KARDİYOVASKÜLER RİSK TAYİNİNDE HDL

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BAKÜ - AZERBAYCAN

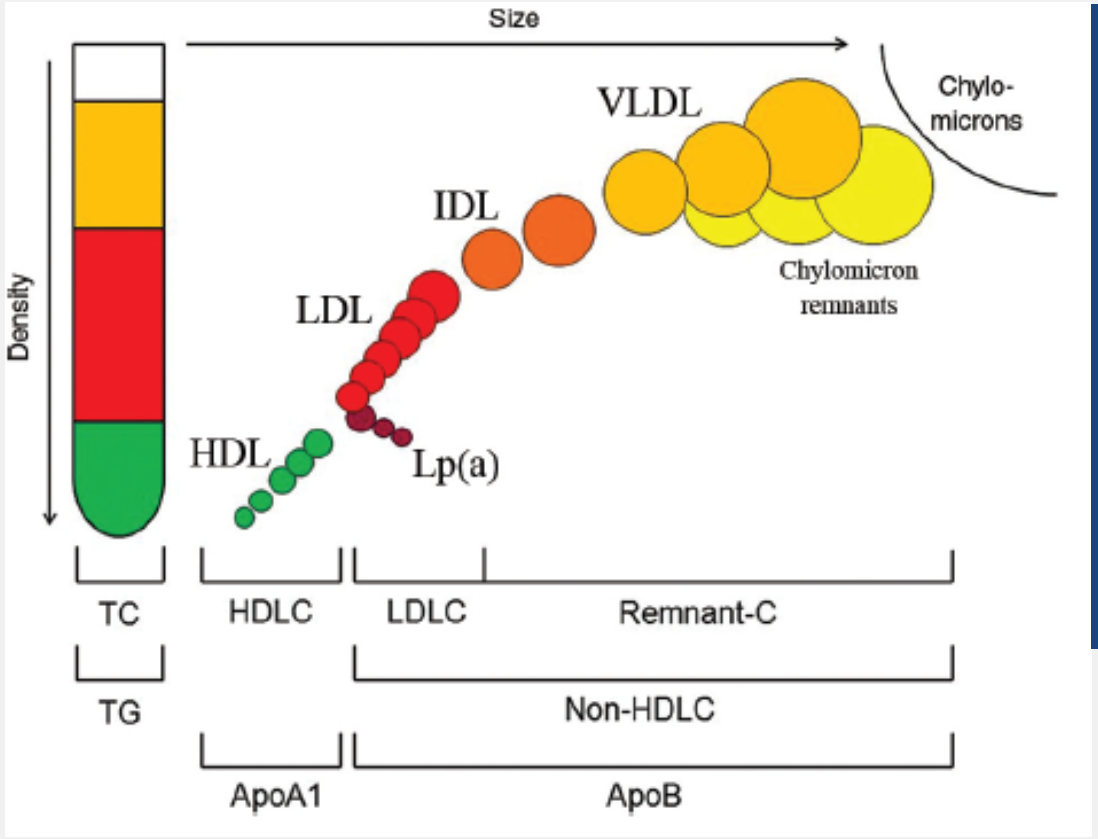
HDL hikayesi- zor sorular

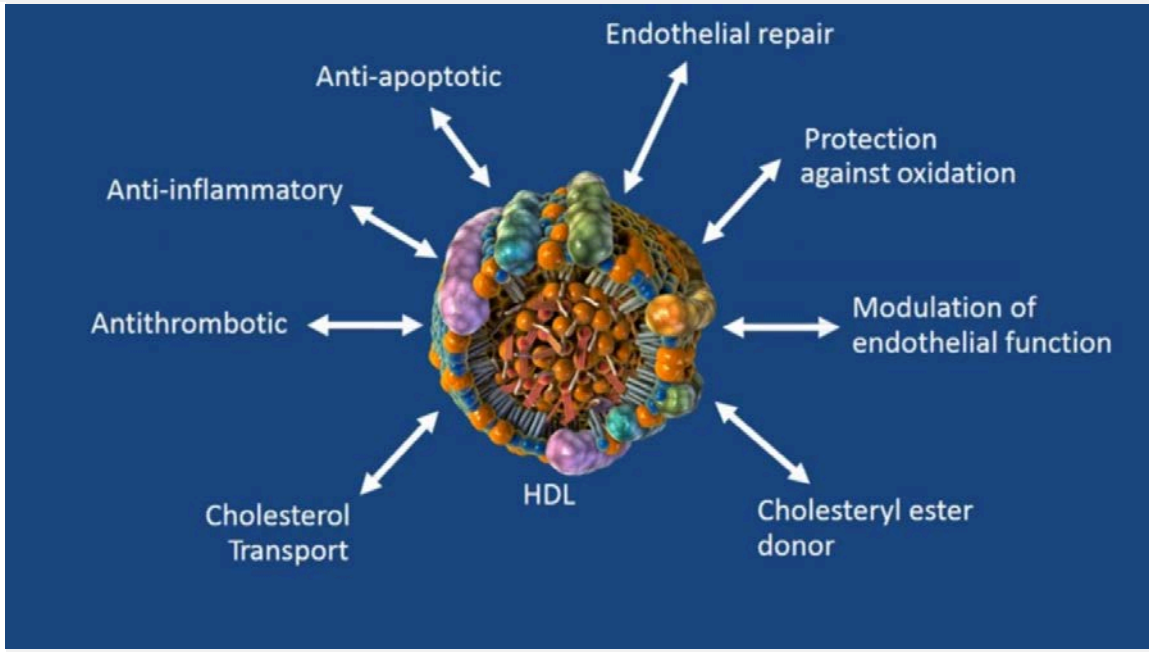
- HDL biyolojisi açıklığa kavuşturuldu mu?
- Sağlık ve hastalık durumlarında HDL?
- Risk tahmininde kullanım - ters kolesterol transportu (RCT)
- HDL metabolizmasının genetik belirleyicileri nelerdir ?
- HDL'nin terapötik hedefleri var mı?

HDL-K: HDL partiküllerinin taşıdığı toplam kolesterol miktarı

HDL fonksiyonu ≠ HDL-K

HDL-K ve non-HDL-K





- **HDL-K ölçümü, HDL tarafından taşınan total kolesterol miktarını göstermektedir.**
- **Non-HDL-K; apoB içeren, aterojenik tüm partiküllerin taşıdığı toplam kolesterol miktarını gösterir.**

Lipidome (200 çeşit)

- Cholesterol esters 35%
- Free cholesterol 15%
- Triacylglycerides 3%
- Phospolipids 50%– en fazla Phosphatidylcholine
- Sphingolipids 5-10%- en fazla sphingomyelin, ceramide

TABLE 1 | Relative distribution of peptides between HDL2 and HDL3.

Preferentially in HDL3	Preferentially in HDL2
Paraoxonase-1 (PON1)	Apolipoprotein CI
Paraoxonase-3 (PON3)	Apolipoprotein CII
Apolipoprotein F	Apolipoprotein CIII
Apolipoprotein L-I	Apolipoprotein E
Apolipoprotein J (clusterin)	
Apolipoprotein M	
Apolipoprotein D	
Apolipoprotein A-IV	
PAF-acetylhydrolase	
Serum amyloid AI and AII	
Haptoglobin related protein	

HDL partikül ağırlığının %15'i kolesteroldür. %85 proteindir.

doi: 10.3389/fphar.2017.00989

HDL metabolizması

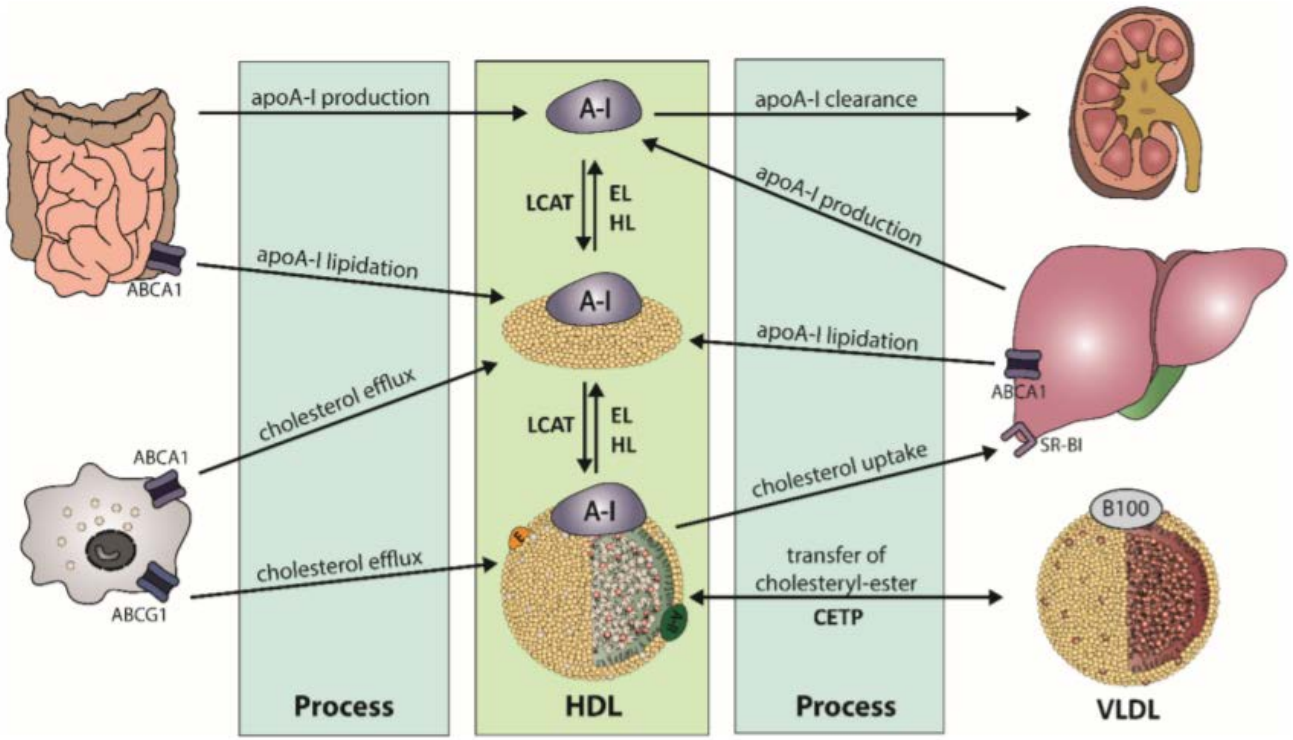
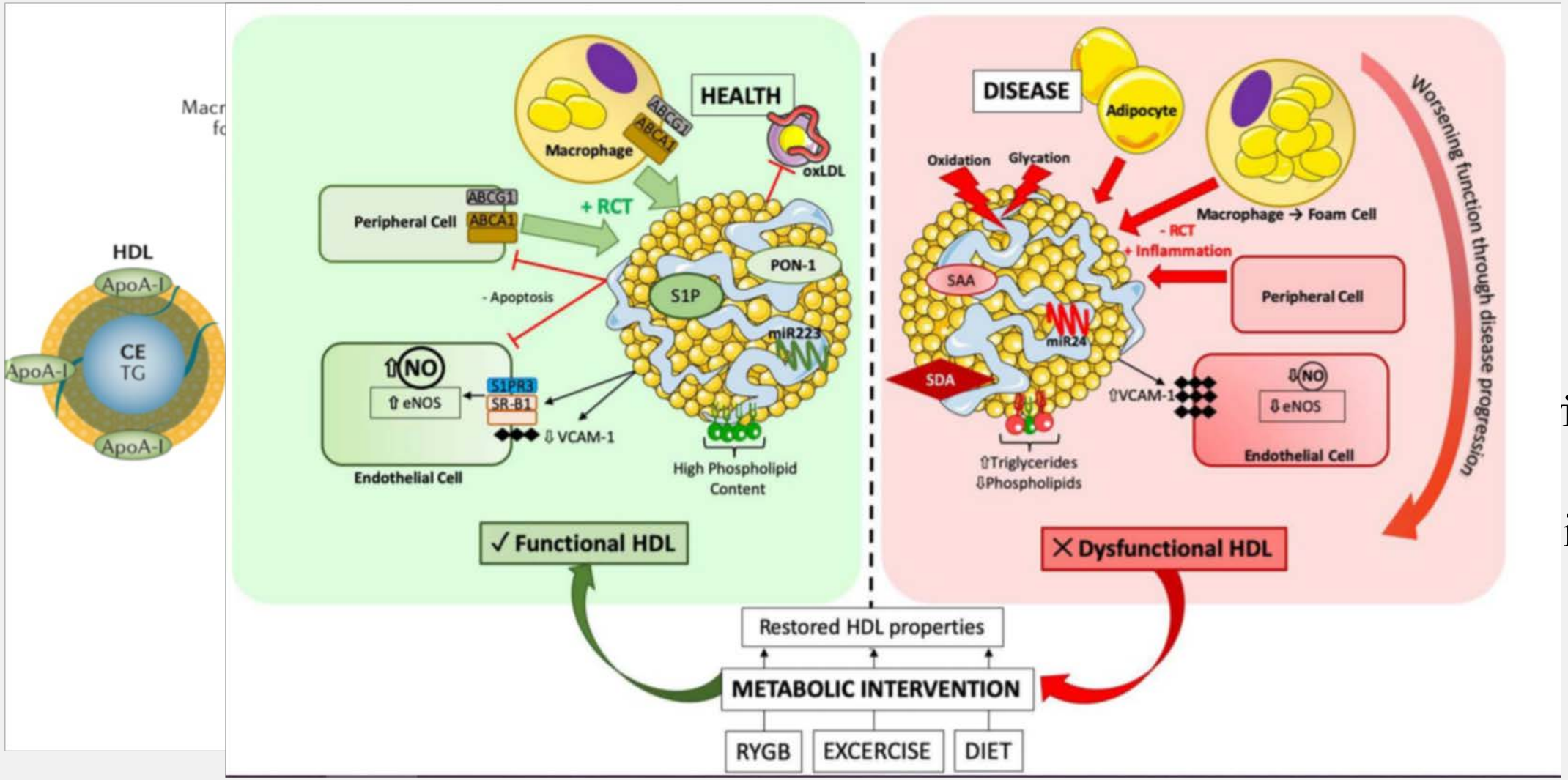


Figure 1. Schematic overview of high-density lipoprotein (HDL) metabolism. Biogenesis of apolipoprotein A-I (apoA-I) takes place in the liver and intestine. After secretion of the lipid-poor apoA-I, it interacts with ATP-binding cassette transporter A1 (ABCA1) to acquire lipids, leading to formation of nascent HDL. The enzyme lecithin-cholesterol-acyl transferase (LCAT) esterifies free cholesterol of nascent HDL to form mature HDL. Cholesteryl-esters are cleared by uptake of the liver by scavenger receptor B1 (SR-BI) or via transfer on triglyceride-rich lipoproteins by cholesteryl-ester transfer protein (CETP), in exchange of triglycerides. Triglyceride-rich HDL is susceptible to hydrolysis by endothelial lipase (EL) or hepatic lipase (HL).

- **ABCA1:** ATP-binding cassette transporter A1
- **SR-B1:** scavanger receptor class B type 1
- **LCAT:** Lecithin-cholesterol acyltransferase
- **CETP:** cholesterol ester transfer protein
- **EL:** endothelial lipase
- **HL:** hepatic lipase
- **PLTP:** Phospholipid transfer protein

Int. J. Mol. Sci. 2020, 21, 732

HDL modifikasyonu



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doi:10.1038/nrcardio.2015.124

HDL-K seviyesi - ASKVH riski ilişkisi

ASCVD Risk Enhancing Factors

- **Family history of premature ASCVD**
  - Males, age <55 years
  - Females, age <65 years
- **Primary hypercholesterolemia**
  - LDL-C 160-189 mg/dL [4.1- 4.8 mmol/L]
  - Non-HDL-C 190-219 mg/dL [4.9-5.6 mmol/L]*
- **Metabolic syndrome**
  Factors: (tally of 3 makes the diagnosis)
  - Increased waist circumference
  - Elevated triglycerides (≥150 mg/dL)
  - Elevated blood pressure
  - Elevated glucose
  - Low HDL-C (< 40 mg/dL in men; < 50 mg/dL in women)
- **Chronic kidney disease**
  - eGFR 15-59 ml/min per1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation
- **Chronic inflammatory conditions**
  - Conditions such as psoriasis, rheumatoid arthritis, or HIV/AIDS
- **History of premature menopause (before age 40) and history of pregnancy-associated conditions that increase later ASCVD risk such as pre-eclampsia**
- **High-risk race/ ethnicities** (e.g. South Asian ancestry)
- **Lipid/biomarkers:** Associated with increased ASCVD risk
  - Persistently* elevated, primary hypertriglyceridemia (≥ 175 mg/dL)
  - If measured:
    - **Elevated high-sensitivity C-reactive protein** (≥ 2.0 mg/L)
    - **Elevated Lp(a)** ≥ 50 mg/dl or ≥ 125 nmol/L constitutes a risk-enhancing factor especially at higher Lp(a)
    - **Elevated apoB** ≥ 130 mg/dl corresponds to an LDL-C > 160 mg/dL and constitutes a risk-enhancing factor
    - **ABI** (ankle-branchial index) < 0.9

*Optimally, three determinations

Normal ölçümler:

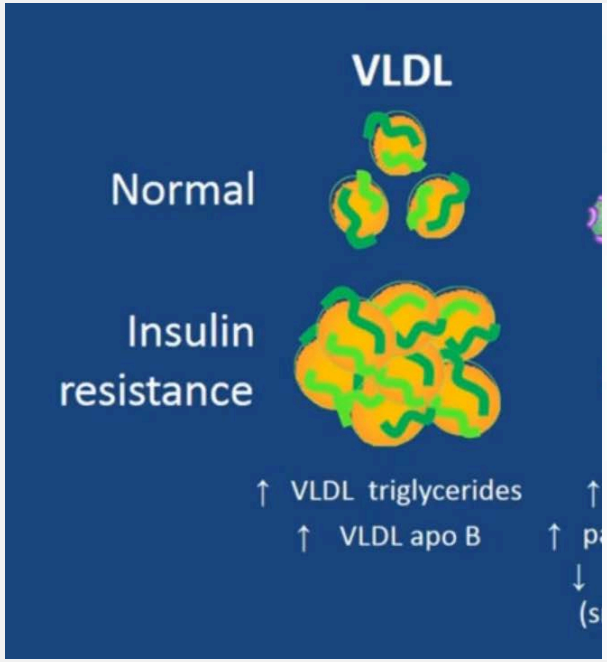
Apo B < 130 mg/dL

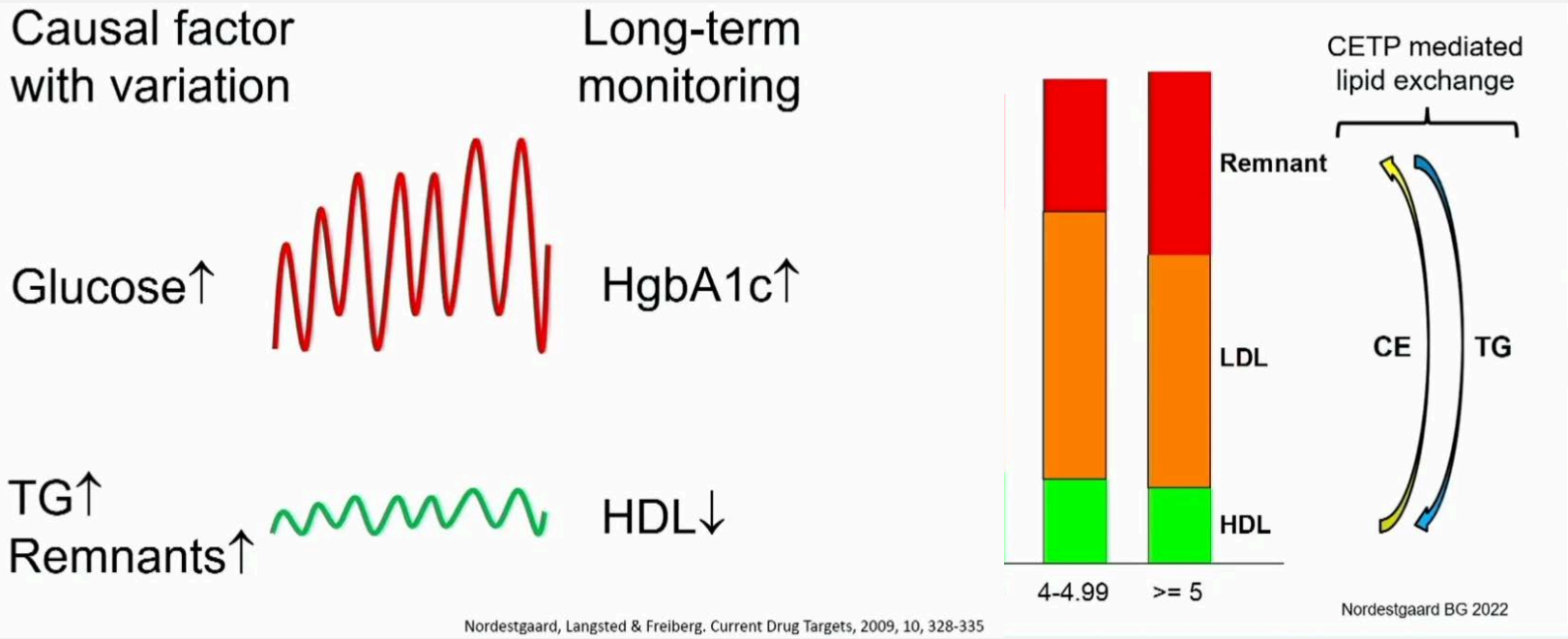
apoA1 erkeklerde: 75-160 mg/dL
apoA1 kadınlarda: 80—175 mg/dL
apoA1 yeni doğanda: < 100 mg/dL

apoB/apoA oranı < 0.8

DOI: 10.1161/CIR.0000000000000678, *doi:10.1093/eurheartj/ehy299*

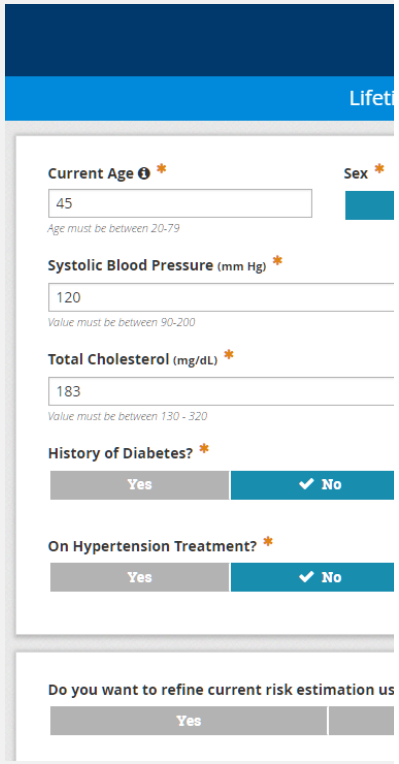
Düşük HDL-K - Aterojenik dislipidemi





- Düşük HDL-K seviyesi, abdominal obezite/DM/insülin direnci gibi ikincil nedenlere bağlı TG'den zengin lipoprotein artışı ve CETP enzimi ile HDL – TRL arasındaki TG ve kolesterol ester değişimi neticesinde gelişir.
- LDL-K seviyesinde yükseklik olmayabilir, kyLDL-k ve apoB yüksekliği artmış KV riskle ilişkilidir.

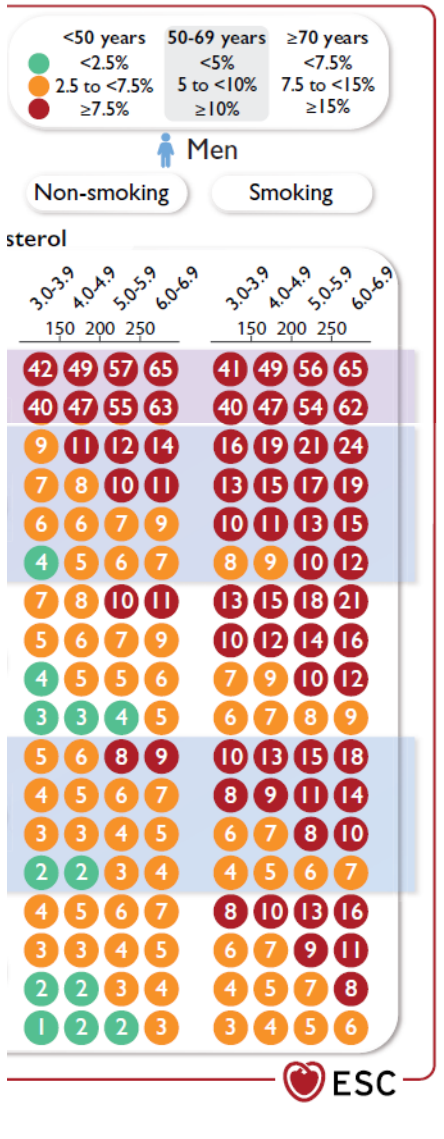
KV risk hesaplanması



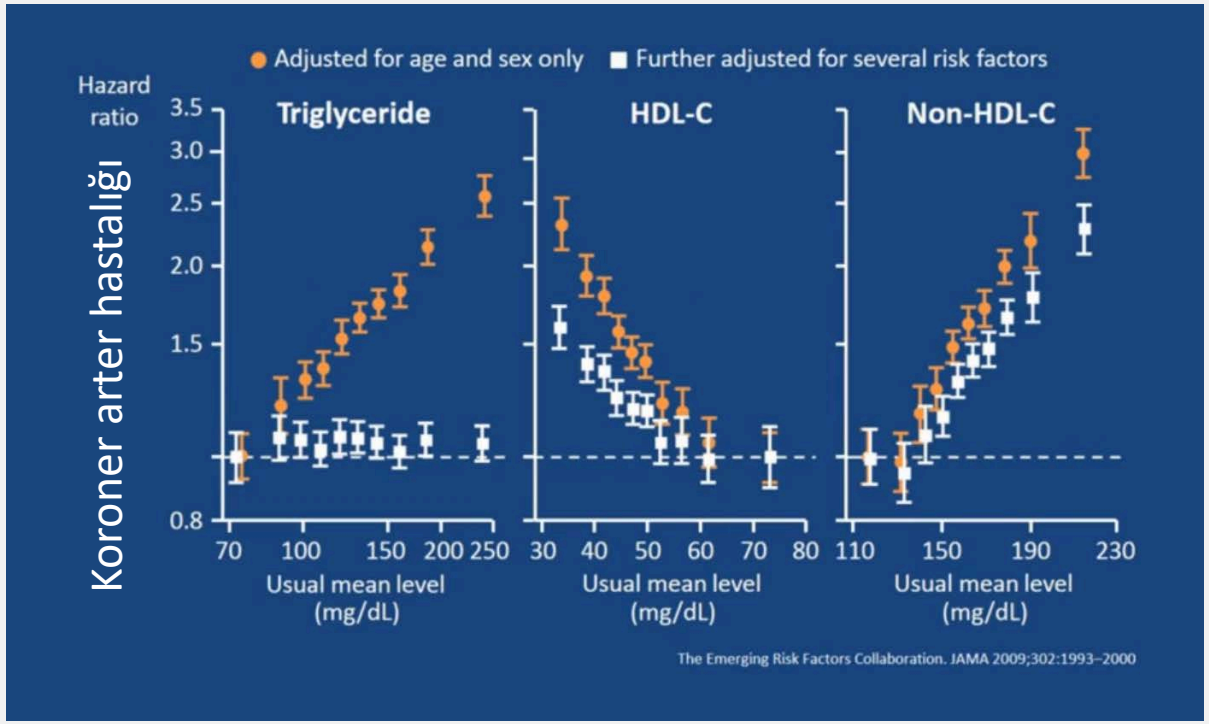
Supplementary Table 1 **Total cardiovascular disease risk assessment systems**

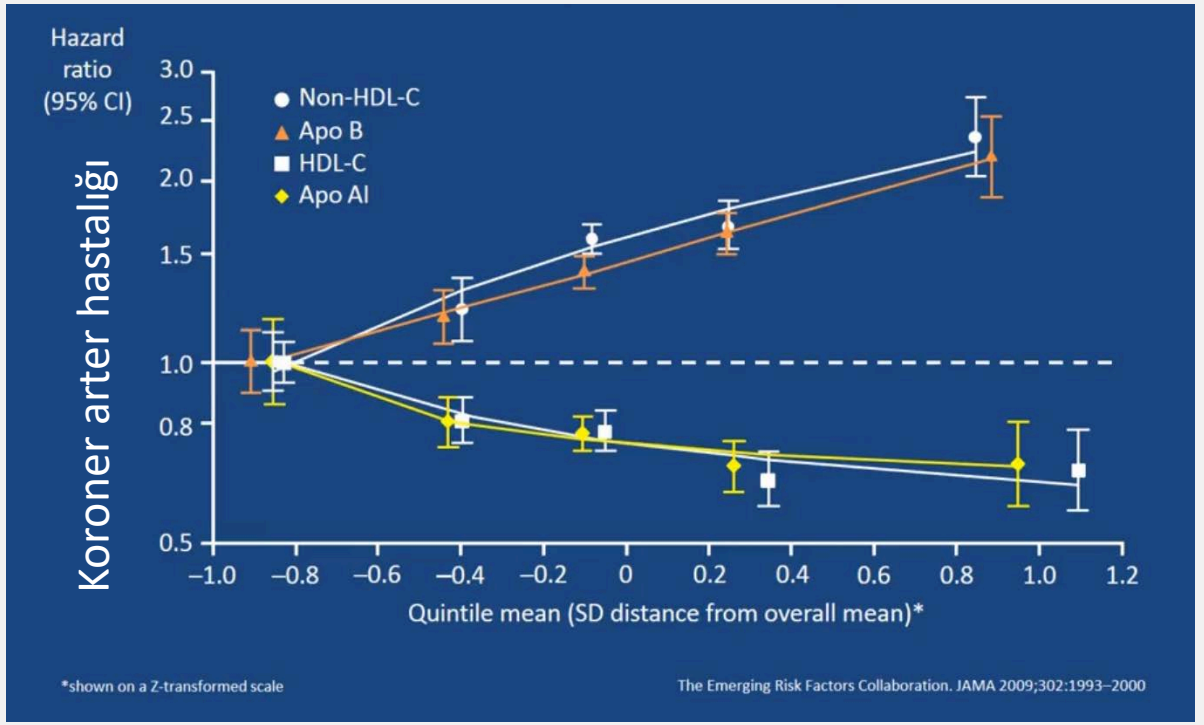
System	Risk	Variables	Reference
Framingham models	10-year risk of CHD events	Gender, age, TC, HDL-C, SBP, smoking status, diabetes, hypertensive treatment	1
Systematic Coronary Risk Estimation (SCORE)	10-year risk of CVD mortality	Gender, age, TC or TC/HDL-C ratio, SBP, smoking status	2
ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network)	10-year risk of first CVD event	Gender, age, TC, HDL-C, SBP, smoking (number of cigarettes), diabetes, area-based index of deprivation, family history	3
QRISK2	10-year risk of first CVD event	Gender, age, TC to HDL-C ratio, SBP, smoking status, diabetes, area-based index of deprivation, family history, BMI, antihypertensive treatment, ethnicity, rheumatoid arthritis, CKD stages 4–5, AF	4
Prospective Cardiovascular Munster Study (PROCAM)	Two separate scores calculate 10-year risk of major coronary events and cerebral ischaemic events	Age, gender, LDL-C, HDL-C, diabetes, smoking, SBP	5
Reynolds Risk Score	10-year risk of incident myocardial infarction, stroke, coronary revascularization, or CV death	Gender, age, SBP, smoking, high-sensitivity C-reactive protein, TC, HDL-C, family history of premature MI (parent aged <60 years), HbA1c if diabetic	6,7
CUORE	10-year risk of first CVD event	Age, gender, TC, HDL-C, diabetes, smoking, SBP, hypertensive treatment	8
Pooled Cohort equations	10-year risk of CVD event	Age, gender, TC, HDL-C, diabetes, smoking, SBP, hypertensive treatment, race	9
Globorisk	10-year risk of CVD mortality	Age, gender, smoking, SBP, diabetes, TC	10

AF = atrial fibrillation; BMI = body mass index; CHD = coronary heart disease; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction, SBP = systolic blood pressure; TC = total cholesterol.



HDL-K – epidemiyolojik çalışmalar- ERFC





- Direkt ölçülen LDL-C: 1.38 (95% CI, 1.09-1.73)
- non–HDL-C: 1.42: (95% CI, 1.06-1.91)
- non–HDL-C/HDL-C oranı: 1.50 (95% CI, 1.38-1.62)
- apo B/apo AI oranı: 1.49 (95% CI, 1.39-1.60)

JAMA. 2009;302(18):1993-2000

HDL-K vs. apoB partikül sayısı

JAMA Cardiology | Original Investigation

Association of Apolipoprotein B–Containing Lipoproteins and Risk of Myocardial Infarction in Individuals With and Without Atherosclerosis

Distinguishing Between Particle Concentration, Type, and Content

Nicholas A. Marston, MD, MPH; Robert P. Giugliano, MD, SM; Giorgio E. M. Melloni, PhD; Jeong-Gun Park, PhD; Valerie Morrill, MS; Michael A. Blazing, MD; Brian Ference, MD, MPhil, MSc; Evan Stein, MD, PhD; Erik S. Stroes, MD, PhD; Eugene Braunwald, MD; Patrick T. Ellinor, MD, PhD; Steven A. Lubitz, MD, MPH; Christian T. Ruff, MD, MPH; Marc S. Sabatine, MD, MPH

Primer korunma kolu:

Statin kullanmayan 390 B kişi, ortalama yaş 59, ortalama takip 11 sene

Sekonder korunma kolu (FOURIER, IMPROVE-IT çalışması

40B hasta, ortalama yaş 63, ortalama takip 2.5 sene

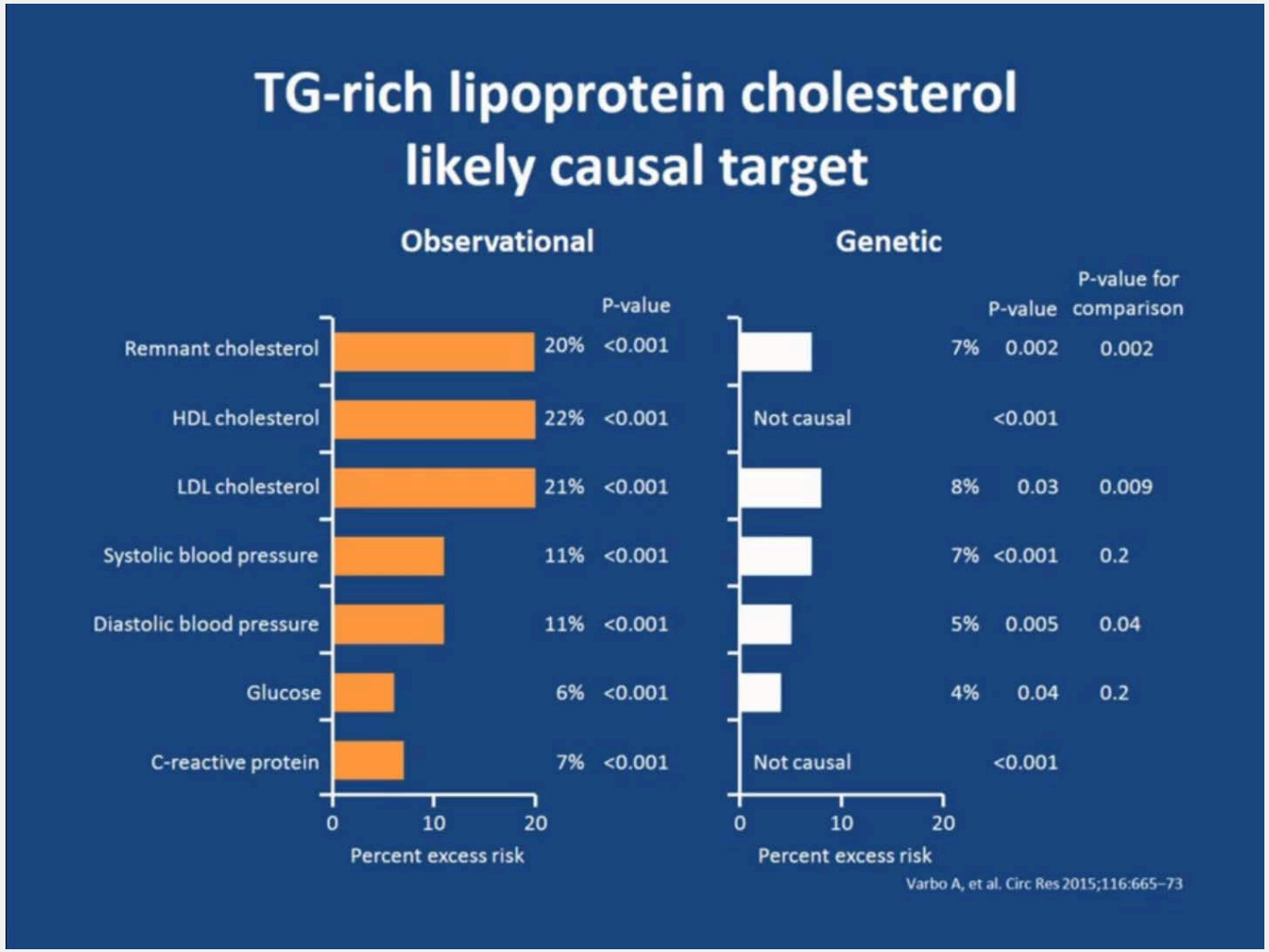
Medical history		
Myocardial infarction	0 (0)	24225 (59.9)
Stroke	0 (0)	5577 (13.8)
Peripheral artery disease	0 (0)	4174 (10.3)
Diabetes	2702 (0.7)	13 205 (32.7)
CKD (eGFR < 60 mL/min/1.73 m^2)	5739 (1.6)	7445 (18.5)
Hypertension	21 930 (5.6)	29 533 (73.1)
Smoking	41 230 (10.6)	12 009 (29.7)
Lipid values, median (IQR), mg/dL		
Apolipoprotein B[d]	105 (90-121)	68 (46-86)
Cholesterol[e]		
Total	226 (199-253)	134 (105-162)
LDL	142 (122-163)	61 (36-85)
HDL	55 (46-66)	46 (38-55)
Non-HDL	168 (143-196)	86 (56-114)
Triglycerides[f]	127 (90-184)	115 (84-163)
Statin use, %	0	99.95

adjustment. All models adjusted for age, sex, body mass index (calculated as

[b] Includes HD

JAMA Cardiol. 2022;7(3):250-256

Epidemiyolojik çalışmalar vs. genetik çalışmalar



Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study

Benjamin F Voight*, Gina M Peloso*, Marju Orho-Melander, Ruth Frikke-Schmidt, Maja Barbalic, Majken K Jensen, George Hindy, Hilma Hólm, Eric L Ding, Toby Johnson, Heribert Schunkert, Nilesh J Samani, Robert Clarke, Jemma C Hopewell, John F Thompson, Mingyao Li, Gudmar Thorleifsson, Christopher Newton-Cheh, Kiran Musunuru, James P Pirruccello, Danish Saleheen, Li Chen, Alexandre F R Stewart, Arne Schillert, Unnur Thorsteinsdottir, Gudmundur Thorgeirsson, Sonia Anand, James C Engert, Thomas Morgan, John Spertus, Monika Stoll,

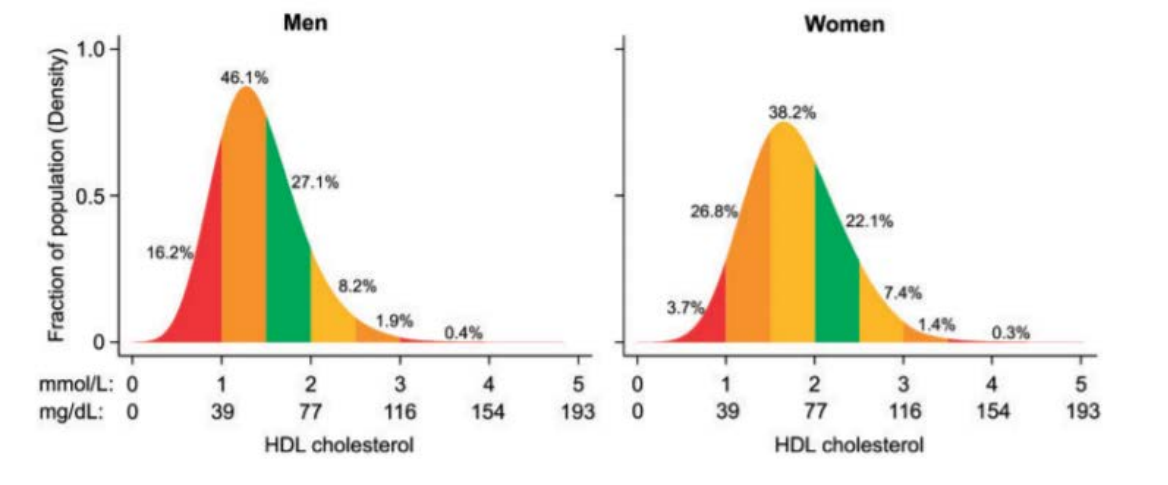
	Odds ratio (95% CI) per SD increase in plasma lipid based on observational epidemiology*	Odds ratio (95% CI) per SD increase in plasma lipid conferred by genetic score†
LDL cholesterol	1·54 (1·45–1·63)	2·13 (1·69–2·69), $p=2\times10^{-10}$
HDL cholesterol	0·62 (0·58–0·66)	0·93 (0·68–1·26), p=0·63

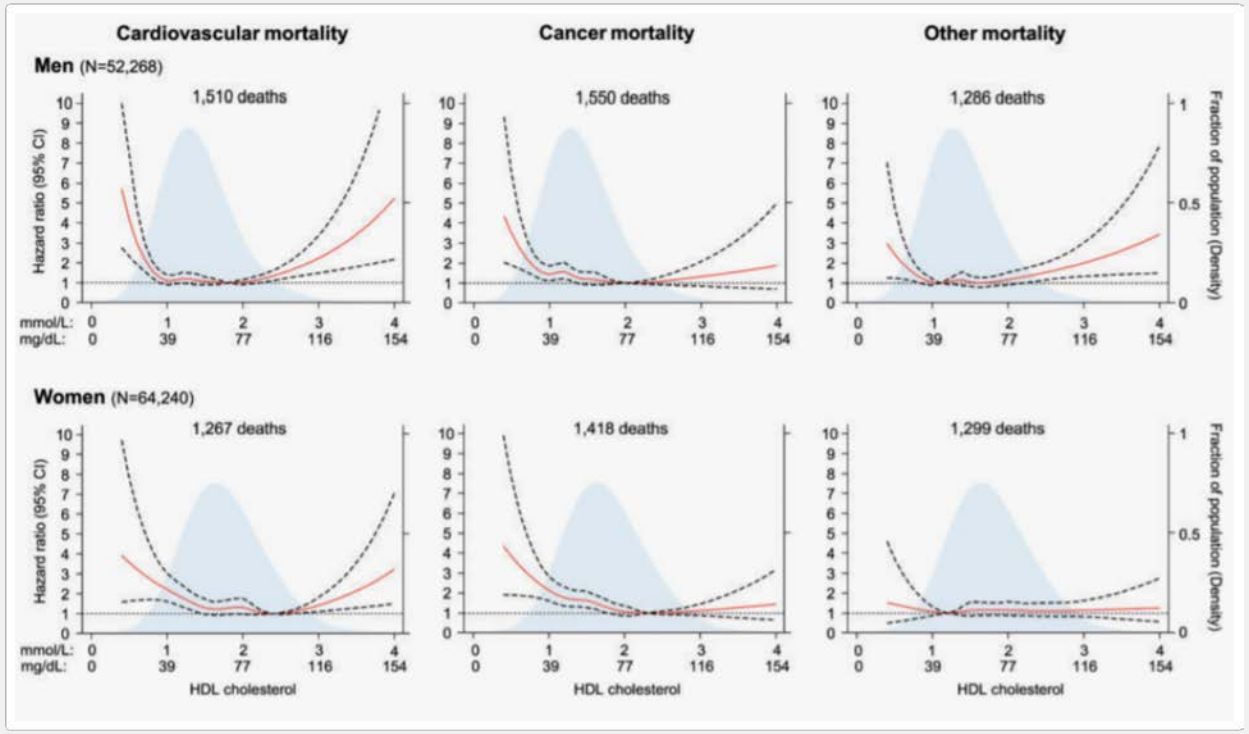
*Observational epidemiology estimates derived from more than 25 000 individuals from prospective cohort studies as shown in the appendix p 22. †LDL genetic score consisting of 13 single nucleotide polymorphisms (SNPs) as shown in the appendix p 27; HDL genetic score consisting of 14 SNPs as shown in the appendix p 28.

Table 4: Estimate of the association of genetically raised LDL cholesterol or HDL cholesterol and risk of myocardial infarction using multiple genetic variants as instruments

Lancet 2012; 380: 572–80

HDL-K seviyesi – mortalite riski





- 52 268 erkek, 64 240 kadın birey
- Erkeklerde HDL-K: 73 mg/dL → mortalite en düşük
- Kadınlarda HDL-K: 93 mg/dL → en düşük mortalite
- < 31 mg/dL ve > 100 mg/dL değerleri artmış enfeksiyon riskiyle ilişkili bulunmuş

sideration as a continuous variable. Clinicians should be aware that at extremely high values [above ~2.3 mmol/L (90 mg/dL)] of HDL-C there appears to be an increased risk of ASCVD, so at such levels HDL-C cannot be used as a risk predictor.

doi:10.1093/eurheartj/ehx163, doi:10.1093/eurheartj/ehx665

HDL-K < 20mg/dL – ASKVH riski nedir?

TABLE 1. Men in the Boston Heart Diagnostics population grouped by HDL-C levels (n = 112,776)

Parameter	Normal HDL-C ≥40 mg/dl (n = 83,812; 74.32%)	Low HDL-C 20–39 mg/dl (n = 28,594; 25.35%)	Severe[a] HDL-C <20 mg/dl (n = 370; 0.33%)	% Difference: Severe vs. Normal
Age (years)	56 (21)	54 (20)	50 (21)	−10.7
BMI (kg/m^2)	28 (7)	31 (7)	32 (9)	+14.3
Weight (lbs.)	195 (48)	218 (56)	215 (60)	+10.3
Lipids and apolipoproteins (mg/dl)				
HDL-C[b]	51 (16)	34 (5)	17 (4)	−66.7
apoA-I[b]	149.5 (29.8)	118.1 (17.7)	79.3 (31.0)	−47.0
TGs	101 (67)	167 (124)	245 (348)	+242.5
LDL-C	116 (54)	113 (54)	86 (60)	−25.9
sdLDL-C	26 (19)	34 (27)	38 (29)	+46.2
apoB	95 (38)	100 (40)	97 (45)	+2.1
HDL subpopulations (mg/dl)				
α1 apoA-I	26.3 (13.6)	14.1 (5.9)	6.0 (4.9)	−77.2
α2 apoA-I	59.8 (13.7)	45.5 (8.6)	29.1 (10.0)	−51.3
α3 apoA-I	22.9 (6.0)	23.2 (6.1)	18.8 (7.1)	−17.9
α4 apoA-I	19.2 (5.7)	18.2 (5.2)	13.8 (10.0)	−28.1
Pre-β1 apoA-I	8.4 (5.4)	6.9 (4.6)	5.3 (1.7)	−36.9

Genetik olarak HDL-K düşüklüğü saptanan hastalarda, ASKVH görülme sıklığı %5,5 ve tanı alma yaşı ortalama 62)

- **258K birey incelenmiş**
- 25 %; HDL-K 20-39 mg/dL
- 504 bireyde (0.2%) HDL-K < 20 mg/dL.
- 206 bireyde (40%), ikincil sebeplere bağlanmış (hyperTG, DM, inflamatuvar hastalık, KC hastalığı, kullandığı ilaçlar)
- 201 bireyde ikincil sebep yok – genetik olarak düşük HDL-K – genetik analiz yapılmış
- 14 homozigot
- 59 heterozigot ; ABCA1 > LCAT > APOA1 > LPL genes
- 128 polijenik

DOI https://doi.org/10.1194/jlr.M088203

HDL-K < 20mg/dL – ne yapalım?

	Very low HDL-C (<5th percentile)	Moderately low HDL-C (<normal laboratory range)
Underlying disease	• Severe hypertriglyceridaemia • Uncontrolled diabetes • Liver failure • Systemic / acute inflammation • Haemato-oncological diseases	• Moderate hypertriglycaemia • Type 2 diabetes • Obesity • Chronic inflammation • Growth hormone excess • Hypercortisolism • Chronic kidney disease
Lifestyle, drugs	• Androgens • Probucol	• Smoking • Physical inactivity • Thiazide-diuretics • Some beta-blockers • Anti-retroviral drugs

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

Düşük HDL-K – Tedavi kılavuzları

Table 10 Corresponding non-high-density lipoprotein cholesterol and apolipoprotein B levels for commonly used low-density lipoprotein cholesterol goals

LDL-C	Non-HDL-C	Apolipoprotein B
2.6 mmol/L (100 mg/dL)	3.4 mmol/L (131 mg/dL)	100 mg/dL
1.8 mmol/L (70 mg/dL)	2.6 mmol/L (100 mg/dL)	80 mg/dL
1.4 mmol/L (55 mg/dL)	2.2 mmol/L (85 mg/dL)	65 mg/dL

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

4.6.2.2 Triglyceride-rich lipoproteins and their remnants

There are no treatment goals for triglycerides, but <1.7 mmol/L (150 mg/dL) is considered to indicate lower risk, whereas higher levels indicate a need to look for other risk factors.

4.6.2.3 High-density lipoprotein cholesterol

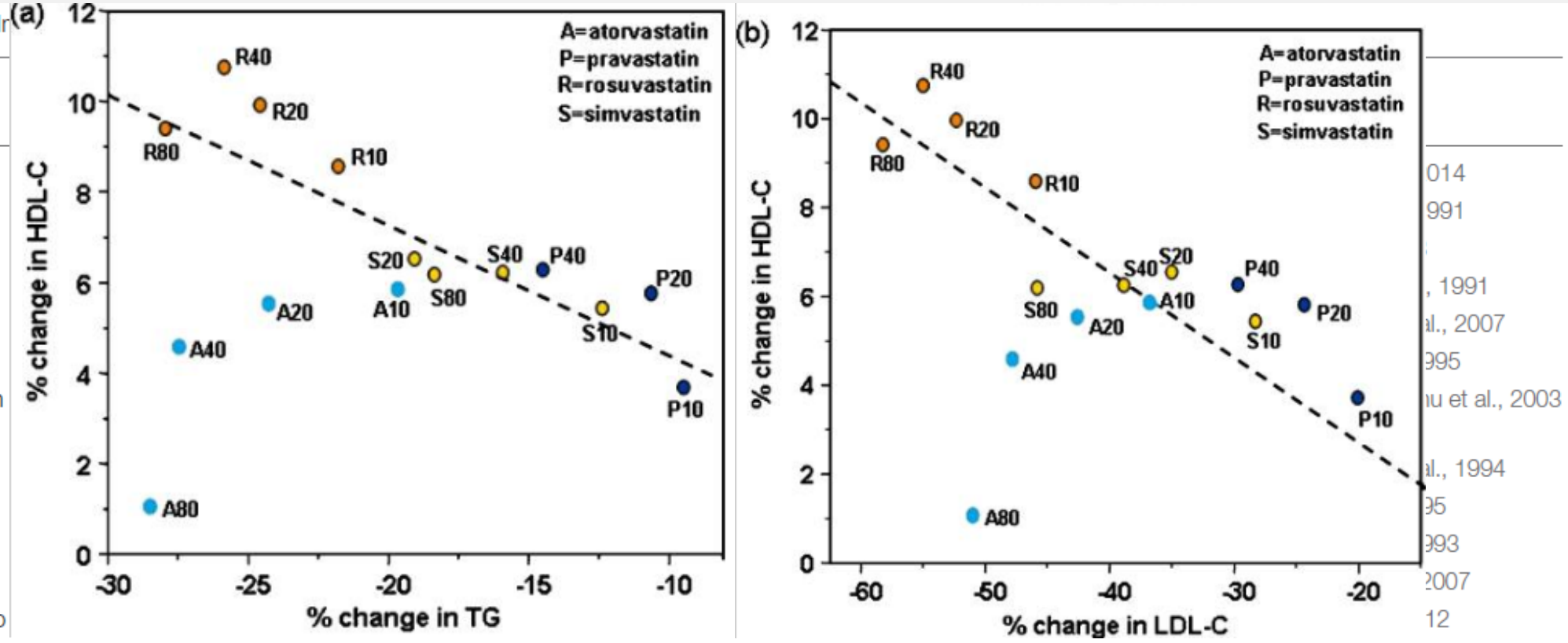
To date, no specific goals for HDL-C levels have been determined in clinical trials, although low HDL-C is associated with (residual) risk in ASCVD patients. PA and other lifestyle factors, rather than drug treatment, remain important means of increasing HDL-C levels.

4.6.1.3 Non-high-density lipoprotein cholesterol

The non-HDL-C value is calculated by subtracting HDL-C from total cholesterol. Non-HDL-C, unlike LDL-C, does not require the triglyceride concentration to be <4.5 mmol/L (400 mg/dL). It also has an advantage in that it is accurate in a non-fasting setting, and may be more accurate in patients with DM. There is evidence for a role of non-HDL-C as a treatment target as it captures the information regarding all apolipoprotein-B-containing lipoproteins.[513] We suggest it as a reasonable alternative treatment goal for all patients, particularly for those with hypertriglyceridaemia or DM. How non-HDL-C levels correspond to commonly used LDL-C goals is shown in *Table 10*.

- **Hastanın risk sınıfına göre öncelikle statin tedavisi – LDL-K hedeflerine ulaşılması önerilmektedir.**
- **LDL-K hedefine ulaşılamadığı durumlarda ezetimib - PCSK9i kombinasyonları kullanılmalıdır.**

Düşük HDL-K – İlaç tedavisi



Statins and CETP inhibitors therapies used to treat cardiovascular disease are summarized regarding their effects on LDL-C and HDL-C as well as HDL subclass specific changes.

- Statinler HDL-K %4-10 arttırır.

doi: 10.3389/fphar.2017.00989

Düşük HDL-K – Klinik çalışmalar

Drug	Disease	LDL-C (%)	HDL-C (%)	HDL2/large HDL (%)	HDL3/small HDL (%)	Reference
Niacin with statin and ezetimbe	CVD	−13	+11	Null	Null	Boden et al., 2011
Niacin and laropiprant with simvastatin	Primary hypercholesterolemia or mixed hyperlipidemia	−45	+20	+38	+14	Ballantyne et al., 2012
Niacin	Dyslipidemia	−35	+15	+82	−4	McKenney et al., 2001
	Primary hypercholesterolemia	−16	+23	+84	Null	Morgan et al., 2003
	Hyperlipidemia	–	–	+102	−2	Toth et al., 2012
Niacin and gemfibrozil	Hyperlipidemia	−20	+32	+90	Null	Superko et al., 2009
Bezafibrate	Coronary artery disease and dyslipoproteinemia	Null	Null	Null	+7	Ruotolo et al., 1998
Ciprofibrate	Hyperlipoproteinemia	−17	+13	Null	+22	Guérin et al., 2003
Fenofibrate	No diabetic patients	Null	+22	−2.3	+1.9	Franceschini et al., 2007

Niacin and fibrate therapies used to treat cardiovascular disease are summarized regarding their effects on LDL-C and HDL-C as well as HDL subclass specific changes.

- Erkeklerde HDL-K <40 mg/dL ve kadınlarda HDL-K < 50 mg/dl altgrup analizinde de tedavi faydasız.

participants
assigned to
niacin–laropiprant

N Engl J Med 2014;371:203-12.

Düşük HDL-K – Klinik çalışmalar

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Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

A. Das Pradhan, R.J. Glynn, J.-C. Fruchart, J.G. MacFadyen, E.S. Zaharris, B.M. Everett, S.E. Campbell, R. Oshima, P. Amarenco, D.J. Blom, E.A. Brinton, R.H. Eckel, M.B. Elam, J.S. Felicio, H.N. Ginsberg, A. Goudev, S. Ishibashi, J. Joseph, T. Kodama, W. Koenig, L.A. Leiter, A.J. Lorenzatti, B. Mankovsky, N. Marx, B.G. Nordestgaard, D. Páll, K.K. Ray, R.D. Santos, H. Soran, A. Susekov, M. Tendera, K. Yokote, N.P. Paynter, J.E. Buring, P. Libby, and P.M Ridker, for the PROMINENT Investigators*

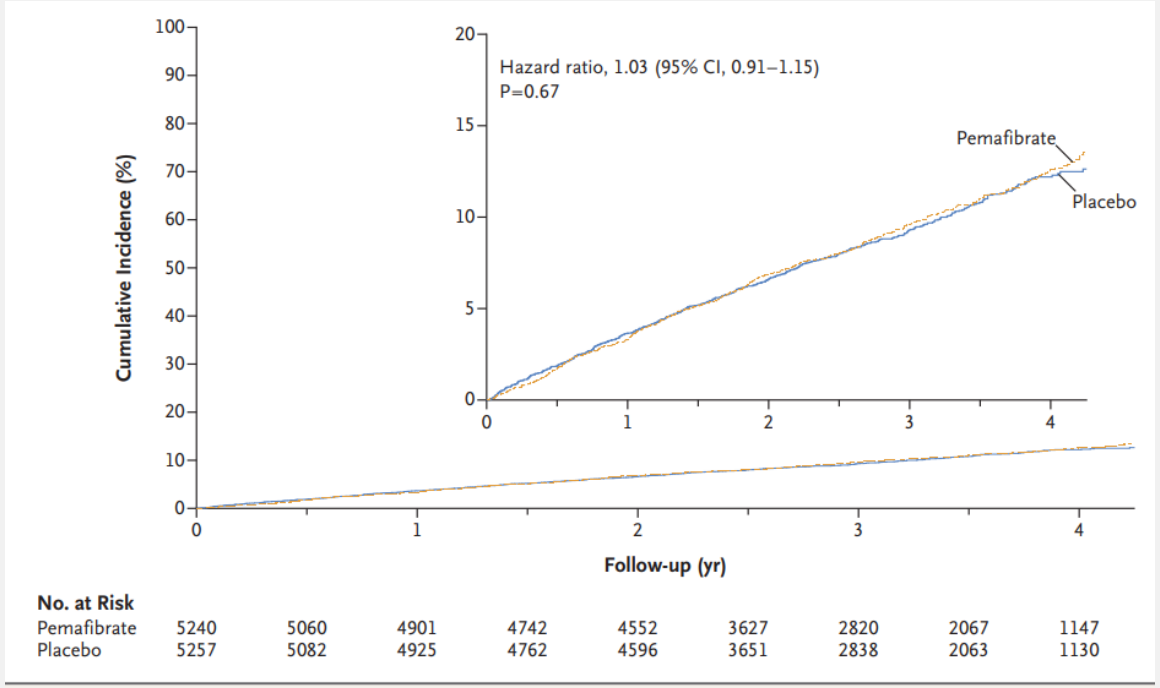

Figure 1. Cumulative Incidence of Cardiovascular Events.

Shown are Kaplan–Meier event curves for the primary trial end point of myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes. The inset shows the same data on an expanded y axis.

- 10.5 B hasta, primer ve sekonder korunma kolları mevcut.
- Pemafibrat 0.2 mg 2x1 vs plasebo randomize, 3.4 sene takip
- Başlangıç TG 271 mg/dL, HDL-K 33 mg/dL, LDL-K 77 mg/dL

- **Aktif tedavi kolunda,**
  - TG %31, VLDL %35, non-HDL-K %2 düşüş
  - **HDL-K %8 artış, LDL-K %14, apoB %3 artış**

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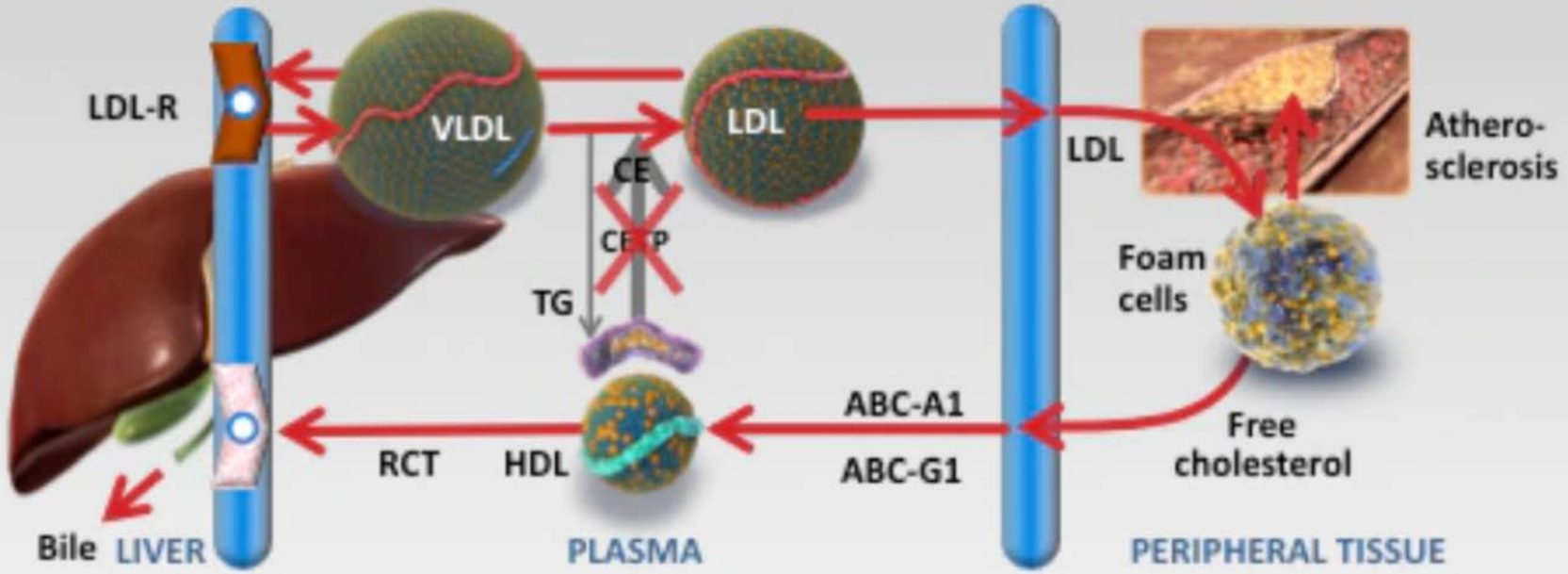
CETP inhibitörleri



- Human CETP deficiency is associated with marked increases in HDL-C[a]
- CETP activity is inversely correlated with plasma HDL-C[a]
- Reduction in CETP activity is associated with a marked reduction in the cholesterol burden in TG-rich particles in both fasting and postprandial phases[b,c]
- Decreasing CETP activity has consistently inhibited atherosclerosis in animal models[a]

ESC European Society of Cardiology

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INVITED REVIEW

Cholesteryl ester transfer protein inhibitors: from high-density lipoprotein cholesterol to low-density lipoprotein cholesterol lowering agents?

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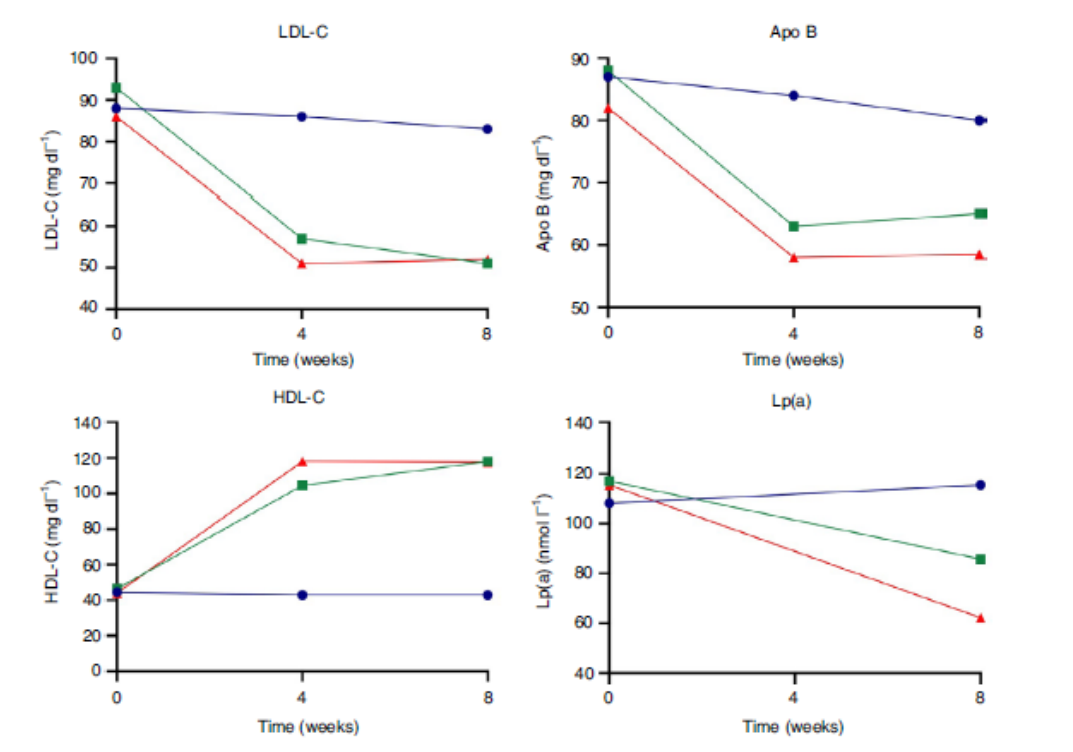
- Tüm lipoproteinler üzerine olumlu etkileri mevcut.
- İlaçlar etkin ancak çalışma süresi kısa – fark istatistiksel anlamlılığa ulaşmamış.

Obicetrapid – PREVAIL çalışması



- HDL-K %165 artış

Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial

Stephen J. Nicholls[1], Marc Ditmarsch[2], John J. Kastelein[3], Scott P. Rigby[4], Douglas Kling[2], Danielle L. Curcio[2], Nicholas John Alp[5] and Michael H. Davidson[2]

- **Yoğun statin tedavisi alan hastalarda, ortalama LDL-K 90 mg/dL**
- **Obicetrapid 5 mg, oral**
  - LDL-C 41 %
  - apoB 25 %
  - Lp (a) 34%
- **Obicetrapid 10 mg, oral**
  - LDL-C 50 %
  - apoB 30 %
  - Lp(a) 56%

HDL-K düşüklüğü – ASKVH için risk belirtecidir.

- HDL-K düşüklüğü, gözlemsel çalışmalarda ASKVH riski ile ilişkili bulunsa da, genetik çalışmalar ve TG düşüren/HDL-K yükselten tedavilerde HDL-K yükseltmenin klinik yararı gösterilememiştir.
- Tedavi kılavuzlarında spesifik HDL-K hedefleri yoktur.
- Obicetrapid tedavisi sadece HDL-K üzerine değil apoB içeren diğer lipoproteinler üzerine de olumlu etki etmektedir. Faz 3 çalışması devam etmektedir.
- ASKVH riskini azaltan tüm tedaviler LDL-K ve apoB içeren lipoproteinleri düşürerek etki göstermektedir.

TEŞEKKÜRLER...