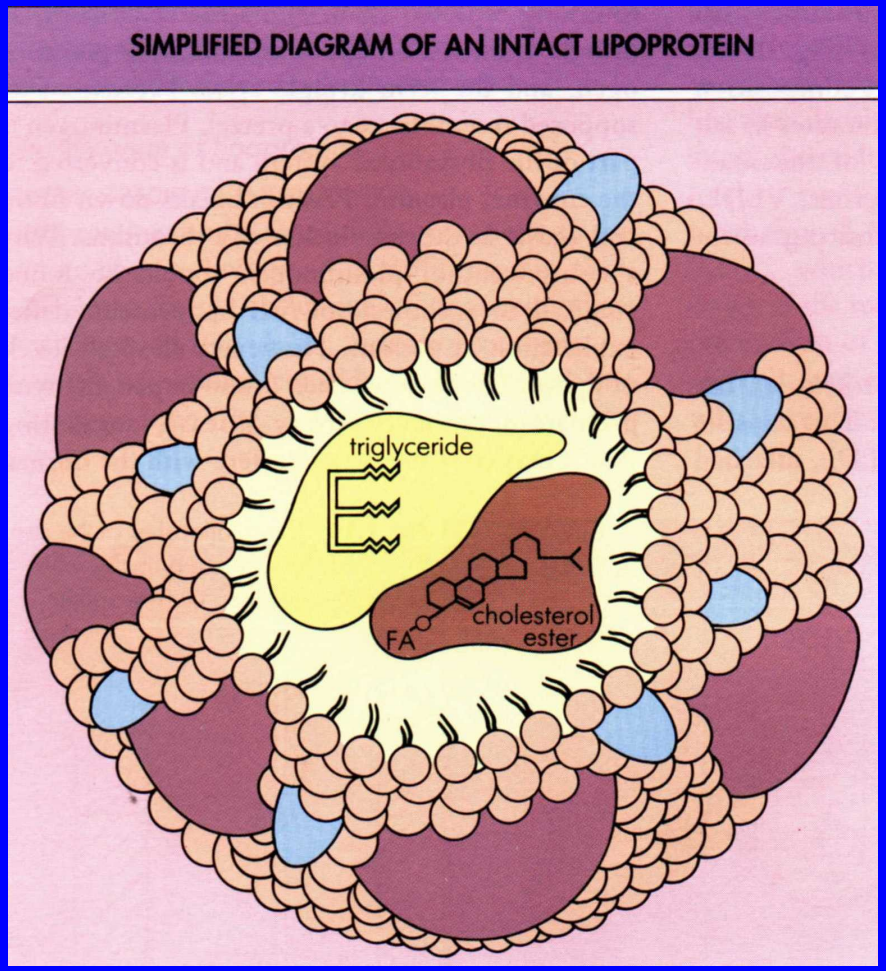
דיסליפידמיה

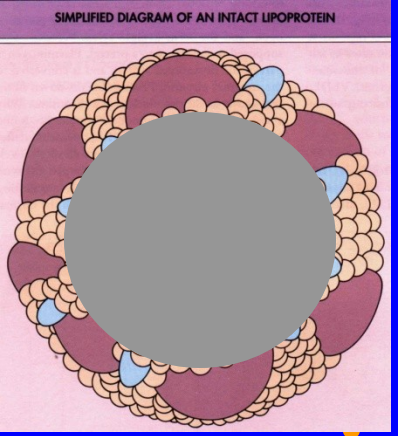
- מטבוליזם
- סינדרומים קליניים
- מחקרים קליניים
- טיפול תזונתי ותרופתי
- הנחיות טיפוליות

יעקב הנקין
המערך הקרדיולוגי
בי"ח סורוקה

Plasma Lipoproteins

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

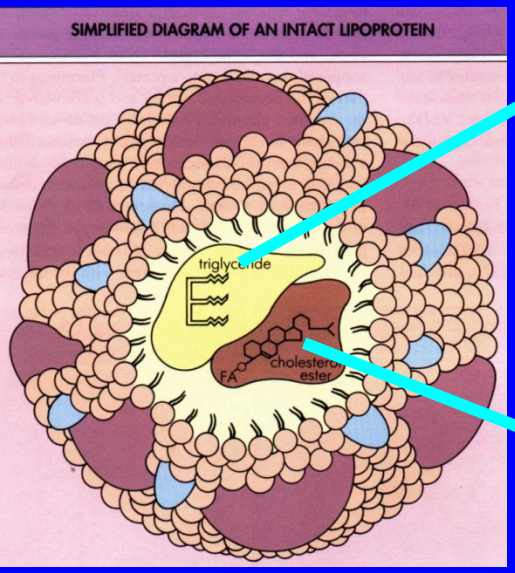




אפופרוטאינים
Apoproteins

- Stabilize lipoproteins (“backbone”)
  - AI ---- 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?

Lipoprotein classes



Trig rich

Chol rich

B48 chylomicron

B100 VLDL

B100 IDL

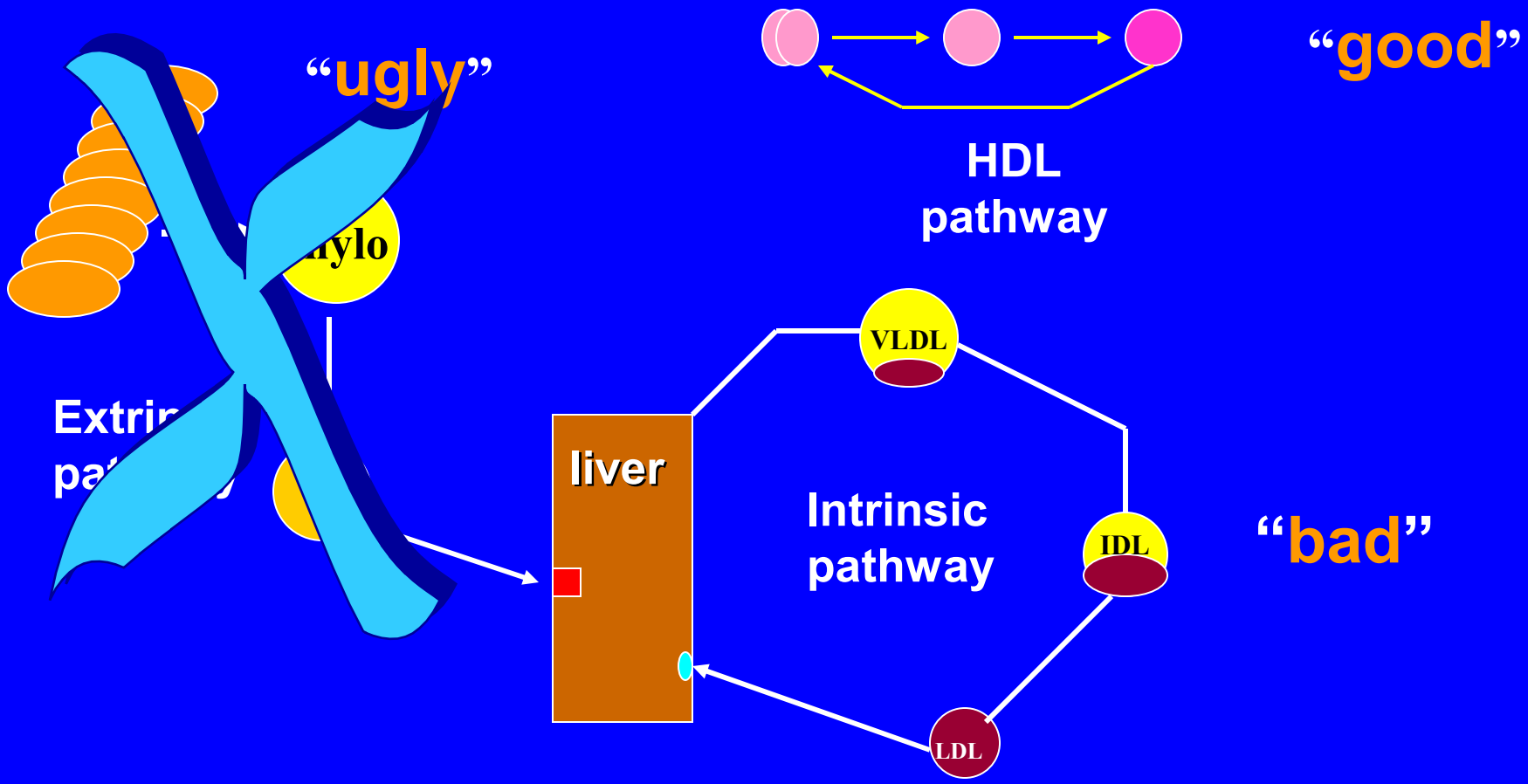
B100 LDL

A HDL

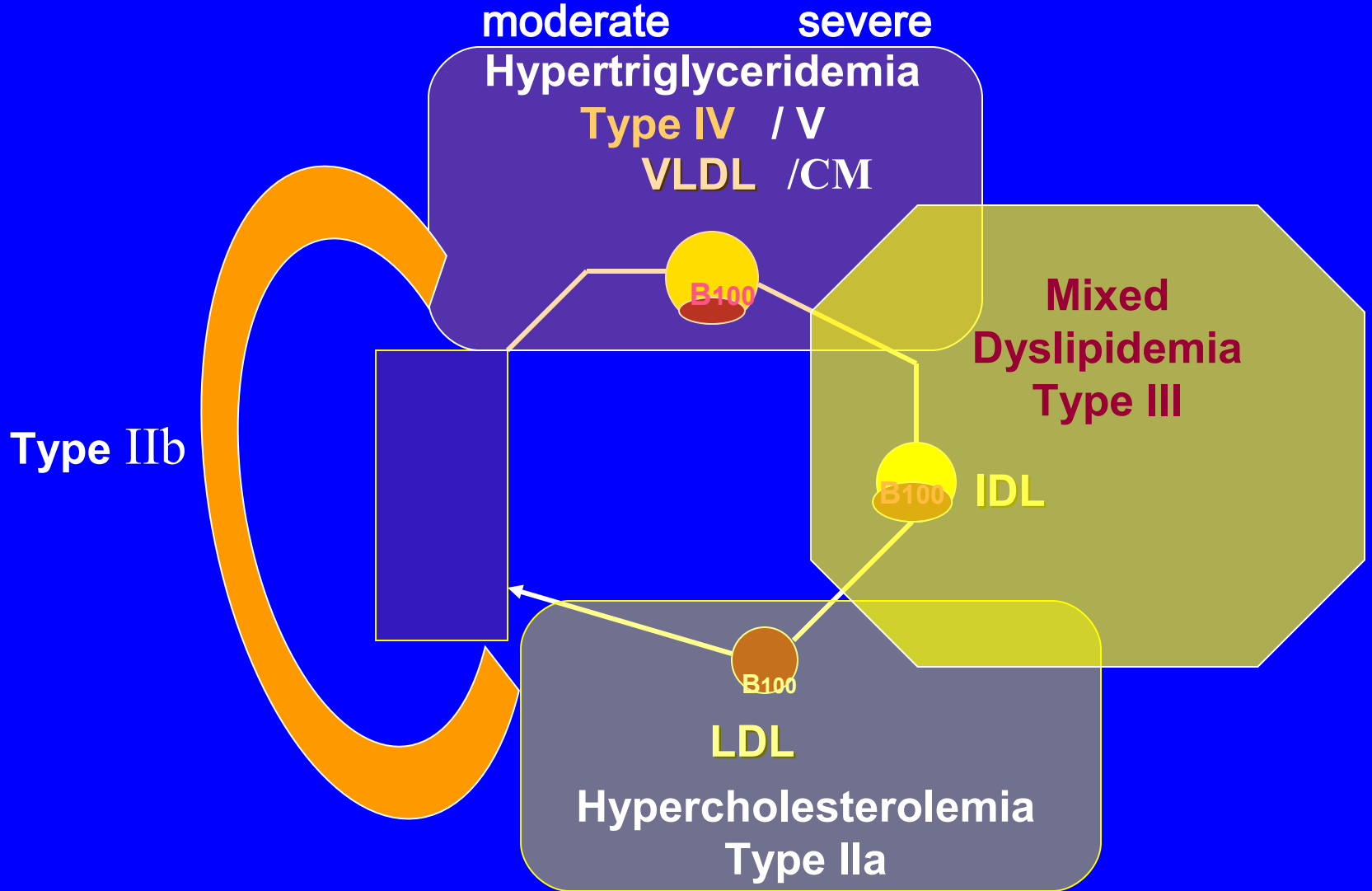
intrinsic

משבולים
וסינדרומים קליניים

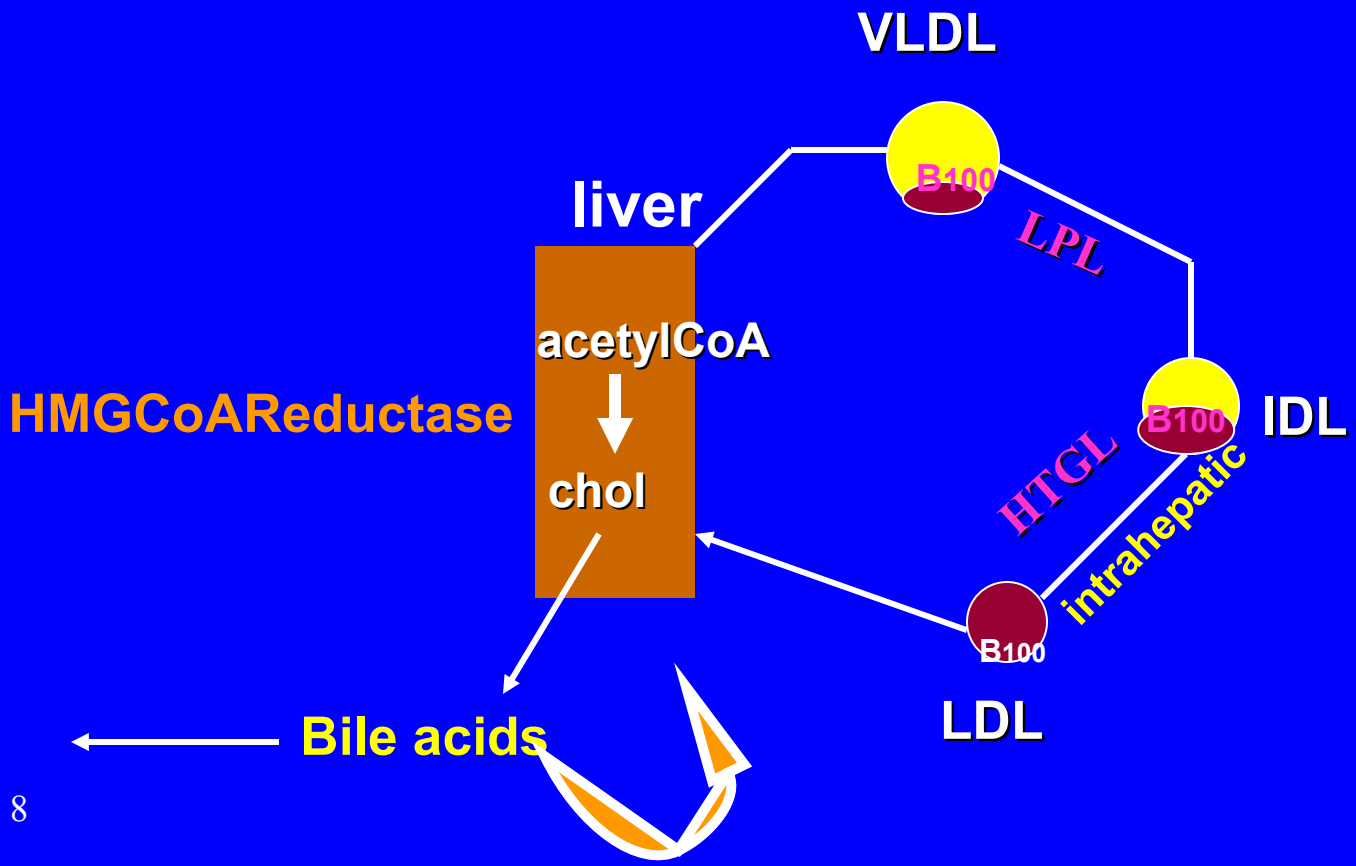
מסלולים מטבוליים



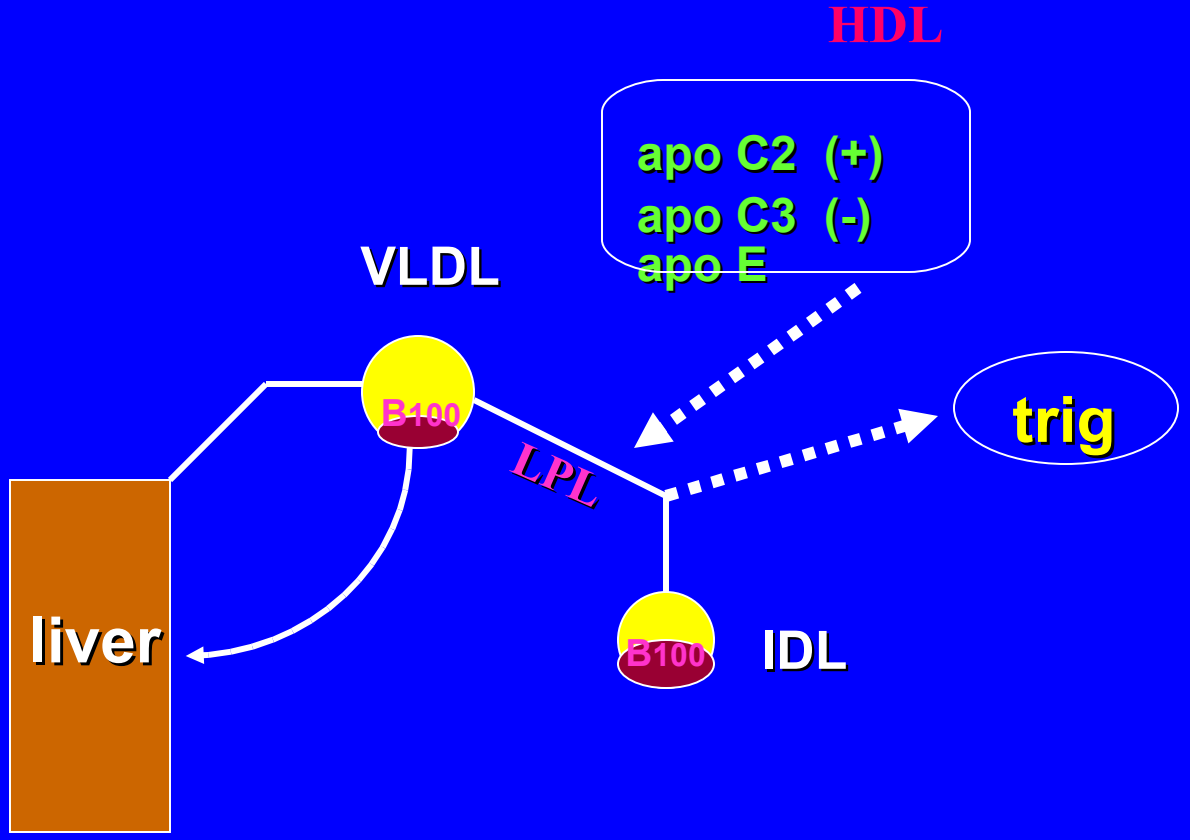
Classification of dyslipidemias



Intrinsic Pathway



VLDL Metabolism 1



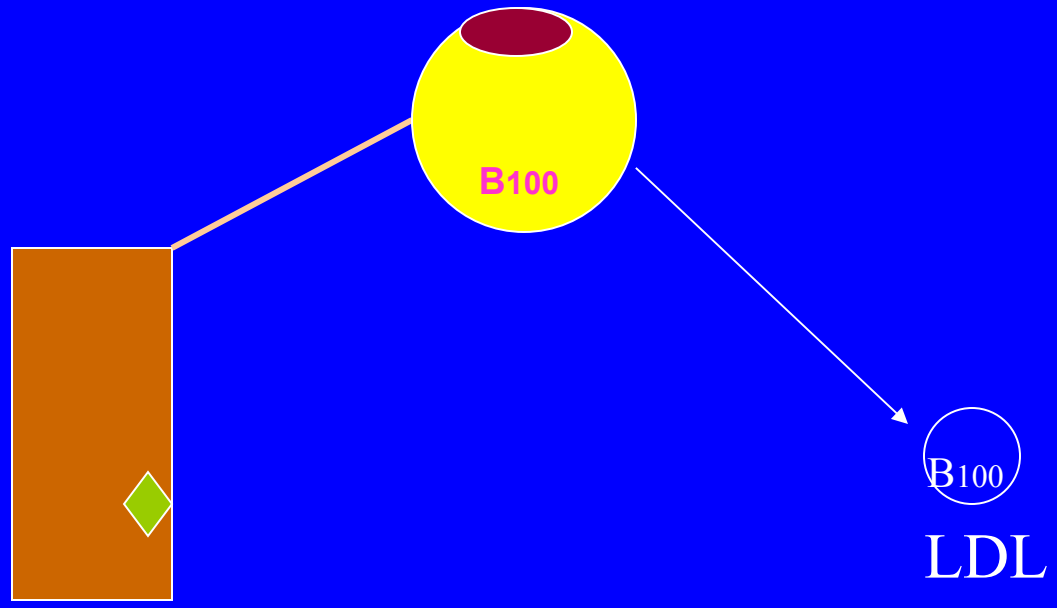
סינדרומים קליניים

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

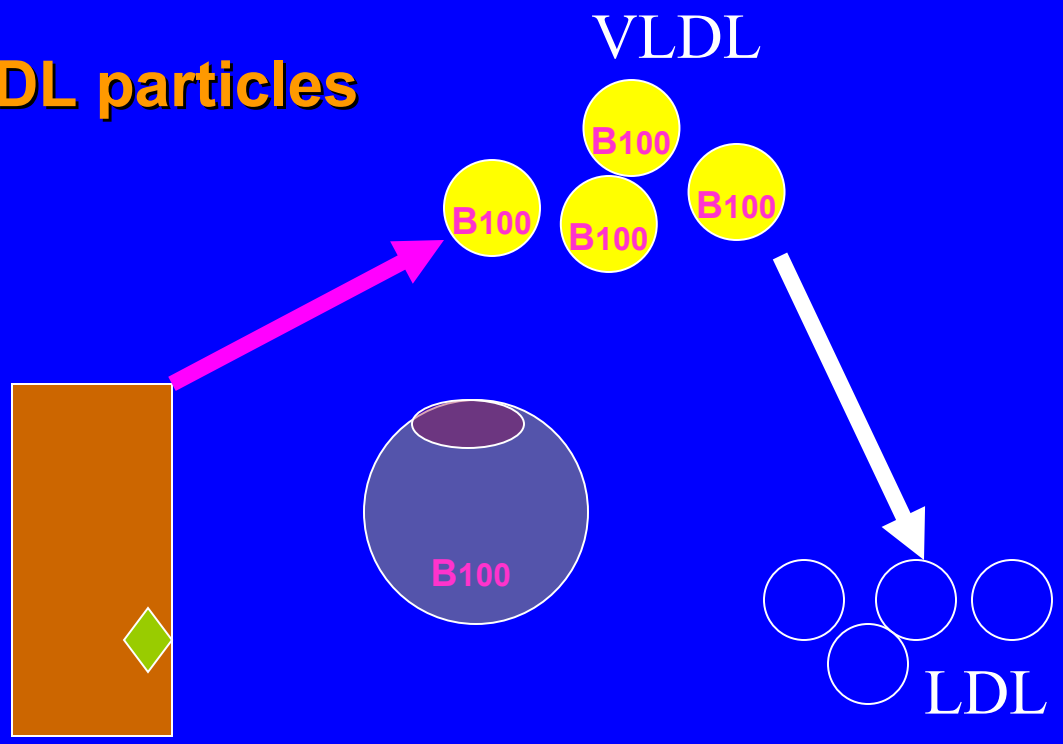
Familial Hypertriglyceridemia

- 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

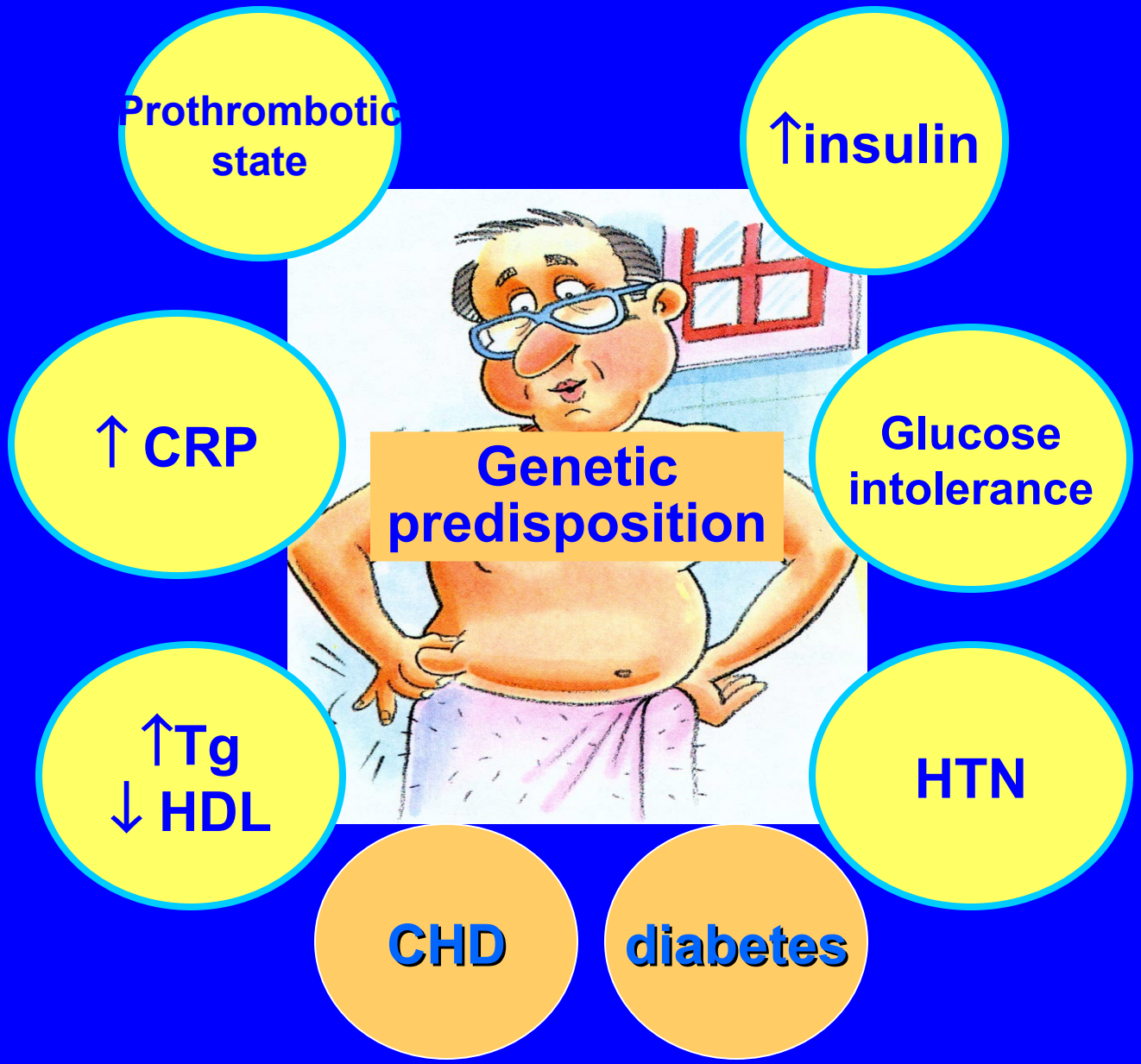


Familial Combined Hyperlipidemia

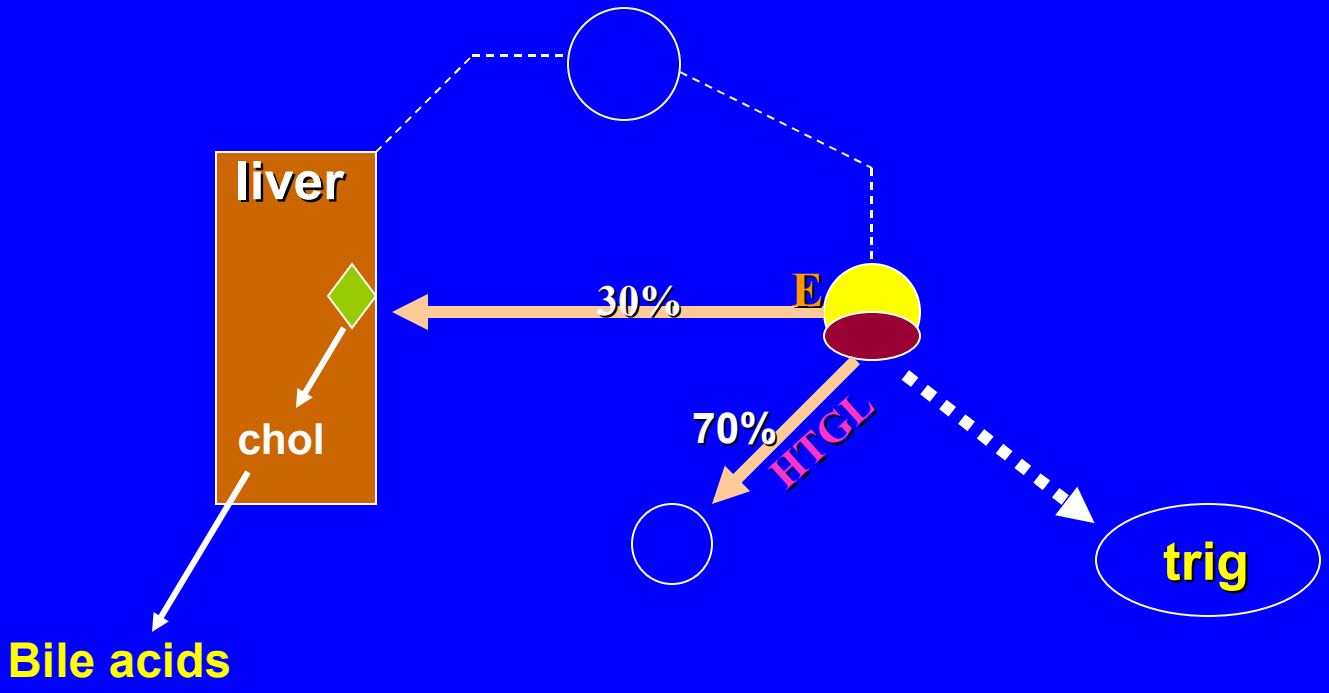
- Autosomal dominant
- usually manifests in adulthood
- elevated chol and/or Tg levels
- overproduction of apo B
- Family: ↑TG or ↑chol or both
  - In 50% of family members
- Many, normal sized VLDL particles
- elevated apo B levels
- increased CHD risk



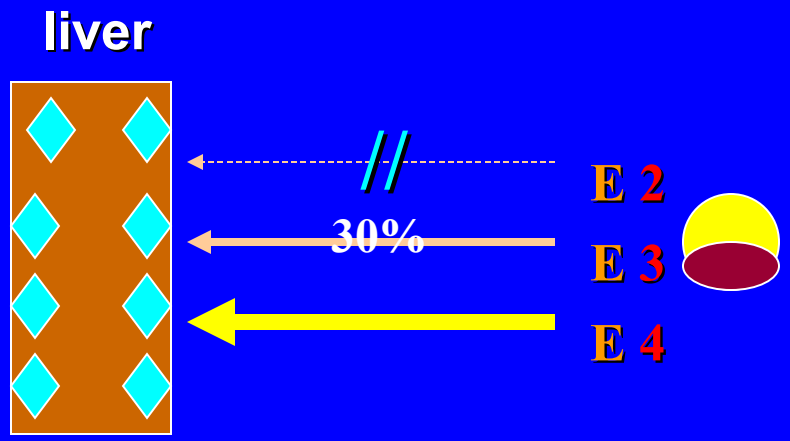
The Metabolic Syndrome



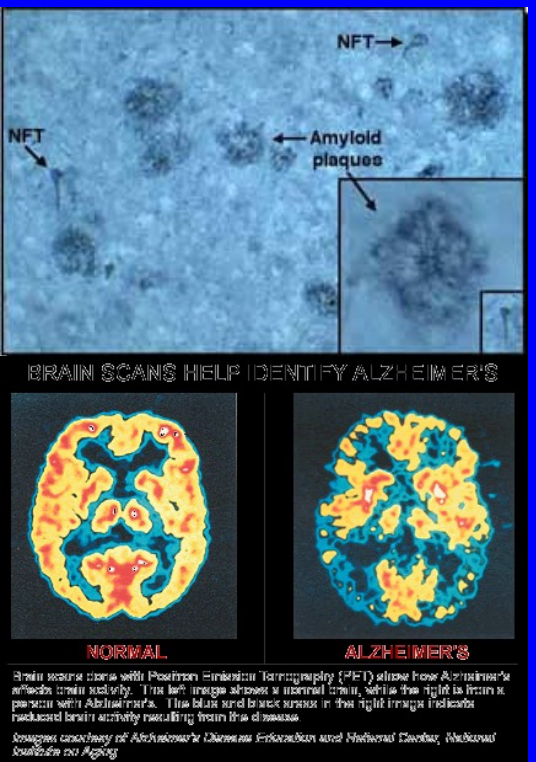
IDL metabolism

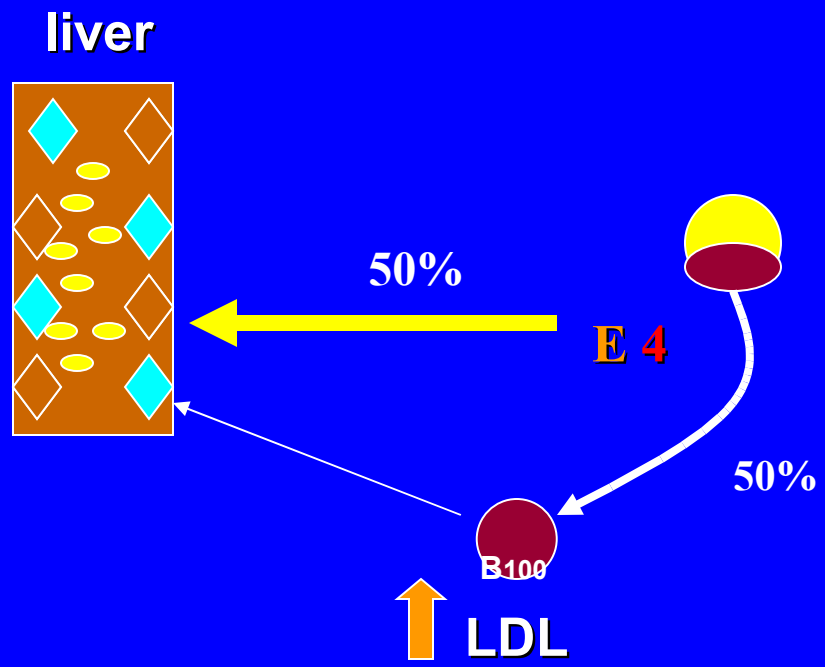


Apo E Phenotypes

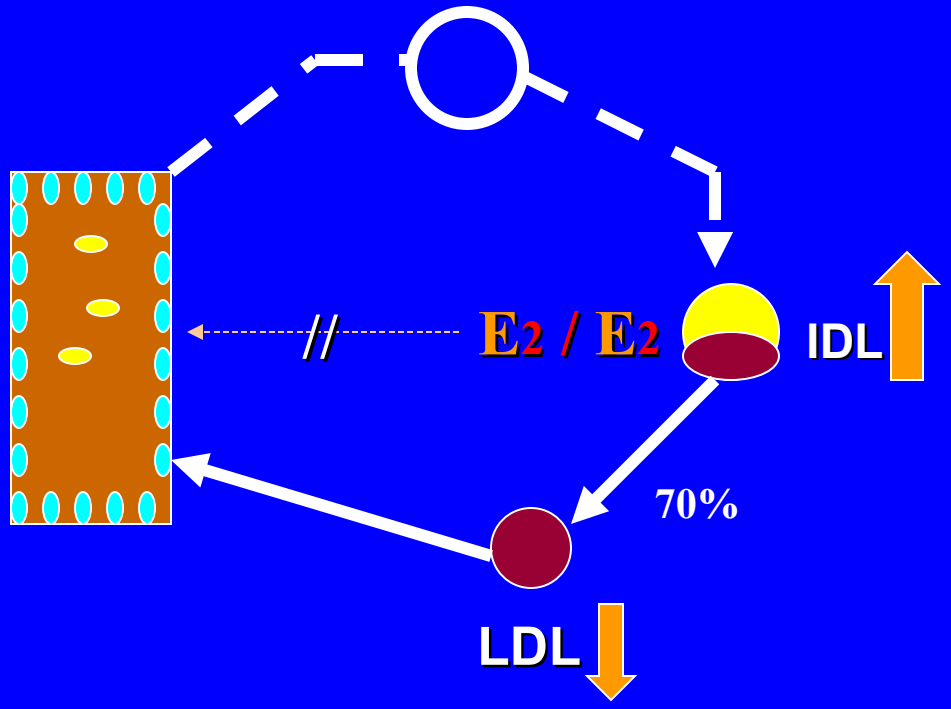


Apo E4 genotype



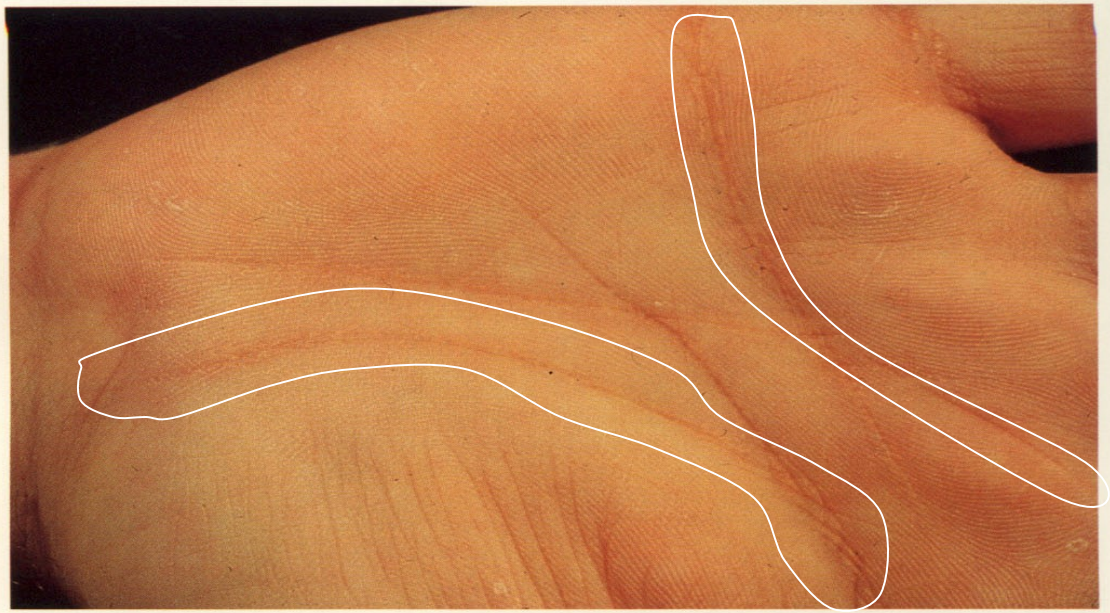


Type III dyslipidemia
Dysbetalipoproteinemia
Broad-beta disease
Remnant disease



Dysbetalipoproteinemia
אפיונים קלינים

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



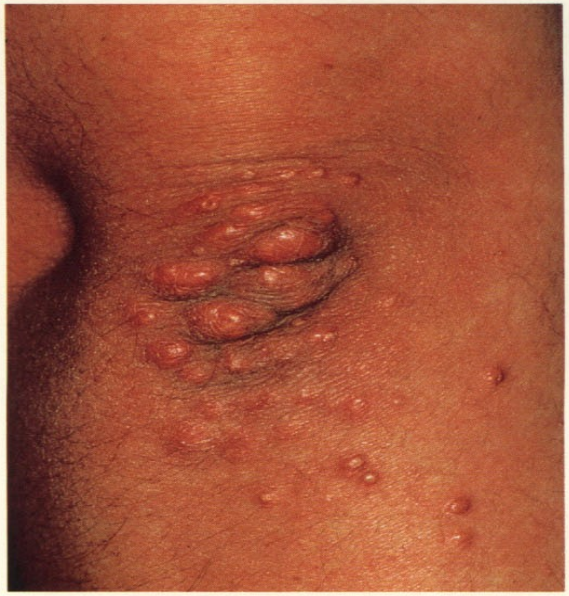
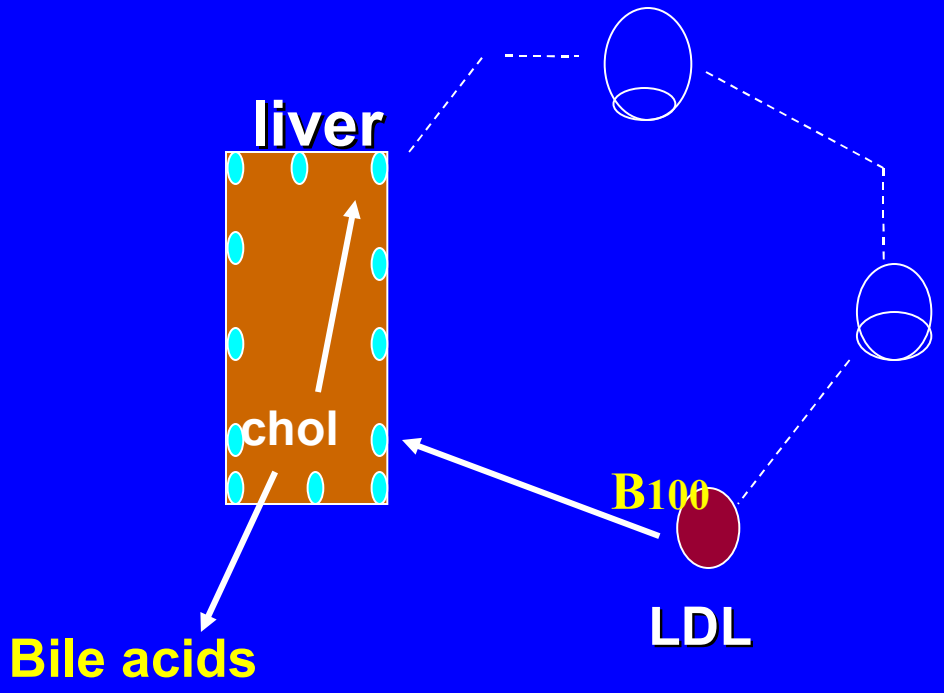
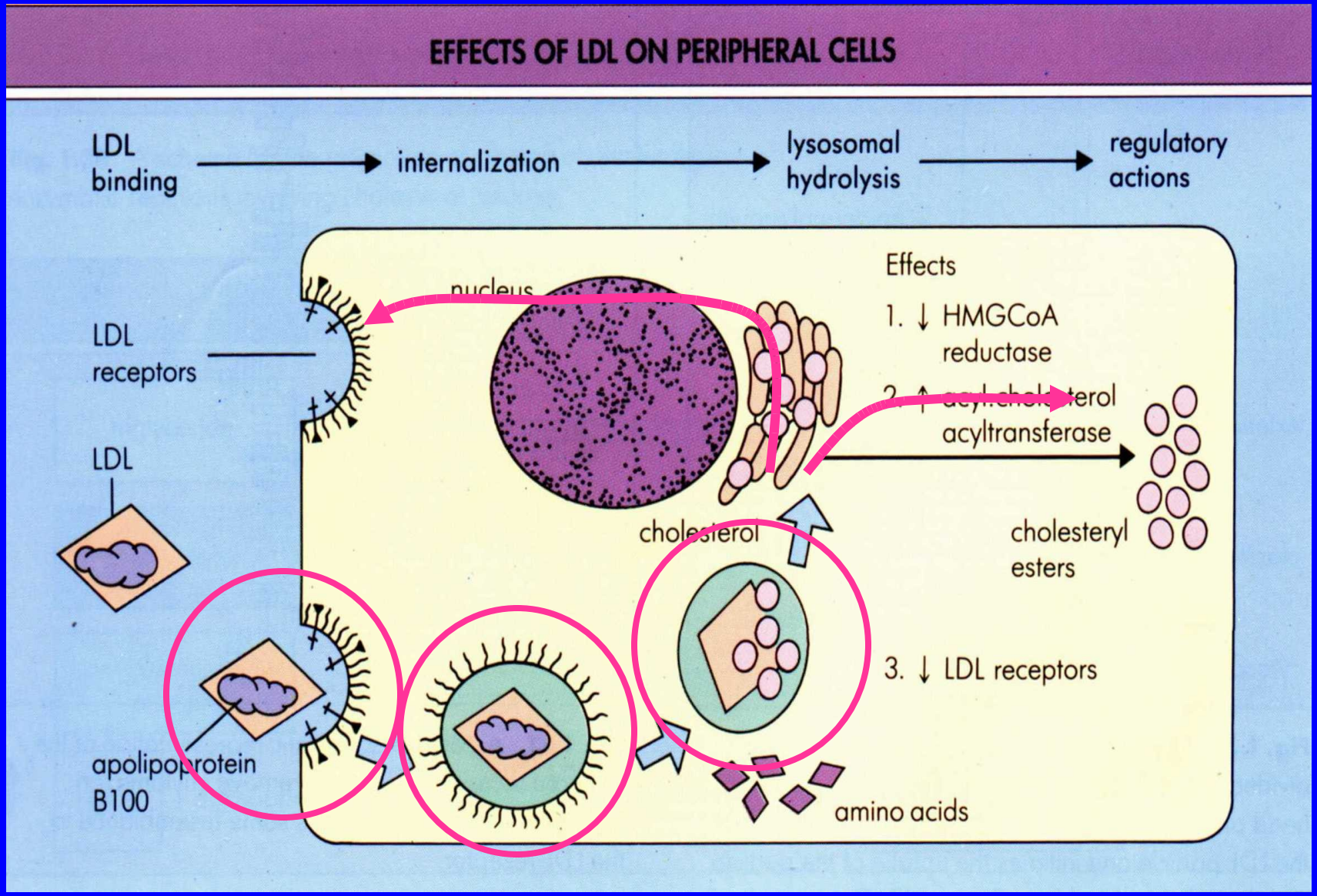


Plate 5.
Xanthoma striata palmaris (top) and tuboeruptive xanthomas (bottom).

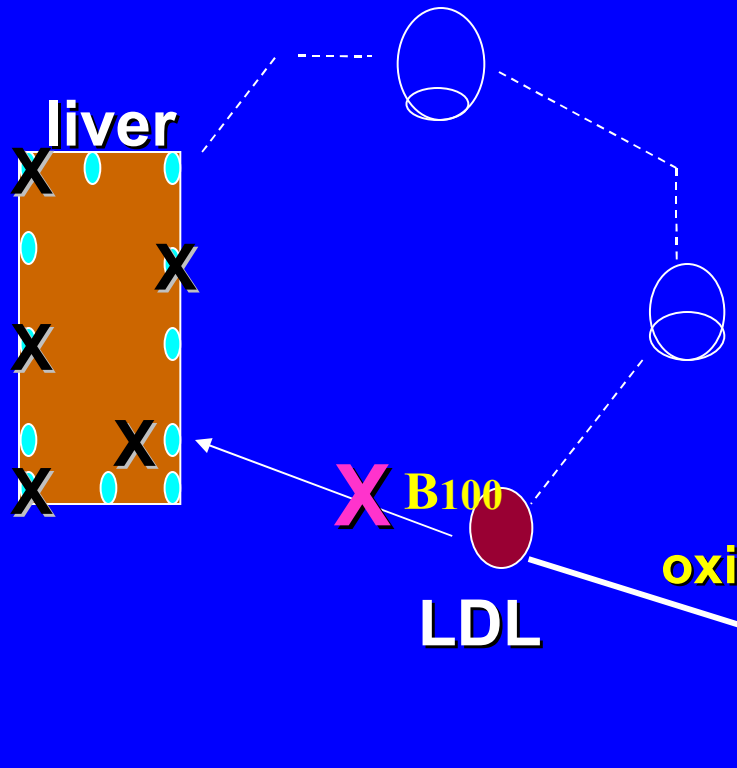
LDL Metabolism



LDL metabolism within Hepatic Cells



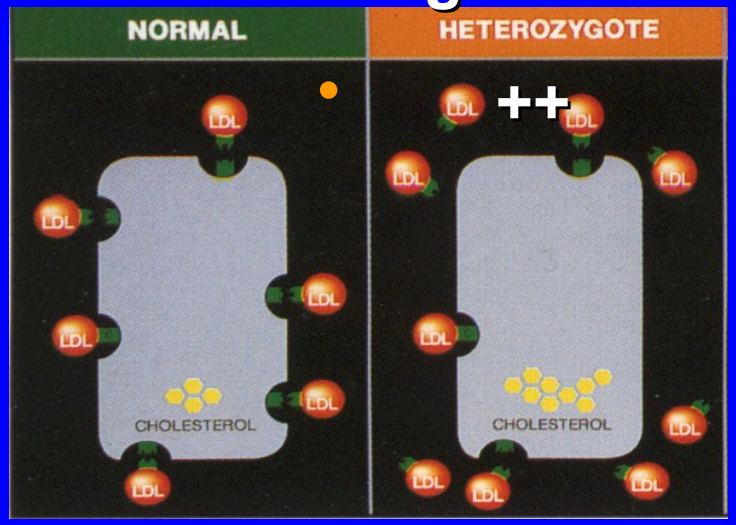
Hyper LDLemia
מנגנונים



Familial Hypercholesterolemia (FH)

- Decreased LDL-receptor
- Autosomal dominant
- Elevated LDL chol (mg/dL)
- Premature CHD
- Tendon Xanthomas
  - hands
  - elbows
  - knees
  - Achilles

	heterozygous	homozygous
	50%	absent
	1:500	1: 106
	250-400	700-1000
	age 35-55	age 15-20
	++	



Tendon Xanthomas

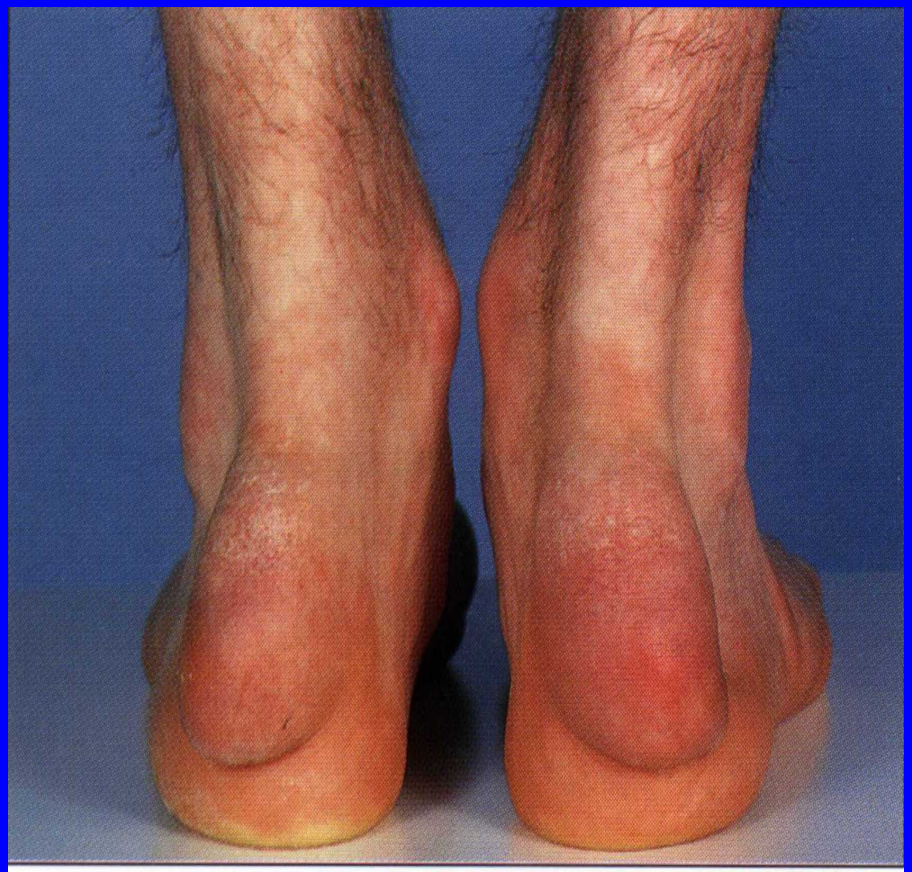


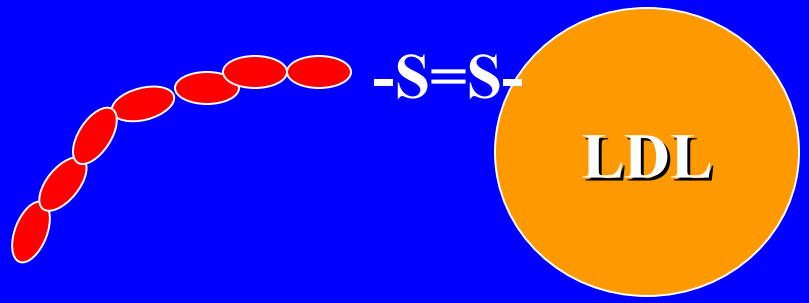
Fig. 5.7 Extensive accumulation of lipids in the Achilles tendon in a patient with Familial Hypercholesterolaemia.

Polygenic (common) hypercholesterolemia

- שילוב של מספר פגמים גנטים ו/או סביבתיים
- חומרה קלה-בינונית
- לא בולט בגיל צעיר
- אין קסנטומות
  - לפעמים ארקוס בקרנית ו/או קסנטלסמות

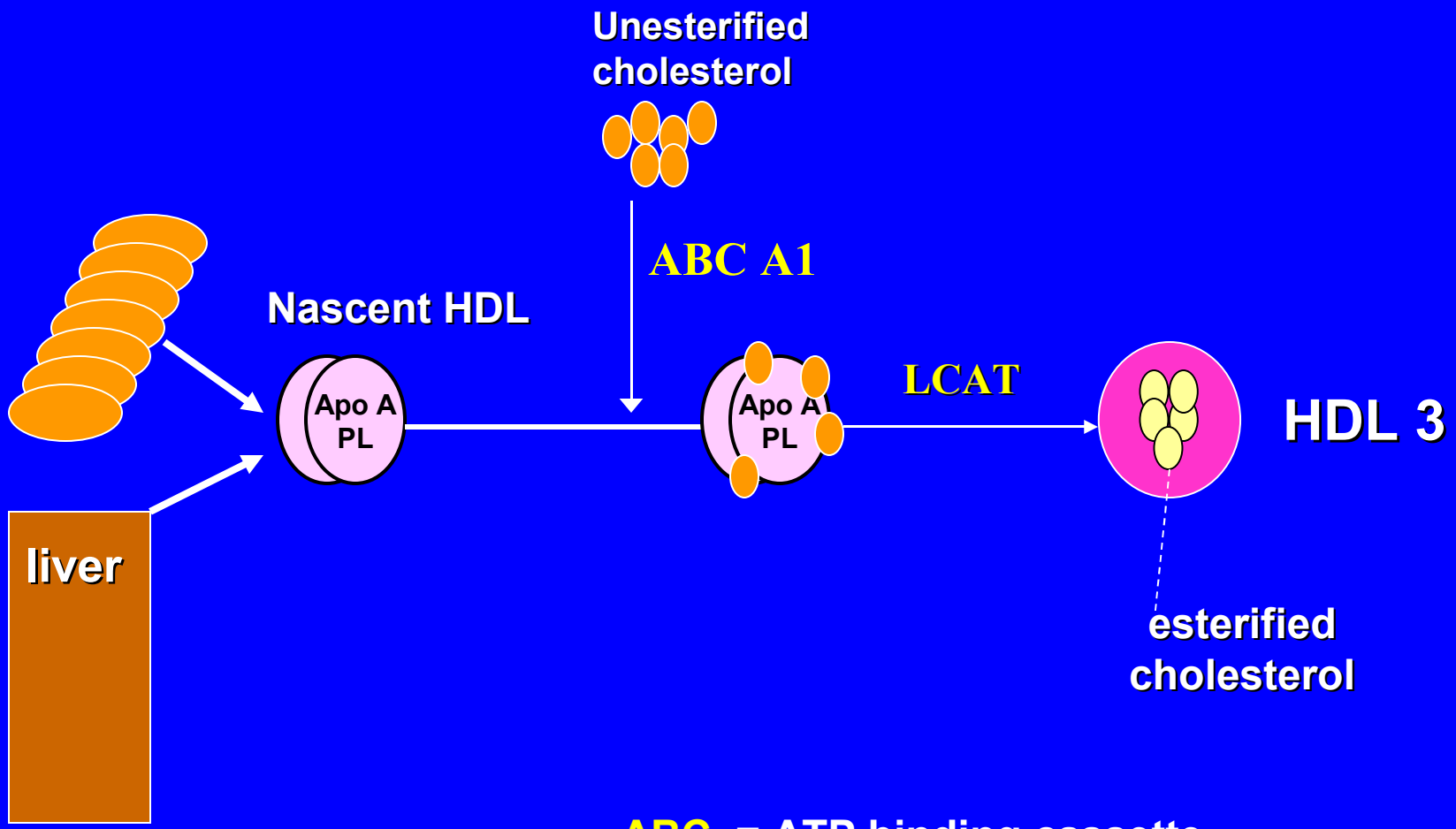
LDL Modifications

- 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



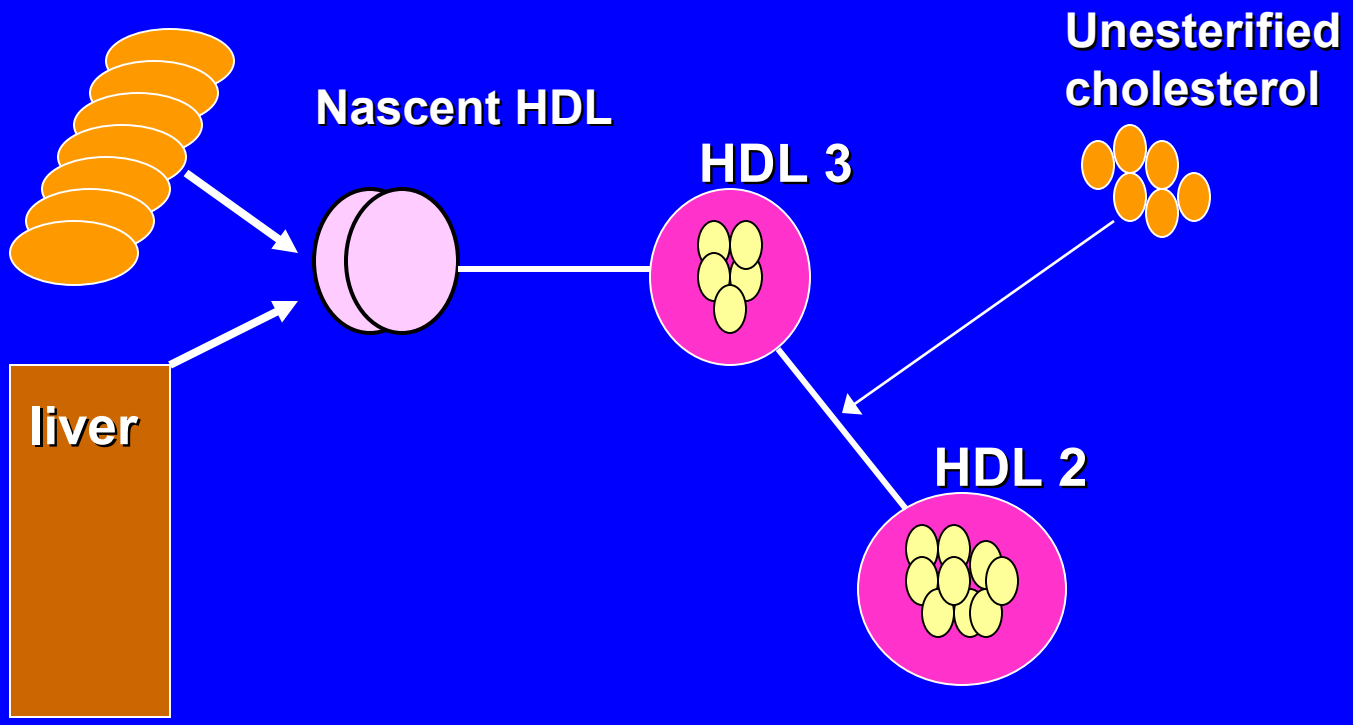
HDL Metabolism 1

Reverse cholesterol transport

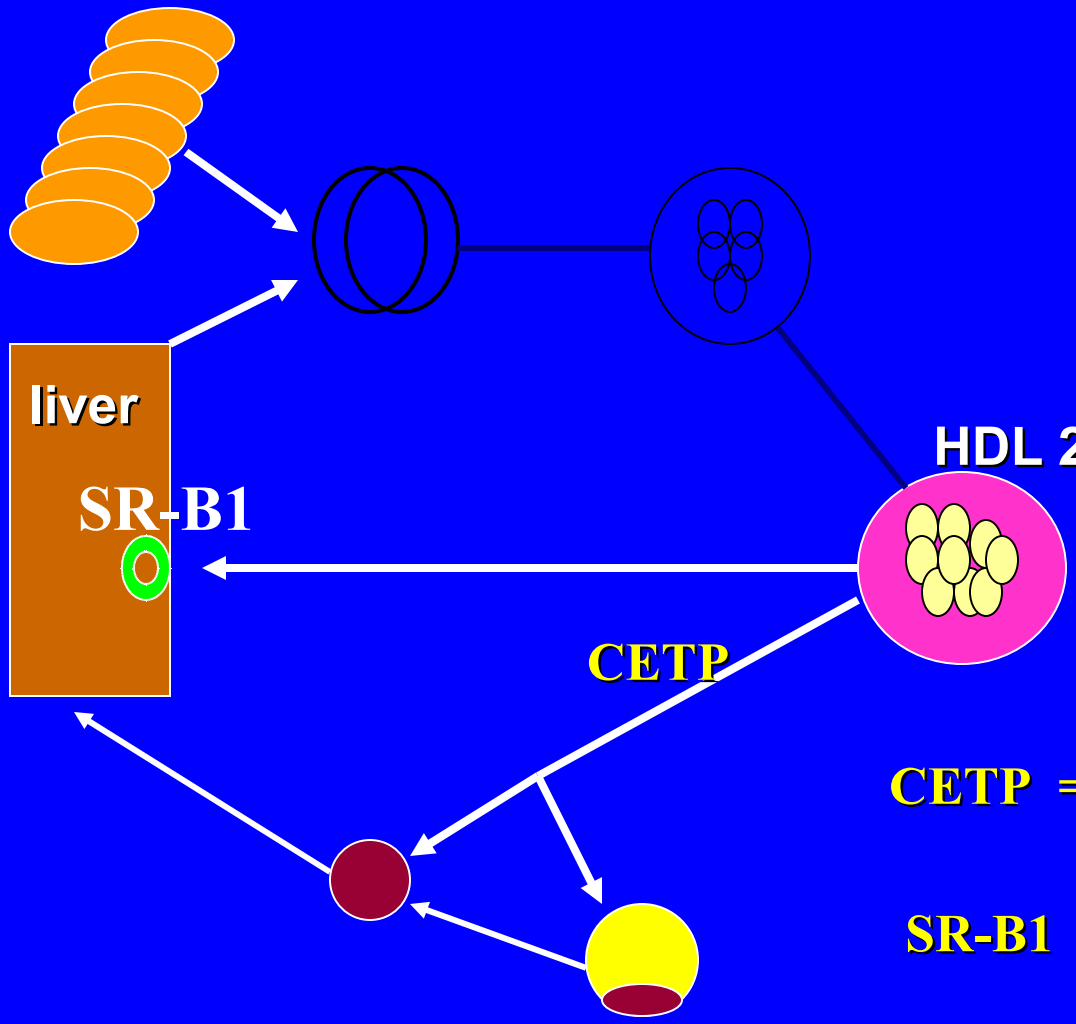


ABC = ATP binding cassette
LCAT = Lecithin:Cholesterol Acetyltransferase

HDL Metabolism 2



HDL Metabolism 3



CETP = Cholesterol Ester Transfer Protein

SR-B1 = Scavenger receptor B1

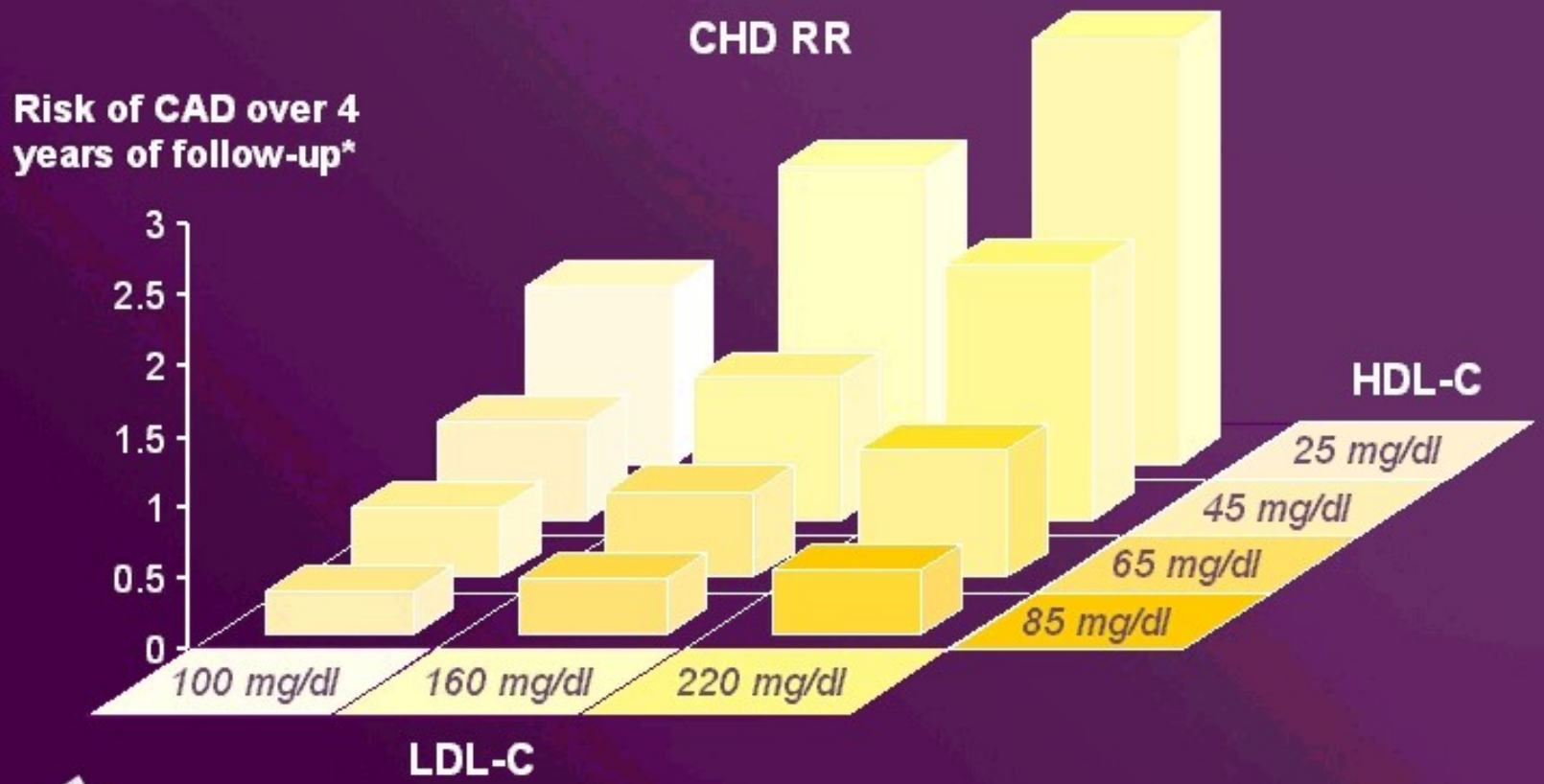
Antiatherosclerotic mechanisms of HDL

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

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

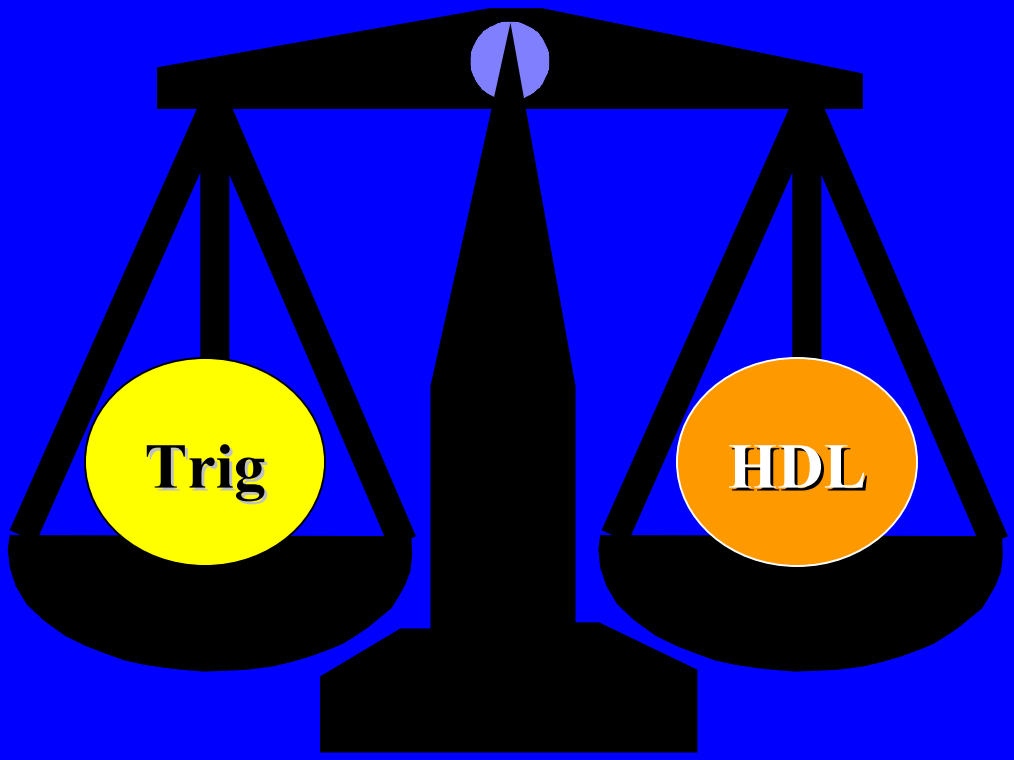
HDL-C vs LDL-C
as a predictor of CHD risk



*Men aged 50–70

Gordon, Castelli et al. Am J Med 1977; 62: 707–714

Relationship between HDL and Triglyceride-rich lipoproteins

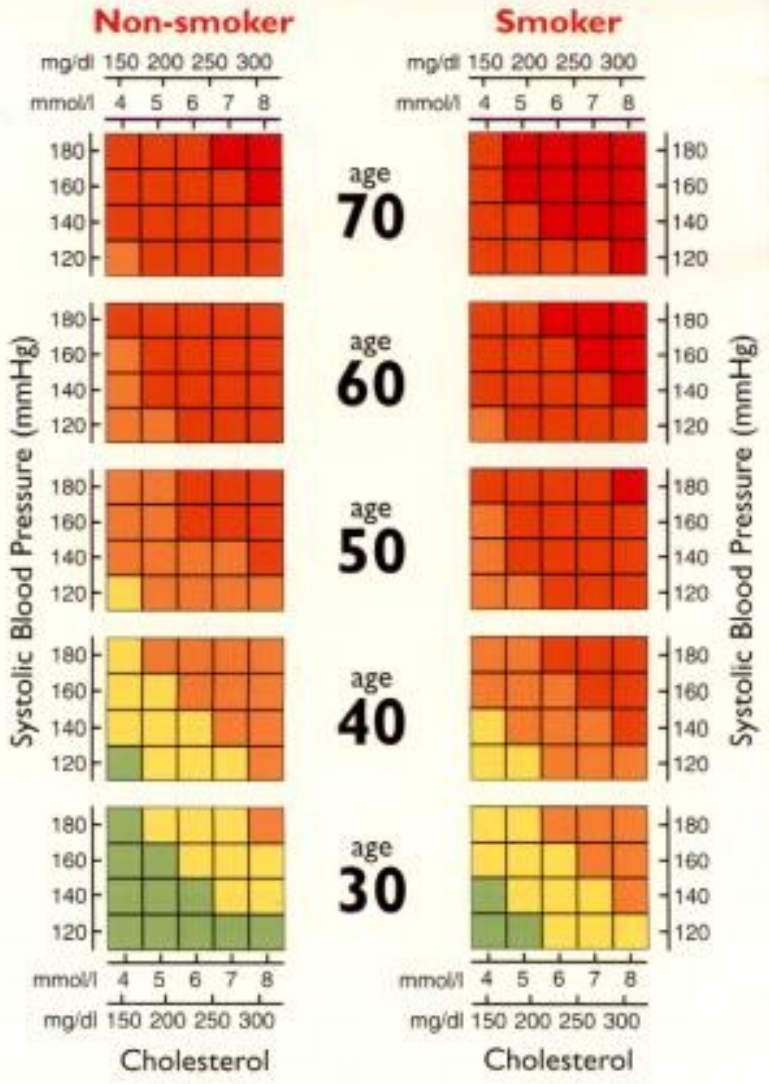


הנחיות קליניות
מניעה ראשונית

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

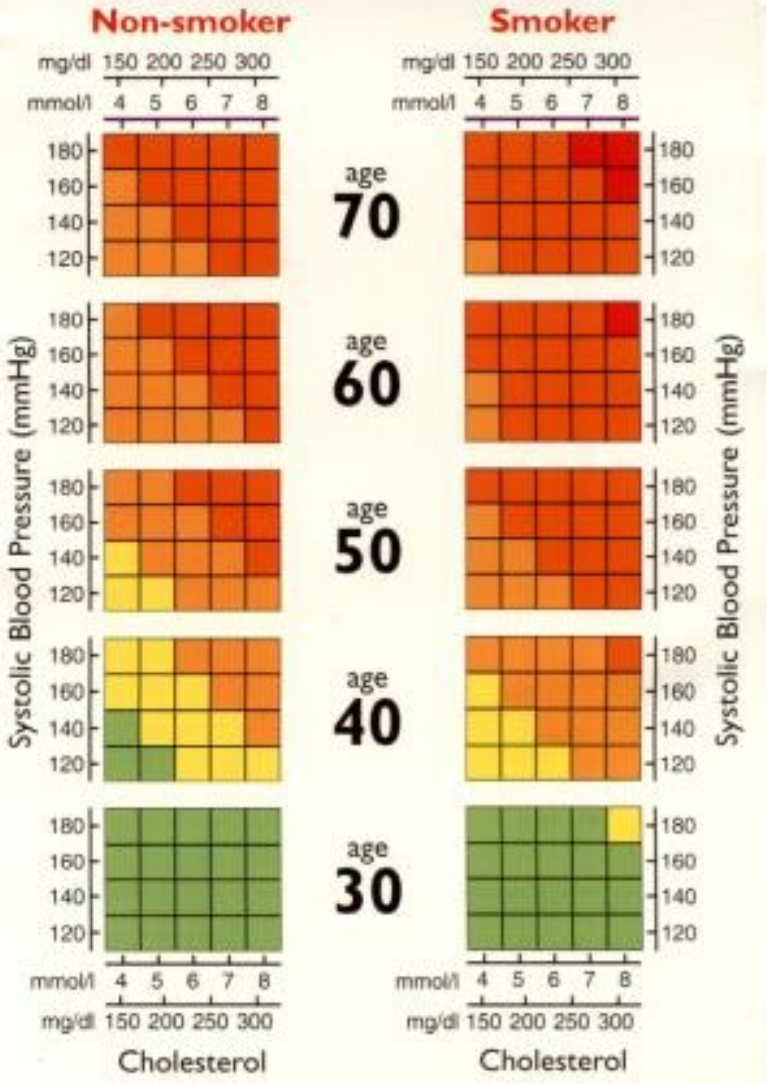
MEN *WITH DIABETES*

Risk of Coronary Heart Disease



WOMEN *WITH DIABETES*

Risk of Coronary Heart Disease



הנחיות קליניות
מניעה שניונית

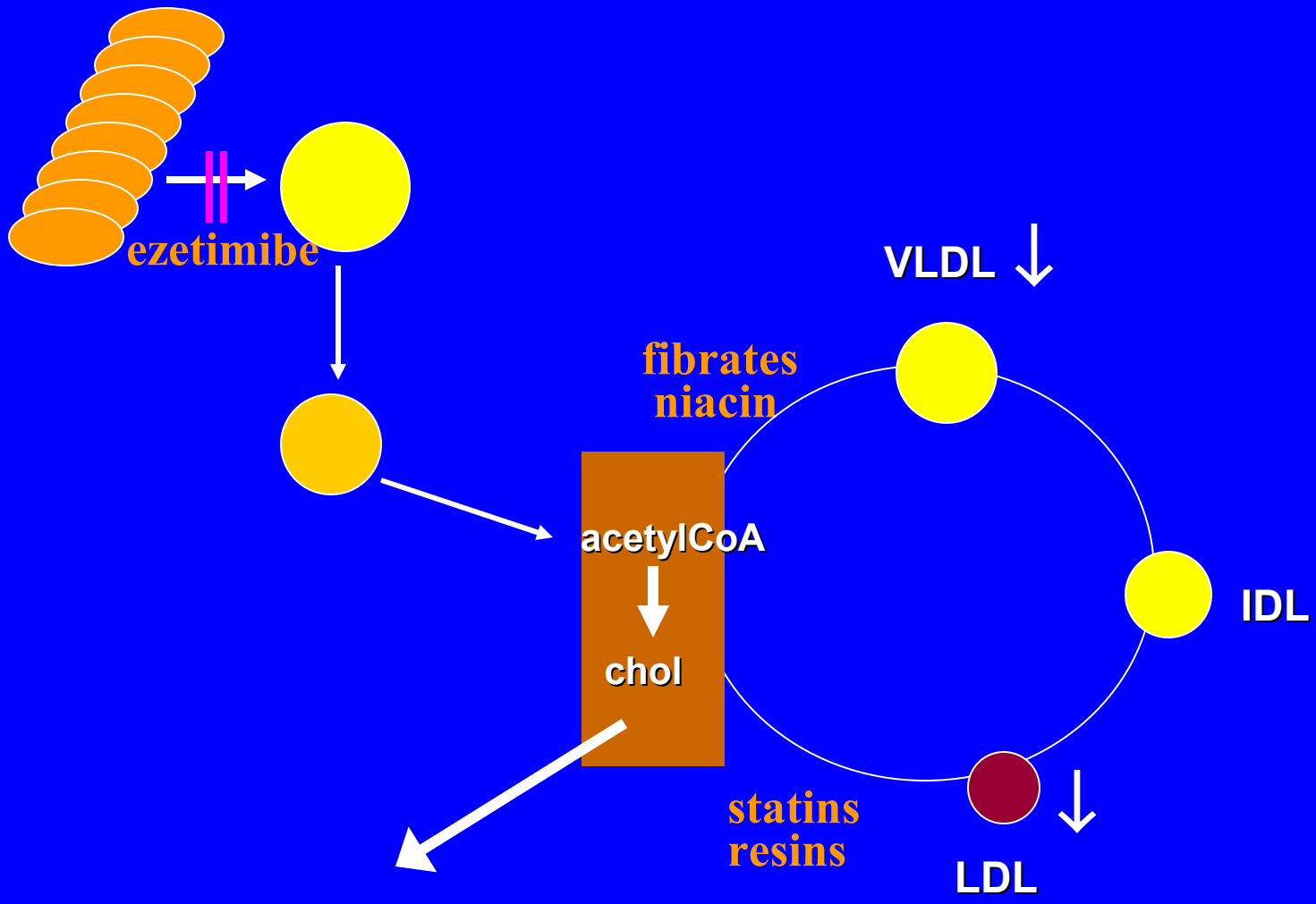
- טיפול בגורמי הסיכון האחרים
- טיפול תזונתי
  - דל שומן / דיאטה "ים-תיכונית"
  - אומגה 31 : גרם ליום
  - פיטוסטרולים: 2 גרם ליום
- טיפול תרופתי
  - תמיד: כאשר LDLc ≥ 100 mg/dL

Risk category	LDL cholesterol goal	Initiate therapeutic lifestyle changes	Consider drug therapy
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL optional goal of <70 mg/dL	≥100 mg/dL	≥100 mg/dL consider drug options if LDL-C <100 mg/dL
Moderately high risk: two + risk factors (10-year risk 10%-20%)	<130 mg/dL optional goal <100 mg/dL	≥130 mg/dL	≥130 mg/dL consider drug options if LDL-C 100-129 mg/dL
Low risk: ≤1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (consider drug options if LDL-C 160-189 mg/dL)

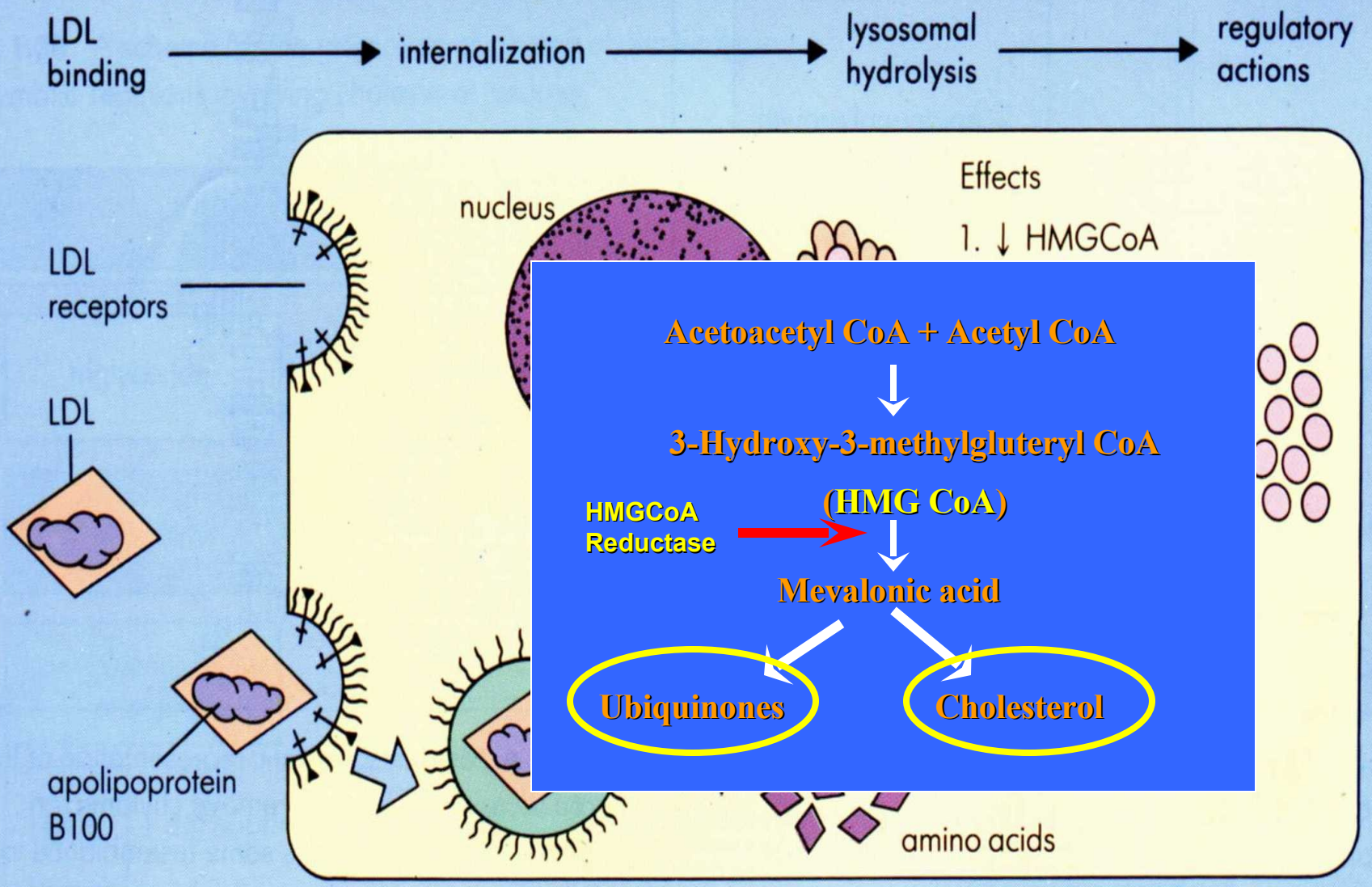
- In high-risk persons
  - recommended LDL-C goal is <100 mg/dL
- when risk is very high
  - an LDL-C goal of <70 mg/dL is a therapeutic option
- This therapeutic option extends also to patients at very high risk who have a baseline LDL-C <100 mg/dL

פרמקולוגיה

מיקום הפעולה של התרופות

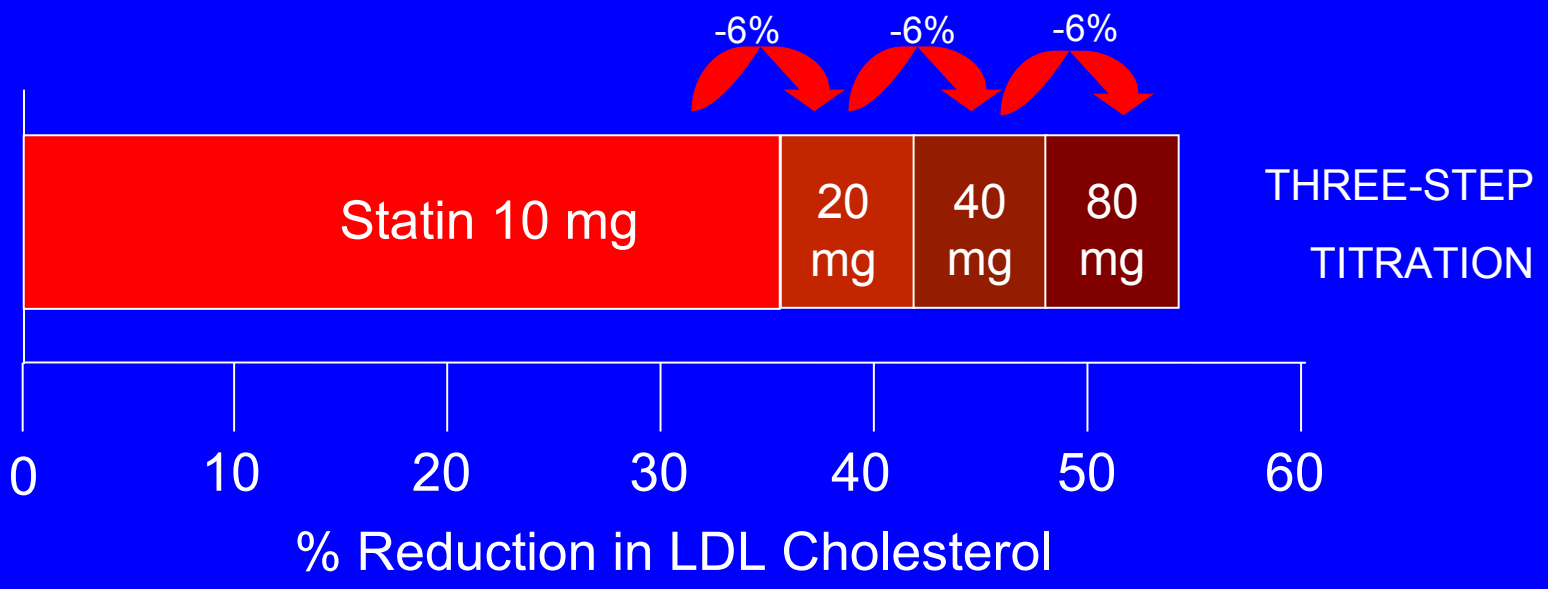


Statins


LDL binding
internalization
lysosomal hydrolysis
regulatory actions
LDL receptors
LDL
apolipoprotein B100
nucleus
Effects
1. ↓ HMGCoA
Acetoacetyl CoA + Acetyl CoA
3-Hydroxy-3-methylgluteryl CoA
(HMG CoA)
HMGCoA Reductase
Mevalonic acid
Ubiquinones
Cholesterol
amino acids

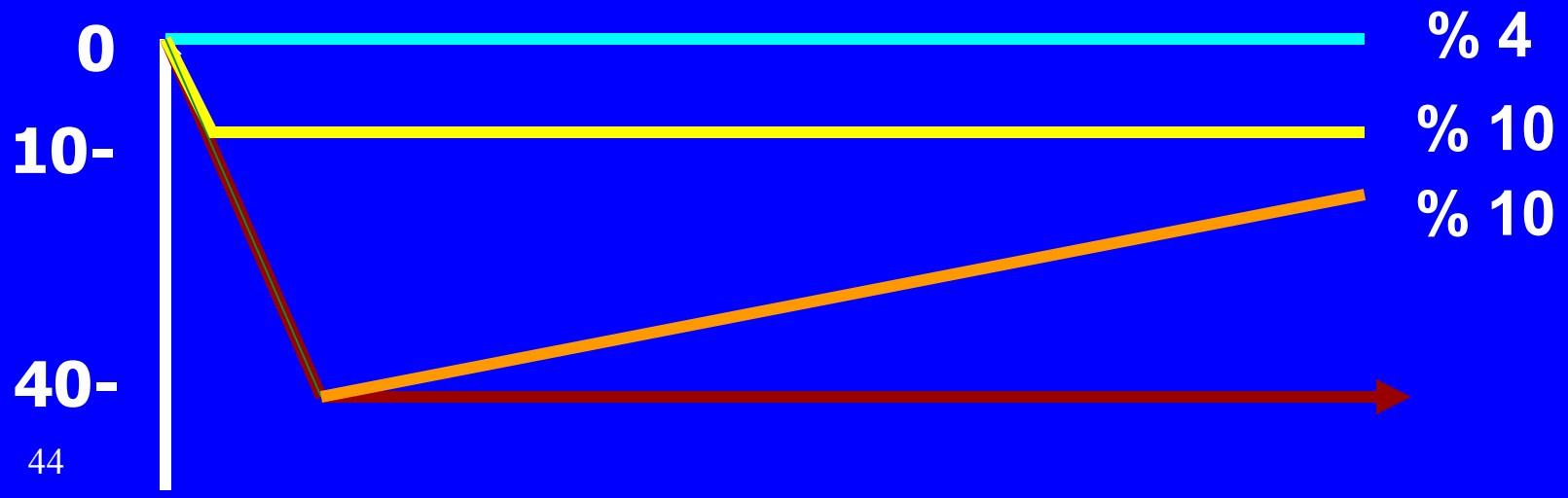
?Why are patients not reaching Goals

Effect of Statin Therapy on LDL-C Levels: "The Rule of 6"

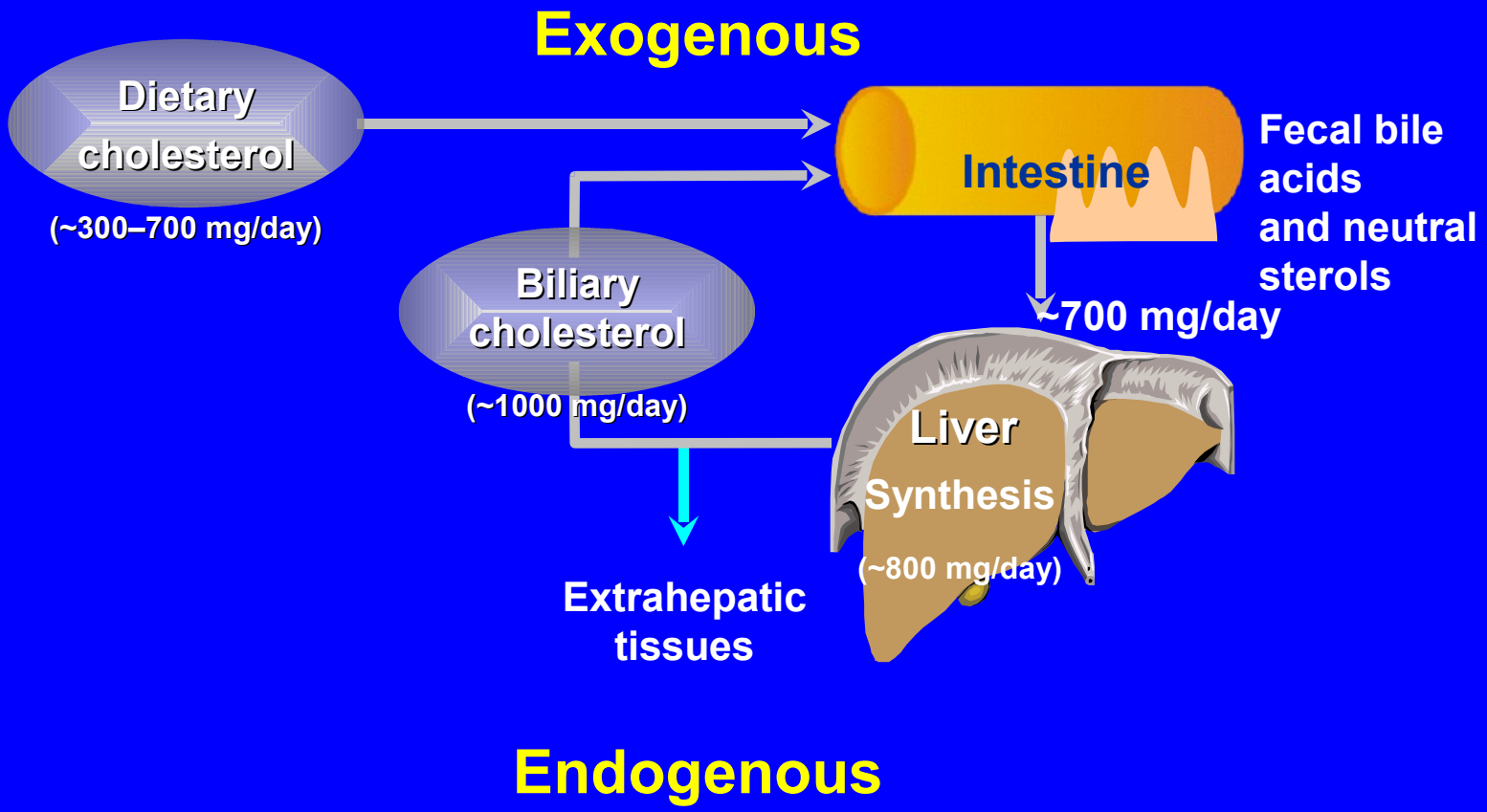


Statin failure

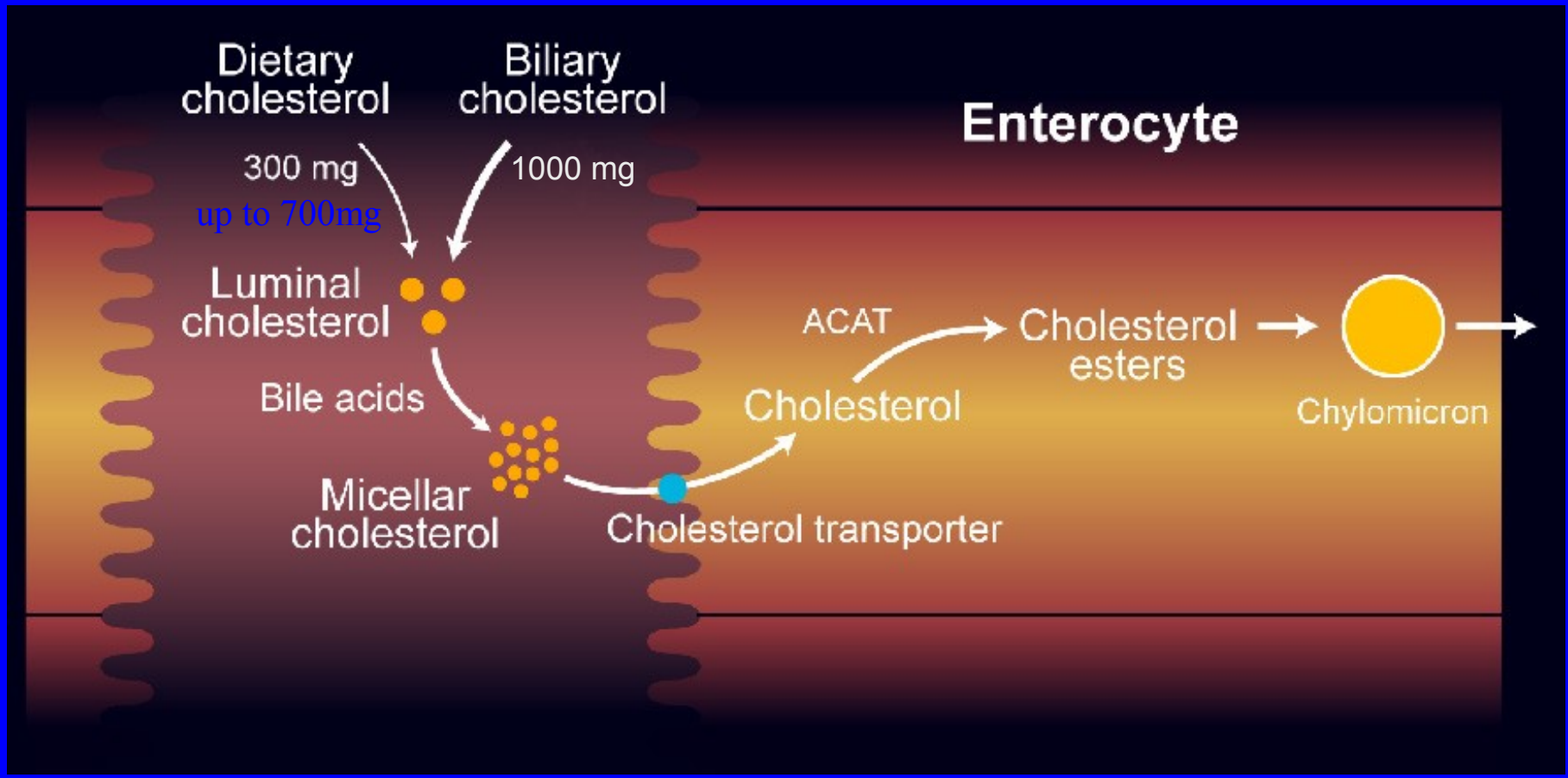
- No response
  - Poor response
  - Lose response over time



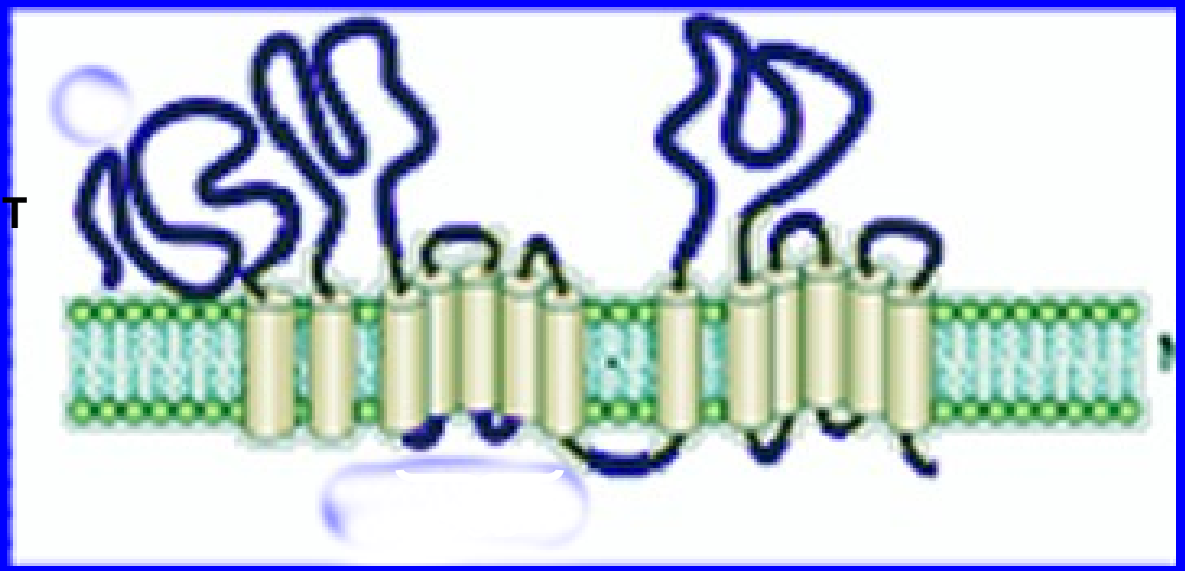
Endogenous and Exogenous Sources of Cholesterol



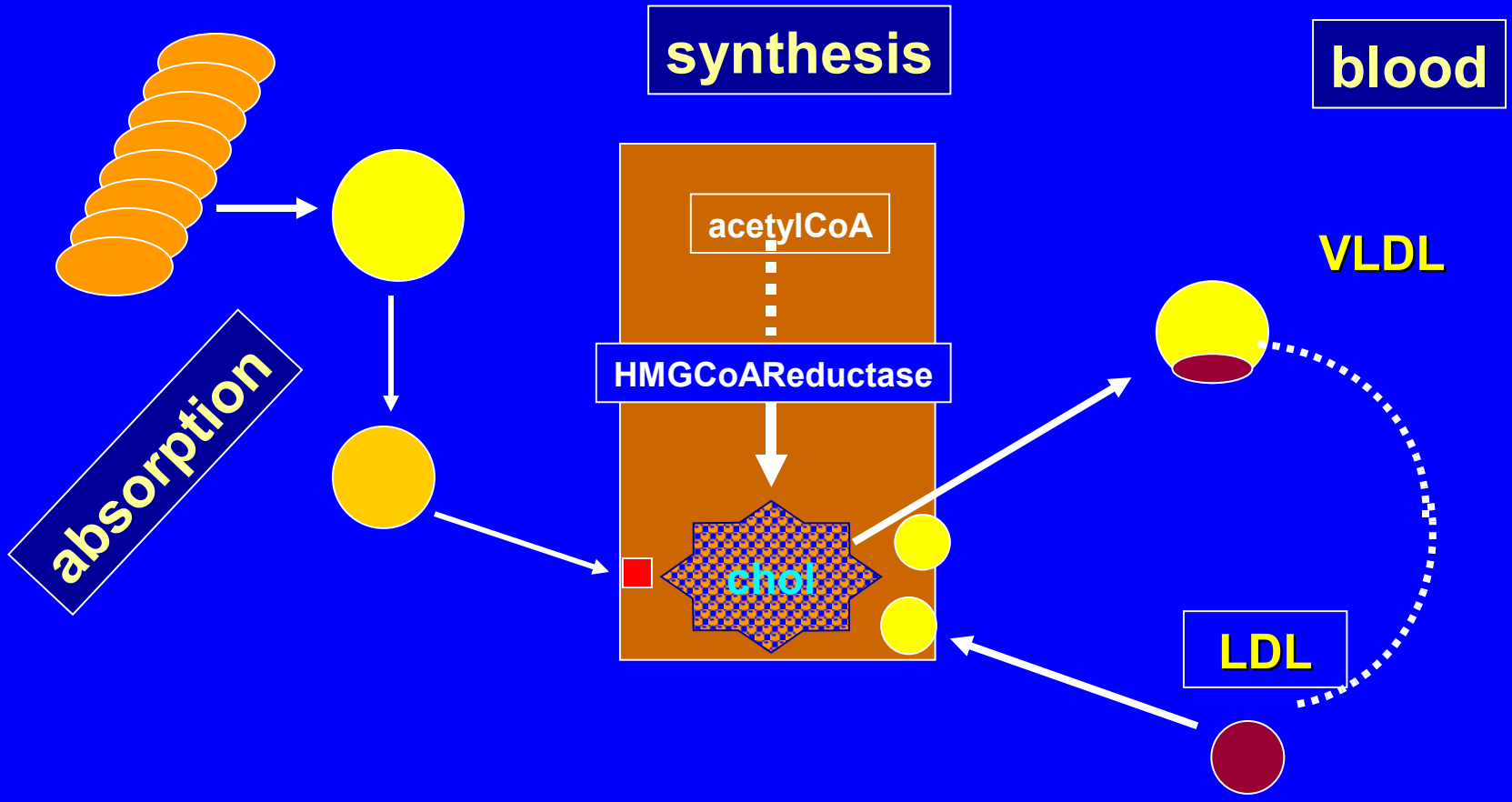
Steps Involved in Cholesterol Absorption



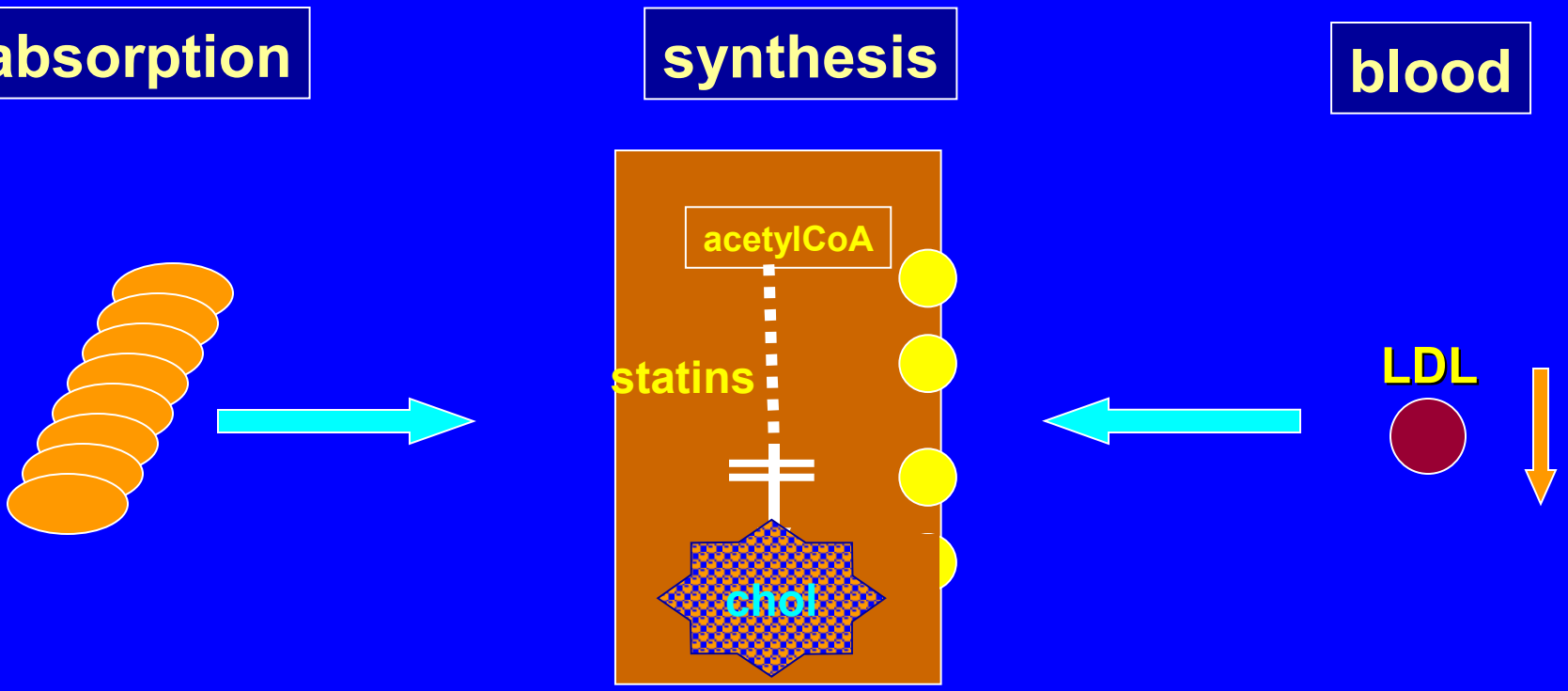
Niemann-Pick C1L1 ((NPC1L1



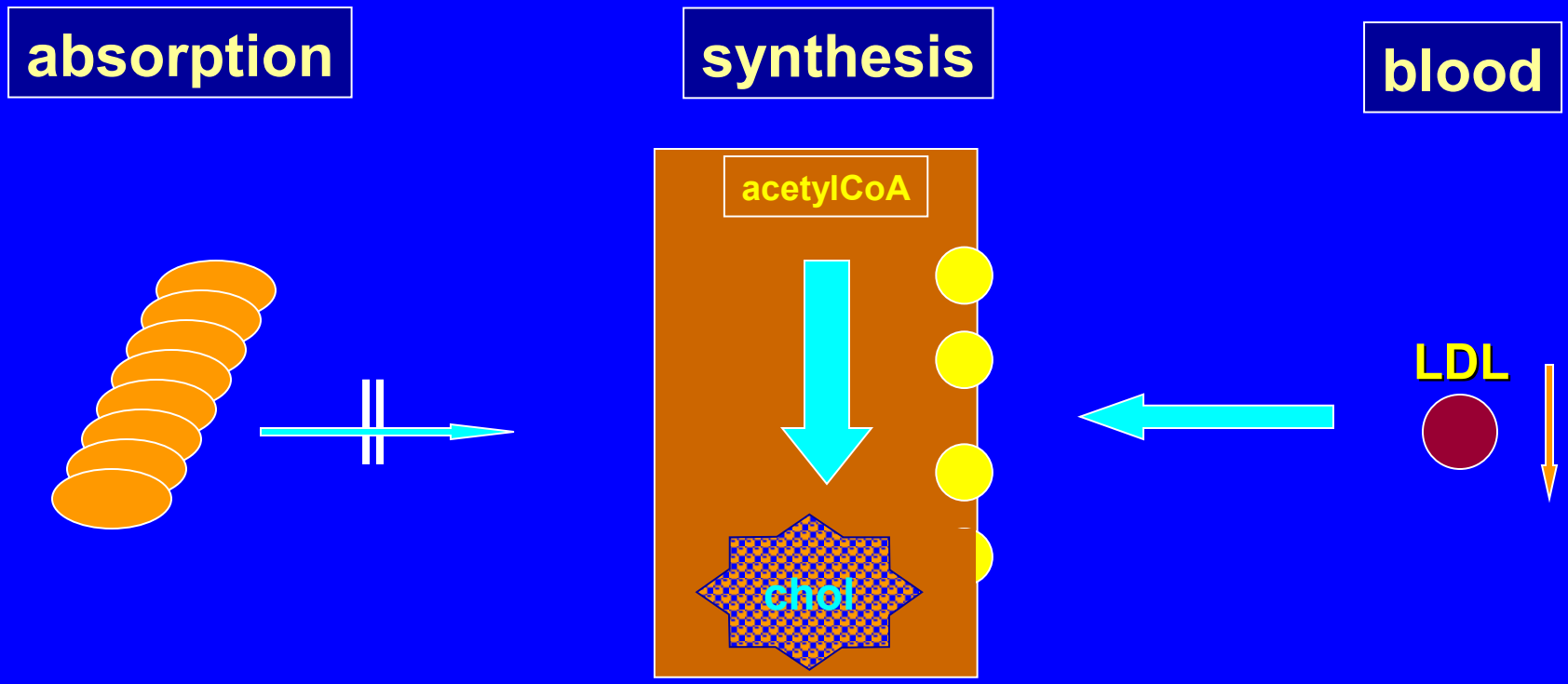
Sources of intra-hepatic cholesterol



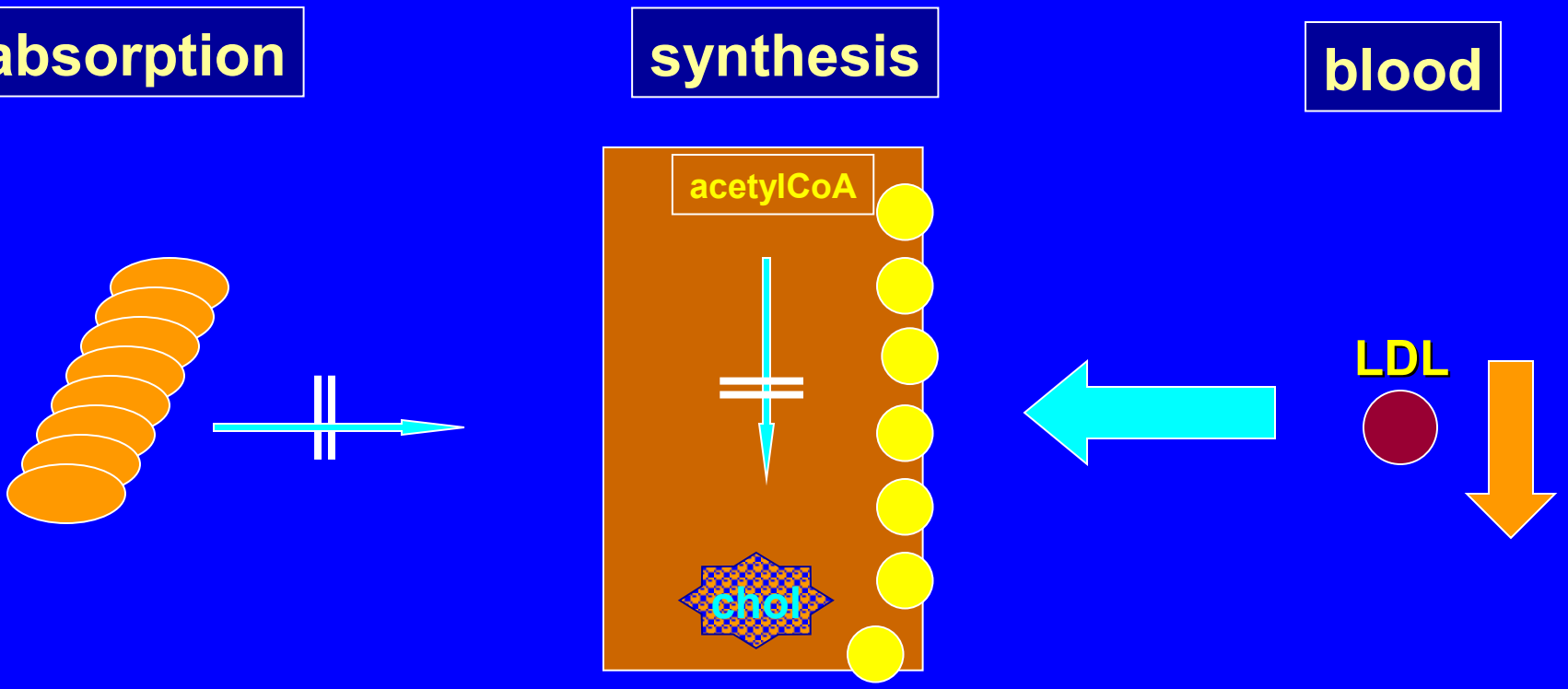
Block synthesis only statins



Block absorption only ezetimibe

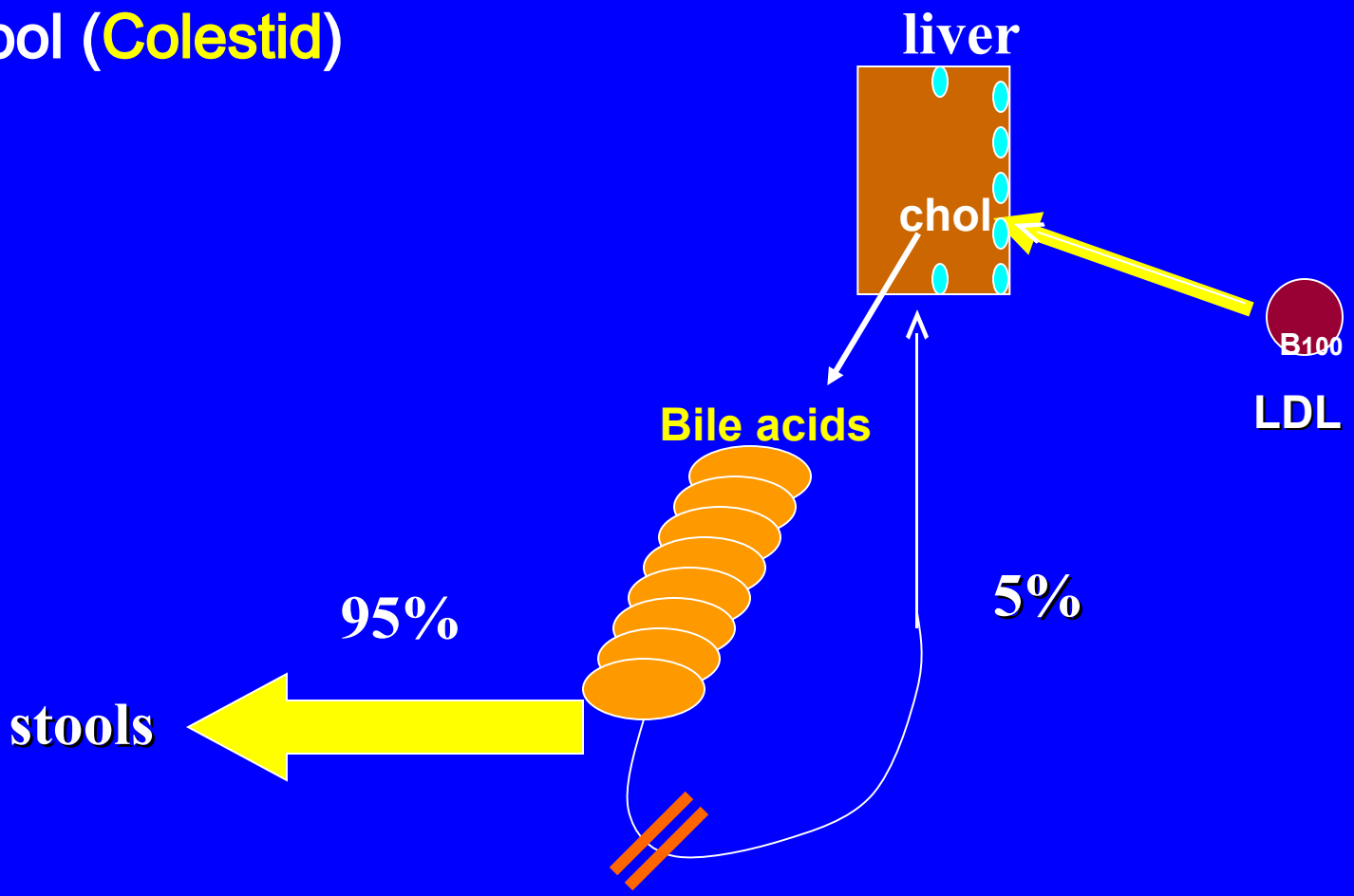


Block absorption & synthesis
ezetimibe + statin



Bile-acid-binding resins
mechanism of action

cholestyramine (Questran)
colestipol (Colestid)

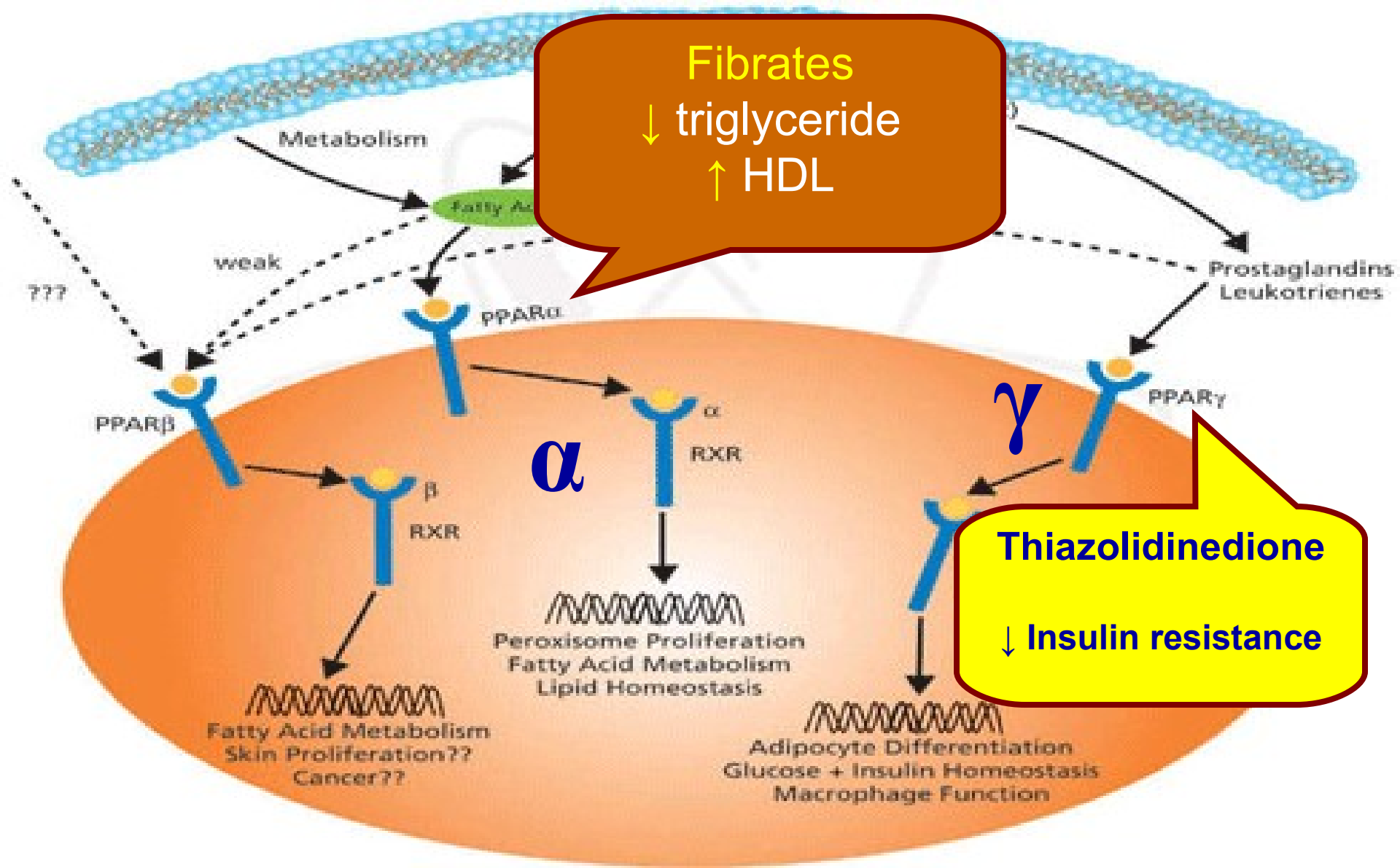


Triglyceride-lowering

- **Fibrates**
  - **Bezafibrate (Bezalip, Norlip)**
  - **Cyprofibrate (Lipanor)**
- **Niacin**

Peroxisome Proliferator Activator Receptors

((PPAR



HDL elevation

- Niacin
- Fibrates
- CETP inhibitors
- Apo A mimetics
  - Apo A Milano

תוספי מזון

- Antioxidants
  - Vitamins E / C / ß carotene
- Homocysteine reduction
  - Folic acid / vitamin B12 / B6

- Omega 3
- Phytosterols

Omega 3

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

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

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

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

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**.

Phytosterols
sterols / stanols

- Plant cholesterols
- Not absorbed from intestine

∀↓ LDLc 10-15%

- Added to margarine, milk products, oily spreads
- Mechanism:
  - Probably competitive inhibition of cholesterol absorption

הנחיות קליניות
מניעה שניונית

- טיפול בגורמי הסיכון האחרים
- טיפול תזונתי
  - דל שומן / דיאטה "ים-תיכונית"
  - אומגה 3 : 1 גרם ליום
  - פיטוסטרולים 2 גרם ליום
- טיפול תרופתי
  - תמיד: כאשר LDLc ≥ 130 mg/dL
  - בחולים בסיכון גבוה במיוחד :
    - בכל רמת LDL
    - HDLc < 40 mg/dL
    - Trig > 200 mg/dL

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

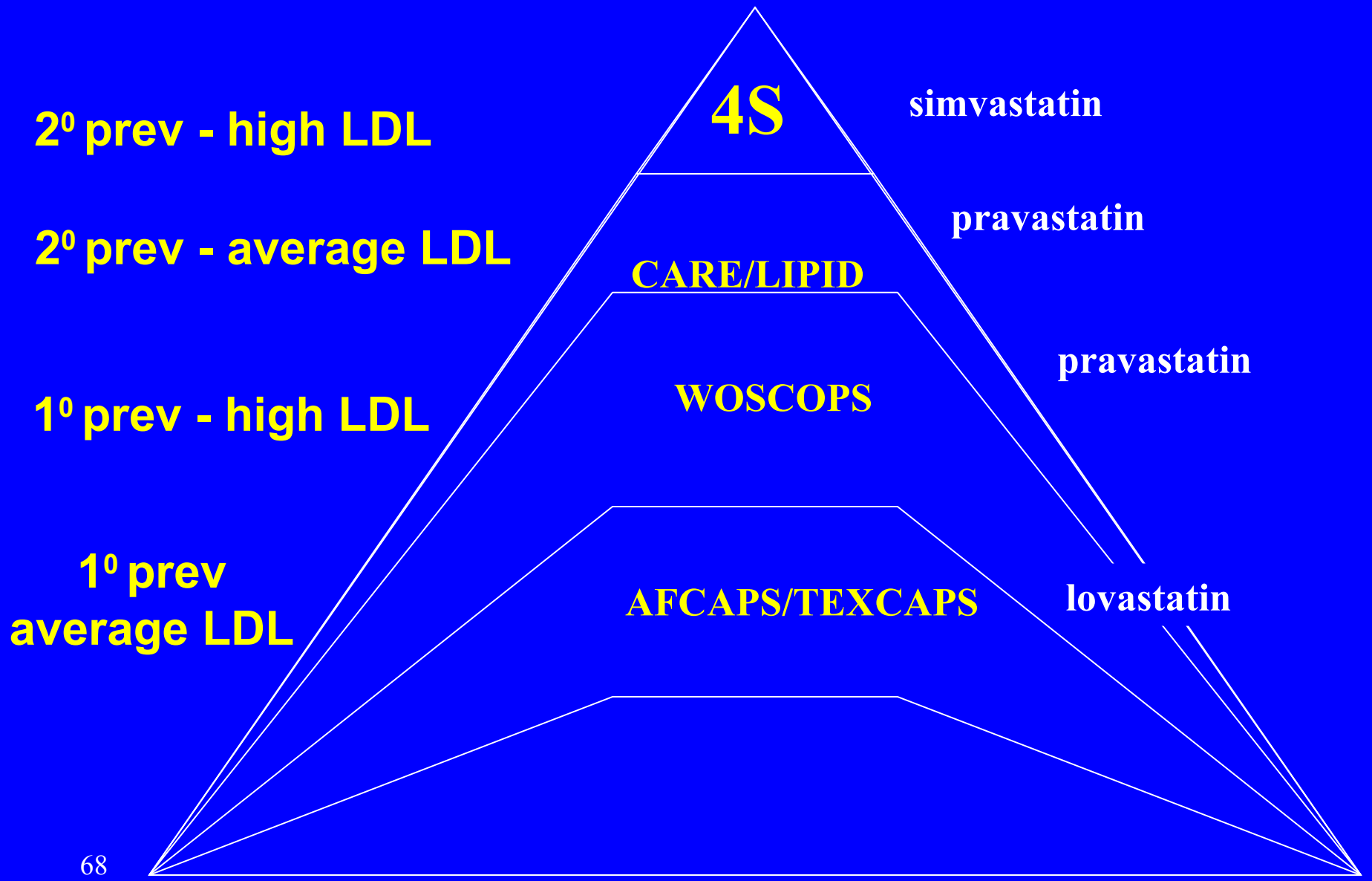

בהצלחה

לקריאה בלבד – לא בהרצאה

Statin Megatrials

- Primary Prevention
  - WOSCOP — prava
  - ACAPS/FCAPS — lova
- Secondary Prevention
  - 4S — simva
  - Care — prava
  - Lipid — prava
  - TNT — atorva
  - AVERT — atorva vs PCI
  - IDEAL — atorva vs simva
- Mixed
  - HPS — simva
- Acute coronary syndrome
  - MIRACLE — atorva
  - PROVE-IT — atorva vs Prava
  - A to Z — simva (low vs high dose)
- IVUS
  - REVERSAL — atorva vs prava
- Hypertensives
  - ALLHAT — prava
  - ASCOT — atorva
- Diabetics
  - CARDS — atorva

Older studies



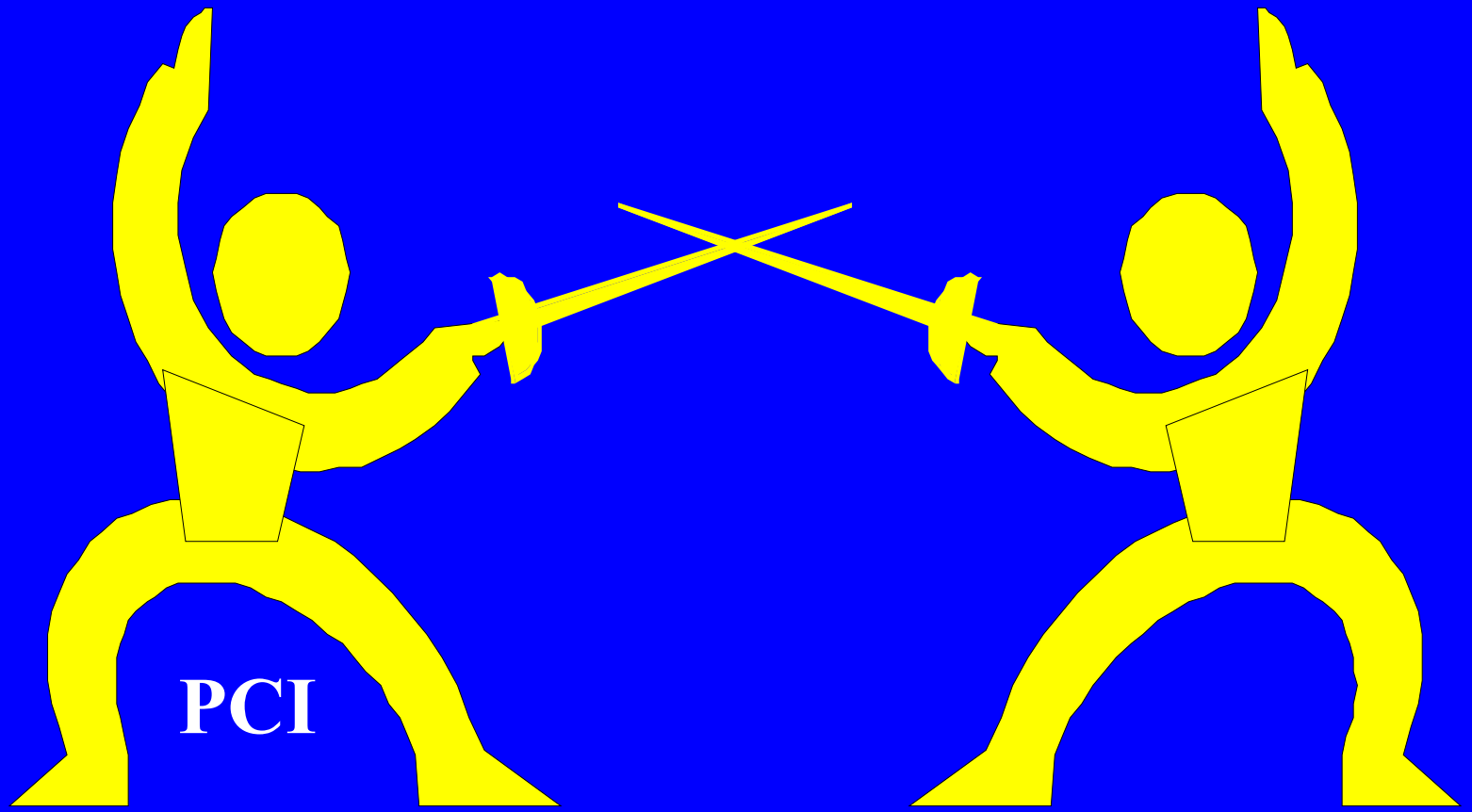
(Heart Protection Study (HPS

- 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)

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	

Statins vs Revascularization



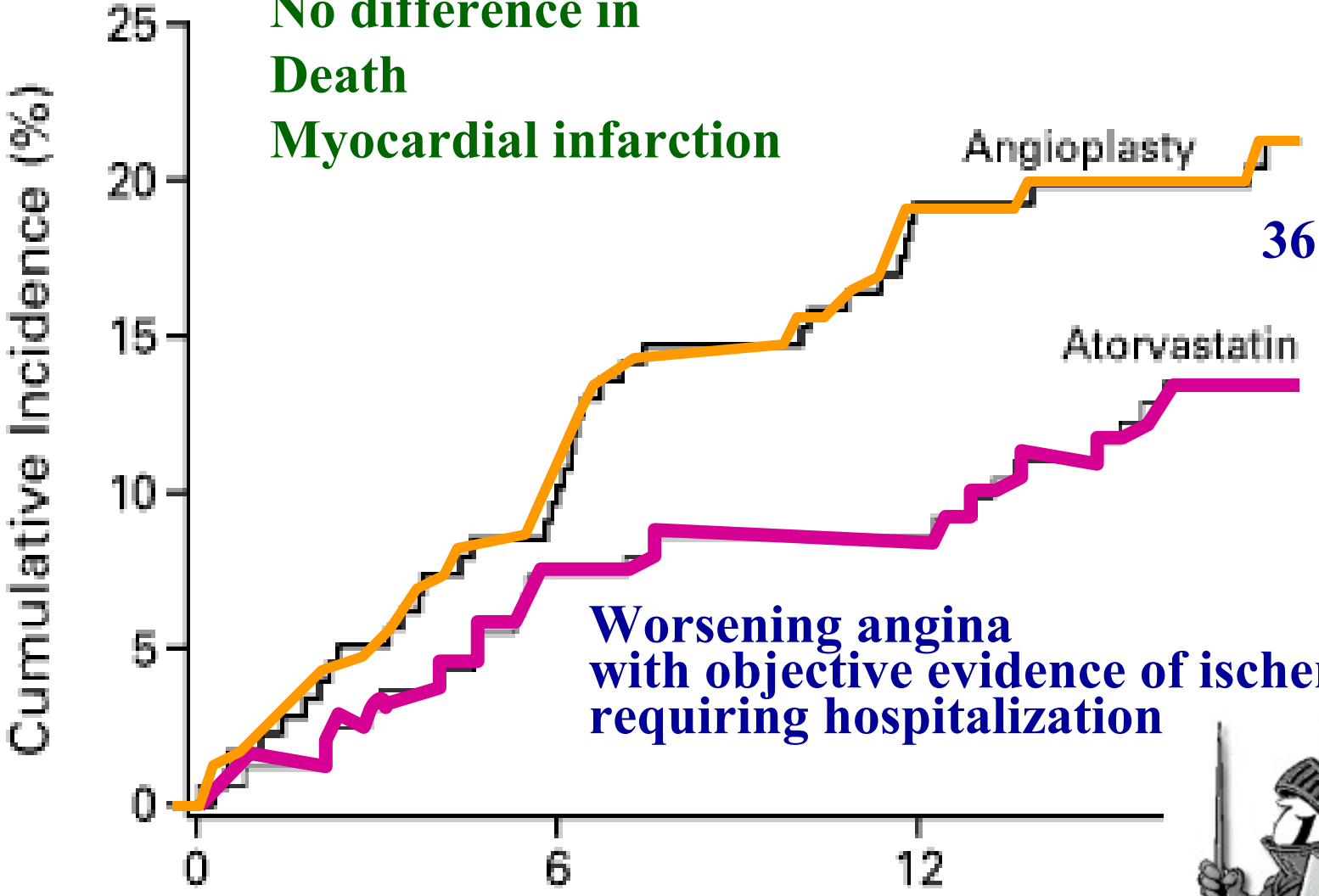
AVERT study
Atorvastatin vs Revascularization

- 18 month, multicenter
- Open label, randomized
- Stable CAD --- referred for PCI

Exclusions:

- 3 vessel CAD, LM disease
- Unstable angina
- MI within previous 2 weeks
- EF < 40%

No difference in
Death
Myocardial infarction



36%

Worsening angina
with objective evidence of ischemia
requiring hospitalization

Statin therapy in acute coronary syndromes

- Increases patient & physician compliance
- Reduces early morbidity & mortality??
- Observational studies:
  - Patients discharged with statins had

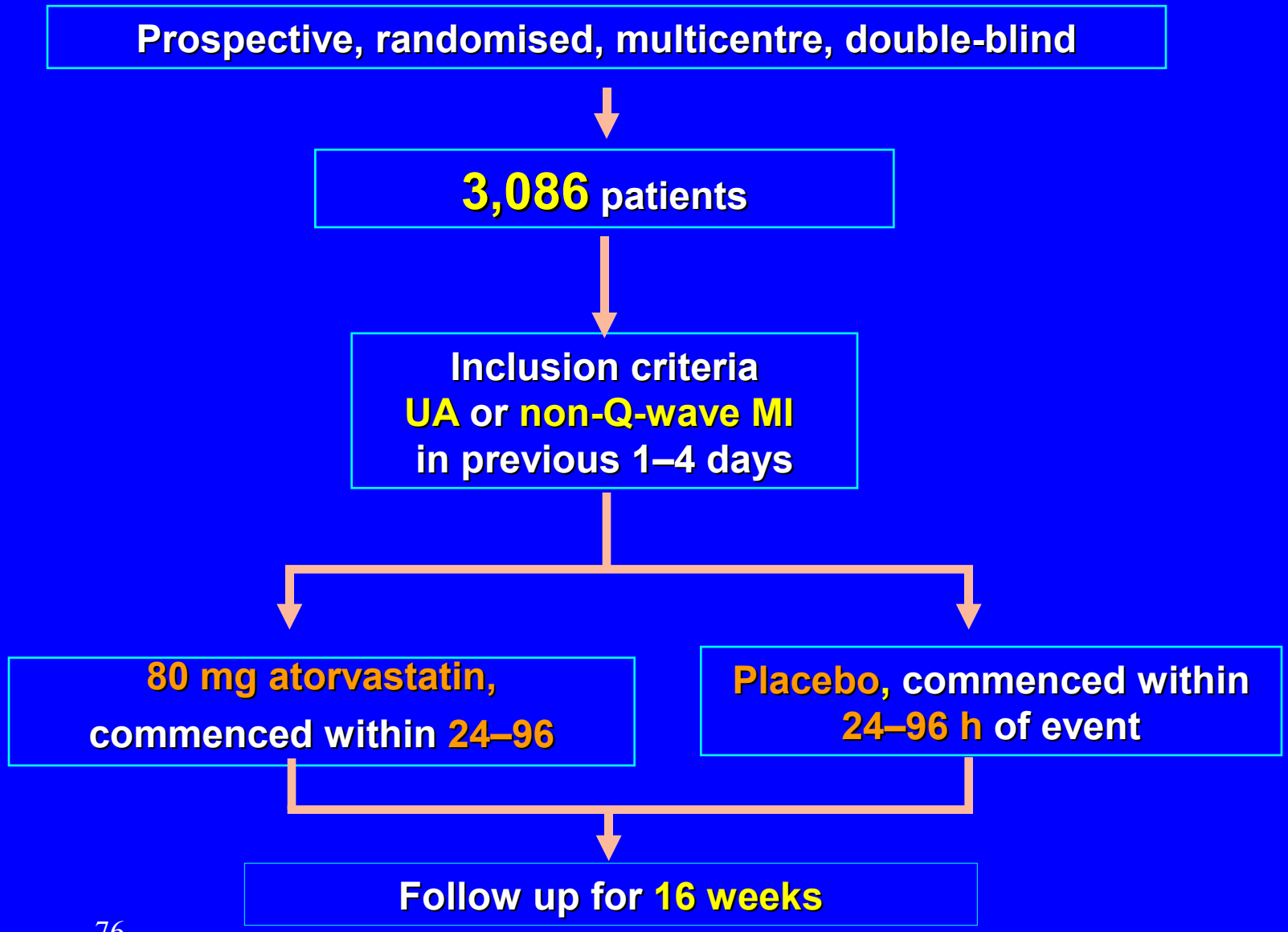
    ~ 50% less mortality over 6-12 months followup

MIRACLE Study

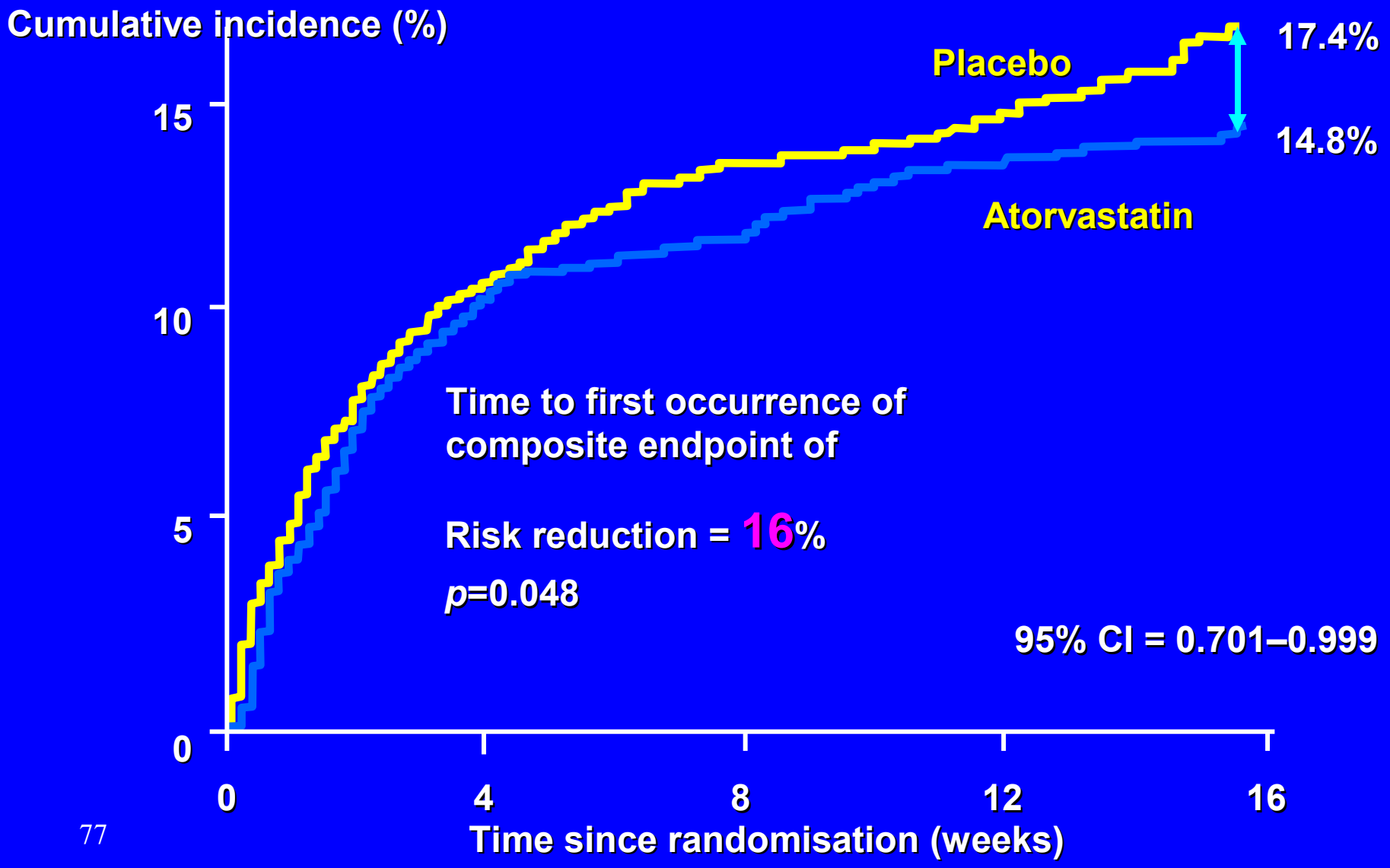
MIRACL

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study

MIRACL study design



Primary efficacy measure



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

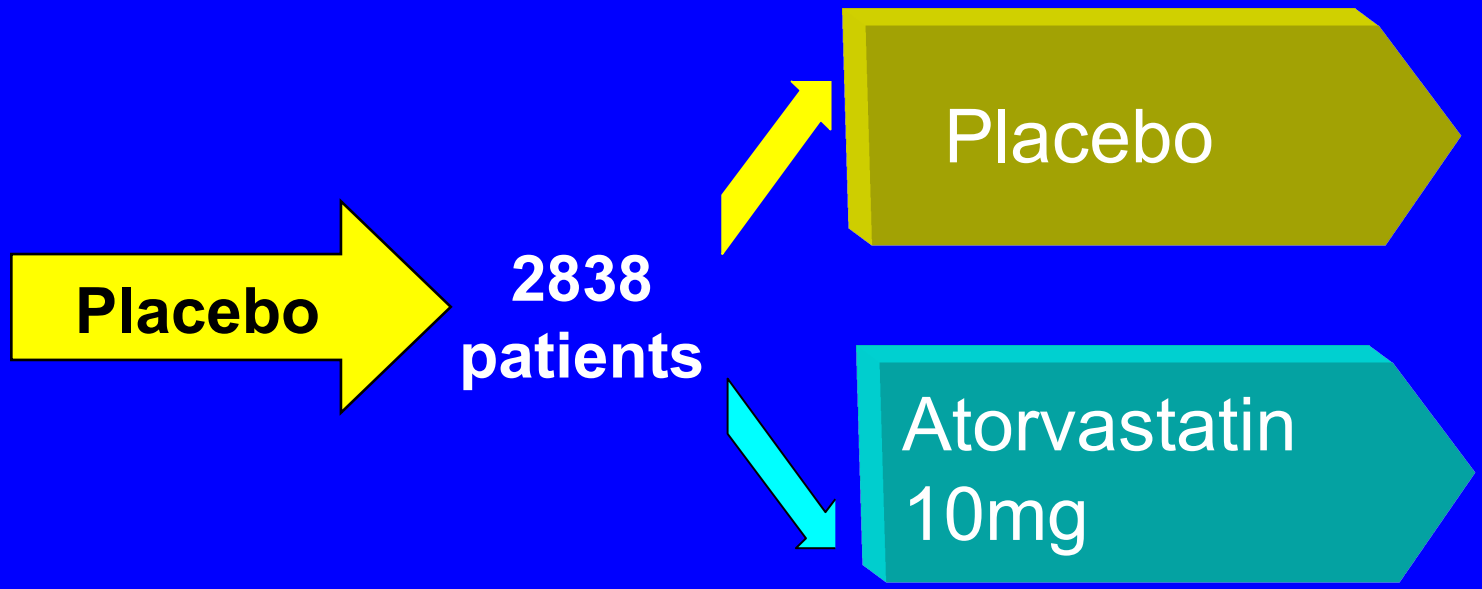
ASCOT

- 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 $p < 0.0005$

Statins in Diabetics

- Heart Protection Study
- CARDS
  - Collaborative Atorvastatin Diabetes Study

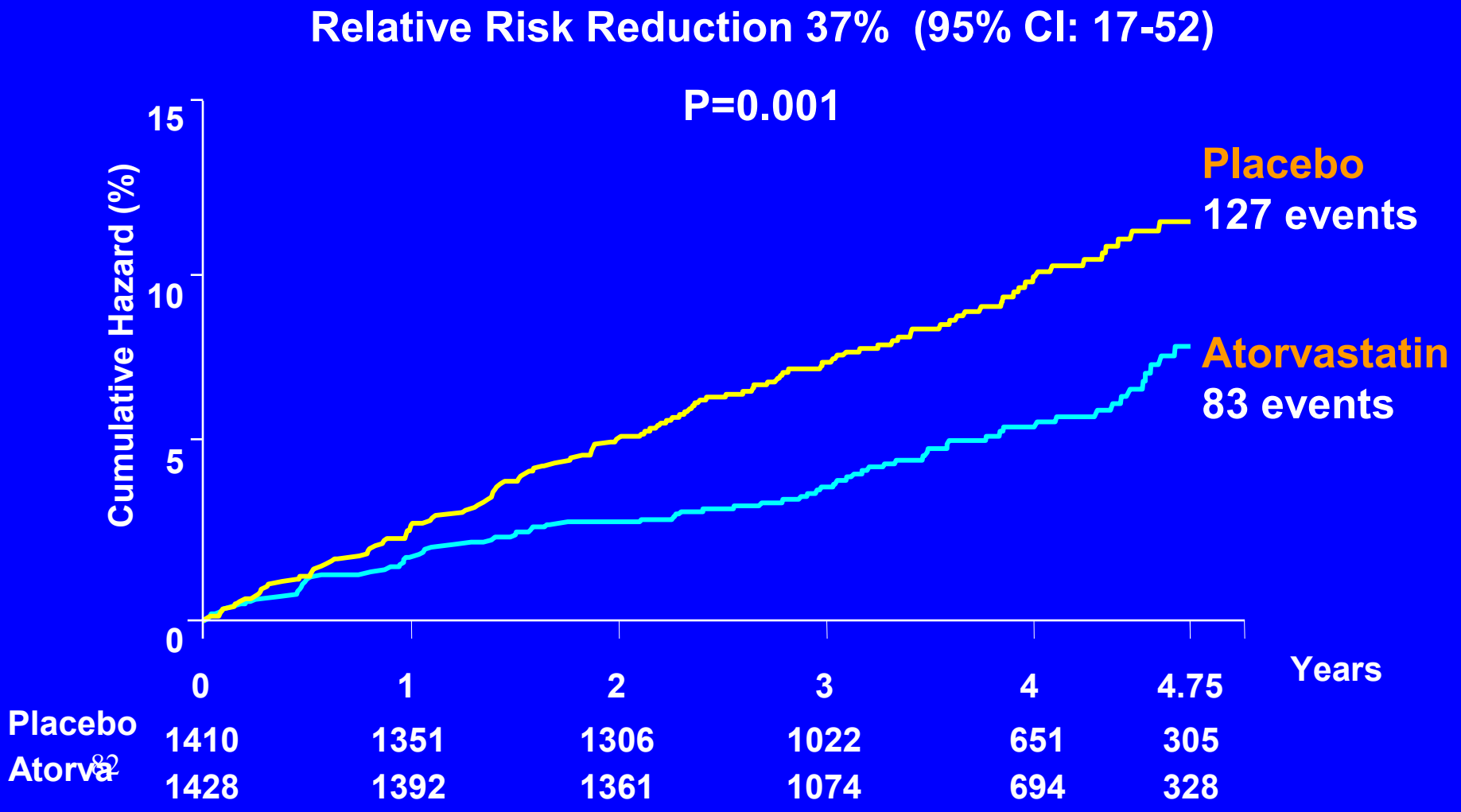
CARDS Design



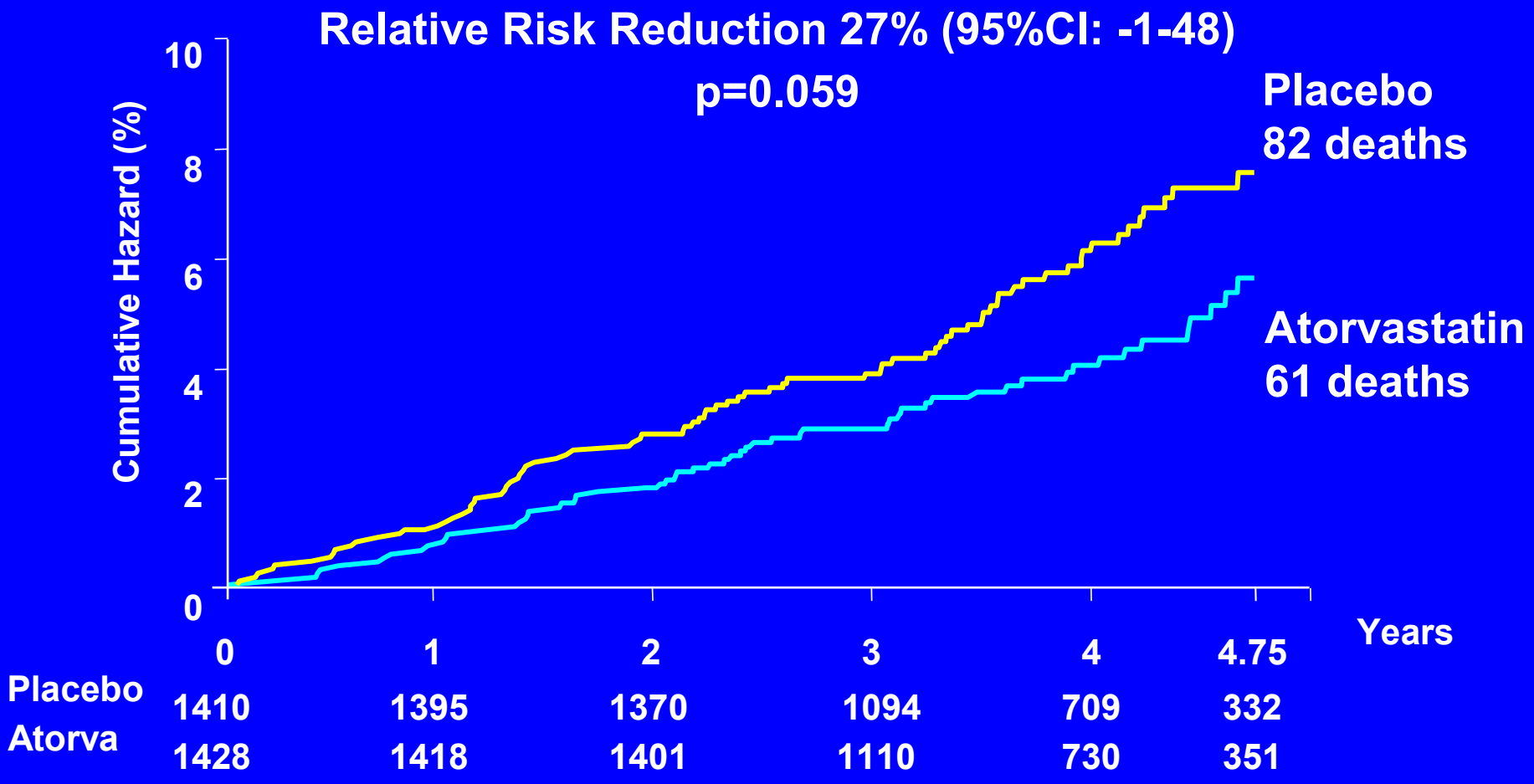
*CARDS Patient Baseline Lipids

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

Cumulative Hazard for Primary Endpoint



Cumulative Hazard for All Cause Mortality



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*

Hypothesis

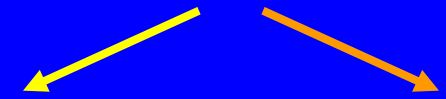
40 mg Lipidal → anti-inflammatory

is not inferior to

80 mg Lipitor → Potent LDL ↓

Design

- 4162 pts with Acute Coronary Syndrome
- within 10 days
  Lipidal 40 mg vs Lipitor 80 mg
- baseline LDLc 106 **mg/dl**



- baseline CRP 12.3 mg/l

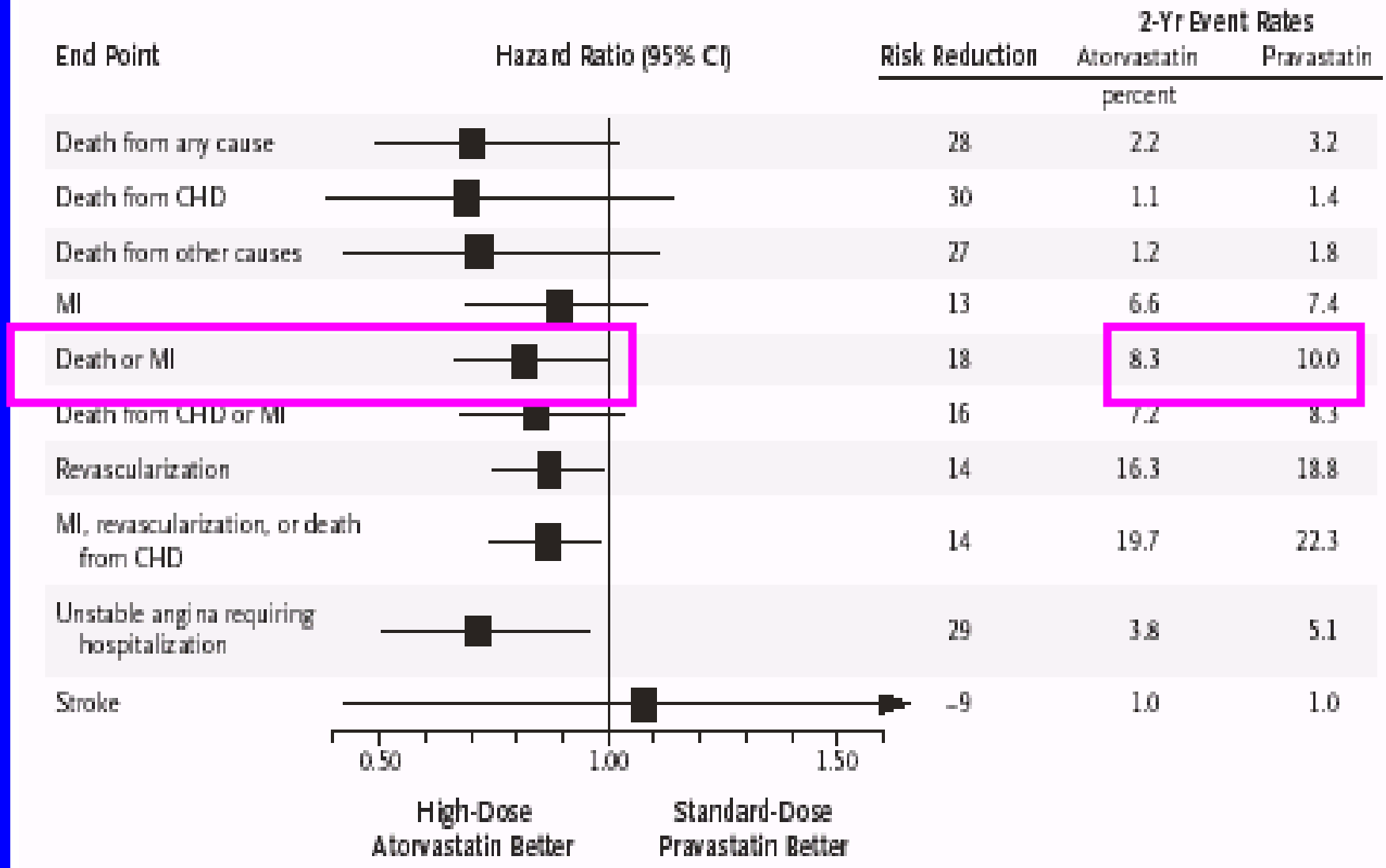
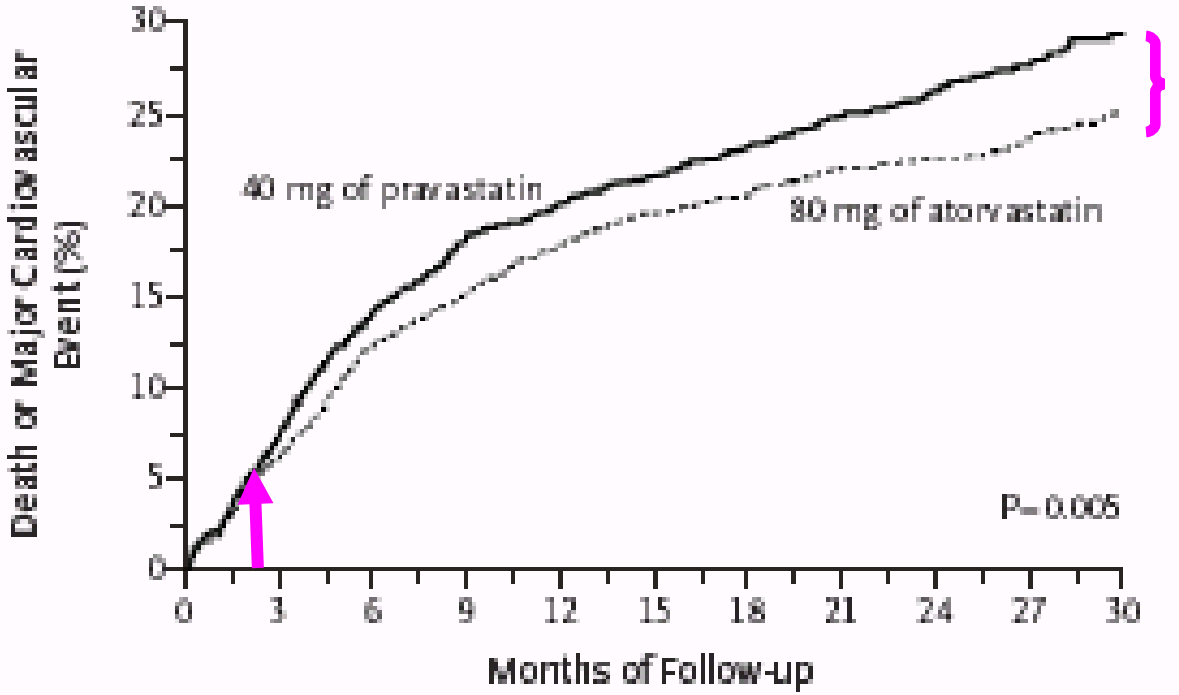


Figure 4. Estimates of the Hazard Ratio for the Secondary End Points and the Individual Components of the Primary End Point in the High-Dose Atorvastatin Group, as Compared with the Standard-Dose Pravastatin Group.



16%

No. at Risk						
Pravastatin	2063	1688	1536	1423	810	138
Atorvastatin	2099	1736	1591	1485	842	133

Figure 2. Kaplan–Meier Estimates of the Incidence of the Primary End Point of Death from Any Cause or a Major Cardiovascular Event.

Intensive lipid lowering with the 80-mg dose of atorvastatin, as compared with moderate lipid lowering with the 40-mg dose of pravastatin, reduced the hazard ratio for death or a major cardiovascular event by 16 percent.

Early Intensive vs a Delayed Conservative Simvastatin Strategy in Patients With Acute Coronary Syndromes

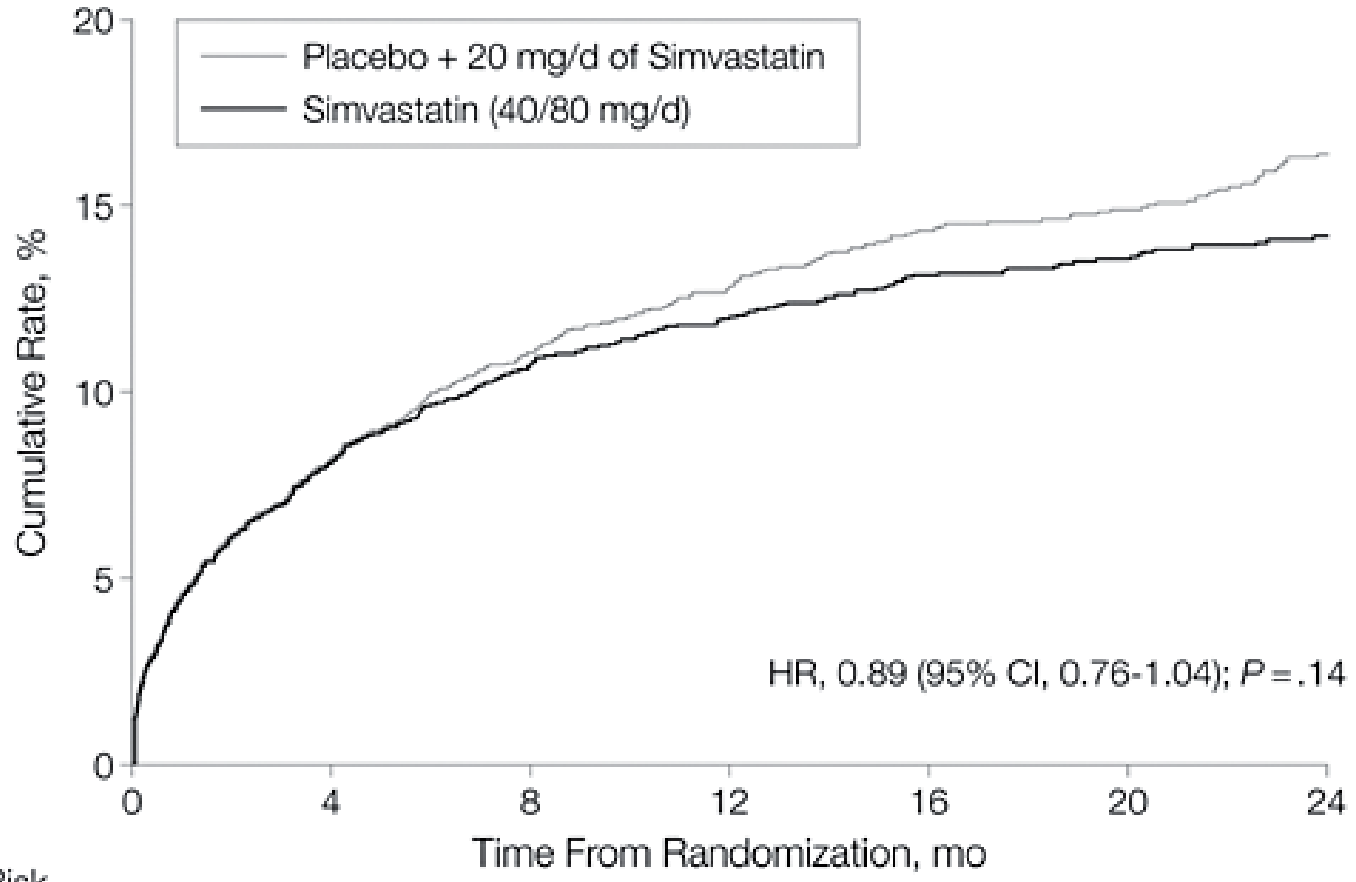
Phase Z of the A to Z Trial

de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, Ramsey KE, Palmisano J, Bilheimer DW, Pfeffer MA, Califf RM, Braunwald E;

JAMA. 2004 Sep 15;292(11):1307-16

Randomization

- early intensive statin treatment strategy
  - 40 mg/d of simvastatin for 30 days
  - then 80 mg/d of simvastatin thereafter
- a less aggressive strategy
  - placebo for 4 months
  - then 20 mg/d of simvastatin thereafter



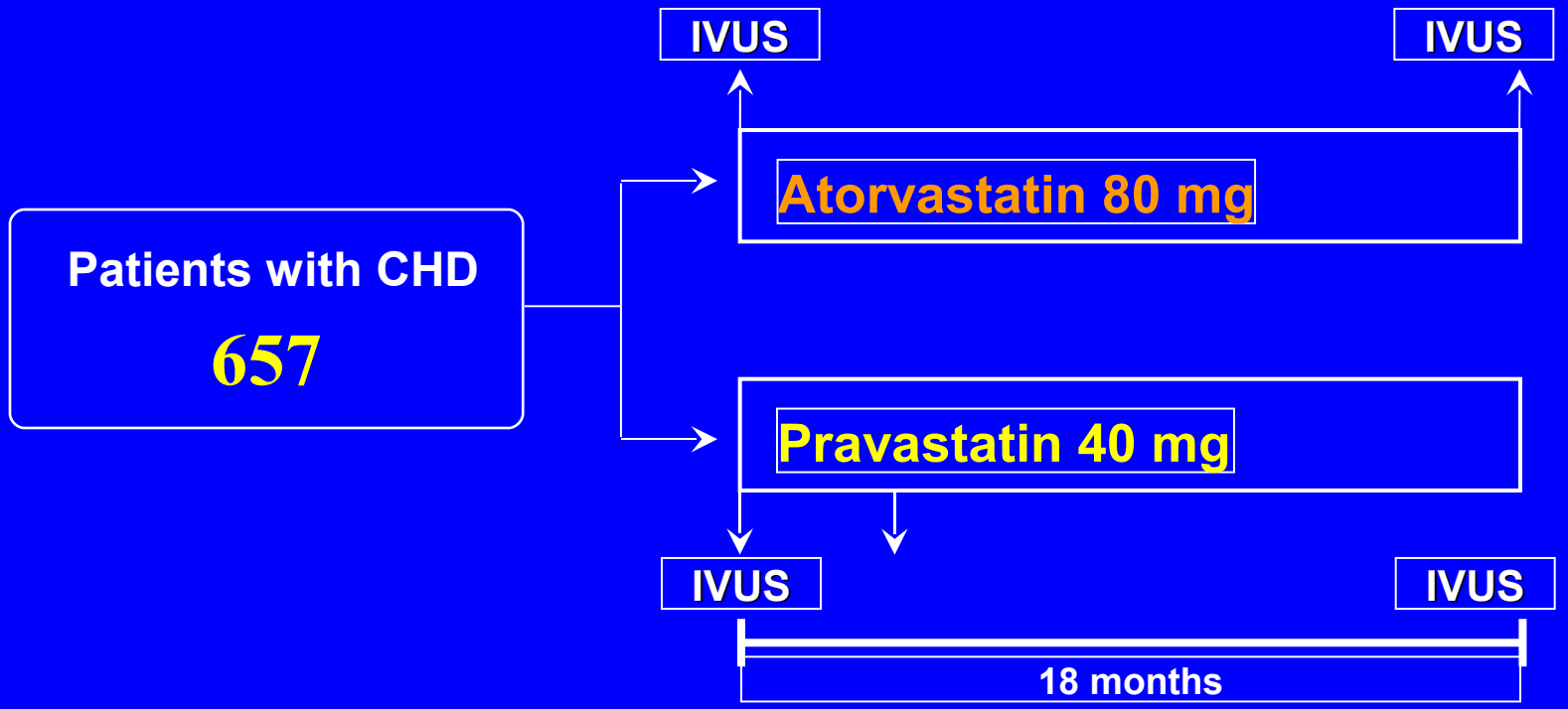
No. at Risk							
Simvastatin (40/80 mg/d)	2265	2039	1950	1855	1632	1377	1020
Placebo + 20 mg/d of Simvastatin	2232	2004	1904	1808	1571	1331	979

REVERSAL Trial

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



Primary endpoint:

- Change in coronary plaque volume by IVUS

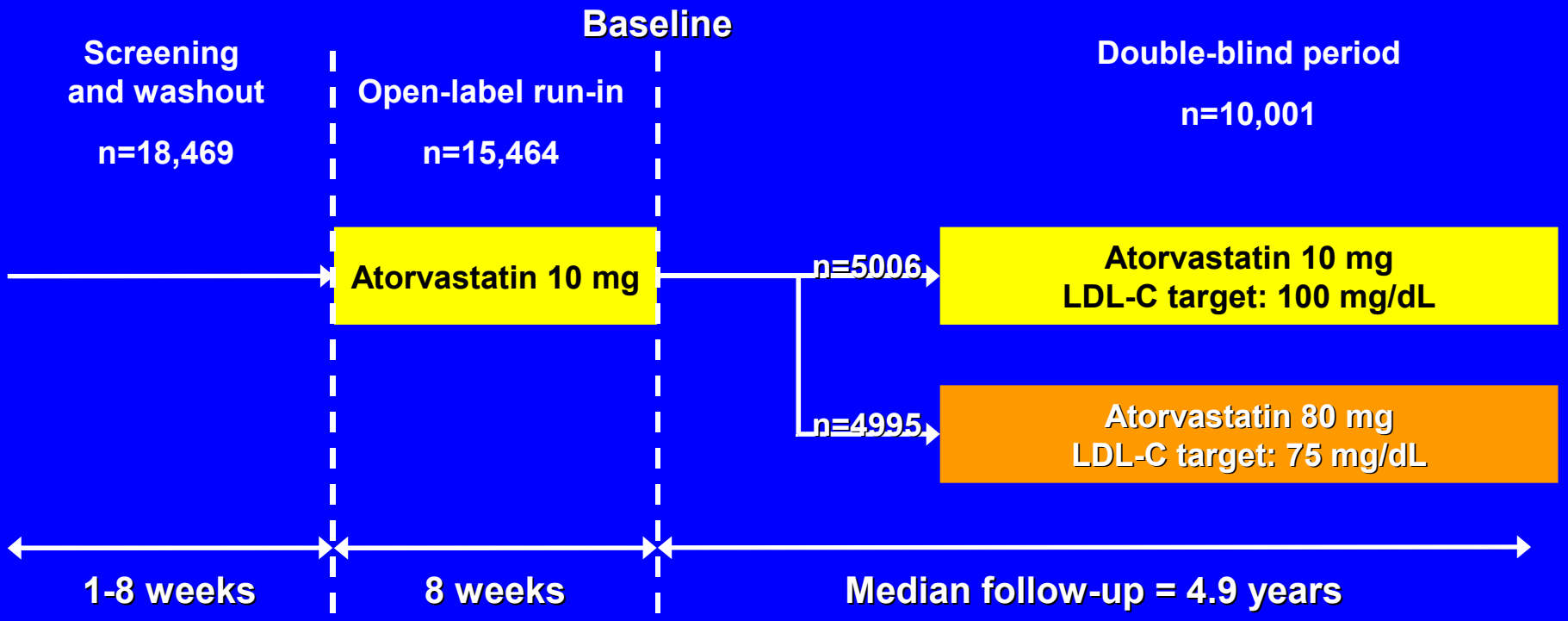
Table 3. Change in Atheroma Volume, Change in Percentage of Atheroma Volume, and Atheroma Volume in 10-mm Subsegment With the Greatest Disease Severity

	Pravastatin (n = 249)	Atorvastatin (n = 253)	*P* Value Between Groups*
	Atheroma Volume, mm³		
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	

TNT: Study Design

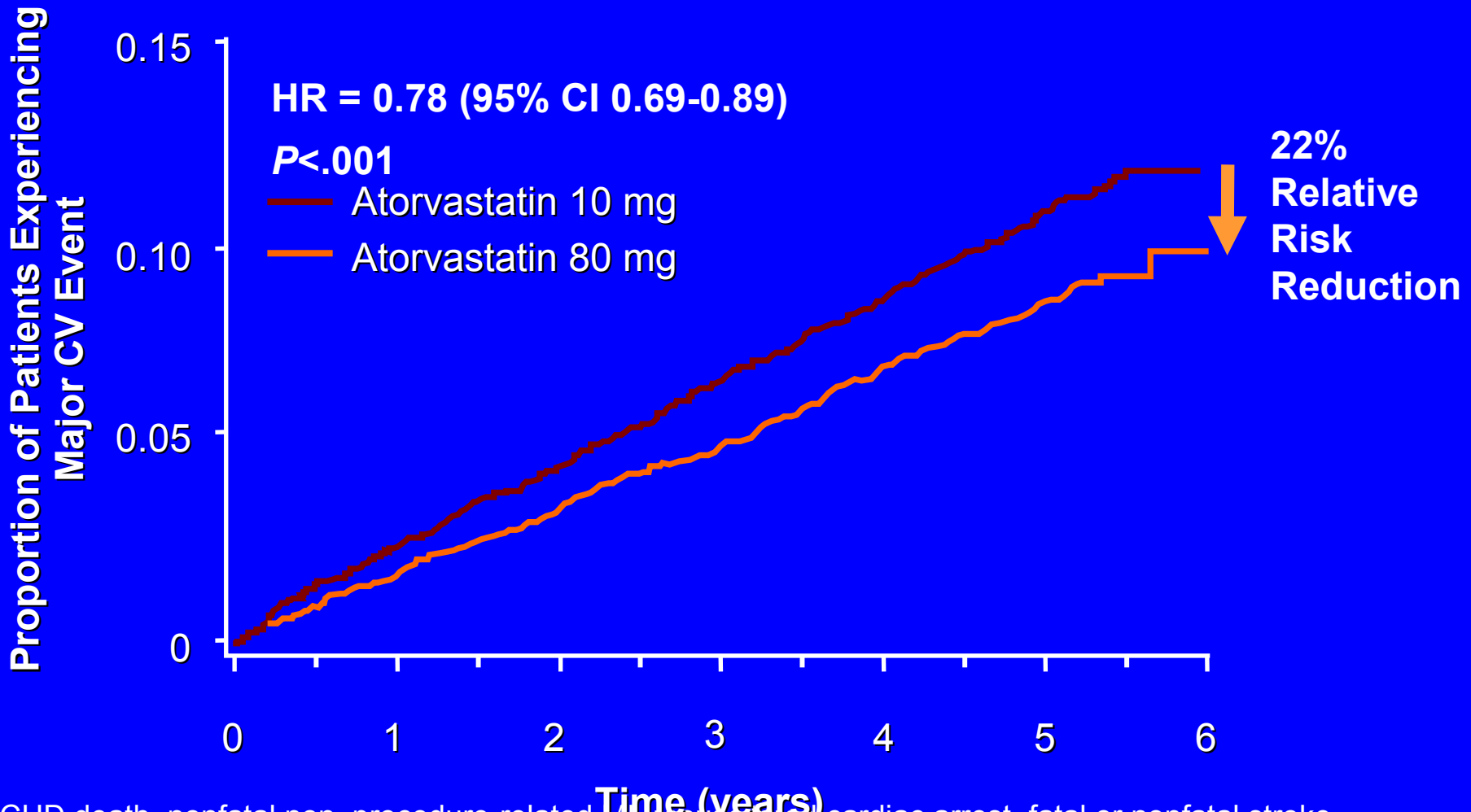
Patient Population
- CHD
- LDL-C: 130-250 mg/dL
- Triglycerides ≤ 600 mg/dL

Primary Efficacy Outcome Measure
- Time to occurrence of a major CV event
  - CHD death
  - Nonfatal, non–procedure-related MI
  - Resuscitated cardiac arrest
  - Fatal or nonfatal stroke



Adapted from LaRosa et al. *N Engl J Med.* 2005;352:1425-1435.

*TNT: Major CV Events



*CHD death, nonfatal non–procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke.

LaRosa et al. *N Engl J Med.* 2005;352:1425-1435.

IDEAL

Primary

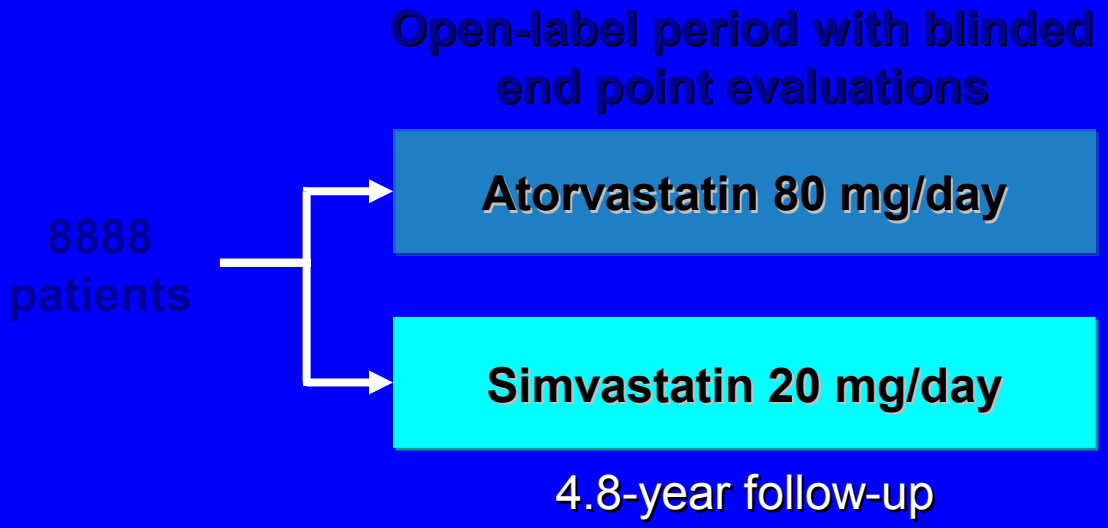
- Time to occurrence of a major coronary event
  - CHD death
  - Nonfatal MI
  - Resuscitated cardiac arrest

Secondary

- Cardiovascular/coronary events
- Cerebrovascular events
- PAD
- Hospitalization with primary diagnosis of CHF
- All-cause mortality

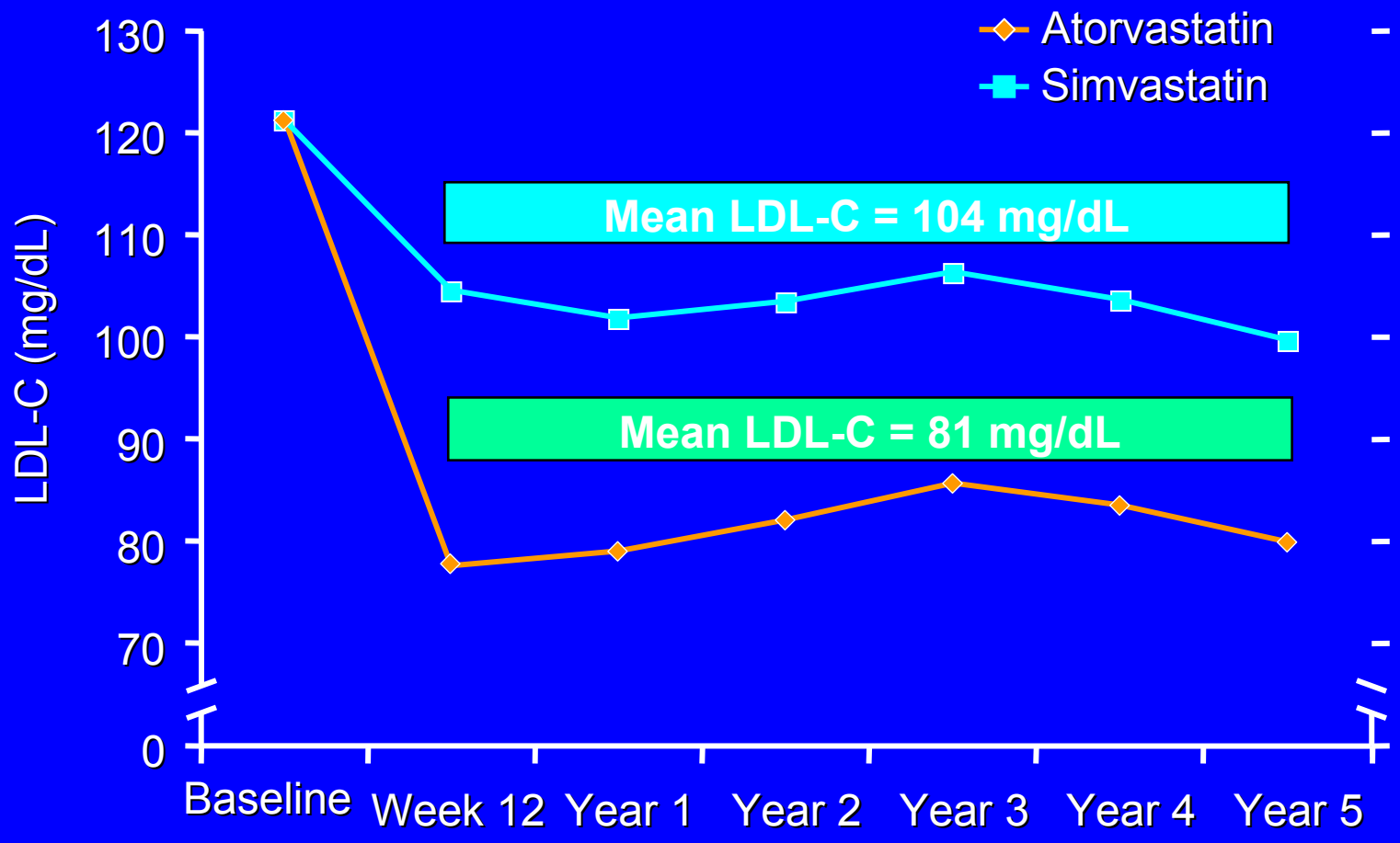
Patient population

- 190 sites throughout Scandinavia and the Netherlands
- Diagnosed with CHD
- Previous hospitalization with MI,



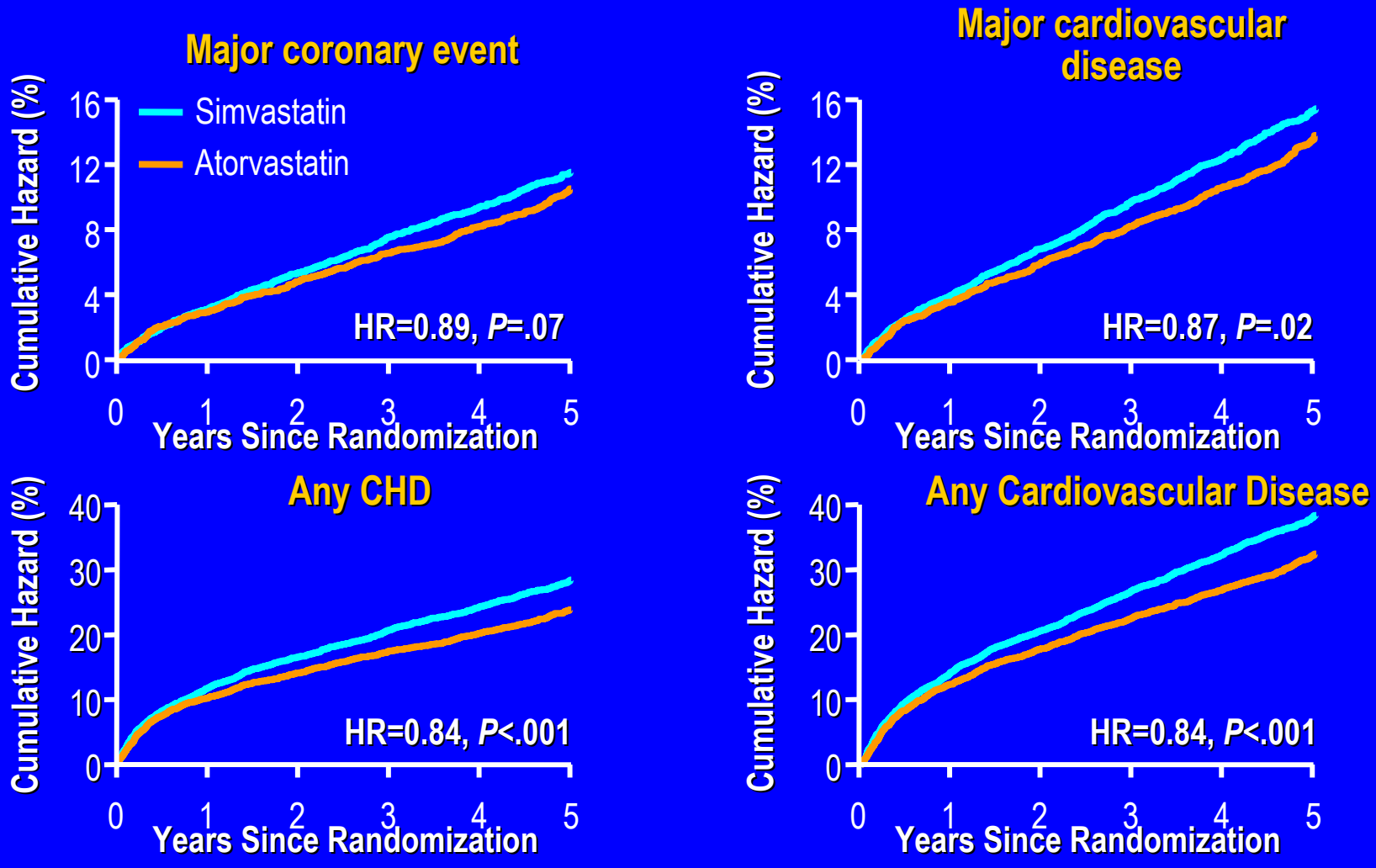
Pedersen et al. *Am J Cardiol*. 2004;94:720-721; Pedersen et al. *JAMA*. 2005;294:2437-2445.

IDEAL: Effect of Treatment On LDL-C



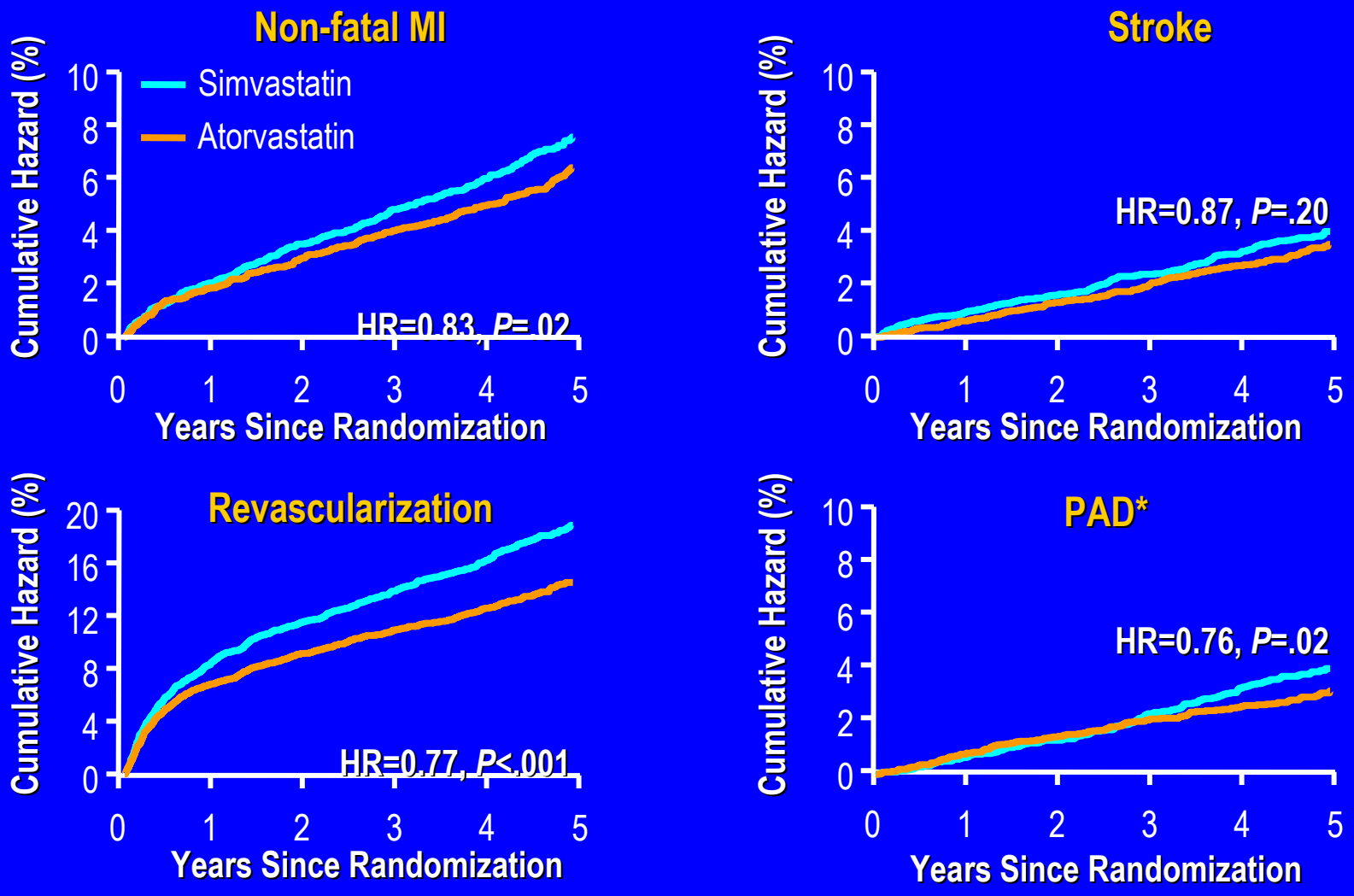
Pedersen et al. *JAMA*. 2005;294:2437-2445.

IDEAL: Composite End Points



Reproduced from Pedersen et al. *JAMA*. 2005;294:2437-2445.

IDEAL: Secondary End Points



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Reproduced from Pedersen et al. *JAMA*. 2005;294:2437-2445.

מחקרים קליניים בהיפרטריגליצרידמיה

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

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

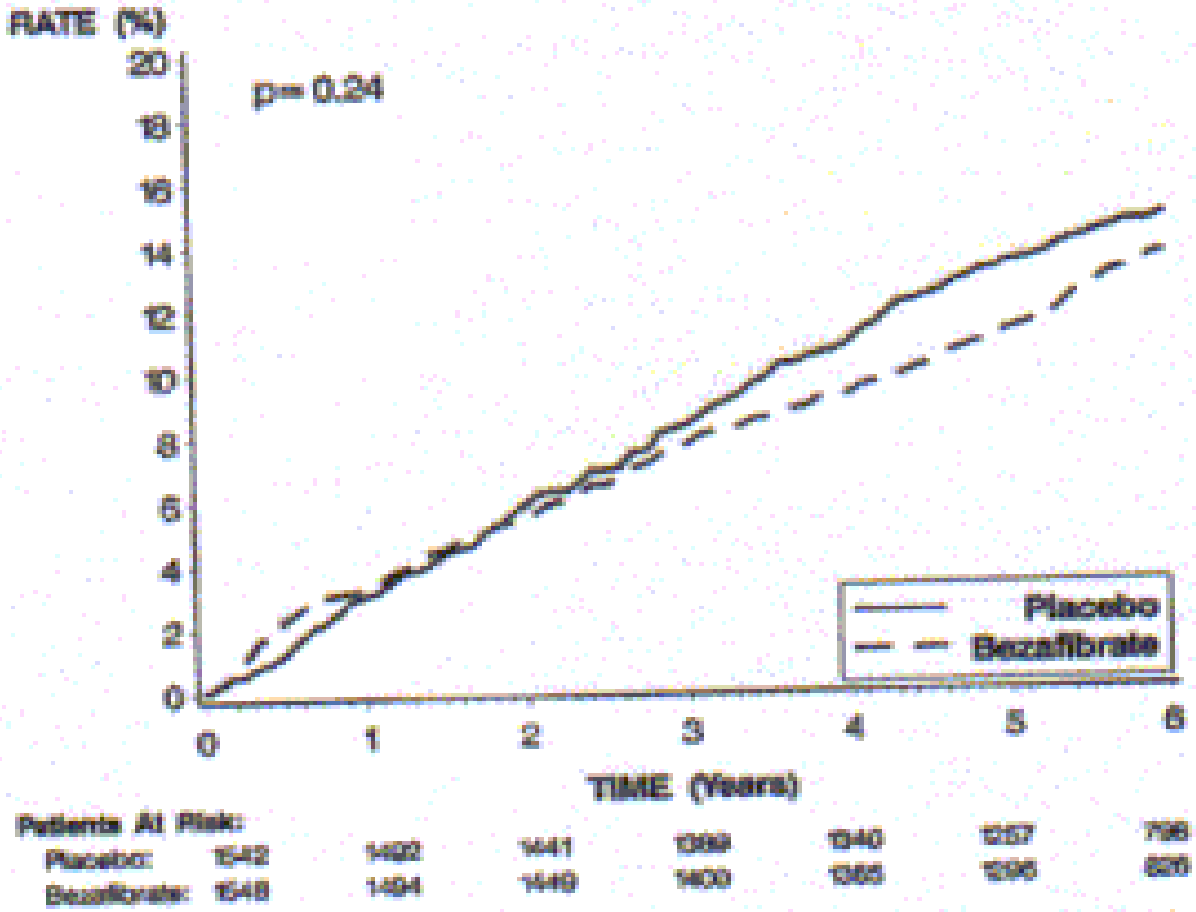

Figure 3. Kaplan-Meier curves for the cumulative probability of the primary end point.

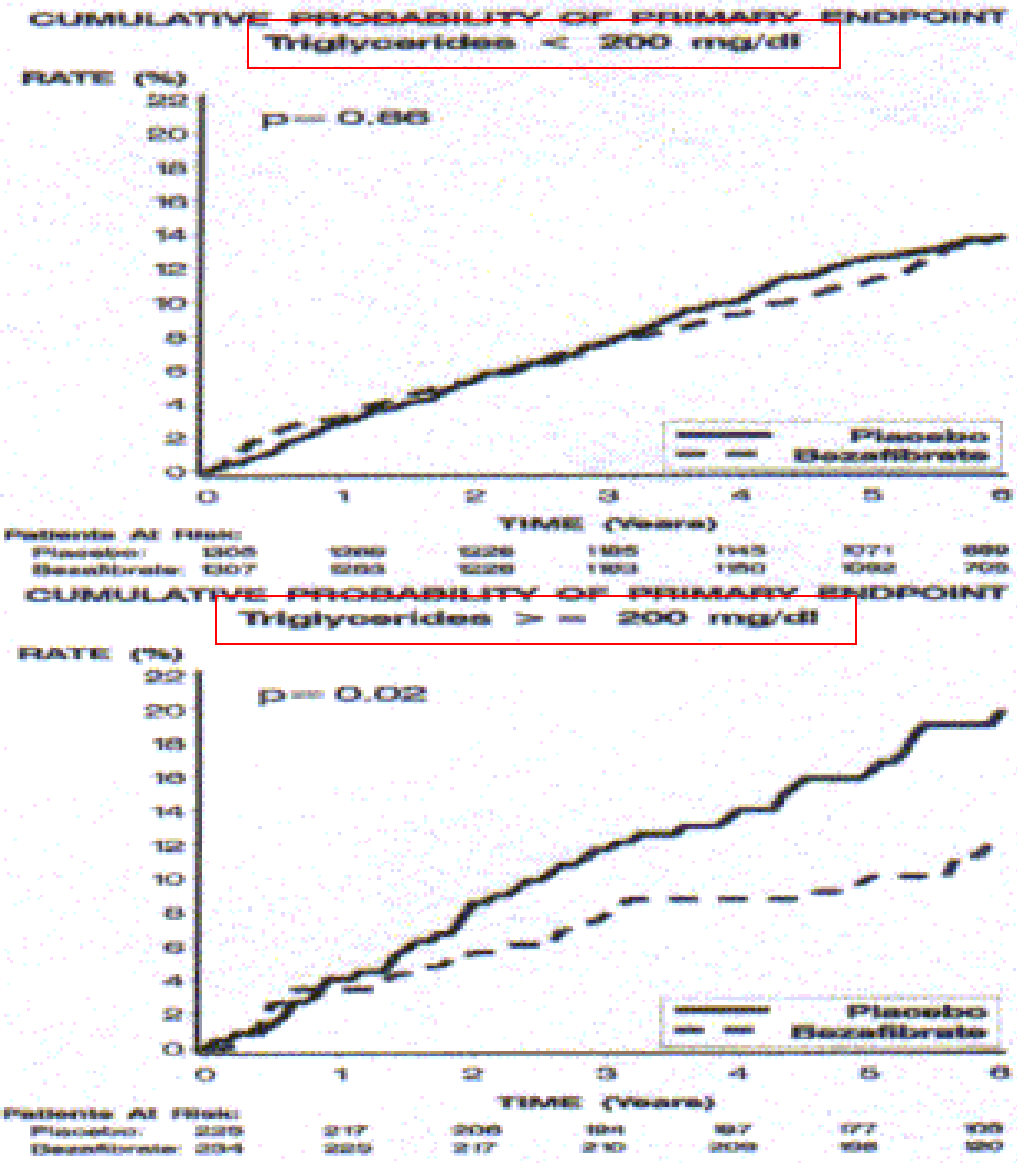

Figure 5. Kaplan-Meier curves for the primary end point in subgroups of patients with baseline triglycerides ≥200 mg/dL and <200 mg/dL.