.

- Among patients with high Lp(a), all cardiovascular risk factors should be optimally addressed as per guideline recommendations.

- Lipoprotein apheresis can be considered in patients with very high Lp(a) and progressive cardiovascular disease despite optimal management of risk factors.

- Niacin and "routine aspirin" are not advised in high Lp(a).
LDL-C reduction needed to mitigate the increased risk of major cardiovascular events caused by high Lp(a)

RED: one genetic risk allele:
Lp(a) 136 nmol/L
LDL-C 3.6 mmol/L

BLUE: reference group:
Lp(a) 16 nmol/L
LDL-C 3.6 mmol/L

GREEN: one genetic risk allele
Lp(a) 135 nmol/L
LDL-C 3.1 mmol/L

0.5 mmol LDL-C reduction required

Data provided by Ference, Catapano et al. using data from the UK Biobank

https://doi.org/10.1093/eurheartj/ehac361
Stronger LDL-C reduction needed to mitigate the increased CV risk caused by high Lp(a), depending on ‘starting age’ of LDL-C lowering

<table>
<thead>
<tr>
<th>Lp(a) nmol/L compared to median</th>
<th>Δ Lp(a) percentile</th>
<th>HR for MCVE due to increased Lp(a)</th>
<th>Intensification of LDL-C reduction (nmol/L) needed to mitigate the increased risk caused by Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>320 nmoL/L</td>
<td>300</td>
<td>99</td>
<td>Begin age 30y: 1.2 mmol/L 1.4 mmol/L 1.7 mmol/L 2.3 mmol/L</td>
</tr>
<tr>
<td>270 nmoL/L</td>
<td>250</td>
<td>97.5</td>
<td>Begin age 40y: 1.0 mmol/L 1.2 mmol/L 1.5 mmol/L 1.9 mmol/L</td>
</tr>
<tr>
<td>220 nmoL/L</td>
<td>200</td>
<td>93.5</td>
<td>Begin age 50y: 0.8 mmol/L 0.9 mmol/L 1.2 mmol/L 1.5 mmol/L</td>
</tr>
<tr>
<td>170 nmoL/L</td>
<td>150</td>
<td>90</td>
<td>Begin age 60y: 0.6 mmol/L 0.7 mmol/L 0.9 mmol/L 1.1 mmol/L</td>
</tr>
<tr>
<td>120 nmoL/L</td>
<td>100</td>
<td>82.5</td>
<td></td>
</tr>
<tr>
<td>70 nmoL/L</td>
<td>50</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>20 nmoL/L</td>
<td>ref.</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

Starting prevention early is KEY

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https://doi.org/10.1093/eurheartj/ehac361
Incremental increase in absolute risk caused by increasing Lp(a) categories

Baseline estimated lifetime risk calculated using the Joint British Societies (JBS3) Lifetime Risk Estimating algorithm

Data provided by Ference, Catapano et al. using data from the UK Biobank

Main part of the risk attributable to Lp(a)

Management of traditional risk factors will be important but will not be enough

Specific Lp(a)-lowering therapies are urgently required
Emerging specific Lp(a)-lowering therapies targeting Lp(a) production

Pelacarsen:
■ Antisense oligonucleotide therapy (ASO): monthly dosing
■ Outcome results from phase 3 are expected in 2025

Olpasiran
■ siRNA technology: longer acting
■ Dose finding study ongoing

SLN360
■ siRNA technology: longer acting
■ Phase 1 finished

Tromp et al.: Expert Opin Investig Drugs 29:483-93, 2020
2022 EAS Consensus on Lp(a)

- Causal continuous association between Lp(a) and ASCVD
- New risk factor for aortic valve stenosis
- Not a risk factor for venous thrombosis
- Very low Lp(a) may associate with type 2 diabetes

EAS

- Lp(a) should be measured at least once in adults
- Interpretation of Lp(a) concentration in the context of absolute global CVD risk
- Intensified risk factor management by lifestyle modification and medications
- Specific Lp(a)-lowering therapies in phase II/III trials

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The EAS appreciates …

The work of the Consensus Panel Members:

The many researchers who provided the evidence and basis for this consensus paper

The study participants and patients of numerous studies

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