Nuevos horizontes en la elevación del C-HDL y Riesgo Cardiovascular:

Colesterol HDL y riesgo cardiovascular ¿Dónde estamos?

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SEC-2011

Colesterol HDL y riesgo cardiovascular
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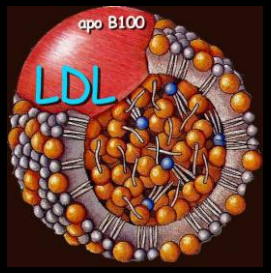


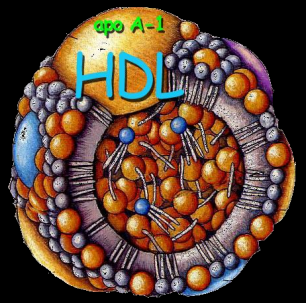
1.IMPACTO DE LAS LDL

2.ESTATINAS Y UMBRAL DE BENEFICIO

3.IMPACTO DE LAS HDL

4.TRANSPORTE REVERSO DE COLESTEROL

5.HDL: CANTIDAD Y/O CALIDAD



6.TRATAMIENTO

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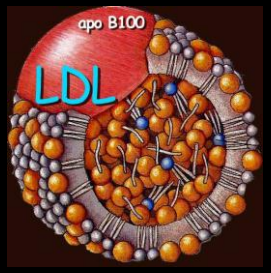

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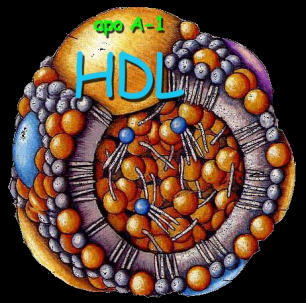
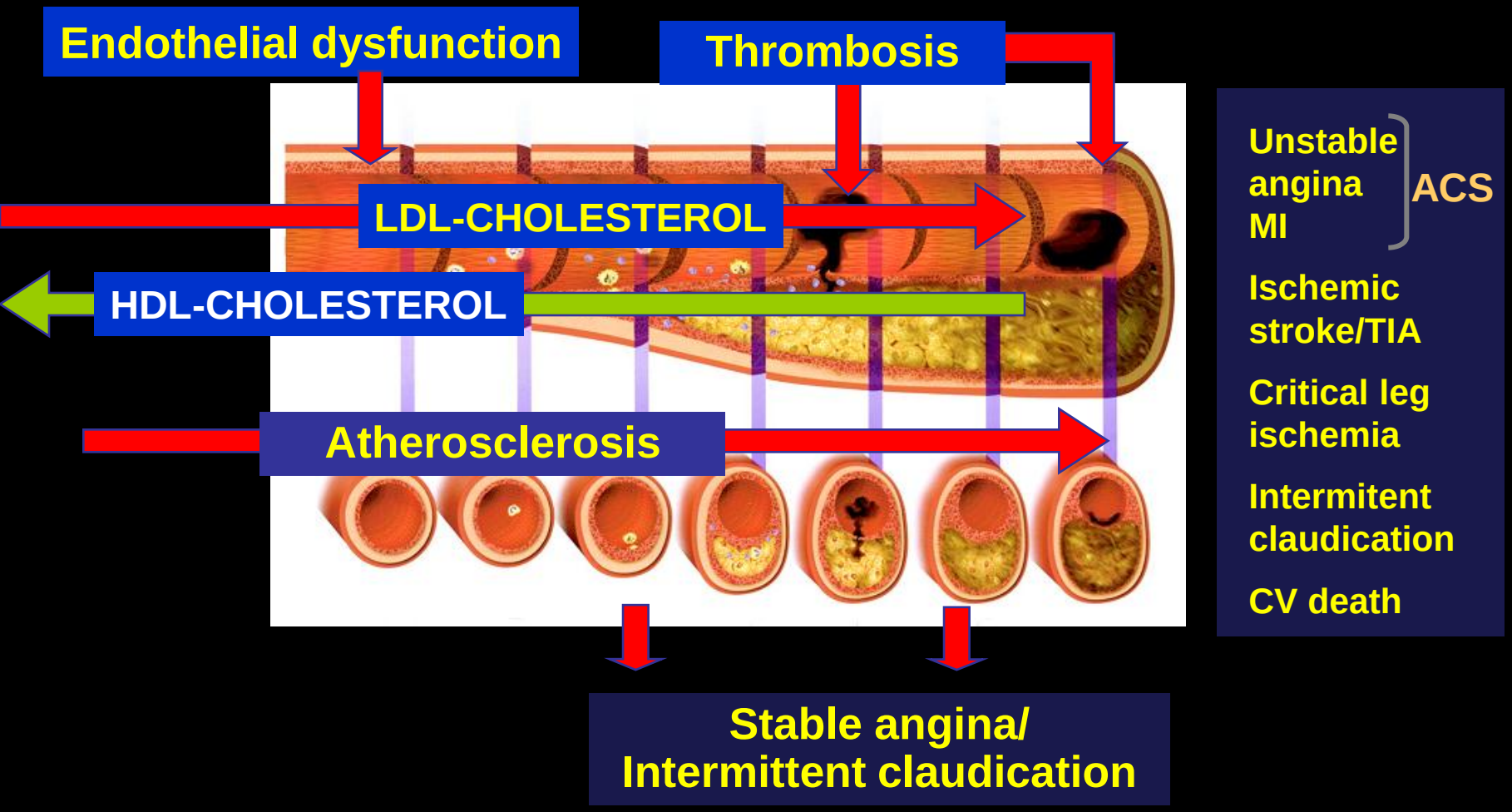


Atherothrombosis: A Generalized and Progressive Process



Major Cardiovascular Risk Factors

↑LDL
↓HDL
↑TGL
Hypertension
Diabetes mellitus
Obesity
(Small LDL, PAI-1, Microalbuminuria)

Metabolic Syndrome

Diet
Smoking
Exercise
Alcohol

Modifiable Risk- factors

Age (menopause)
Gender
Genes/Family History

Non-Modifiable Factors

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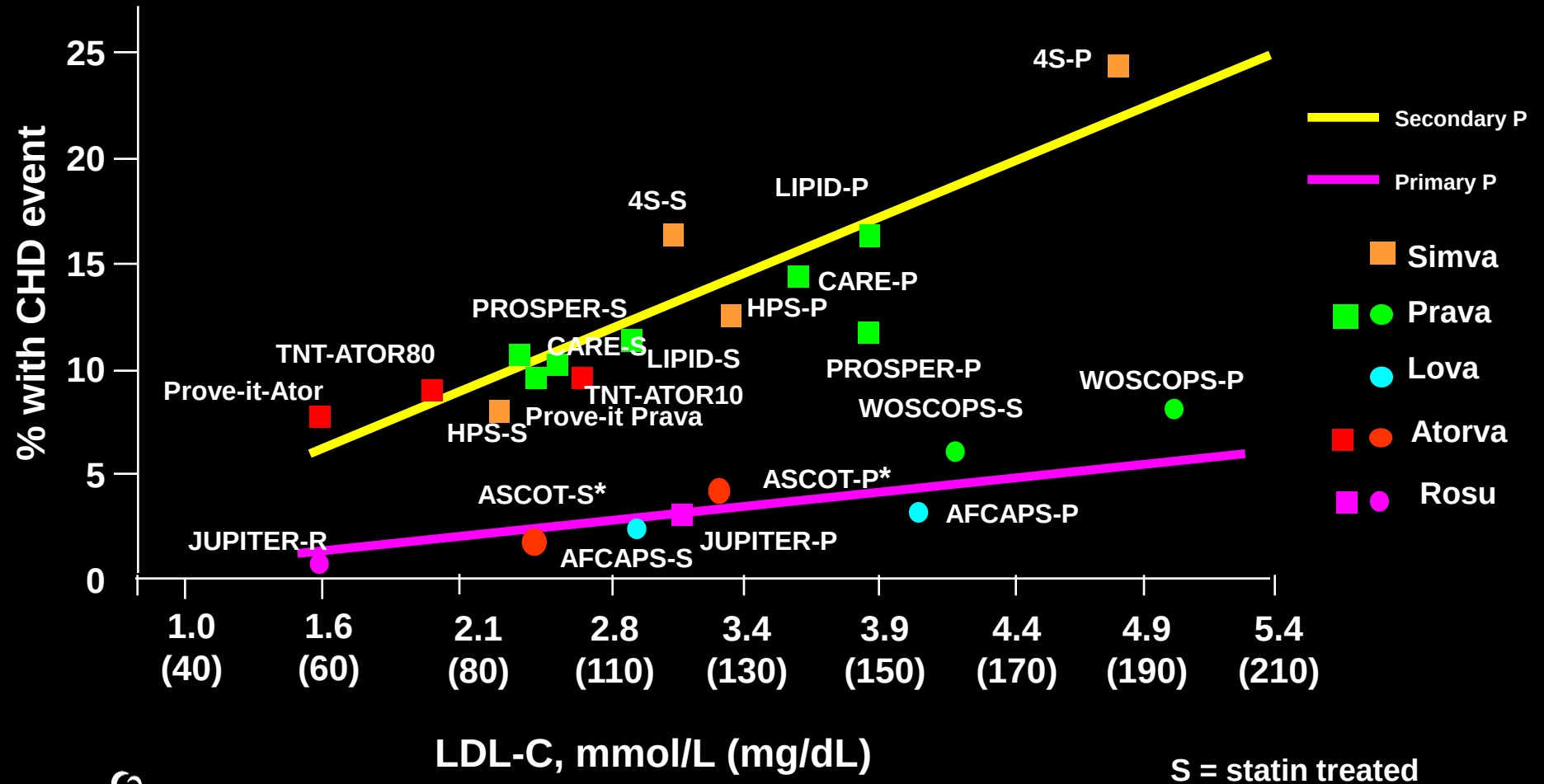
LDL-C Levels versus Events in Landmark Statin Trials



S = statin treated
P = placebo treated

*Extrapolated to 5 years

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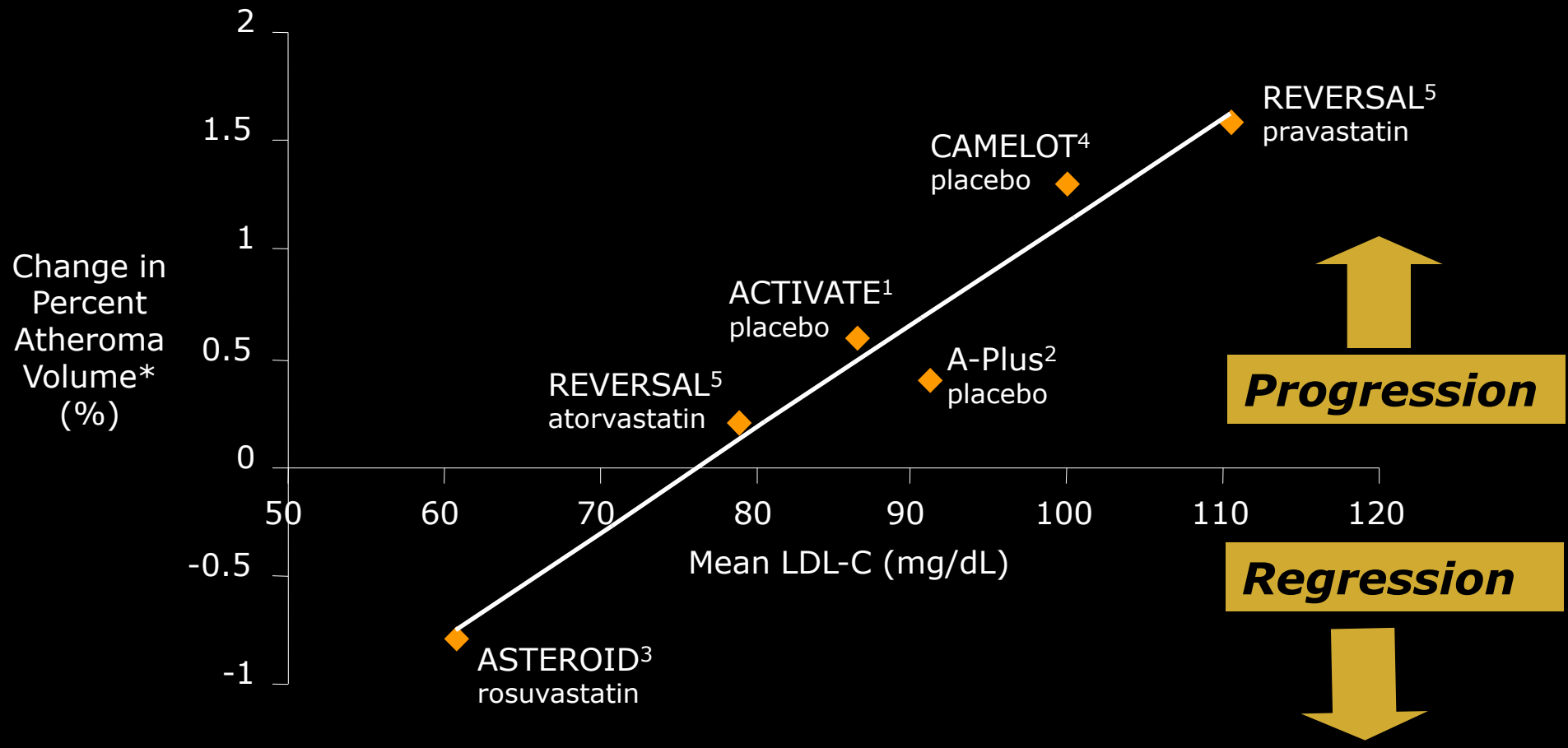
LDL-C and change in percent atheroma volume (IVUS)†



†ASTEROID and REVERSAL investigated active statin treatment; A-PLUS, ACTIVATE AND CAMELOT investigated non-statin therapies but included placebo arms who received background statin therapy (62%, 80% and 84% respectively).

*Median change in PAV from ASTEROID and REVERSAL; LS mean change in PAV from A-PLUS, ACTIVATE AND CAMELOT

1 Nissen S et al. N Engl J Med 2006;354:1253-1263. **2** Tardif J et al. Circulation 2004;110:3372-3377. **3** Nissen S et al. JAMA 2006;295 (13):1556-1565 **4** Nissen S et al. JAMA 2004;292: 2217–2225. **5** Nissen S et al. JAMA 2004; 291:1071–1080

INTER-HEART Study: Risk Factors for MI

Risk Factor	Odds Ratio adjusted for all other risk factors
APO-B/APO-A1 (Quintile 5 vs 1)	3.25 (2.81 - 3.76)
Current smoking	2.87 (2.58 - 3.19)
Diabetes	2.37 (2.07 – 2.71)
Hypertension	1.91 (1.74 – 2.10)
Abdominal obesity	1.62 (1.45 – 1.80)
Psychosocial stress	2.67 (2.21 – 3.22)
Daily vegetables/fruit	0.70 (0.62 – 0.79)
Exercise	0.86 (0.76 – 0.97)
Alcohol Usage	0.91 (0.82 – 1.02)

Yusuf S et al. Lancet. 2004;364:937-952

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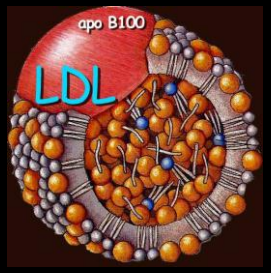

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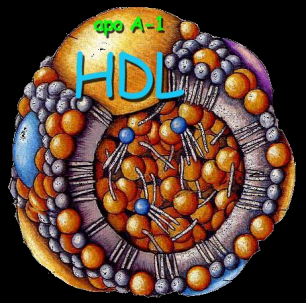


Limitations of Statin Monotherapy on CHD Events

Trial	Drug	N	Events,* n		Risk Reduction, %†	Events not Avoided, %
			Control Group	Statin Group		
4S WOSCOPS CARE AFCAPS LIPID	Simvastatin Pravastatin Pravastatin Lovastatin Pravastatin	30,817	2,042	1,490	26	74
HPS	Simvastatin	20,586	1,212	898	26	74
PROSPER	Pravastatin	5,804	356	292	19	81
ASCOT-LLA	Atorvastatin	10,305	154	100	36	64
Total		**67,462**	**3,764**	**2,780**	**27**	**73**

* Nonfatal MI and CHD death; AFCAPS also included unstable angina
† Weighted average

Reprinted from Bays H. *Expert Rev Cardiovasc Ther* 2004; 2:89-105, with permissions from Future Science Group.

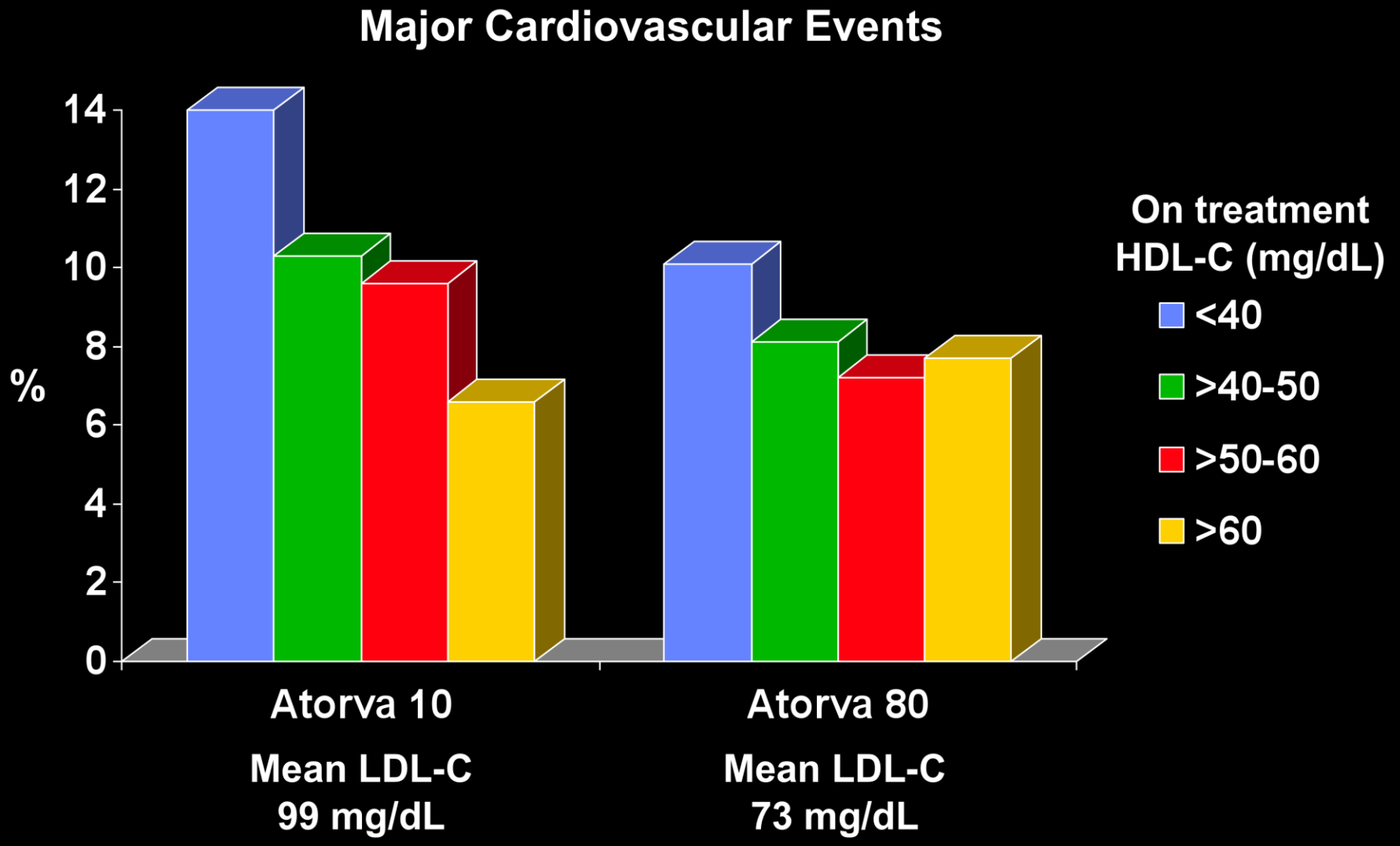
RESIDUAL RISK after LDL lowering

Frequency of Low HDL-C in Men With Premature CHD

Risk factor	Controls (n = 601)	Cases (n = 321)
Cigarette smoking	29%	67%*
HDL-C $<$ 35 mg/dL	19%	57%*
Hypertension	21%	41%*
LDL-C $\geq$ 160 mg/dL	26%	34%*
Diabetes mellitus	1%	12%*

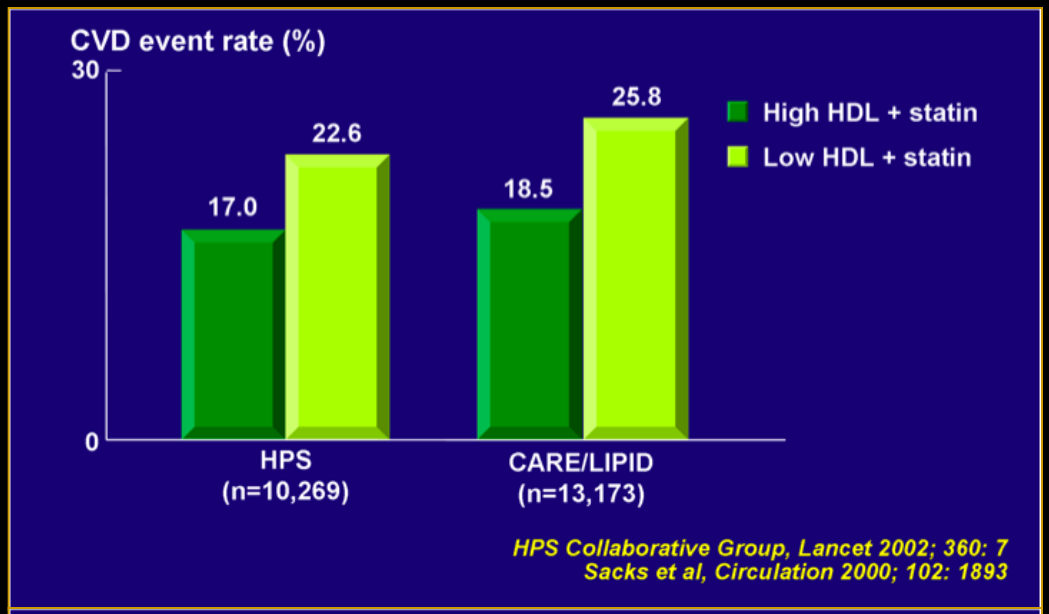
*Significantly different from controls ($P < 0.001$)
Genest JJ et al. *Am J Cardiol* 1991;67:1185–1189

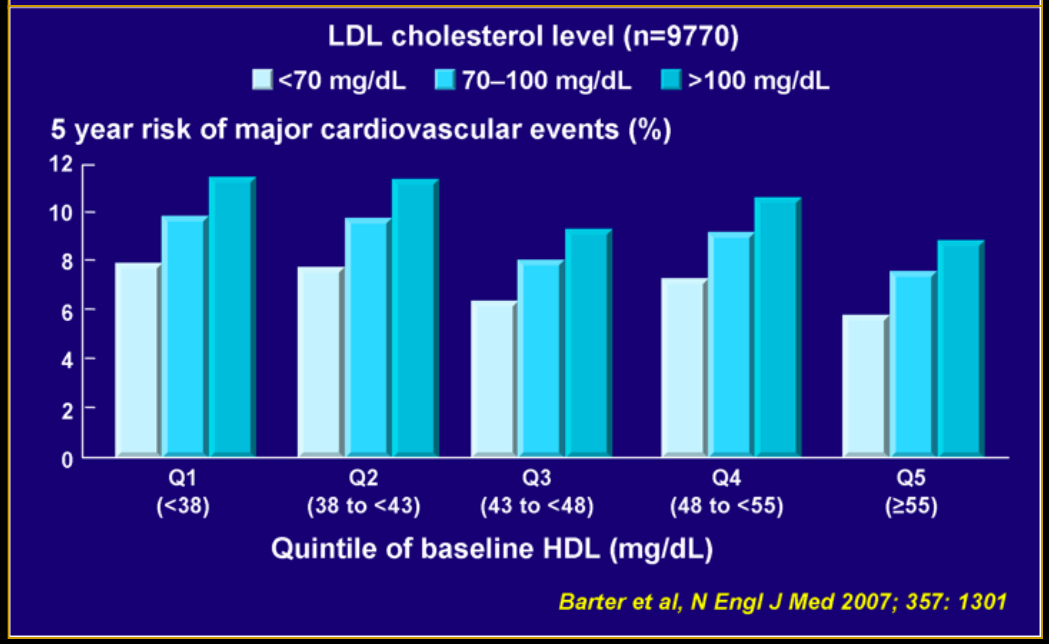
"On-treatment" HDL-C Predicts Cardiovascular Events: TNT



Barter et al. ACC 2006. Abstract 914-203.

CV events and HDL despite statins





Residual high risk for CV events despite statin therapy among patients with low HDL-C levels

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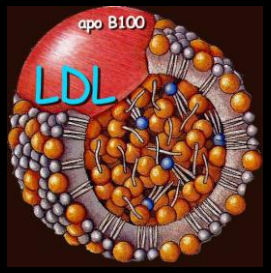

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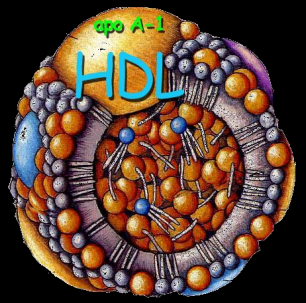
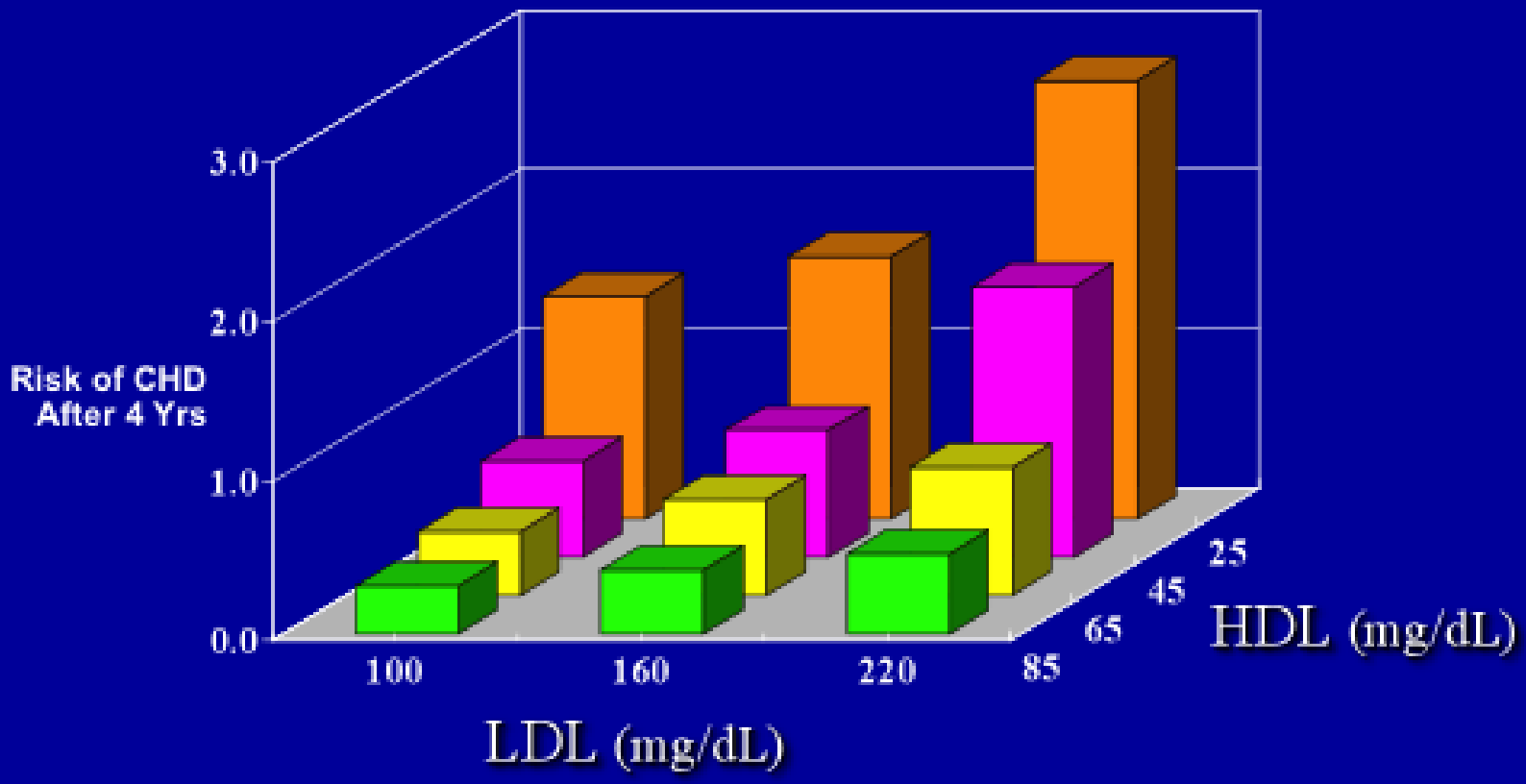


Low HDL-C is a Risk Factor for CHD Even When LDL-C Levels are Well Controlled



Am J Med 1977;62:707-714

Low HDL, even in statin-treated patients, associated with increased CVD risk

Estimated number of additional events for every 10-mg/dL decrease in HDL cholesterol

Outcome	Statin-treated patients, median events (95% CI)	Control participants, median events (95% CI)	p
MI*	7.1 (6.8–7.3)	8.3 (8.1–8.5)	0.57
Cardiovascular disease	4.1 (3.5–4.5)	5.4 (4.8–5.8)	0.21
Coronary heart disease death	2.6 (2.5–2.7)	2.3 (2.2–2.4)	0.31
Cardiovascular death	9.1 (8.0–10.1)	9.5 (8.5–10.5)	0.36
All-cause death	2.9 (2.2–3.4)	2.6 (1.7–3.1)	0.10

*After adjustment for LDL-cholesterol levels and age, a 10-mg/dL decrease in HDL-cholesterol levels was associated with 7.1 more MIs per 1000 patient-years in statin-treated patients and 8.3 MIs per 1000 patient-years among healthy controls.

Jafri H, Alsheikh-Ali AA, Karas RH. Meta-analysis: Statin therapy does not alter the association between low levels of high-density lipoprotein cholesterol and increased cardiovascular risk. Ann Intern Med 2010; 153:800-808.

HDL and CAD

54.6% of CAD hospitalizations have low HDL levels (<40mg/dl) independently of LDL levels

(Fonarow ACC 2007)

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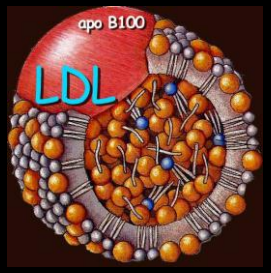

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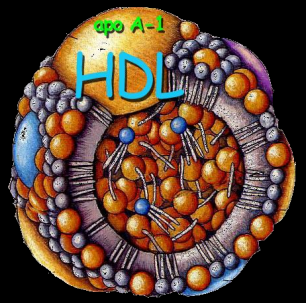


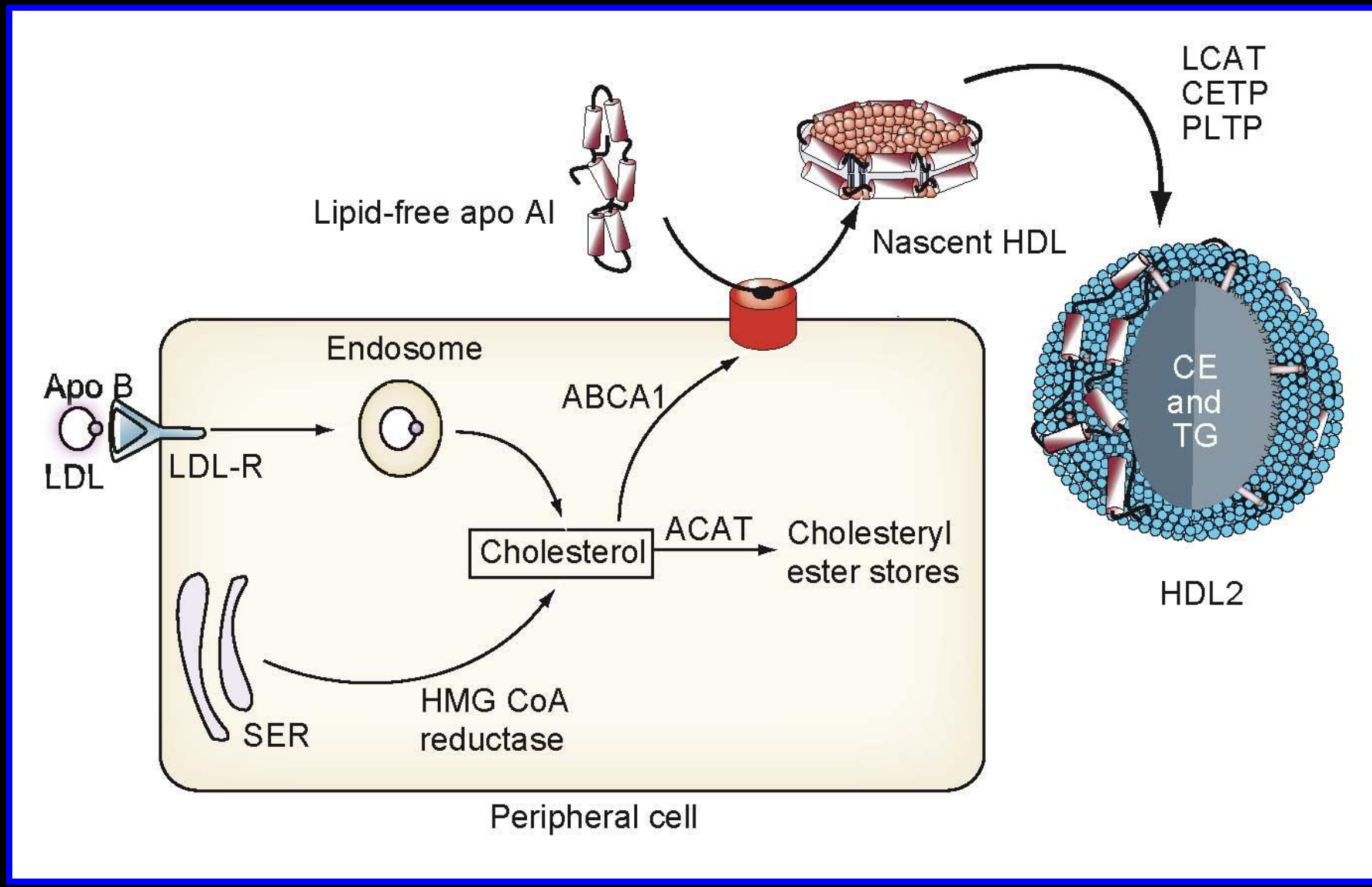
REVERSE CHOLESTEROL TRANSPORT (RCT)

- MULTISTEP PROCESS RESULTING IN THE NET MOVEMENT OF CHOLESTEROL FROM THE PERIPHERAL TISSUES BACK TO THE LIVER

- CHOLESTEROL FROM NON-HEPATIC PERIPHERAL TISSUES IS TRANSFERRED TO HDL BY THE ABCA1 (ATP-binding cassette transporter) - - APO A-1 ACTS AS AN ACCEPTOR, AND THE PHOSPHOLIPIDS OF HDL ACT AS A RESERVOIR FOR THE MOBILIZED CHOLESTEROL

- CHOLESTEROL IS CONVERTED IN CE BY THE ENZYME LCAT

- CE CAN BE TRANSFERRED TO OTHER LIPOPROTEINS (such as LDL) AND THESE LIPOPROTEINS CAN BE TAKEN UP BY THE LIVER VIA THE LDLR



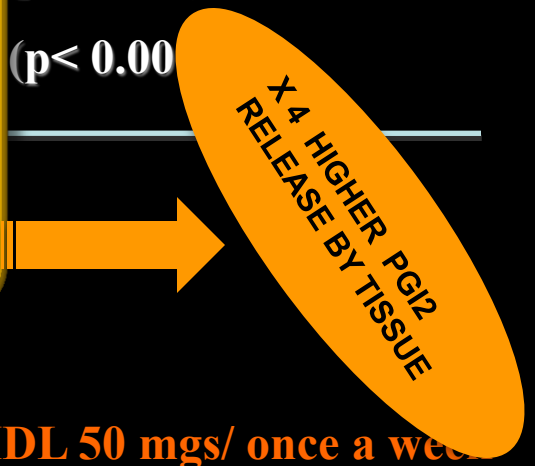
Marcil M, Expert Rev Cardiov Ther 2004 2 (3) 417-30

HDL - Experimental Atherosclerosis

	CONTROL	PLACEBO	TREATED	P
Progession[1]	—	38 ± 6	15 ± 2	(p< 0.001)
Regression[2]	34 ± 4	39 ± 5	18 ± 4	(p< 0.00

(*) = Cholesterol diet (0.5%) —Sudan IV positive area

- Homologous HDL-VHDL preps



1 = Placebo 8 weeks (*) — Treated 8 weeks (*), HDL-VHDL 50 mgs/ once a week

Badimon JJ, Badimon L, Fuster V. Lab Inv 60: 455, 1989

2 = Control: 8 weeks (*) — Placebo and treated: 8 and 4 weeks

Badimon JJ, Badimon L, Fuster V. J Clin Invest 85: 1234, 1990

These observations have been later supported by several transgenic models

Apo A-1

•The major protein component of HDL
•Chylomicrons secreted from the intestinal enterocytes contain ApoA1 which is transferred to HDL in the bloodstream

FUNCTIONS

•Interacts with cellular SR-B1 for bidirectional cholesterol fluxes

•Source of CE for triglycerides

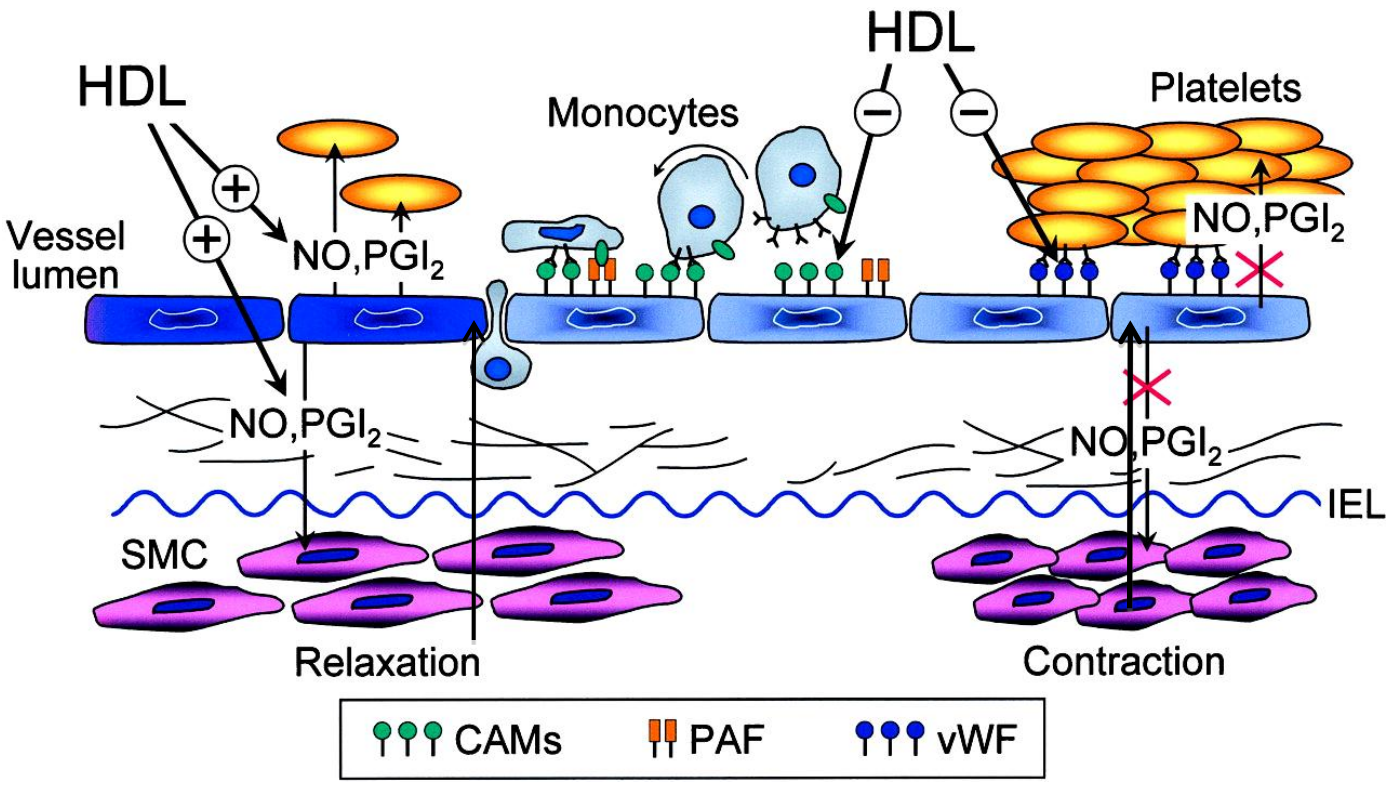
•Interact with ABCG-1 to accept free cholesterol

•Accepts free cholesterol and phospholipids from cellular ABCA-1

•Promotes cholesterol flux to the liver for excretion

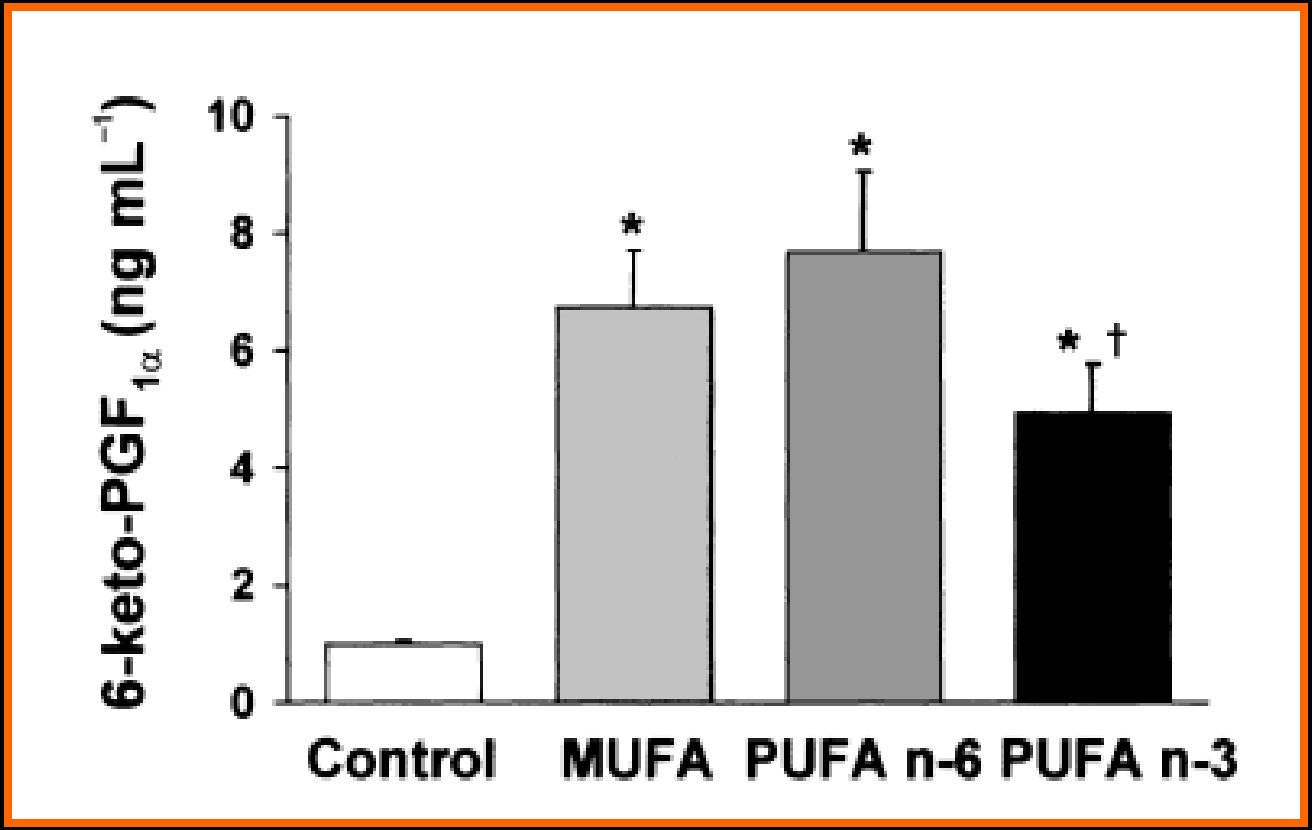
•Acts as cofactor for LCAT which is responsible fro the formation of most of the plasma cholesteryl-esters

MULTIPLE BIOLOGICAL ACTIONS OF HDL ON THE VASCULAR WALL



Gonzalez-Diez M, Badimon L, Martinez-Gonzalez *J Thromb Haemost.* 2008
Martinez Gonzalez J, Badimon L. *Atherosclerosis* 174 (2004) 305–313
Escudero I, Badimon L. *Eur J Clin Invest.* 2003 33 (9) 779-86
Calabresi, L. et al. *Arterioscler Thromb Vasc Biol* 2003;23:1724-1731
Cockerill GW, et al.*ArterioscIerThrombVascBiol.1999;19:910 –917*
Vinals M , Badimon L. *Arterioscler Thromb Vasc Biol* 1999;19:2405-2411
Vinals M, Badimon L. *Arterioscler Thromb Vasc Biol 1997*; 17:3481-3488
Pomerantz KB, Summers B, Hajjar D. P. *Biochemistry. 1993;32:13624–13635*

HDL-induced PGI2 in human smooth muscle cells
Serum from individuals on diets rich in the different fatty-acids



Escudero I, Martinez J,Alonso R, Mata P, Badimon L. Eur J Clin Invest. 2003 33 (9) 779-86

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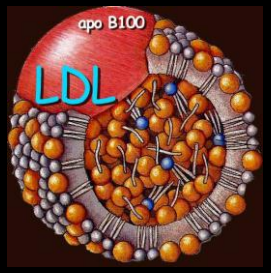

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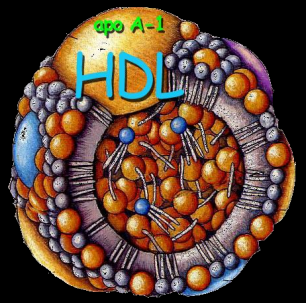


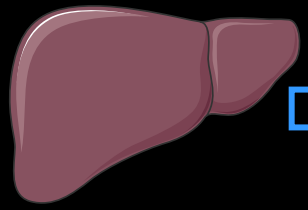
HDL FUNCTIONALITY

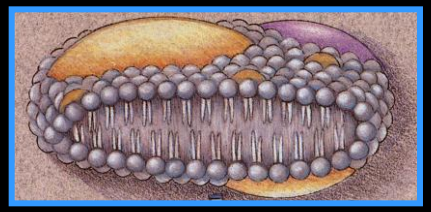
- Low HDL-C is an independent risk factor for CAD in men and women

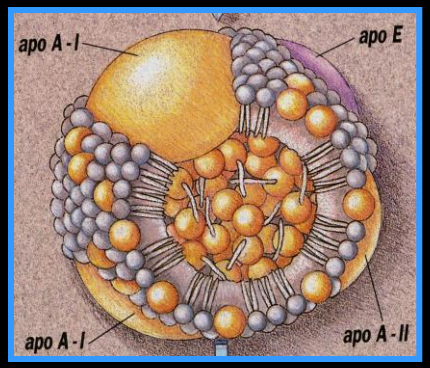
- HDL particles have a complex structure that has diverse protective and pro-inflammatory functions

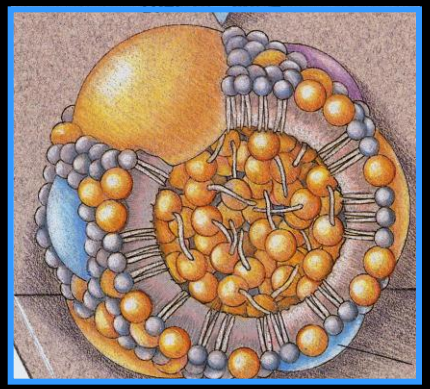
- Diverse studies continue to investigate the role of HDL quantity and quality on cardiovascular risk reduction

HDL: Cantidad *vs.* Calidad









Hígado

HDL "nascent"

HDL3

HDL2

HDL 2 and HDL 3

	HDL3	HDL2
características	↓ diámetro ↑ densidad	↑ diámetro ↓ densidad
composición lipídica	↓ colesterol ↓ fosfolípidos	↑ colesterol ↑ fosfolípidos
actividad	Transporte reverso colesterol Anti-trombótica Anti-oxidante Anti-inflamatoria Cito-protectora	Transporte reverso colesterol Anti-trombótica

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Caracterización proteoma HDL

Plasma EDTA

Ultracentrifugation in Density Gradient

HDL fraction

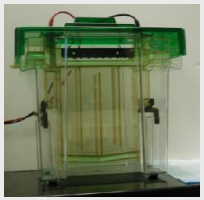
Dialysis (24h)

Characterization by Electrophoresis Gel

Protein Quantification by BCA Kit

2D Electrophoresis

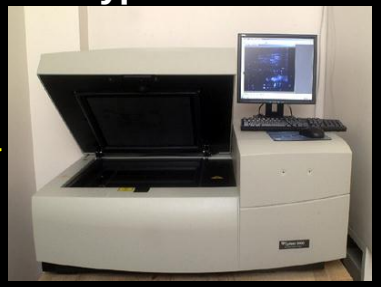
IEF



2D-PAGE

Fluorescent staining

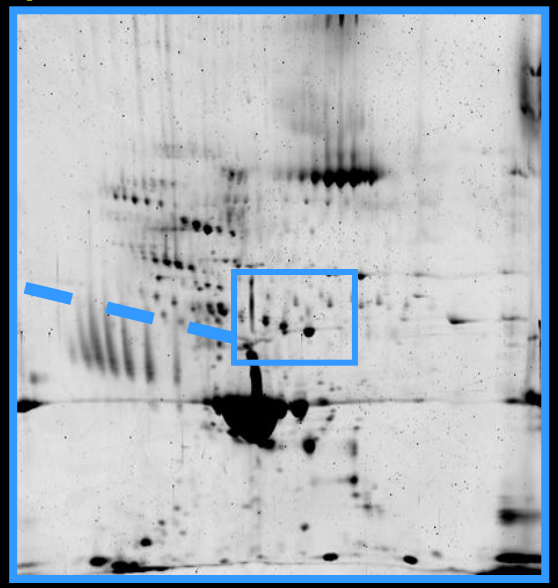
Typhoon 9400

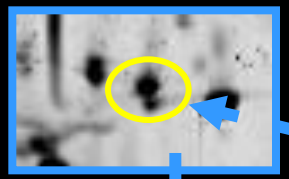


pH 4 → 7

120 kDa

10





Protein

Trypsin digest

Peptides

Protein identification

Mass spectrometry

LC/MS/MS

MALDI-TOF

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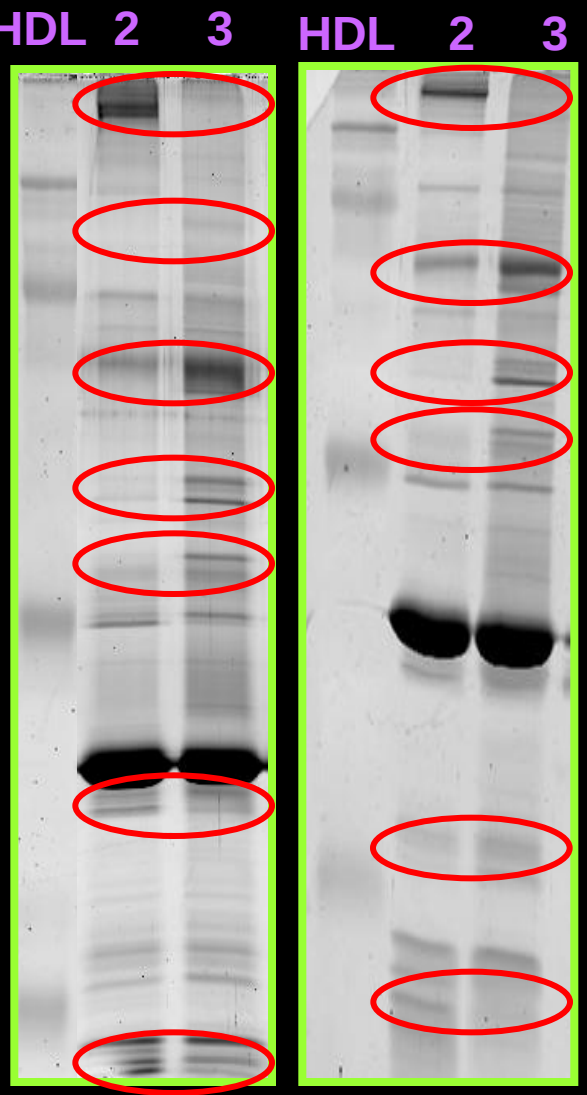
HDL: Quantity *vs.* Quality – (1-DE Analysis)



Differential Band Pattern By 1DE

Differential protein content in HDL

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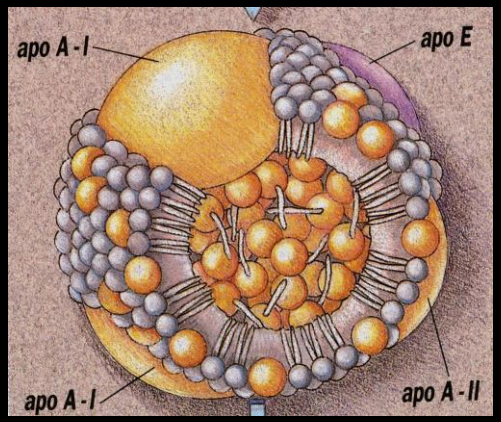
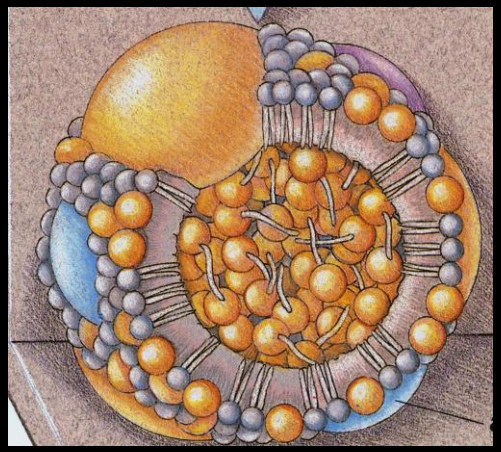
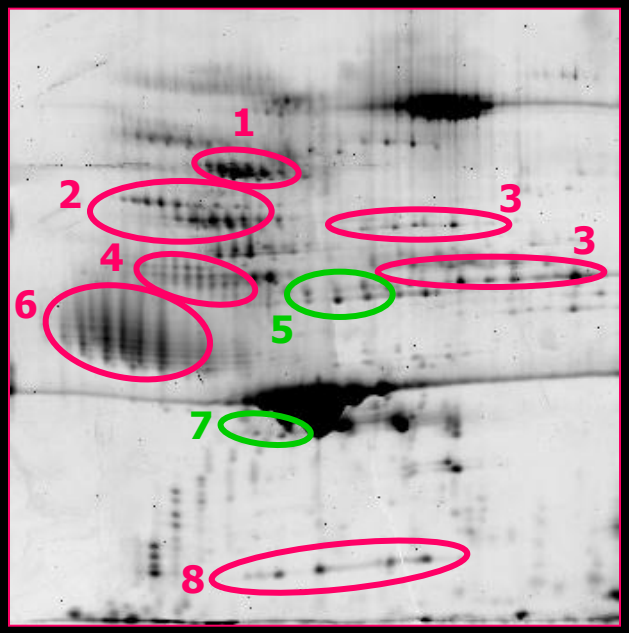
HDL: Quantity *vs.* Quality – (2-DE Analysis)

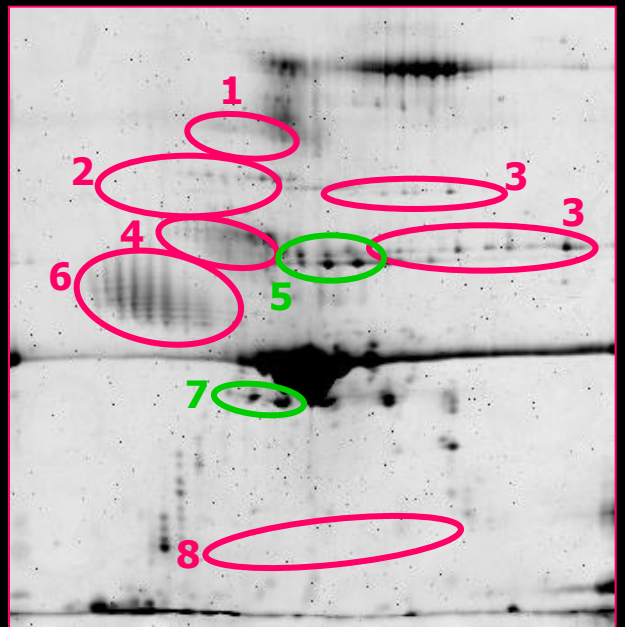
HDL 3



HDL 2







1. Alfa-1-antitripsin
2. Paraoxonase-1
3. Apolipoprotein L1
4. Apolipoprotein J
5. Apolipoprotein E
6. Apolipoprotein D
7. Apolipoprotein AIV
8. Transtirhetin

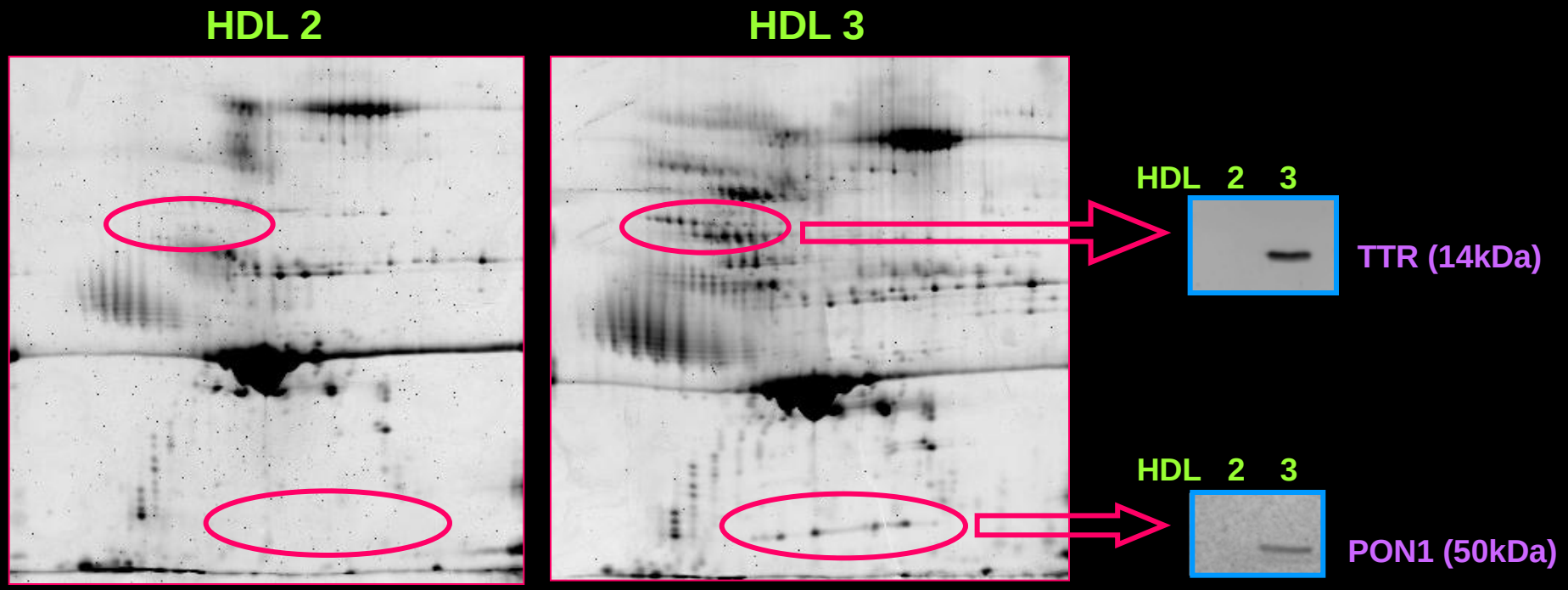
Differential protein contents

Antioxidants

Cytoprotectors

Antiinflammatory

HDL: Quantity *vs.* Quality – (WB validation)

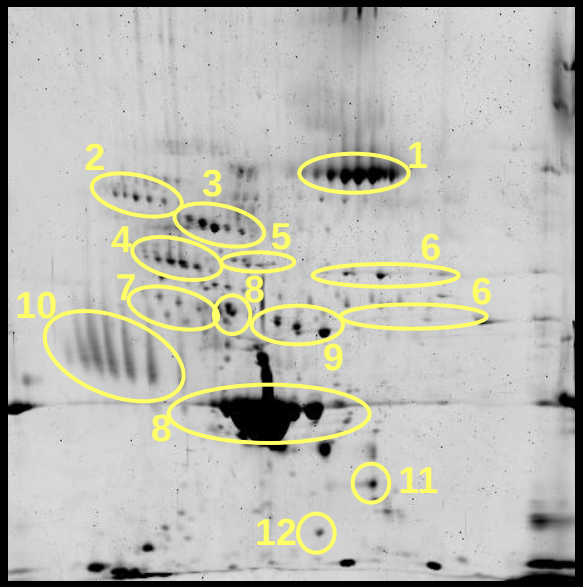


TTR o Transtirhetin → Acute phase reactant protein
Transport of thyroid hormons
Transport of RBP4

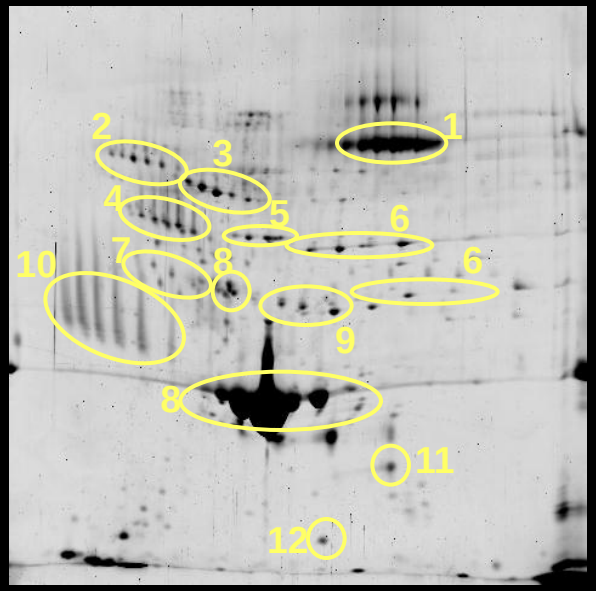
PON1 o Paraoxonasa-1 → Antioxidant properties

Differential HDL patterns in patients with high LDL (hFH)

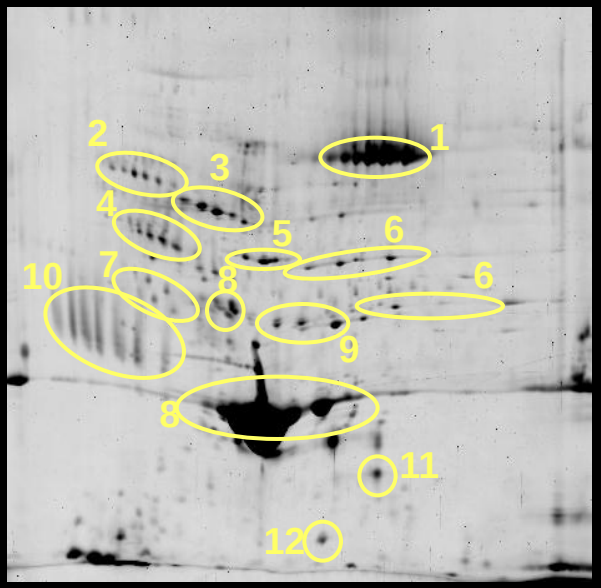
+ Mut + CAD



- Mut - CAD



+ Mut - CAD



18 families analyzed (3 persons in each one)

212 spots validated

96 spots identified

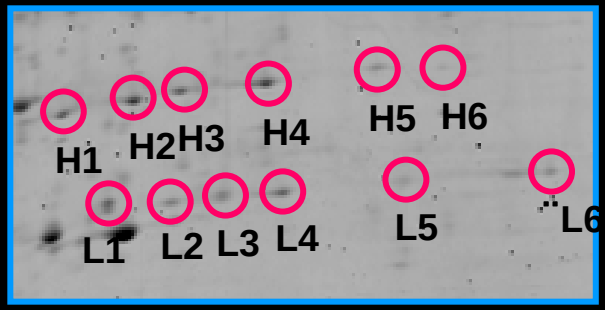
+/- mutation (Mut)

+/- coronary artery disease (CAD)

1. Albumin	7. Apo J
2. LCAT	8. Apo A-I
3. Alpha-1-antitrypsin	9. Apo E
4. PON-1	10. Apo D
5. Apo A-IV	11. Apo M
6. Apo L-1	12. TTR

Differential Apo L1 pattern in hFH patients

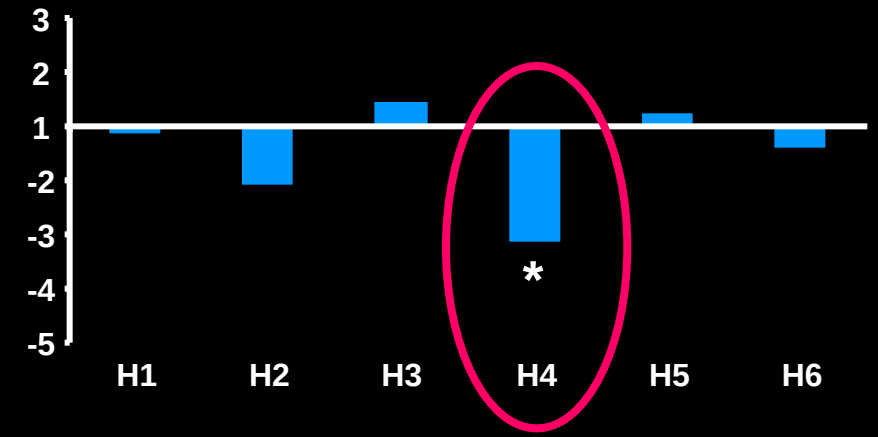
Apo L1: Apoptosis -related protein

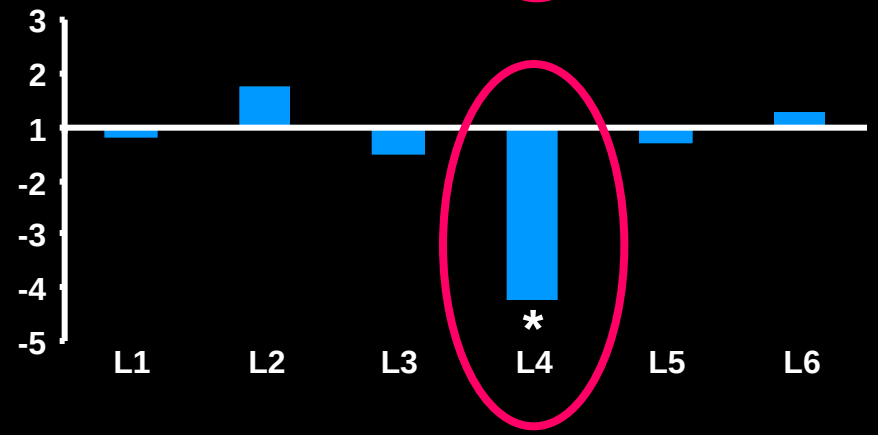


Chain of spots of 45 kDa (high MW)

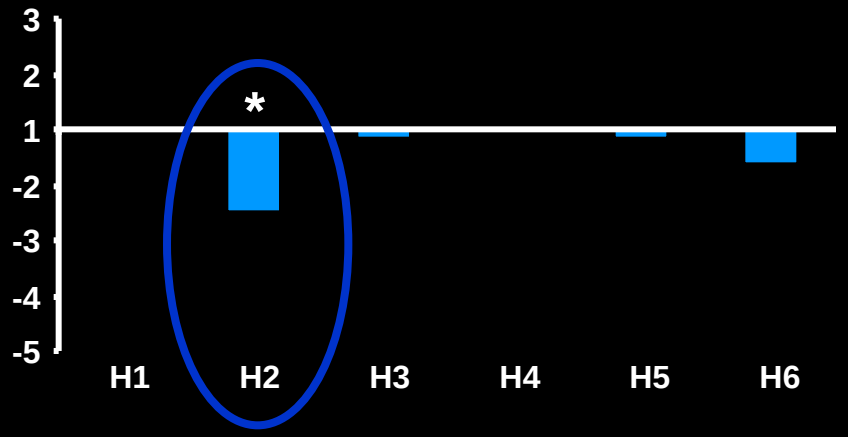
Chain of spots of 38 kDa (low MW)
Truncated form

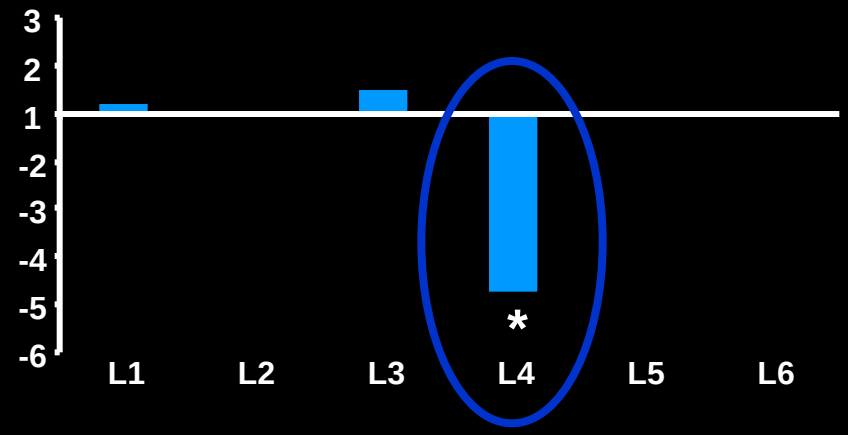
Mut CAD vs. Mut No CAD
Effect of the pathology





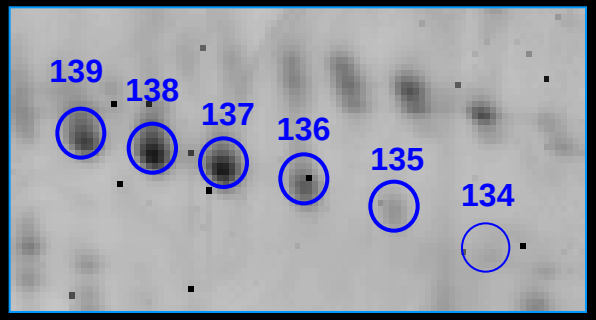
Mut-CAD and Mut-NoCAD vs. Control
Effect of the mutation



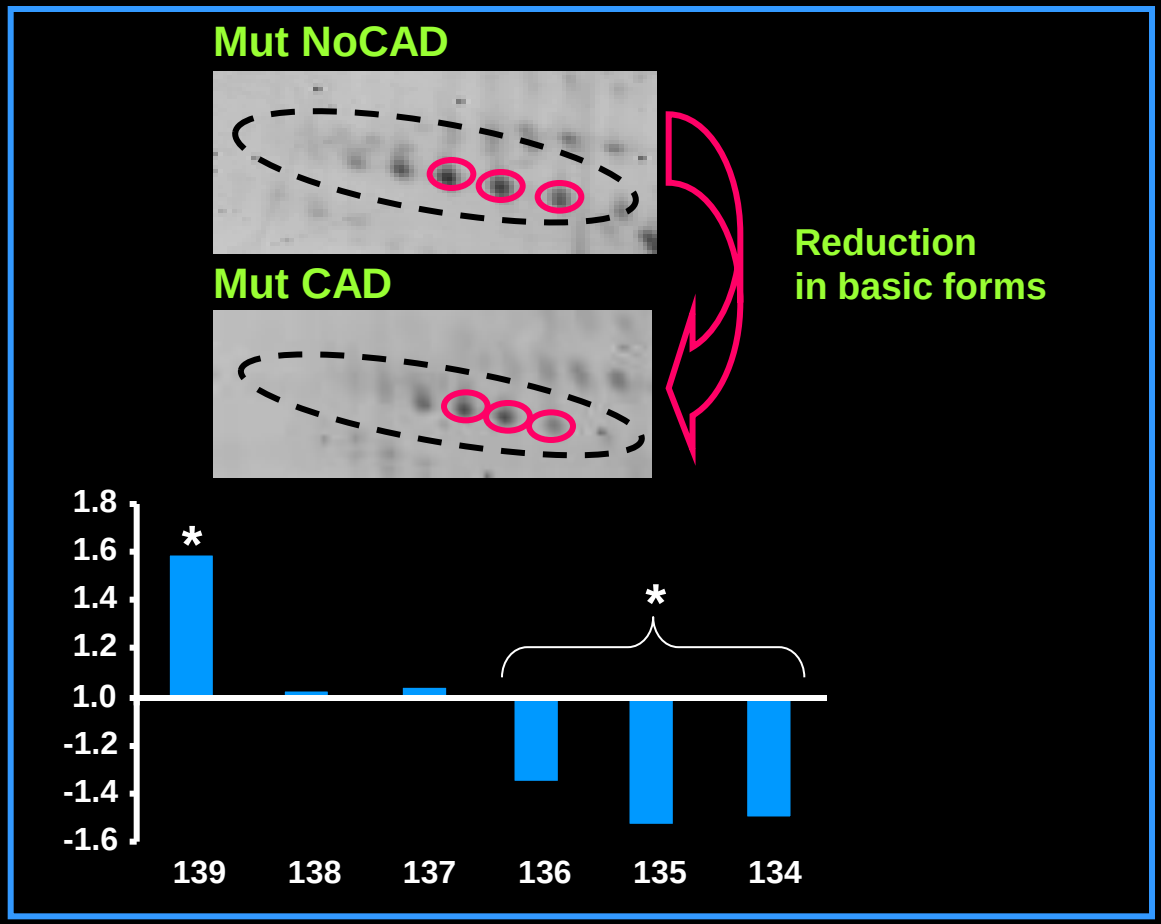


Differential LCAT patterns in hFH patients

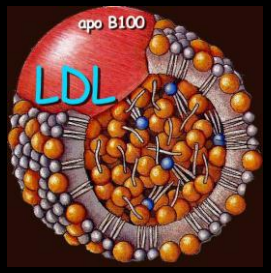
Six differential spots



Post transductional modifications:
4 N-glicosilation spots
2 O-glicosilation spots



Colesterol HDL y riesgo cardiovascular
¿Dónde estamos?



1.IMPACTO DE LAS LDL

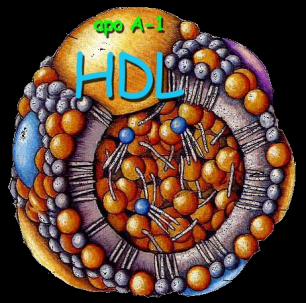
2.ESTATINAS Y UMBRAL DE BENEFICIO

3.IMPACTO DE LAS HDL

4.TRANSPORTE REVERSO DE COLESTEROL

5.HDL: CANTIDAD Y/O CALIDAD

6.TRATAMIENTO



Trial evidence supporting the raise of HDL

CORONARY DRUG PROJECT (NIACIN ↑ 25% HDL)
LIPID RESEARCH CLINICAL TRIAL (CHOLESTRYRAMINE ↑ 3% HDL)
HELSINKY HEART TRIAL (GENFIBROZIL ↑10% HDL)
VETERANS HDL INTERVENTION TRIAL (GENFIBROZIL ↑6% HDL)

Imaging/Angiographic studies

FATS (nicotinic acid)
HATS (nicotinic acid)
REVERSAL (statin)
ASTEROID (statin)
Apo A-I Milano (Apo A-I)
ERASE (rHDL)

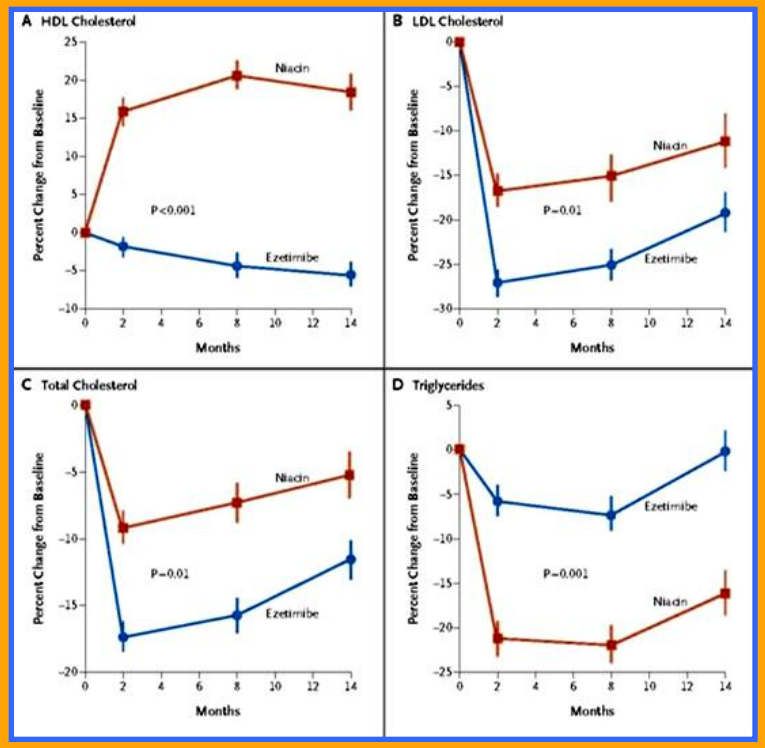
Emerging Strategies to raise HDL

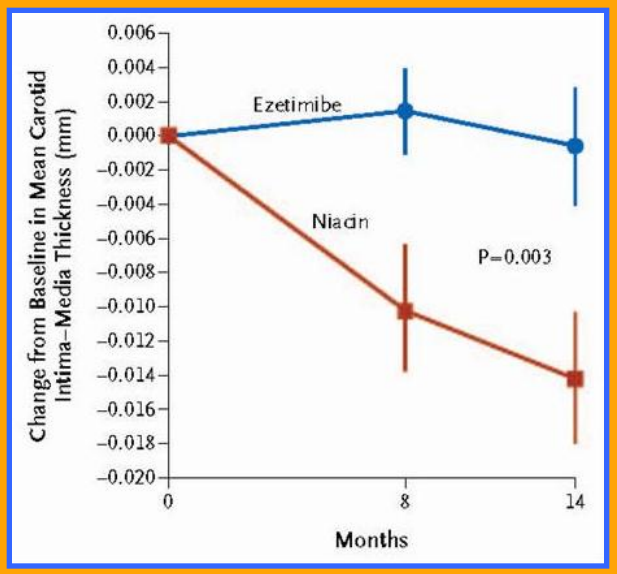
Apo A-I Milano
PPAR's Agonists
alpha - fibrates
Non-flushing Niacin
(Niacin-Laropiprant)
CETP Inhibitors

Apo A-I mimetics
LXR/RXR activation
SR-B1 overexpression
ABC 1 gene overexpression

ARBITER 6

At Baseline
CHO 146 mg/dl HDL 43 mg/dl LDL 82 mg/dl TGL 124 mg/dl





Taylor AJ, N engl j med 361;22, 2009

AIM - HIGH

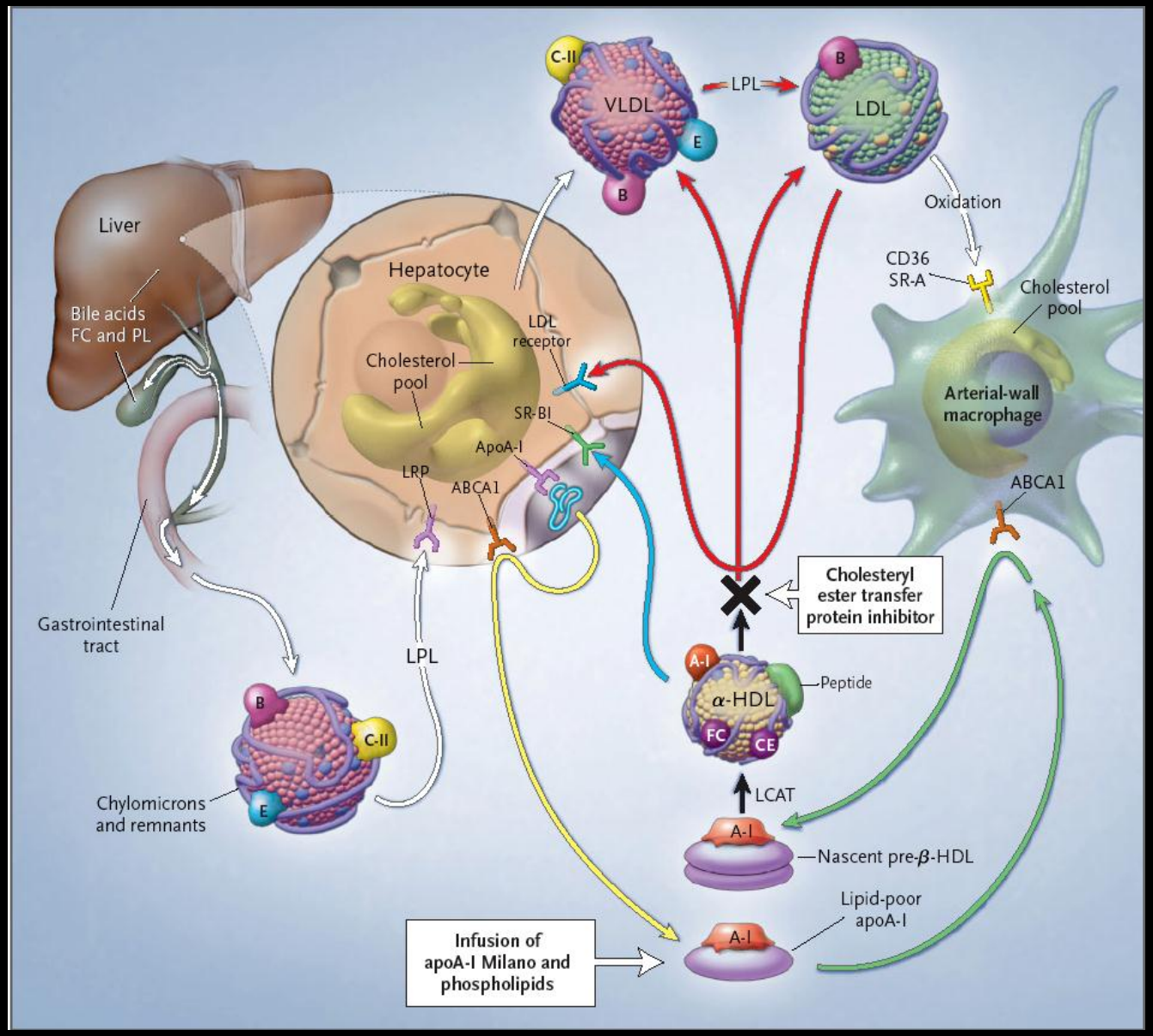
Atherothrombosis Intervention in Metabolic Syndrome with Low HDL-C/High Triglycerides and Impact on Global Health Outcomes

- Randomized trial on niacin vs placebo in the background of simvastatin therapy in approximately 3300 patients with cardiovascular disease, low HDL and high triglycerides
- AIM was stopped for FUTILITY with about 2/3 of the events already occurred
- HDL levels were higher and triglycerides lower in the niacin group with the LDL levels very low and equal in the two groups
- There were more strokes in the niacin group

LIMITATIONS IN TRIAL DESIGN

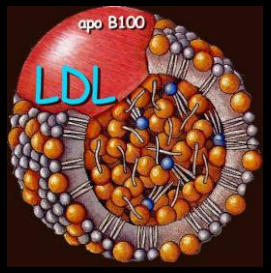
- Mechanisms of action can not be determined from clinical trials if the agent has multiple effects
- AIM-HIGH was inadequately powered (<3500 patients)
- AIM-HIGH was not targeted at patients who would benefit the most(those with high TGL and low HDL)

Reverse Cholesterol Transport and CETP



Brewer B, NEJM 2004;350:1491

Colesterol HDL y riesgo cardiovascular
¿Dónde estamos?



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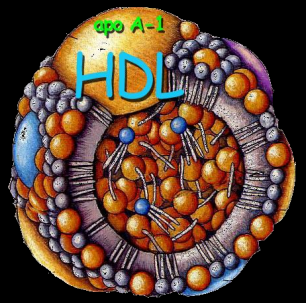
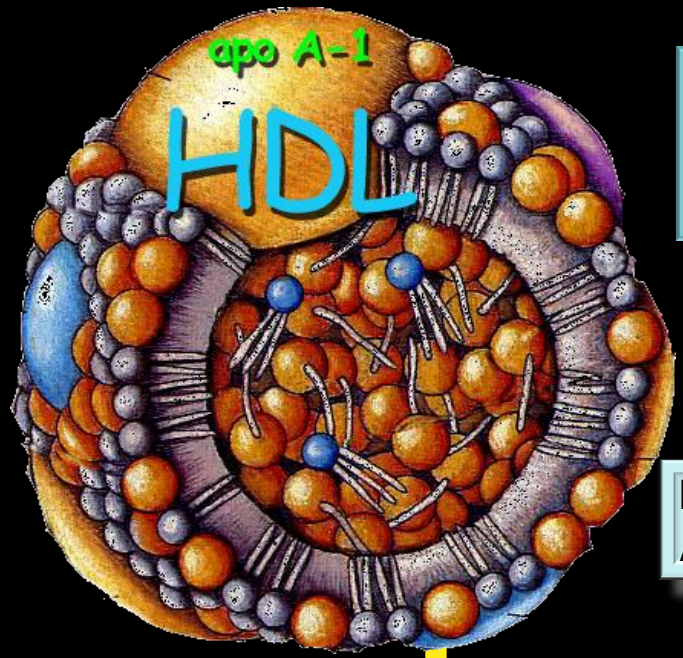


6.TRATAMIENTO

ANTI-ATHEROTHROMBOTIC ACTIVITIES OF HDL PARTICLE COMPONENTS

CARRIER OF ACTIVE MOLECULES

PARTICLE SIZE-ASSOCIATED FUNCTIONALITY



Antioxidant

Normalization of EC function
Antithrombotic effects

Antiapoptotic

Antiinflammatory

Fibrinolysis

PGI2

NO

REVERSE CHO TRANSPORT

Badimon et al 1990-2005
Viñals et al 1997,1998
Escudero et al 2003


BARCELONA CARDIOVASCULAR RESEARCH CENTER
CSIC-ICCC
HOSPITAL DE LA SANTA CREU I SANT PAU