Lipoprotein (a): Emerging Risk Factor That is Actionable Now

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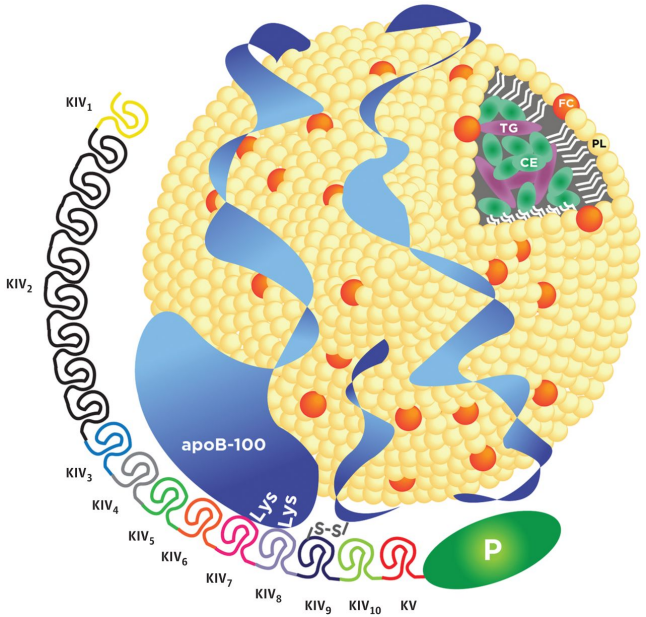
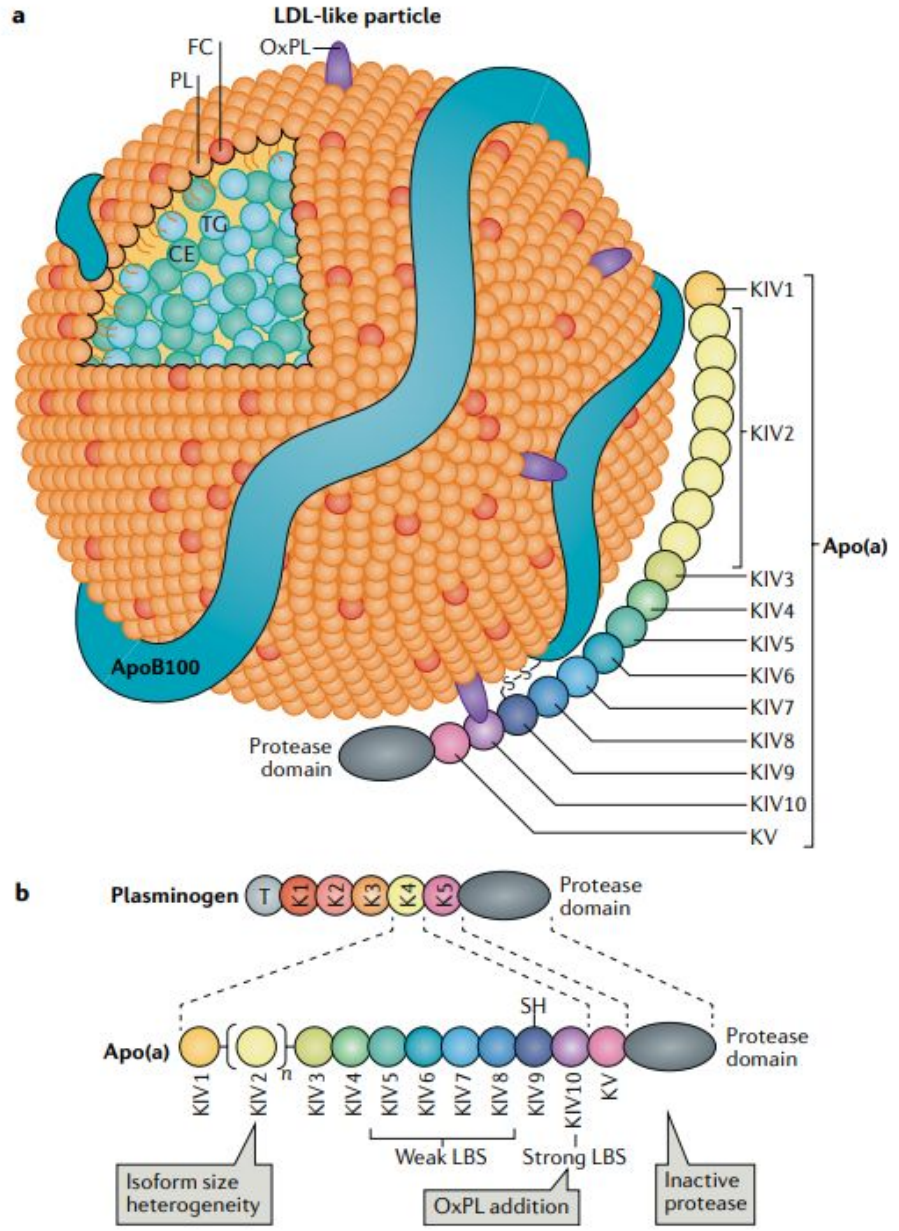


Disclosures

- Dr. Michos reports advisory boards for Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Edwards Life Science, Esperion, Medtronic, Novo Nordisk, Pfizer

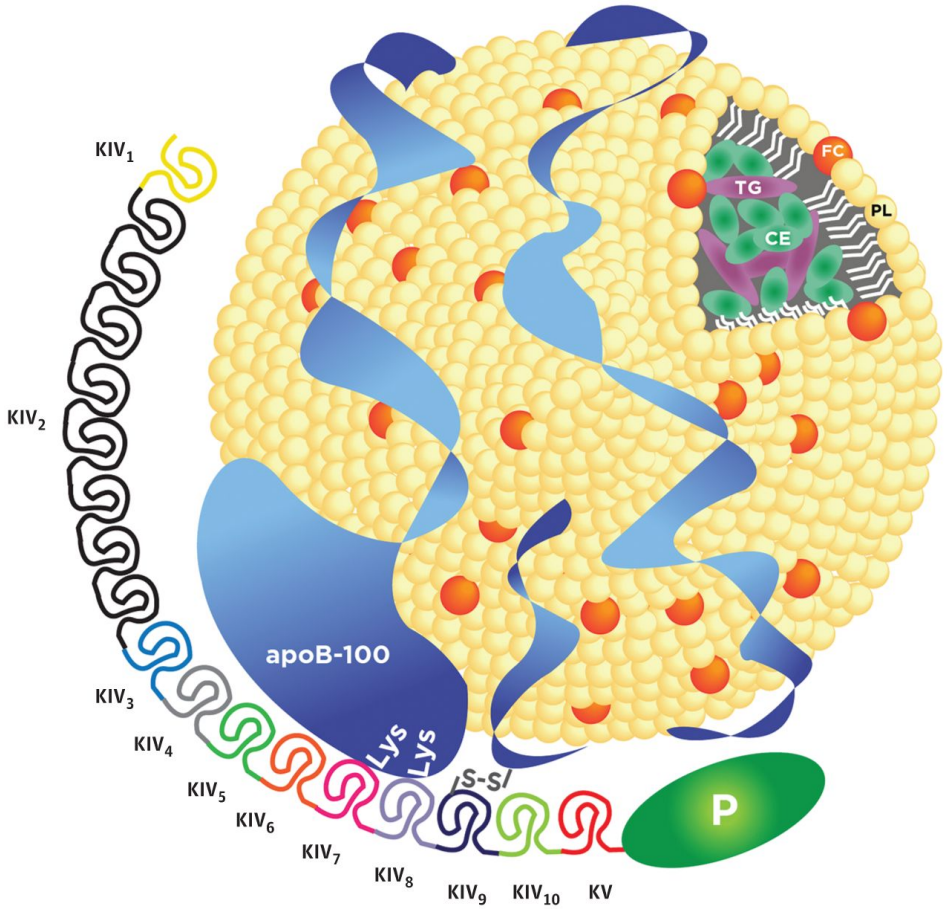
Structure of Lp(a)

- Lp(a) is a LDL-like particle with an apoB100 bound to apo(a)
- Major lipoprotein carrier of pro-inflammatory and pro-calcific oxidized phospholipids (OxPL)
- Apo(a) is highly homologous to plasminogen
- The apo(a) part consists of 10 subtypes of kringle domain IV (KIV_{1-10}), a kringle domain V (KV) and an inactive protease domain.



Boffa and Koschinsky, Nat Rev Cardiol 2019;16:305-318

Structure of Lipoprotein (a)

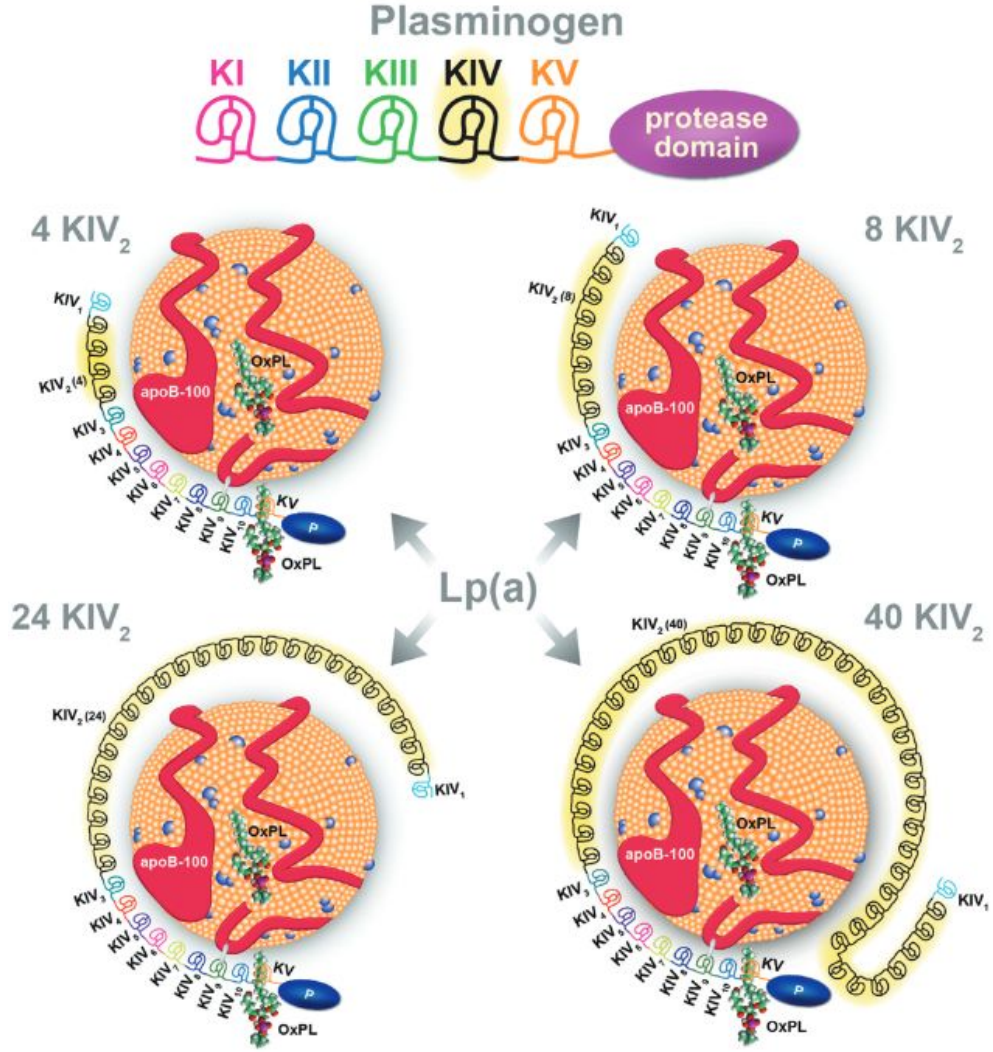


Duarte Lau F, et al. *JAMA Cardiol*. 2022;7(7):760-769.

- .Highly genetically determined
- Apo(a) gene accounts for >90% of variation in LP(a) levels
- KIV_2 can expand into more than 40 identically repeated copies.
- Within a population, there is significant heterogeneity in apo(a) size and thus different Lp(a) size
- 80% of individuals carry 2 different-sized apo(a) iso-forms, each inherited from 1 parent

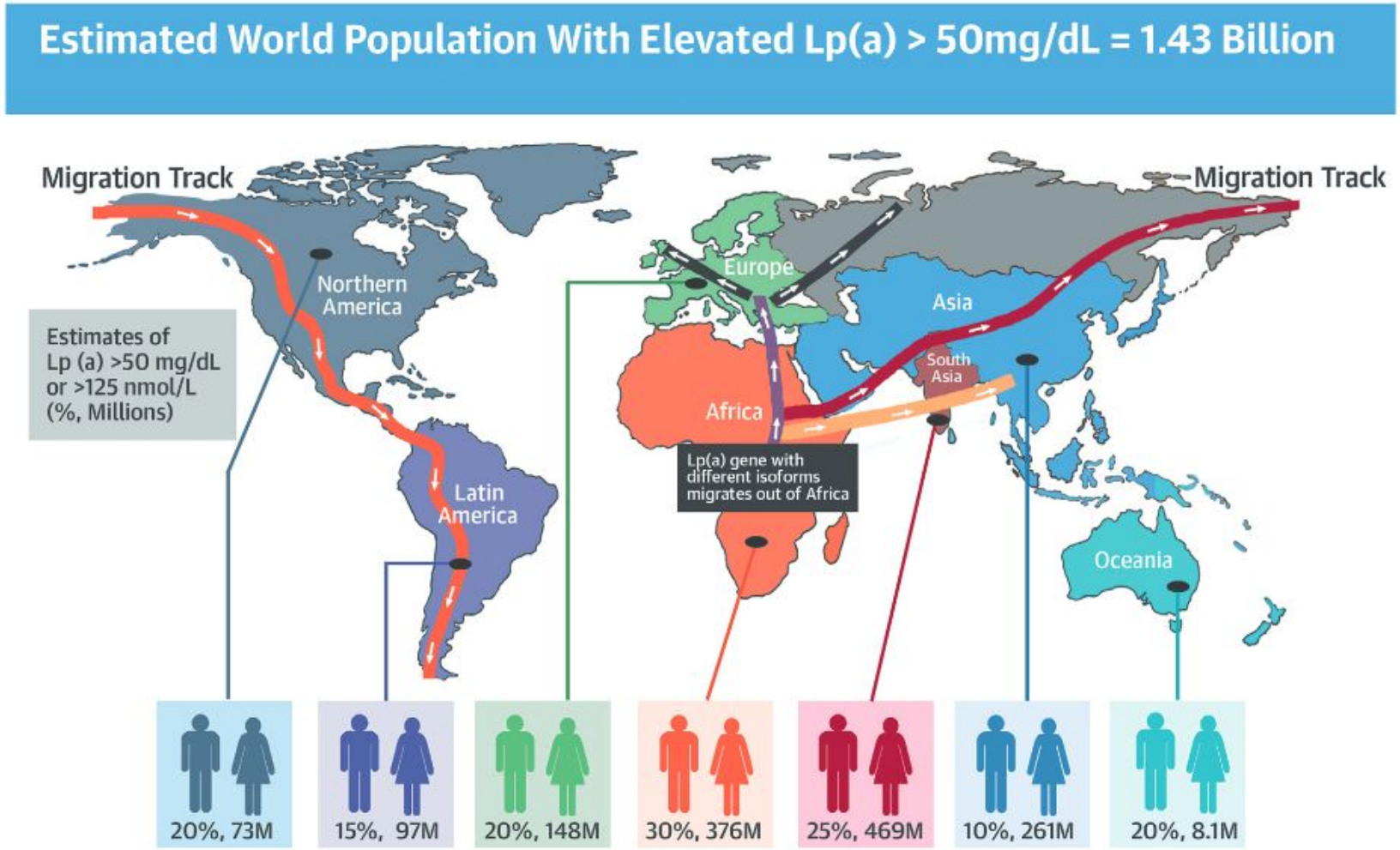
Structure of Lp(a)

- Significant inverse association between the number of kringle-IV (KIV) type 2 repeats in apo(a) and plasma Lp(a) concentrations.
- The size heterogeneity of apo(a) impairs the accuracy of antibody-mediated immunoassays to measure the true Lp(a) burden.
- Direct conversion between Lp(a) mass (mg/dL) and concentration (nmol/L) is an imprecise approximation since all conversion factors are inherently isoform dependent.
- Should be measured by isoform insensitive assay and reported in nmol/L



Tsimikas S. *J Am Coll Cardiol.* 2017;69:692-711.

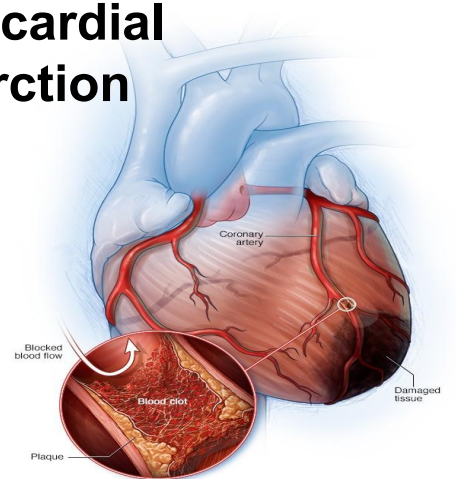
An estimated 20% to 25% of the global population have Lp(a) levels of 50 mg/dL (~125 nmol/L) or higher

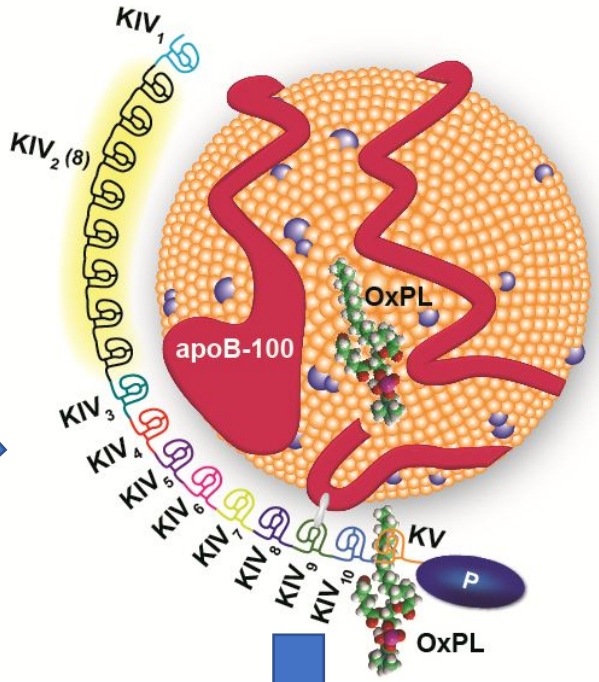


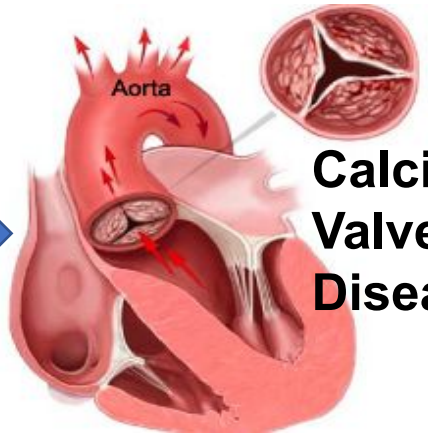
Tsimikas S. et al. *J Am Coll Cardiol.* 2018;71:177-192.

Lp(a) and cardiovascular disease (CVD) risk

Myocardial infarction



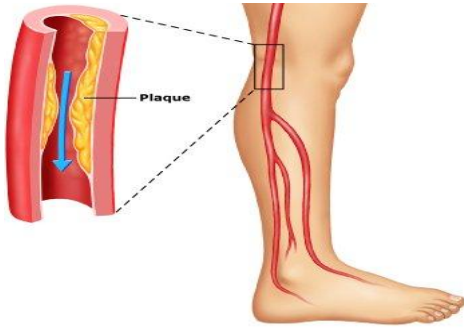




Calcific Aortic Valve Disease

Stroke

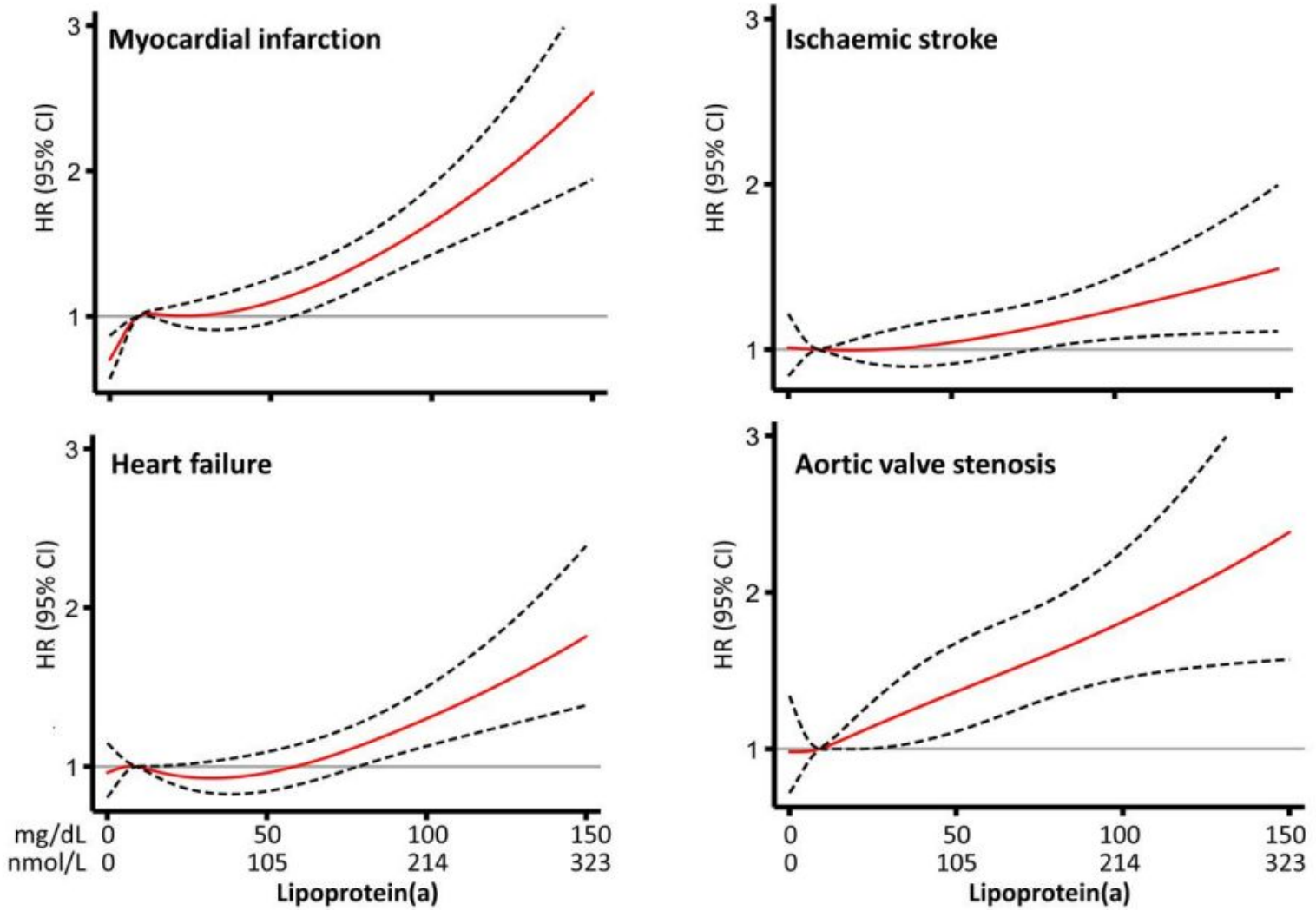
Peripheral Arterial Disease



Mortality

Risk of clinical outcomes with Lp(a) concentration.

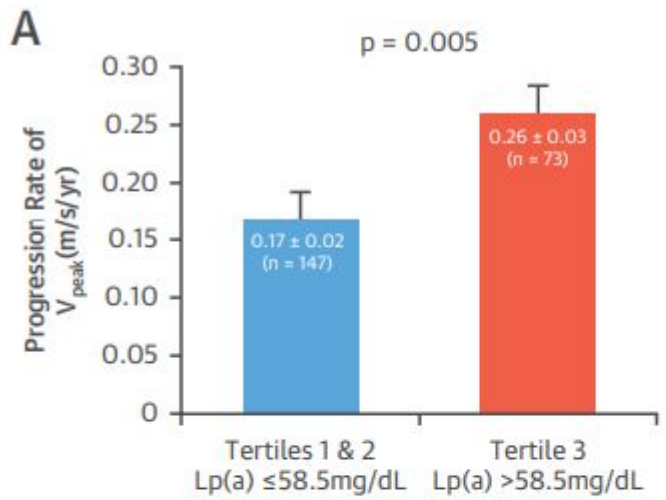
Based on data from 70 286 White individuals in the Copenhagen General Population Study with a median 7.4 years of follow-up.



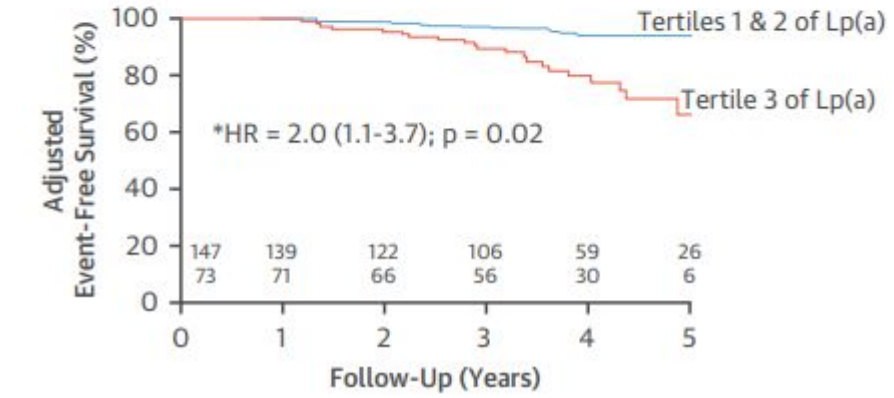
Kronenberg F et al. Eur Heart J. 2022; 43(39):3925–3946.

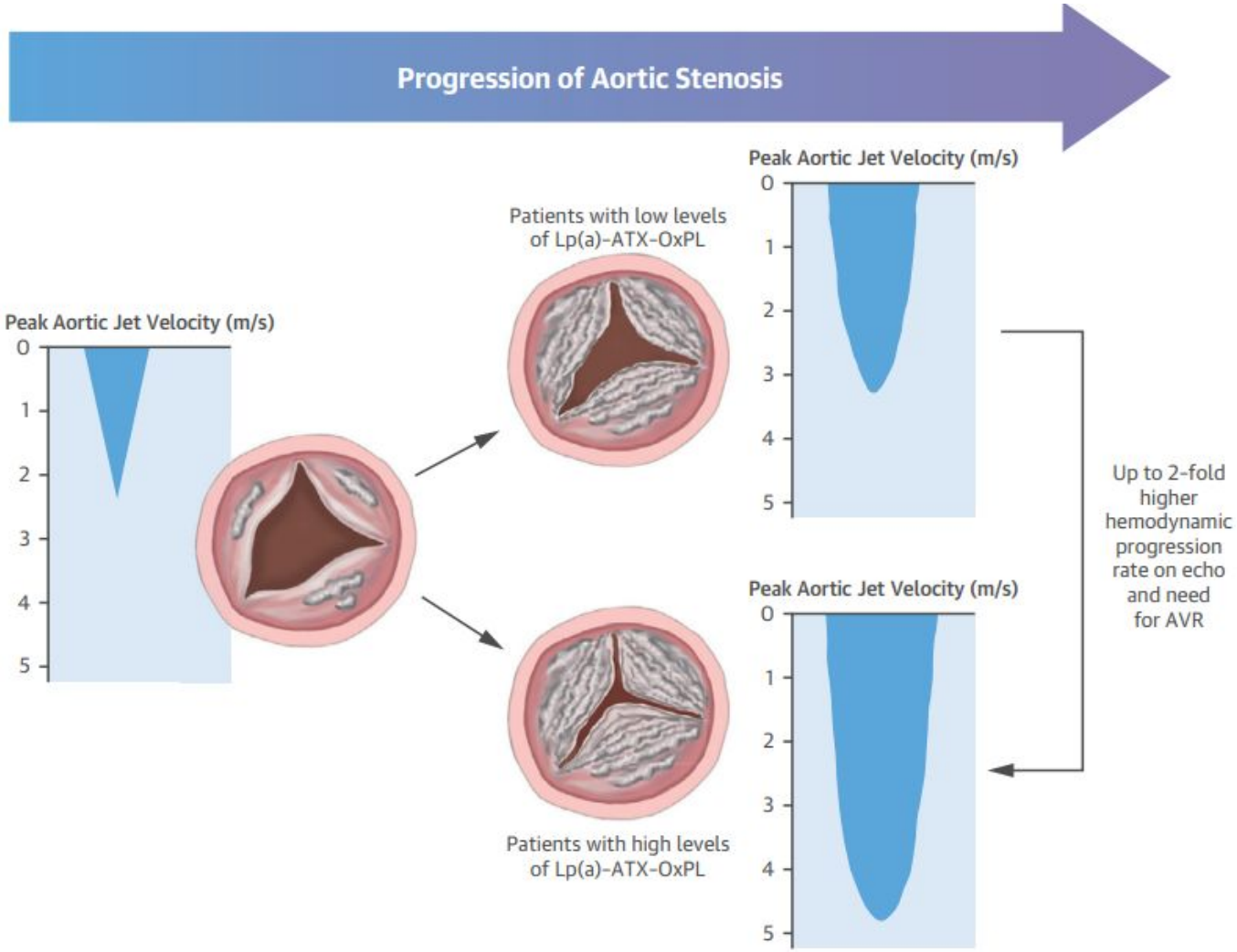
Lp(a) and calcific aortic stenosis

Progression of aortic valve peak velocity



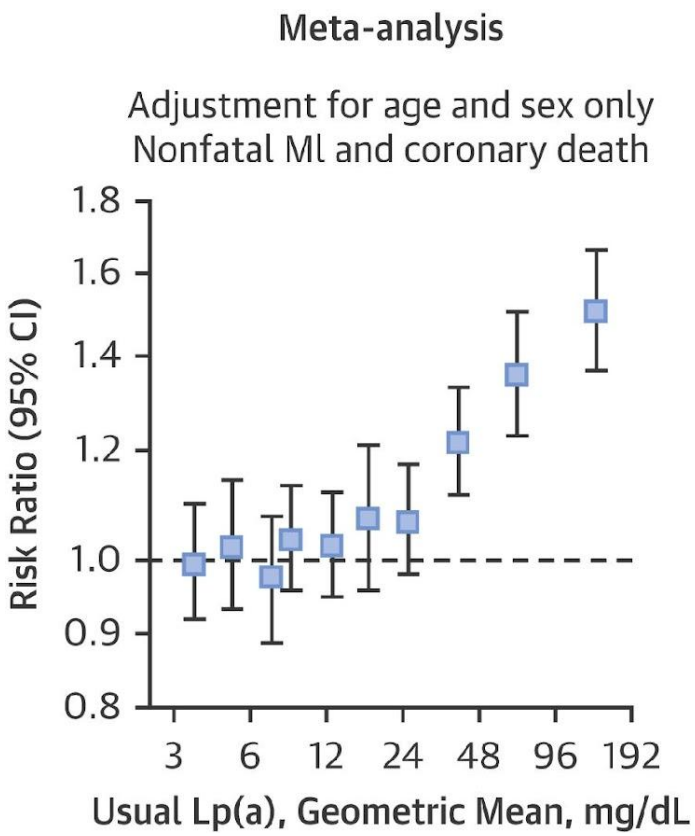
Survival free of AVR

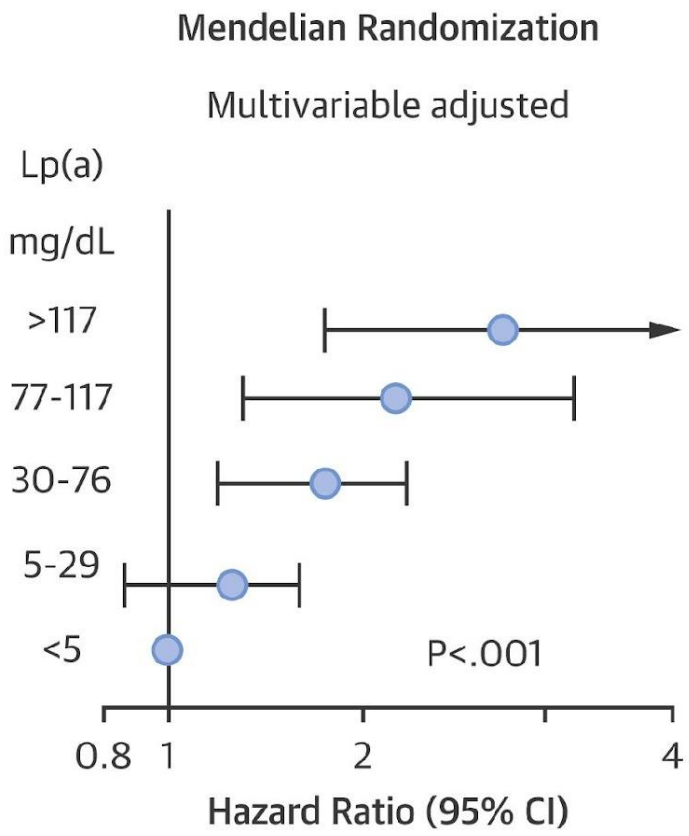


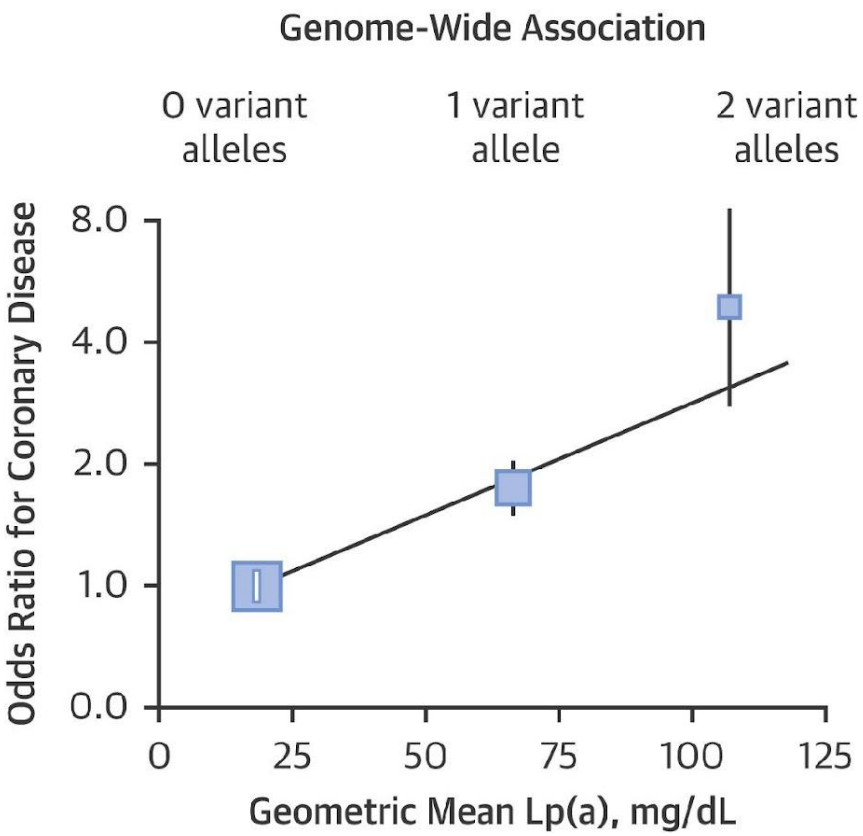


Tsimikas S et al. *J Am Coll Cardiol.* 2017;69:692-711.

Evidence Base for Lp(a) as an Independent, Causal, Genetic Risk Factor for CVD

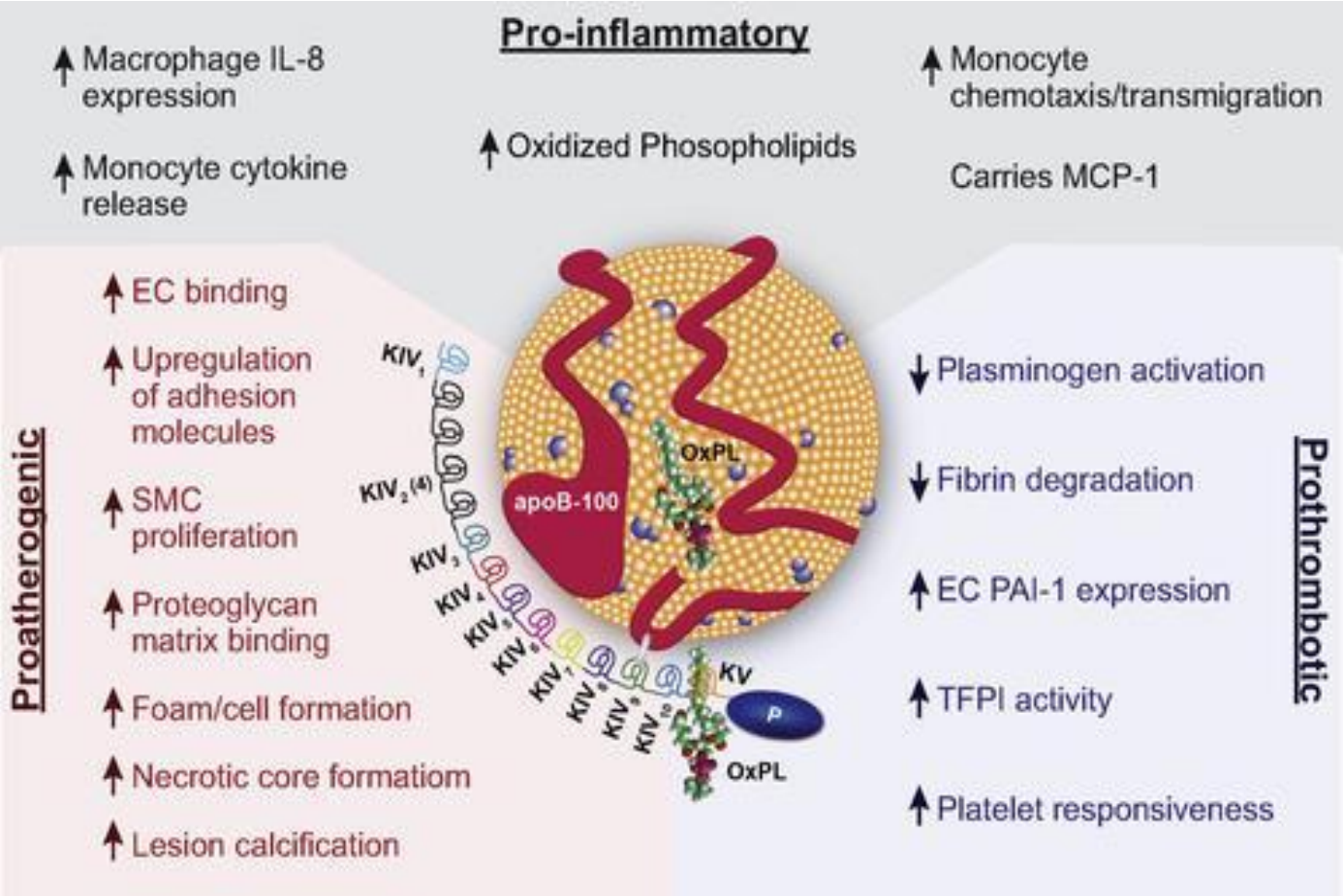






Tsimikas S et al. *J Am Coll Cardiol.* 2017;69:692-711.

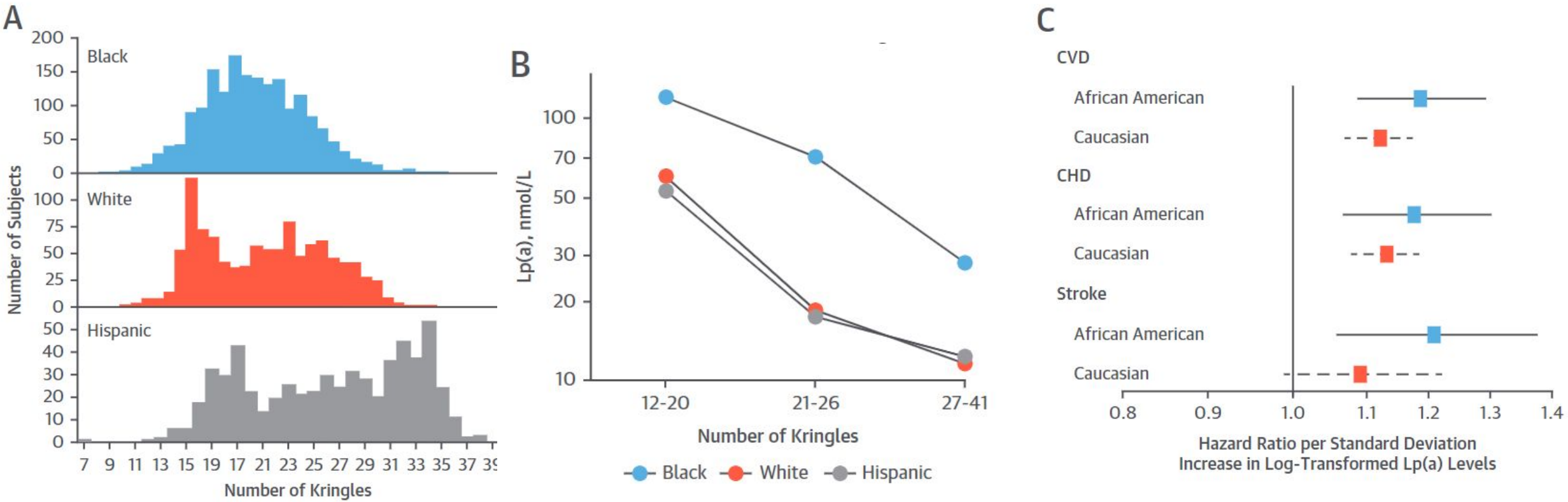
Pathogenic Mechanisms of Lp(a)



- Epidemiologic and genetic studies suggest a potentially causal association between elevated Lp(a) levels, ASCVD and aortic valve stenosis.
- Major lipoprotein carrier of pro-inflammatory oxidized phospholipids
- Promotes CVD through 4 mechanisms:
  - Vascular inflammation
  - Atherogenesis
  - Calcification
  - Thrombosis.

Tsimikas S et al. *J Am Coll Cardiol.* 2017;69:692-711.

Apo(a) Isoform Differences, Lp(a) Values, and CVD Events in Different Racial Groups

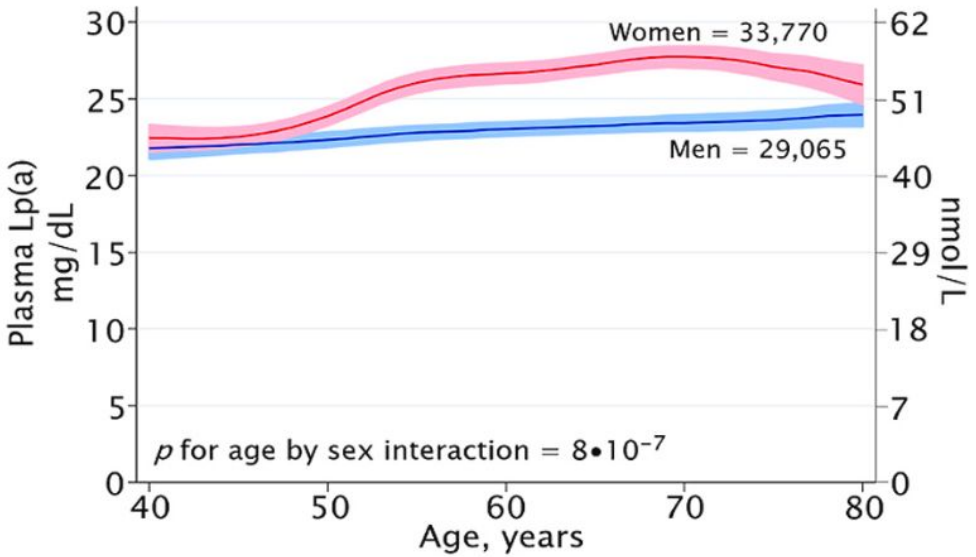


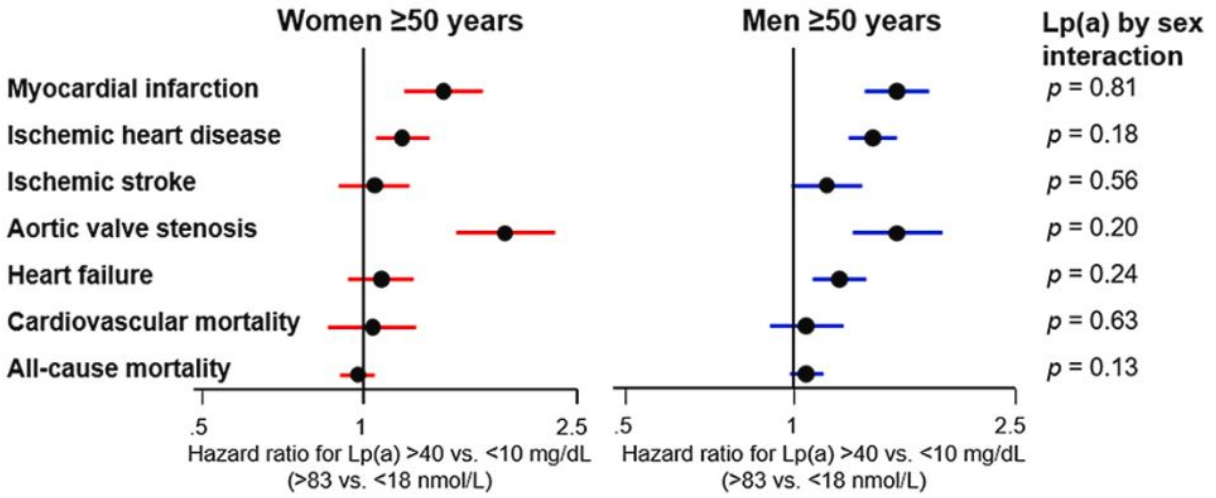
Tsimikas S et al. *J Am Coll Cardiol*. 2017;69:692-711.

Lipoprotein (a) in women

Copenhagen General Population Study (37,545 women & 32,497 men)

Lipoprotein(a) levels increase selectively around age 50 in women.





Similar risk of morbidity and mortality for lipoprotein(a) >40 mg/dL (83 nmol/L) versus <10 mg/dL (18 nmol/L) in women and men above age 50.

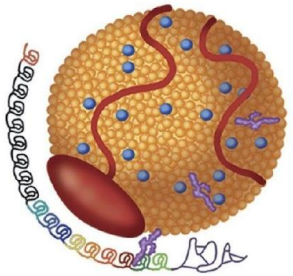
Together, this implies that elevated lipoprotein(a) above age 50 is a relatively more common cardiovascular risk factor in women than in men, pointing toward repeat measurement in women above age 50.

Simony SB et al. Atherosclerosis 2022; 355: 76–82

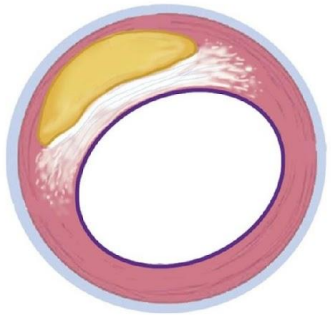
Joint association of Lp(a) and CAC

CENTRAL ILLUSTRATION: Joint Association of Lipoprotein(a) and CAC Score With Atherosclerotic Cardiovascular Disease Risk

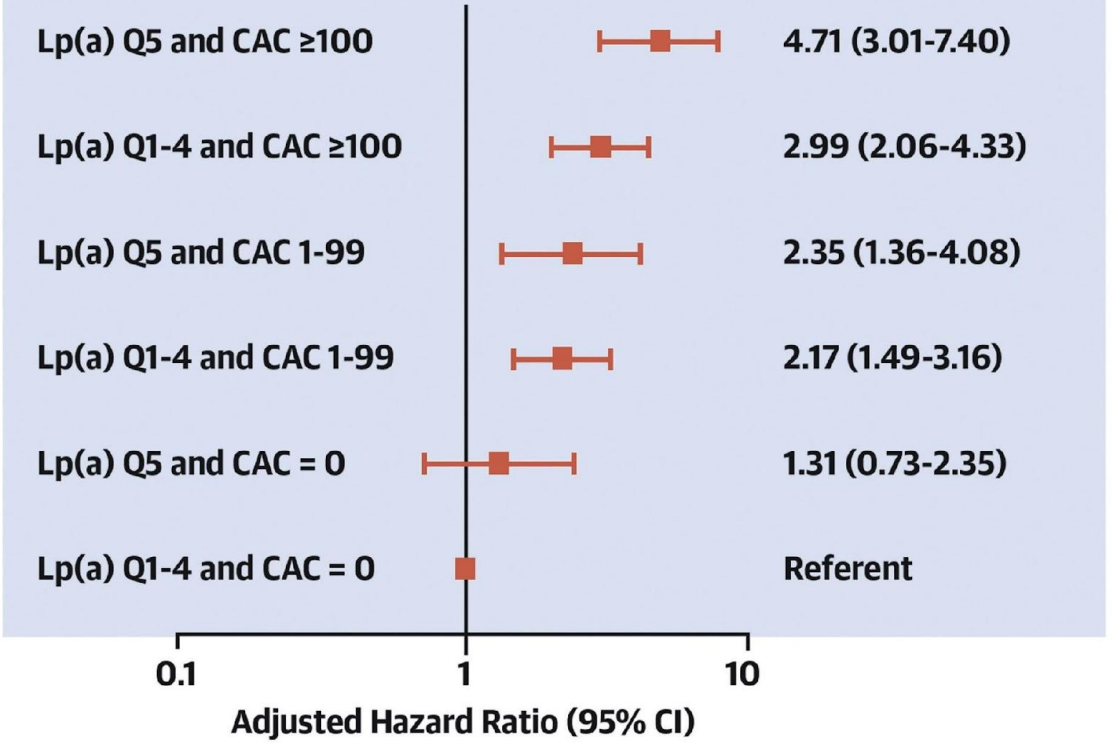
Lipoprotein(a)



CAC Score



Joint Association of Lp(a) and CAC Score With ASCVD Risk



Mehta, A. et al. J Am Coll Cardiol. 2022;79(8):757-768.

When to Measure Lipoprotein(a) (Lp[a]) and Thresholds for Treatment Across Guidelines

2018 American College of Cardiology/American Heart Association Cholesterol Guidelines[19]

- ASCVD not explained by major risk factors
- Family history of premature ASCVD[a]
- Lp(a) levels ≥125 nmol/L (≥50 mg/dL) are considered an ASCVD risk-enhancing factor

2019 National Lipid Association Scientific Statement[20]

- Personal or family history of premature ASCVD[a]
- Personal or family history of severe hypercholesterolemia (LDL-C ≥190 mg/dL) or suspected familial hypercholesterolemia
- Family history of elevated Lp(a)
- Borderline (5% to 7.4%) and intermediate (7.5% to 19.9%) 10-year ASCVD risk (for statin consideration)
- At very high risk of ASCVD (for PCSK9 consideration)[b]
- Partial response to LDL-C–lowering therapy
- Recurrent or progressive ASCVD, despite optimal lipid-lowering therapy
- Calcific aortic valve stenosis
- Lp(a) levels ≥100 nmol/L (≥50 mg/dL) are considered an ASCVD risk-enhancing factor

2019 European Society of Cardiology/European Atherosclerosis Society Guidelines for the Management of Dyslipidaemias[21]

- Measure at least once in each adult person's lifetime (universal screening)
- Lp(a) levels >430 nmol/L (>180 mg/dL) are considered very high risk

2019 HEART UK Consensus Statement[22]

- Personal or family history of premature ASCVD[c]
- First-degree relatives with serum Lp(a) levels >200 nmol/L
- Familial hypercholesterolemia or other genetic dyslipidemias
- Calcific aortic valve stenosis
- Borderline increased (but <15%) 10-year ASCVD risk
- Lp(a) levels >90 nmol/L are considered high risk

2020 Endocrine Society Lipid Management Guidelines[23]

- Family history of premature ASCVD or high Lp(a)
- Personal history of ASCVD
- Lp(a) levels ≥125 nmol/L (≥50 mg/dL) are considered an ASCVD risk-enhancing factor

2021 Canadian Guidelines for the Management of Dyslipidemia[24]

- Measure at least once in each adult person's lifetime (universal screening)
- Lp(a) levels ≥100 nmol/L (≥50 mg/dL) are considered high risk

Duarte Lau F et al. *JAMA Cardiol*. 2022;7(7):760-769.

Risk-Enhancing Factors

Lloyd-Jones DM, et al.
J Am Coll Cardiol 2022
Oct 4;80(14):1366-1418.

Family history of premature ASCVD
(men aged <55 years; women aged <65 years)

Chronic inflammatory conditions

History of premature menopause
(before age 40 years) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia

Primary hypercholesterolemia

High-risk races/ethnicities
(eg, South-Asian ancestry)

Chronic kidney disease

Metabolic syndrome

Lipids/biomarkers associated with increased ASCVD risk

Persistently elevated, primary hypertriglyceridemia (≥175 mg/dL)

If measured:

1. **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
2. **Elevated Lp(a)** ≥50 mg/dL (≥125 nmol/L)
3. **Elevated apoB** ≥130 mg/dL
4. **ABI <0.9**

Incorporating Lp(a) into clinical risk assessment

Lp(a) can be incorporated into 10 year estimated ASCVD risk using the following formula:

Predicted 10-y risk×[1.11$^{\text{(patient's Lp(a) level in nmol/L/50)}}$]

Patient example: For a patient with 10-y risk estimate of 10.0%, who has an Lp(a) level of 250 nmol/L, the updated predicted risk estimate would be:

10.0 %×1.11$^{(250\ /50)}$ =

10.0%×1.11^{5} =

10.0%×1.69 = 16.9%

Reyes-Soffer G et al, ATVB 2022;42(1):e48-e60.

EAS recommendations: Intervention strategies as a function of total cardiovascular risk and untreated Lp(a) concentration.

B

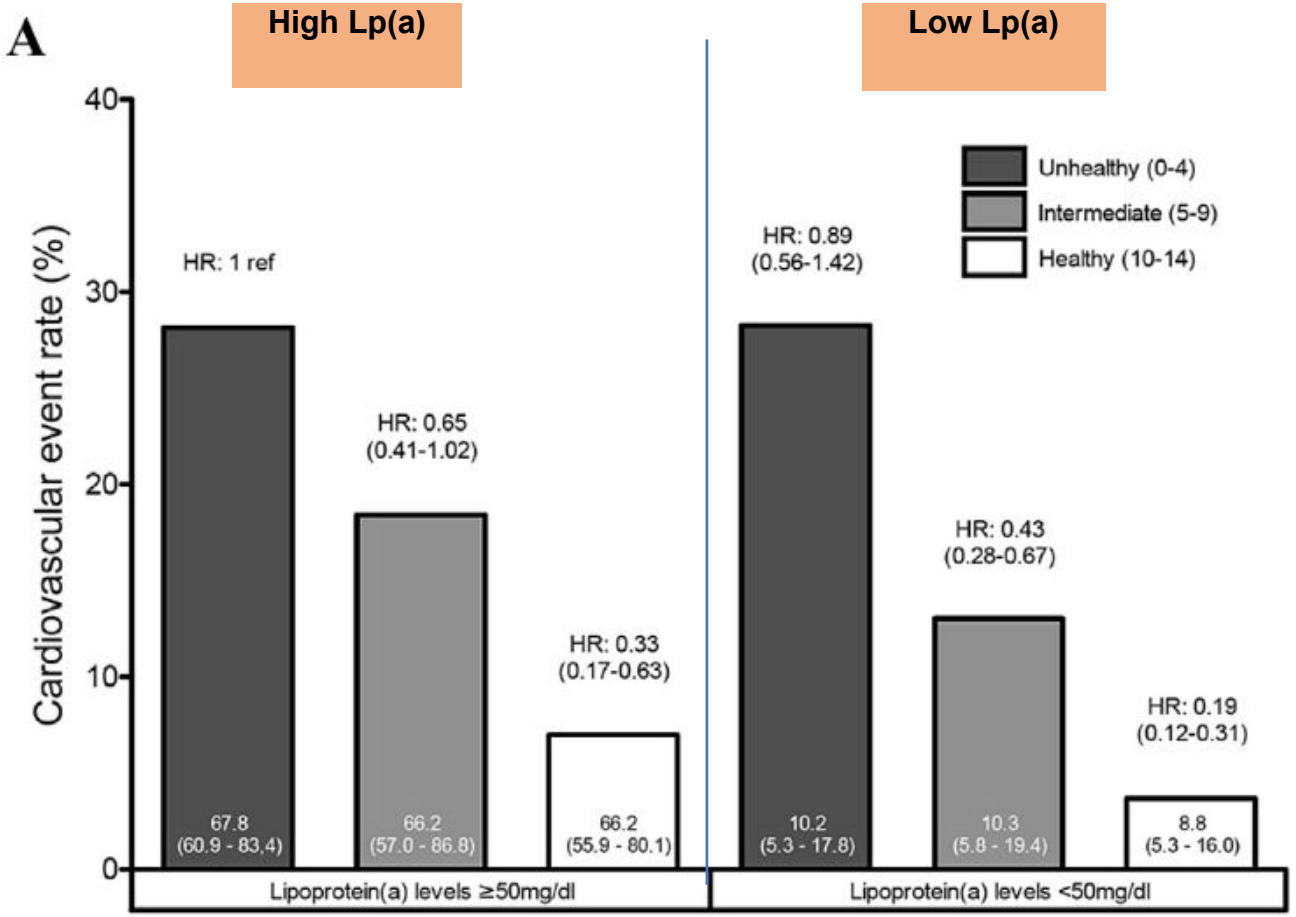
	Total CV risk (SCORE) %	Untreated Lp(a) concentrations					
		< 10 mg/dL < 25 nmol/L	10 to <30 mg/dL 25 to <75 nmol/L	30 to <50 mg/dL 75 to <125 nmol/L	50 to <75 mg/dL 125 to <188 nmol/L	75 to <100 mg/dL 188 to <250 nmol/L	≥100 mg/dL ≥250 nmol/L
Primary Prevention	< 1 low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
Primary Prevention	≥1 to <5, or moderate-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
Primary Prevention	≥5 to <10, or high- risk	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
Primary Prevention	≥10, or at very-high risk due to a risk condition	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
Secondary Prevention	Very-high-risk	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)

Kronenberg F et al. Eur Heart J. 2022; 43(39):3925–3946.

Ideal cardiovascular health influences cardiovascular disease risk associated with high lipoprotein(a) levels

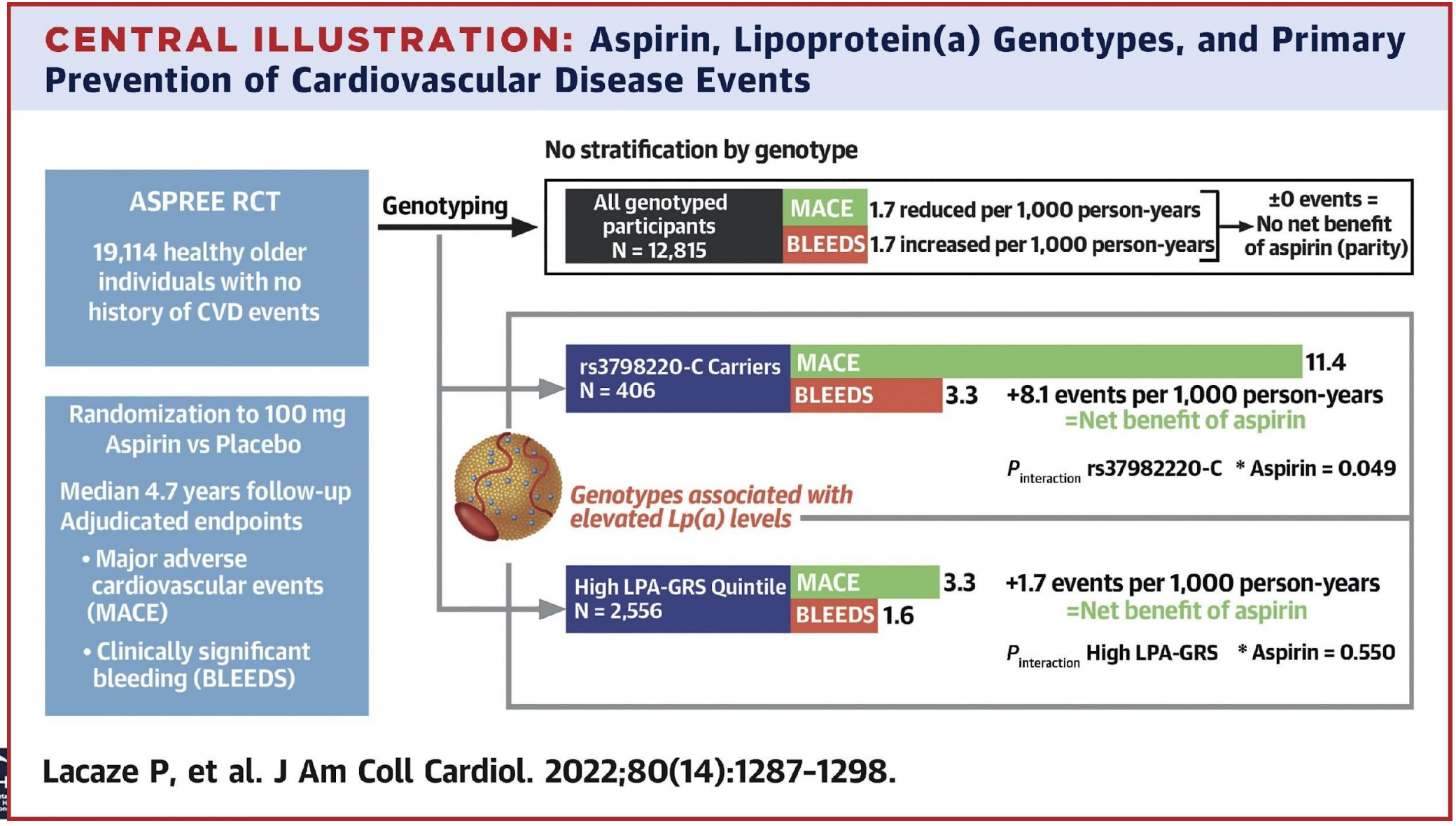
14,051 participants of the EPIC-Norfolk study followed for 11.5 years

CVD Events



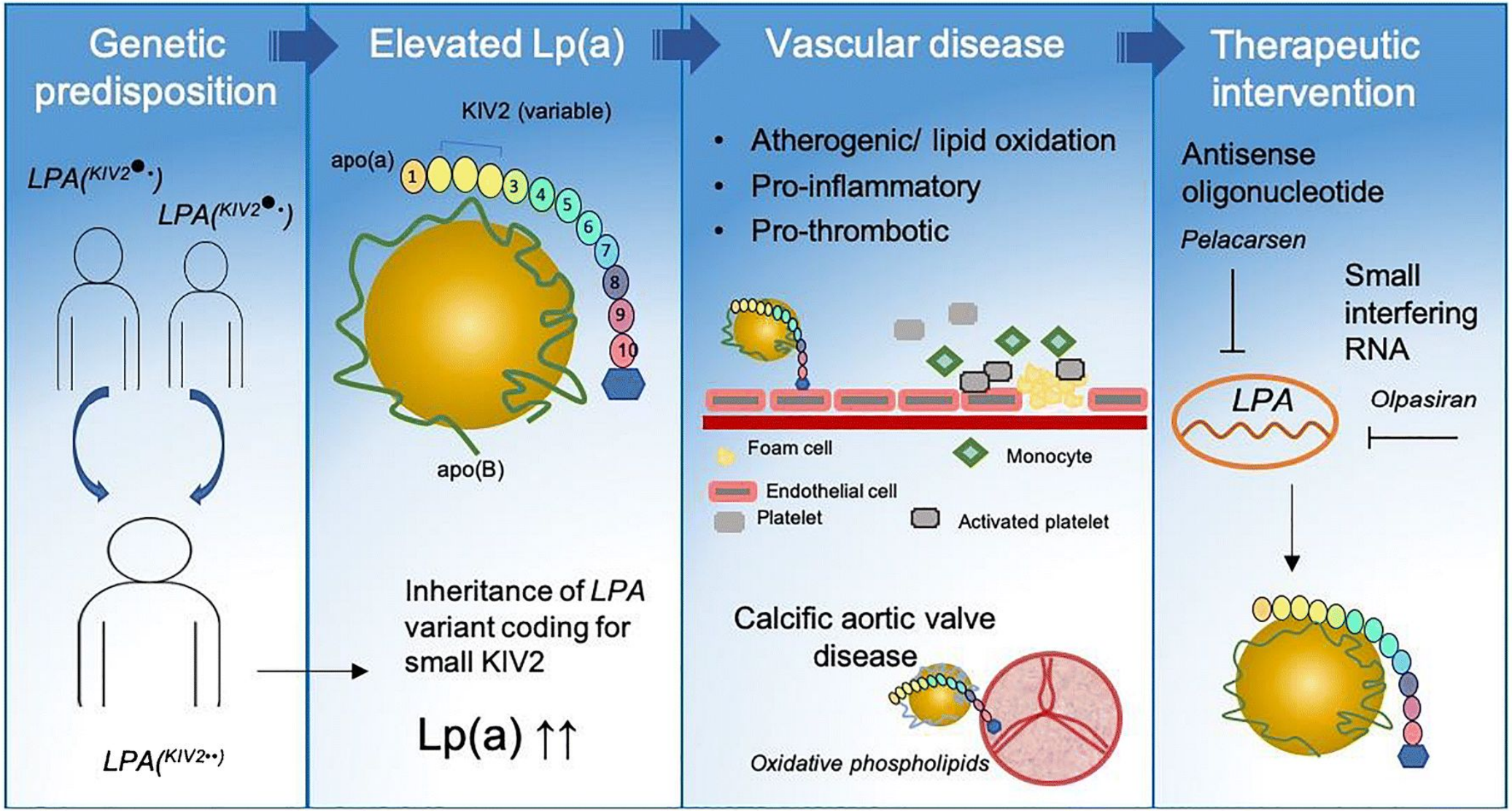
Perrot N et al. Atherosclerosis 2017; 256: 47-52.

Aspirin may benefit older individuals with elevated lipoprotein(a) genotypes in primary prevention.



Lacaze P, et al. J Am Coll Cardiol. 2022;80(14):1287-1298.

Lp(a) – emerging risk factor

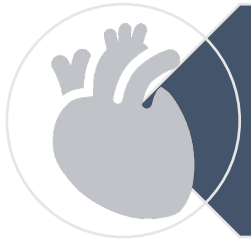


Nicholls SJ et al. Curr Cardiol Report 2021

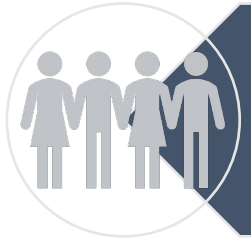
Why measure Lipoprotein (a)?

Identify individuals with very high Lp(a)

Reclassify borderline, intermediate, and high risk individuals



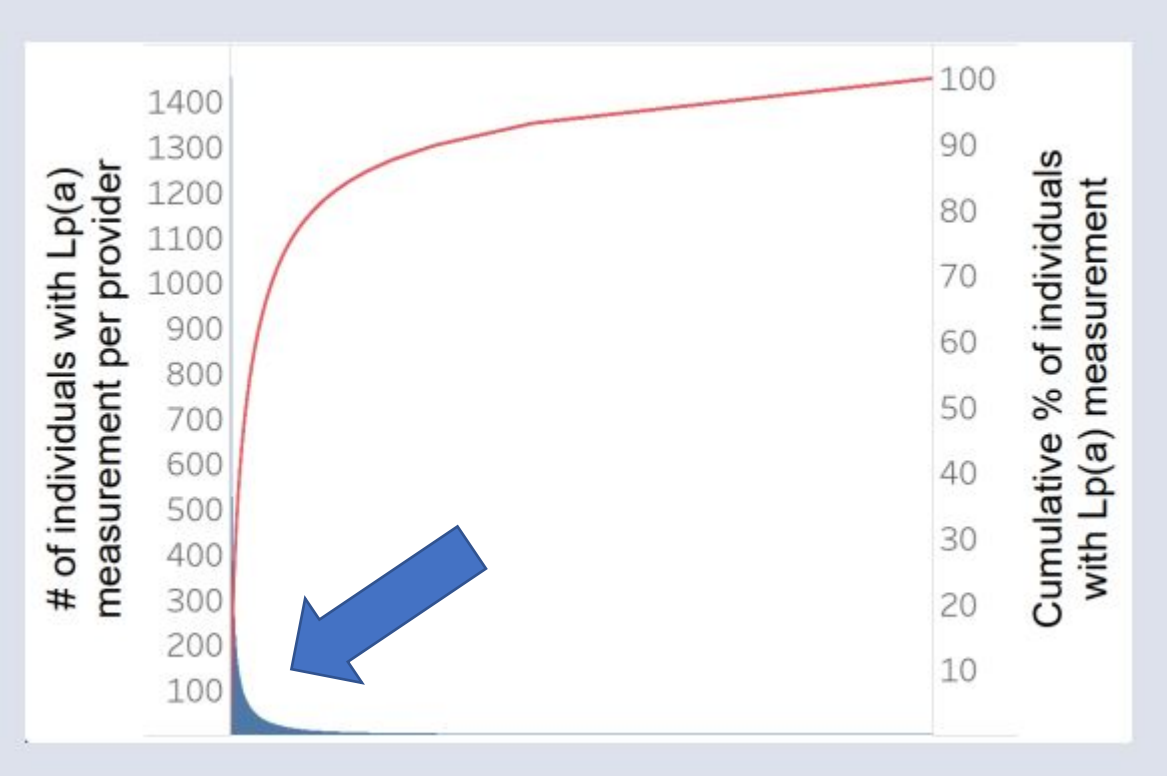
Optimize management and treatment of other CVD risk factors

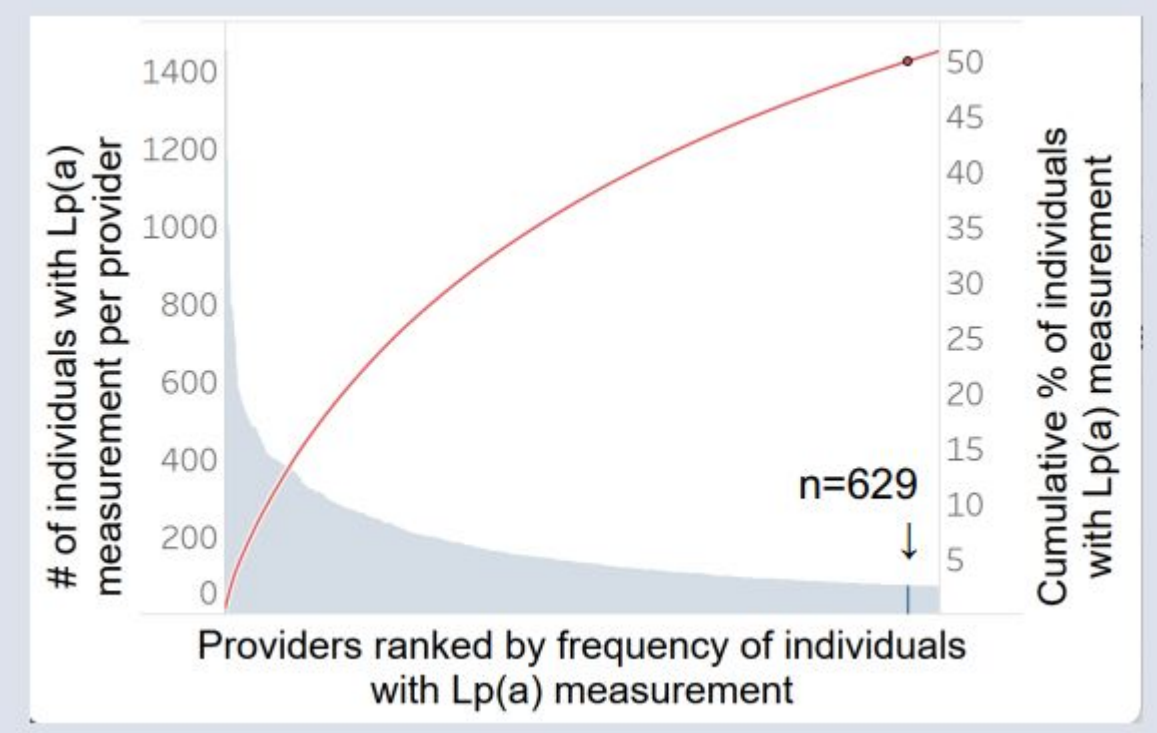


Identify familial risk, cascade testing

Measurement of Lp(a) was rare within a large US health care dataset

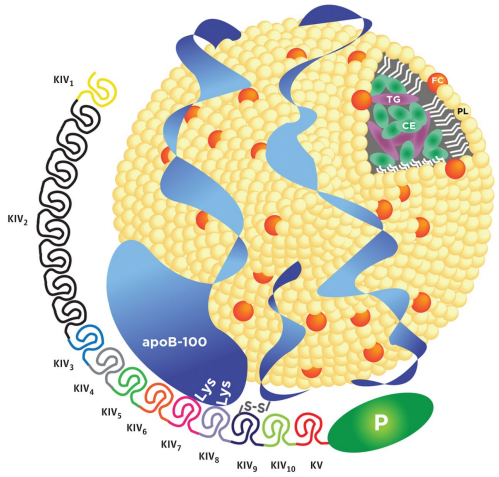
- Out of >112 million Americans with claims data for ASCVD screening or treatment from 2012-2019, **only 0.3% received Lp(a) screening**.
- Of HCPs in the U.S., **<0.1%** (n=629 of 810,119) **are responsible for ordering 50% of Lp(a) tests**





MacDougall DE, McGowan MP, Wilemon KA, Ahmed CD, Myers KD. Characterization of Lp(a) Measurement In a Large U.S. Health Care Dataset. *J Clin Lipidol*. 2022;16:e36-e37. Presentation at the National Lipid Association Scientific Sessions, June 2023.

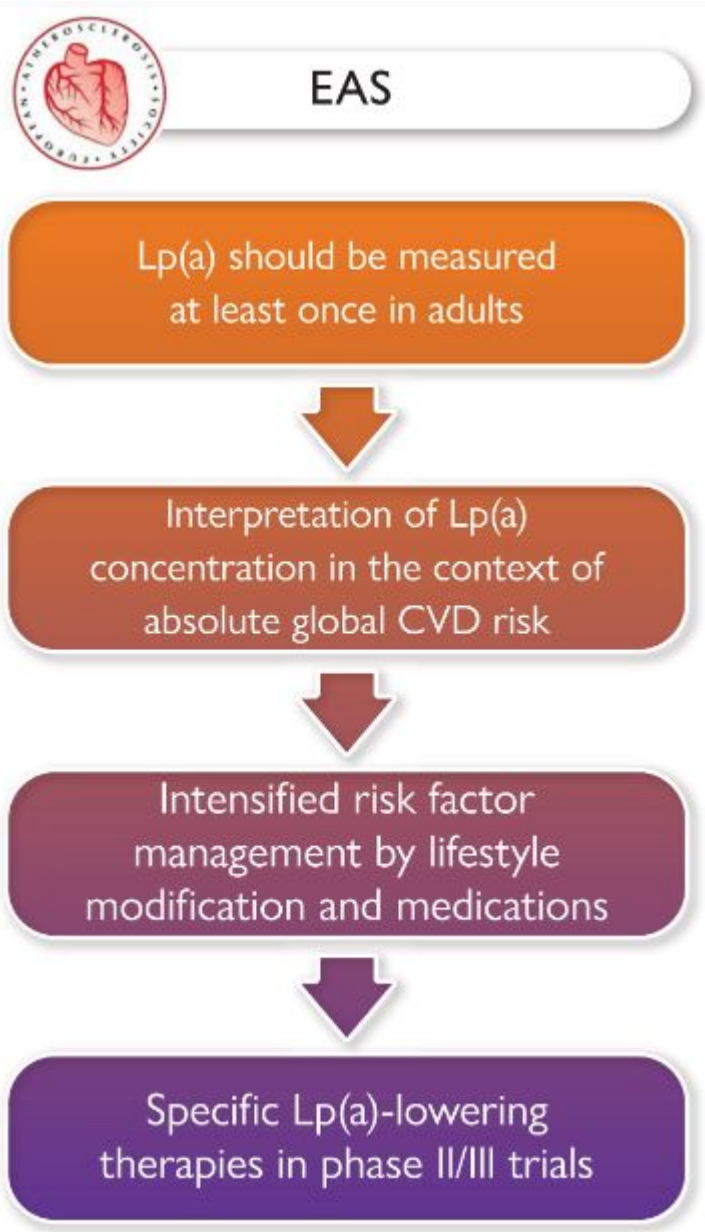
How should one measure Lp(a)?



- Use isoform insensitive assay, reported in nmol/L
- Lp(a) test costs between $25 to $100 dollars, which is comparable to a standard lipid profile,
  - a once in a lifetime measurement of Lp(a) potentially may be cost-effective
- CPT® code 83695 for Lp(a) test
- ICD-10 code for personal or family history of ASCVD may help with insurance overage
- There are also two ICD-10 codes for Lp(a);
  - E78.41 [Elevated Lp(a)] and Z83.430 [Family history of elevated Lp(a)]

Conclusions

- Lp(a) has pro-inflammatory and pro-atherosclerotic properties, which may partly relate to the OxPLs carried by Lp(a).
- High Lp(a) induces the expression of inflammatory and calcification genes in vascular and valvular cells and associates with increased incidence and progression of AV stenosis.
- In the absence of specific Lp(a)-lowering therapies, early risk factor management is recommended for individuals with elevated Lp(a), taking into account their absolute global cardiovascular risk and Lp(a) level.



Kronenberg F et al. Eur Heart J. 2022; 43(39):3925–3946.

Current and emerging treatments for elevated Lp(a)

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Houston, Texas

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Financial Disclosure

- **Grant/Research Support:** Abbott Diagnostic, Akcea, Amgen, Arrowhead, Esperion, Ionis, Merck, New Amsterdam, Novartis, Novo Nordisk, Regeneron, Roche Diagnostic, NIH, AHA, ADA (all paid to institution, not individual)
- **Consultant:** Abbott Diagnostics, Alnylam Pharmaceuticals, Althera, Amarin, Amgen, Arrowhead, Astra Zeneca, Denka Seiken, Esperion, Genentech, Gilead, Illumina, Ionis, Matinas BioPharma Inc, Merck, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, TenSixteen Bio

Impact of LDL-lowering therapies on Lp(a)

No/minimal impact

- Diet[1] (saturated fat may lower slightly)[2]
- Bempedoic acid[3]
- Ezetimibe[3]
  - Possible reduction, 0-5%

Reduction

- Niacin[3]
  - ~20% (no benefit RCT + statin)
- **PCSK9 inhibitors (mAb/siRNA)[3]**
  - **20-25% (benefit RCT + statin)**
- Lipoprotein apheresis[3]
  - 70-80% (benefit in observational data)
- Lomitapide[4] (HoFH only)
  - ~13% (no outcomes data)

Possible increase

- Statins[3]
  - Possible increase, 0-10%

There are currently no approved pharmacological therapies for lowering Lp(a).

HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, randomised control trial; siRNA, small interfering RNA.

1. Enkhmaa B et al. *Nutrients*. 2020;12(7):2024; **2.** Ginsberg HN et al. *Arterioscler Thromb Vasc Biol.* 1998;18(3):441-449; **3.** Schwartz GG, Ballantyne CM. *Atherosclerosis.* 2022;349:110-122; **4.** Rader DJ, Kastelein JJP. *Circulation* 2014;129(9):1022-1032.

Treatment options for reduction of CV events in patients with elevated Lp(a) levels

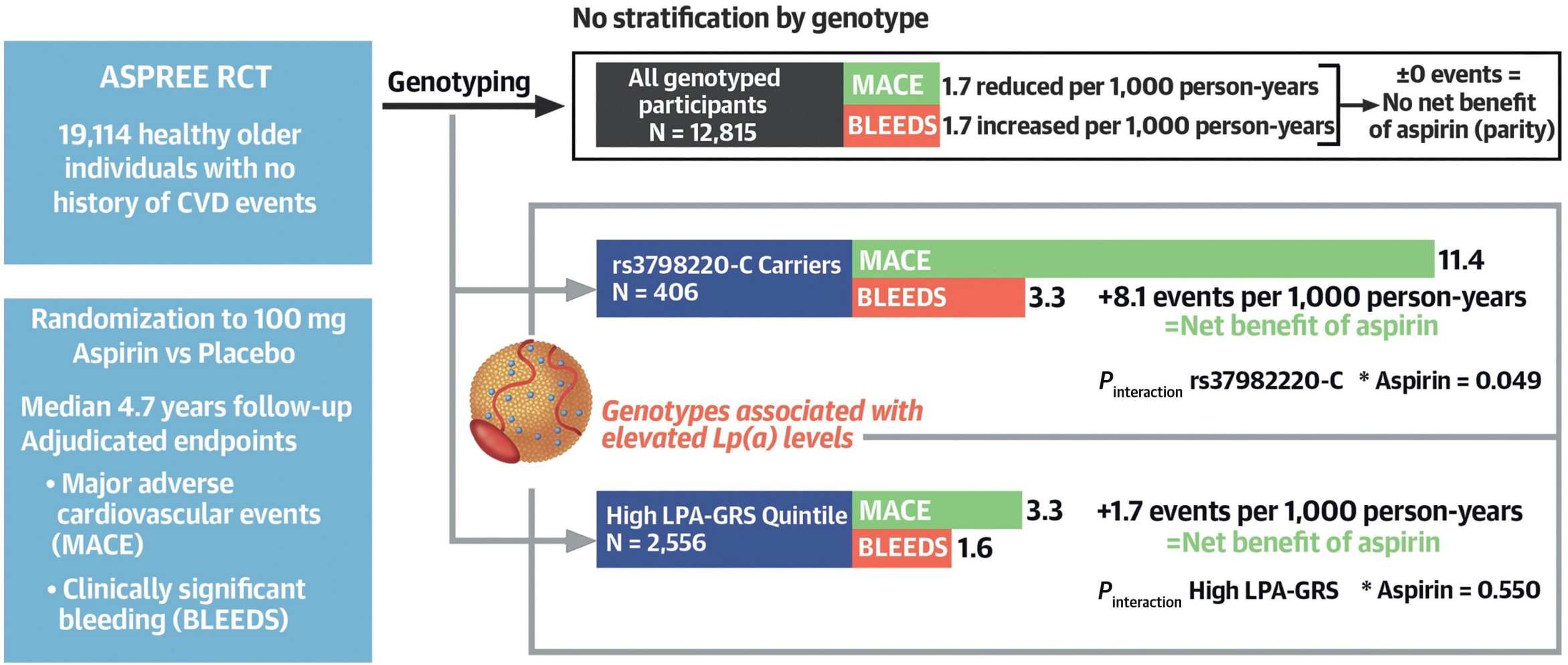
Treatment	Status of analyses
Aspirin[1]	Post hoc analyses, observational data
Statins[2]	Post hoc analyses from more than one study
PCSK9 inhibitors (mAbs and siRNA)[2]	Post hoc analyses
Lipoprotein apheresis[1]	Post hoc analyses

There are currently no approved pharmacological therapies for lowering Lp(a).

CV, cardiovascular; Lp(a), lipoprotein(a); mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA.

1. Schwartz GG, Ballantyne CM. *Atherosclerosis.* 2022;349:110-122; **2.** Hoogeveen RC et al. *Clin Chem.* 2021;67(1):143-153.

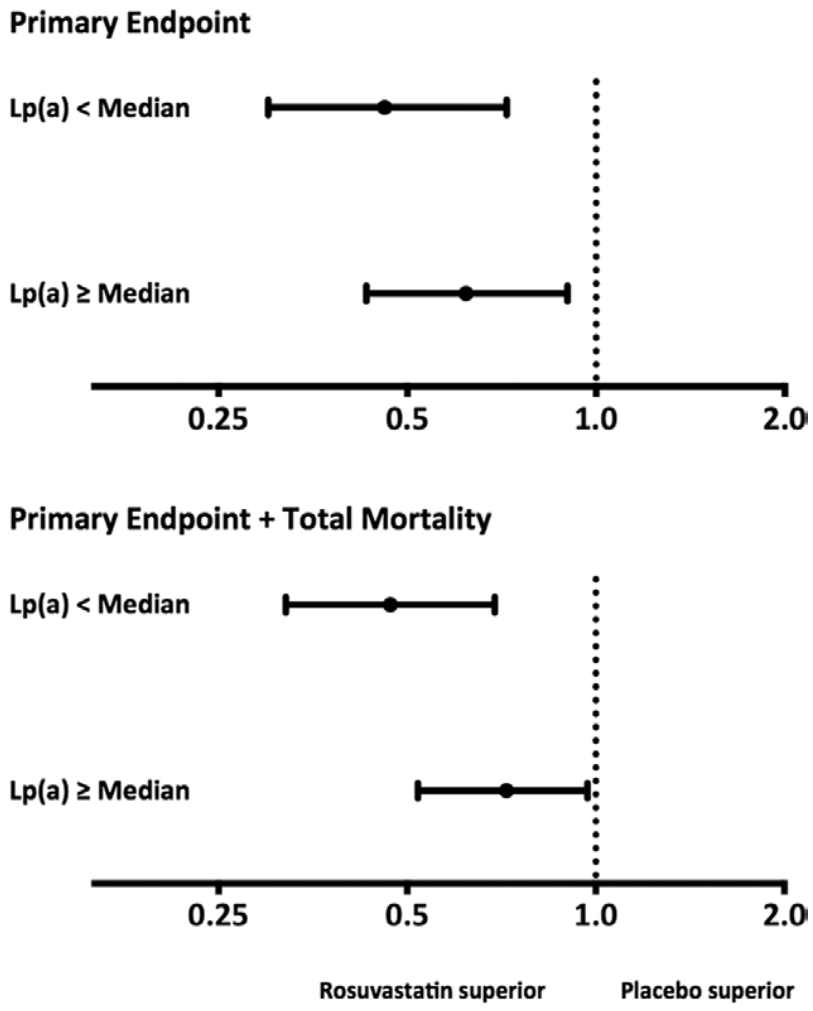
Aspirin may be beneficial for primary prevention in older patients with elevated Lp(a)



CVD, cardiovascular disease; Lp(a), lipoprotein(a); LPA-GRS, lipoprotein(a) genomic risk score; MACE, major adverse cardiovascular events; RCT, randomised controlled trial.

Figure used with permission from Lacaze P et al. *J Am Coll Cardiol.* 2022;80(14):1287-1298.

JUPITER: Lp(a) and Residual Risk with Rosuvastatin



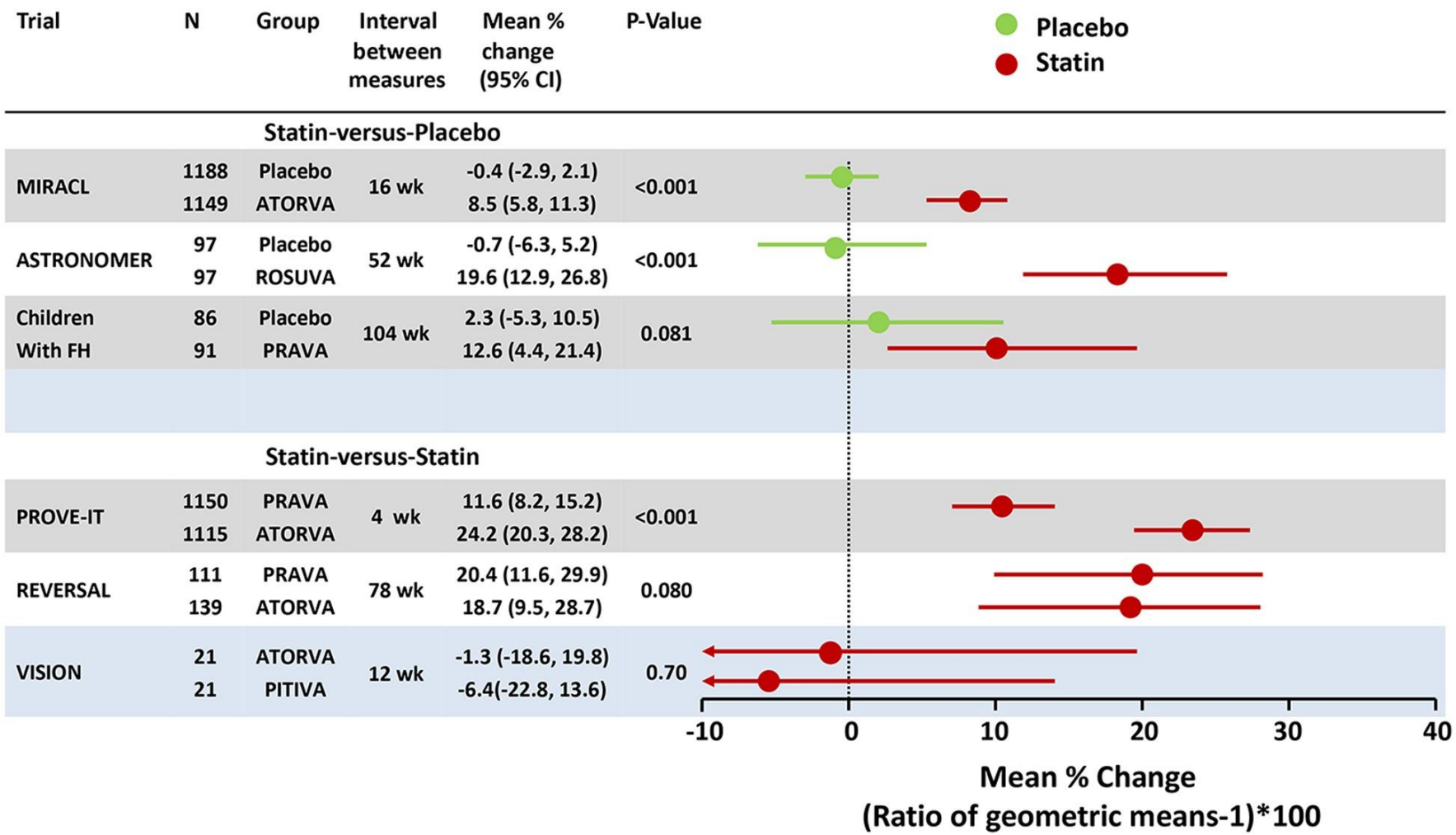
Khera AV et al. *Circulation* 2014;129:635-642.

JUPITER trial (n = 9612): Lp(a) was a significant determinant of residual risk in White patients treated with rosuvastatin

- Median change in Lp(a) with rosuvastatin and placebo was 0
- However, rosuvastatin resulted in small statistically significant positive shift in overall Lp(a) distribution in White patients
- Baseline and on-statin Lp(a) concentrations were associated with increased CV risk
- Rosuvastatin significantly reduced incident CVD regardless of baseline Lp(a)
- **On-statin Lp(a) concentrations were associated with residual risk of CVD, independent of LDL-C and other factors in White patients**

CV, cardiovascular; CVD, cardiovascular disease; Lp(a), lipoprotein(a); LDL-C, low-density lipoprotein cholesterol.
Khera AV et al. *Circulation.* 2014;129(6):635-642.

Effect of Statins on on Lp(a) Level: Meta-Analysis of 6 Studies (5256 Participants)



Tsimikas S et al. *Eur Heart J* 2020;41:2275-2284.

Effect of Statins on on Lp(a) Level: Meta-Analysis of 39 Studies (24,448 Participants)

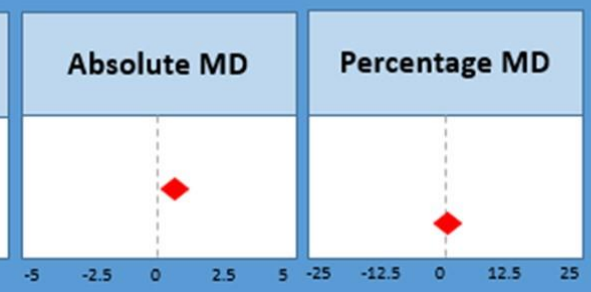
The effect of statins vs. placebo on Lp(a) levels

Conclusion
Statin therapy does not lead to clinically important differences in Lp(a) levels as compared to placebo

39 Randomized controlled trials
24,448 participants

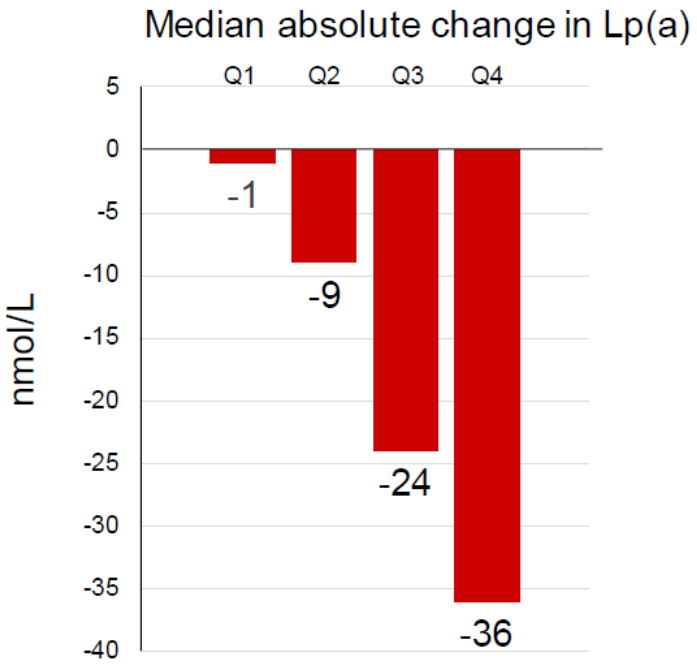
Statin arms	Placebo arms
12,411 participants	11,221 participants

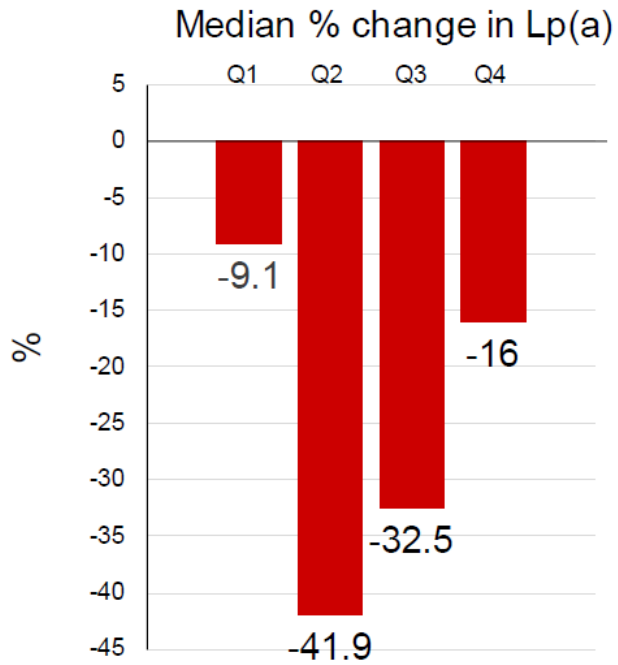
Comparison	Mean Difference (95% CI)	Absolute MD	Percentage MD	Certainty of Evidence (GRADE)
Statins vs. Placebo				
Absolute change	1.1 mg/dl (0.5 to 1.6)			⊕⊕⊕◯ Moderate
Percentage change	0.1% (-3.6 to 4.0)			⊕⊕⊕◯ Moderate

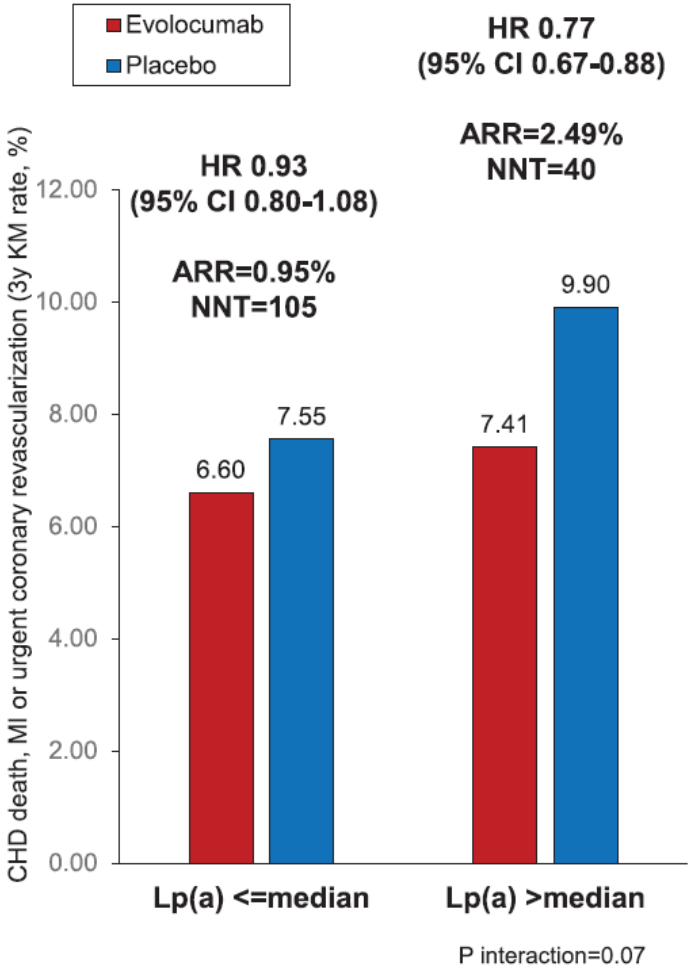


DeBoer LM et al. *Eur J Prev Cardiol* 2022;29:779-792.

FOURIER trial: Evolocumab reduces Lp(a) and risk of CV outcomes







ARR, absolute risk reduction; CV, cardiovascular; HR, hazard ratio; KM, Kaplan-Meier; Lp(a), lipoprotein(a); MI, myocardial infarction; NNT, number needed to treat.
Figures used with permission from O'Donoghue ML et al. *Circulation.* 2019;139(12):1483-149.

ODYSSEY Outcomes: Greater absolute effect of alirocumab on MACE with higher baseline Lp(a)

Subgroup	MACE Incidence Alirocumab n/N (%)	MACE Incidence Placebo n/N (%)	HR (95% CI) ($p_{interaction}$ = 0.55)	Absolute Risk Reduction (95% CI) ($p_{interaction}$ = 0.0011)
Quartile 1	211/2,327 (9.1)	228/2,403 (9.5)	0.95 (0.79, 1.15)	0.4% (-1.2, 2.1)
Quartile 2	219/2,438 (9.0)	239/2,293 (10.4)	0.85 (0.71, 1.03)	1.4% (-0.3, 3.1)
Quartile 3	212/2,356 (9.0)	269/2,373 (11.3)	0.79 (0.66, 0.94)	2.3% (0.6, 4.1)
Quartile 4	261/2,341 (11.2)	316/2,393 (13.2)	0.83 (0.70, 0.98)	2.1% (0.2, 3.9)
Overall	903/9,462 (9.5)	1,052/9,462 (11.1)	0.85 (0.78, 0.93)	1.6% (0.7, 2.4)

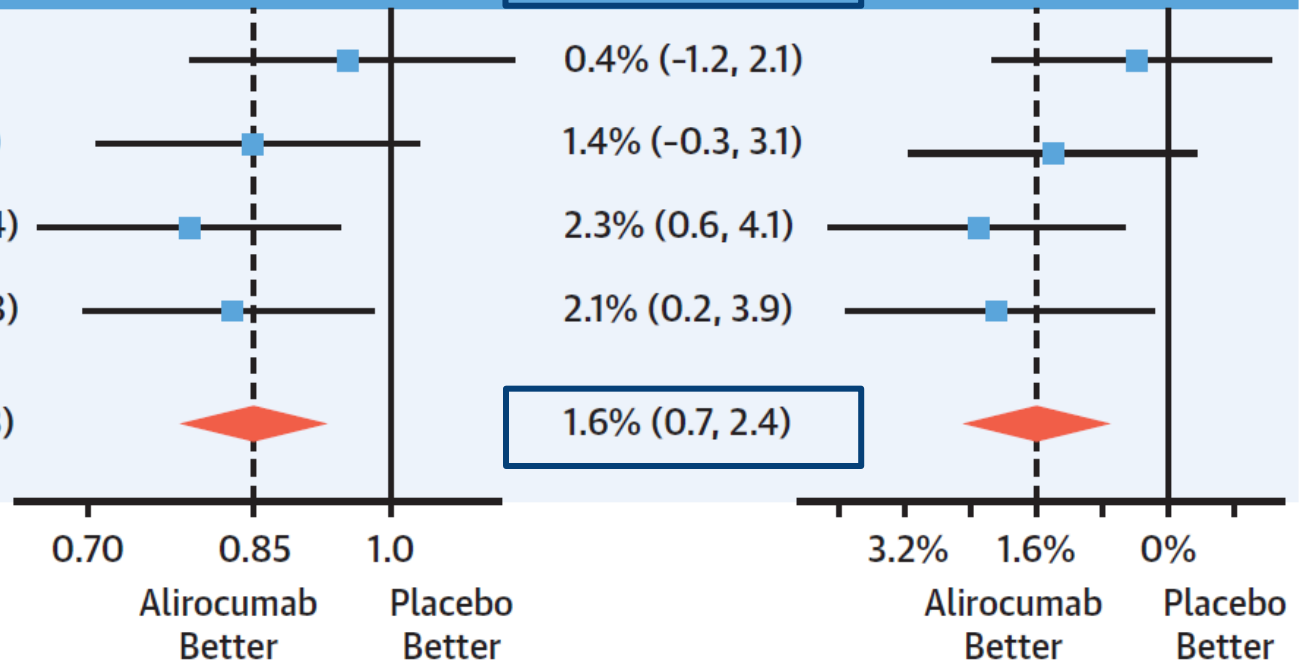
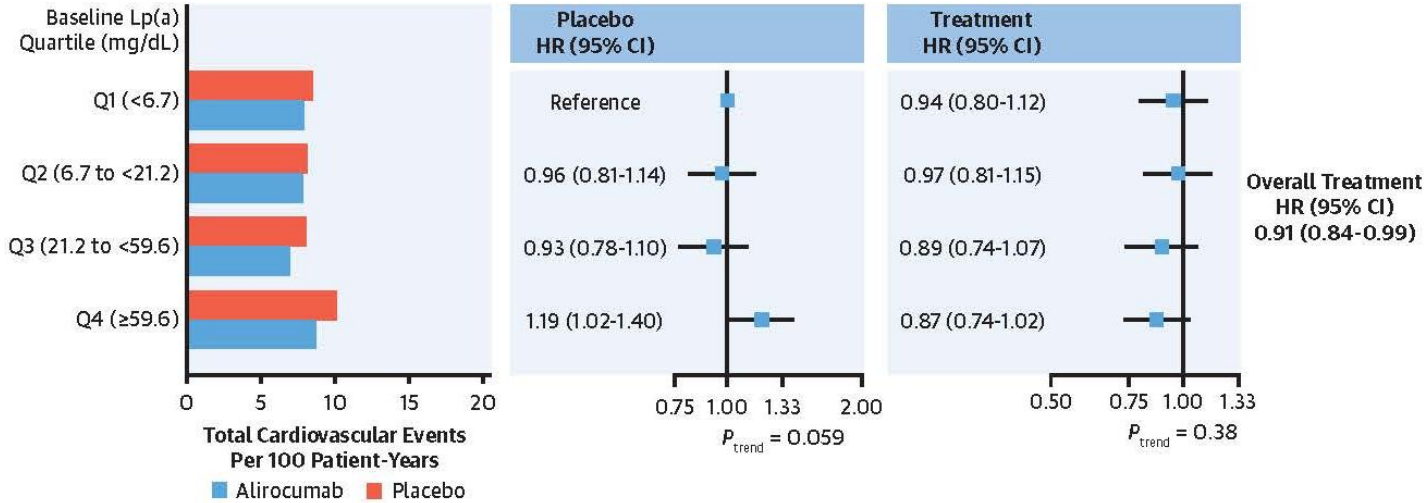


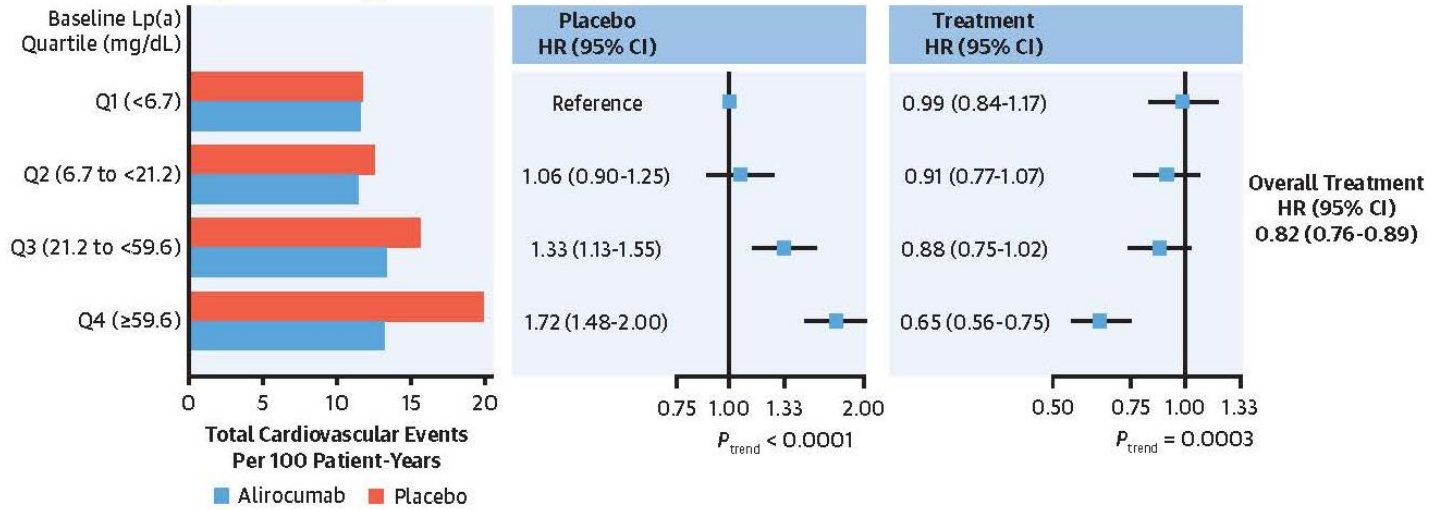
Figure used with permission from Bittner VA, et al. *Journal of the American College of Cardiology*. 2020;75(2):133-44.

ODYSSEY Outcomes trial: Elevated hsCRP amplifies the relationship of Lp(a) with risk of CV events after ACS and the reduction in that risk with alirocumab

Baseline hsCRP <2 mg/L n = 10,323



Baseline hsCRP ≥2 mg/L n = 10,323



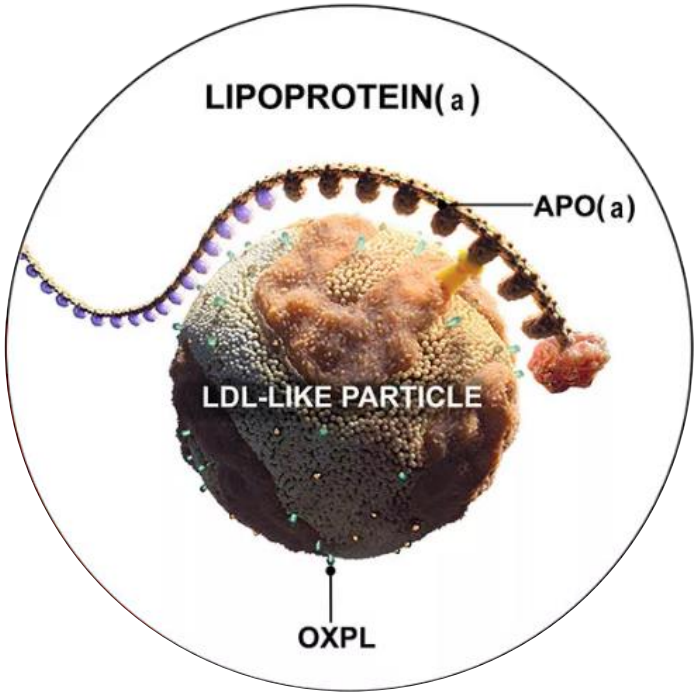
ACS, acute coronary syndrome; CV, cardiovascular; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein(a).

Figure used with permission from Schwartz GG et al. *J Am Coll Cardiol.* 2022;80(24):2356-2359.

Lipoprotein Apheresis
FDA approved for Lp(a) lowering

Manage all of your risk factors for heart attack and stroke

- Manage cholesterol levels
- Manage blood glucose
- Manage blood pressure
- Emerging risk factors



- Maintain healthy diet
- Maintain healthy weight
- Regular exercise
- No smoking

Apo(a), apolipoprotein A; LDL, low-density lipoprotein; OXPL, oxidized phospholipids.

Garcia M et al. *Circ Res.* 2016;1(8):1273-1293.

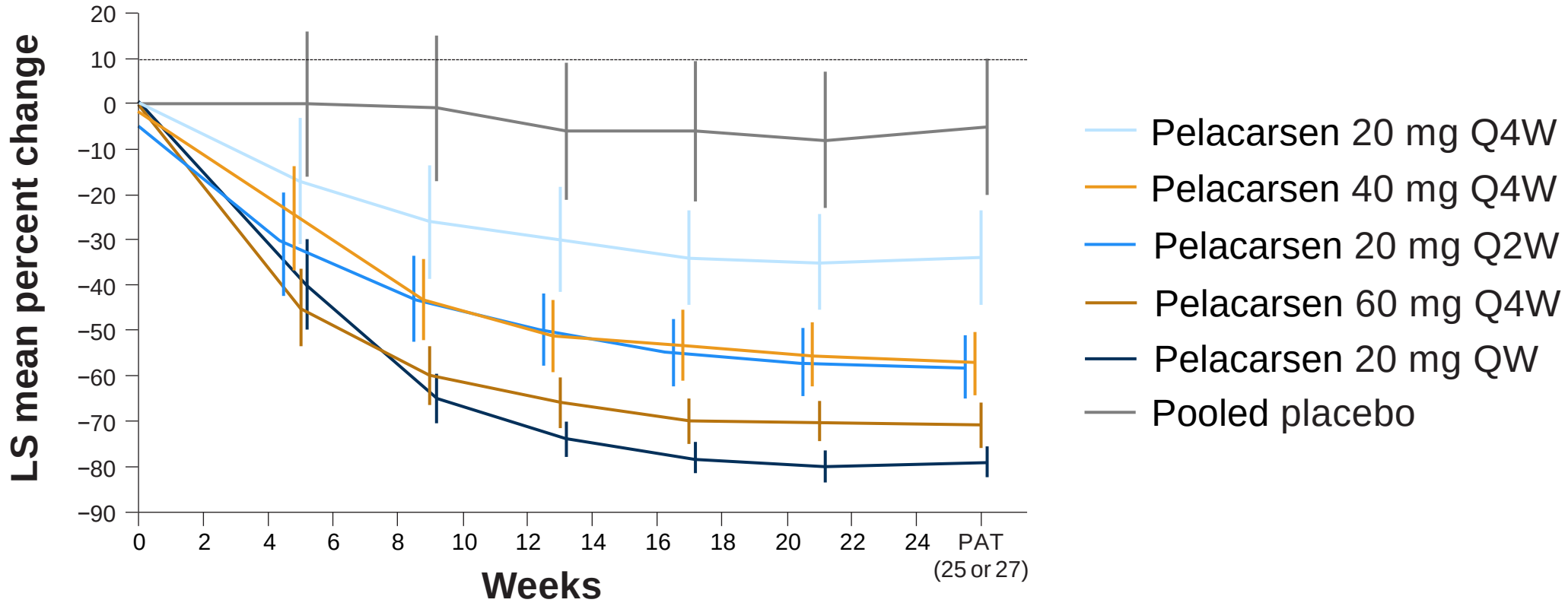
Lp(a) therapies in development

Agent	Mechanism of Action	Clinical Trial Phase	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	↓ 35–80%
Olpasiran (formerly AMG 890, ARO-LPA)	siRNA to apo(a)	3: OCEAN(a) outcomes trial now enrolling	↓ 70–99%
Zerlasiran (SLN360)	siRNA to apo(a)	2: ALPACAR-360 enrolled	↓ 46–98%
Muvalaplin (LY3473329)	Oral small molecule binds to apo(a)	2: KRAKEN recruiting; 1 published	↓ 50–65%
LY3819469	siRNA to apo(a)	2: enrolled	

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.

Phase 2: The Lp(a)-lowering effect of pelacarsen was apparent by week 4, with a near-maximal effect reached by week 16

Change from baseline over time in Lp(a) level

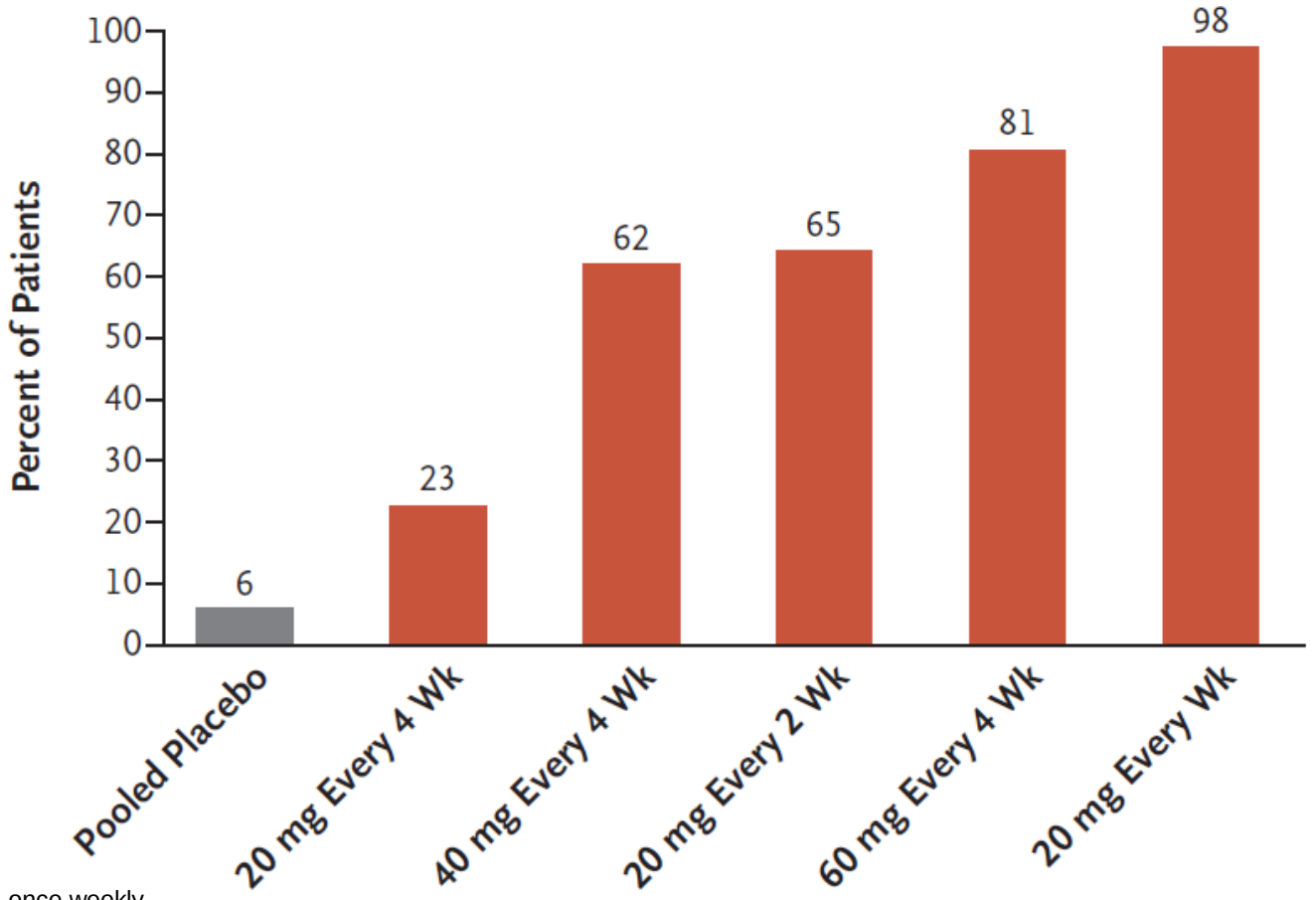


LS, least-squares mean; Lp(a), lipoprotein(a); QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.
Error bars represent 95% CIs; PAT = primary analysis timepoint at week 25 (groups that received monthly doses) or week 27 (groups that received more frequent doses).

Tsimikas S et al. *N Engl J Med* 2020;382:244-255.

Phase 2: Patients receiving pelacarsen attained target Lp(a) levels

Patients with Lp(a) levels of <50 mg/dL at primary analysis timepoint[1]



98%

Of patients reached target Lp(a) levels[1,2,3] with 20 mg QW at primary analysis timepoint[a]

Lp(a), lipoprotein(a); QW, once weekly.

[a]Primary analysis timepoint at week 25 (groups that received monthly doses) or week 27 (groups that received more frequent doses).

1. Figure used with permission from Tsimikas S et al. *N Engl J Med.* 2020;382(3):244-255; **2.** Mach F et al. *Eur Heart J.* 2020;41(1):111-188; **3.** Grundy SM et al. *J Am Coll Cardiol.* 2019;73(24):3168-3209.

Lp(a)HORIZON

8324 men and women aged 18–80 years with Lp(a) ≥70 mg/dL at screening and established CVD

Randomized to receive pelacarsen (formerly TQJ230, AKCEA-APO(a)-LRx) 80 mg or placebo monthly injected subcutaneously

Primary efficacy measures:

- Time to first occurrence of expanded MACE (CV death, nonfatal MI, nonfatal stroke, urgent coronary revascularization requiring hospitalization) in patients with Lp(a) ≥70 mg/dL
- Time to first occurrence of expanded MACE in patients with Lp(a) ≥90 mg/dL

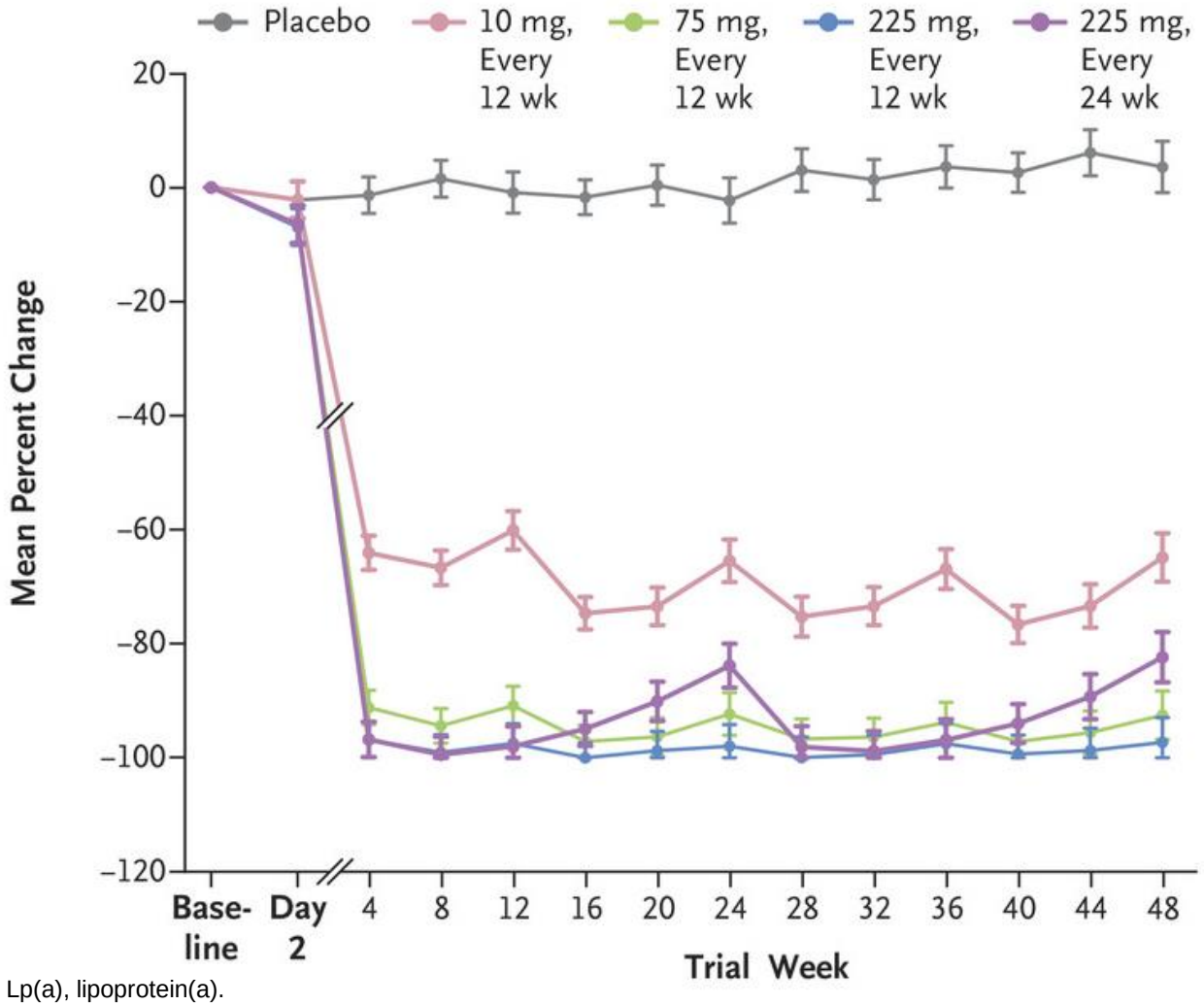
Duration: ~4 years

Estimated primary completion date: May 29, 2025

Estimated study completion date: May 30, 2025

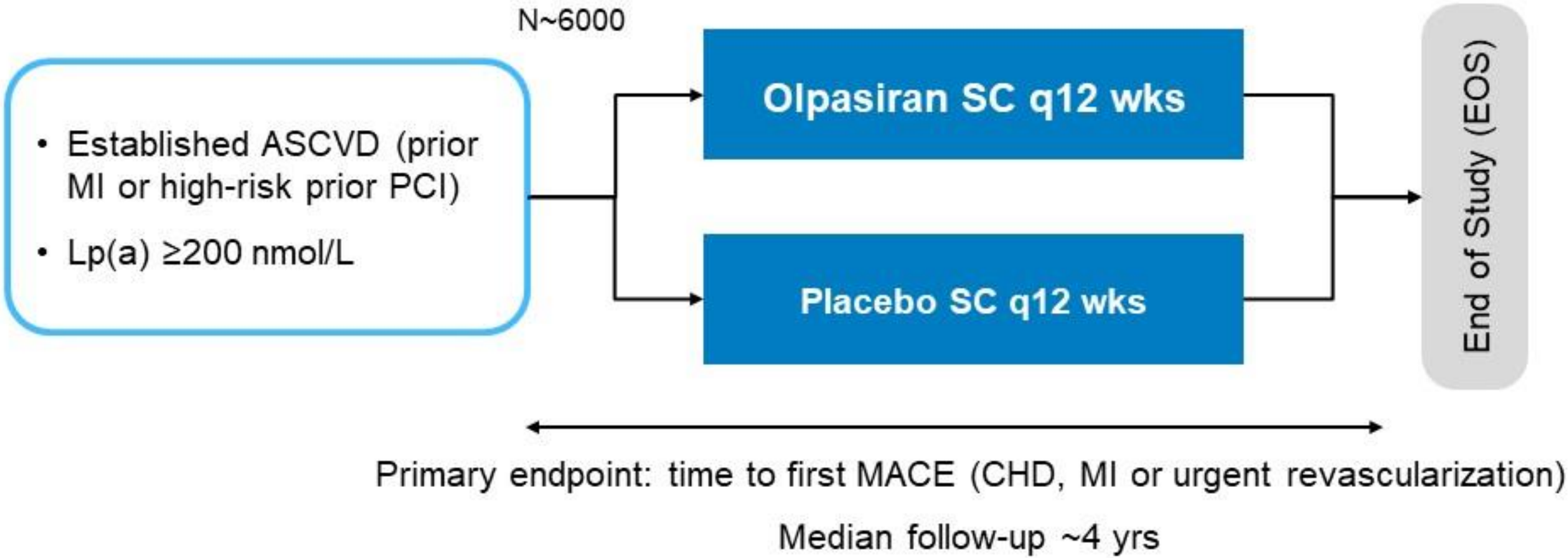
https://clinicaltrials.gov/ct2/show/NCT04023552

OCEAN(a)-dose Phase 2 trial: Olpasiran reduced Lp(a) levels in patients with ASCVD



ASCVD, atherosclerotic cardiovascular disease; Lp(a), lipoprotein(a).
Figure used with permission from O'Donoghue ML et al. *N Engl J Med.* 2022;387(20):1855-1864.

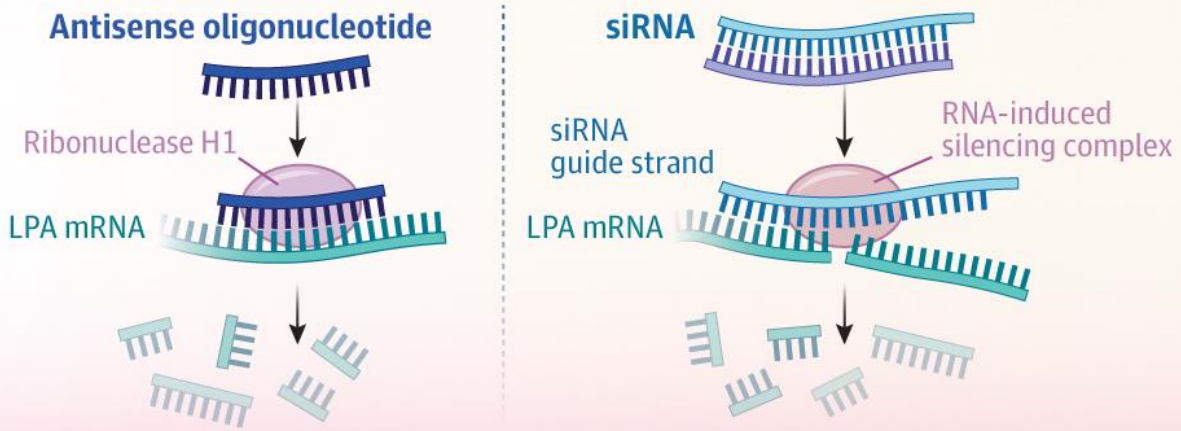
Olpasiran Trials of Cardiovascular Events and Lipoprotein(a) Reduction [OCEAN(a)] - Outcomes Trial



https://clinicaltrials.gov/ct2/show/NCT05581303

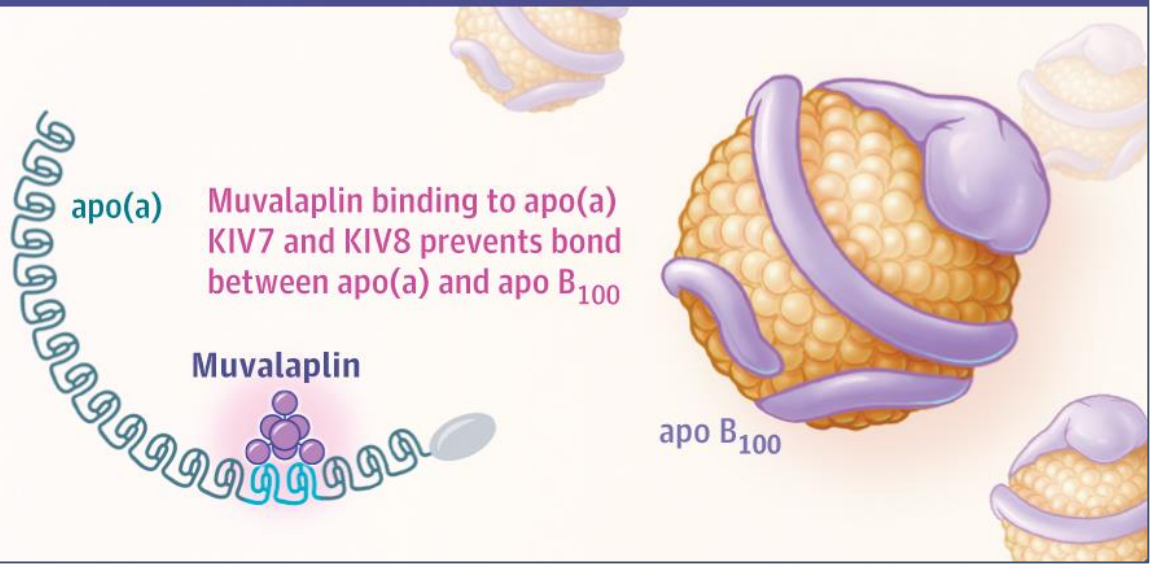
Therapeutic Approaches to Lower Lipoprotein(a)

Injectable RNA-based therapies: Antisense oligonucleotides and small interfering RNA (siRNA) prevent translation of *LPA* messenger RNA (mRNA)



LPA mRNA degradation blocks production of apo(a) necessary for Lp(a) synthesis

Oral small molecule inhibitor therapy: Muvalaplin binds to apo(a) to prevent formation of Lp(a)



Nicholls SJ et al. *JAMA* 2023;330:1042-1053.

Conclusions

1. Patients with high levels of Lp(a) with increased risk for CVD should receive comprehensive risk factor reduction
2. Statin and PCSK9 inhibitors have been shown in post hoc analyses to have benefits in reducing CVD events in patients with elevated levels of Lp(a)
3. Lipoprotein apheresis is the only currently approved therapy for Lp(a) in high-risk patients
4. Ongoing clinical trials with novel highly effective therapies to specifically reduce Lp(a) are in progress

Patrick M. Moriarty

Professor of Medicine

Director of Clinical Pharmacology and

The Atherosclerosis and Lipid-apheresis Center

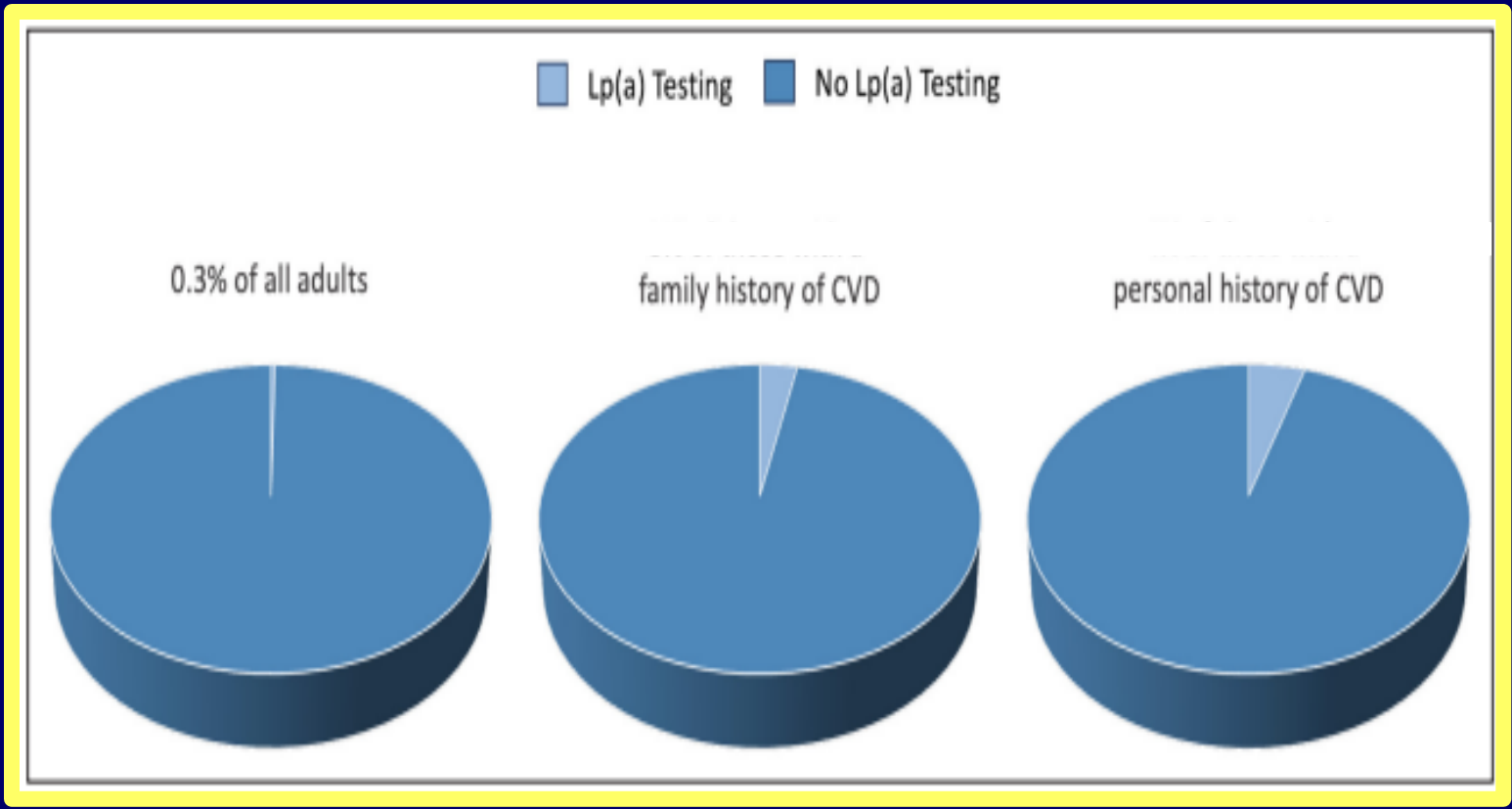
(University of Kansas)

Disclosures

- **Regeneron---------- Research, Consultant**
- **Amgen---------- Research, Consultant**
- **Esperion---------- Research, Consultant, Executive Committee**
- **Kaneka---------- Research, Consultant**
- **Novartis---------- Research, Advisory Board**
- **Vascular Health Foundation-- Research, Advisory Board**
- **Ionis---------- Research**
- **FH Foundation---------- Research**
- **Aegerion---------- Research**
- **Merck---------- Research**
- **Editas Medicine---------- Consultant**

Who have had Lp(a) testing?

A) All Adults
B) Family history of CVD*
C) A personal history of CVD



*** CVD = Cardiovascular Disease**

Bhatia H. S., et al. JAHA. 2023

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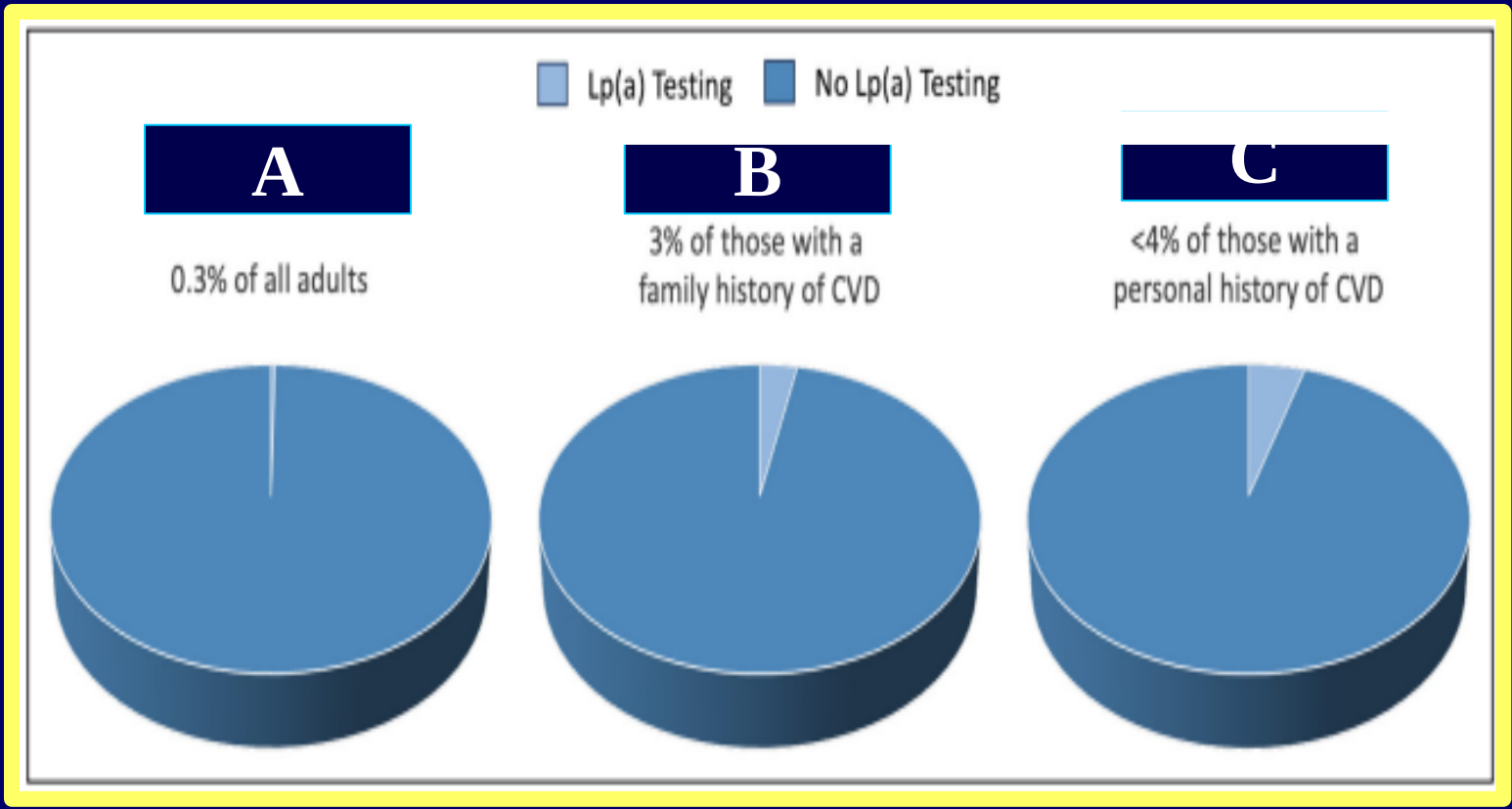

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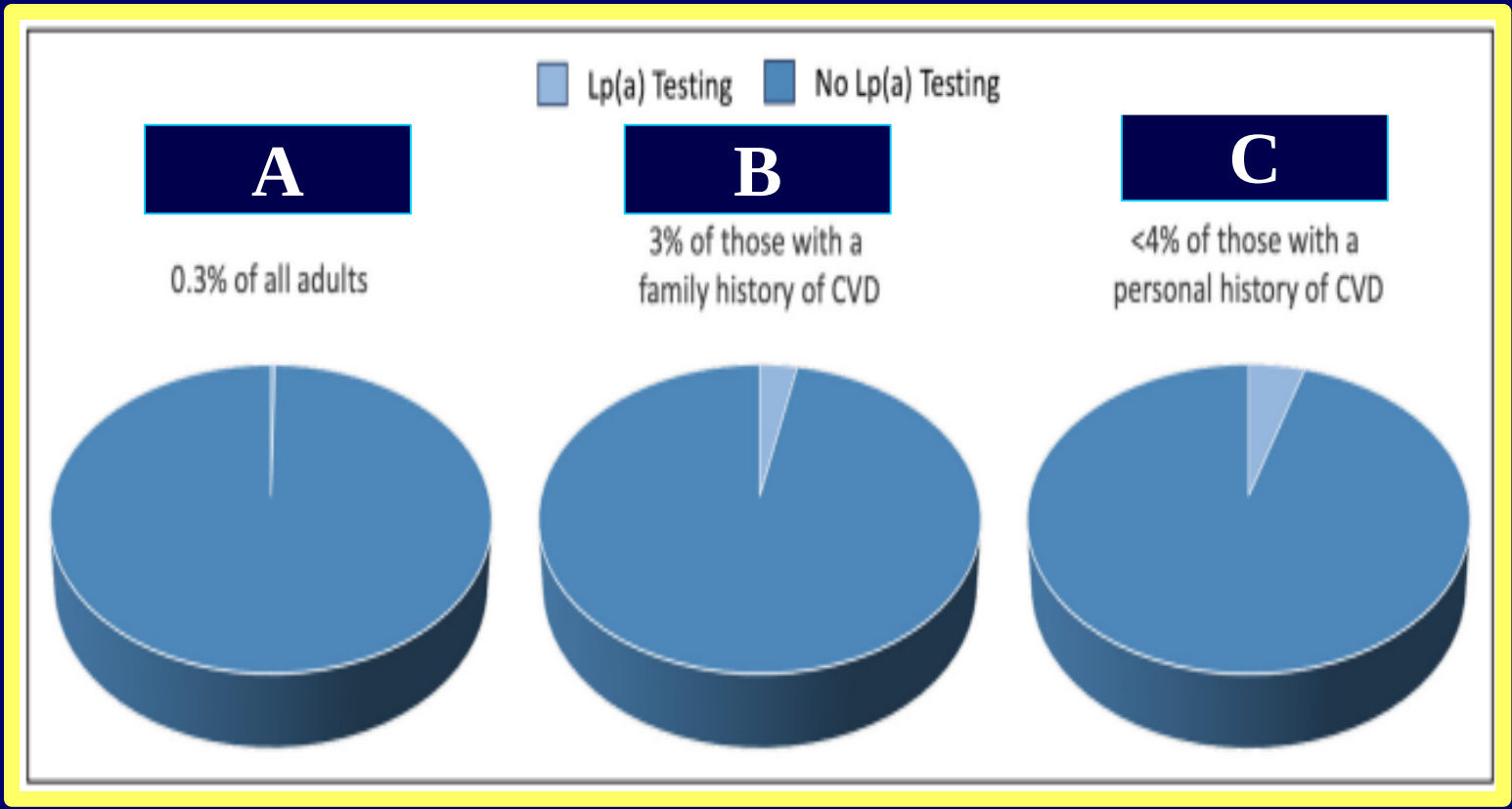

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Bhatia H. S., et al. JAHA. 2023

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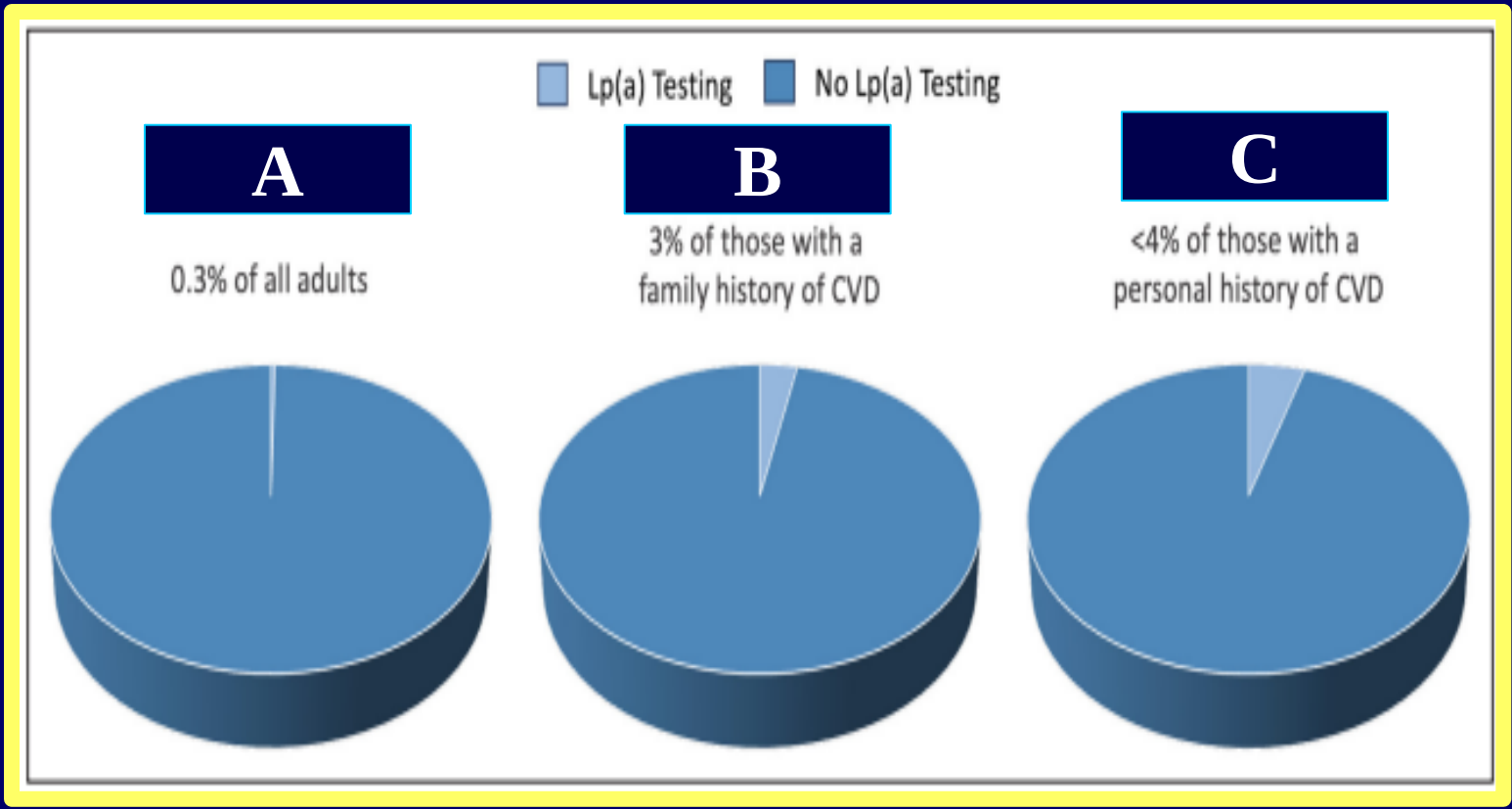


*** CVD = Cardiovascular Disease**

Bhatia H. S., et al. JAHA. 2023

Case Report:
Male Child with Elevated Lp(a) Leading to Acute Ischemic Stroke

Moriarty P.M., et al. JCA. 2017

Case Presentation

Demographics

- 11 year old Male
- Symptom Duration 5 days before being brought to Childrens Hospital

Symptoms

- Dizziness
- Headache
- Lethargy
- Altered Mental Status

History

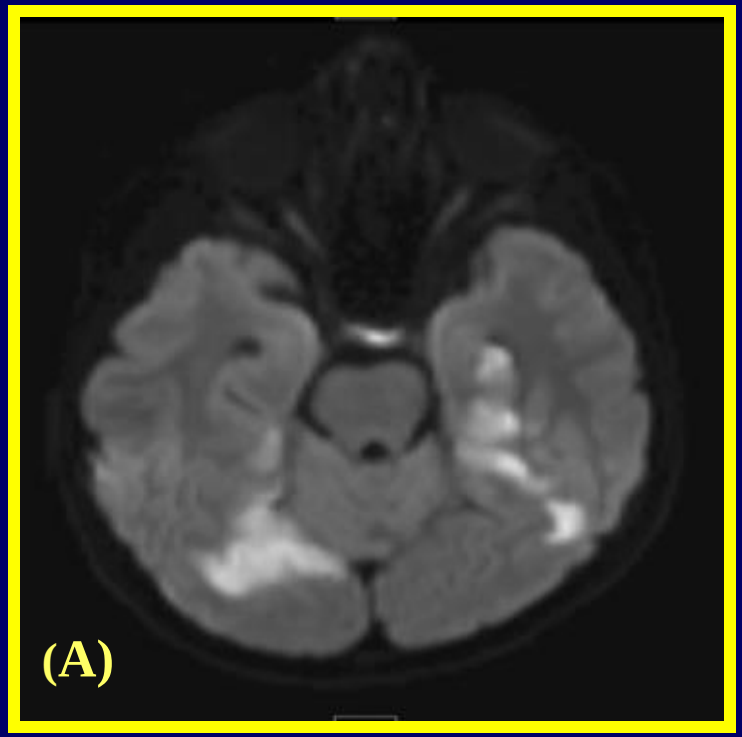
- No history of any CNS trauma or deficits
- Past medical/surgical history- unremarkable
- Birth History- Unremarkable
- Normal Developmental History
- Allergies- NKDA
- Medications: Amoxetin 25 mg for ADHD
- No family history of strokes, Parents and younger sister alive and well

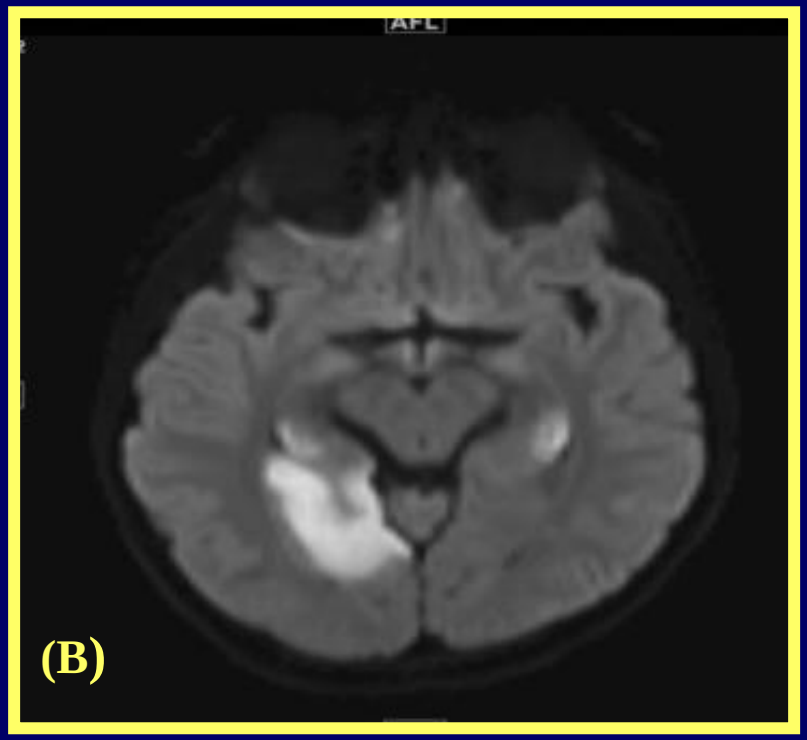
Physical Examination

Neurological

- **Speech fluent**
- **Pupils: asymmetric (Right > Left); both constricted; Right responsive to light**
- **Disconjugate eye movements and rotary nystagmus**
- **Right facial droop present**
- **Right UE/LE responsive to pain only**
- **Left UE/LE responsive to pain**

Initial MRI revealing Several Infarcted Areas

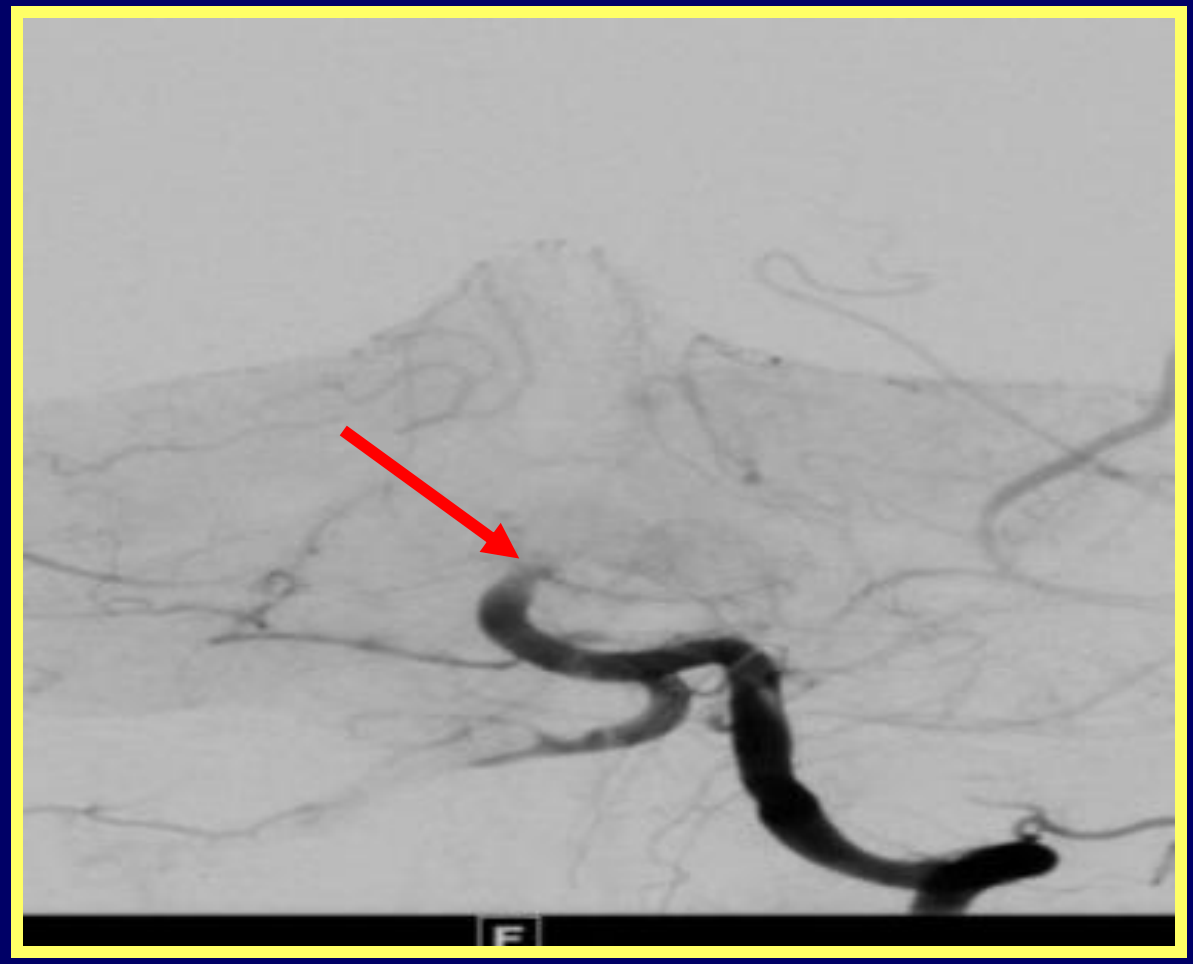




A) Infarcts in basal/lateral occipital lobes and left mesial temporal lobe.
B) Right occipital lobe and basal/lateral hippocampal infarct.

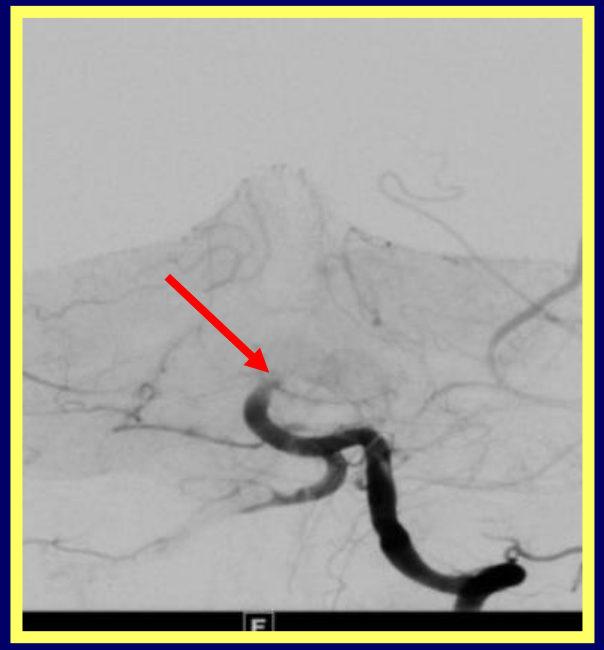
Moriarty P.M., et al. JCA. 2017

Cerebral Angiogram displayed P1 Bilateral Segment Occlusion

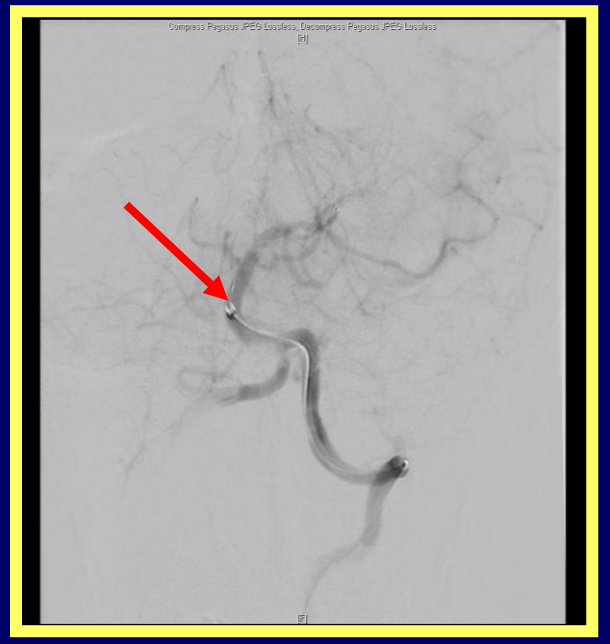


Moriarty P.M., et al. JCA. 2017

Basilar Artery Pre/ Post Thrombectomy



Pre-thrombectomy



Post-thrombectomy

Moriarty P.M., et al. JCA. 2017

Physical Examination Post Basilar Artery Thrombectomy

Neurological

- **Unable to open eyes**
- **Progression of Right facial droop**
- **Right UE/LE responsive to pain only**
- **Left UE/LE responsive to pain**

Initial Lab Work Up

COAGULATION Factors	
APTT	27.9 sec
INR	1
Fibrinogen	405 mg/dL
D-Dimer	264 ng/ml
Factor 5 Leiden	Negative
Factor 8	152%
Cardiolipin IgG	5.5 GPL/ml
Cardiolipin IgM	8.2 MPL/ml
Prothrobin Gene analysis	G/G
Factor 2 mutation	Negative

Additional Lab Work Up

BLOOD COUNTS	
Hemoglobin	13.3 g/dL
Hematocrit	39.4%
Platelet Count	422 K/UL
WBC Count	9.2 K/UL
Neutrophils	72%
Lymphocytes	24%
Monocytes	4%
Eosinophils	0%
Basophils	0%
RBC	4.71 M/UL
MCV	83.5 FL
MCHC	33.7 G/DL
MPV	7.2 FL
RDW	13.3%
ESR	16 mm/hr

GENERAL CHEMISTRY	
Sodium	136 mmol/L
Potasium	132 mmol/L
Chloride	3.5 mmol/L
Calcium	
CO2	24mmol/ L
Albumin	98 mmol/L
Anion Gap	10
BUN	12 mg/dl
Creatinine	0.50mg/dl
Glucose	120 mg/dl
Total Bilirubin	4.4 g/L
Total Protein	0.5 mg/dl
AST (SGOT)	7.4 g/L
ALT (SGPT)	63 U/L
ALP	126 U/L
CK	34

LIPID PROFILE	
Cholesterol	135 mg/dL
Triglycerides	90 mg/dL
LDL	60 mg/dL
HDL	62 mg/dL
Non HDL-C	73 mg/dL
Lipoprotein a	148 mg/dL
LDL-P	657 mg/dL
SD LDL	14
HDL-P	25.5
HDL2	33
Apo B100	47
Apo B/ A1 Ratio	0.36
Free Fatty Acids	0.80

BIOSIGNAL Trial:
Recurrent Cerebrovascular Events (1 year Follow-Up) for Lp(a) Levels < and > 100nmol/L (40mg/dL)

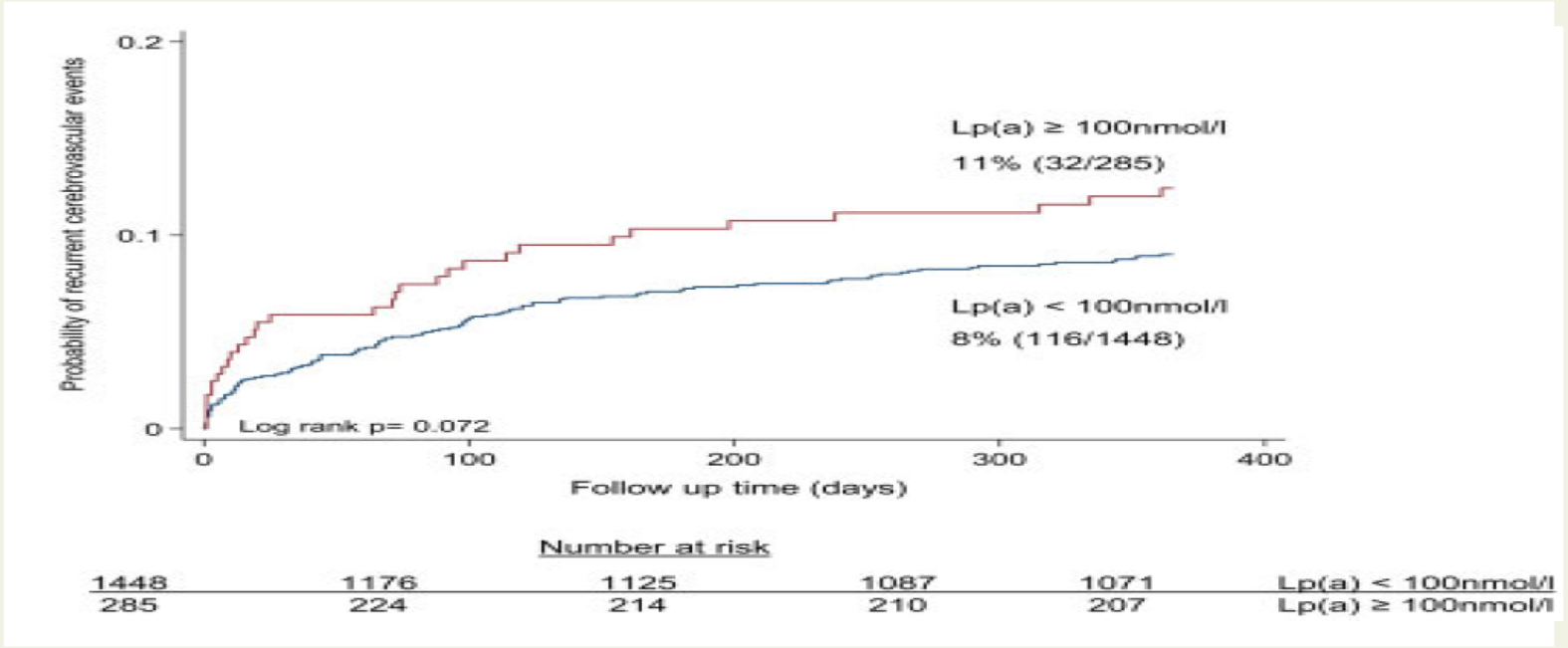


Figure 2 Kaplan–Meier failure estimates for recurrent cerebrovascular events. Kaplan–Maier failure estimates for recurrent cerebrovascular events (ischaemic stroke or transient ischaemic attack, $n = 148$) during a 12-month follow-up for Lp(a) levels below and above 100 nmol/L. In four patients with recurrent cerebrovascular events Lp(a) levels were missing. Lp(a), Lipoprotein(a)

Arnold M., et al. EHJ. 42: 2186-96. 2021

BIOSIGNAL Trial:
Subgroup Analysis

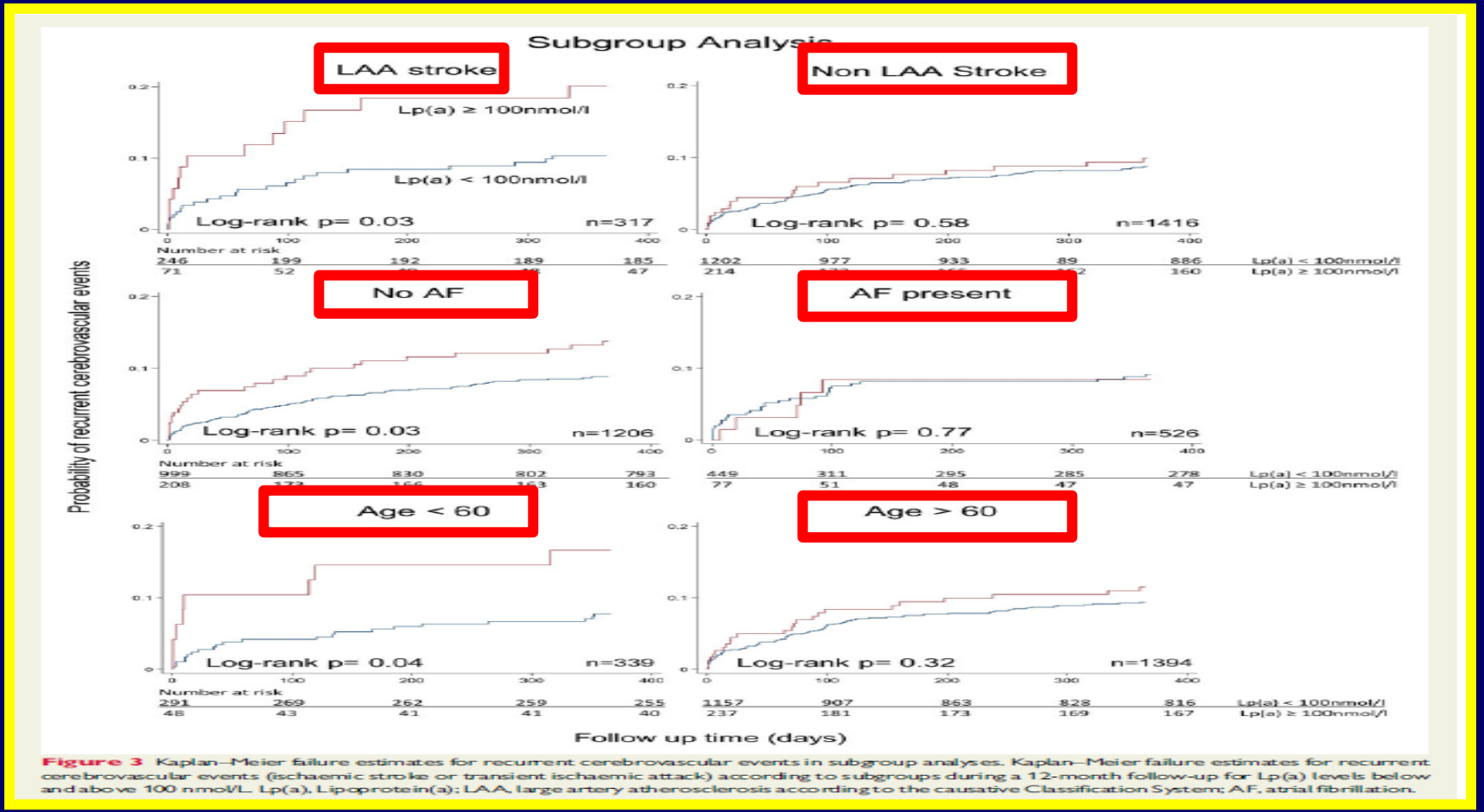


Figure 3 Kaplan–Meier failure estimates for recurrent cerebrovascular events in subgroup analyses. Kaplan–Meier failure estimates for recurrent cerebrovascular events (ischaemic stroke or transient ischaemic attack) according to subgroups during a 12-month follow-up for Lp(a) levels below and above 100 nmol/L. Lp(a), Lipoprotein(a); LAA, large artery atherosclerosis according to the causative Classification System; AF, atrial fibrillation.

LAA= Large Artery Atherosclerosis

AF= Atrial Fibrillation

Arnold M., et al. EHJ. 42: 2186-96. 2021

Ischemic Strokes in Young Adults

- In adults the majority of thrombotic stroke is associated to atherosclerosis compared to only 2% for the pediatric patient.
- In patients under 55 years, cryptogenic strokes account for almost 40% of all ischemic strokes.
- Children with an elevated Lp(a) level have a fourfold increased risk of AIS and the risk of recurrent ischemic strokes (nl: 5-15%) is increased more than ten-times in patients with an elevated Lp(a) (>90th percentile).

Sultan S.M., et al. Int. J. of Stroke. 2014, 79-87.
Nave A.H., et al. *Atherosclerosis* 2015 242.
Goldenberg N. A., et al. *Haematologica.* 2013;98(5).

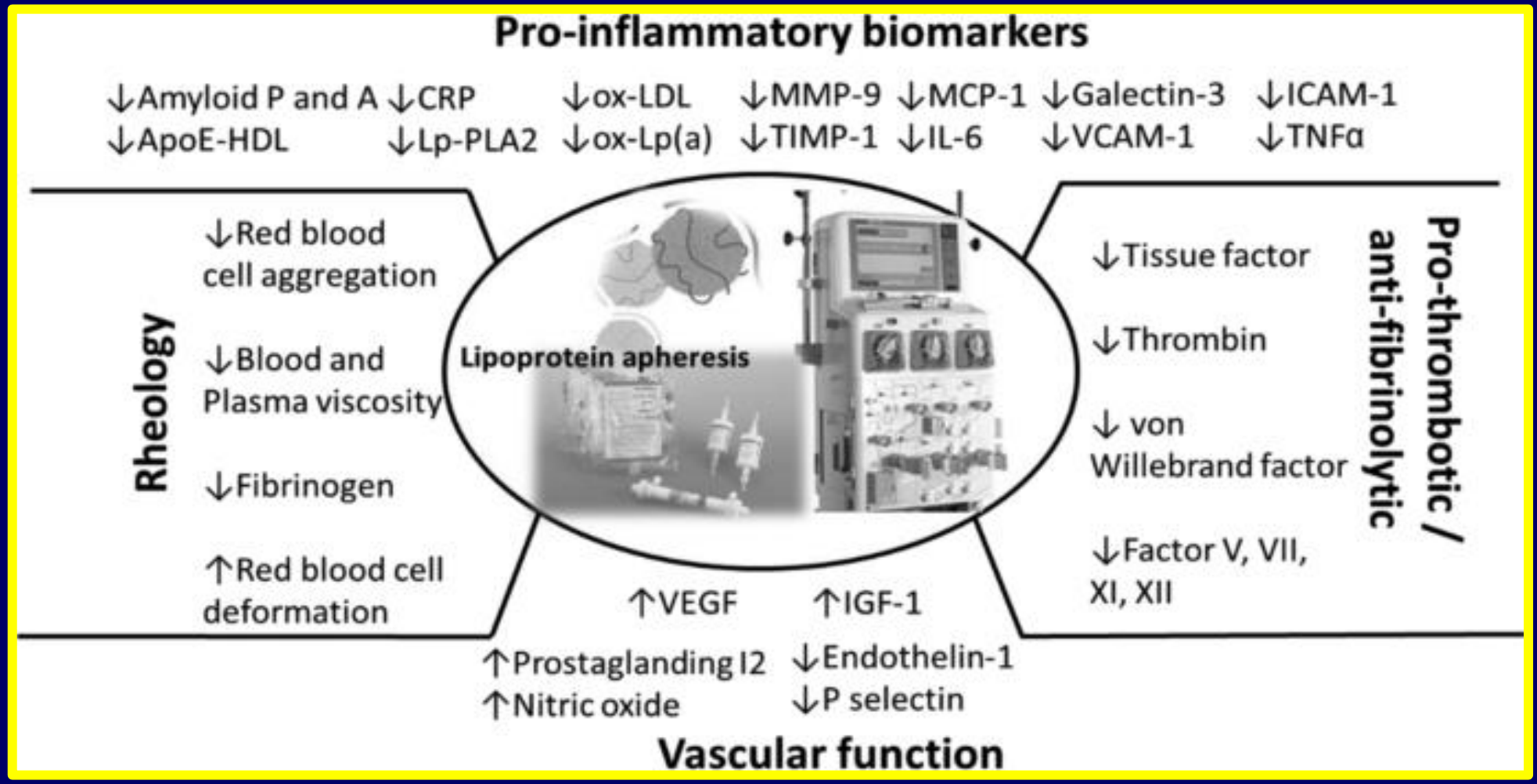
FDA Approval for Lipoprotein-Apheresis
(after maximum Lipid-modifying therapy)

Group A&B – Functional Hypercholesterolemic (FH) with LDL-C ≥300 mg/dL.

Group C – Functional FH with LDL-C ≥100 mg/dL and either coronary artery disease (CAD) or peripheral artery disease (PAD).

Group D – Functional FH with LDL-C ≥ 100 mg/dl and lipoprotein(a) [Lp(a)] ≥ 60mg/dL, and either CAD or PAD.

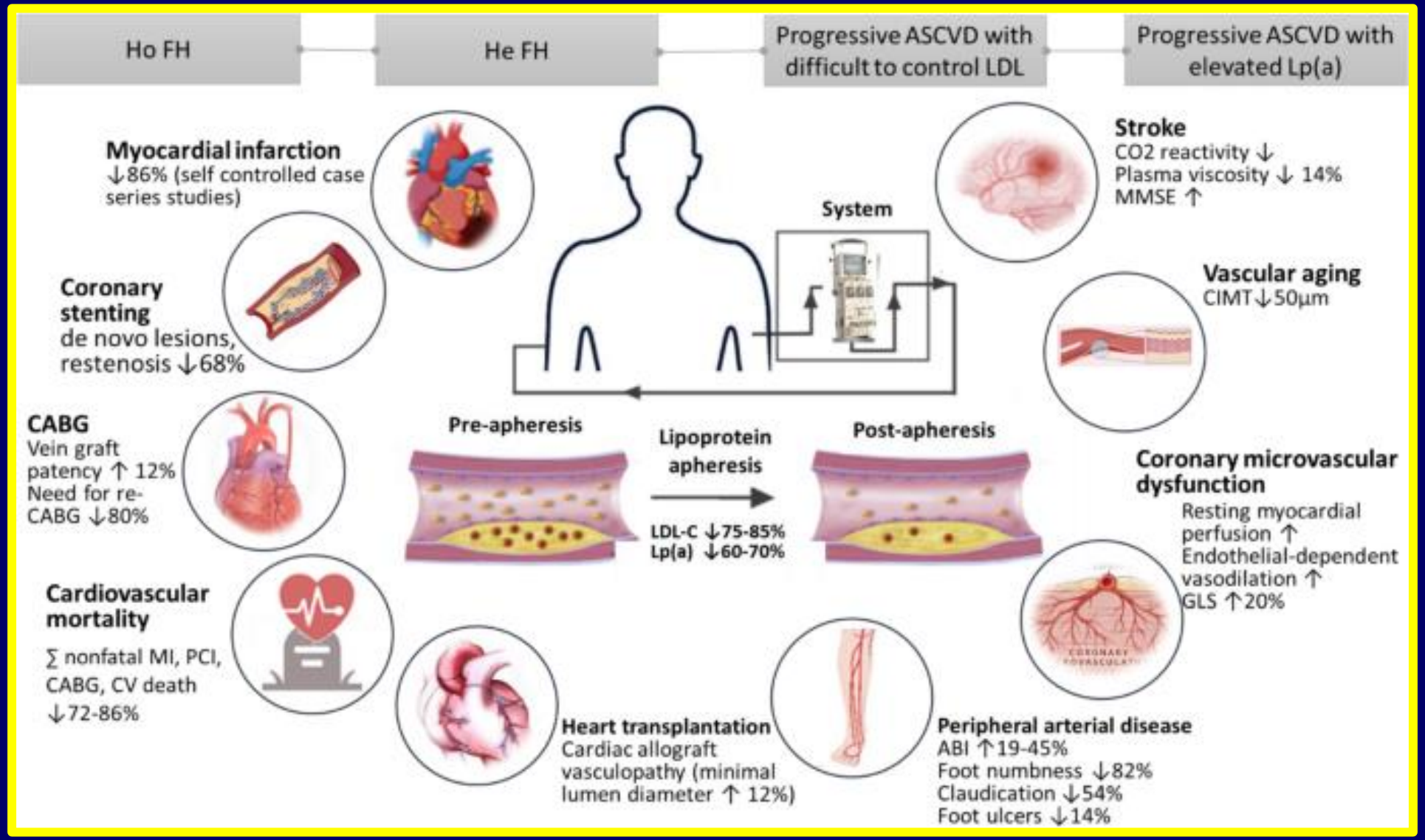
Changes in Markers of ASCVD* with Lipid-apheresis



***ASCVD= Atherosclerosis Cardiovascular Disease**

Safarova MS, Moriarty PM. Current Atherosclerosis Reports (2023) 25:391-404.

A Summary of ASCVD Outcomes in Patients treated with Lipid-apheresis



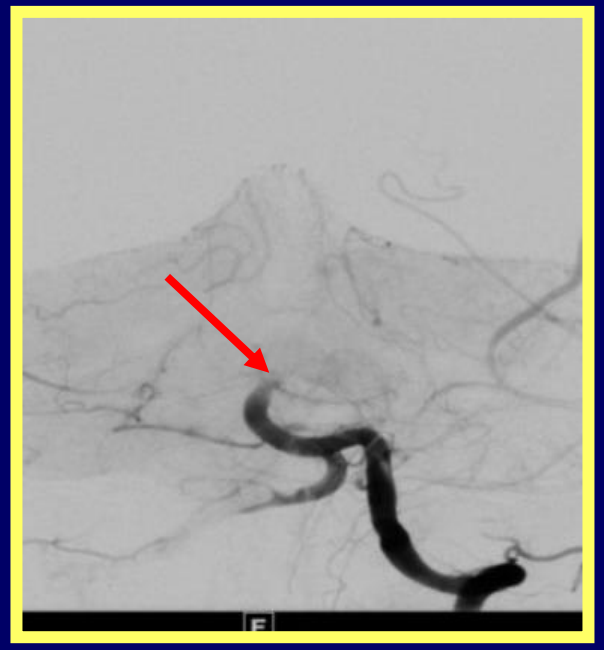
Safarova MS, Moriarty PM. Current Atherosclerosis Reports (2023) 25:391-404.

Case Report:
Change in Lipoproteins Following LA

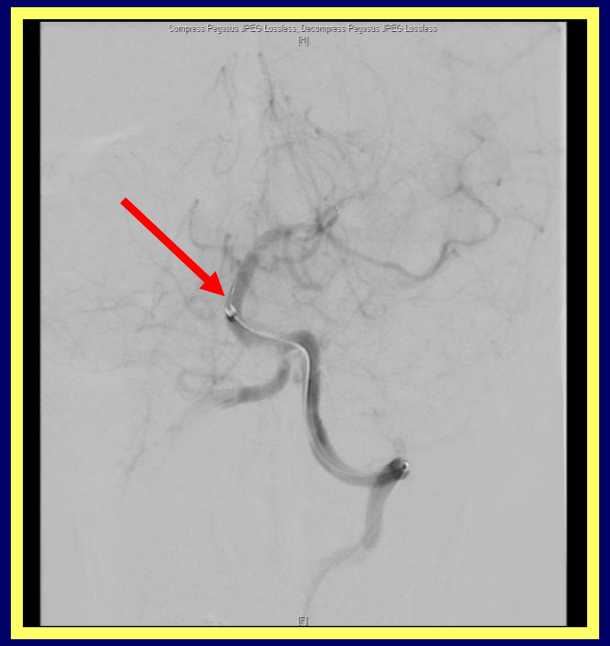
Lipoproteins (mg/dL)	Pre-LA	Post-LA	% Change
LDL-C	55	9	84
HDL-C	61	53	13
Triglycerides	45	14	69
ApoB	40	< 5	88
Lp(a)-Mass	148	28	81

Moriarty P.M., et al. JCA. 2017

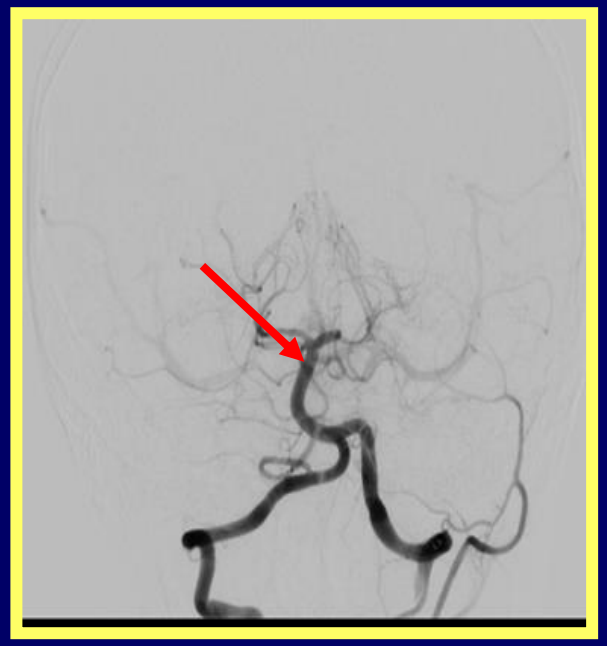
Basilar Artery Pre/ Post Thrombectomy and Lipoprotein-Apheresis



Pre-thrombectomy



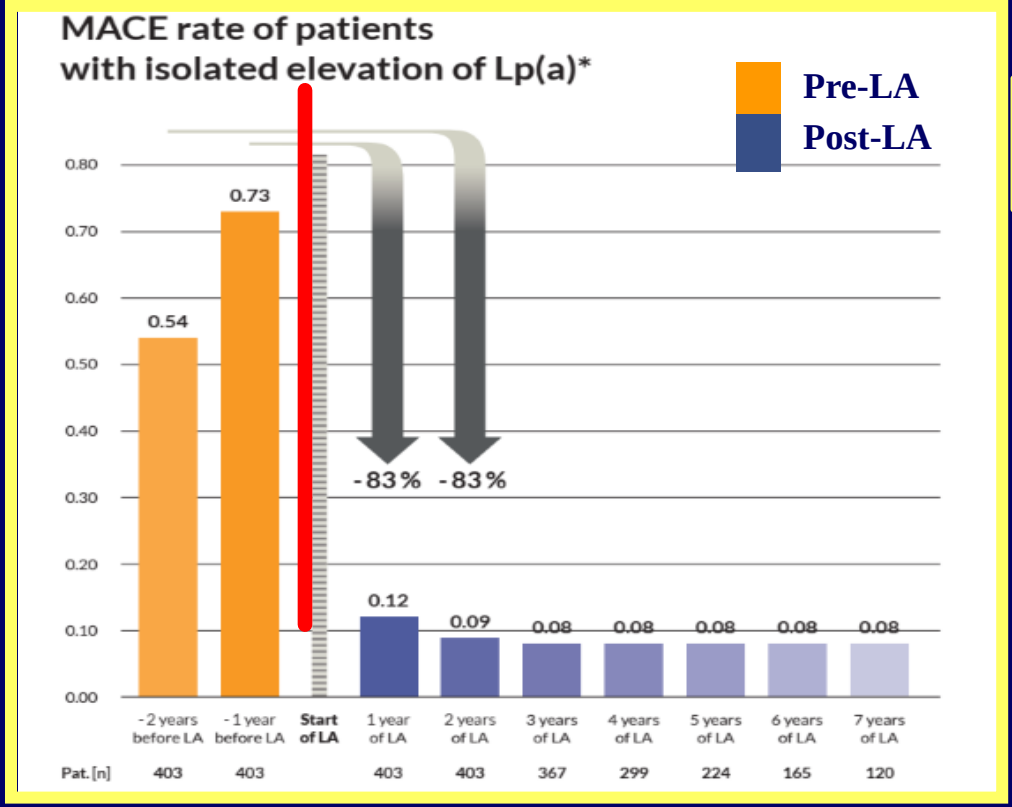
Post-thrombectomy



Post-Apheresis

Moriarty P.M., et al. JCA. 2017

GLAR* Analysis of MACE** in LA Patients with Isolated Elevation in Lp(a)



Patients with LDL-C<100 mg/dL) and Lp(a)> 60 mg/dl (>120 nmol/L)

- **Median acute reduction over the years:**
  LDL-C = 68.1%
  Lp(a) = 75.6%
- **First 2 years: 83% decrease in MACE.**

***GLAR = German Lipid-Apheresis Registry**

****MACE= Major Adverse Cardiac Events**

Schettler V., et al. *Ther Apher Dial*. 2022

Lipid-apheresis for Patients (n=14, Age 11-66) with an elevated Lp(a) and CVD

(KU Atherosclerosis Prevention and Lipid-apheresis Center)

	Retrospective Period	Prospective Period
	Before initiating LA therapy	Ongoing LA treatment
LDL-C mg/dL	80	29 (-64%)
Lp(a) mg/dL	138	51 (62%)
Mean Duration	6 years	4 years
MACE*	36	2 (-94%)
MI**	10	0
CABG***	12	0
Stent	10	2
Stroke	4	0

*MACE: Major Adverse cardiovascular Event

**MACE: Myocardial Infarction

***CABG: Coronary Artery By-pass Graft

Moriarty PM, et al. JCL: 2019

Patient Follow up (9 Years)

- Continues to receive biweekly apheresis therapy.
- On Neurological examination :

  -Eye movements significantly improved.

  -Speech, weakness and headaches all greatly improved.

  -Walks without assistance.

  -Eating a regular diet and is able to dress himself.

  -Graduated high school and is now working at Walmart.

  -No cerebrovascular accidents for the past 9 years.

Understanding the Role of Lp(a) as a CV Risk Marker to Therapeutic Target in the Prevention of ASCVD

Panel Discussion & Q/A

Chair:
Patrick M. Moriarty, MD

Faculty:
Christie M. Ballantyne, MD
Erin D. Michos, MD, MHS, FACC, FAHA, FASE, FASEPC