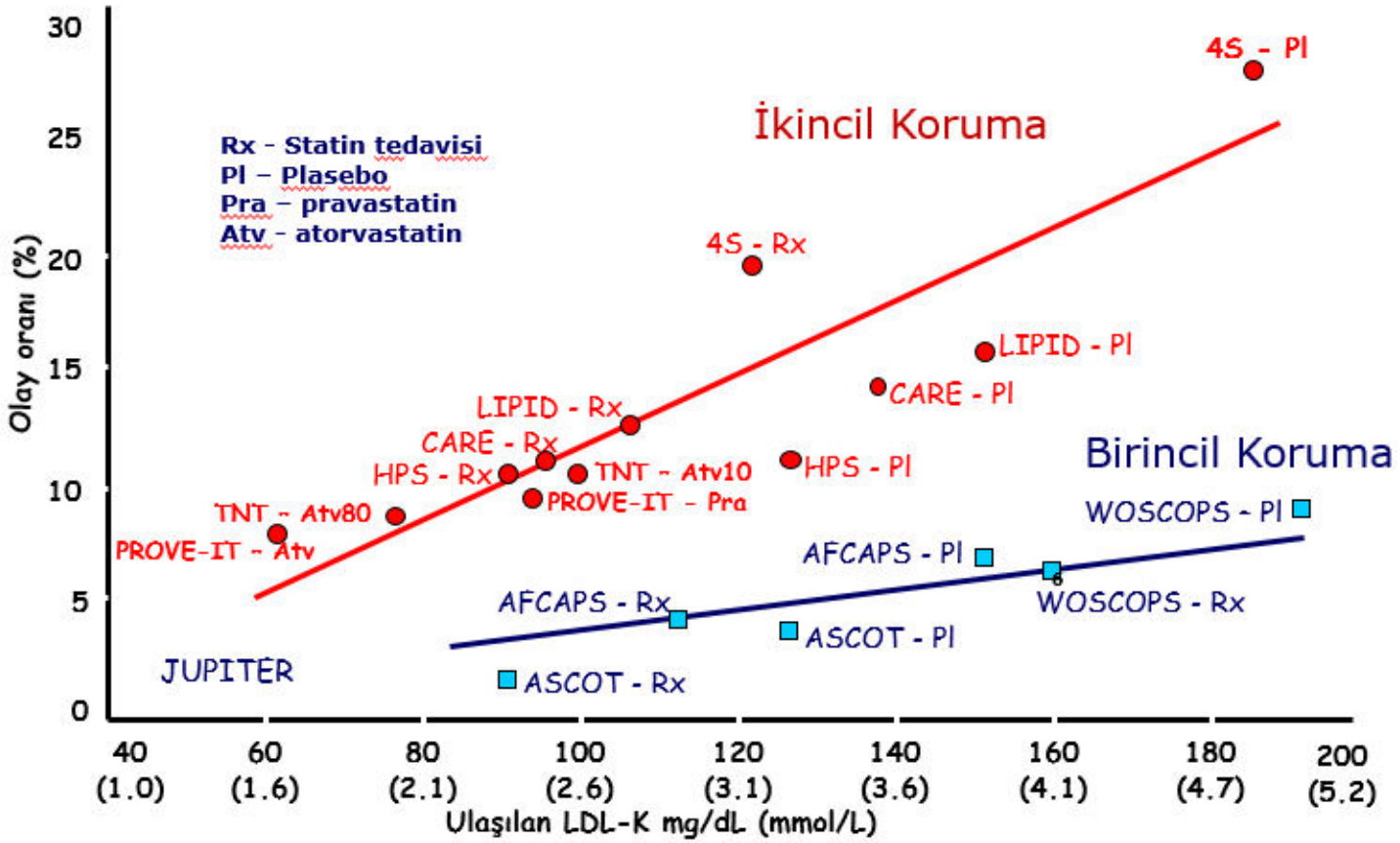
Statin tedavisinde doğrular ve yanlışlar

Dr. Ahmet Temizhan
SBÜ Ankara Bilkent Şehir Hastanesi Kardiyoloji Kliniği
SBÜ 6.İç Hastalıkları Kongresi

Statin bize hiç yanlış yapmadı!

Kedi olalı bir fare tuttuk

İkincil ve birincil korunmada statinler;
LDL-K düşüşüyle paralel olarak KVO gelişimini azaltır



Rosenson RS. *Exp Opin Emerg Drugs* 2004;**9**(2):269-279, LaRosa JC *et al. N Engl J Med* 2005;**352**:1425-1435.

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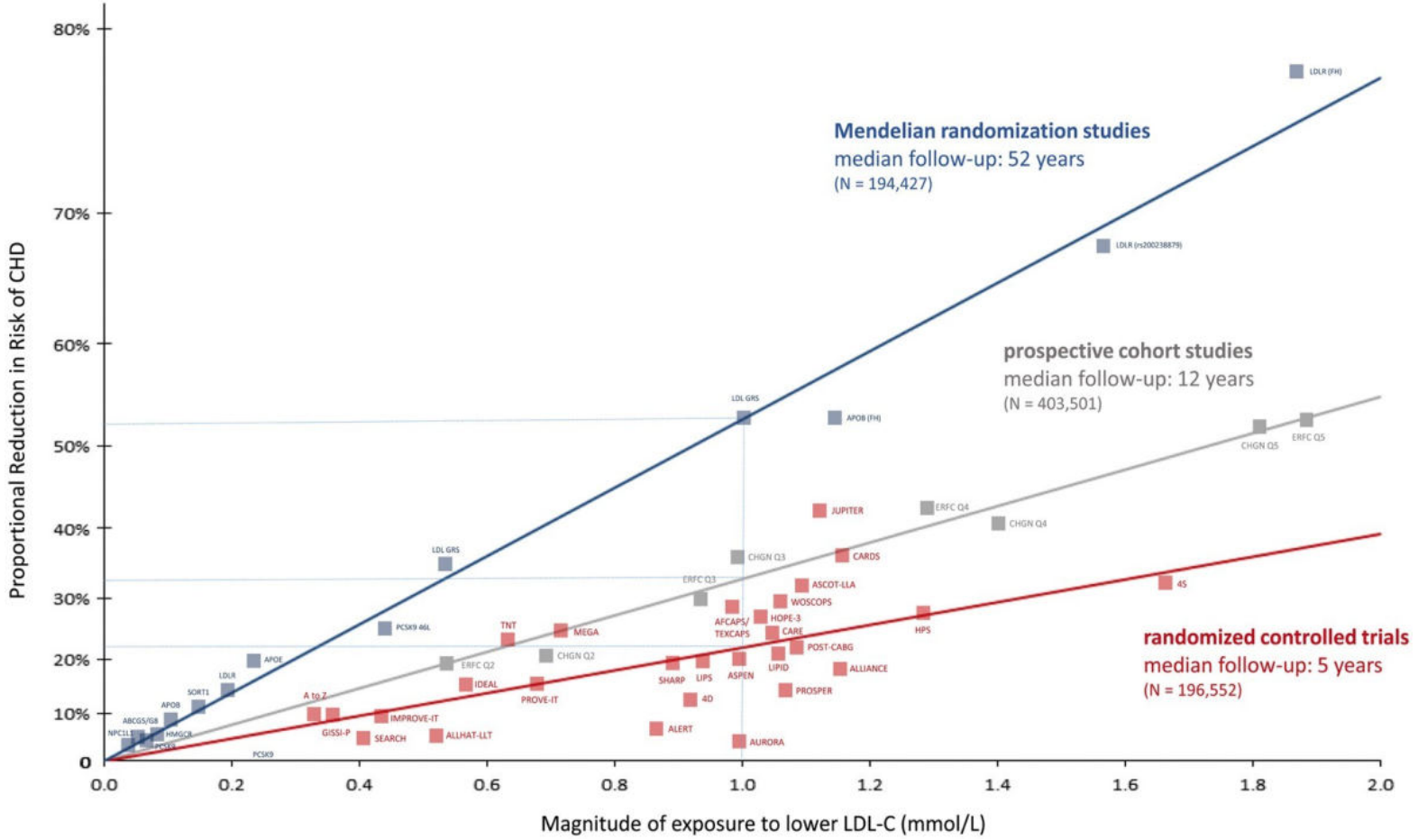
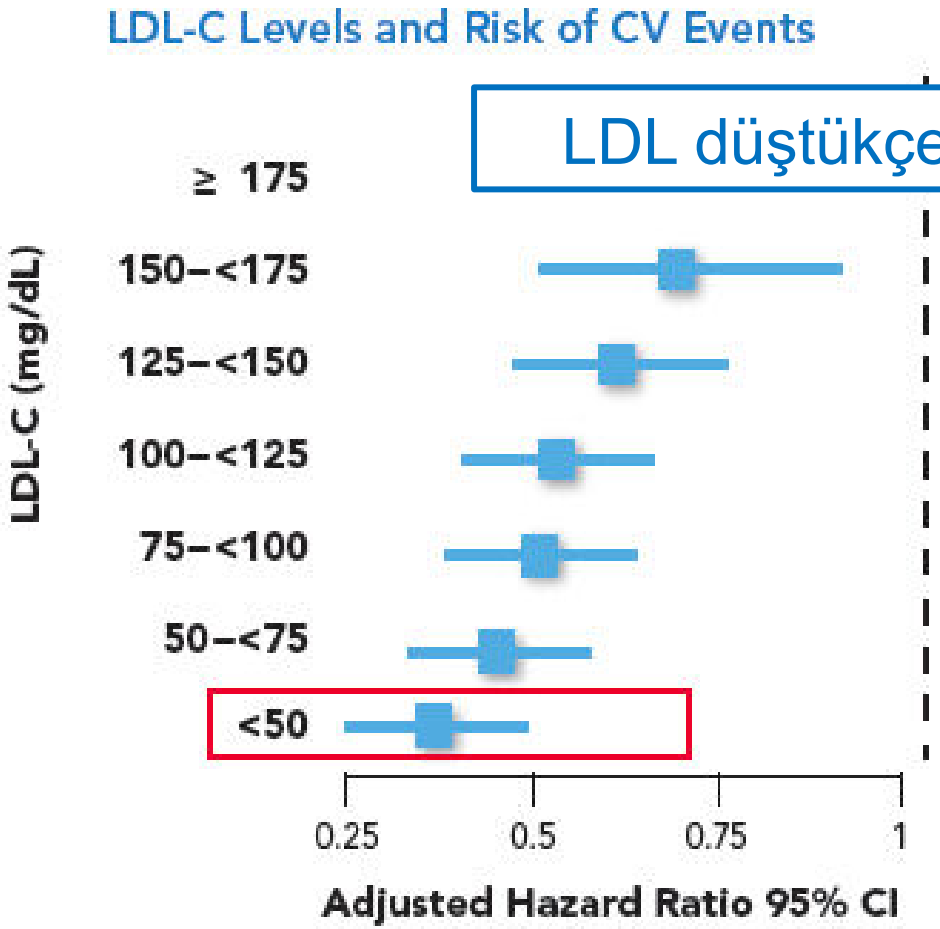


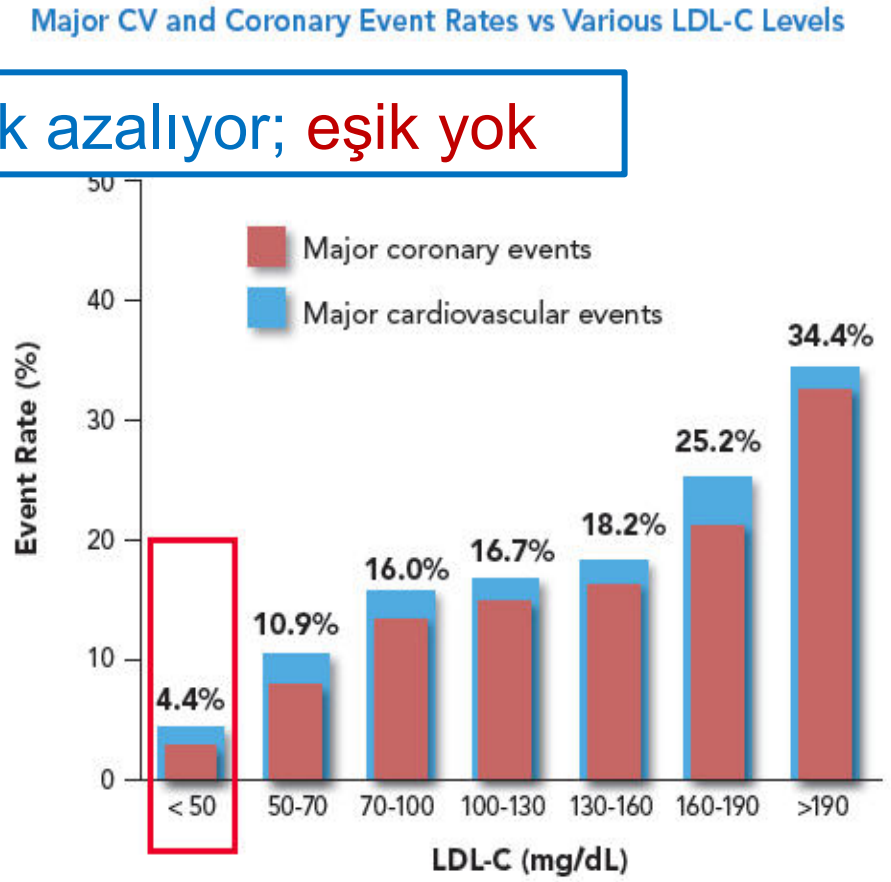
Eur Heart J, Volume 38, Issue 32, 21 August 2017, Pages 2459–2472,
https://doi.org/10.1093/eurheartj/ehx144

LDL-K düştükçe major KV olaylar azalıyor, eşik yok

38153 hasta metaanalizi



LDL düştükçe risk azalıyor; eşik yok



J Am Coll Cardiol 2014;64:485–94.

Statin ile LDL'de 1 mmol/L (38.67 mg/dL) azalma ve 5 yıllık takip;

Major koroner olaylar %23 ↓

KAH ilişkili ölümler %20 ↓

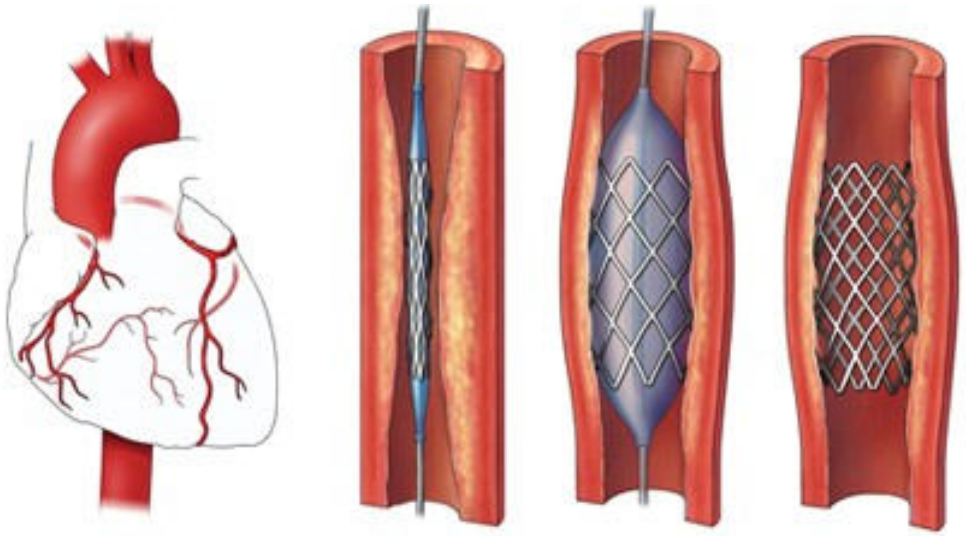
Total inme %17 ↓

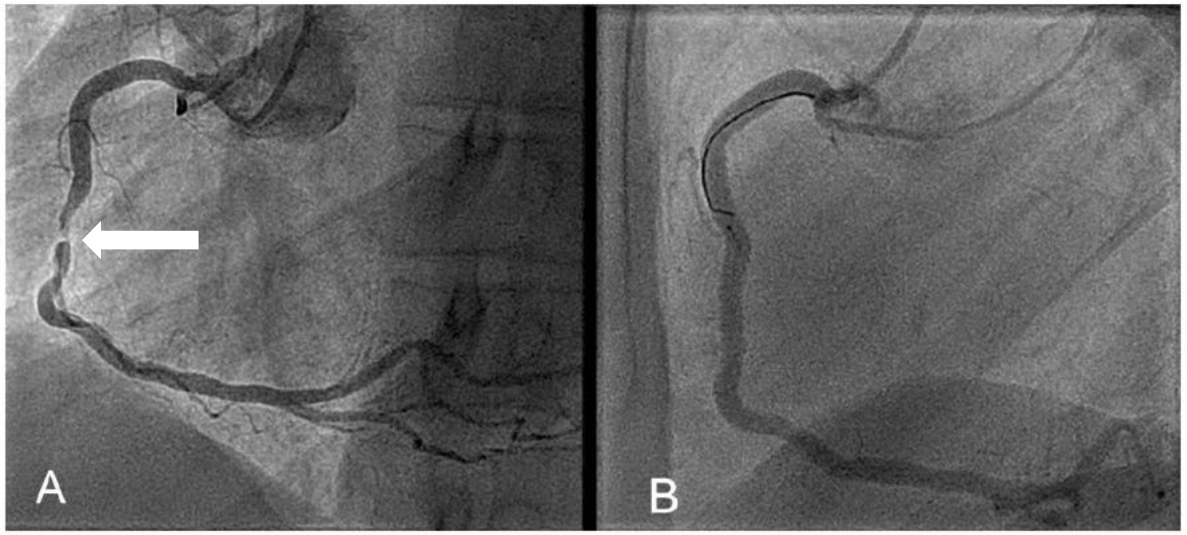
Total mortalite %10 ↓

Böyle bir silahımız varken

KAH stent ile tedavi (!) edilmeye çalışılıyor

Koroner stent anginayı azaltılabiliyor

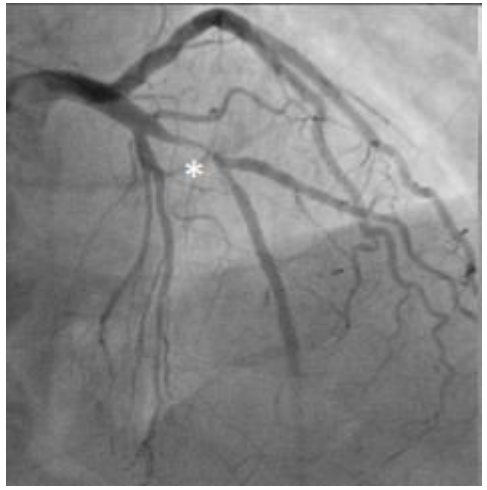




Mİ gelişimini engellenebiliyor mu?

Initial Invasive or Conservative Strategy for Stable Coronary Disease

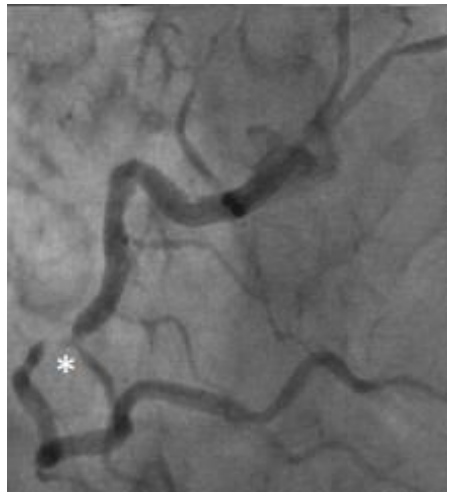
ISCHEMIA



Stabil KAH
Orta veya ciddi iskemi

N:2588

N:2591



İnvaziv yaklaşım
OMT+KAG+optimal revaskülarizasyon

Konservatif yaklaşım
OMT

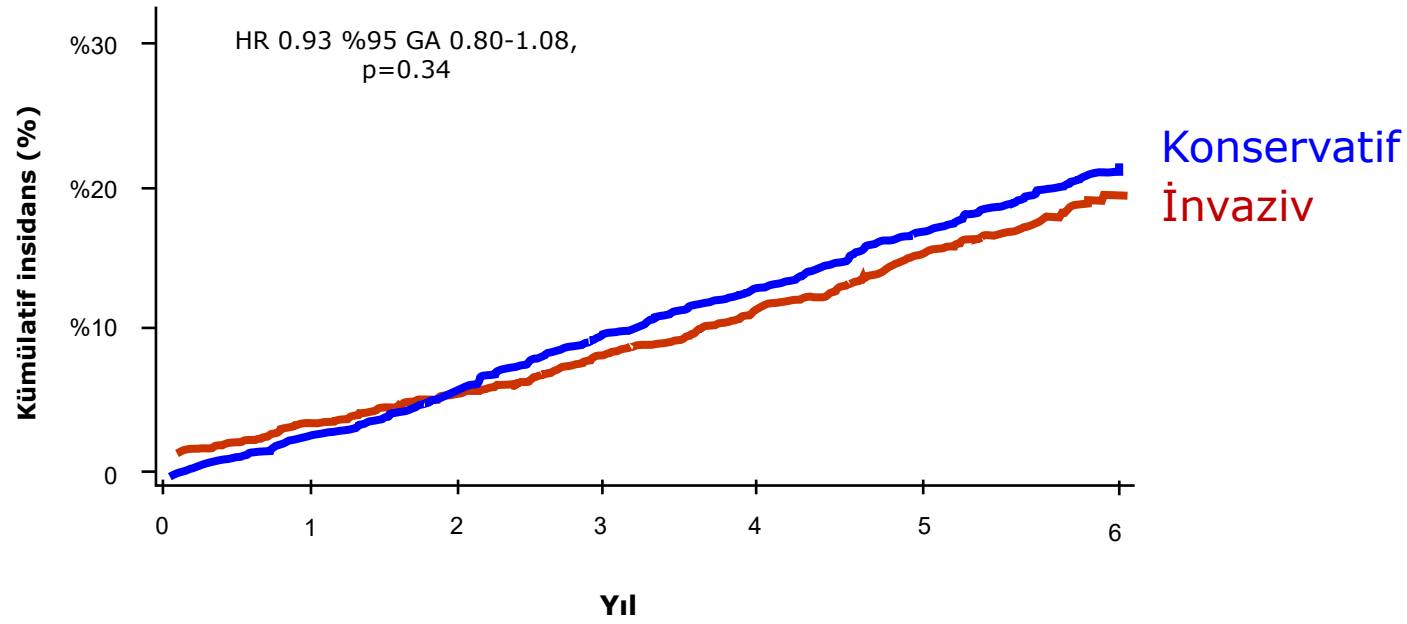
3.2 yıl takip

Birincil sonlanım; KV nedenli ölüm, Mİ, veya USAP, KY nedeniyle yatış veya resuste edilen kardiyak arrest

30 Mart 2020, NEJM

ISCHEMIA

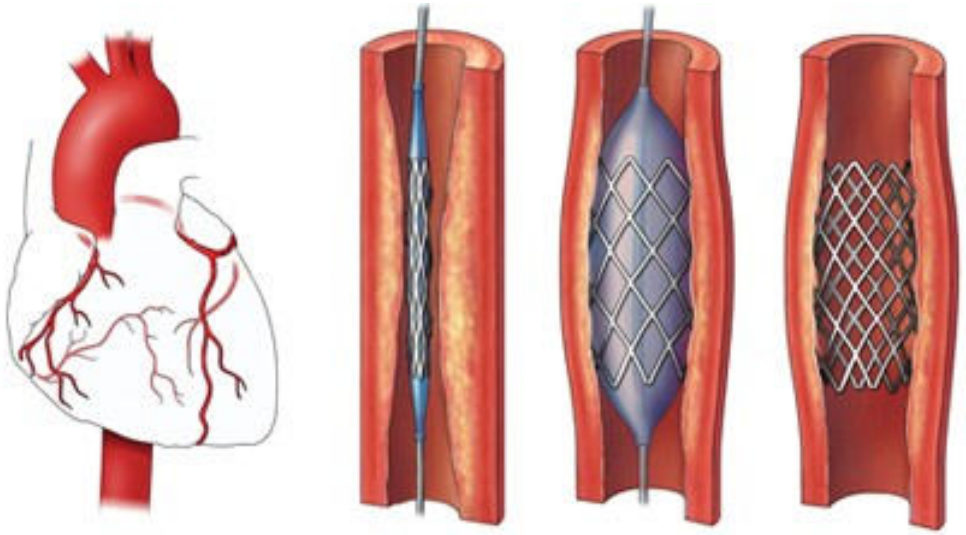
Birincil sonlanım; KV nedenli ölüm, Mİ, veya USAP, KY nedeniyle yatış veya resuste edilen kardiyak arrest

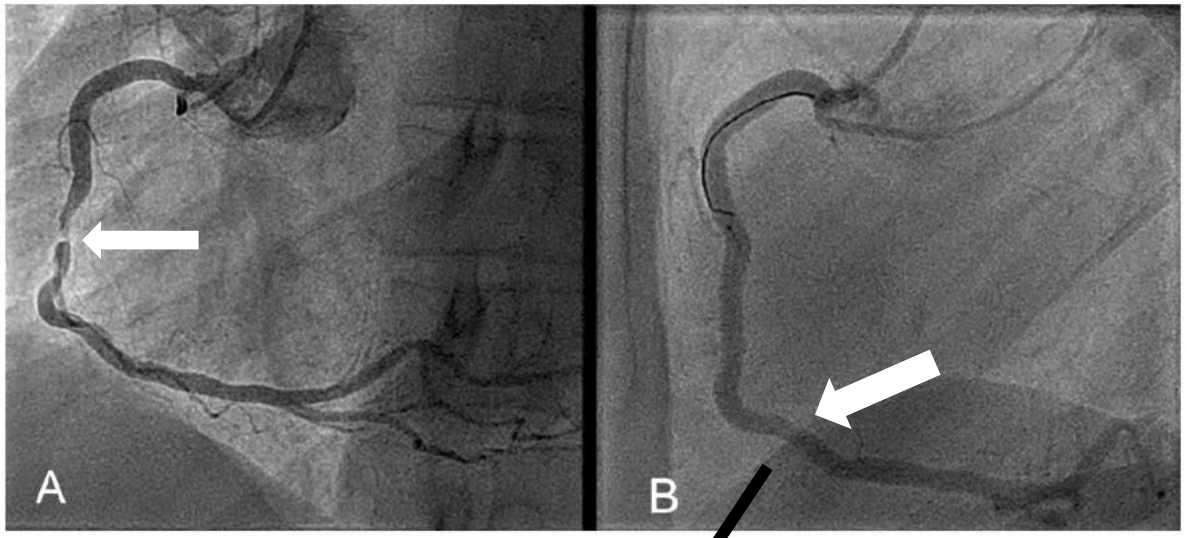


OMT (statin) tedavisi çok önemli

30 Mart 2020, NEJM

Koroner stentler Mİ gelişimini niçin engelleyemiyor?

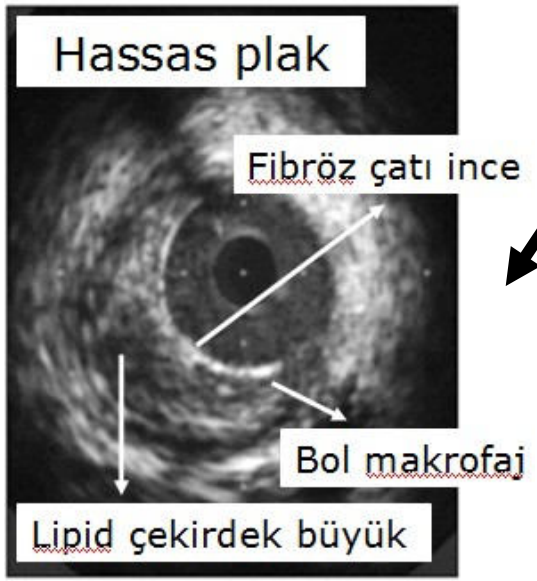




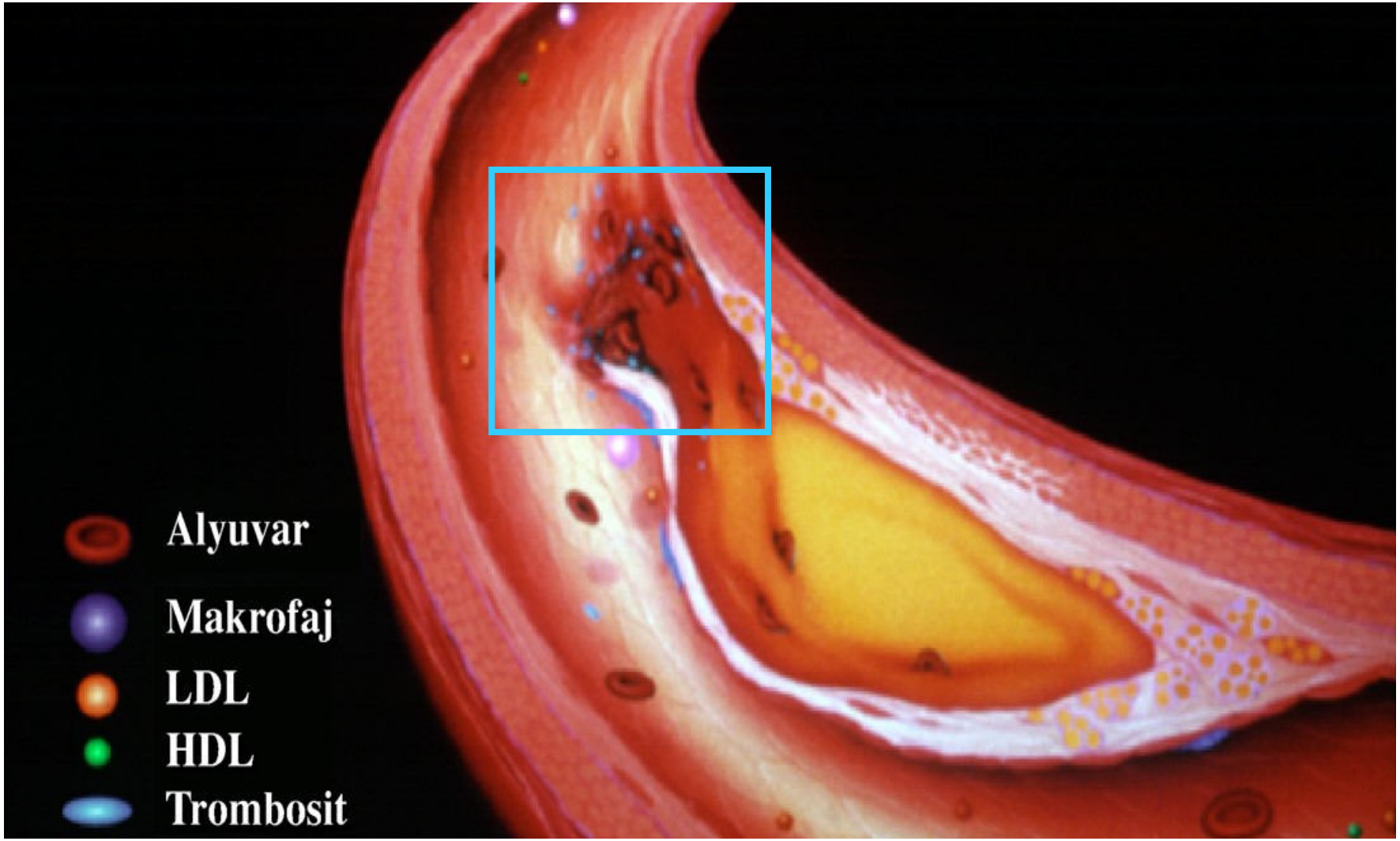
Stent restenozu denen bir sorun var!

Mİ ciddi darlık yapmayan plaklardan da (hatta daha çok) kaynaklanıyor

Koroner plakların fibröz çatısını sağlamlaştırmak gerek

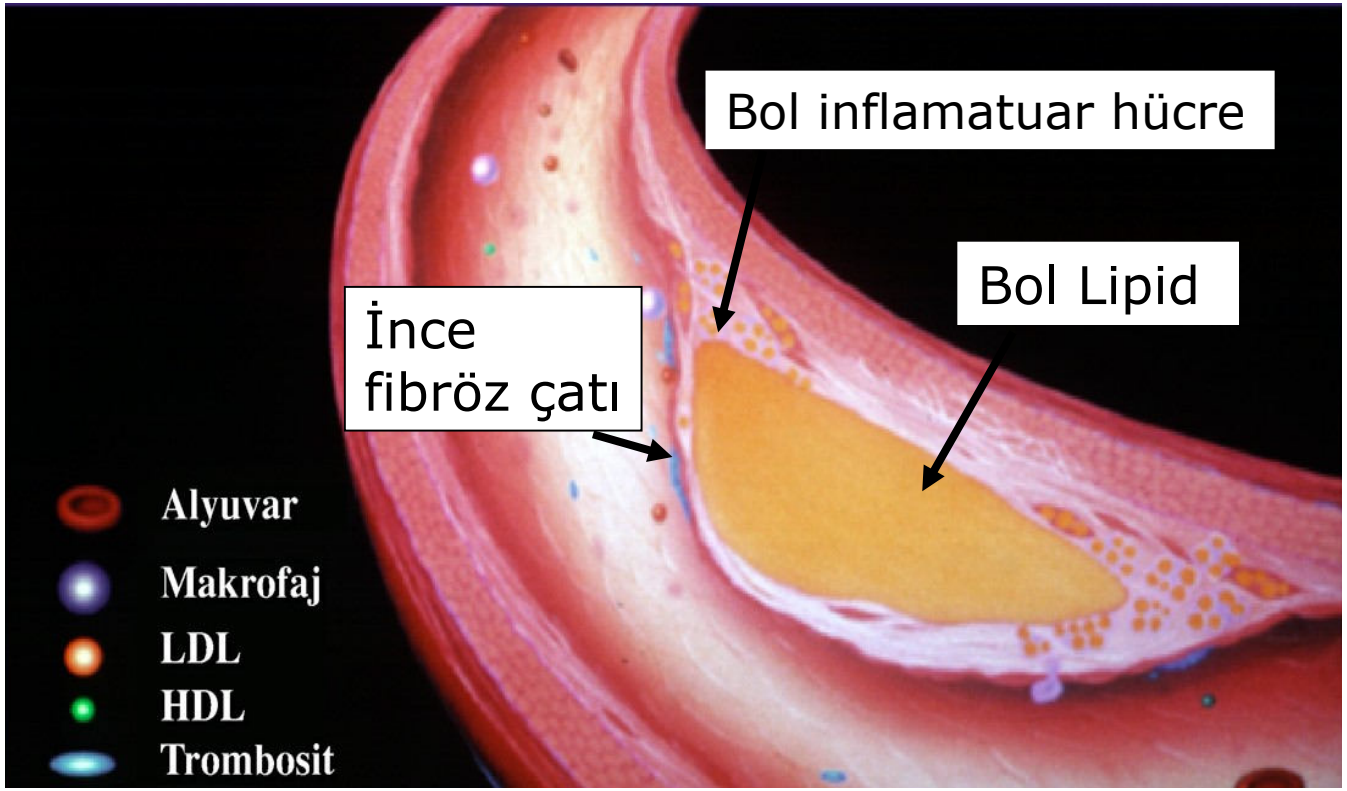


Ateroskleroz ve progresyonu



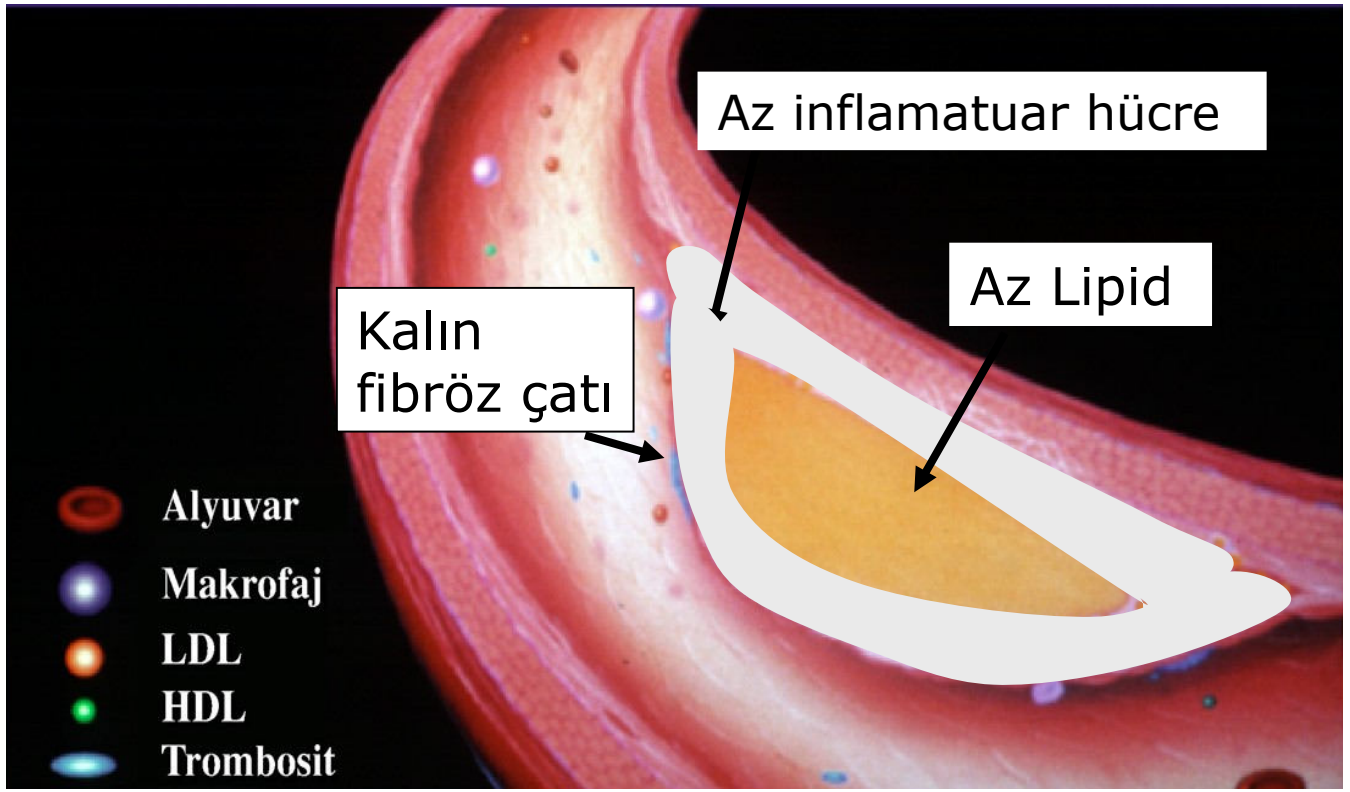
Libby P, New Perspectives in Lipid Education, Lipid Lowering and the Atherosclerotic Plaque: New Insights

Hassas: koroner plak



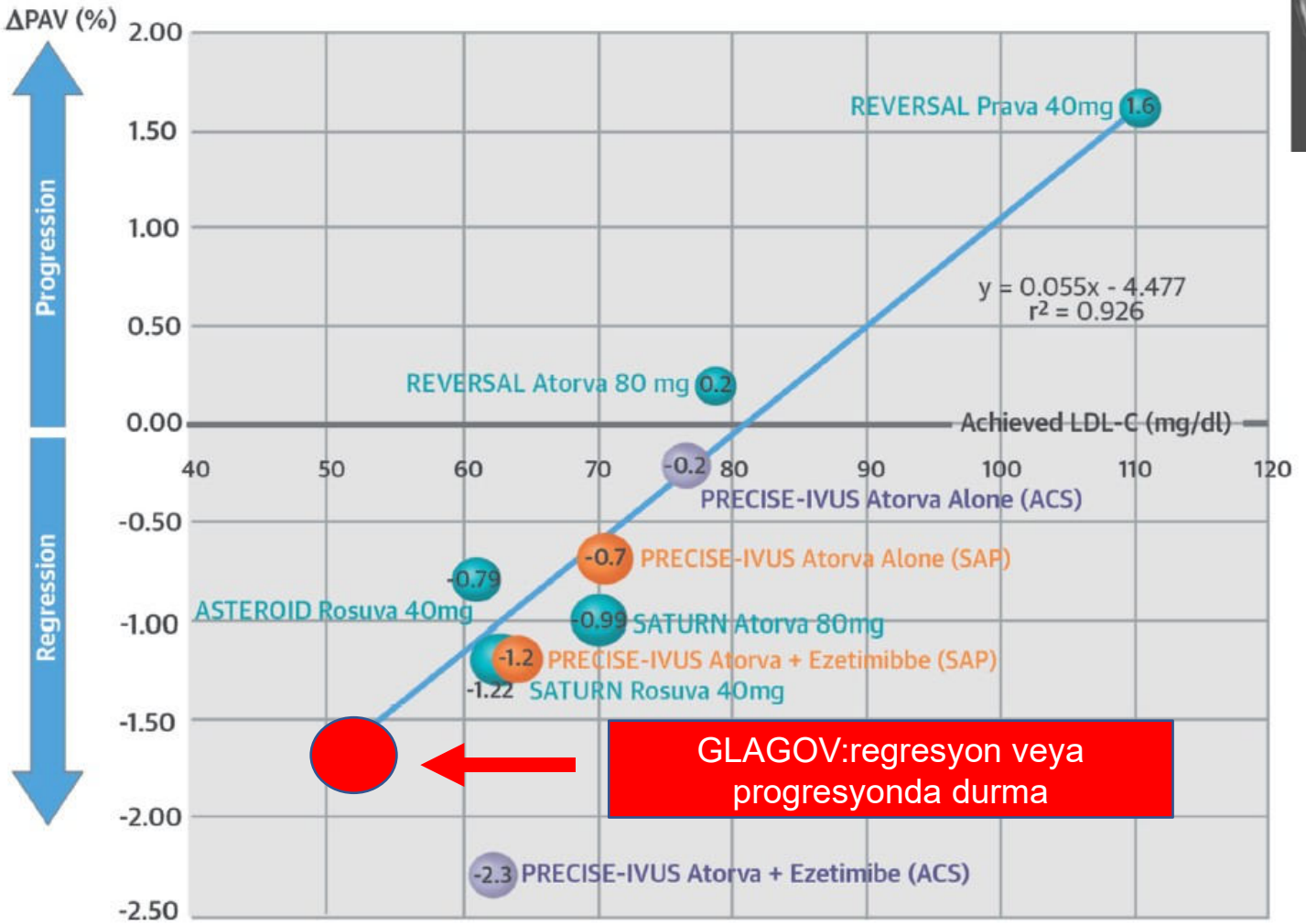
Statin ile

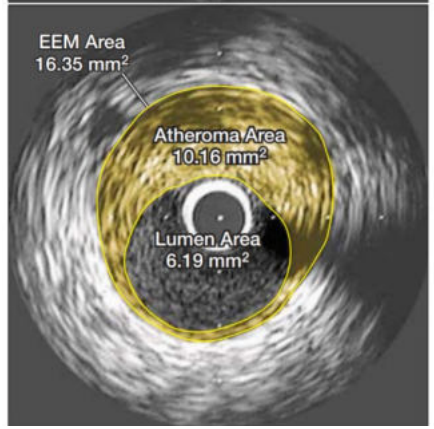
Sağlam: koroner plak

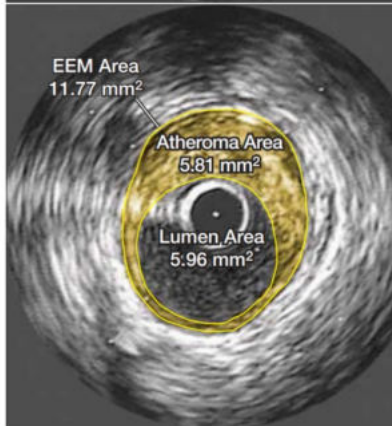


Statin aterosklerotik plaklarda yaptığı değişiklikleri gözle görebiliyor muyuz?

IVUS ile regresyon ve LDL







Eur Heart J 2020;41:111-188

JAMA Cardiology | Original Investigation

Association of Statin Treatment With Progression of Coronary Atherosclerotic Plaque Composition

Alexander R. van Rosendael, MD; Inge J. van den Hoogen, MD; Umberto Gianni, MD; Xiaoyue Ma, MSc; Sara W. Tantawy, MD; A. Maxim Bax, BS; Yao Lu, MSc; Daniele Andreini, MD, PhD; Mouaz H. Al-Mallah, MD; Matthew J. Budoff, MD; Filippo Cademartiri, MD, PhD; Kavitha Chinnaiyan, MD; Jung Hyun Choi, MD, PhD; Edoardo Conte, MD; Hugo Marques, MD, PhD; Pedro de Araújo Gonçalves, MD, PhD; Ilan Gottlieb, MD, PhD; Martin Hadamitzky, MD; Jonathon A. Leipsic, MD; Erica Maffei, MD; Gianluca Pontone, MD, PhD; Sanghoon Shin, MD; Yong-Jin Kim, MD, PhD; Byoung Kwon Lee, MD, PhD; Eun Ju Chun, MD, PhD; Ji Min Sung, PhD; Sang-Eun Lee, MD, PhD; Renu Virmani, MD; Habib Samady, MD; Yu Sato, MD; Peter H. Stone, MD; Daniel S. Berman, MD; Jagat Narula, MD, PhD; Ron Blankstein, MD; James K. Min, MD; Fay Y. Lin, MD; Leslee J. Shaw, PhD; Jeroen J. Bax, MD, PhD; Hyuk-Jae Chang, MD, PhD

IMPORTANCE The density of atherosclerotic plaque forms the basis for categorizing calcified and noncalcified morphology of plaques.

OBJECTIVE To assess whether alterations in plaque across a range of density measurements provide a more detailed understanding of atherosclerotic disease progression.

DESIGN, SETTING, AND PARTICIPANTS This cohort study enrolled 857 patients who underwent serial coronary computed tomography angiography 2 or more years apart and had quantitative measurements of coronary plaques throughout the entire coronary artery tree. The study was conducted from 2013 to 2016 at 13 sites in 7 countries.

MAIN OUTCOMES AND MEASURES The main outcome was progression of plaque composition of individual coronary plaques. Six plaque composition types were defined on a voxel-level basis according to the plaque attenuation (expressed in Hounsfield units [HU]): low attenuation (−30 to 75 HU), fibro-fatty (76-130 HU), fibrous (131-350 HU), low-density calcium (351-700 HU), high-density calcium (701-1000 HU), and 1K (>1000 HU). The progression rates of these 6 compositional plaque types were evaluated according to the interaction between statin use and baseline plaque volume, adjusted for risk factors and time interval between scans. Plaque progression was also examined based on baseline calcium density. Analysis was performed among lesions matched at baseline and follow-up. Data analyses were conducted from August 2019 through March 2020.

857 hasta

Seri koroner CT anjiografi çekilmiş

↓

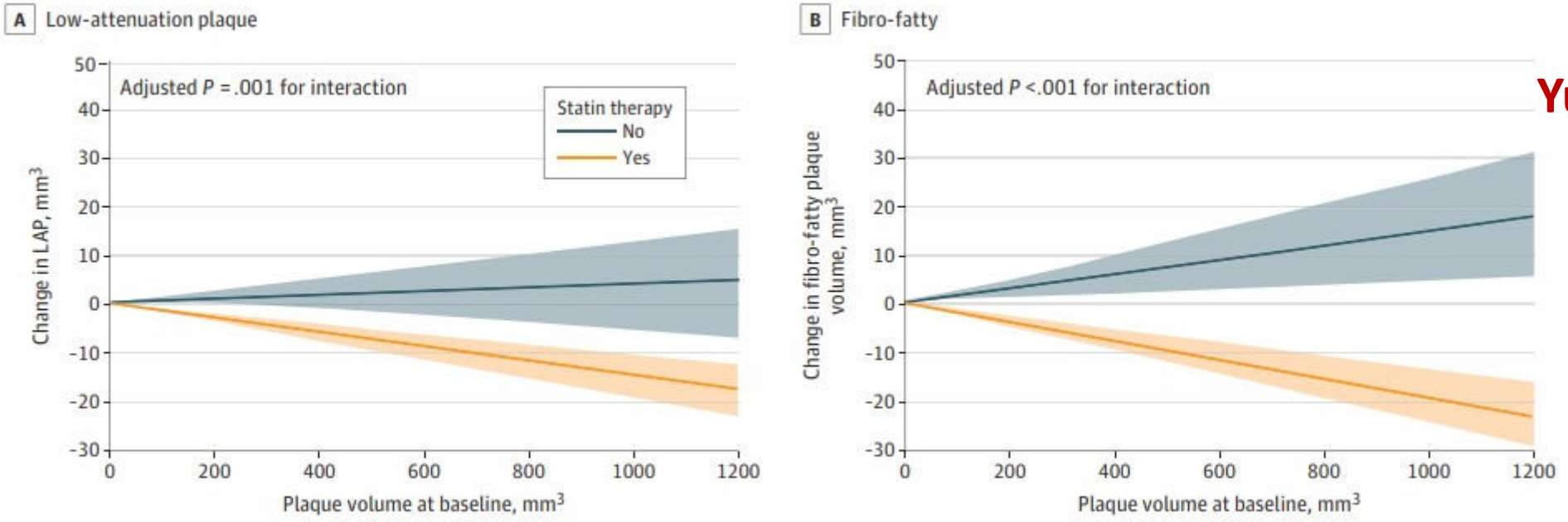
Statin alan

Statin almayan

↓

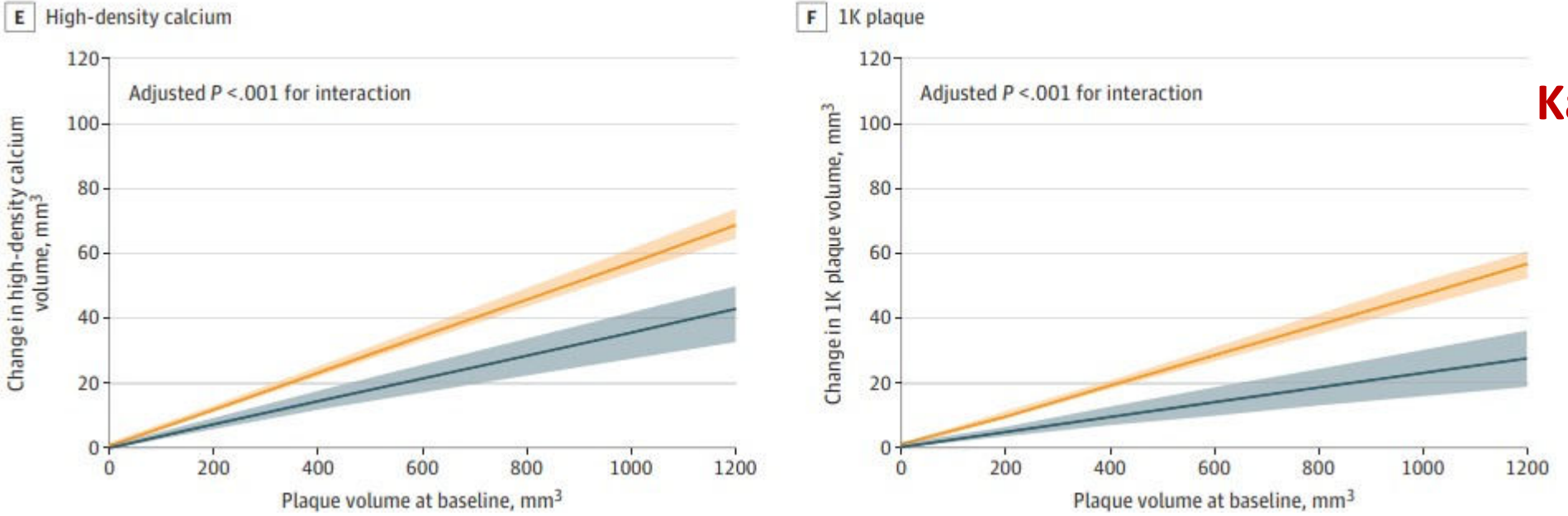
2-6 yıl süre içinde koroner plaklarda oluşan değişim

JAMA Cardiol. 2021;6(11):1257-1266



Yumuşak plak ↓

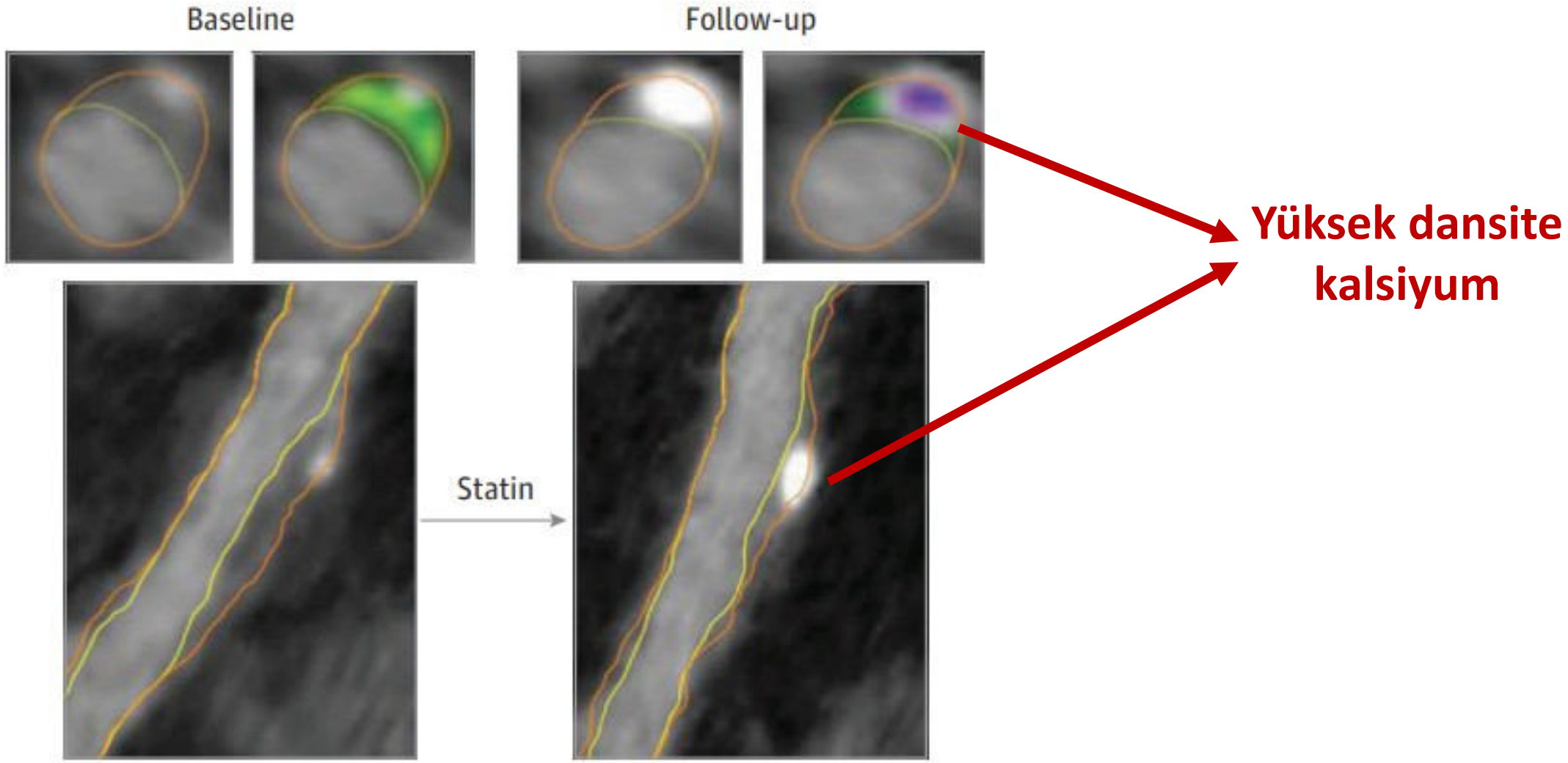
LDL-K düzeyi:88 mg/dL vs 110 mg/dL



Kalsifiye plak ↑

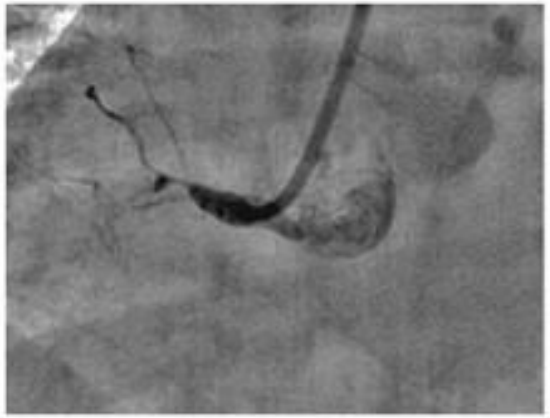
JAMA Cardiol. 2021;6(11):1257-1266

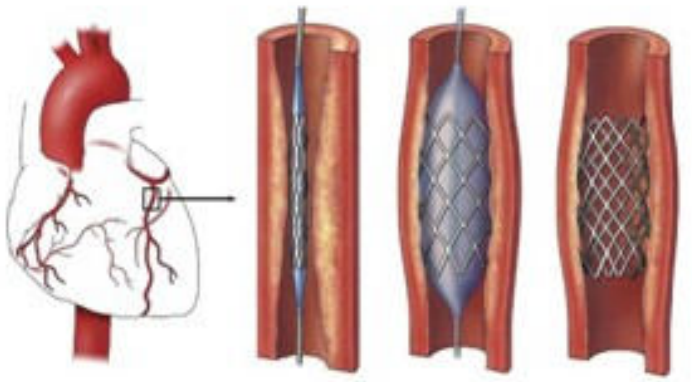
Statin aterosklerotik plağı sertleştiriyor

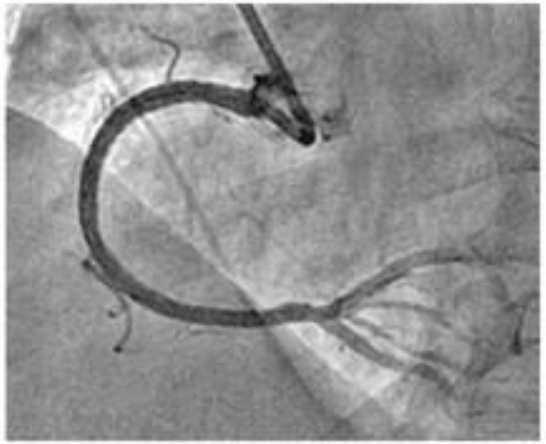


JAMA Cardiol. 2021;6(11):1257-1266

Statin bu özelliğinden AMİ hastalarının tedavisinde de faydalanıyoruz







22 sene önce; AKS'da yüksek doz statin

Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes

The MIRACL Study: A Randomized Controlled Trial

Gregory G. Schwartz, MD, PhD
Anders G. Olsson, MD, PhD
Michael D. Ezekowitz, MD, PhD
Peter Ganz, MD
Michael F. Oliver, MD
David Waters, MD
Andreas Zeiher, MD
Bernard R. Chaitman, MD
Sally Leslie, PhD
Theresa Stern, PhD
for the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators

Context Patients experience the highest rate of death and recurrent ischemic events during the early period after an acute coronary syndrome, but it is not known whether early initiation of treatment with a statin can reduce the occurrence of these early events.

Objective To determine whether treatment with atorvastatin, 80 mg/d, initiated 24 to 96 hours after an acute coronary syndrome, reduces death and nonfatal ischemic events.

Design and Setting A randomized, double-blind trial conducted from May 1997 to September 1999, with follow-up through 16 weeks at 122 clinical centers in Europe, North America, South Africa, and Australasia.

Patients A total of 3086 adults aged 18 years or older with unstable angina or non–Q-wave acute myocardial infarction.

Interventions Patients were stratified by center and randomly assigned to receive treatment with atorvastatin (80 mg/d) or matching placebo between 24 and 96 hours after hospital admission.

Main Outcome Measures Primary end point event defined as death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization.

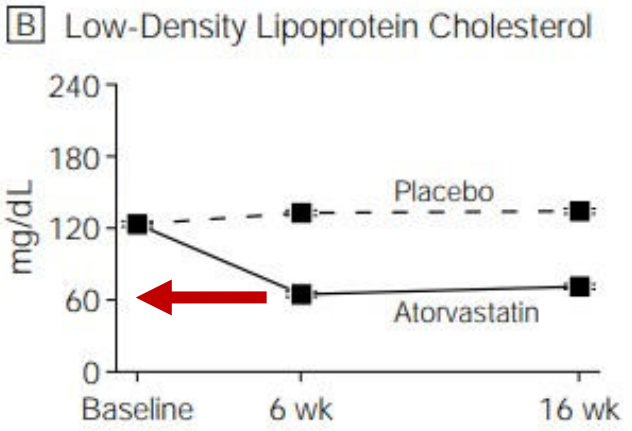
Results A primary end point event occurred in 228 patients (14.8%) in the atorvastatin group and 269 patients (17.4%) in the placebo group (relative risk [RR], 0.84; 95% confidence interval [CI], 0.70-1.00; $P=.048$). There were no significant differences in risk of death, nonfatal myocardial infarction, or cardiac arrest between the atorvastatin group and the placebo group, although the atorvastatin group had a lower risk of symptomatic ischemia with objective evidence and requiring emergency rehospitalization (6.2% vs 8.4%; RR, 0.74; 95% CI, 0.57-0.95; $P=.02$). Likewise, there were no significant differences between the atorvastatin group and the placebo group in the incidence of secondary outcomes of coronary revascularization procedures, worsening heart failure, or worsening angina, although there were fewer strokes in the atorvastatin group than in the placebo group (12 vs 24 events; $P=.045$). In the atorvastatin group, mean low-density lipoprotein cholesterol level declined from 124 mg/dL (3.2 mmol/L) to 72 mg/dL (1.9 mmol/L). Abnormal liver transaminases (>3 times upper limit of normal) were more common in the atorvastatin group than in the placebo group (2.5% vs 0.6%; $P<.001$).

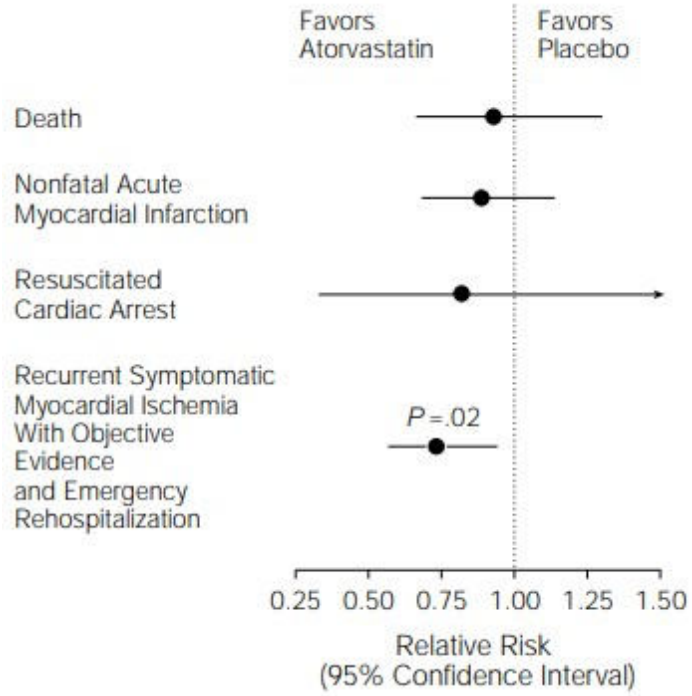
Conclusion For patients with acute coronary syndrome, lipid-lowering therapy with atorvastatin, 80 mg/d, reduces recurrent ischemic events in the first 16 weeks, mostly recurrent symptomatic ischemia requiring rehospitalization.

JAMA. 2001;285:1711-1718 www.jama.com

BLOOD CHOLESTEROL LOWERing with statins has been regarded as a long-term strategy to reduce death and ischemic cardiovascular events in patients with stable coronary heart disease, with significant effects evident after approximately 2 years of treatment.[1-3] Previous trials excluded patients who had experienced recent unstable angina or acute myocardial infarction (MI). However, it is within the early period after an acute coronary syndrome (ACS) that patients experience the highest rate of death and recurrent ischemic events.[4,5] To date, it has not been determined whether initiation of treatment with a

USAP veya Non-Q MI 3086 hasta
<u>İlk 24-96 saat içinde</u>
LDL-K değerine bakılmaksızın
Atorvastatin 80 mg vs plasebo





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

PROVE IT–TIMI 22

Christopher P. Cannon, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Daniel J. Rader, M.D., Jean L. Rouleau, M.D., Rene Belder, M.D., Steven V. Joyal, M.D., Karen A. Hill, B.A., Marc A. Pfeffer, M.D., Ph.D., and Allan M. Skene, Ph.D., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 Investigators*

ABSTRACT

BACKGROUND

Lipid-lowering therapy with statins reduces the risk of cardiovascular events, but the optimal level of low-density lipoprotein (LDL) cholesterol is unclear.

METHODS

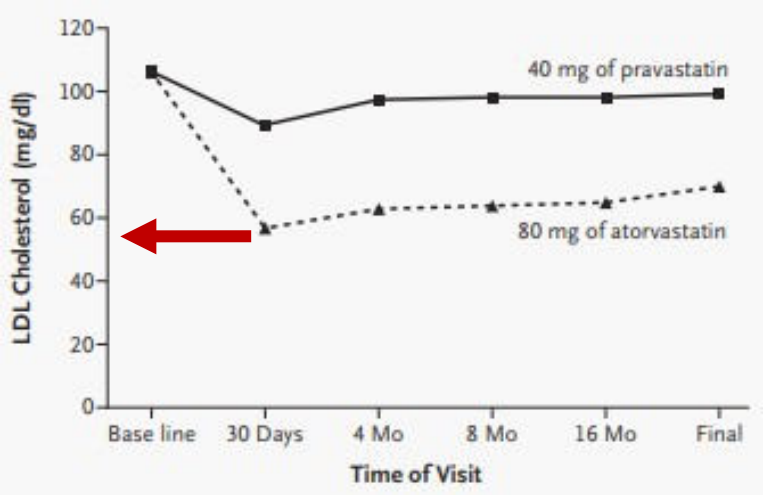
We enrolled 4162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and compared 40 mg of pravastatin daily (standard therapy) with 80 mg of atorvastatin daily (intensive therapy). The primary end point was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. The study was designed to establish the noninferiority of pravastatin as compared with atorvastatin with respect to the time to an end-point event. Follow-up lasted 18 to 36 months (mean, 24).

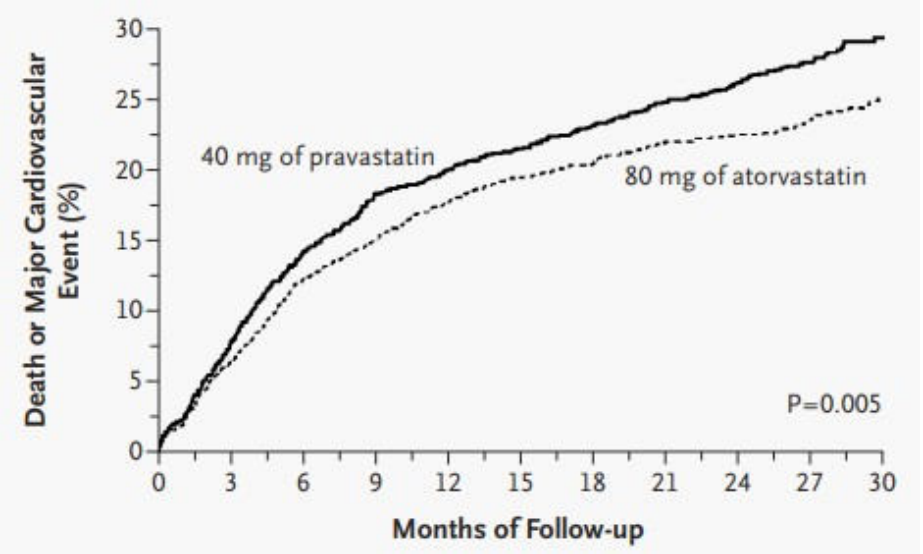
RESULTS

The median LDL cholesterol level achieved during treatment was 95 mg per deciliter (2.46 mmol per liter) in the standard-dose pravastatin group and 62 mg per deciliter (1.60 mmol per liter) in the high-dose atorvastatin group (P<0.001). Kaplan–Meier estimates of the rates of the primary end point at two years were 26.3 percent in the pravastatin group and 22.4 percent in the atorvastatin group, reflecting a 16 percent reduction in the hazard ratio in favor of atorvastatin (P=0.005; 95 percent confidence interval, 5 to 26 percent). The study did not meet the prespecified criterion for equivalence but did identify the superiority of the more intensive regimen.

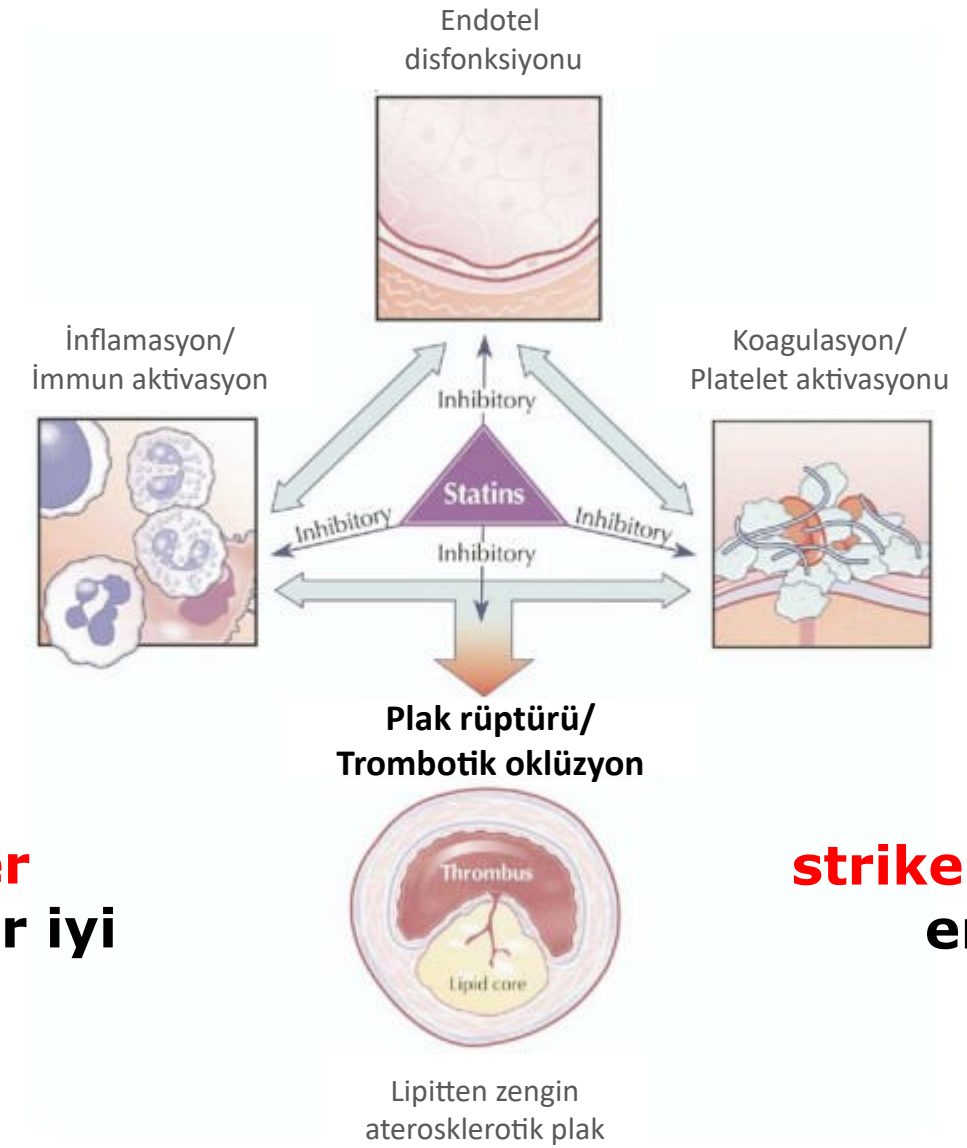
NEJM 2004;350

USAP, NSTEMI, STEMI 4162 hasta
İlk 10 gün içinde
LDL-K değerine bakılmaksızın
Atorvastatin 80 mg vs Pravastatin 40 mg





%16 RRA



the lower, the better
ne kadar düşük o kadar iyi

strike early and strike strong
erken vur, güçlü vur

2019 ESC/ EAS guidelines for the management of dyslipidaemias. Eur Heart J 2020;41:111–188
Eur Heart J, Acute Cardiovascular Care 2022; 11: 939–949

Statin tedavisinde yanlışlar

Kolesterolümü statin ile değil diyet ve egzersizle düşüreyim…

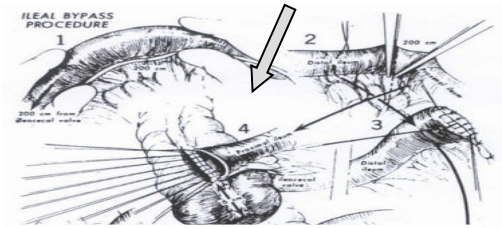
(Statin endikasyonu olan hastalar için)

POSCH – Çalışması
emilim yüzeyinin azaltılması

Buchwald et al., NEJM 1990

1975-83, 838 AMI, LDL>140

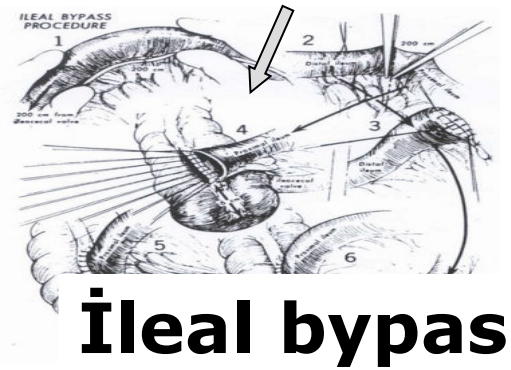
Diyet



Diyet +
ileal bypass

POSCH – Çalışması
5 yıl takip

emilim yüzeyinin azaltılması



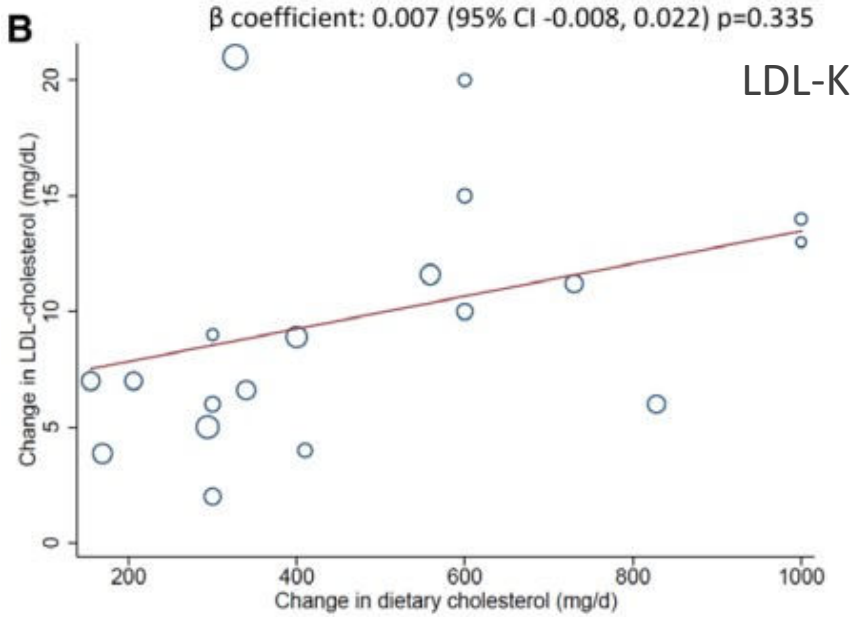
	diyet	**İleal bypass diyet**	
Toplam mortalite	106	84	(-%25)
KAH mortalitesi	70	49	(-%34)
PTCA / Bypass	201	106	(-%59)

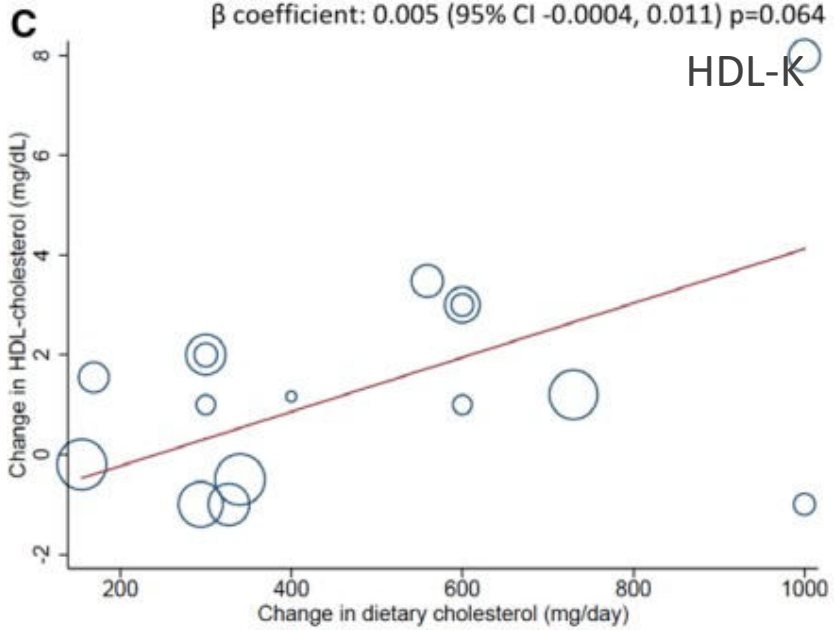
Buchwald et al, Arch of Int Med 1998; 158:1253-61

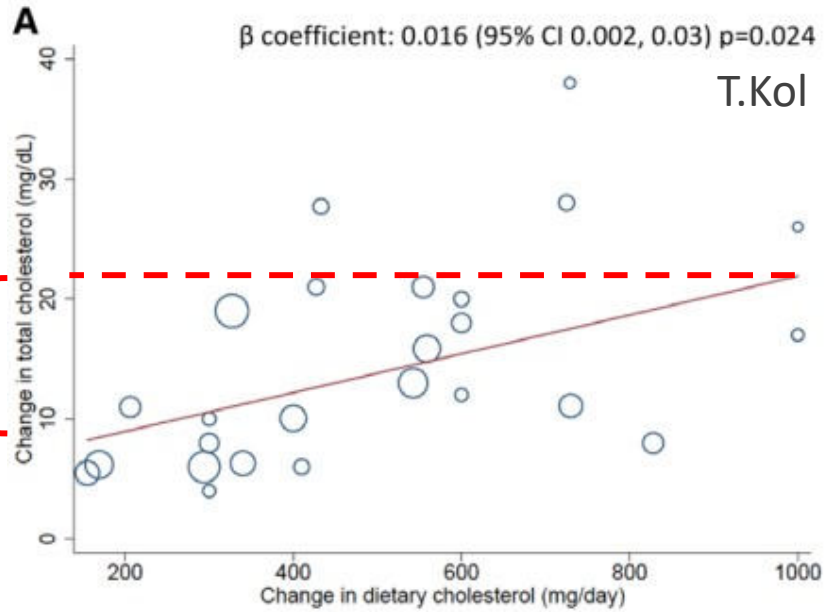
Bağırsakları devre dışı bırakamayız!

Diyetle aldığımız kolesterolü azaltmak işe yarıyor mu?

Diyet ile alınan kolesterol miktarı 155 - 1000 mg/gün

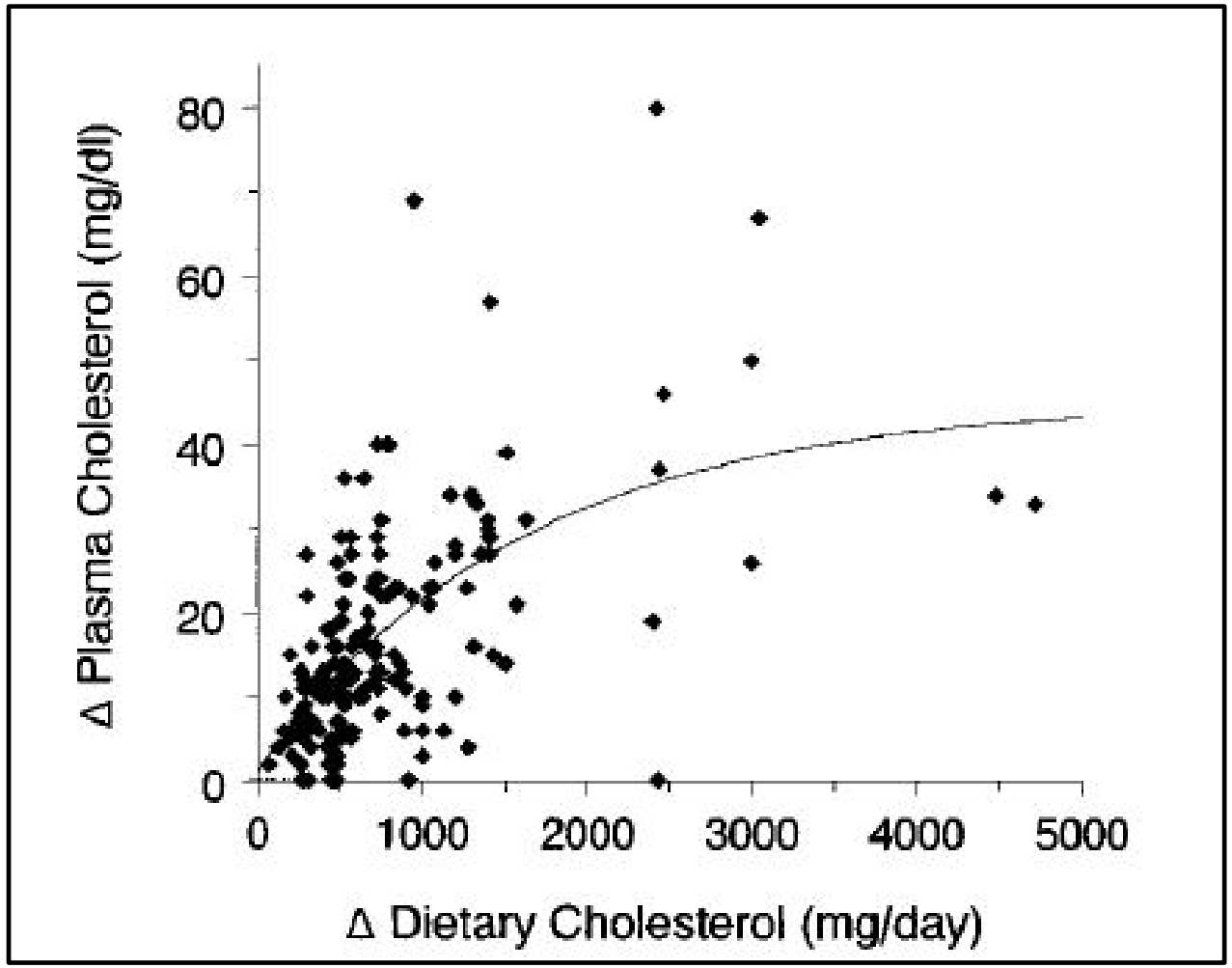






Circulation 2020;141(3):e39-e53

Kolesterol alımı çok yüksek ise emilim azalıyor…



Journal of the American College of Nutrition, 2000; 19: 540S–548S

Kilosu az olanlar kolesterolden daha çok etkileniyor…

Akdeniz tipi beslenenlerde
Vejetaryenlerde fazla

*:Endojen kol sentezi kilo ile ilişkili. Düşük kilolularda sentez az olduğu için emilim için feedback veremiyor…

Am J Epidemiol 137:171–177, 1993.

Amerikan

+ yumurta
kan kolesterolünü çok değiştirmez

Akdeniz veya vejetaryen

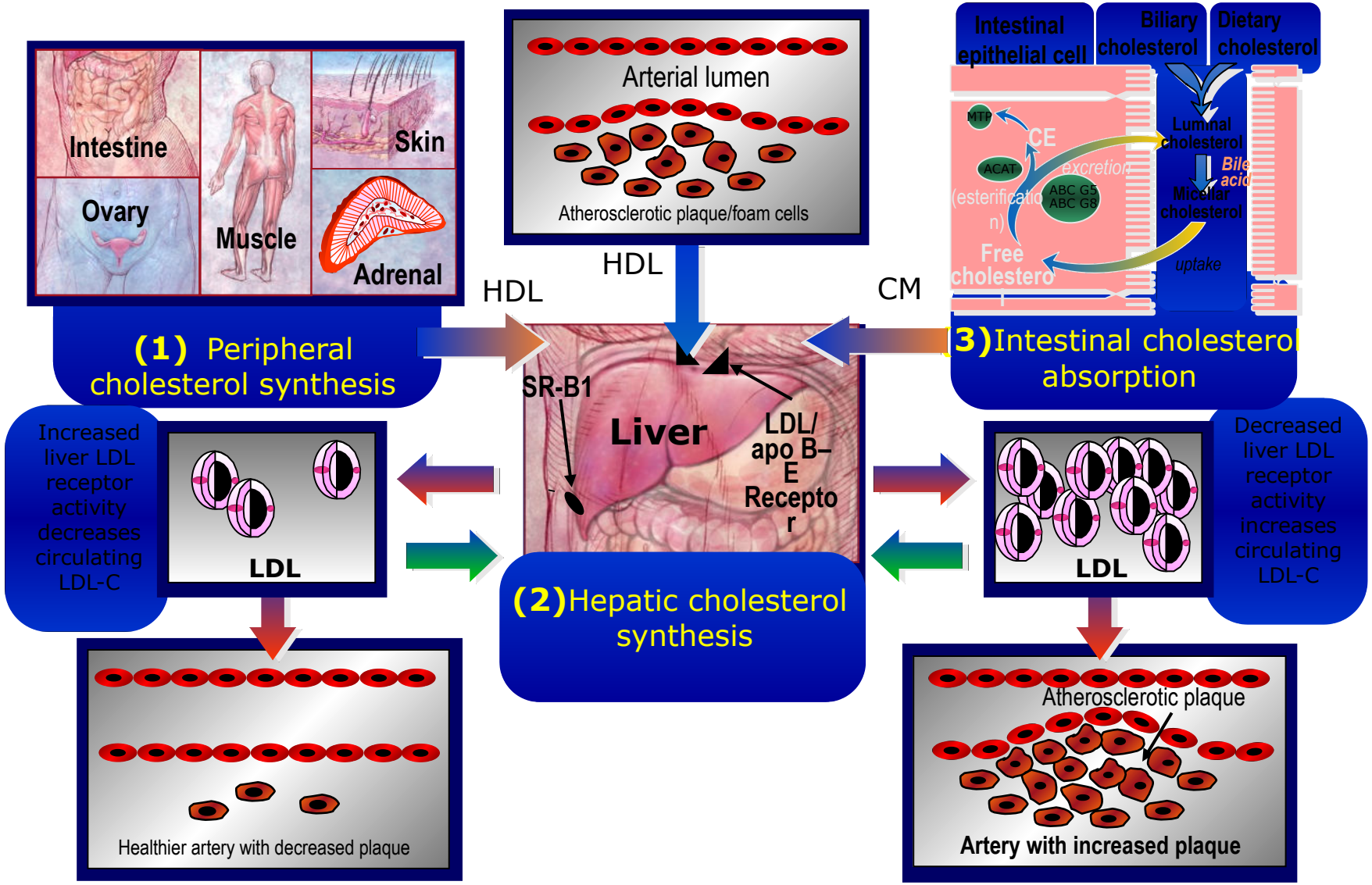
+ yumurta
kan kolesterolünü daha fazla arttırır

Barsaktan kolesterol emilim çok heterojen
Toplumun %70'i hipo-responder…

J Am Coll Nutr 2000; 19: 540S–548S

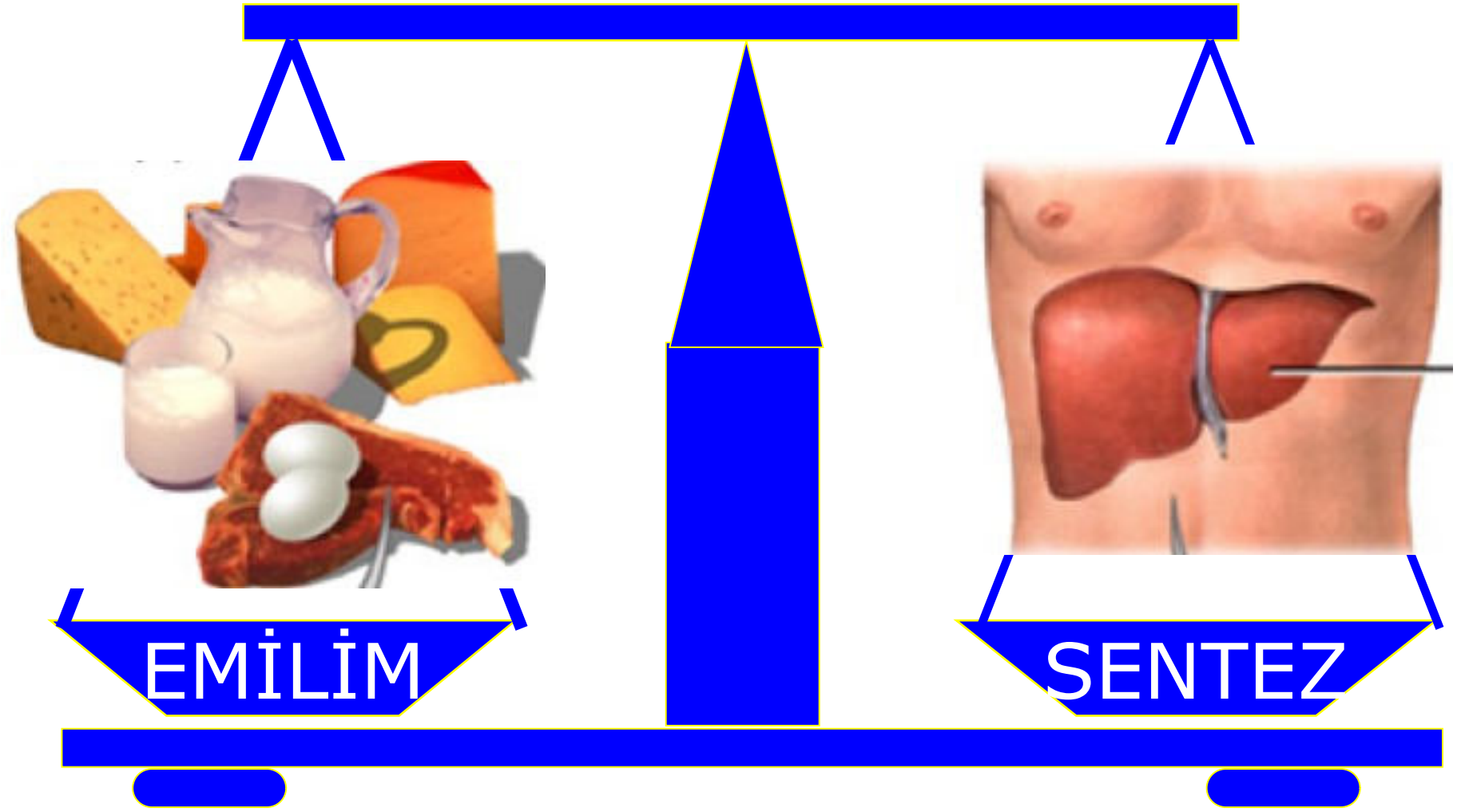
Circulation 2020;141(3):e39-e53

Kolesterolün çoğunlukla vücutta üretiliyor

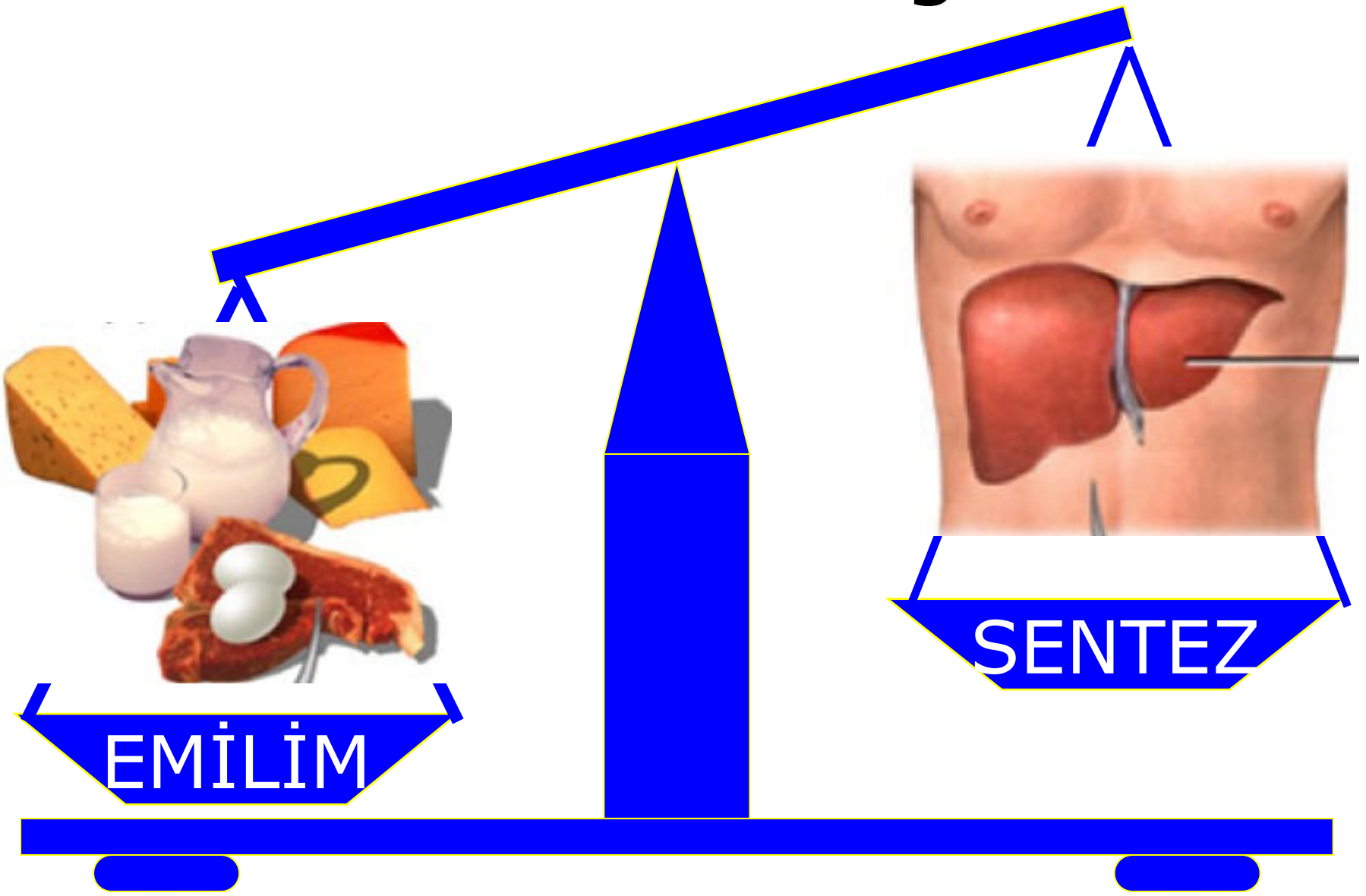


Bays H et al. Expert Opin Pharmacother 2003;4:779-790.

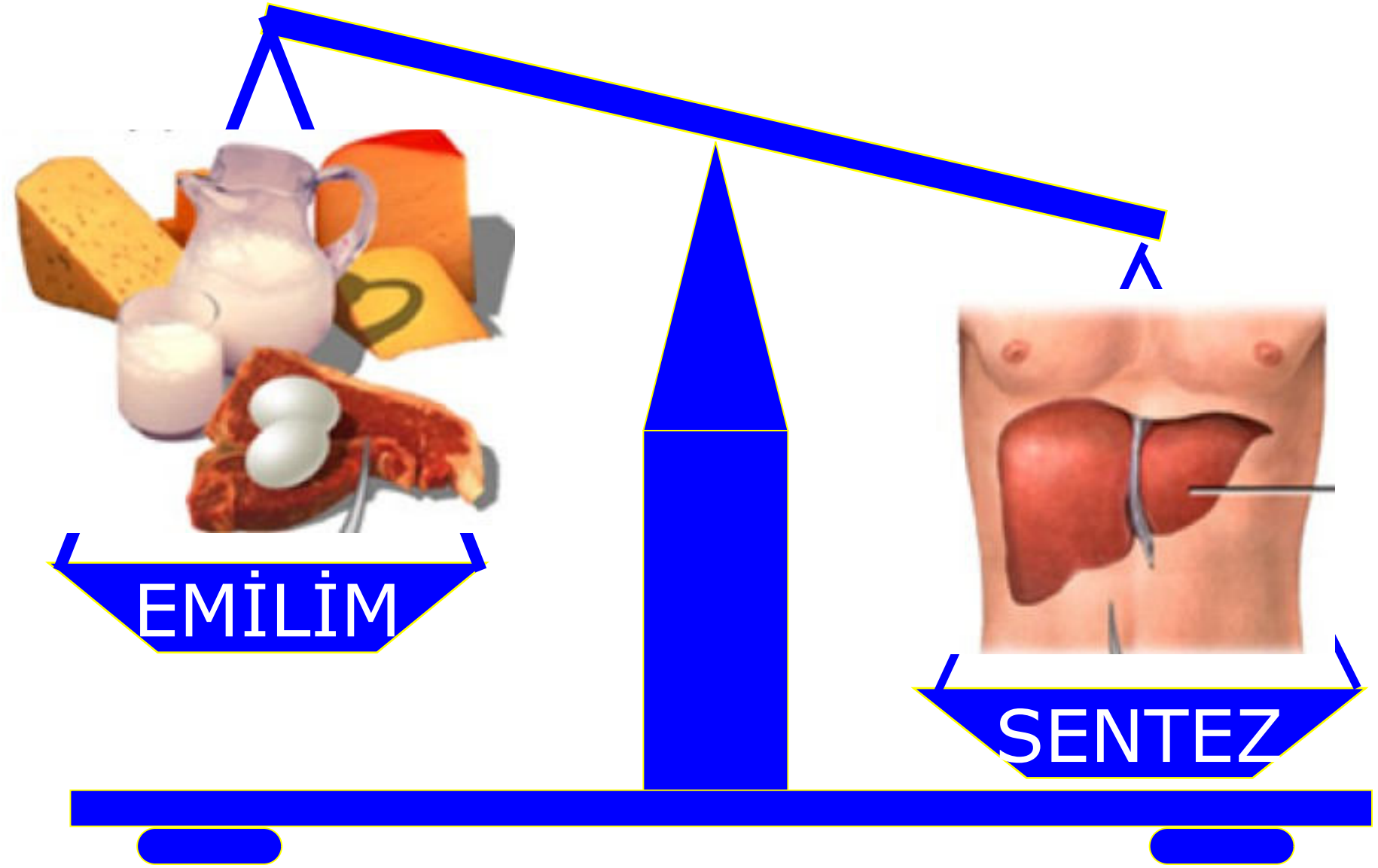
Kolesterol dengesi



Kolesterol dengesi



Kolesterol dengesi



AHA/ACC Prevention Guideline

OPEN

2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

"There is insufficient evidence to determine whether lowering dietary cholesterol reduces LDL-C."

" Available evidence shows no appreciable relationship between consumption of dietary cholesterol and serum cholesterol, consistent with the conclusions of the AHA/ACC report. Cholesterol is not a nutrient of concern for overconsumption."

Mevcut kanıtlar, AHA/ACC raporunun sonuçlarıyla tutarlı olarak diyet kolesterolü tüketimi ile serum kolesterolü arasında kayda değer bir ilişki olmadığını gösteriyor. Kolesterol aşırı tüketim için endişe edilecek bir besin değildir.

Diyet kılavuzları sağlıklı diyet uygulamalarına (Akdeniz diyeti, DASH [Dietary Approaches to Stop Hypertension]–diyeti) yönlenmelidir.

Plazma kolesterol seviyesini belirleyen toplam yağdan ziyade yağ asitleridir…

Meta-analiz; 60 çalışma- 1672 gönüllü

Am J Clin Nutr 2003;77:1146–55

ESC European Society of Cardiology
European Heart Journal (2020) **41**, 111–188
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

" Avoiding any consumption of trans fat is a key measure of the dietary prevention of CVD. "

" The cholesterol intake in the diet should be reduced (<300 mg/day), particularly in people with high plasma cholesterol levels. "

"Diet plus physical activity"

Egzersizle koroner olay riski düşüyor…

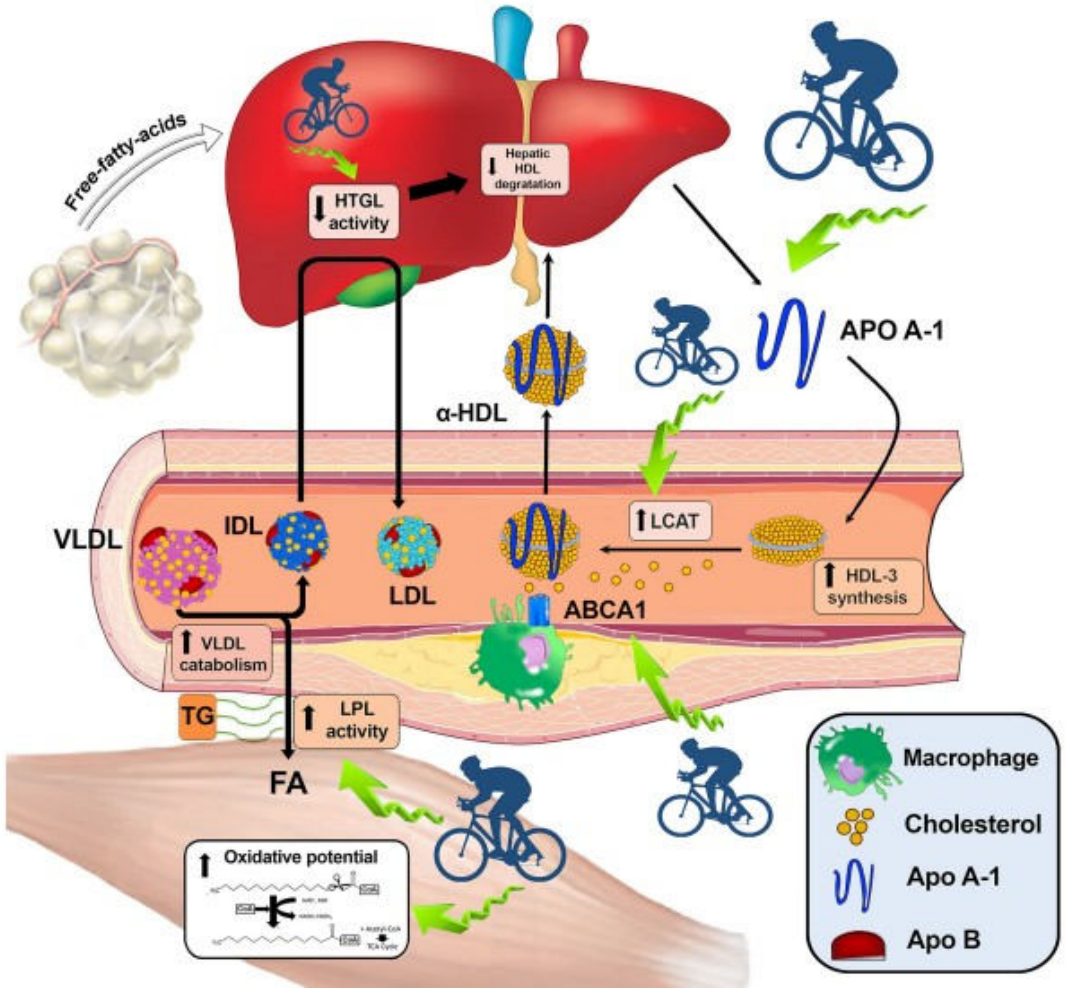
41053 kişi (25–64 yaş), 10 yıllık risk

P<0,001

ERKEK KADIN

European Heart Journal 2007: 28: 492–498

Düzenli-dirençli egzersiz ile;



HDL-K %4.6 artıyor (HDL2)
TG %3,7 düşer
LDL-K %5 düşer (ky LDL)
T. Kol %1 düşer
Visseral yağ azalır

Am J Physiol Heart Circ Physiol 2020;319: H76–H88

Ann Intern Med 2000;133:92-103

Metabolism 1992;41:1249-1256

Medicine & Science in Sports & Exercise

Statin tedavisinde yanlışlar

Kolesterolümü statin ile değil diyet ve egzersizle düşüreyim…

(Statin endikasyonu olan hastalar için)

Statinin yan etkisi çok…

- Hepatotoksite
- Kas hasarı
- Yeni diyabet gelişimi
- Nörokognitif fonksiyonlara etki

Statin tedavisi sırasında;

Karaciğer transaminazlarında hafif artış %0.5–2.0

İlk 3 ay içinde olur-geçicidir

Kalıcı transaminaz yüksekliği (>3x NÜS)

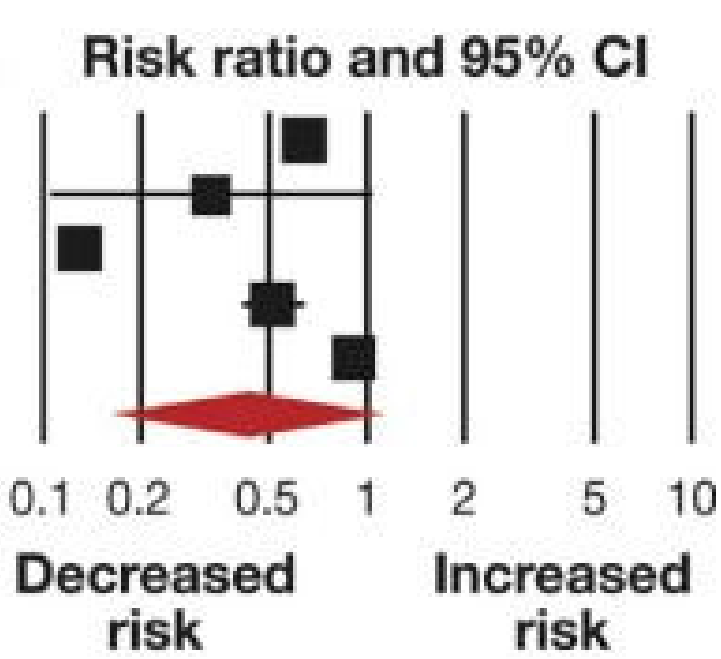
- Atorvastatin 10 mg ile %0.1
- Atorvastatin 80 mg ile %0.6
- Plasebo ile %0.2

Eur Heart J 2018; 39: 2526–2539

Meta-analiz
121,058 kronik karaciğer hastası

Statin ile fibrozisin progresyonu veya siroz gelişim riski artmıyor

Study name	Risk ratio	Lower limit	Upper limit	*P*-value
Simon 2016	0.64	0.57	0.72	.00
Simon 2015	0.33	0.11	1.03	.06
Yang 2015	0.13	0.12	0.14	.00
Huang 2016	0.51	0.41	0.63	.00
Oliver 2016	0.91	0.80	1.04	.16
	0.42	0.16	1.11	.08

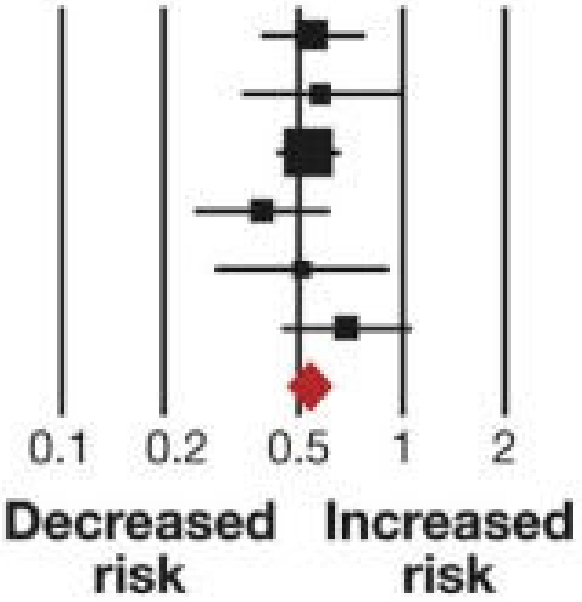


Clin Gastroenterol Hepatol 2017;15:1521–1530

Meta-analiz
121,058 kronik karaciğer hastası

Statin ile sirozun dekompanse olma riski artmıyor

Study name	Risk ratio	Lower limit	Upper limit	*P*-value
Mohanty 2015 -HCV	0.55	0.39	0.78	.00
Kumar 2014 - mixed	0.58	0.34	0.98	.04
Huang 2016 - HBV	0.53	0.43	0.66	.00
Chang 2017 - HBV	0.39	0.25	0.61	.00
Chang 2017 - HCV	0.51	0.28	0.91	.02
Chang 2017 - EtOH	0.69	0.45	1.06	.09
	0.54	0.46	0.62	.00

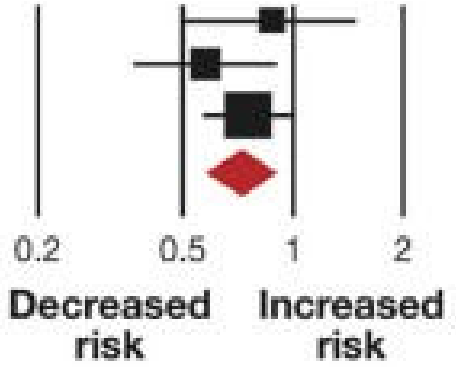


Clin Gastroenterol Hepatol 2017;15:1521–1530

Meta-analiz
121,058 kronik karaciğer hastası

Statin ile portal hipertansiyonun progresyon riski artmıyor

Study name	Risk ratio	Lower limit	Upper limit	*P*-value	Statins	Placebo
Abraldes 2016	0.87	0.51	1.50	.63	17/69	22/78
Pollo-Flores 2015	0.58	0.37	0.91	.02	8/14	20/20
Abraldes 2009	0.76	0.57	1.02	.07	19/28	24/27
	0.73	0.59	0.91	.01	44/111	66/125



Clin Gastroenterol Hepatol 2017;15:1521–1530

Karaciğer enzimlerinin takibi

Rutin periyodik takip önerilmiyor

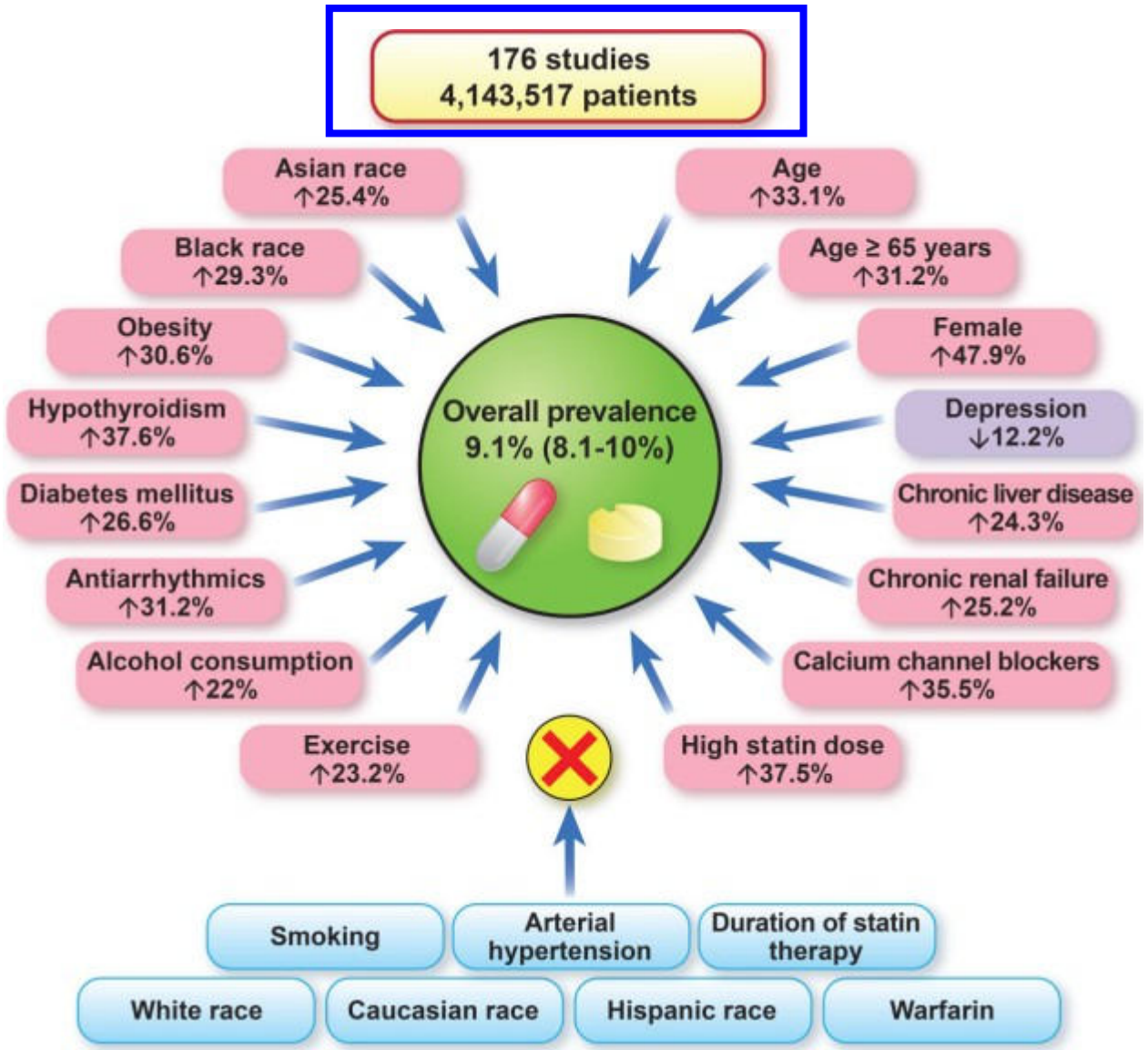
-olur da hekim ALT, AST veya GGT düzeylerinde izole bir atış görüp statini gereksiz keser ve hastanın KVO riski artar diye…

Hepatotoksiteye dair semptomlar varsa (beklenmedik halsizlik veya güçsüzlük, iştah kaybı, karın ağrısı, koyu renkli idrar veya ciltte/sklereda sararma) bakılmalıdır

ALT >3 NÜS ise statine ara verilmelidir. Diğer nedenler dışlanmalıdır

Eur Heart J 2018; 39: 2526–2539
Eur Heart J 2020;41:111-188

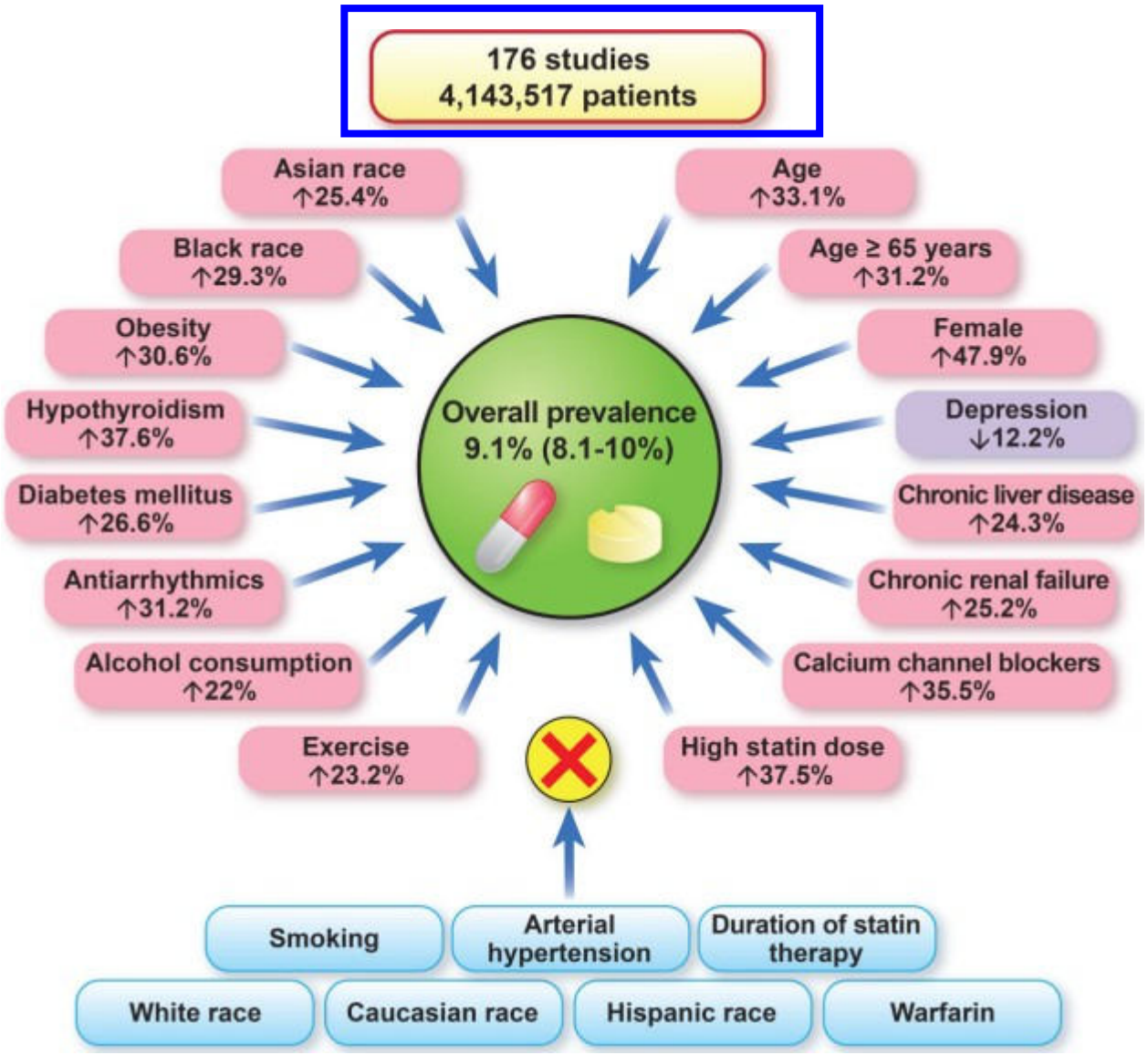
Statin ile ilişkili kas semptomları=statin intoleransı



Statin intoleransı KV risk artışı ile yakından ilişkili

Eur Heart J 2022;43: 3213–3223

Statin ile ilişkili kas semptomları=statin intoleransı



Gerçek yaşam verilerinde daha yüksek oranda görülüyor
%17 (14–19%)

<u>Statin intoleransı tanımı</u>

National Lipid Association (NLA)

International Lipid Expert Panel (ILEP)

European Atherosclerosis Society (EAS)

Eur Heart J 2022;43: 3213–3223

National Lipid Association (NLA) statin intoleransı tanımı

1)En az 2 farklı statini tolere edememeli

-bir tanesi önerilen en düşük dozu olmalı (rosuva 5 mg, atorva 10 mg, simva 10 mg, lova 20 mg, prava 40 mg, fluva 40 mg, and pitava 2 mg)

-diğeri herhangi bir günlük dozda olabilir

2) Objektif semptomlar veya anormal laboratuvar olmalı, statin kesilince düzelmeli

3) Başka nedenler (hipotiroidizm, ilaç etkileşimi, eşlik eden hastalıklar, belirgin egzesiz artışı veya altta yatan kas hastalığı) dışlanmalı

J Clin Lipidol 2014;8: S72-S81

Statin ilişkili kas semptomları;kesin tanımı ve testi yok

-Simetrik

-Proksimal bölgede

-Geniş kas gruplarında

  -Kalçalar

  -Kaba etler

  -Baldırlar

  -Sırt kaslar

-4-6 hafta içinde başlar

-%90'da başka bir statine geçince düzelir

Nosebo etkisi mi?

Nocebo

Placebo

Negatif etki beklentisi

Pozitif etki beklentisi

Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase

Lancet 2017;389:2473-2481

ASCOT-LLA
Atorvastatin vs plasebo (çift kör)

↓

Kas semptomları
plasebo ile aynı

ASCOT-LLA
Atorvastatin (açık etiket)

↓

Kas semptomlarında
belirgin artış

NOCEBO ETKİSİ

Statin tedavisi güvenlidir

	Placebo (n = 8,150)		Rosuvastatin: No LDL-C <50 mg/dl (n = 4,000)			Rosuvastatin: LDL-C <50 mg/dl (n = 4,154)			
	n	Rate	n	Rate	p Value vs. Placebo	n	Rate	p Value vs. Placebo	p Value vs. No LDL-C <50 mg/dl
ALT >3 × ULN	84	0.5	56	0.7	0.06	66	0.7	0.007	0.78
CK >10 × ULN	1	0.005	1	0.01	0.45	1	0.01	0.84	1.00
≥2+ proteinuria	387	2.2	210	2.5	0.01	251	2.6	0.13	0.29
≥2+ hematuria	531	3.0	295	3.6	0.008	346	3.7	0.003	0.56
eGFR change, ml/min/1.73 m^2, mean (SD)	−9.0 (13.5)		−9.1 (14.1)		0.004	−7.9 (13.1)		0.04	0.50
Musculoskeletal/connective tissue disorders	2,930	21.7	1,489	24.4	0.006	1,691	24.3	0.0001	0.23
Myalgia	559	3.2	317	4.0	0.03	326	3.5	0.08	0.49
Muscular weakness	61	0.3	43	0.5	0.03	30	0.3	0.75	0.11
Rhabdomyolysis*/myopathy/myositis	9	0.05	3	0.04	0.61	7	0.07	0.56	0.56
Nervous system disorders	1,431	8.8	628	8.3	0.10	720	8.3	0.27	0.60
Peripheral neuropathy†	40	0.2	18	0.2	0.79	20	0.2	0.53	0.72
Amyotrophic lateral sclerosis	2	0.01	0	0	0.10	1	0.01	—	—
Parkinson's disease	13	0.1	5	0.1	0.78	8	0.1	0.80	0.63
Memory impairment‡	33	0.2	21	0.2	0.13	12	0.1	0.23	0.041
Psychiatric disorders	619	3.6	307	3.8	0.67	296	3.2	0.15	0.23
Insomnia††	205	1.1	104	1.2	0.79	118	1.2	0.40	0.52
Depression‡‡	217	1.2	103	1.2	0.83	83	0.9	0.005	0.01
Anxiety§§	158	0.9	66	0.8	0.29	65	0.7	0.09	0.54
Anger‖ ‖	4	0.02	0	0	—	1	0.01	—	—
Diabetes mellitus	209	1.2	105	1.2	0.025	151	1.6	0.06	0.70
Hepatobiliary disorders	177	1.0	71	0.8	0.35	108	1.1	0.43	0.27

J Am Coll Cardiol 2011;57:1666–75

Yeni diyabet gelişimi

-Primer korumada yıllık %1 ihtimalle yeni DM gelişir

(MetS, prediyabet, obez, yaşlı, yüksek doz statin)

-LDL-K 1–2 mmol/L düşmesi 150-300/10.000 kişide majör vasküler olay gelişimini engelliyor

European Heart Journal (2018) 39, 2526–2539

Statin tedavisinde yanlışlar

Kolesterolümü statin ile değil diyet ve egzersizle düşüreyim…

(Statin endikasyonu olan hastalar için)

Statinin yan etkisi çok…

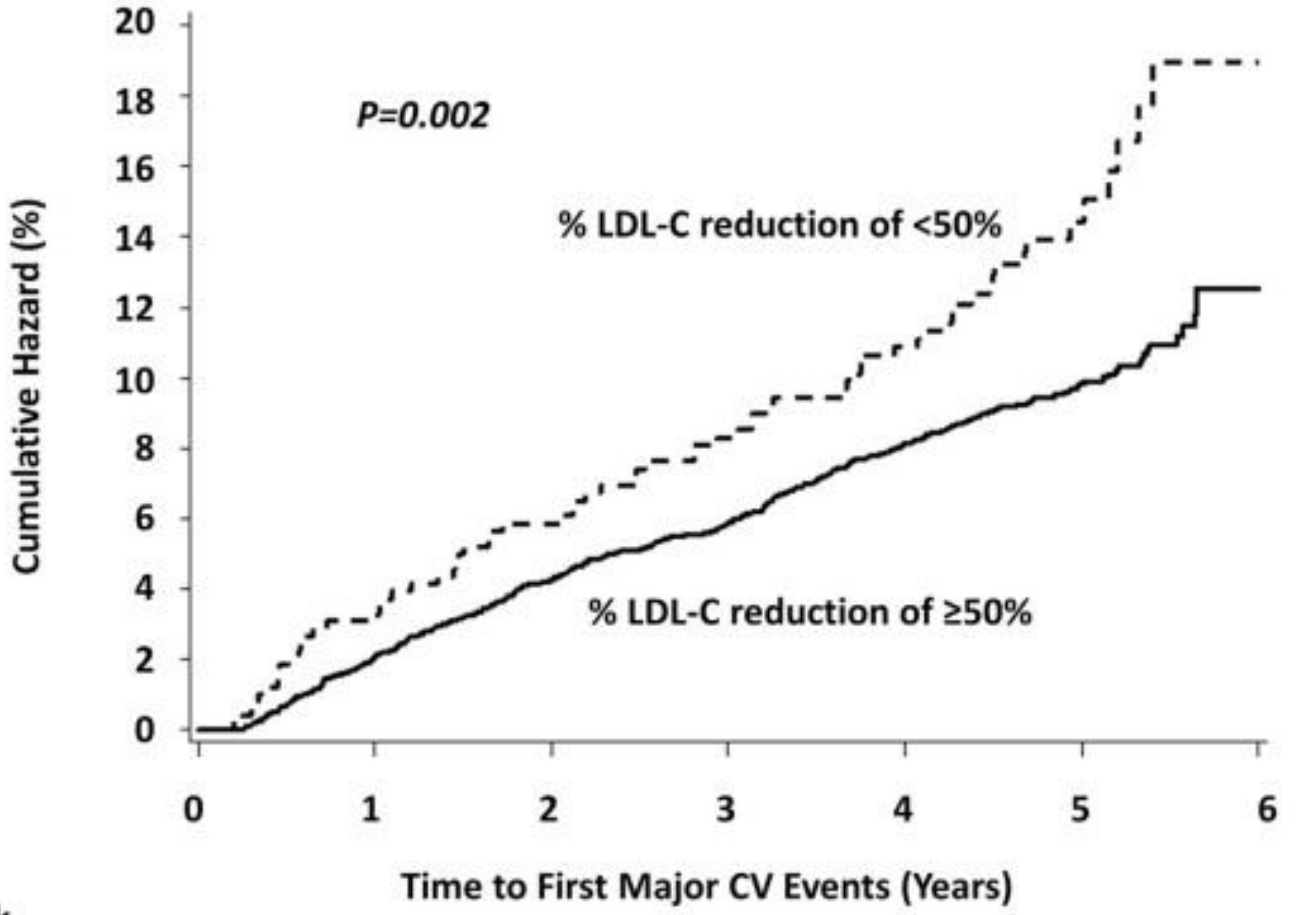
Hedef LDL-K (<70 veya <55 mg/dL) ulaşmak yeterli…

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Öneri	Sınıf	Kanıt
İkincil korumada çok yüksek riskli hastalarda LDL-K bazale göre ≥%50 düşürülmeli ve hedef LDL-K değeri olan <55 mg/dL ulaşılmalıdır	1	A
Birincil korumada çok yüksek riskli hastalarda (Ailesel HK değil) LDL-K bazale göre ≥%50 düşürülmeli ve hedef LDL-K değeri olan <55 mg/dL ulaşılmalıdır	1	C
Birincil korumada yüksek riskli hastalarda LDL-K bazale göre ≥%50 düşürülmeli ve hedef LDL-K değeri olan <70 mg/dL ulaşılmalıdır	1	A

Eur Heart J 2020;41:111-188

LDL-K ≤70mg/dL hedefine ulaşılan hastalar



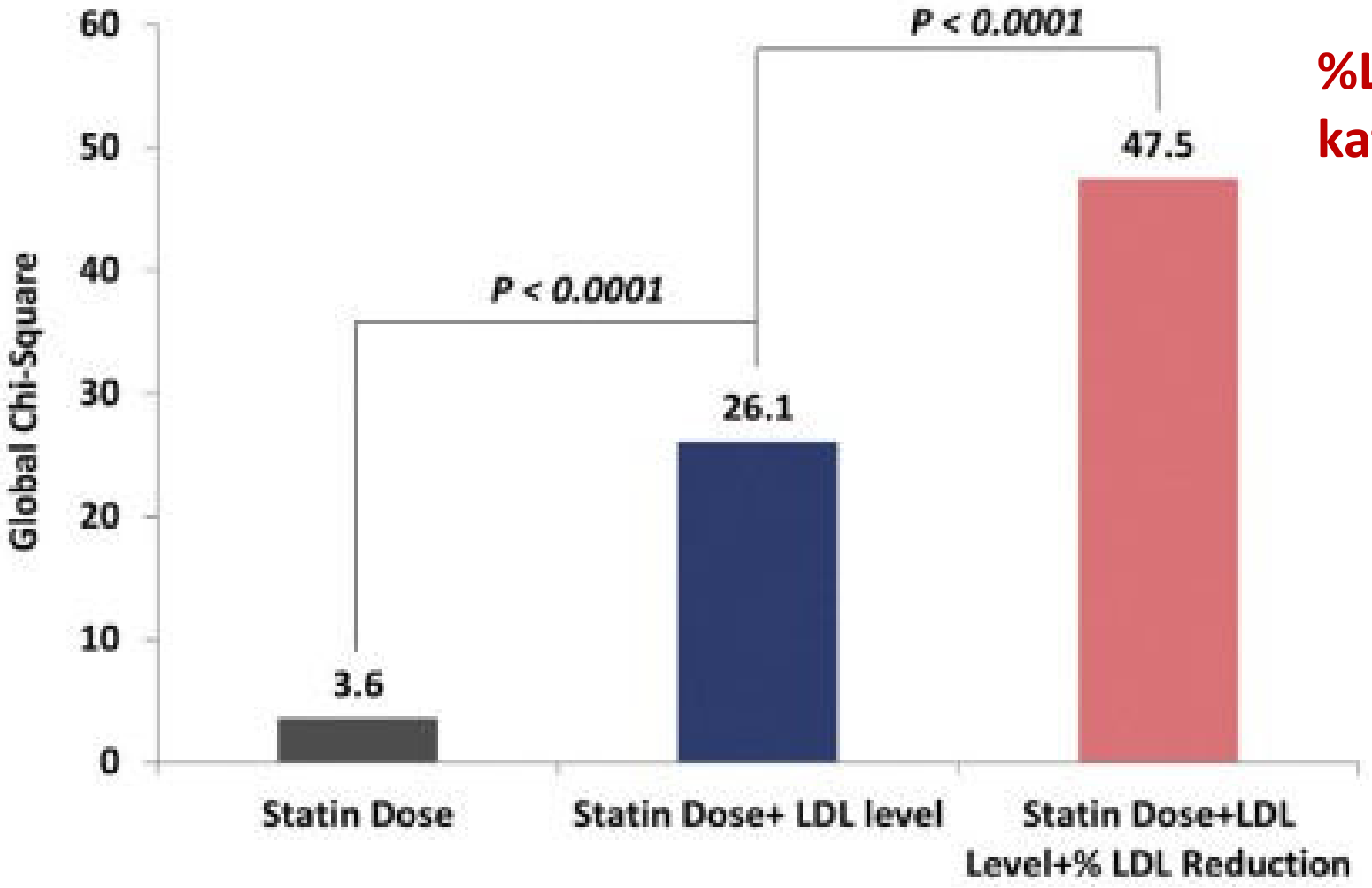
Major KVO %51 ↑

No. at Risk

%LDL-C ≥ 50%	4538	4426	4298	4188	4048	1937	71
%LDL-C <50%	494	475	456	439	419	170	9

Am J Med 2016; 129: 384-391

LDL-K ≤70mg/dL hedefine ulaşılan hastalar



%LDL-K düşüşü ilave katkı sağlıyor

Am J Med 2016; 129: 384-391

Statin tedavisinde yanlışlar

Kolesterolümü statin ile değil diyet ve egzersizle düşüreyim…

(Statin endikasyonu olan hastalar için)

Statinin yan etkisi çok…

Hedef LDL-K (<70 veya <55 mg/dL) ulaşmak yeterli…

Statin dozunu 2 katına çıkınca 2 katı düşüş sağlarım

Statin dozunu 2 katına çıkınca etkinliği 2 kat artmıyor

Hedef LDL-K <100mg/dl

	%6	%6	%6
117mg/dl ➡	106 ➡	95 ➡	84
Atorvastatin 10mg	20mg	40mg	80mg

Statin tedavisinde yanlışlar

Kolesterolümü statin ile değil diyet ve egzersizle düşüreyim…

(Statin endikasyonu olan hastalar için)

Statinin yan etkisi çok…

Hedef LDL-K (<70 veya <55 mg/dL) ulaşmak yeterli…

Statin dozunu 2 katına çıkınca 2 katı düşüş sağlarım

Kolesterol çok düşerse hücre içi enzimatik işlevler bozulur

A Receptor-Mediated Pathway for Cholesterol Homeostasis

MICHAEL S. BROWN AND JOSEPH L. GOLDSTEIN

IN 1901, AFTER STUDYING A PATIENT WITH BLACK URINE, a physician named Archibald Garrod suggested that a single mutant gene can produce a discrete block in a biochemical pathway, which he called an "inborn error of metabolism." Garrod's brilliant insight anticipated by 40 years the one gene–one enzyme concept of Beadle and Tatum. Similarly, the chemist Linus Pauling and the physician Vernon Ingram, through study of patients with sickle cell anemia, showed that mutant genes alter the amino acid sequences of proteins. Clearly, many fundamental advances in biology were spawned by perceptive studies of human genetic diseases (*1*).

We began our work in 1972 in an attempt to understand a human genetic disease, familial hypercholesterolemia (FH). In patients with this disease, the concentration of cholesterol in the blood is elevated many times above normal and heart attacks occur early in life. We postulated that this dominantly inherited disease results from a failure of end-product repression of cholesterol synthesis. The possibility fascinated us because genetic defects in feedback regulation had not been observed previously in humans or animals, and we hoped that study of this disease might throw light on fundamental regulatory mechanisms.

Our approach was to apply the techniques of cell culture to unravel the postulated regulatory defect in FH. These studies led to the discovery of a cell surface receptor for a plasma cholesterol transport protein called low density lipoprotein (LDL) and to the elucidation of the mechanism by which this receptor mediates feedback control of cholesterol synthesis (*2, 3*). FH was shown to be caused by inherited defects in the gene encoding the LDL receptor; these defects disrupt the normal control of cholesterol metabolism. Study of the LDL receptor in turn led to an understanding of receptor-mediated endocytosis, a general process by which cells communicate with each other through internalization of regulatory and nutritional molecules (*4*). Receptor-mediated endocytosis differs from previously described biochemical pathways because it depends on the continuous and highly controlled movement of membrane-embedded proteins from one cell organelle to another in a process termed receptor recycling (*4*). Many of the mutations in the LDL receptor that occur in FH patients disrupt the movement of the receptor between organelles. These mutations define a new type of cellular defect that has broad implications for normal and deranged human physiology.

The authors are from the Department of Molecular Genetics, University of Texas Health Science Center, Southwestern Medical School, Dallas, TX 75235. This article is adapted from the lecture they delivered in Stockholm, Sweden, 9 December 1985, when they received the Nobel Prize in Physiology or Medicine. This article is published here with the permission of the Nobel Foundation and will also be included in the complete volume of *Les Prix Nobel en 1985* as well as in the series *Nobel Lectures* (in English) published by the Elsevier Publishing Company, Amsterdam and New York.

The Problem of Cholesterol Transport

Cholesterol is the most highly decorated small molecule in biology. Thirteen Nobel Prizes have been awarded to scientists who devoted major parts of their careers to cholesterol (*5*). Ever since it was first isolated from gallstones in 1784, cholesterol has exerted an almost hypnotic fascination for scientists from the most diverse areas of science and medicine. Its complex four-ring structure and its

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The 1985 Nobel Prize in Medicine— Michael S. Brown and Joseph L. Goldstein Have Revolutionized Our Knowledge About Cholesterol Metabolism and Heart Disease

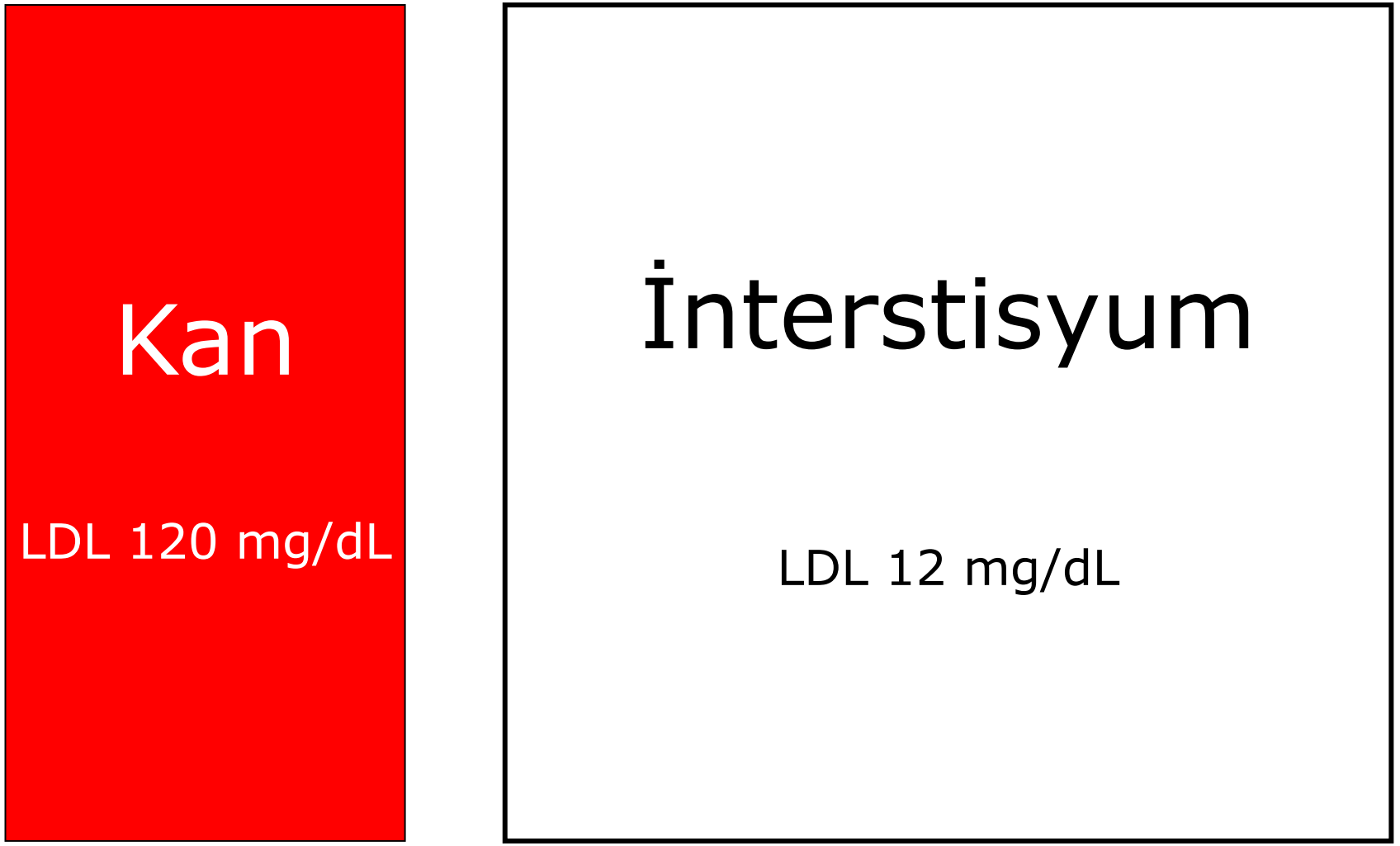
Number 38 September 22, 1986

Photo from the Nobel Foundation archive.

Michael S. Brown

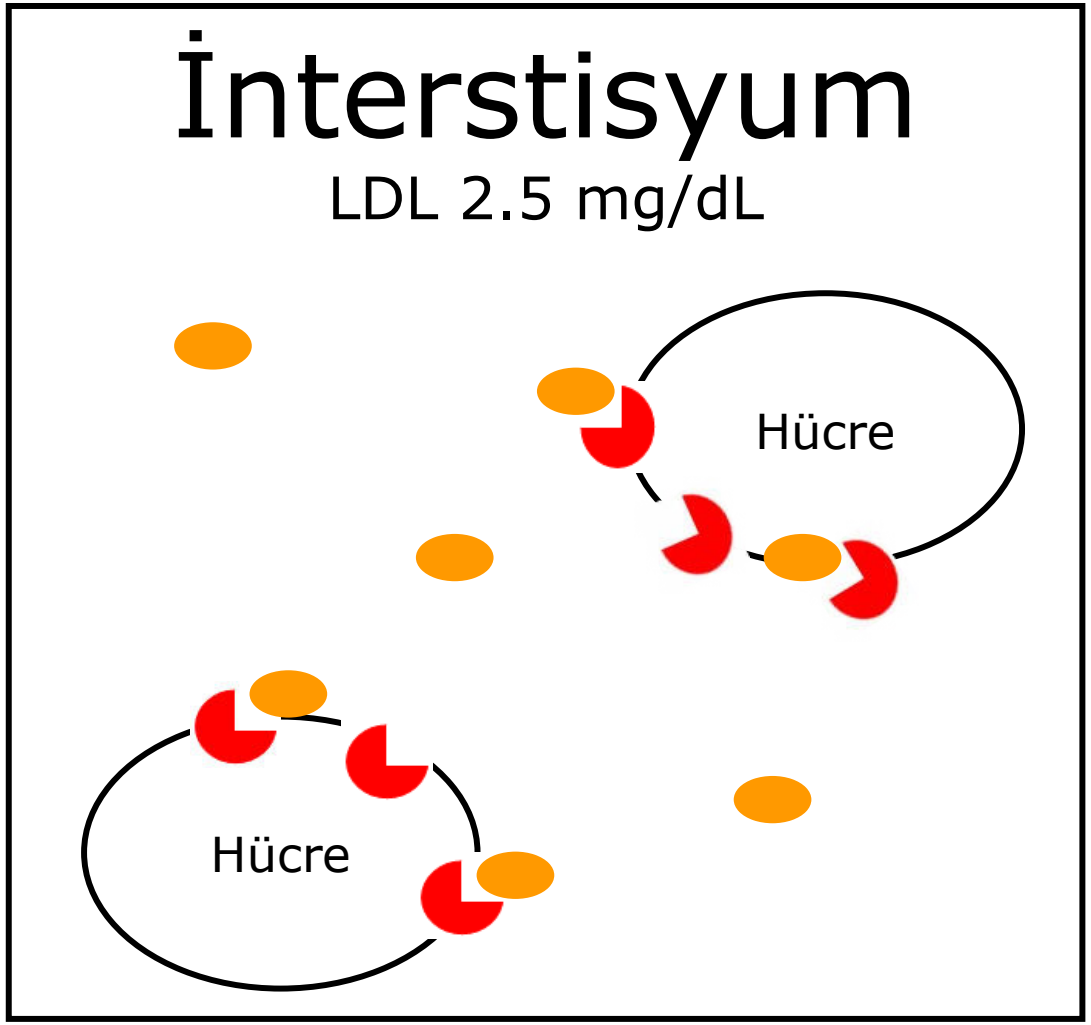
Photo from the Nobel Foundation archive.

Joseph L. Goldstein


Kan
LDL 120 mg/dL
İnterstisyum
LDL 12 mg/dL

Kan

LDL 25 mg/dL



Statin bize hiç yanlış yapmadı!

Kedi olalı bir fare tuttuk