Lp(a) in Practice: Challenges in Testing and Opportunities in Care

Leslie J. Donato, Ph.D., D (ABCC)
Co-Director Clinical Specialty Laboratory
Co-Director Hospital Clinical Laboratory and Point of Care
Associate Professor, Laboratory Medicine and Pathology
Department of Laboratory Medicine and Pathology at Mayo Clinic

Howard S Weintraub, MD, FACC, FAHA, FASPC
Clinical Professor of Medicine
NYU Grossman School of Medicine
Clinical Director, NYU Center for the Prevention of Cardiovascular Disease

American Heart Association.

Disclaimer

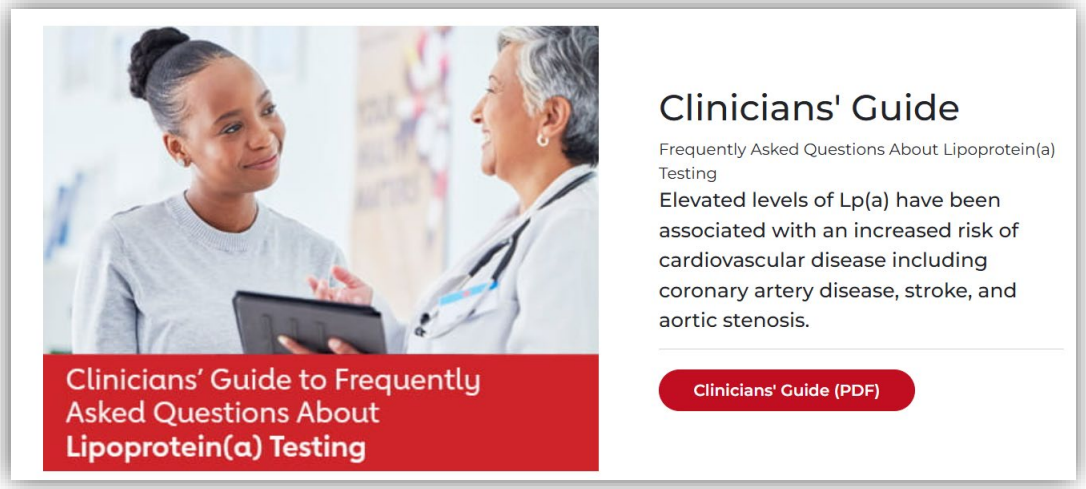
The recommendations and opinions presented by our guest speakers may not represent the official position of the American Heart Association. The materials are for educational purposes only, and do not constitute an endorsement or instruction by AHA/ASA. The AHA/ASA does not endorse any product or device.

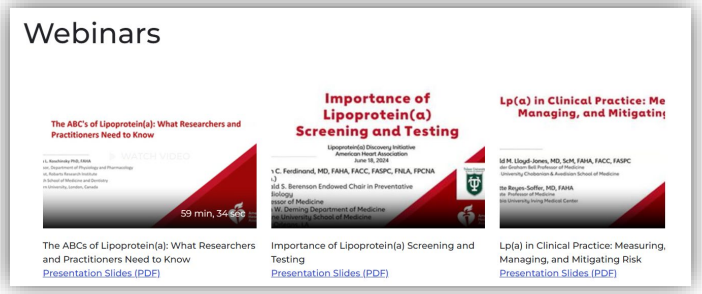
Lp(a) Discovery Project

High Lp(a) levels are a genetically inherited and are a common independent risk factor for heart disease, affecting approximately 1 in 5 people worldwide.

The American Heart Association (AHA) launched a 3-year national initiative, the **Lp(a) Discovery Project**, to increase Lp(a) testing by improving processes across care settings through national education.

As an enhancement to this work, the AHA launched the **Lp(a) Federally Qualified Health Center (FQHC) Discovery Project** which seeks to identify various approaches and barriers to Lp(a) testing within FQHCs and develop national education to improve knowledge and increase awareness surrounding Lp(a).





MAYO CLINIC

Leslie J. Donato, Ph.D., DABCC

Associate Professor, Department of Laboratory Medicine and Pathology

Co-Director Clinical Specialty Laboratory

Co-Director Hospital Clinical Laboratory and Point of Care

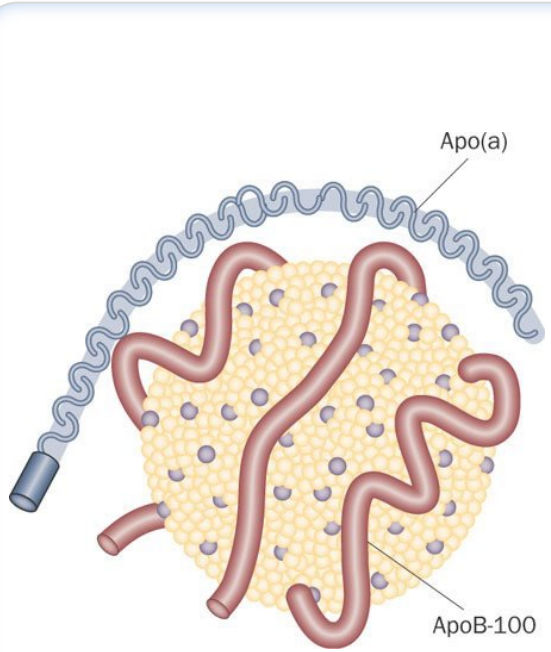
Mayo Clinic, Rochester, MN

Disclosures

Presenter	Conflicts
Leslie J. Donato	Novartis: Paid speaker Helena Laboratories: Paid speaker Bosch Healthcare Solutions Gm: Consultant

Lipoprotein(a):
An apoB Family Member
Mediates CV Risk Through 3 Main Pathways

- Apo(a) unique apolipoprotein
- Plasma Lp(a) concentrations correlate highly with apo(a) production
- Variable size dependent on number of repeating KIV_2 domains (3 to >40)
- More atherogenic than LDL on a particle basis



Proinflammatory

↑ Macrophage IL-8 expression
↑ Monocyte migration
↑ OxPLs

Prothrombotic

↓ Plasminogen activation
↓ Fibrinolysis
Clot persistence

Proatherogenic

↑ Expression of adhesion molecules
↑ Retention in arterial wall
↑ Foam cell formation

Sotirios Tsimikas (2017) JACC

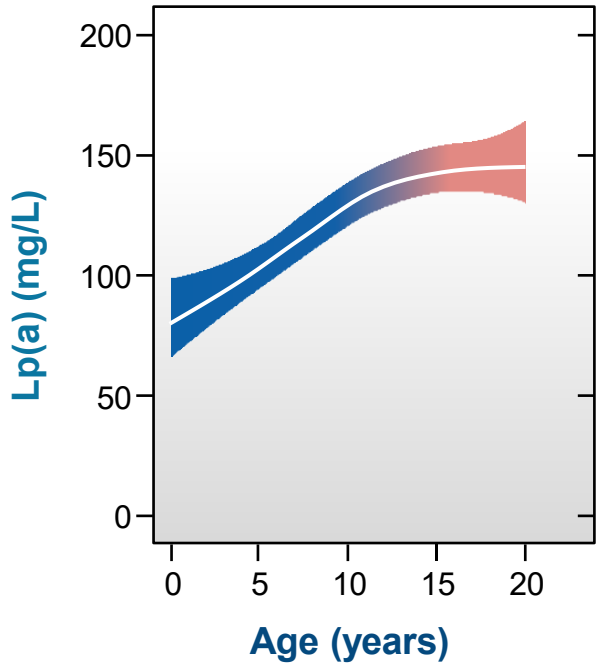
Lp(a) Expression

Detected within first year of life

Recent data: increases throughout childhood

Expression fairly stable in adulthood

Lp(a) with increasing age

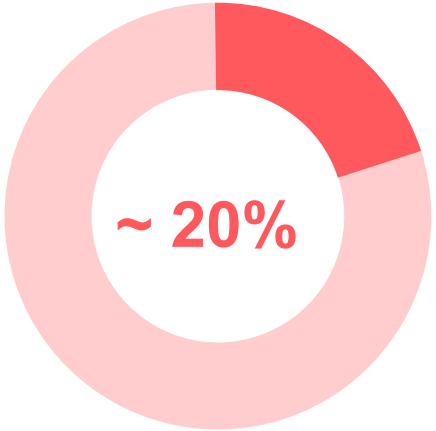


5–10% higher in women
17% higher in post-menopausal women

Ethnic differences: *LPA* gene variants differ according to ancestry and geography

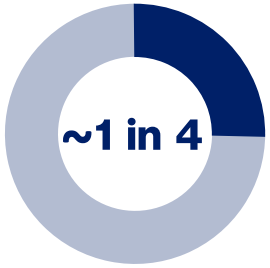
1. de Boer LM et al. *Atherosclerosis*. 2022;349:227-232. **2**. Kronenberg F et al. *Eur Heart J*. 2022;43(39):3925-3946.
3. Nordestgaard BG, Langsted A. *Lancet*. 2024;404(10459):1255-1264. **4.** Tsimikas S, Marcovina SM. *J Am Coll Cardiol*. 2022;80(9):934-946.

Elevated Lp(a) Is Observed in:



~1.5 billion people (globally)

~67 million people (US)

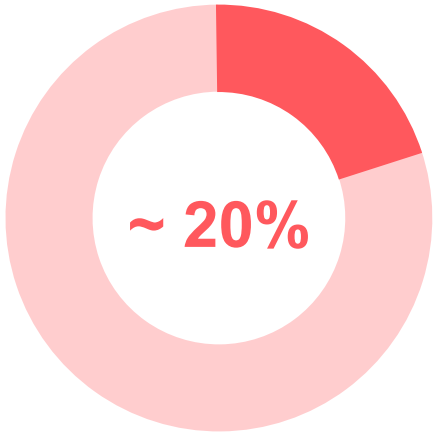


individuals with ASCVD

individuals with premature ASCVD

Tsimikas S, Marcovina SM. *J Am Coll Cardiol*. 2022;80(9):934-946.
Nissen SE et al. *Open Heart*. 2022;9(2):e002060.
Altmann C et al. *Clin Res Cardiol*. Published online April 15, 2024. doi:10.1007/s00392-024-02427-0

Elevated Lp(a) Is Observed in:



individuals worldwide

TESTING

- **Help reclassify a patient's risk of CVD**
- **Allows for intensive management of CVD risk factors**
- **May help to improve ASCVD risk prediction**
- **May motivate patient to adhere to risk mitigation strategies**
- **May inform about familial CV risk**

1. de Boer LM et al. *Atherosclerosis*. 2022;349:227-232. **2**. Kronenberg F et al. *Eur Heart J*. 2022;43(39):3925-3946.
3. Nordestgaard BG, Langsted A. *Lancet*. 2024;404(10459):1255-1264. **4.** Tsimikas S, Marcovina SM. *J Am Coll Cardiol*. 2022;80(9):934-946.

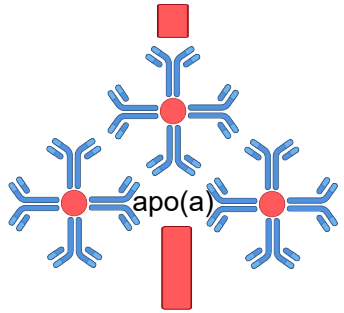
Let’s test for it!

Laboratory Testing for Lp(a) Concentration

- A routine blood draw is sufficient
- Fasting is not required
- Lp(a) concentration can be reported as nmol/L or mg/dL
- Testing may only be required once in an individual's lifetime

Measuring Lp(a) Blood Concentration

<u>Several methodologies</u>
RIA
ELISA
Immunonephelometry*
Immunoturbidimetry*
Mass Spectrometry
*most common commercially



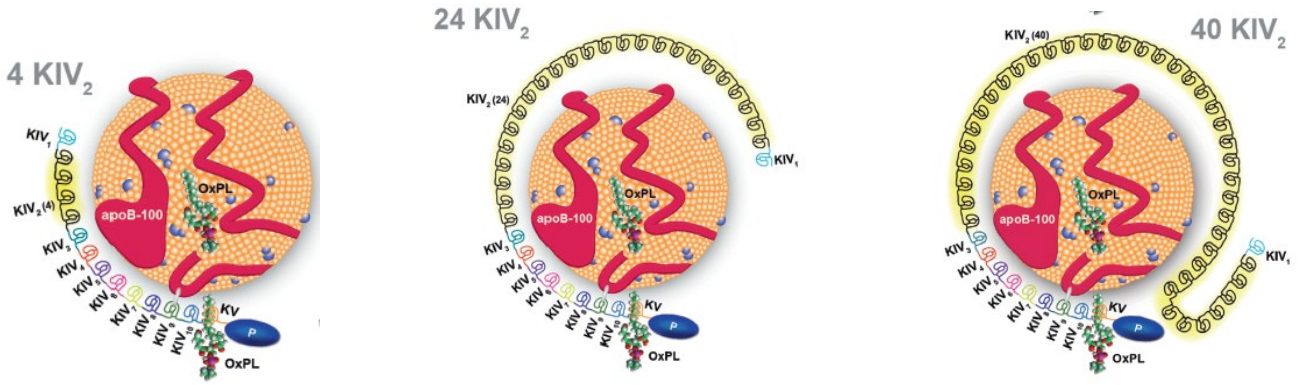
ICD-10-CM code:
E78.41 elevated Lp(a)
Z83.430 family history of elevated Lp(a)

CPT® code:
83695
Lp(a) blood test

It's easy (sort of)

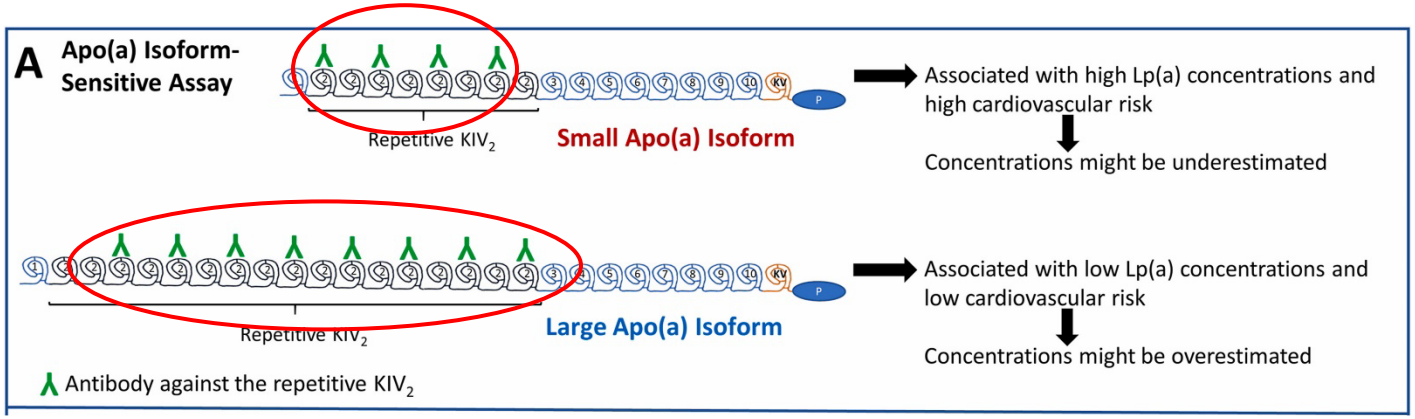
Challenges for Accurately Measuring Lp(a)

- Molecular weight can range from 300 to 800 kDa
- Polyclonal immunoassays: variable numbers of antigenic epitopes
- Depending on size of Lp(a) calibrator, assays over-estimate or under-estimate Lp(a) concentration



Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. J Am Coll Cardiol. 2017;69(6):692-711.

Problem with Accuracy



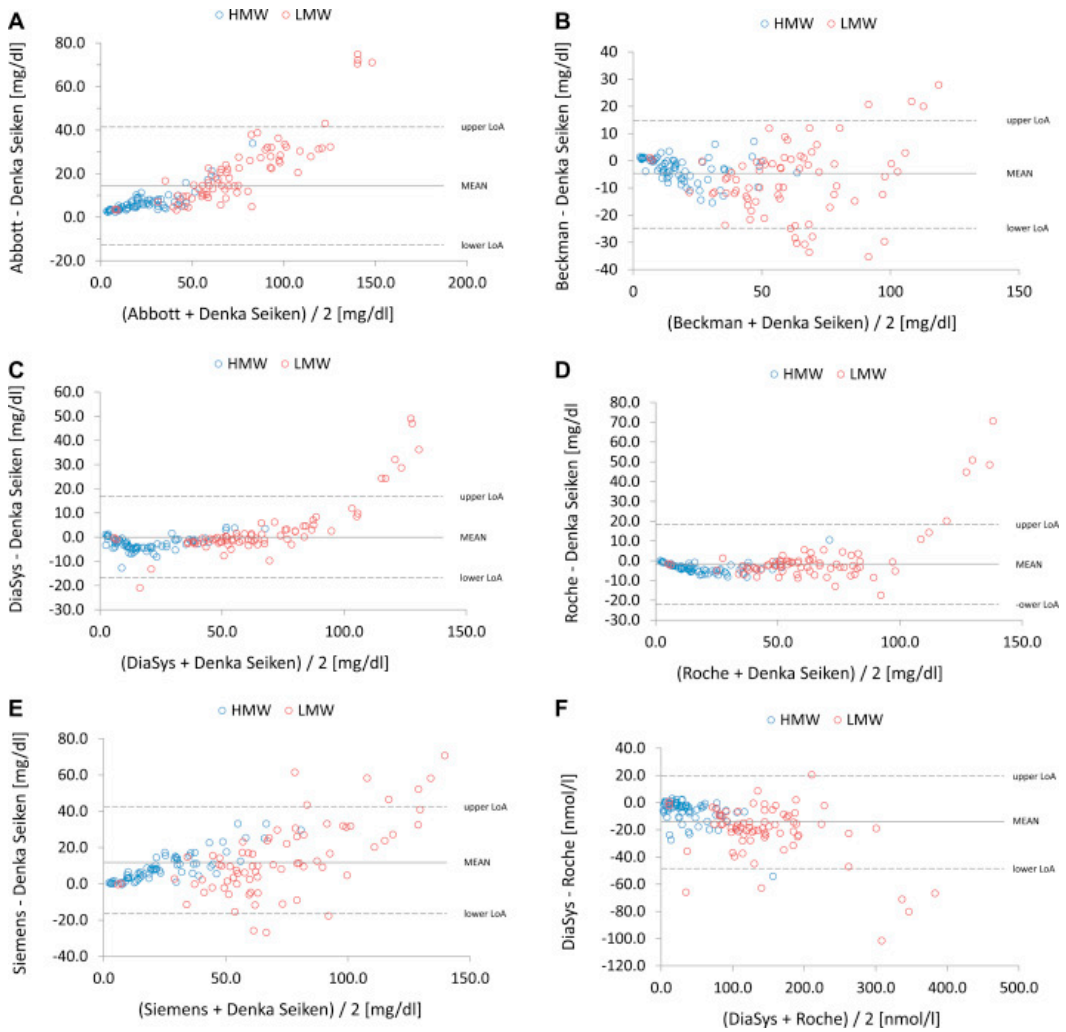
Best commercial assays use 5-point calibration and a mixture of Lp(a) sizes in the calibrator

- Use molar assay if possible.
- But mass assay is still acceptable

Testing is BETTER than not testing!!

Kronenberg F. Lipoprotein(a) measurement issues: Are we making a mountain out of a molehill? Atherosclerosis. 2022;349:7-9. doi:10.1016/j.atherosclerosis.2022.04.012

Lp(a) Assays are NOT Harmonized



Kronenberg F. Lipoprotein(a) measurement issues: Are we making a mountain out of a molehill? Atherosclerosis. 2022;349:7-9. doi:10.1016/j.atherosclerosis.2022.04.012

Are we testing for it?

Guidelines: Lp(a) Testing Recommendations

Statements/Guidelines	At least once in all patients' lifetimes	Family history of premature ASCVD	Personal history of premature ASCVD	Moderate-to-high ASCVD risk	Refractory elevation of LDL-C despite LLT	Patients with a personal history of aortic valve stenosis
NLA (2024/2019)	✓	✓	✓	✓	✓	✓
ACC (2022)		✓				
AACE/ACE (2020)		✓	✓	✓	✓	✓
AHA/ACC (2019)		✓	✓			

Premature events	NLA (2024/2019) AACE/ACE (2020) AHA/ACC (2019)		AAS (2023)	BHS (2022)	EAS (2022) ESC/EAS (2019)	EAS (2022)	CCS (2021)	LAI (2023)	HEART UK (2019)
Once in adult patient's lifetimes	NLA 2024	SEA (2024)		BHS (2022)	EAS (2022) ESC/EAS (2019)		CCS (2021)	LAI (2023)	

NLA 2024 Focused Update on Nonstatin Therapies. J Clin Lipidol. 2024;18(3):e77–e111.
ACC 2022 Expert Consensus on Nonstatin LDL-C Therapies. J Am Coll Cardiol. 2022;80(14):1366–1418.
AACE/ACE 2020 Dyslipidemia Guideline Update. Endocr Pract. 2020;26(1):1–87.
AHA/ACC 2019 Cholesterol Management Guideline. Circulation. 2019;139(25):e1082–e1143.
SEA 2024 Standards for Global Control of Vascular Risk. *Clin Invest Arterioscler.* 2024.
BHS 2022 Lipoprotein(a) Consensus Statement. *Br J Cardiol.* 2022.
EAS 2022 Consensus on Lipoprotein(a). *Eur Heart J.* 2022;43:3925–46.
2019 ESC/EAS Dyslipidaemias Guideline. *Eur Heart J.* 2020;41(1):111–188.
CCS 2021 Dyslipidemia Guideline. *Can J Cardiol.* 2021;37(8):1129–1150.
LAI 2023 Risk Assessment & Lipid Mgmt Update. *J Assoc Physicians India.* 2023.
Heart UK 2019 Lp(a) Consensus.

Lp(a) Testing Rates Remain Low

6 University of California medical centers
(n = 5,553,654)

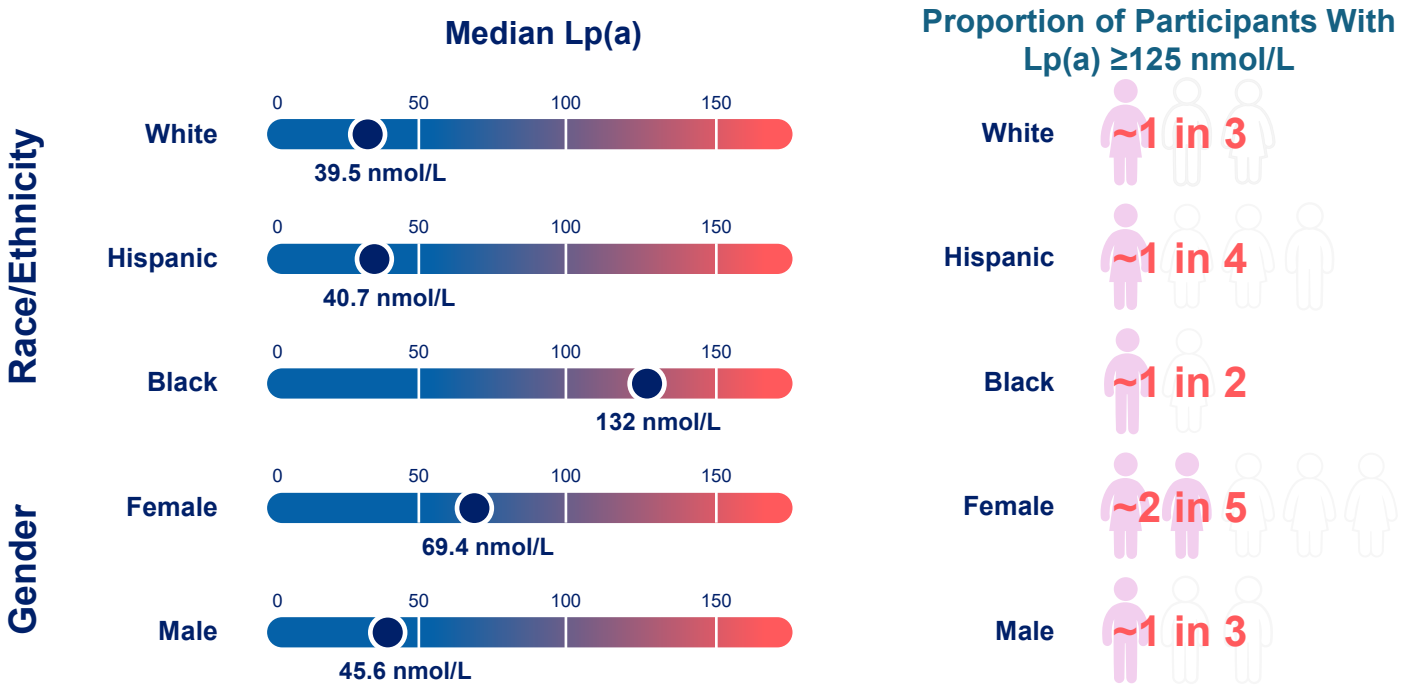
0.3% Overall testing rate

<4% Patients with personal history of CVD

3.3% Patients with family history of CVD

Bhatia HS et al. *J Am Heart Assoc.* 2023;12(18):e031255.

Prevalence of Elevated Lp(a) Varies



Differences in Lp(a) levels between populations are largely determined by the distribution of *LPA* gene variants, which differs according to ancestry and geography

Shapiro MD et al. *J Clin Lipidol*. 2025;19(1):28-38.

Unfortunate Trend

Patients at higher risk of CV events are least likely to be tested for Lp(a)

Patient Characteristics Associated With a Decreased Likelihood of Undergoing Lp(a) Testing

	OR (95% CI)
Black race	0.83 (0.80-0.85)
Hispanic or Latinx ethnicity	0.77 (0.73-0.80)
Rural neighborhood	0.91 (0.89-0.93)
CDC Social Vulnerability Index 0.75-1.00	0.70 (0.68-0.72)

1. Chen T et al. *JAMA Netw Open*. 2025;8(1):e2453300. **2.** Bhatia HS et al. *J Am Heart Assoc*. 2023;12(18):e031255. **3.** Kelsey MD et al. *Am J Prev Cardiol*. 2023;14:100478. **4.** Shah NP et al. *J Am Heart Assoc*. 2024;13:e035610.

Lp(a) Testing Rates Remain Low

Why?

- Lack of awareness
- Not included in standard lab orders
- Reimbursement problems
- No current targeted treatment

We need to do better!

How to interpret the results?

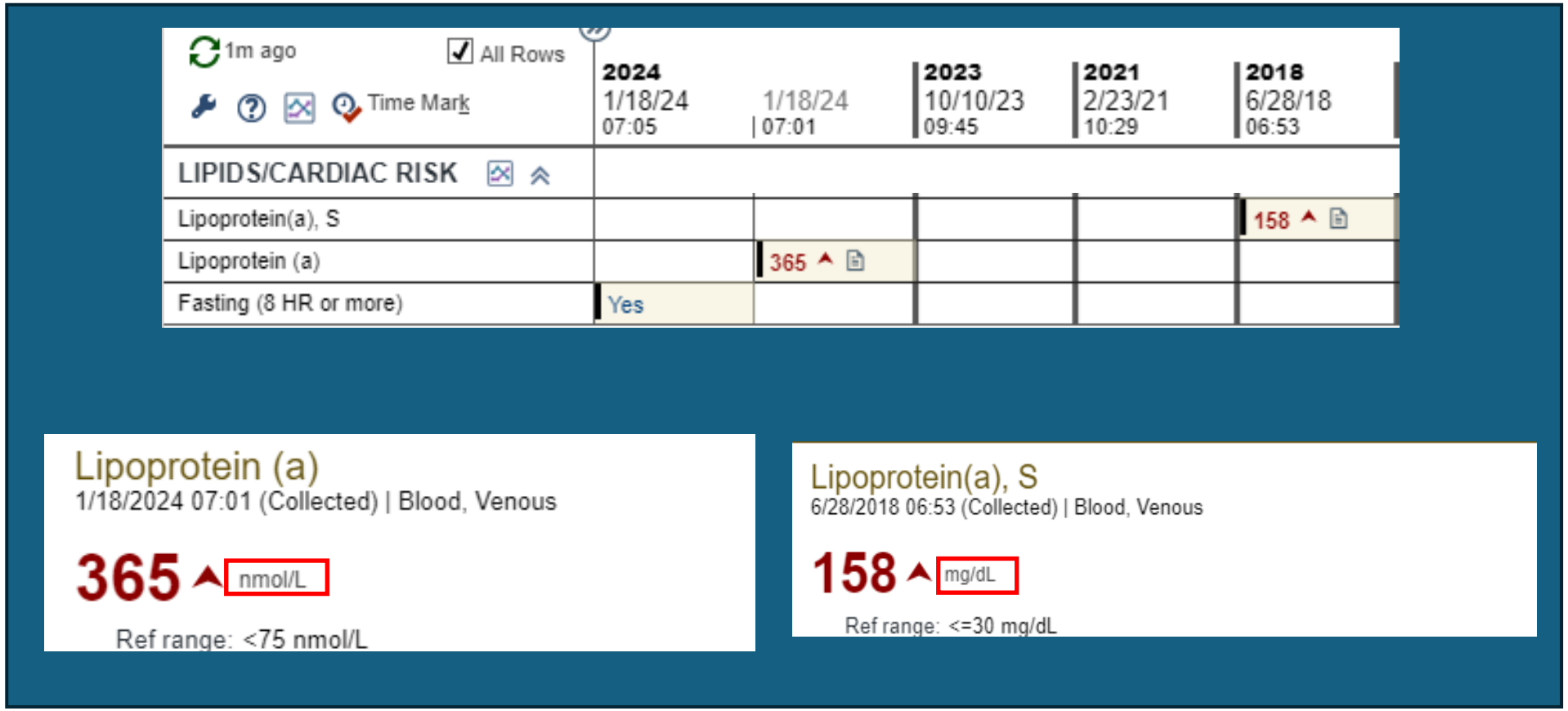
Different “Flavors” of Lp(a) Measurements

	Particle Concentration Assays	Apo(a) Mass Assays
Units reported	nmol/L	mg/dL
Characteristic measured	Number of actual particles, regardless of apo(a) size or lipid content	Total mass, which varies depending on the size of the Lp(a) isoform (eg, number of kringle repeats, cargo)
Influence of apo(a) isoform size	Less susceptible to inaccuracies from isoform size	Most susceptible to inaccuracies from isoform size

National and international guidance documents: nmol/L preferred over mg/dL;
But: measuring in mg/dL is better than no Lp(a) measurement

1. McConnell JP et al. *J Clin Lipidol*. 2014;8(6):550-553. **2.** Tsimikas S et al. *J Am Coll Cardiol*. 2018;71(2):177-192. **3.** Koschinsky ML et al. *J Clin Lipidol*. 2024;18(3):e308-e319. **4.** Cao J et al. *J Appl Lab Med*. 2024;9(5):1040-1056.

Beware of assay units



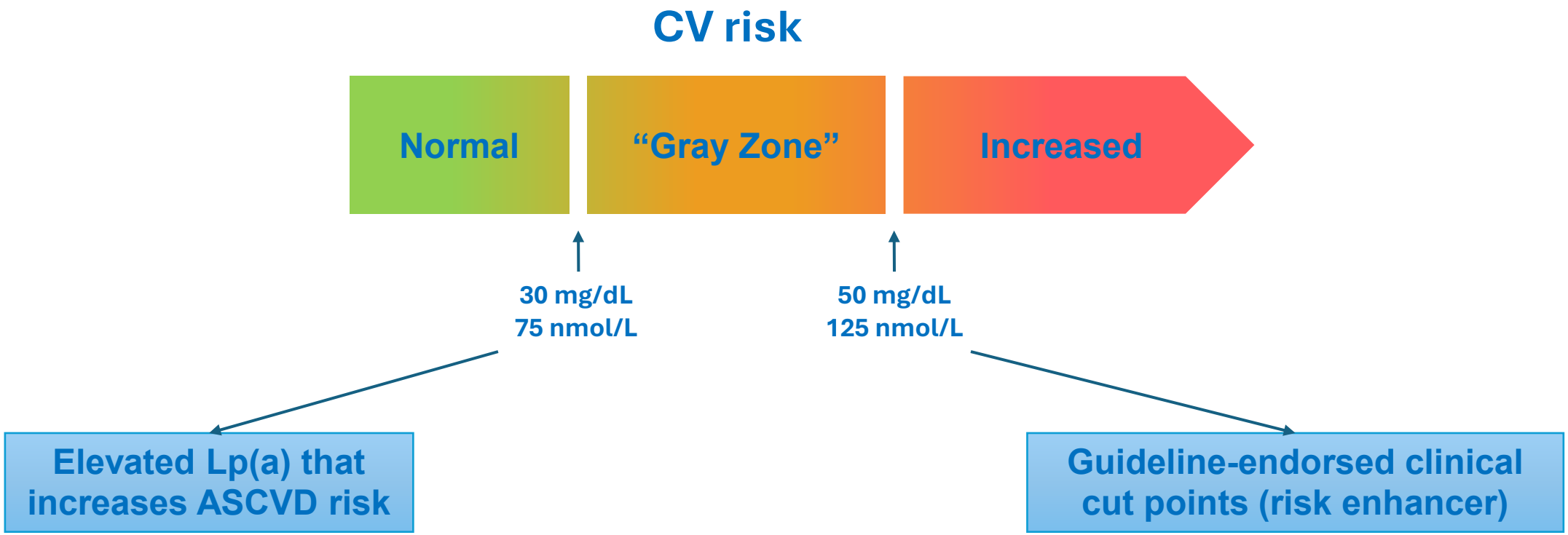
Lp(a) Measurement Methods Needs Harmonization

Ideal Lp(a) assays should:
Do not convert results obtained in mass units to molar units
Choose assay that utilizes isoform-independent antibodies
Utilize the WHO/IFCC SRM-2B reference material (new reference materials are being developed)
Check the assay has been certified for accuracy
Until the assays are harmonized, it is best to stick to testing using one assay

1. Cegla J et al. *Ann Clin Biochem.* 2021;58(1):16-21. **2.** Koschinsky ML et al. *J Clin Lipidol*. 2024;18(3):e308-e319.

Lp(a) Test Reporting/Interpretation

What Are Testing Labs To Do? Where To Flag?



J Appl Lab Med. 2024 Sep 3;9(5):1040-1056.

Even without targeted treatment-

Lp(a) testing at least once in a lifetime
(ideally at an early age and in combination with LDL cholesterol)

Lp(a) < 30 mg/dL (<62 nmol/L)	Lp(a) 30-50 mg/dL (62-105 nmol/L)	Lp(a) >50 mg/dL (>105 nmol/L)
Reclassification of CVD risk		
No major risk increase from Lp(a) → Usual CVD risk factor control	Slight risk increase from Lp(a) → Might increase in higher risk category (e.g. by kidney impairment, hypothyroidism, menopause, …) → Improve management of traditional risk factors	The higher the concentration, → the higher the CVD risk → Reclassification into higher risk category and more stringent manage-ment of traditional CVD risk factors

Invite family members for cascade and reverse cascade Lp(a) testing
(e.g. parents, siblings, children)

Management of high Lp(a) with early preventive measures

- ✓ Lifestyle changes (stop smoking, more exercise, better diet, weight loss, …)
- ✓ Lower LDL-cholesterol (possibly lower treatment target)
- ✓ Improve blood pressure control
- ✓ Better control of diabetes and prediabetes

Lower the global CVD risk of the given person

The global risk of an individual depends on presence of traditional risk factors plus the Lp(a) concentration and the management strategy is derived from this combination.

Atherosclerosis 2025 May 5:119218.

NYU Langone Health

Leon H. Charney Division of Cardiology
NYU Center for the Prevention of Cardiovascular Disease

Howard Weintraub, MD, FAHA, FACC

Clinical Director, NYU Center for the Prevention of Cardiovascular Disease

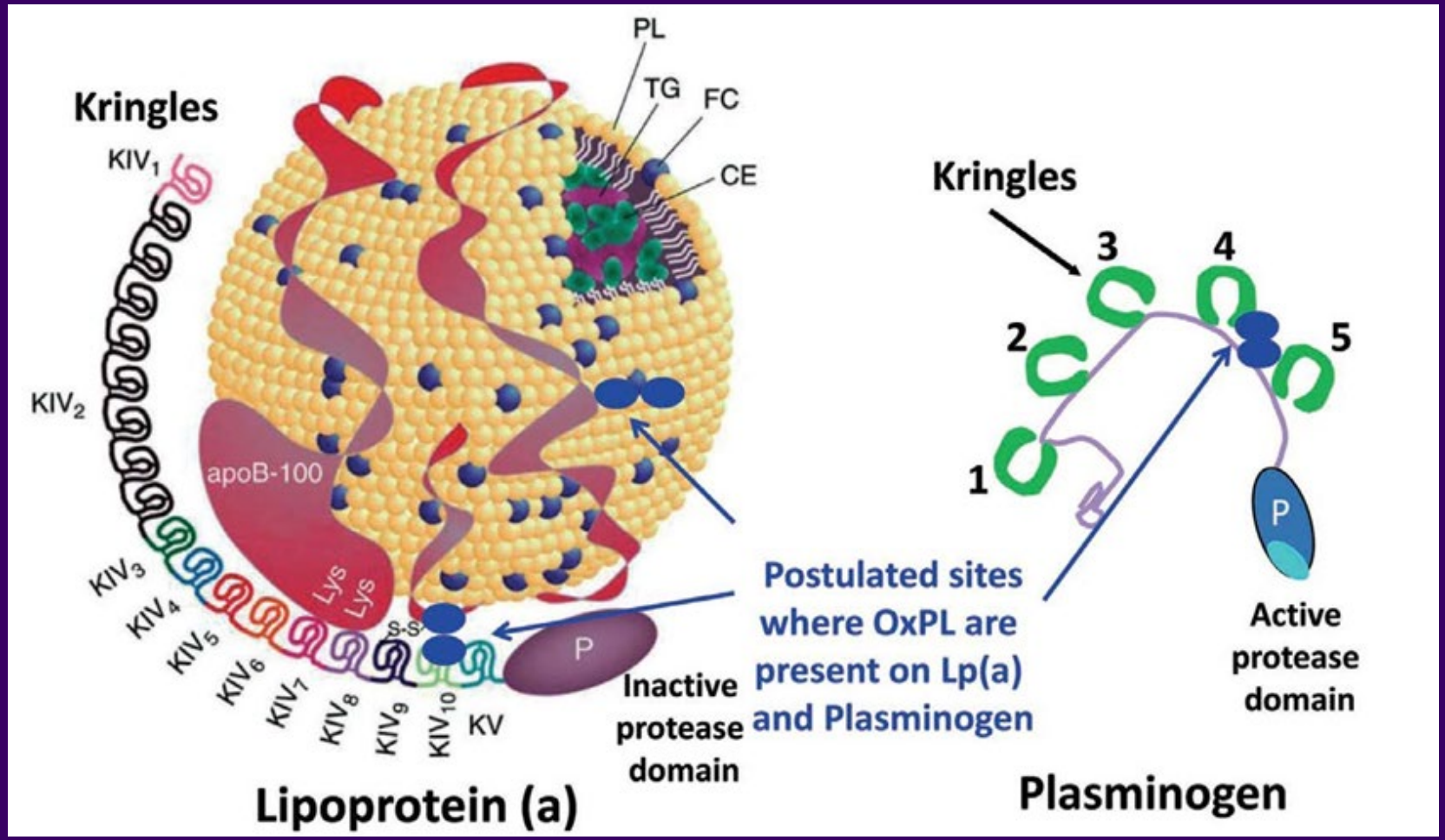
Disclosures

Presenter	Conflicts
Howard Weintraub	NovoNordisk: Consultant Amgen: Research Novartis: Research Lily: Research

NYU Langone Health

Determinants of binding of oxidized phospholipids on apolipoprotein (a) and lipoprotein (a)[1]

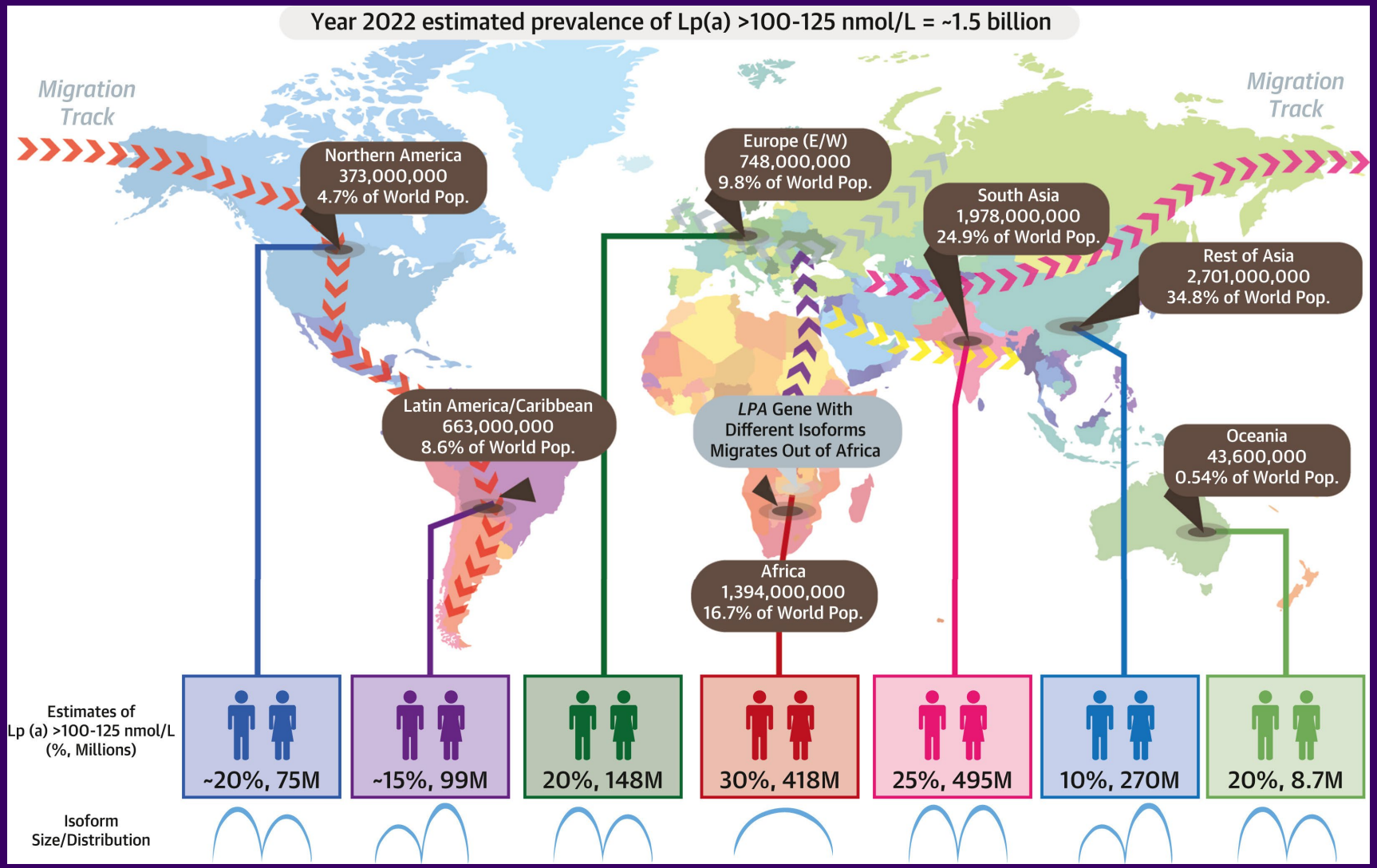
Gregor Leibundgut,*,† Corey Scipione,§ Huiyong Yin,** Matthias Schneider,†† Michael B. Boffa,§ Simone Green,* Xiaohong Yang,* Edward Dennis,§§ Joseph L. Witztum,* Marlys L. Koschinsky,§ and Sotirios Tsimikas[2,*]



NYU Langone Health

Leibundgut et al JACC 2012 and JLR 2013

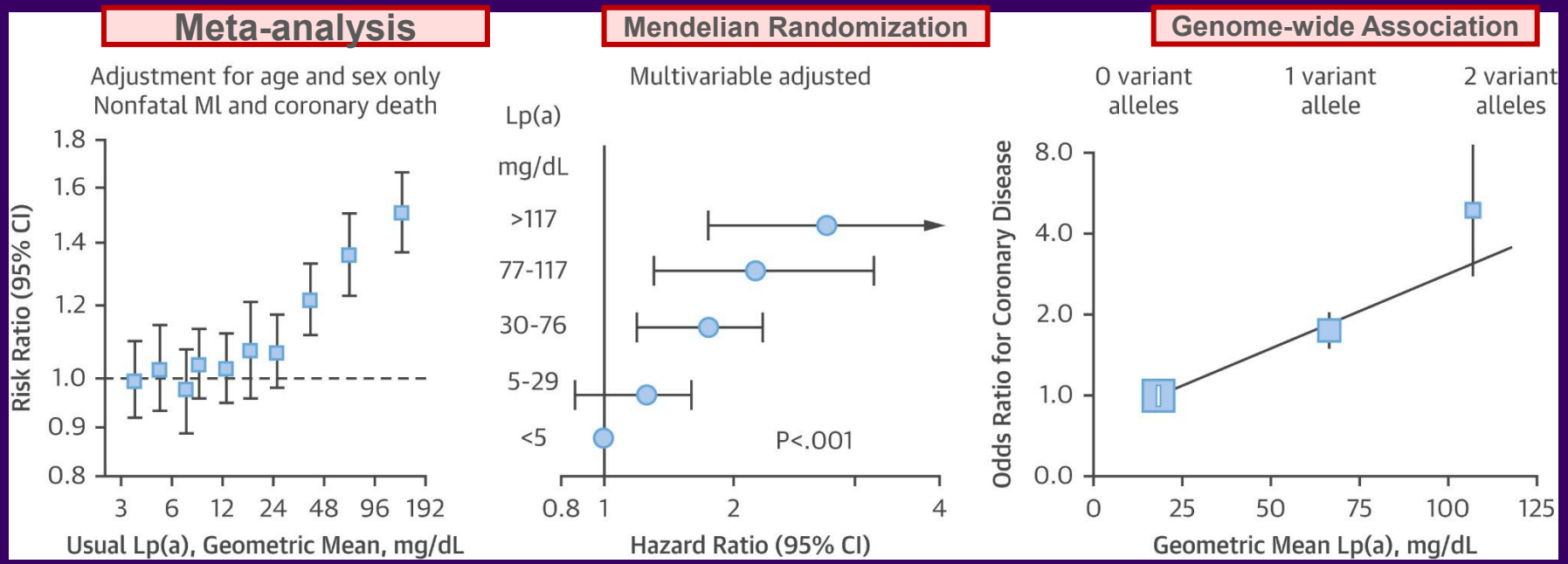
Prevalence of global elevated Lp(a)



NYU Langone Health

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

Evidence base for Lp(a) - ASCVD



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

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

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

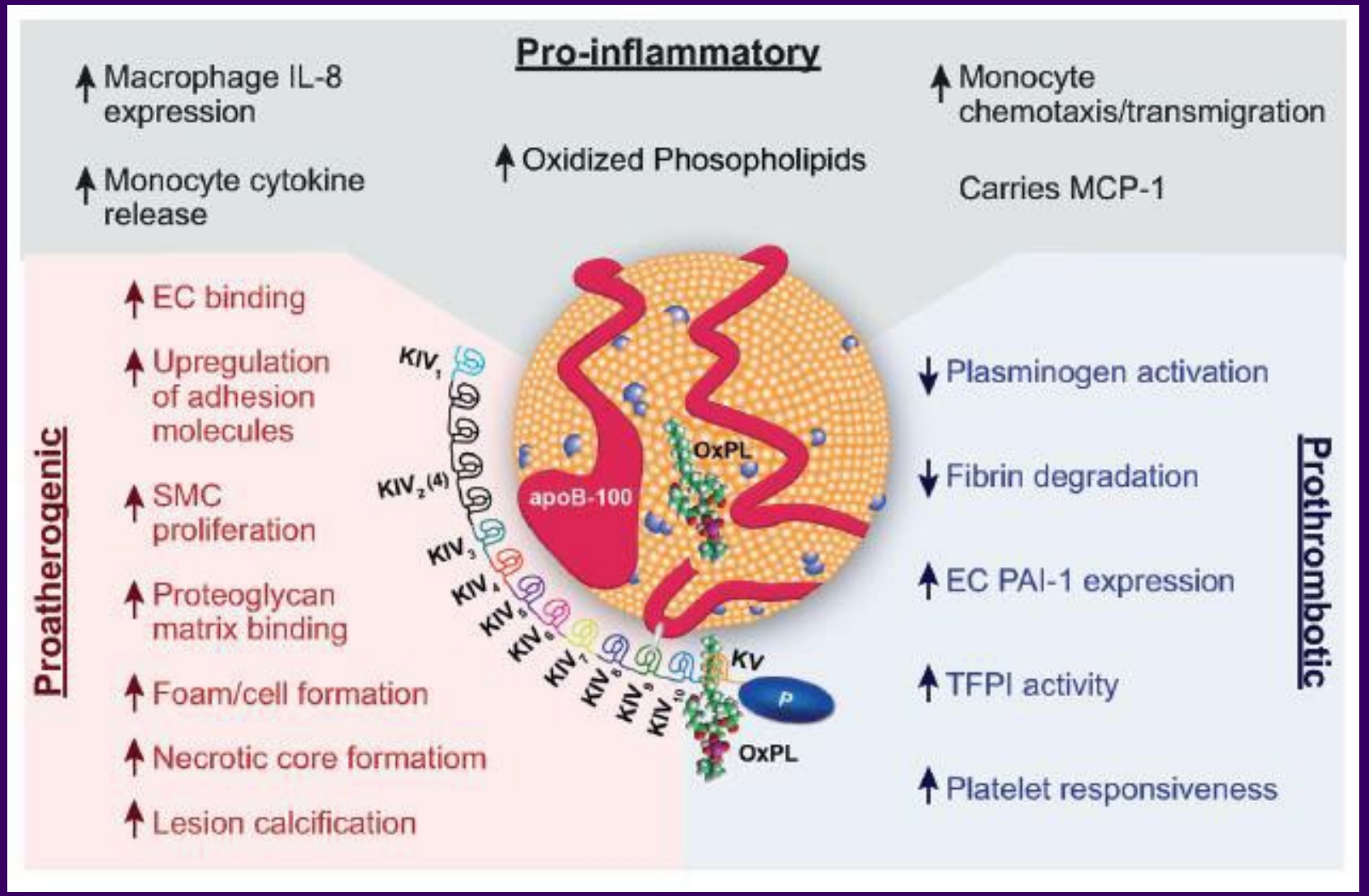
Identification of variants in LPA associated with CAD (Clarke et al., NEJM 2009; 361:2518)

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

NYU Langone Health

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

What are the mechanisms through which Lp(a) mediates CVD and ASCVD



NYU Langone Health

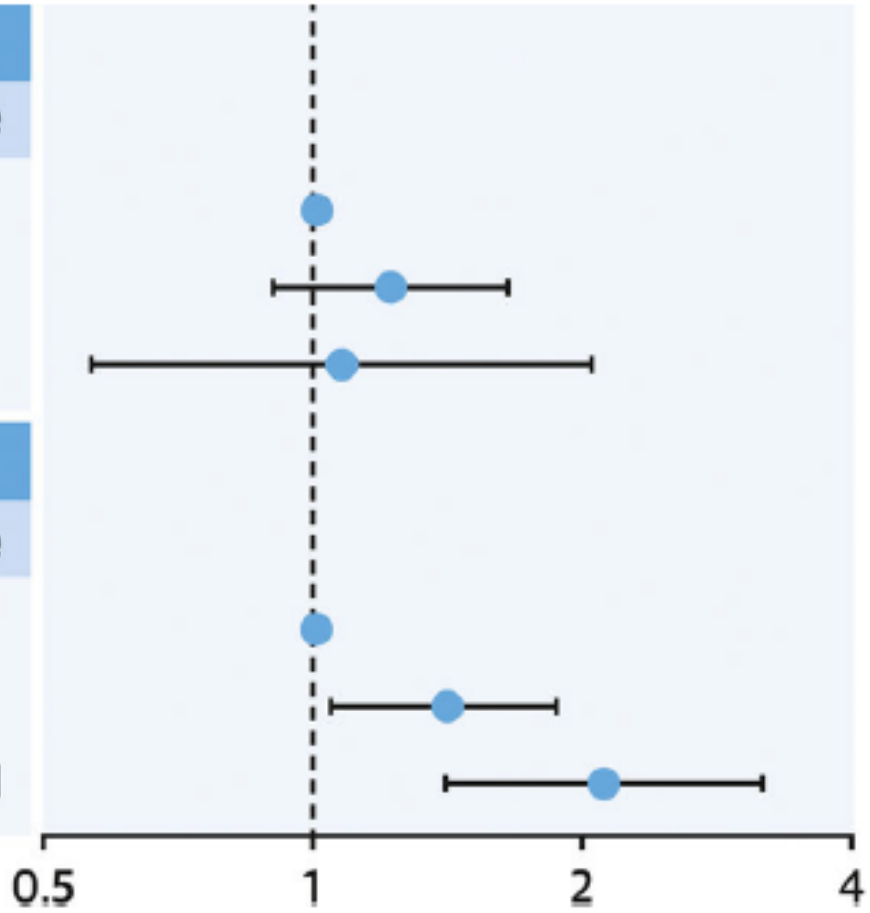
Tsimikas JACC 2017;69:692-711

hsCRP Modifies Impact of Lp(a) on CV Health

A

hsCRP <2 mg/L			
Lp(a) Strata	Events/Total (%)	HR (95% CI)	*P* Value
<50 mg/dL	268/1,960 (13.7)	1.00 (reference)	NA
50-99.9 mg/dL	55/332 (16.5)	1.21 (0.89-1.64)	0.21
≥100 mg/dL	11/85 (12.9)	1.10 (0.58-2.08)	0.77

hsCRP ≥2 mg/L			
Lp(a) Strata	Events/Total (%)	HR (95% CI)	*P* Value
<50 mg/dL	256/1,788 (14.3)	1.00 (reference)	NA
50-99.9 mg/dL	62/359 (17.3)	1.36 (1.02-1.81)	0.03
≥100 mg/dL	28/111 (25.2)	2.09 (1.40-3.13)	< 0.001

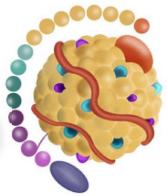


NYU Langone Health

Zhang, W. et al. JACC. 9/2021

Lp(a) Influence on ASCVD

Copenhagen General Population Study (68,090 individuals)

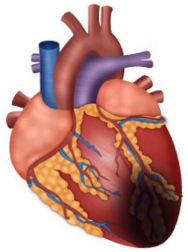


Hazard ratio (95%CI) for ASCVD, myocardial infarction, and aortic valve stenosis

	ASCVD	Myocardial infarction	Aortic valve stenosis
CRP <2 mg/l	1.61 (1.43–1.81)	2.08 (1.76–2.45)	2.01 (1.59–2.55)
CRP ≥2 mg/l	1.57 (1.36–1.82)	1.65 (1.34–2.04)	1.73 (1.31–2.27)
Interaction	P=0.87	P=0.15	P=0.18

HR (95% CI) for Lp(a) top 10% versus bottom 33%

Absolute 10-year risk of ASCVD and aortic valve stenosis



ASCVD

♂ 34%

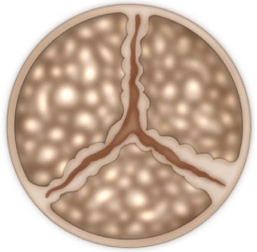
♀ 20%

Age 70-79
and
CPR ≥2 mg/l
and
Lp(a)
≥70 mg/dl
≥147 mmol/l

Aortic valve stenosis

13% ♂

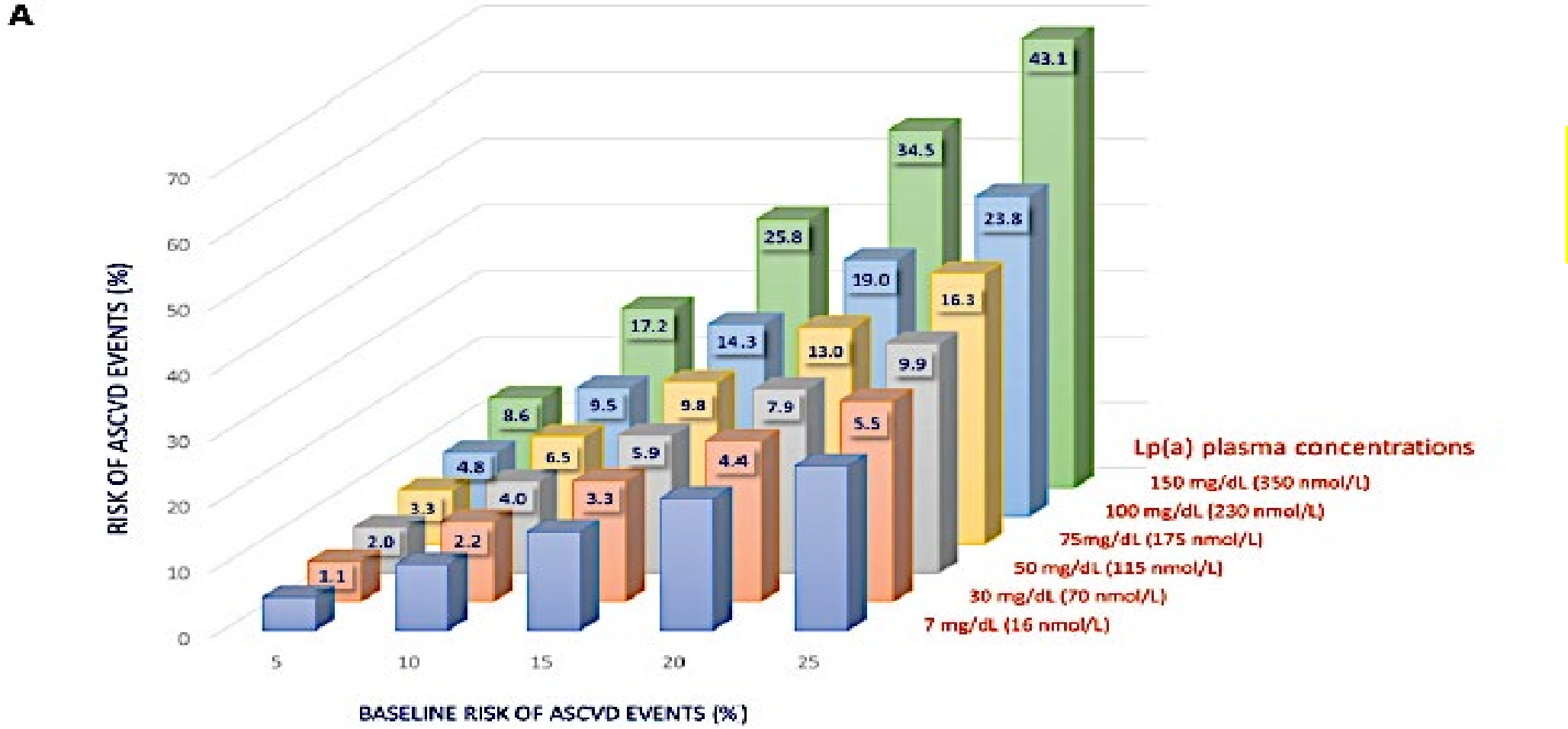
8% ♀



NYU Langone Health

Nordestgaard, B. et al. EHJ. 2023

Effect of Increasing Lp(a) Levels and Estimated Baseline Absolute Risk for Major CVE's

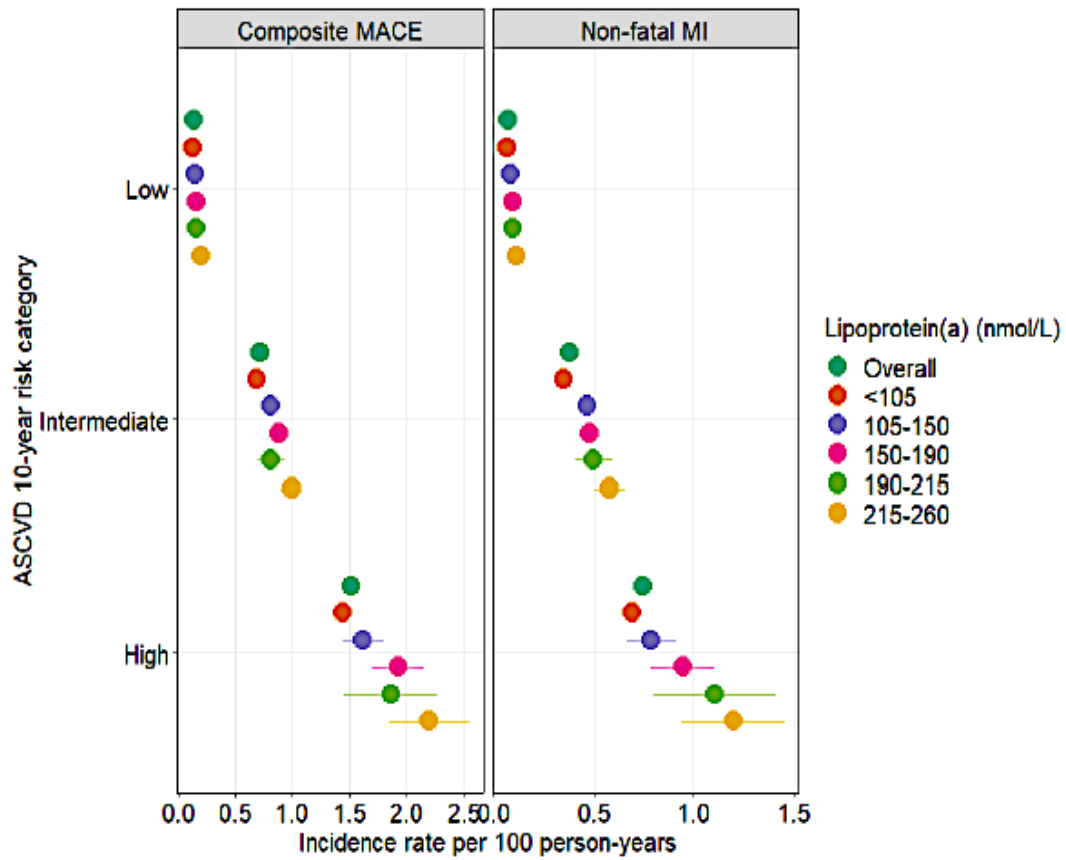


UK Biobank
N=415,274

Kronenberg, F. et al. EHJ 2022

NYU Langone Health

Incident Rates of MACE-Relative to Risk Scores and Lp(a)



IRs of MACE and non-fatal MI, stratified by Lp(a) and ASCVD 10-year risk score

IRs of MACE and non-fatal MI associated with risk score

- IRs of MAC and non-fatal MI were significantly higher in the high-risk category than in intermediate and low-risk

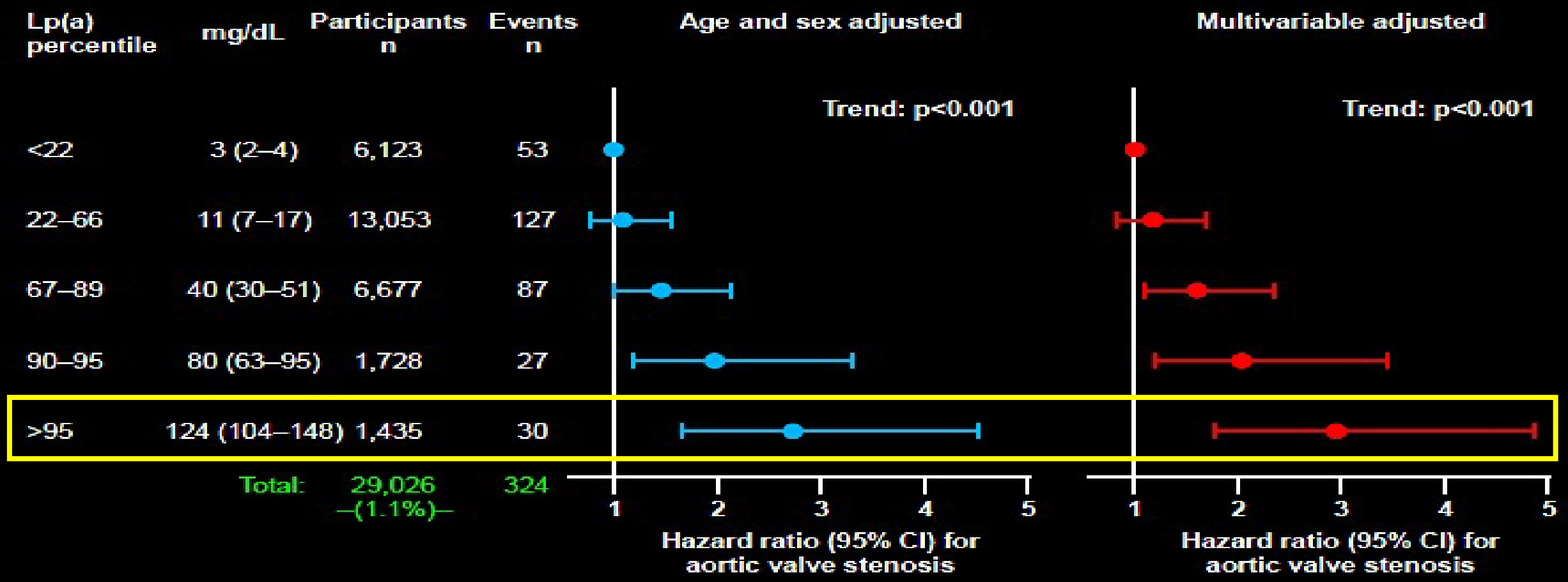
IRs of MACE and non-fatal MI associated with Lp(a)

- Within risk categories, Lp(a) levels above 105 nmol/L caused significant increase in IR of MACE and non-fatal MI by up to 82%

NYU Langone Health

Costa-Scharplatz, Madlaina et al. AHA 2023

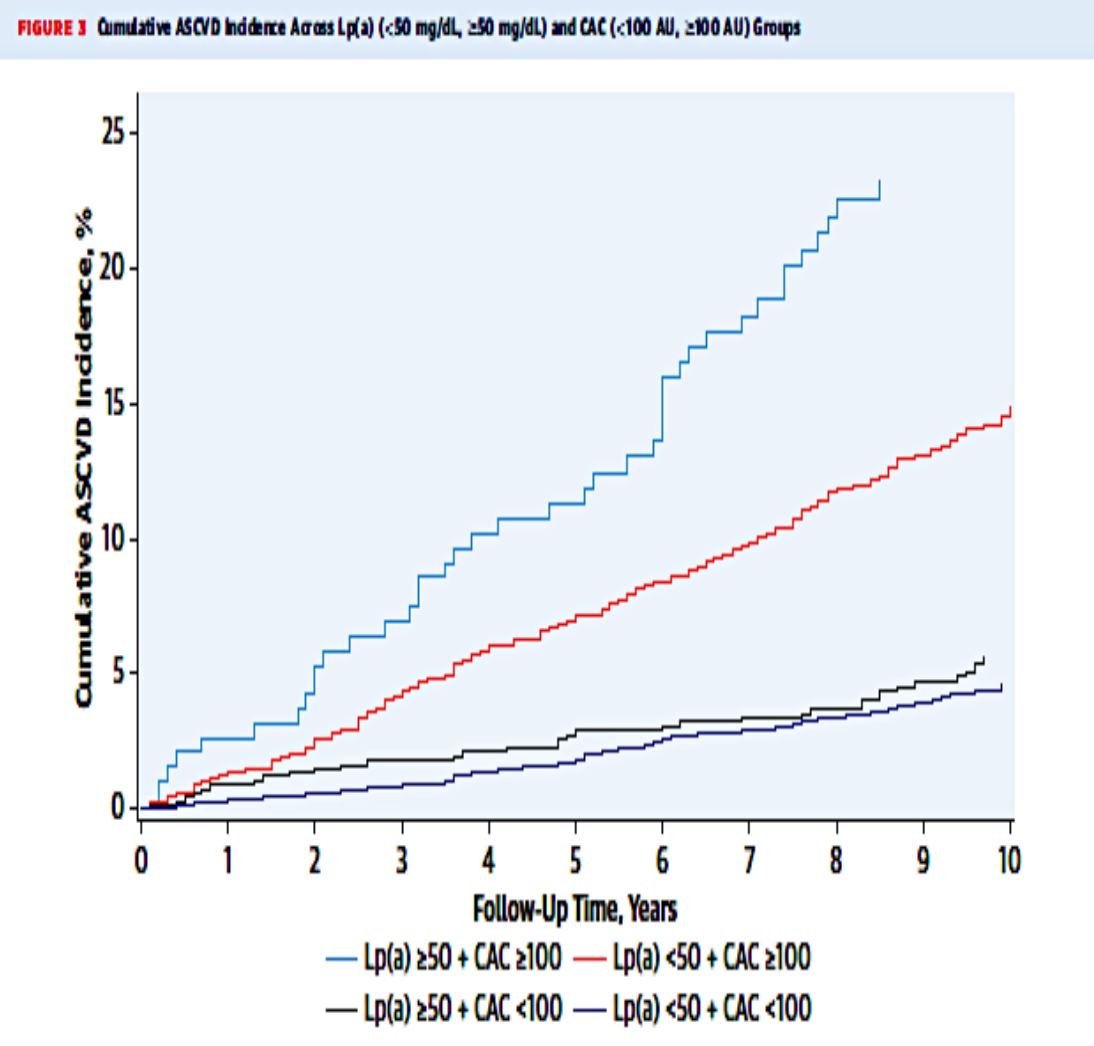
Risk of aortic valve stenosis as a function of elevated Lp(a) levels

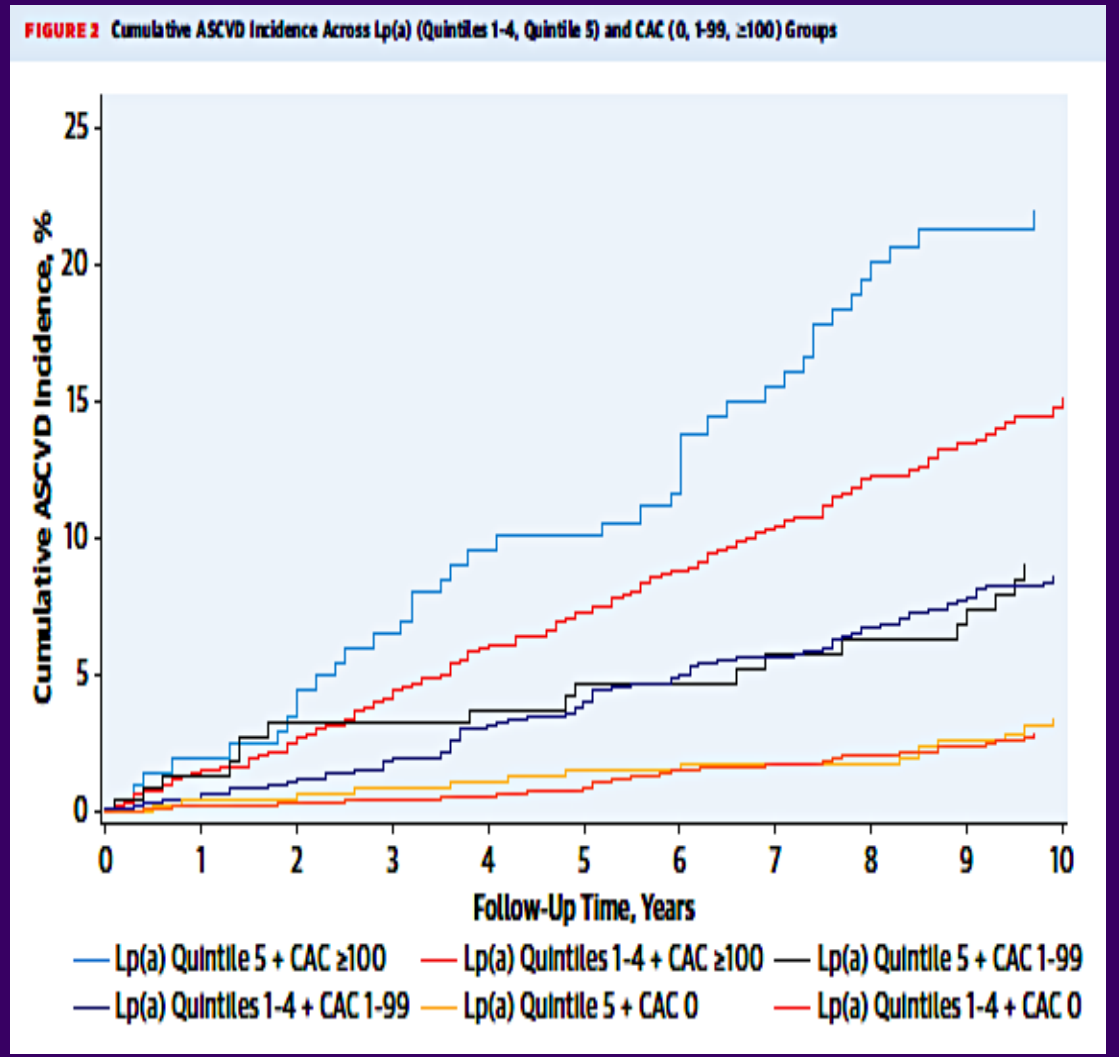


Lp(a): lipoprotein(a); CI, confidence interval; HDL, high density lipoprotein
Analyses were adjusted for age and sex, or multivariable adjusted additionally for total cholesterol, HDL cholesterol, systolic blood pressure, smoking, and diabetes; Lp(a) in mg/dL is shown as median (interquartile range)

1. Kamstrup PR *et al.* J Am Coll Cardiol. 2013 Oct 10. doi: 10.1016/j.jacc.2013.09.038. [Epub ahead of print]

Increasing CAC and Lp(a) and Incidence of ASCVD



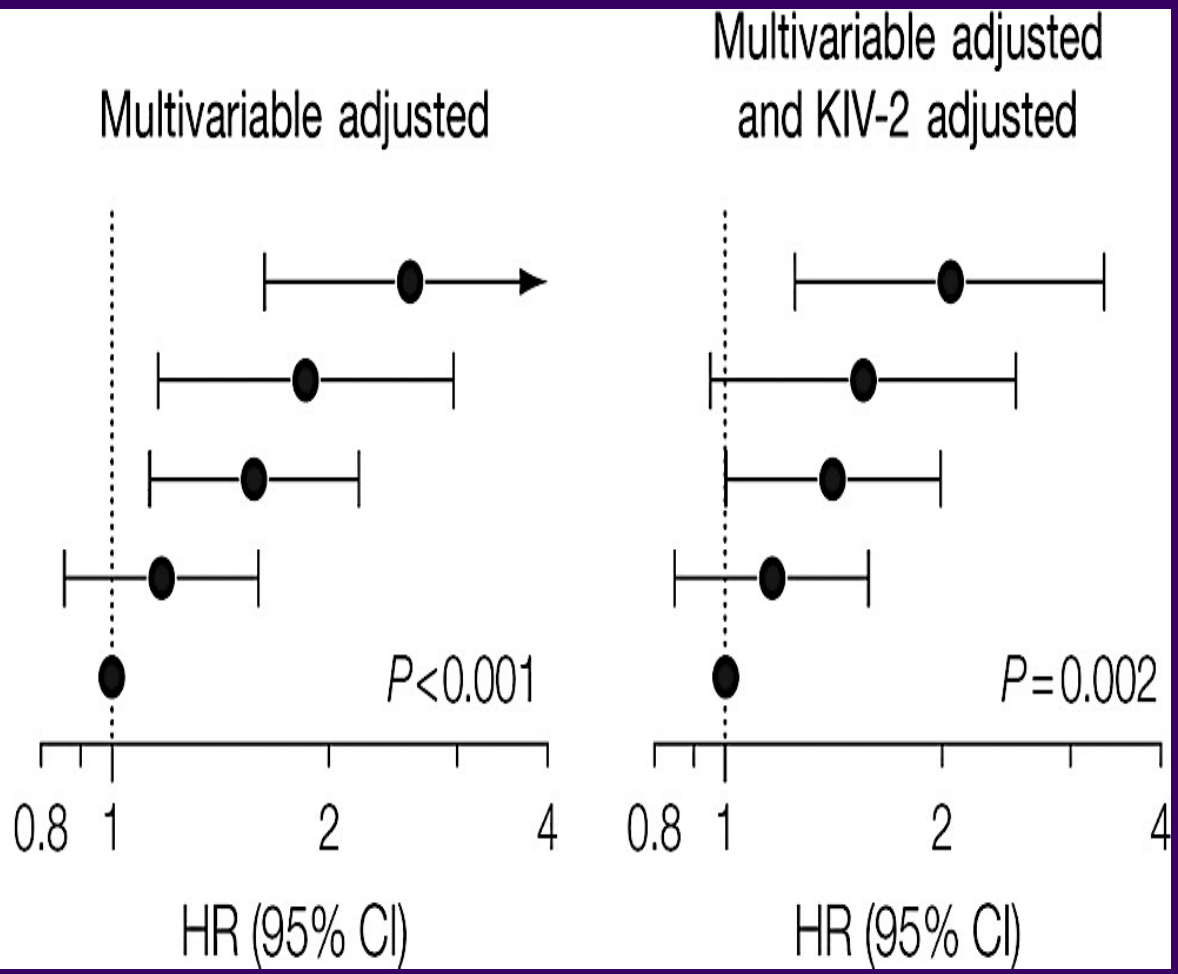


NYU Langone Health

Mehta, A. et al. JACC. 3/2022

Risk of myocardial infarction by levels of lipoprotein(a) in the general population

Lipoprotein(a)		Participants	Events
Percentile	mg/dL	(no).	(no).
>95th	>117	376	46
90th–95th	77–117	450	46
67th–89th	30–76	1731	155
22nd–66th	5–29	3385	241
<22nd [reference]	<5	1582	104

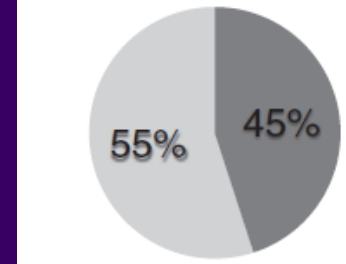


NYU Langone Health

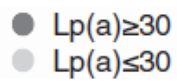
Nordestgaard B G et al. Eur Heart J 2010;31:2844-2853

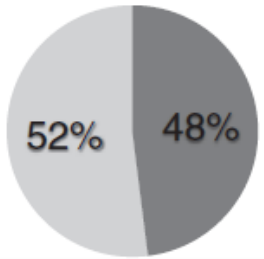
Lipoprotein(a) screening in patients with controlled traditional risk factors undergoing percutaneous coronary intervention

Matthew C. Weiss, MD, Jeffrey S. Berger, MD, Eugenia Gianos, MD, Edward Fisher, MD, MPH, PhD, Arthur Schwartzbard, MD, James Underberg, MD, Howard Weintraub, MD*



Percent abnormal Lp(a) in all-comers, n=113.





Percent Lp(a) ≥30mg/dL in those with LDL-C ≤70 *and* non-HDL ≤100mg/dL, n=38.

Lp(a) (mg/dL)	Mod. or High Intensity Statin (n=67)	LDL-C ≤70mg/dL (n=41)	Non-HDL ≤100mg/dL (n=54)	LDL-C ≤70 *and* non-HDL ≤100mg/dL (n=38)	"Corrected LDL-C" ≤70 *and* non-HDL ≤100mg/dL
<30	33 (49%)	24 (59%)	30 (56%)	21 (55%)	21 (42%)
≥30	34 (51%)	17 (41%)	19 (35%)	17 (45%)	29 (58%)
≥50	25 (43%)	13 (32%)	16 (30%)	16 (42%)	24 (48%)
Mean Lp(a) mg/dL	56±56	50±59	48±57	52±61	53±28

NYU Langone Health

Journal of Clinical Lipidology, Vol 11, No 5, October 2017

Lipid Lowering and Lp(a) Directed Therapies

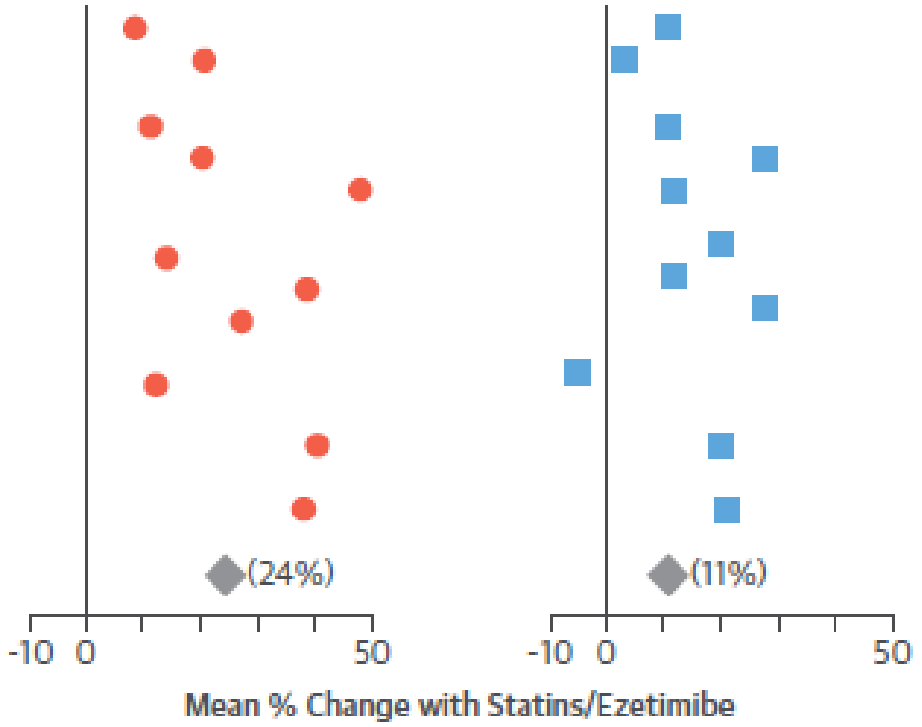
Drug/class name	Drug target	Development stage	Lp(a) reduction	LDL-C reduction	References
Approved lipid lowering therapies					
Statins	HMGCR	Available	No change	20–50%	[28, 47, 48]
Ezetimibe	NPC1L1	Available	0–7% (on top of statins)	18–22% (on top of statins)	[29, 30, 49]
Lipoprotein apheresis	Plasma lipoprotein removal	Available	63%	64%	[32]
Bempedoic acid	ACLY	Available	No change	17–21%	[34, 50–52]
PCSK9i monoclonal antibodies	PCSK9	Available	23–27% (on top of statins + ezetimibe)	50–60% (on top of statins + ezetimibe)	[35, 36]
Inclisiran	PCSK9	Available	22%	50%	[42]
Lp(a)-directed therapies					
Pelacarsen	ASO with GalNAc3 conjunction	Phase 3	80%	10–20%	[43, 44••, 53]
Olpasiran	siRNA	Phase 2	Up to 90%	No change	[45•]
SLN360	siRNA	Phase 1	Up to 98%	Up to 25%	[46•]

NYU Langone Health

Nurmohamed, N, et al. Current Atherosclerosis Reports. 2022

Statins modestly increase Lp(a) levels
UCSD Lp(a) data from clinical trials

Statin	Study		
Atorvastatin 10mg	Ky *et al*	2008	(n=29)
	Yoshida *et al*	2012	(n=21)
Atorvastatin 80mg	Tsimikas *et al* (MIRACL)	2004	(n=1151)
	Ky *et al*	2008	(n=26)
	Choi *et al* (REVERSAL)	2008	(n=108)
Pravastatin 40mg	Rodenberg *et al*	2006	(n=90)
	Choi *et al* (REVERSAL)	2008	(n=106)
	Ky *et al*	2008	(n=24)
Pitivastatin 2mg	Yoshida *et al*	2012	(n=21)
Rosuvastatin 40mg	Capoulade *et al* (ASTRONOMER)	2015	(n=134)
Simvastatin/Ezetimibe	Yeang *et al*	2016	(n=162)
			(n=1850)



NYU Langone Health

Yeang et al J Clin Lipidology 2016, Tsimikas JACC 2017

Table 1 Non-genetic influences on lipoprotein(a) concentration

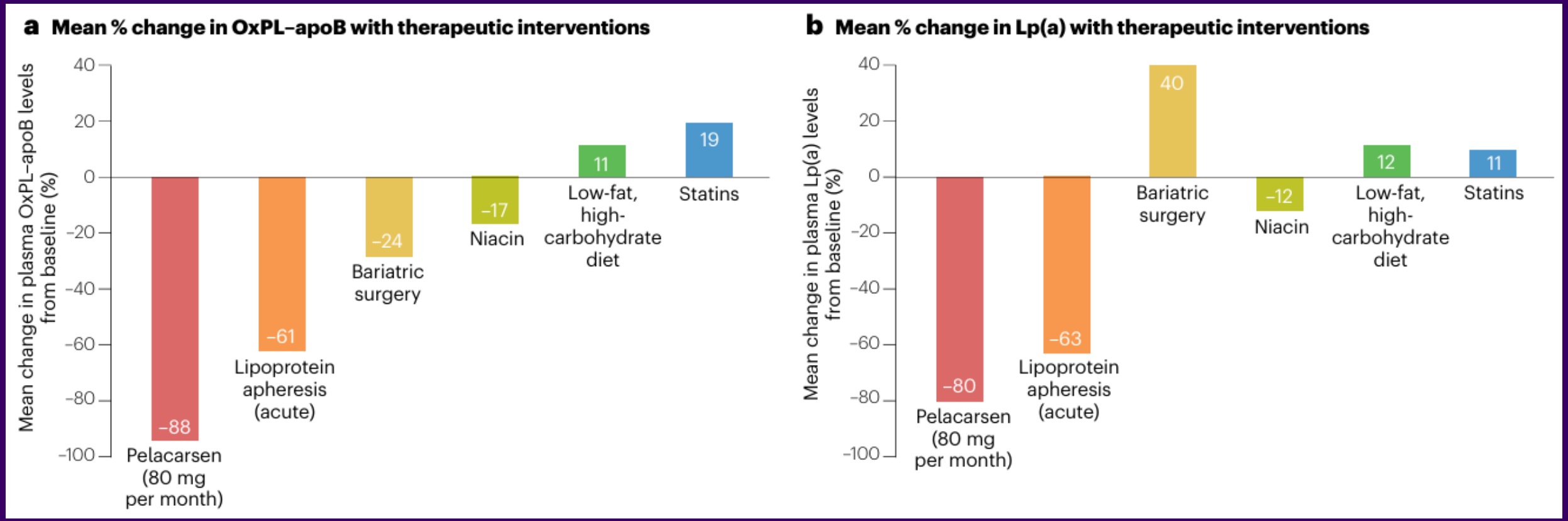
Condition/intervention	Effect on Lp(a) levels
Lifestyle	
Replacement of dietary saturated fat with carbohydrate or unsaturated fat[32]	~10%–15% increase
Low carbohydrate diet high in saturated fat[33]	~15% decrease
Fasting[34]	None
Physical activity[35]	None/minimal
Hormones and related conditions	
Hyperthyroidism[36]	Decrease; 20%–25% increase with thyrostatic treatment or radioactive iodine therapy
Hypothyroidism[36]	Increase; 5%–20% decrease with replacement therapy
Growth hormones[37]	2x increase with therapy
Endogenous sex hormones[31]	None/minimal
Pregnancy[38,39]	2x increase
Menopause[31]	None/minimal
Postmenopausal hormonal replacement therapy[40]	~25% decrease
Surgical or biochemical castration in males[48]	Small increase
Ovariectomy, oestrogen receptor antagonist[49]	Small increase
Chronic kidney disease[41,42]	
Nephrotic syndrome[50,63]	3–5 x increase (vs. control)
Peritoneal dialysis patients[51]	2 x increase (vs. control)
Haemodialysis treatment and chronic kidney disease[51,52,64]	Increases in large apo(a) isoform carriers
Kidney transplantation[43]	~Normalization of levels
Hepatic impairment[44,59]	Decrease, depending on cause
Liver transplantation[53]	Changes of apo(a) isoform to that of the donor, with corresponding changes in Lp(a) levels
Inflammation and related conditions[55,60]	
Severe, life-threatening acute-phase conditions (sepsis, severe burns)[46]	Decrease
Several inflammatory conditions[45]	Increase
Tocilizumab (interleukin-6 inhibitor)[47,61]	~30%–40% decrease
Protease inhibitors or antiretroviral therapy[56,57]	Increase
Statins[65–68]	May slightly increase Lp(a) (but reports are heterogeneous)
Air pollution (fine particulate, PM2.5)[58]	Slight increase

Changes are based on limited data; studies referenced are representative examples.

Non-Genetic Influences on Lp(a) Concentration

Kronenberg, F. et al.
EHJ. 2022

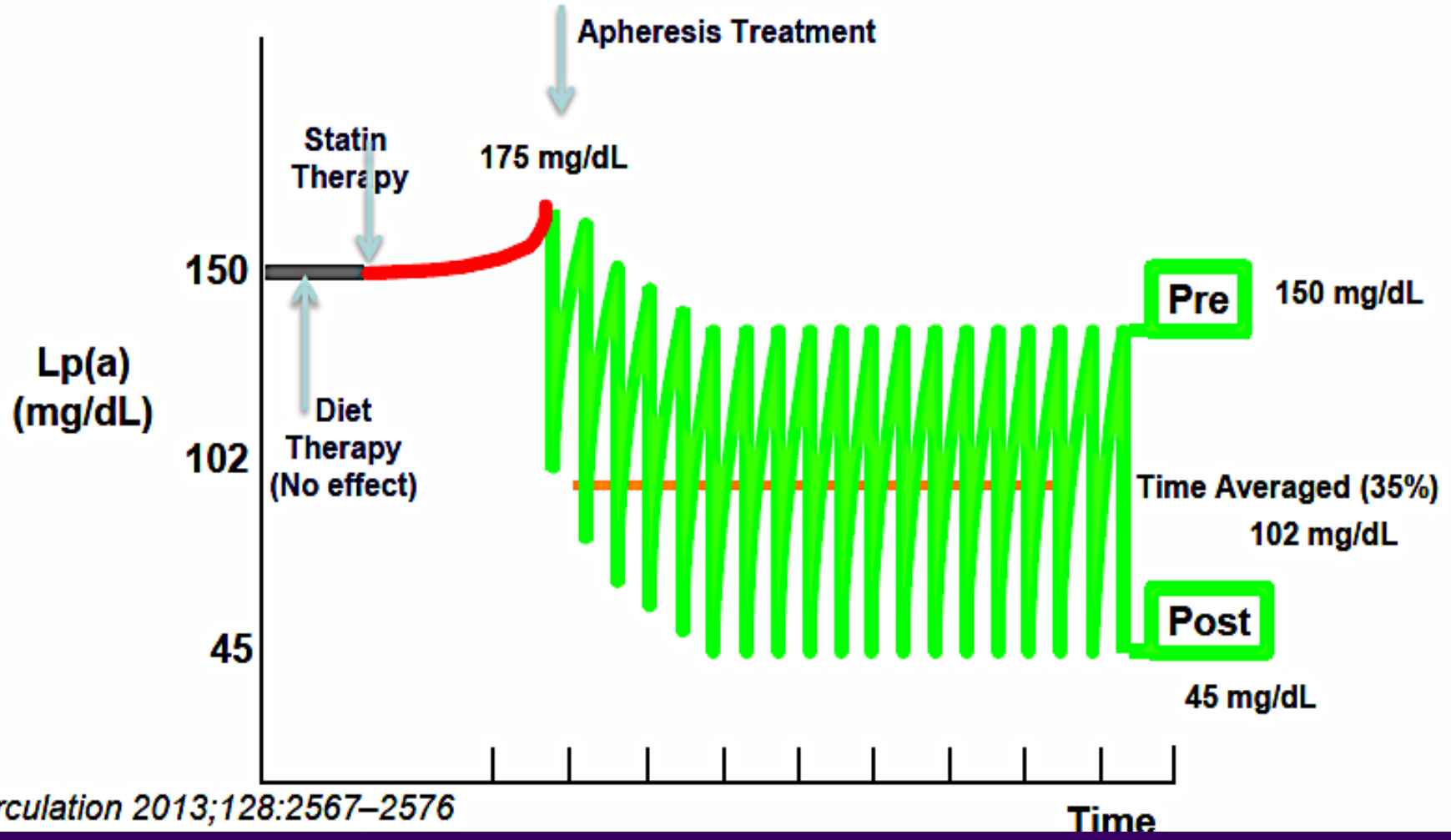
Effect of Therapeutic Interventions on Plasma Levels of Ox-PL- apoB and Lp(a)



NYU Langone Health

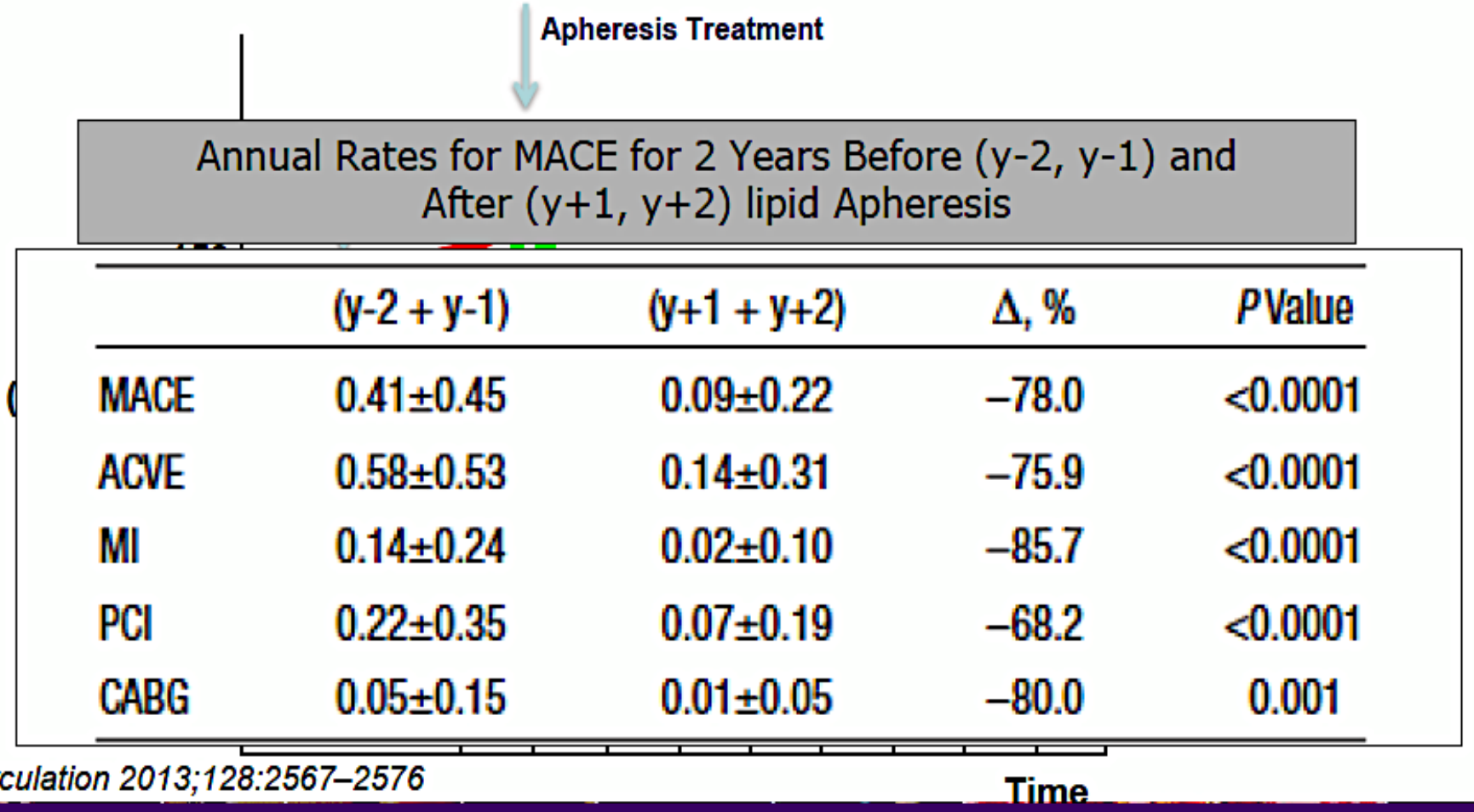
Tsimikas, S; Witzum, JL. Nat Rev Cardiol. 2023

Lipid apheresis and Lp(a)



Leebman et al. *Circulation 2013;128:2567–2576*

Lipid apheresis and Lp(a)



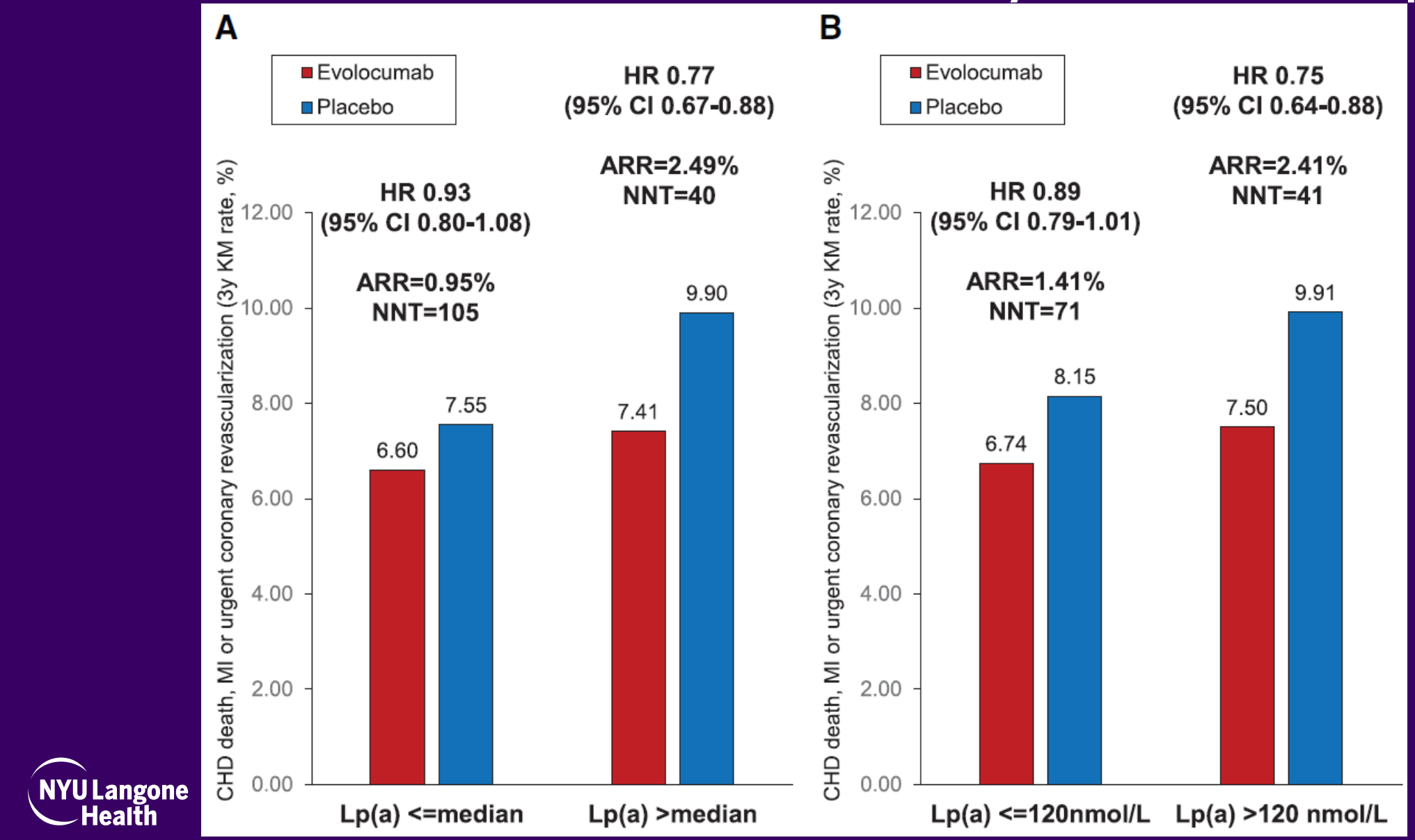
Annual Rates for MACE for 2 Years Before (y-2, y-1) and After (y+1, y+2) lipid Apheresis

	(y-2 + y-1)	(y+1 + y+2)	Δ, %	*P* Value
MACE	0.41±0.45	0.09±0.22	−78.0	<0.0001
ACVE	0.58±0.53	0.14±0.31	−75.9	<0.0001
MI	0.14±0.24	0.02±0.10	−85.7	<0.0001
PCI	0.22±0.35	0.07±0.19	−68.2	<0.0001
CABG	0.05±0.15	0.01±0.05	−80.0	0.001

Leebman et al. *Circulation 2013;128:2567–2576*

NYU Langone Health

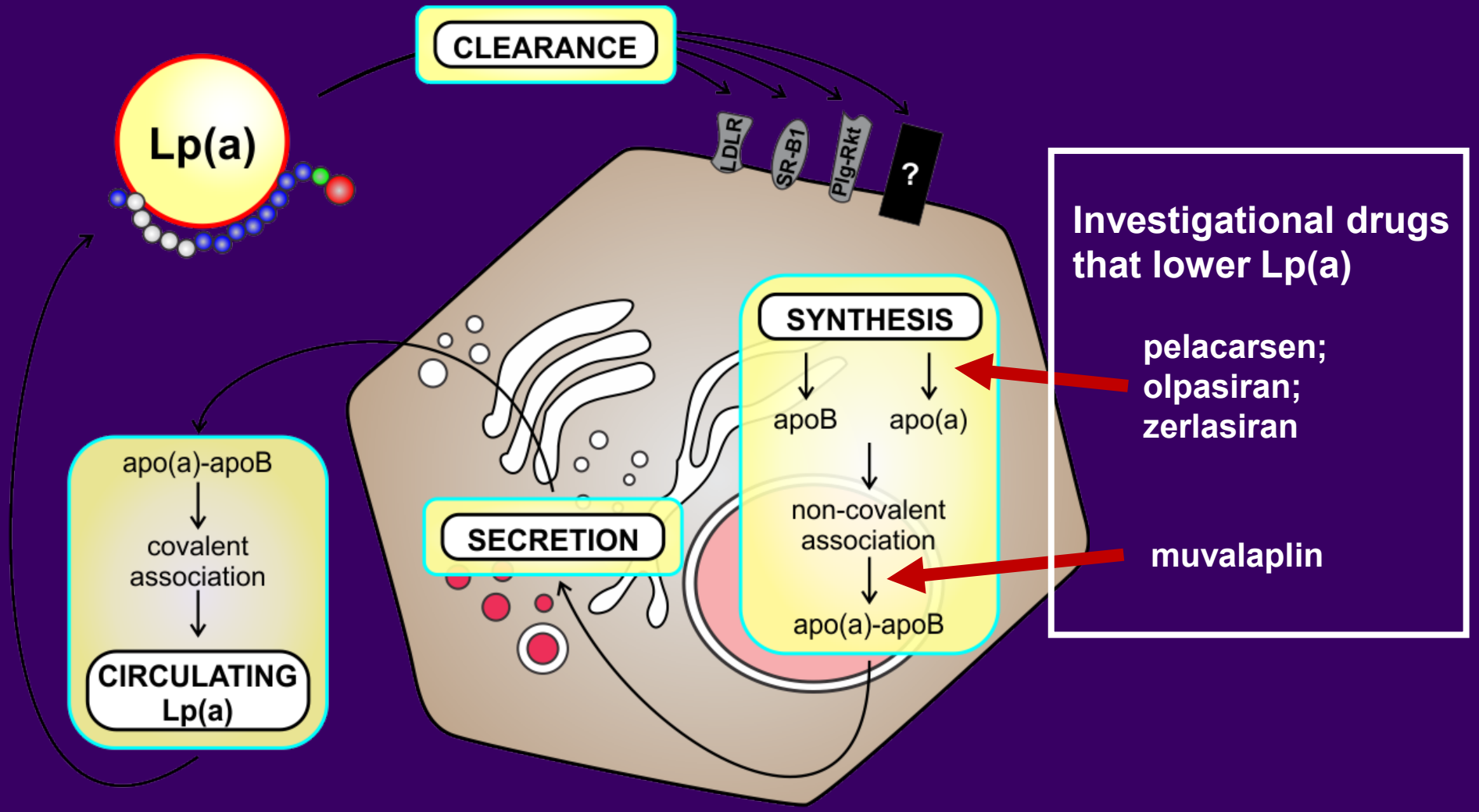
FOURIER: Treatment Effect by Baseline Lp(a)



NYU Langone Health

O'Donoghue et. al. Circulation 2019;139:1483–1492

Biosynthesis and catabolism of Lp(a)



NYU Langone Health

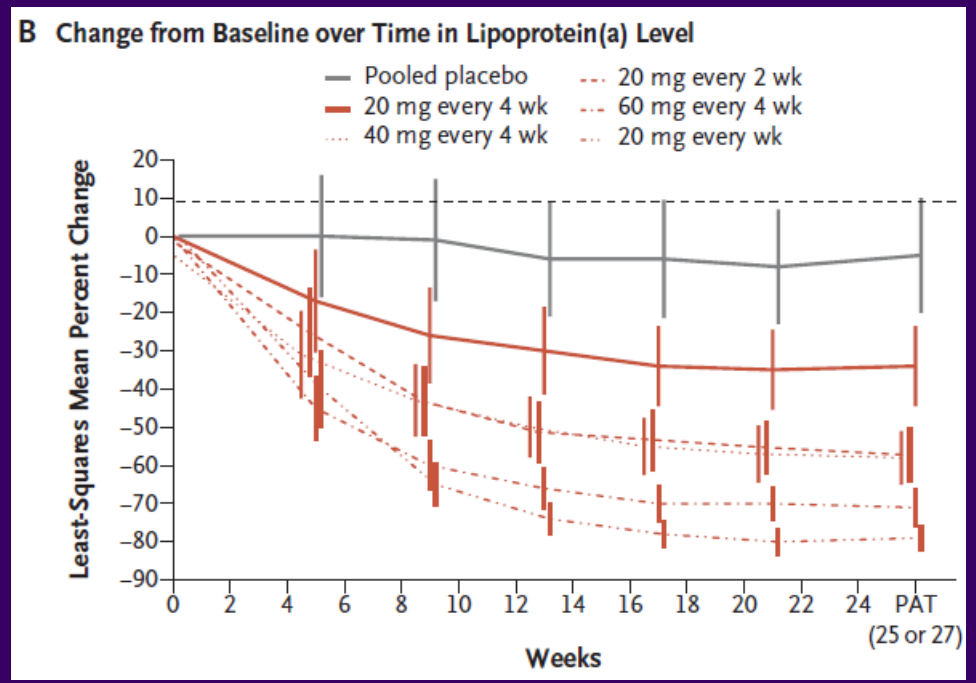
Koschinsky ML, unpublished image; The ABC'S of Lp(a)-Lp(a) Discovery Webinar

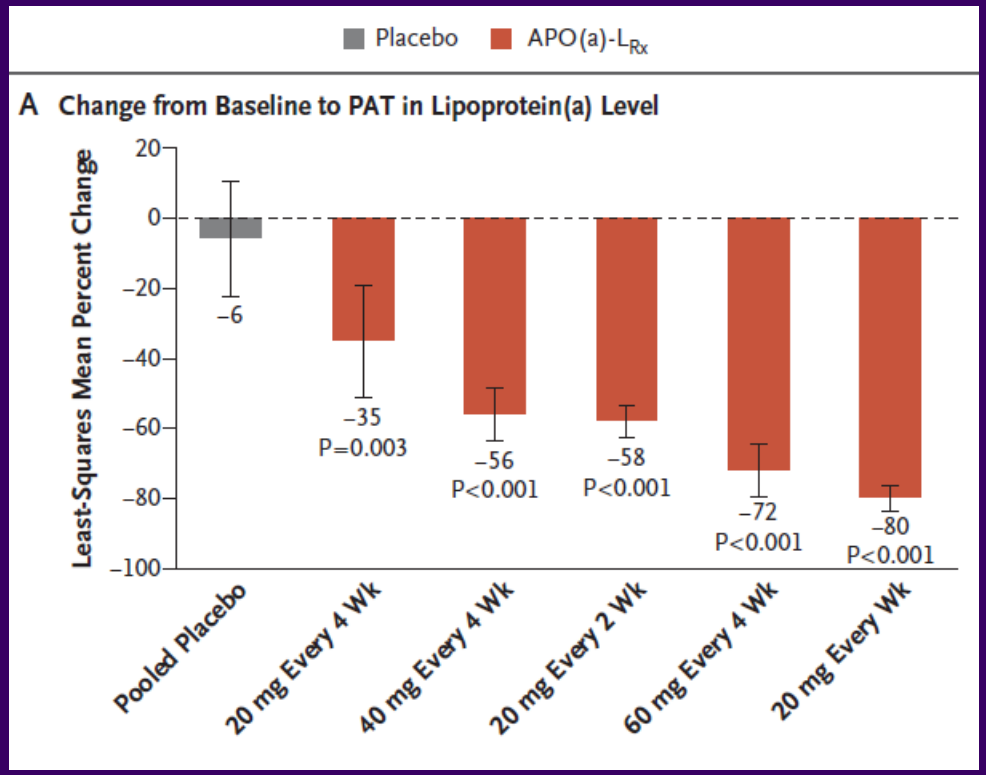
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lipoprotein(a) Reduction in Persons with Cardiovascular Disease

Sotirios Tsimikas, M.D., Ewa Karwatowska-Prokopczuk, M.D., Ph.D., Ioanna Gouni-Berthold, M.D., Jean-Claude Tardif, M.D., Seth J. Baum, M.D., Elizabeth Steinhagen-Thiessen, M.D., Michael D. Shapiro, D.O., Erik S. Stroes, M.D., Patrick M. Moriarty, M.D., Børge G. Nordestgaard, M.D., D.M.Sc., Shuting Xia, M.S., Jonathan Guerriero, M.B.A., Nicholas J. Viney, B.Sc., Louis O'Dea, M.B., B.Ch., B.A.O., and Joseph L. Witztum, M.D., for the AKCEA-APO(a)-L_{Rx} Study Investigators*





We did not observe marked changes in platelet, renal, or liver function, nor a between-group difference in the risk of influenza-like symptoms. The most common adverse events among patients who received APO(a)-L_{Rx} were injection-site reactions, which were generally mild.

NYU Langone Health

Olpasiran

Phase 2

- siRNA based therapy
- Safe and efficacious
- Reduction in Lp(a) up to -100.5% at the highest dose at 36 weeks

O'Donoghue ML, et al. NEJM 2022

Pelacarsen

Phase 2

- ASO based therapy
- Safe and efficacious
- Reduction in Lp(a) up to -80% at the highest dose at 27 weeks

Tsmikas S, et al. NEJM 2020

Phase 3 trials ongoing!

NYU Langone Health

Zerlasiran (SLN360)

- siRNA based therapy
- Reduction in Lp(a) up to -96%

Nissen S, Wolski K.et al. JAMA 2022

Lepodisran

- siRNA based therapy
- Safe and efficacious
- Reduction in Lp(a) >-90% at the highest doses at 27 weeks

Nissen S, Linnebjerg H.et al. JAMA 2023

Muvalaplin (oral agent)

- Oral therapy to disrupts creation of Lp(a)
- Reduction in Lp(a) up to -86%

Nicholls SJ, Ni W.et al. JAMA 2024

NYU Langone Health

Synopsis of various guidelines

- **Lp(a) should be measured in subjects with intermediate or high risk for CVD or CHD**
  - Personal history of premature CVD (especially when no other risk factors are present)
  - In persons with moderate to high risk of CVD using various scoring systems
  - Recurrent CVD despite statin therapy
  - Familial hypercholesterolemia or other genetic genetic dyslipidemias
  - Family history of premature CVD
  - Family history of high Lp(a)

But there are changes going on …

NYU Langone Health

New dyslipidemia guidelines

2019 ESC/EAS Guidelines

Lp(a) measurement should be considered at least once in each adult person's lifetime

Eur.Heart J. 41:111-188, 2020

2021 Canadian Cardiovascular Society

We recommend measuring Lp(a) level once in a person's lifetime as a part of the initial lipid screening.

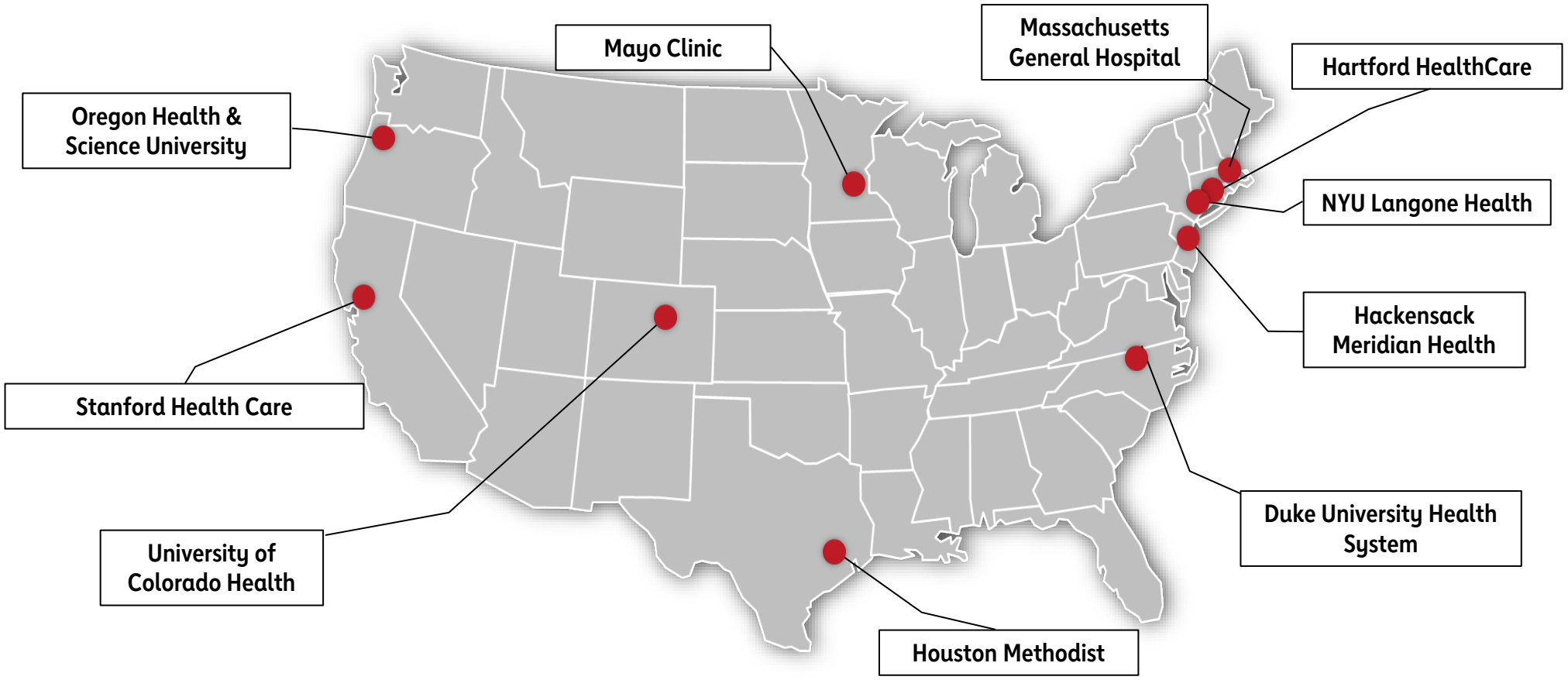
Can.J.Cardiol (in press)

doi: 10.1016/j.cjca.2021.03.016

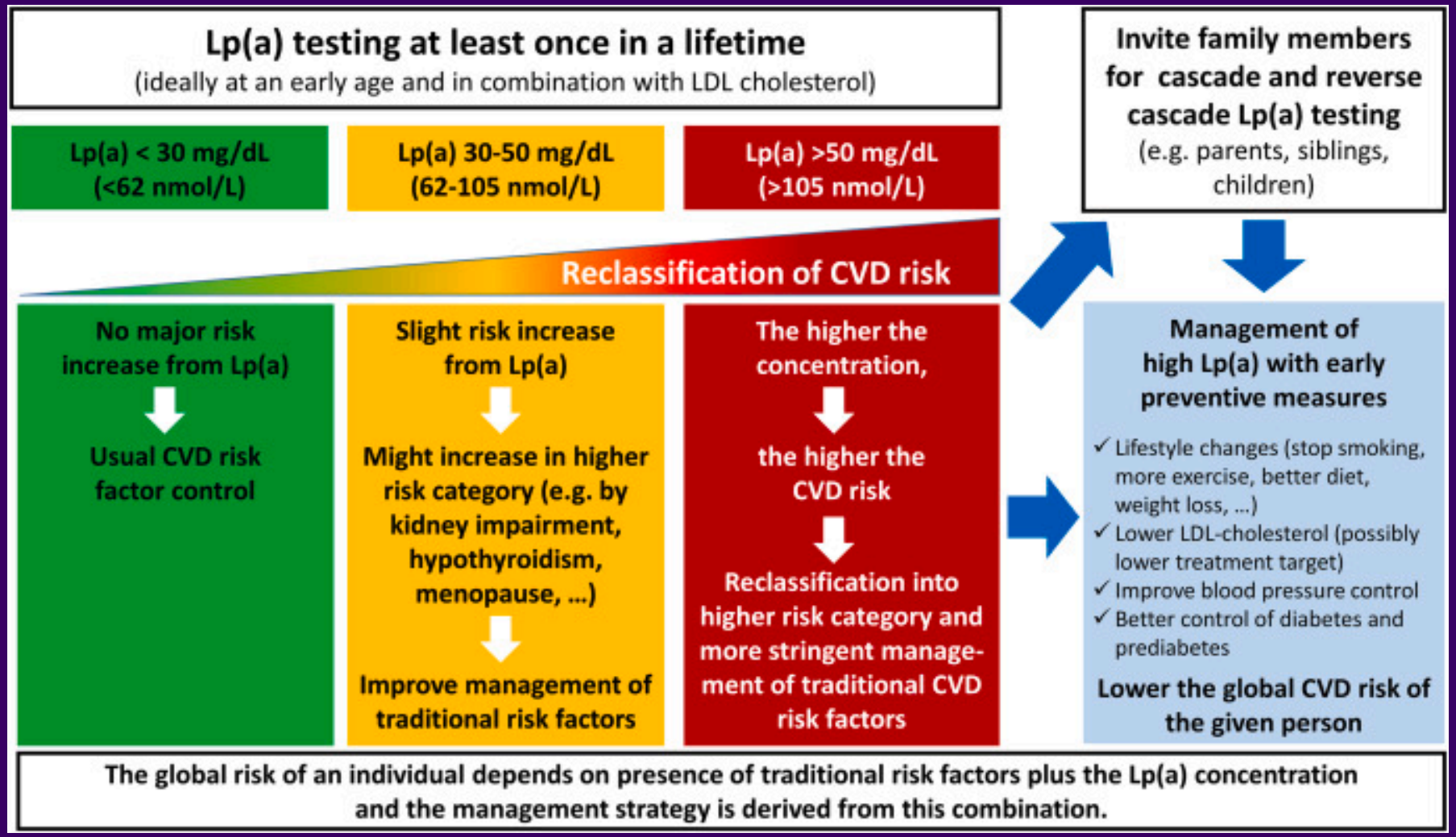
Idea behind: don't wait until the first event occurs

NYU Langone Health

Lp(a) Discovery Project Health Systems



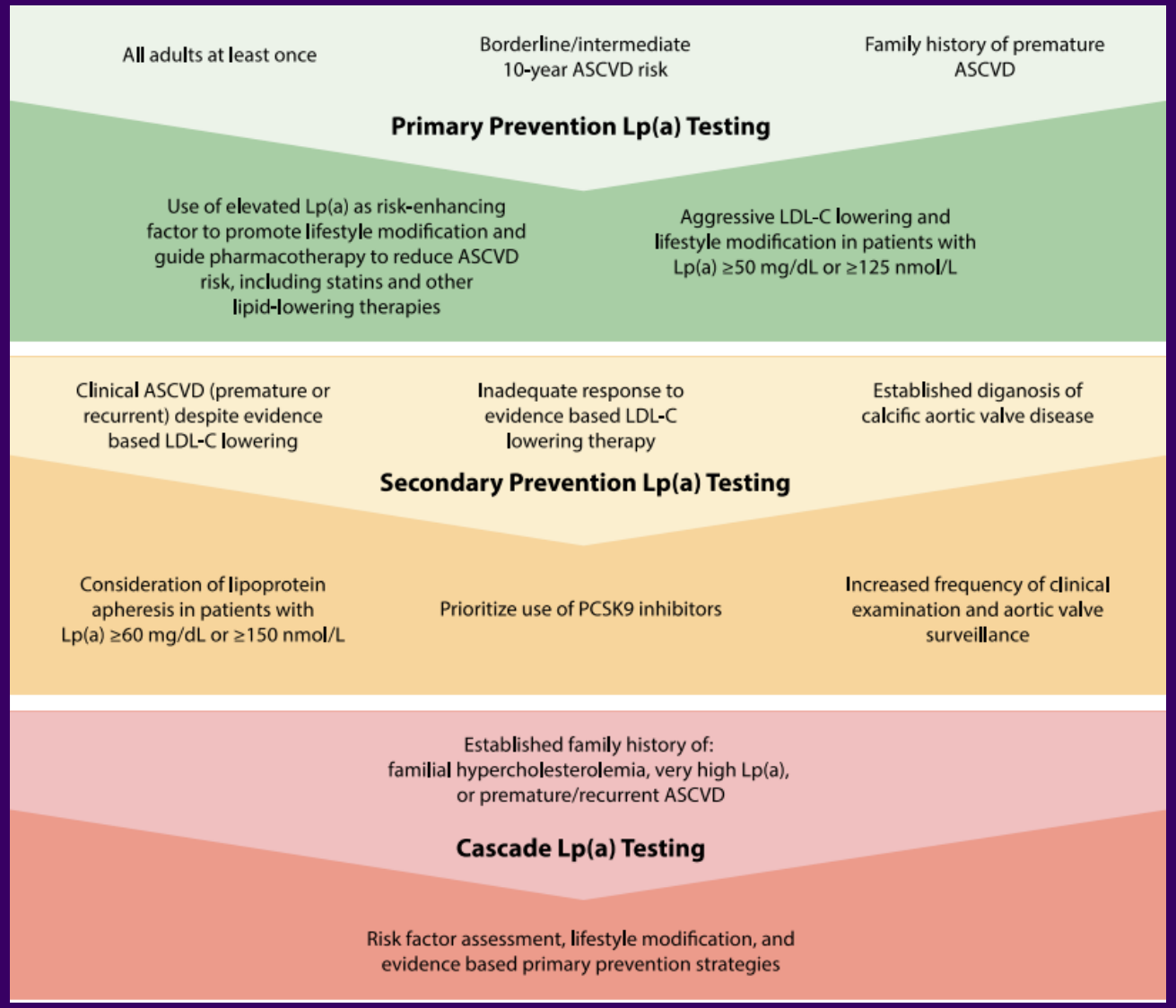
Lp(a) Action Plan for Clinicians



NYU Langone Health

Atherosclerosis 2025 May 5:119218.

Lp(a) Action Plan for Clinicians



NYU Langone Health

Ma, GS et al. Curr Cardiol Reports; August 2023

THANK YOU

NYU Langone Health

Questions and Discussion

Lp(a) Resources