Penn Medicine

Lp(a) cholesterol – what was once old, is the new frontier

Jedrek Wosik, MD, MMCi
Associate Chief Health Information Officer
Assistant Professor, Cardiovascular Medicine, University of Pennsylvania
Medical Director, Population Health, Penn Medicine

October 7th, 2025

Lp(a) vs LDL-C

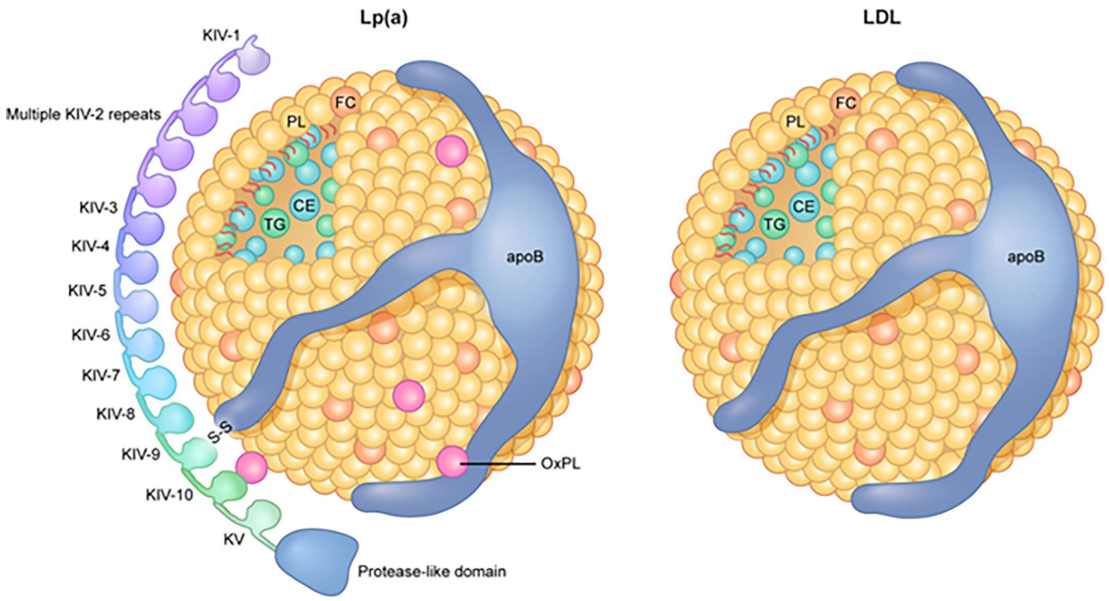
SIMILAR BUT DISTINCT

Lipoprotein particle

- Contains one molecule of **apolipoprotein B-100 (apoB-100)** (just like LDL),
- a unique **apolipoprotein(a)** (**apo(a)**) with loop-like structures (kringle)

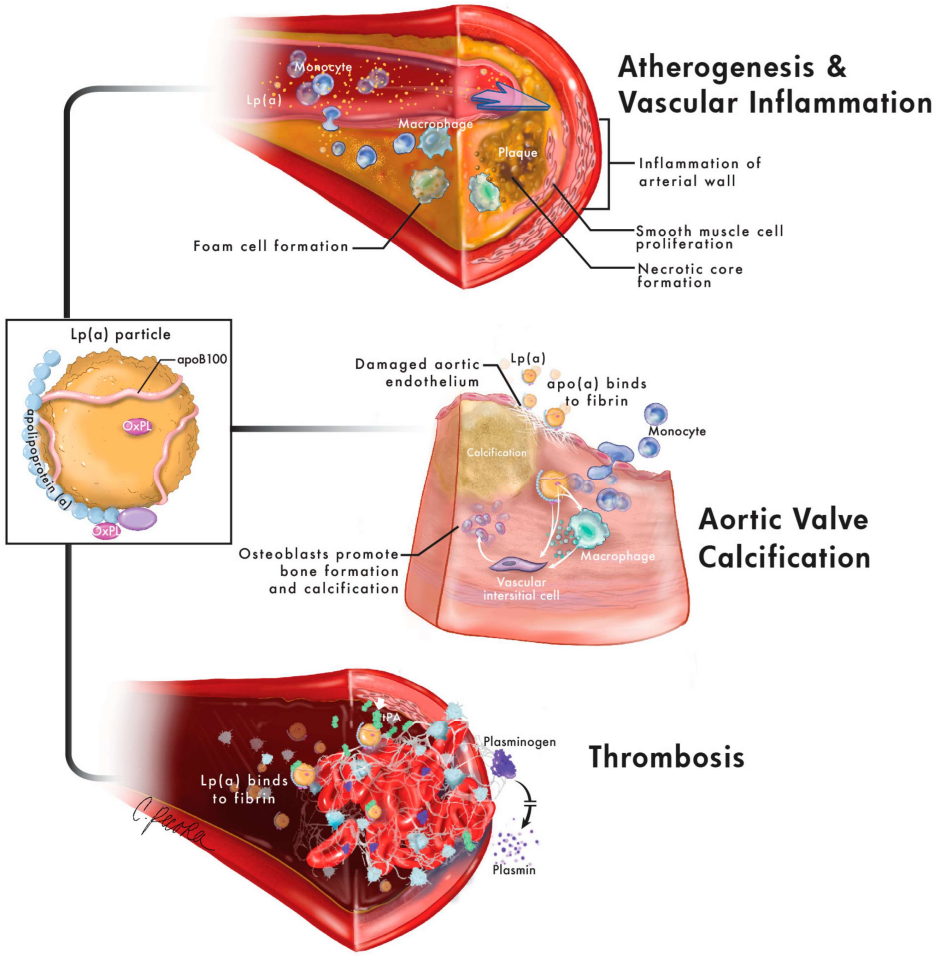
Smaller isoform (fewer KIV-2 repeats) → higher Lp(a) levels

Larger isoform (more repeats) → lower Lp(a) levels

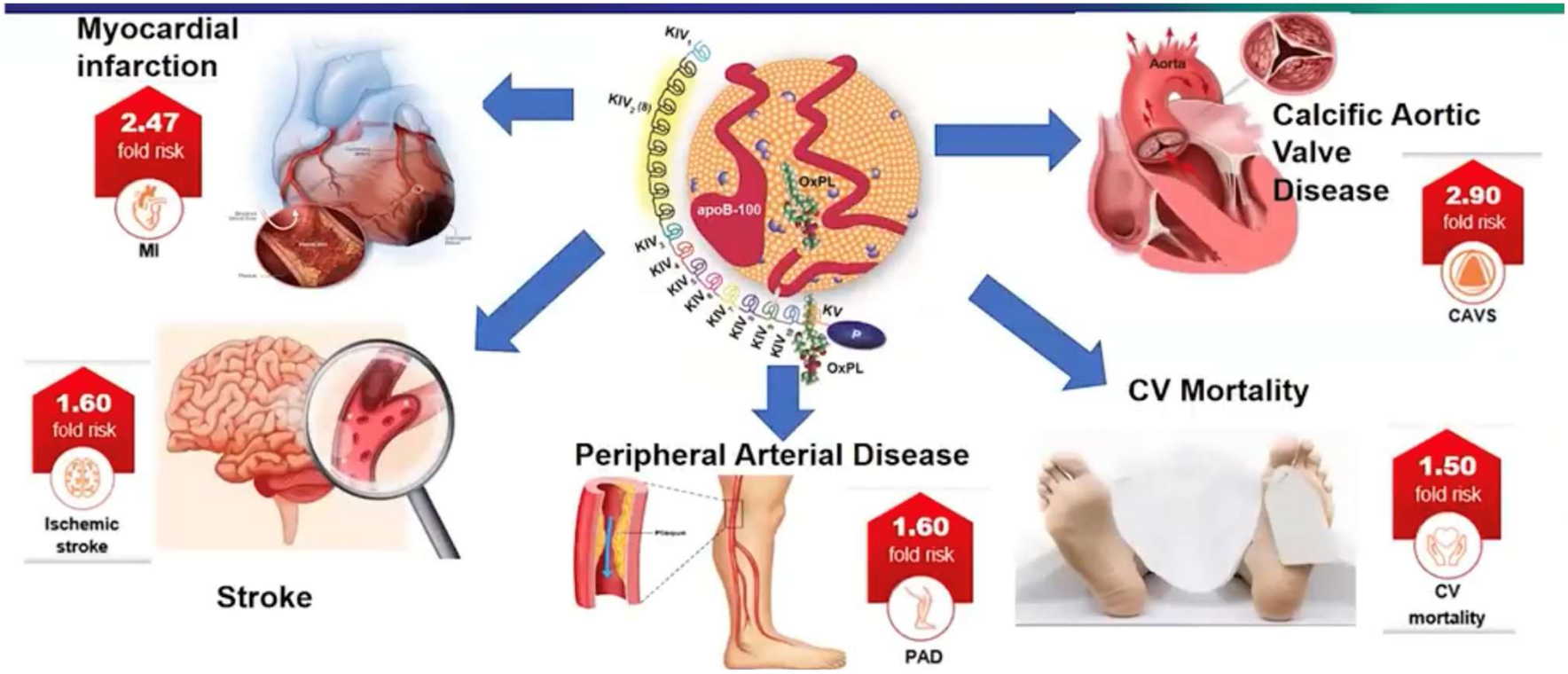


Smaller isoforms are secreted more efficiently → plasma Lp(a) concentration can be 10×–100× higher.

Volgman. 2023 JAHA

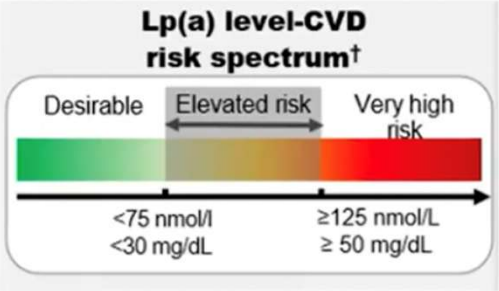


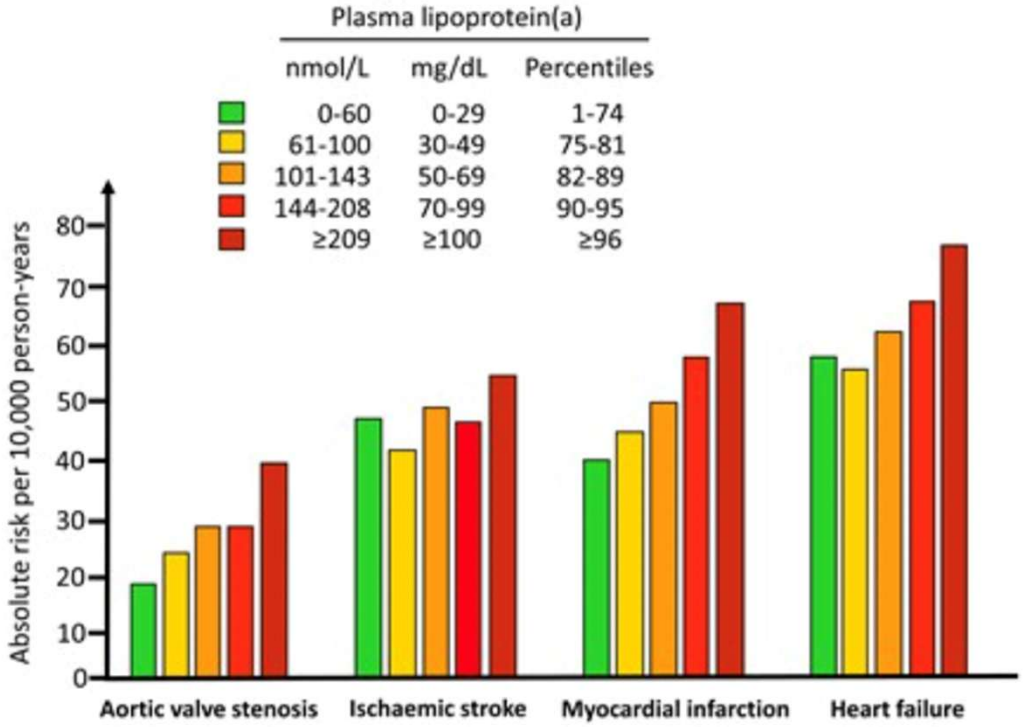
Bhattia, JCM 2022



[4] Reyes-Soffer, G, AJPC 2024

Clinical risk is continuous





Kronenberg, F EHJ 2022

1963 and Kåre Berg

b

Prof. Dr. G. G. Wendt

To be printed in

ACTA PATHOLOGICA ET MICROBIOLOGICA SCANDINAVICA
Vol. 59. Fasc. 3. 1963

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

Prof. Dr. G.G. Wendt mit den besten Grüssen für Kåre Berg

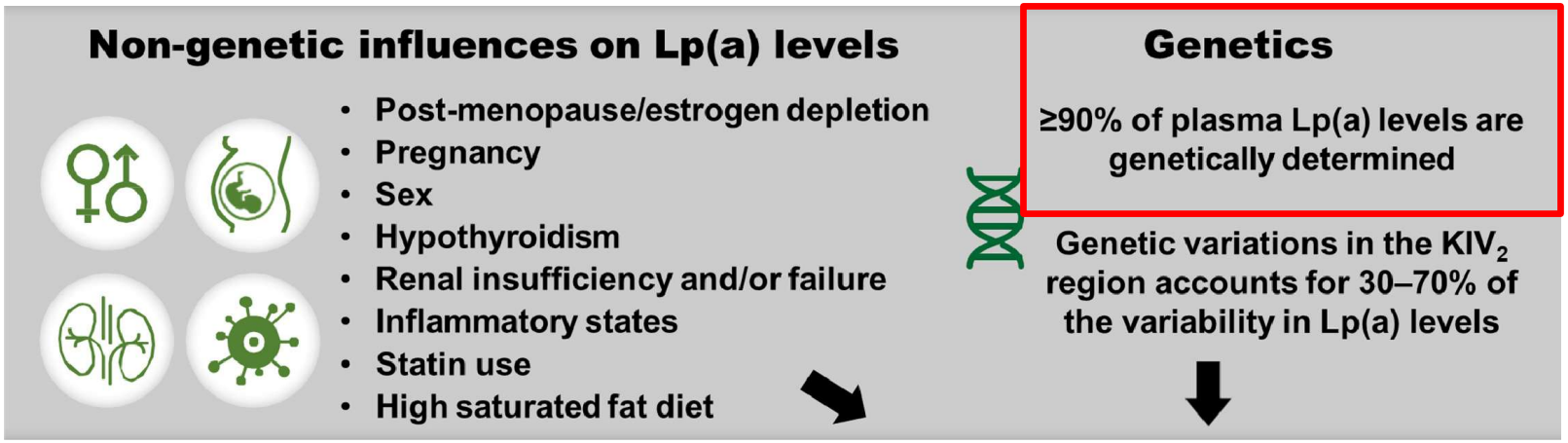
A NEW SERUM TYPE SYSTEM IN MAN—THE Lp SYSTEM

By

KÅRE BERG

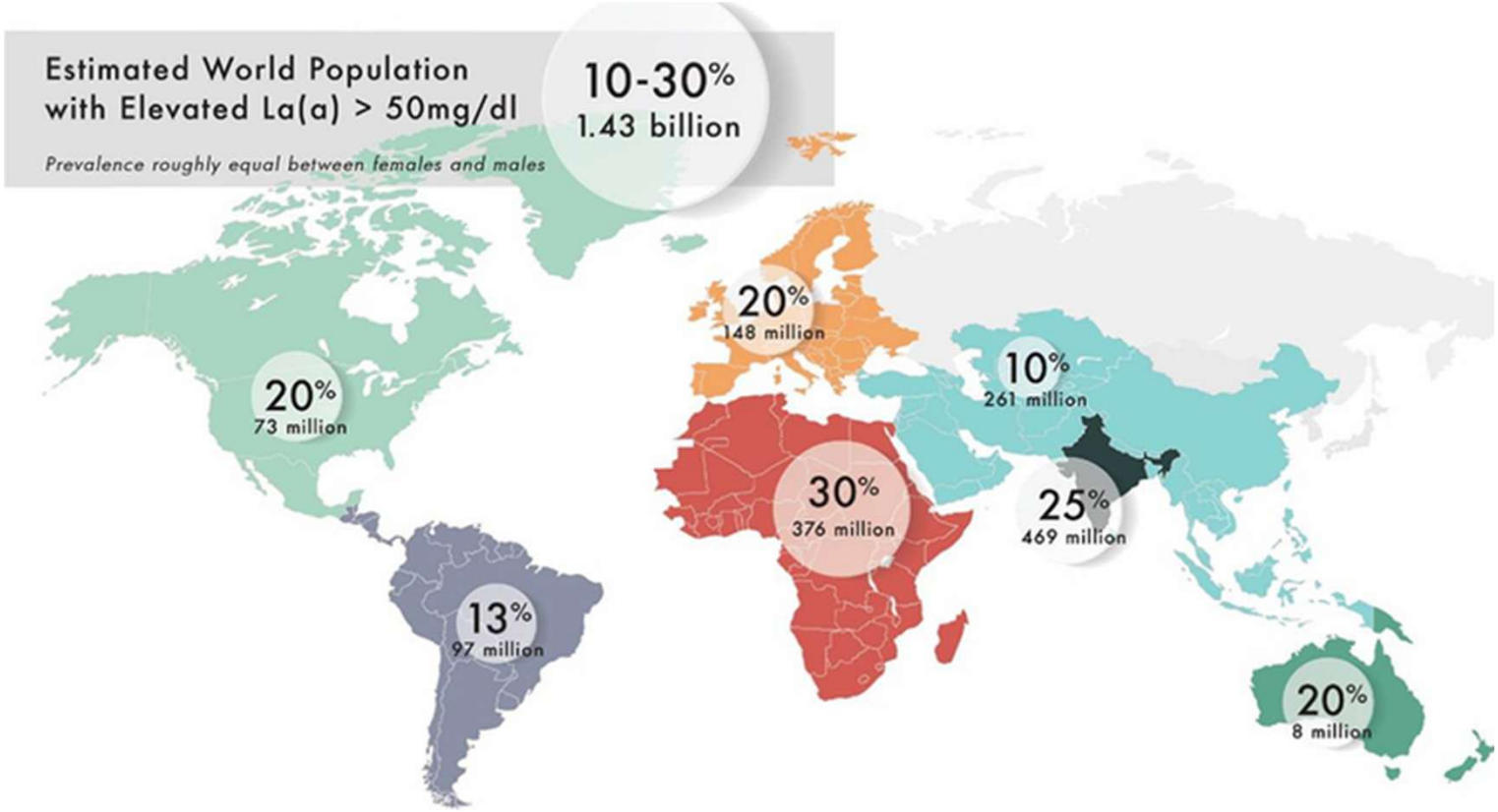
Received 25.iii.63

>90% of levels are genetically determined



[7] Reyes-Soffer, G, AJPC 2024

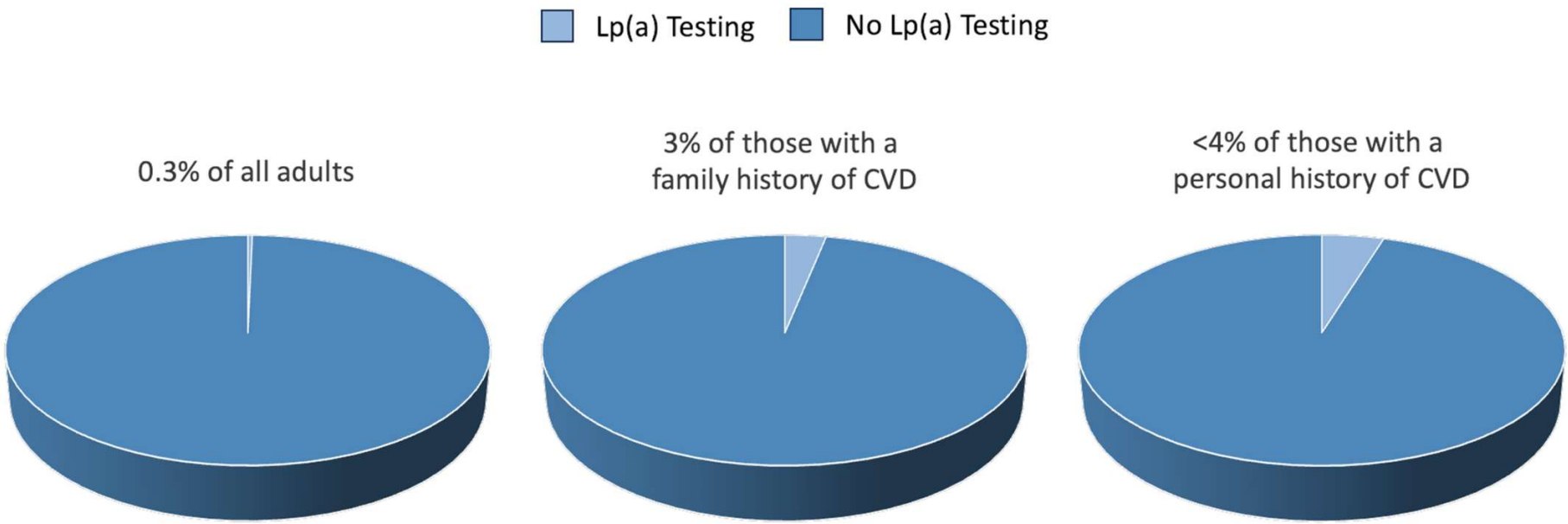
Many people with elevated lp(a)



Patel, N, Current Cardiovascular Risk Reports 2022

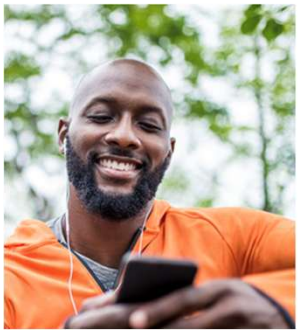
[9] Reyes-Soffer, G, AJPC 2024

Not widely tested



10 Bhattia JAHA 2023

Testing options



Lipoprotein(a) Test

5.0 ★★★★★ 1 Review

Learn more about your risk for heart disease and stroke with a simple blood test.

More than 80% of premature heart attacks and strokes are preventable.1 A high Lipoprotein(a), or Lp(a), level can lead to atherosclerosis (hardening of the arteries) a... Read More

$49

Add To Cart

<u>Insurance coverage: (varies)</u>

- Known ASCVD
- Familial hypercholesteremia
- Family history of early ASCVD (before 55 in men and 65 in women)
- Family history of elevated lp(a)
- Mixed hyperlipidemia

FAMILY HEART FOUNDATION

Lipoprotein(a) & Familial Hypercholesterolemia

The Family Heart Foundation offers free heart health screening — why it matters

How it Works

1 **Request Your Kit: Sign up below to get your at-home screening kit† supplied by Endless Health. We will ship it directly to you within 5 to 7 business days.**

2 **Receive and Use Your Kit: Follow the simple instructions included with your kit for hassle-free screening at home.**

3 **Find Your Results: Please return the kit by mail to receive your results. Returns are always free. Your detailed results will be available on the results portal, providing you with clear action steps and advice.**

Talk to your medical team or a Family Heart Foundation Care Navigator for more support.

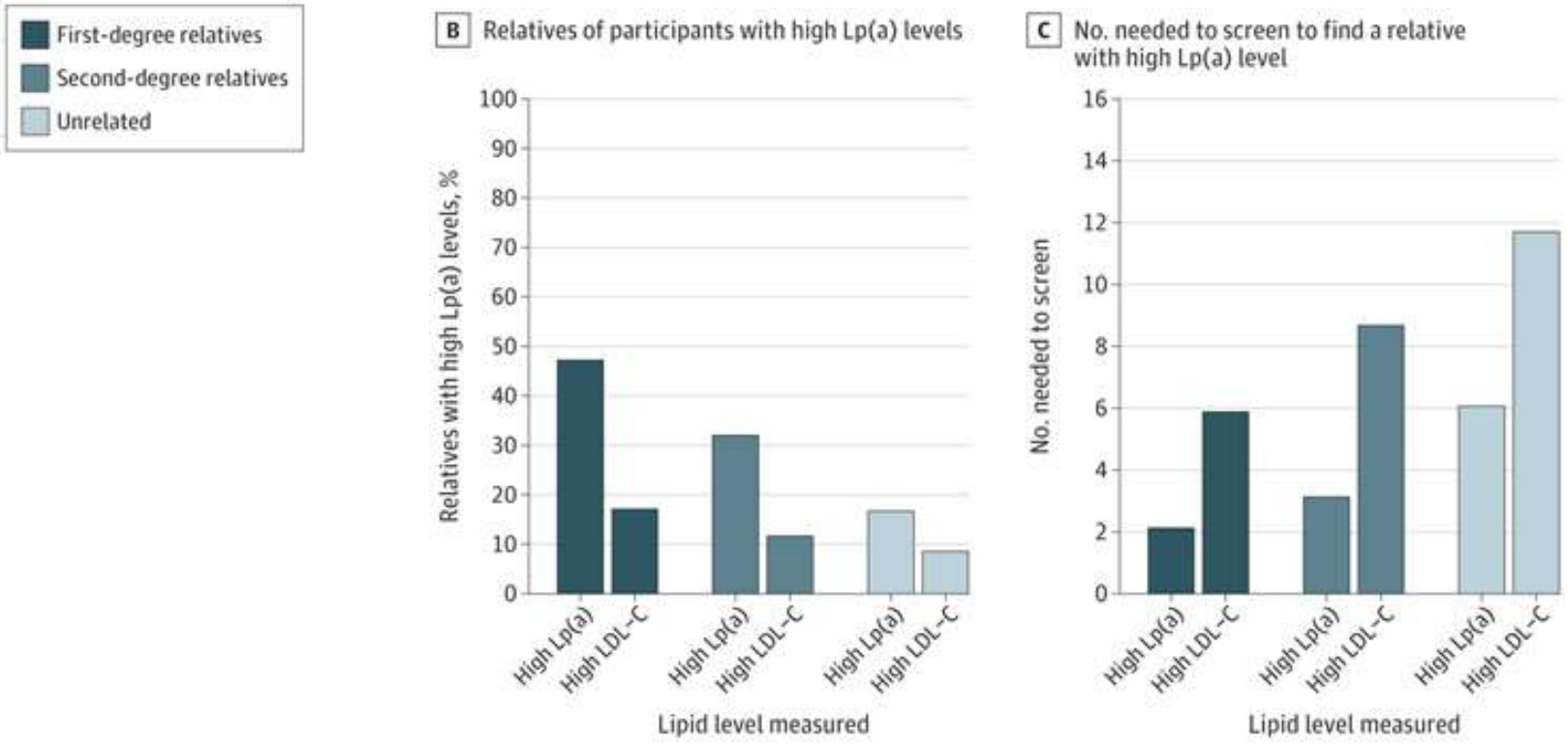
† Unfortunately, we are unable to send at-home screening kits to New Jersey, New York and Rhode Island. Currently, these States have legislation that doesn't allow at-home collection and screening.

Do you have questions about your screening kit? The Family Heart Foundation Care Navigators are here to help you.

With our support, you will understand your current heart health status and learn how to enhance it through lifestyle changes and expert advice.

Are you in danger due to high LDL-C? Learn how to reach your LDL Safe Zone.

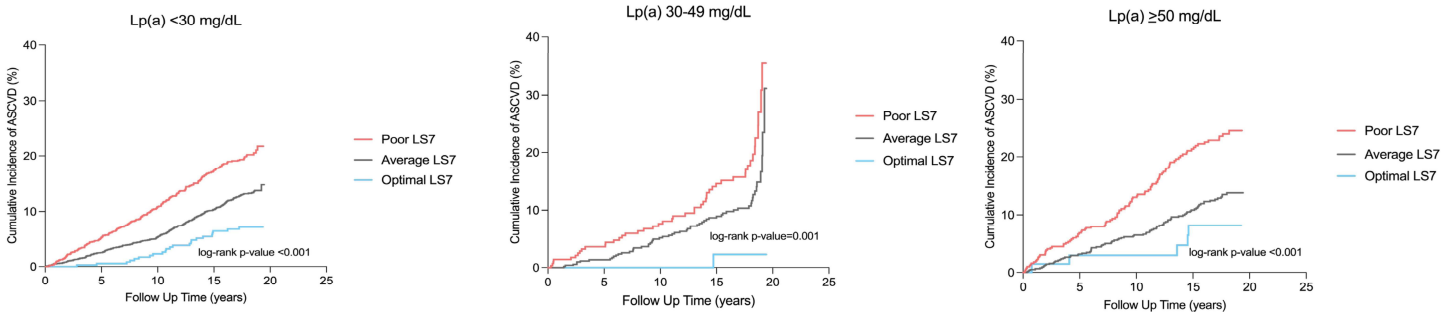
Screen relatives



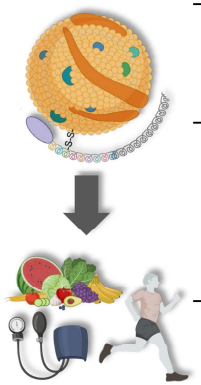
[12] Reskamp, JAMA 2023

Traditional Risk Factors, Optimal Cardiovascular Health, and Elevated Lipoprotein(a)

Cumulative Incidence of ASCVD According to Life's Simple 7, Stratified by Lipoprotein(a)



Association Between Life's Simple 7 and ASCVD Events, Stratified by Lipoprotein(a)



	Lp(a) <30 mg/dL		Lp(a) 30-49 mg/dL		Lp(a) ≥50 mg/dL		P-Interaction †
	HR (95% CI) *	P-Value	HR (95% CI) *	P-Value	HR (95% CI) *	P-Value	
Poor LS7 (0-7)	Ref	-	Ref	-	Ref	-	
Average LS7 (8-11)	0.65 (0.53, 0.78)	<0.001	0.60 (0.39, 0.93)	0.02	0.54 (0.39, 0.74)	<0.001	0.60
Optimal LS7 (12-14)	0.45 (0.28, 0.71)	<0.001	0.12 (0.02, 0.89)	0.04	0.35 (0.13, 0.99)	0.04	

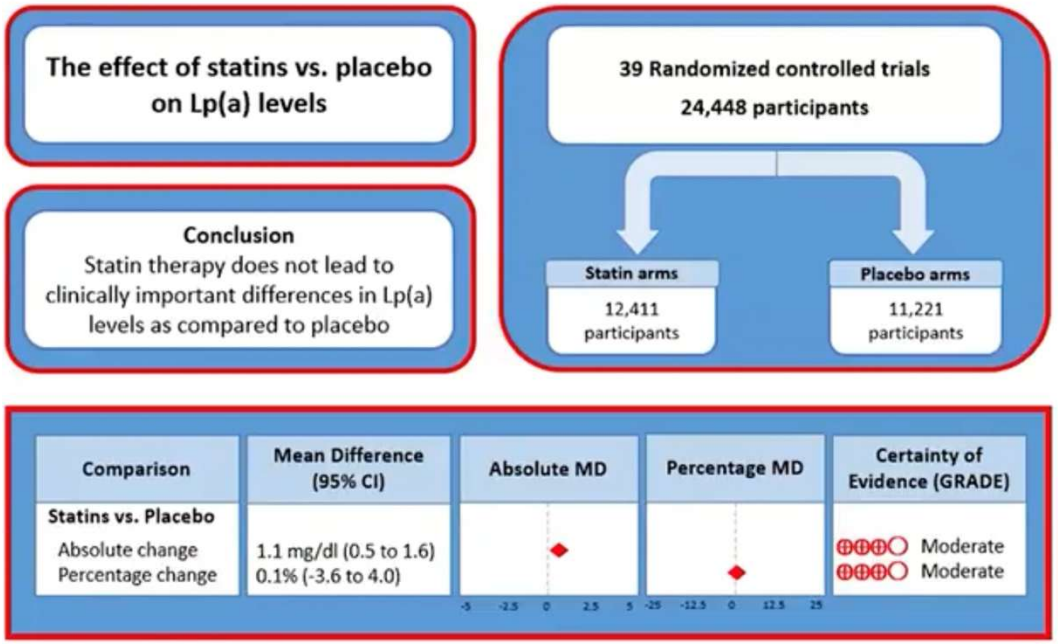
*models include: age, sex, race/ethnicity, MESA site, education health care insurance status, baseline Lp(a), time-varying statin therapy, time-varying aspirin therapy, and Life's Simple 7 score
†represents p-interaction for three-level Lp(a) variable (<30, 30-49, ≥50 mg/dL) and Life's Simple 7 score

Ravazi, European Journal of Preventive Cardiology 2024

Effects of statins on lp(a) level

Modest increase

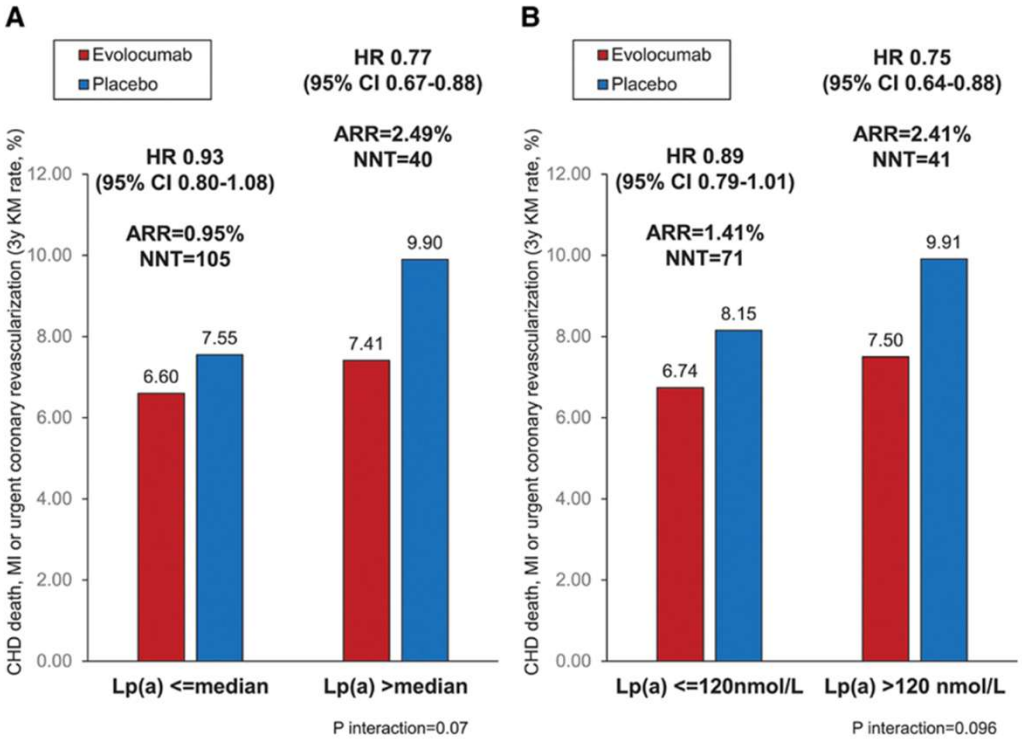
Not a reason not use statin in patients with high lp(a)



[14]de Boer, L. EJPC 2022

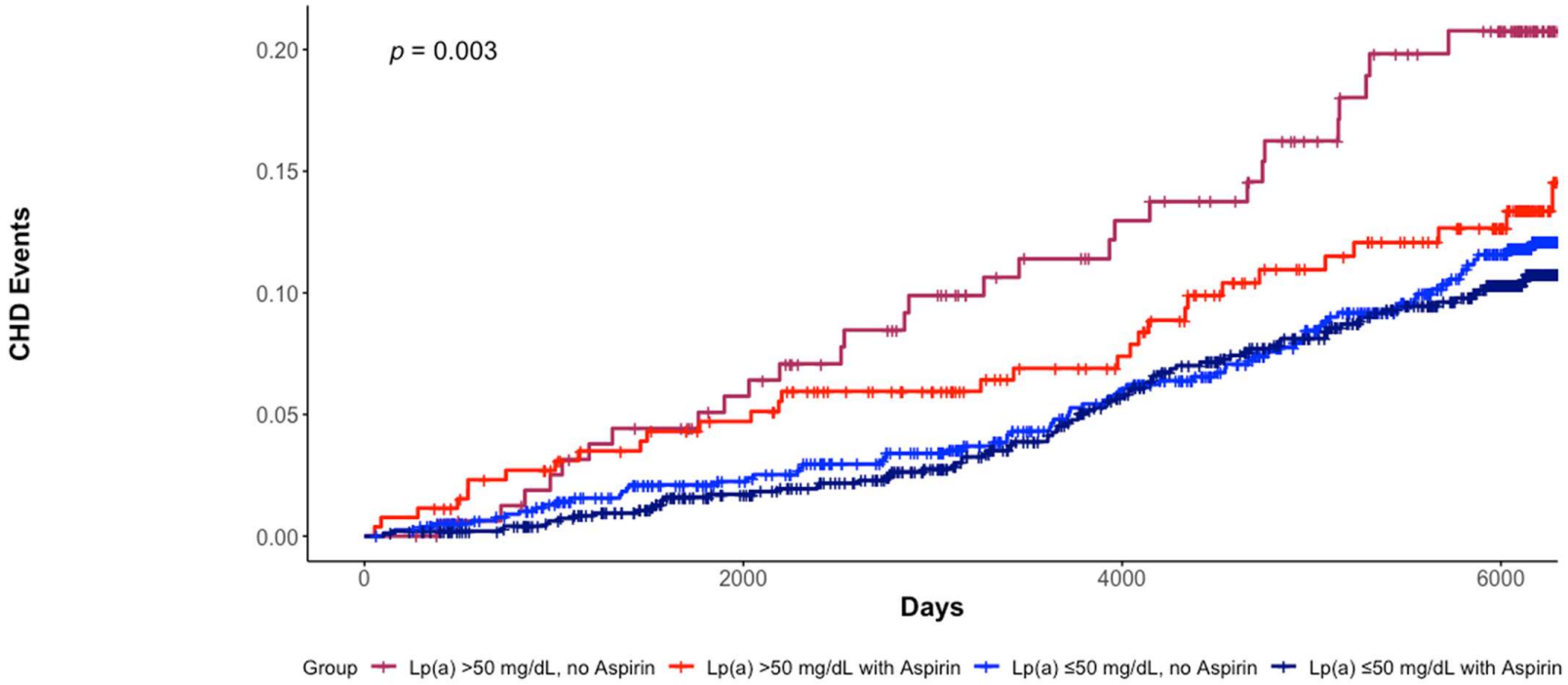
PCSK9i reduces lp(a)

EVOLUCUMAB/REPATHA REDUCED LP(A) BY A MEDIAN (IQR) OF 26.9% (6.2-46.7%)



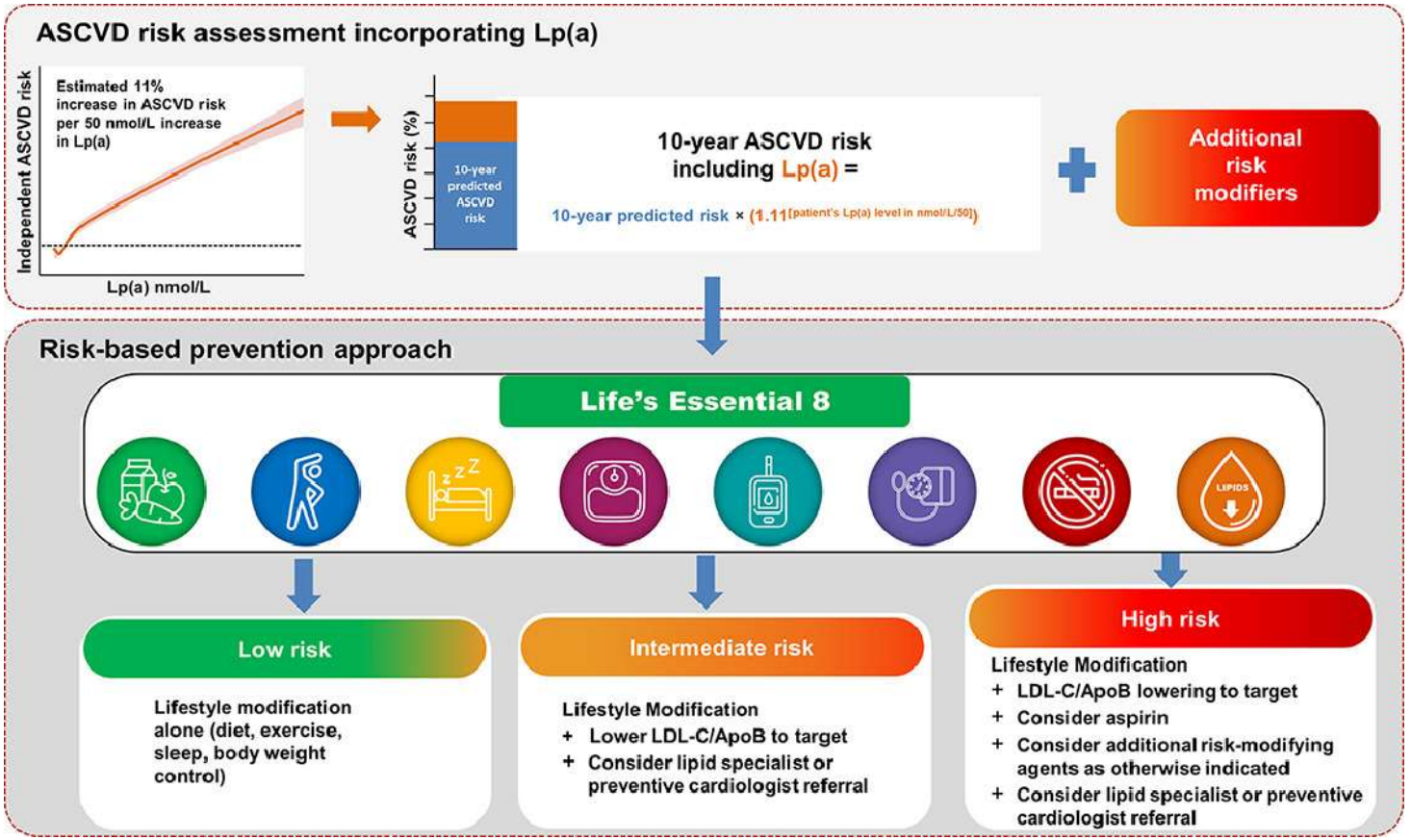
[15] O'Donoghue, Circulation 2019

Consider aspirin if lp(a) is high



[16]Bhatia, JAHA 2024

Risk based strategies



[17] Reyes-Soffer, G, AJPC 2024

Lp(a)-targeting therapies in development

Agent	Mechanism of Action	Clinical Trial Phase (est. study completion)	Effect on Lp(a)
Pelacarsen (formerly IONIS-APO(a)-L_{RX}, AKCEA-APO(a)-L_{RX}, TQJ230)	Antisense to apo(a)	3: Lp(a)HORIZON outcomes trial enrolled (~5/2025)	↓ 35–80%
Olpasiran (formerly AMG 890, ARO-LPA)	siRNA to apo(a)	3: OCEAN(a) outcomes trial enrolled (~12/2026)	↓ 70–99%
Lepodisiran (LY3819469)	siRNA to apo(a)	3: ACCLAIM-Lp(a) outcomes trial recruiting (~3/2029)	↓ 41–94%
Zerlasiran (SLN360)	siRNA to apo(a)	2: ALPACAR-360 published	↓ 46–98%
Muvalaplin (LY3473329)	Oral small molecule binding to apo(a)	2: KRAKEN published	↓ 50–65%

Hussain A et al. *Annu Rev Med* 2021;72:431–446.
Hoogeveen RC et al. *Clin Chem* 2021;67:143–153.
Schwartz GG, Ballantyne CM. *Atherosclerosis* 2022;349:110–122.
https://clinicaltrials.gov/study/NCT04023552.
https://clinicaltrials.gov/study/NCT05581303.
https://www.clinicaltrials.gov/study/NCT06292013
Nissen SE et al. *NEJM* 2025 (ePub).
Nissen SE et al. *JAMA* 2024;332:1992-2002.
Nicholls SJ et al. *JAMA* 2025;333:222-231.

Lp(a) testing in rural health population

Widely available

Test most people once

Most assays are accurate

High prevalence of elevated levels

Associated with MI, aortic stenosis, HF and stroke

Manage today – optimize risk factors (use statin, pcsk9i)

Cascade screening

Future therapies and outcomes coming soon

Penn Medicine

ADDENDUM

Rise in Popularity (1960s–1990s)

In the 1970s–80s, Lp(a) became a hot topic because:

- It **resembled LDL** but carried an extra glycoprotein, **apolipoprotein(a)**, covalently linked to apoB-100.
- Apo(a) had **structural homology to plasminogen**, suggesting a role in **thrombosis and atherosclerosis** — a "two-hit" molecule linking lipid and clot risk.
- Epidemiologic studies (especially by Utermann, Scanu, and Berg's group) showed **high Lp(a)** predicted premature coronary artery disease, even in those with normal cholesterol.

By the late 1980s, it was viewed as a **causal, independent risk factor**, and assays for Lp(a) appeared in lipid labs.

Fall from Favor (1990s–2000s)

Interest waned for several reasons:

1. **Assay variability:** Different labs gave wildly inconsistent results due to apo(a) size polymorphisms (kringle repeats), making cross-study comparisons unreliable.

2. **No therapy:** Statins had no meaningful effect on Lp(a), so clinicians couldn't act on the result.

3. **Confounding skepticism:** Some epidemiologists argued that Lp(a) merely tracked with LDL or inflammation markers, not causally with events.

4. **Focus shift:** The lipid world turned to LDL-C targets, statins, and later HDL and triglyceride biology.

By 2005, Lp(a) was rarely measured outside of academic centers.

Resurgence (2010s–Today)

1.Genetic proof:

1. *Mendelian randomization* and GWAS showed LPA variants causally increase atherosclerotic risk — independent of LDL-C or other lipids.
2. This firmly established Lp(a) as a **genetically determined, causal risk factor**.

2.Improved assays:

1. Standardized **isoform-insensitive assays** in nmol/L clarified epidemiologic thresholds (≈ <75 nmol/L normal, >125 nmol/L elevated).

3.New therapies:

1. **Antisense oligonucleotides (pelacarsen, olpasiran, SLN360)** can reduce Lp(a) by 80–95%, leading to ongoing large outcomes trials (*Lp(a)HORIZON*, *OCEAN(a)*).
2. Clinicians once again have a potential **actionable biomarker**.

Meanwhile, increased awareness of "residual risk" after statins (MI, stroke, calcific aortic stenosis) rekindled attention to Lp(a) as an unaddressed pathway.