What's on the HORIZON with Lp(a): Comparing the Nearly Completed Lp(a) Trials

Michael J. Blaha, MD, MPH
Professor of Cardiology and Epidemiology
Director of Clinical Research
Director of Cardiometabolic Clinic
Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease
Director of the Preventive Cardiology fellowship at Johns Hopkins
Baltimore, MD

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Disclosure

Advisory Board: Bayer; Boehringer Ingelheim; Eli Lilly; Idorsia; Merck; New Amsterdam; Novartis; Novo Nordisk

Consultant: Scene Health

Research Grant: AHA; Bayer; FDA; NIH (National Institutes of Health); Novo Nordisk

Speaker's Bureau: Boehringer Ingelheim; Novo Nordisk

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Learning Objectives

1. Describe the unmet need for dedicated therapies aimed at lowering lipoprotein(a).
2. List the ongoing cardiovascular outcomes trials of lipoprotein(a) reducing therapies.
3. Explain the expected outcomes of these trials and their potential effect on clinical practice.

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Introduction

- Lp(a) discovered by Norwegian medical geneticist, Professor Kåre Ingmar Berg, as an antigenic variant of LDL-C
- Lp(a) recognised as genetically linked

- International guidelines incorporate Lp(a) as a risk factor or risk-enhancing factor for atherosclerotic cardiovascular disease (ASCVD), and make recommendations for testing
- Apo(a) gene (*LPA*) cloned and sequenced
- Lp(a) structure elucidated

1963 | 1974 | 1987 | 2000-2020 | 2020 onwards

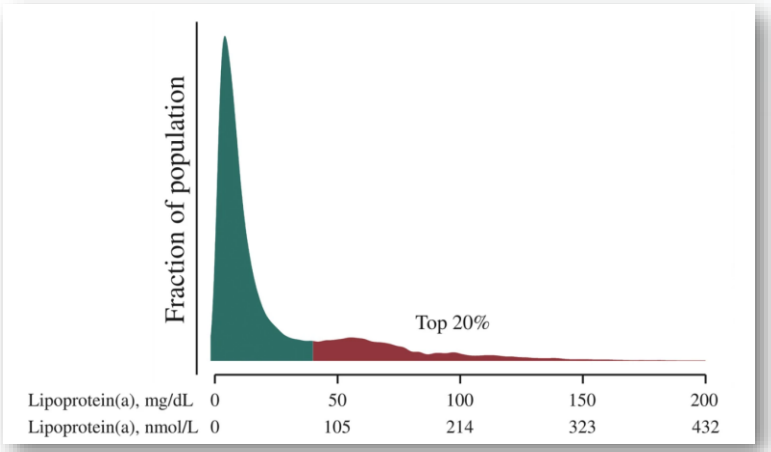
- Lp(a) linked to coronary heart disease
- Multiple epidemiological and Mendelian randomisation studies demonstrate Lp(a) importance as an independent risk factor for myocardial infarction (MI), calcific aortic valve stenosis (CAVS), heart failure, ischaemic stroke, peripheral artery disease (PAD), cardiovascular and all-cause mortality
- Research starts to establish mechanisms through which Lp(a) promotes atherosclerosis

Sources: Witztum JL, Ginsberg HN. Lipoprotein (a): Coming of Age at Last. J Lipid Res. 2016 Mar;57(3):336-9; Kronenberg F, Mora S, Stroes ESG et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J. 2022 Oct 14;43(39):3925-3946; Grundy SM, Stone NJ, Bailey AL et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Jun 18;139(25):e1082-e1143

Lp(a) FORUM

4

Distribution of Lp(a) in the Population



Langsted, A., Nordestgaard, B.G. (2022). Lipoprotein(a). In: Shapiro, M.D. (eds) Cardiovascular Risk Assessment in Primary Prevention. Contemporary Cardiology. Humana, Cham.

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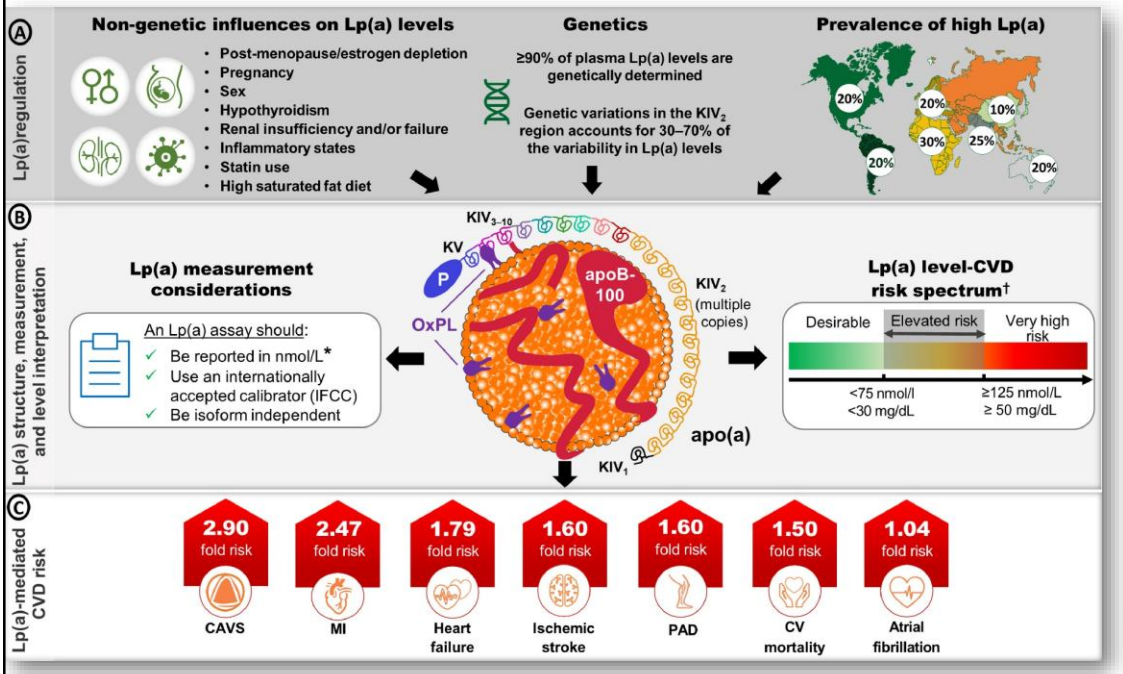


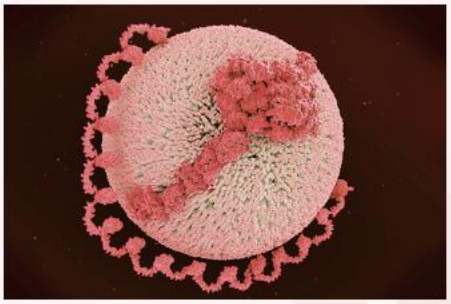
Reyes-Soffer et al, AJPC 2024

6

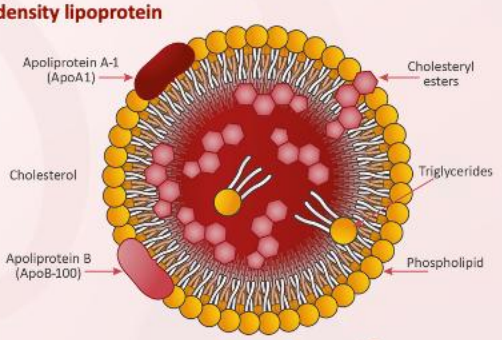
Genetic studies show Lp(a) is highly atherogenic

- A Mendelian randomisation study using UK Biobank data from almost 500,000 people compared the per particle atherogenicity of Lp(a) and LDL in terms of coronary heart disease (CHD) risk, based on their component apoB
- Lp(a) was approximately 6-7 times more atherogenic per particle than LDL
  - Lp(a) competes with plasminogen and tissue plasminogen activator (tPA) for binding to fibrin
  - Lp(a) upregulates plasminogen activator inhibitor type 1 (PAI-1) within endothelial cells and associates with increased α1-antitrypsin synthesis, both of which inhibit tPA
  - Lp(a) can bind to α2-macroglobulin, a non-specific plasmin inhibitor

Lp(a)



Low-density lipoprotein



Source: Björnson E, Adiels M, Taskinen MR et al. Lipoprotein(a) Is Markedly More Atherogenic Than LDL: An Apolipoprotein B-Based Genetic Analysis. J Am Coll Cardiol. 2024 Jan 23;83(3):385-395

Lp(a) FORUM

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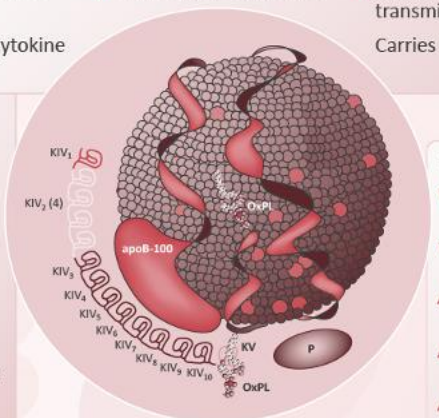
Lp(a) exerts proatherogenic, proinflammatory and prothrombotic activities

Proinflammatory

- Macrophage IL-8 expression
- Oxidised phospholipids
- Monocyte chemotaxis/ transmigration
- Monocyte cytokine release
- Carries MCP-1

Proatherogenic

- EC binding
- Upregulation of adhesion molecules
- SMC proliferation
- Proteoglycan matrix binding
- Foam/cell formation
- Necrotic core formation
- Lesion calcification



Prothrombotic

- Plasminogen activation
- Fibrin degradation
- EC PAI-1 expression
- TFPI activity
- Platelet responsiveness

EC: Endothelial cell; SMC: Smooth muscle cell; MCP-1: Monocyte chemoattractant protein-1; PAI-1: Plasminogen activator inhibitor type 1; TFPI: tissue factor pathway inhibitor

Source: Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. J Am Coll Cardiol. 2017 Feb 14;69(6):692-711

Lp(a) FORUM

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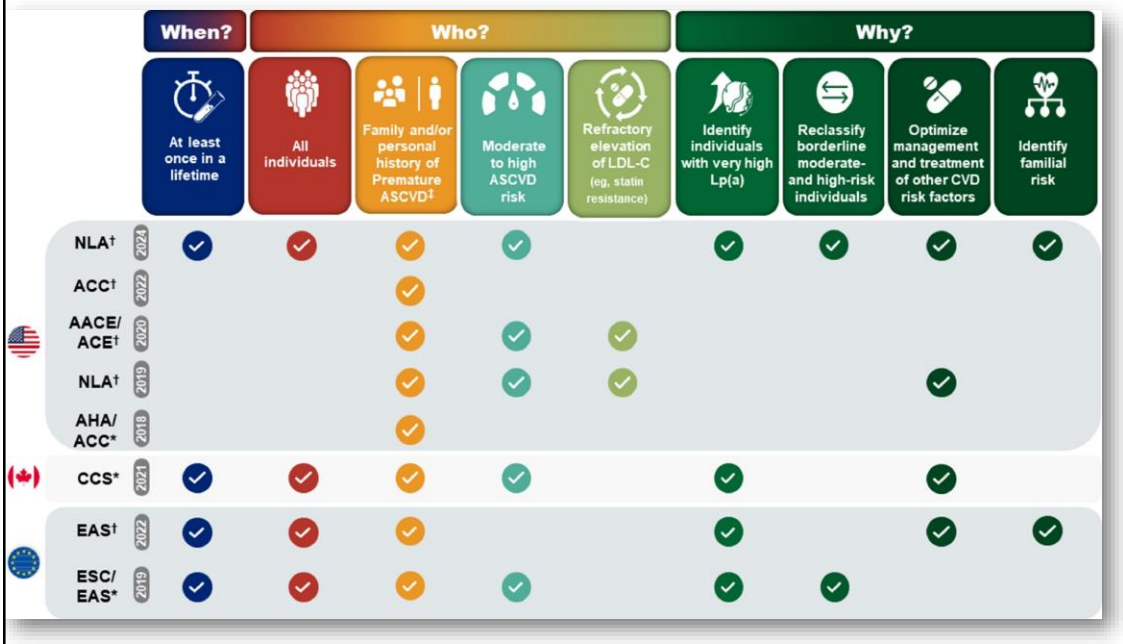

Reyes-Soffer et al, AJPC 2024

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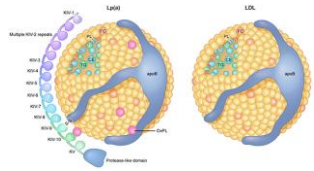
New: Measure Lipoprotein(a) Once in All Adults



Lp (a) in nmol/L	ASCVD relative risk
450	4x
375	3x
250	2x
125	1.4x
75	Reference

Screening with Lp(a)

Measurement of Lp(a) in all adults is recommended at least once for ASCVD risk assessment (1)

In those with FH, premature ASCVD, or high Lp(a), cascade testing of 1st- degree relatives is recommended (1)

Lp(a) particles consist of an LDL-cholesterol-like particle bound to an apo(a) protein

Lp(a) levels are largely genetically determined and stable over one's lifetime

Repeat testing is generally not needed

If Lp(a) is elevated, intensify LDL-C lowering and aggressively control other ASCVD risk factors

Blumenthal RS, et al. J Am Coll Cardiol. 2026;Epub ahead of print.

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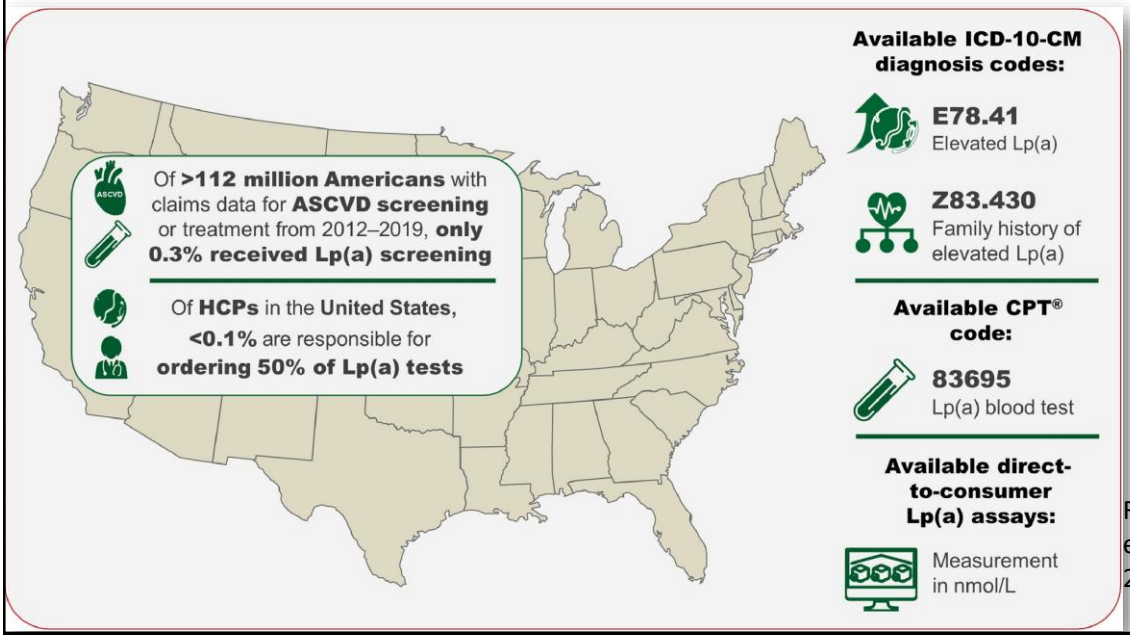

Reyes-Soffer et al, AJPC 2024

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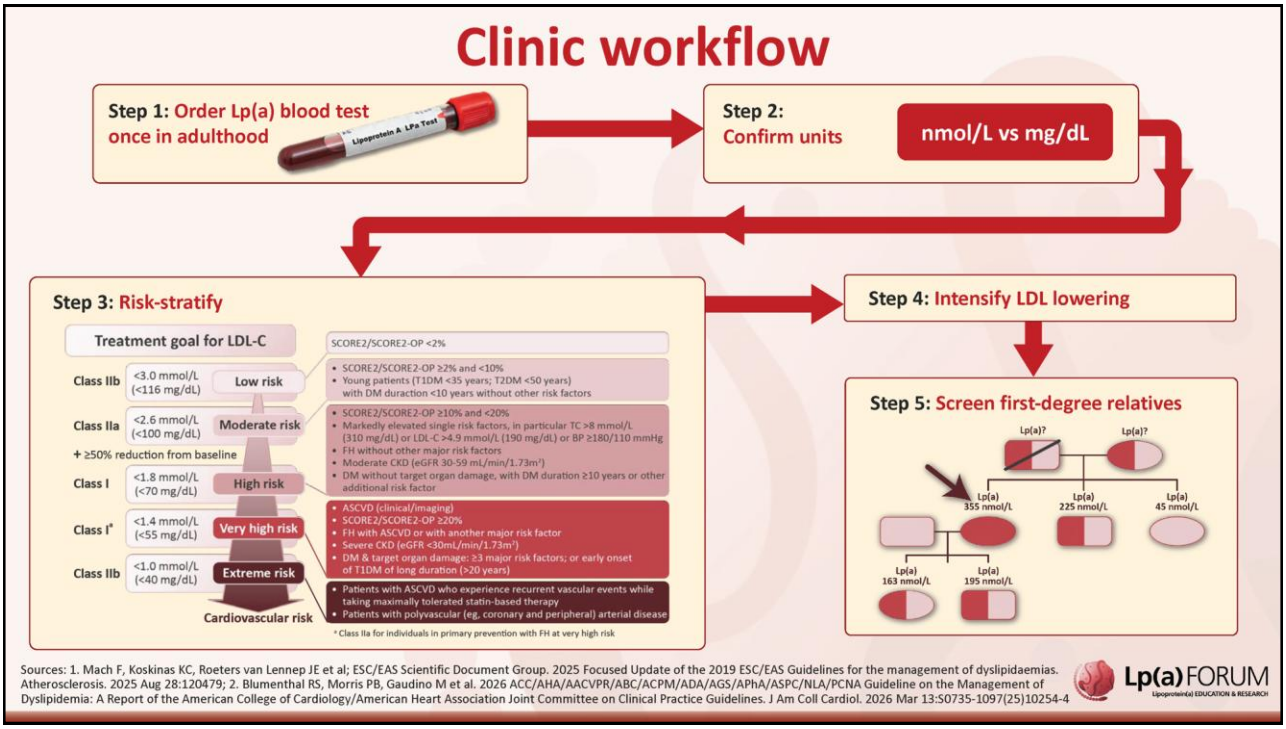

Sources: 1. Mach F, Koskinas KC, Roeters van Lennep JE et al; ESC/EAS Scientific Document Group. 2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias. Atherosclerosis. 2025 Aug 28:120479; 2. Blumenthal RS, Morris PB, Gaudino M et al. 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2026 Mar 13:S0735-1097(25)10254-4

Lp(a) FORUM Lipoprotein(a) EDUCATION & RESEARCH

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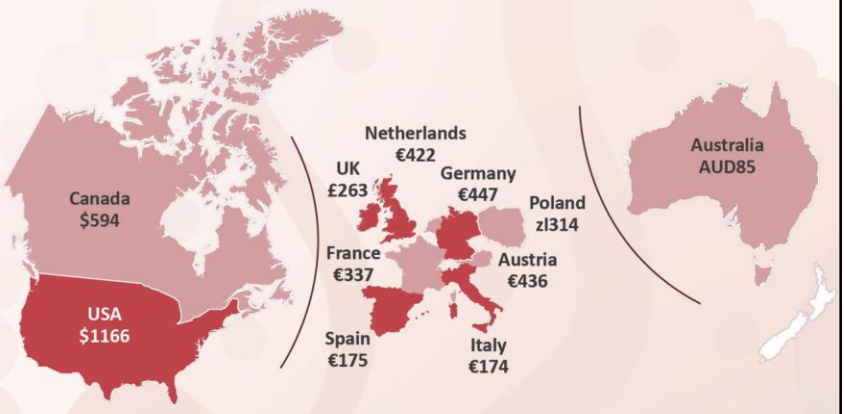
Cost effectiveness of Lp(a) testing

- Lp(a) testing is cost effective for primary CV prevention in high income countries[1]
- In a study of 10,000 people aged 40-69 years without CVD randomly selected from UK Biobank, Lp(a) testing led to treatment modification in 1,807 individuals
- Based on direct healthcare and indirect costs in the Australian and UK national healthcare systems, treatment modification led to 217 and 255 quality-adjusted life years gained in Australia and the UK, respectively
- From a societal perspective, Lp(a) testing saved $85 and £263 per person in Australia and the UK, respectively
- In a cost adaptation analysis, Lp(a) testing was cost-saving among multiple European countries, Canada and the USA

Cost adaptation to other countries: Costs saved per person



Source: Morton JI, Kronenberg F, Daccord M et al; Lp(a) International Taskforce (ITF) initiative. Lp(a) testing for the primary prevention of cardiovascular disease in high-income countries: a cost-effectiveness analysis. Atherosclerosis. 2025 Oct;409:120447.

Lp(a) FORUM Lipoprotein(a) EDUCATION & RESEARCH

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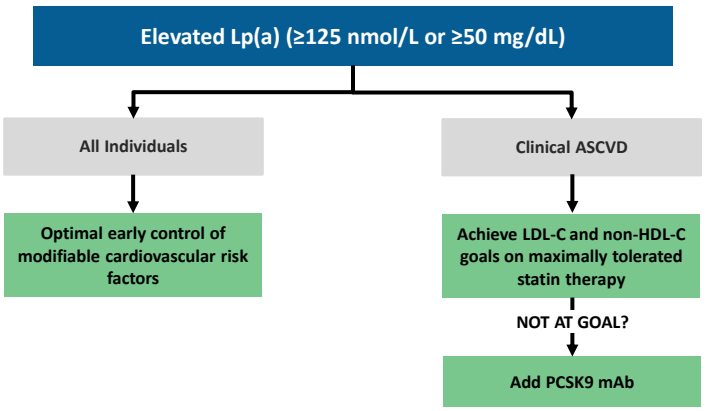
Approach to Patients with Elevated Lp(a)



American Heart Association.

Abbreviations: ASCVD indicates atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein-cholesterol; Lp(a), lipoprotein(a); mAb, monoclonal antibody; and PCSK9, Proprotein Convertase Subtilisin/Kexin type 9.

Blumenthal, R.S., Morris, P.B., et al. 2026 ACC/AHA Guideline on the Management of Dyslipidemia. *Circulation*.

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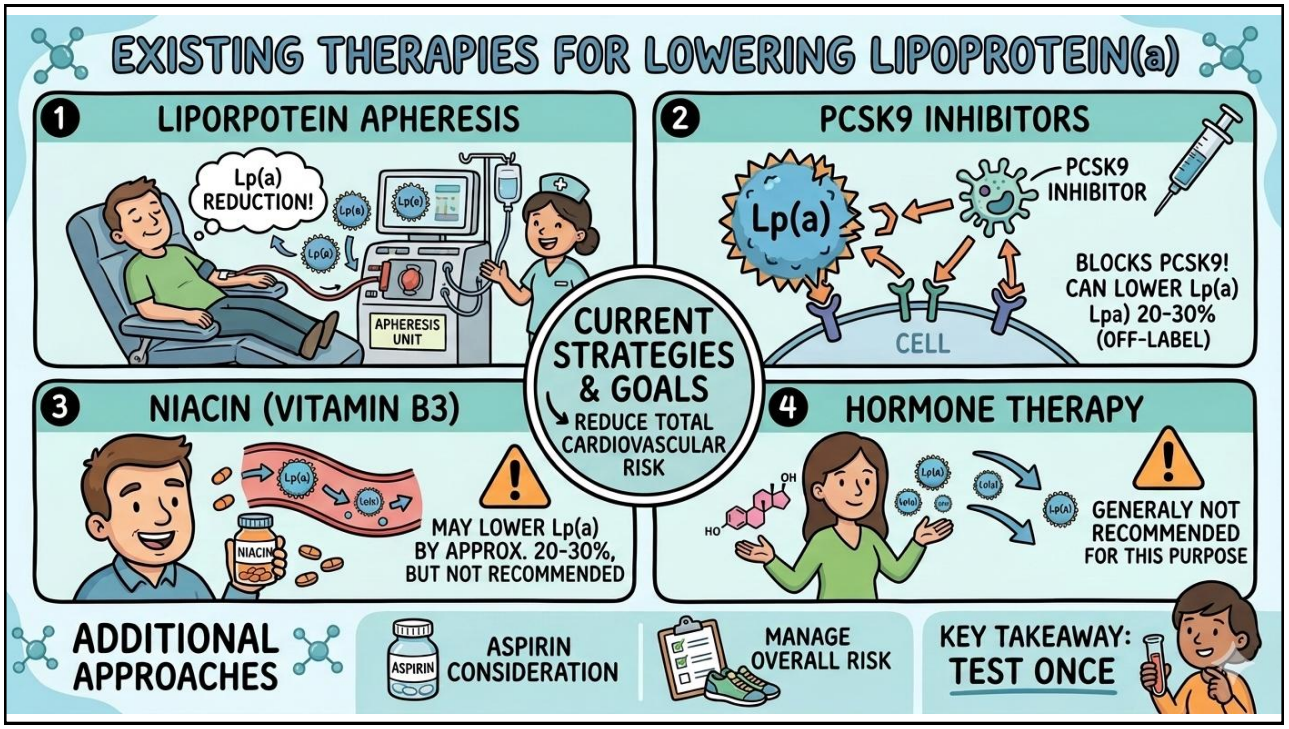
EXISTING THERAPIES FOR LOWERING LIPOPROTEIN(a)
1 LIPORPOTEIN APHERESIS
Lp(a) REDUCTION!
APHERESIS UNIT
2 PCSK9 INHIBITORS
Lp(a)
PCSK9 INHIBITOR
CELL
BLOCKS PCSK9! CAN LOWER Lp(a) Lpa) 20-30% (OFF-LABEL)
CURRENT STRATEGIES & GOALS
REDUCE TOTAL CARDIOVASCULAR RISK
3 NIACIN (VITAMIN B3)
NIACIN
MAY LOWER Lp(a) BY APPROX. 20-30%, BUT NOT RECOMMENDED
4 HORMONE THERAPY
GENERALY NOT RECOMMENDED FOR THIS PURPOSE
ADDITIONAL APPROACHES
ASPIRIN
ASPIRIN CONSIDERATION
MANAGE OVERALL RISK
KEY TAKEAWAY: TEST ONCE

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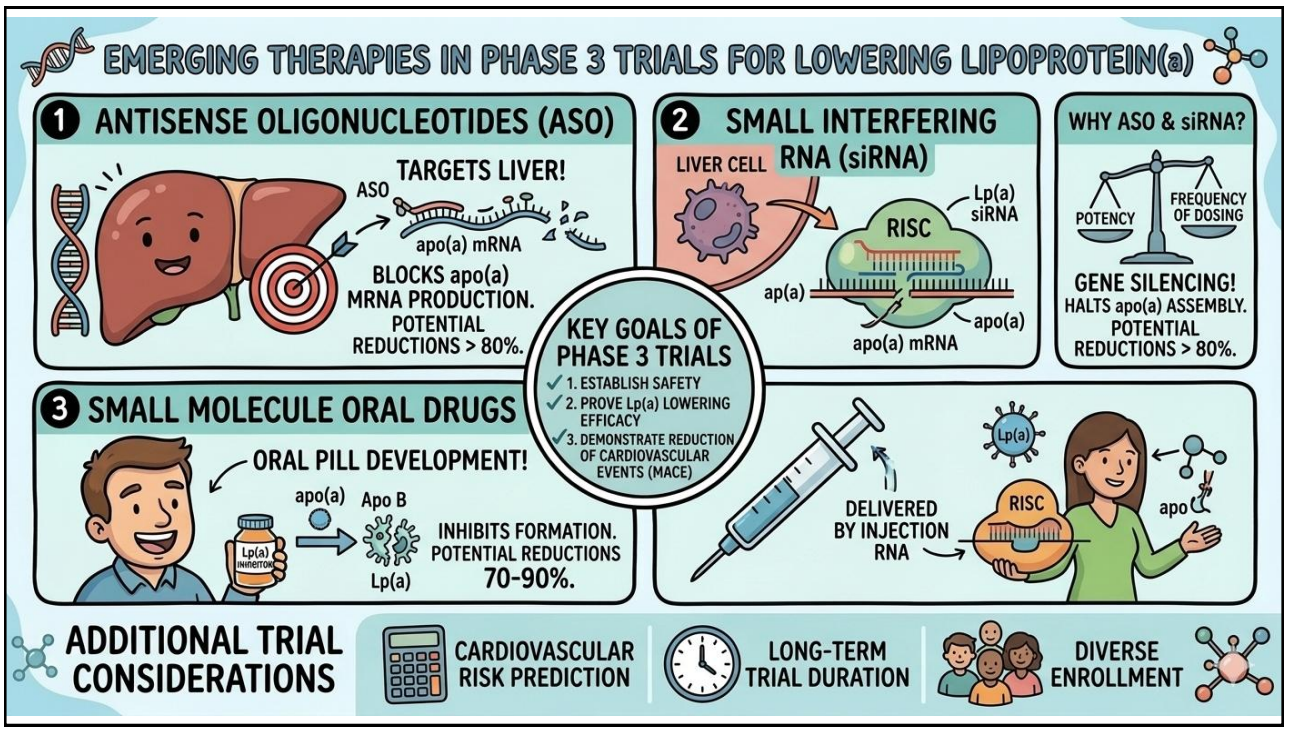
EMERGING THERAPIES IN PHASE 3 TRIALS FOR LOWERING LIPOPROTEIN(a)
1 ANTISENSE OLIGONUCLEOTIDES (ASO)
TARGETS LIVER!
ASO
apo(a) mRNA
BLOCKS apo(a) MRNA PRODUCTION. POTENTIAL REDUCTIONS > 80%.
2 SMALL INTERFERING RNA (siRNA)
LIVER CELL
Lp(a) siRNA
RISC
ap(a)
apo(a)
apo(a) mRNA
WHY ASO & siRNA?
POTENCY
FREQUENCY OF DOSING
GENE SILENCING!
HALTS apo(a) ASSEMBLY. POTENTIAL REDUCTIONS > 80%.
KEY GOALS OF PHASE 3 TRIALS
1. ESTABLISH SAFETY
2. PROVE Lp(a) LOWERING EFFICACY
3. DEMONSTRATE REDUCTION OF CARDIOVASCULAR EVENTS (MACE)
3 SMALL MOLECULE ORAL DRUGS
ORAL PILL DEVELOPMENT!
apo(a)
Apo B
Lp(a)
INHIBITS FORMATION. POTENTIAL REDUCTIONS 70-90%.
DELIVERED BY INJECTION
RNA
Lp(a)
RISC
apo
ADDITIONAL TRIAL CONSIDERATIONS
CARDIOVASCULAR RISK PREDICTION
LONG-TERM TRIAL DURATION
DIVERSE ENROLLMENT

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HOW MUCH DO YOU NEED TO LOWER LIPOPROTEIN(A) TO SEE A POTENTIAL MACE BENEFIT?

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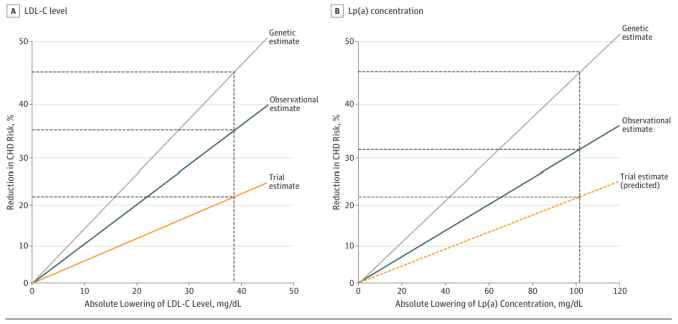
JAMA Cardiology | Original Investigation

Association of *LPA* Variants With Risk of Coronary Disease and the Implications for Lipoprotein(a)-Lowering Therapies
A Mendelian Randomization Analysis

Stephen Burgess, PhD; Brian A. Ference, MD, MPhil, MSc; James R. Staley, PhD; Daniel F. Freitag, PhD; Amy M. Mason, PhD; Sune F. Nielsen, PhD; Peter Willeit, MD, PhD; Robin Young, PhD; Praveen Surendran, PhD; Savita Karthikeyan, MSc; Thomas R. Bolton, MSc; James E. Peters, MD; Pia R. Kamstrup, MD, PhD; Anne Tybjærg-Hansen, MD, PhD, DMSc; Marianne Benn, MD, PhD, DMSc; Anne Langsted, MD, PhD; Peter Schnohr, MD; Signe Vedel-Krogh, MD; Camilla J. Kobylecki, PhD; Ian Ford, PhD, FRSE, FRCP; Chris Packard, DSc; Stella Trompet, PhD; J. Wouter Jukema, MD; Naveed Sattar, MD, FRCP; Emanuele Di Angelantonio, MD; Danish Saleheen, MD; Joanna M. M. Howson, PhD; Børge G. Nordestgaard, MD, PhD, DMSc; Adam S. Butterworth, PhD; John Danesh, DPhil, FMedSci; for the European Prospective Investigation Into Cancer and Nutrition–Cardiovascular Disease (EPIC-CVD) Consortium

Figure 3. Estimates of Coronary Heart Disease (CHD) Risk Reduction With Lowering of Low-Density Lipoprotein Cholesterol (LDL-C) Level and Lipoprotein(a) (Lp[a]) Concentration



Genetic estimates of lifelong lowering from mendelian randomization (brown line), observational estimates from prospective cohort studies (blue line), and (A) trial estimate from short-term statin trials (for LDL-C) or (B) predicted trial estimate (for Lp[a]) (orange line). The vertical line is at 38.67 mg/dL (ie, 1 mmol/L) for LDL-C level and at 101.5 mg/dL for Lp(a) concentration, the estimated equivalent lowering in Lp(a) for the same reduction in CHD risk. To convert LDL-C to millimoles per liter, multiply by 0.0259.

CONCLUSIONS AND RELEVANCE The clinical benefit of lowering Lp(a) is likely to be proportional to the absolute reduction in Lp(a) concentration. Large absolute reductions in Lp(a) of approximately 100 mg/dL may be required to produce a clinically meaningful reduction in the risk of CHD similar in magnitude to what can be achieved by lowering LDL-C level by 38.67 mg/dL (ie, 1 mmol/L).

Across 2 key studies, it is estimated that Lp(a) is needed to be reduced by 66-90 mg/dL to reduce ASCVD ~20%.

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ONGOING CARDIOVASCULAR OUTCOMES TRIALS

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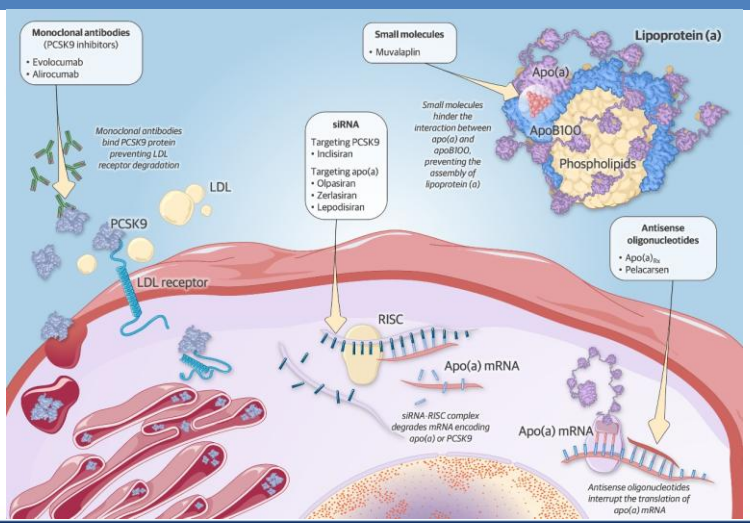
Pelacarsen – *An Anti-Sense Oligonucleotide*



Greco A, Capodanno D, et al. Circulation. 2025 Feb 11;151(6):400-415.

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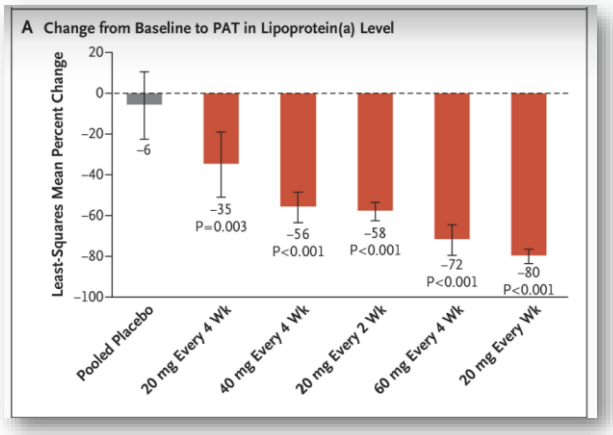
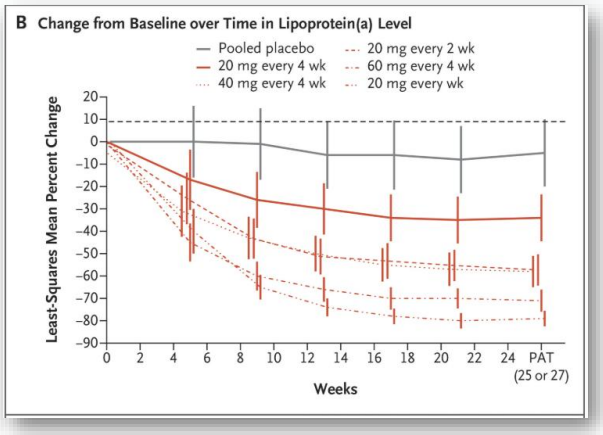
Pelacarsen – *Phase 2 Data*





Tsimikas S, et al. N Engl J Med. 2020 Jan 16;382(3):244-255.

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Pelacarsen – *Lp(a) HORIZON CVOT*

- Phase 3, randomized, double-blind, placebo-controlled cardiovascular outcomes trial
- Enrolled **8,323 patients** with established cardiovascular disease (MI, ischemic stroke, or peripheral artery disease) and elevated baseline Lp(a) levels of **≥70 mg/dL**
- 4-component **MACE** (CV death, nonfatal MI, nonfatal stroke, or urgent coronary revascularization)
- Planned subpopulation analysis in patients with baseline Lp(a) **≥90 mg/dL**
- The event-driven study aiming for 993 primary CV events, with top-line results anticipated in **H2 2026**.

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Pelacarsen – *Lp(a) HORIZON CVOT*

Design and Rationale of Lp(a)HORIZON Trial: Assessing the Effect of Lipoprotein(a) Lowering With Pelacarsen on Major Cardiovascular Events in Patients With CVD and Elevated Lp(a)

Leslie Cho, MD[a], Stephen J. Nicholls, MBBS, PhD[b], Børge G. Nordestgaard, MD, DMSc[c], Ulf Landmesser, MD[d], Sotirios Tsimikas, MD[e], Michael J. Blaha, MD, MPH[f], Eran Leitersdorf, MD[g], A. Michael Lincoff, MD[a], Anastasia Lesogor, MD[h], Brian Manning, Pharm D[i], Plamen Kozlovski, MD[h], Hui Cao, MD[i], Jing Wang, MD, PhD[i], and Steven E. Nissen, MD[a]

Trial Registration NCT 04023552. (Am Heart J 2025;287:1–9.)

- Age ~60 years
- 73% male
- 78% White
- ~79% with Lp(a) ≥90 mg/dL
- ~81% with prior MI
- ~78% with high intensity statin use
- ~57% on ezetimibe
- Mean LDL ~65 mg/dl!

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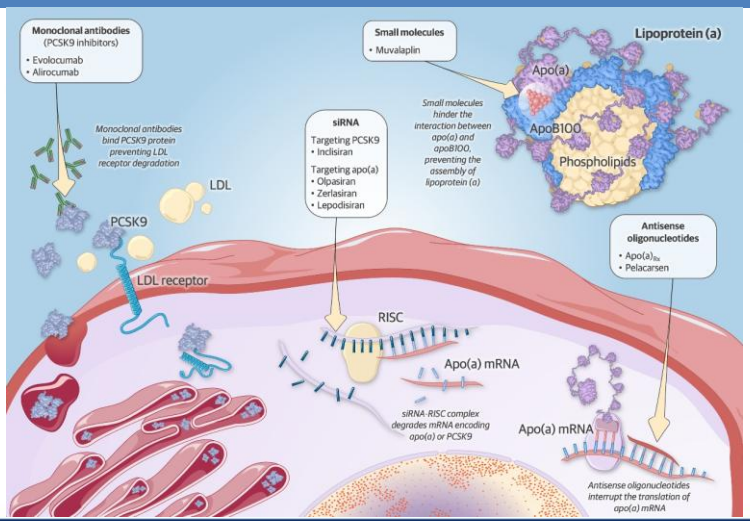
Olpasiran – *A Small Interfering RNA*



Greco A, Capodanno D, et al. Circulation. 2025 Feb 11;151(6):400-415.

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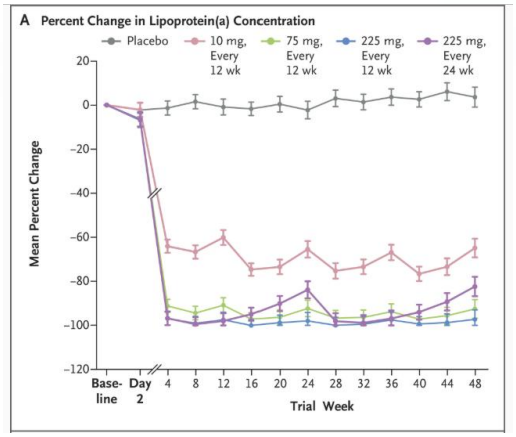
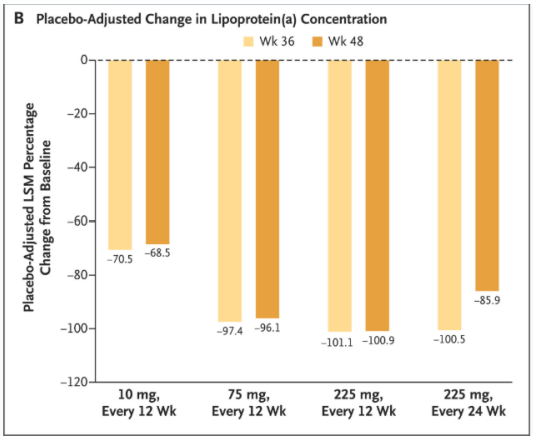
Olpasiran – *Phase 2 Data*





O'Donoghue ML, et al. N Engl J Med. 2022 Nov 17;387(20):1855-1864.

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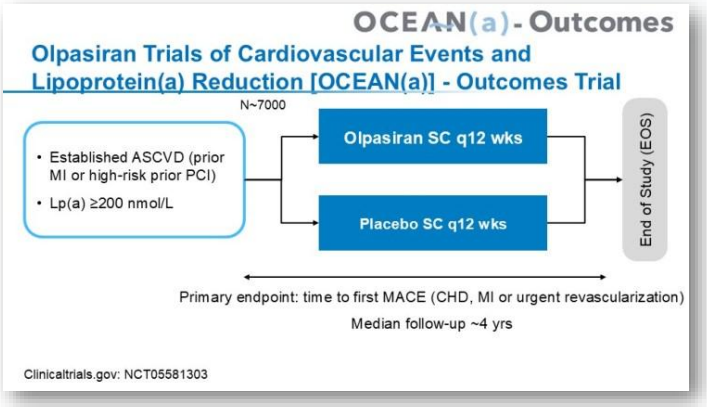
Olpasiran – *OCEAN(a) CVOT*



- Every 3 month dosing
- Includes high risk PCI patients
- Notably excludes stroke from the primary endpoint

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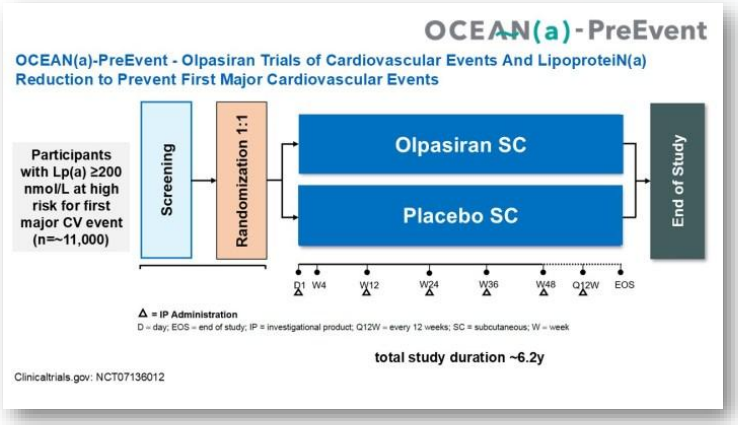
Olpasiran – *OCEAN(a) PREVENT CVOT*



- Larger and longer trial
- Aimed at patients at high risk for a first ASCVD event
- Multiple risk factors or **evidence of atherosclerosis**

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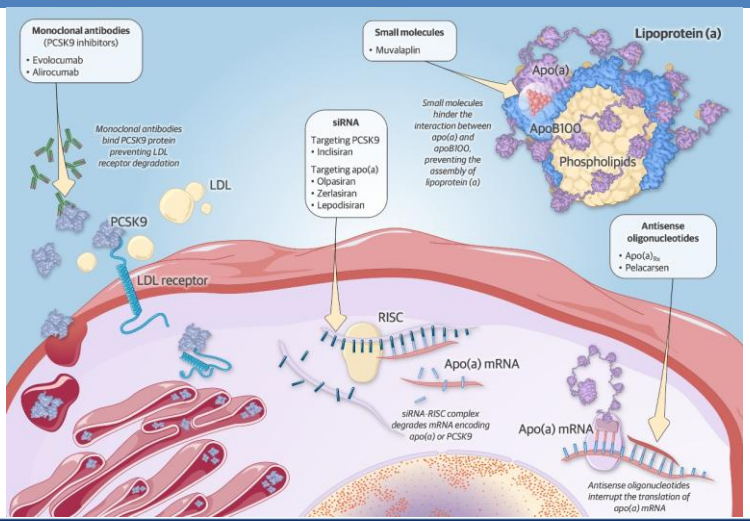
Lepodisiran – *A Small Interfering RNA*



Greco A, Capodanno D, et al. Circulation. 2025 Feb 11;151(6):400-415.

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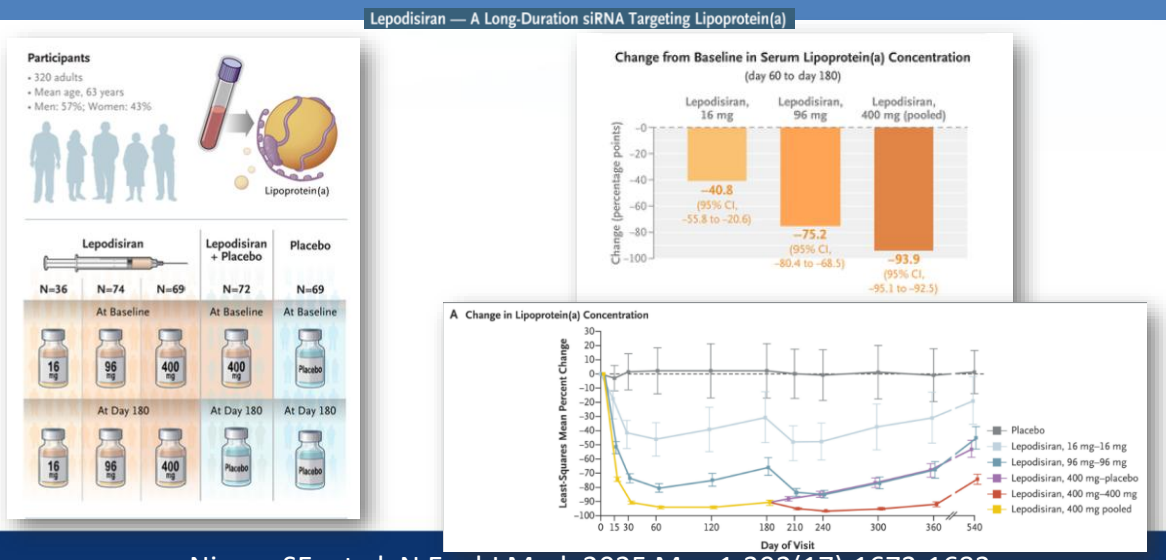
Lepodisiran – *Phase 2 Data*



Nissen SE, et al. N Engl J Med. 2025 May 1;392(17):1673-1683.

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Lepodisiran – *ACCLAIM-Lp(a) CVOT*

- Adults with high levels of Lp(a) ≥175 nmol/L who either have established heart disease **or are age 55+ and at high risk for their first cardiovascular event**.
- The trial began in March 2024 and is expected to conclude around March 2029.
- Event-driven study aiming to enroll approximately 12,500 participants globally with 1,276 4-pt MACE events.
- Lepodisiran first three doses are given **six months apart**, followed by subsequent doses **every 12 months**.

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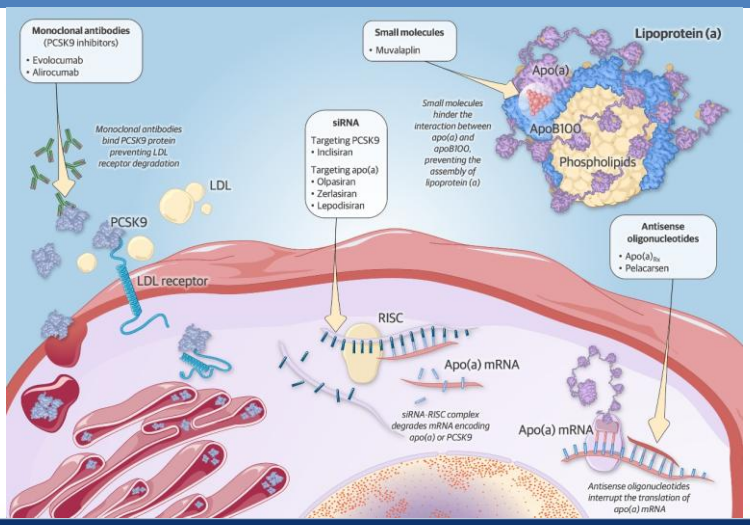
Muvalaplin – *A Small Molecule*



Greco A, Capodanno D, et al. Circulation. 2025 Feb 11;151(6):400-415.

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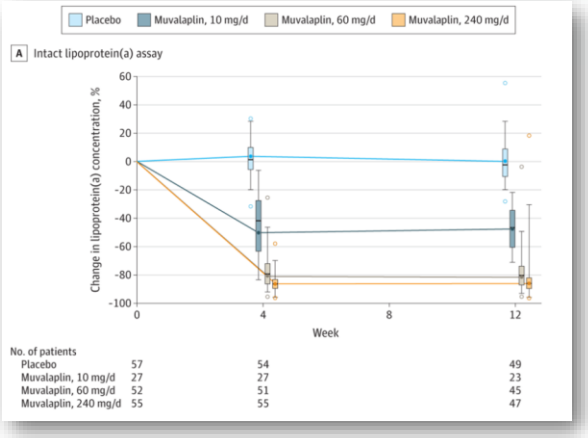
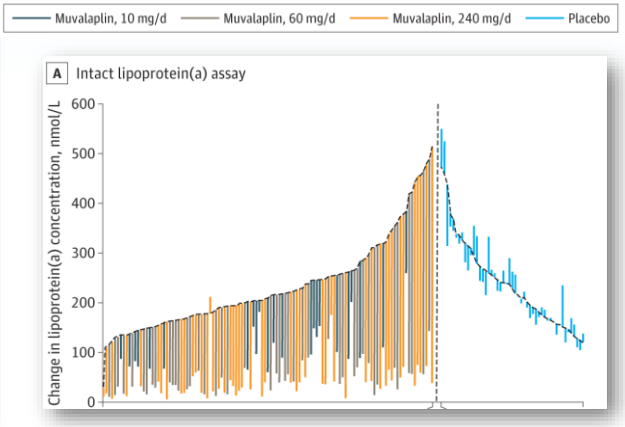
Muvalaplin – *Phase 2 Data*





Nicholls SJ, et al. JAMA. 2025 Jan 21;333(3):222-231.

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Muvalaplin – *MOVE-Lp(a) CVOT*

- **Lipoprotein(a) Threshold**: Must have levels of ≥**175 nmol/L**.
- Inclusion Criteria
  - Previous history of heart attack, stroke, or revascularization procedure.
  - High risk for a first event due to conditions like coronary artery disease, reduced kidney function with diabetes, or high coronary artery calcium (CAC) score.
- Oral muvalaplin once daily
- 10,450 patients followed for 4-point MACE in event-driven design
- Estimated to conclude in 2031

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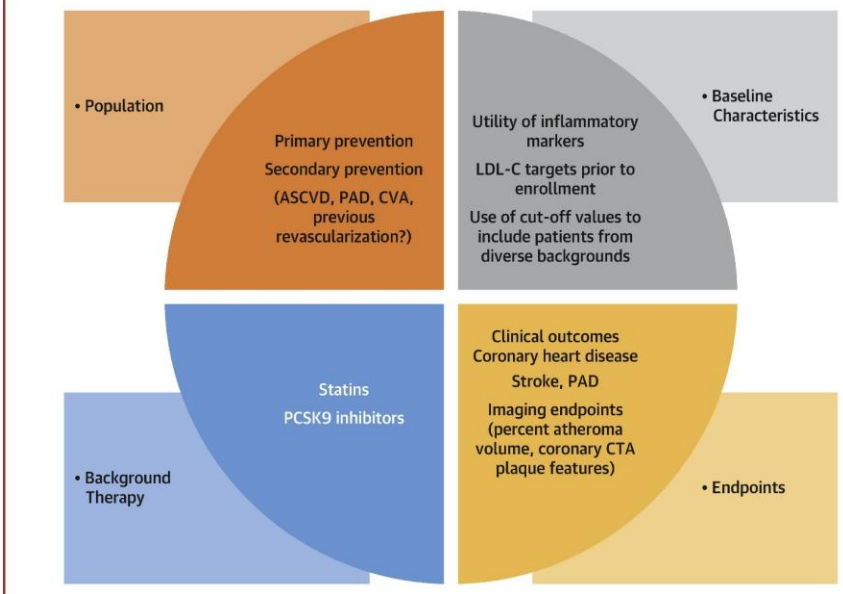
CENTRAL ILLUSTRATION: Clinical Trial Considerations for Lipoprotein(a)-Lowering Therapies



Malick WA, et al. J Am Coll Cardiol. 2023;81(16):1633-1645.

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CENTRAL ILLUSTRATION: Global Variation in Lipoprotein(a) Levels Among Patients With Coronary Heart Disease From the INTERASPIRE Study

Purpose: To assess variation in Lp(a) levels among coronary heart disease (CHD) patients across the globe and estimate eligibility for future Lp(a)-lowering therapies

3,928 patients with CHD → From 13 countries and 6 WHO regions (INTERASPIRE Lp(a) 2020-2023) → Both centralized and standardized measurements of Lp(a)

Eligibility rates for Lp(a)-lowering therapies across regions/countries

	Lp(a) ≥150 nmol/L (Lp(a)HORIZON)	Lp(a) ≥175 nmol/L (ACCLAIM-Lp(a))	Lp(a) ≥200 nmol/L (OCEAN(a)-OUTCOMES)
Africa-Kenya	21.0%	15.3%	8.9%
Africal-Nigeria	15.2%	10.3%	6.7%
Africa-Tanzania	10.7%	6.5%	4.7%
Americas-Argentina	15.5%	12.3%	9.6%
Americas-Colombia	18.6%	14.5%	9.4%
Europe-Poland	16.0%	11.5%	8.7%
Europe-Portugal	25.5%	18.3%	11.6%
Southeast Asia-Indonesia	12.1%	8.5%	6.8%
Eastern Mediterranean-UAE	6.0%	3.3%	1.0%
Western Pacific-China	13.4%	10.8%	8.5%
Western Pacific-Malaysia	13.8%	9.5%	5.3%
Wetern Pacific-Philippines	4.3%	2.5%	1.3%
Western Pacific-Singapore	8.8%	6.8%	4.3%

25% 20% 15% 10% 5%

Median Lp(a) levels

Median Lp(a) levels overall: 32 nmol/L (11-89)

17.6% having levels ≥125 nmol/L

Eligibility rates for Lp(a)-lowering therapies

13% Lp(a) ≥150 nmol/L (Lp(a)HORIZON)

9.3% Lp(a) ≥175 nmol/L (ACCLAIM-Lp(a))

6.2% Lp(a) ≥200 nmol/L (OCEAN(a)-OUTCOMES)

Median Lp(a) in CHD patients is below common risk thresholds and varies by region and country which may impact equitable access to Lp(a)-lowering therapies.

Barkas F, et al. JACC. 2025;85(21):2028-2042.

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Summary Thoughts – Part 1

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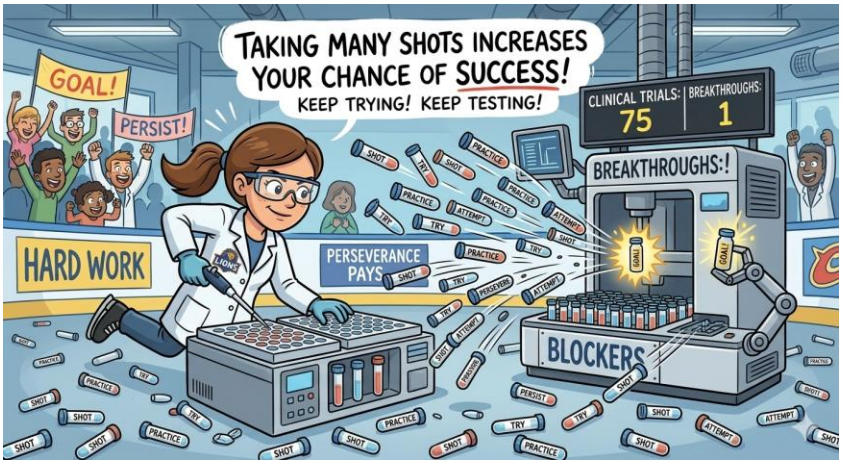

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Summary Thoughts – Part 2

- We will be able to lower Lp(a) to basically whatever level we want.
- HORIZON – ultimate scientific experiment, but some risky elements that may diminish chance of success
- However, after first three trials, we will definitely know if Lp(a) lowering via this general approach decreases MACE
- Question is degree of RRR – 15% or up to 30%?? Stroke? Mortality?
- Therapy for high-risk 2^{o} prevention – as soon as late 2026/early 2027
- Broad use in high-risk 1^{o} prevention – probably wait until 2031
- Therefore, in interim, potential role in primary prevention for PCSK9i drugs like oral enlicitide (or possibly obicetrapib)

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Summary Thoughts – Part 3

- What if these trials are negative?
- Too little residual risk after modern treatment?
- Something we don't fully understand about Lp(a) beyond simple serum particle or cholesterol concentration?
- OxPL or inflammation?

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Presentation Summary

- High Lp(a) is common, mechanistically linked to ASCVD and AS, but woefully undermeasured
- New Class I recommendation for at least one-time measurement
- Remarkable new therapies that should lower Lp(a) sufficiently to reduce MACE
- MANY ongoing trials, extending from secondary to high-risk primary prevention with monthly to yearly injections or oral small molecule therapies
- Story will begin to unfold in second half of 2026

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