Bakü, 29.04.2023

Liporotein (a): Aterosklerozda rolü, Tanı ve Tedavi hedefi kim?

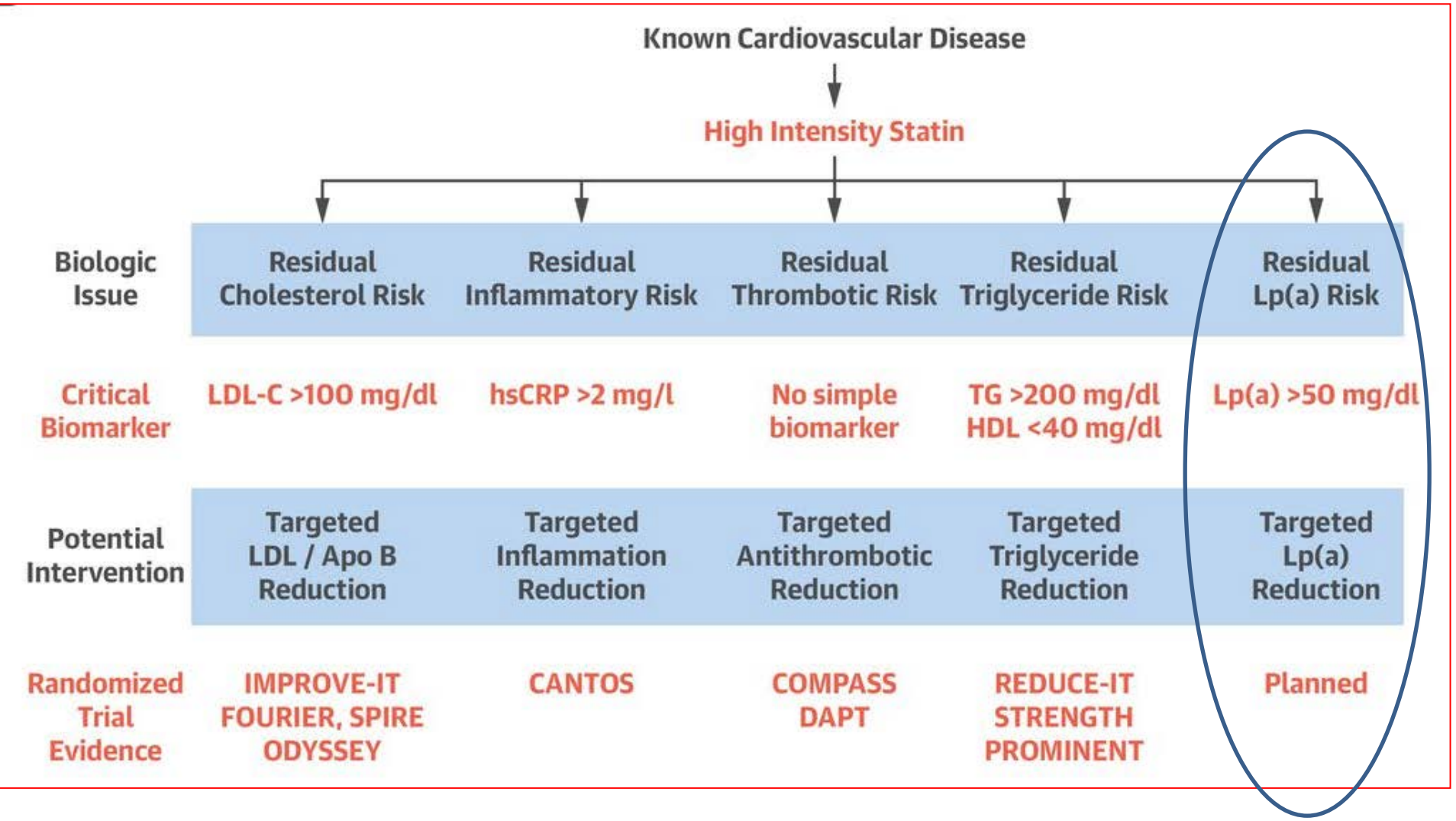
Prof. Dr. Öner ÖZDOĞAN

SBU. İzmir Tıp Fakültesi

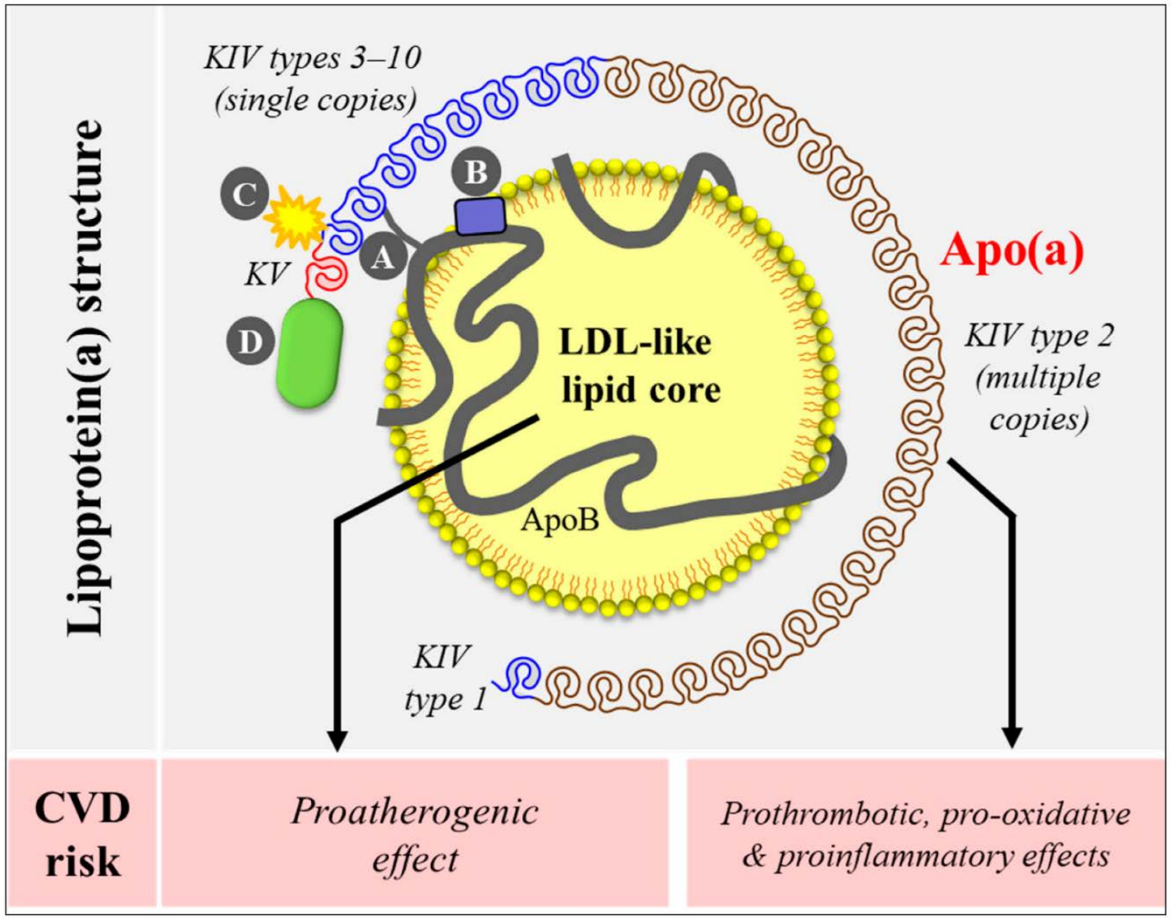
Tepecik SUAM

Kardiyoloji AD

Rezidual Risk

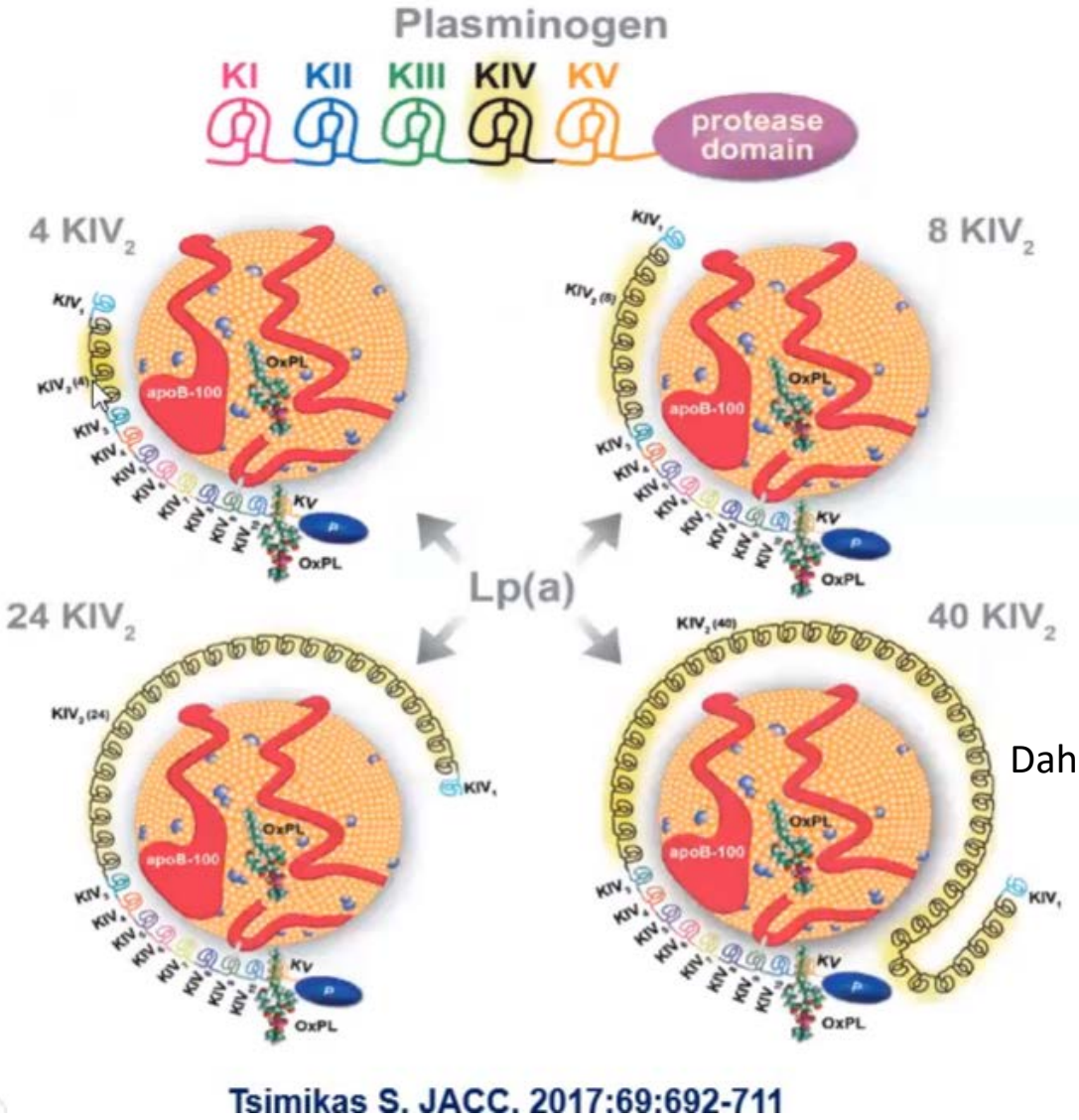


Ridker, P.M. J Am Coll Cardiol. 2018;72(25):3320-31.



Enkhmaa et al., 2020, Nutrients

Farklı Lp(a) izoformları



Tsimikas S. JACC. 2017:69:692-711

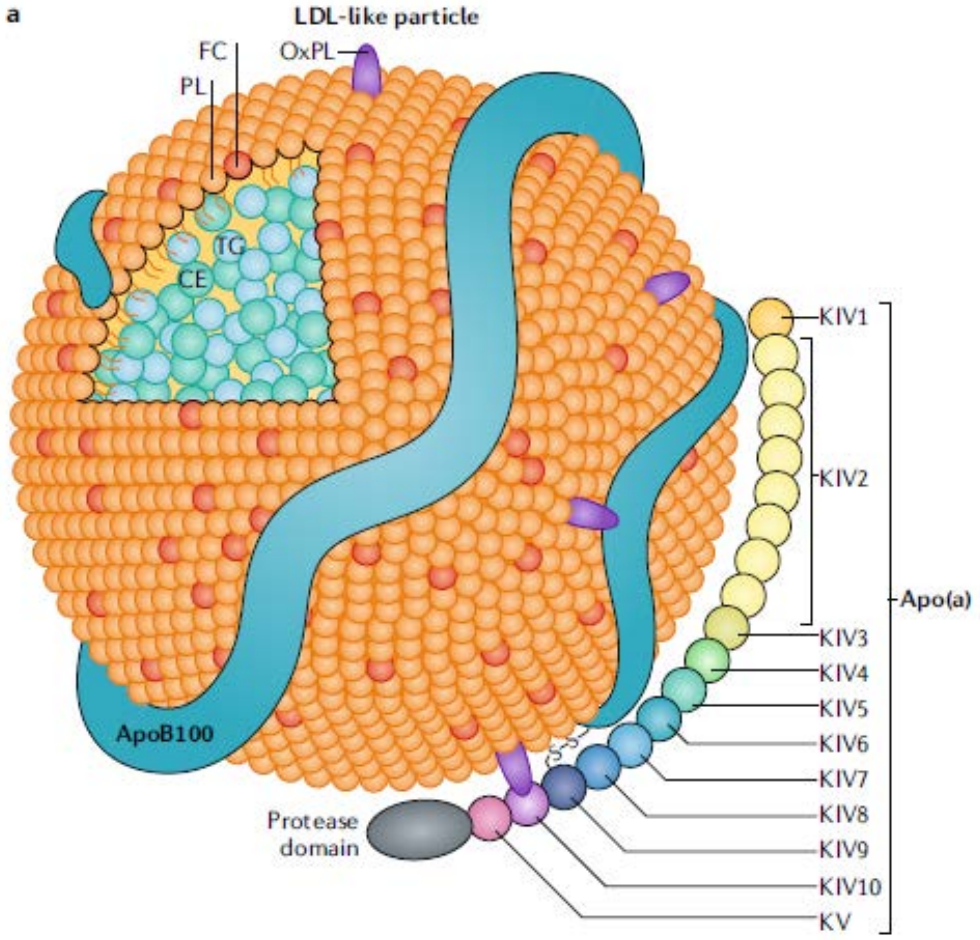
Apo (a) çeşitli sayıda Kringle IV tip-2 (KIV-2) tekrarına sahiptir

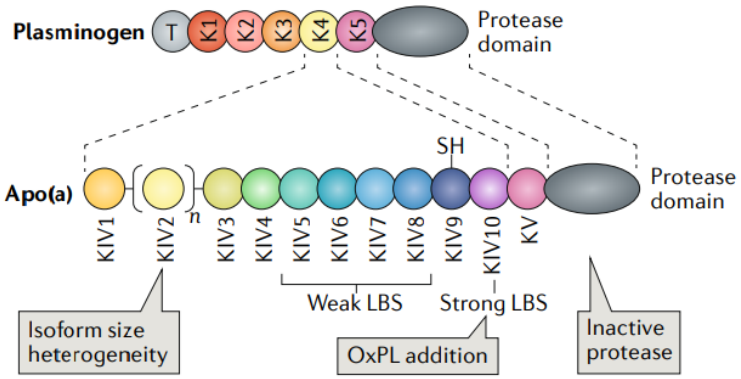
KVH için en önemli genetik risk faktörlerindendir ve çok heterojendir

Lp(a) konsantrasyonu, daha küçük Apo(a) izoformları varlığında KC sentez oranı farklılıklarına bağlı olarak yükselir

Daha küçük Lp(a) partikülleri daha aterojeniktir

Lp(a) okside Phospholipidlerin majör taşıyıcısı





Boffa et al., 2019, Nature Rev Cardiol

1987

LPA geni klonlandı ve plasminojen ile benzerliği gösterildi.

Published: 18 November 1987

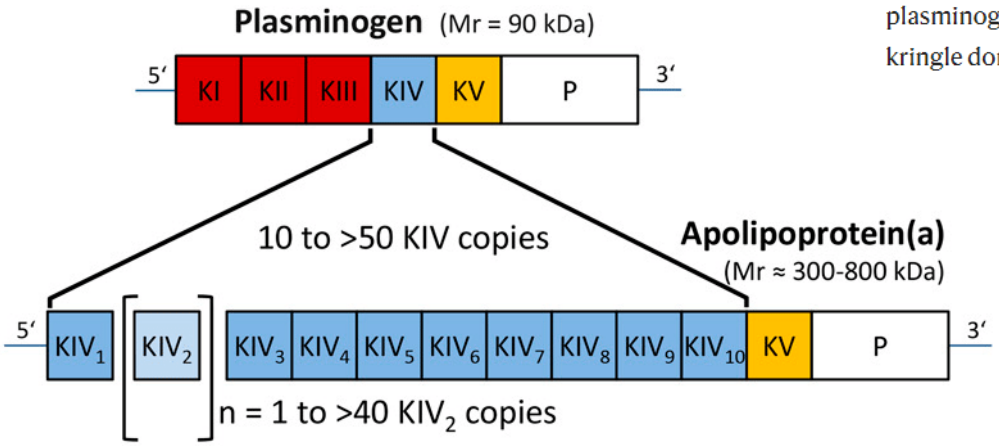
cDNA sequence of human apolipoprotein(a) is homologous to plasminogen

John W. McLean, James E. Tomlinson, Wun-Jing Kuang, Dan L. Eaton, Ellson Y. Chen, Gunther M. Fless, Angelo M. Scanu & Richard M. Lawn

Nature **330**, 132–137 (1987) | Cite this article

Abstract

Lipoprotein(a) is an LDL-like lipoprotein whose concentration in plasma is correlated with atherosclerosis. The characteristic protein component of lipoprotein(a) is apolipoprotein(a) which is disulphide-linked to apolipoprotein B-100. Sequencing of cloned human apolipoprotein(a) complementary DMA shows that it is very similar to human plasminogen. It contains a serine protease domain and two types of plasminogen-like kringle domains, one of which is present in 37 copies.

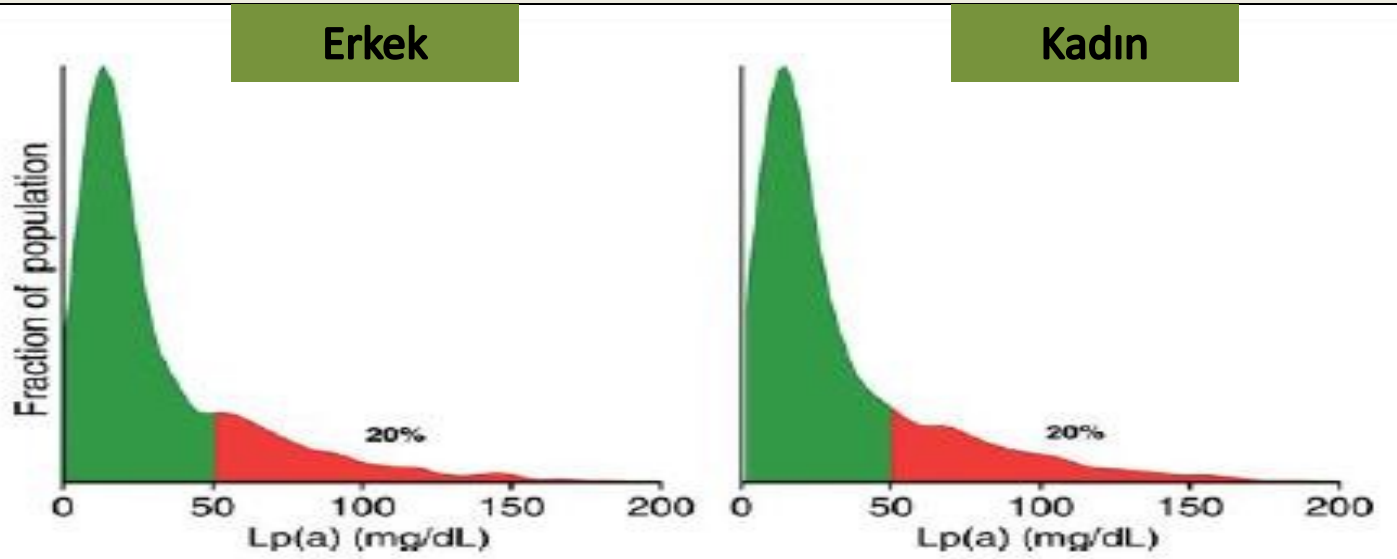


Apo(a)

Apo(a) gene (LPA) in chromosome 6q26-27

10 subtypes of KIV repeats, composed of 1 copy each of KIV1, KIV3-10 and KV, multiple (1 to > 40) copies of KIV2, as well as an inactive protease-like domain

Lp(a) Dağılım eğrisi



Copenhagen General Population Çalışmasından

- Siyahlarda ve familyal hiperkolesterolemi ve Kronik böbrek hastalarında daha yüksek Lp(a) düzeyleri mevcut

Nordestgaard P et al. EHJ 2010; 31(23), 2844-2853

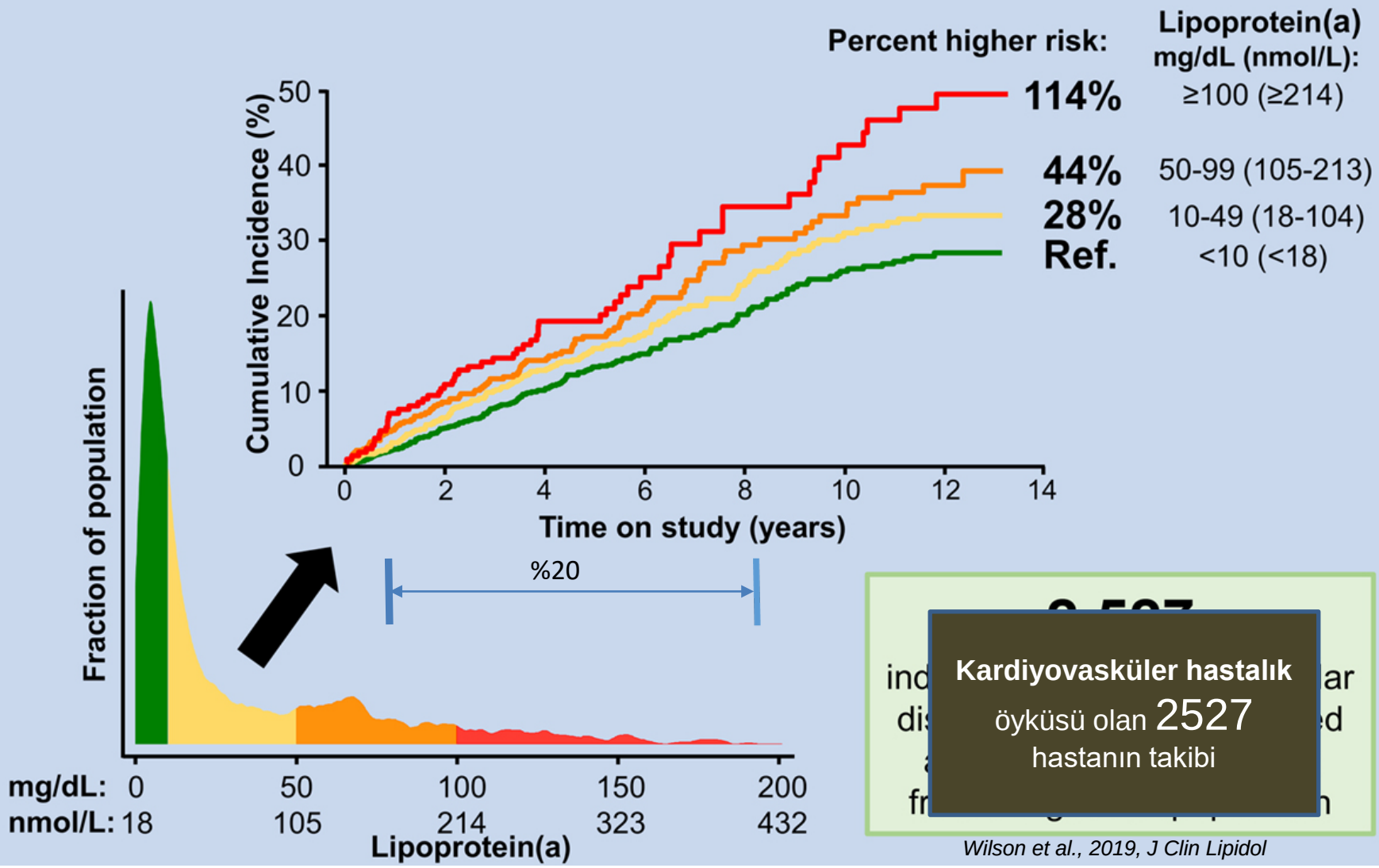
Table 3 Distribution of Lp(a) levels by ethnic group*

Ethnic group	N	Lp(a) Level by percentile (nmol/L)					
		10th	50th	75th	80th	98th	95th
Caucasian Americans	2929	1	20	73	100	154	209
African Americans	1899	16	75	130	148	199	234
Japanese American	1379	3	19	40	49	75	103

*Data from Marcovina, 2016.

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

Risk of major adverse cardiovascular event (MACE)



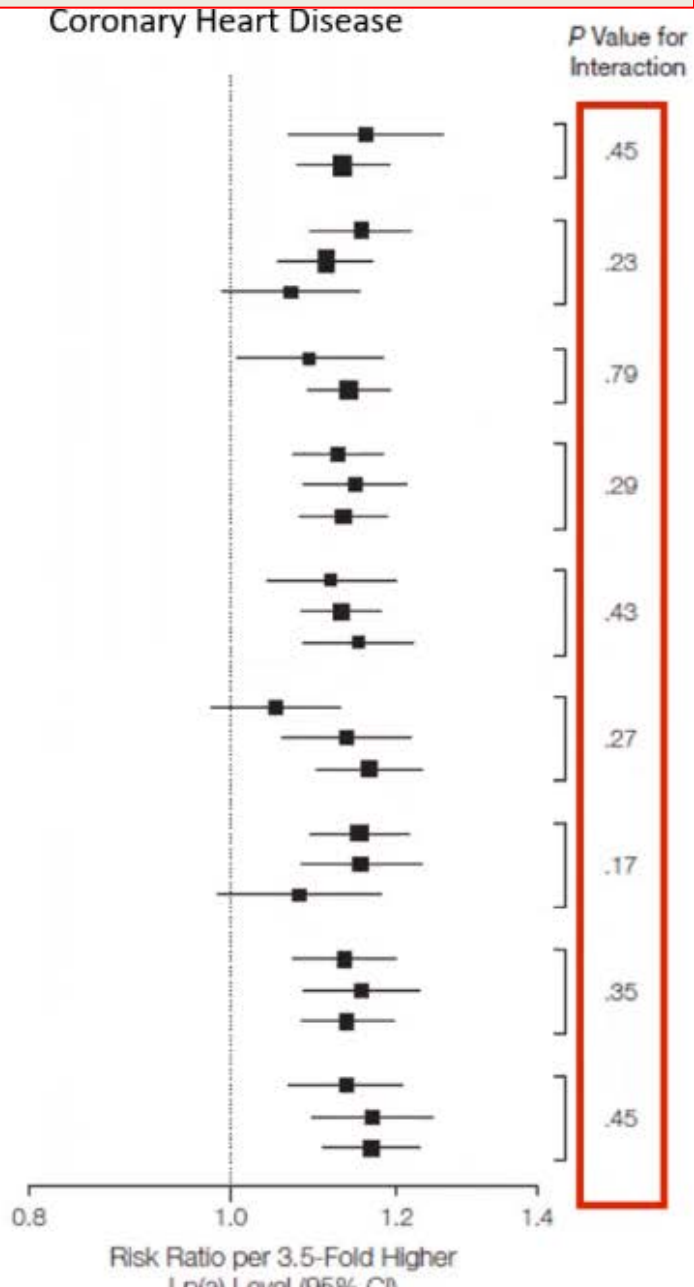
Wilson et al., 2019, J Clin Lipidol

Christian M. Madsen, Pia R. Kamstrup, Anne Langsted, Anette Varbo, Børge G. Nordestgaard Arteriosclerosis, Thrombosis, and Vascular Biology. 2020;40:255–266

Hangi hastalarda Lp(a) açısından risk daha fazla?

Risk faktörlerinden bağımsız

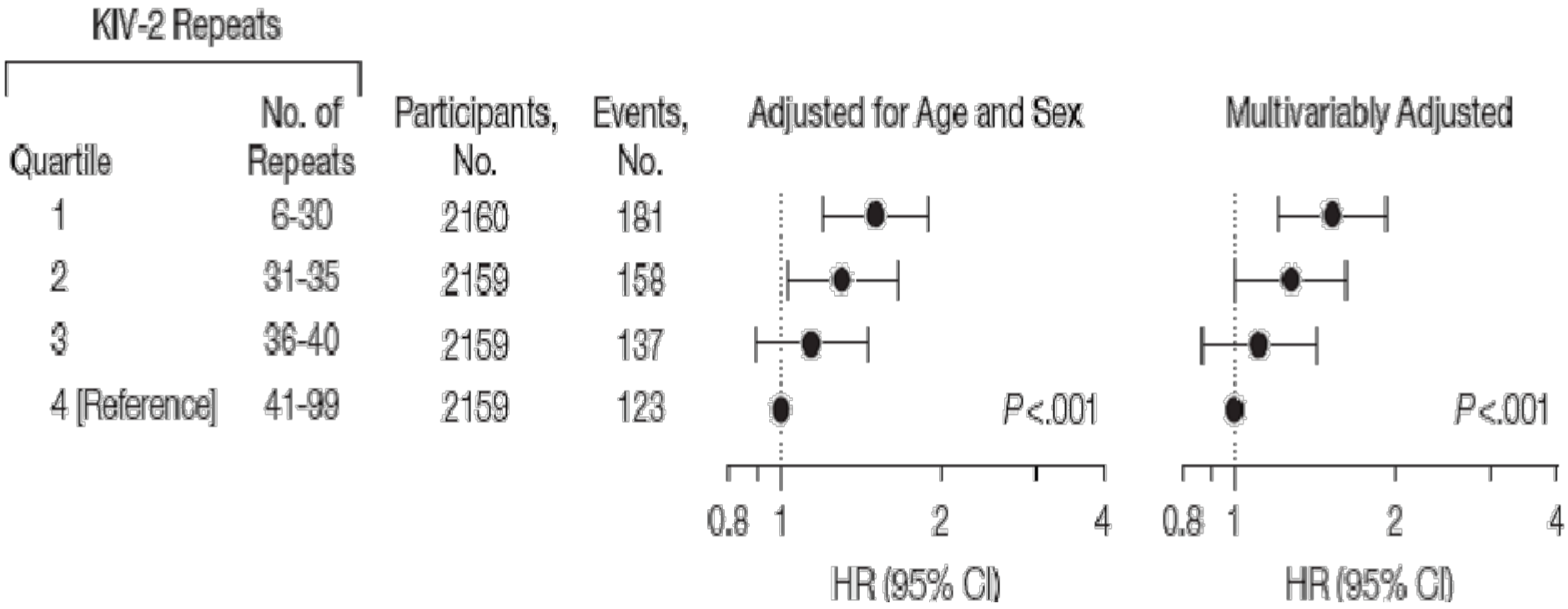
Characteristics	No. of Studies	No. of Individuals	No. of Cases	Risk Ratio (95% CI)
Sex				
Female	16	50016	2197	1.16 (1.07-1.26)
Male	27	56694	6255	1.13 (1.07-1.19)
Age at survey, y				
40-59	26	74315	5310	1.15 (1.09-1.22)
60-69	24	19359	1900	1.11 (1.05-1.17)
≥70	15	7939	1010	1.07 (0.99-1.15)
History of diabetes				
Yes	27	6372	941	1.09 (1.01-1.18)
No	28	100212	7495	1.14 (1.09-1.19)
Systolic blood pressure, mm Hg				
<122	30	38682	2212	1.12 (1.07-1.18)
122-135	30	39277	2848	1.15 (1.08-1.21)
>135	30	29653	3413	1.13 (1.08-1.19)
Body mass index[a]				
<24	30	36098	2338	1.12 (1.04-1.20)
24-27	30	35814	2883	1.13 (1.08-1.18)
>27	30	35700	3252	1.15 (1.08-1.22)
Non–HDL-C, mg/dL				
<148	27	32834	1307	1.05 (0.98-1.13)
148-187	27	32452	1983	1.14 (1.06-1.22)
>187	27	32438	2816	1.16 (1.10-1.23)
HDL-C, mg/dL				
<43	26	33944	2816	1.15 (1.09-1.21)
43-55	26	32335	1880	1.15 (1.08-1.23)
>55	26	31321	1389	1.08 (0.99-1.18)
Triglycerides, mg/dL				
<97	29	35792	1988	1.13 (1.07-1.20)
97-150	29	35220	2678	1.15 (1.08-1.23)
>150	29	35134	3365	1.14 (1.08-1.19)
Corrected total cholesterol, mg/dL[b]				
<198	30	35885	2053	1.13 (1.07-1.21)
198-235	30	35870	2757	1.17 (1.09-1.25)
>235	30	35857	3663	1.17 (1.11-1.23)



Lipoprotein(a) Concentration and the Risk of Coronary Heart Disease, Stroke, and Nonvascular Mortality. The Emerging Risk Factors Collaboration. JAMA. 2009;302(4):412-423

Lp(a)'nın Farklı izoformlarının MI riskinde önemi

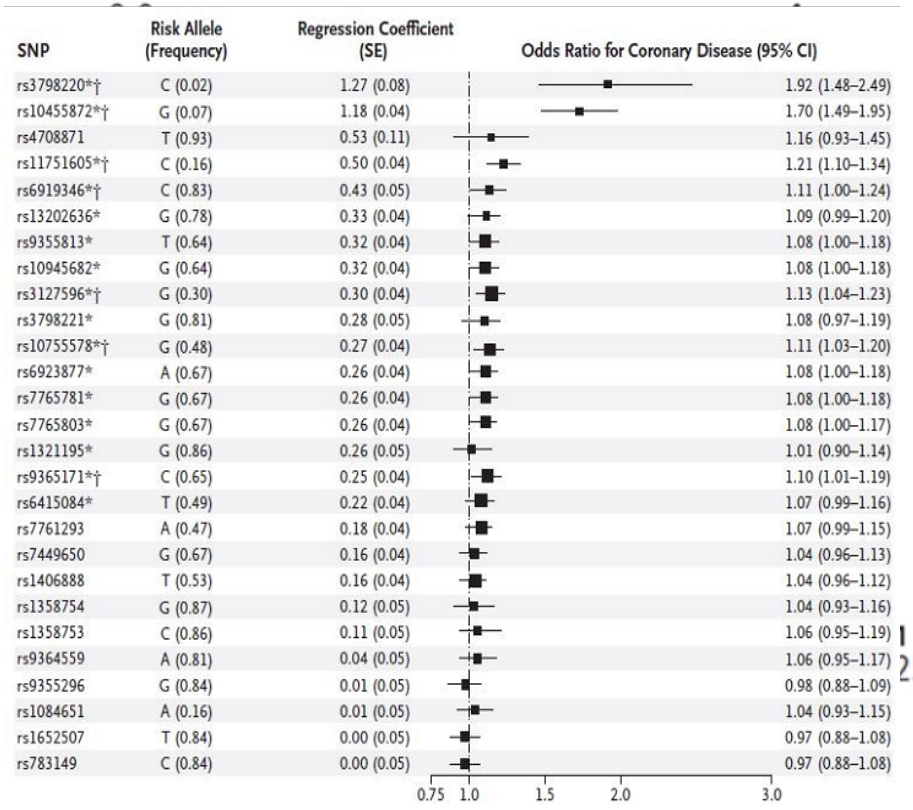
Apo(a) KIV-2 Tekrarlarına göre Quartiller ve MI riski, Copenhagen Heart Study



Daha küçük Apo(a) izoformlarının artmış riskle korelasyonu

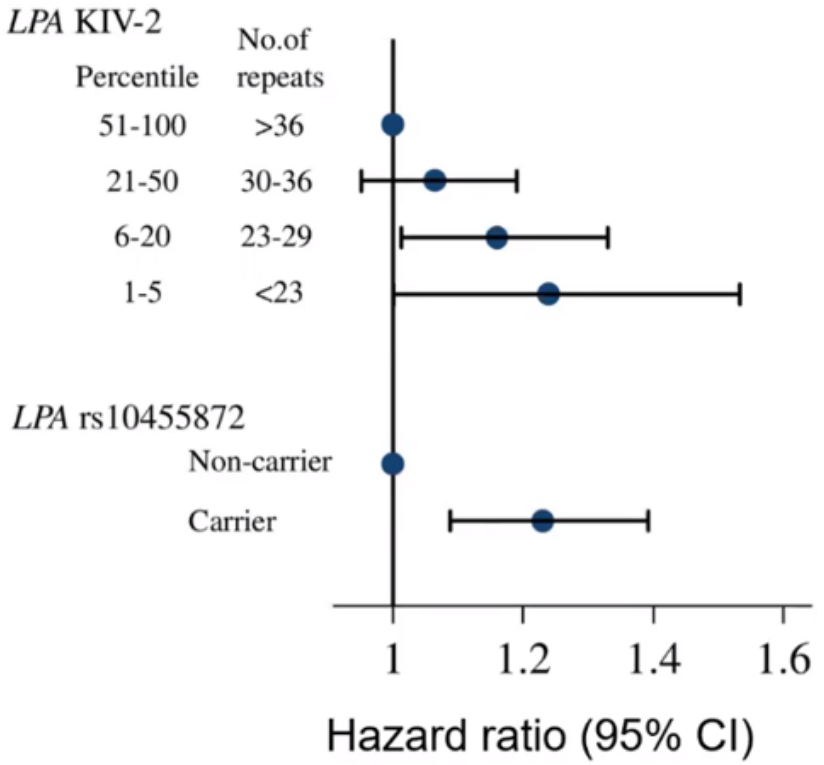
Kamstrup et al., JAMA 2009;301(22);2331-9

Lp(a) ve KVH ile ilişkili genetik varyant



SNP	Risk Allele (Frequency)	Regression Coefficient (SE)	Odds Ratio for Coronary Disease (95% CI)
rs3798220*†	C (0.02)	1.27 (0.08)	1.92 (1.48–2.49)
rs10455872*†	G (0.07)	1.18 (0.04)	1.70 (1.49–1.95)
rs4708871	T (0.93)	0.53 (0.11)	1.16 (0.93–1.45)
rs11751605*†	C (0.16)	0.50 (0.04)	1.21 (1.10–1.34)
rs6919346*†	C (0.83)	0.43 (0.05)	1.11 (1.00–1.24)
rs13202636*	G (0.78)	0.33 (0.04)	1.09 (0.99–1.20)
rs9355813*	T (0.64)	0.32 (0.04)	1.08 (1.00–1.18)
rs10945682*	G (0.64)	0.32 (0.04)	1.08 (1.00–1.18)
rs3127596*†	G (0.30)	0.30 (0.04)	1.13 (1.04–1.23)
rs3798221*	G (0.81)	0.28 (0.05)	1.08 (0.97–1.19)
rs10755578*†	G (0.48)	0.27 (0.04)	1.11 (1.03–1.20)
rs6923877*	A (0.67)	0.26 (0.04)	1.08 (1.00–1.18)
rs7765781*	G (0.67)	0.26 (0.04)	1.08 (1.00–1.18)
rs7765803*	G (0.67)	0.26 (0.04)	1.08 (1.00–1.17)
rs1321195*	G (0.86)	0.26 (0.05)	1.01 (0.90–1.14)
rs9365171*†	C (0.65)	0.25 (0.04)	1.10 (1.01–1.19)
rs6415084*	T (0.49)	0.22 (0.04)	1.07 (0.99–1.16)
rs7761293	A (0.47)	0.18 (0.04)	1.07 (0.99–1.15)
rs7449650	G (0.67)	0.16 (0.04)	1.04 (0.96–1.13)
rs1406888	T (0.53)	0.16 (0.04)	1.04 (0.96–1.12)
rs1358754	G (0.87)	0.12 (0.05)	1.04 (0.93–1.16)
rs1358753	C (0.86)	0.11 (0.05)	1.06 (0.95–1.19)
rs9364559	A (0.81)	0.04 (0.05)	1.06 (0.95–1.17)
rs9355296	G (0.84)	0.01 (0.05)	0.98 (0.88–1.09)
rs1084651	A (0.16)	0.01 (0.05)	1.04 (0.93–1.15)
rs1652507	T (0.84)	0.00 (0.05)	0.97 (0.88–1.08)
rs783149	C (0.84)	0.00 (0.05)	0.97 (0.88–1.08)

0.75 1.0 1.5 2.0 3.0



PROCARDIS, Clarke et al., NEJM 2009;361:2518-28

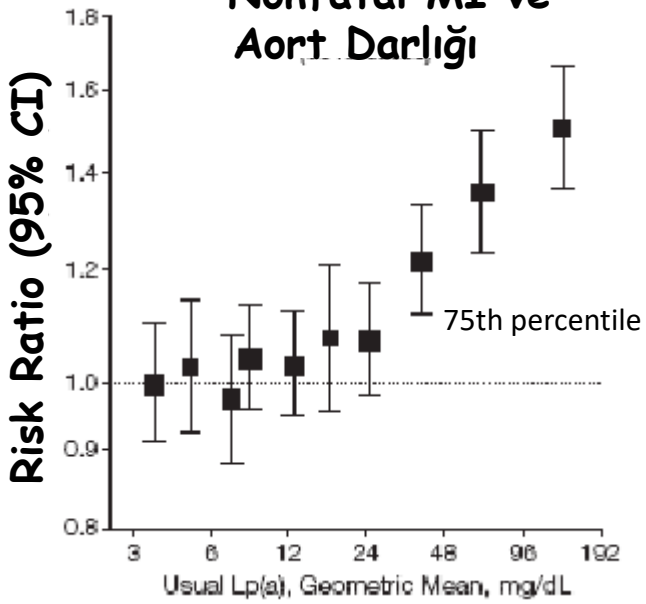
Nedenselliğin genetik kanıtı

LPA geni KVH ile ilişkili

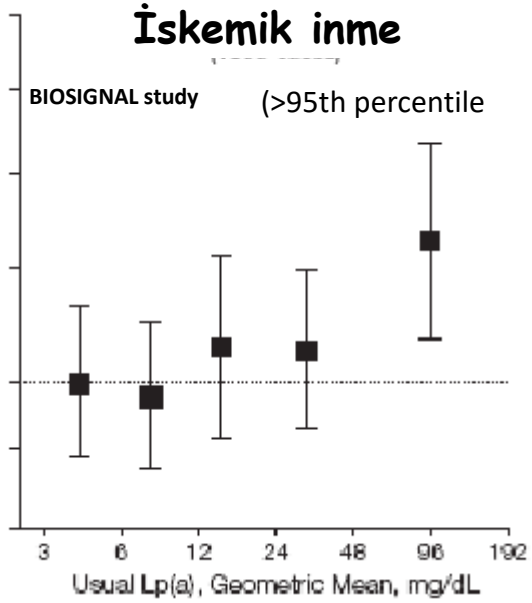
2LPA SNP; yüksek Lp(a)KVH ile ilişkili

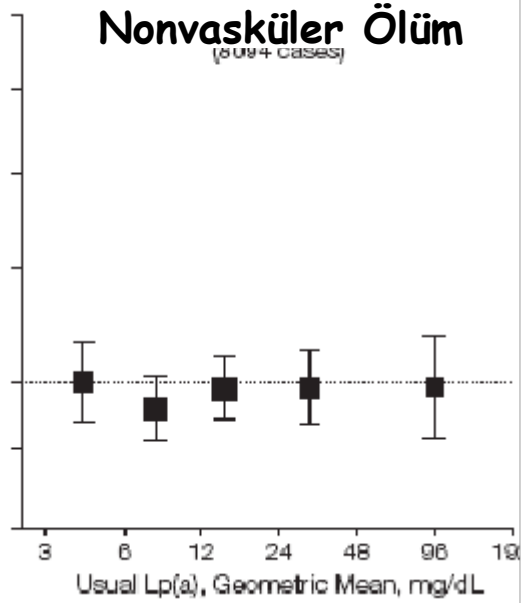
Primer korumada Miyokard İnfarktüsü Riski ile Lp(a)'nın Epidemiyolojik İlişkisi

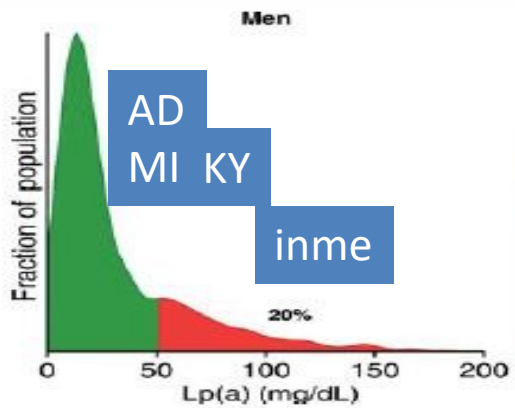
gençlerde

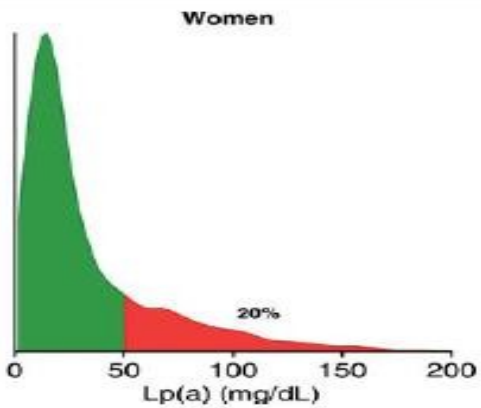


~50 mg/dl





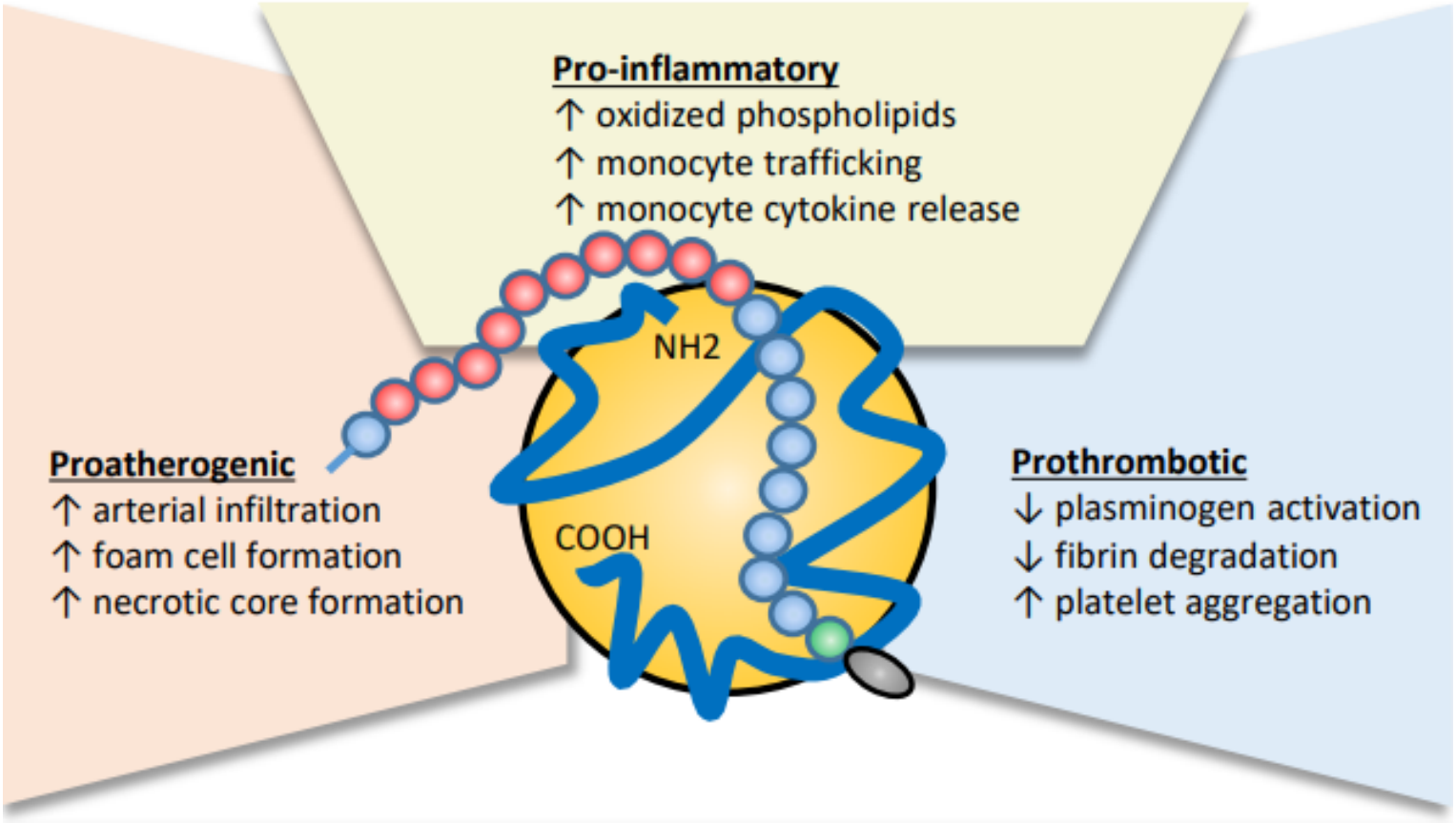




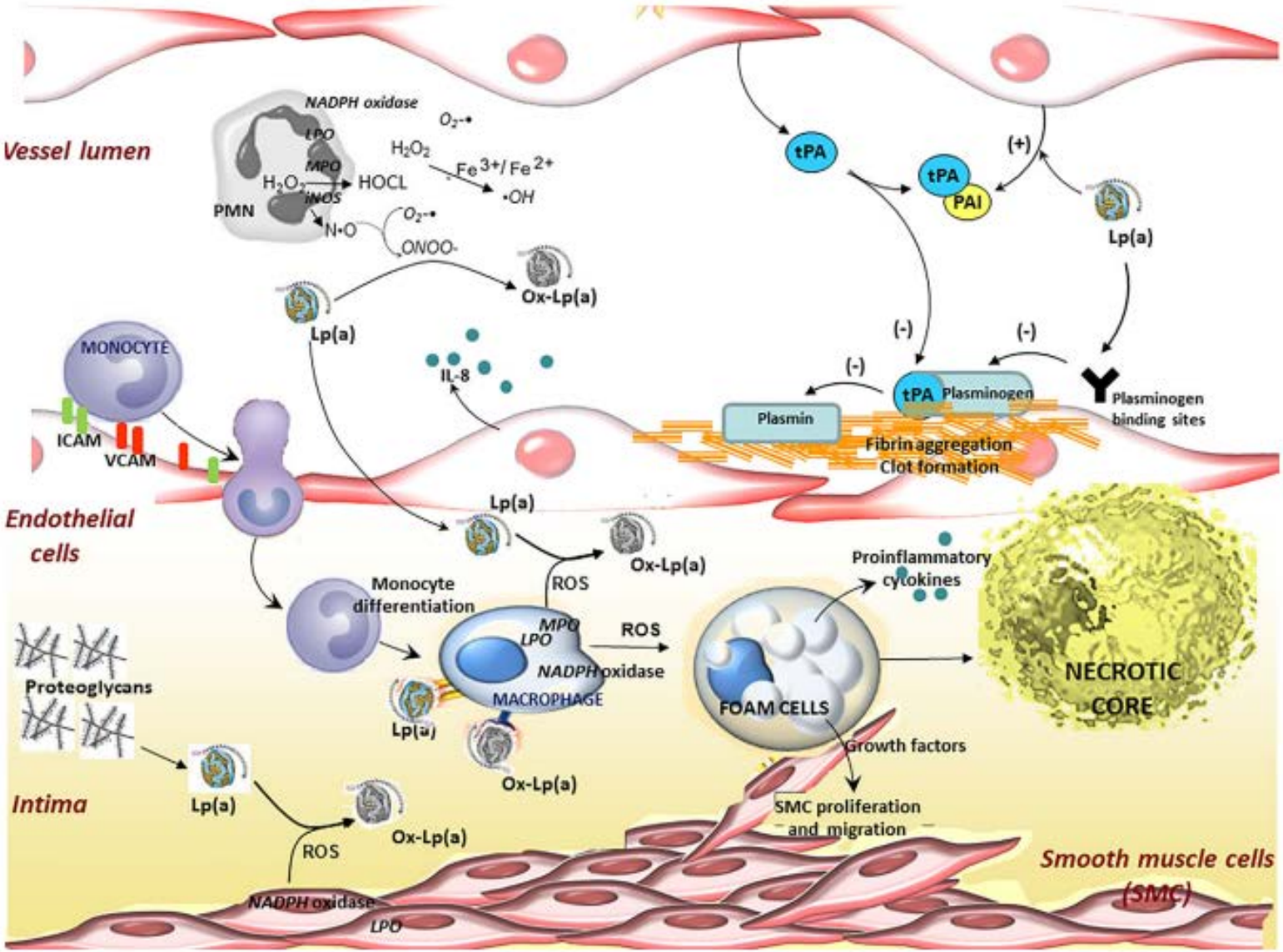
The Emerging Risk Factors Collaboration *JAMA*. 2009;302(4):412-23

Lp(a) ve ASKVH-AD ilişkisi

Lp(a) Patofizyoloji

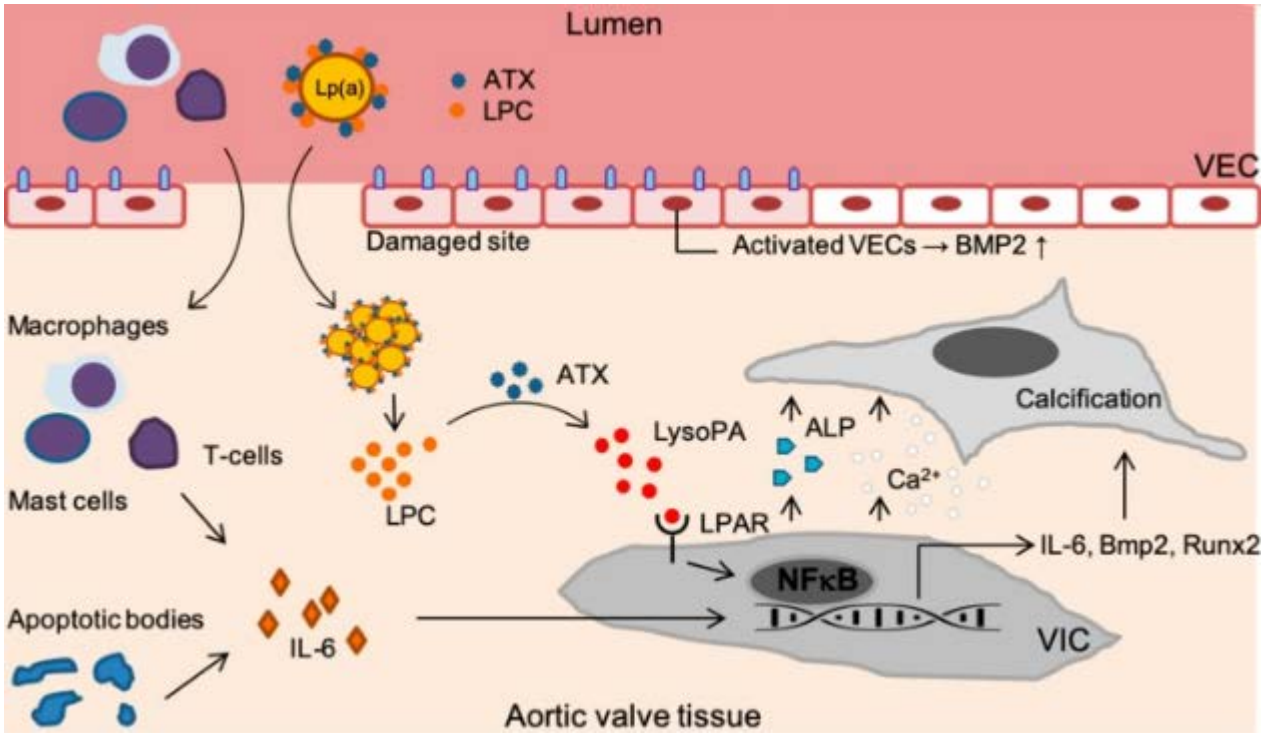


Patofizyolojik mekanizmalar



Ferretti G, et al. J Cell Physiol. 2018;233:2966-2981

Aort Darlığı ve Lp(a)



Yüksek Lp(a) *hem damar hem kapak hücrelerinde* inflamatuar ve kalsifikasyon genlerinin ekspresyonunu arttırır

Biomolecules, 2019 Dec; 9(12): 760.

Lp(a) kimde ölçelim?

2019 HEART-UK	2020 EAS & EFLM
Premature ASCVD (men <55 years, women <60 years)	Premature ASCVD (men <55 years, women <60 years)
Family history of premature ASCVD and/or elevated Lp(a)	Family history of premature ASCVD and/or elevated Lp(a)
Familial hypercholesterolemia	Familial hypercholesterolemia
Recurrent ASCVD even under optimal statin treatment	Recurrent ASCVD even under optimal statin treatment
Aortic valve stenosis	Aortic valve stenosis
	Individuals who have first-degree relatives with Lp(a)> 200 nmol/l
	For those with a borderline but <15% 10-year cardiovascular event risk

European Federation of Clinical Chemistry and Laboratory Medicine (**EFLM**)

Lp(a)

EAS ESC European Society of Cardiology

Lp(a) ölçümü, 180 mg/dL (430 mmol/L) seviyesinin üstünde yüksek kalıtsal Lp(a) seviyelerine sahip, heterozigot ailevi hiperkolesterolemi riskine eşdeğer, hayat boyu sürecek bir ASKVH'si olanları belirlemek için her yetişkin kişinin yaşamında en az bir kez göz önünde bulundurulmalıdır.	IIa	C
Lp(a), aile öyküsünde prematüre KVH olan seçilmiş hastalarda ve orta yüksek risk arasında sınırda olan kişilerde yeniden sınıflandırma için düşünülmelidir.	IIa	C

Lp(a) düzeylerinin %90'ı kalıtımsal
Lp(a) >180 mg/dL =HeFH ve 2 kat daha sık

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Statin kullanan ve LDL-K düşük hastalar

Li et al. BMC Cardiovasc Disord (2021) 21:41
https://doi.org/10.1186/s12872-021-01861-6

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

The correlation between lipoprotein(a) and coronary atherosclerotic lesion is stronger than LDL-C, when LDL-C is less than 104 mg/dL

Chuang Li[1,2], Qiwen Chen[3], Mei Zhang[2*], Yin Liu[4*], Yushun Chu[2], Fanpeng Meng[2], Jianyu Wang[2], Jie Tang[2], Jian Luo[2], Xiulong Niu[2] and Maoti Wei[1]

Even the Guideline recommended LDL-C concentration was strict for patients at very-high CVD risk, < 55 mg/dl, in both primary and secondary prevention [16]. The data in the secondary prevention of vascular disease showed that the recurrent 10-year risk of vascular events is still over 30% in 9% patients with vascular disease, who's risk factors were all at guideline-recommended targets [19]. Lp(a) may contribute to the residual risk. In a recently published epidemiological study, Hu etc. fund the Lp(a) co-contributed with LDL-C to the incidence of acute myocardial infarction in Chinese people [20]. In this study, we found the same trend, especially in patients with LDL-C < 100 mg/dL. In the subgroup analysis of Low-LDL-C Group in this study, near 43% patients were taking statin, the pathogenicity of Lp(a) may partly due to the effect of statins on Lp(a) increasing.

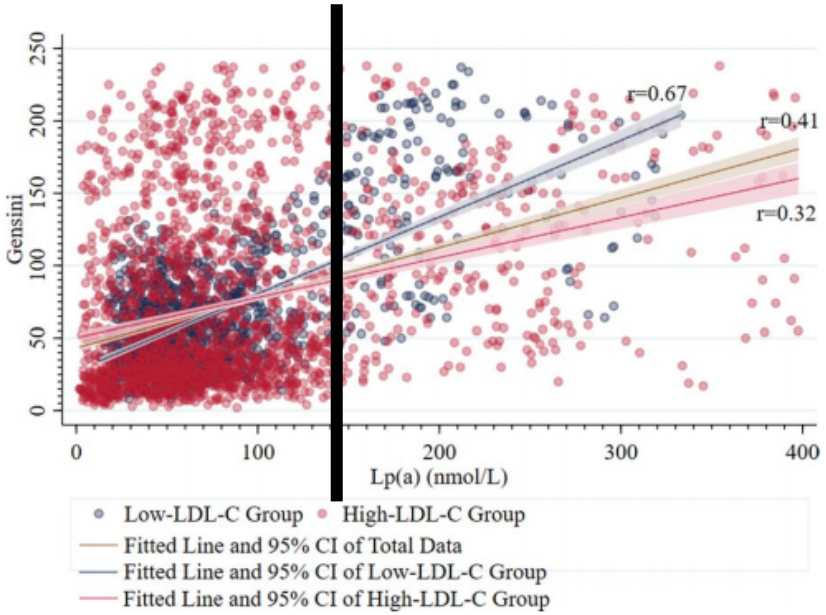


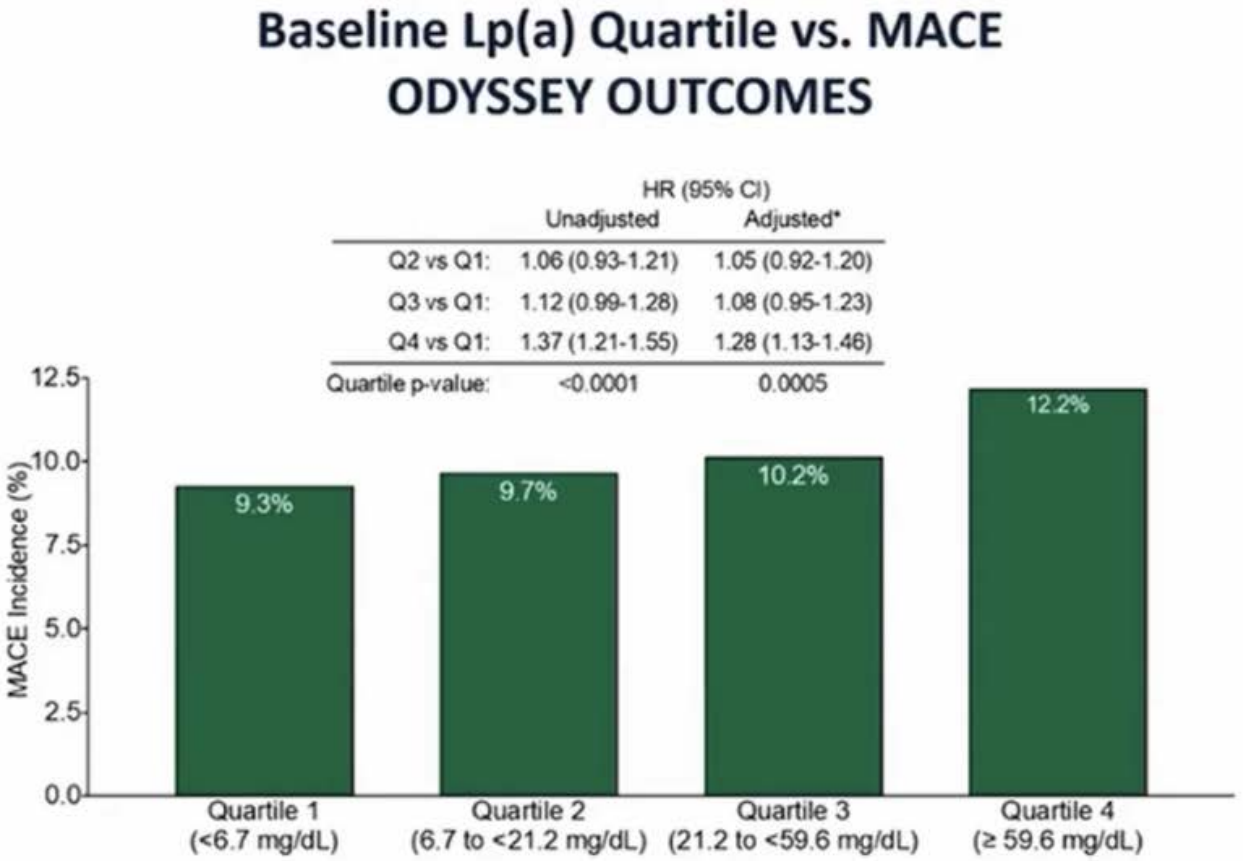
Fig. 3 Scatter Plot of Lp(a)-Gensini Correlation in Low-LDL-C Group, High-LDL-C Group and Total Patients. The LDL-C concentration was converted from mg/dL to mmol/L to facilitate the determination of the LDL intervals, with LDL-C (mmol/L) = 0.0259 * LDL-C (mg/dL). r-LDL-C-Gensini: correlation coefficient r in the Spearman correlation analysis of LDL-C and Gensini; r-Lp(a)-Gensini: correlation coefficient r in the Spearman correlation analysis of Lp(a) and Gensini

Li et al., 2021,BMC Cardiovasc Disord.

Lp(a)-corrected LDLC should be assessed at least once in patients with suspected or known high Lp(a), or if the patient shows a poor response to LDL-lowering therapy.

Nordestgaard et al., 2020, Atherosclerosis

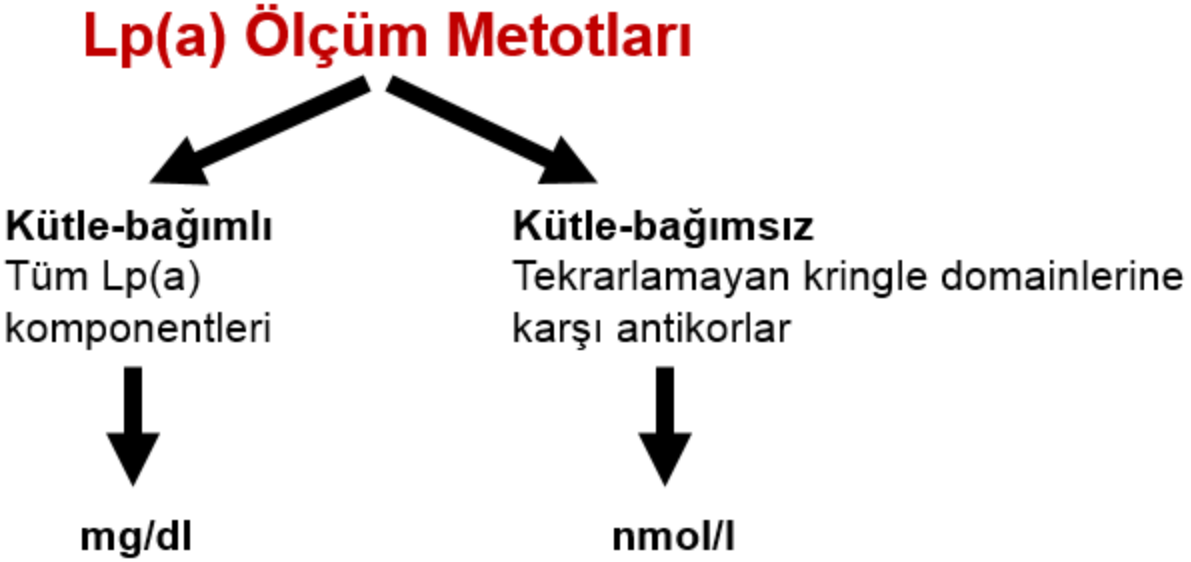
Lp(a) is a risk factor even at very low LDL-C concentrations



Nasıl ölçelim?

Farklı ölçüm yöntemleri bulunmaktadır.

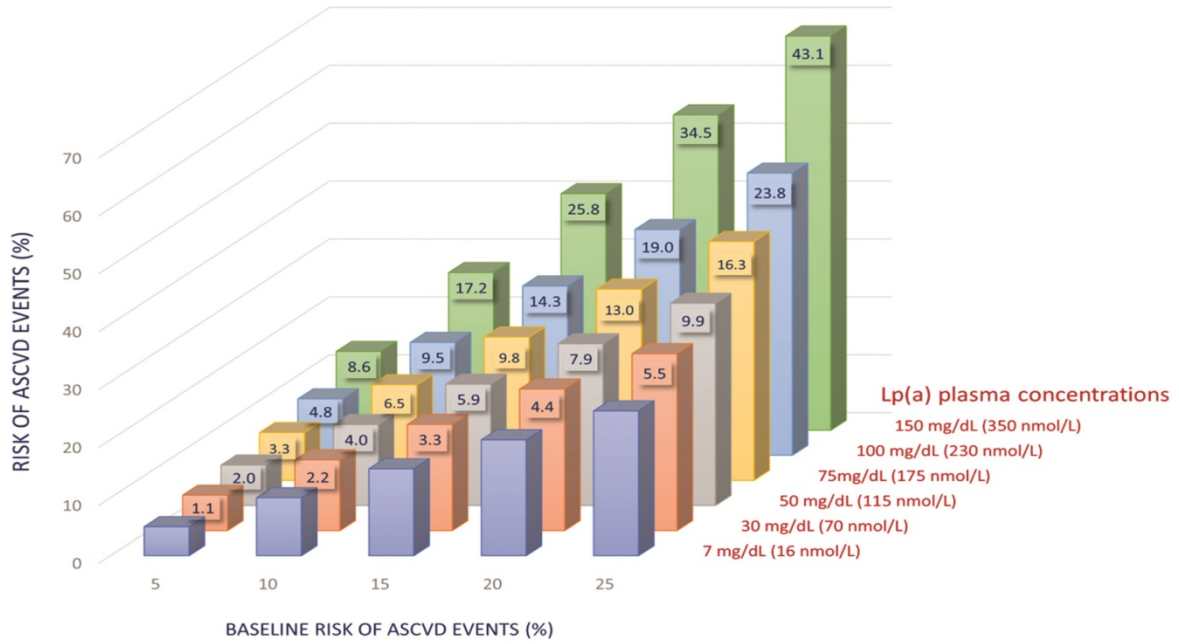
Lp(a) molar konsantrasyon **(ELISA)**
Lp(a) kitle konsantrasyonu
Lp(a) kolesterol düzeyi (nephelometry)



Tedavi

Yüksek Lp(a)nın majör CV olay riski üzerine etkisi

A



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 inter-vention, 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 inter-vention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle inter-vention, 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 inter-vention, 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 inter-vention, 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 inter-vention, 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)

Eur Heart J. Volume 43. Issue 39. 14 October 2022. Pages 3925–3946

İlk yaklaşım

Yoğun risk faktörü yönetimi

- KB
- Glu
- Yaşam tarzı değişiklikleri

Tedavi

III. Treatment		
1. In adults aged 40-75 y with a 10-y ASCVD risk of 7.5%–19.9%, the finding of an Lp(a) ≥50 mg/dL or ≥100 nmol/L **is reasonable** to be used as a risk-enhancing factor to favor initiation of a moderate- or high-intensity statin in those with on-treatment LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL).[26,36]	IIa	B-NR
2. In high-risk* or very-high-risk** patients, with Lp(a) ≥50 mg/dL or ≥100 nmol/L, it **is reasonable** to consider more intensive LDL-C lowering to achieve greater ASCVD risk reduction.[21,50,53]	IIa	A
3. In very-high-risk** patients, taking a maximally tolerated statin with Lp(a) ≥50 mg/dL or ≥100 nmol/L, the addition of ezetimibe **is reasonable** in those with on-treatment LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL).[117]	IIa	B-R
4. In high-risk* patients taking a maximally tolerated statin, with Lp(a) ≥50 mg/dL or ≥100 nmol/L, the addition of ezetimibe **may be reasonable** in those with on-treatment LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL).[117]	IIb	B-R
5. In very-high-risk** patients taking a maximally tolerated statin and ezetimibe, with an LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL) and an Lp(a) of ≥50 mg/dL or ≥100 nmol/L, the addition of a PCSK9 inhibitor **is reasonable**.[74,99,106,116]	IIa	B-R
6. Niacin, which lowers Lp(a) concentration, **is not recommended** to reduce ASCVD risk in patients receiving moderate- to high-intensity statins +/− ezetimibe and an on-treatment LDL-C <80 mg/dL.[54,72]	III (harm)	A
7.	III (harm)	B-R

HRT
- Lp(a) %10-15 azalma
- YE: meme kanseri, tromboz, inme

Wilson et al., 2019, J Clin Lipidol.

Çok yüksek riskli hstlarda Lp(a) ≥100 nmol/L ise daha yoğun LDL-K düşürücü tedavi önerilir
Max statine ek olarak Ezetimibe-PCSK9 inh

Statin therapy increases lipoprotein(a) levels

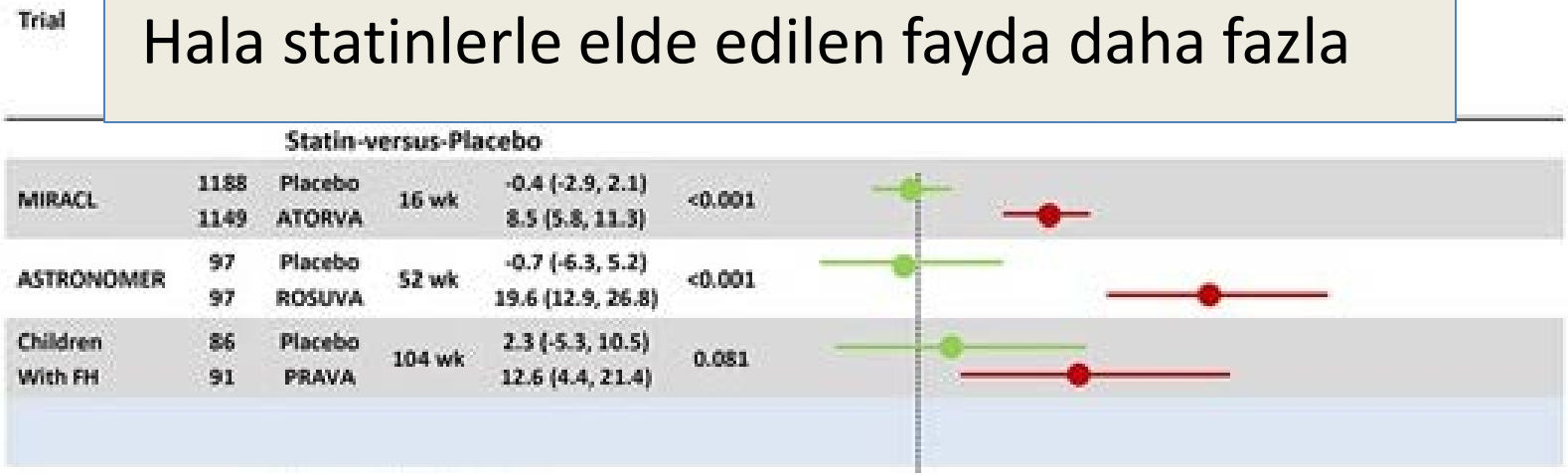
Sotirios Tsimikas ✉, Philip L S M Gordts ✉, Chelsea Nora, Calvin Yeang, Joseph L Witztum

European Heart Journal, Volume 41, Issue 24, 21 June 2020, Pages 2275–2284, https://doi.org/10.1093/eurheartj/ehz310

Published: 20 May 2019 **Article history** ▾

($P < 0.0001$). The mean percent change from baseline ranged from 11.6% to 20.4% in the pravastatin group and 18.7% to 24.2% in the atorvastatin group. Incubation of HepG2 hepatocytes with atorvastatin showed an increase in expression of *LPA* mRNA and apolipoprotein(a) protein.

Hala statinlerle elde edilen fayda daha fazla



LPA mRNA hepatik ekspresyonunu artıyor

Tsimikas et al., 2020, Eur Heart J.

Tedaviye erken başlamak önemli

https://doi.org/10.1093/eurheartj/ehac361

Stronger LDL-C reduction needed to mitigate the increased CV risk caused by high Lp(a), depending on '*starting age' of LDL-C lowering*

Lp(a) nmol/L	Δ Lp(a) compared to median	Lp(a) percentile	HR for MCVE due to increased Lp(a)	Intensification of LDL-C reduction (nmol/L) needed to mitigate the increased risk caused by Lp(a)			
				Begin age 30y	Begin age 40y	Begin age 50y	Begin age 60 y
320	300	99	2.56	1.2 mmol/L	1.4 mmol/L	1.7 mmol/L	2.3 mmol/L
270	250	97.5	2.19	1.0 mmol/L	1.2 mmol/L	1.5 mmol/L	1.9 mmol/L
220	200	93.5	1.87	0.8 mmol/L	0.9 mmol/L	1.2 mmol/L	1.5 mmol/L
170	150	90	1.60	0.6 mmol/L	0.7 mmol/L	0.9 mmol/L	1.1 mmol/L
120	100	82.5	1.37	0.4 mmol/L	0.5 mmol/L	0.6 mmol/L	0.8 mmol/L
70	50	75	1.17	0.2 mmol/L	0.2 mmol/L	0.3 mmol/L	0.4 mmol/L
20	ref.	50	ref.	ref.	ref.	ref.	ref.

Starting prevention early is KEY

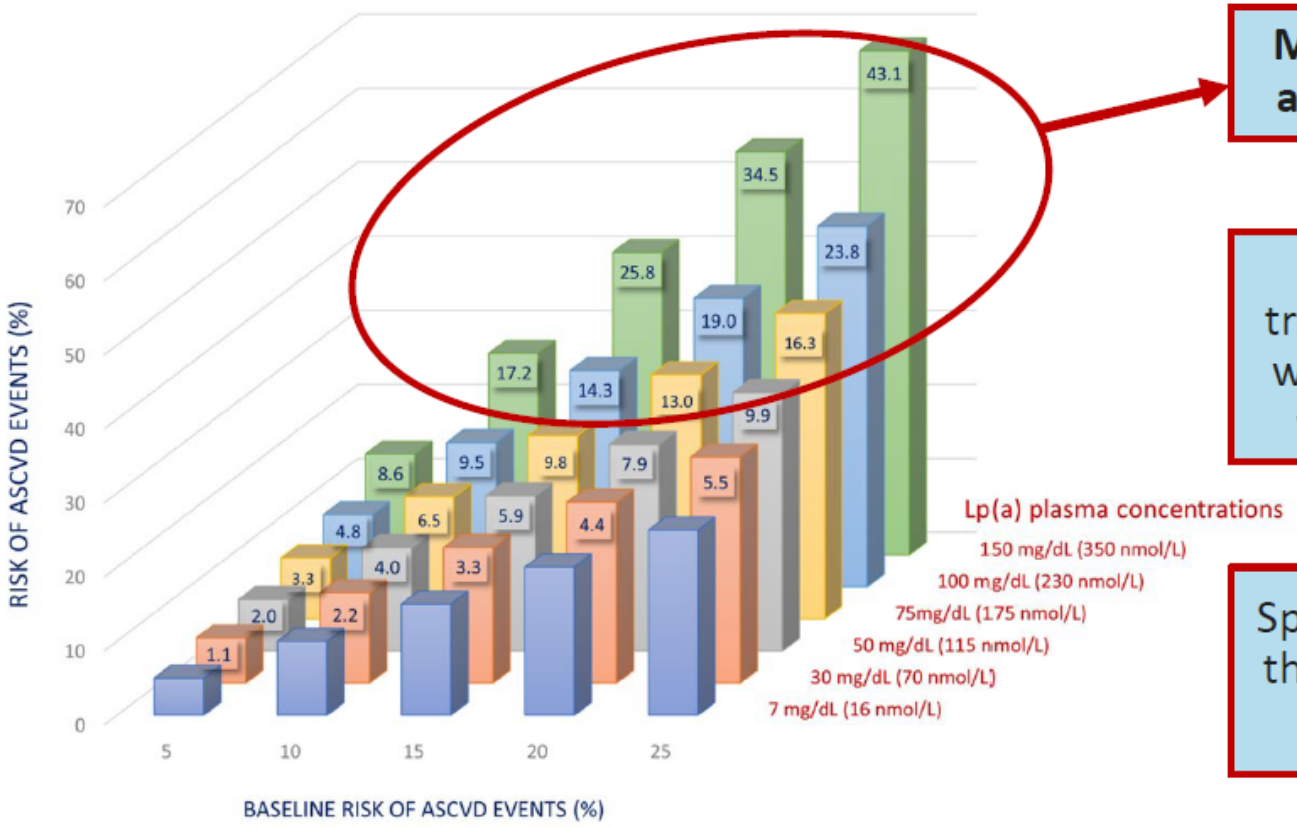
Data provided by Ference, Catapano et al. using data from the UK Biobank

EAS

Spesifik Lp(a) düşürücü tedavi gerekli

https://doi.org/10.1093/eurheartj/ehac361

Incremental increase in absolute risk caused by increasing Lp(a) categories



Main part of the risk attributable to Lp(a)

Management of traditional risk factors will be important but will not be enough

Specific Lp(a)-lowering therapies are urgently required

Baseline estimated lifetime risk calculated using the Joint British Societies (JBS3) Lifetime Risk Estimating algorithm

EAS

Data provided by Ference, Catapano et al. using data from the UK Biobank

Tedavi

III. Treatment		
1. In adults aged 40-75 y with a 10-y ASCVD risk of 7.5%–19.9%, the finding of an Lp(a) ≥50 mg/dL or ≥100 nmol/L **is reasonable** to be used as a risk-enhancing factor to favor initiation of a moderate- or high-intensity statin in those with on-treatment LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL).[26,36]	IIa	B-NR
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7.	III (harm)	B-R

HRT

- Lp(a) %10-15 azalma
- YE: meme kanseri, tromboz, inme

Wilson et al., 2019, J Clin Lipidol.

Niacin Lp(a) %20 azaltır
AIM - HIGH

Niasin ile gözlenen iskemik inmeler nedeniyle çalışma erken sonlandırıldı

Boden WE. *N Engl J Med.*

ASA verelim mi?

Randomized Controlled Trial > Atherosclerosis. 2009 Apr;203(2):371-6.
doi: 10.1016/j.atherosclerosis.2008.07.019. Epub 2008 Jul 26.

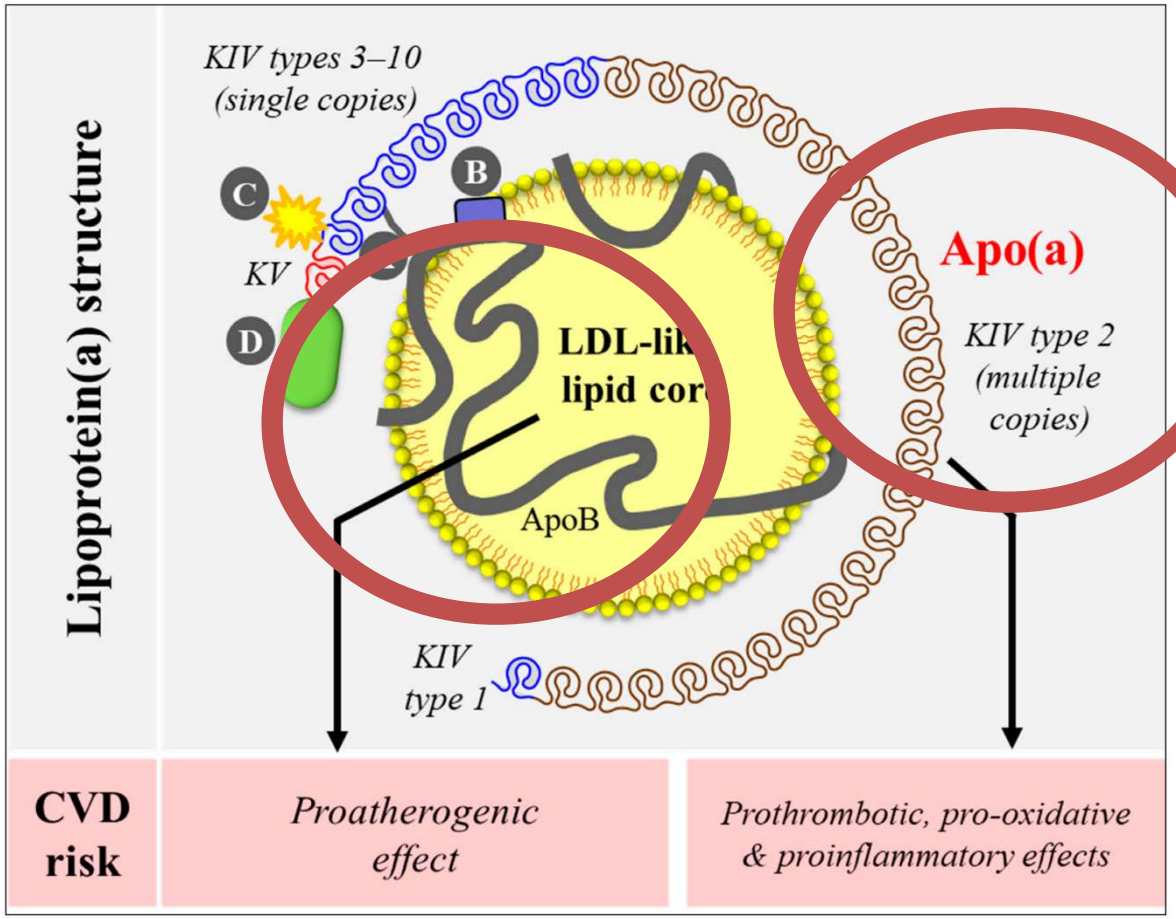
Polymorphism in the apolipoprotein(a) gene, plasma lipoprotein(a), cardiovascular disease, and low-dose aspirin therapy

Daniel I Chasman [1], Dov Shiffman, Robert Y L Zee, Judy Z Louie, May M Luke, Charles M Rowland, Joseph J Catanese, Julie E Buring, James J Devlin, Paul M Ridker

Klinik çalışmalarda yüksek Lp(a) düzeyleri VTE ile ilişkili bulunmadı

J. Clin. Med. 2019, 8, 2073

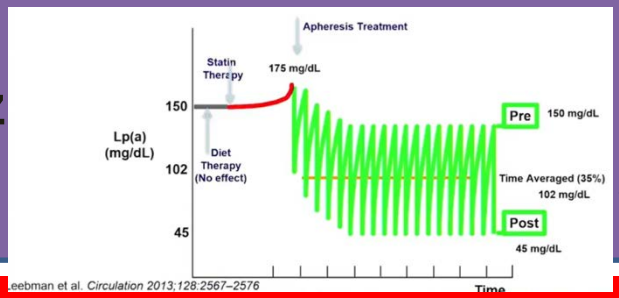
Lp(a) Spesifik Tedavi



Enkhmaa et al., 2020, Nutrients

Tedavi - Lipoprotein Aferezi (LA)

Aferez



%70 (ortalama %35). Kardiyovasüler risk azalması ile ilişkili

Leebmann J et al. Circulation 2013;128:2567-2576

The Heart UK Lp aferez rehberi:

İlerleyici KAH, Lp(a) >150 nmol/L(60 mg/dL) ve LDL-K >125 mg/dL (max ted rağmen)

Almanya rehberi:

İlerleyici KAH ve Lp(a) >150 nmol/L(60 mg/dL)

Simultane kontrol grup Ø gerçek fayda belli değil

Parameter	Lp(a) nmol/L	% in Comparison with 1. LA	LDL-C mmol/L	% in Comparison with 1. LA
1st LA session	243.5	baseline	2.7	baseline
pre session	177	–27.3	2.3	–12.8
post session	43.5	–82.1	0.7	–75
IMV	121.6	–50	1.9	–29.5

Tedavi - Lipoprotein Aferezi (LA)

- RKÇ Ø Etik kurul zor- LDL-K düşüşü dışı fayda?
- LA etkinliğini öncesi-sonrası karşılaştırma tek seçenek

İki çalışmada KV olaylar %90 azalmış ve NNT sadece: 3

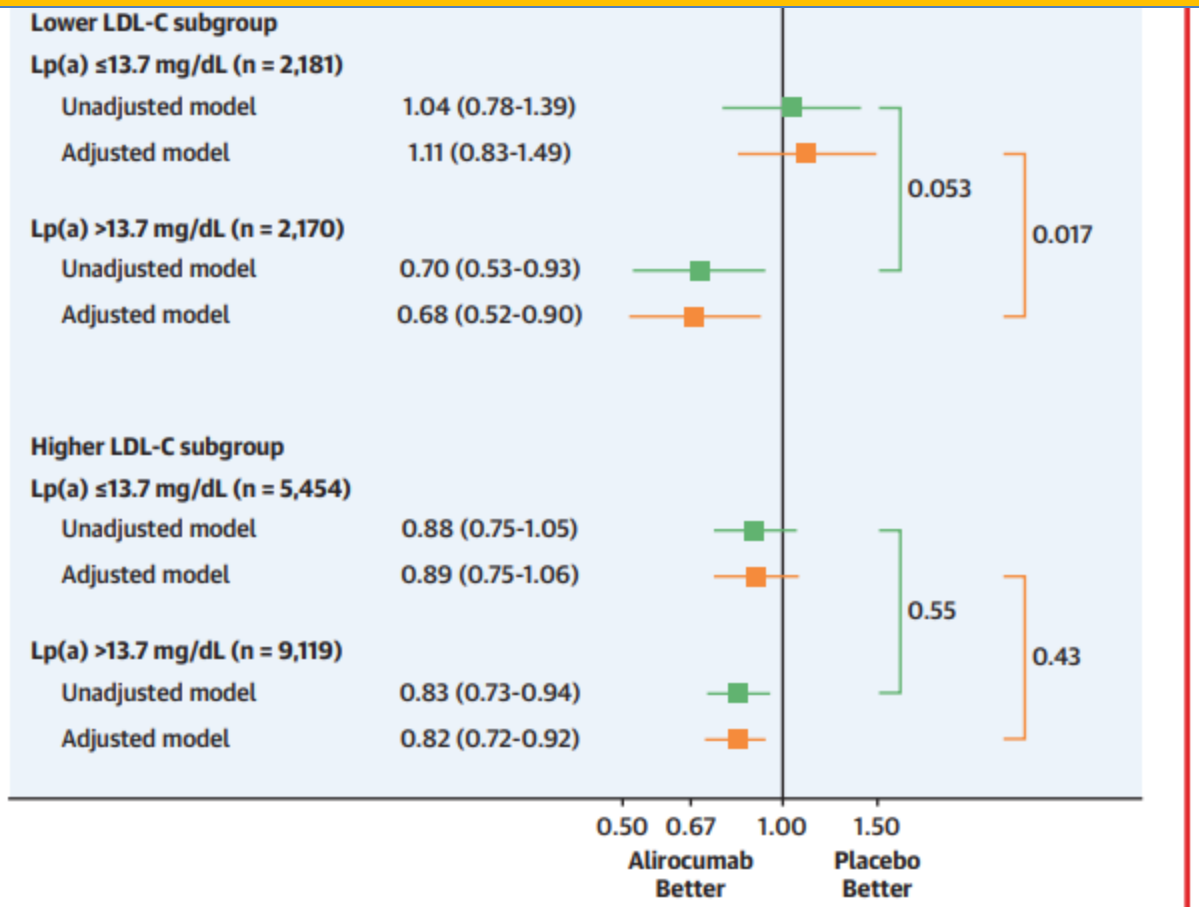
i. *Jaeger çalışması*

ii. *Pro (a) Life çalışması*

Lipoprotein(a) and Benefit of PCSK9 Inhibition in Patients With Nominally Controlled LDL Cholesterol

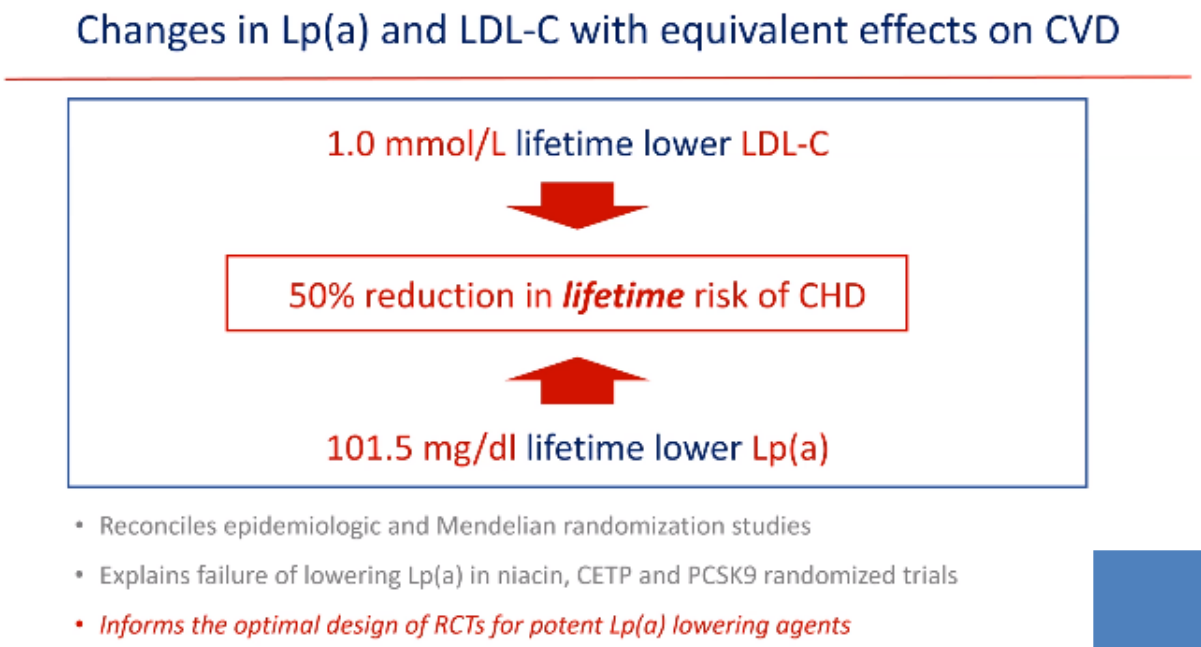
Gregory G. Schwartz, MD, PhD,[a] Michael Szarek, PhD,[b,c] Vera A. Bittner, MD, MSPH,[d] Rafael Diaz, MD,[e]

PCSK9 inh tedavisinden fayda görecek hastaları belirlemek için Lp(a) düzeyini ölçmek faydalı olabilir



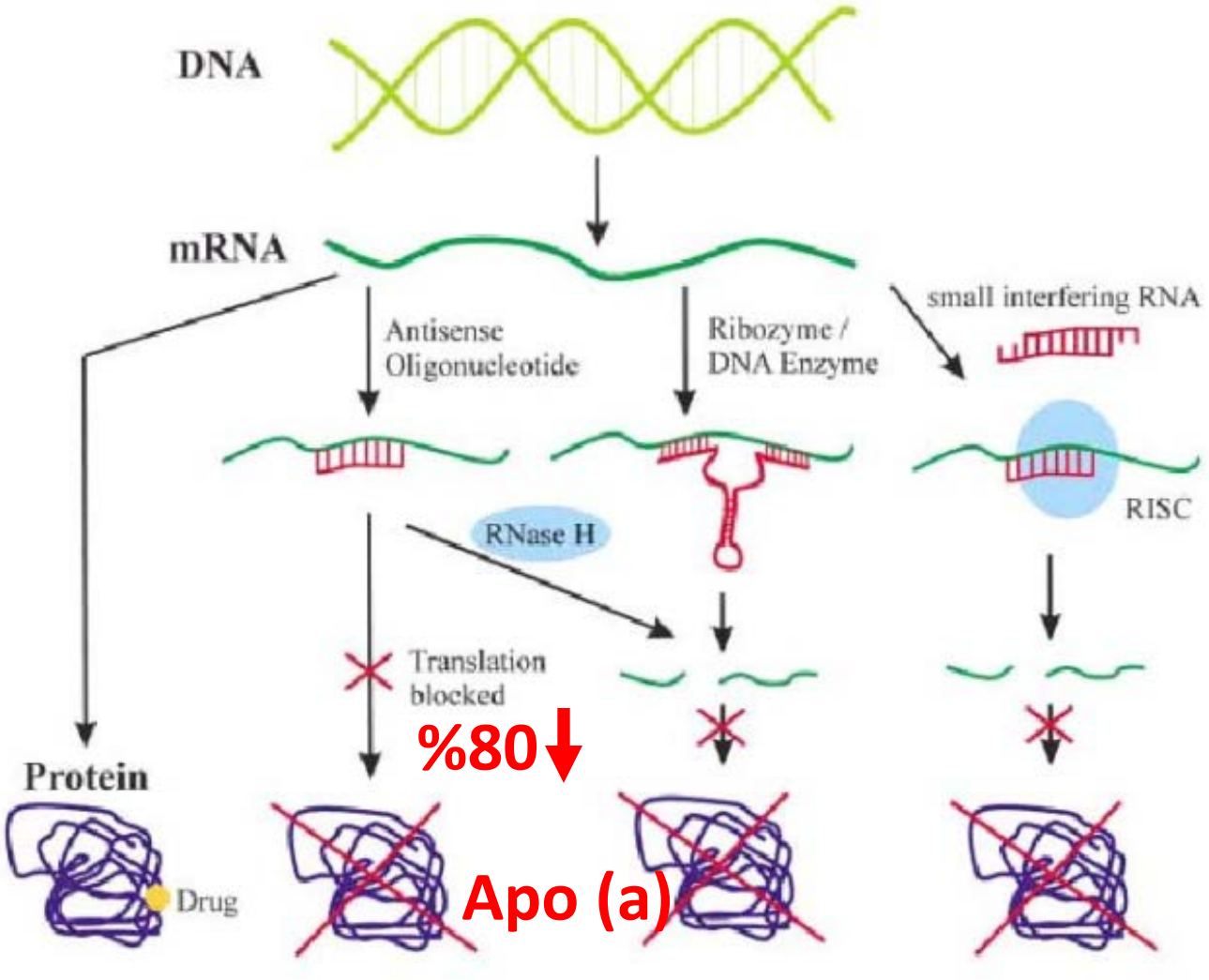
Schwartz, G.G. et al. J Am Coll Cardiol. 2021;78(5):421-33.

Mendelyan randomize çalışmalara göre



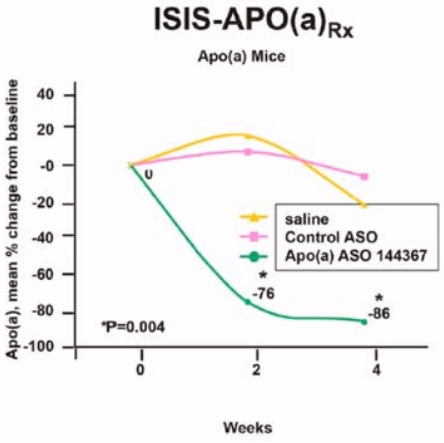
	Lp(a) azalması
Evolucumab, Alirocumab	**≈%30**
Inclisiran	**%26**
Mipomersen	**%39**
Lomitapide	**%33**

Antisense Teknolojileri - *pelacarsen*

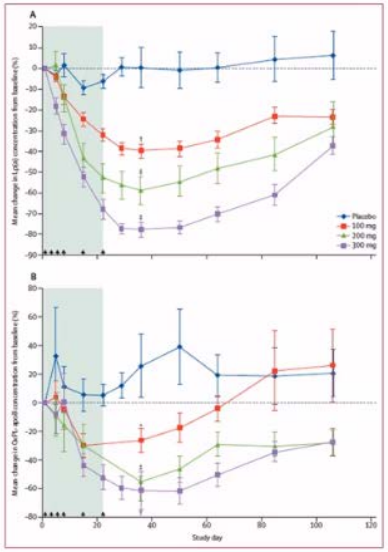


The Second Birth of ASO Therapy for Lp(a)

Reduction in Lp(a) levels with ASO to apo(a)

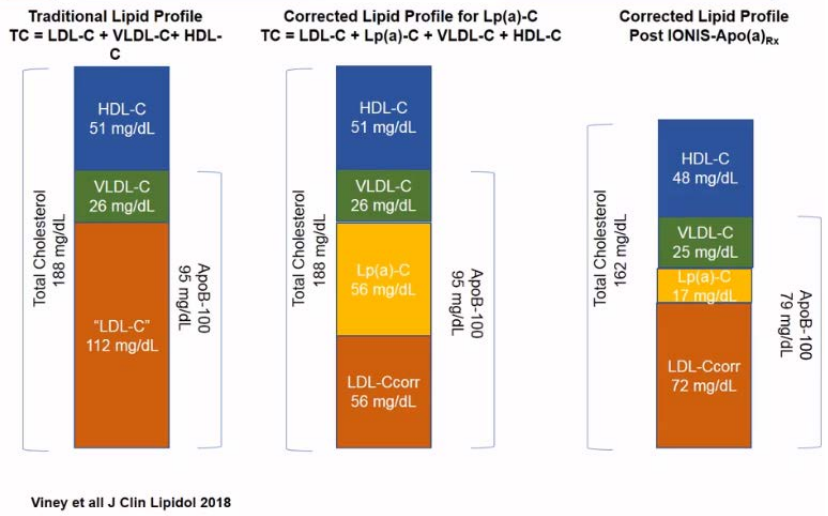


Merki et al. JACC 2011;57:1611–2



Tsimikas et al Lancet 2015

Additional Net Reduction of Atherogenic LDL-ApoB-100 with ASO to Apo(a)

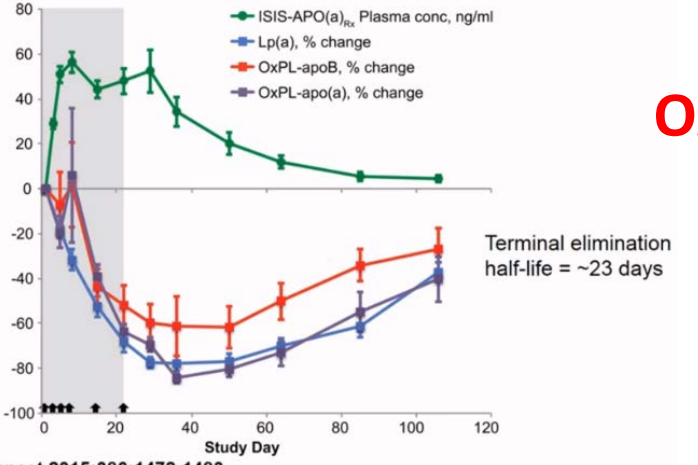


Viney et all J Clin Lipidol 2018

% 80 Lp(a) azalma **20 mg/hf**

%72 Lp(a) azalma **60mg/ay**

Relationship of Plasma ISIS-APO(a)Rx Trough Concentrations and Mean Percent Change in Lp(a), OxPL-apoB and OxPL-apo(a) - 300 mg



OxPL %41

Tsimikas et al Lancet 2015;386:1472-1483

ORIGINAL ARTICLE

Lipoprotein(a) Reduction in Persons with Cardiovascular Disease

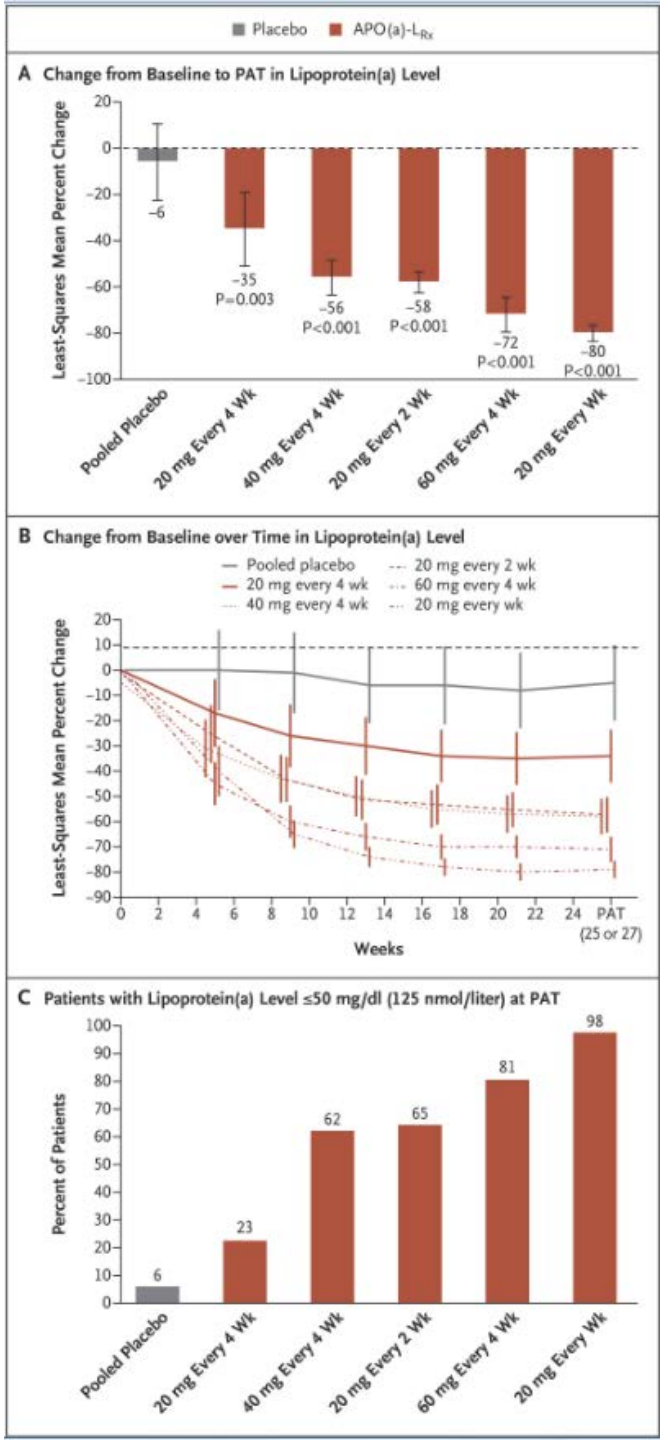
Sotirios Tsimikas, M.D., Ewa Karwatowska-Prokopczuk, M.D., Ph.D., Ioanna Gouni-Berthold, M.D., Jean-Claude Tardif, M.D., Seth J. Baum, M.D., Elizabeth Steinhagen-Thiessen, M.D., Michael D. Shapiro, D.O., Erik S. Stroes, M.D., Patrick M. Moriarty, M.D., Børge G. Nordestgaard, M.D., D.M.Sc., Shuting Xia,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

January 16, 2020
N Engl J Med 2020; 382:244-255
DOI: 10.1056/NEJMoa1905239

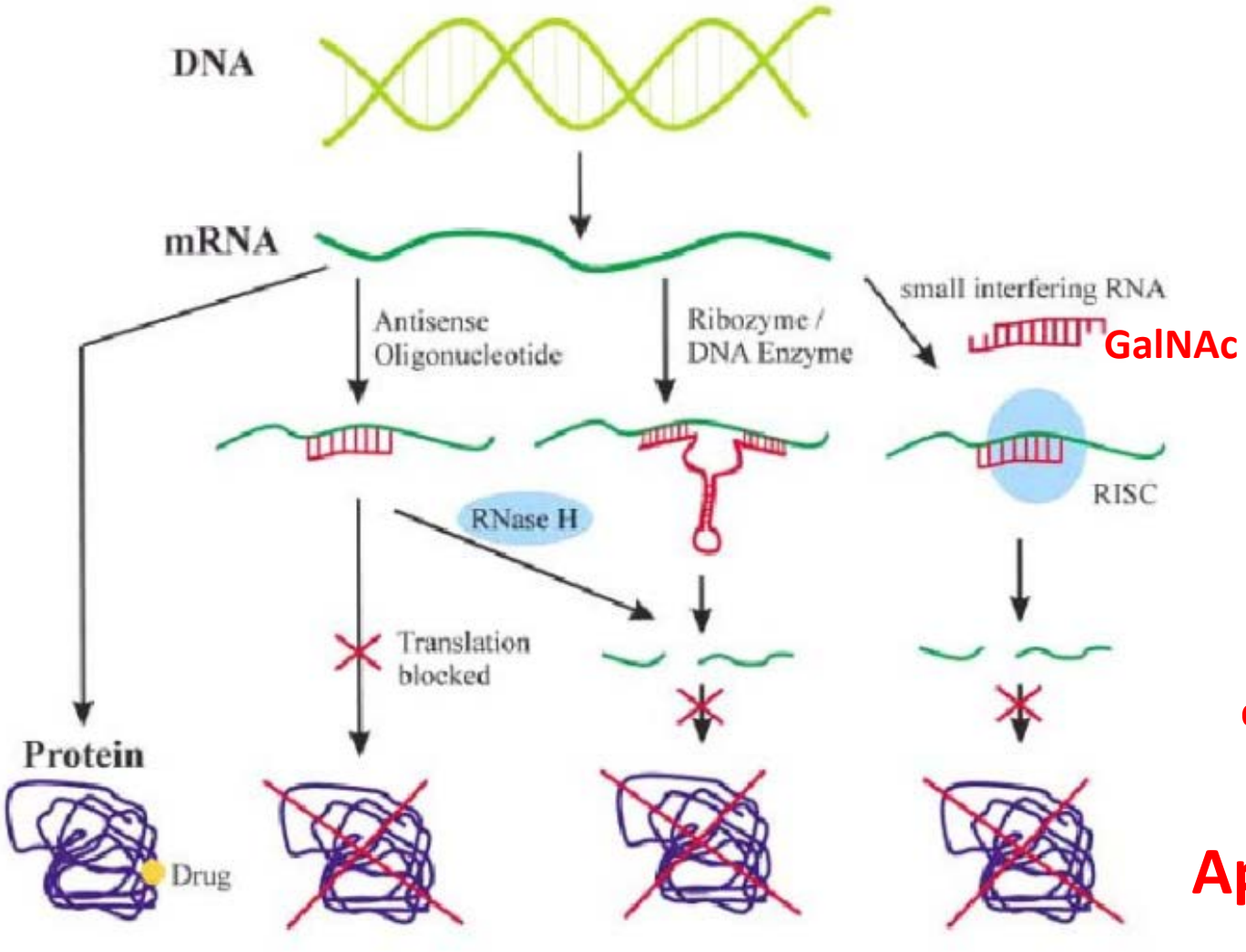
HORIZON –faz III

CV olay ve Lp(a)>70, 80 mg ayda bir

Phase III cardiovascular-outcome study with AKCEA-APO(a)-LRX



Antisense Teknolojileri – *siRNA - Olpasiran*



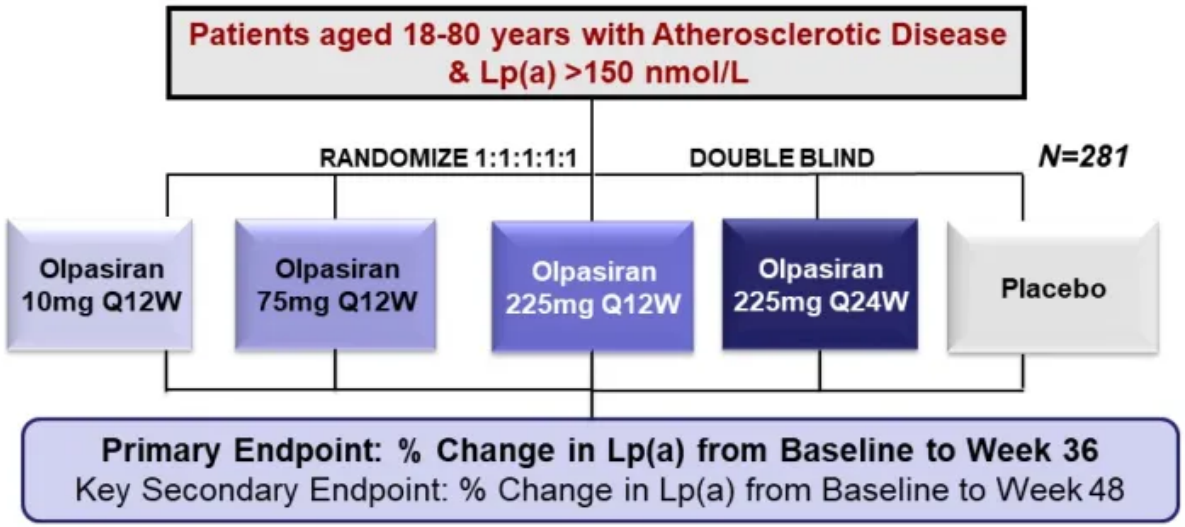
%90↓

Apo(a)

Olpasiran-AMG 890-siRNA

Faz II

OCEAN(a)-DOSE:
Study to Evaluate Efficacy, Safety, and Tolerability of Olpasiran (AMG890, a small interfering RNA) in Subjects with Elevated Lipoprotein(a)



Clinicaltrials.gov:
NCT04270760

Silence Therapeutics, 88 hst, 30-900 mg

Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease

Michelle L. O'Donoghue, M.D., M.P.H., Robert S. Rosenson, M.D., Baris Gencer, M.D., M.P.H., J. Antonio G. López, M.D., Norman E. Lepor, M.D., Seth J. Baum, M.D., Elmer Stout, M.D., Daniel Gaudet, M.D., Ph.D., Beat Knusel, Ph.D., Julia F. Kuder, M.A., Xinhui Ran, M.S., Sabina A. Murphy, M.P.H., Huei Wang, Ph.D., You Wu, Ph.D., Helina Kassahun, M.D., and Marc S. Sabatine, M.D., M.P.H., for the OCEAN(a)-DOSE Trial Investigators*

ABSTRACT

BACKGROUND
Lipoprotein(a) is a presumed risk factor for atherosclerotic cardiovascular disease. Olpasiran is a small interfering RNA that reduces lipoprotein(a) synthesis in the liver.

METHODS
We conducted a randomized, double-blind, placebo-controlled, dose-finding trial involving patients with established atherosclerotic cardiovascular disease and a lipoprotein(a) concentration of more than 150 nmol per liter. Patients were randomly assigned to receive one of four doses of olpasiran (10 mg every 12 weeks, 75 mg every 12 weeks, 225 mg every 12 weeks, or 225 mg every 24 weeks) or matching placebo, administered subcutaneously. The primary end point was the percent change in the lipoprotein(a) concentration from baseline to week 36 (reported as the placebo-adjusted mean percent change). Safety was also assessed.

RESULTS
Among the 281 enrolled patients, the median concentration of lipoprotein(a) at baseline was 260.3 nmol per liter, and the median concentration of low-density lipoprotein cholesterol was 67.5 mg per deciliter. At baseline, 88% of the patients were taking statin therapy, 52% were taking ezetimibe, and 23% were taking a proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor. At 36 weeks, the lipoprotein(a) concentration had increased by a mean of 3.6% in the placebo group, whereas olpasiran therapy had significantly and substantially reduced the lipoprotein(a) concentration in a dose-dependent manner, resulting in placebo-adjusted mean percent changes of −70.5% with the 10-mg dose, −97.4% with the 75-mg dose, −101.1% with the 225-mg dose administered every 12 weeks, and −100.5% with the 225-mg dose administered every 24 weeks ($P<0.001$ for all comparisons with baseline). The overall incidence of adverse events was similar across the trial groups. The most common olpasiran-related adverse events were injection-site reactions, primarily pain.

CONCLUSIONS
Olpasiran therapy significantly reduced lipoprotein(a) concentrations in patients with established atherosclerotic cardiovascular disease. Longer and larger trials will be necessary to determine the effect of olpasiran therapy on cardiovascular disease. (Funded by Amgen; OCEAN(a)-DOSE ClinicalTrials.gov number, NCT04270760.)

Lp(a) ve DM riski

Clin Chem. 2010 August ; 56(8): 1252–1260. doi:10.1373/clinchem.2010.146779.

Lipoprotein(a) and Risk of Type 2 Diabetes

Samia Mora, MD, MHS, Pia R. Kamstrup, MD, PhD, Nader Rifai, PhD, Børge G. Nordestgaard, MD, DMSc, Julie E. Buring, ScD, and **Paul M Ridker, MD, MPH**

Study populations

The Women's Health Study (WHS) is a completed randomized, double-blinde controlled clinical trial of low-dose aspirin and vitamin E in US female healthc professionals (15). Eligible participants were apparently healthy women, ages 45 years or older, who were free of self-reported cardiovascular disease or cancer at study entry (1992–1995). At the time of enrollment, participants gave written informed consent, completed questionnaires on demographics, medical history, medications, and lifestyle factors. They were also asked to provide a blood sample, if they were willing. Participants were requested, but not required, to have the sample drawn in the morning before eating, and reported the number of hours since their last meal before the blood draw. For the present analysis, we excluded women with prevalent diabetes (N=770), baseline hemoglobin A_{1c} (HbA_{1c}) ≥6.5% (N=270), or missing lipid measurements (N=237), resulting in 26,746 women for analysis. We also repeated the analyses after excluding the 164 women with HbA_{1c} ≥6.0% and <6.5%. The study was approved by the institutional review boards of the Brigham and Women's Hospital (Boston, Mass). We replicated our findings in a general population of 9,652 men and women (Copenhagen City Heart Study [CCHS])(14) in relation to prevalent type 2 diabetes (N=419).

Paige *et al. Cardiovasc Diabetol (2017) 16:38*
DOI 10.1186/s12933-017-0520-z

Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

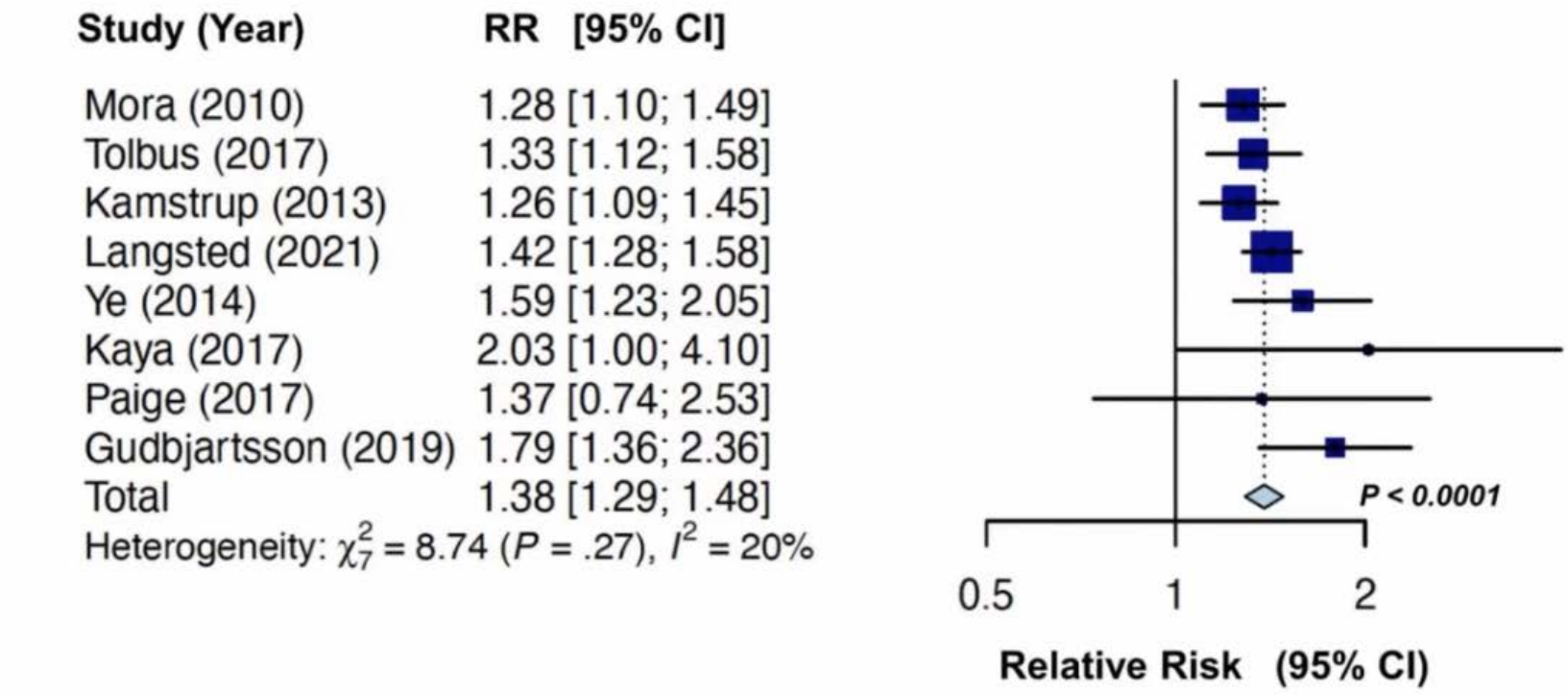
Lipoprotein(a) and incident type-2 diabetes: results from the prospective Bruneck study and a meta-analysis of published literature

Our study provides evidence to support the hypothesis that Lp(a) concentration is inversely associated with development of type-2 diabetes, in people without previous diabetes. That we only observed an increased risk of diabetes in people with Lp(a) concentrations in the lowest two quintiles (~mean Lp(a) levels of <7 mg/dL) suggest that the use of Lp(a) lowering therapies would not be in conflict with these findings if provided therapies do not lower Lp(a) levels beyond those observed in these lowest two quintiles.

Conclusion—Lp(a) was associated inversely with risk of type 2 diabetes independent of risk factors, in contrast to prior positive associations of Lp(a) with cardiovascular risk.

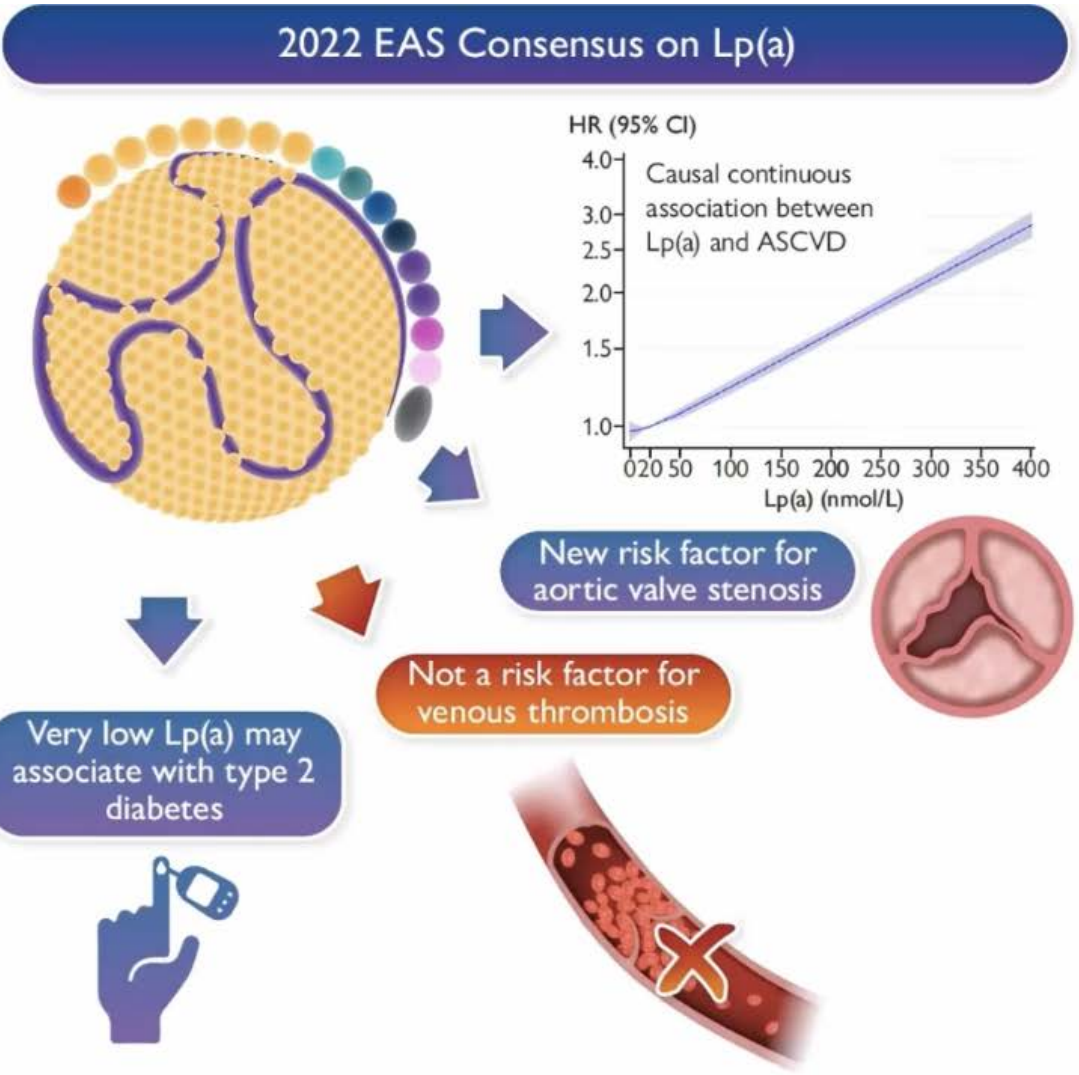
Sadece çok düşük Lp(a) ile ilişkili bulunmuş <7mg/dL

Meta-analysis of available studies showed a 38% higher risk of diabetes for the bottom quintile vs. top quintile of Lp(a)



Eur Heart J 2022

Özet



***Yüksek Lp(a) ASKVH ve KV mortalite nedenselliği**

***Lp(a) ve KV sonlanım ilişkisi doğrusal ve sürekli**

***Çok düşük LDL düzeylerinde bile risk faktörü**

***İskemik inme ve KY daha yüksek Lp(a) düzeylerinde**

Teşekkürler