The ABC's of Lipoprotein(a): What Researchers and Practitioners Need to Know

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Disclosures

Presenter	Conflicts
Marlys L. Koschinsky	Novartis Canada: Advisory Board Novartis: Consultant Eli Lilly: Consultant and Research Contract

Learning Objectives

1. Describe the key features of lipoprotein(a) [Lp(a)] structure and how Lp(a) levels in plasma are determined
2. Understand the evidence for Lp(a) as an independent and causal risk factor for disease
3. Appreciate the mechanisms through which Lp(a) may be pathogenic in the vasculature
4. Identify the key features of Lp(a) production and removal from circulation
5. Be familiar with approaches in development for Lp(a) lowering
6. Recognize how Lp(a) can be used in the clinic

Arteriosclerosis, Thrombosis, and Vascular Biology 2022;42:e48-e60

AHA SCIENTIFIC STATEMENT

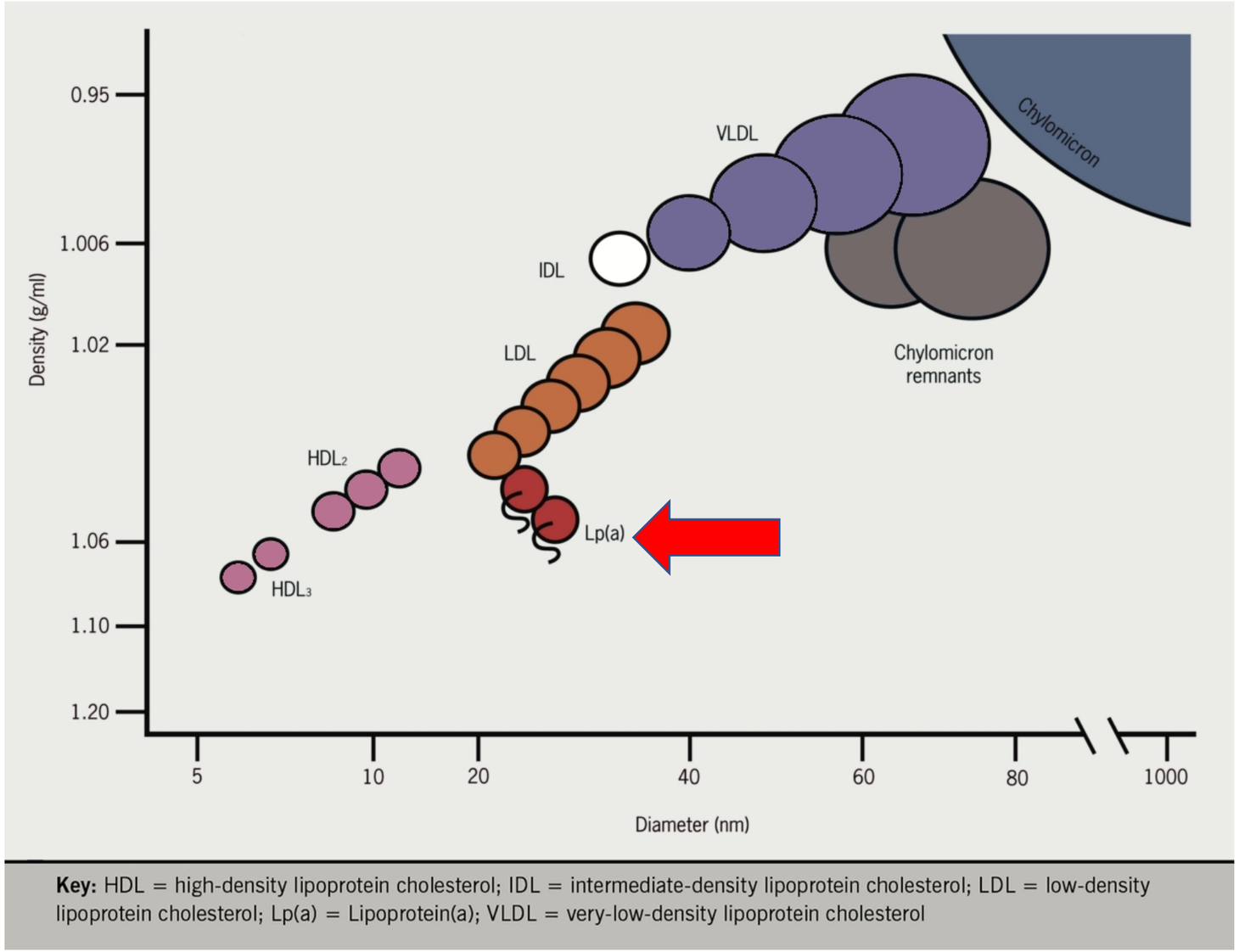
Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association

The International Atherosclerosis Society endorses this statement.

Gissette Reyes-Soffer, MD, FAHA, Chair; Henry N. Ginsberg, MD, FAHA; Lars Berglund MD, PhD; P. Barton Duell, MD, FAHA; Sean P. Heffron, MD, MS, MSc; Pia R. Kamstrup, MD, PhD; Donald M. Lloyd-Jones, MD, ScM, FAHA; Santica M. Marcovina, PhD, ScD, FAHA; Calvin Yeang, MD, PhD; Marlys L. Koschinsky PhD, FAHA, Co-Chair; on behalf of the American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; and Council on Peripheral Vascular Disease

Part 1: Structure of Lp(a) and Determination of Lp(a) Levels

Lp(a) size and density compared to other lipoproteins

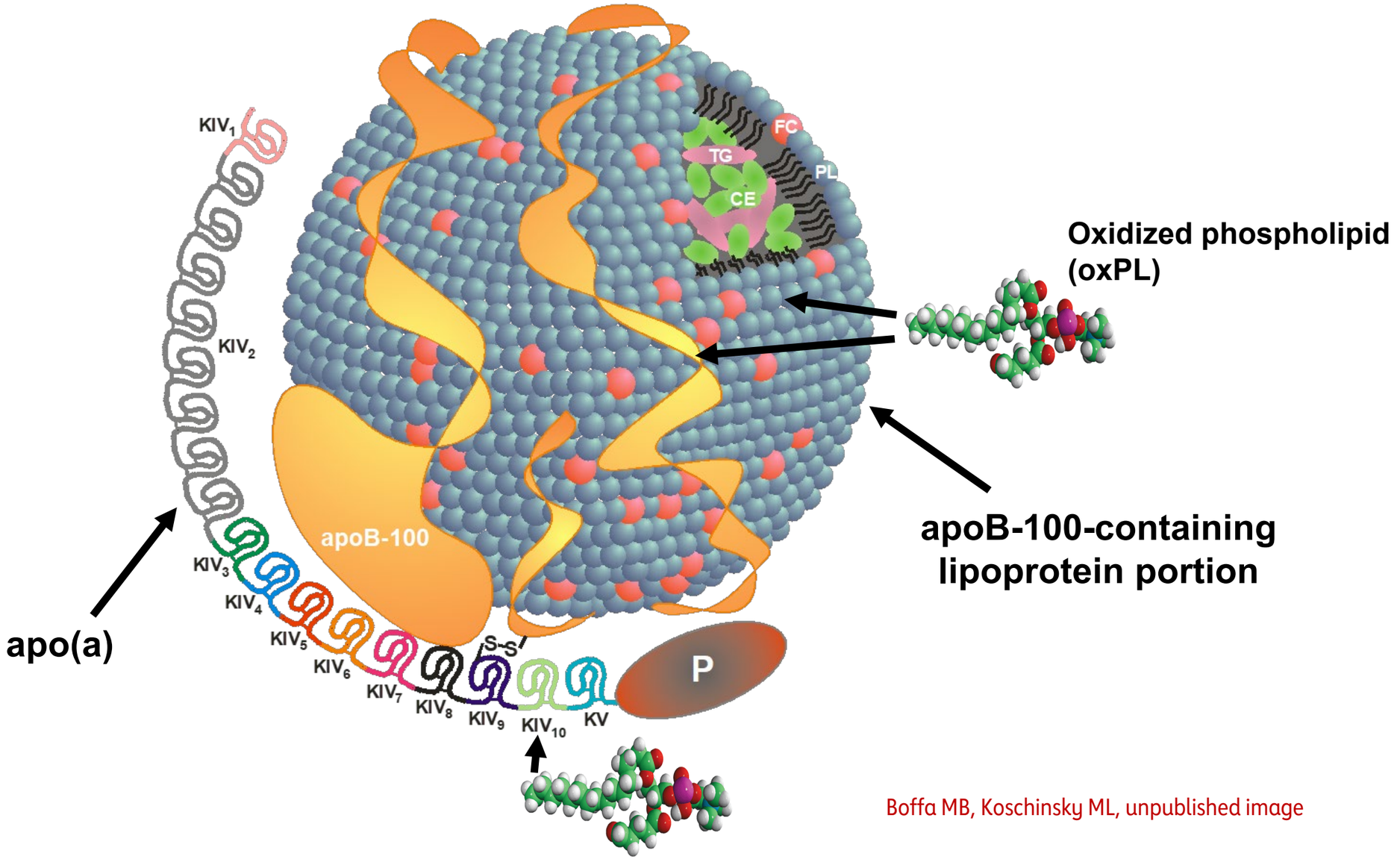


Key: HDL = high-density lipoprotein cholesterol; IDL = intermediate-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; Lp(a) = Lipoprotein(a); VLDL = very-low-density lipoprotein cholesterol

The density of Lp(a) is increased by the presence of the large glycoprotein apo(a)

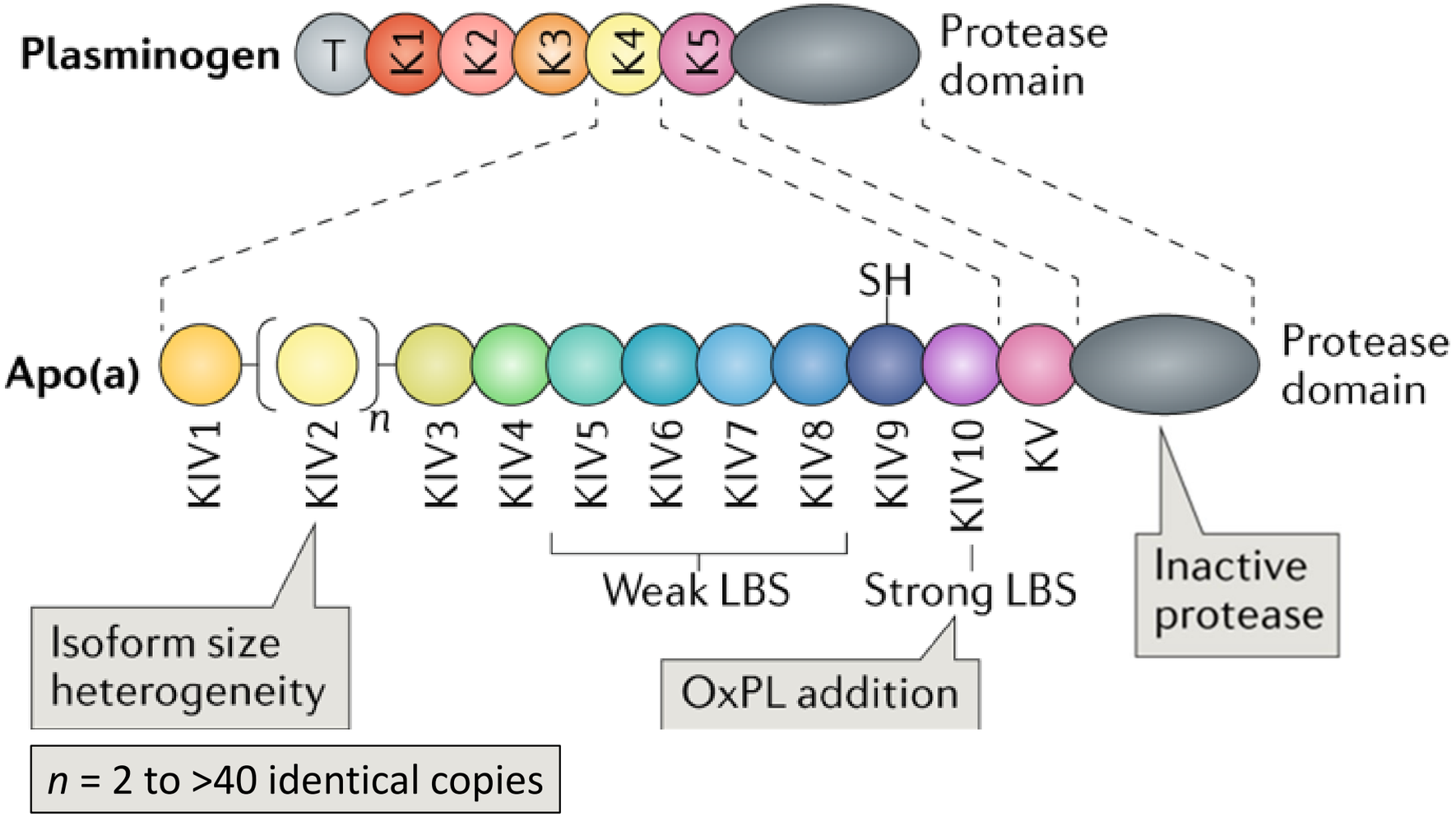
Lipids module 1: lipid metabolism and its role in atherosclerosis (bjcardio.co.uk)

Structure of circulating Lp(a)



Boffa MB, Koschinsky ML, unpublished image

Relationship between apo(a) and plasminogen



Adapted from Boffa MB, Koschinsky ML. Nat Rev Cardiol 2019;16:305

Lp(a) levels

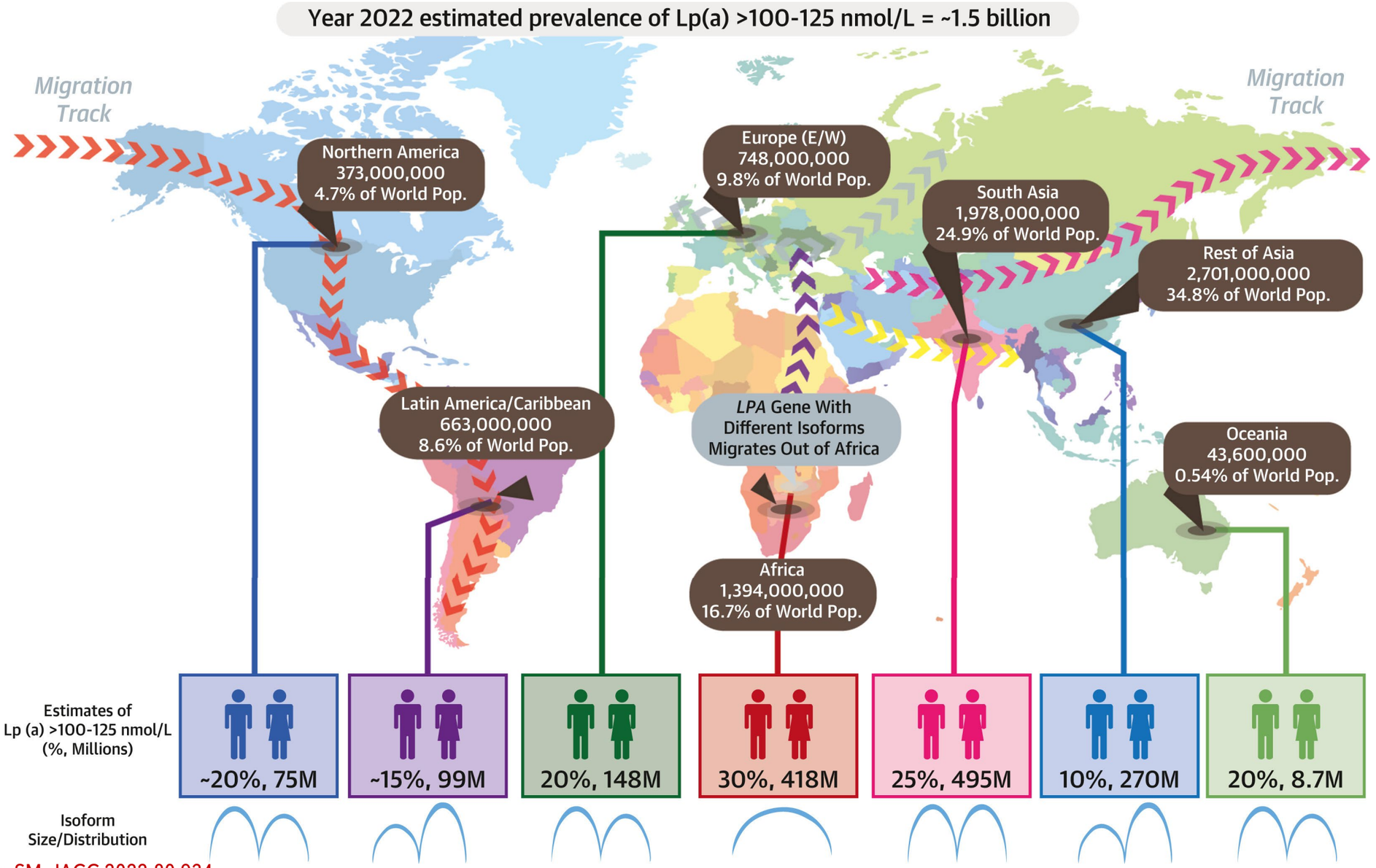
- Plasma Lp(a) levels vary more than 100-fold in the population from <1 to >100 mg/dL (<1 to >250 nmol/L)

- Lp(a) levels are primarily genetically determined
  - Up to 90% of observed variability from *LPA* itself (variability in different ethnic groups)
    - *Bulk of this from inverse correlation between apo(a) isoform size and Lp(a) levels*
  - Lp(a) levels are determined largely by production rather than catabolism of the particle
  - Lp(a) levels comparatively resistant to conventional methods for LDL lowering
    - *Little evidence for a role for lifestyle changes; statins are not effective for Lp(a) lowering and may in fact slightly increase it*

- Elevated plasma Lp(a) (> 30 – 50 mg/dL; > 75 – 125 nmol/L) is an independent, causal, risk factor for a variety of cardiovascular diseases
  - Greatest effect: CHD, CAVD

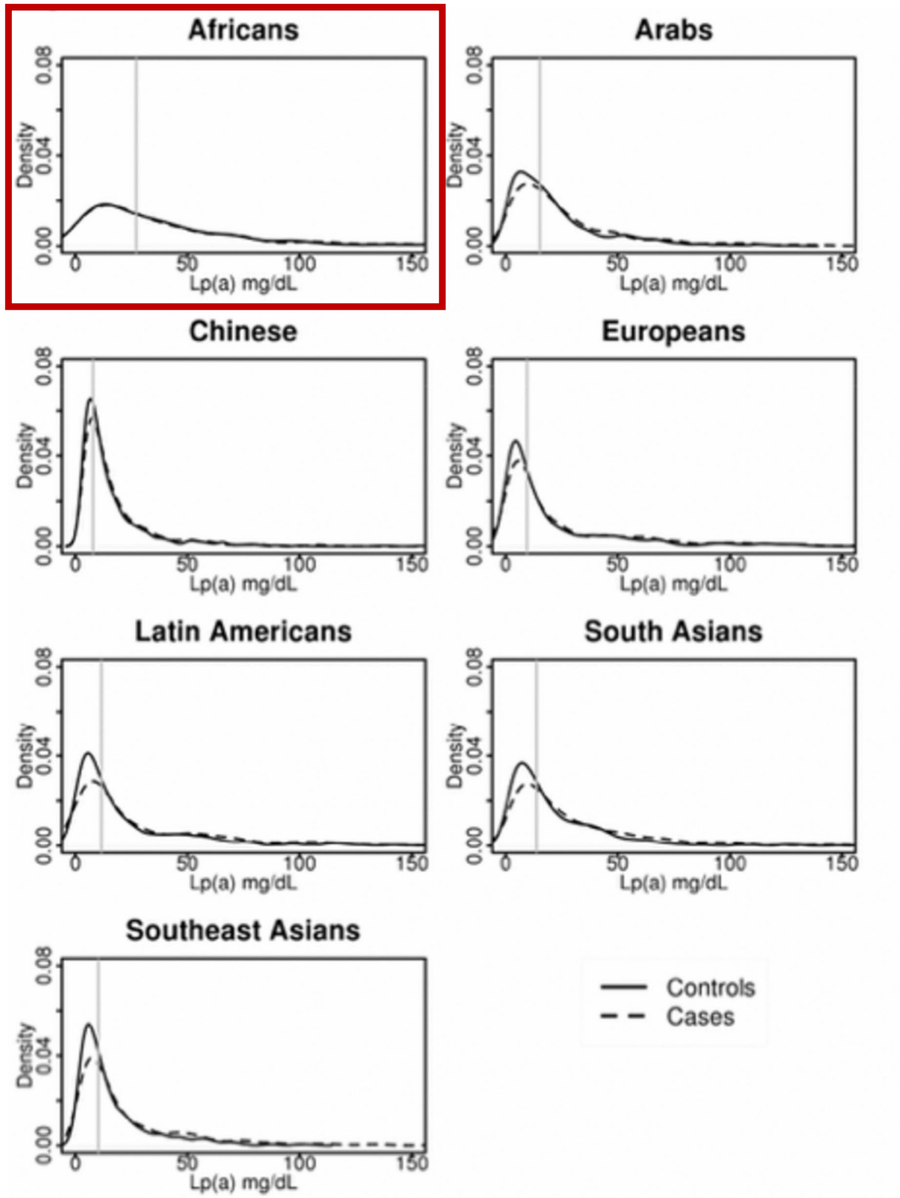
Wilson DP, et al. J Clin Lipidol. 2019;13(3):374-392
Reyes-Soffer G, et al. Arterioscler Thromb Vasc Biol. 2022;42:e48-e60
Kronenberg F, et al. Eur Heart J. 2022;43:3925-3946

Prevalence of elevated Lp(a)



Tsimikas S, Marcovina SM. JACC 2022;80:934

Distribution of Lp(a) levels



Skewed distribution observed in most populations

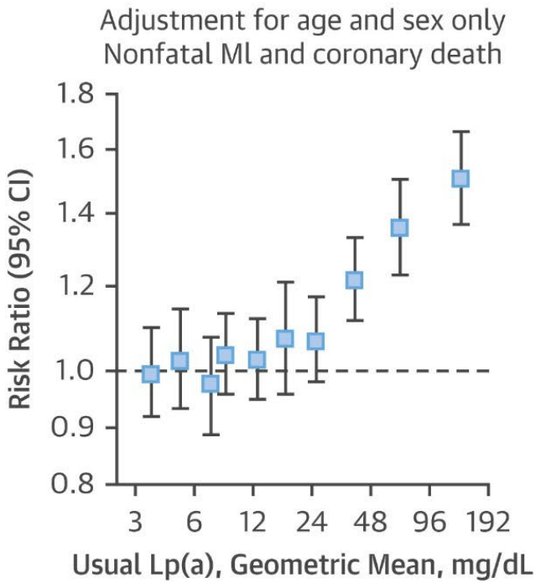
Pare G, et al. Circulation 2019;139:1472

American Heart Association.

Part 2: Elevated Lp(a) and Risk for Cardiovascular Disease

Evidence base for Lp(a) - ASCVD

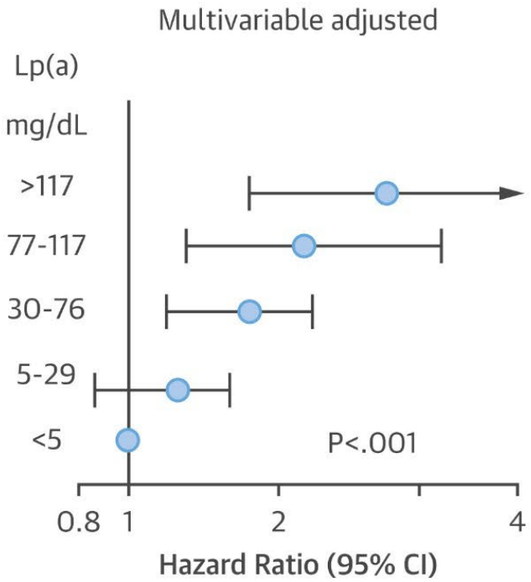
Meta-analysis



Independent risk factor for CHD and stroke (Erqou et al., JAMA 2009;302:412)

- Meta-analysis of prospective studies
- Curvilinear risk relationship beginning at approximately 30 mg/dL

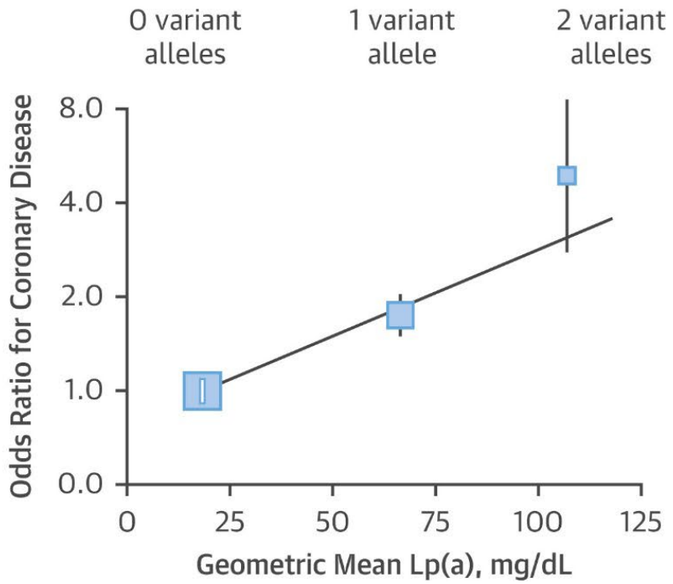
Mendelian Randomization



Causal Risk factor for CHD (Kamstrup et al., JAMA 2009; 301:2331)

- Mendelian randomization approach
- Genetically-elevated Lp(a) levels increased risk

Genome-wide Association



Identification of variants in LPA associated with CAD (Clarke et al., NEJM 2009; 361:2518)

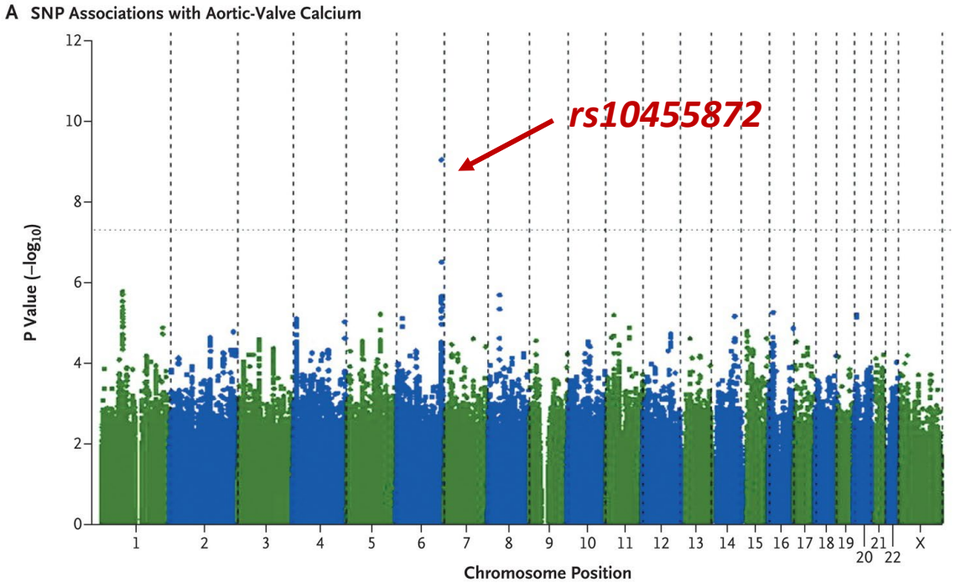
- GWAS identified *LPA* as strongest locus associated with CHD
- 2 variants increased risk almost 2-fold individually and over 4-fold combined

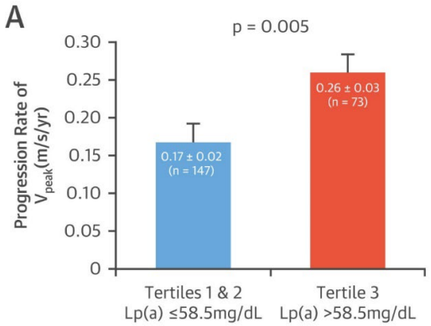
A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies | Journal of the American College of Cardiology (jacc.org)

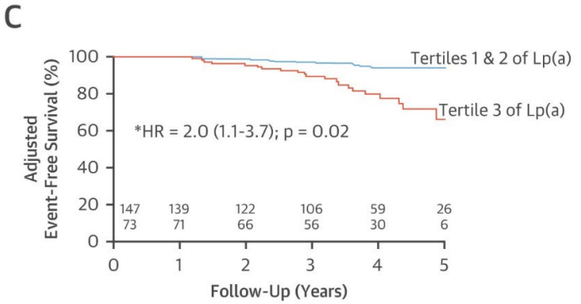
Evidence base for Lp(a) - CAVD

- LPA the only gene identified in GWAS associated with CAVD (Thanassoulis et al., NEJM 2013;368:503)
  - rs10455872 associated with aortic valve calcification
  - Mendelian randomization: genetically-elevated Lp(a) levels associated with incident aortic valve stenosis

- Data from the ASTRONOMER trial (Capoulade et al., JACC 2015; 66:1236)
  - Increased rate of AS progression in top tertile of Lp(a) (and OxPL-apoB)
  - Lower event-free survival (valve replacement) in top tertile of Lp(a) (and OxPL-apoB)

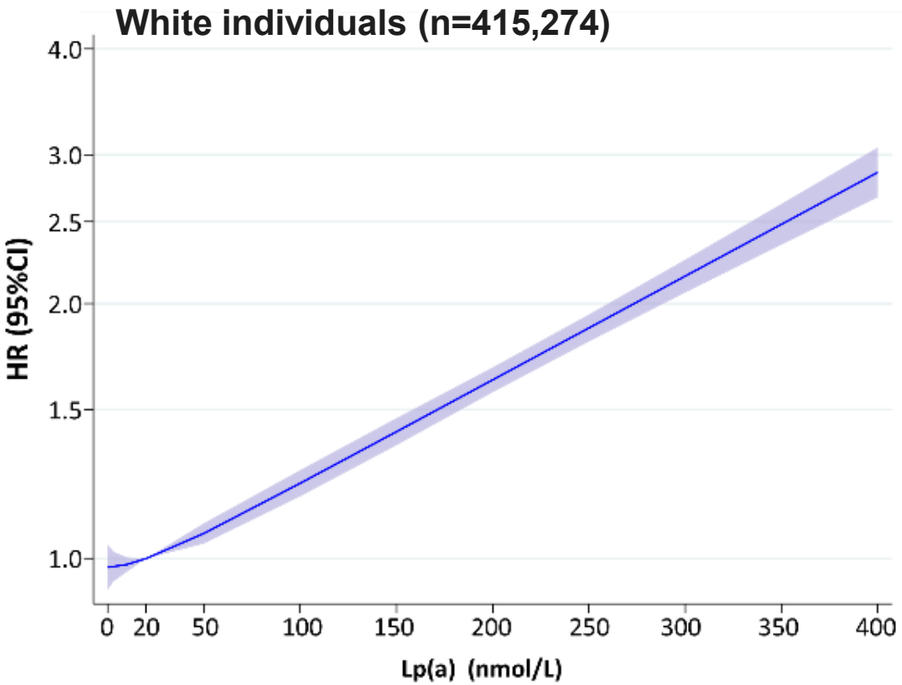


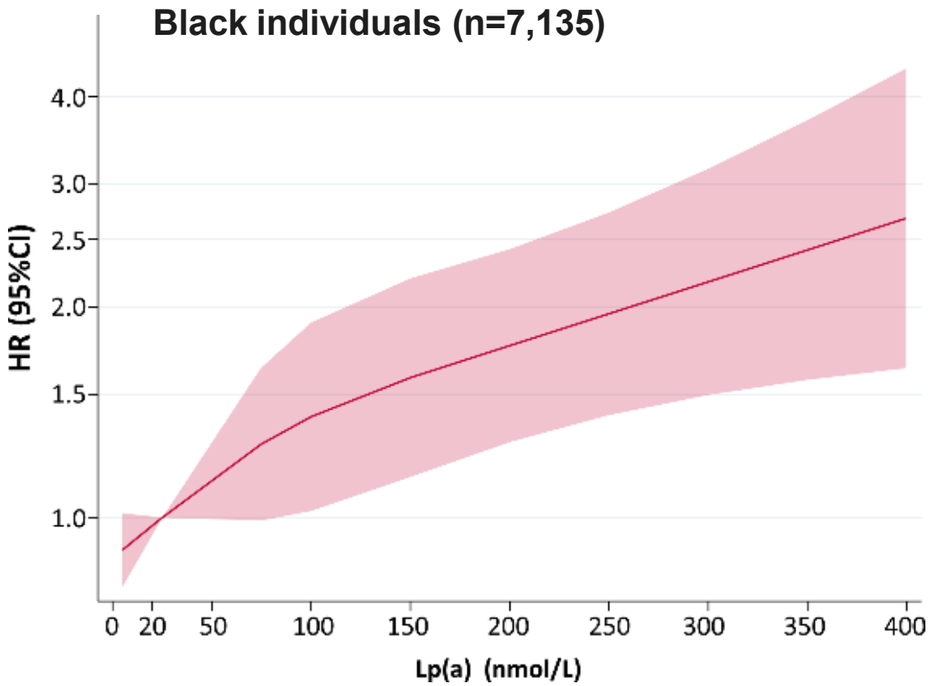




[Oxidized Phospholipids, Lipoprotein(a), and Progression of Calcific Aortic Valve Stenosis]

The association between Lp(a) and major CVD* outcomes is continuous independent of ethnicity





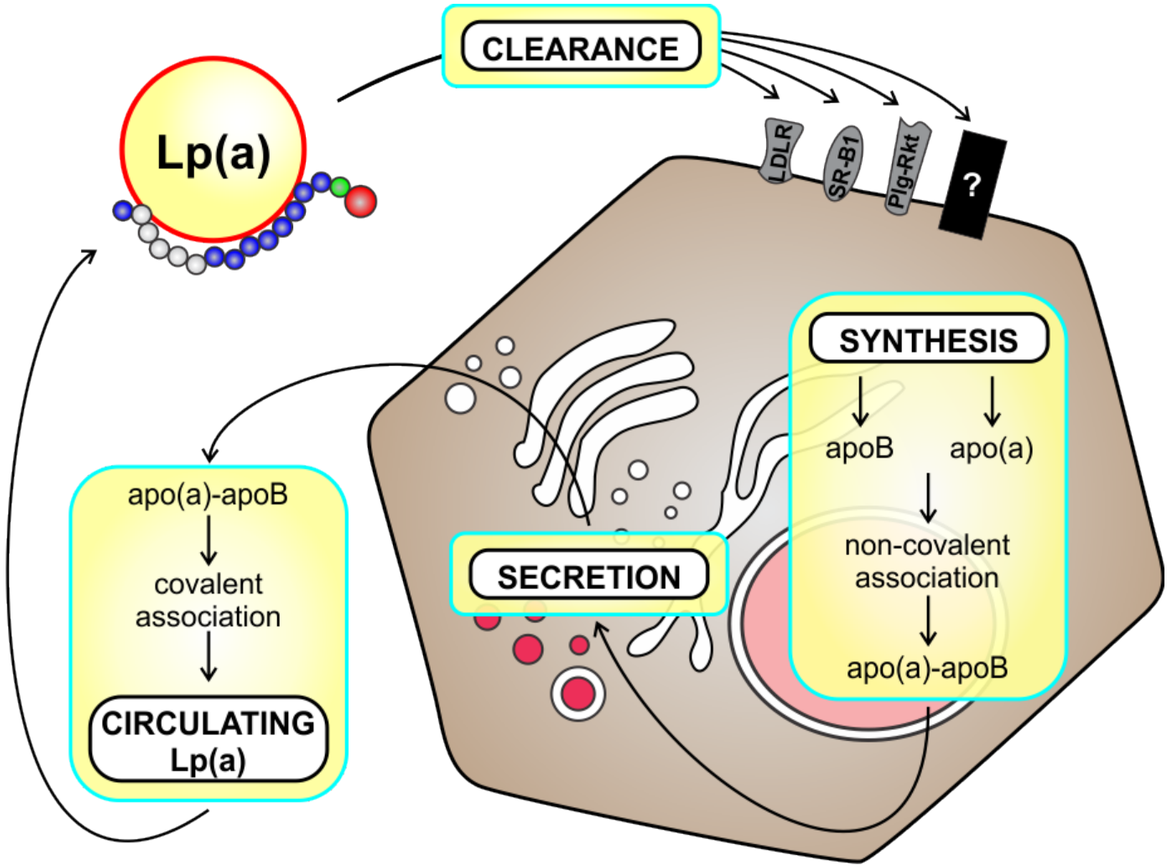
*defined as the composite of the first occurrence of fatal or non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, or coronary revascularization [percutaneous coronary intervention or coronary artery bypass graft surgery]

Analysis provided by Prof. Brian Ference using data from the UK Biobank

Kronenberg F, et al. Eur Heart J 2022;43:3925

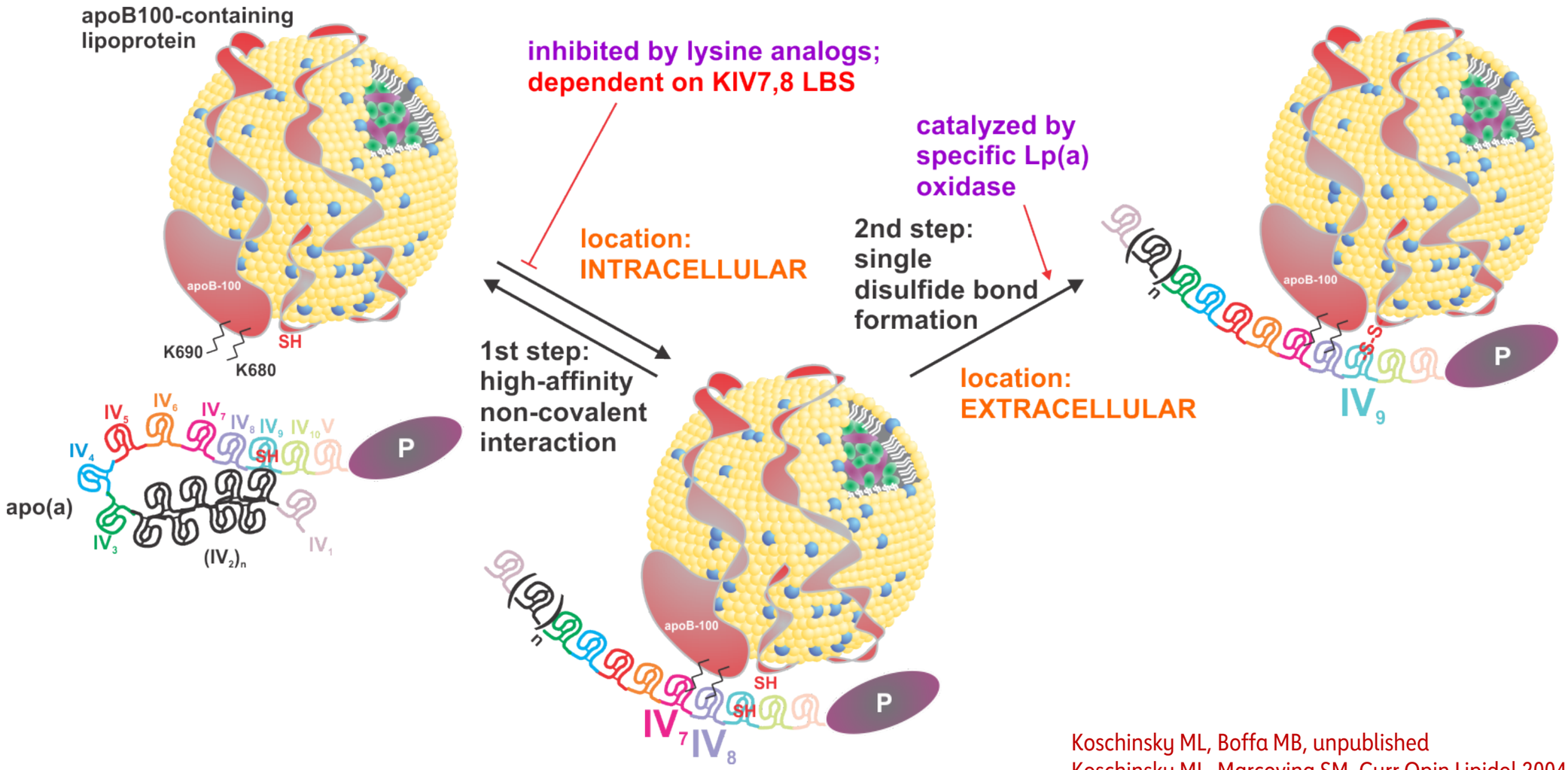
Part 3: Biosynthesis and Catabolism of Lp(a)

Biosynthesis and catabolism of Lp(a) - Overview



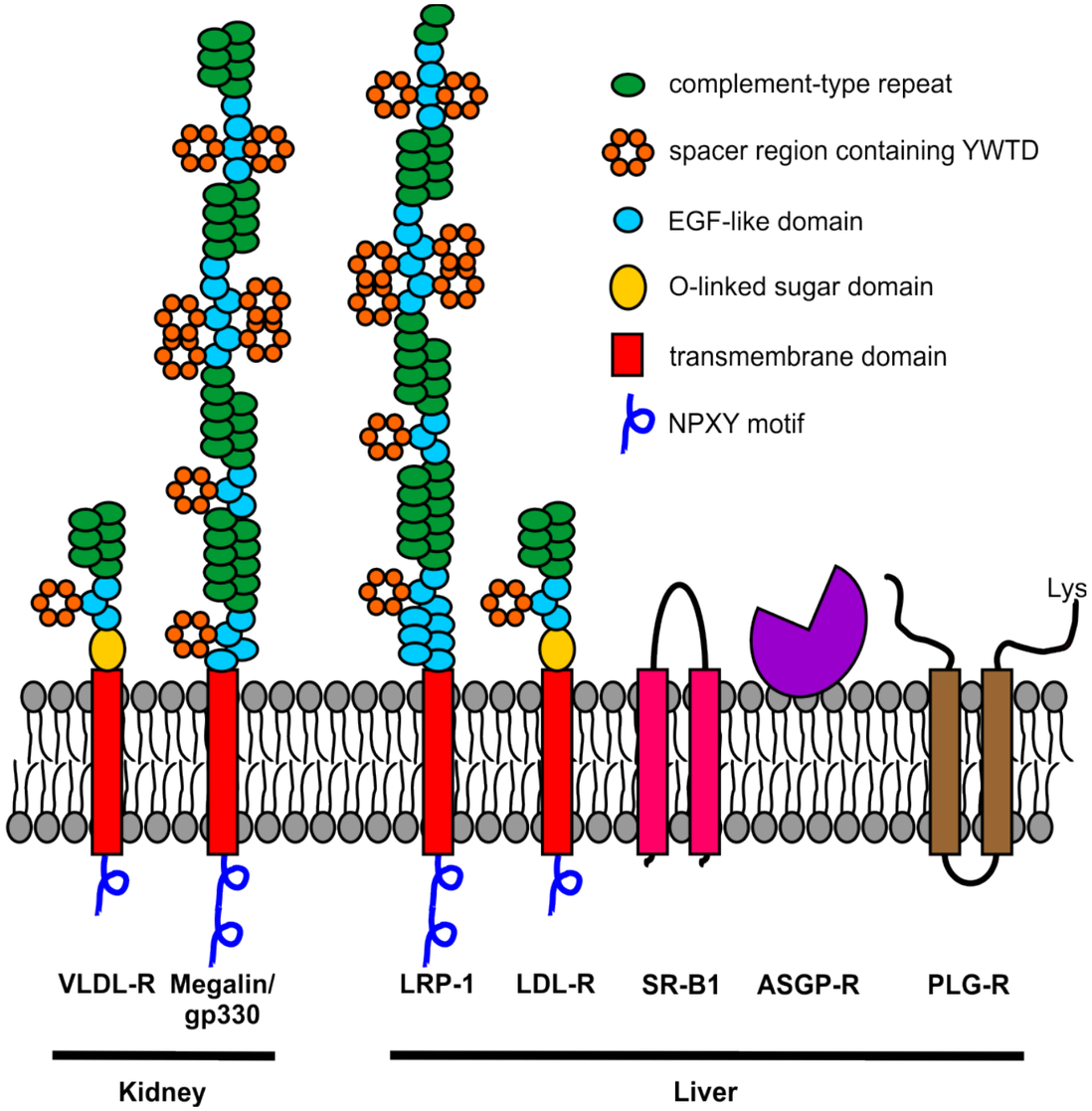
Koschinsky ML, unpublished image

Assembly of Lp(a) particles



Koschinsky ML, Boffa MB, unpublished
Koschinsky ML, Marcovina SM. Curr Opin Lipidol 2004;15:167

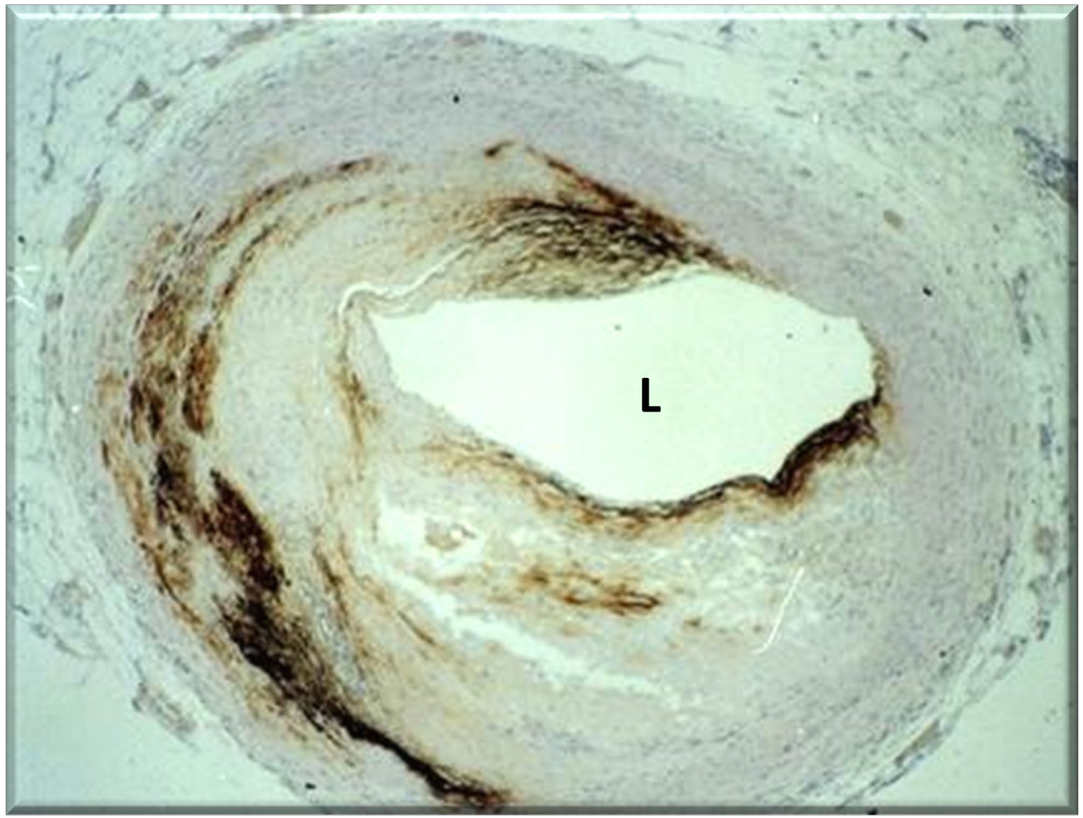
Lp(a) catabolism: Which receptor is responsible for Lp(a) uptake in liver cells?



Koschinsky ML, Boffa MB, unpublished

Part 4: Pathogenic Mechanisms of Lp(a)

How does Lp(a) cause ASCVD?

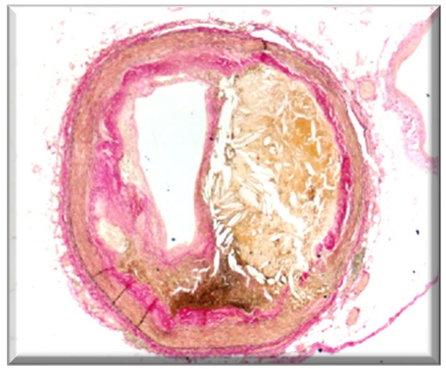


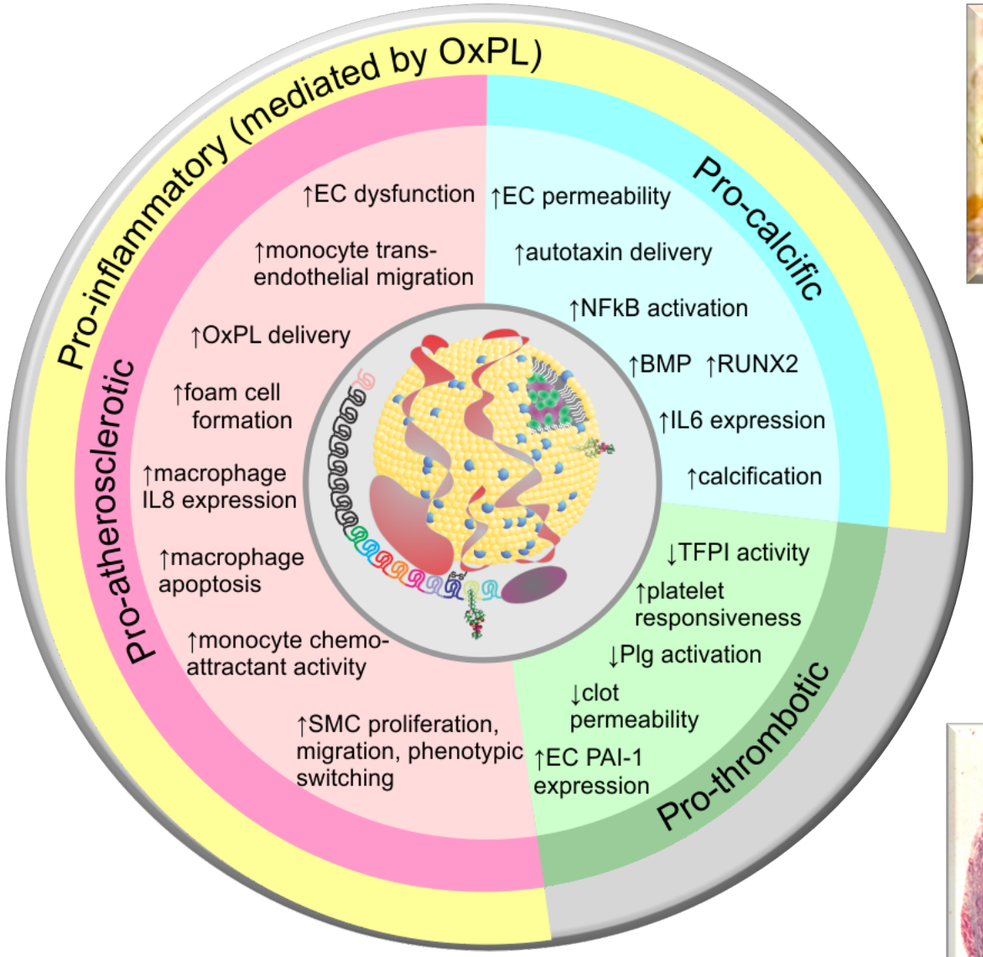
63-year-old male; coronary artery cross section immunostained for apo(a) (brown)

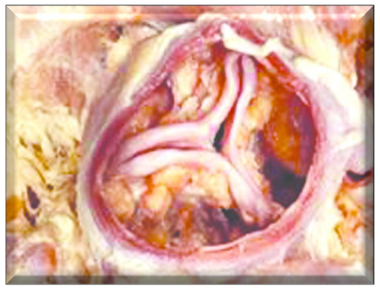
- Lp(a) accumulates in atherosclerotic lesions to an extent that is proportional to its plasma concentrations
- Lp(a) is selectively related in this milieu (relative to LDL) owing it its apo(a)-mediated interactions with cells and extracellular matrix

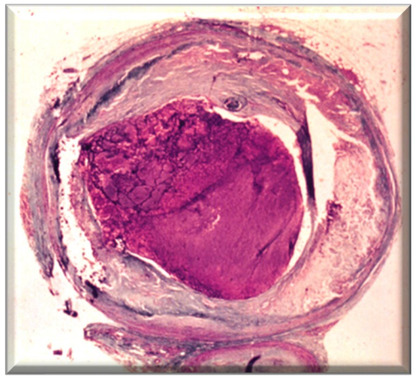
Koschinsky ML, unpublished
Presented at the 42nd Annual Meeting of the American Society of Hematology, 2000

Proposed mechanisms of Lp(a) pathogenicity



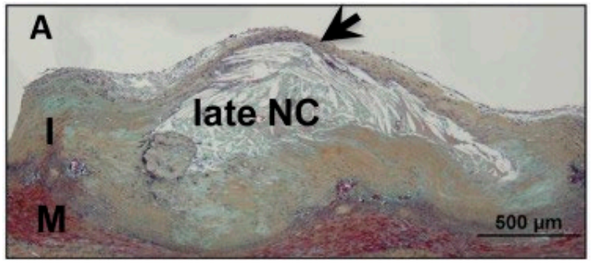






Modified from Kronenberg F, et al. Eur Heart J 2022;43:3925

Lp(a) accumulates in atheromas in association with oxidation-specific epitopes



Apo(a) associates with OxPL epitopes in vulnerable plaques

Van Dijk RA, et al. J Lipid Res 2012;53:2773

Oxidized phospholipids (OxPL) and Lp(a)

Atherogenicity of Lp(a) may be mediated in part by its association with proinflammatory OxPL (present on apo(a) and LDL)

- Tsimikas S, et al. NEJM 2005;353:46

In plasma, OxPL preferentially associates with Lp(a); apo(a) major carrier

- Bergmark S, et al. J Lipid Res 2008;49:2230

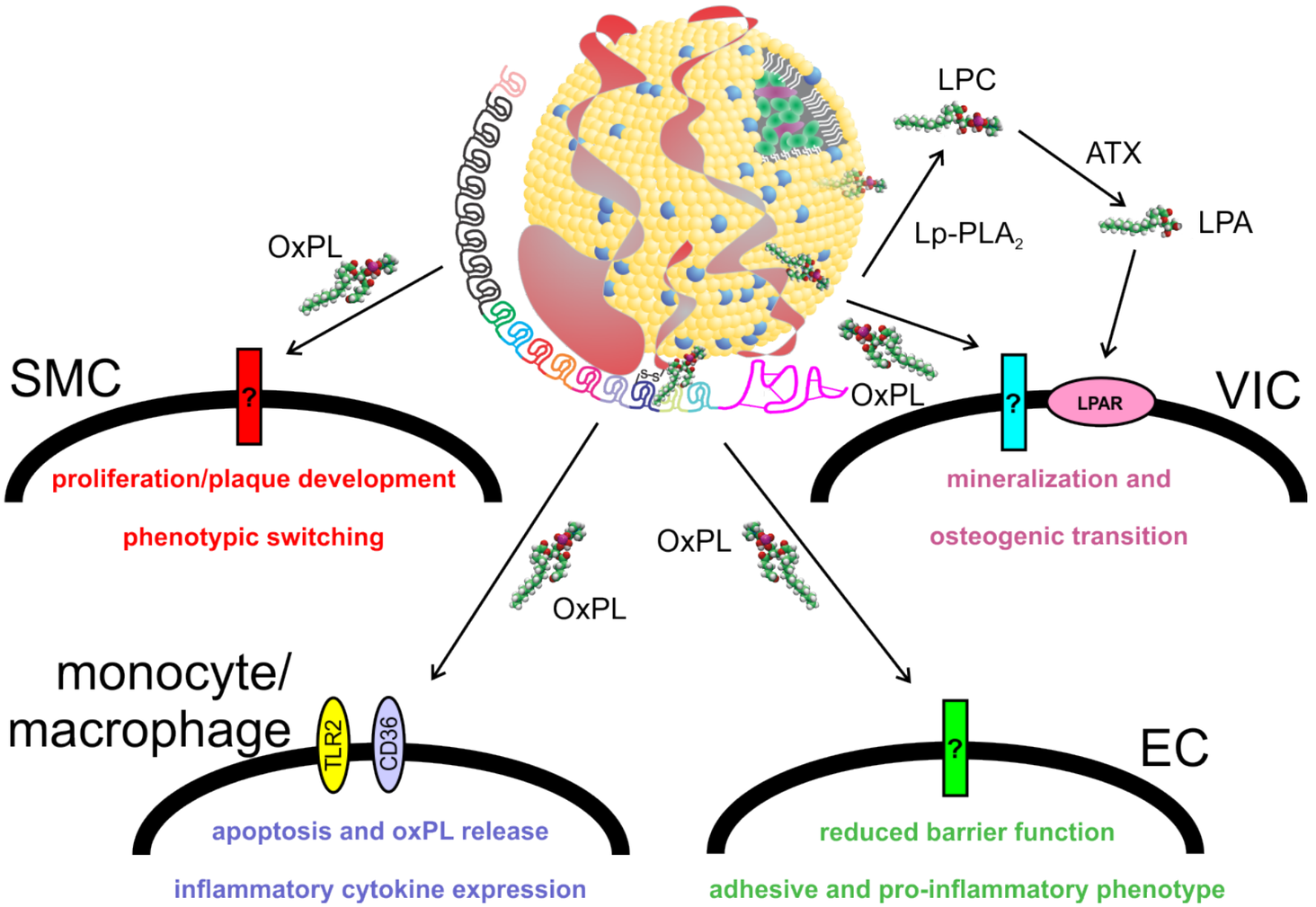
OxPL attaches covalently to the KIV10 domain in apo(a) (dependent on lysine-binding site)

- Leibundgut G, et al. J Lipid Res 2013;54: 2815

OxPL on apo(a):

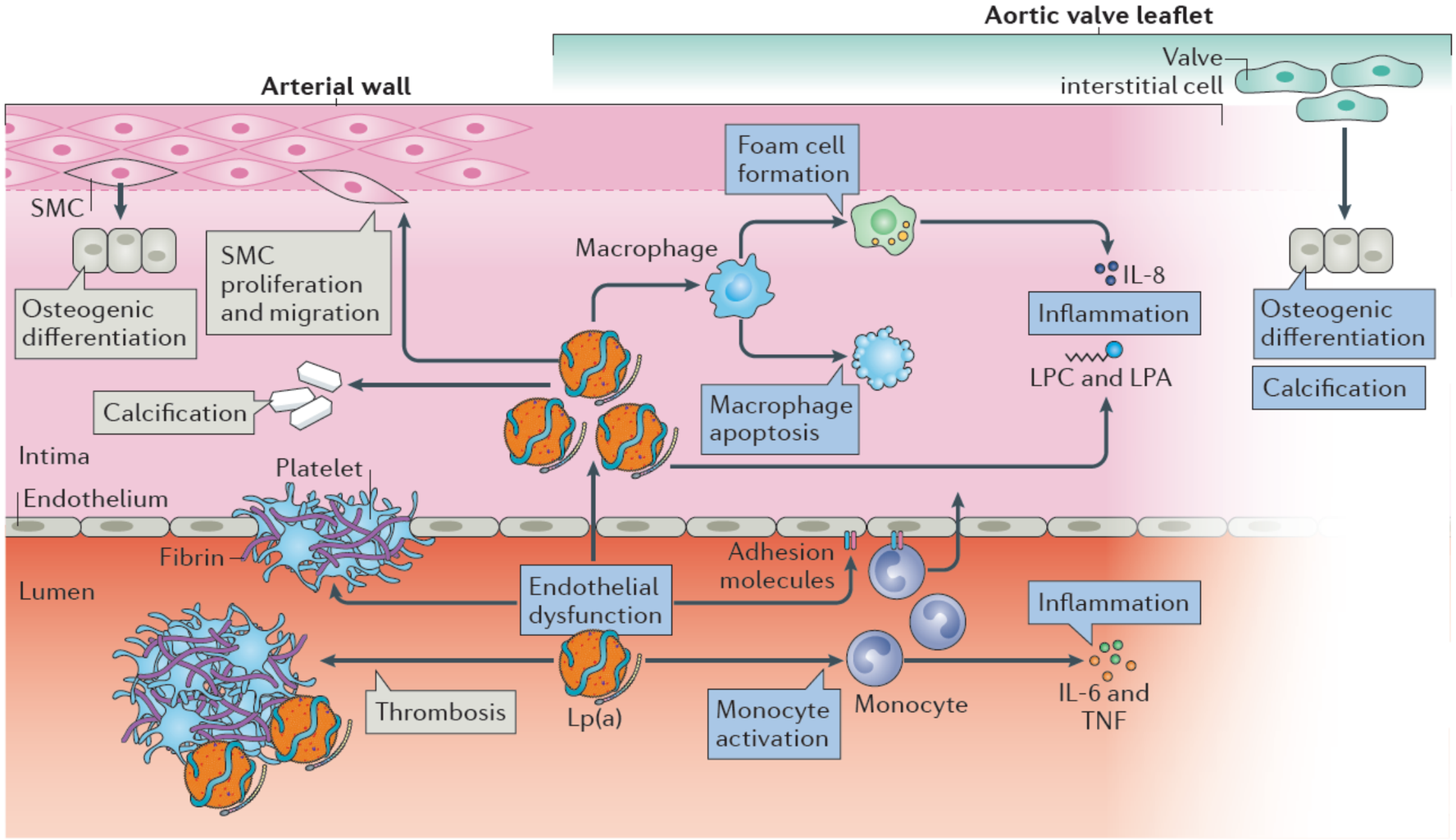
- Promote macrophage apoptosis
  - Seimon TA, et al. Cell Metab 2010;12:467
- Promote macrophage IL- 8 expression
  - Scipione C, et al. J Lipid Res 2015;56:2273
- Elicit arterial wall inflammation and an inflammatory monocyte response in humans
  - Van der Valk F, et al. Circulation 2016;134:611
- Promote valve calcification through pro-inflammatory and pro-osteogenic effects on valve interstitial cells
  - Zheng KH, et al. JACC 2019;73:2150
- Increase vascular endothelial cell glycolysis, facilitating inflammation and leukocyte extravasation
  - Schnitzler JG, et al. Circ Res 2020;126:1346

Lp(a)-OxPL signaling in vascular and inflammatory cells



Adapted from: Koschinsky ML, Boffa MB. Atherosclerosis 2022;349:92-100

OxPL as a unifying theory for the role of Lp(a) in ASCVD and CAVD



Boffa MB, Koschinsky ML. Nat Rev Cardiol 2019;16:305

Nature Reviews | Cardiology

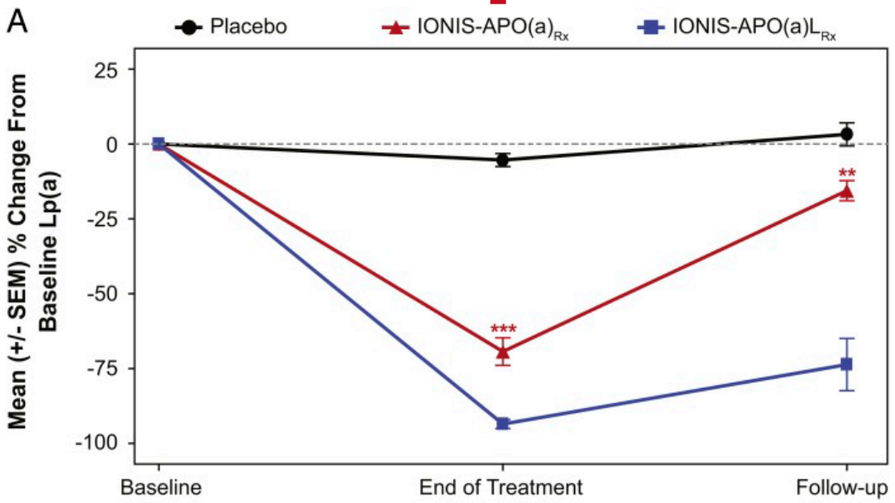
High Lp(a) as a risk factor for thrombosis

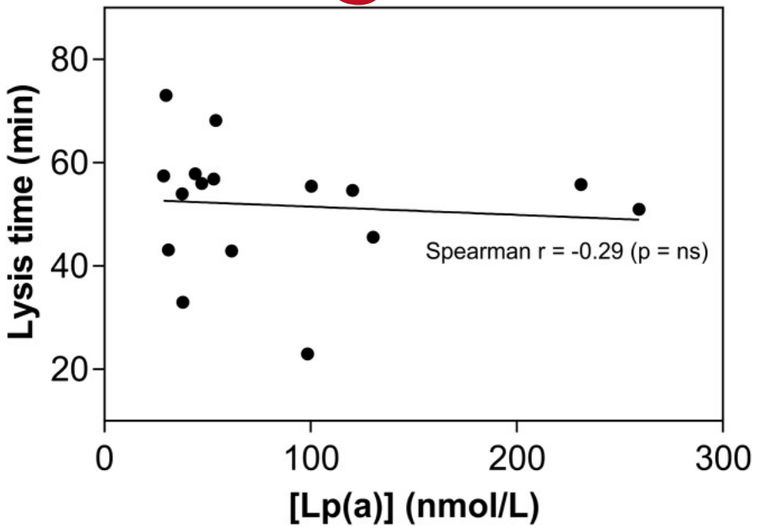
Venous thrombosis	
For	**Against**
• Fibrinolysis assays *in vitro* and in animal models • Association studies in humans (some)	• Association studies in humans (some) • Mendelian randomization studies (large)

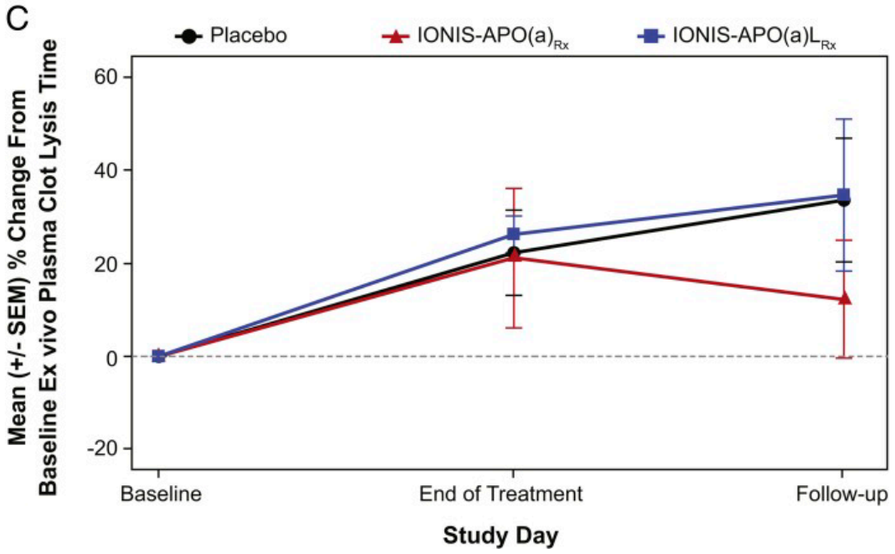
Arterial thrombosis	
For	**Against**
• Fibrinolysis assays *in vitro* and in animal models using apo(a) • Imaging studies of arterial lesions • Epidemiological studies showing high Lp(a) predicts resistance to endogenous fibrinolysis • Role of Lp(a) in pediatric stroke	• No effect of elevated Lp(a) on response to thrombolytic therapy (AMI or ischemic stroke) • (Lack of role of high Lp(a) in venous thrombosis taken as evidence of lack of role in arterial thrombosis – DEBATABLE) • Fibrinolysis assays *in vitro* using Lp(a)

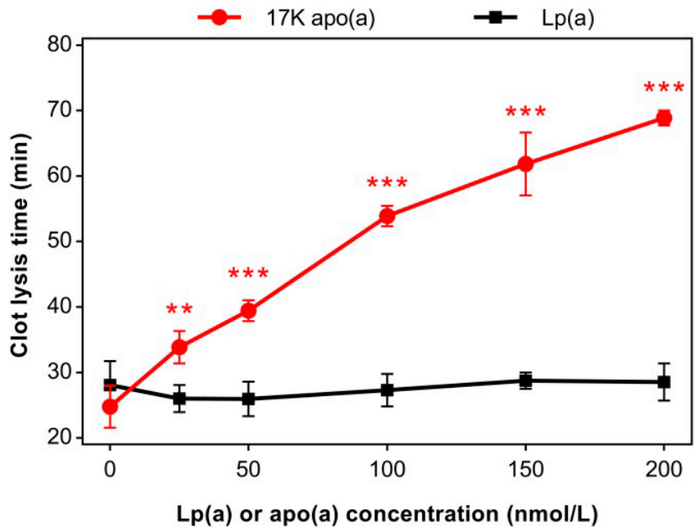
Boffa MB, Koschinsky ML. J Lipid Res 2016;57:745

Lp(a) lowering by antisense oligonucleotides does not impact ex vivo fibrinolysis





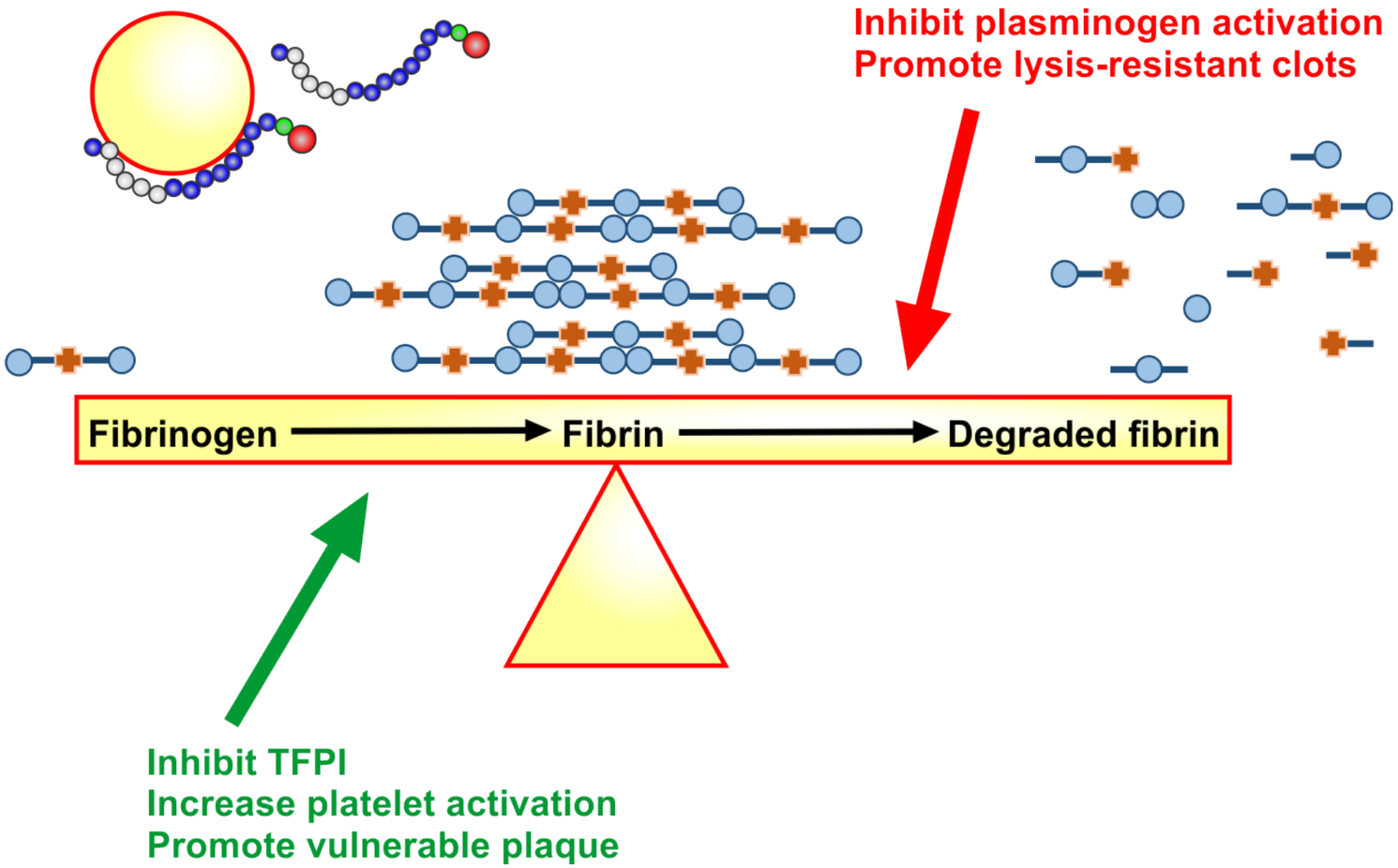




Effect of Lp(a) on thrombosis may be at level of platelet activation or coagulation

Boffa MB, et al. J Lipid Res 2019;60:2082

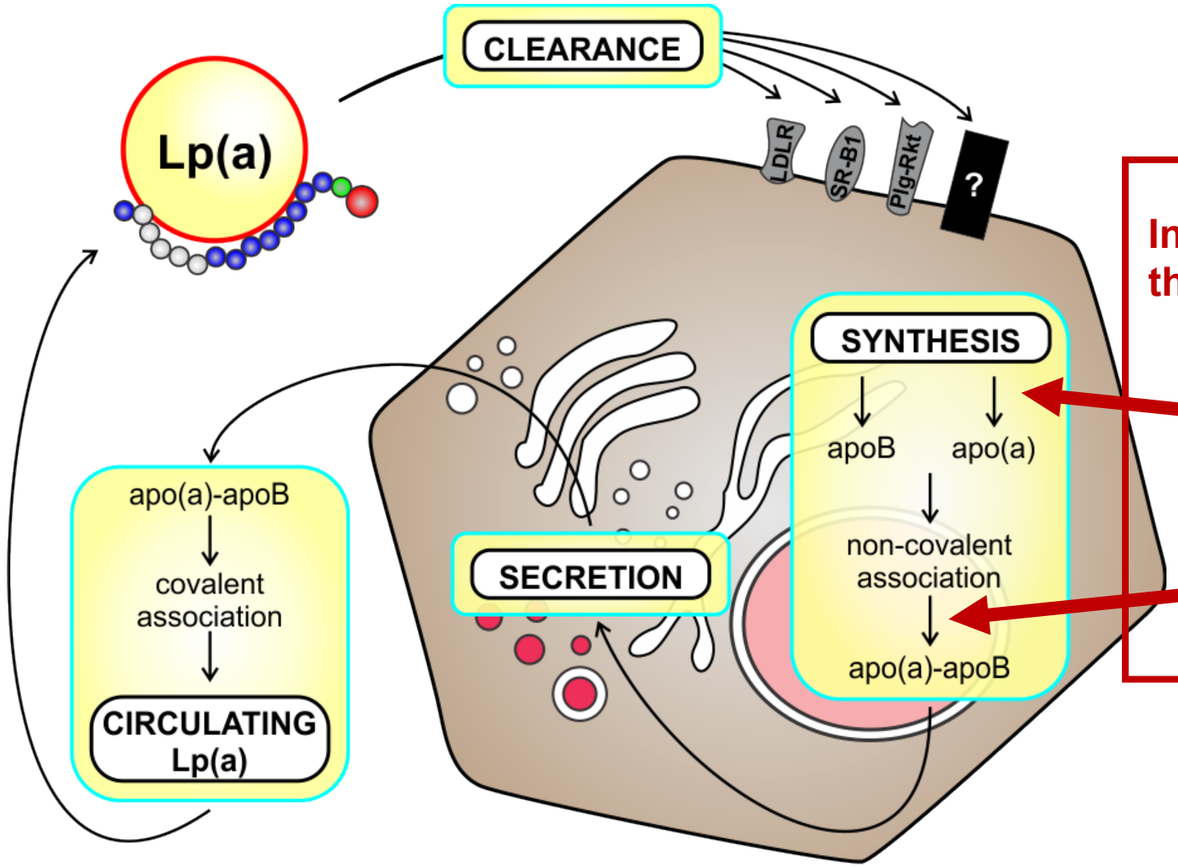
Lp(a) and thrombosis: possible mechanisms



TFPI = tissue factor pathway inhibitor.
Boffa MB, Koschinsky ML, unpublished image

Part 5: Pharmacological Lowering of Lp(a)

Biosynthesis and catabolism of Lp(a)



Investigational drugs that lower Lp(a)

pelacarsen; olpasiran; zerlasiran

muvalaplin

Koschinsky ML, unpublished image

Phase 3 cardiovascular outcomes trials

Pelacarsen: Lp(a)HORIZON (NCT04023552)

- n = 8323; randomized, double-blind, placebo-controlled
- 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)
- Recruitment completed; anticipated study end is May 2025

Olpasiran: OCEAN(a) (NCT05581303)

- n = 7000 (est.); randomized, double-blind, placebo-controlled
- Key inclusion criteria: Lp(a) ≥ 200 mg/dL; history of ASCVD
- Primary endpoint: time to CHD death, myocardial infarction, or urgent coronary revascularization
- Recruitment ongoing; anticipated study end is December 2026

Lipoprotein apheresis for Lp(a) lowering

- Lowers Lp(a) by 50 – 85% (rebounds within 2 weeks) (also lowers LDL-C by 60 – 85%)

- FDA approved for Lp(a) lowering when:
  - Patient has functional familial hypercholesterolemia
    and
  - LDL-C > 100 mg/dL
    and
  - Patient has established coronary artery disease
    and
  - Lp(a) > 60 mg/dL

- Limited clinical trial data suggest that Lp(a) lowering with lipoprotein apheresis may reduce the risk of ASCVD events, but definitive studies are needed

Reyes-Soffer G, Ginsberg HN, Berglund L, et al. Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association. Arterioscler Thromb Vasc Biol. 2022;42(1):e48-e60. doi:10.1161/ATV.0000000000000147

Part 6: Use of Lp(a) in Clinical Practice

Lp(a) in clinical practice

Why would a clinician measure Lp(a)?
Elevated Lp(a) is a common independent atherosclerotic cardiovascular disease risk factor that is not measured in the majority of affected patients
The only currently available method to know if someone has elevated Lp(a) is to measure Lp(a) with a simple blood test that is relatively inexpensive
Awareness of the presence of elevated Lp(a) is important, because high Lp(a) increases atherosclerotic cardiovascular disease risk and could inform clinical decision-making regarding risk management
Cascade screening of family members of patients with elevated Lp(a) may identify additional individuals with elevated Lp(a) because of its autosomal codominant inheritance pattern

How should one measure Lp(a)?
Prefer:
Isoform size-insensitive assay with 5-point calibrator
In units of nmol/L
Conversion from mg/dL to nmol/L and correction of LDL-C for Lp(a)-C not recommended

Reyes-Soffer G, et al. ATVB 2022;42:e48

Clinical implementation of Lp(a) levels in risk assessment for primary prevention of ASCVD

- Current ACC/AHA guidelines recommend that risk assessment for primary prevention of atherosclerotic cardiovascular disease should begin with 10-yr risk estimation using the Pooled Cohort Equations (or similar well-validated equation for the patient population).
- If the patient is in the borderline (5%–7.4%) or intermediate (7.5%–19.9%) 10-yr risk group, personalization and recalibration of the risk estimate should be attempted during a patient-clinician discussion that considers risk-enhancing factors, including family history of premature atherosclerotic cardiovascular disease, chronic kidney disease, and other chronic conditions.
- If measured, the Lp(a) level can be used as a risk-enhancing factor in this scenario. Based on the data from Patel et al, the clinician could adjust the 10-y risk estimate based on the following formula to provide an approximate updated 10-yr risk estimate: Predicted 10-yr risk×$[1.11^{(\text{patient's Lp(a) level in nmol/L}/50)}]$

Patient example: For a patient with 10-yr risk estimate of 10.0%, who has an Lp(a) level of 250 nmol/L, the updated predicted risk estimate would be 16.9%: $10.0\%\times1.11^{(250/50)}=10.0\%\times1.115=10.0\%\times1.69=16.9\%$

Reyes-Soffer G, et al. ATVB 2022;42:e48

Key Messages

1. **Hallmark features of lipoprotein(a) [Lp(a)] structure and how Lp(a) levels in plasma are determined**
   - Consists of the unique apo(a) and an apoB-containing lipoprotein particle
   - Is most similar in size and density to LDL but is metabolically distinct
   - Biosynthesis (production) is main driver of Lp(a) levels and reflects their strong genetic determination
   - Elevated Lp(a) is present in approximately 20% of the global population
   - Elevated Lp(a) is a causal and independent risk factor for cardiovascular diseases
2. **Oxidized phospholipid modification of apo(a) is a large contributor to the pathogenicity of Lp(a)**
   - Apo(a)-associated OxPL accounts for many of the proinflammatory effects of Lp(a) in vascular cells (ex. vascular endothelial cells, smooth muscle cells, macrophage and aortic valve cells)
   - Lp(a) may also have prothrombotic properties
3. **Lp(a) measurement can be useful in the clinic**
   - Identification of patients with elevated Lp(a) levels (> 30 – 50 mg/dL; > 75 – 125 nmol/L) can improve CVD risk prediction and inform risk management
   - Elevated Lp(a) in an individual may prompt cascade screening of primary relatives

Questions and Discussion