Use of Lipoprotein(a) in Clinical Practice: A Biomarker Whose Time Has Come.

A Scientific Statement from the National Lipid Association
Lipoprotein (a)  
... an independent risk marker for ASCVD.

- What are the causal links between increased circulating concentrations of Lp(a) and 1) ASCVD and 2) valvular aortic stenosis?
- How should we measure and report Lp(a)?
- Who should have Lp(a) measured and when?
- How does the level of Lp(a) affect treatment?
Use of Lipoprotein(a) in Clinical Practice: A Biomarker Whose Time Has Come.

<table>
<thead>
<tr>
<th>NLA Oversight Committee</th>
<th>Expert Panel</th>
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<tr>
<td>• Terry A. Jacobson, MD</td>
<td>• Marlys L. Koschinsky, PhD</td>
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<td>• Peter H. Jones, MD</td>
<td>• Catherine J. McNeal, MD, PhD</td>
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<tr>
<td>• Carl E. Orringer, MD</td>
<td>• Borge G. Nordestgaard, MD, DMSc</td>
</tr>
<tr>
<td>• Don P. Wilson, MD</td>
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</table>
Disclosures

- Dr. Wilson has received speaking honorarium from Osler Institute, research grants from Merck Sharp & Dohme and Novo Nordisk, and has participated on the advisory board for Alexion Pharmaceuticals.
- Dr. Jacobson has received consulting fees from Amarin, Amgen, AstraZeneca, Esperion, Sanofi Regeneron, and Novartis.
- Dr. Jones has received advisory board honorarium from Amgen, Sanofi Regeneron, and AstraZeneca.
- Dr. Koschinsky has received speaker and consulting honorarium from Eli Lilly, speaker honorarium from Pfizer, consulting honorarium from Amgen, and independent contractor fees from Pfizer, Eli Lilly, Cardiovax and Ionis.
- Dr. McNeal has nothing to disclose.
- Dr. Nordestgaard has received consulting honorarium from Akcea, Amgen, Regeneron, Sanofi, and Kowa.
- Dr. Orringer has nothing to disclose.
### ACC/AHA Recommendation System:

**Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care**

(Updated August 2015)

<table>
<thead>
<tr>
<th>CLASS (STRENGTH) OF RECOMMENDATION</th>
<th>LEVEL (QUALITY) OF EVIDENCE</th>
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<tbody>
<tr>
<td><strong>CLASS I (STRONG)</strong></td>
<td><strong>LEVEL A</strong></td>
</tr>
<tr>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td>High-quality evidence from more than 1 RCT</td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>Meta-analyses of high-quality RCTs</td>
</tr>
<tr>
<td>• Is recommended</td>
<td>One or more RCTs corroborated by high-quality registry studies</td>
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<tr>
<td>• Is indicated/useful/effective/beneficial</td>
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<td>• Should be performed/administered/other</td>
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<tr>
<td>• Comparative Effectiveness Phrases:</td>
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<tr>
<td>• Treatment/strategy A is recommended/indicated in preference to treatment B</td>
<td></td>
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<tr>
<td>• Treatment A should be chosen over treatment B</td>
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| **CLASS IIa (MODERATE)**           | **LEVEL B-R**                |
| Benefit >> Risk                    | (Randomized)                 |
| Suggested phrases for writing recommendations: | Moderate-quality evidence from 1 or more RCTs |
| • Is reasonable                     | Meta-analyses of moderate-quality RCTs |
| • Can be useful/effective/beneficial |                          |
| • Comparative Effectiveness Phrases: |                          |
| • Treatment/strategy A is probably recommended/indicated in preference to treatment B |                          |
| • It is reasonable to choose treatment A over treatment B |                          |

| **CLASS IIb (WEAK)**               | **LEVEL B-NR**               |
| Benefit > Risk                     | (Nonrandomized)              |
| Suggested phrases for writing recommendations: | Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies |
| • May/might be reasonable           | Meta-analyses of such studies |
| • May/might be considered           |                          |
| • Unfounded/effectiveness in unknown/unclear/uncertain or not well established |                          |

| **CLASS III: No Benefit (MODERATE)** | **LEVEL C-LD**               |
| Benefit = Risk                      | (Limited Data)               |
| Suggested phrases for writing recommendations: | Randomized or nonrandomized observational or registry studies with limitations of design or execution |
| • It is not recommended             | Meta-analyses of such studies |
| • It is not indicated/useful/effective/beneficial |                          |
| • Should not be performed/administered/other |                          |

| **CLASS III: Harm (STRONG)**       | **LEVEL C-EO**               |
| Risk > Benefit                     | (Expert Opinion)             |
| Suggested phrases for writing recommendations: | Consensus of expert opinion based on clinical experience |
| • Potentially harmful               |                          |
| • Causing harm                     |                          |
| • Associated with excess morbidity/mortality |                          |
| • Should not be performed/administered/other |                          |

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CIR and LCE are determined independently (any CIR may be paired with any LCE).

A recommendation with CIR C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although CIRs are analytical, there may be a very clear clinical consensus that a particular test or therapy is useful or ineffective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

1 For comparative-effectiveness recommendations (CLASS I and IIa; LCE A and B only), studies that support the use of comparator texts should involve direct comparisons of the treatments or strategies being evaluated.

2 The method of assessing quality is evolving, including the application of standards, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of theEvidence ReviewCommittee.

CIR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LCE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Acknowledgement

• The authors would like to acknowledge Vivian Grifantini, Luke Hamilton and Dena Hanson for their assistance in preparing and editing this manuscript.

• A special thanks to Dr. Patrick Moriarty, who provided insightful comments and thoughtful suggestions during manuscript development.
Use of Lipoprotein(a) in Clinical Practice: A Biomarker Whose Time Has Come.

• Introduction - Don P. Wilson, MD
• Laboratory Measurement of lipoprotein(a) - Marlys Koschinsky, PhD
• Lipoprotein(a) testing and Treatment in Clinical Practice Adults
  • Primary Prevention - Peter Jones, MD
  • Secondary Prevention - Carl Orringer, MD
• Youth - Catherine McNeal, MD, PhD
• Questions and Answers - Panel
Use of Lipoprotein(a) in Clinical Practice: A Biomarker Whose Time Has Come.

Laboratory Measurement of Lp(a)

Marlys L. Koschinsky, PhD FAHA FNLA
Scientific & Executive Director
Robarts Research Institute
Professor, Dept. of Physiology & Pharmacology
Schulich School of Medicine & Dentistry
The University of Western Ontario
What are the Major Issues Surrounding Lp(a) Measurement?

1. Units of measurement
   - mg/dL versus nmol/L

2. Lack of standardization/harmonization of assays
   - Potential for isoform-dependent bias

3. Absence of evidence-based cutpoints
   - Different risk groups
   - Different ethnic populations
   - Co-morbidities
Potential for Isoform-Dependent Bias

Panel A: Apo(a) size-sensitive assay (using antibodies to repeating K-IV subunits)
- Repeating subunit
- Non-repeating subunit

Reference Standard
- Signal underestimates Lp(a) concentration
- Reference Standard
- Signal accurately reflects Lp(a) concentration

LMW Test Sample (less signal)
- Signal overestimates Lp(a) concentration
- LMW Test Sample (same signal)
- Signal accurately reflects Lp(a) concentration

HMW Test Sample (more signal)
- Signal overestimates Lp(a) concentration
- HMW Test Sample (same signal)
- Signal accurately reflects Lp(a) concentration

Bias can be minimized by usage of calibrator containing a variety of different isoforms.

Units of Measurement

• Recommend adoption of particle concentration (nmol/L) versus mass concentration (mg/dL)
  ➢ Cannot interconvert accurately between the two units
Units of Measurement

• Advantages of particle concentration (nmol/L)

➢ NOTE: Secondary reference material (PRM-2B) is in units of nmol/L

➢ Allow standardization/harmonization of assays

➢ Harmonize future clinical studies

➢ Facilitate establishment of evidence-based guidelines
Choice of Lp(a) Assay

• Recommendation is to select assay with all of the following characteristics, where possible:

  ➢ Reports results in nmol/L

  ➢ Utilizes a 5-point calibrator (or similar)

  ➢ Calibrated against WHO/IFCCLM secondary reference material
Evidence-Based Cutpoints for Risk Assessment?

- Ethnic group-specific?
  - Largest studies have compared African-Americans and whites (inconsistent results)
- Sex?
  - Some evidence for lower risk in women (not replicated in larger studies)
- Primary versus secondary prevention?
  - Some evidence for higher cutpoint in secondary prevention
- Comorbidities?
  - Thrombophilia
  - Diabetes
  - FH
  - Renal disease

EVIDENCE BASE IS INCOMPLETE
Use of Lipoprotein(a) in Clinical Practice: A Biomarker Whose Time Has Come.

Lipoprotein(a) Testing in Primary Prevention

Peter H. Jones MD, FNLA
Associate Professor
Baylor College of Medicine
Case Presentation

- 48-yr-old Hispanic male in for annual prevention exam. He has no physical complaints and takes no prescribed medications. He does not smoke; no regular exercise plan.
- Family history: Mother with PCI at age 62 and doing well at age 69. He thinks she has a high cholesterol. Father (70) has T2DM, and sister (45) has no medical problems but did have GDM. He has 2 children age 18 and 16.
- Baseline labs: All normal, with A1C 5.7%.
  
  Lipids:  
  - TC 252 mg/dL
  - HDL-C 38 mg/dL
  - TG 260 mg/dL
  - LDL-C 162 mg/dL
  - non-HDL-C 214 mg/dL

  Pooled cohort: 6.6% 10 year risk
Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

- **Age 0-19 y**
  - Lifestyle to prevent or reduce ASCVD risk
  - Diagnosis of Familial Hypercholesterolemia → statin

- **Age 20-39 y**
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
  - Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

- **Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus**
  - 10-year ASCVD risk percent begins risk discussion

- **Age >75 y**
  - Clinical assessment, Risk discussion

**ASCVD Risk Enhancers:**
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

**Lipid/Biomarkers:**
- Persistently elevated triglycerides (≥175 mg/dL, ≥2.0 mmol/L)
- In selected individuals if measured:
  - hs-CRP ≥2.0 mg/L
  - Lp(a) levels >50 mg/dL or >125 nmol/L
  - apoB ≥130 mg/dL
  - Ankle-brachial index (ABI) <0.9

**Risk discussion:**
- <5% “Low Risk”
- 5% - <7.5% “Borderline Risk”
- ≥7.5% - <20% “Intermediate Risk”
- ≥20% “High Risk”

- Risk discussion: Emphasize lifestyle to reduce risk factors (Class I)
- Risk discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIb)
- Risk discussion: If risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% (Class I)
- Risk discussion: Initiate statin to reduce LDL-C ≥50% (Class I)

If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥25th percentile, initiate statin therapy
## Risk-Enhancing Factors for Clinician - Patient Risk Discussion

<table>
<thead>
<tr>
<th>Risk-Enhancing Factors</th>
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<tbody>
<tr>
<td><strong>Family history of premature ASCVD</strong> (men, age &lt;55 y; women, age &lt;65 y)</td>
</tr>
<tr>
<td><strong>Primary hypercholesterolemia</strong> (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*</td>
</tr>
<tr>
<td><strong>Metabolic syndrome</strong> (increased waist circumference, elevated triglycerides [&gt;175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [&lt;40 mg/dL in men; &lt;50 in women mg/dL] are factors; tally of 3 makes the diagnosis)</td>
</tr>
<tr>
<td><strong>Chronic kidney disease</strong> (eGFR 15–59 mL/min/1.73 m² with or without albuminuria; not treated with dialysis or kidney transplantation)</td>
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<tr>
<td><strong>Chronic inflammatory conditions</strong> such as psoriasis, RA, or HIV/AIDS</td>
</tr>
<tr>
<td><strong>History of premature menopause</strong> (before age 40 y) and <strong>history of pregnancy-associated conditions</strong> that increase later ASCVD risk such as preeclampsia</td>
</tr>
<tr>
<td><strong>High-risk race/ethnicities</strong> (e.g., South Asian ancestry)</td>
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## Risk-Enhancing Factors for Clinician - Patient Risk Discussion

### Risk-Enhancing Factors

- **Lipid/biomarkers**: Associated with increased ASCVD risk
  - Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);
  - If measured:
    - **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
    - **Elevated Lp(a)**: A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).
    - **Elevated apoB** ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
    - **ABI** <0.9
### Examples of Candidates for CAC Measurement Who Might Benefit From Knowing Their CAC Score Is Zero

<table>
<thead>
<tr>
<th>CAC Measurement Candidates Who Might Benefit from Knowing Their CAC Score Is Zero</th>
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<tr>
<td>• Patients reluctant to initiate statin therapy who wish to understand their risk and potential for benefit more precisely</td>
</tr>
<tr>
<td>• Patients concerned about need to reinstitute statin therapy after discontinuation for statin-associated symptoms</td>
</tr>
<tr>
<td>• Older patients (men, 55-80 y of age; women, 60-80 y of age) with low burden of risk factors who question whether they would benefit from statin therapy</td>
</tr>
<tr>
<td>• <strong>Middle-aged adults (40-55 y of age)</strong> with PCE-calculated 10-year risk of ASCVD 5% to &lt;7.5% with factors that increase their ASCVD risk, although they are in a borderline risk group</td>
</tr>
</tbody>
</table>
II. Lipoprotein(a) Testing in Clinical Practice

1. **Adults (> 20 years of age)**

   Measurement of Lp(a) **is reasonable** to refine risk assessment for ASCVD events in:

1) Individuals with a family history of 1st degree relatives with premature ASCVD (<55 years of age in men; <65 years of age in women)  
   - Rallidis, 2018

2) Individuals with premature ASCVD (<55 years of age in men and <65 years of age in women), particularly in the absence of traditional risk factors.  
   - Erqou, 2009; Kamstrup, 2013; Clarke 2009; CARDIoGRAMplus C4D Consortium, 2013; Genest, 1992

3) Individuals with primary severe hypercholesterolemia (LDL ≥190mg/dL) or suspected familial hypercholesterolemia.  
   - Pérez de Isla, 2017; Ellis, 2016; Langsted 2016; Ellis, 2019

4) Individuals at very high** ASCVD risk to better define those who are more likely to benefit from PCSK9 inhibitor therapy  
   - O'Donoghue, 2018; Bittner, 2018
II. Lipoprotein(a) Testing in Clinical Practice

1. **Adults (> 20 years of age)**

   Measurement of Lp(a) may be reasonable with:

1) Intermediate (7.5-19.9%) 10-year ASCVD risk when the decision to use a statin is uncertain, to improve risk stratification in primary prevention.

2) Borderline (5-7.4%) 10-year ASCVD risk when the decision to use a statin is uncertain, to improve risk stratification in primary prevention.

3) Less-than-anticipated LDL-C lowering, despite good adherence to therapy.

4) A family history of elevated Lp(a).

5) Calcific valvular aortic stenosis.

6) Recurrent or progressive ASCVD, despite optimal lipid-lowering therapy.
Case

• After a discussion about appropriate lifestyle changes and the possibility of taking a moderate intensity statin, we focused on potential genetic lipid contributors to his risk and his mother’s ASCVD.

He agreed to test for Lp(a).

Lp(a) is 82 mg/dL.

Should his children be screened?
• The Importance of Shared Decision Making

• A decision to measure Lp(a) should be made after a thoughtful benefit-risk discussion between the patient and his/her healthcare provider. Shared decision-making should reflect an individual’s preferences and values. Decisions should also be based upon family history, the presence of comorbid conditions, race/ethnicity, and/or concern of future risk. In the absence of an acute illness, the level of Lp(a) is stable throughout an individual’s lifetime and unaffected by lifestyle. Therefore, a case could be made to measure Lp(a) in all individuals, at least once in a lifetime, based upon strong support for the association between elevated Lp(a) levels and increased risk, together with genetic findings that indicate elevated Lp(a) is causally related to premature ASCVD and VAS. However, there is no current evidence to substantiate the benefit of such an approach, and there is currently no targeted treatment(s) to lower Lp(a) levels that have been proven to affect ASCVD outcomes or progression of VAS. Therefore, although some panel members supported it, a recommendation for universal testing of Lp(a) was not made at this time. The Scientific Statement Committee acknowledges that there is likely little harm from a universal screening approach and that the cost of the test is relatively inexpensive compared to other cardiovascular disease screening tests. As more data become available in the future, the potential role of universal testing should be re-evaluated.
Use of Lipoprotein(a) in Clinical Practice: A Biomarker Whose Time Has Come.

Lipoprotein(a) Testing in Secondary Prevention

Carl E. Orringer, MD, FNLA
2019 NLA Annual Scientific Sessions
May 17, 2019
A Lipid Consultation Challenge

- 41 year old man with LDL-C 140 mg/dL, but no other ASCVD risk factors had an MI at age 40 and 2nd MI without PCI 3 months ago. Cardiac cath: 2 vessel CAD.
- Brother: CABG, then graft closure age 48.
- Rx: atorvastatin 80 mg, ezetimibe 10 mg ASA 81 mg and clopidogrel 75 mg daily.
- LDL-C 68 mg/dL. Lp(a) 200 nmol/L.
- He read that niacin lowers Lp(a) and began niacin ER 2000 mg daily
- His doctor repeated his blood testing: LDL-C 55 mg/dL. Lp(a) 150 nmol/L

Which would you recommend?

A. Switch to rosuva 40 mg daily
B. Increase niacin to 2500 mg daily and repeat Lp(a)
C. Discontinue niacin and continue atorva and ezetimibe
D. Discontinue niacin, recheck LDL-C and consider addition of PCSK9 inhibitor
E. Call Alan Brown
Lp(a) Testing in Patients with ASCVD

- In which ASCVD patients may measurement of Lp(a) be reasonable?
- Does clinician knowledge of Lp(a) level help to predict risk in statin-treated patients?
- In which ASCVD patients might knowledge of Lp(a) level aid in therapeutic decision making?
In Which ASCVD Patients May Measurement of Lp(a) Be Reasonable?

• Younger ACS patients\(^1\): Independent risk factor for those patients
  • Age <45 years (OR 2.88, 95% CI 1.7-4.6)
  • Age 45-60 years (OR 2.06, 95% CI 1.4-3.2)

• Recurrent coronary events
  • Target vessel re-stenosis after PCI\(^2\)
  • Bypass graft failure\(^3\)

• Recurrent ischemic stroke\(^4\)
  • Case control studies (high vs. low) (OR 1.41, 95% CI 1.26-1.57)
  • Prospective studies (OR 1.29, 95% CI 1.06-1.58)

---

Does Clinician Knowledge of Lp(a) Predict ASCVD Risk in Statin-Treated Patients?

• Patient level data from 7 placebo controlled statin RCT’s were examined for expanded MACE and hazard ratios for CV events estimated for each trial across pre-defined Lp(a) levels vs those with Lp(a) <15 mg/dL.

• After multivariate adjustment, association of on-statin Lp(a) with MACE risk was stronger than on-placebo Lp(a) and was more pronounced at younger ages.

• Thus, elevated Lp(a) in statin-treated patients signifies increased ASCVD risk not addressed by statins

RCT Evidence Supporting Drug Therapy in High and Very High Risk Patients, with or without Elevated Lp(a)

• Statins
  – Cholesterol Treatment Trialists Collaboration meta analysis¹

• Ezetimibe
  – IMPROVE-IT²

• PCSK9 inhibitors
  – FOURIER³
  – ODYSSEY-OUTCOMES⁴

• Icosapent Ethyl in patients with triglycerides 150-499 mg/dL
  – REDUCE-IT⁵

Drug Therapy Specific to Lp(a) Related Risk in High or Very High Risk ASCVD Patients

• Statins
  – Associated with minimal or mild ↑ in Lp(a). ASCVD outcomes worse in those with ↑Lp(a), but rosuvastatin 20 mg daily reduced ASCVD risk equally in all ethnicities regardless of whether Lp(a) was above or below median\(^1\)

• Ezetimibe
  – Associated with minimal reduction in Lp(a) as monotherapy (7%)\(^2\)

• PCSK9 inhibitors
  – Evolocumab reduces Lp(a) by median of 27%; reduces risk of CHD death, MI or urgent revascularization by 23% in those with Lp(a) >37 nmol/L (NNT\(_{3y}\) 40) vs. 7% in those with Lp(a) ≤ 37 nmol/L (NNT\(_{3y}\) 105)\(^3\)
  – Presentation at ACC19 on Lp(a) in ODYSSEY-OUTCOMES (V. Bittner) indicated that alirocumab improved ASCVD outcomes the most in those with highest Lp(a), and that Lp(a) reduction contributed to improved outcomes, independently of LDL-C

### What Does the NLA Lp(a) Expert Panel Advise?

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<td></td>
<td>III (harm)</td>
<td>A</td>
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<tr>
<td>6.</td>
<td>Niacin, which lowers Lp(a) concentration, <strong>is not recommended</strong> to reduce ASCVD risk in patients receiving moderate-to-high intensity statins +/- ezetimibe and an on-treatment LDL-C &lt;80 mg/dL</td>
<td>Albers, 2013; Parish, 2018</td>
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<tr>
<td>2.</td>
<td>In high* or very high** risk patients, with Lp(a) ≥50 mg/dL or ≥100 nmol/L(^5), it <strong>is reasonable</strong> to consider more intensive LDL-C lowering to achieve greater ASCVD risk reduction.</td>
<td>Ila</td>
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## What Does the NLA Lp(a) Expert Panel Advise?

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<td>3.</td>
<td>In very high** risk patients, taking a maximally tolerated statin with ( \text{Lp(a)} \geq 50 \text{ mg/dL or } \geq 100 \text{ nmol/L} ), the addition of ezetimibe is reasonable in those with on-treatment LDL-C ( \geq 70 \text{ mg/dL} ) (or non-HDL-C ( \geq 100 \text{ mg/dL} )).</td>
<td>Ila</td>
</tr>
<tr>
<td>5.</td>
<td>In very high risk** patients taking a maximally tolerated statin and ezetimibe, with an LDL-C ( \geq 70 \text{ mg/dL} ) (or non-HDL-C ( \geq 100 \text{ mg/dL} )) and an ( \text{Lp(a)} ) of ( \geq 50 \text{ mg/dL} ) or ( \geq 100 \text{ nmol/L} ), the addition of a PCSK9 inhibitor is reasonable.</td>
<td>Ila</td>
</tr>
<tr>
<td>4.</td>
<td>In high* risk patients taking a maximally tolerated statin, with ( \text{Lp(a)} \geq 50 \text{ mg/dL or } \geq 100 \text{ nmol/L} ), the addition of ezetimibe may be reasonable in those with on-treatment LDL-C ( \geq 70 \text{ mg/dL} ) (or non-HDL-C ( \geq 100 \text{ mg/dL} )).</td>
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Lipoprotein(a) testing and treatment <20 years of age

Catherine McNeal, MD, PhD
Division of Cardiology, Department of Internal Medicine
Baylor Scott & White Health
Temple, TX
A healthy 10-yr-old boy undergoes routine cholesterol screening and is found to have an LDL-C of 200 mg/dL.

In addition to:

• Family history
• Medical history and physical examination
• Exclusion of secondary causes of hypercholesterolemia, including medications

Would measurement of Lp(a) be indicated?
With respect to Lp(a):

• More than 90% of the Lp(a) concentration is explained by an autosomal dominant pattern of inheritance.
• The gene is fully expressed by 1-2 years of age.
• Reaches adult levels by ~5 years of age.
• Levels are stable throughout the lifespan, independent of age, gender or lifestyle habits.
If measured, how would an elevated level impact clinical-decision making?

• Since Lp(a) is inherited with high fidelity, when a child is found to have an elevated level of Lp(a), reverse cascade screening (siblings and parents) is recommended.

• Even in the absence of approved Lp(a)-lowering medications, youth found to have an elevated level of Lp(a) should be encouraged to adopt a lifelong heart-healthy lifestyle. Family members should as well.

• The need for smoking avoidance or cessation should be emphasized.
A 5-yr-old female experiences an unexplained ischemic stroke. In addition to general supportive care and use of anticoagulants or antiplatelet agents in the acute setting:

Should Lp(a) be measured?

- Measurement of Lp(a) in youth with a history of ischemic stroke may be reasonable.
- Paucity of data due to rare occurrence (2 in 100,000 per year excluding neonatal strokes) and varied etiologies.
• A consistent positive association between elevated lipoprotein (a) and ischemic stroke in youth has been reported (OR 4.24 (2.94–6.11) in high vs low Lp(a) concentrations)

• Levels may be influenced by the presence of acute inflammatory conditions including stroke.
### Table of Recommendation

<table>
<thead>
<tr>
<th>Measurement of Lp(a) may be reasonable with:</th>
<th>Class of Rec (strength)</th>
<th>Levels of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. A family history of 1st-degree relatives with premature ASCVD (&lt;55 yrs of age in men, &lt;65 yrs of age women).</td>
<td>IIb</td>
<td>C-LD</td>
</tr>
<tr>
<td>4. A parent or sibling found to have an elevated Lp(a).</td>
<td>IIb</td>
<td>C-LD</td>
</tr>
</tbody>
</table>
Use of Lipoprotein(a) in Clinical Practice: A Biomarker Whose Time Has Come.

A Scientific Statement from the National Lipid Association.

Questions