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.

NLA Oversight Committee

- Terry A. Jacobson, MD
- Peter H. Jones, MD
- Carl E. Orringer, MD
- Don P. Wilson, MD

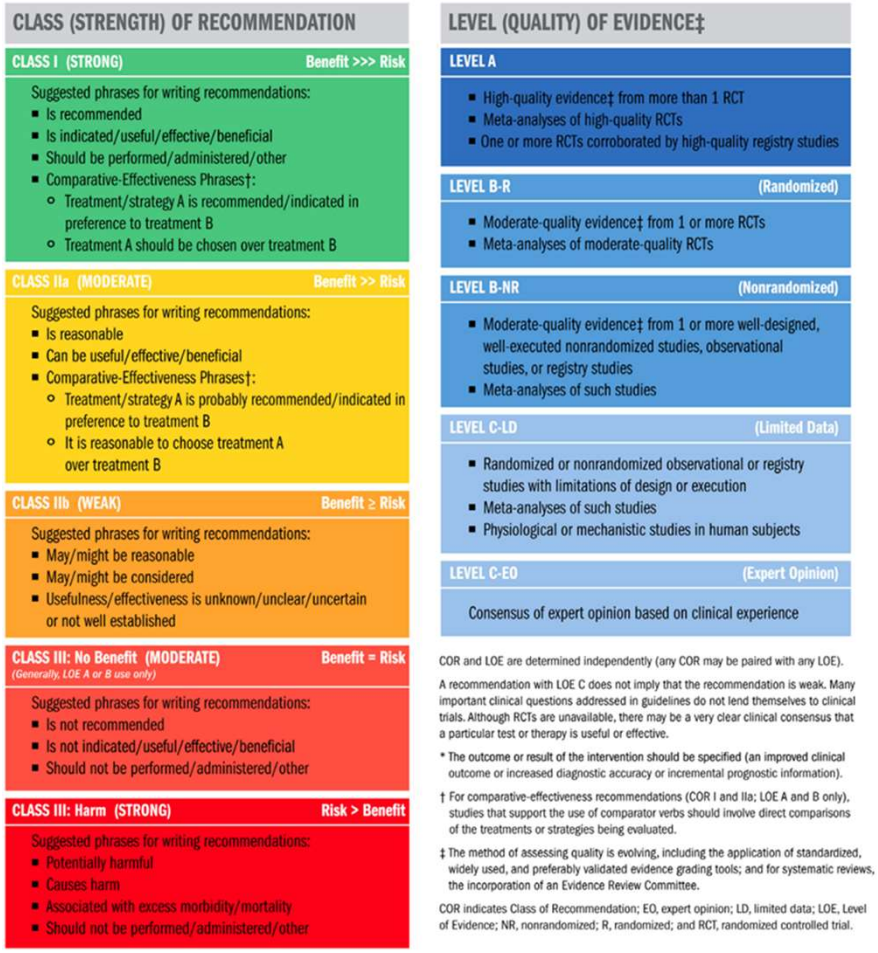
Expert Panel

- Marlys L. Koschinsky, PhD
- Catherine J. McNeal, MD, PhD
- Borge G. Nordestgaard, MD, DMSc

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 he 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)



CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — Benefit >> Risk

Suggested phrases for writing recommendations:
- Is reasonable
- 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) — Benefit ≥ Risk

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — Benefit = Risk
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — Risk > Benefit

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

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

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

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

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

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

Reference: Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;67:1572–4

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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)

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Scientific & Executive Director
Robarts Research Institute
Professor, Dept. of Physiology & Pharmacology
Schulich School of Medicine & Dentistry
The University of Western Ontario

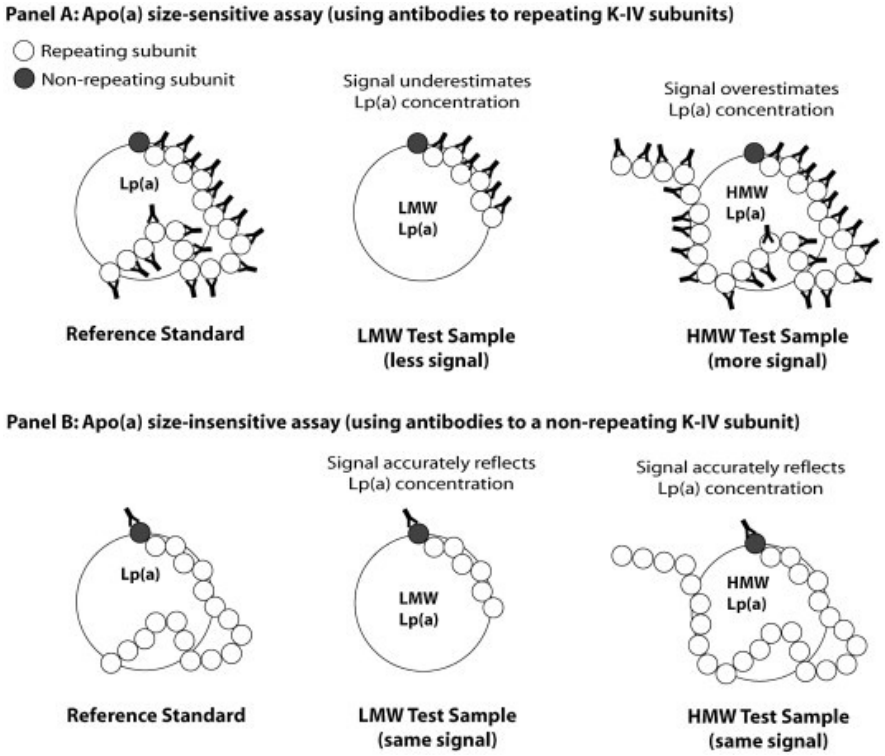
What are the Major Issues Surrounding Lp(a) Measurement?

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

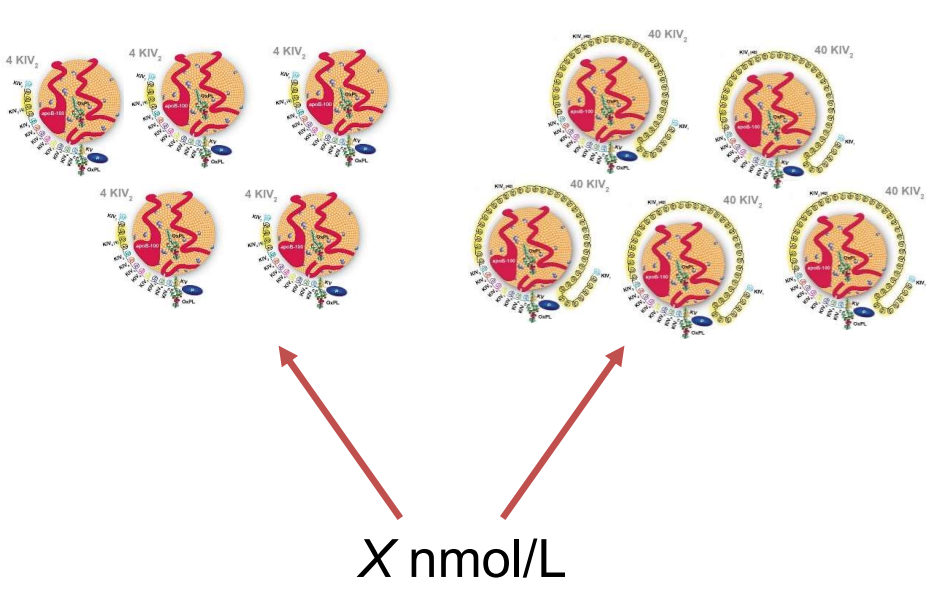


Bias can be minimized by usage of calibrator containing a variety of different isoforms

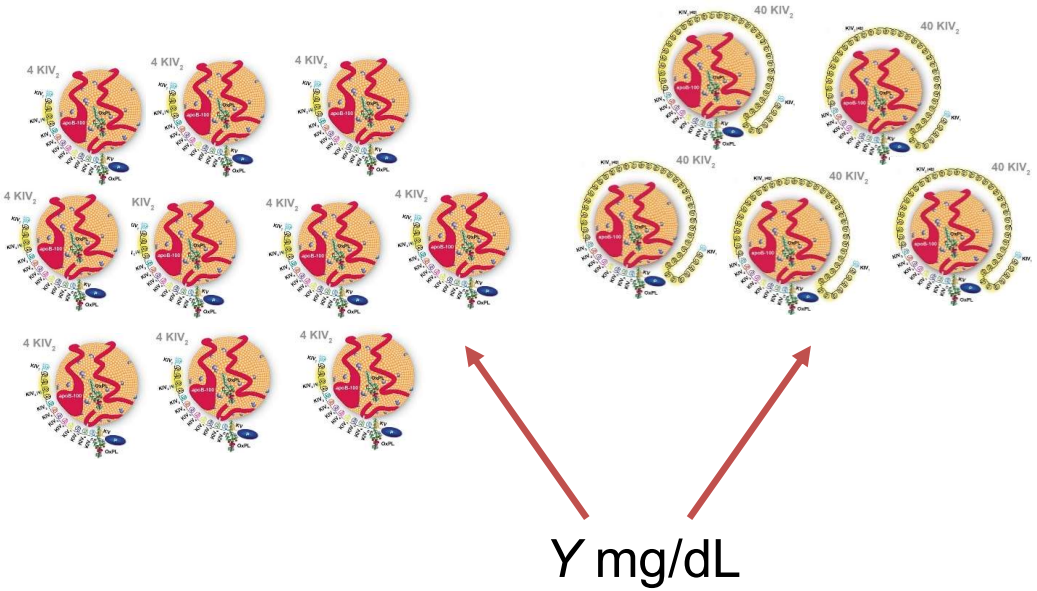
Longenecker JC, et al. Clin Chim Acta. 2008;397:36

Units of Measurement

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



X nmol/L

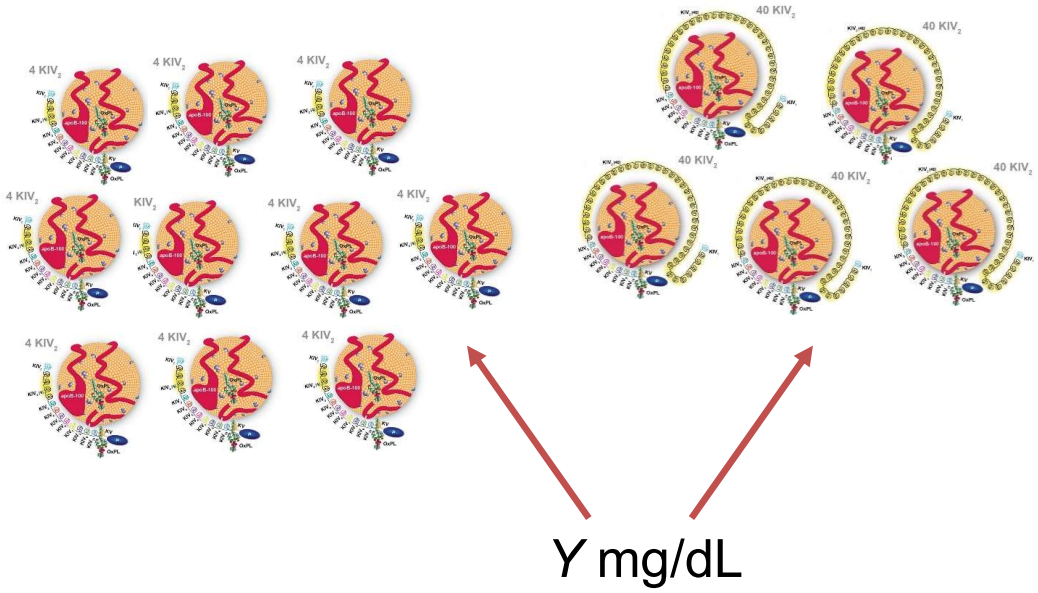


Y mg/dL

Units of Measurement

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

Multiplying by a common conversion factor (to nmol/L) tends to <u>underestimate</u> the smaller isoforms



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?
  - Are the cutpoints different?
- 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

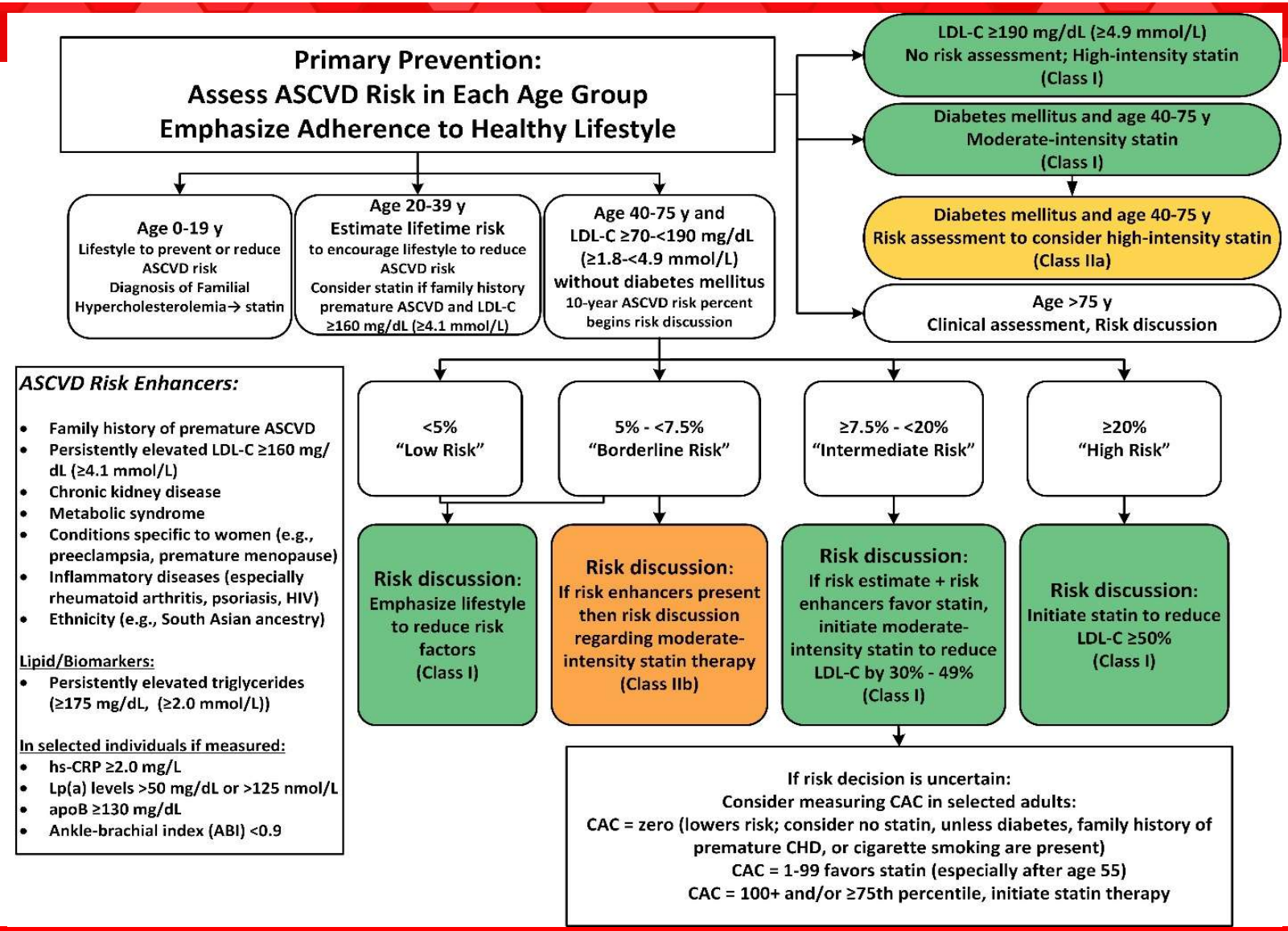
Peter H. Jones MD, FNLA
Associate Professor
Baylor College of Medicine

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.
- Exam: BP 144/88, BMI 27. Normal physical exam.
- 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
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
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
<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 estimate + 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 ≥75th percentile, initiate statin therapy

Risk-Enhancing Factors for Clinician - Patient Risk Discussion

Risk-Enhancing Factors
• **Family history of premature ASCVD** (men, age <55 y; women, age <65 y) • **Primary hypercholesterolemia** (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])* • **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis) • **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation) • **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS • **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia** • **High-risk race/ethnicities** (e.g., South Asian ancestry)

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

CAC Measurement Candidates Who Might Benefit from Knowing Their CAC Score Is Zero
• Patients reluctant to initiate statin therapy who wish to understand their risk and potential for benefit more precisely • Patients concerned about need to reinstitute statin therapy after discontinuation for statin-associated symptoms • 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 • Middle-aged adults (40-55 y of age) with PCE-calculated 10-year risk of ASCVD 5% to <7.5% with factors that increase their ASCVD risk, although they are in a borderline risk group

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)	IIa	C-LD	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.	IIa	B NR	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.	IIa	B-NR	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	IIa	B-NR	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.	IIa	B-NR	Nave, 2015; Willeit 2014; Grundy 2018; Wei, 2018; Kamstrup, 2013
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.	IIb	B-NR	Nave, 2015; Willeit 2014; Grundy 2018; Wei, 2018; Kamstrup, 2013
3)	Less-than-anticipated LDL-C lowering, despite good adherence to therapy.	IIb	C-LD	Yeang 2016; CARDIoGRAMplus C4D Consortium 2013; Langstead 2016
4)	A family history of elevated Lp(a).	IIb	C-LD	Clarke 2009; CARDIoGRAMplus C4D Consortium 2013; Langsted 2016
5)	Calcific valvular aortic stenosis.	IIb	C-LD	Thanassoulis 2013; Kamstrup 2014; Arsenault 2014; Vongpromek 2015; Capoulade 2015
6)	Recurrent or progressive ASCVD, despite optimal lipid-lowering therapy.	IIb	C-LD	Albers 2013; Khera 2014; Nestel 2013;

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.

NLA Scientific Statement on Clinical Utility of Lipoprotein a: Secondary Prevention

Carl E. Orringer, MD, FNLA

2019 NLA Annual Scientific Sessions

May 17, 2019

Clinical Utility of Lp(a)Testing in Patients with ASCVD Key Questions

- In which ASCVD patients does measurement of Lp(a) provide a plausible etiology for MACE?
- Does Lp(a) level predict risk for MACE in statin-treated patients?
- How do evidence-based lipid therapies affect Lp(a) levels?
- Is there evidence that any currently available lipid therapies alter Lp(a)-related risk?

Lp(a) as a Plausible Etiology for MACE

- Coronary artery disease
  - ACS: Risk in those with Lp(a) >50 is tripled in those age<45 and doubled age 45-60
  - Cardiac death and non-fatal ACS after PCI[2] (N=1336, Lp(a) >22 mg/dL vs. < 22)
  - Bypass graft stenosis[3] (N=135, Lp(a) 33 mg/dL vs 17)
- 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)

1. Rallidis LS et al. Atherosclerosis 2018;269:29-34 2. Suwa S et al. J Atheroscler Thromb 2017;24:1125-31
3. Hoff HF et al. Circulation 1988;77: 1238-44 4. Nave AH et al. Atherosclerosis 2015;242: 496-503

Lp(a) as a Risk Marker for MACE in Statin-Treated Patients

- Patient-level data from 7 placebo controlled statin RCT's (N=29,069) was examined for fatal or non fatal CHD, stroke or revascularization across Lp(a) tertiles compared to Lp(a) <15 mg/dL, with multivariate adjustment
- MACE risk more strongly associated with on-statin Lp(a) than on-placebo Lp(a), especially at younger ages
- **Elevated Lp(a) in statin-treated patients signifies increased risk**

Willeit P et al. Lancet 2018;392:1311-20.

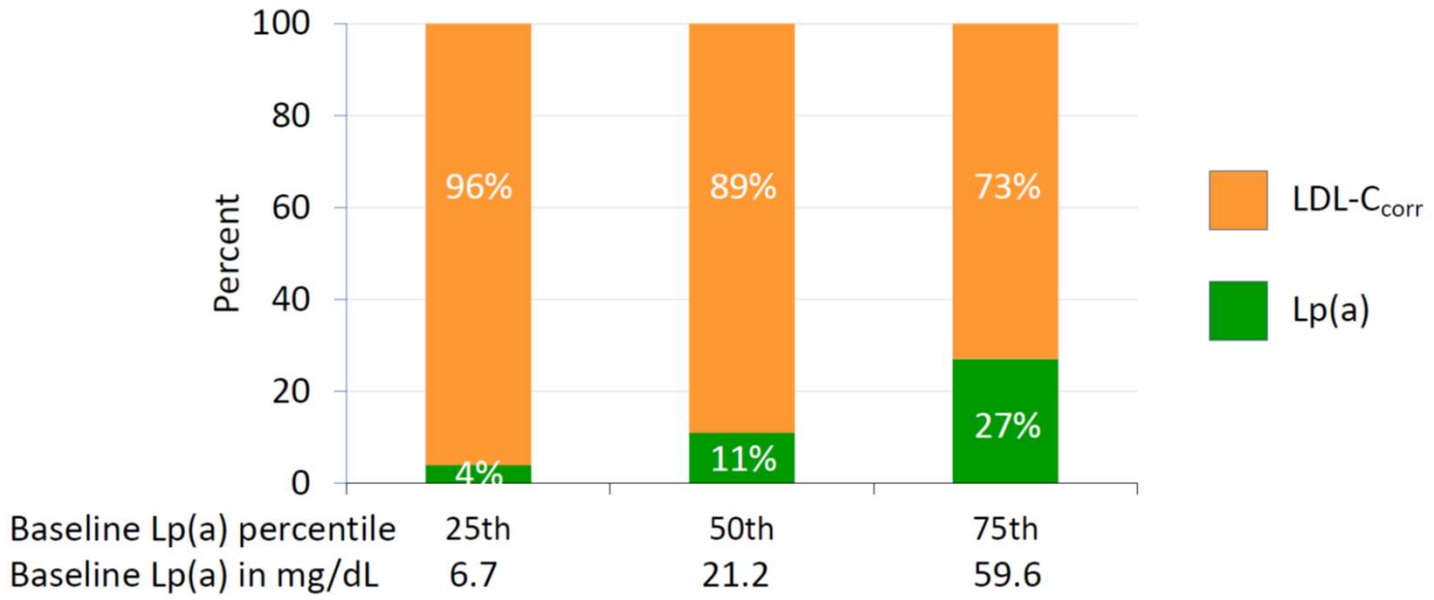
Does Drug Therapy Affect Risk in ASCVD patients with ↑Lp(a)?

	Impact on Lp(a)	Effect on ASCVD Outcomes
Statins	Minimal or mild ↑	Rosuvastatin 20 mg daily reduced ASCVD risk equally in all ethnicities, whether Lp(a) above or below median[1]
Ezetimibe	Minimal ↓ as monotherapy[2]	Unknown
PCSK9 inhibitors	Evolocumab ↓ by median 27%	Reduces RR of CHD death, MI or urgent revascularization 23% if Lp(a) >37 nmol/L (NNT_{3y} 40) vs. those with Lp(a) ≤37 (NNT_{3y} 105)[4]
	Alircomab ↓ by median 29%[3]	Proportion of MACE reduction attributable to changes in Lp(a) greatest in those with Lp(a) >59.6 mg/dL[5]

1. Khera AV et al. Circulation. 2014 Feb 11;129(6):635-42. 2. Awad K et al. Drugs 2018;78:453-62.
3. Gaudet D et al. Am J Cardiol 2017;119: 40-64. 4. O'Donoghue M et al. Circulation. 2019;139:1483–1492
5. Presented by V. Bittner ACC19

ODYSSEY OUTCOMES

Proportion of MACE Reduction Attributable to Changes in Lp(a) and Corrected LDL-C



From model with baseline and change in Lp(a), baseline and change in LDL-C_{corr} (Model 2)

Presented by Vera Bittner, ACC19

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

6. Niacin, which lowers Lp(a) concentration, ***is not recommended*** to reduce ASCVD risk in patients receiving moderate-to-high intensity statins +/- ezetimibe and an on-treatment LDL-C <80 mg/dL	III (harm)	A	Albers, 2013 ; Parish, 2018

2. In high* or very high** risk patients, with Lp(a) ≥50 mg/dL or ≥100 nmol/L[§], it ***is reasonable*** to consider more intensive LDL-C lowering to achieve greater ASCVD risk reduction.	IIa	A	Willeit, 2018); Khera, 2014; Baigent, 2000

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

3. In very high** risk patients, taking a maximally tolerated statin with Lp(a) ≥50 mg/dL or ≥100 nmol/L§, the addition of ezetimibe ***is reasonable*** in those with on-treatment LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL).	IIa	B-R	Cannon, 2015
5. In very high risk** patients taking a maximally tolerated statin and ezetimibe, with an LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL) and an Lp(a) of ≥50 mg/dL or ≥100 nmol/L§, the addition of a PCSK9 inhibitor ***is reasonable***.	IIa	B-R	O'Donoghue,2018; Bittner, 2018; Sabatine, 2017; Schwartz, 2018
4. In high* risk patients taking a maximally tolerated statin, with Lp(a) ≥50 mg/dL or ≥100 nmol/L§, the addition of ezetimibe ***may be reasonable*** in those with on-treatment LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL).	IIb	B-R	Cannon, 2015

Lp(a) and Secondary Prevention: Summary

- Be aware of Lp(a)-associated increased risk for recurrent events
- Continue to follow Guideline based therapies, as most lipid-related risk is still attributable to LDL-C
- Consider more aggressive LDL-C lowering for ASCVD patients with increased Lp(a)
- Consider earlier use of PCSK9 inhibitors in ASCVD patients with elevated Lp(a)

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

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	Class of Rec (strength)	Levels of Evidence
Youth (< 20 years of age)		
Measurement of Lp(a) may be reasonable with:		
1. Clinically suspected or genetically confirmed FH.	IIb	C-LD
2. A family history of 1st-degree relatives with premature ASCVD (<55 yrs of age in men, <65 yrs of age women).	IIb	C-LD
3. An unknown cause of ischemic stroke.	IIb	C-LD
4. A parent or sibling found to have an elevated Lp(a).	IIb	C-LD

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Questions