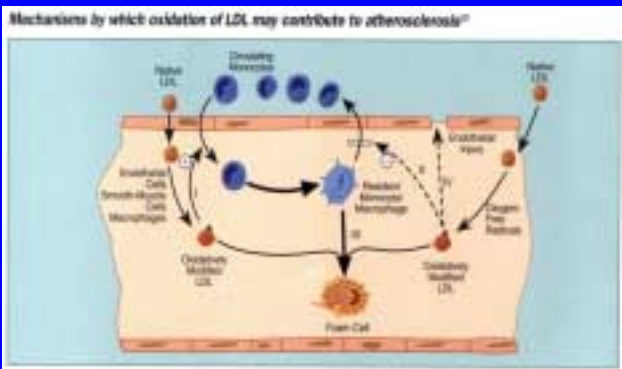


יצירת הפלק הטרשתי השלב הראשוני



דיסליפידמיה

- מטבוליזם
- סינדרומים קליניים
- טיפול תזונתי ותרופתי
- מחקרים קליניים
- הנחיות טיפוליות

ד"ר יעקב הנקין
המערך הקרדיולוגי
בי"ח סורוקה

1

אפופרוטאינים Apoproteins

- Stabilize lipoproteins ("backbone")
 - ♦ A1 ---- HDL
 - ♦ B48 ---- chylo
 - ♦ B100 ---- VLDL, IDL, LDL
- modulate enzymatic activity
 - ♦ catalyze (CII ---- LPL, A1 ---- LCAT)
 - ♦ inhibit (CIII ---- LPL)
- Facilitate lipoprotein entry into cells (ligands)
 - ♦ B100 ---- LDL
 - ♦ E ---- chylo, VLDL & IDL, HDL?

4

Plasma Lipoproteins

- Spherical particles
- Non-polar core:
 - ♦ cholesterol ester
 - ♦ triglyceride
- Polar outer coat:
 - ♦ unesterified chol
 - ♦ phospholipids
 - ♦ proteins (apo)



3

מטבוליזם וסינדרומים קליניים

6

Chylomicron

trig > 90 %
chol 1-2 %
apo < 1 %

B 48

VLDL

trig 60 %
chol 12 %
apo 10 %
PL 18 %

B 100

IDL

LDL

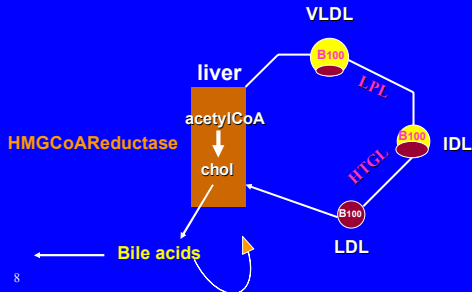
trig 5 %
chol 50 %
apo 25 %
PL 20 %

HDL

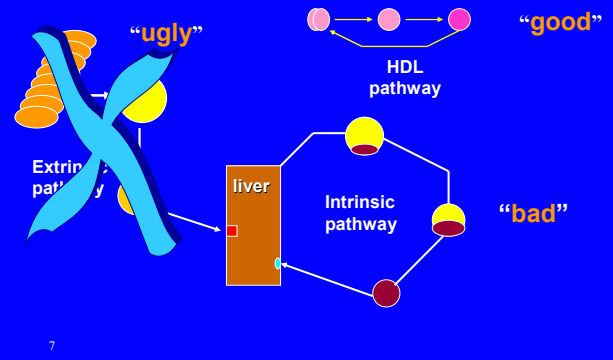
chol 20 %
apo 50 %
PL 25 %

5

Intrinsic Pathway



מסלולים מטבוליים

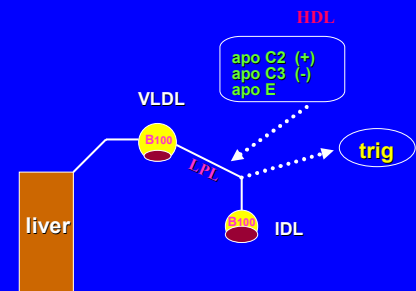


Etiology of elevated VLDL type IV dyslipidemia

- **Primary (genetic)**
 - ♦ Familial Hypertriglyceridemia (FHTG)
 - ♦ Familial Combined Hyperlipidemia (FCHL)
- **Secondary (acquired)**
 - ♦ Obesity
 - ♦ Diabetes mellitus
 - ♦ Insulin resistance syndrome
 - ♦ Chronic renal failure
 - ♦ high carbohydrate diets
 - ♦ Ethanol
 - ♦ Drugs: estrogen, beta-blockers, retinoids

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VLDL Metabolism 1



9

Familial Hypertriglyceridemia

- Autosomal dominant
- elevated Tg levels only
- increased CHD risk ??
- Family: ↑TG in 50% of family members
- Few, large sized VLDL particles
- overproduction of triglyceride
- normal apo B levels

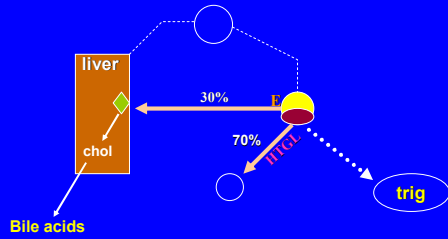
12

Familial Combined Hyperlipidemia

- Autosomal dominant
- usually manifests in adulthood
- elevated chol and/or Tg levels
- increased CHD risk
- Family: ↑TG or ↑chol or both
 - ♦ In 50% of family members
- Many, normal sized VLDL particles
- overproduction of apo B
- elevated apo B levels

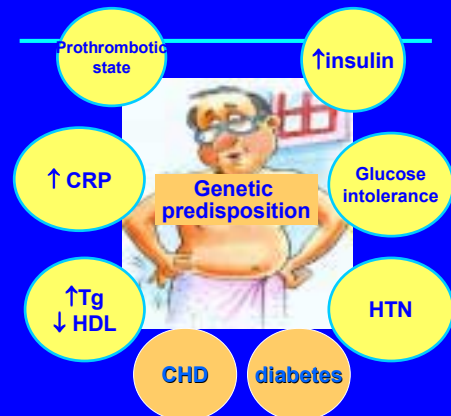
11

IDL metabolism



14

The Metabolic Syndrome



13

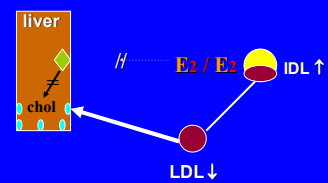
Dysbetalipoproteinemia אפיונים קליניים

- Xanthomas:
 - ♦ palmar
 - ♦ tuberous (elbows, knees)
- Premature atherosclerosis
 - ♦ coronary (myocardial infarction, anginal syndromes)
 - ♦ cerebrovascular (carotid artery disease, CVA)
 - ♦ peripheral vascular (limb ischemia)

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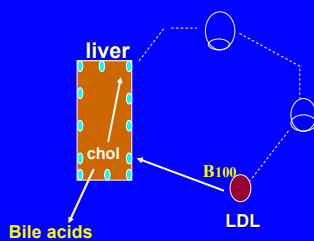
Type III dyslipidemia Dysbetalipoproteinemia

Broad-beta disease
Remnant disease



15

LDL Metabolism



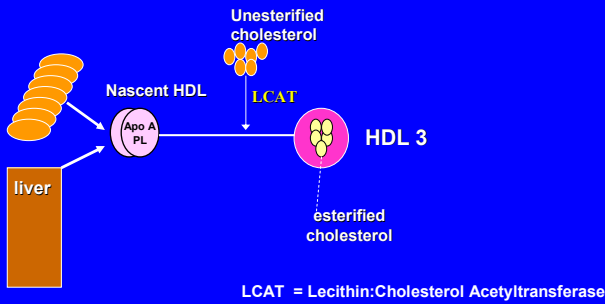
18



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HDL Metabolism 1

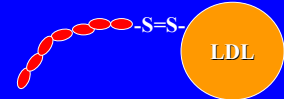
Reverse cholesterol transport



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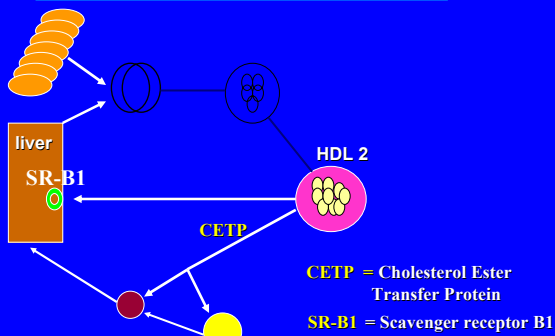
LDL Modifications

- **LDL Oxidation**
 - ♦ inadequate methods to measure tissue oxidation
 - ♦ antioxidants ??
- **LDL size & density**
 - ♦ type A: large, buoyant
 - ♦ type B: small, dense
 - ▼ hyper TG, DM, insulin resistance
 - ▼ familial combined hyperlipidemia
 - ▼ CHD patients
- **Lp(a)**
 - ♦ atherogenic
 - ♦ thrombogenic



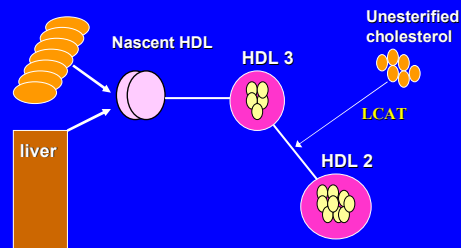
25

HDL Metabolism 3



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HDL Metabolism 2



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Causes of low HDL-C

- Genetic
- Hypertriglyceridemia
- Obesity
- Diabetes mellitus
- Insulin resistance syndrome
- cigarette smoking
- Diet: high CHO, high PUFA
- Drugs
 - ♦ Anabolic steroids (testosterone, progestins)
 - ♦ beta adrenergic blockers

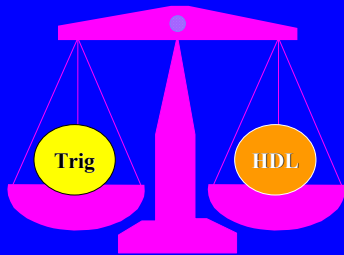
30

Antiatherosclerotic mechanisms of HDL

- Reverse Cholesterol Transport
 - ♦ direct (SRAP)
 - ♦ indirect (via LDL, VLDL)
- Prevents LDL Oxidation
 - ♦ paraoxinase
- Prevents synthesis of prothrombotic prostaglandins
- Increases synthesis of antithrombotic prostaglandins
 - ♦ prostacycline

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Relationship between HDL and Triglyceride-rich lipoproteins



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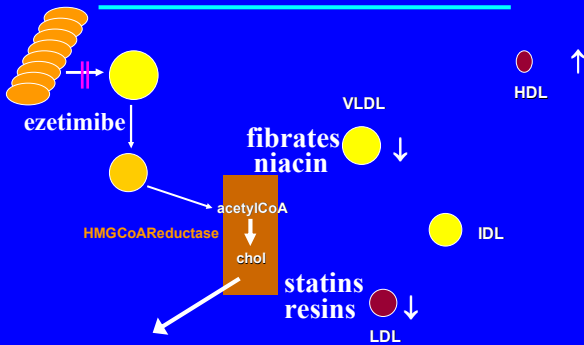
HDL-C vs LDL-C as a predictor of CHD risk



*Men aged 55-75

Source: Castelli et al. (1976) Circulation 53:600

מיקום הפעולה של התרופות



34

פרמקולוגיה

33

הנחיות קליניות מניעה ראשונית

- טיפול בגורמי הסיכון האחרים
- טיפול תזונתי
- חישוב ה- global risk

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Potential Mechanisms by Which Omega-3 Fatty Acids May Reduce Risk for Cardiovascular Disease

- Reduce susceptibility to ventricular arrhythmia
- Antithrombogenic
- Hypotriglyceridemic (fasting and postprandial)
- Retard growth of atherosclerotic plaque
- Reduce adhesion molecule expression
- Reduce platelet-derived growth factor
- Antiinflammatory
- Promote nitric oxide-induced endothelial relaxation
- Mildly hypotensive

38

Omega 3

- AHA Scientific Statement.
- Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease.
- Circulation. 2002;106:2747.

37

Omega 3 AHA recommendations

Population

Recommendation:

- Patients without documented CHD Eat a variety of (preferably oily) fish at least twice a week. Include oils and foods rich in linolenic acid (flaxseed, canola, and soybean oils; flaxseed and walnuts)
- Patients with documented CHD Consume 1 g of EPA+DHA per day, preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician.
- Patients needing Tg lowering 2-4 grams of EPA+DHA per day provided as capsules under a physician's care

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Side Effects

	GI Upset	Clinical Bleeding	Fishy Aftertaste	Worsening Glycemia*	Rise in LDL-C [†]
> 1 g/d	Very low	Very low	Low	Very low	Very low
1 to 3 g/d	Moderate	Very low	Moderate	Low	Moderate
>3 g/d	Moderate	Low	Likely	Moderate	Likely

*Usually only in patients with impaired glucose tolerance and diabetes.

[†] usually only in patients with hypertriglyceridemia.

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Target endpoints

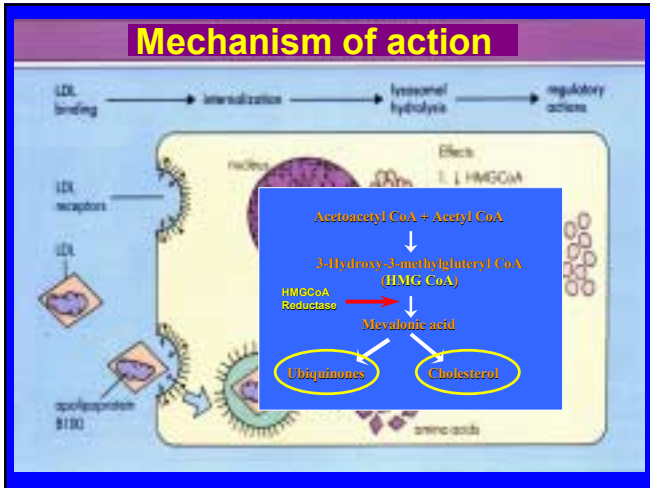
- LDLc < 100 mg/dL
- HDLc > 40 mg/dL
- Triglycerides < 200 mg/dL

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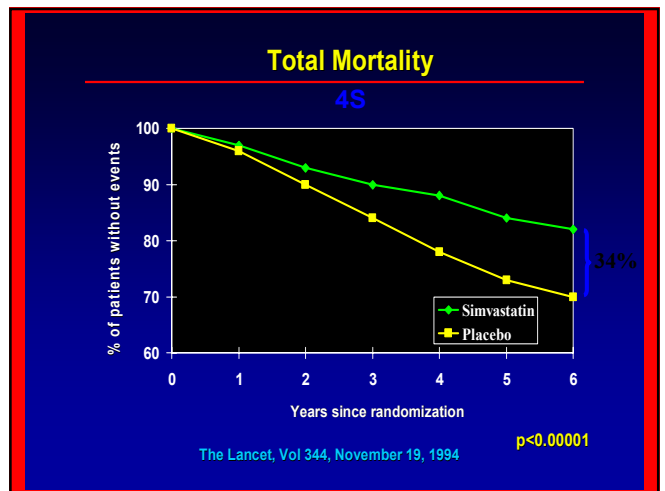
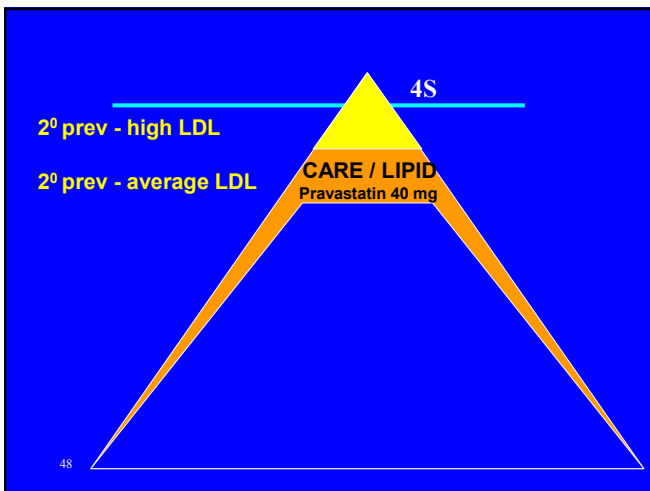
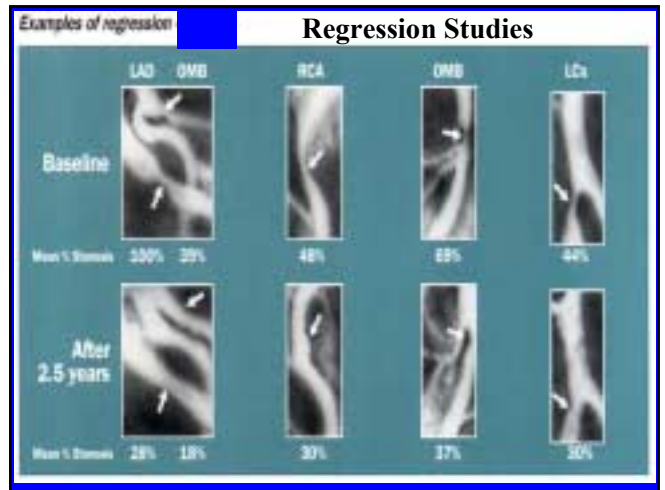
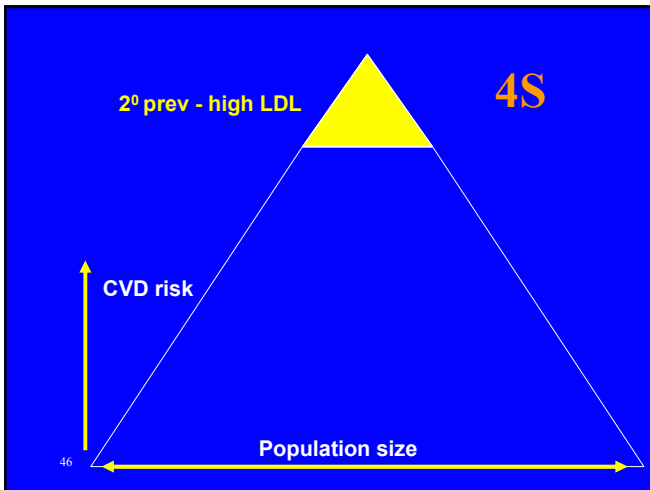
הנחיות קליניות מניעה שניונית

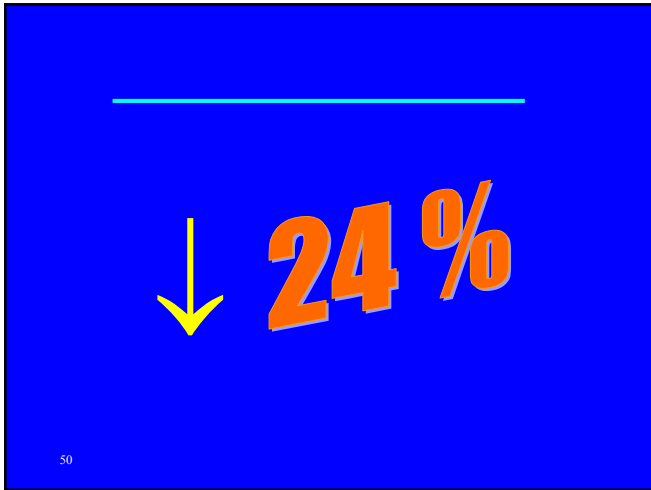
- טיפול בגורמי הסיכון האחרים
- טיפול תזונתי
 - ♦ דל שומן / דיאטה "ים-תיכונית"
 - ♦ אומגה 3 : 1 גרם ליום
- טיפול תרופתי
 - ♦ תמיד : כאשר LDLc ≥ 130 mg/dL

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- ### Megatrials showing statin efficacy
- **Primary Prevention**
 - ♦ WOSCOP prava
 - ♦ ACAPS/FCAPS lova
 - **Secondary Prevention**
 - ♦ 4S simva
 - ♦ Care prava
 - ♦ Lipid prava
 - **Mixed**
 - ♦ HPS simva
 - **Comparative**
 - ♦ PROVE-IT, REVERSAL atorva vs Prava
 - **Hypertensives**
 - ♦ ALLHAT prava
 - ♦ ASCOT atorva
 - **Diabetics**
 - ♦ CARDS atorva
- 43



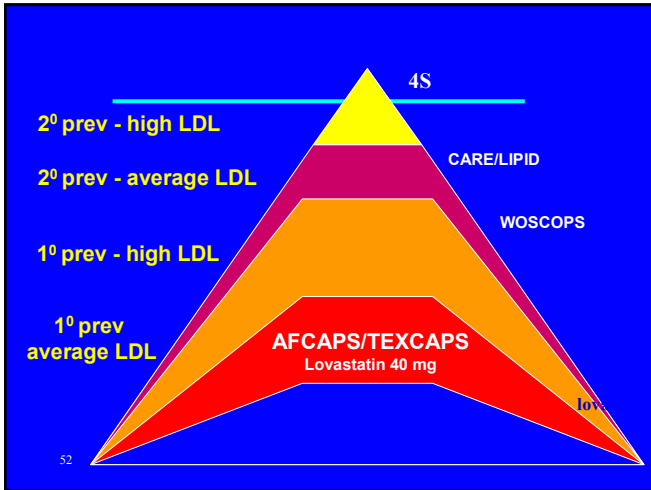


50

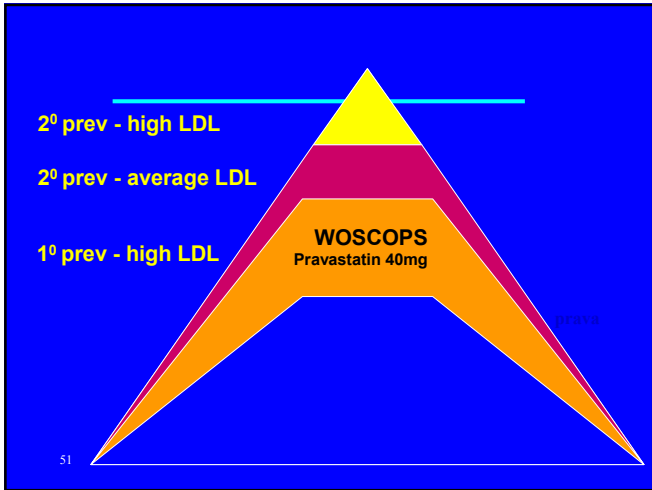
Pravastatin 40 mg

	CARE	LIPID
• Type	2 ^o	2 ^o
• Place	USA	Aust / NZ
• No.	4159	9014
• Ages	21-75	31-75
• Sex	M&F	M&F
• Length (y)	5	6.1
• Baseline LDL	115-174	130-170
	139	150

49



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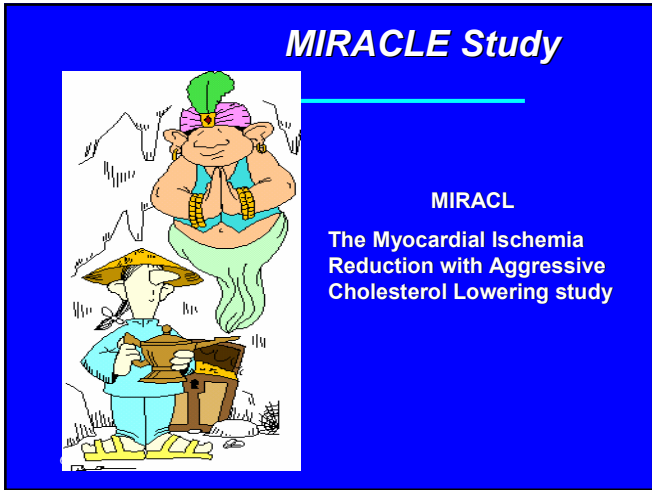
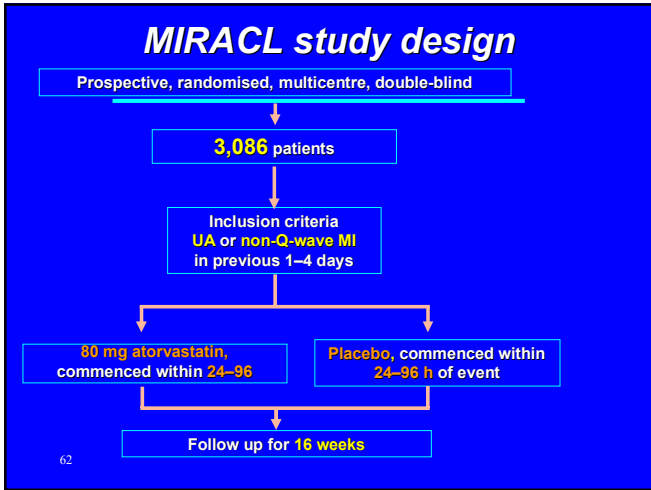
HPS - results

	Simvastatin	Placebo	relative reduction
• All cause mortality	12.9	14.6	12%
• CVD death	7.7	9.2	17%
• Major CVD events	19.9	25.4	22%
• Non-CVD mortality	5.2	5.5	
• Stroke	4.4	6.0	27%
• CPK X10	0.1	0.05	
• ALT X3	0.8	0.6	

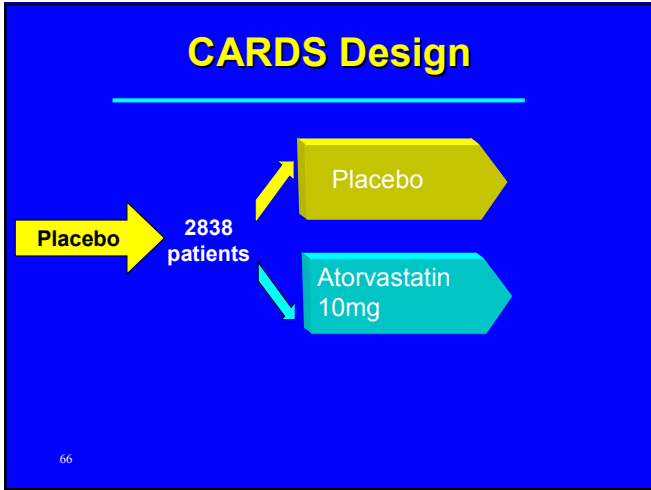
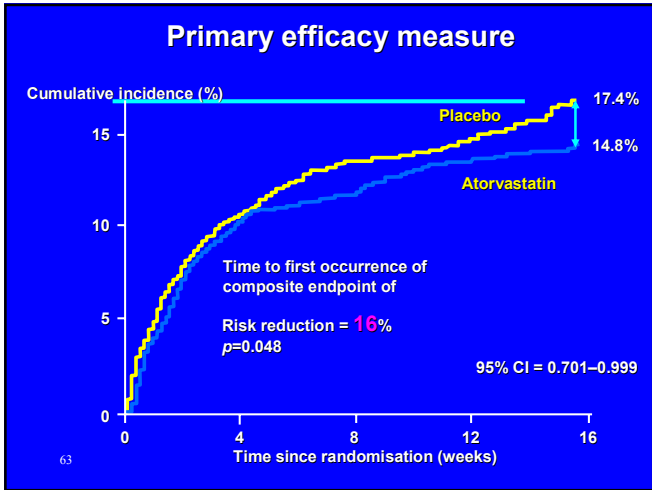
54

- ### Heart Protection Study (HPS)
- Largest ever cholesterol-lowering study
 - Funded by the British Medical Council & BHF
 - 20,000 M&F, age 40-80
 - High CHD risk – declined statins by physician
 - ♦ Below average cholesterol
 - ♦ Women
 - ♦ Age > 70
 - ♦ Non-coronary arterial disease
 - Simvastatin 40 mg vs placebo
 - 5.5 years
 - 2 by 2 design (also randomized to antioxidants)

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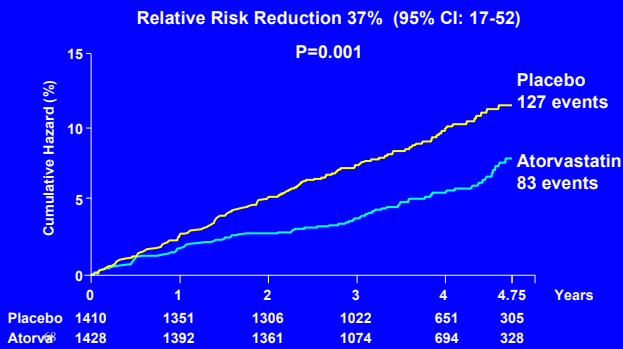


- ### Statins in Hypertensives
- #### ALLHAT
- 33 357 pts age 50+
 - HTN + 1 risk factor
 - Randomized to chlorthalidone vs lisinopril vs amlodipin
 - lipid-lowering arm:
 - ♦ 10355 pts with LDL-C 120 - 189 mg/dL
 - ♦ Pravastatin 40mg vs usual care
 - ♦ No difference in outcome: total or CV mortality
- #### ASCOT
- 19342 pts age 40-79
 - HTN + 3 risk factors
 - Randomized to beta-blocker vs amlodipin
 - lipid-lowering arm:
 - ♦ 10305 pts with total cholesterol < 260 mg/dL
 - ♦ Atorvastatin 10mg vs placebo
 - ♦ Stopped pre-maturely after 3.3 years
 - ♦ ↓ 36% events, ↓ 29% total mortality $p < 0.0005$
- 64



- ### Statins in Diabetics
- Heart Protection Study
 - CARDS
 - ♦ Collaborative Atorvastatin Diabetes Study
-
- 65

Cumulative Hazard for Primary Endpoint



CARDS Patient Baseline Lipids*

	Placebo Median (IQR)	Atorvastatin Median (IQR)
Total cholesterol	207	207
LDL-cholesterol	118 (100-137)	119 (100-138)
HDL-cholesterol	53	52

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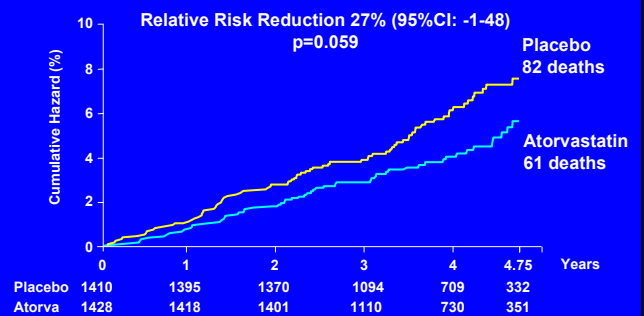
LDL in secondary Prevention:

How low
is low ?



70

Cumulative Hazard for All Cause Mortality



69

Hypothesis

40 mg Lipidal → anti-inflammatory

is not inferior to

80 mg Lipitor → Potent LDL ↓

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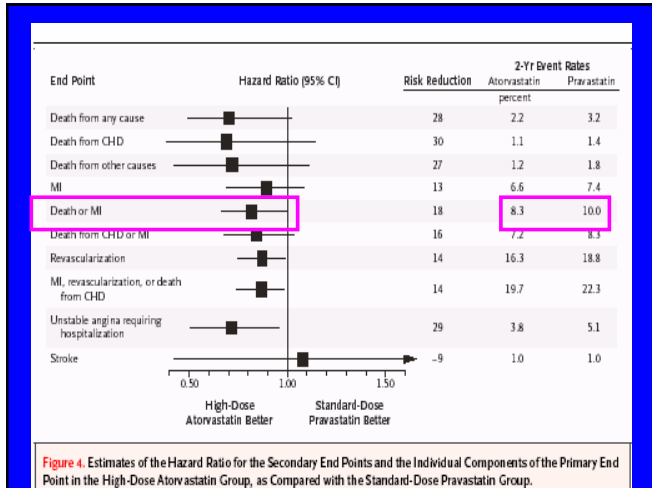
PROVE-IT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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*



Design

- 4162 pts with Acute Coronary Syndrome
- within 10 days
Lipidal 40 mg vs Lipitor 80 mg
- baseline LDLc 106 mg/dl
 - 95 (Lipidal)
 - 62 (Lipitor)
- baseline CRP 12.3 mg/l
 - 2.1 (Lipidal)
 - 1.3 (Lipitor)

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REVERSAL Trial

JAMA Effect of Intensive Compared With Moderate Lipid-Lowering Therapy on Progression of Coronary Atherosclerosis
A Randomized Controlled Trial
March 3, 2004—Vol 291, No. 9

Reversing Atherosclerosis with Aggressive Lipid Lowering

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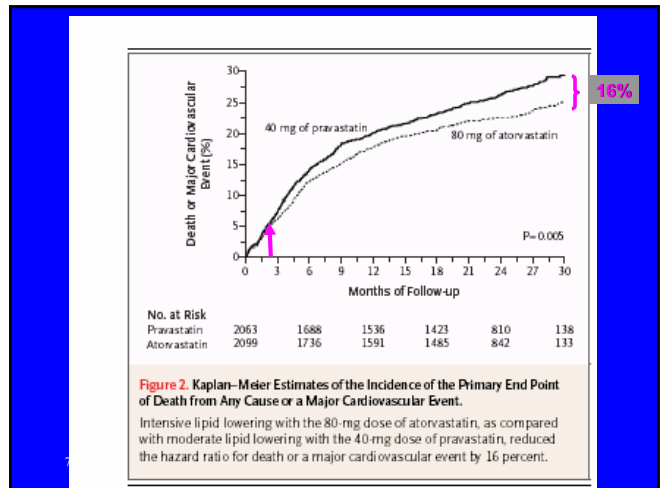
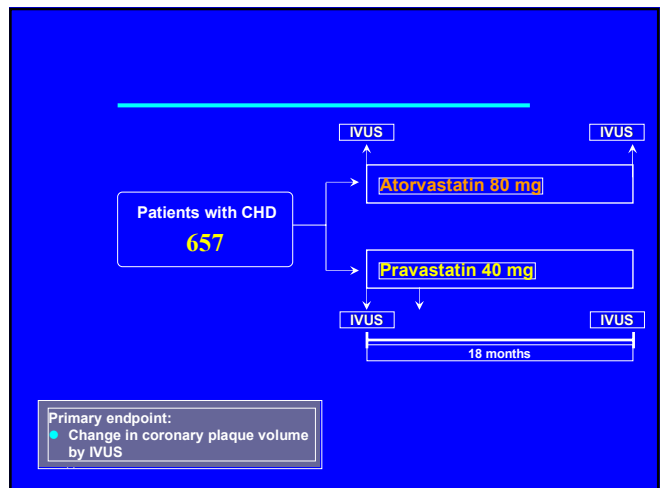


Table 3. Change in Atheroma Volume, Change in Percentage of Atheroma Volume, and Atheroma Volume in 10-mm Subsegment With the Greatest Disease Severity

	Pravastatin (n = 249)	Atorvastatin (n = 253)	P Value Between Groups ^a
Atheroma Volume, mm ³			
Baseline			
Mean (SD)	194.5 (114.8)	184.4 (115.7)	
Median (IQR)	168.6 (117.4 to 246.2)	161.9 (111.0 to 228.2)	.20
Follow-up			
Mean (SD)	199.6 (112.3)	183.9 (108.8)	
Median (IQR)	180.0 (125.5 to 255.3)	160.9 (107.4 to 240.3)	.05
Nominal change			
Mean (SD)	+5.1 (1.4)	-0.4 (1.8)	
Median (95% CI)	4.4 (0.1 to 6.0)	-0.9 (-3.5 to 1.6)	.02†
P value compared with baseline‡	.01	.72	

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BIP Study

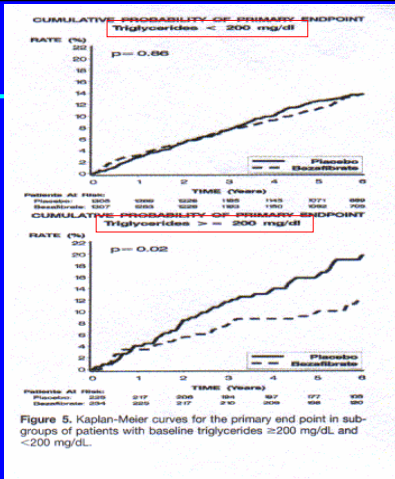
- Multicenter
- Randomized
- Double-blind
- Placebo-controlled
- Bezafibrate SR 400 mg
- 1992-1998
- Men & women
- Age 45-74
- Post MI
- Stable angina, (+) imaging
- LDL-C < 180/160 mg/dL
- HDL-C < 45 mg/dL
- Trig < 300 mg/dL

80

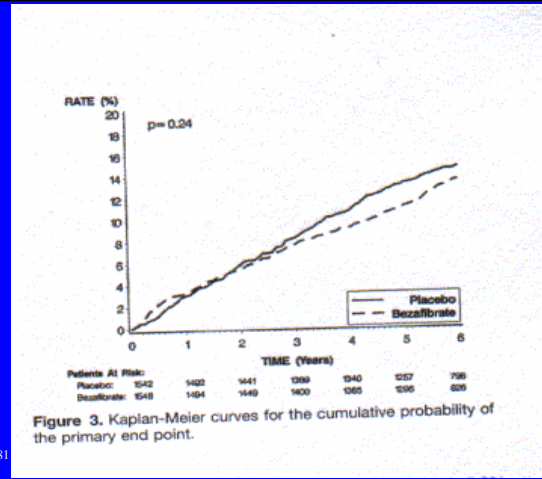
מחקרים קליניים בהיפרטריגליצרידמיה

- מניעה ראשונית
- מניעה שניונית
- Helsinki heart Study
- Coronary Drug Project (CDP): niacin
- Stockholm Heart Study: niacin + colestipol
- Bezafibrate Intervention Study (BIP)
- Hypertriglyceridemia Intervention Study (HIT)
- מחקרים אנגיוגרפיים
- BECAIT

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81

Target endpoints

- LDLc < 100 mg/dL
- HDLc > 40 mg/dL
- Triglycerides < 200 mg/dL

בחולים בסיכון גבוה במיוחד:

- LDLc < 70 mg/dL
- At least 30-40% reduction

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הנחיות קליניות מניעה שניונית

- טיפול בגורמי הסיכון האחרים
- טיפול תזונתי
 - דל שומן / דיאטה "ים-תיכונית"
 - אומגה 3 : 1 גרם ליום
- טיפול תרופתי
 - תמיד: כאשר $LDLc \geq 130$ mg/dL
 - בחולים בסיכון גבוה במיוחד:
 - בכל רמת LDL
 - HDLc < 40 mg/dL
 - Trig > 200 mg/dL

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חוששים לפרנסה שלכם
כקרדיולוגים?
אל תדאגו
זה לא יקרה !!

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המניעה השניונית

יעילה
פשוטה
Cost-effective



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