Lipoprotein(a): an important value or just a number?

Albert Lopez DO FASPC FACP
FOMA Convention 2026

Disclosures:

NOVARTIS – THE HERITAGE TRIAL, CTQJ 230A12001- PELACARSEN; Lp(a) PREVALENCE IN CARDIOVASCULAR DISEASE

NOVARTIS – THE HORIZON TRIAL; PELACARSEN (TQJ 230); IMPACT OF LOWERING Lp(a) WITH PELACARSEN ON MAJOR CARDIOVASCULAR EVENTS IN PATIENTS WITH ESTABLISHED CARDIOVASCULAR DISEASE.

LIB THERAPEUTICS, LIB003-005 LDL-C LOWERING FOR CAD; LIBERATE H2H TRIAL, LERODALCIBEP 3RD GEN PSCK9

LIB THERAPEUTICS, LIB003-006 LDL-C LOWERING FOR CAD, LIBERATE H2H TRIAL.

LIB THERAPEUTICS, LIB003-007 LDL-C LOWERING FOR CAD

LIB THERAPEUTICS, LIB003-011 LDL-C LOWERING FOR CAD

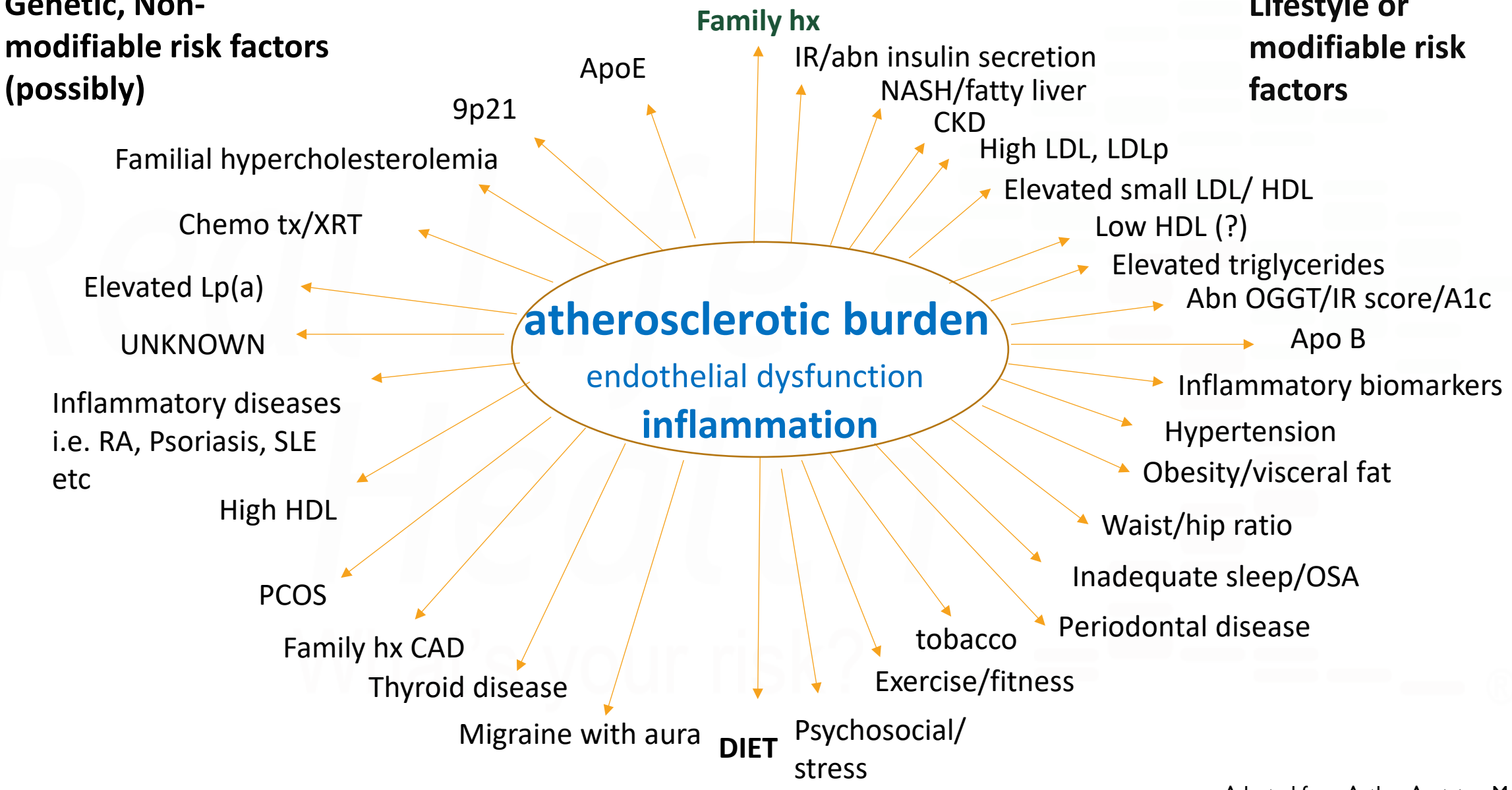
AMGEN, OBSERVATIONAL STUDY FOR OLPASIRAN -SMALL INTERFERING RNA REDUCING LIPOPROTEIN A

AMGEN, 2021-0057 Lp(a) AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE – OLPASIRAN. OCEAN(A) TRIAL.

NOVARTIS, CKJX839B12302, VICTORION- 2 PREVENT - CVD STUDY- INCLISIRAN.

ELI LILY, EFFECT OF LEPODISIRAN ON THE REDUCTION OF ADVERSE CARDIOVASCULAR EVENTS IN ADULTS WITH ELEVATED LIPOPROTEIN (a) WHO HAVE ESTABLIHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE OR ARE AT RISK FOR A FIRST CARDIOVASCULAR EVENT. ACCLAIM-Lp(a) TRIAL.

ASTRA ZENICA; AZURE TRIAL, ASSESS AZD0780 ON MAJOR ADVERSE CV EVENTS IN PATIENTS WITH A HISTORY OF ASCVD EVENTS OR AT HIGH RISK FOR A FIRST EVENT- REDUCING THE RISK OF MACE-PLUS IN PATIENTSWITH ESTABLISHED ASCVD OR AT HIGH RISK FOR A FIRST ASCVD EVENT.



Adapted from Arthur Agatston M.D.

Endothelial function

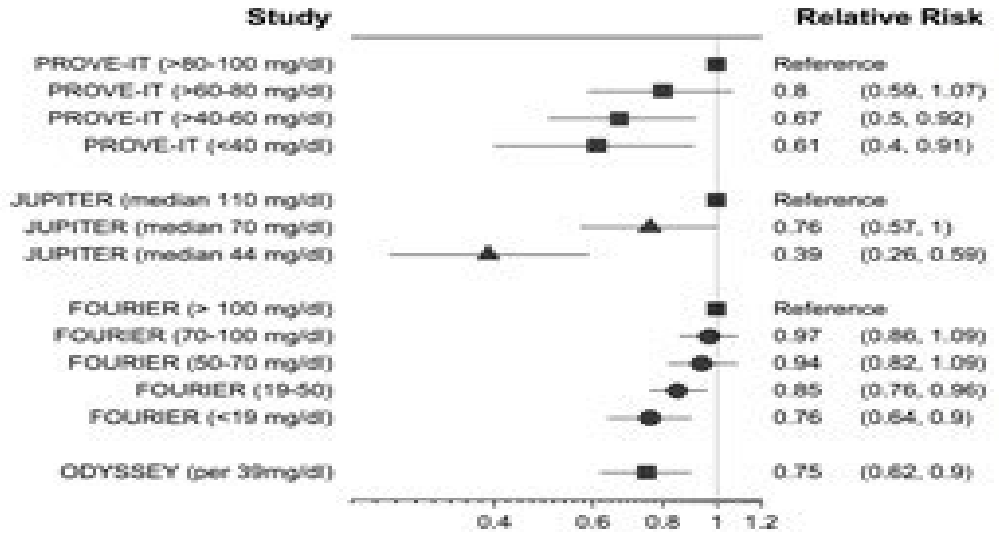
Oxidative stress

Inflammation

LDL-C reduction

The ealier the better, the lower the better for longer

- Stroke/TIA
- Myocardial infraction
- Mesenterie ischemia
- Lower extremity
- Amputation
- Erectile dysunction
- Ischemic cardiomyopathy
- Renal ischemia



- Neurodegenerative disorders
- Vascular dementia
- Alzheimer's disease
- Parkinson's disease

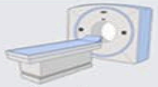
ATHEROSCLEROSIS
(coronary artery diseases; peripheral vascular disease; renal artery discase; mesenteric artery disease; cerebrovascular disease)

Aortic aneurysms, aortic valve sclerosis

American Journal of Preventive Cardiology
Volume 26, April 2026, 101417

State-of-the-Art Review:

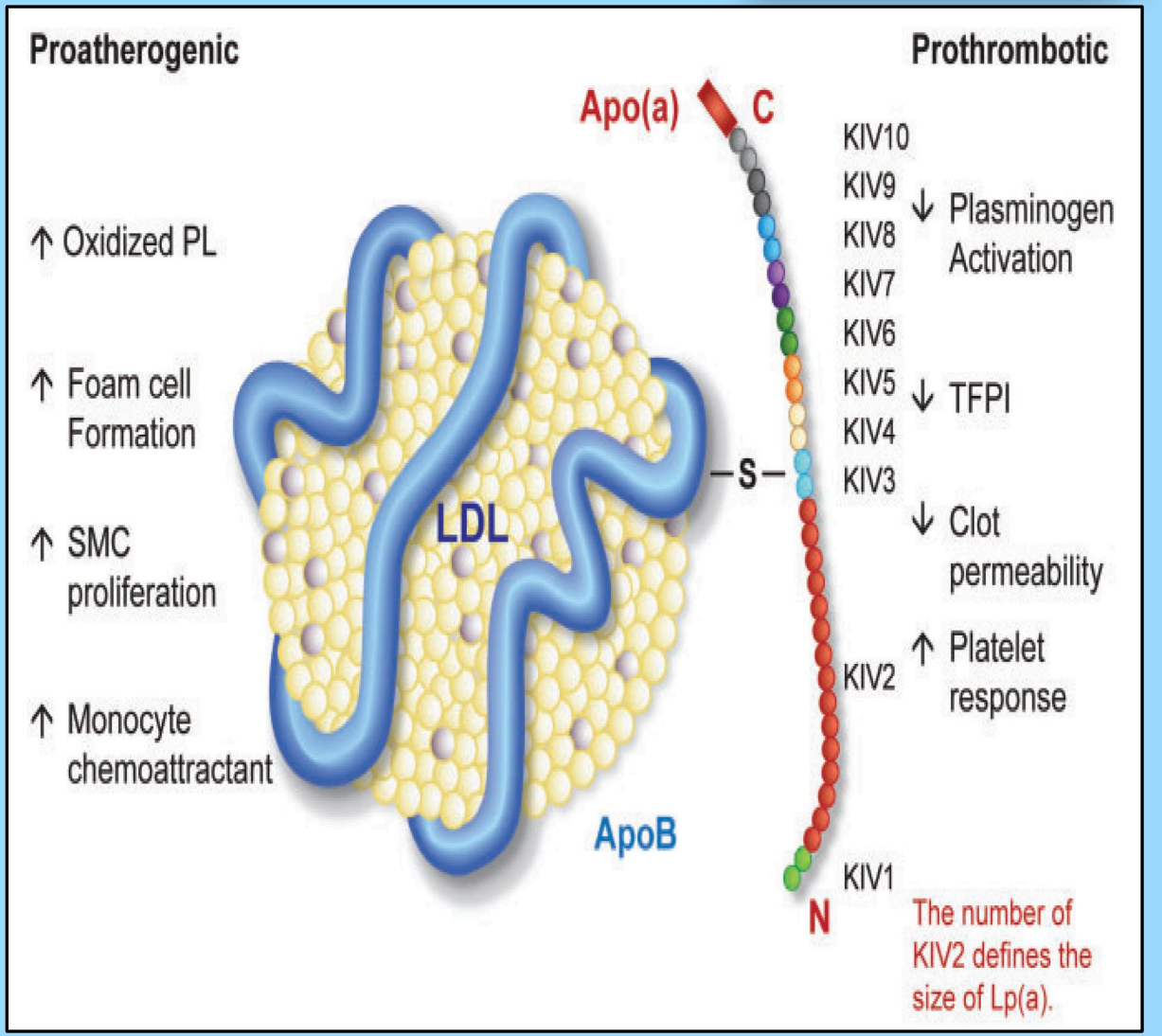
Progress in risk assessment and management: Forecasting updates across international cholesterol guidelines

	Current Guideline Recommendations	Future Directions to Consider	Data to Support Future Directions
Risk Assessment 	Pooled Cohort Equations (2013)	PREVENT Equations (2024) (Likely lower risk thresholds)	Development and Validation of AHA PREVENT Equations
Subclinical Atherosclerosis Imaging 	CAC to Guide Statin Eligibility	CAC to Guide Statin Eligibility and LDL-C Goals	CorCal, CAUGHT-CAD, NOTIFY-1, DANCAVAS
Combination Lipid Lowering Therapy 	Ezetimibe as First Choice After Maximally Tolerated Statin Therapy	Lower threshold for addition of PCSK9i in order to achieve lower LDL-C goals	RACING, FOURIER-OLE, VESALIUS-CV
LDL-C Targets 	<70 mg/dL in Secondary Prevention <55 mg/dL in Very High Risk	<70 mg/dL for High Risk <55 mg/dL in Very High Risk <30 mg/dL in Extremely High Risk	FOURIER-OLE, Observational Data from CAC Consortium
Lipoprotein(a) 	Select Testing as a Risk Enhancer	Universal Testing Prioritize PCSK9i if Lp(a) Elevated	Post-Hoc Analyses of FOURIER & ODYSSEY OUTCOMES

Alexander C. Razavi ,Mark Sokolsky, Matthew Belanger, Cameron Blazoski, Jared A. Spitz, Laurence S. Sperling, Roger S. Blumenthal, Seamus P.Whelton.
https://doi.org/10.1016/j.ajpc.2026.101417

Lp(a)

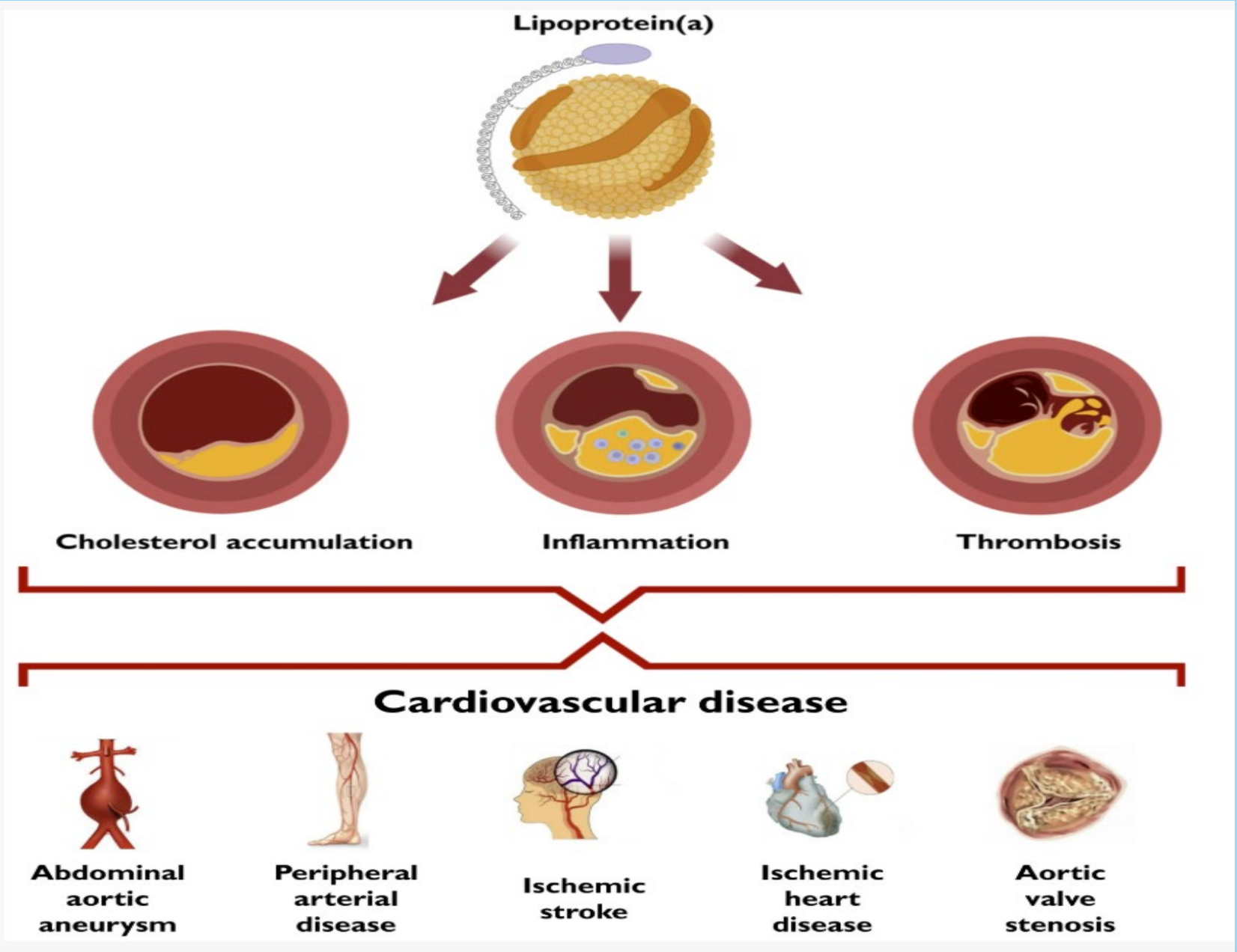
- **Lp(a) excess represents a lifelong, genetically determined, causal risk factor independent of all other known risk factors for CVD, arterial stenosis, and CV mortality**



THE TRIPLE THREAT OF ELEVATED LP(A)

- PRO-ATHEROGENIC
- PRO-THROMBOTIC
- PRO-INFLAMMATORY

CURRENT THOUGHTS ON MECHANISM OF LP(A) AS CAUSE FOR ATHEROSCLEROSIS



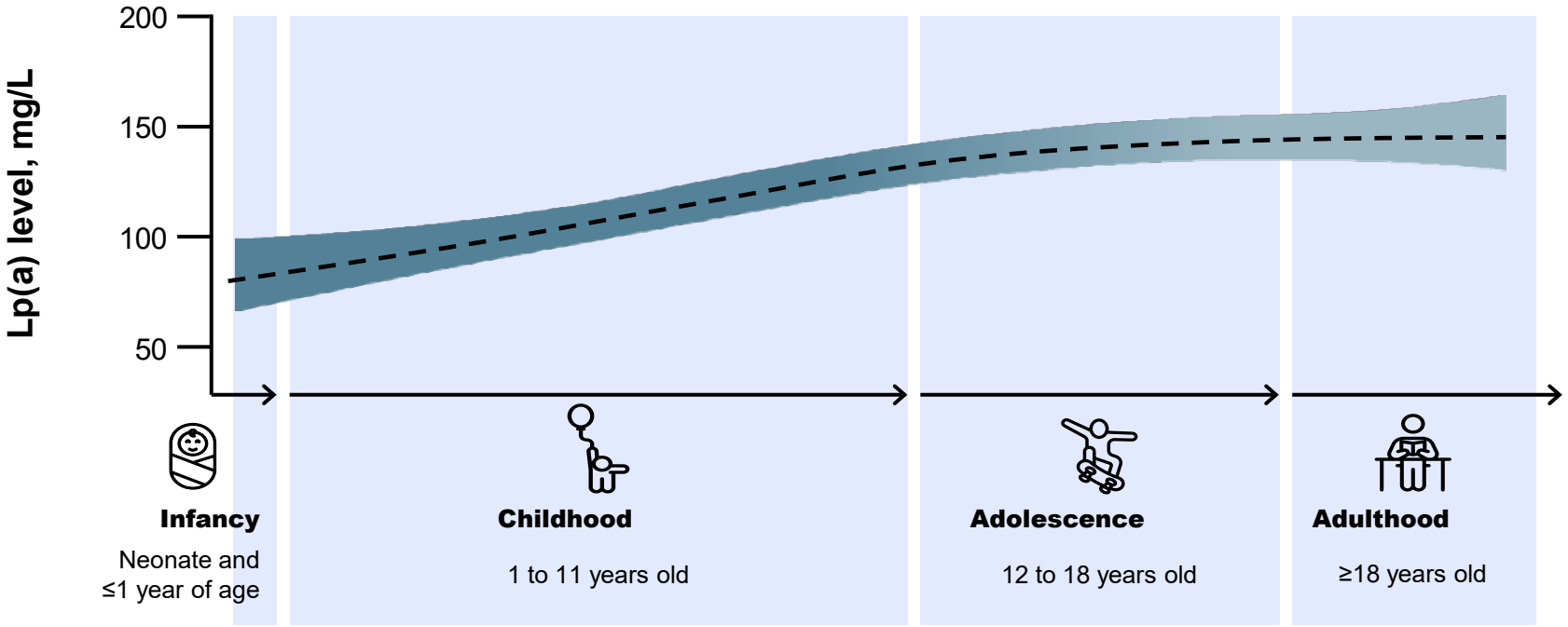
Thomas PE, Vedel-Krogh S, Kamstrup PR, Nordestgaard BG. Lipoprotein(a) in cardiovascular disease with focus on peripheral arterial disease, major adverse limb events, abdominal aortic aneurysms and interaction with low-grade inflammation. Adv Lipoprotein(a) Res. 2026;1:202504. https://doi.org/10.70401/alr.2025.0004

A DANGEROUS PLAYER

Genetically determined Lp(a) levels are continually and linearly a related risk of CVD independent of other modifiable risk factors such as lifestyle and lipid levels.

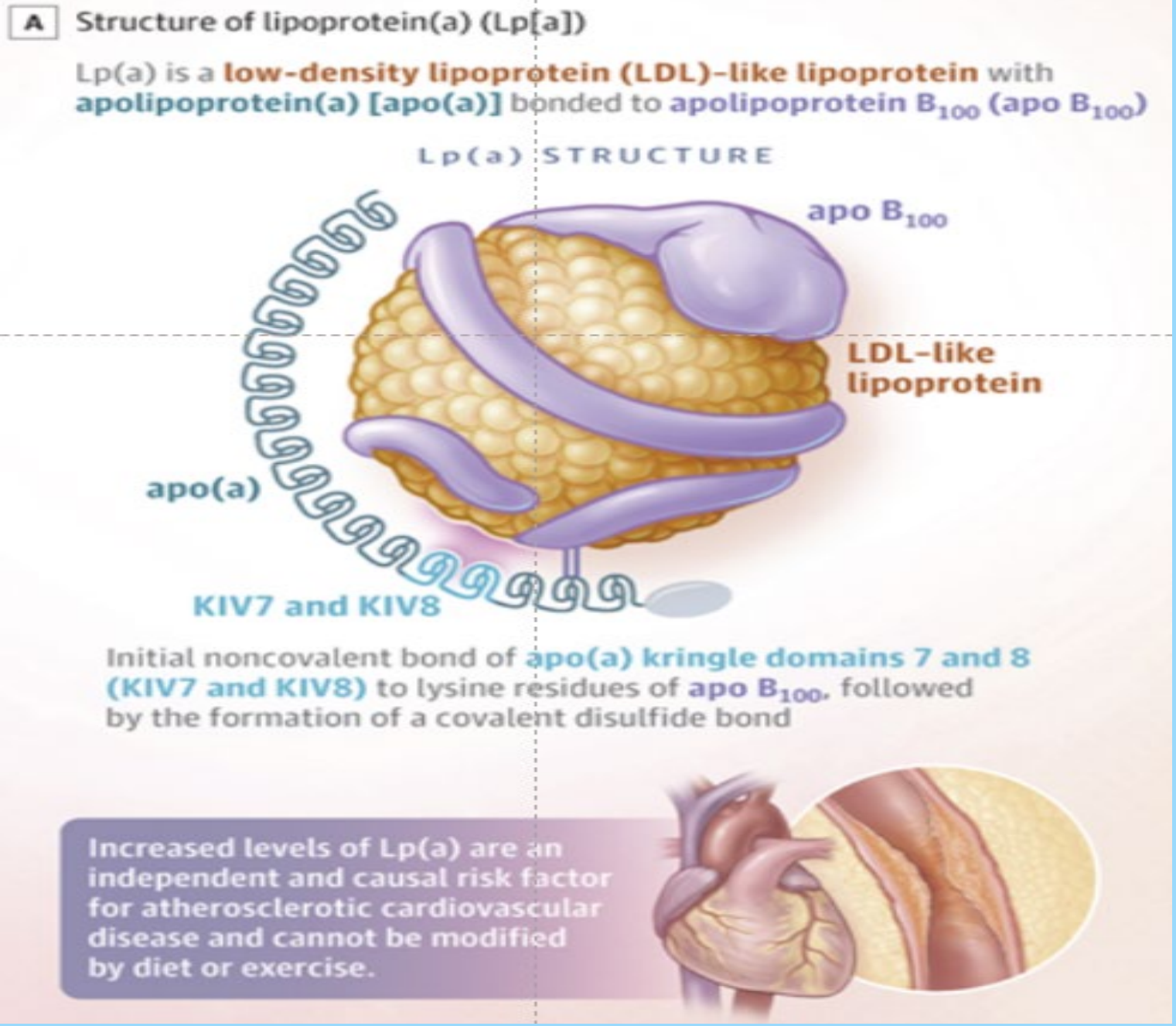
Lp(a) Levels Are >90% Genetically Determined[1-3]

Lp(a) Is Detected Within One's First Year of Life and Increases Throughout Childhood, but Expression Is Fairly Stable in Adulthood[4]



Lipoprotein a or Lp(a)

- Individuals with elevated Lp(a) face a lifelong increased risk of premature cardiovascular events despite the absence of other risk factors.
- Elevated Lp(a) is an independent causal risk factor – increasing the risk for ASCVD
- Lp(a) is 6 x more atherogenic than LDL
- Mug photo courtesy of Dr Sam Tsimikas



Lp(a) measurement is complicated by the unique structure of apolipoprotein(a).

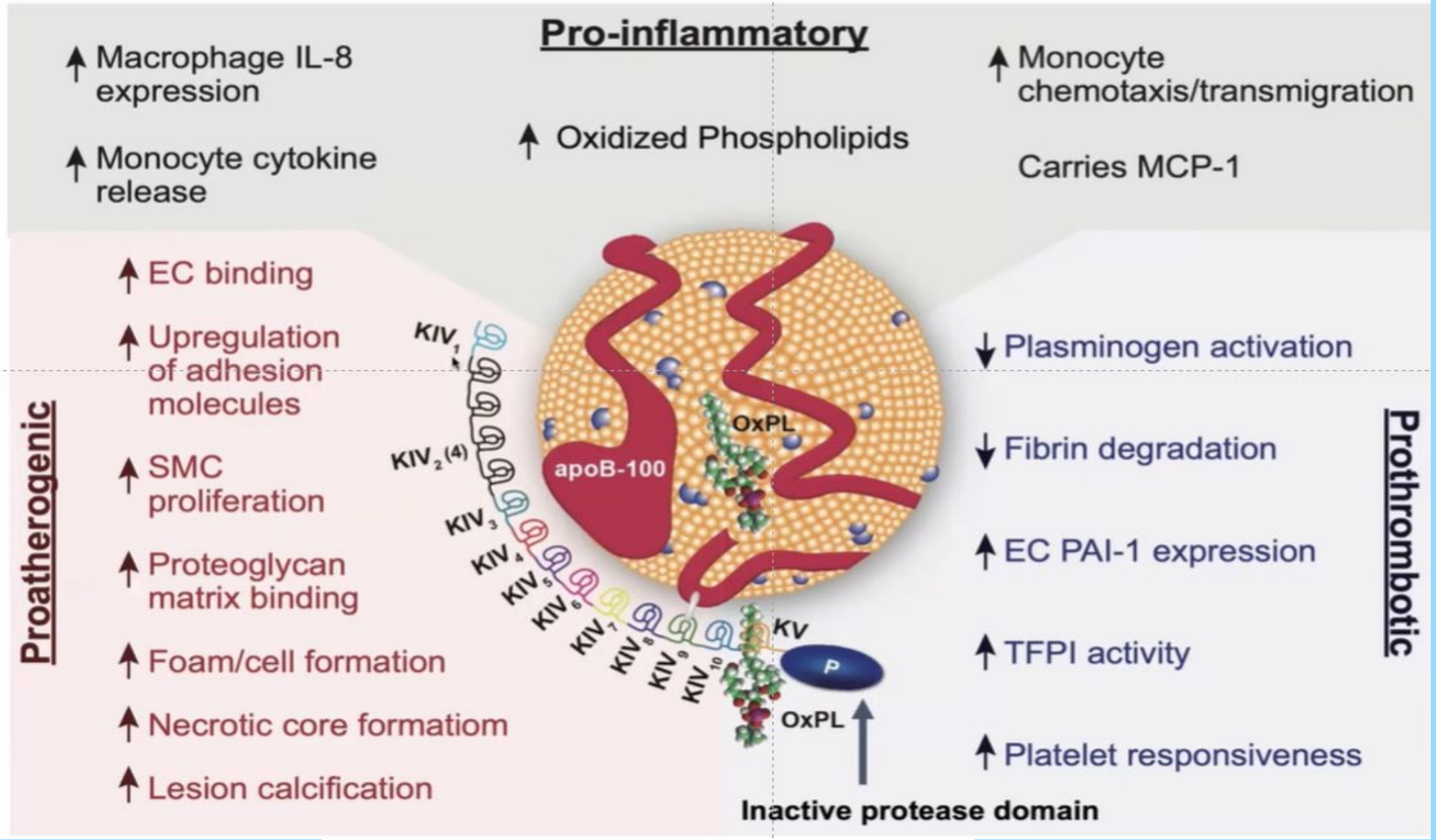
Apo(a) is characterized by a variable number of identically repeated kringle IV type 2 (KIV2) sequences (ranging from 3 to > 40 copies) that correspond to differently sized isoforms of Lp(a).

Therefore, antibodies that recognize epitopes in the KIV2 sequence tend to underestimate the concentrations of smaller Lp(a) isoform sizes (which tend to be associated with higher Lp(a) levels and higher ASCVD risk), while overestimating those of larger isoforms.

Nicholls SJ, Nissen SE, Fleming C, et al. Muvalaplin, an Oral Small Molecule Inhibitor of Lipoprotein(a) Formation: A Randomized Clinical Trial. *JAMA.* 2023;330(11):1042–1053. doi:10.1001/jama.2023.16503

Is Lp(a)-associated cardiovascular risk independent of that associated with LDL-C?

Key Mechanisms Through Which Lp(a) Mediates CVD



Tsimikas JACC 2017;69:692-711

HOW COMMON IS LP(A)?
WHO IS AT RISK ?

We estimate 20-30% of the population have elevated Lp(a).

That's 2-3 per 10 people

6.4 million people in the US

1.4 billion people worldwide

If you have elevated Lp(a), your children have a **50% chance** of inheriting elevated Lp(a).

Screening and therapies could prevent up to 1 in 3 heart attacks and 1 in 2 cases of aortic valve disease in patients with high Lipoprotein(a).

Centre universitaire de santé McGill
Institut de recherche

McGill University Health Centre
Research Institute

From the study **Estimating the Population Impact of Lp(a) Lowering on the Incidence of Myocardial Infarction and Aortic Stenosis** published in *Arteriosclerosis, Thrombosis, and Vascular Biology*

Who should get tested for Lpa?

- Early history of heart attack, stroke or peripheral vascular disease; women younger than 65 ; men younger than 55.
- Early or rapid progression of Aortic valvular disease
- "Statin resistant " patients; high LDL despite medication
- Strong family history of "heart" disease or stroke
- Cardiovascular disease with normal cholesterol, or no other risk factors
- Family member with high Lp(a)
- Diabetics/ insulin resistant (IFG)
- Familial Hypercholesterolemia; FH
- Pro-thrombotic states not identified in classic hypercoagulable work-up
- Individuals of African or South Asian descent
- Everyone; once in a lifetime
- ? When?

Scientific statements

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

Marlys L. Koschinsky, PhD[a] · Archna Bajaj, MD, MSCE[b] · Michael B. Boffa, PhD[a] · … · Michael J. Wilkinson, MD[k] · Don P. Wilson, MD[l] · Christie M. Ballantyne, MD[m]

NATIONAL LIPID ASSOCIATION

- 

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

Florian Kronenberg , Samia Mora , Erik S G Stroes , Brian A Ference , Benoit J Arsenault , Lars Berglund , Marc R Dweck , Marlys Koschinsky , Gilles Lambert , François Mach ..et.al.

ESC European Society of Cardiology

Lp(a)

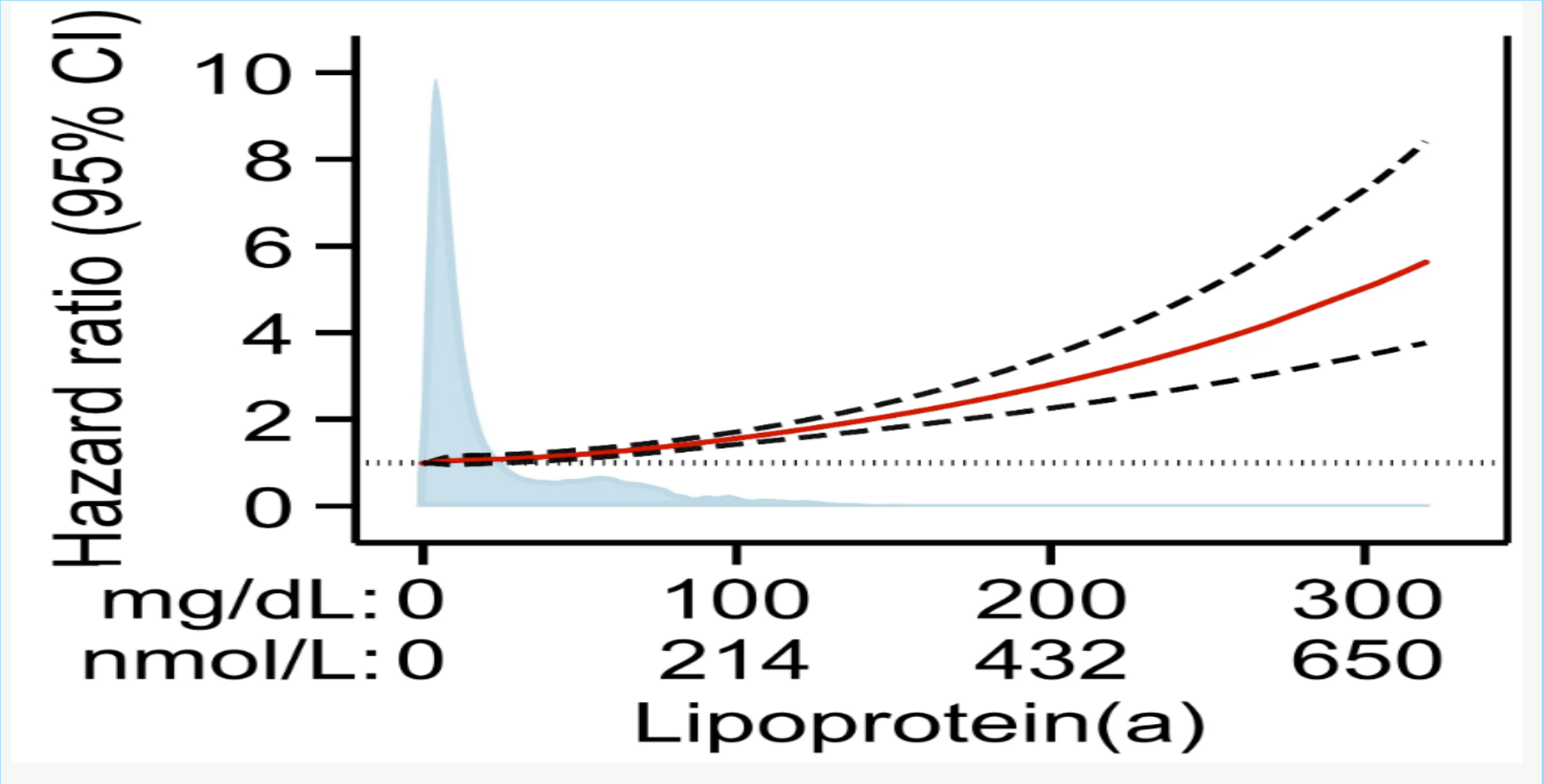
The relationship between Lp(a) level and cardiovascular disease risk is continuous and log-linear

- Rather than a single cut-point defining a risk threshold, Lp(a) levels represent a continuum of cardiovascular disease risk spanning low, intermediate, and high risk

- Lp(a) should be measured and reported in nmol/L; Lp(a) values should not be converted between mg/dL and nmol/L using a fixed conversion factor

A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice. Koschinsky, Marlys L. et al. Journal of Clinical Lipidology, Volume 18, Issue 3, e308 - e319

RISK OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE BY PLASMA LIPOPROTEIN A



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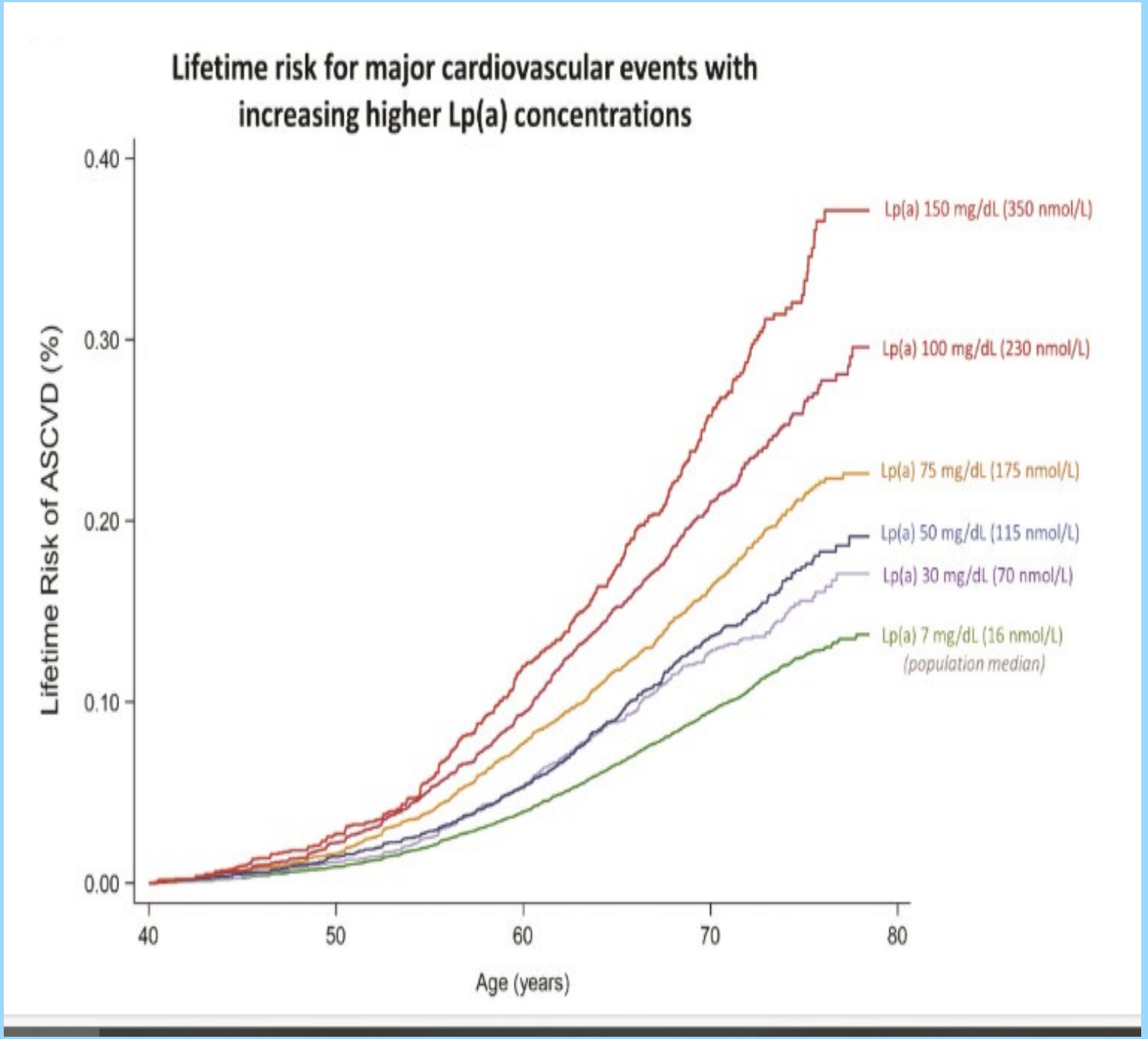
LP(A)

Individuals with Lp(a) levels:

<75 nmol/L (30 mg/dL) may be considered low risk,

individuals with Lp(a) levels ≥125 nmol/L (50 mg/dL) may be considered high risk,

individuals with Lp(a) levels in the “gray zone” between 75 and 125 nmol/L (30–50 mg/dL) are at intermediate risk and may warrant repeat measurement



Lipid analyses for CVD risk estimation

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.

Lp(a) > 50-75 mg/dl imparts risk

Lp(a) > 180 mg/dl = risk of FeFH patient

www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

- Lp(a) should be measured and reported in nmol/L; Lp(a) values should not be converted between mg/dL and nmol/L using a fixed conversion factor

Lp(a) readings: Check the units

Labs report lipoprotein(a) values in two different units. The preferred method is nanomoles per liter (nmol/L), but many labs still use milligrams per deciliter (mg/dL). Currently, there's no universal consensus on what constitutes an abnormal Lp(a) level, but the thresholds shown below are commonly used.

Lp(a)	**nmol/L**	**mg/dL**
Normal	Below 75	Below 30
High	125 and above	50 and above

LP(A)

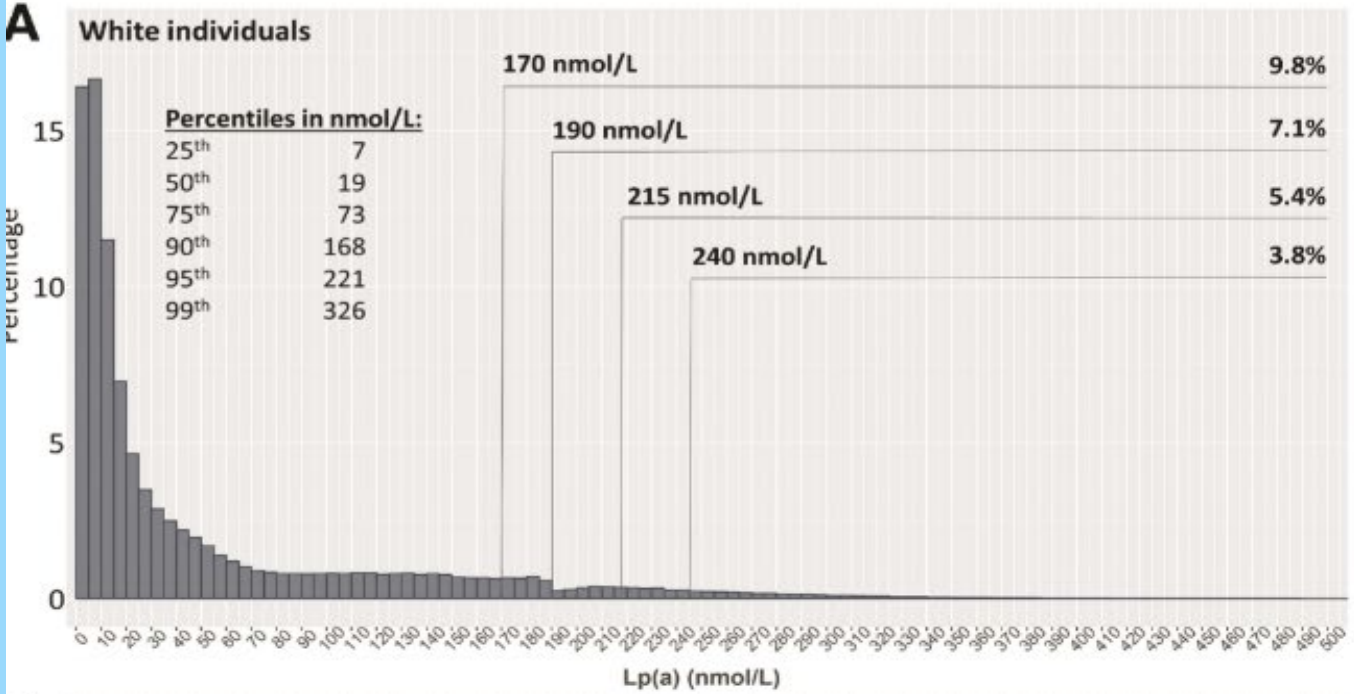
- Lp(a) risk categories apply across races and ethnicities

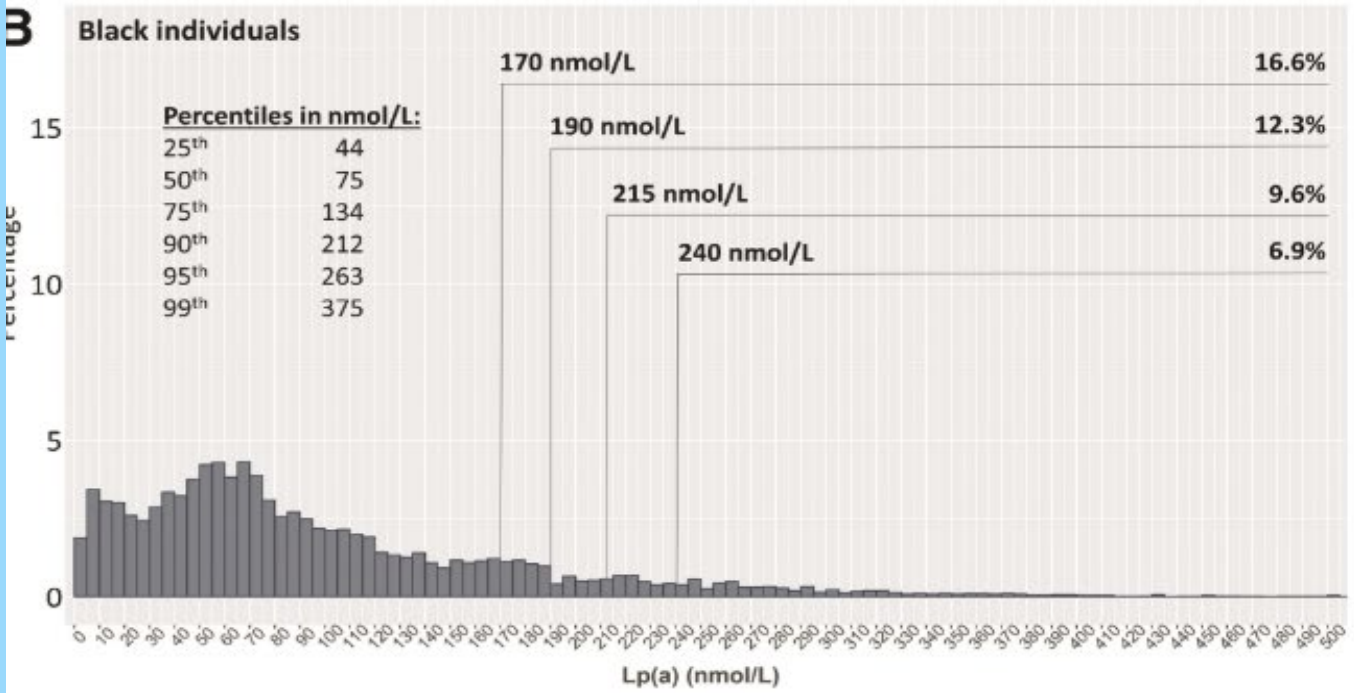
  persons from African ancestry

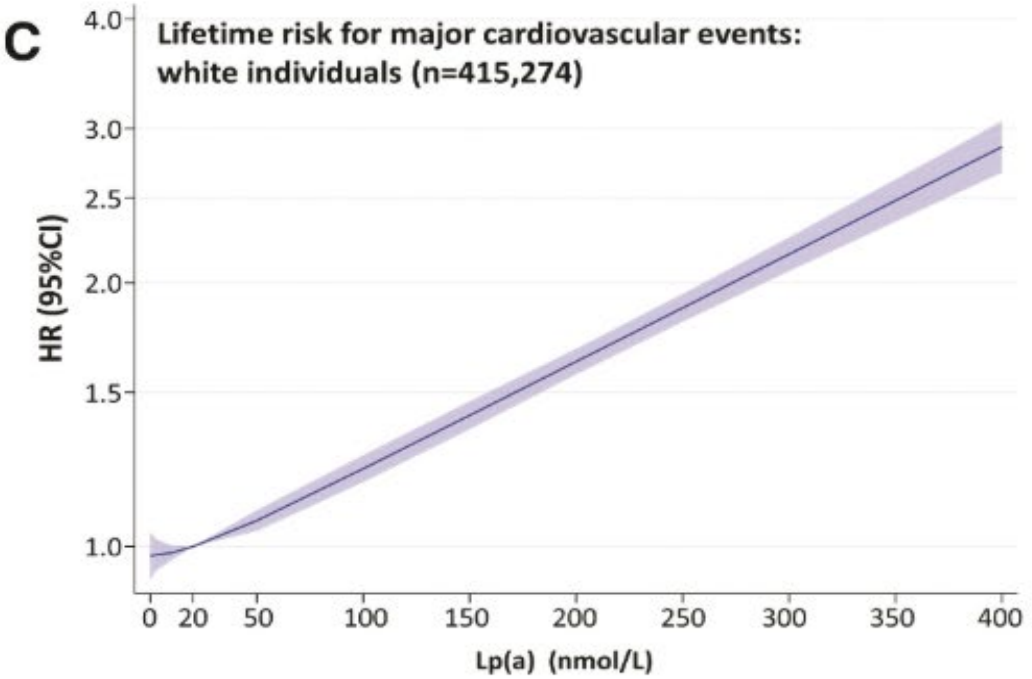
  South Pacific Islanders

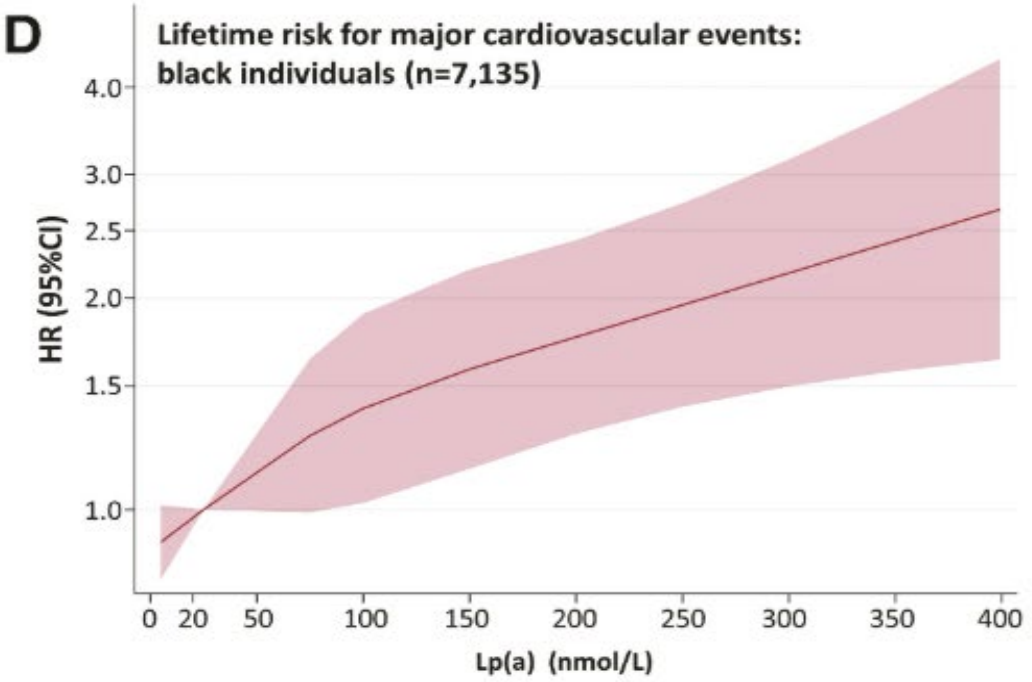
  South Asian subcontinent

- Lp(a) should be measured at least once in every adult for cardiovascular risk assessment


A
White individuals
170 nmol/L
9.8%
190 nmol/L
7.1%
215 nmol/L
5.4%
240 nmol/L
3.8%
Percentiles in nmol/L:
25th 7
50th 19
75th 73
90th 168
95th 221
99th 326
Percentage
Lp(a) (nmol/L)


B
Black individuals
170 nmol/L
16.6%
190 nmol/L
12.3%
215 nmol/L
9.6%
240 nmol/L
6.9%
Percentiles in nmol/L:
25th 44
50th 75
75th 134
90th 212
95th 263
99th 375
Percentage
Lp(a) (nmol/L)


C
Lifetime risk for major cardiovascular events:
white individuals (n=415,274)
HR (95%CI)
Lp(a) (nmol/L)


D
Lifetime risk for major cardiovascular events:
black individuals (n=7,135)
HR (95%CI)
Lp(a) (nmol/L)

Lp(a) Testing Rates in the US Are Currently Very Low and Disparities Exist

Multiple studies, including surveys and retrospective analyses, have reported very low Lp(a) testing rates.[1-3]

People of color and **women** were less likely to undergo Lp(a) testing, highlighting the disparity in testing.[1-3]

Those who underwent Lp(a) testing were more likely to have **CVD** or **CVD risk factors**

- Testing rates were markedly higher in 1 large-scale survey for those with **CVD (<4%)** or a family history of **CVD (3%)** compared with the **total patient population (0.3%)**[2]

CVD, cardiovascular disease; Lp(a), lipoprotein(a).

1. Kelsey MD et al. *Am J Prev Cardiol*. 2023;14:100478. **2.** Bhatia HS et al. *J Am Heart Assoc*. 2023;12(18):e031255. **3.** Shah NP et al. Poster Sa3192 presented at: American Heart Association Scientific Sessions; November 11-13, 2023; Philadelphia, PA.

Consensus key points: Proposed mechanisms for the pathogenicity of Lp(a) in ASCVD and AVS (aortic valve stenosis)

- Lp(a) has pro-inflammatory and pro-atherosclerotic properties, which may partly relate to the OxPLs (oxidized phospholipids) carried by Lp(a).

- Lp(a) is the major carrier of plasma oxidized phospholipids (OxPL) – biomarkers for oxidative lipid burden and predictive of cardiovascular risk.

- A potential role for Lp(a) in pro-thrombotic and anti- fibrinolytic activity in vivo remains unproven.

- High Lp(a) induces the expression of inflammatory and calcification genes in vascular and valvular cells and associates with increased incidence and progression of AVS- aortic valvular stenosis.

Florian Kronenberg, Samia Mora, Erik S G Stroes, Brian A Ference, Benoit J Arsenault, Lars Berglund, Marc R Dweck, Marlys Koschinsky, Gilles Lambert, François Mach, Catherine J McNeal, Patrick M Moriarty, Pradeep Natarajan, Børge G Nordestgaard, Klaus G Parhofer, Salim S Virani, Arnold von Eckardstein, Gerald F Watts, Jane K Stock, Kausik K Ray, Lale S Tokgözoğlu, Alberico L Catapano, **Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement, European Heart Journal, Volume 43, Issue 39, 14 October 2022, Pages 3925–3946, https://doi.org/10.1093/eurheartj/ehac361**

Inflammatory Biomarkers With Associations With Lp(a)

	Pathophysiological Effect	Relationship With Lp(a)	Clinical Evidence
hsCRP	Known inflammatory biomarker with prognostic value for ASCVD Synthesized in the liver, acute phase reactant, potent inducer of inflammation in vascular smooth muscle, and may contribute to increased atherothrombosis	Increased hsCRP (>2 mg/L) is associated with increased incidence of ASCVD in patients with elevated Lp(a)	Puri et al[29] Zhang et al[30]
IL-1	Proinflammatory cytokine active in the course of an inflammatory response, acute or chronic Can be produced by endothelial cells, smooth muscle cells, macrophages, and monocytes	Proinflammatory IL-1 genotypes modulate the contribution of OxPL and Lp(a) toward atherosclerosis and incident ASCVD	Tsimikas et al[28]
IL-6	Cytokine of innate immunity involved in host defense, immune cell regulation, proliferation, and differentiation Involved in atherogenesis and systemic atherothrombosis	IL-6 has been found to modulate levels of Lp(a) as inhibitors of IL-6 decrease Lp(a), indicating a mechanism by which inflammation modulates atherothrombotic risk	Müller et al[31] Ridker et al[32]
IL-8	Chemoattract cytokine that attracts and activates neutrophils in inflammatory regions	The apo(a) component of Lp(a) stimulates IL-8 expression in macrophages	Scipione et al[23]
MCP-1	Chemokine that plays a key role in the regulation of migration and infiltration of monocytes/macrophages	MCP-1 binds OxPL on Lp(a) thereby increasing monocyte recruitment to vascular endothelium	Wiesner et al[24]

ASCVD = atherosclerotic cardiovascular disease; hsCRP = high-sensitivity C-reactive protein; IL = interleukin; Lp(a) = lipoprotein(a); MCP = monocyte chemoattractant protein; OxPL = oxidized phospholipids.

Clinical Trial Design for Lipoprotein(a)-Lowering Therapies: *JACC* Focus Seminar 2/3
Authors: Waqas A. Malick, Sascha N. Goonewardena, Wolfgang Koenig, and Robert S. Rosenson Robert.rosenson@mssm.eduAUTHORS INFO & AFFILIATIONS
Publication: JACC Volume 81, Number 16

Lp(a) is associated with an increased risk of incident ASCVD

- - even in the absence of a family history of heart disease.
- - is independent of LDL-C and is attributed to the atherogenic, proinflammatory, and prothrombotic properties of Lp(a).

Systematic universal Lp(a) screening can improve health outcomes by increasing awareness of, and enabling precision in, ASCVD prevention strategies and individualization of therapy selection.

Preventive strategies with healthy lifestyle and LDL-C/apolipoprotein B (apoB) lowering pharmacotherapies (especially statins) reduce risk across almost all patient groups, and incorporation of Lp(a) into risk assessment can inform decision-making for these patients since treatment is tied closely to overall risk.

Koschinsky et al, A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.03.001

Lp(a) levels provide incremental and independent prognostic information to C-reactive protein levels for risk estimates of ASCVD, MI, and CAVS.

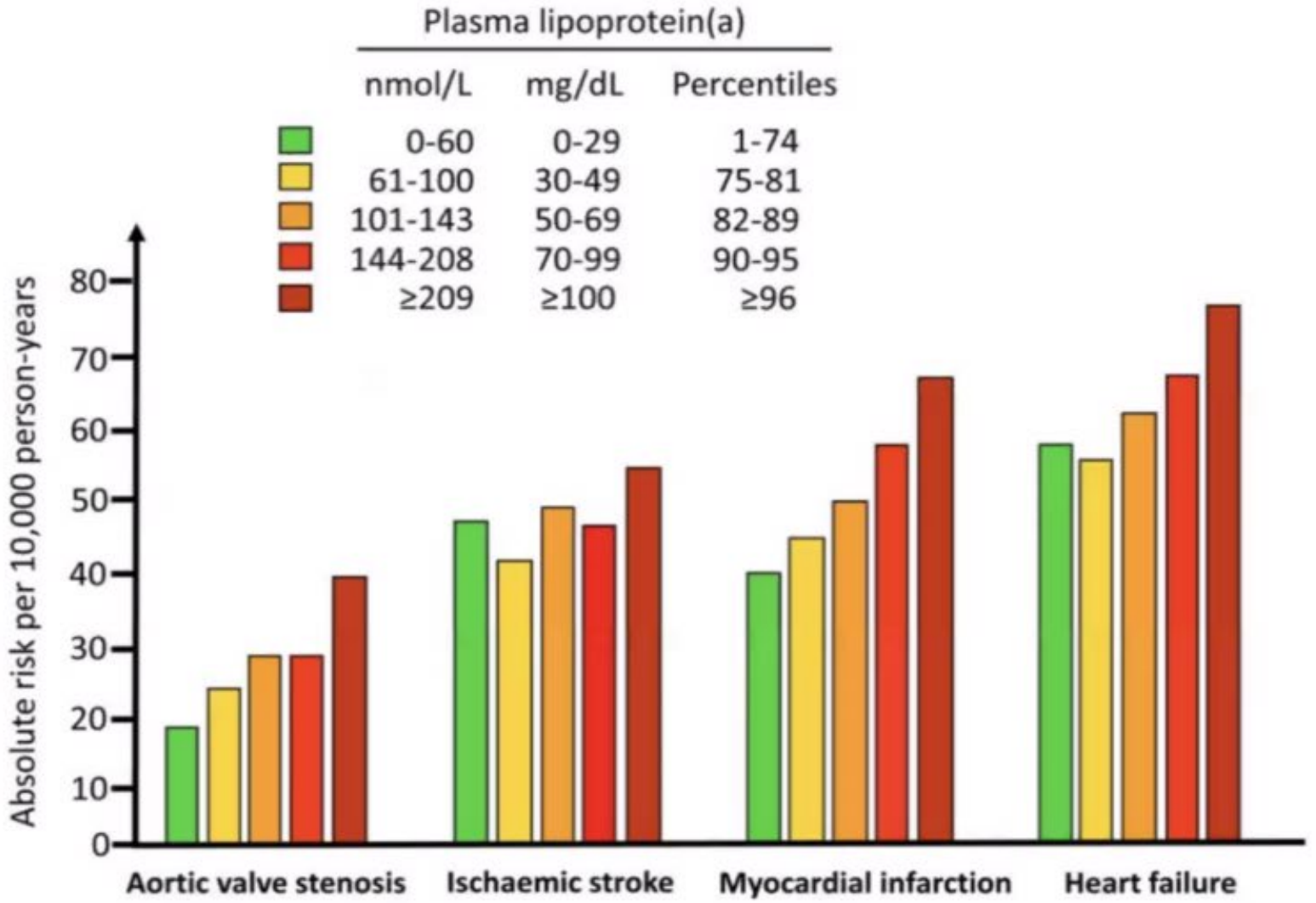
Elevated Lp(a) remains a risk factor for ASCVD even with aggressive LDL-C lowering by statins and nonstatins (proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors, bempedoic acid, and ezetimibe).

Nonetheless, early and more-intensive management of modifiable risk factors, including LDL-C and non–high-density lipoprotein cholesterol (non-HDL-C) levels, is warranted in at-risk patients who have elevated Lp(a), as their risk is potentiated to a greater extent at a given Lp(a) concentration.

Estimates of the incremental reduction in LDL-C needed to mitigate the additional risk posed by elevated Lp(a), based on the patient's age …, have been published ; however, these estimates have not been tested in randomized controlled outcomes trials.

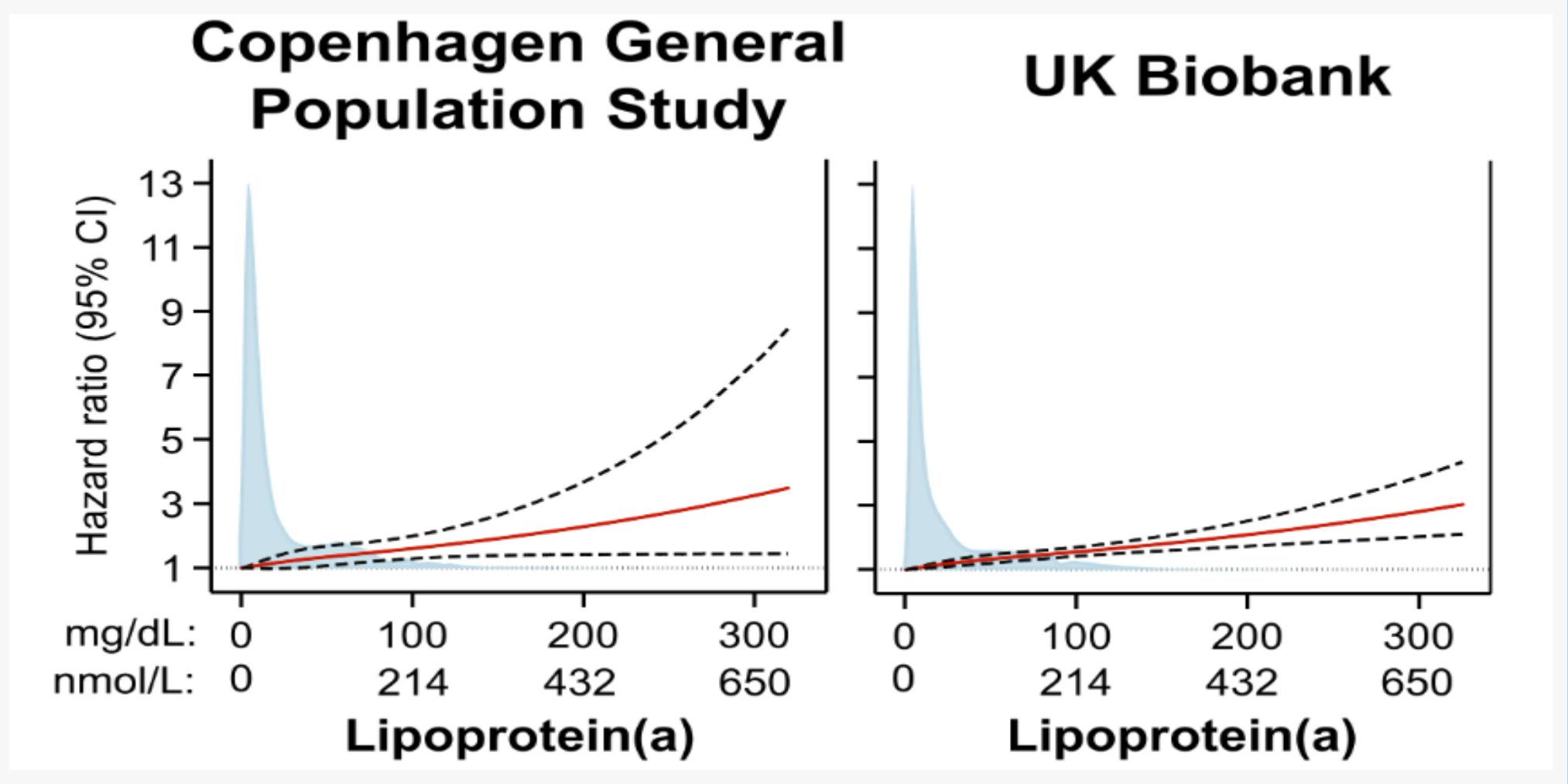
Koschinsky et al, A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.03.001

Risk of clinical outcomes associated with Lp(a)



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

RISK OF AAA BY PLASMA LIPOPROTEIN A



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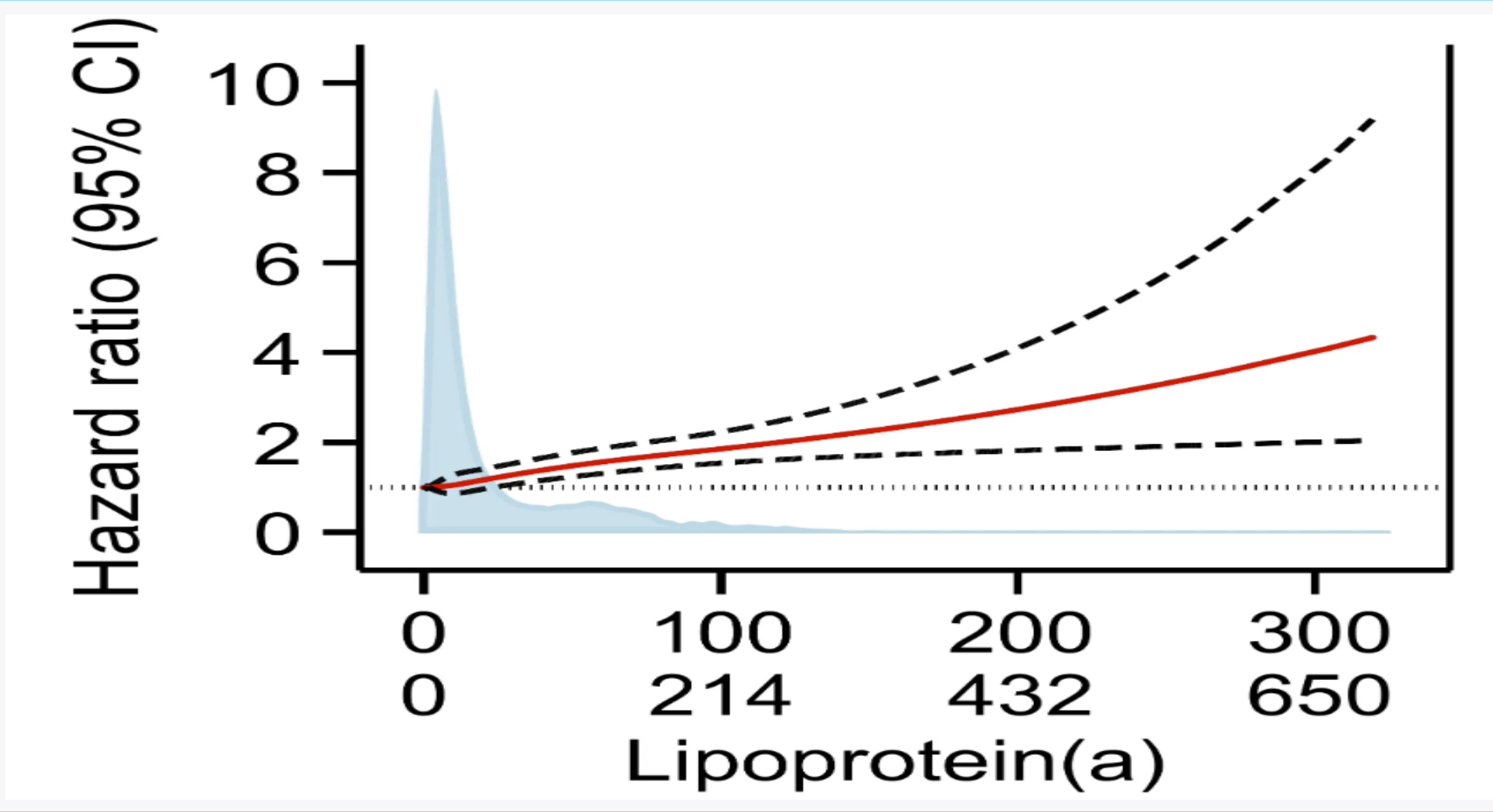
RISK OF AORTIC STENOSIS BY LIPOPROTEIN (A), IN THE COPENHAGEN GENERAL POPULATION STUDY



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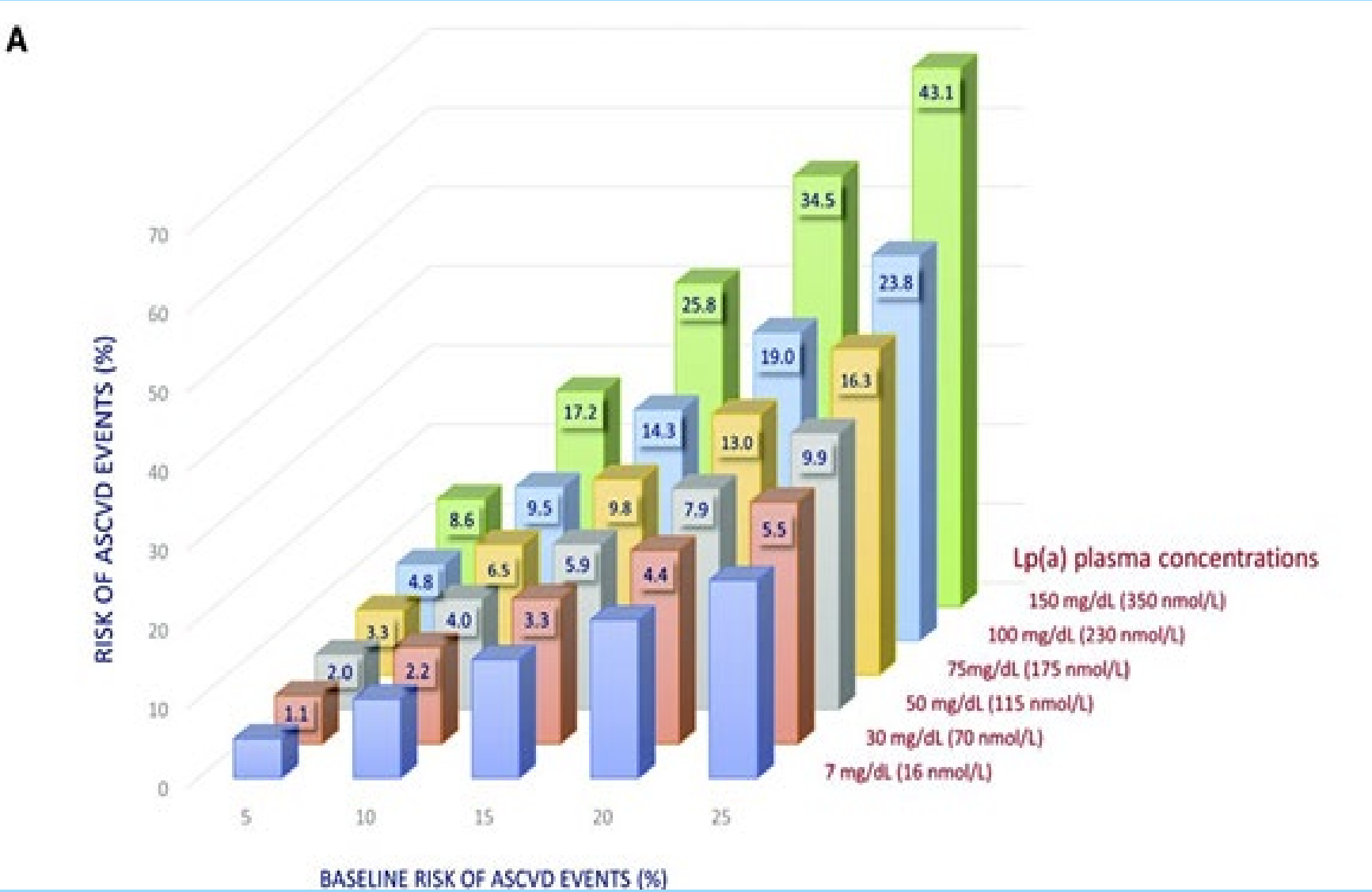
Effect of increasing Lp(a) levels and estimated baseline absolute risk for major cardiovascular events.



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Consensus key points: Lp(a) and clinical outcomes

•Observational and genetic evidence convincingly demonstrates that high Lp(a) concentration is causal for ASCVD, AVS and cardiovascular and all-cause mortality in men and women and across ethnic groups.

• The relation between Lp(a) concentration and these outcomes is continuous; elevated Lp(a) is a risk factor even at very low LDL-C concentration.

• The risk of ischaemic stroke and heart failure increases at higher Lp(a) levels than those associated with the risk of myocardial infarction and AVS. • In children, an Lp(a) >30 mg/dL (>75 nmol/L) is associated with increased risk of (recurrent) arterial ischaemic stroke.

• Lp(a) is not a risk factor for venous thromboembolism

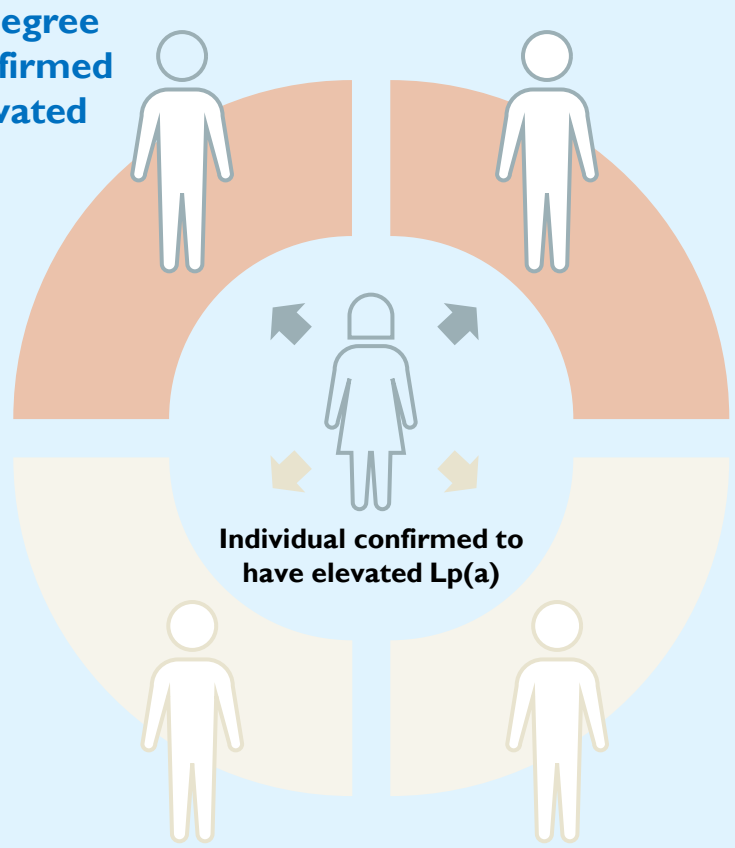
However, whether Lp(a)-specific therapies reduce ASCVD risk in adulthood is an ongoing subject of intensive investigation.

Cascade testing for high Lp(a) is recommended in the settings of FH, family history of (very) high Lp(a), and personal or family history of ASCVD

Florian Kronenberg, Samia Mora, Erik S G Stroes, Brian A Ference, Benoit J Arsenault, Lars Berglund, Marc R Dweck, Marlys Koschinsky, Gilles Lambert, François Mach, Catherine J McNeal, Patrick M Moriarty, Pradeep Natarajan, Børge G Nordestgaard, Klaus G Parhofer, Salim S Virani, Arnold von Eckardstein, Gerald F Watts, Jane K Stock, Kausik K Ray, Lale S Tokgözoğlu, Alberico L Catapano, **Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement, European Heart Journal, Volume 43, Issue 39, 14 October 2022, Pages 3925–3946, https://doi.org/10.1093/eurheartj/ehac361**

ONCE ELEVATED LP(A) IS CONFIRMED, CASCADE SCREENING SHOULD BE CONSIDERED FOR FIRST-DEGREE RELATIVES[1,2]

- Elevated Lp(a) and family history of elevated Lp(a) are both important components of a patient's medical history
- The National Lipid Association recommends cascade screening in first-degree family members of patients with elevated Lp(a) to identify additional individuals at risk who require intervention



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The previously proposed correction factor for Lp(a)-C used to adjust LDL-C calculation may lead to the undertreatment of high-risk patients and therefore should not be used

Although statins may increase Lp(a) levels, concerns about Lp(a) elevation should not be a reason to discourage or discontinue statins

- In high-risk patients with elevated Lp(a) who need additional LDL-C lowering after maximally tolerated statin therapy, a PCSK9 inhibitor may address residual risk from both LDL-C and Lp(a)

- Lipoprotein apheresis was approved by the FDA for use in patients with clinically diagnosed heterozygous familial hypercholesterolemia and either documented coronary artery disease or documented peripheral artery disease who have Lp(a) level ≥60 mg/dL (~150 nmol/L) and LDL-C ≥ 100 mg/dL despite maximally tolerated lipid-lowering therapy

A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice. Koschinsky, Marlys L. et al. Journal of Clinical Lipidology, Volume 18, Issue 3, e308 - e319

Lipoprotein(a) [Lp(a)] is not just about coronary disease

Robust genetic and population data confirm Lp(a) as a causal risk factor across multiple vascular beds

Peripheral Arterial Disease (PAD):

Rising Lp(a) levels show a clear, stepwise association with PAD risk—up to ~3-fold higher risk at extreme concentrations.

Major Adverse Limb Events (MALE):

In patients with PAD, high Lp(a) markedly increases the risk of amputations and repeat revascularizations.

Abdominal Aortic Aneurysm (AAA):

Elevated Lp(a) is consistently associated with higher AAA risk, supported by Mendelian randomization.

Inflammation matters—but doesn't negate Lp(a) risk:

Lp(a)-associated cardiovascular risk persists independently of hsCRP levels, in both primary and secondary prevention.

Clinical takeaway:

Lp(a) identifies residual vascular risk beyond LDL-C and traditional factors—supporting routine measurement and future targeted therapy.

Phase 3 Lp(a)-lowering outcome trials may redefine prevention across coronary and non-coronary vascular disease.

adapted from Pablo Corral MD

What is new since the 2010 EAS consensus statement?

- Strong evidence for a causal association between Lp(a) concentration and cardiovascular outcomes in different ethnicities.
- This association is continuous even at low levels of low-density lipoprotein cholesterol.
- Lp(a) is a new risk factor for aortic valve stenosis.
- Evidence does not support Lp(a) as a risk factor for venous thromboembolism and impaired fibrinolysis.
- Lifelong very low Lp(a) concentrations may associate with diabetes mellitus.
- Lp(a) should be measured at least once in adults.
- A high Lp(a) concentration should be interpreted in the context of other risk factors and absolute global cardiovascular risk, and addressed through intensified lifestyle and risk factor management.
- Specific effective Lp(a)-lowering therapies are in Phase II/III clinical trials.

Florian Kronenberg, Samia Mora, Erik S G Stroes, Brian A Ference, Benoit J Arsenault, Lars Berglund, Marc R Dweck, Marlys Koschinsky, Gilles Lambert, François Mach, Catherine J McNeal, Patrick M Moriarty, Pradeep Natarajan, Børge G Nordestgaard, Klaus G Parhofer, Salim S Virani, Arnold von Eckardstein, Gerald F Watts, Jane K Stock, Kausik K Ray, Lale S Tokgözoğlu, Alberico L Catapano, **Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement, European Heart Journal, Volume 43, Issue 39, 14 October 2022, Pages 3925–3946, https://doi.org/10.1093/eurheartj/ehac361**

GENES LEAD THE WAY: THE ADVANCEMENT OF LIPIDOMICS

- Identification of genetic pathways has lead to bio-technology development of new treatment targets:
- Protein targets- Small molecules
- Human monoclonal antibodies
  - I.E PCSK9 inhibitors
- RNA silencing approaches

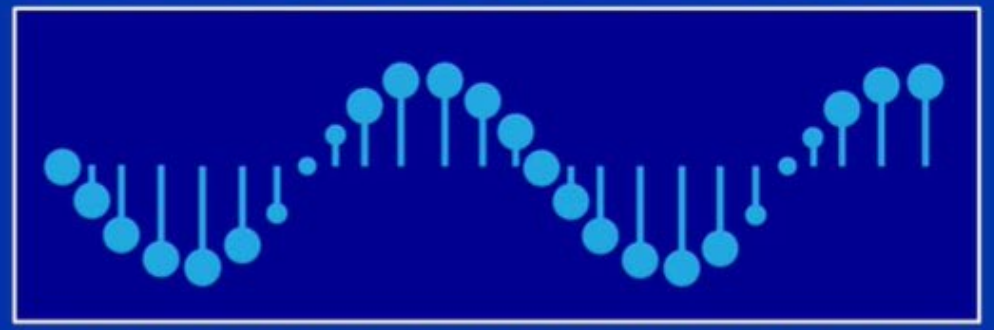
  small interfering RNA

  anti-sense oligonucleotide

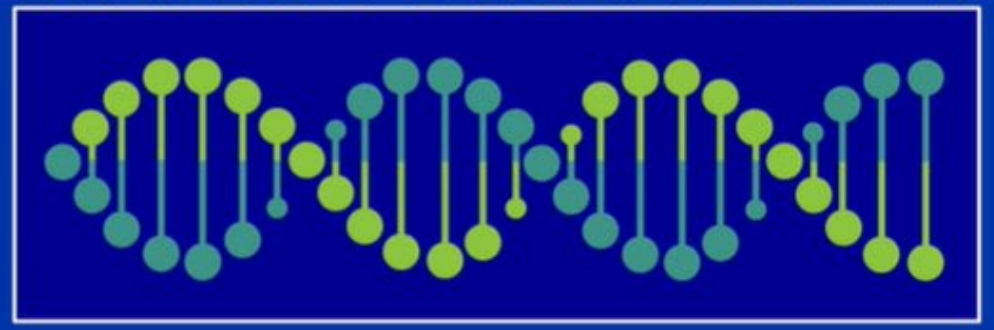
  Gene based editing; CRISPER

Current Approaches: Gene Silencing and Disruptors

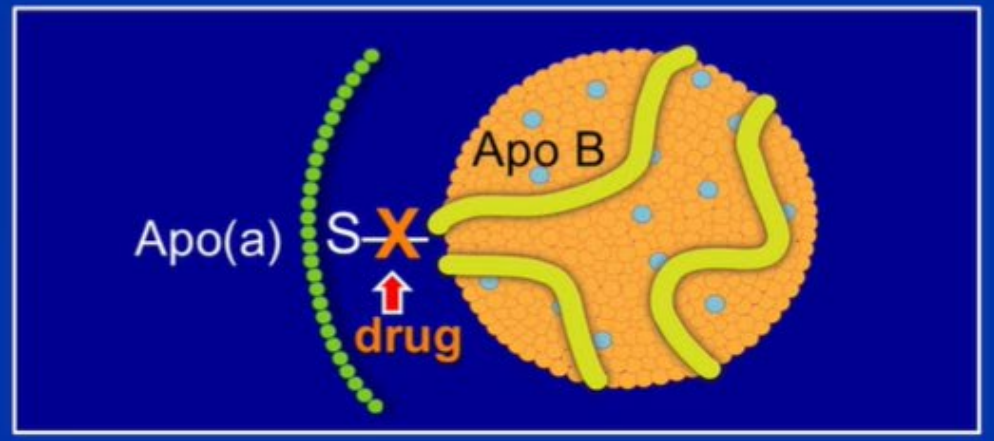
Antisense Oligonucleotide
Single Stranded DNA

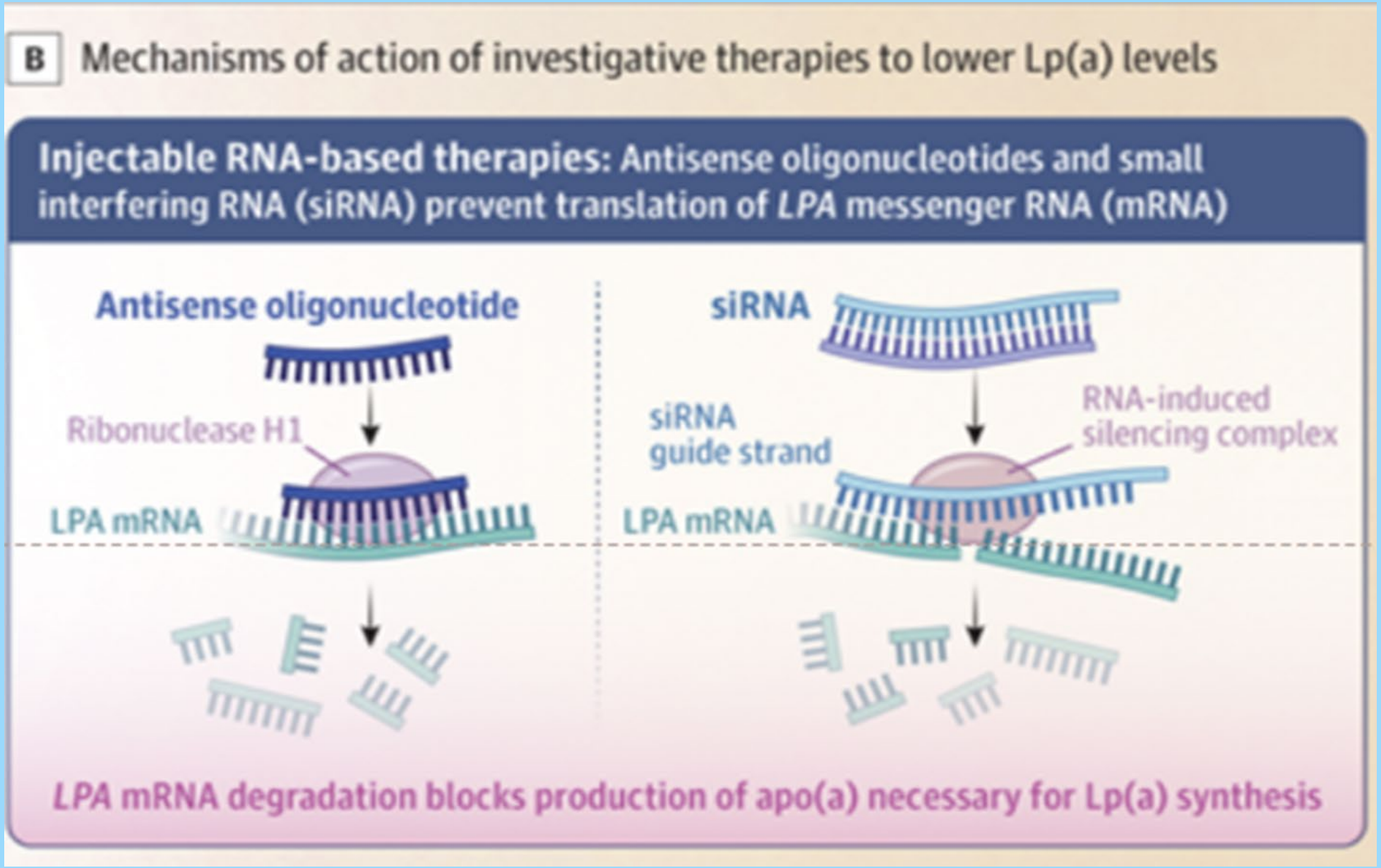


siRNA
Double Stranded RNA

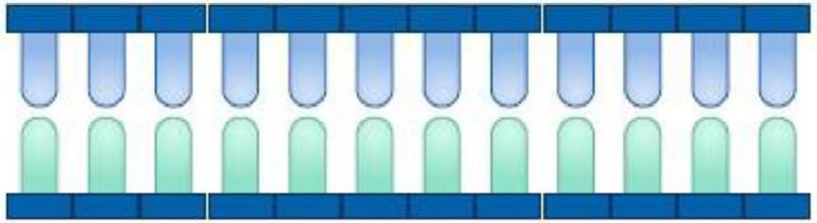


Disruptor: Blocks Association of Apo(a) and Apo B

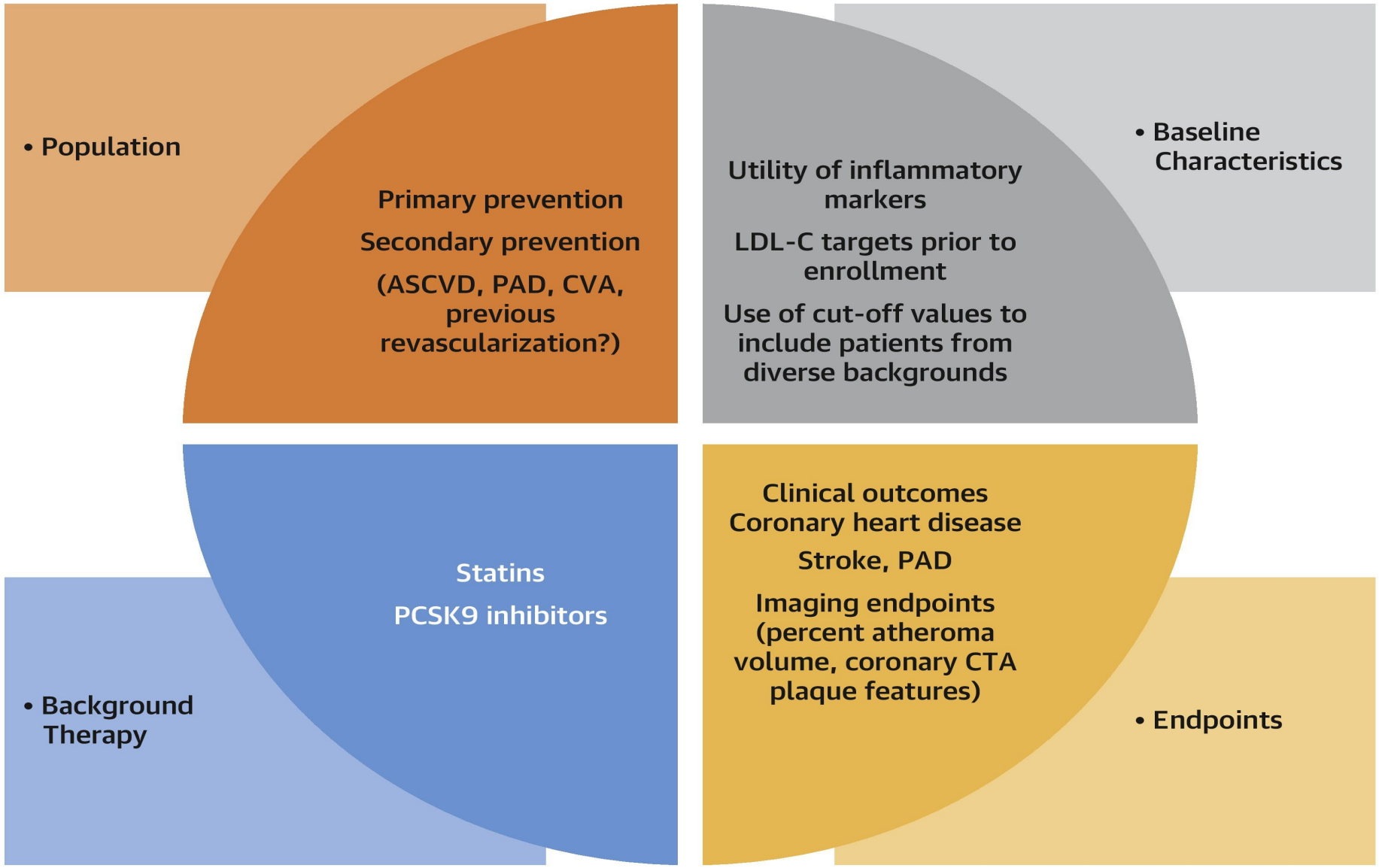




Nicholls SJ, Nissen SE, Fleming C, et al. Muvalaplin, an Oral Small Molecule Inhibitor of Lipoprotein(a) Formation: A Randomized Clinical Trial. *JAMA*. 2023;330(11):1042–1053. doi:10.1001/jama.2023.16503

Antisense oligonucleotide	Small interfering RNA
	
Single stranded	Double stranded
16–20 nucleotides	19–29 nucleotides
Amphipathic (Hydrophilic & hydrophobic)	Hydrophilic
Act in the nucleus	Act in the cytoplasm
Lp(a)-lowering ASOs in development: **Pelacarsen**	Lp(a)-lowering siRNAs in development: **Olpasiran** **Lepodisiran** **Zerlasiran**

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



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

ASCVD = atherosclerotic cardiovascular disease; CTA = computed tomography angiography; CVA = cerebrovascular accident; LDL-C = low-density lipoprotein cholesterol; PAD = peripheral arterial disease; PCSK9 = proprotein convertase subtilisin/kexin type 9

The Lp(a)-lowering effects of currently available therapies.

Agent/technique	Effect on Lp(a)
Procedural therapies	
Lipoprotein apheresis[a]	• ~60%-75% reduction (single session) • ~25%-40% decreased mean interval (weekly or biweekly apheresis)[109]
Pharmacological therapies	
Statins (inhibition of HMG-CoA reductase)	• Do not reduce and may increase Lp(a) concentration from 8.5% to 19.6% depending on the statin[58]
Ezetimibe (cholesterol absorption inhibitor)	• 7% reduction[110] or no effect (monotherapy or combination with a statin)[111]
Niacin (hepatocyte diacylglycerol acyltransferase-2 inhibitor)	• ~10%-20% reduction[112,113]
Alirocumab, evolocumab (anti-PCSK9 mAbs)	• Up to 27% reduction[51,60]
Inclisiran (siRNA PCSK9 inhibitor)	• 21.9% reduction[63]
Bempedoic acid (ACL inhibitor)	• 2.4% reduction[114]
Estrogen (HRT)	• Up to 20% reduction among postmenopausal women[115]
Lomitapide[b] (MTP inhibitor)	• 17% reduction[116]
Evinacumab[b] (anti-ANGPTL3 mAb)	• 16.5% reduction[117]

Pelacarsen: Mechanism of action and Lp(a)-lowering effect
Harpreet S. Bhatia MD, Archna Bajaj MD, Sascha N. Goonewardena MD c, Patrick M. Moriarty MD

Journal of Clinical Lipidology
Volume 19, Issue 5, September–October 2025, Pages 1208-1222

TRIALS OF NOVEL THERAPIES TARGETING LP(A)GENE TRANSCRIPTION VIA SIRNA & GENE TRANSLATION WITH ASO

Study Name, Phase (Therapy)	Therapy Mechanism	Therapy Formulation	Population	Outcome
OCEAN(a) DOSE,[a] phase 2 (olpasiran [AMG 890])	siRNA that reduces Lp(a) synthesis in the liver	SC injection of 10, 75, or 225 mg every 12 weeks, or 225 mg every 24 weeks	• 281 participants • 18-80 years of age • Lp(a) >150 nmol/L • Evidence of ASCVD	• Percent change in Lp(a) level at 36 weeks • Preliminary results: percent reduction of 70.5% to 110.5%
SLN360,[b] phase 2 (SLN360)	Double-stranded siRNA targeting *LPA* mRNA	SC injection of 30, 100, 300, or 600 mg vs. placebo	• BMI 18-32 kg/m2 • Lp(a) level >125 nmol/L • At high risk of ASCVD events	• Change of Lp(a) level from baseline
ORION-11,[c] phase 3 (inclisiran)	siRNA that inhibits PCSK9 synthesis	SC injection of 300 mg on day 1 and day 90, then every 6 months vs. placebo	• ≥18 years of age • LDL-C level ≥70 mg/dL • History of ASCVD	• Secondary outcome evaluating effect of inclisiran on Lp(a) level • Preliminary results: percent reduction of Lp(a) level by 28.5%
Lp(a)HORIZON,[d] phase 3 (pelacarsen [TQJ230])	ASO against Apo(a)	SC injection of 80 mg monthly vs. placebo	• 8,323 participants • 18-90 years of age • Lp(a) level ≥70 mg/dL • Established CVD	• Time to occurrence of MACE in 4 years

Apo(a) = apolipoprotein(a); ASCVD = atherosclerotic cardiovascular disease; ASO = antisense oligonucleotide; BMI = body mass index; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); LPA = lipoprotein(a) gene; MACE = major adverse cardiovascular events; mRNA = messenger RNA; PCSK9 = proprotein convertase subtilisin/kexin 9; SC = subcutaneous; siRNA = small interfering RNA.

Clinical Trial Design for Lipoprotein(a)-Lowering Therapies: *JACC* Focus Seminar 2/3
Authors: Waqas A. Malick, Sascha N. Goonewardena, Wolfgang Koenig, and Robert S. Rosenson Robert.rosenson@mssm.edu**AUTHORS INFO & AFFILIATIONS**
Publication: JACC Volume 81, Number 16

Trials of Novel therapies targeting Lp(a)gene transcription via SiRNA & gene translation with ASO

AKCEA-APO(a)-LRx,[e] phase 2 (pelacarsen [ISIS 681257])	ASO against Apo(a)	SC injection of 20, 40, or 60 mg every 4 weeks; 20 mg every 2 weeks; or 20 mg every week vs. placebo for 6-12 months	• 286 participants • 18-10 years of age • Lp(a) level ≥60 mg/dL • Diagnosed CVD • Must be on standard-of-care preventive therapy for CVD risk factors other than elevated Lp(a) levels	• Percent change from baseline Lp(a) level • Preliminary results: dose-dependent reduction ranging 35-80%
TQJ230,[f] phase 3 (pelacarsen [TQJ230])	ASO against Apo(a)	SC injection of 80 mg monthly vs. placebo	• 60 participants • Established ASCVD • Currently undergoing lipoprotein apheresis for isolated Lp(a)	• Superiority of pelacarsen over placebo in reducing the rate of lipoprotein apheresis sessions
KRAKEN,[g] phase 2 (LY3473329) muvalaplin	siRNA-based approach targeting Apo(a)	Daily oral dose vs. placebo	• 233 participants • Lp(a) level ≥175 nmol/L • At high risk of ASCVD	• Percent change from baseline Lp(a) level to week 12
LY3819469,[h] phase 2 (LY3819469) zerlasiran	siRNA-based approach targeting Apo(a)	SC injections in four different doses vs. placebo	• 254 participants • >40 years of age • Lp(a) level ≥175 nmol/L at screening	• Percent change from baseline in time-averaged Lp(a) level

Apo(a) = apolipoprotein(a); ASCVD = atherosclerotic cardiovascular disease; ASO = antisense oligonucleotide; BMI = body mass index; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); LPA = lipoprotein(a) gene; MACE = major adverse cardiovascular events; mRNA = messenger RNA; PCSK9 = proprotein convertase subtilisin/kexin 9; SC = subcutaneous; siRNA = small interfering RNA.

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Approaches that result in lowering of both Lp(a) and LDL

Lipoprotein Apheresis (LA):

Reduced LDL and Lp(a) with significant reduction of future CVD events

94% over mean tx period of 48 months

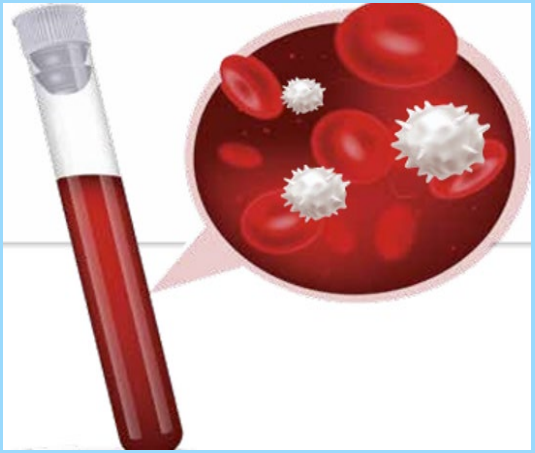
Prospective 5 year follow-up Lpa was reduced by 68%

PCSK9 inhibitors

reduce LDL-C by 43% to 64%

lower Lp(a) by 20% to 30%

ODYSSEY OUTCOMES and FOURIER outcomes trials showed enhanced benefit from PCSK9 inhibitor therapy in patients with elevated Lp(a) despite more modest (16-22%) Lp(a) percent lowering in this group



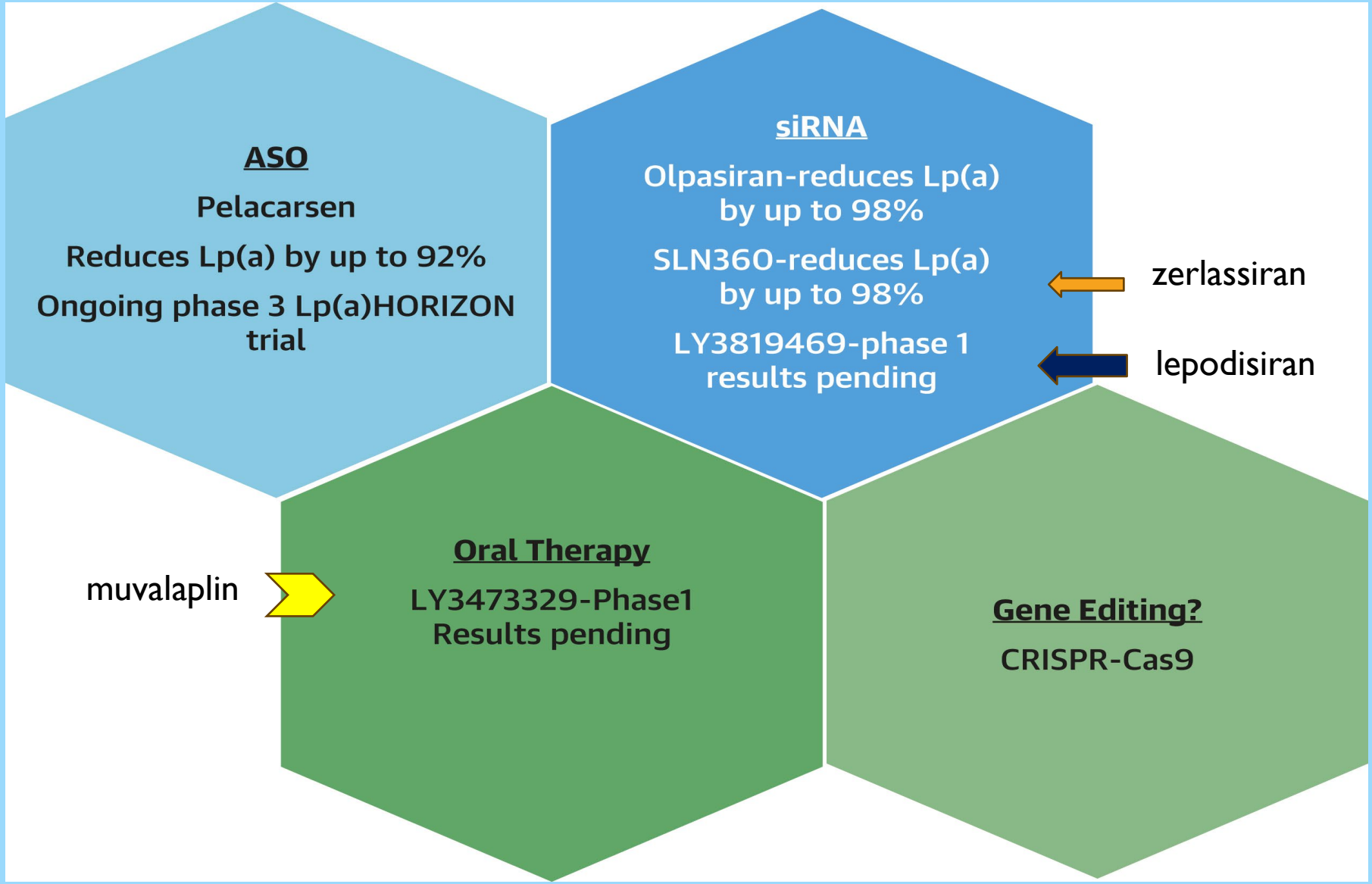
Inclisiran

a small interfering RNA molecule that targets PCSK9 messenger RNA, has been evaluated in people with high risk for CVD and elevated LDL-C.

Inclisiran reduced Lp(a) by 25.6% in the ORION-10 trial evaluating inclisiran in patients with ASCVD and by 18.6% in the ORION-11 trial that enrolled subjects with an ASCVD equivalent

Adapted from AHA Lp(a):A Toolkit for Health Care Professionals

Emerging Therapeutics for Lp(a)



Pelacarsen is an antisense oligonucleotide (ASO) currently being tested in a phase 3 clinical trial. Olpasiran, a small-interfering RNA (siRNA), has begun testing in a phase 3 clinical trial. SLN360 (Muvalaplin) and LY3819469 (Zerlasiran) are other siRNAs being evaluated. Oral therapy with LY3473329 (muvalaplin) has also completed phase 3 enrollment. Gene editing is a therapy on the horizon.

Lp(a) = lipoprotein(a); Lp(a)HORIZON = Assessing the Impact of Lipoprotein (a) Lowering with TQJ230 on Major Cardiovascular Events in Patients With CVD trial.

Clinical Trial Design for Lipoprotein(a)-Lowering Therapies: *JACC* Focus Seminar 2/3 April 2023
Authors: Waqas A. Malick, Sascha N. Goonewardena, Wolfgang Koenig, and Robert S. Rosenson Robert.rosenson@mssm.eduAUTHORS INFO & AFFILIATIONS
Publication: JACC Volume 81, Number 16

Emerging Therapies that specifically and effectively lower Lp(a)

There are five compounds; pelacarsen, olpasiran, lepodisiran, zerlasiran, and muvalaplin that are in Phase 3 clinical trials.

There is one in phase 2 trial HRS-5346 as an oral to reduce Lp(a).

Pelacarsen
an antisense oligonucleotide (ASO) that targets apo(a) messenger RNA and lowers Lp(a) by ~80%.

This compound is currently being tested in a Phase 3 cardiovascular outcomes trial (Lp(a) HORIZON; NCT04023552). 8323 participants; 42 countries
randomized, double-blind, placebo-controlled trial

Key inclusion criteria: Lp(a) ≥ 70 mg/dL; pre-existing ASCVD
Primary endpoint: time to expanded MACE (Lp(a) ≥ 70 mg/dL or ≥ 90 mg/dL)

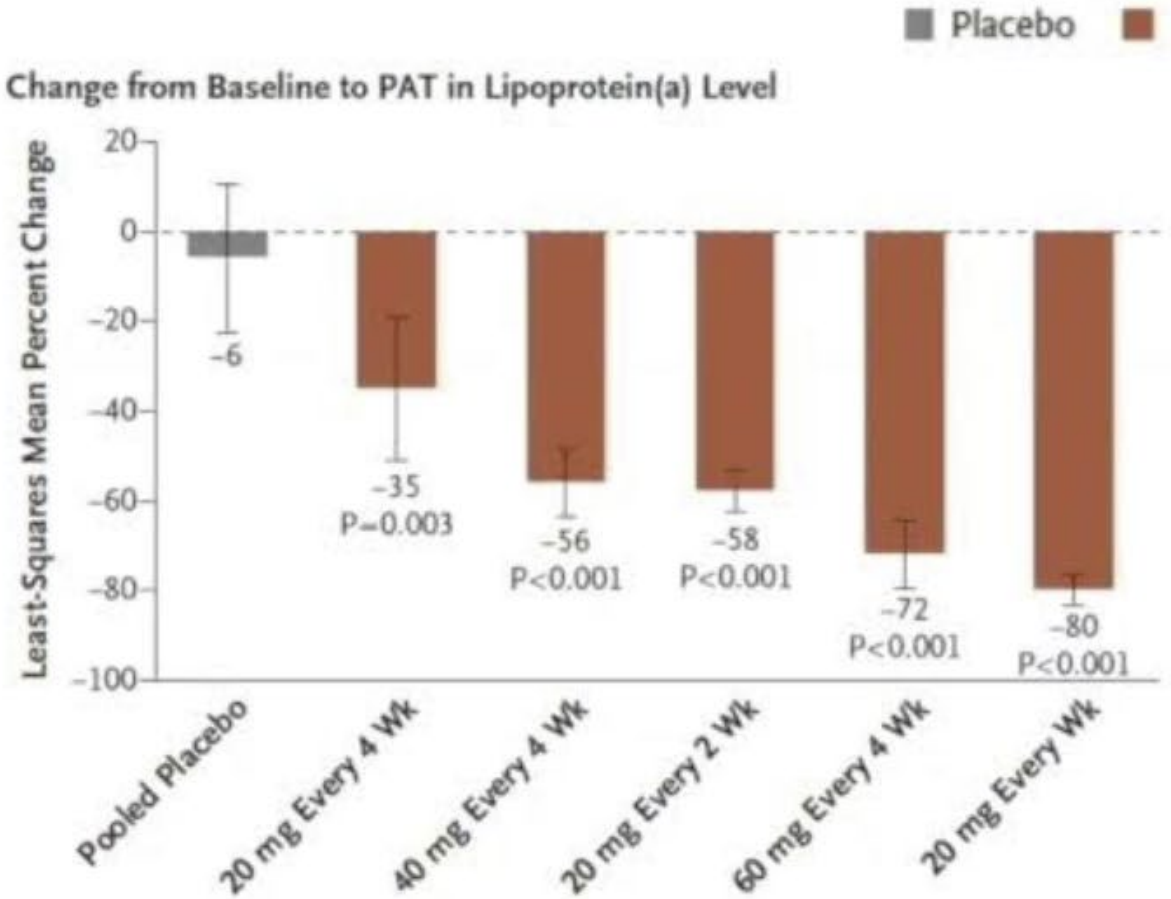
Anticipated study completion date last qtr 2026 to 1st qtr 2027

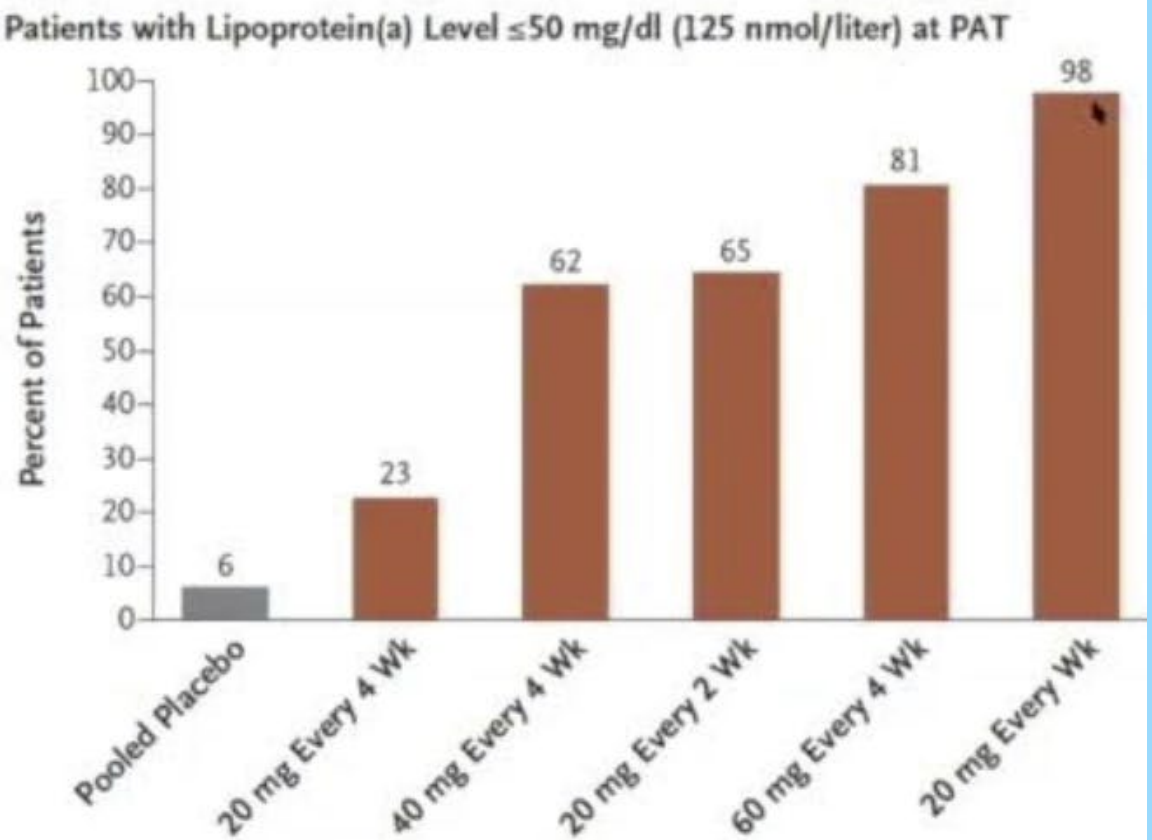
Adapted from AHA Lp(a):A Toolkit for Health Care Professionals

Pelacarsen – mean 80% reduction in Lp(a)

98% of patients reached goals of <50 mg/dL (<125 nmol/L)

No significant differences in liver or renal function or platelet count





Tsimikas et al N Engl J Med 2020;382:244-55

Emerging Therapies that specifically and effectively lower Lp(a)

Olpasiran

a silencing RNA compound (siRNA) that targets apo(a) messenger RNA and lowers Lp(a) by >90%.

This compound is currently being tested in a Phase 3 cardiovascular outcomes trial (OCEAN(a); NCT05581303) 7297 participants; randomized, double-blind, placebo-controlled trial

Key inclusion criteria: Lp(a) ≥ 200 nmol/L; history of ASCVD

Primary endpoint: time to CHD death, myocardial infarction, or urgent coronary revascularization

Anticipated study completion date 2026-2027

Adapted from AHA Lp(a):A Toolkit for Health Care Professionals

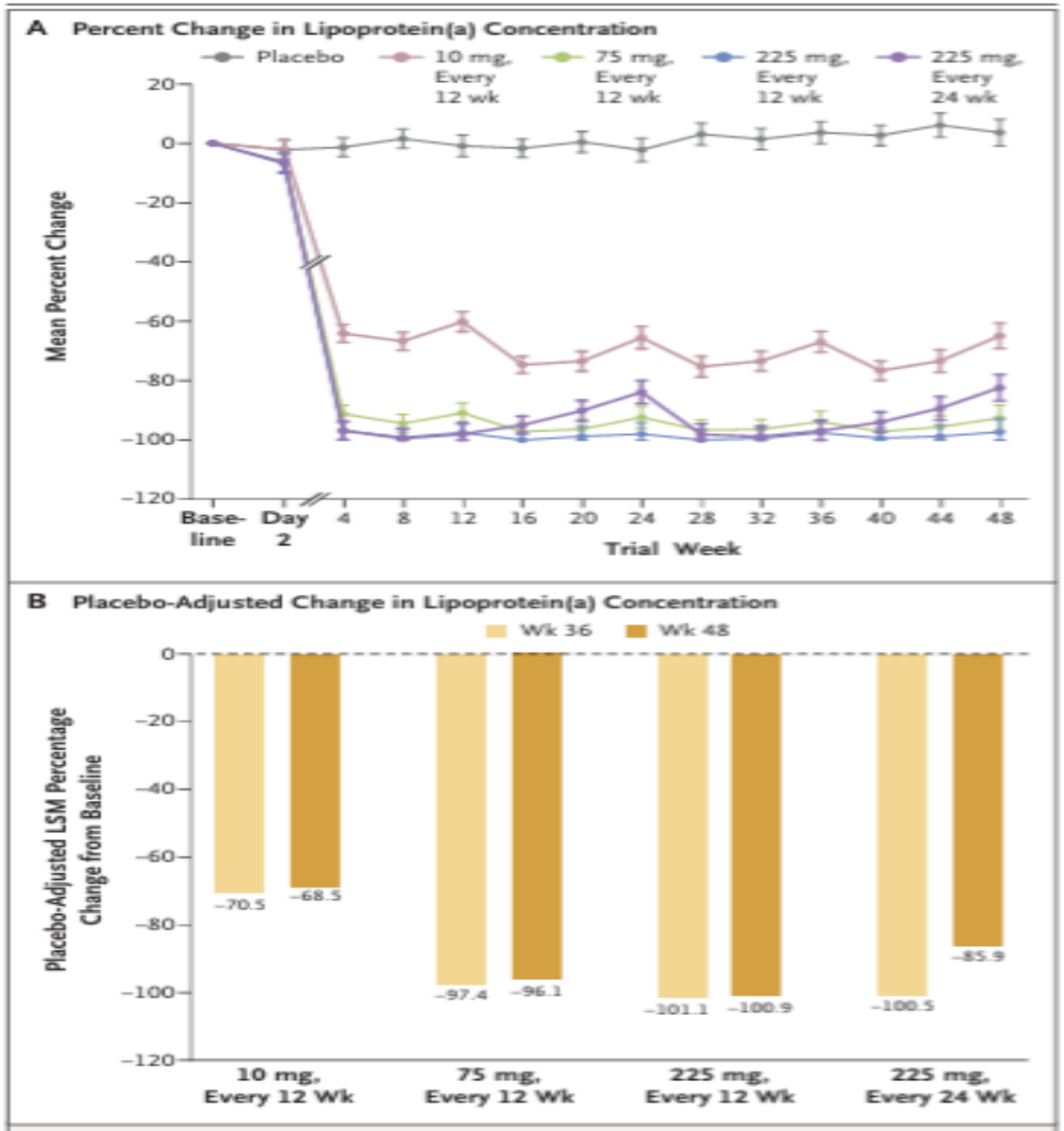


Figure 1. Percent Change in Lipoprotein(a) Concentration and the Placebo-Adjusted Mean Percent Change from Baseline in the Lipoprotein(a) Concentration with Olpasiran at Weeks 36 and 48.

Panel A shows the mean percent change in the lipoprotein(a) concentration over time according to trial group. I bars indicate 95% confidence intervals. Panel B shows the placebo-adjusted least-squares mean (LSM) percent change from baseline in the lipoprotein(a) concentration for the four olpasiran dose groups at weeks 36 and 48.

Emerging Therapies that specifically and effectively lower Lp(a)

Lepodisaran

a silencing RNA compound long acting SiRNA that targets apo(a) messenger RNA.

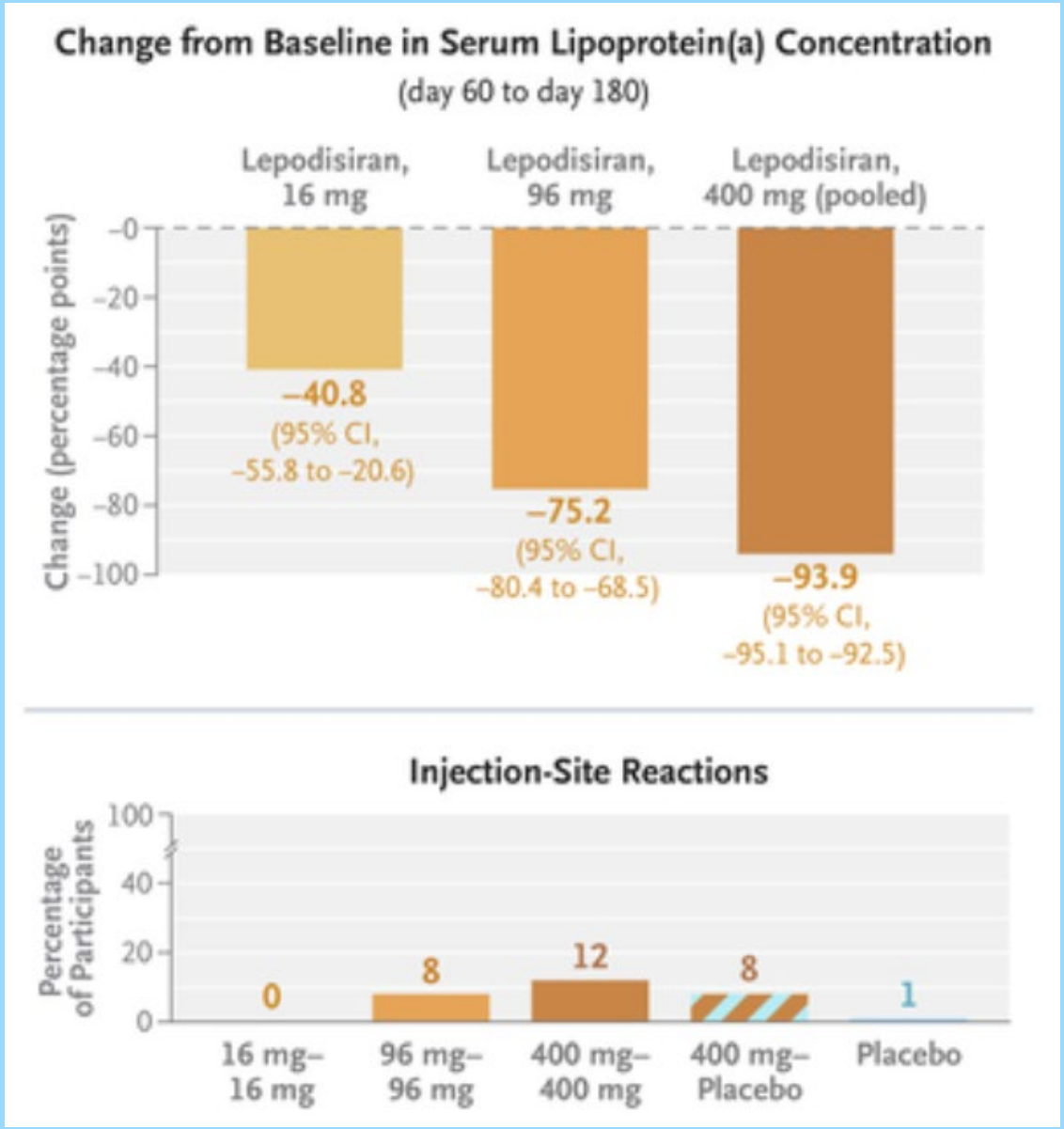
It is being tested in a Phase 3 cardiovascular outcomes trial (ACCLAIM-Lp(a) ;
NCT06292013 (recently ended recruiting) and ALPACA trial- their phase 2 trial)

68% patients had CV risk, 48% has CAD, 31% prior MI
74% on statin, 33% on ezetimibe, 6% on PCSK9

Post 1 year Lp(a) remained < 91% lower that initial measurement

anticipated study completion date of March 2029.

Adapted from AHA Lp(a):A Toolkit for Health Care Professionals



Lilly's ALPACA trial lepodisiran reduced levels of genetically inherited heart disease risk factor, lipoprotein(a), by nearly 94% from baseline at the highest tested dose in adults with elevated levels

March 30, 2025

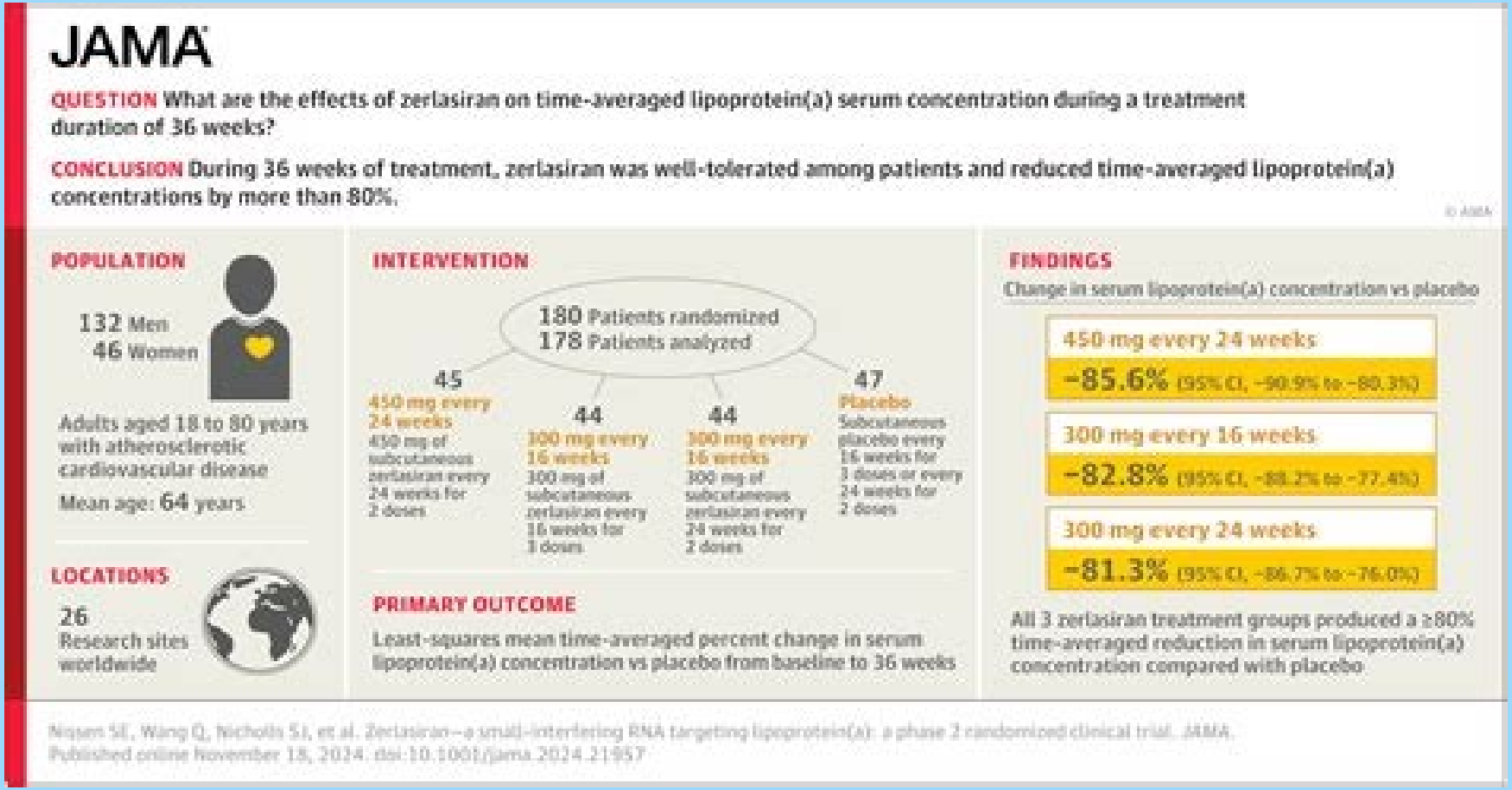
In Phase 2 ALPACA results, lepodisiran significantly reduced levels of genetically inherited cardiovascular risk factor, with some patients sustaining reductions for nearly 1.5 years.

These data were presented at the American College of Cardiology 2025 Scientific Sessions and simultaneously published in the New England Journal of Medicine (NEJM)

On Going ALPACA Phase 3 Randomized Double-Blind Placebo-Controlled Study to Investigate the Effect of Lepodisiran on the Reduction of Major Adverse Cardiovascular Events in Adults with Elevated Lipoprotein(a) who have Established Atherosclerotic Cardiovascular Disease or Are at Risk for a First Cardiovascular Event ACCLAIM-Lp(a)

Emerging Therapies that specifically and effectively lower Lp(a)

zerlasiran, (SLN360)another siRNA compound against apo(a) mRNA Phase 2 completed, phase 3 ongoing
up to 96% Lp(a) lowering



JAMA

QUESTION What are the effects of zerlasiran on time-averaged lipoprotein(a) serum concentration during a treatment duration of 36 weeks?

CONCLUSION During 36 weeks of treatment, zerlasiran was well-tolerated among patients and reduced time-averaged lipoprotein(a) concentrations by more than 80%.

POPULATION

132 Men
46 Women

Adults aged 18 to 80 years with atherosclerotic cardiovascular disease

Mean age: 64 years

LOCATIONS

26
Research sites worldwide

INTERVENTION

180 Patients randomized
178 Patients analyzed

45
450 mg every 24 weeks
450 mg of subcutaneous zerlasiran every 24 weeks for 2 doses

44
300 mg every 16 weeks
300 mg of subcutaneous zerlasiran every 16 weeks for 3 doses

44
300 mg every 16 weeks
300 mg of subcutaneous zerlasiran every 24 weeks for 2 doses

47
Placebo
Subcutaneous placebo every 16 weeks for 3 doses or every 24 weeks for 2 doses

PRIMARY OUTCOME

Least-squares mean time-averaged percent change in serum lipoprotein(a) concentration vs placebo from baseline to 36 weeks

FINDINGS

Change in serum lipoprotein(a) concentration vs placebo

450 mg every 24 weeks
−85.6% (95% CI, −90.9% to −80.3%)

300 mg every 16 weeks
−82.8% (95% CI, −88.2% to −77.4%)

300 mg every 24 weeks
−81.3% (95% CI, −86.7% to −76.0%)

All 3 zerlasiran treatment groups produced a ≥80% time-averaged reduction in serum lipoprotein(a) concentration compared with placebo

Nissen SE, Wang Q, Nicholls SJ, et al. Zerlasiran—a small-interfering RNA targeting lipoprotein(a): a phase 2 randomized clinical trial. JAMA. Published online November 18, 2024. doi:10.1001/jama.2024.21957

Adapted from AHA
Lp(a):A Toolkit for Health Care Professionals

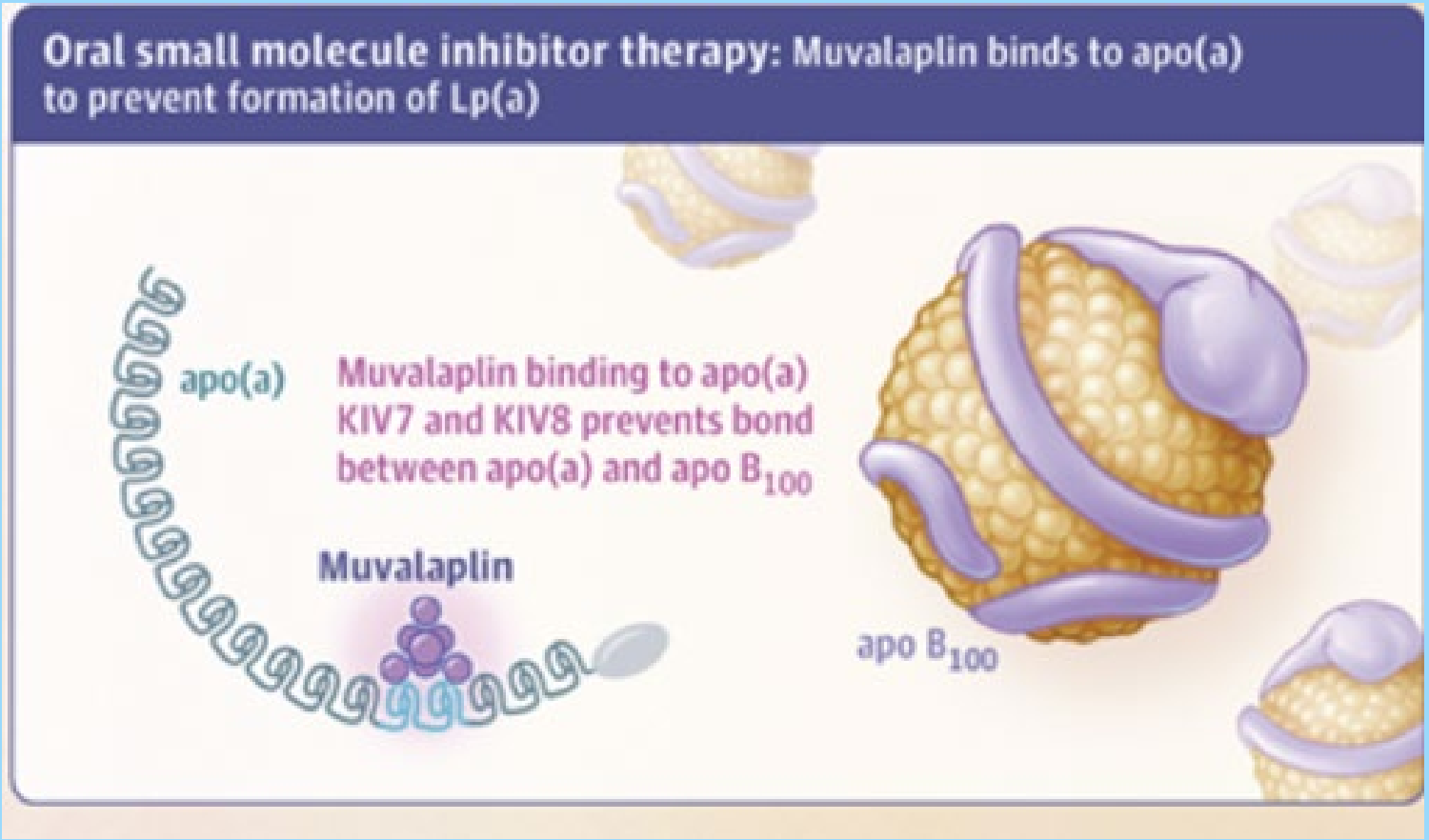
Emerging Therapies that specifically and effectively lower Lp(a)

muvalaplin

a small molecule that disrupts Lp(a) formation preventing bond between apo(a) & apoB100

Completed Phase 2, ongoing phase 3 trial – Kraken trial (NCT05563246), oral agent

up to 65% Lp(a) reduction observed



Adapted from AHA Lp(a):A Toolkit for Health Care Professionals

Nicholls SJ, Nissen SE, Fleming C, et al. Muvalaplin, an Oral Small Molecule Inhibitor of Lipoprotein(a) Formation: A Randomized Clinical Trial. *JAMA.* 2023;330(11):1042–1053. doi:10.1001/jama.2023.16503

JAMA®

QUESTION Can the oral small molecule lipoprotein(a) inhibitor muvalaplin reduce lipoprotein(a) levels in patients with elevated lipoprotein(a) concentrations at high risk of cardiovascular events?

CONCLUSION Muvalaplin was well tolerated and produced substantial reductions in lipoprotein(a) levels in patients at high risk of cardiovascular events. The effect of muvalaplin on cardiovascular events requires further investigation.

POPULATION

157 Men
76 Women

Patients with lipoprotein(a) concentrations ≥175 nmol/L and at high risk of cardiovascular events

Median age: **66** years

LOCATION

43
Sites in Asia, Australia, Europe, Brazil, and the US

INTERVENTION

233 Patients randomized
232 Patients analyzed

- **34** Muvalaplin, 10 mg/d
- **63** Muvalaplin, 60 mg/d
- **68** Muvalaplin, 240 mg/d
- **67** Placebo

All groups received 4 oral tablets once daily for 12 weeks

PRIMARY OUTCOME

Placebo-adjusted percentage change in lipoprotein(a) from baseline to week 12, measured by an intact lipoprotein(a) assay (assay 1) and by an apolipoprotein-based assay (assay 2)

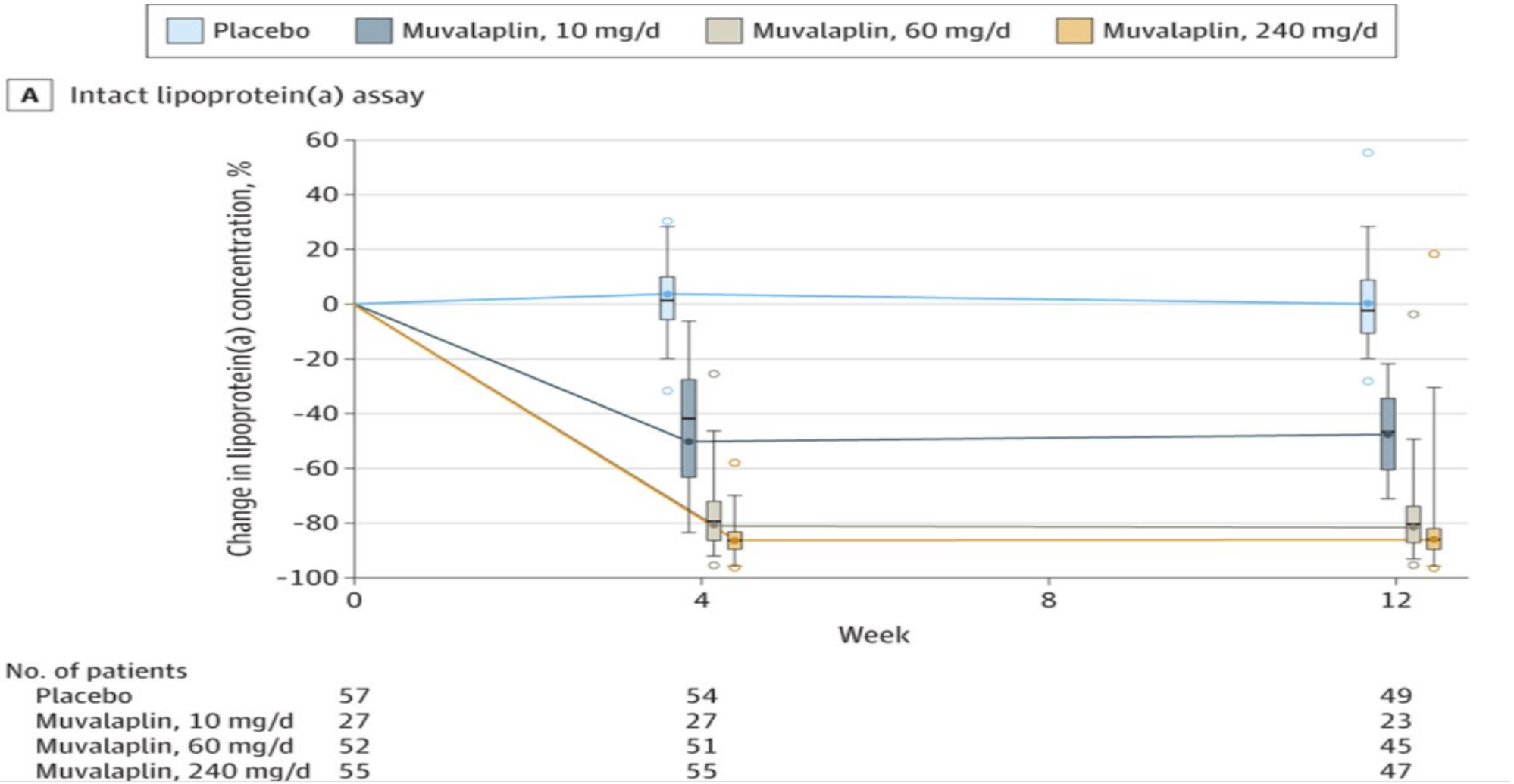
FINDINGS

Placebo-adjusted reductions in lipoprotein(a) by assay 1 and assay 2

Muvalaplin, 10 mg/d	Assay 1: **47.6%** (95% CI, 35.1% to 57.7%) Assay 2: **40.4%** (95% CI, 28.3% to 50.5%)
Muvalaplin, 60 mg/d	Assay 1: **81.7%** (95% CI, 78.1% to 84.6%) Assay 2: **70.0%** (95% CI, 65.0% to 74.2%)
Muvalaplin, 240 mg/d	Assay 1: **85.8%** (95% CI, 83.1% to 88.0%) Assay 2: **68.9%** (95% CI, 63.8% to 73.3%)

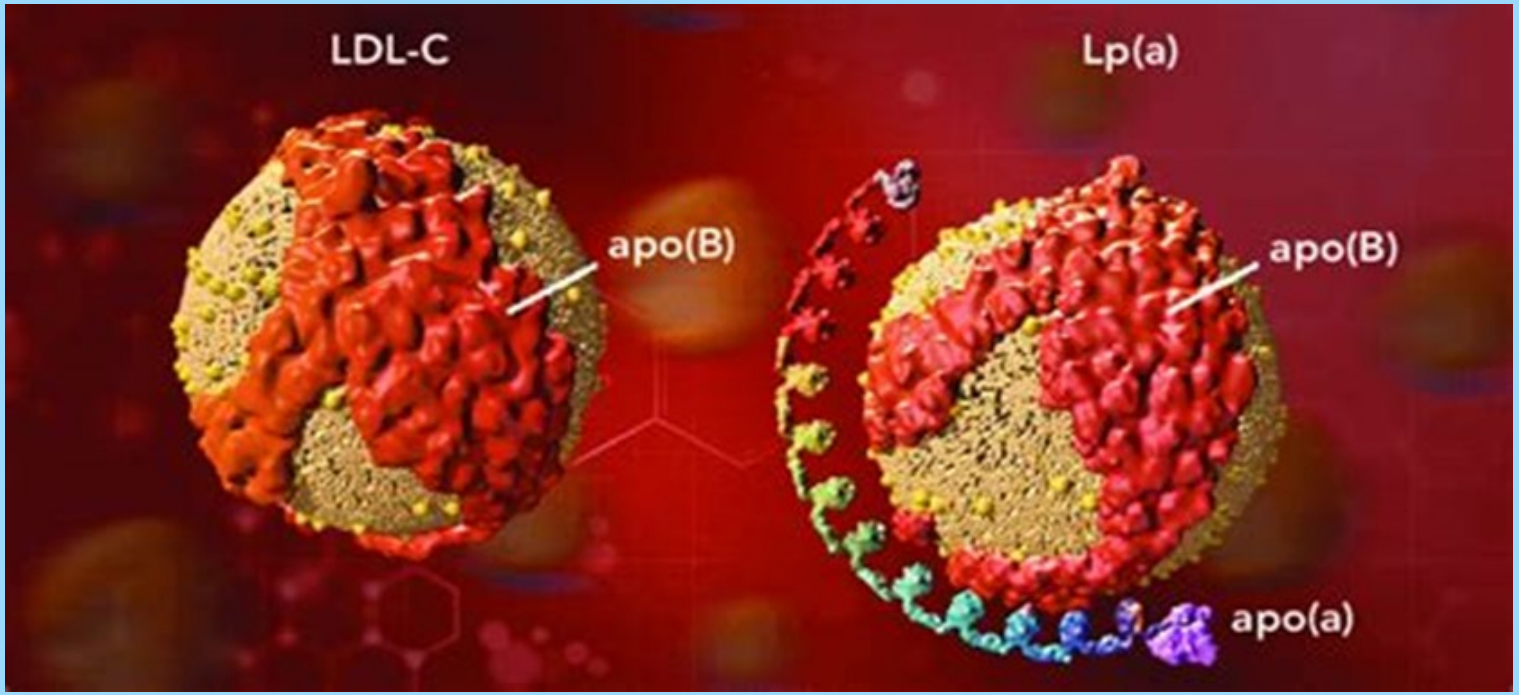
Muvalaplin at all dosages reduced lipoprotein(a) compared with placebo using both assays.

Nicholls SJ, Ni W, Rhodes GM, et al. Oral muvalaplin for lowering of lipoprotein(a): a randomized clinical trial. *JAMA*. Published online November 18, 2024. doi:10.1001/jama.2024.24017



Nicholls SJ, Ni W, Rhodes GM, et al. Oral Muvalaplin for Lowering of Lipoprotein(a): A Randomized Clinical Trial. JAMA. 2025;333(3):222–231. doi:10.1001/jama.2024.24017

SUMMARY
CLOSING THOUGHTS



LIPOPROTEIN (A)

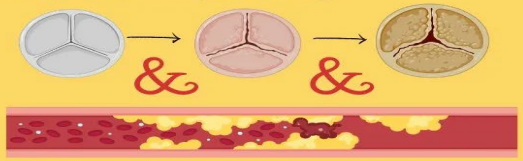
Creator: @CFAndersenMD, Editors: @Gurleen_Kaur96, @AmitGoyalMD, @RichardAFerraro, @Dr_DanMD

Biochemistry

Lp (a) is a LDL-like particle bound to Apo(a) and ApoB

Manifestations

1) Calcific aortic stenosis (dose-dependent)
2) ASCVD (possibly dose-dependent)

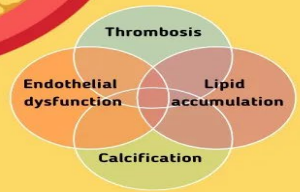


Genetics

Lp (a) levels are 90% genetically determined and remain stable throughout an individual's lifetime

20-25% globally believed to have Lp (a) ⩾ 50 mg/dL, levels noted to raise CV risk (1)

Pathophys



Lp (a) carries oxidized phospholipids into injured vessels and AV causing:
1) Endothelial dysfunction
2) Lipid accumulation,
3) Calcification
4) Thrombosis

Therapeutics

Niacin, fibrates, vitamin C, diet	Ineffective and/or confer ↑ side effect profile	+/-
PCSK-9 inhibitors	Moderate Lp (a) ↓ of 15-25%	+
⁘ **Pelacarsen, Olpasiran**	Significant Lp (a) ↓ of up to 80%	+++

⁘ *Pelacarsen is an anti-sense oligonucleotide currently in Phase 3 clinical trial, HORIZON-Lp (a)*

Future Directions

Nucleic acid-based therapies to target Lp (a) mRNA, including anti-sense oligonucleotides (pelacarsen) and small-interfering RNA (olpasiran)

Additional trials assessing effect of ↓ Lp (a) on ASCVD and AS (e.g. HORIZON-Lp(a), OCEAN(a)-DOSE)

When to measure Lp (a) ?

1) ASCVD not explained by major risk factors
2) Family history of premature ASCVD (2)
3) Everyone , esp those at risk

Clinical evaluation of high Lp (a)

Lp (a) levels ⩾ 50 mg/dL are considered an ASCVD ⁘⁘ risk-enhancing factor which may warrant therapy (2)

(1) 2019 ESC/EAS guidelines for the management of dyslipidaemias
(2) 2018 ACC/AHA Cholesterol Guidelines

⁘⁘ Of note, there remains no direct clinical evidence of Lp (a) reduction conferring improved mortality or ↓ CV outcomes.

Horizon trial – peilcarsen (ASO)

Ocean(a) – olparsiran (siRNA)

SLN360- (siRNA) zerlasiran

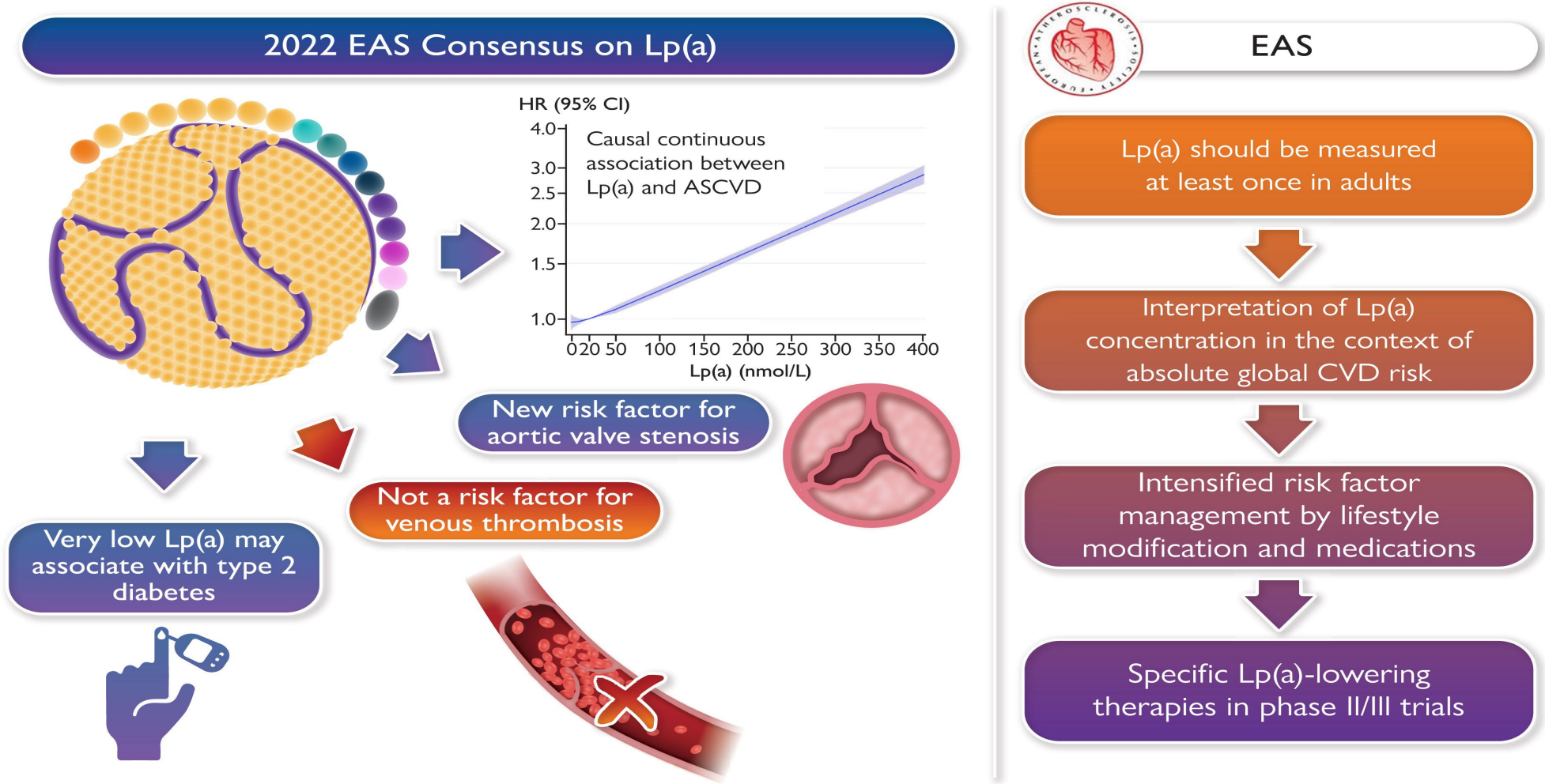
Orion-11 Inclisiran (siRNA)

AKCEA APO(a)-LRx pelicarsen

KRAKEN LY3473329 siRNA muvalaplin

Alpaca trial Zelasiran, siRNA

ACCLAIM-Lp(a) – Lepodisiran- siRNA



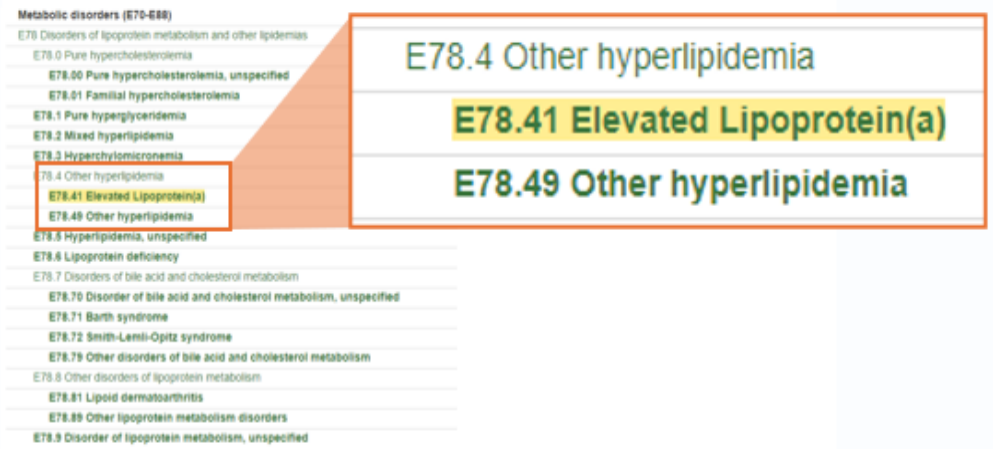
Florian Kronenberg, Samia Mora, Erik S G Stroes, Brian A Ference, Benoit J Arsenault, Lars Berglund, Marc R Dweck, Marlys Koschinsky, Gilles Lambert, François Mach, Catherine J McNeal, Patrick M Moriarty, Pradeep Natarajan, Børge G Nordestgaard, Klaus G Parhofer, Salim S Virani, Arnold von Eckardstein, Gerald F Watts, Jane K Stock, Kausik K Ray, Lale S Tokgözoğlu, Alberico L Catapano, **Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement, European Heart Journal, Volume 43, Issue 39, 14 October 2022, Pages 3925–3946, https://doi.org/10.1093/eurheartj/ehac361**

Elevated Lp(a) Is Recognized by ICD-10 Codes and a CPT Code

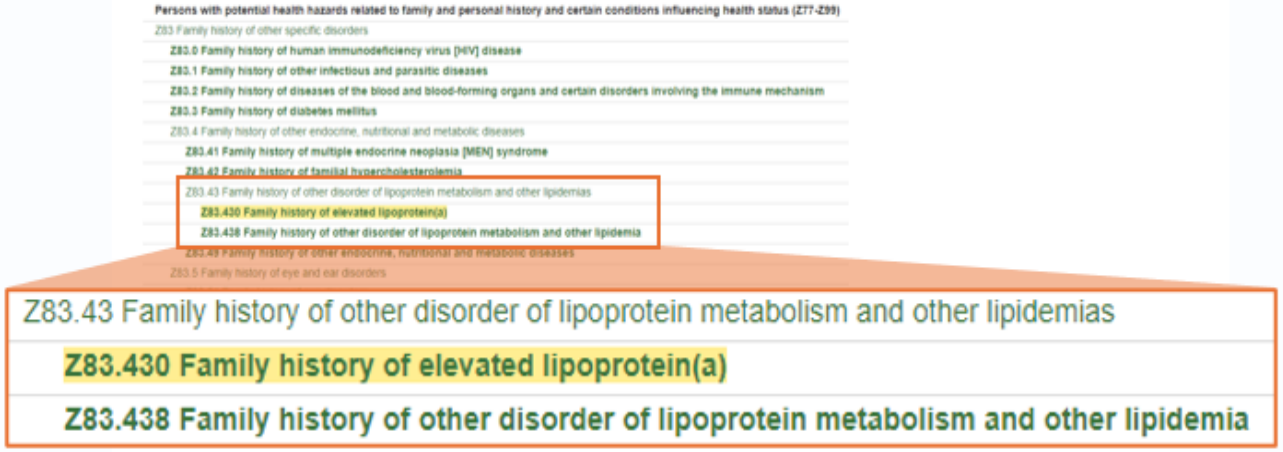
- **ICD-10 codes E78.41 and Z83.430 identify patients with elevated Lp(a) and family history[1]**
- **CPT code 83695 is assigned for Lp(a) blood testing[2]**

ICD-10-CM[3]

Chapter 4: Endocrine, Nutritional, and Metabolic Diseases



Chapter 21: Factors Influencing Health Status and Contact With Health Services



The availability of these ICD-10 codes may help:

- **Support the justification for Lp(a) testing[4]**
- **Identify elevated Lp(a) as an independent/causal and genetic risk factor for CVD[5,6]**
- **Enhance diagnoses of patients at risk of Lp(a)-mediated disease[7]**
- **Allow familial/inherited risk to be assigned[7]**

CPT, Current Procedural Terminology; CVD, cardiovascular disease; ICD-10-CM, International Classification of Diseases, 10th revision, Clinical Modification; Lp(a), lipoprotein(a).

1. Engler RJ et al. *Fed Pract.* 2019;36(suppl 7):S19-S31. **2.** Bhatia HS et al. *J Am Heart Assoc.* 2023;12(18):e031255. **3.** Centers for Disease Control and Prevention. ICD-10-CM browser tool. Accessed July 4, 2024. https://icd10cmtool.cdc.gov/?fy=FY2024 **4.** Wilson DP et al. *J Clin Lipidol.* 2022;16(5):e77-e95. **5.** Tsimikas S. *J Am Coll Cardiol.* 2017;69(6):692-711. **6.** Reyes-Soffer G et al. *Arterioscler Thromb Vasc Biol.* 2022;42(1):e48-e60. **7.** Tsimikas S et al. *J Am Coll Cardiol.* 2018;71(2):177-192.

A Focused Update to the 2019 NLA Scientific Statement on Use of Lipoprotein(a) in Clinical Practice

Measure Lp(a) at least Once in all Adults and Selected High-risk Children

Action Items to Consider if High Risk:

- More intensive risk factor management, including LDL-C (Lp(a) is a risk-enhancing factor)
- Cascade screening
- Lifestyle modifications
- Therapies such as statin, PCSK9 inhibitor, asprin; apheresis if severe

Authors: Marlys Koschinsky, PhD, Archna Bajaj, MD, MSCE, Michael Boffa, PhD, Dave Dixon, PharmD, CLS, FNLA, Keith Ferdinand, MD, Samuel Gidding, MD, Edward Gill, MD, Terry Jacobson, MD, MNLA, Erin Michos, MD, MHS, Maya Safarova, MD, PhD, Daniel Soffer, MD, Pam Taub, MD, Michael Wilkinson, MD, Don Wilson, MD, Christie Ballantyne, MD

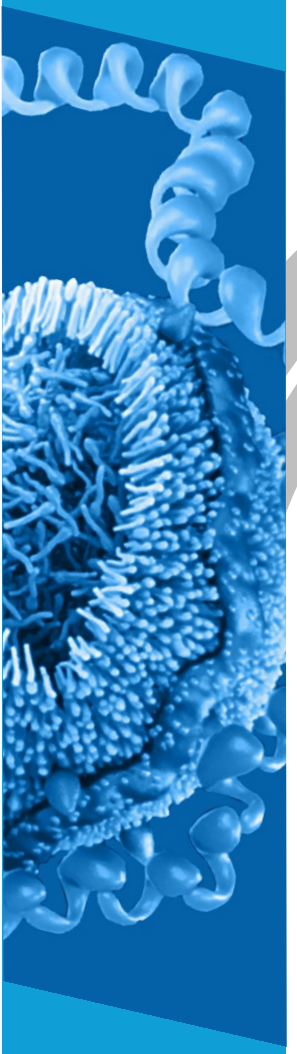
A Focused Update to the 2019 NLA Scientific Statement on Use of Lipoprotein(a) in Clinical Practice

Recommendations to Consider Offering to Patients

1. Lifestyle modification
2. Statins
3. Ezetimibe
4. PCSK9-directed therapies
5. Aspirin
6. Lipoprotein apheresis

7. New emerging treatments in phase 3 trials

Patient Case Summary and Next Steps



Patient has likely been exposed to elevated levels of Lp(a) since early childhood.[1]

Black individuals and women are more likely to have elevated Lp(a).[2]

The patient has elevated Lp(a) and a family history of premature MI, which translate to a higher risk of MI and ASCVD.[3]

HCP should order an Lp(a) test for this patient based on US guidelines and scientific statements.[4]

As there are no approved pharmacotherapies to reduce Lp(a), the patient should be managed through a risk-based prevention approach and control of their modifiable risk factors.[5,6]

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, CV disease; HCP, health care professional; Lp(a), lipoprotein(a); MI, myocardial infarction.

1. Ciffone N et al. *Am Heart J Plus*. 2024;38:100350. **2.** Shapiro MD et al. *J Clin Lipidol*. 2025;19(1):28-38. **3.** Hedegaard BS et al. *J Am Coll Cardiol*. 2022;80(21):1998-2010. **4.** Reyes-Soffer G et al. *Am J Prev Cardiol*. 2024;18:100651. **5.** Kronenberg F. *Curr Atheroscler Rep*. 2024;26(3):75-82. **6.** Ciffone N et al. *Am Heart J Plus*. 2024;38:100350.

2025 — A Year of New Insights in Lp(a) Science

❤️ Lp(a) drives atherosclerosis events
Elevated Lp(a) levels were associated with continuously increased risk of recurrent atherosclerotic cardiovascular disease events, irrespective of sex and ethnicity, highlighting the unmet need for Lp(a) lowering therapy in diverse populations.

❤️ Therapeutic Insights
Further Phase 2 data supported the efficacy and safety of Lp(a) targeting agents, and recruitment to major Phase 3 cardiovascular outcomes trials of Lp(a) lowering therapies gathered pace

❤️ Making clinical trials more inclusive
Breaking down the barriers for inclusion of typically underrepresented populations in cardiovascular clinical trials can pay off, as shown by the rapid, successful recruitment to the Lp(a)FRONTIERS EXPANSION trial.

🔬 Understanding Lp(a) Variability
Researchers found that major fluctuations in Lp(a) levels in individuals were mainly due to technical issues rather than biological fluctuations, underscoring the need for optimal quality control in laboratory measurement.

📊 Broader Evidence from Earlier 2025 Studies
Earlier in the year, studies reported that:

- Lp(a) testing is cost effective in high-income countries.
- Waist-to-hip ratio modifies Lp(a) cardiovascular risk.
- Inflammatory pathways may influence Lp(a) risk, and
- apo(a) isoform size affects Lp(a) response to lipid-lowering therapy.

📈 Overall, 2025 was a year of validation, clinical insights, and forward-looking evidence — moving us closer to better understanding, management, and ultimately treatment of elevated Lp(a) across diverse populations. Read more on >> https://lpaforum.org/

The key questions that remain unanswered are:

•In the race to find Lp(a) level-lowering therapies, will reduced levels translate to reduced CV risk in randomized placebo-controlled trials?

•Which standardized assay(s) for measurement of Lp(a) level should be used globally?

•Should there be a threshold for risk prediction and treatment?

•Should future therapy target all persons with elevated Lp(a) levels irrespective of demographics?

•Should a subset of people with added risk (perhaps individuals in persistent inflammatory states) be started on therapy irrespective of ASCVD risk?

•In risk stratification, should there be different cutoffs for different race/ethnic groups?

•Given its bidirectional relationship with CRP, is there a role for anti-inflammatory agents in therapy?

Clinical Trial Design for Lipoprotein(a)-Lowering Therapies: *JACC* Focus Seminar 2/3
Authors: Waqas A. Malick, Sascha N. Goonewardena, Wolfgang Koenig, and Robert S. Rosenson Robert.rosenson@mssm.edu**AUTHORS INFO & AFFILIATIONS**
Publication: JACC Volume 81, Number 16

A Focused Update to the 2019 NLA Scientific Statement on Use of Lipoprotein(a) in Clinical Practice

Conclusion:

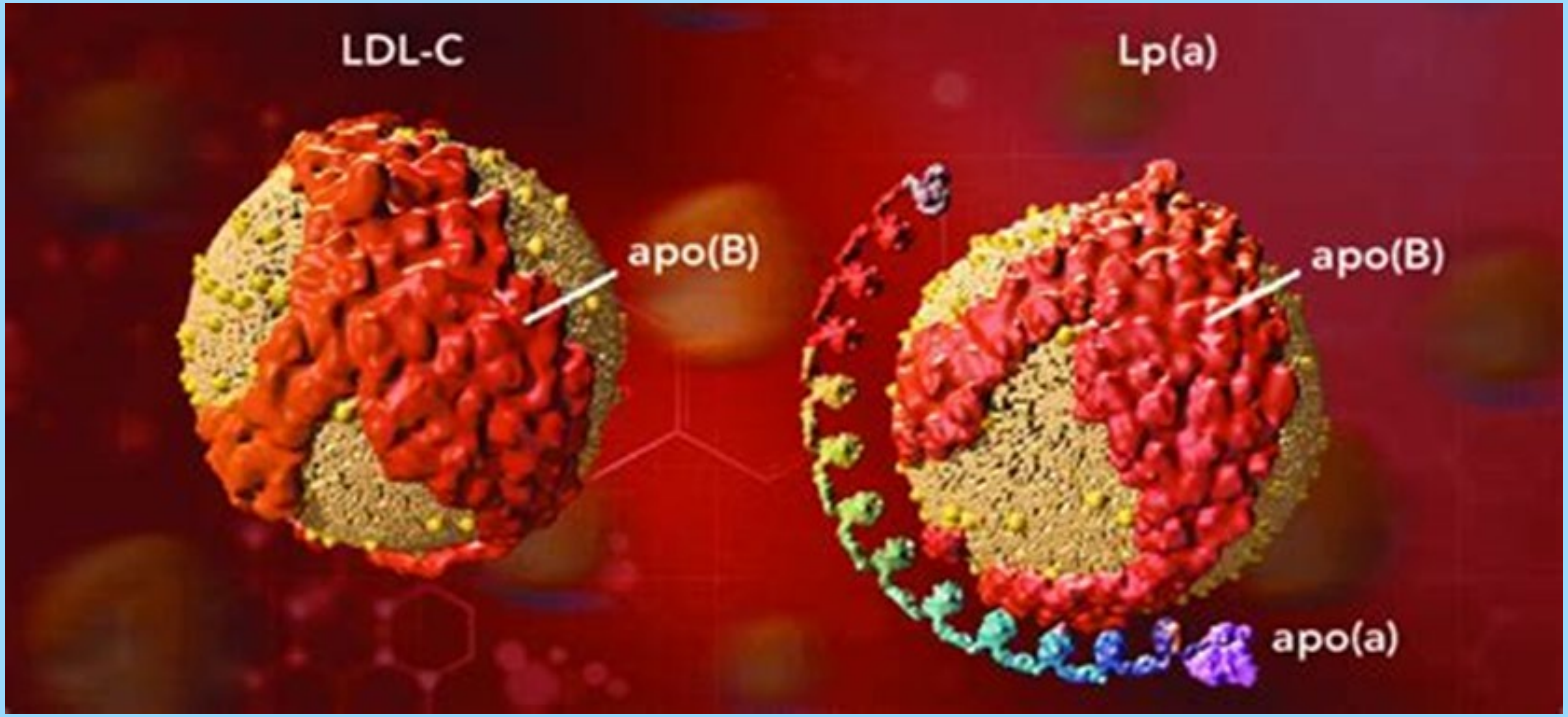
While specific Lp(a)-lowering therapies are not currently available, elevated Lp(a) is actionable now.

Early and intensive risk factor management can be implemented in patients with elevated Lp(a) while considering their absolute global lifetime CVD risk and their magnitude of Lp(a) elevation.

As such, Lp(a) level should be measured at least once in all adults to identify individuals with high Lp(a) levels.

Authors: Marlys Koschinsky, PhD, Archna Bajaj, MD, MSCE, Michael Boffa, PhD, Dave Dixon, PharmD, CLS, FNLA, Keith Ferdinand, MD, Samuel Gidding, MD, Edward Gill, MD, Terry Jacobson, MD, MNLA, Erin Michos, MD, MHS, Maya Safarova, MD, PhD, Daniel Soffer, MD, Pam Taub, MD, Michael Wilkinson, MD, Don Wilson, MD, Christie Ballantyne, MD

THANK YOU



Albert A Lopez DO FASPC FACP

- The relationship between Lp(a) level and cardiovascular disease risk is continuous and log-linear
- Rather than a single dichotomous cutpoint defining a risk threshold, Lp(a) levels represent a continuum of cardiovascular disease risk spanning low, intermediate, and high risk
- Individuals with Lp(a) levels <75 nmol/L (30 mg/dL) may be considered low risk, individuals with Lp(a) levels ≥ 125 nmol/L (50 mg/dL) may be considered high risk, and individuals with Lp(a) levels in the "gray zone" between 75 and 125 nmol/L (30–50 mg/dL) are at intermediate risk and may warrant repeat measurement
- Lp(a) risk categories apply across races and ethnicities
- Lp(a) should be measured at least once in every adult for cardiovascular risk assessment
- Lp(a) should be measured and reported in nmol/L; Lp(a) values should not be converted between mg/dL and nmol/L using a fixed conversion factor
- The previously proposed correction factor for Lp(a)-C used to adjust LDL-C calculation may lead to the undertreatment of high-risk patients and therefore should not be used
- Although statins may increase Lp(a) levels, concerns about Lp(a) elevation should not be a reason to discourage or discontinue statins
- In high-risk patients with elevated Lp(a) who need additional LDL-C lowering after maximally tolerated statin therapy, a PCSK9 inhibitor may address residual risk from both LDL-C and Lp(a)
- Lipoprotein apheresis was approved by the FDA for use in patients with clinically diagnosed heterozygous familial hypercholesterolemia and either documented coronary artery disease or documented peripheral artery disease who have Lp(a) level ≥ 60 mg/dL (~ 150 nmol/L) and LDL-C ≥ 100 mg/dL despite maximally tolerated lipid-lowering therapy

Please cite this article as: Koschinsky et al, A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.03.001

With Federica Fogacci and Giuseppe Cicero we state the case that
testing for Lipoprotein (a) [Lp(a)] is not a dilemma but a mandate.

If ye seek, ye shall find in your practice a surprising number of individuals with higher Lp(a) concentrations.

I have heard from respected peers that one time universal testing of this causal risk factor for atherosclerotic events and aortic stenosis is not warranted because we have no proven therapies to treat elevations.

I respectfully but strongly disagree for 3 major reasons that inform my conversations with patients. 1) Those with Lp(a) elevation should be encouraged to manage aggressively other risk factors. 2) As Lp(a) is so strongly determined genetically, I discuss cascade screening with patients, so that their offspring and sibs can be informed and choose to heighten their own preventive measures. 3) I tell those with high Lp(a) "Help is on the way."

There are now multiple novel therapeutics that can lower Lp(a) effectively, and large scale outcome studies currently in progress will determine safety of two (now 5) of these agents, and their efficacy in event reduction.

We need further studies of such agents in those who have not sustained a prior myocardial infarction, and following aortic valve endpoints as well. But we will have initial safety and efficacy information about Lp(a) reduction in short order that will provide an evidence base for our management strategies and shared decision making with our patients.

J Clin Lipidol 2025; 19:1520-1522

Central Illustration: Clinician Awareness, Testing, and Treatment for Lipoprotein(a): Results from a Large US National Survey

2002

US clinicians, 5% lipid specialists

AWARENESS

agree Lp(a) is a significant risk factor for CVD

77% agree ↑ risk stratification

75% agree ↑ patient engagement

TESTING

Cardiologists VS Primary care physicians

1.56x more likely to support Lp(a) testing for premature ASCVD

1.63x more likely to support testing for FHx of premature ASCVD

TREATMENT

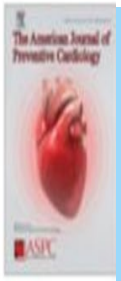
Most likely to prescribe Lp(a)-targeted therapy with proven CVD benefit :

51% Recurrent CVD

47% Premature CVD

Lp(a) testing enhances risk assessment and patient engagement
Premature/recurrent CVD patients are most likely to receive testing and therapy

American Journal of Preventive Cardiology
Volume 25, March 2026, 101388



Clinician awareness, testing, and treatment for lipoprotein(a): Results from a large US national survey

Nathan D. Wong [a], Yihang Fan [a], Wenjun Fan [a], Jonathan H Ward [b], Belinda Schludi [b], Xingdi Hu [b]

- Strong evidence for a causal association between Lp(a) concentration and cardiovascular outcomes in different ethnicities.
- This association is continuous even at low levels of low-density lipoprotein cholesterol.
- Lp(a) is a new risk factor for aortic valve stenosis.
- Evidence does not support Lp(a) as a risk factor for venous thromboembolism and impaired fibrinolysis.
- Lifelong very low Lp(a) concentrations may associate with diabetes mellitus.
- Lp(a) should be measured at least once in adults.
- A high Lp(a) concentration should be interpreted in the context of other risk factors and absolute global cardiovascular risk, and addressed through intensified lifestyle and risk factor management.
- Specific effective Lp(a)-lowering therapies are in Phase II/III clinical trials.

Florian Kronenberg, Samia Mora, Erik S G Stroes, Brian A Ference, Benoit J Arsenault, Lars Berglund, Marc R Dweck, Marlys Koschinsky, Gilles Lambert, François Mach, Catherine J McNeal, Patrick M Moriarty, Pradeep Natarajan, Børge G Nordestgaard, Klaus G Parhofer, Salim S Virani, Arnold von Eckardstein, Gerald F Watts, Jane K Stock, Kausik K Ray, Lale S Tokgözoğlu, Alberico L Catapano, Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement, ***European Heart Journal*, Volume 43, Issue 39, 14 October 2022, Pages 3925–3946**, https://doi.org/10.1093/eurheartj/ehac361