Lipoprotein A,
An emerging CVD risk factor

Joseph Poole, MD PhD
CV Conference 2020
Lipoprotein (a): an emerging risk factor for atherosclerosis.

Hegele RA¹.
Lipoprotein(a) - the cardiovascular risk factor: significance and therapeutic possibilities.

Bláha V.

Abstract
About 20% of the population has raised Lp(a) concentrations and evidence suggests that high levels of Lp(a) are an independent cardiovascular risk factor. Both the European Society of Cardiology and the European Atherosclerosis Society recommend measuring Lp(a) values in intermediate to high-risk patients for risk stratification, as well as in patients already under statin treatment and with recurrent clinical events as a residual risk factor that calls for lipid-lowering therapy intensification. Strategies used to lower Lp(a) concentrations have either been partially disappointing in the past or lack cardiovascular outcome data. Therefore, Lp(a) has often been considered as a nonmodifiable cardiovascular risk factor. New and consistent data retrieved from the PCSK9 inhibitor trials now suggest that Lp(a) can be decreased effectively by roughly 30%, while emerging data from apo(a) antisense therapy trials suggest that selective and potent Lp(a) reduction is a feasible treatment approach in the future. The impact of such decreases on the occurrence of cardiovascular outcomes, independent from LDL-C, could, if established, herald Lp(a) in the treatment of atherosclerosis. Key words: alirocumab - atherosclerosis - cardiovascular disease - evolocumab - hypercholesterolaemia - lipoprotein(a) - lipoprotein apheresis.
Lipoprotein A, 
**STILL** An emerging CVD risk factor AGAIN

Joseph Poole, MD PhD
CV Conference 2020
None

Financial Disclosures
• Discovered in 1963 by Kare Berg’s group in Norway
• Lp(a) shares antigens with low-density lipoprotein (LDL)
• Lp(a) includes a single molecule of apolipoprotein B covalently linked to apo(a)
• Levels of Lp(a) determined by the rate of de novo hepatic synthesis
• Although Lp(a) has an LDL-receptor binding region, the hepatic LDL receptor plays a negligible role in Lp(a) catabolism
• Cleared largely by the kidney and spleen
Lipoprotein(a) consists of an LDL-like particle to which apolipoprotein(a) is covalently linked.

Nordestgaard B G et al. Eur Heart J 2010;31:2844-2853
• Apo(a) has a region homologous to plasminogen and competitively antagonizes plasminogen binding
• Likely evolved due to advantageous promotion of hemostasis and wound healing at sites of arterial injury, promoting thrombosis and coagulation
• Direct atherogenic effect: Arterial deposition of oxidized phospholipids by apo B
• Lp(a) animation
• Elevated Lp(a) has been identified to be an independent, causal risk factor for CVD
Nonfatal MI and coronary death (9318 cases)

Risk Ratio (95% CI)

Usual Lp(a), Geometric Mean, mg/dL

• You inherit it
• LPA gene located on chromosome 6
• Inherited in a codominant autosomal pattern
• 30 different isoforms of apo(a)
• Apo(a) sequence composed of 3-50 repeated plasminogen-like kringle IV domains, the fewer the repeats, the higher the Lp(a) level

How do you get it?
• No, it’s inherited.
• Diet, exercise, smoking and other traditional risk factors for hyperlipidemia do not impact Lp(a) levels.

What about diet, exercise, etc?
What is a high Lp(a) level?

- >50 mg/dL
  Or
- >125 nmol/L
• Niacin therapy is the only lipid pharmacological treatment that consistently, markedly and dose-dependently lower Lp(a)
• In clinical trials, daily doses of 1 gram or higher lowers Lp(a) up to 40%
• Doses of Niacin 2-4 gm per day have been associated with further Lp(a) lowering
• Mechanism of action:
  • Decreases mobilization of free fatty acids from adipose tissue
  • Attenuates hepatic synthesis of apo B

How do you get rid of it?
Does lowering Lp(a) save lives?

- Probably
- A large systematic review and meta-regression analysis of 11 RCTs totally 10,000 patients revealed:
  - Niacin treatment up to 2gms/day was associated with a significant decline in CVD events (P=.007).
  - Post-hoc analyses mixed
  - Greatest benefit exists for patients in the highest quartile of Lp(a)

Lavigne and Karas, J Am Coll Cardiol 2013;61(4):440-446
A case

- 29 year male, Non-smoker, HLD on statin tx
- Family history CAD in uncle and grandfather
- Acute chest tightness while walking
- Stuttering symptoms over 5 hours
- Presents to ER
- EKG: NSR rate 99, non-specific ST TW changes precordium
- Trop 0.05, 0.15, 0.22
- High risk NST with 20-25% anterior ischemia
- Taken to the cath lab
A case

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- EKG: NSR rate 99, non-specific ST TW changes precordium
- Trop 0.05, 0.15, 0.22
- High risk NST with 20-25% anterior ischemia
- Taken to the cath lab
- 99% proximal LAD stenosis=> successful PCI
<table>
<thead>
<tr>
<th>Year</th>
<th>Meds</th>
<th>Notes</th>
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<tbody>
<tr>
<td>2009</td>
<td>Simvastatin 40</td>
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<tr>
<td></td>
<td>Niacin 500mg bid</td>
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<tr>
<td>2016</td>
<td>Changed to Crestor 40</td>
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<tr>
<td></td>
<td>Lp(a) = 93 mg/dL</td>
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<td></td>
<td>Niacin increased to 750mg bid</td>
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<td>2017</td>
<td>2018</td>
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<td>----------------------------------------------------------------------</td>
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<tr>
<td>• Lp(a) = 81 mg/dL</td>
<td>• Lp(a) = 51 mg/dL</td>
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<tr>
<td>• Niacin increased to 1000mg bid</td>
<td>• Niacin increased to 1500mg bid</td>
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<td></td>
<td>• Lp(a) rechecked 6 months later = 33 mg/dL</td>
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<tr>
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<td>• Pt maintained on Niacin 1500mg bid</td>
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ACC/AHA CLINICAL PRACTICE GUIDELINE


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• ASCVD = atherosclerotic cardiovascular disease

• Includes:
  • Myocardial infarction
  • Stable or unstable angina
  • Arterial revascularization
  • Stroke/transient ischemic attack
  • Peripheral arterial disease
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)

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

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
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) without diabetes mellitus

**Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L)**
Risk assessment to consider high-intensity statin (Class IIa)

**Diabetes mellitus and age 40-75 y**
Moderate-intensity statin (Class I)

**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:**
- Low Risk (5% - <7.5%)
  - Emphasize lifestyle to reduce risk factors (Class I)

**Intermediate Risk (≥7.5% - <20%)**
- Risk discussion:
  - If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIb)

**High Risk (≥20%)**
- Risk discussion:
  - Initiate moderate-intensity statin to reduce LDL-C by 30% - 49% (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
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
• Family history of premature ASCVD before 55 years of age in a first-degree male relative or before 65 years of age in a first-degree female relative
ASCVD Risk Enhancers:

- Family history of premature ASCVD
- Persistently elevated LDL-C \( \geq 160 \text{ mg/dL} \) (\( \geq 4.1 \text{ mmol/L} \))
- 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 \( (\geq 175 \text{ mg/dL}, \geq 2.0 \text{ mmol/L}) \)

In selected individuals if measured:
- hs-CRP \( \geq 2.0 \text{ mg/L} \)
- Lp(a) levels \( >50 \text{ mg/dL} \) or \( >125 \text{ nmol/L} \)
- apoB \( \geq 130 \text{ mg/dL} \)
- Ankle-brachial index (ABI) \( <0.9 \)
Typical distributions of lipoprotein(a) levels in the general population.

Nordestgaard B G et al. Eur Heart J 2010;31:2844-2853
• Lp(a) is a particularly atherogenic lipid that is an independent, causal risk factor for CVD events
  • Genetically determined
  • Not part of a routine fasting lipid profile
  • Not lowered by statins or heart healthy habits
  • Improved by Niacin tx
  • Check Lp(a) in patients with premature CVD or in patients with a 1st degree relative with premature CVD
  • Use Lp(a) level as an ASCVD ‘risk enhancer’ when determining a patient’s primary prevention plan
  • Pay attention to units (>50 mg/dl or >125 nmol/L)
  • Know your own Lp(a) level

Take home message
• Enjoy the refreshments and visit the vendors
• Please return to your seats at the announced time

Break time
Possible national championship has jump rope club jumping for joy