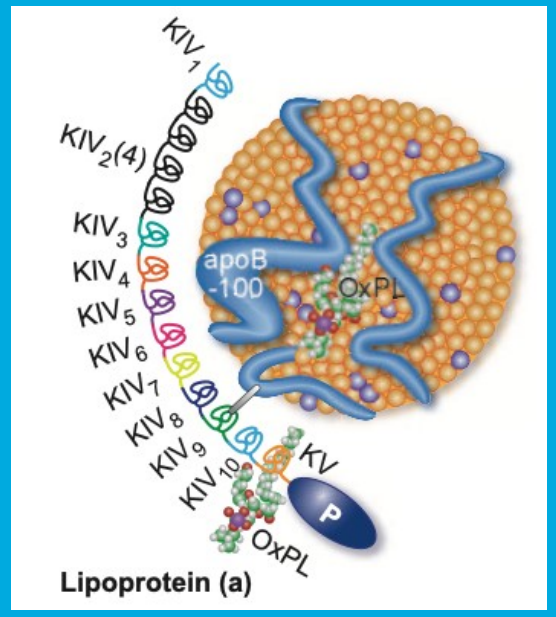
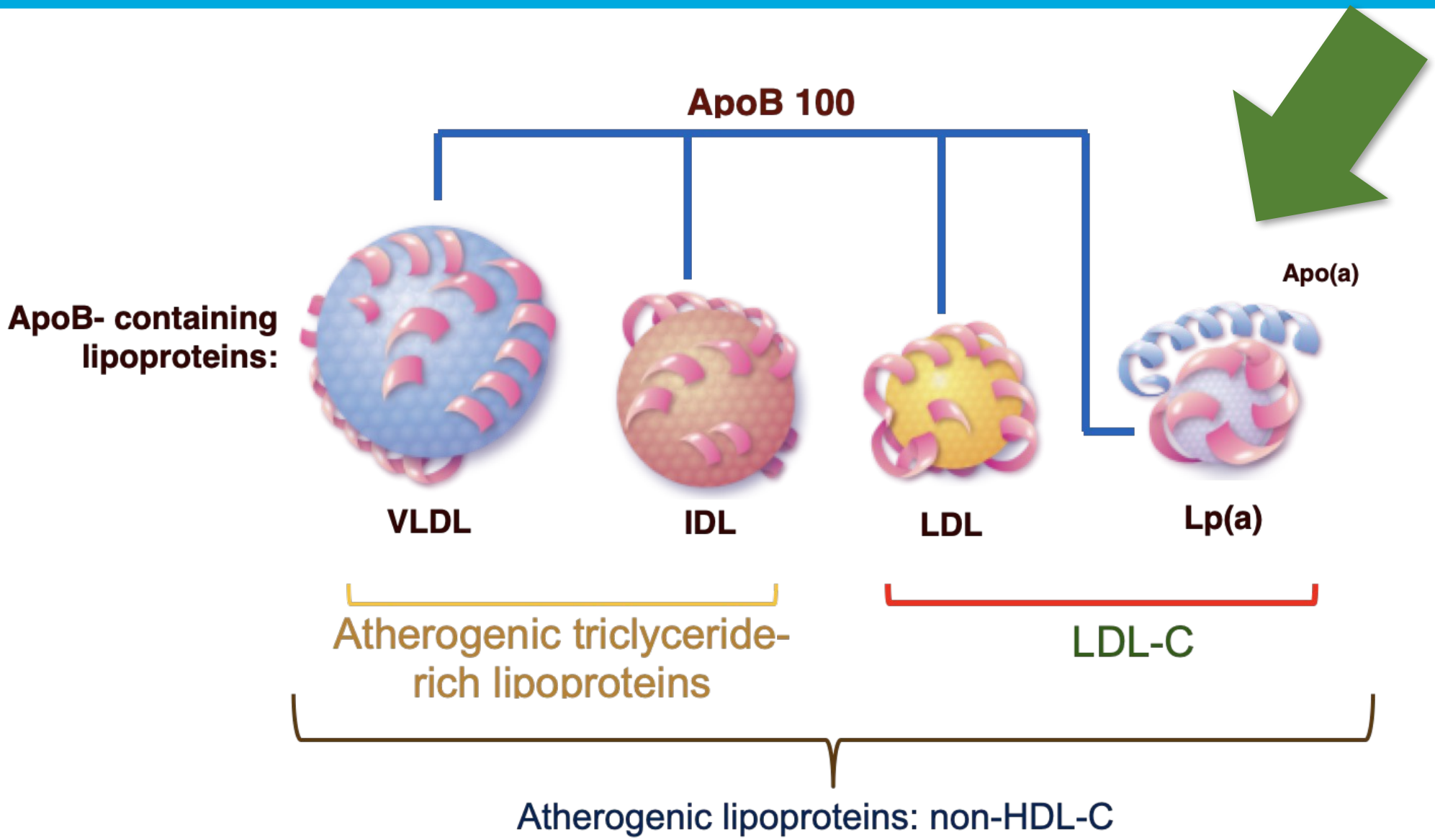


Lipoproteïne (a)
Het volgende doelwit

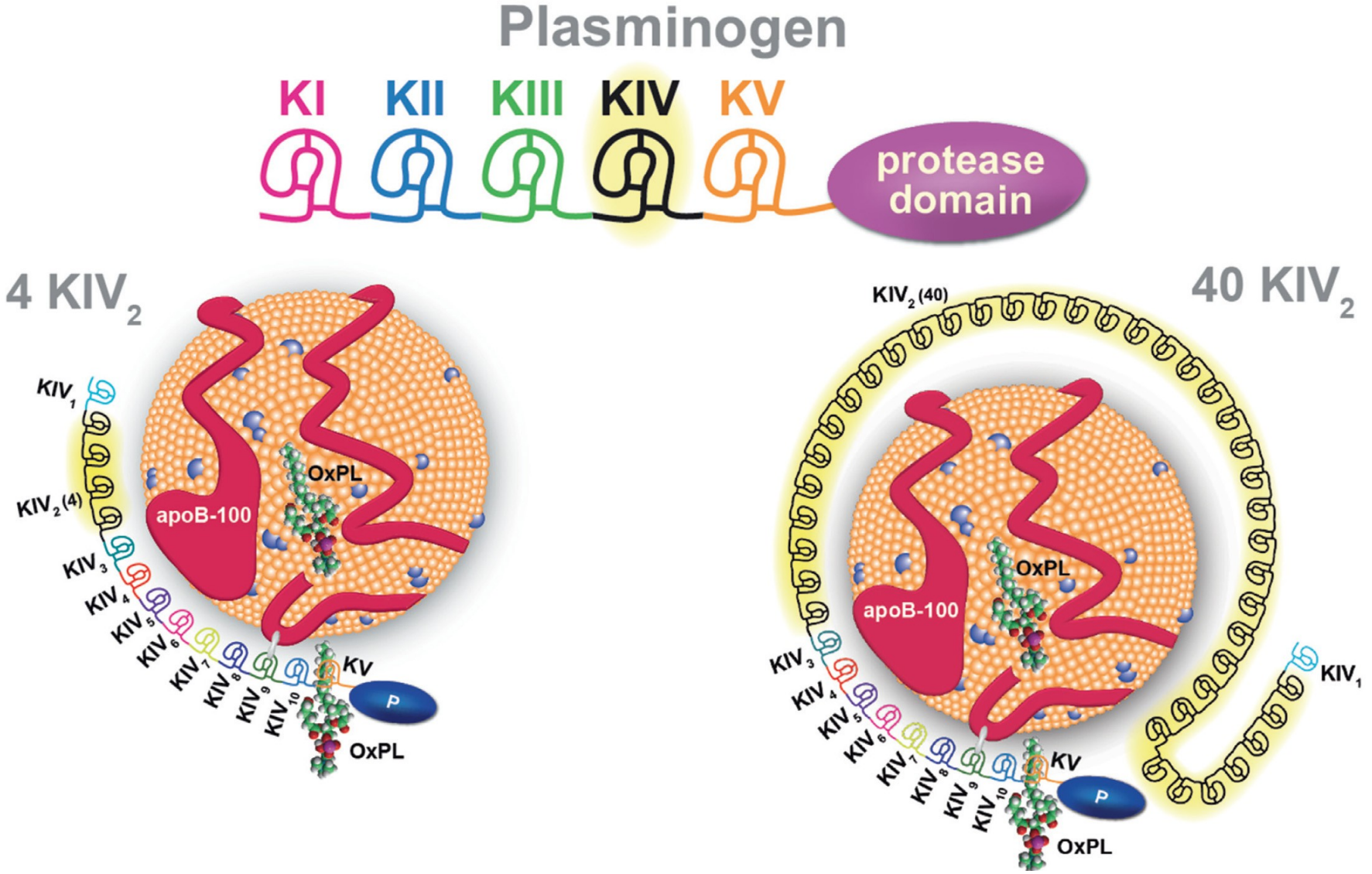
Peter R Sinnaeve, MD PhD FESC

UZ LEUVEN

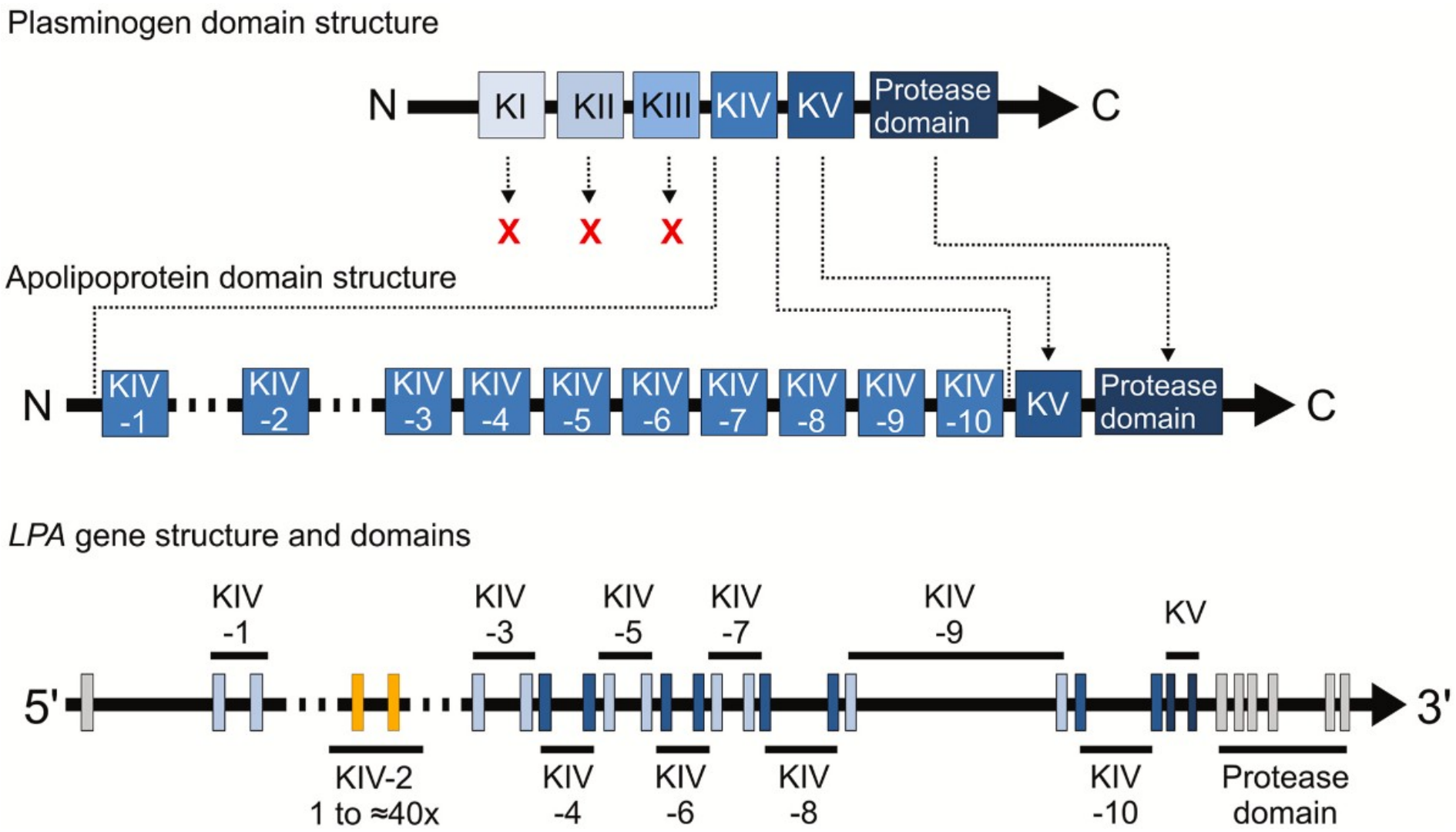
Lipoproteine (a) *[liepopròteejiene kleinə aa]*



Lipoproteine (a) genetisch bepaalde spiegels

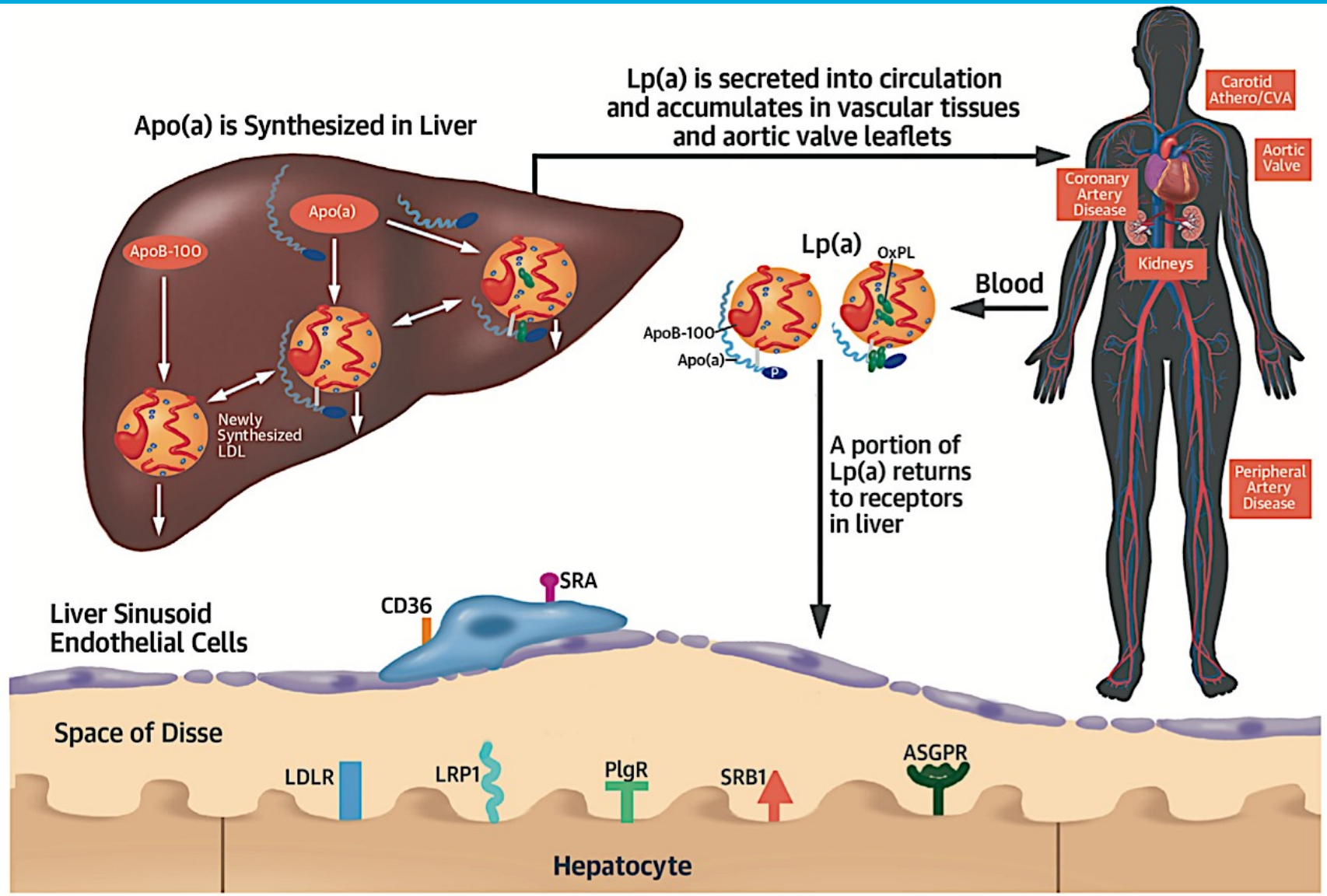


Lipoproteine (a) genetisch bepaalde spiegels & evolutie



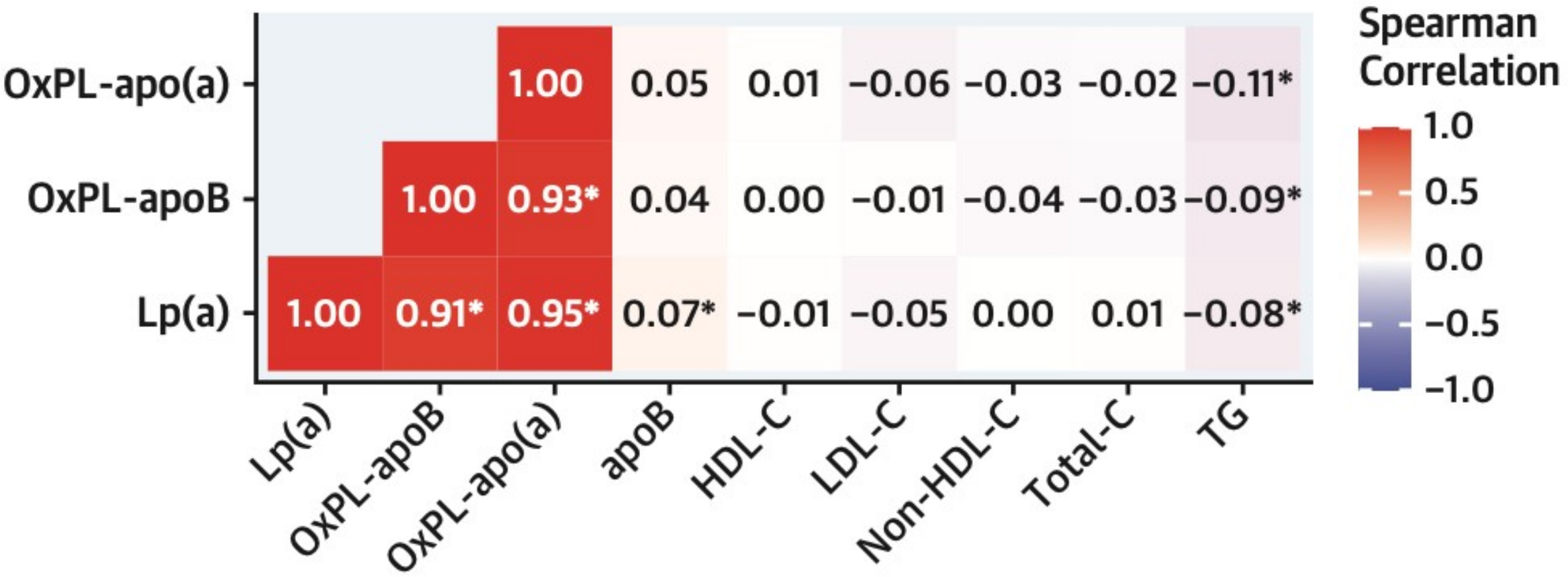
Coassin et al Atherosclerosis 2022;349:17

Lipoproteine (a) *metabolism*



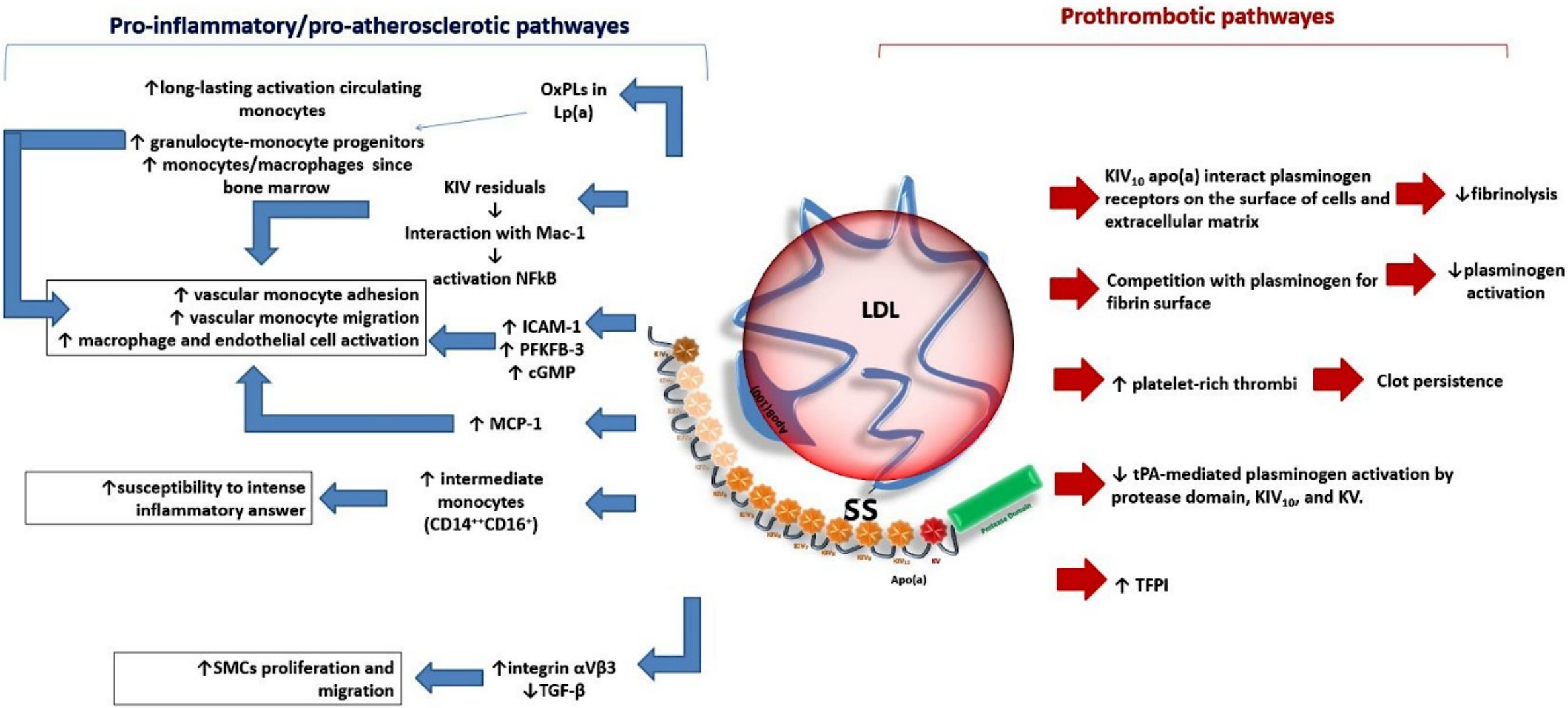
Tsimikas et al JACC 2018;71:177

Lp (a) spiegels & geoxideerde fosfolipiden



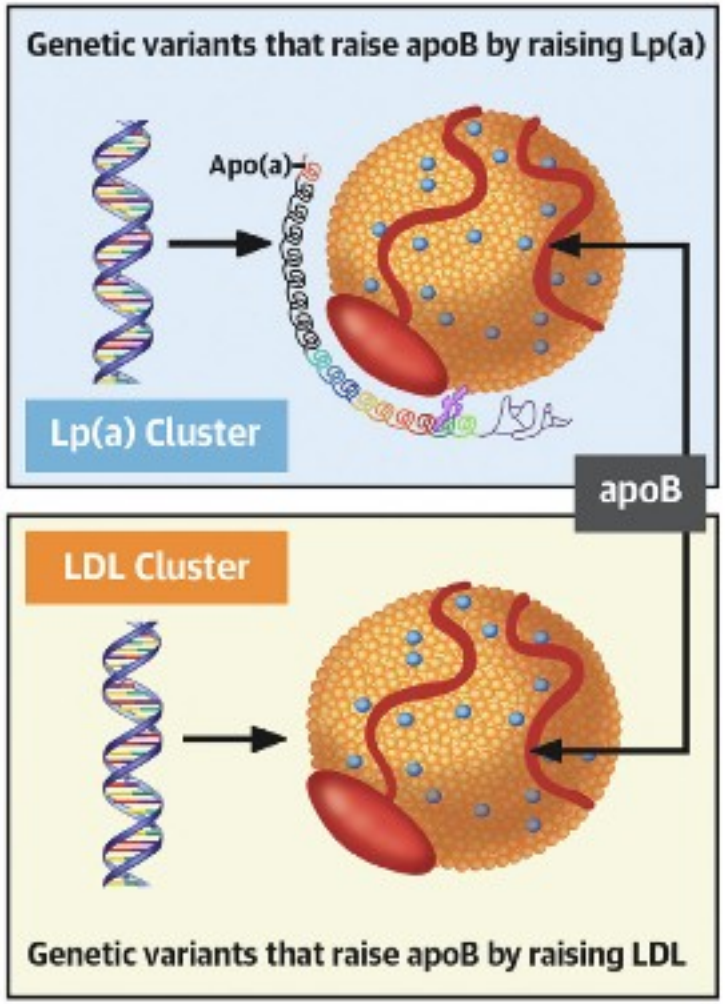
Gilliland et al JACC;2023:81:1780

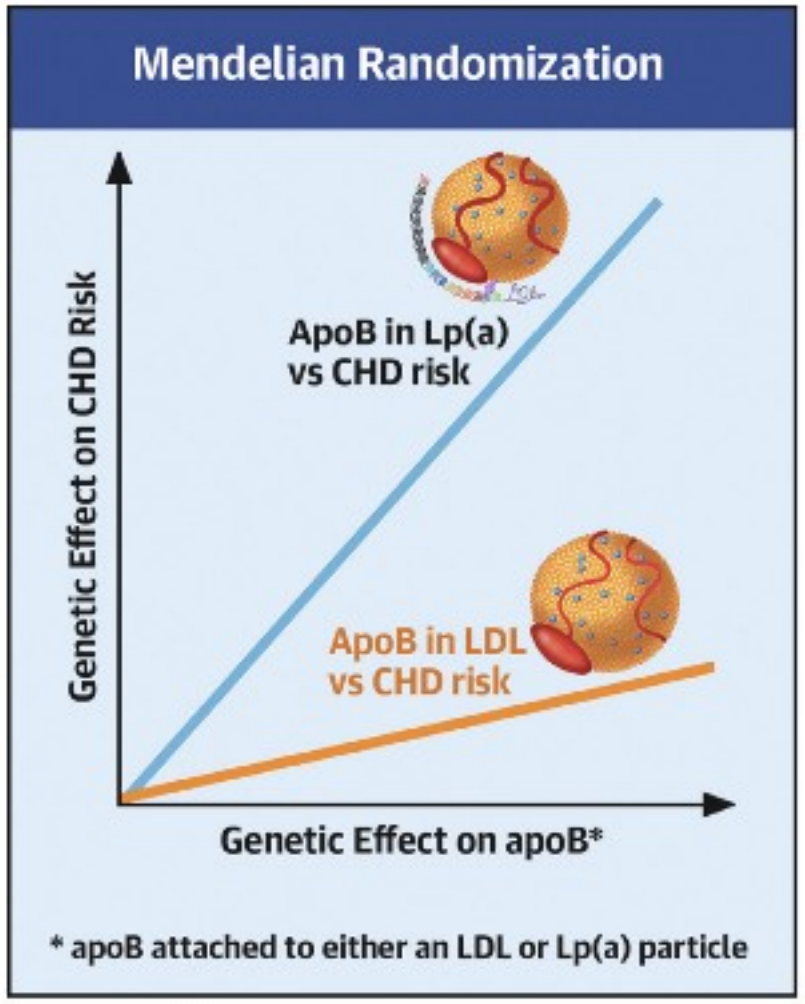
Lipoproteine (a) pathofysiologie



Di Fusco et al J Clin Med 2023;12:2529

Lp (a) atherogeniciteit





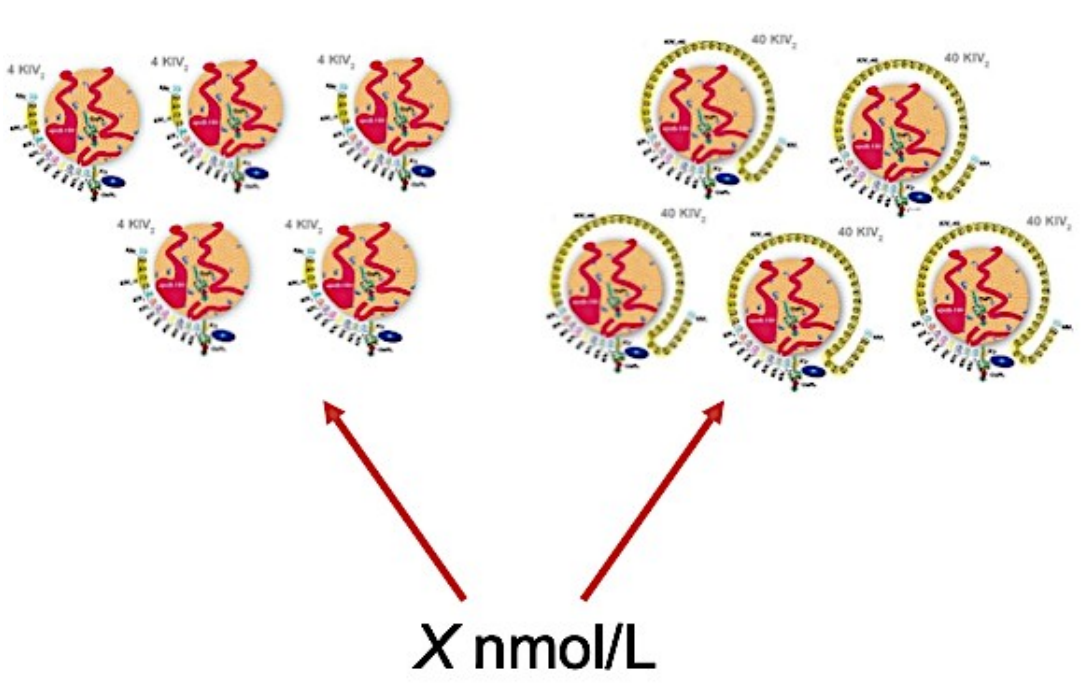
x

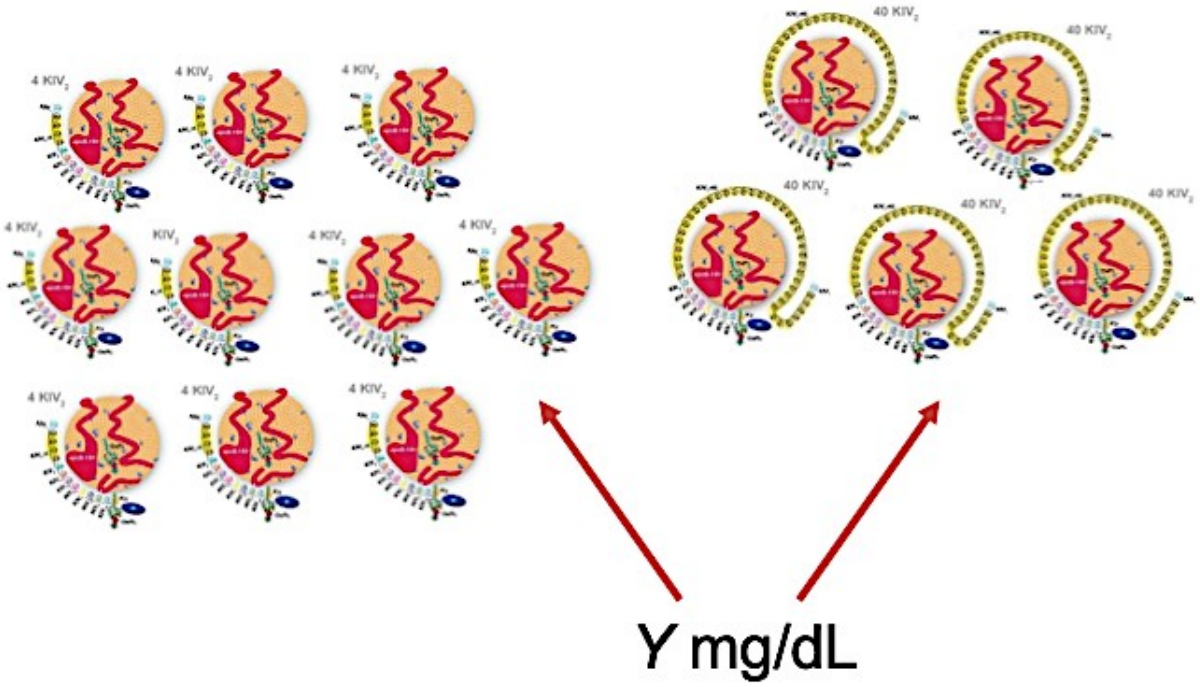
6

atherogeen
per partikel

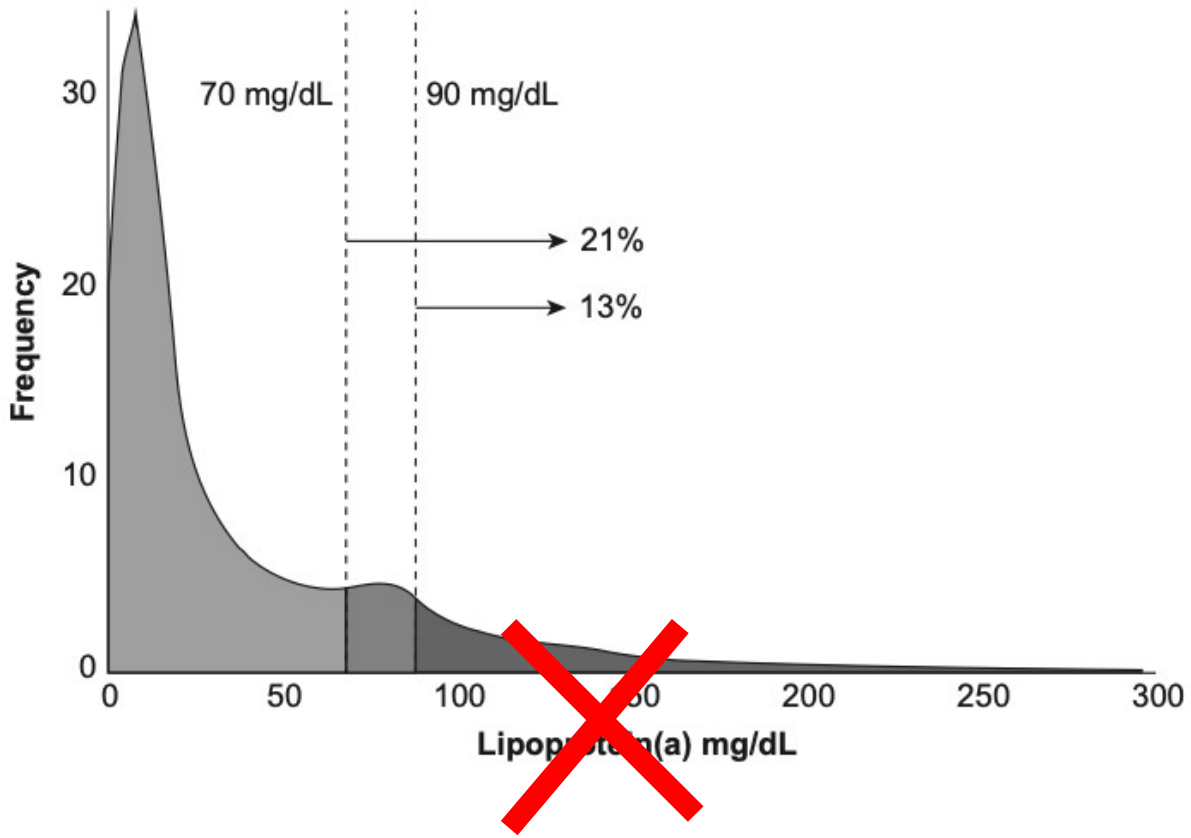
Björnsson et al JACC 2024;83:385

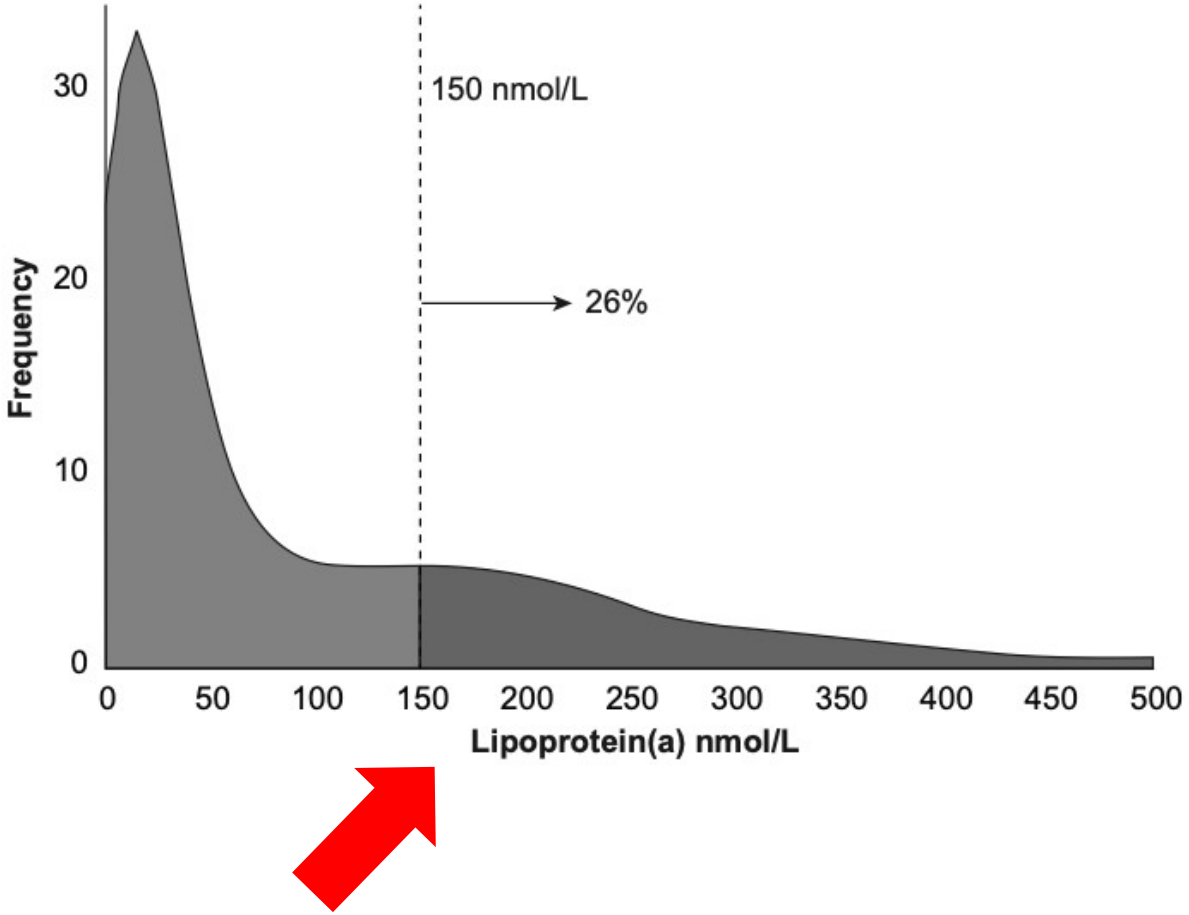
Lipoproteine (a) Géén (weinig) meet-standardisatie





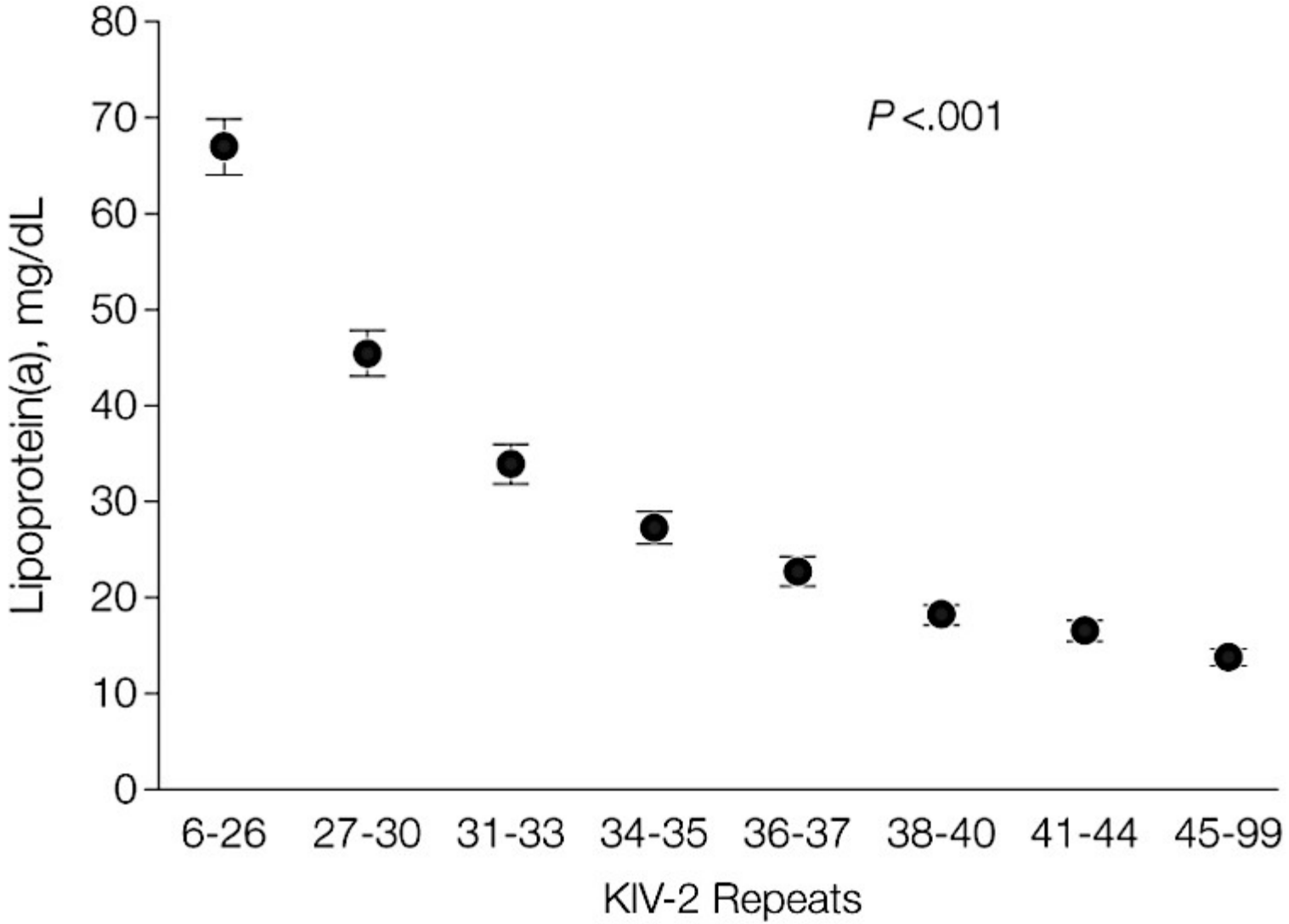
Lp (a) spiegels asymmetrisch & genetisch bepaald





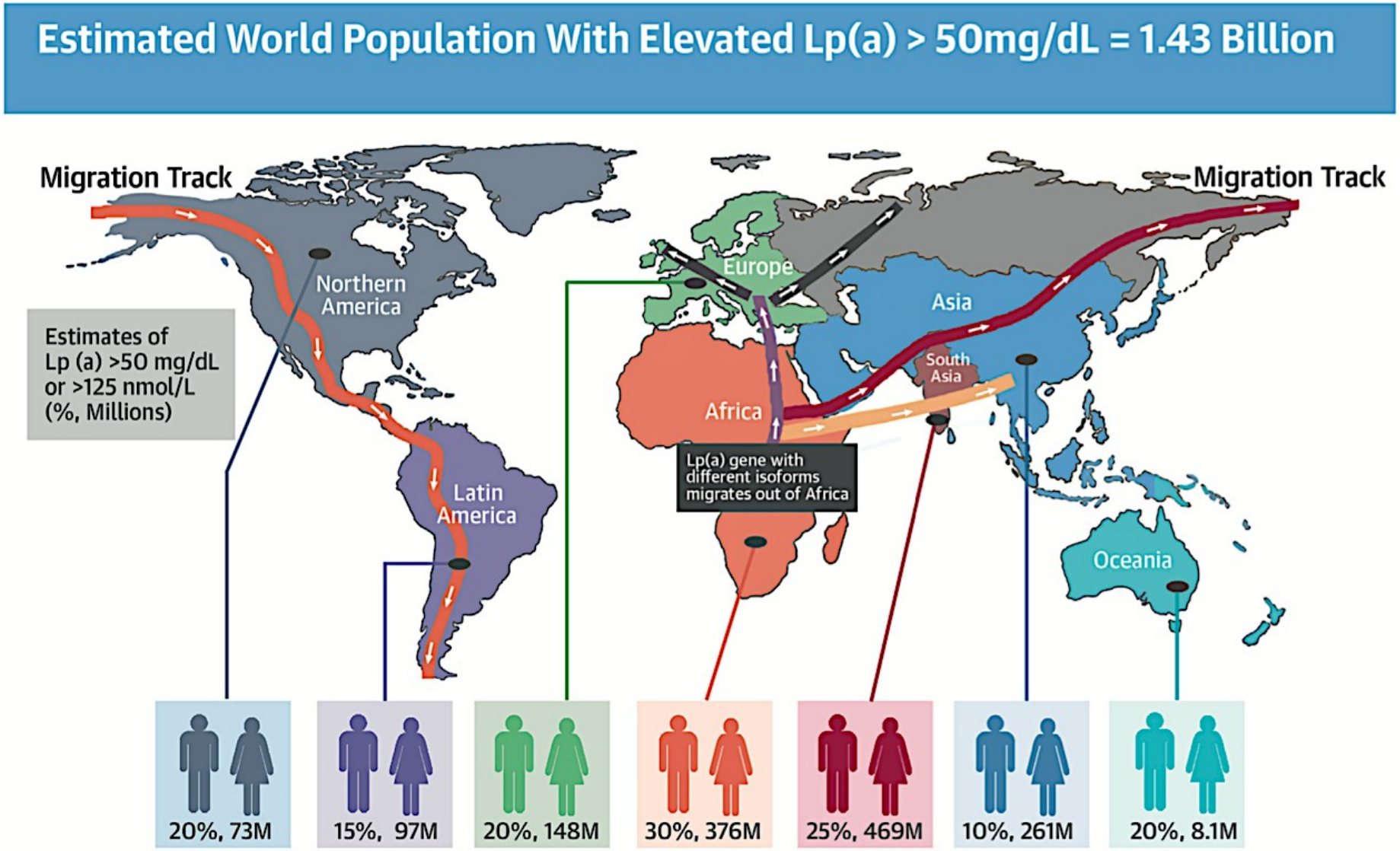
Nissen et al Open Heart 2022;9:e002060

Lp (a) spiegels Spiegel omgekeerd evenredig met KIV2 repeats



Kamstrup et al JAMA 2009;301:2331

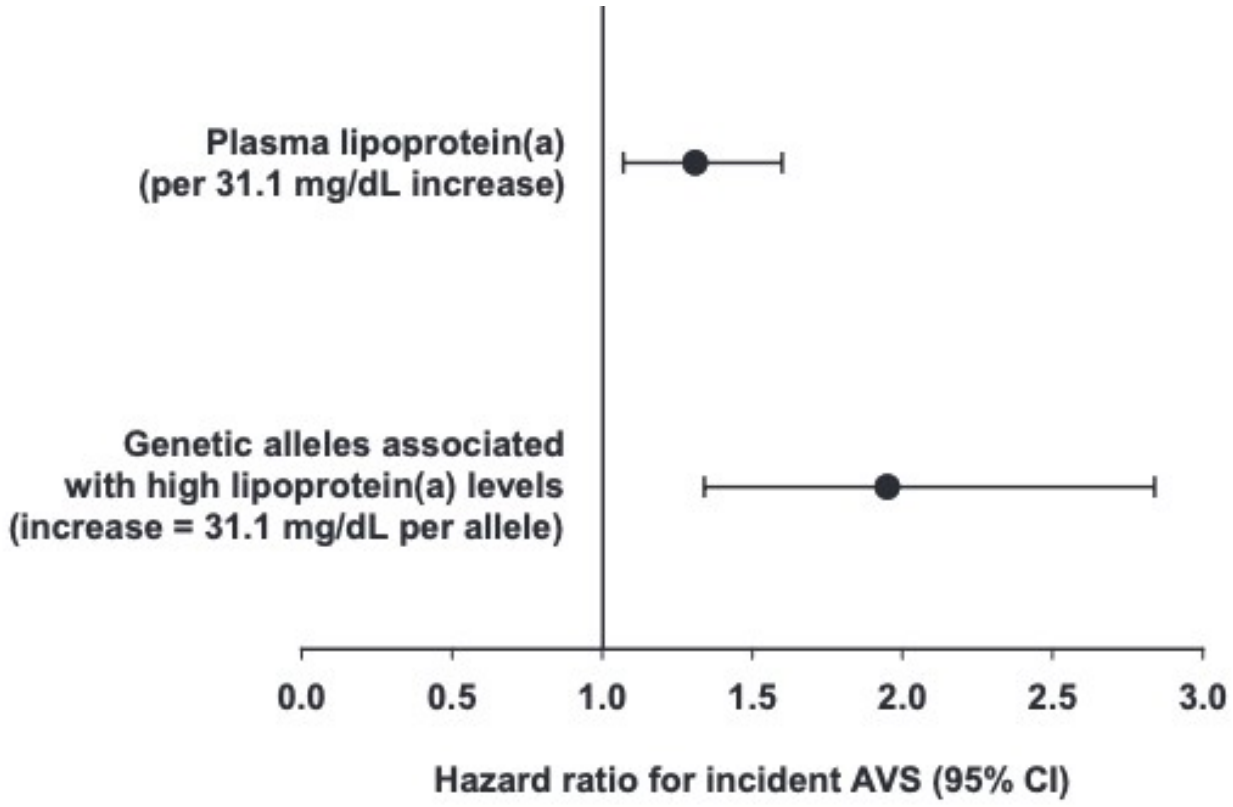
Lp (a) spiegels ethnische heterogeniciteit



Tsimikas et al JACC 2018;71:177

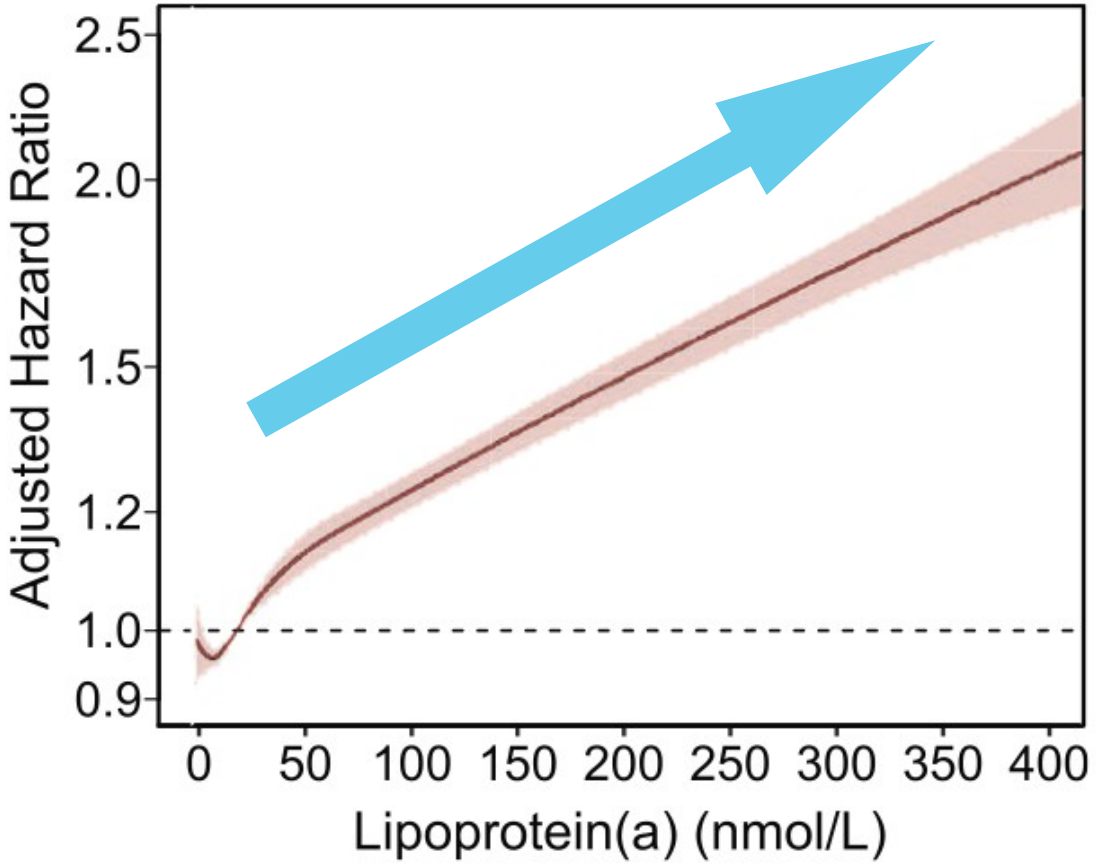
Lp (a) spiegels lineaire prognose

Aortastenose



Arsenault et al JACC 2014;7:204

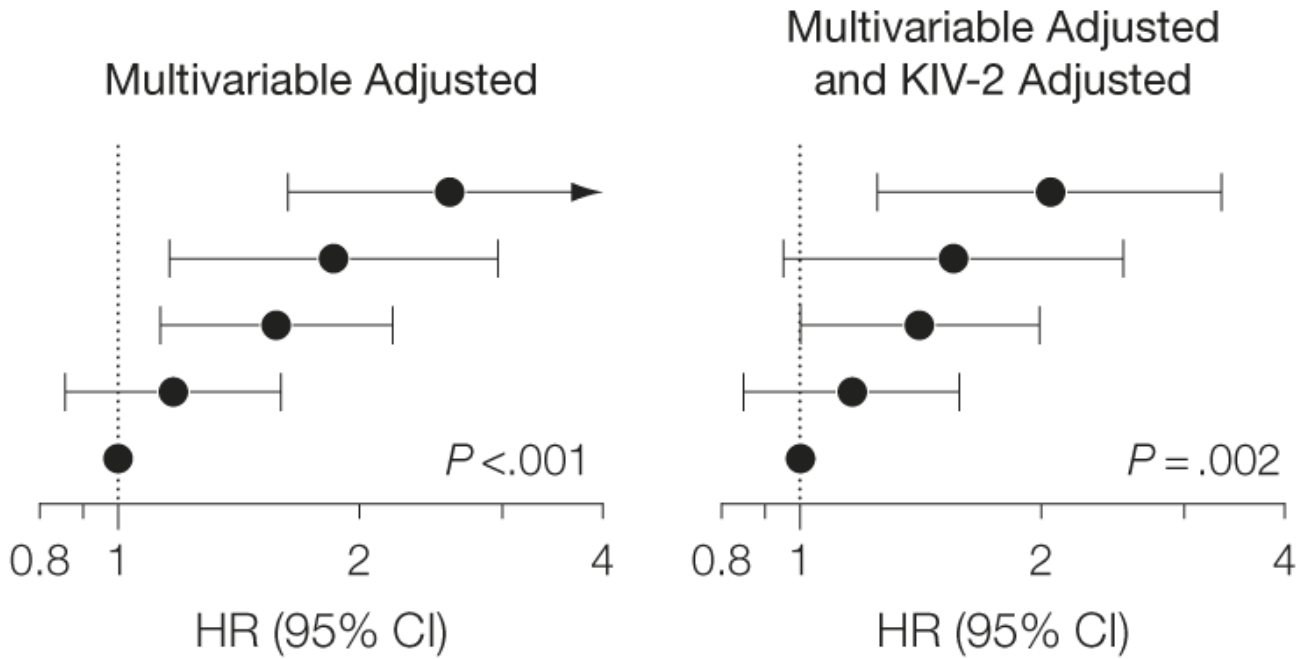
AsCVD



Patel et al ATVB 2021;41:465

Lp (a) spiegels lineaire prognose (risico zelfs bij héél laag LDL)

Lipoprotein(a) Percentile	mg/dL	Participants, No.	Events, 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

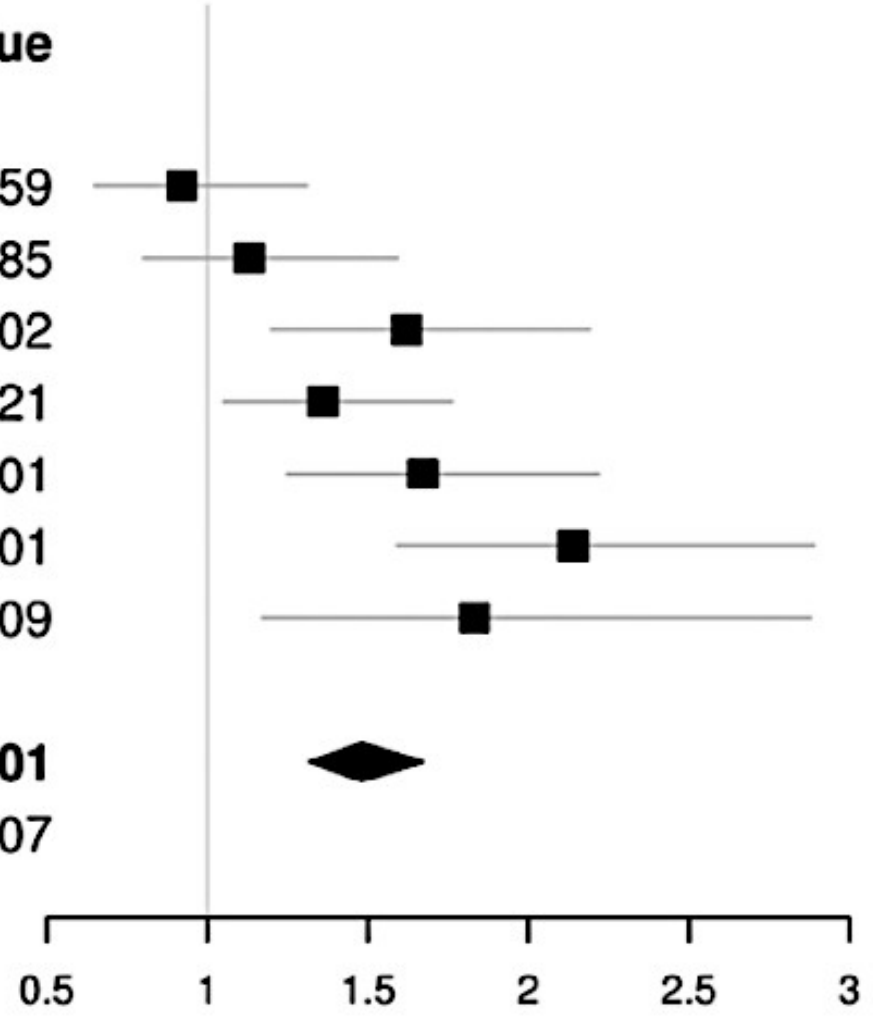


Risico op myocardinfarct

Kamstrup et al JAMA 2009;301:2331

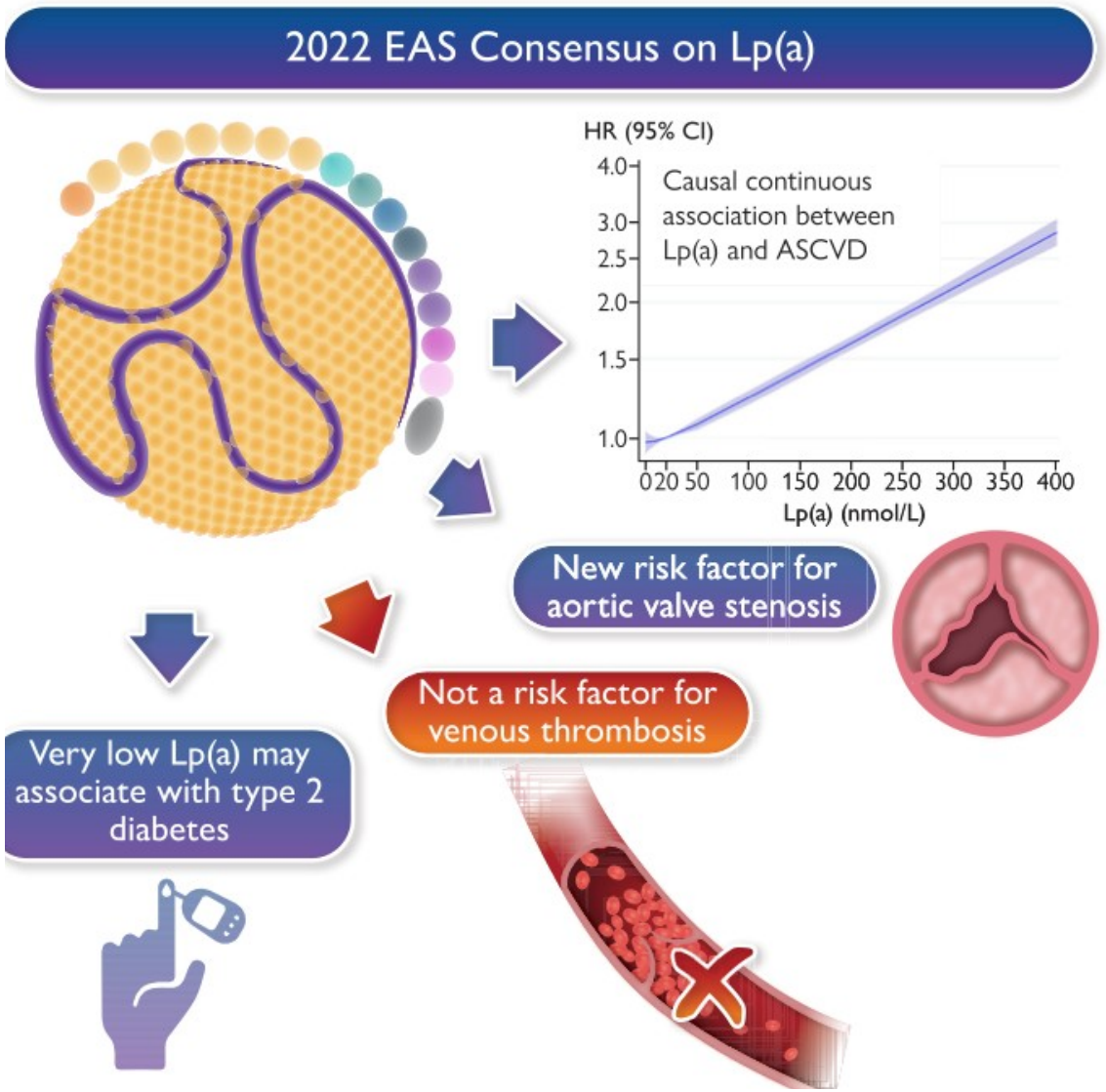
Lp (a) spiegels ethnische variatie in risico op myocardinfarct

Ethnicity	Case	Control	OR[95% CI]	P-value
Africans	294	474	0.92(0.65-1.31)	0.659
Arabs	528	822	1.13(0.80-1.59)	0.485
Chinese	2034	2385	1.62(1.20-2.19)	0.002
Europeans	951	897	1.36(1.05-1.76)	0.021
Latin Amercians	731	732	1.67(1.25-2.22)	<0.001
South Asians	948	870	2.14(1.59-2.89)	<0.001
Southeast Asians	600	607	1.83(1.17-2.88)	0.009
Summary	**6086**	**6787**	**1.48(1.32-1.67)**	**<0.001**
Heterogeneity				0.007



Paré et al Circulation 2019;139:1472 – INTERHEART data

Lp (a) in de praktijk – *Onafhankelijke risicofactor*



EAS

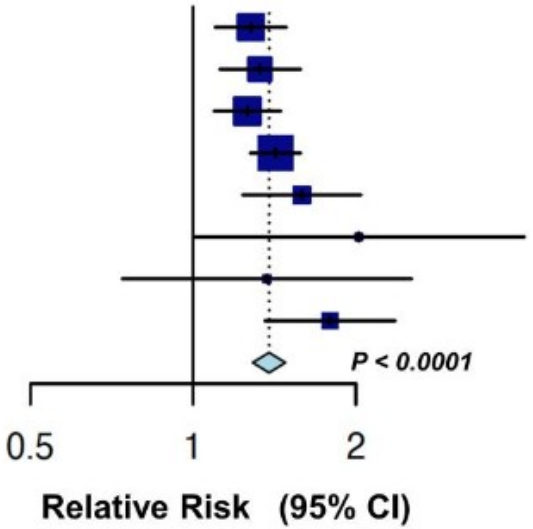
- Lp(a) should be measured at least once in adults
- Interpretation of Lp(a) concentration in the context of absolute global CVD risk
- Intensified risk factor management by lifestyle modification and medications
- Specific Lp(a)-lowering therapies in phase II/III trials

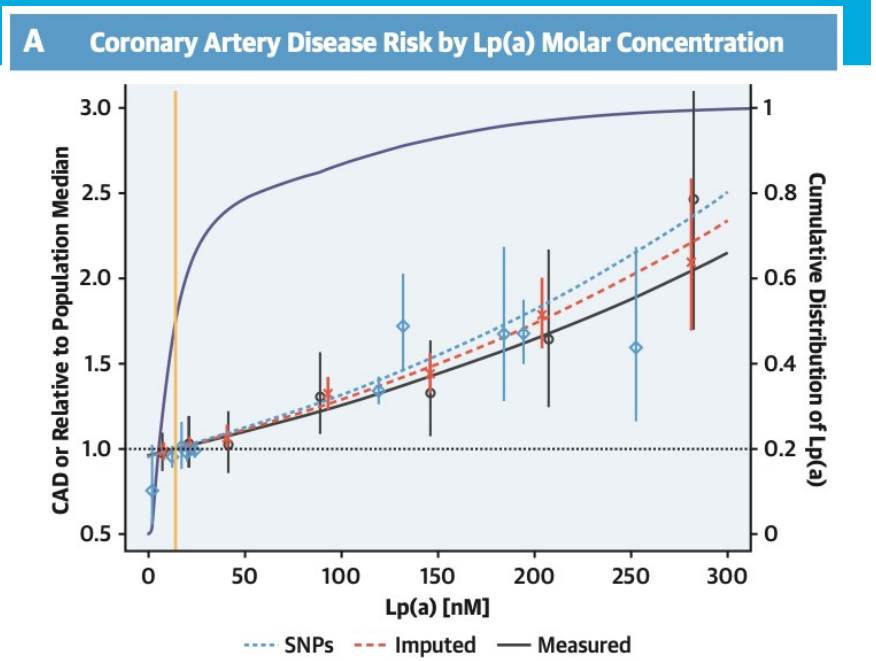
Kronenberg et al EHJ 2022;43:3925

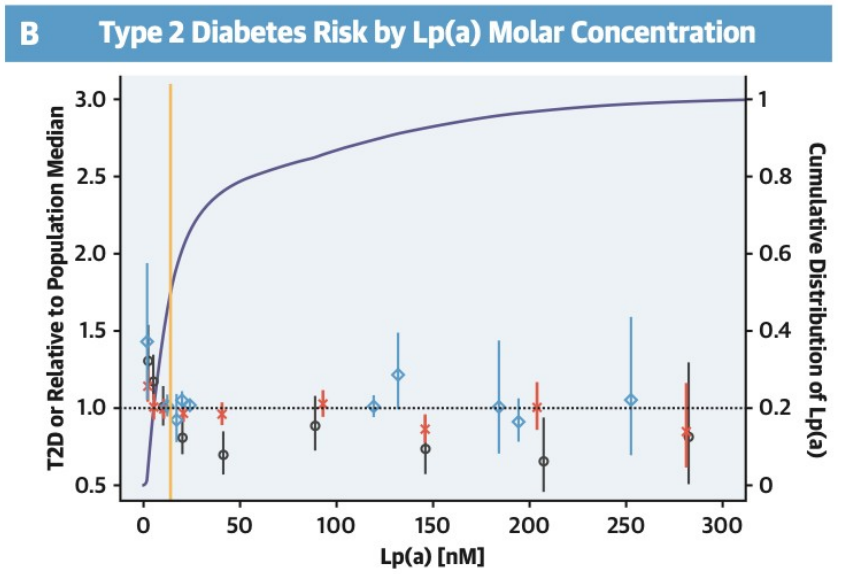
Lp (a) & diabetes ?

Study (Year)	RR [95% CI]
Mora (2010)	1.28 [1.10; 1.49]
Tolbus (2017)	1.33 [1.12; 1.58]
Kamstrup (2013)	1.26 [1.09; 1.45]
Langsted (2021)	1.42 [1.28; 1.58]
Ye (2014)	1.59 [1.23; 2.05]
Kaya (2017)	2.03 [1.00; 4.10]
Paige (2017)	1.37 [0.74; 2.53]
Gudbjartsson (2019)	1.79 [1.36; 2.36]
Total	1.38 [1.29; 1.48]

Heterogeneity: $\chi^2_7 = 8.74$ ($P = .27$), $I^2 = 20\%$







Role of homozygous LoF mutations

Kronenberg et al EHJ 2022;43:3925 & Gudbjartsson JACC

Lp (a) in de praktijk – *Maar wie screen je ? En wanneer…? Iair*

- Bij bij individuen met een familielid met prematuur AsCVD (<55j M, <65 V)
- Bij prematuur AsCVD, zeker zo geen/weinig andere risicofactoren
- Bij erg hoog LDL (>190 mg/dL) of vermoeden FH
- Bij héél hoog AsCVD risico ev ter beoordeling van ev PCSK9

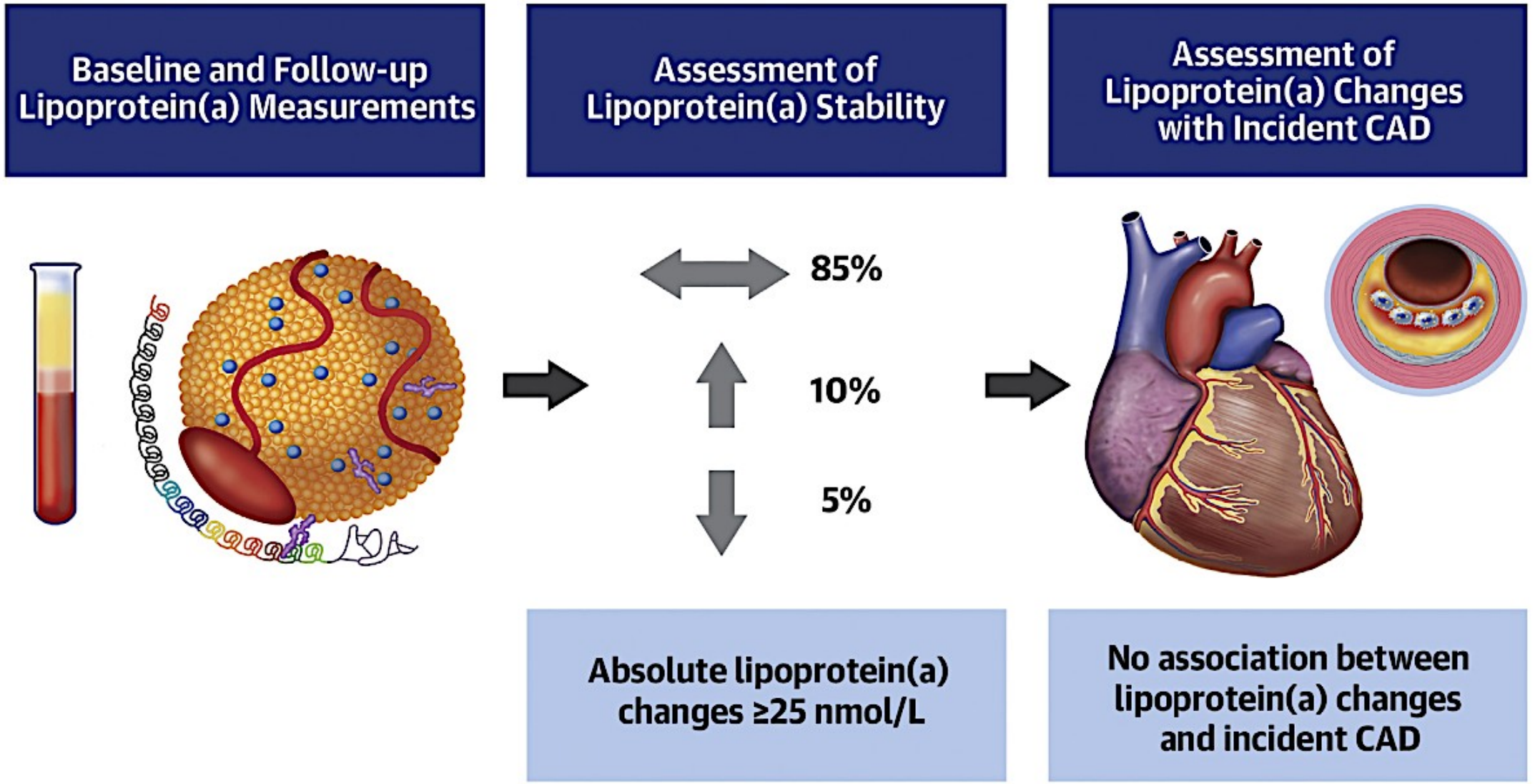
- Intermediair 10j AsCVD risico als statine-indicatie niet duidelijk
- Weinig respons op LLT ondanks therapietrouw
- Verhoogd Lp(a) in de familie
- Gecalcifieerde AS

Lp (a) in de praktijk – *Maar wie screen je ? En wanneer…? Ilair*

- Nog nuttig zo al op LLT (statine, PCSK9i,…) ?
- Recurrente/progressieve AsCVD ondanks optimale LLT & preventie
- Overweeg agressievere LLT therapie en preventie zo Lp(a) ↑
- Overweeg (eerder gebruik van) PCSK9i zo ook Lp(a) ↑

- Cave ↑ als acute fase reactie na bvb acuut myocardinfarct

Lp (a) in de praktijk – *Is re-screenen nodig ?*



Trinder et al JACC 2022;79:617

Statine & Lp(a): minimale impact (mild ↑)

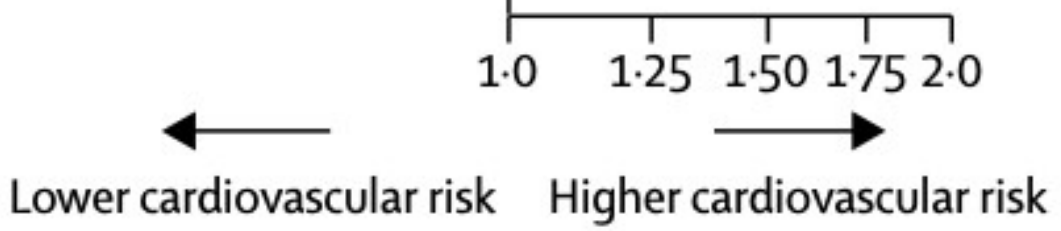
Statine verbetert outcome onafhankelijk van Lp(a) spiegel



Khera et al Circ 2014;129:635 – Data from JUPITER

Lp (a) risico als reeds op statine

	Trials (n)	Patients (n)	Events (n)	Hazard ratio (95% CI) for lipoprotein(a) ≥50 mg/dL *vs* 50 mg/dL	$p_{interaction}$
Age-adjusted and sex-adjusted					
On-statin	7	14536	2603	1·48 (1·23–1·78)	0·010
On-placebo	7	14533	3148	1·23 (1·04–1·45)	
Multivariable adjusted*					
On-statin	6	13883	2561	1·47 (1·25–1·73)	0·031
On-placebo	6	13881	3088	1·26 (1·06–1·50)	



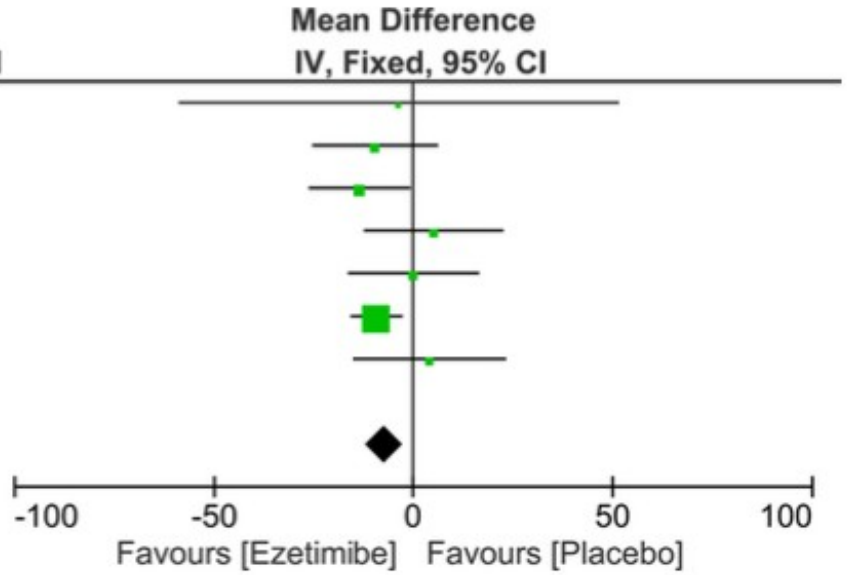
Willeit et al Lancet 2018;392:1331-20

Ezetimibe & Lp(a): minimale impact (mild↓)

	Ezetimibe			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Ballantyne et al. 2003	12.4	158.83	65	16.1	156.47	60	0.8%	-3.70 [-59.00, 51.60]
Davidson et al. 2002	0.8	46.08	61	10.4	46.85	70	9.4%	-9.60 [-25.54, 6.34]
Dujovne et al. 2002	2.83	94.71	666	16.32	82.68	226	14.2%	-13.49 [-26.45, -0.53]
Goldberg et al. 2004	-2.5	52.6	48	-7.7	33.4	51	7.8%	5.20 [-12.28, 22.68]
Kerzner et al. 2003	2	50.91	72	2	48	64	8.6%	0.00 [-16.63, 16.63]
Knopp et al. 2003	-7.5	46.35	621	1.76	41.13	204	52.8%	-9.26 [-15.98, -2.54]
Melani et al. 2003	15	55.2	64	10.9	56.44	65	6.4%	4.10 [-15.17, 23.37]
Total (95% CI)			**1597**			**740**	**100.0%**	**-7.06 [-11.95, -2.18]**

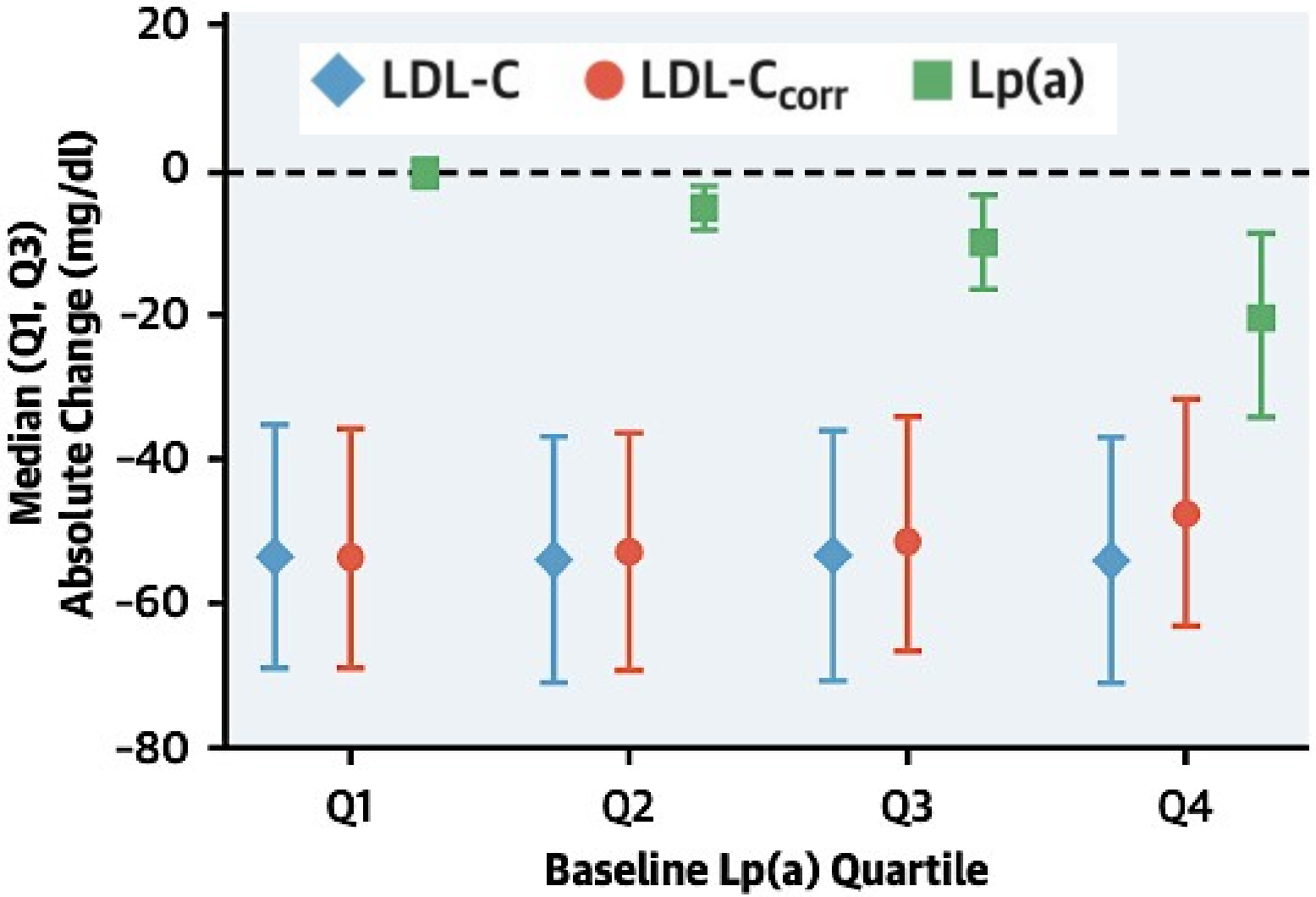
Heterogeneity: Chi² = 5.34, df = 6 (P = 0.50); I² = 0%

Test for overall effect: Z = 2.84 (P = 0.005)



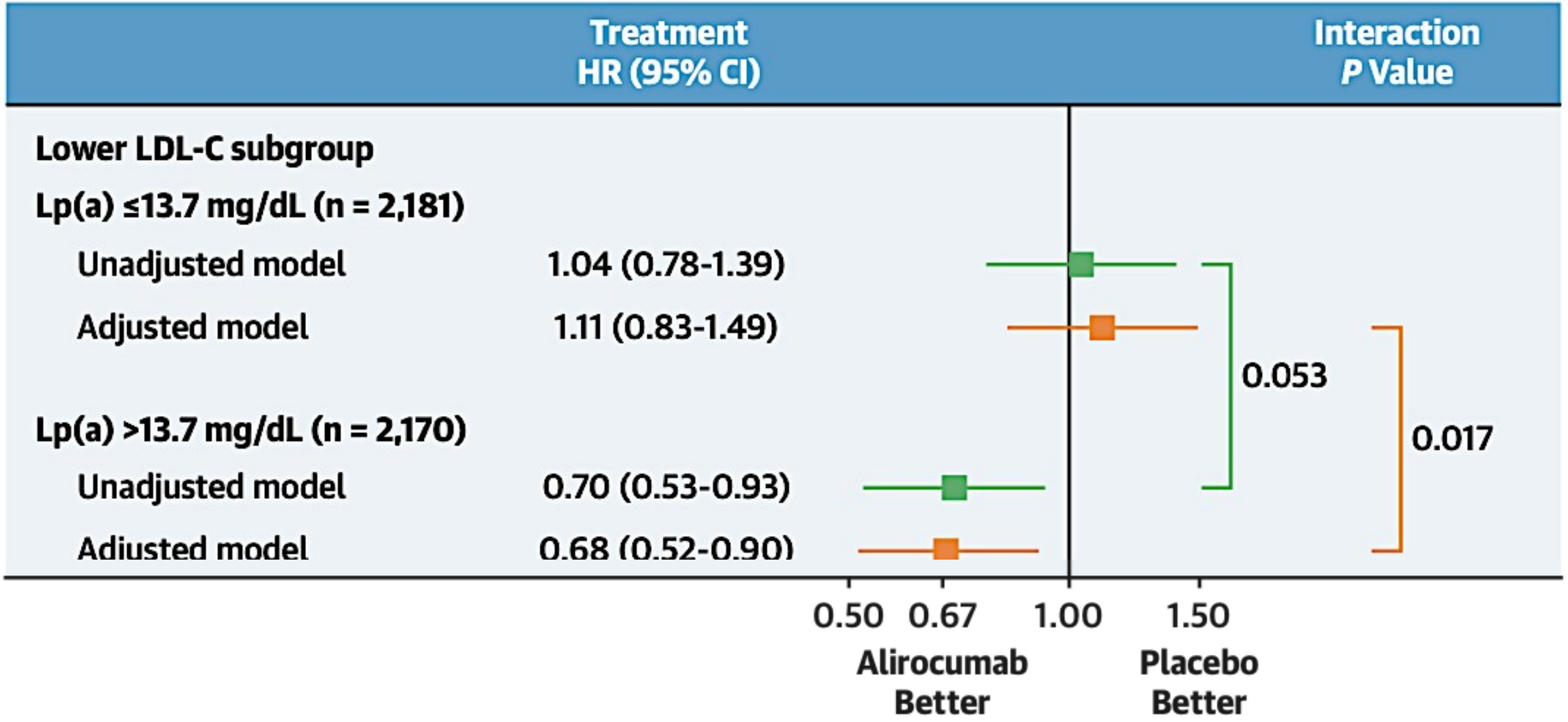
Awad et al Drugs 2018;78:453-62

PCSK9i & Lp(a): onafhankelijke impact (1) – ODYSSEY & alirocumab



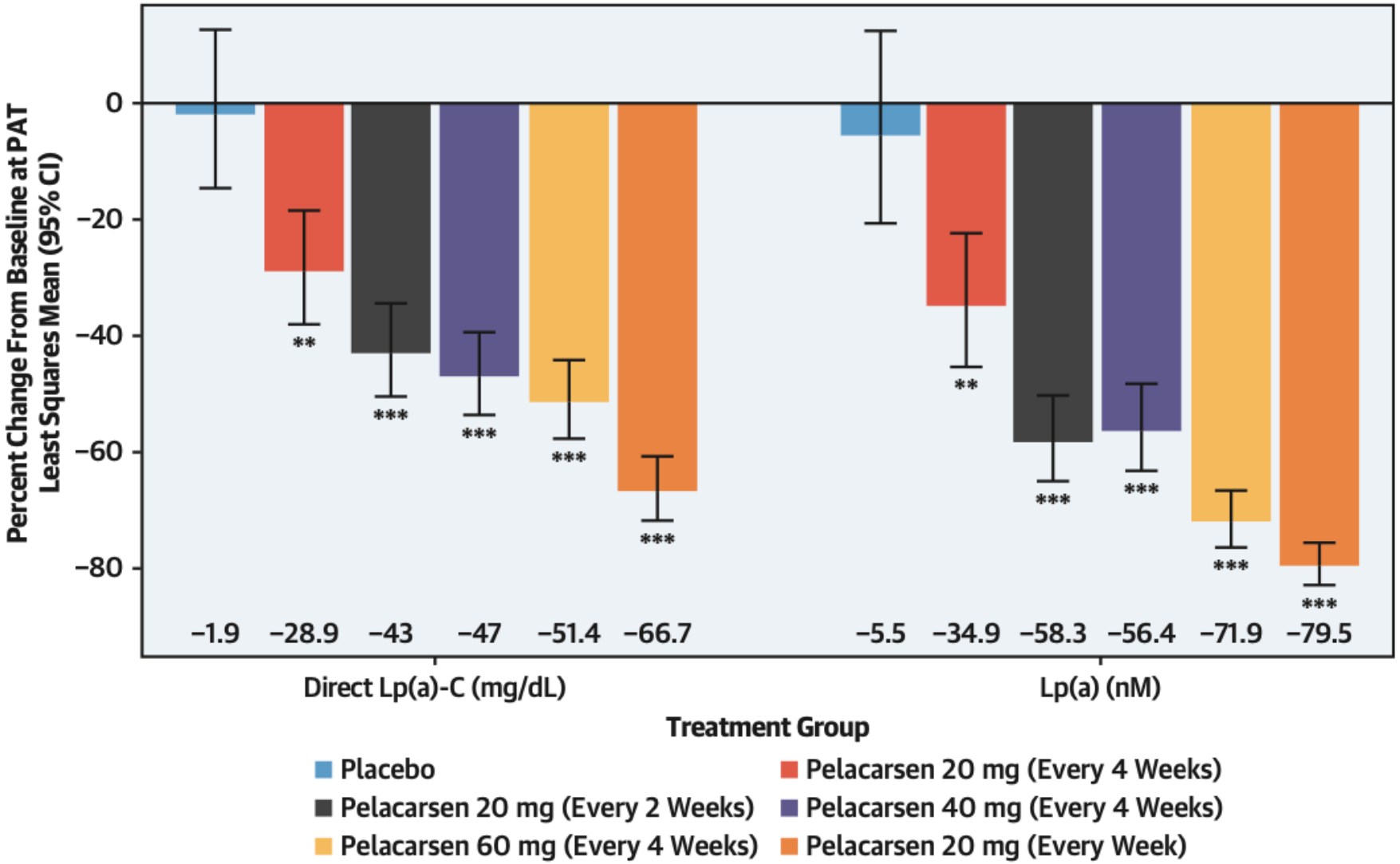
Bittner et al JACC 2020;75:133

PCSK9i & Lp(a): onafhankelijke impact (2) - ODYSSEY



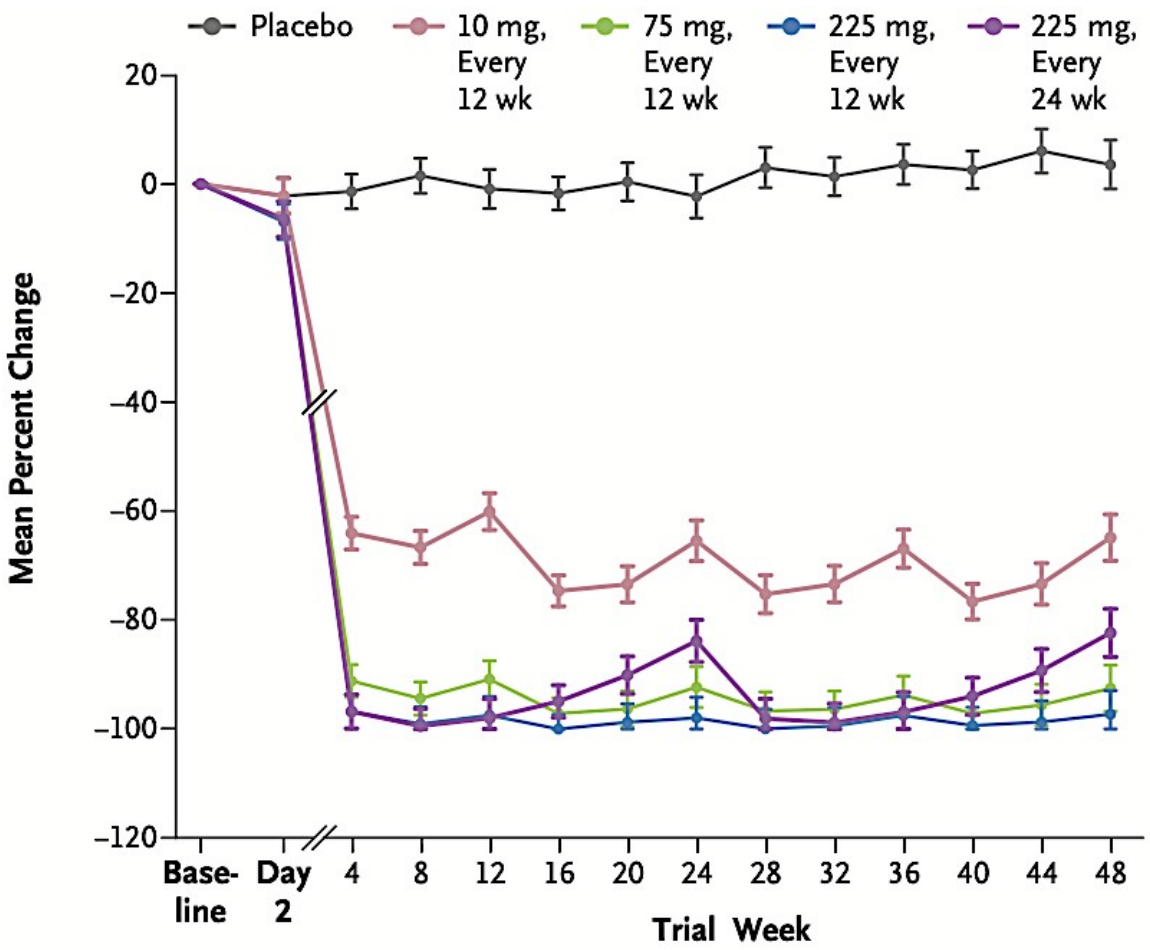
Schwartz et al JACC 2021;78:421

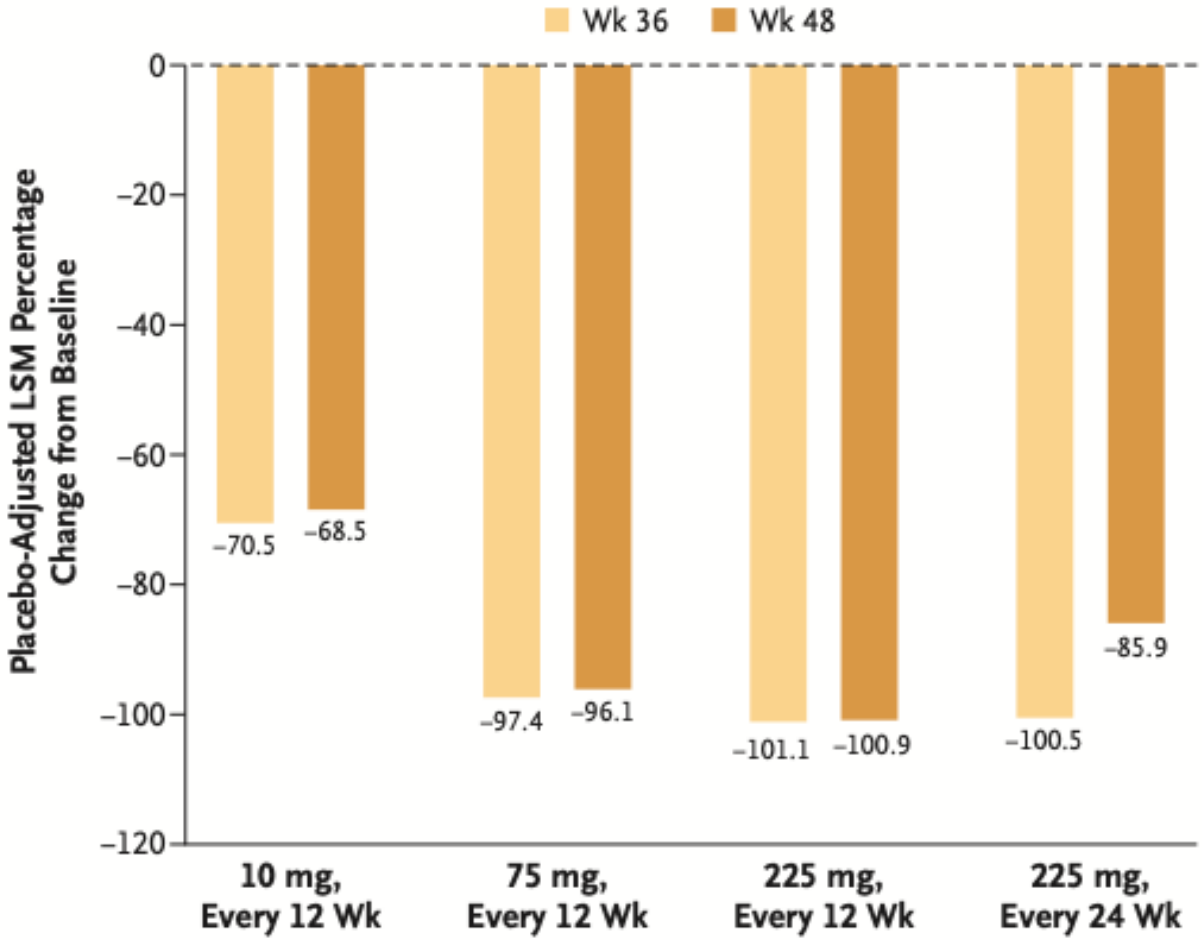
Lp(a) inhibitie met pelacarsen *(Lp(a)HORIZON, n=8300, 80 mg/mnd, ≥70 mg/dL)*



Yeang et al JACC 2022;79:1035

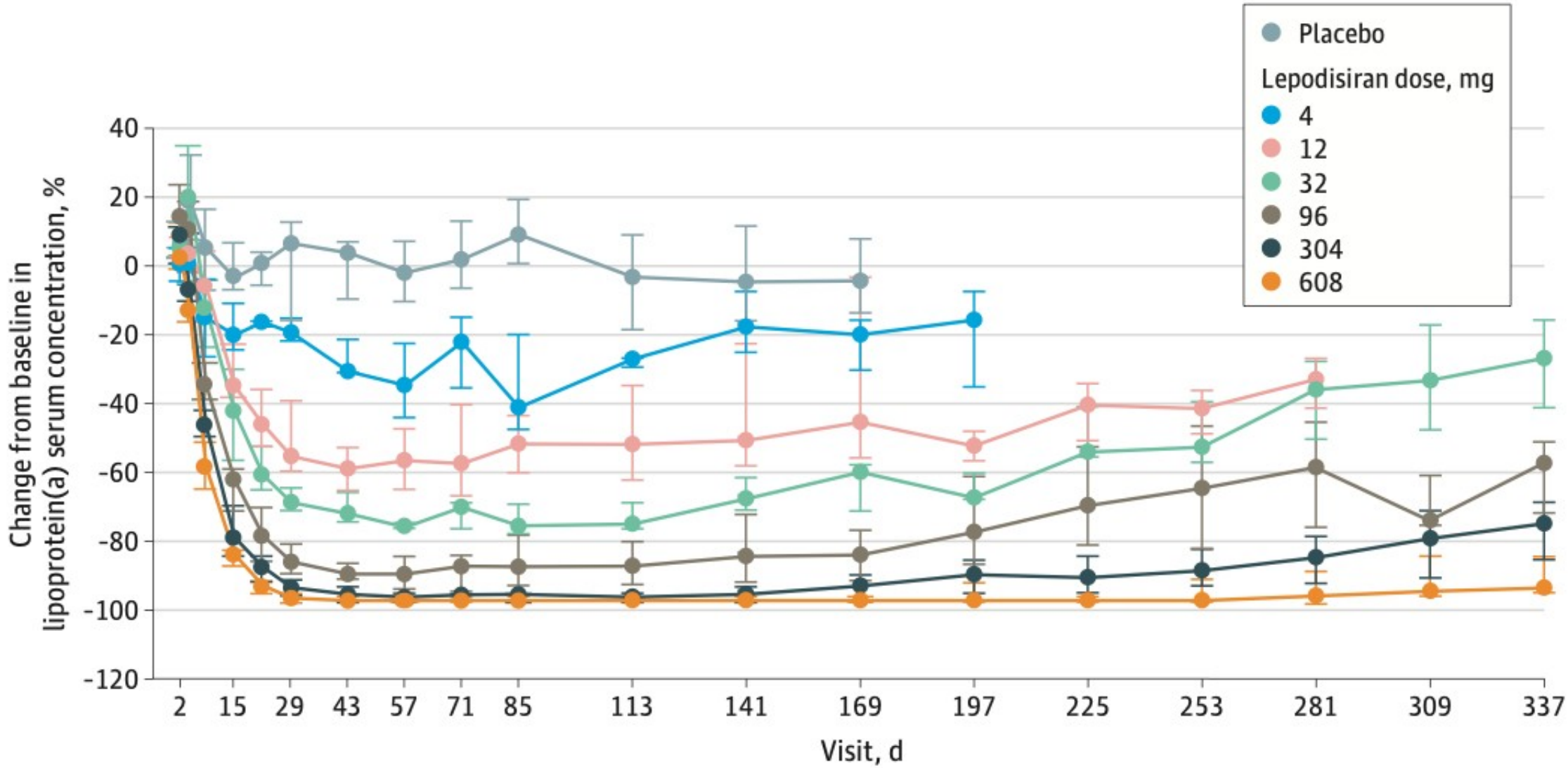
Lp(a) inhibitie met olpasiran *(OCEAN-Lp(a), n=6000, ≥200 nmol/L, 150 mg/3mnd)*



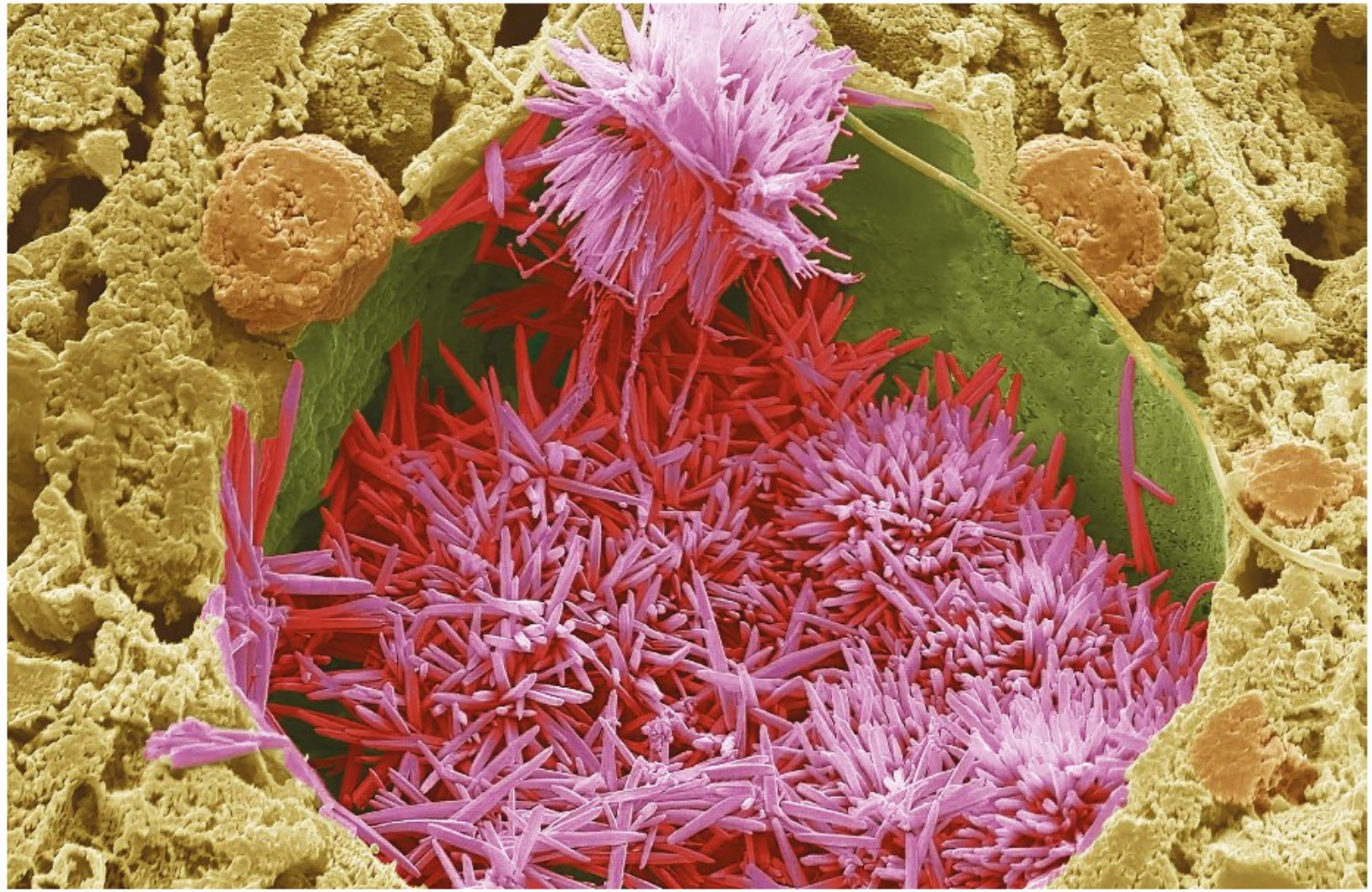


O'Donoghue et al NEJM 2023

Lepodisiran *(ACCLAIM-Lp(a), n=12,500 , …)*



Nissen et al JAMA 2023;33:2080



Cholesterol crystals (red) in a lipid droplet in a human liver.

FIRST TRIAL OF 'BASE EDITING' IN HUMANS LOWERS CHOLESTEROL — BUT RAISES SAFETY CONCERNS



Dankuwel !

UZ LEUVEN

SEDES SAPIENTIAE + VNIVERSITAS CATHOLICA LOVANIENSIS
1425