Lipoprotein(a) and Cardiovascular Disease

Calvin Yeang, MD, PhD
Cardiovascular Institute
University of California San Diego
April 25, 2021

Disclosures

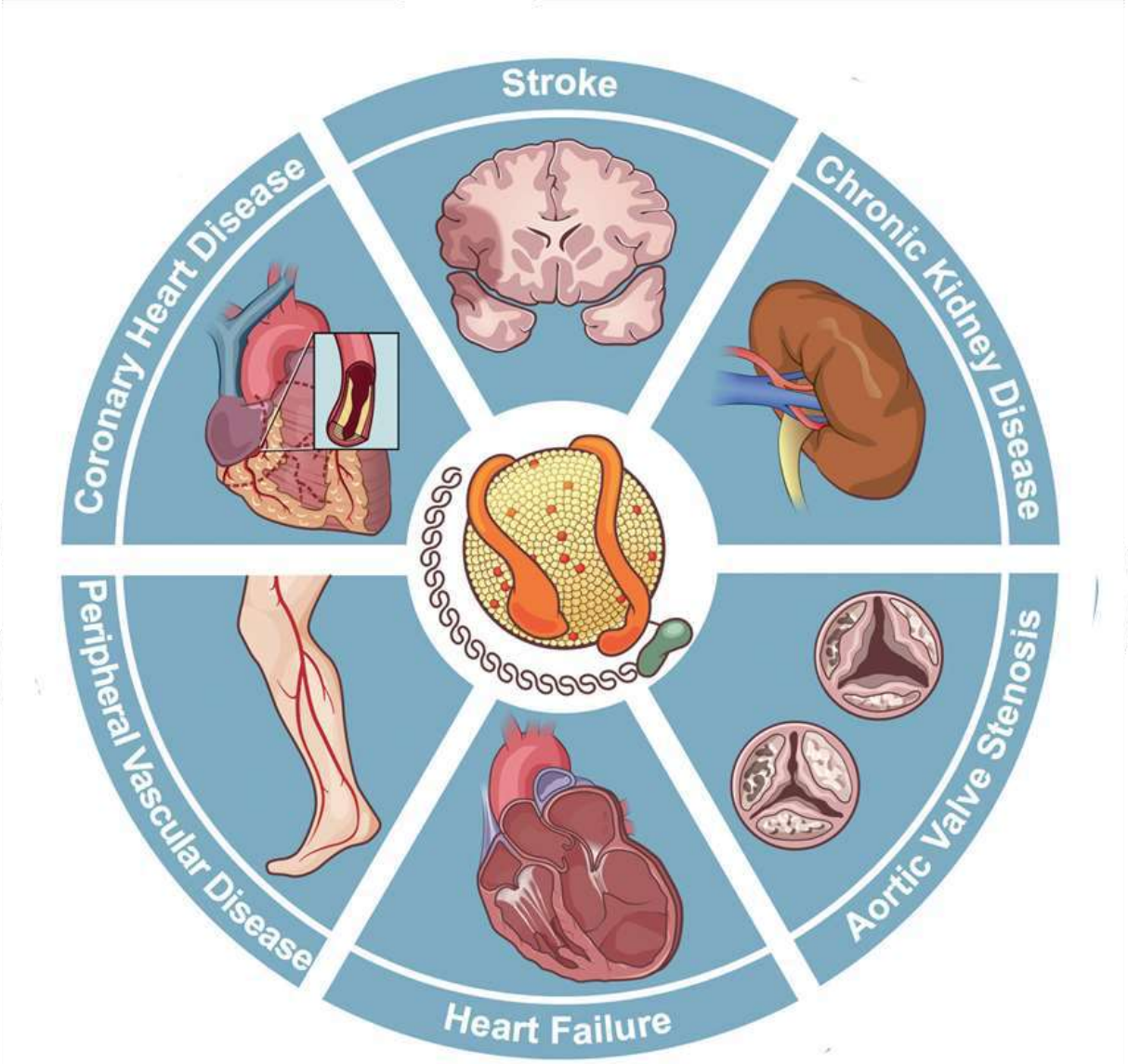
Research Funding

NIH/NHLBI

Kaneka Corporation

Ionis Pharmaceuticals

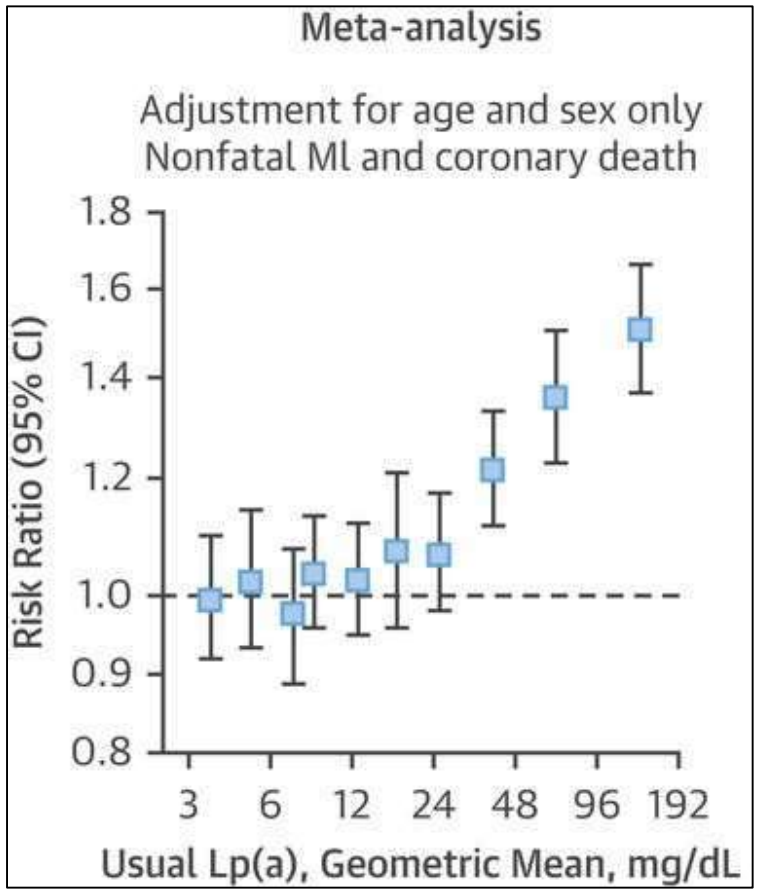
Lipoprotein(a) [Lp(a)]: Likely Causal ASCVD, and CAVD Risk Factor

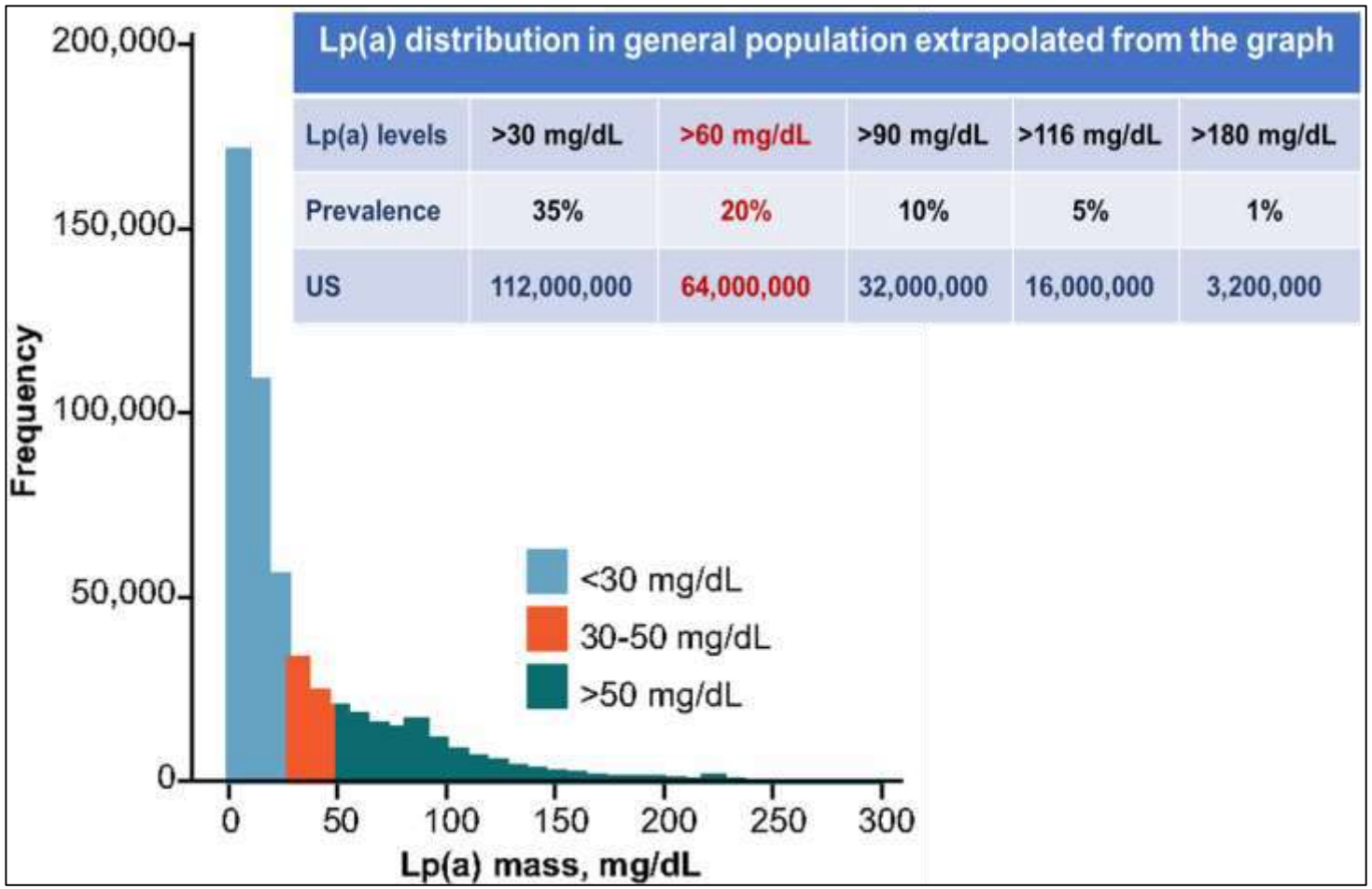


Modified from Emdin et al JACC 2016

With permission

Prevalence of Elevated Lp(a) Levels in the United States

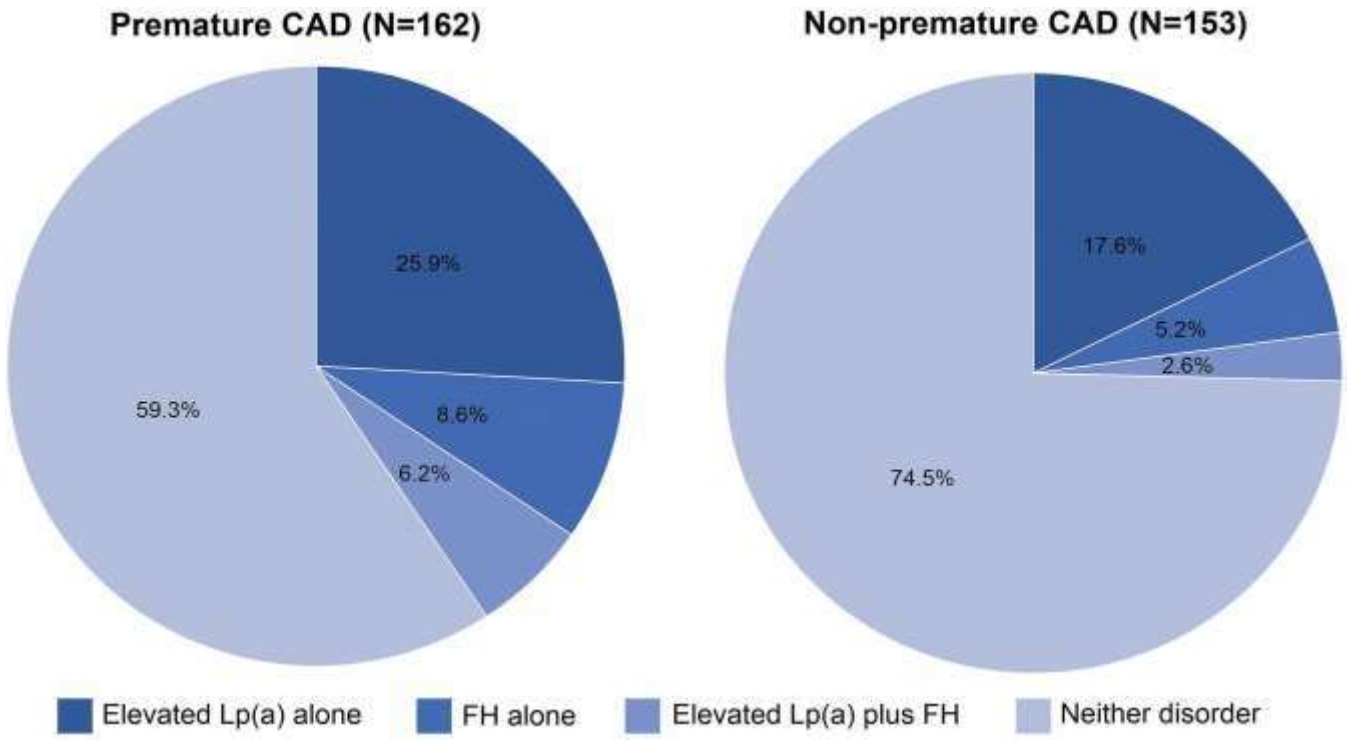




Erqou et al. JAMA 2009

Varvel et al. Arterioscler Thromb Vasc Biol 2016

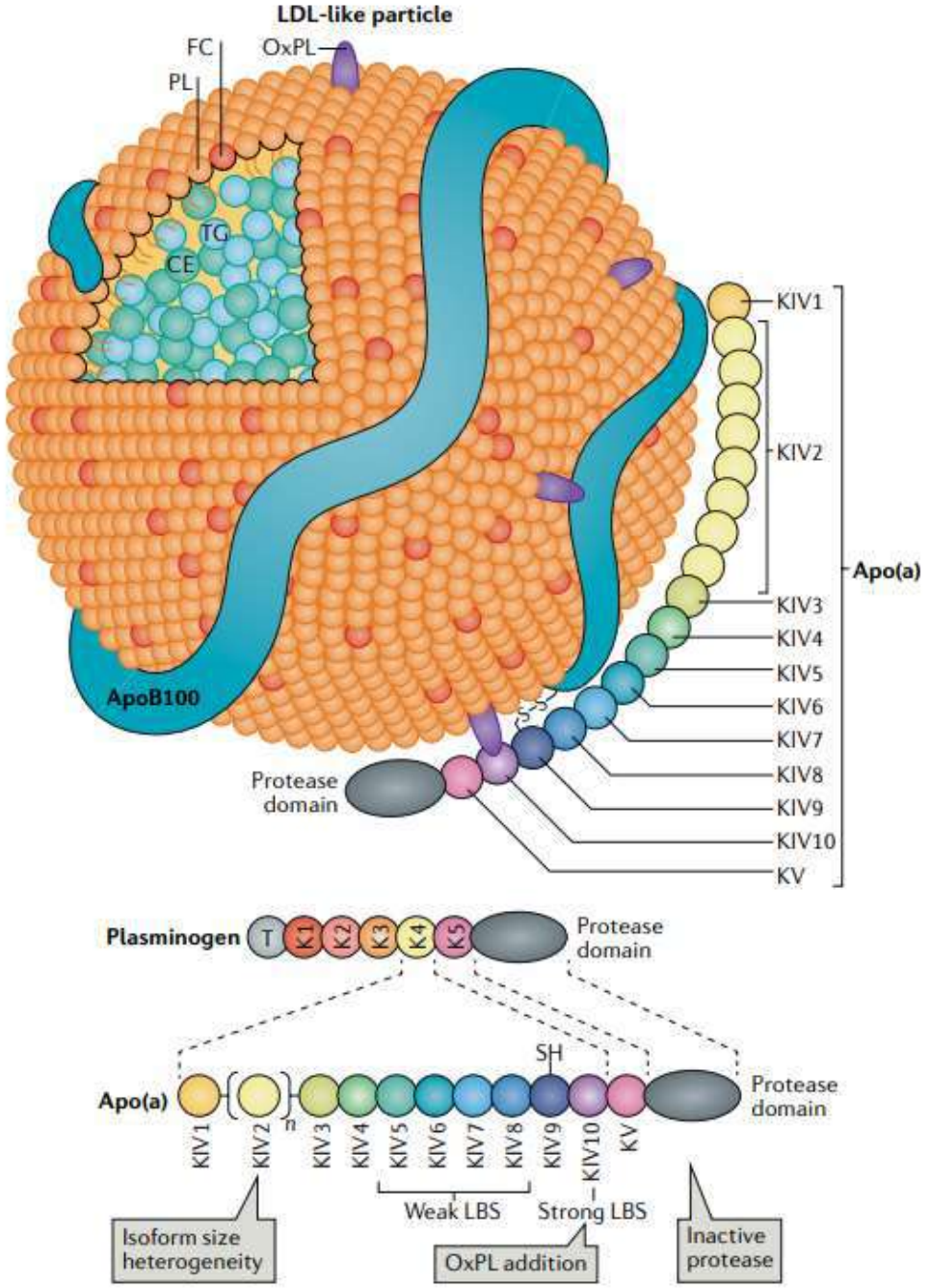
Prevalence of Lp(a) and Familial Hypercholesterolemia in Premature CAD



Ellis et al. Clinical Cardiology. 2018. 41:378-384

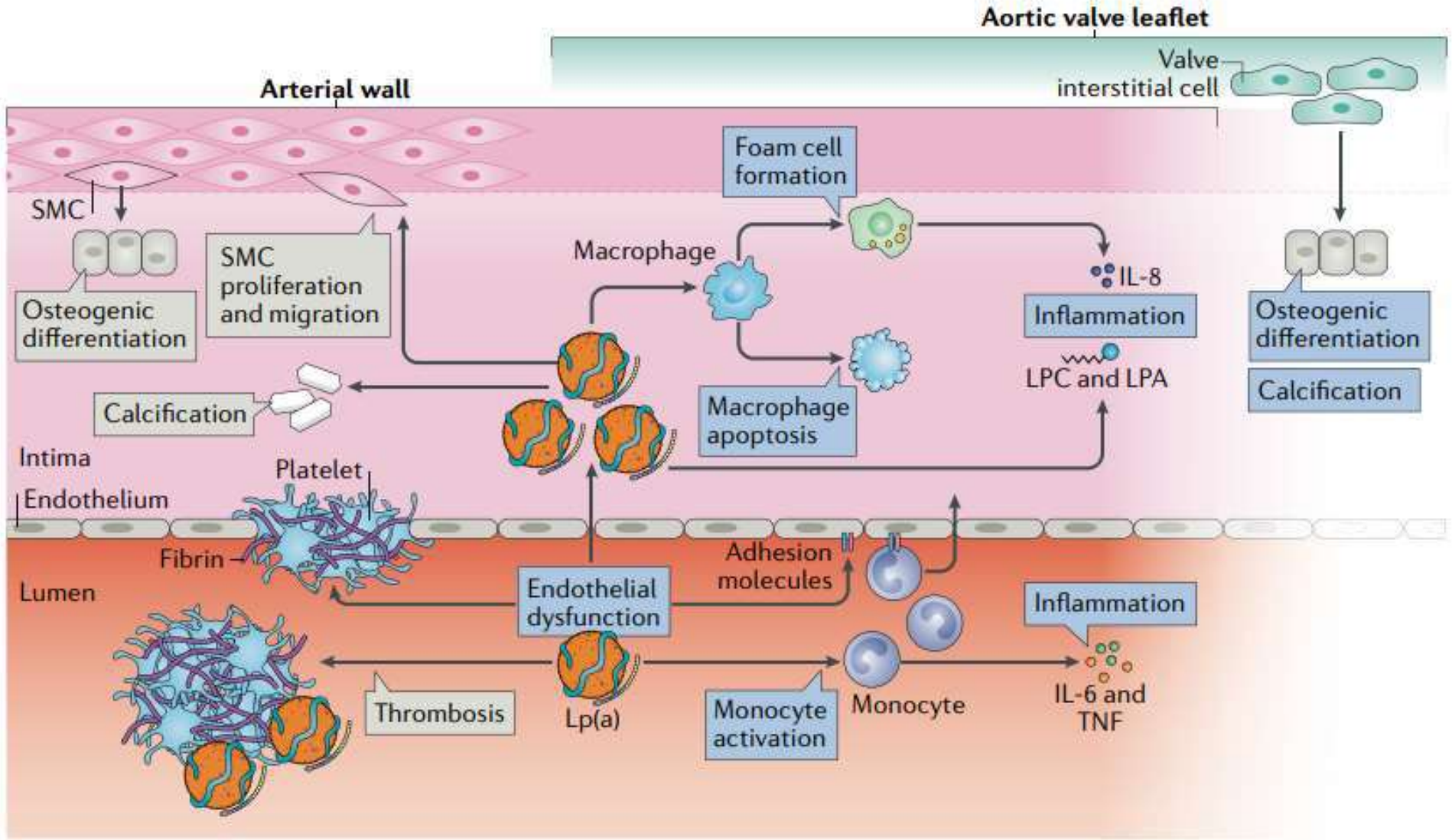
Lipoprotein(a)

- Composed of LDL-like lipid moiety and covalently bound apo(a)
- Major lipoprotein carrier of pro-inflammatory and pro-calcific oxidized phospholipids (OxPL)
- Apo(a) is highly homologous to plasminogen
- Heritability index = 0.9
- Autosomal co-dominant inheritance
- Genetic determinants of Lp(a) levels include:
  - apo(a) isoform size
  - *LPA* SNPs



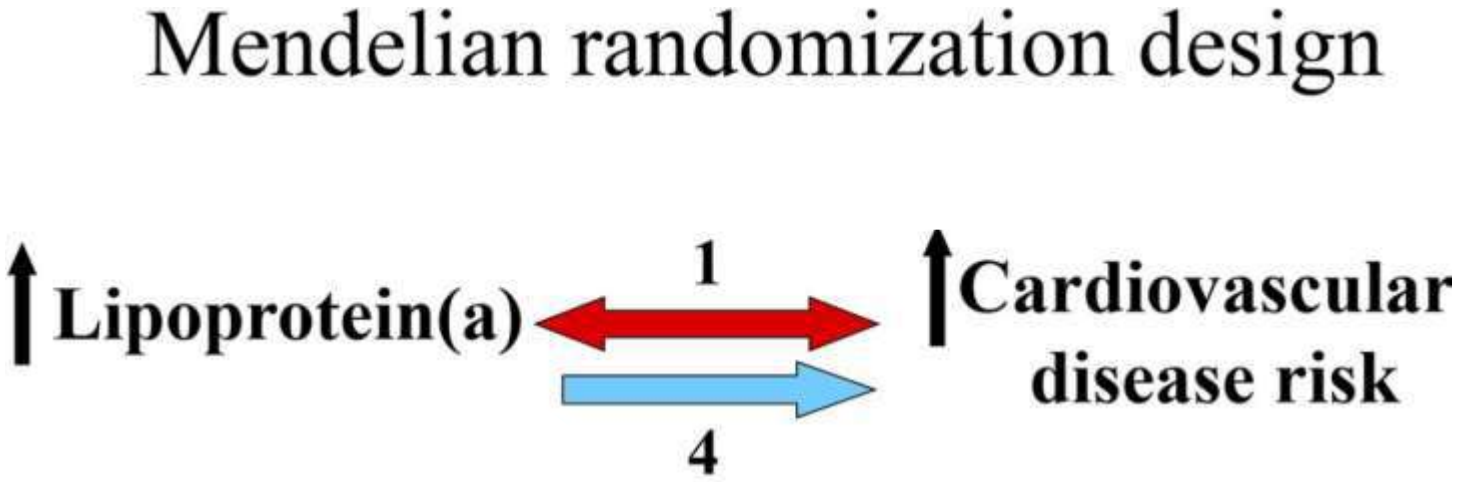
Boffa and Koschinsky, Nat Rev Cardiol 2019;16:305-318

Lp(a) Pathophysiology



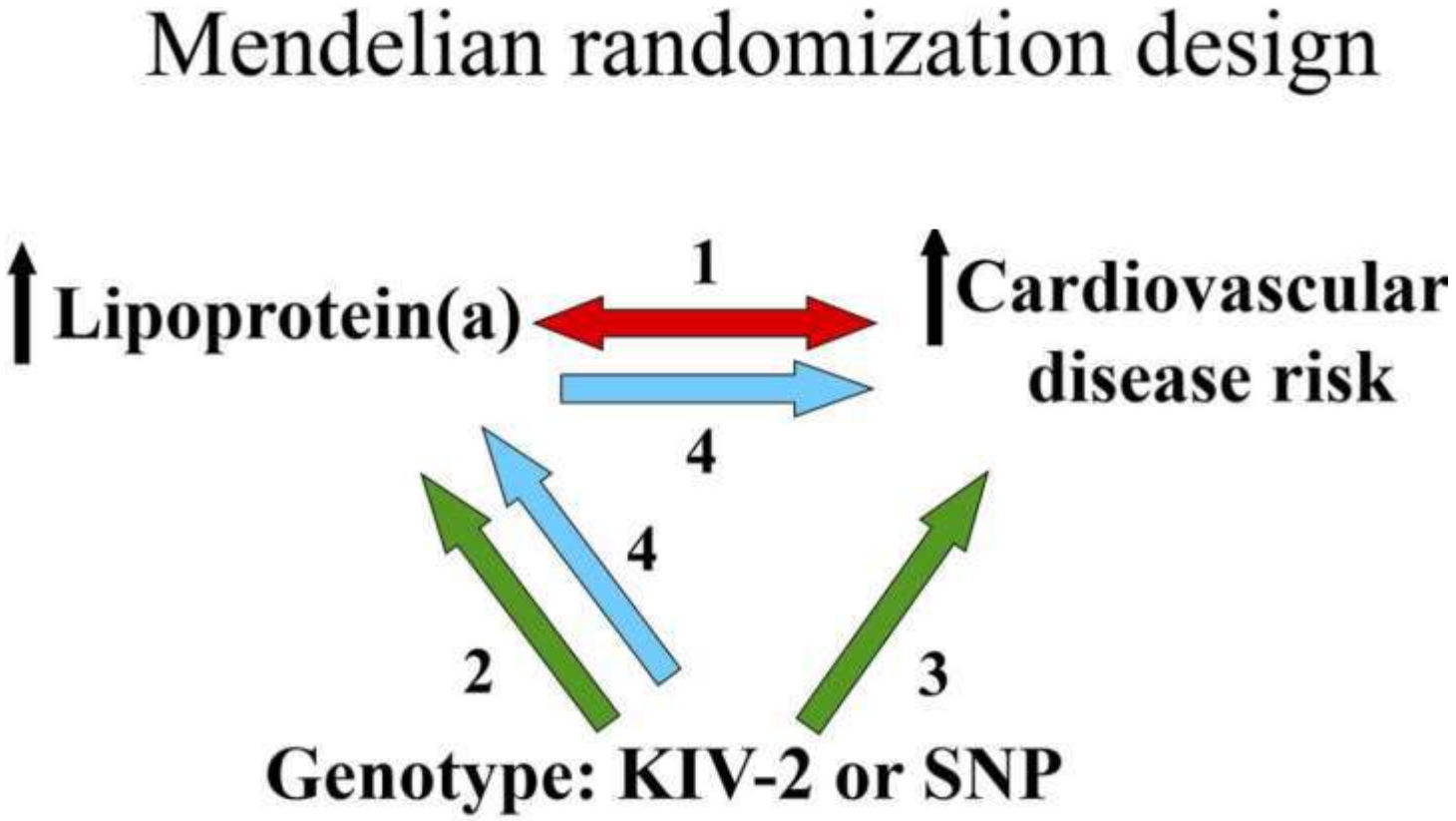
Boffa and Koschinsky, Nat Rev Cardiol 2019;16:305-318

Lp(a) – A Likely Causal ASCVD and CAVD Risk Factor



Nordestgaard and Langsted. JLR 2016. 57(11):1953-1975

Lp(a) – A Likely Causal ASCVD and CAVD Risk Factor



Nordestgaard and Langsted. JLR 2016. 57(11):1953-1975

Lp(a) – A Likely Causal ASCVD and CAVD Risk Factor

	Atherosclerotic cardiovascular disease					
High-quality data source:	Myocardial Infarction	Ischemic stroke	Atherosclerotic stenosis*	Aortic valve stenosis	Cardiovascular mortality	All-cause mortality
Meta-analyses of observational studies	Yes	Yes	No	No	No	No
Large observational studies.†**	Yes	Yes	Yes	Yes	Yes	Yes
Large Mendelian randomization studies	Yes	Yes	Yes	Yes	Yes	Yes
Large genome-wide association studies	Yes	No	Yes	Yes	No	No

*Clinical symptoms in the form of stable angina pectoris or intermittent claudication or documented atherosclerotic stenosis in coronary, femoral, or carotid arteries.

†Using isoform insensitive Lp(a) measurements.

NLA scientific statement on Lp(a), JCL 2019

Lp(a) Reclassifies ASCVD Risk

ACC/AHA risk

Controls

ACC/AHA risk	ACC/AHA risk with Lp(a) 0-5%	5-7.5%	>7.5%	
0-5%	5,405	873	342	6,620
5-7.5%	796	638	436	**1,870**
>7.5%	0	545	6,066	6,611
	6,201	2,056	6,844	**15,101**

Cases

ACC/AHA risk	ACC/AHA risk with Lp(a) 0-5%	5-7.5%	>7.5%	
0-5%	92	17	21	130
5-7.5%	31	30	28	**89**
>7.5%	0	46	1,291	1,337
	123	93	1,340	**1,556**

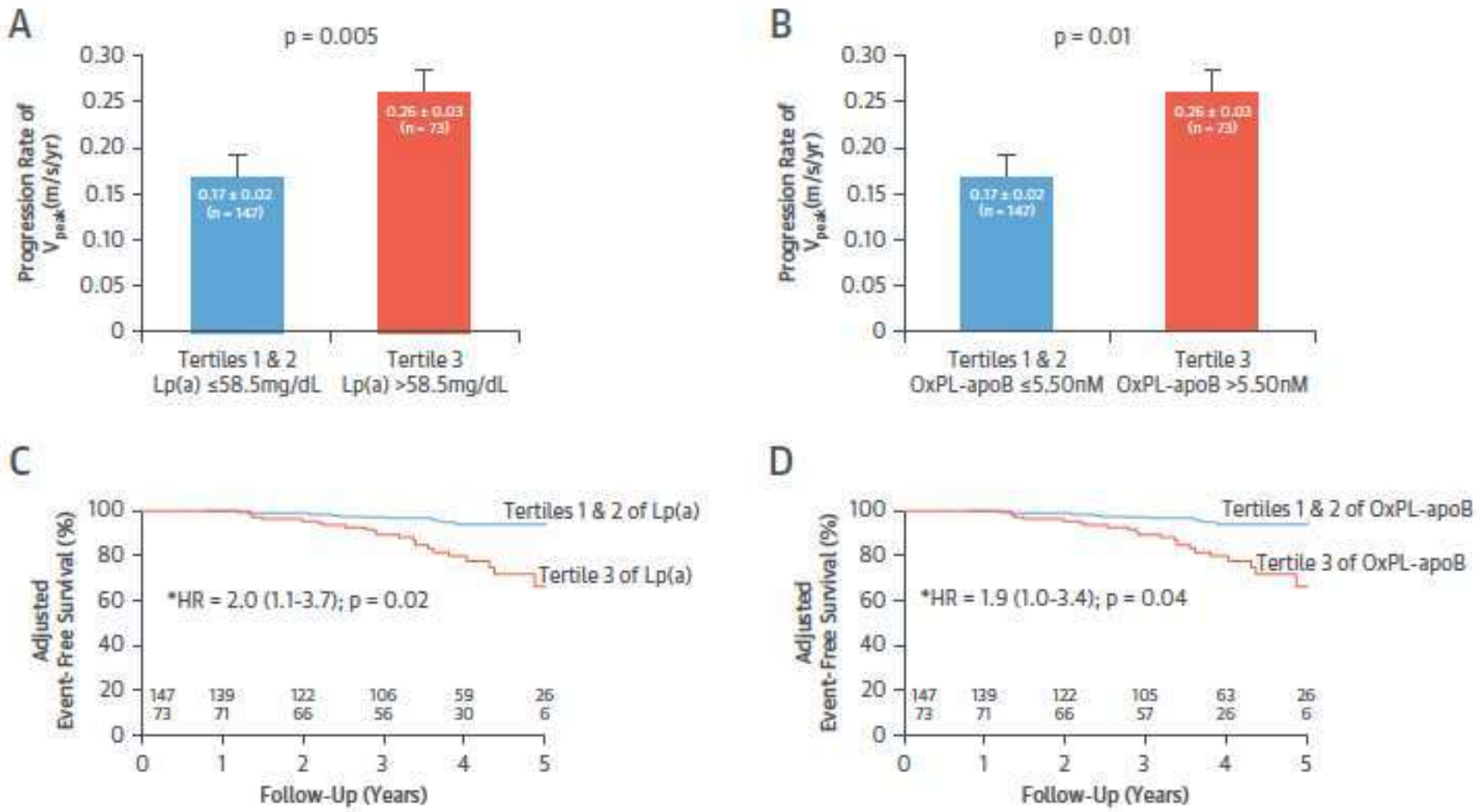
NRI

Controls	(796+0+545) - (873+342+436) / **15,101**	-2.05%
Cases	(17+21+28) - (31+0+46) / **1,556**	-0.71%
Total		**-2.76%**

Intermediate Risk NRI		
Controls	(796) - (436) / **1,870**	19.25%
Cases	(28) - (31) / **89**	-3.37%
Total		**15.88%**

Verbeek et al. JACC 2017;11:1513-0

Elevated Lp(a) and Progression of Aortic Stenosis

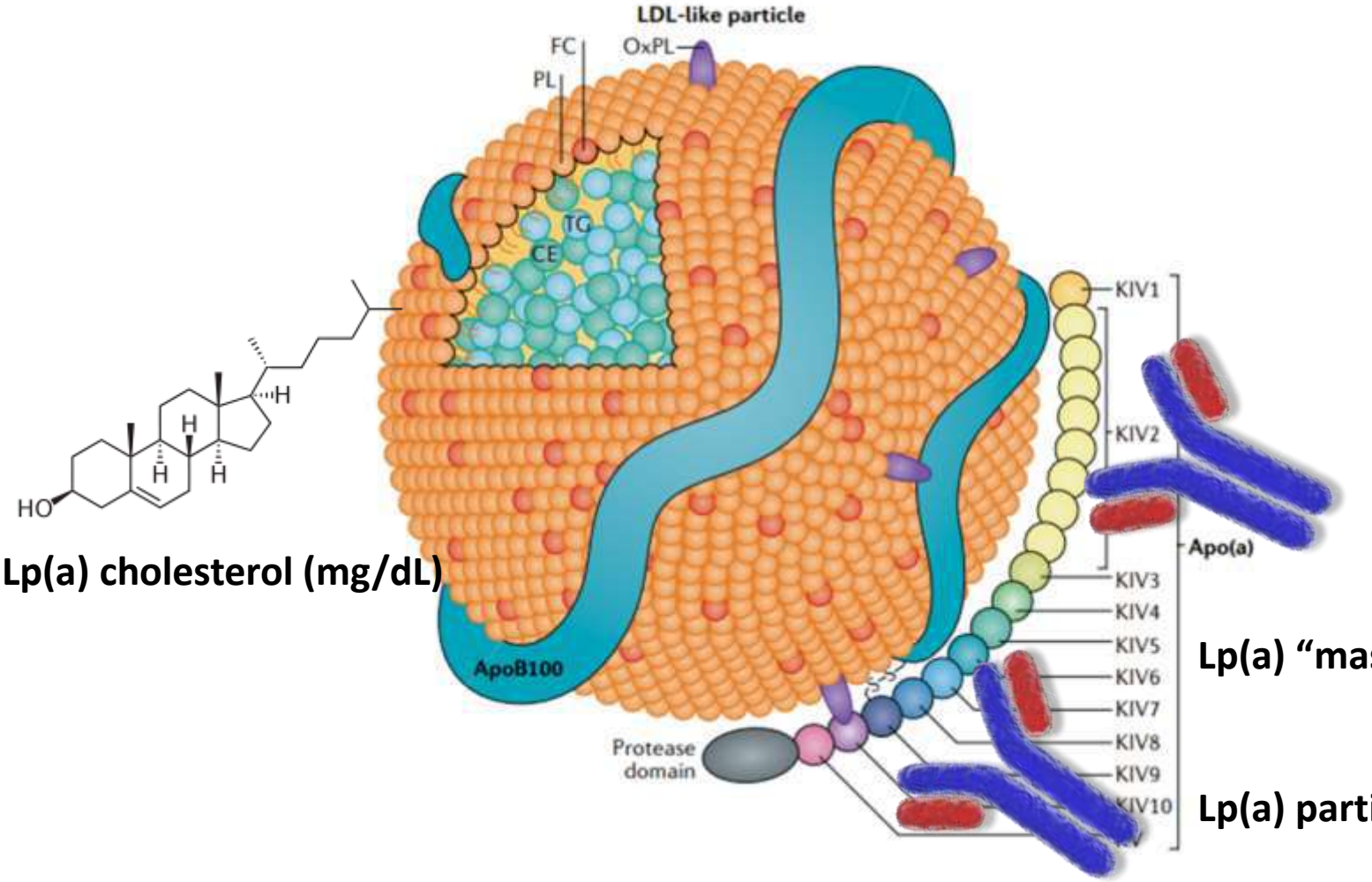


Capoulade et al. JACC 2015;66:1236-46

Societal Guidelines on Measuring Lp(a)

Guideline	Year	Recommendation
American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines	2019	Family history of premature CVD or personal history of CVD not explained by major risk factors. Constitutes a risk-enhancing factor especially at levels > 50 mg/dL or > 125 nmol/L.
European Society of Cardiology and European Atherosclerosis Society	2019	Lp(a) should be measured at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels > 180 mg/dL (> 430 nmol/L) who may have a lifetime risk of CVD equivalent to the risk associated with heterozygous familial hypercholesterolemia.
National Lipid Association	2019	To define risk assessment in adults with first-degree relatives with premature CVD, a personal history of premature CVD, primary severe hypercholesterolemia (LDL-C > 190 mg/dL) or suspected FH. To aid in the clinician-patient discussion about whether to prescribe a statin in those aged 40–75 years with borderline (5%–7.4%) 10-year CVD risk, to identify a possible cause for a less-than-anticipated LDL-C lowering to evidence-based LDL-C–lowering therapy, to use in cascade screening of family members with severe hypercholesterolemia, and to identify those at risk for progressive aortic stenosis
HEART UK consensus statement	2019	Lp(a) should be measured in adults with a personal or family history of premature atherosclerotic CVD; those with first-degree relatives who have Lp(a) levels > 200 nmol/L patients with familial hypercholesterolemia; patients with calcific aortic valve stenosis and those with borderline (but < 15%) 10- year risk of a cardiovascular event.
Canadian Cardiovascular Society	2016	Lp(a) might aid risk assessment in subjects with intermediate risk scores or with a family history of premature coronary artery disease.

Interpreting Lp(a) Measurements



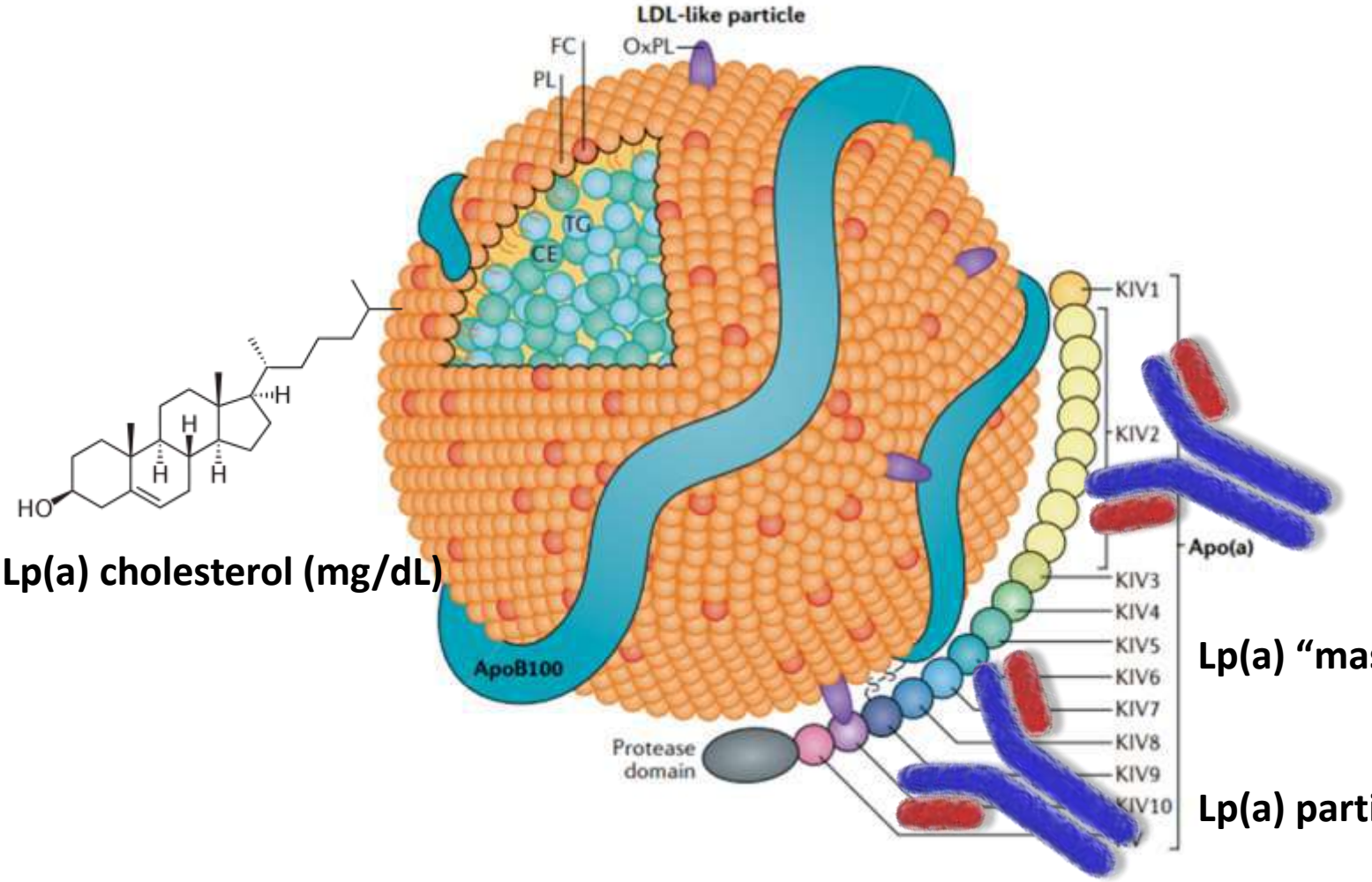
Lp(a) cholesterol (mg/dL)

Lp(a) "mass" (mg/dL)

Rough conversion factor
X 2.4

Lp(a) particle number (nM)

Interpreting Lp(a) Measurements



Lp(a) cholesterol (mg/dL)

Lp(a) particle number (nM)	# Samples	Lp(a) particle number/mass assay ratio
All levels	1635	2.42 (1.25)/2.30 (1.63–3.02)
<75	494	1.82 (1.44)/1.54 (1.10–2.22)
75–<125	296	2.32 (1.31)/2.07 (1.63–2.64)
125–<175	239	2.33 (0.76)/2.24 (1.77–2.71)
175–<225	242	2.62 (0.97)/2.49 (2.06–3.02)
225–<275	127	2.80 (0.67)/2.76 (2.30–3.16)
275–<325	70	3.00 (0.58)/2.93 (2.55–3.35)
≥325	167	3.64 (0.78)/3.45 (3.09–4.03)

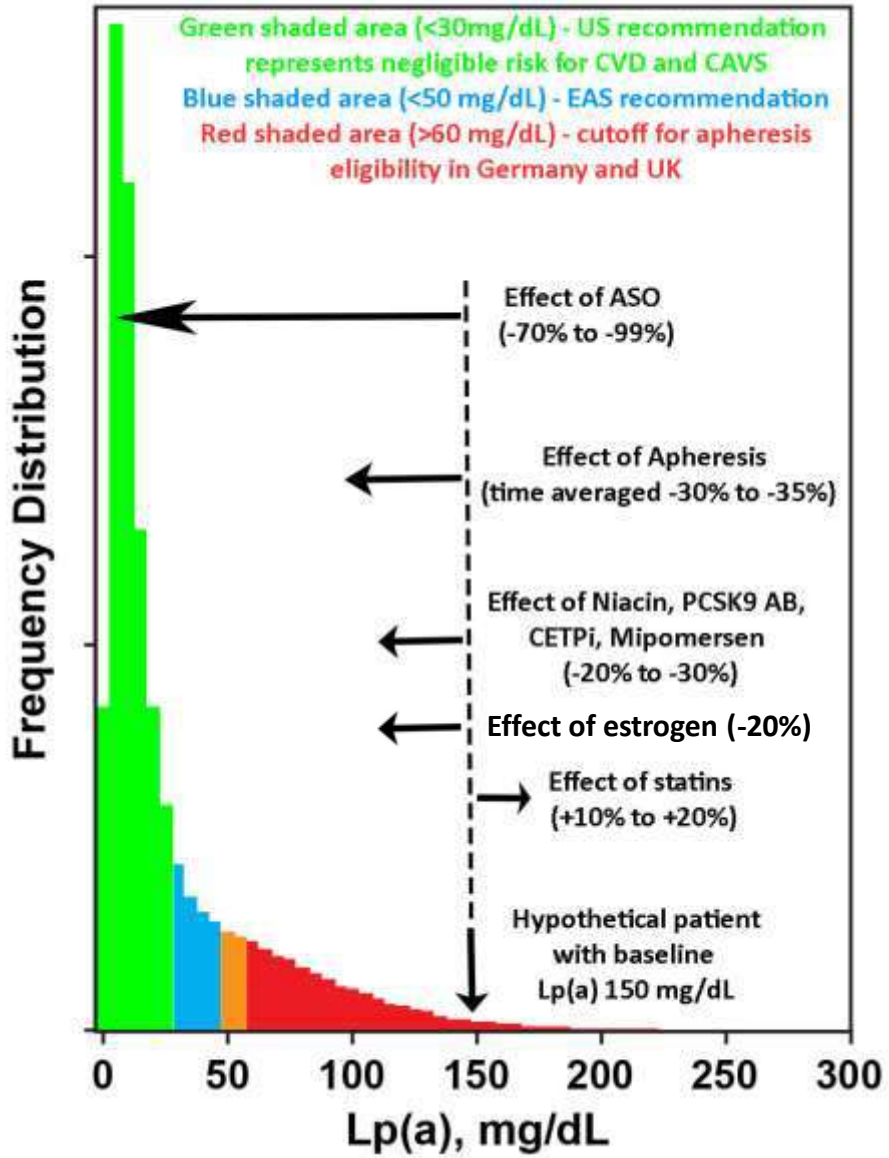
Tsimikas et al. JCL 2018;12:1313-23

Lp(a) "mass" (mg/dL)

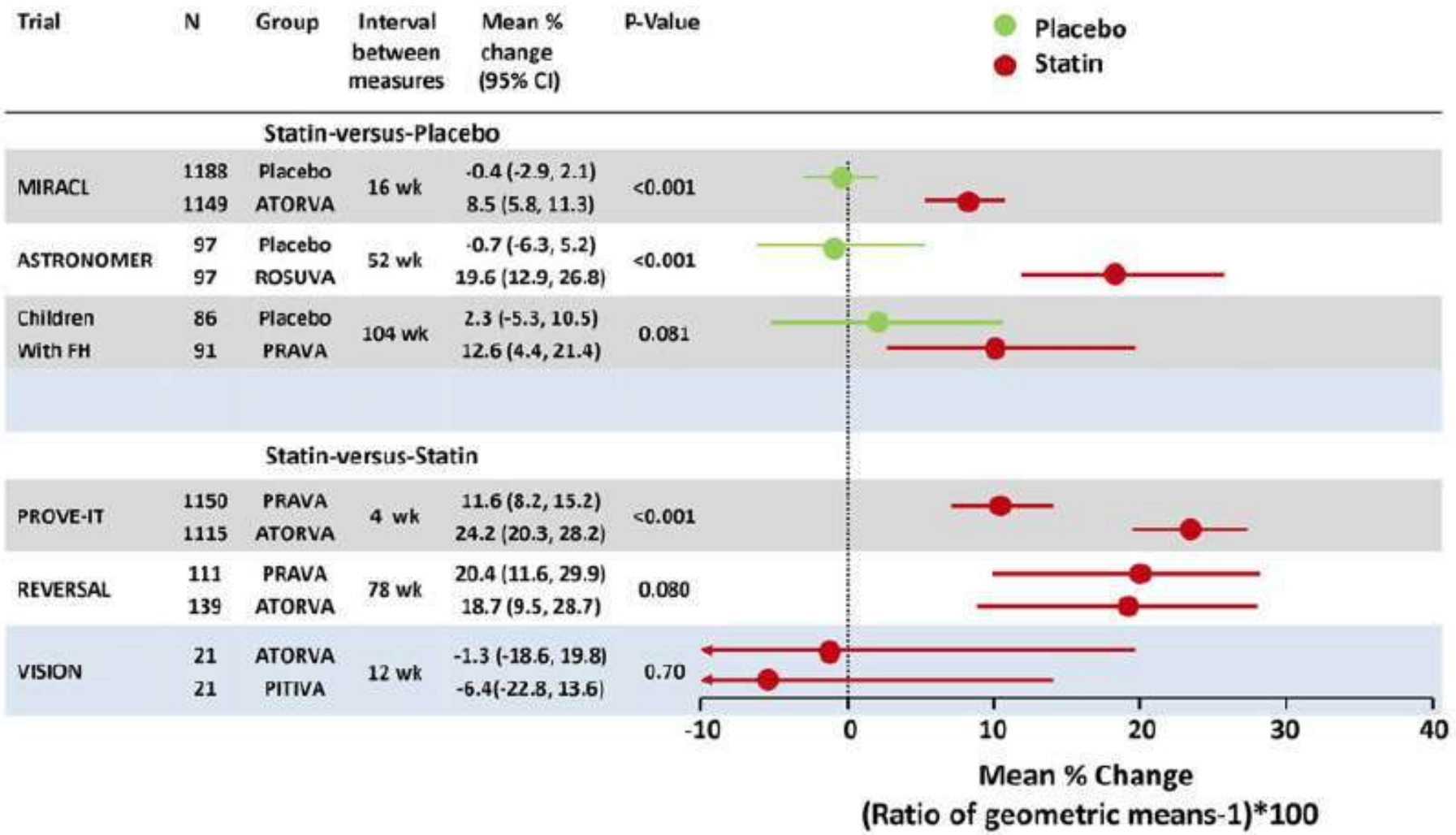
Rough conversion factor
X 2.4

Lp(a) particle number (nM)

Emerging Concepts: Lp(a) lowering therapies



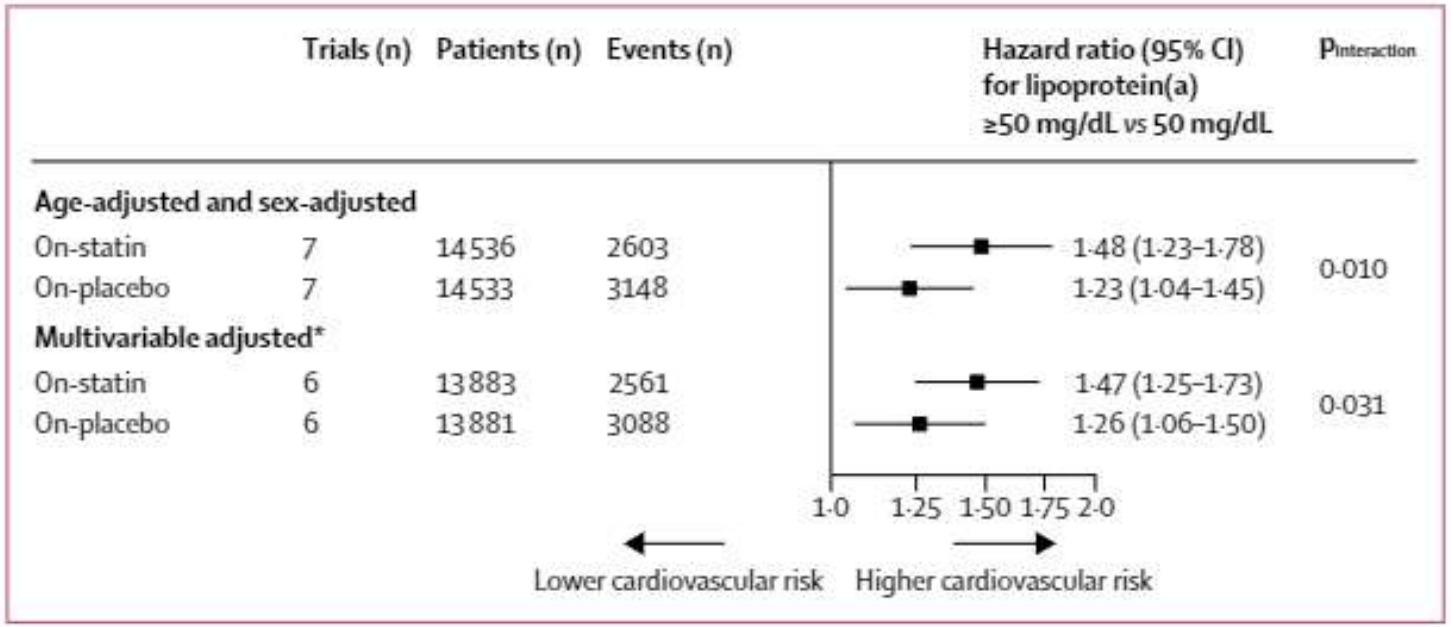
Statins Do Not Lower Lp(a)



Tsimikas et al Eur Heart J 2019

Statins and Lp(a) Attributed Risk

- Patient level meta-analysis of landmark statin trials (AFCAPS, CARDS, 4D, JUPITER, LIPID, MIRACL, and 4S)
- 26,069 patients; 5751 CVD events; 95,576 person-years at risk

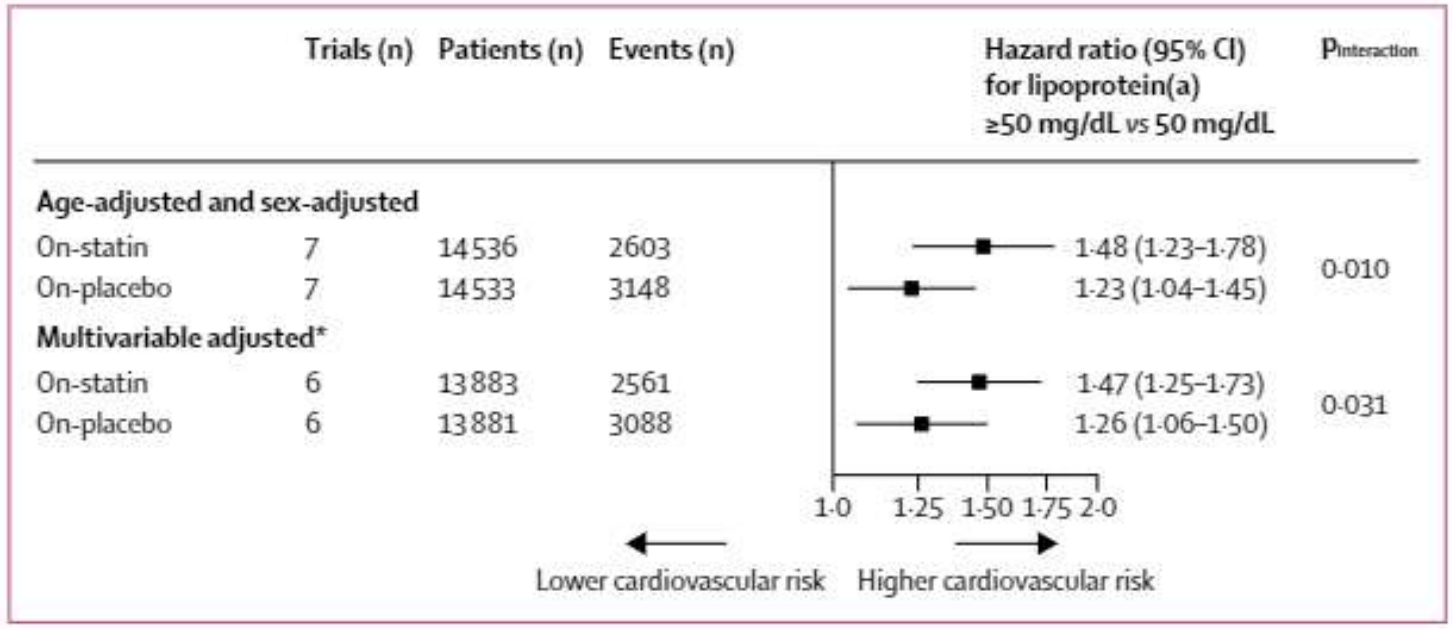


Willeit et al. Lancet 2018;392:1311-20

Statins and Lp(a) Attributed Risk

- Patient level meta-analysis of landmark statin trials (AFCAPS, CARDS, 4D, JUPITER, LIPID, MIRACL, and 4S)
- 26,069 patients; 5751 CVD events; 95,576 person-years at risk

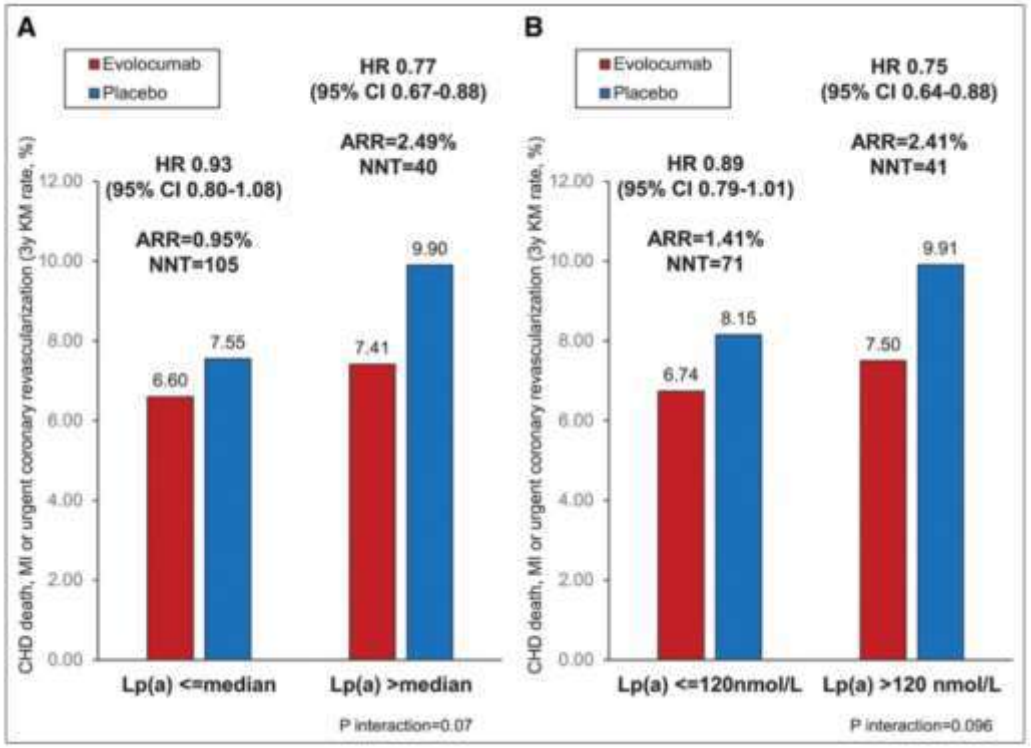
"When LDL-attributable risk is reduced with statin treatment, lipoprotein(a)-associated risk becomes an even stronger predictor of residual risk."



Willeit et al. Lancet 2018;392:1311-20

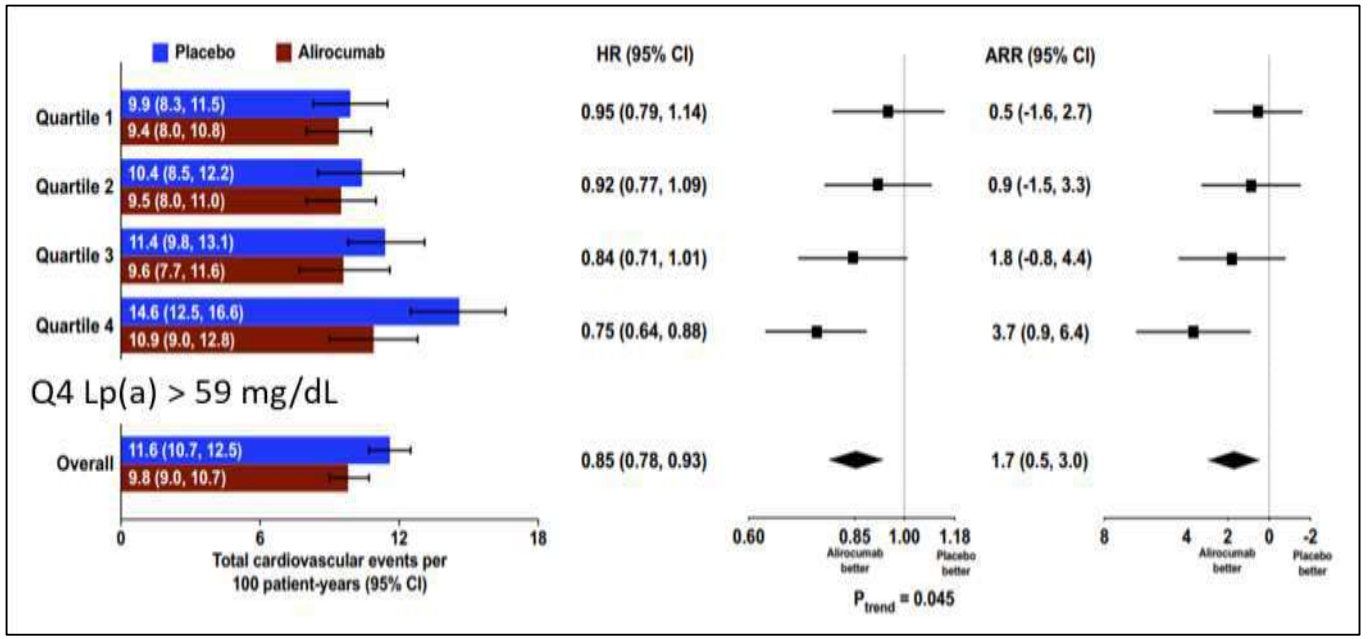
PCSK9i and Lp(a) Attributed Risk

Evolocumab



O'Donoghue et al. Circulation 2019;139:1483-92

Alirocumab



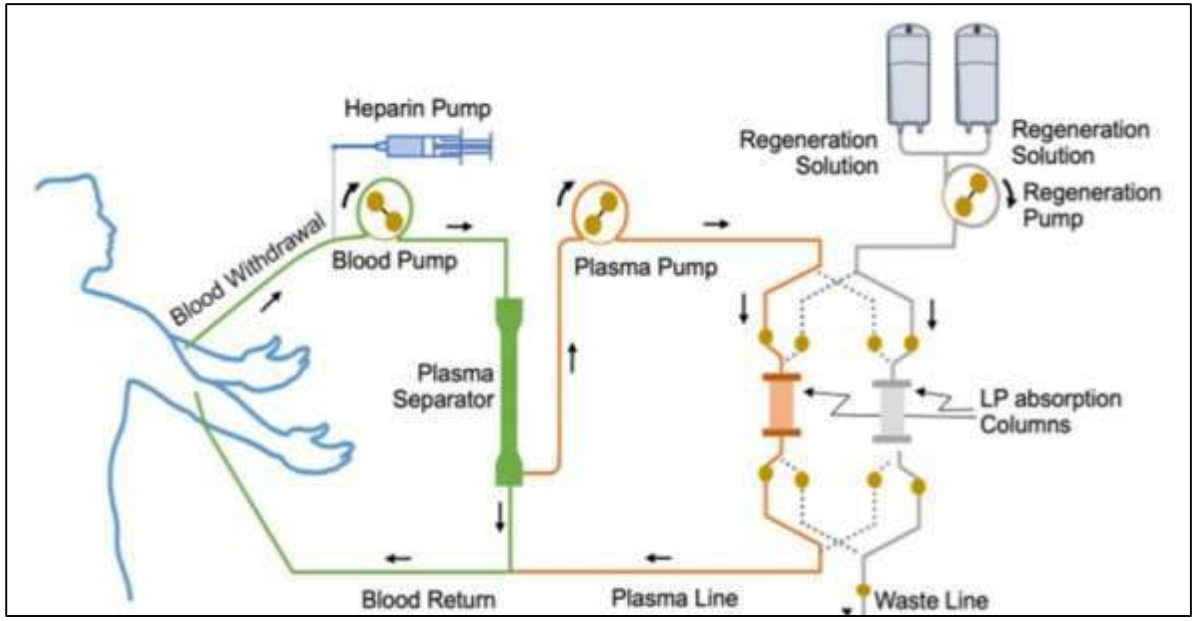
Szarek et al. ESC 2020;41:4245-55

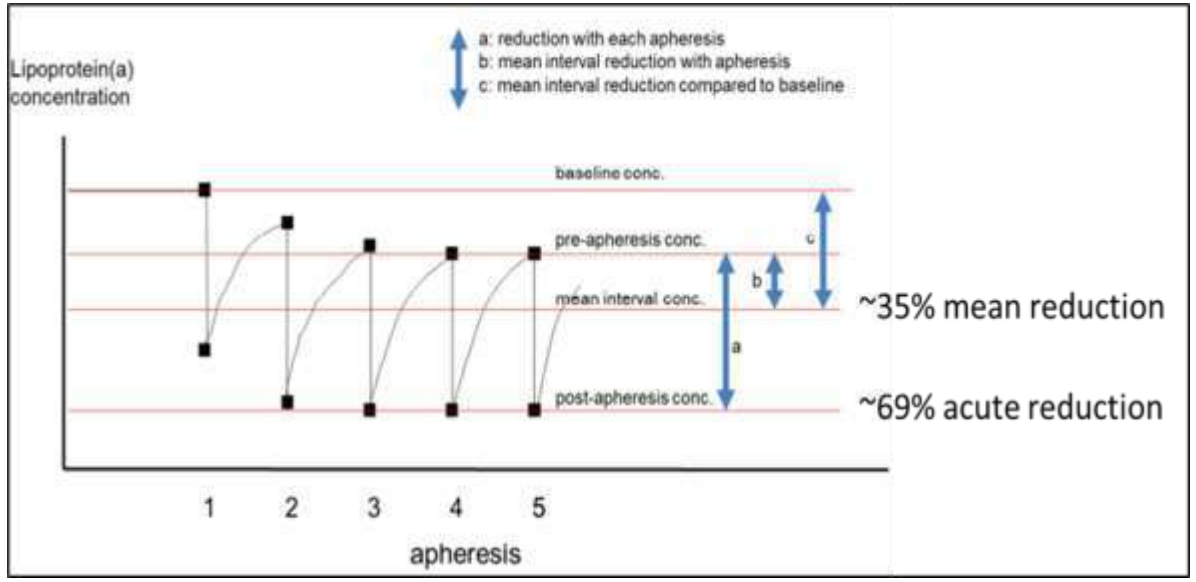
Lipoprotein Apheresis

FDA approved indications for lipoprotein apheresis

The LIPOSORBER LA-15 System is indicated for use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated:

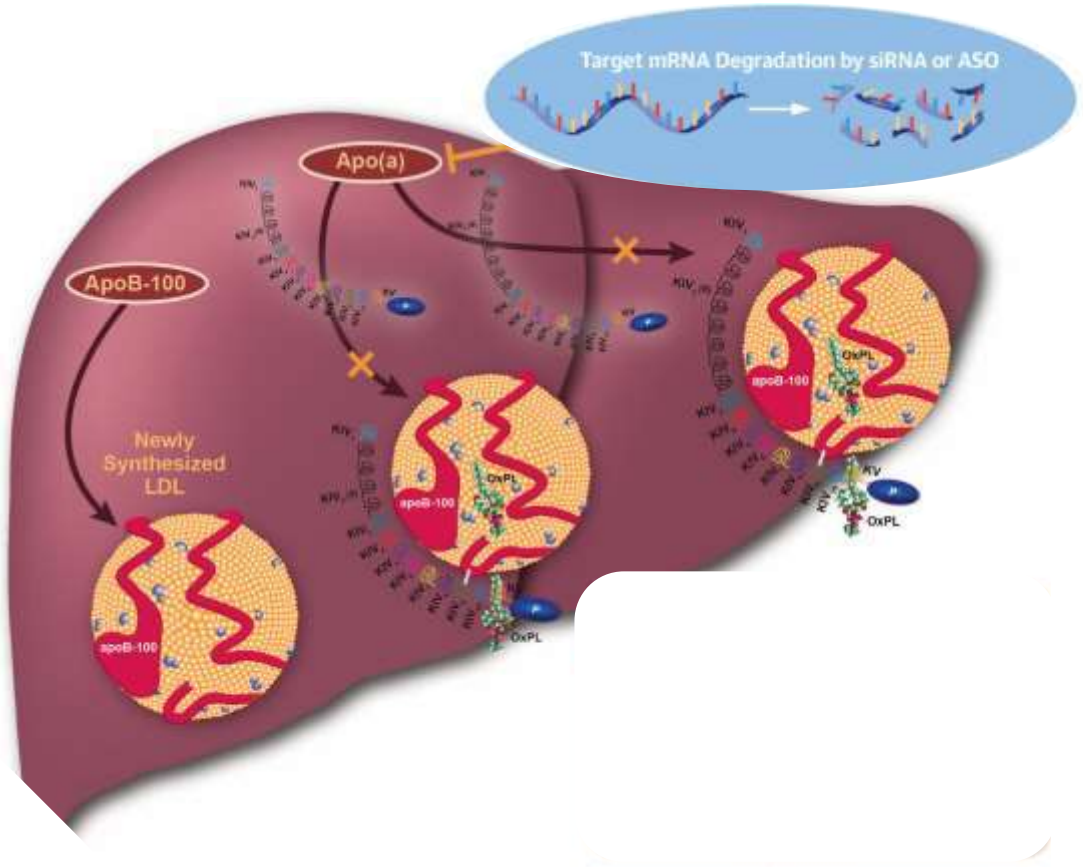
- Group A – Functional Hypercholesterolemic Homozygotes with **LDL-C >500 mg/dL**;
- Group B – Functional Hypercholesterolemic Heterozygotes with **LDL-C ≥300 mg/dL**; and
- Group C – Functional Hypercholesterolemic Heterozygotes with **LDL-C ≥100 mg/dL** and either documented **coronary artery disease** or documented **peripheral artery disease**.
- Group D – Functional Hypercholesterolemic Heterozygotes with **LDL-C ≥ 100 mg/dl** and lipoprotein(a) [**Lp(a)] ≥ 60 mg/dL**, and either documented **coronary artery disease** or documented **peripheral artery disease**.



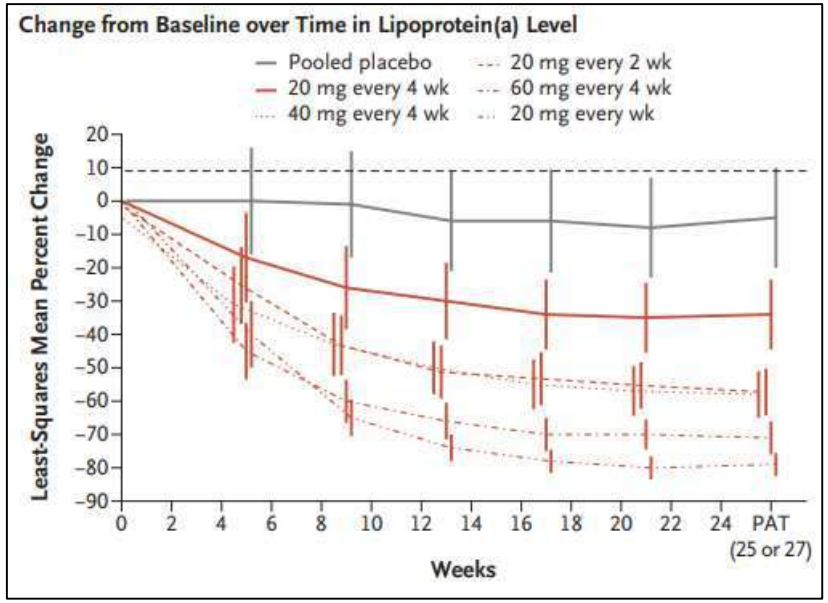


Modified from Waldmann and Parhofer. JLR 2016

Lp(a) Lowering by RNAi

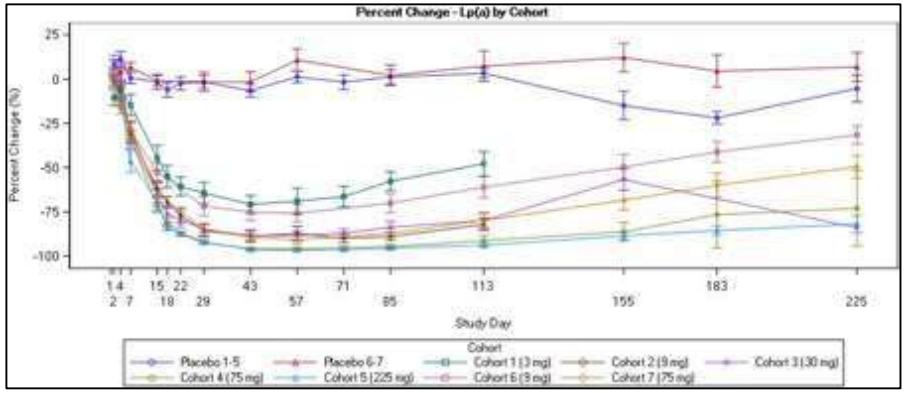


Pelacarsen



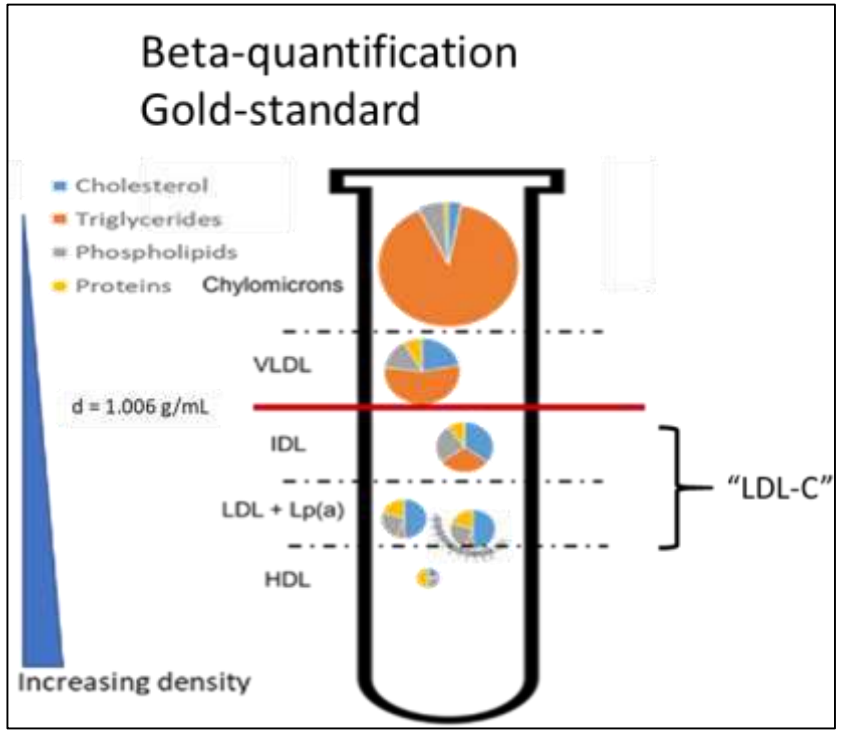
Tsimikas et al. NEJM 2020;382:244-55

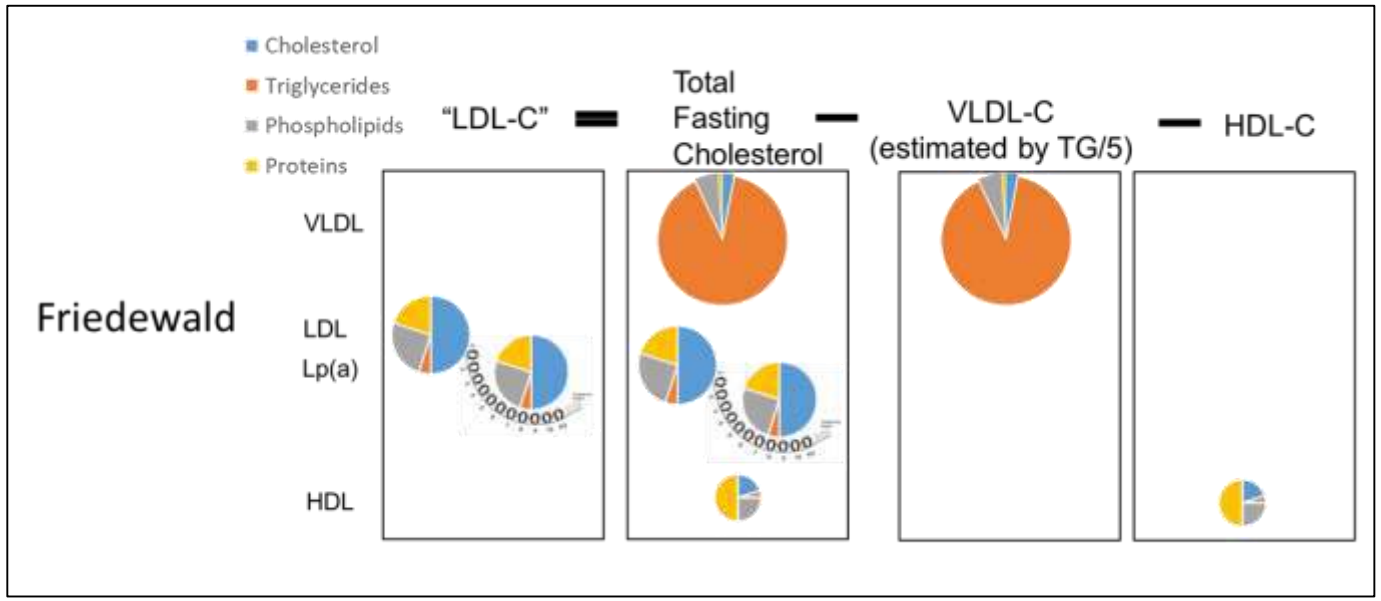
ARO-LPA

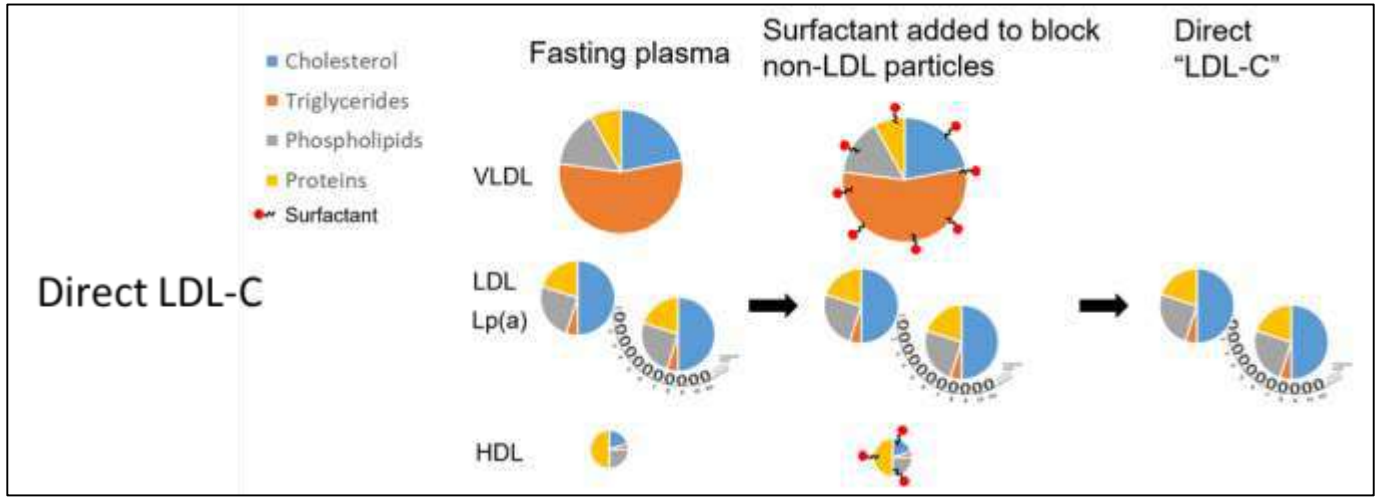


Koren et al. Abstract presented at ATVB 2020

Emerging Concepts: Lp(a) and LDL Attributed Risk
“LDL-C” = Lp(a)-C + correct LDL-C

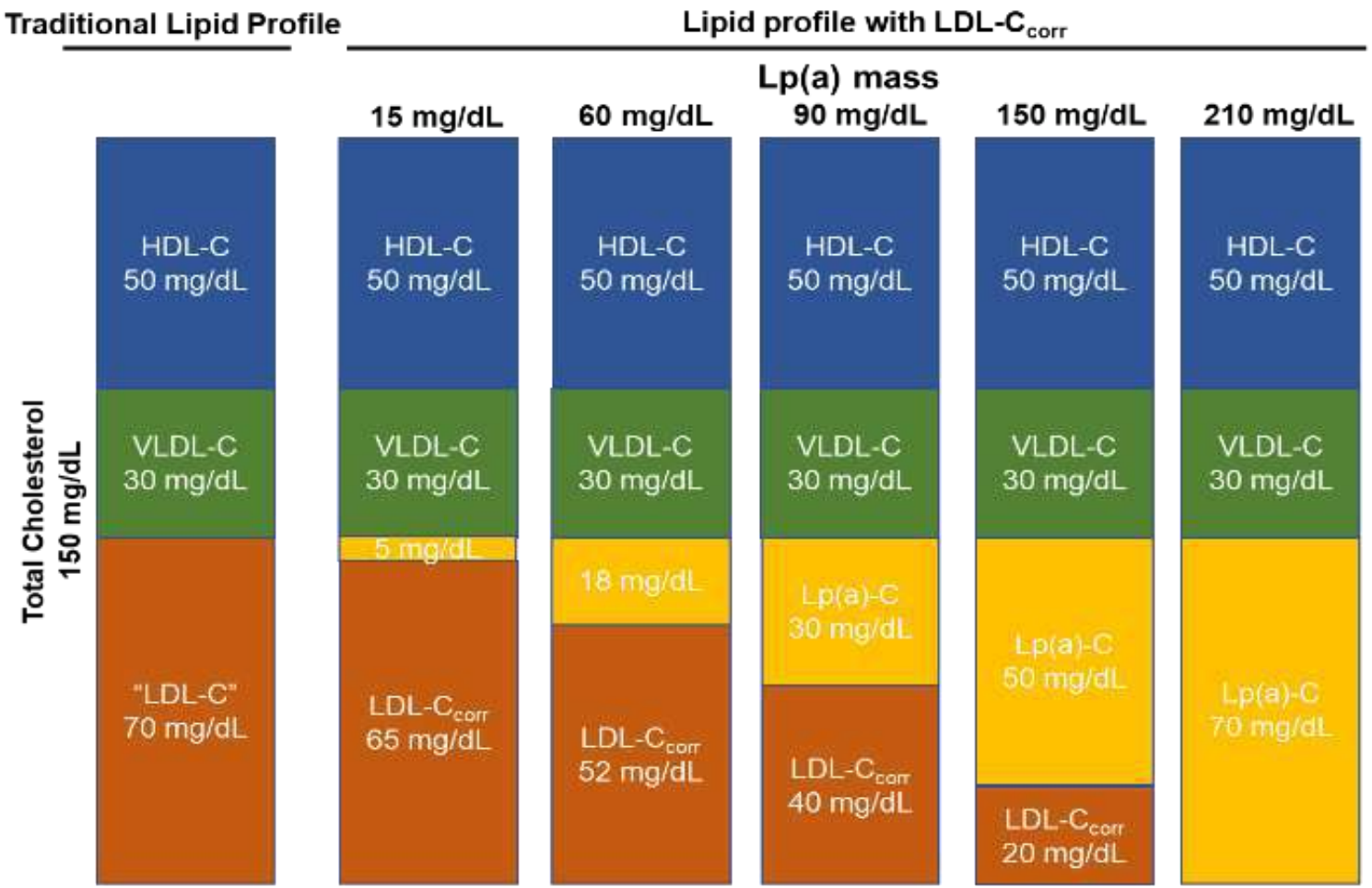






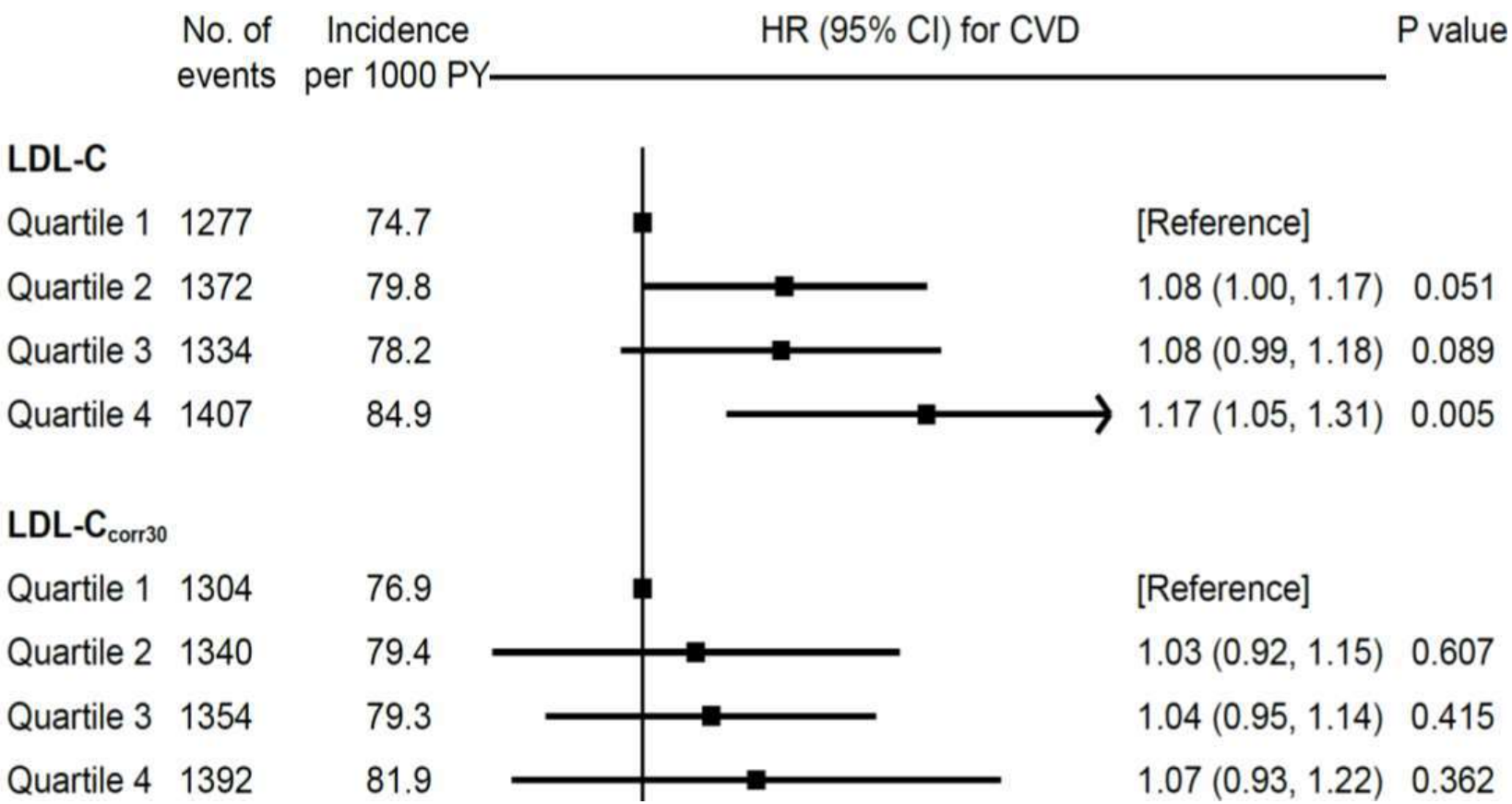
Lp(a) heterogeneity and “LDL-C” inaccuracy

*IDL-C not shown



Willeit and Yeang et al, JAHA 2020

“LDL-C” vs correct LDL-C and CVD risk



Willeit and Yeang et al, JAHA 2020

Thank you!

UCSD Specialized Center for Atherosclerosis (SCOR) group

Miller/Tsimikas/Witztum/Yeang labs