JOHNS HOPKINS
MEDICINE

Lipid Screening: How to Use Lipoprotein(a)

Thorsten Leucker, MD, PhD

Patient Case

- 44 y/o man with HTN (on ARB), hyperlipidemia and family history of ASCVD (not premature)

- Lipid panel:

Total Cholesterol	193 mg/dL	5.0 mmol/L
Triglycerides	90 mg/dL	1.0 mmol/L
HDL-C	55 mg/dL	1.4 mmol/L
LDL-C	119 mg/dL	3.1 mmol/L

ESC 2022 Risk Calculator: Causal AI in Precision Cardiovascular Health

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Enter your health information below

Cholesterol units: ◉ mmol/L ○ mg/dL

Height units: ◉ cm ○ in

Weight units: ◉ kg ○ lbs

Sex: Male | Female

Height (cm): 190

Age (ages 30-75): 44

Weight (kg): 95

Lipoprotein(a) = 365 nmol/L

LDL Cholesterol (mmol/L) (range 2.0 - 5.0): 3.1

Do you have diabetes? No | Yes

HDL Cholesterol (mmol/L) (range 0.6 - 2.8): 1.4

Do you currently smoke? No | Yes

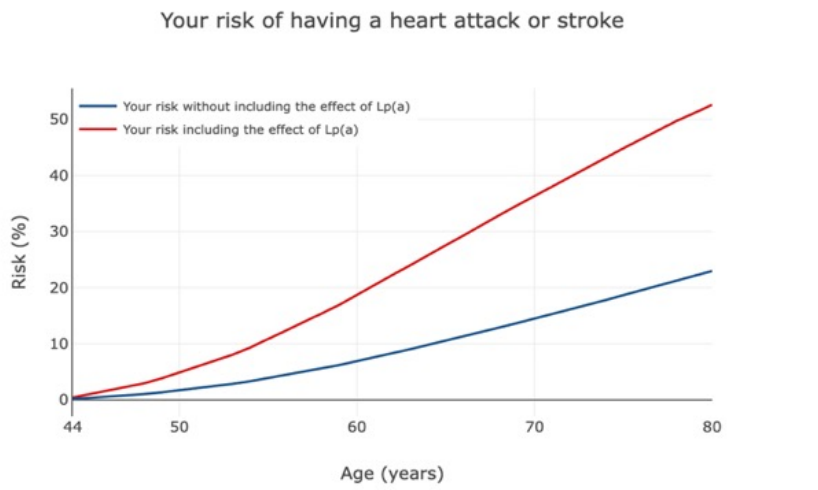
Systolic Blood Pressure (mmHg) (range 90 - 200): 130

Have you ever smoked? No | Yes

Are you taking a medicine to lower blood pressure? No | Yes

Has anyone in your family had a heart attack or stroke? No | Yes

Impact of including Lp(a) as a risk factor



Your risk of having a heart attack or stroke up to age 80 is: 23.0%

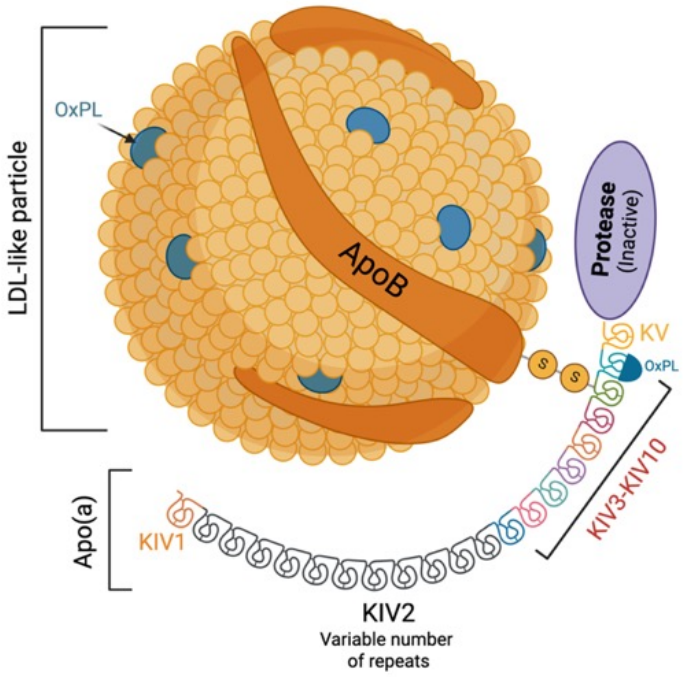
With an Lp(a) level of 365 nmol/L, your estimated risk of having a heart attack or stroke up to age 80 changes from 23.0% to: 52.6%

Lp(a) risk categories: normal <75 nmol/L; intermediate 75-125 nmol/L; high >125 nmol/L

Talk Overview: Why Lp(a) Matters

- Residual CVD risk persists despite optimal LDL-C lowering
- Lp(a) is a common, inherited risk factor not captured by traditional lipid panels
- Lp(a) influences lifetime and absolute CV risk, particularly in higher-risk individuals
- Guidelines now support routine measurement and incorporation into personalized risk assessment
- Novel Lp(a)-lowering therapies are emerging, with major implications for prevention

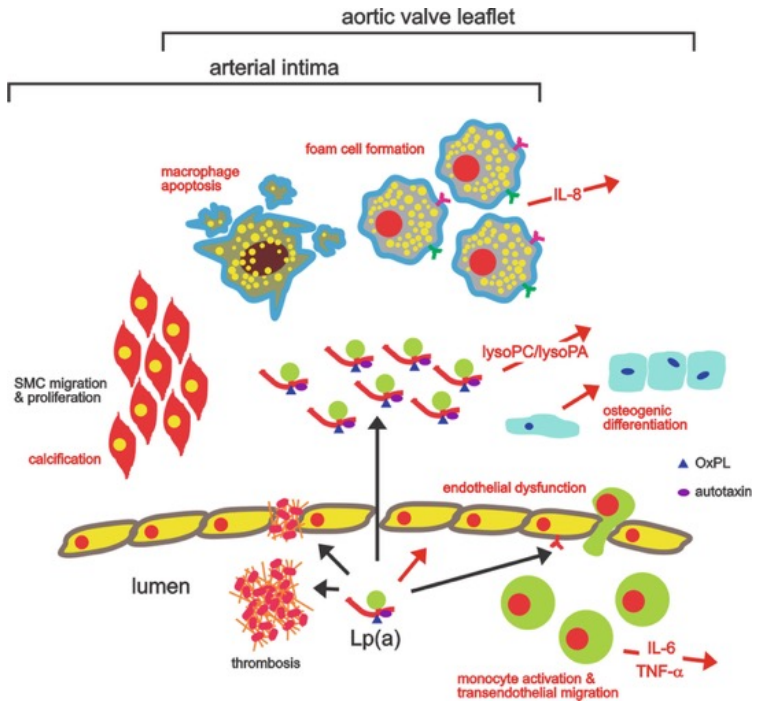
Structure of Lp(a): A Genetically Controlled Lipoprotein



- Apo(a) + LDL-like particle
- Kringle IV repeats

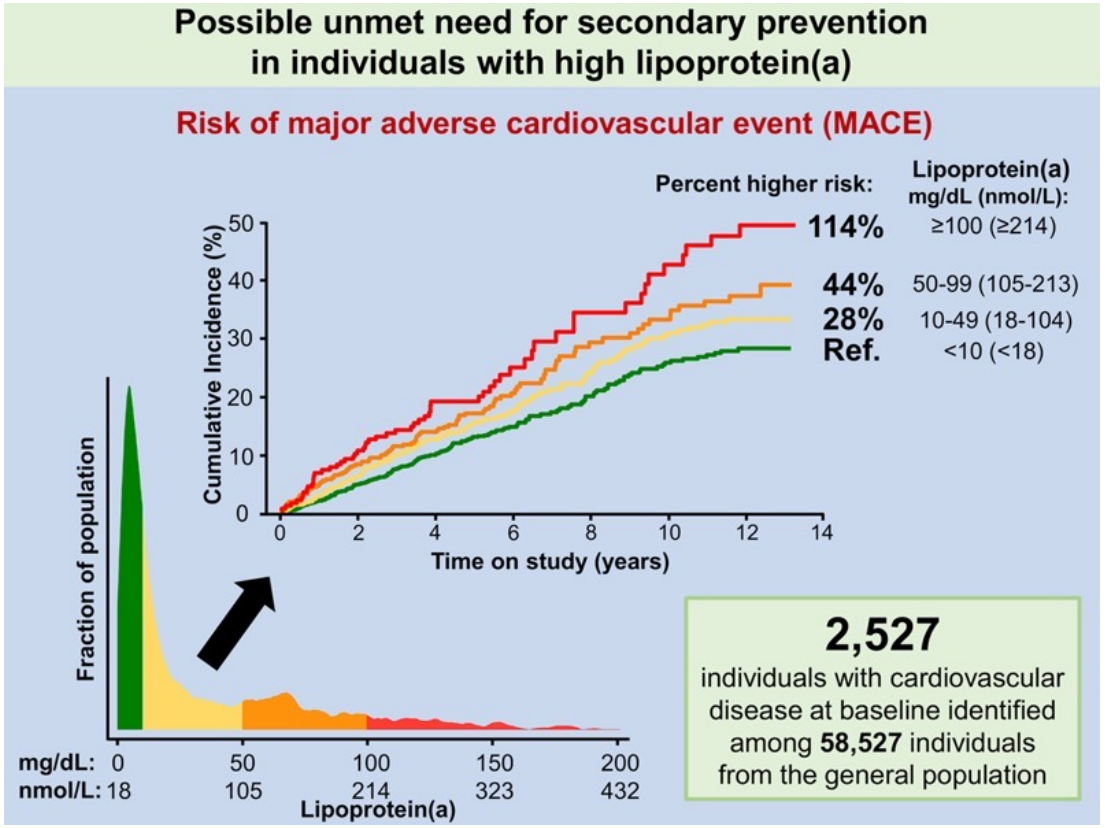
Atherogenic, Pro-Inflammatory, and Pro-Thrombotic Roles of Lp(a)

- Lp(a) carries oxidized phospholipids
  → inflammation
- Enhances monocyte/macrophage activation
- Blocks fibrinolysis, increasing thrombosis risk



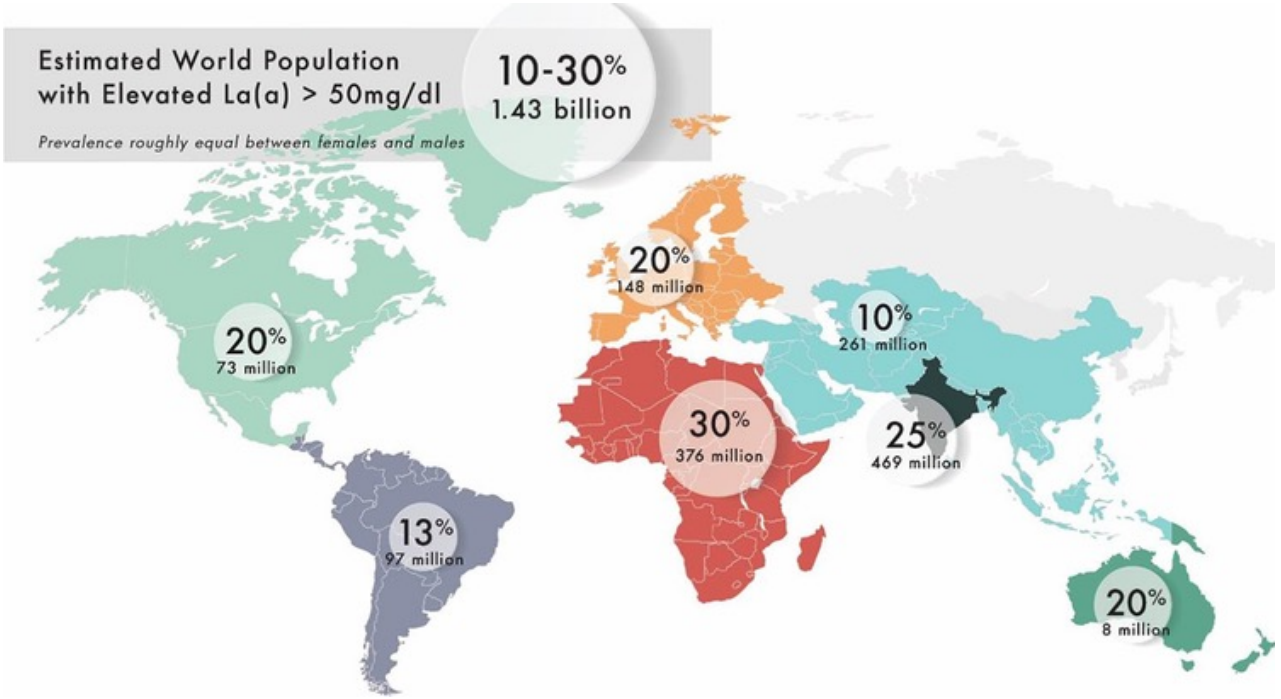
Lipoprotein(a). Contemporary Cardiology. Humana, Cham. https://doi.org/10.1007/978-3-031-24575-6_10

Elevated Lp(a) is associated with high risk of recurrent CVD



Arterioscler Thromb Vasc Biol. 2020;40:255–266.

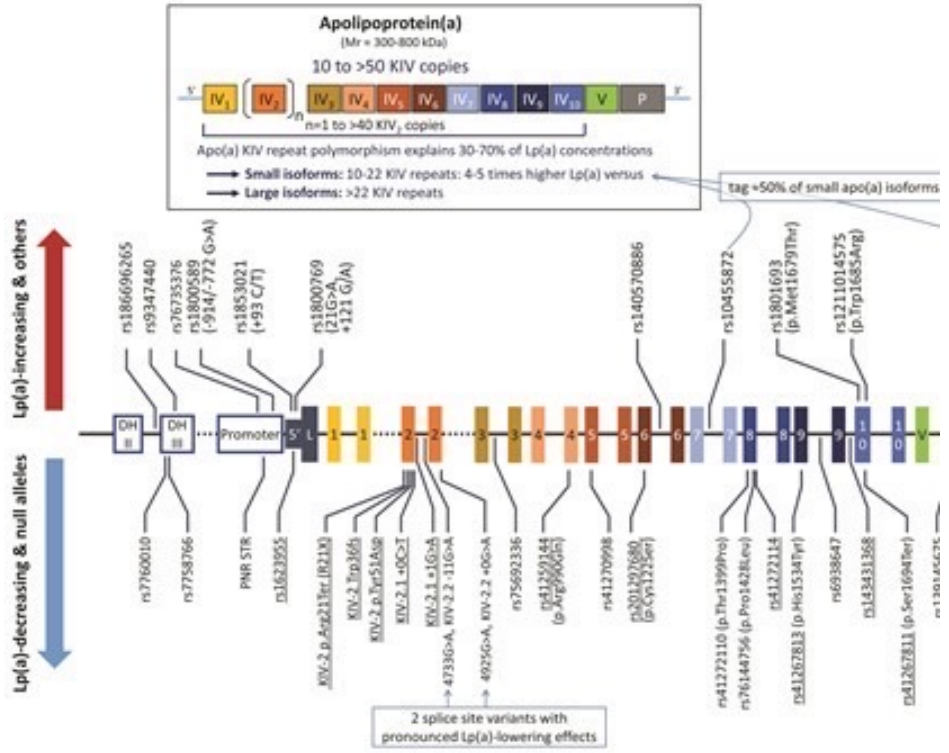
Estimated Prevalence of Elevated Lp(a) Globally



Curr Cardiovasc Risk Rep 16, 111–120 (2022)

Determinants of Lp(a)

- Genetics (90%)
- Ethnicity
- Kidney dysfunction ↑
- Liver dysfunction ↓
- Gender
  - Slight increase after menopause
- Hormones
  - Thyroid-, growth-, and sex-hormones
- Inflammation, IL-6 promoter

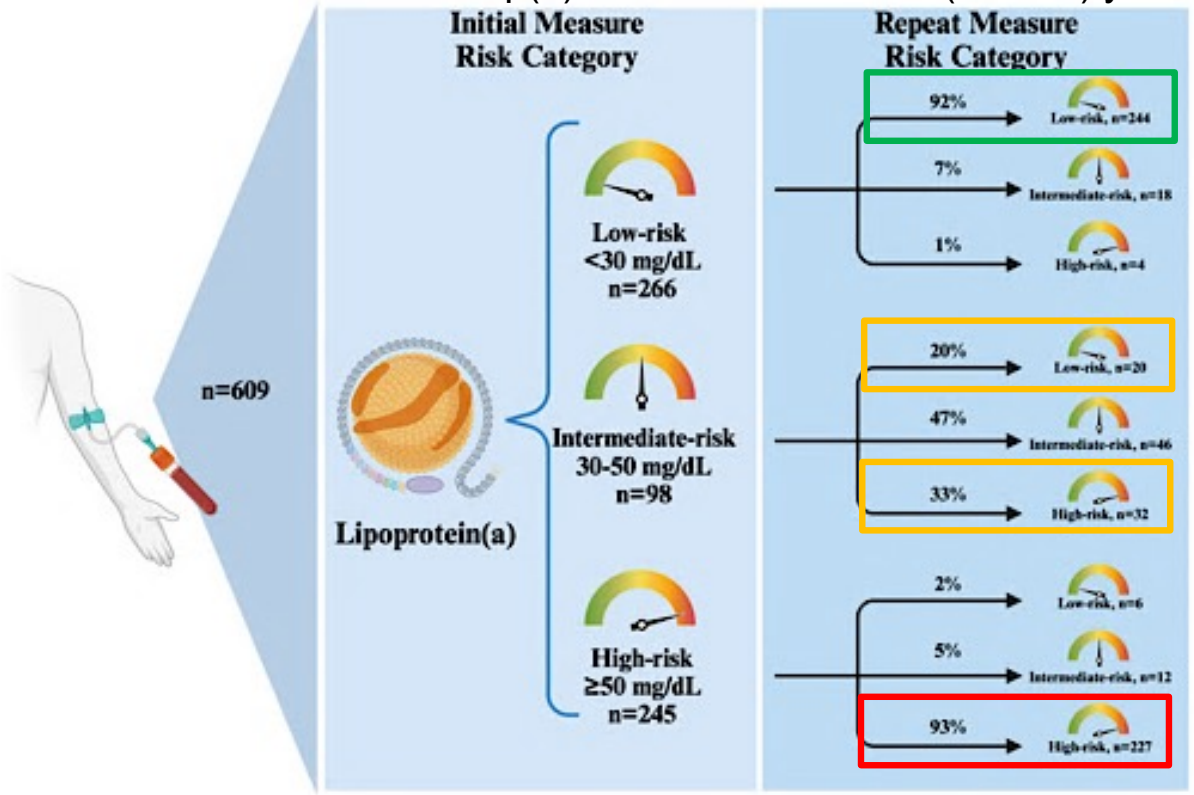


Atherosclerosis. 2022 May:349:17-35.

Variability in Lp(a) Levels

Median time between the two Lp(a) measures was 1.07 (0.5-2.1) years

A



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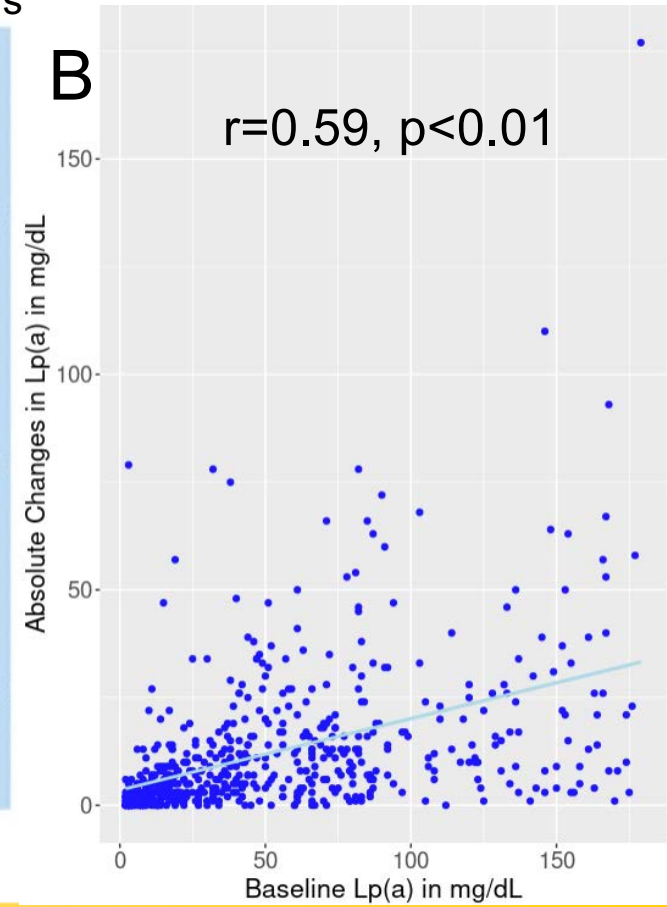
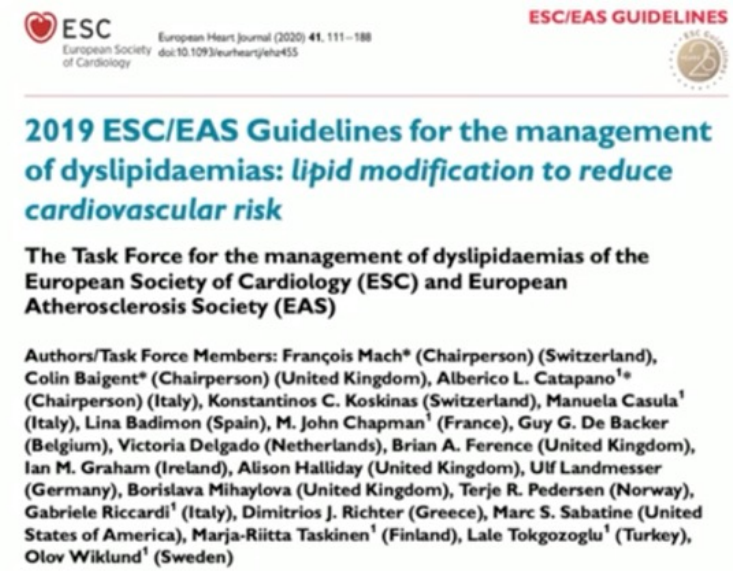


Eur Heart J Open. 2024 Aug

Lp(a) was First Mentioned in the 2019 ESC-EAS Guidelines



ESC European Society of Cardiology

European Heart Journal (2020) 41, 111–188 doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Authors/Task Force Members: François Mach* (Chairperson) (Switzerland), Colin Baigent* (Chairperson) (United Kingdom), Alberico L. Catapano[†*] (Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula[†] (Italy), Lina Badimon (Spain), M. John Chapman[†] (France), Guy G. De Backer (Belgium), Victoria Delgado (Netherlands), Brian A. Ference (United Kingdom), Ian M. Graham (Ireland), Alison Halliday (United Kingdom), Ulf Landmesser (Germany), Borislava Mihaylova (United Kingdom), Terje R. Pedersen (Norway), Gabriele Riccardi[†] (Italy), Dimitrios J. Richter (Greece), Marc S. Sabatine (United States of America), Marja-Riitta Taskinen[†] (Finland), Lale Tokgozoglu[†] (Turkey), Olov Wiklund[†] (Sweden)

ESC European Society of Cardiology

European Heart Journal (2022) 43, 3925–3946 https://doi.org/10.1093/eurheartj/ehac361

SPECIAL ARTICLE
Miscellaneous

Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement

Florian Kronenberg[1], Samia Mora[2], Erik S.G. Stroes[3], Brian A. Ference[4], Benoit J. Arsenault[5], Lars Berglund[6], Marc R. Dweck[7], Marlys Koschinsky[8], Gilles Lambert[9], François Mach[10], Catherine J. McNeal[11], Patrick M. Moriarty[12], Pradeep Natarajan[13], Børge G. Nordestgaard[14,15], Klaus G. Parhofer[16], Salim S. Virani[17], Arnold von Eckardstein[18], Gerald F. Watts[19], Jane K. Stock[20], Kausik K. Ray[21], Lale S. Tokgözoğlu[22], and Alberico L. Catapano[23,24]

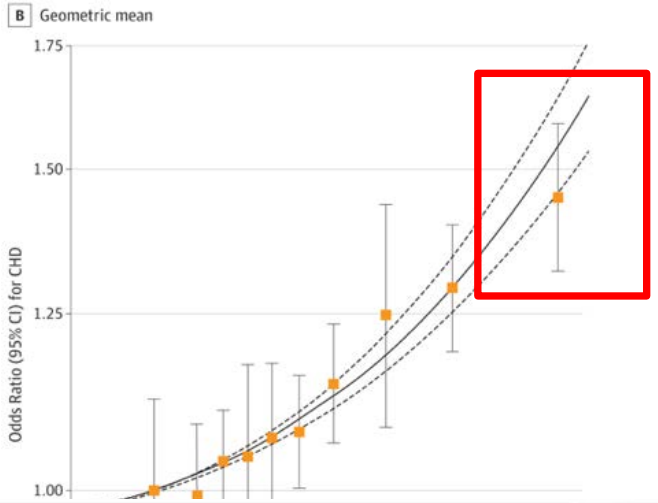
A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice

Marlys L. Koschinsky, PhD, Archna Bajaj, MD, MSCE, Michael B. Boffa, PhD, Dave L. Dixon, PharmD, Keith C. Ferdinand, MD, Samuel S. Gidding, MD, Edward A. Gill, MD, Terry A. Jacobson, MD, Erin D. Michos, MD, MHS, Maya S. Safarova, MD, PhD, Daniel E. Soffer, MD, Pam R. Taub, MD, Michael J. Wilkinson, MD, Don P. Wilson, MD, Christie M. Ballantyne, MD*

When Should Lp(a) be Measured

- 2019 ESC guidelines based on MR from 5 studies with external validation from 48 studies

- Individuals with **very high Lp(a)** (>180 mg/dL or >430 nmol/L) have lifetime ASCVD risk equivalent to untreated heterozygous fam



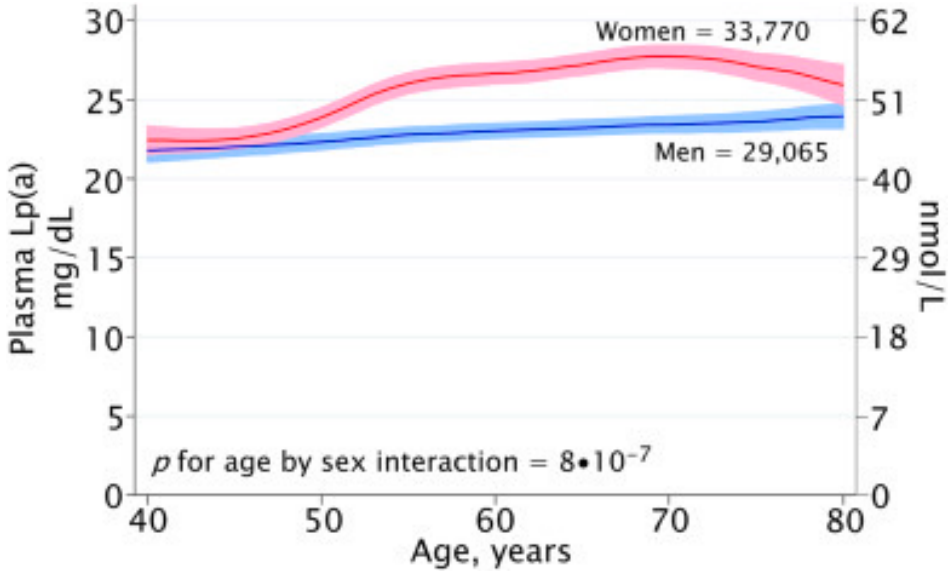
GUIDELINE

Recommendations	Class	Level
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.	IIa	C
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	IIa	C

Ap

2025 ESC Recommendations for Lp(a) Screening

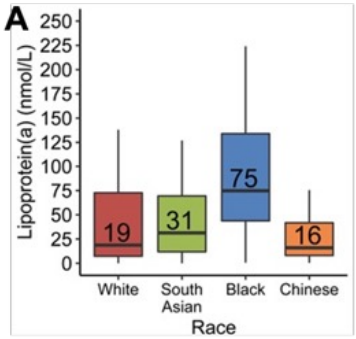
- After menopause a second measurement is reasonable, particularly if the pre-menopausal levels were borderline.



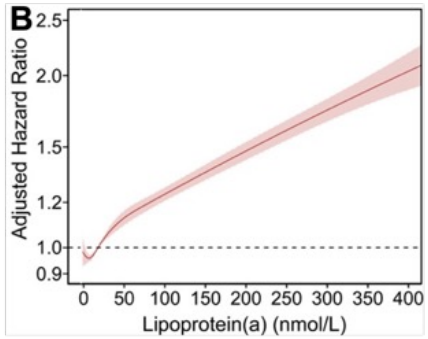
Lp(a) Concentrations and Incident Atherosclerotic Cardiovascular Disease

460,506 adults in the UK Biobank → Lipoprotein (a) concentrations → ASCVD

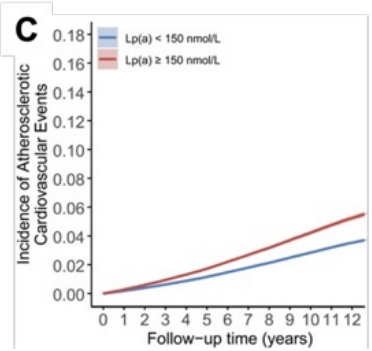
Significant differences in Lp(a) concentrations according to race



Linear rise in ASCVD risk with Increasing Lp(a) concentration

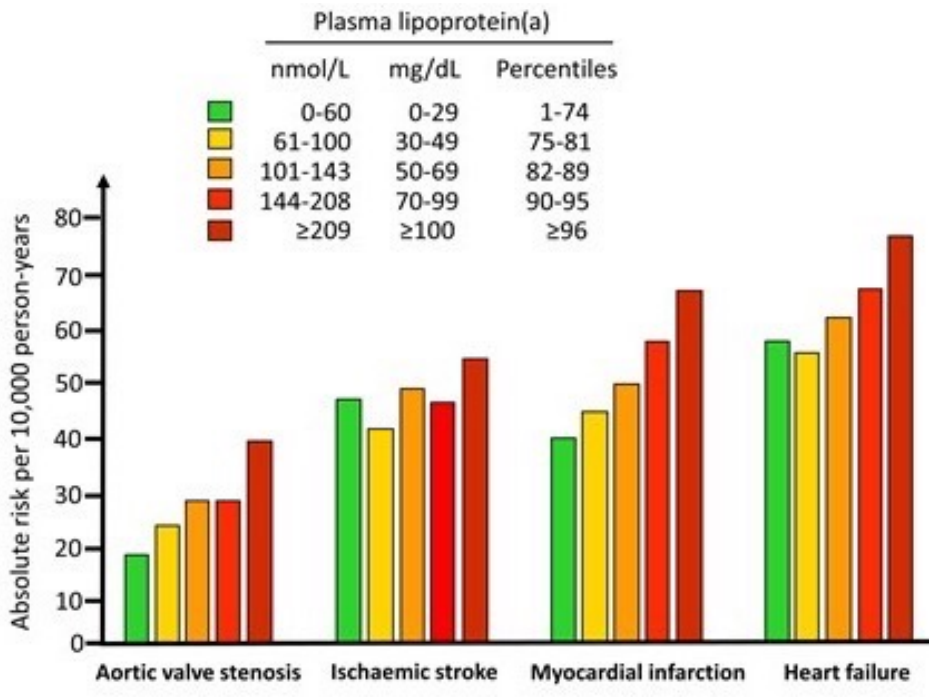


Modest increase in ASCVD risk for high Lp(a) across racial groups



Arterioscler Thromb Vasc Biol. 2021 Jan;41(1):465-474

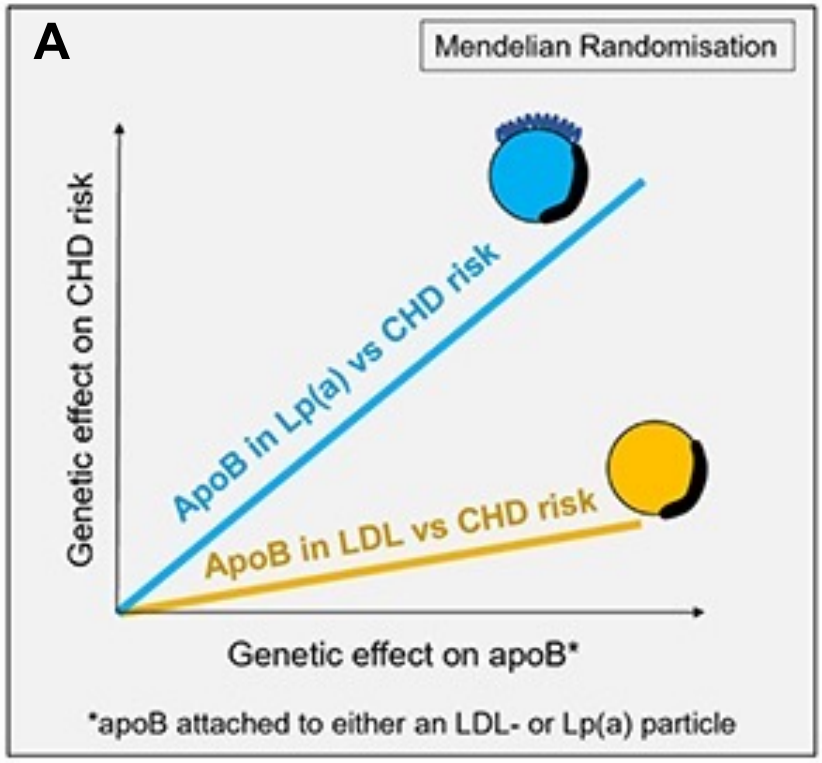
CVD Risk Increases with Increasing Lp(a) in the General Population

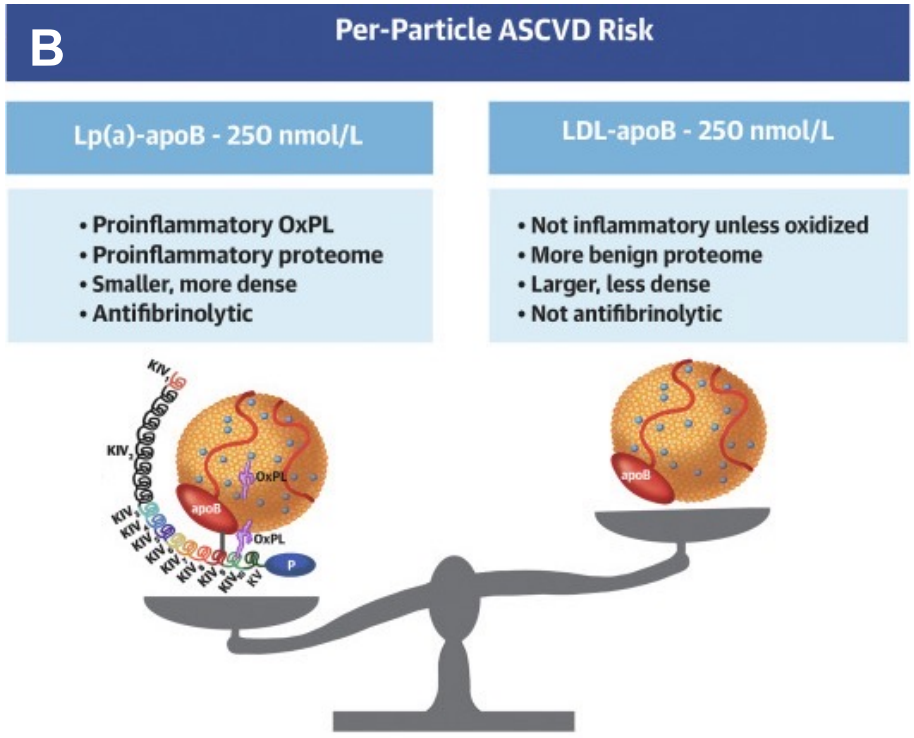


- >75th percentile: increases the risk for aortic valve stenosis and MI
- >90th percentile: increased risk for heart failure
- >95th percentile: increased risk for cardiovascular mortality and ischemic stroke

European Heart Journal, **43**(39), 3925-3946.

Lp(a) more Atherogenic than LDL-c?

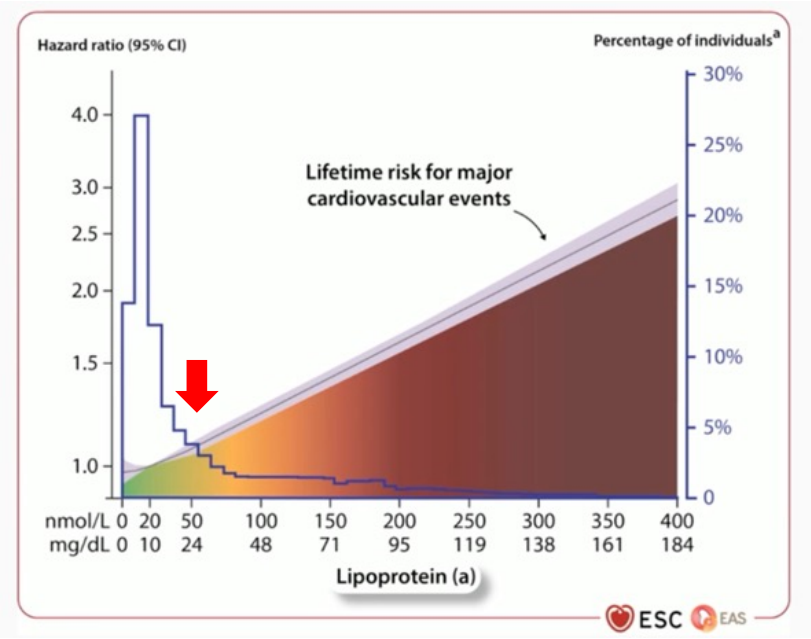




J Am Coll Cardiol. 2024 Jan 23;83(3):385-395.

What is the New (2025) Definition of High Lp(a)

- Lp(a) risk increases modestly at 30–50 mg/dL (62–105 nmol/L)
- Becomes clinically significant >50 mg/dL (105 nmol/L)
- Higher levels → progressively greater CV risk



GUIDELINE

Recommendation	Class	Level
Lp(a) levels above 50 mg/dL (105 nmol/L) should be considered in all adults as a CV risk-enhancing factor, with higher Lp(a) levels associated with a greater increase in risk.	IIa	B

Challenges with Lp(a) Measurement

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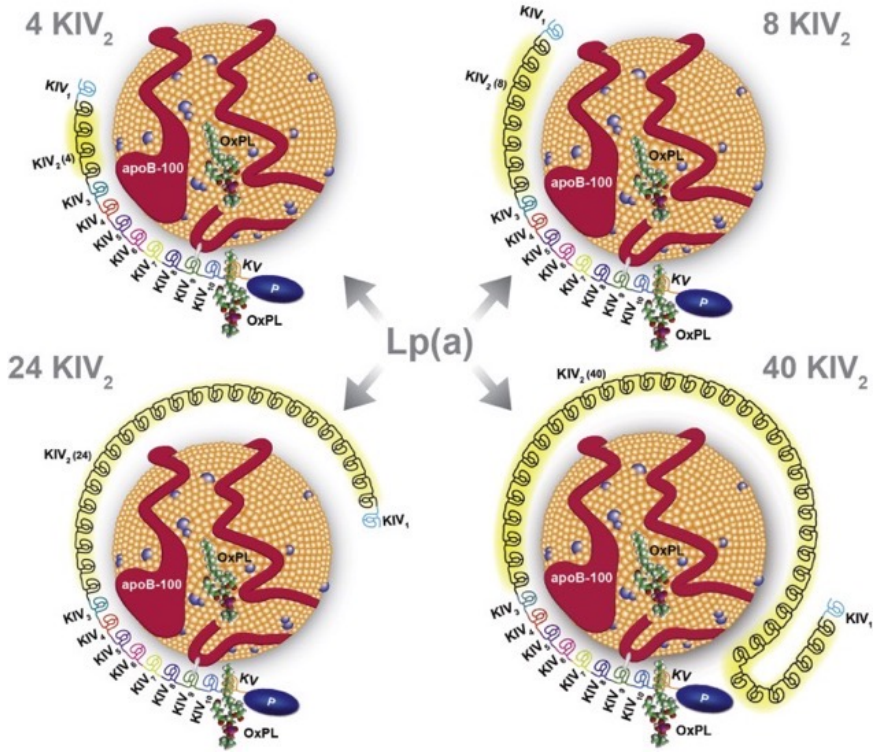
Key Considerations for Lp(a) Measurement

- Substantial variability exists among assays due to differences in apo(a) structure and Kringle-IV repeats, which can under- or overestimate Lp(a) levels.

- Molar units (nmol/L) are preferred for standardization; mass units (mg/dL) remain acceptable for clinical use.



J Am Coll Cardiol. 2017 Feb 14;69(6):692-711.

How does Lp(a) Contribute to Risk Assessment?

- **Previous ESC 2019 approach:**
  Adding Lp(a) to risk algorithms only marginally improves risk discrimination because of its skewed distribution.

- **New ESC 2025 approach:**
  Estimate how much the Lp(a) level increases the individual's overall risk of ASCVD, taking into account both Lp(a) and baseline **absolute global risk of ASCVD**.

Lp(a) Prognostic Value Depends on Baseline Cardiovascular Risk

The Additive Prognostic Value of Lipoprotein(a) for All-cause and Cardiovascular Mortality Across the Traditional Cardiovascular Risk Continuum: Analysis from NHANES III (1988–1994) with Follow-Up to 2019

This study aims to evaluate the association between Lp(a) levels and all-cause & CV mortality, stratified by baseline CV risk.

Population

A nationally representative cohort of 55,050,155 U.S. adults from NHANES III (1988–1994)

Study Design

Retrospective cohort study with mortality follow-up through 2019

Baseline CV Risk*

Low (<5%)	Borderline-Moderate (5.0–19.9%)	High (≥20%)
7.4%	41.2%	51.5%

*Calculated using the PREVENT equations for 30-year total–CVD risk

Lipoprotein(a)

Lp(a) (>50 mg/dL) was present in 15% overall, more commonly in the high-risk group (15% vs 11% in low-risk)

Outcomes

Over a mean follow-up of 22.4 years (±7.07), there were 17,301,805 all-cause and 4,965,456 CV deaths.

		All-cause Mortality	Cardiovascular Mortality
Lp(a) >75 mg/dL	Low Baseline Risk	aHR: 1.02; 95% CI: 0.12–8.75	sHR: 1.04; 95% CI: 0.64–1.69
	Borderline-Intermediate Baseline Risk	aHR: 0.78; 95% CI: 0.39–1.53	sHR: 0.30; 95% CI: 0.04–2.20
	High Baseline Risk	**aHR: 1.25; 95% CI: 1.02–1.53**	**sHR: 1.21; 95% CI: 1.09–1.36**
		All-cause Mortality	**Cardiovascular Mortality**
Lp(a) 50–75 mg/dL	Low Baseline Risk	aHR: 1.29; 95% CI: 0.28–5.87	sHR: 1.02; 95% CI: 0.70–1.49
	Borderline-Intermediate Baseline Risk	aHR: 1.09; 95% CI: 0.75–1.59	sHR: 1.06; 95% CI: 0.51–2.20
	High Baseline Risk	**aHR: 1.16; 95% CI: 1.00–1.34)**	**sHR: 1.06; 95% CI: 0.98–1.15**

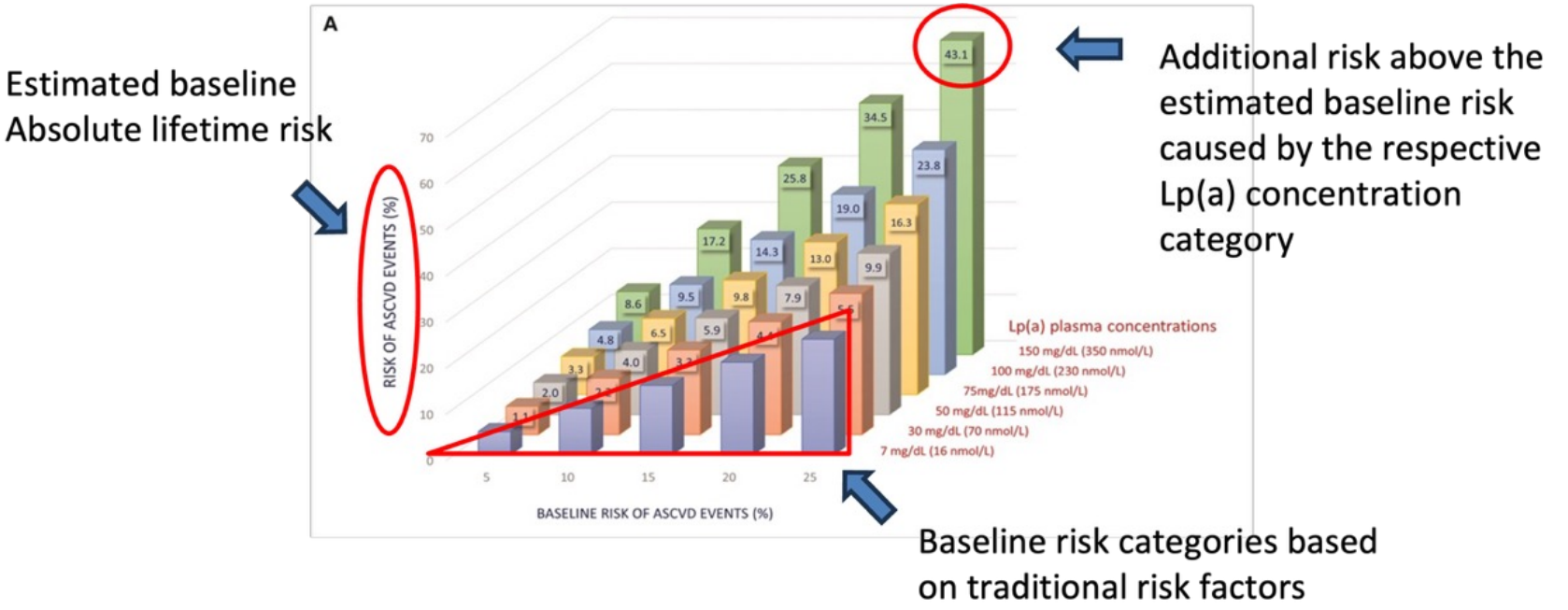
Models adjusted for Sex, Age, Total Cholesterol, HDL Cholesterol, LDL Cholesterol, Systolic Blood Pressure, Body Mass Index, Estimated Glomerular Filtration Rate, Diabetes, Smoking.

Elevated Lp(a) levels (> 75 mg/dL) are associated with increased all-cause and CV mortality among individuals with high baseline traditional CV risk, as defined by the AHA's PREVENT score, independent of traditional risk factors. Our findings highlight the value of Lp(a) particularly among those with elevated baseline risk, where its prognostic utility appears greatest.

Mustafa Al-jarshawi[1], Nicholas Chew[2], Marc P Bonaca[3], Kausik K Ray[4], Mamas A. Mamas[1] Eur J Prev Cardiol. 2026 Jan 14

Incremental Increase in Absolute Risk Caused by Increasing Lp(a) Categories

Baseline estimated lifetime risk calculated using the Joint British Societies (JBS3) Lifetime Risk Estimating algorithm

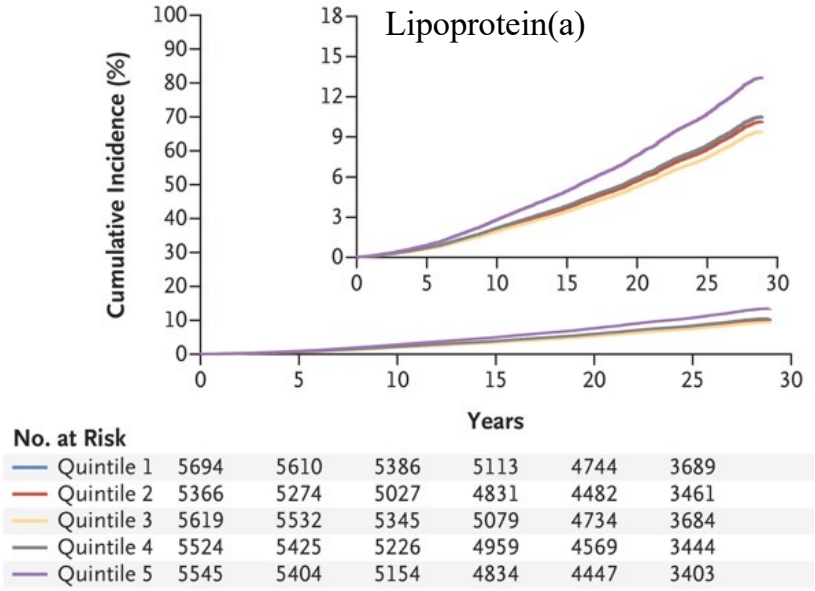


Incremental Increase in Absolute Risk Caused by Increasing Lp(a) Categories

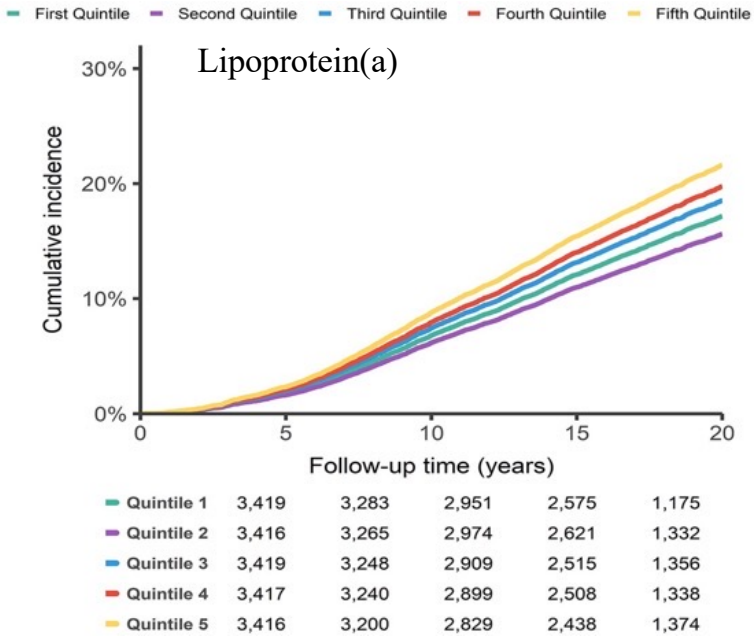
If Lp(a) is not considered, the absolute risk might be substantially underestimated

High Lp(a) Contributes to Lifetime CV Risk

Inflammation, Cholesterol, Lp(a), and 30-Year CVD Risk in Women



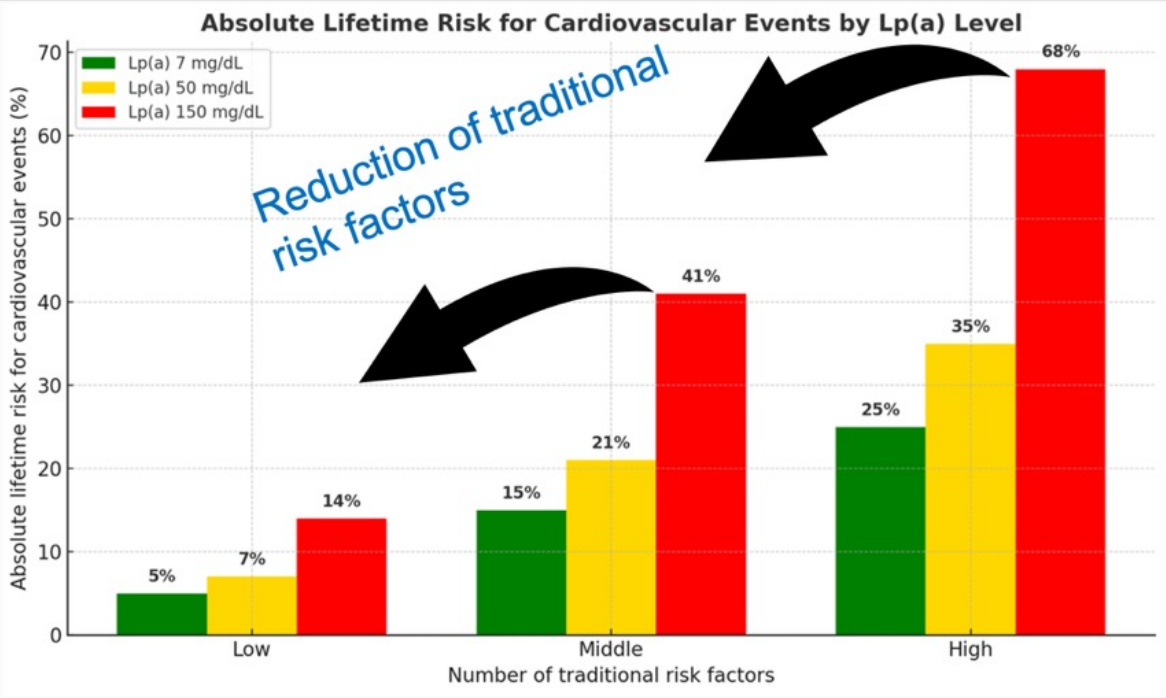
EPIC-Norfolk Study



N Engl J Med. 2024;391(22):2087-2097. & Eur Heart J. 2025. DOI: 10.1093/eurheartj/ehaf209

How Should Lp(a) be Incorporated into Clinical Decision-Making to Mitigate Risk?

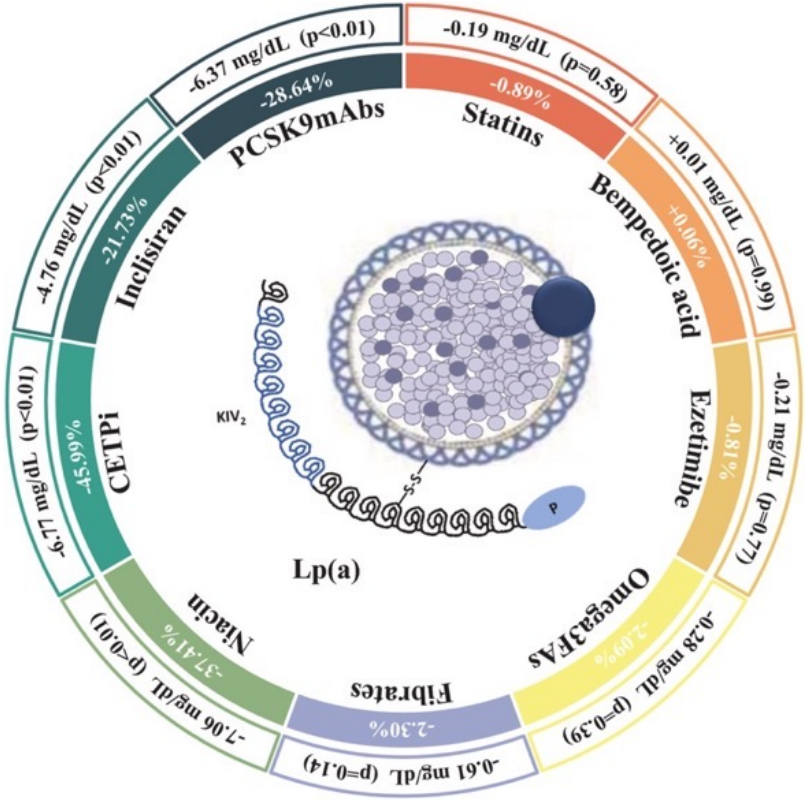
More intensive risk factor management with increasing Lp(a) concentration and increasing baseline risk



Atherosclerosis. 2023; 374:107-120.

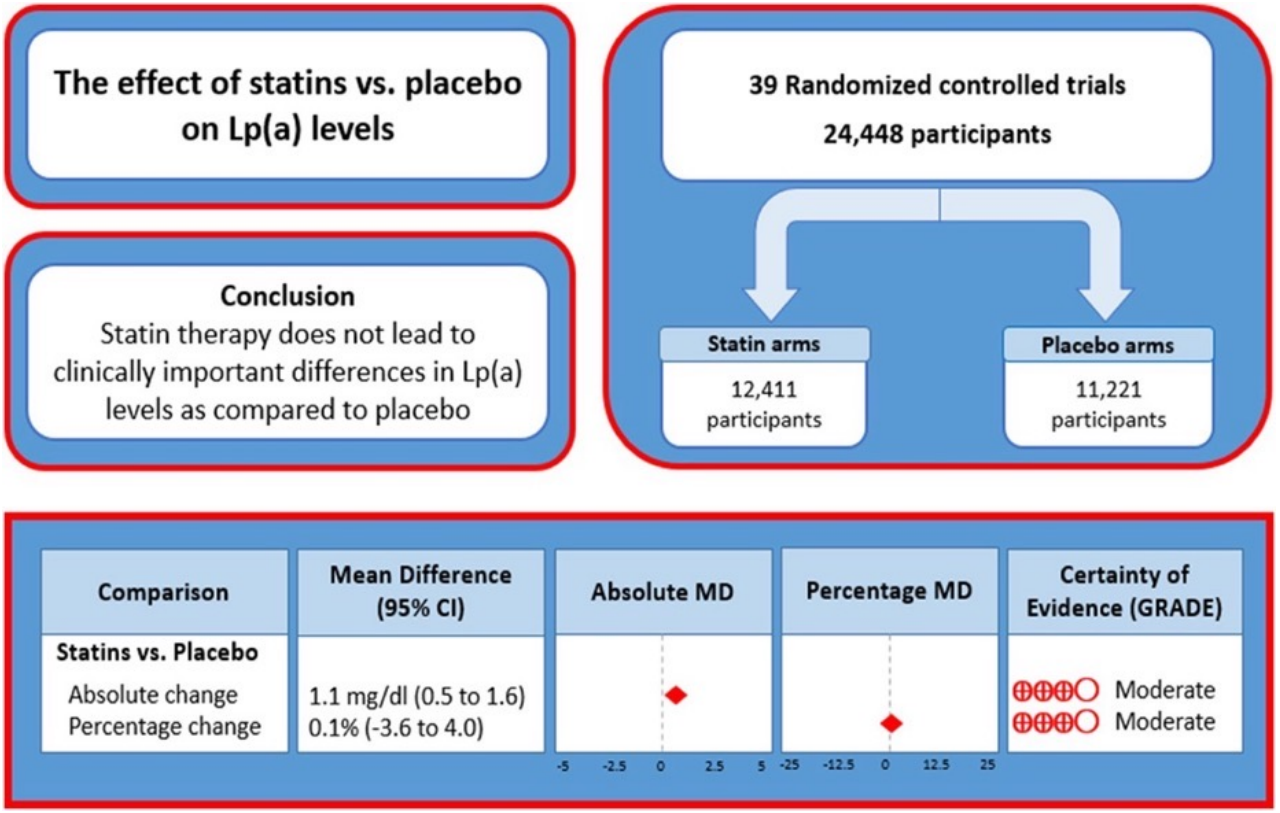
Effect of Lipid Lowering Therapies on Lp(a)

- Lifestyle: No change
- High-intensity statin: no change
- Ezetimibe, Bempedoic acid: no change
- PCSK9 inhibitor: decrease by 25%
- Niacin: decrease by 25% but no clinical benefit
- Obicetrapib: decrease by 30-50 % ? (in progress)
- Apheresis: decrease up to 70 %
- Specific Lp(a) lowering therapies awaited



Atherosclerosis. 2025 Sep;408:120420.

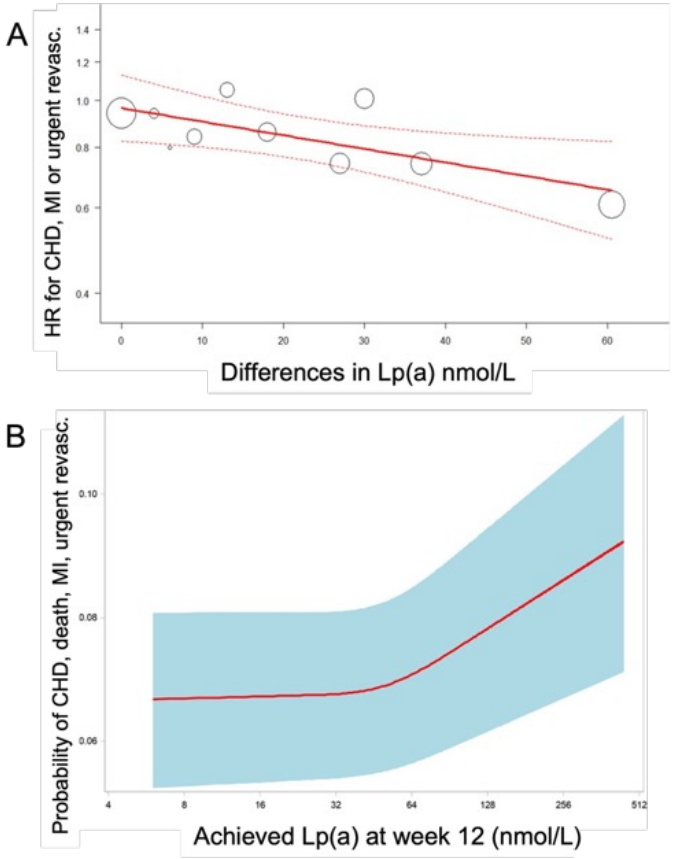
Statins and Lp(a)



Eur J Prev Cardiol. 2022 May 5;29(5):779-792.

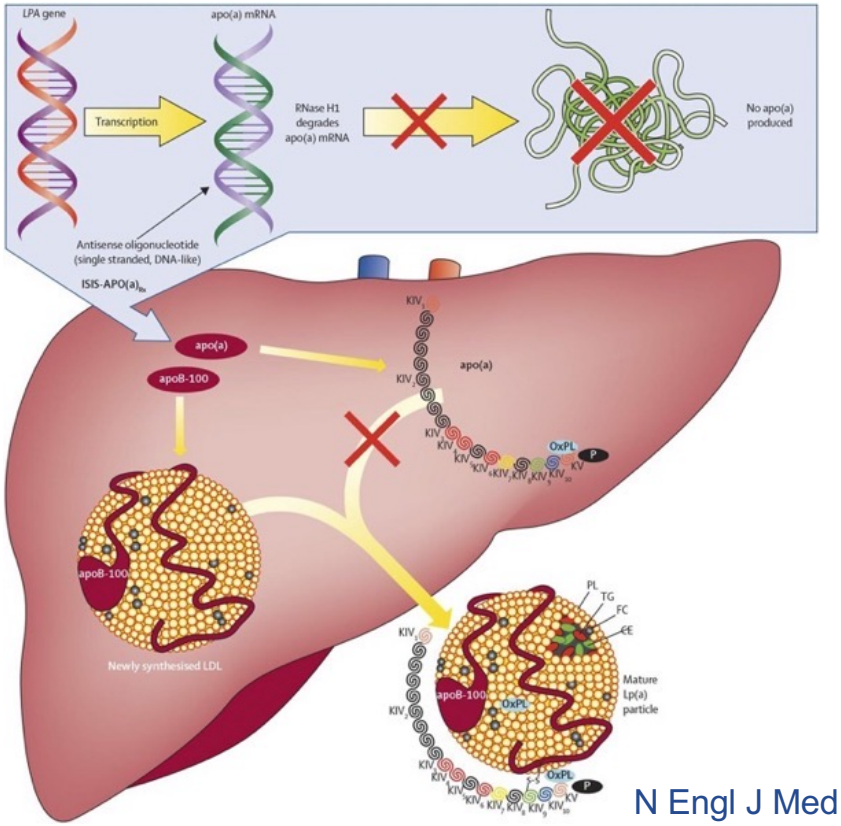
Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk

- FOURIER: 25,096 ASCVD patients on statins, randomized to evolocumab vs placebo
- Higher Lp(a) → ↑ coronary risk independent of LDL-C
- Evolocumab ↓ Lp(a) ~27% (greater absolute drop at higher baseline)
- Greater benefit in high-Lp(a) pts: 23% ↓ events (NNT 40 vs 105)
- Dual lowering of LDL-C + Lp(a) → lowest residual CV risk

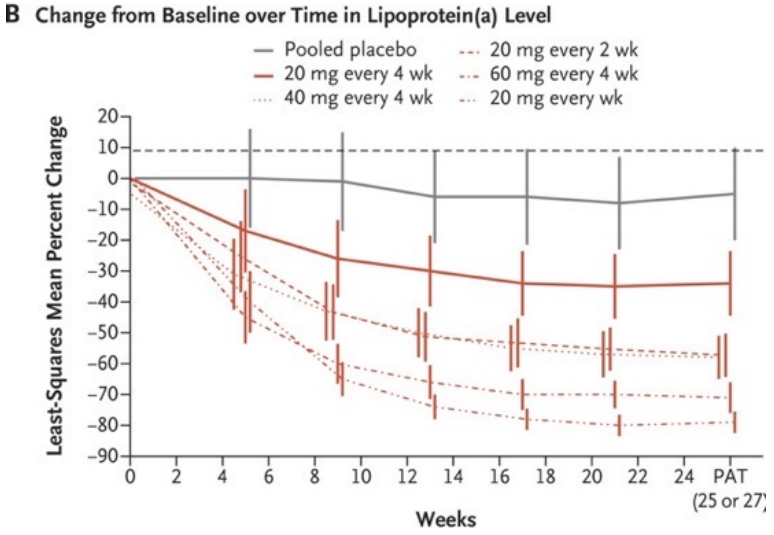


Circulation. 2019;139:1483–1492

New Horizons in Lp(a) Lowering – Pelacarsen Lp(a) ASO



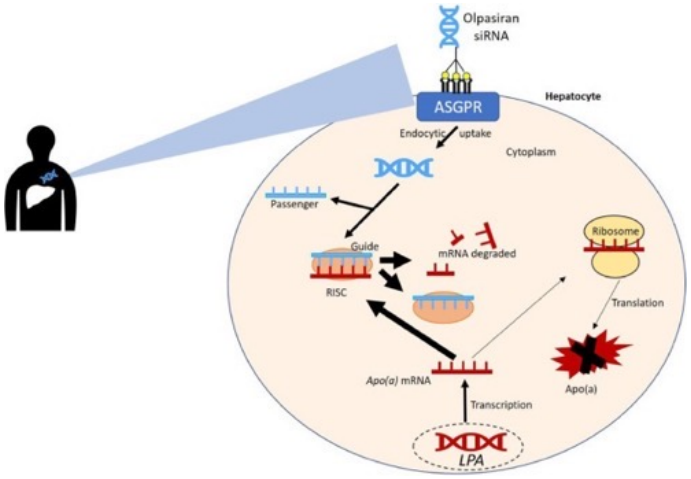
- 286 patients with ASCVD and Lp(a) levels ≥ 60 mg/dL (150 nmol/L)
- -> Up to 80% Lp(a) reduction

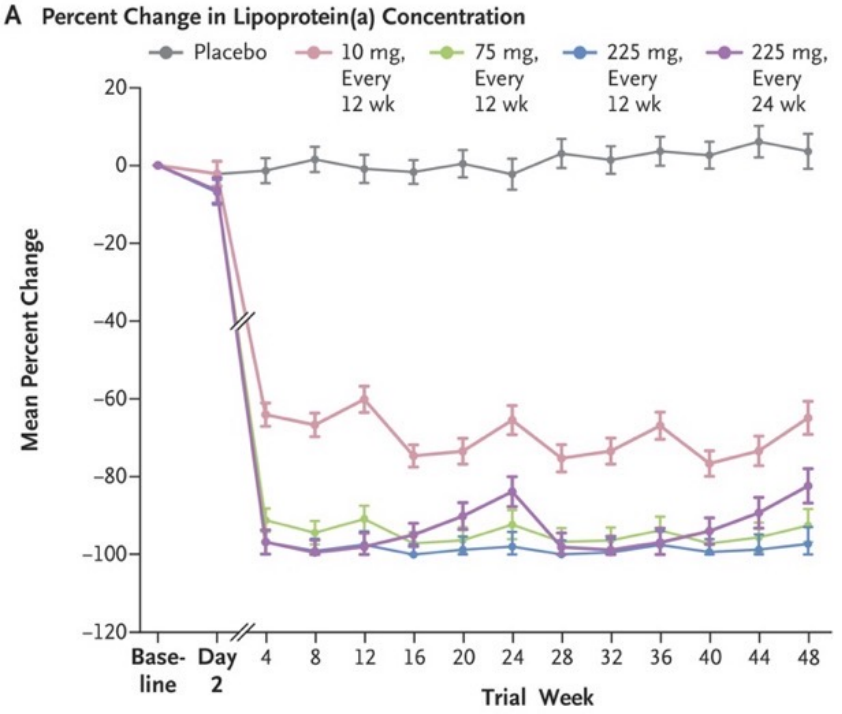


N Engl J Med 2020; 382:244-255

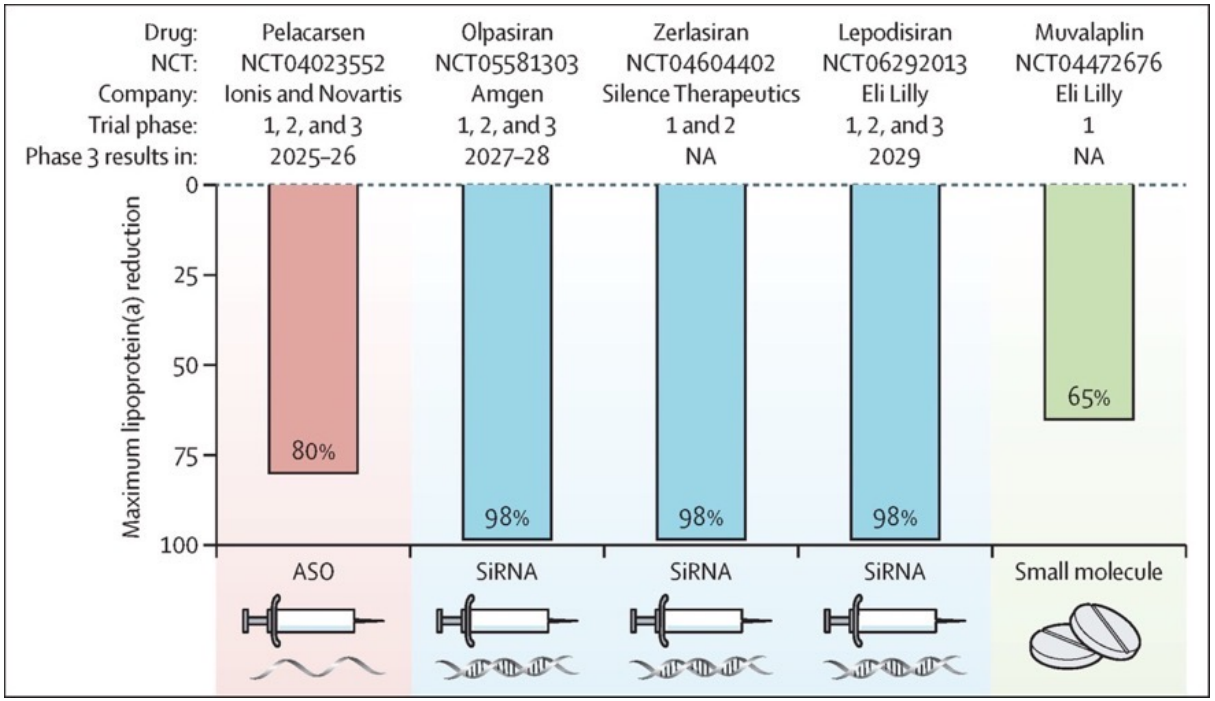
Small Interfering RNA Targeting Lp(a) Synthesis — Olpasiran

- 281 enrolled patients with ASCVD
- Median lipoprotein(a) at baseline was 260.3 nmol/L
- -> 60-100% reduction of Lp(a)





Specific Lp(a)-Lowering Therapies being Tested in Randomized Clinical Trials



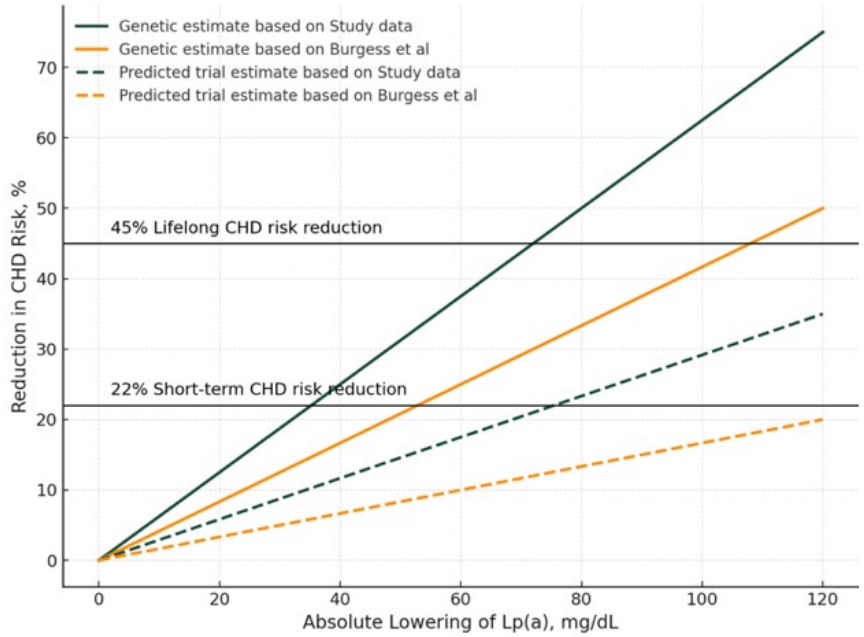
Lancet. 2024 Sep 28;404(10459):1255-1264.

What Should the Clinician do in the Absence of Specific Lp(a)-Lowering Therapies?

- Early risk factor management
- More intensive risk factor control, including LDL-C lowering considering both absolute CV risk and Lp(a) levels.

Gaps in Knowledge

- Will lowering Lp(a) reduce the risk of ASCVD and AV stenosis progression?
- What is the extent of Lp(a) lowering required for clinical benefit?

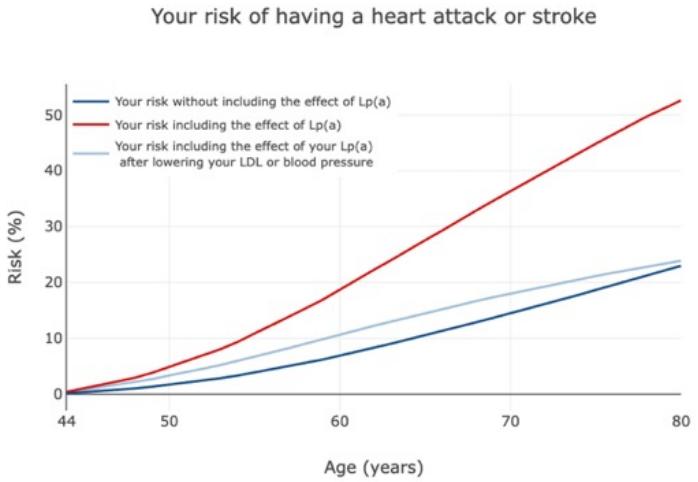


For a 22% RRR, genetic estimates vary from 66 to 101 mg/dL(~ 158-242 nmol/L) reduction required

JAMA Cardiology. 2018; 3(7):619–627.

Back to Our Case:

Lipoprotein(a) = 365 nmol/L



With an Lp(a) level of 365 nmol/L, your estimated risk of having a heart attack or stroke up to age 80 changes from 23.0% to:

52.6%

With an Lp(a) of 365 nmol/L and an estimated risk of 52.6%, lowering your LDL by 1.3 mmol/L and your SBP by 10 mmHg beginning at age 44 will reduce your risk of having a heart attack or stroke to:

23.9%

- Impact of risk factor control:
  - Lowering
    - LDLc < 70 mg/dL (1.8mmol/L)
  - Sys. BP to
    - ~ 120mmHg

Summary: Lp(a) in Contemporary CV Risk Assessment

- 🧬 **Lp(a) is a genetically determined, causal risk factor** for ASCVD and AV stenosis, with pro-atherogenic, pro-inflammatory, and pro-thrombotic effects independent of LDL-C.
- 🌍📈 **Elevated Lp(a) is common (10–30% globally)** and confers **substantial lifetime CV risk**, particularly at levels >50 mg/dL (>105 nmol/L), with progressively higher risk at extreme levels.
- ⚖️ **Risk attributable to Lp(a) is context-dependent**--its prognostic impact is greatest in individuals with higher baseline absolute CV risk and meaningfully increases lifetime and absolute risk estimates.
- 🩺 **Guidelines now emphasize measuring Lp(a) at least once in adulthood** and incorporating its level into individualized risk estimation rather than simple risk reclassification.
- 💊 **In the absence of approved Lp(a)-specific therapies**, management focuses on **early and intensive control of modifiable risk factors** (especially aggressive LDL-C/ApoB100 lowering), while **potent Lp(a)-lowering agents (ASOs, siRNA)** are in late-stage clinical development.

Patient referral

- Lp(a) >200 nmol/L (~80 mg/dL)
- No prior MI or CVA
- Non 0 CAC

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