Cardiovascular Today Updates on Lipoprotein (a)

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Agenda

- Background on Lipoprotein (a)
- Clinical Significance
- Emerging Treatments

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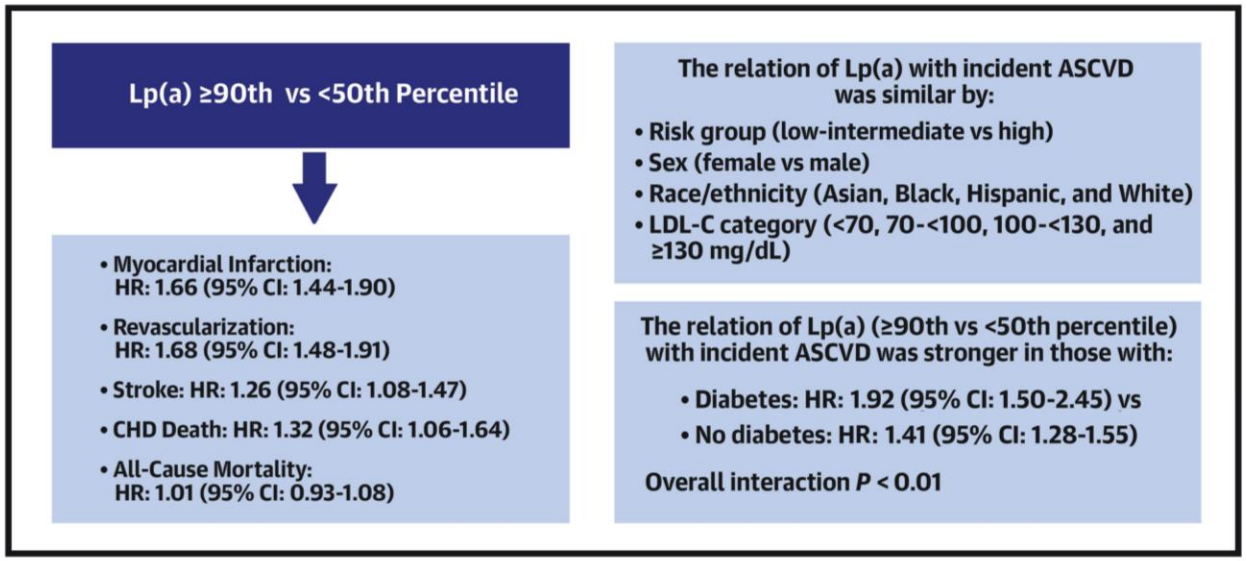
Why Do We Care?

- Significant increase in Atherosclerotic CV Disease
  - Proinflammatory
  - Proatherosclerotic
  - Antifibrinolytic



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Wong, et al. JACC. April 2024

Background

- Lipoprotein (a) was first identified in the 1960s
  - Distinct but similar to LDL

FROM THE INSTITUTE OF FORENSIC MEDICINE, UNIVERSITY HOSPITAL, RIKSHOSPITALET, OSLO, NORWAY

A NEW SERUM TYPE SYSTEM IN MAN—THE Lp SYSTEM

By

KÅRE BERG

Received 25.iii.63

The hypothesis for the study was that animals, when given relatively large doses of an isolated protein from one single donor, might be able to develop antibodies against several antigenic groups on this protein, including possible type-specific factors, and that antibodies against all but the latter could be removed by proper absorptions.

The purpose of the present article is to describe a procedure by means of which a specific antibody was produced in rabbits. This antibody

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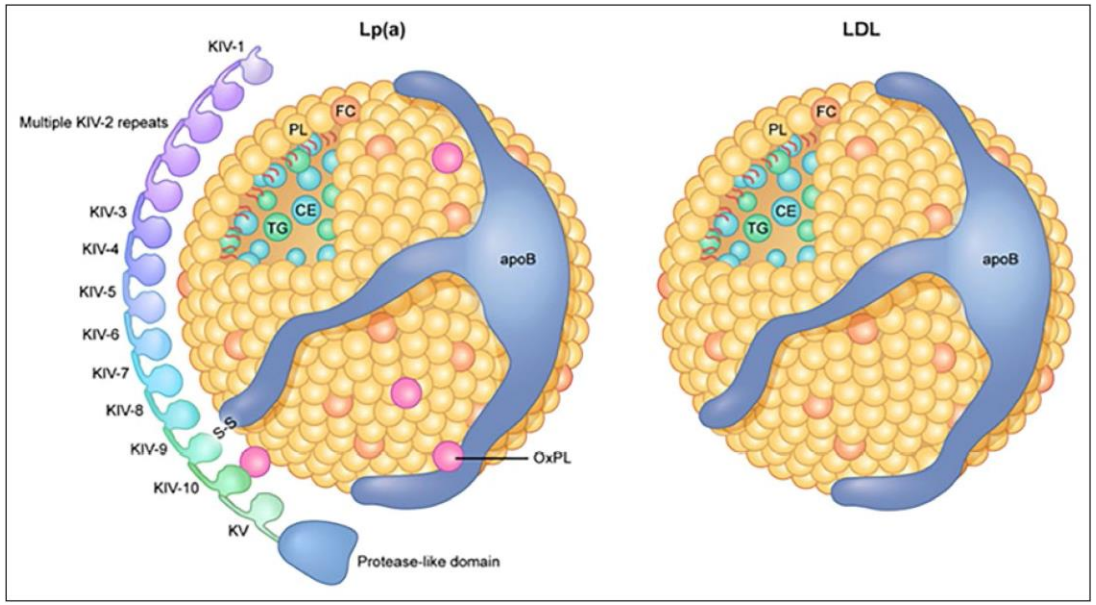
Background

- Lipoprotein (a) was first identified in the 1960s
  - Distinct but similar to LDL
  - Lipid-rich molecule (like LDL), but with an apolipoprotein molecule attached.



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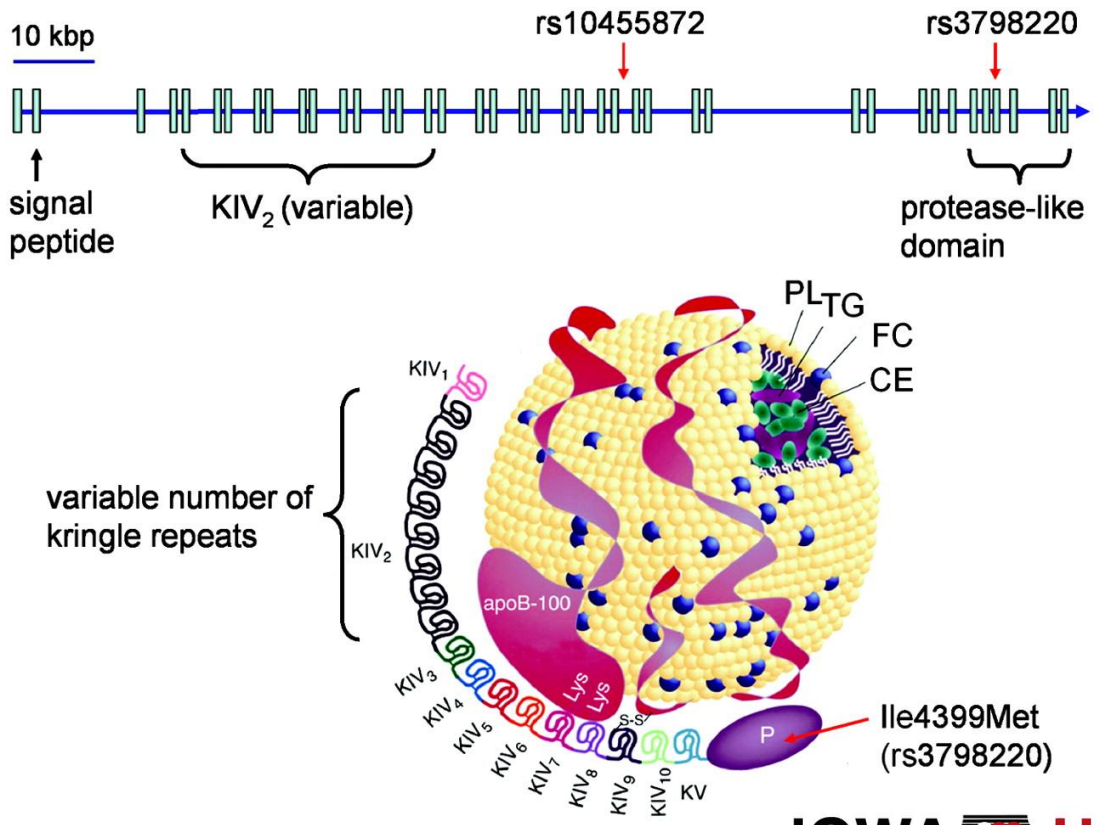
Background

- Predominately Genetically Determined
  - 70%-90% Lp(a) levels are based on expression of the LPA gene



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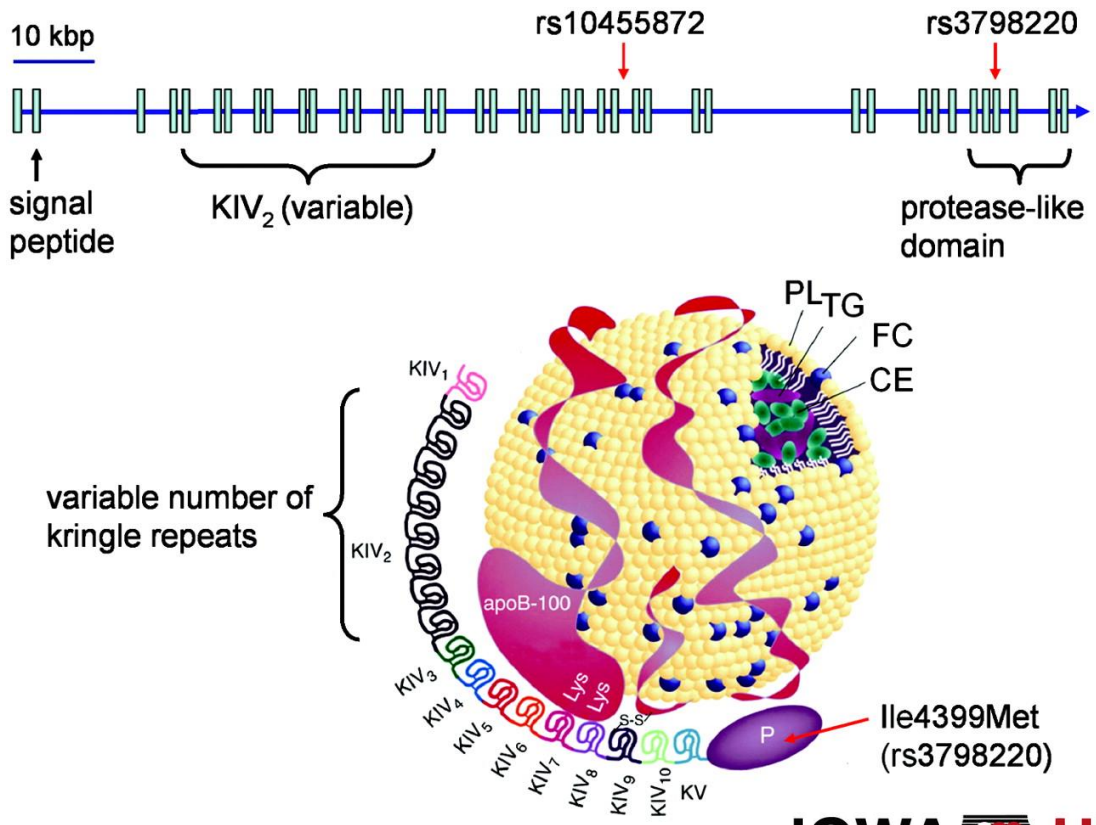
Yonghong, et al. Circulation. Oct 2011

Background

- Predominately Genetically Determined
  - 70%-90% Lp(a) levels are based on expression of the LPA gene
  - African / South Asia lineage have higher levels across population
  - Diet / Exercise have limited roles in treatment



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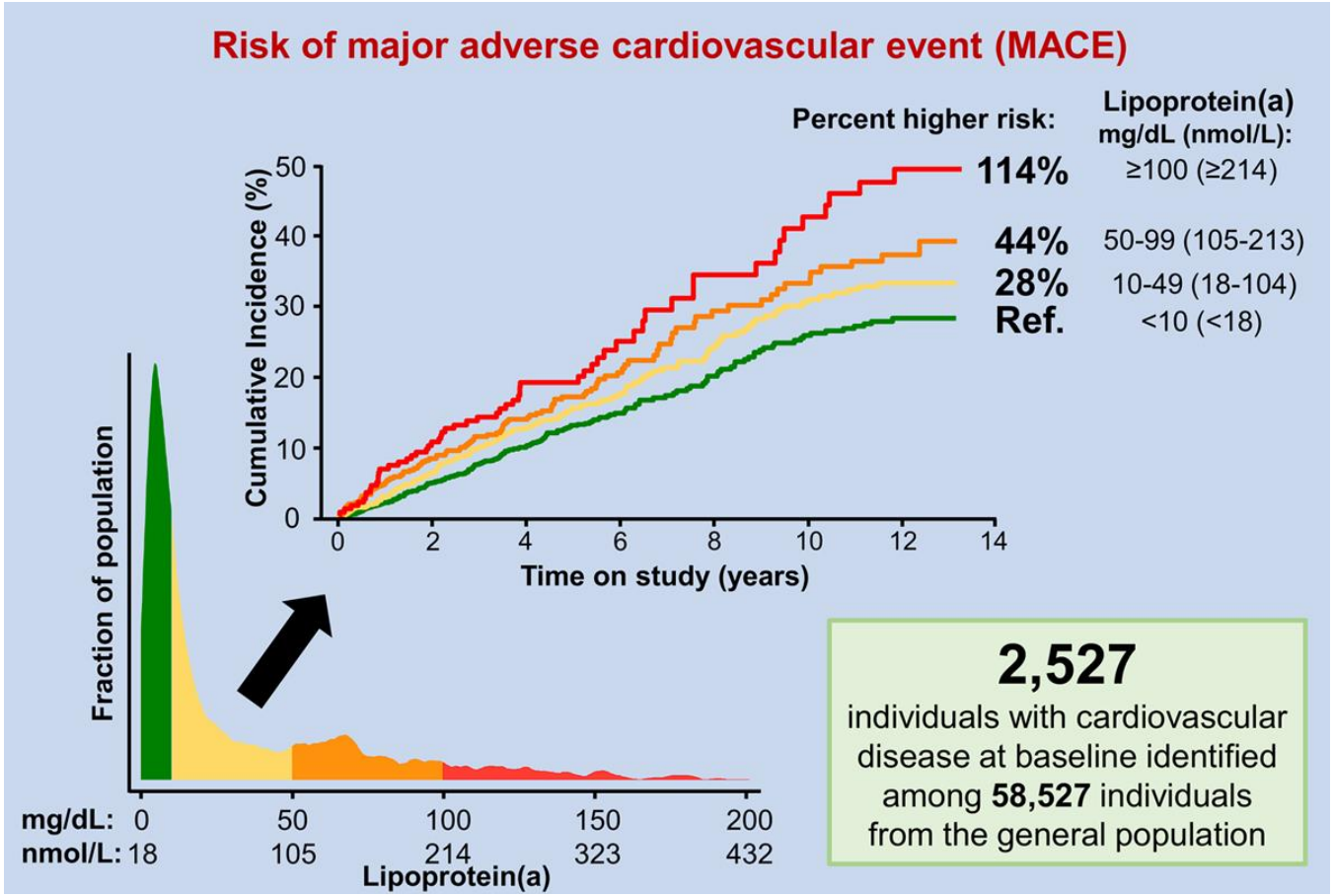
Yonghong, et al. Circulation. Oct 2011

Clinical Significance

- Clinical risk increases with higher levels of Lp(a) [mg/dL]
  - American College of Cardiology: ≥ 50 abnormal
  - Canadian Cardiovascular Society: ≥ 50 abnormal
  - European Atherosclerotic Society: < 30 normal, 30-50 intermediate risk, > 50 abnormal
  - National Lipid Association (US): > 50 abnormal

Clinical Significance



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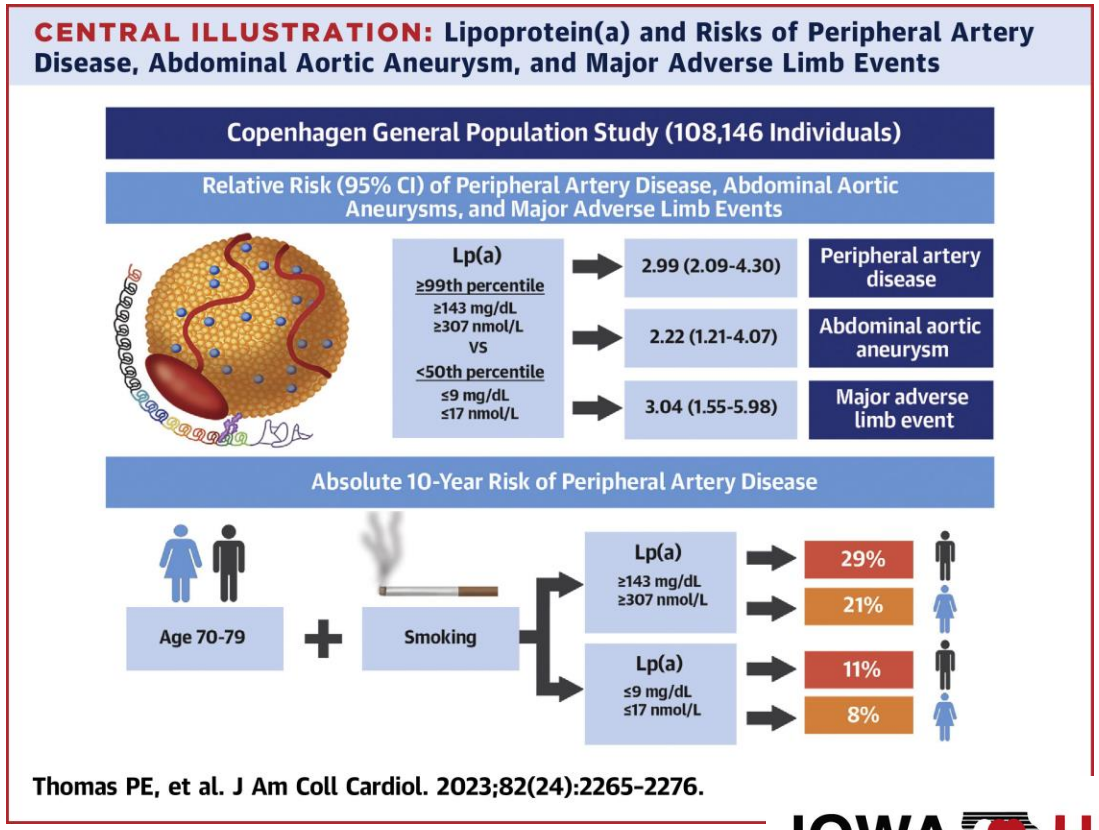
Clinical Significance

- Peripheral Artery Disease
  - Lp(a) > 70 (90th percentile): 2 x increase in risk of PAD
  - Lp(a) > 143 (99th percentile): ~ 3 x increase in PAD including major adverse limb event



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Emerging Treatments

- Lifestyle modification (dietary change, increase in exercise, weight management)
  - No consistent effect on Lp(a) levels.

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Emerging Treatments

- Lifestyle modification (dietary change, increase in exercise, weight management)
  - No consistent effect on Lp(a) levels.
- HMG-CoenzymeA Reductase Inhibitors (statins)
  - Neutral to slight increase in Lp(a) levels.

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Emerging Treatments

- PCSK9i & mRNA-PCSK9i
  - Alirocumab (Praluent)
    - 23-27% reduction in Lp(a)

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Schwartz, et al. JACC. Aug 2021
O'Donoghue, et al. Circulation. Mar 2019

Emerging Treatments

- PCSK9i & mRNA-PCSK9i
  - Alirocumab (Praluent)
    - 23-27% reduction in Lp(a)
  - Inclisiran (Leqvio)
    - 22% reduction in Lp(a)

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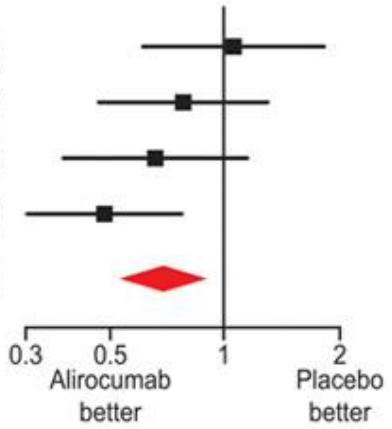
Emerging Treatments

PAD events: lipoprotein(a)

Subgroup	PAD incidence: Alirocumab n/N (%)	PAD incidence: Placebo n/N (%)	Relative risk reduction: HR (95% CI)
Quartile 1	26/2327 (1.1)	25/2403 (1.0)	1.05 (0.61-1.83)
Quartile 2	28/2438 (1.1)	33/2293 (1.4)	0.78 (0.47-1.29)
Quartile 3	21/2356 (0.9)	33/2373 (1.4)	0.66 (0.38-1.14)
Quartile 4	26/2341 (1.1)	54/2393 (2.3)	0.48 (0.30-0.77)
Overall	**101/9462 (1.1)**	**145/9462 (1.5)**	**0.69 (0.54-0.89)**

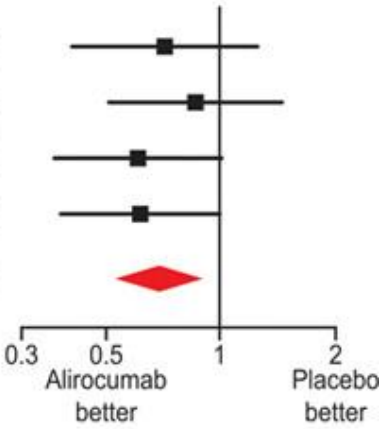
P_{trend} = .03



PAD events: LDL-$C_{corrected}$

Subgroup	PAD incidence: Alirocumab n/N (%)	PAD incidence: Placebo n/N (%)	Relative risk reduction: HR (95% CI)
Quartile 1	21/2338 (0.9)	30/2393 (1.3)	0.72 (0.41-1.26)
Quartile 2	27/2364 (1.1)	31/2368 (1.3)	0.86 (0.52-1.45)
Quartile 3	25/2372 (1.1)	41/2360 (1.7)	0.61 (0.37-1.00)
Quartile 4	28/2388 (1.2)	43/2341 (1.8)	0.62 (0.39-1.00)
Overall	**101/9462 (1.1)**	**145/9462 (1.5)**	**0.69 (0.54-0.89)**

P_{trend} = .50



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Schwartz, et al. JACC. Aug 2021

Emerging Treatments

- Phase III Trials
  - ACCLAIM-Lp(a)
    - Lepodisiran – Lilly
      - Small mRNA therapy inhibiting production of apolipoprotein
      - Reduction in Lp(a) by ~95% in phase II report

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Nissen, et al. NEJM. March 2025

Emerging Treatments

- Phase III Trials
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  - OCEAN(a)-DOSE
    - Olpasiran – Amgen
      - Small mRNA therapy inhibiting apolipoprotein mRNA production
      - Enrollment complete: ~100% reduction in phase II; ~50% reduction 1 year after last treatment

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O'Donoghue, et al. JACC. Aug 2024

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  - KRAKEN
    - Muvalaplin – Lilly
      - Small molecule prevents binding of apolipoprotein to ApoB
      - Reduction in Lp(a) by ~85% in phase II

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Nicholls, et al. JAMA. Nov 2024

Summary

- Lipoprotein(a) is an independent risk factor for ASCVD.
  - With thresholds of > 50mg/dL and especially > 100mg/dL, significant increase in CAD & PAD
  - Does not respond to lifestyle modification.
  - Novel therapies specifically targeting Lp(a) emerging with trials emerging.
    - Strongly consider checking Lp(a) in patients with early CAD, family history of early CAD, or familial hyperlipidemia.

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  - Novel therapies specifically targeting Lp(a) emerging with trials emerging.
    - Strongly consider checking Lp(a) in patients with early CAD, family history of early CAD, or familial hyperlipidemia.

- Questions?

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