Proyecto Prometeo

Alteraciones de los lípidos en postrasplante renal

Metabolismo de los Lípidos: Actualización

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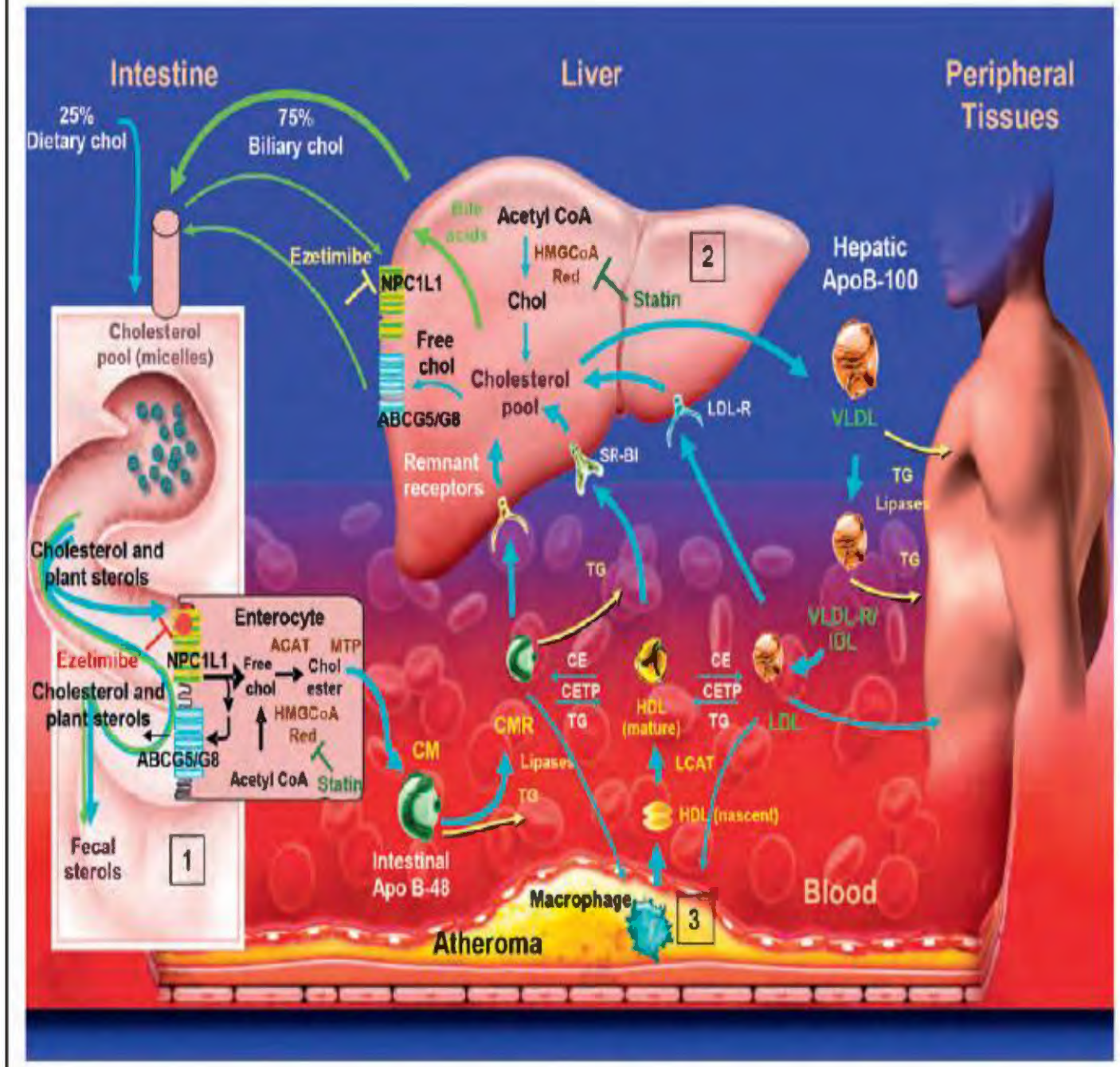
Alcalá de Henares, 19 de octubre de 2012

Hospital Universitario Miguel Servet

Instituto Aragonés de Ciencias de la Salud

Vías de transporte de lípidos

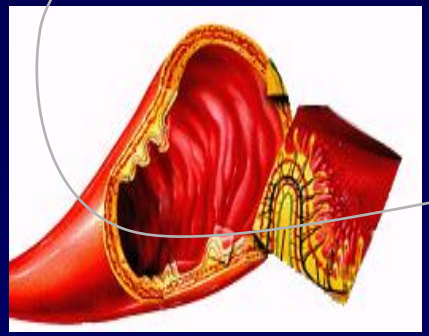
- Exógena: Dieta → Hígado
- Endógena: Hígado → Tejidos periféricos
- T. Reverso: Tejidos periféricos → Hígado


Intestine
Liver
Peripheral Tissues
25% Dietary chol
75% Biliary chol
Ezetimibe
NPC1L1
Bile acids
Acetyl CoA
HMGCoA Red
Statin
Chol
2
Free chol
ABCG5/G8
Cholesterol pool
LDL-R
Hepatic ApoB-100
VLDL
TG
Lipases
Remnant receptors
SR-BI
Cholesterol pool (micelles)
Cholesterol and plant sterols
Enterocyte
ACAT
MTP
Free chol
Chol ester
HMGCoA Red
Acetyl CoA
Statin
CE
CETP
TG
VLDL-R/ IDL
CM
CMR
HDL (mature)
LDL
LCAT
HDL (nascent)
Intestinal Apo B-48
Fecal sterols
1
Macrophage
3
Blood
Atheroma

Metabolismo lipídico. Transporte exógeno

Ingesta
(TG, FL, CE)

Absorción intestinal



Síntesis de QMn

HDL

Apo E,
CII, CIII

CL
FL

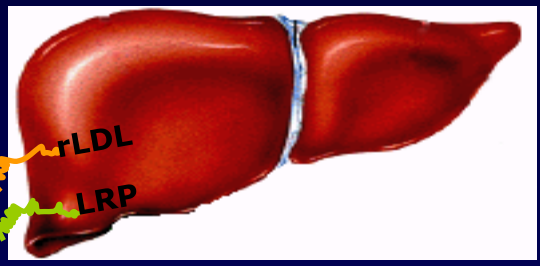
Endotelio

HSPG

PTEC

EC

QMr



Apo C

Apo E

Apo B48

QMn

LPL

AGL
Glicerol

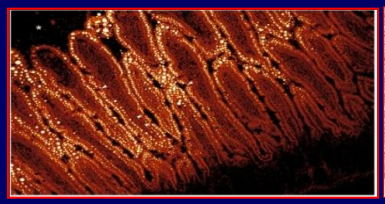
Albúmina

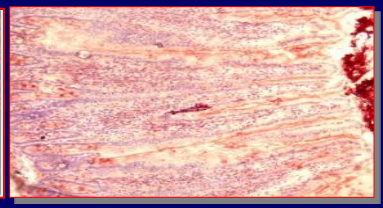
Endotelio

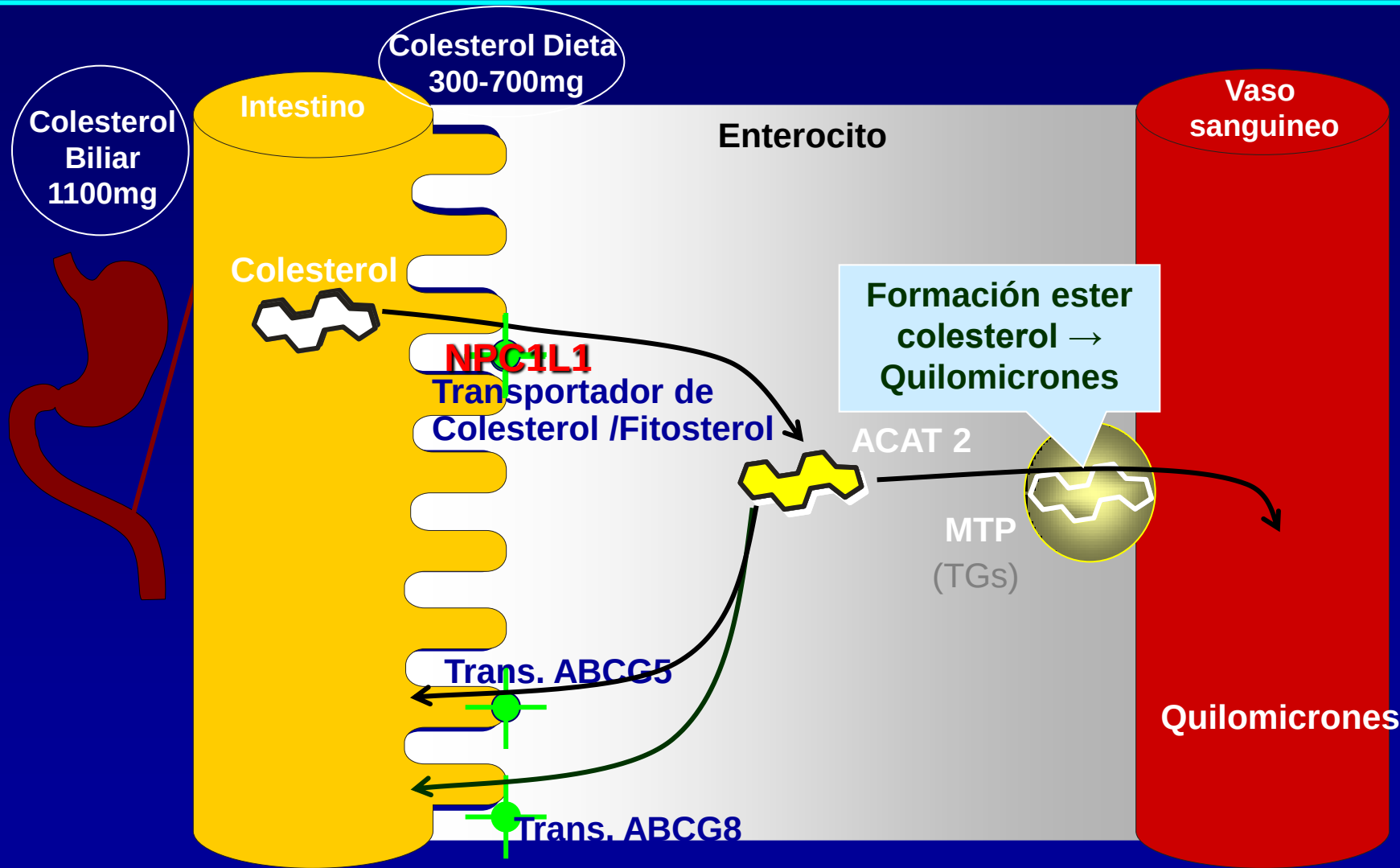
Tejidos periféricos

Universidad de Zaragoza

Absorción intestinal del Colesterol



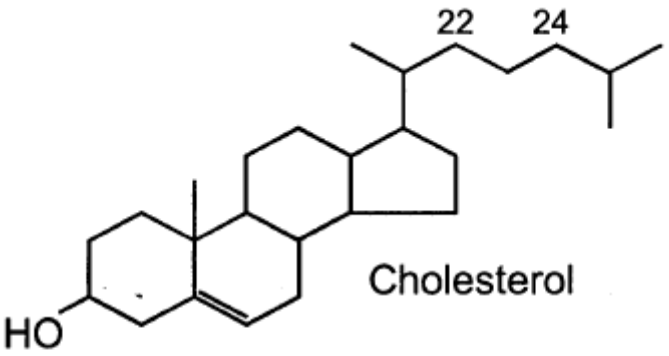




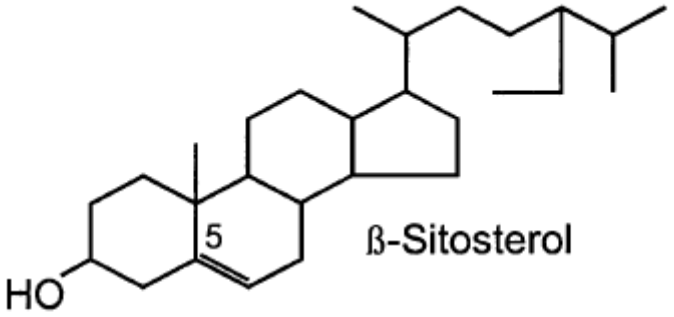
ESTEROLES

- Los esteroles son lípidos esenciales de las membranas de las células eucariotas y ausentes en las procariotas
- Elementos fundamentales en el control de las propiedades de las membranas celulares
- Especialmente las funciones de barrera de las membranas están vinculadas con el nivel de esteroles

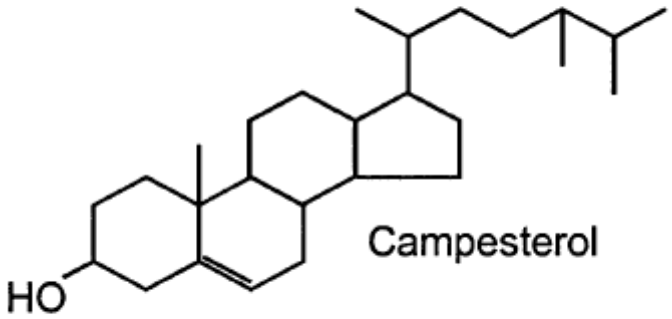
Esteroles



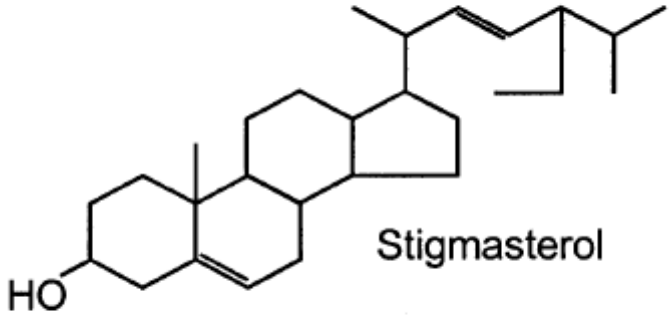
Cholesterol



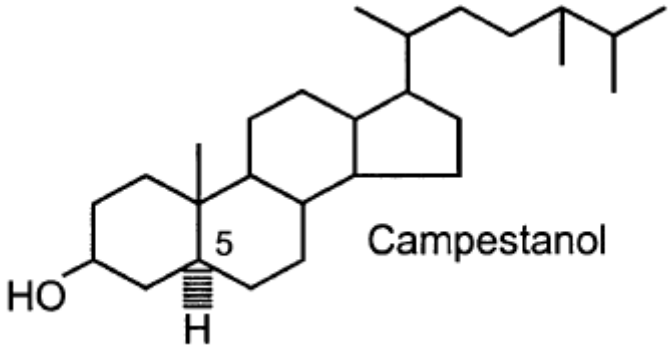
ß-Sitosterol



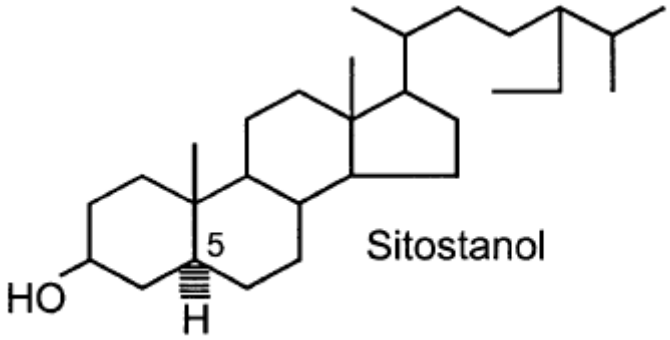
Campesterol



Stigmasterol



Campestanol



Sitostanol

PRINCIPALES ESTEROLES EN PLASMA

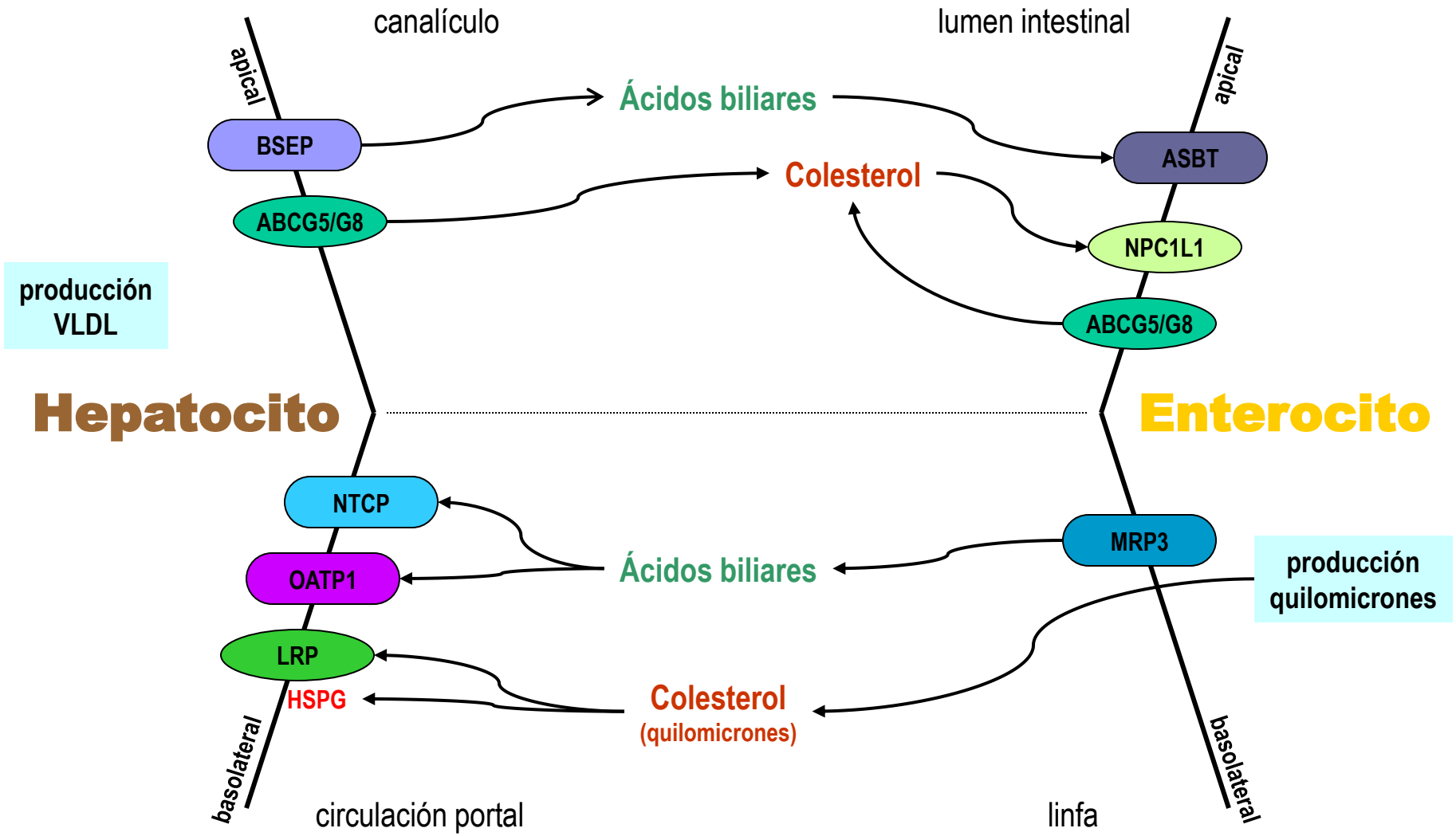
- **Precursores síntesis de colesterol**
  - **Escualeno**
  - **Colestenol**
  - **Desmosterol**
  - **Latosterol**
- **Colesterol**
- **Esteroles no colesterol**
  - **Colestanol**
  - **Esteroles vegetales**
    - **Campesterol**
    - **Sitosterol**
    - **Avenasterol**

ASPECTOS COMPARATIVOS

	Colesterol	Fitosteroles	Fitostanoles
Ingesta/día	300-500 mg	200-400 mg	<10 mg
Fuente	huevos, carne, mantequilla,	Aceites vege. semillas,	Ac. Coco, tallos, industria
Síntesis endog.	800-1200 mg	No	No
Absorción	40-60%	< 5%	0,1-2%
Concentración	140-300 mg/dl	0.3-1.7 mg/dl	0.3-0.6 mg/dl
Excreción	40-60%	>95%	>98%

Clifton P. Atherosclerosis Supplements 2002;3:5

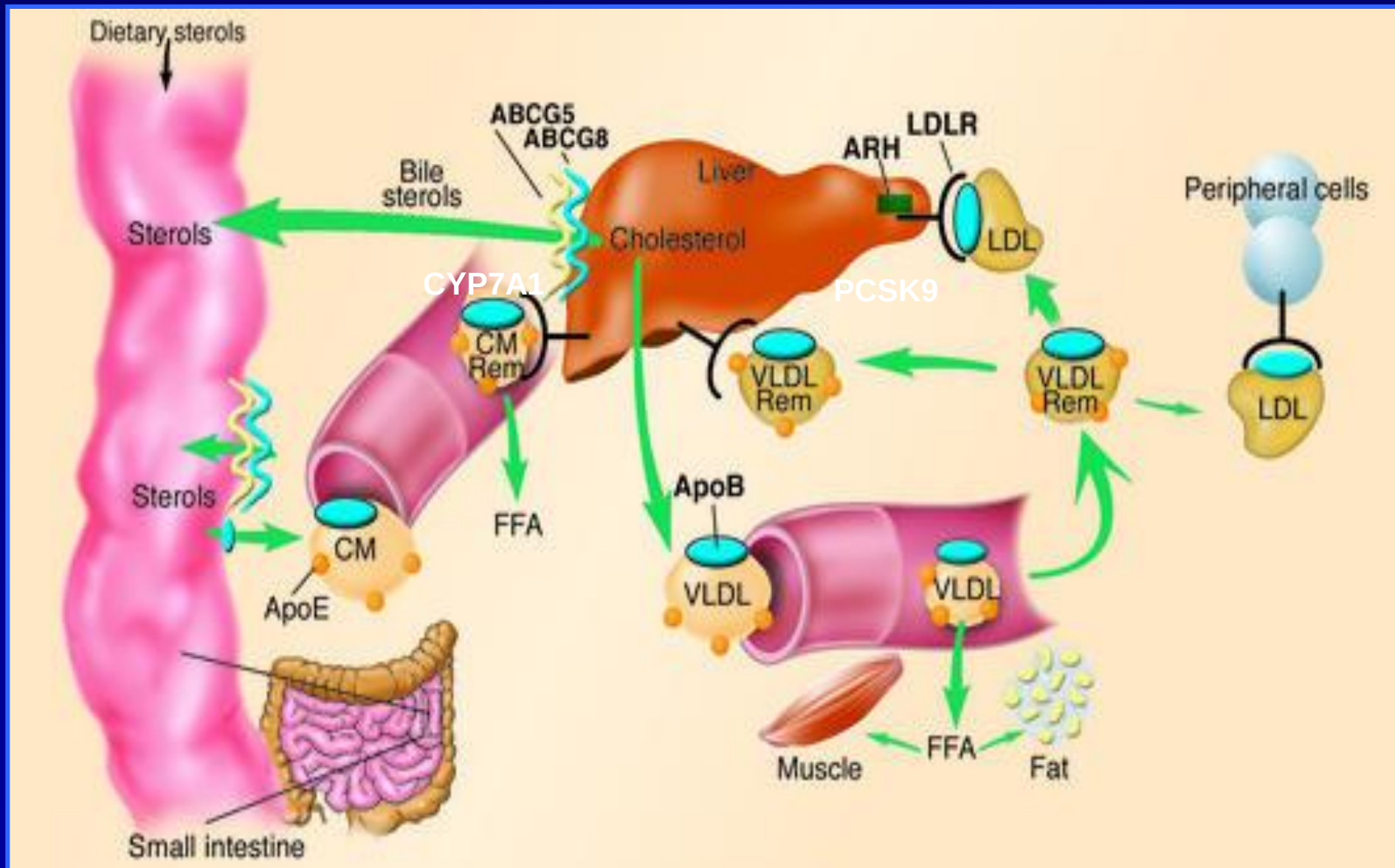
Mecanismo molecular

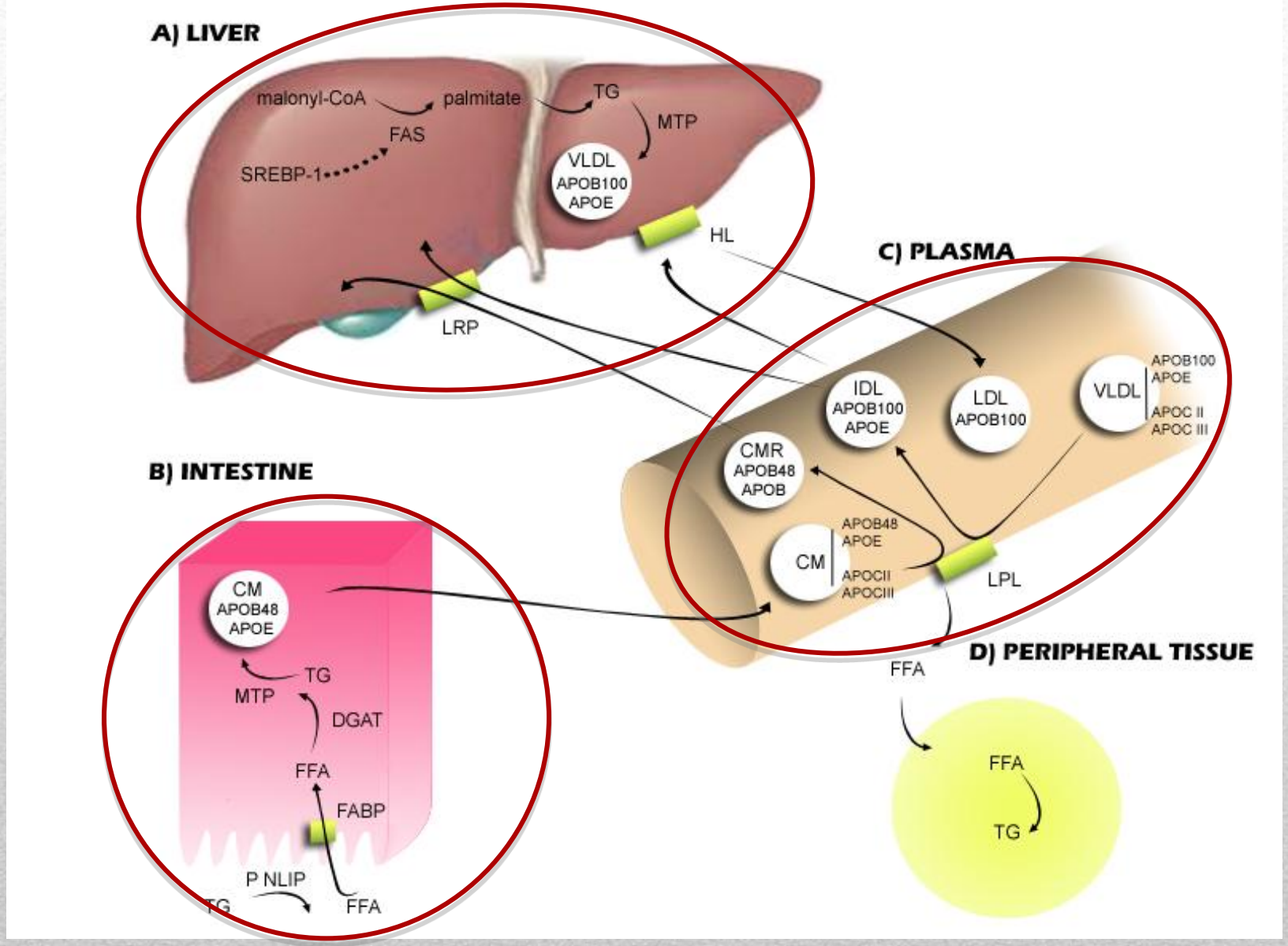


UTILIDAD CLINICA DETERMINACIÓN ESTEROLES EN SANGRE

- Colesterol: riesgo coronario
- Fitosteroles: riesgo coronario ?
- Marcadores absorción intestinal
  - Colestanol
  - Fitosteroles
- Marcadores síntesis endógena de colesterol
  - Escualeno
  - Colestenol
  - Desmosterol
  - Latosterol
- Cocientes: absorción/síntesis
  - Clasificación hipercolesterolemias
  - Respuesta a estatinas, ezetimiba,...

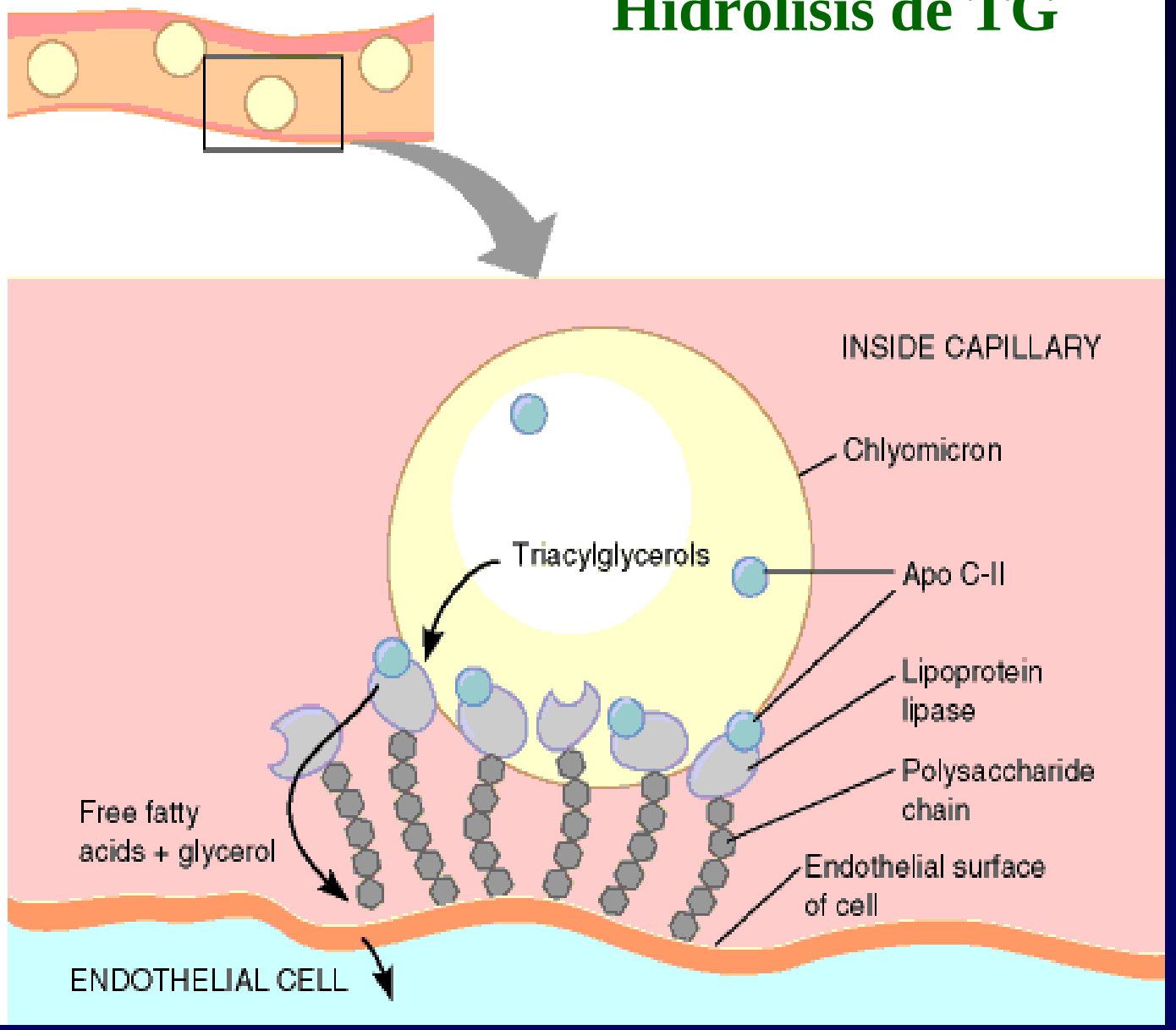
Metabolismo lipídico

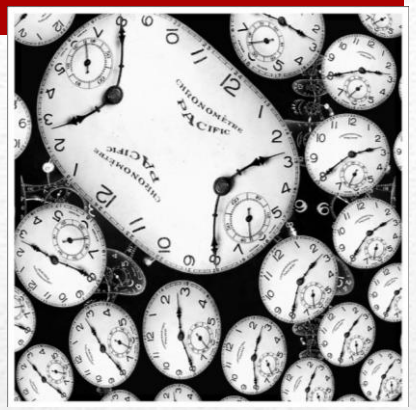




Metabolismo de los triglicéridos

Hidrólisis de TG





APO-CII	APOAI-CIII-AIV	LPL	APO-AV	LMF1 y GPIHBP1
FINALES ‘70	80-90s	’90s	2000	2007-2011

Historia de la genética de las HTG

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Novel LMF1 Nonsense Mutation in a Patient with Severe Hypertriglyceridemia

Angelo B. Cefalù, Davide Noto, Maria Luisa Arpi, Fen Yin, Rossella Spina, Hannele Hilden, Carlo M. Barbagallo, Antonio Carroccio, Patrizia Tarugi, Sebastiano Squatrito, Riccardo Vigneri, Marja-Riitta Taskinen, Miklós Péterfy and Maurizio R. Averna

J. Clin. Endocrinol. Metab. 2009 94:4584-4590 originally published online Oct 9, 2009; , doi: 10.1210/jc.2009-0594

Presenta mutación W464X en homocigosis Exón 9 de LMF1

- Probando de 42 años con HTG desde los 32 (no tiene una clara respuesta a tratamientos).
- TG = 2.400 mg/dl CT = 374 mg/dl HDL-c = 44 mg/dl
- Episodios recurrentes de pancreatitis y Diabetes tipo II.
- No presentó mutaciones en LPL, APOC2 ni APOA5.
- La actividad LPL se vio reducida en un 76% respecto a normolipémicos, y la HL en un 27%.

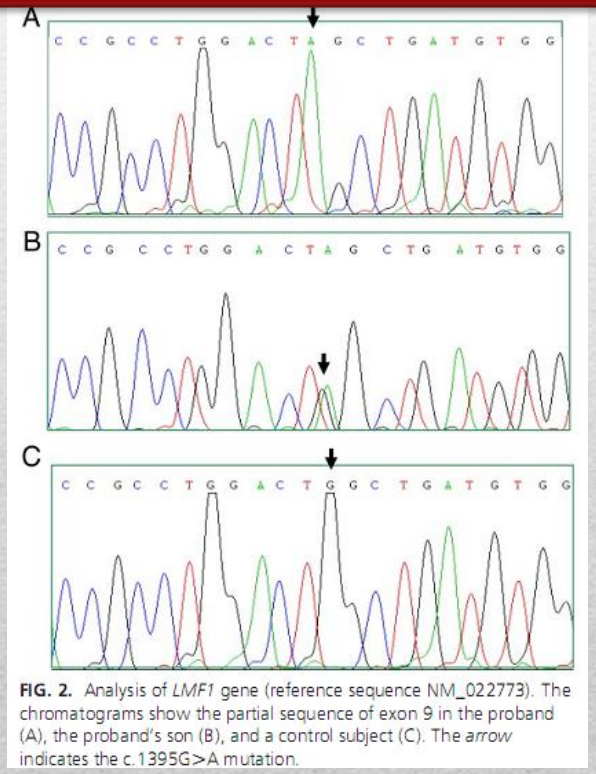
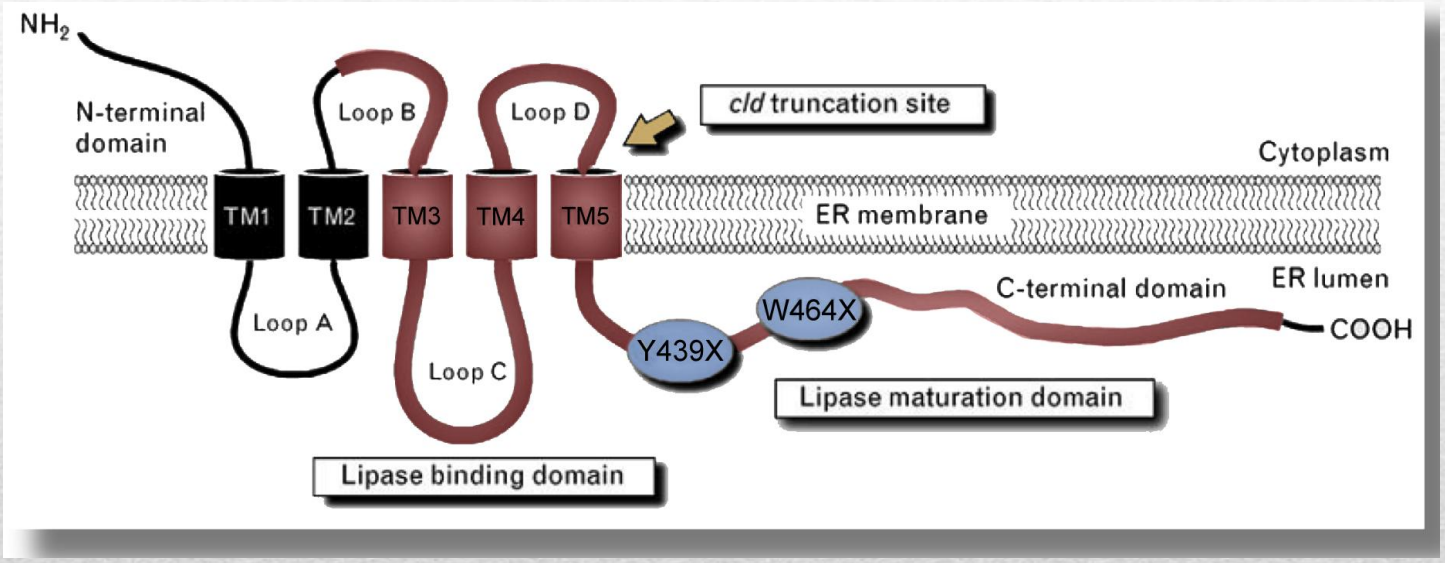
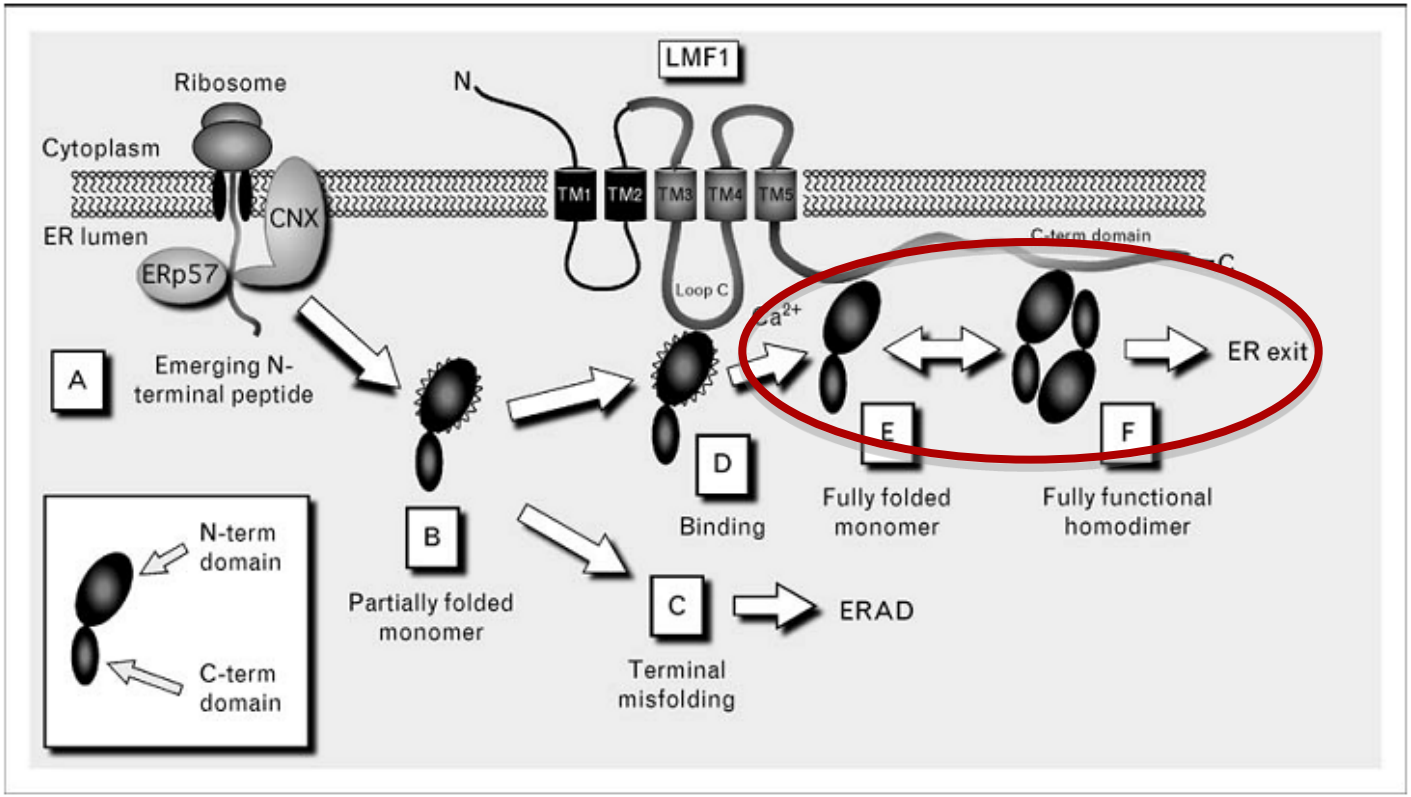


FIG. 2. Analysis of *LMF1* gene (reference sequence NM_022773). The chromatograms show the partial sequence of exon 9 in the proband (A), the proband's son (B), and a control subject (C). The *arrow* indicates the c.1395G>A mutation.

LMF1 es una proteína de membrana, que se localiza en el RE en interviene en la maduración y ensamblaje de las lipasas homodiméricas.





The inset illustrates the N-folding and C-folding domains comprising the lipase monomer; wavy lines indicate an N-terminal domain that is partially folded. Only the homodimer exhibits enzyme activity and exits the endoplasmic reticulum ; all other lipase forms are inactive and are retained in the endoplasmic reticulum. Terminally misfolded forms are destined for endoplasmic reticulum-associated degradation (ERAD). CNX, calnexin; ERp57, 57-kDa endoplasmic reticulum protein; LMF1, Lipase maturation factor 1.

Doolittle et al. *Curr Opin Lipidol* 2010;21:198-203

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Author Manuscript
Cell Metab. Author manuscript; available in PMC 2008 April 4.

Published in final edited form as:
Cell Metab. 2007 April ; 5(4): 279–291.

Glycosylphosphatidylinositol-anchored high density lipoprotein–binding protein 1 plays a critical role in the lipolytic processing of chylomicrons

Anne P. Beigneux[1,*], **Brandon S. J. Davies**[1], **Peter Gin**[1], **Michael M. Weinstein**[1], **Emily Farber**[1], **Xin Qiao**[1], **Franklin Peale**[2], **Stuart Bunting**[2], **Rosemary L. Walzem**[3], **Jinny S. Wong**[4], **William S. Blaner**[5], **Zhi-Ming Ding**[6], **Kristan Melford**[7], **Nuttaporn Wongsiriroj**[5], **Xiao Shu**[7], **Fred de Sauvage**[2], **Robert O. Ryan**[7], **Loren G. Fong**[1], **André Bensadoun**[8], and **Stephen G. Young**[1,*]

1Department of Medicine/Division of Cardiology, David Geffen School of Medicine, University of California, Los Angeles, CA 90095

Ratones *Gpihbp1*$^{-/-}$

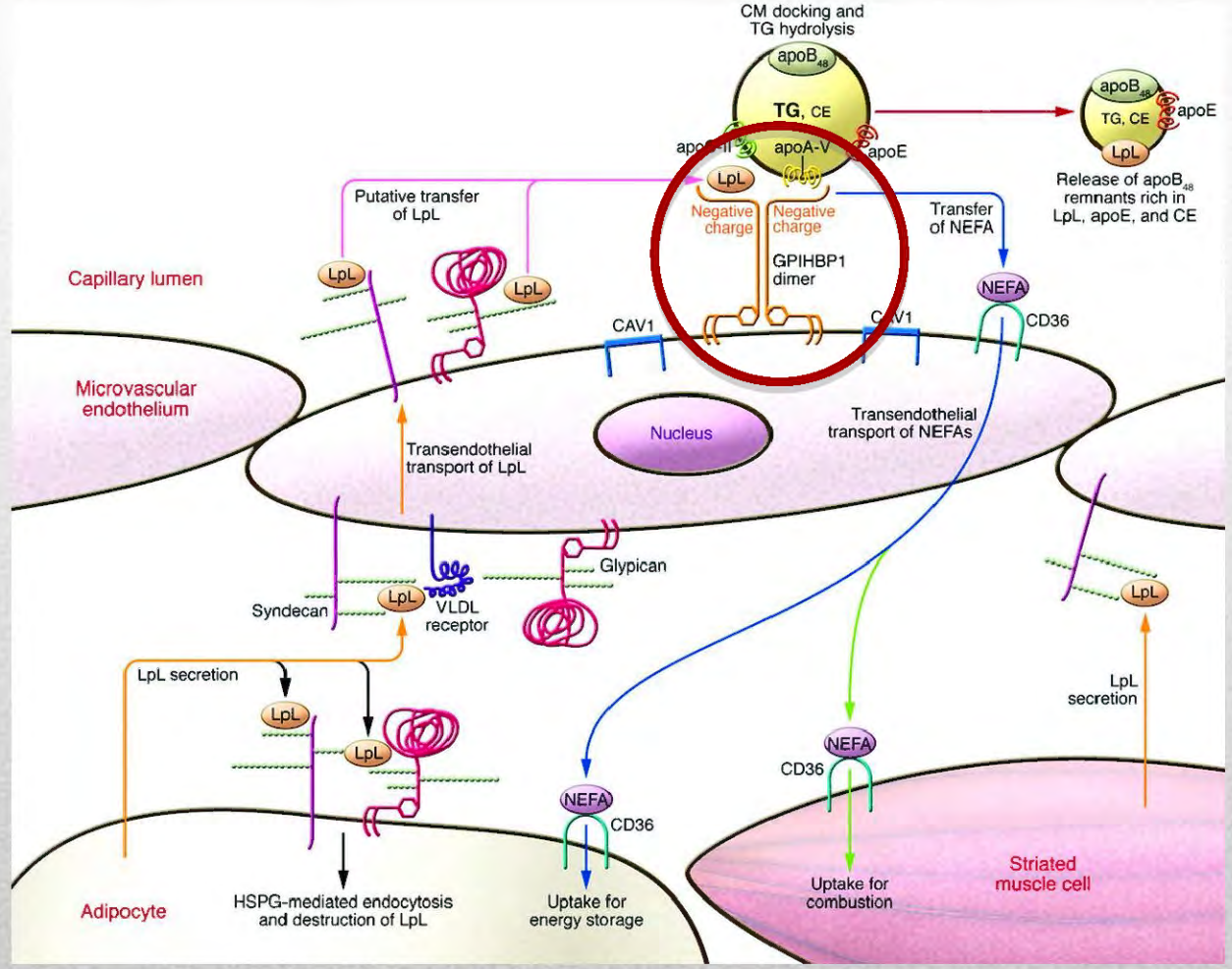
GPIHBP1 fue inicialmente identificada como una proteína de superficie celular que se unía a HDLs.
P… GPI-anchored Ly6 (como UPAR y CD59).

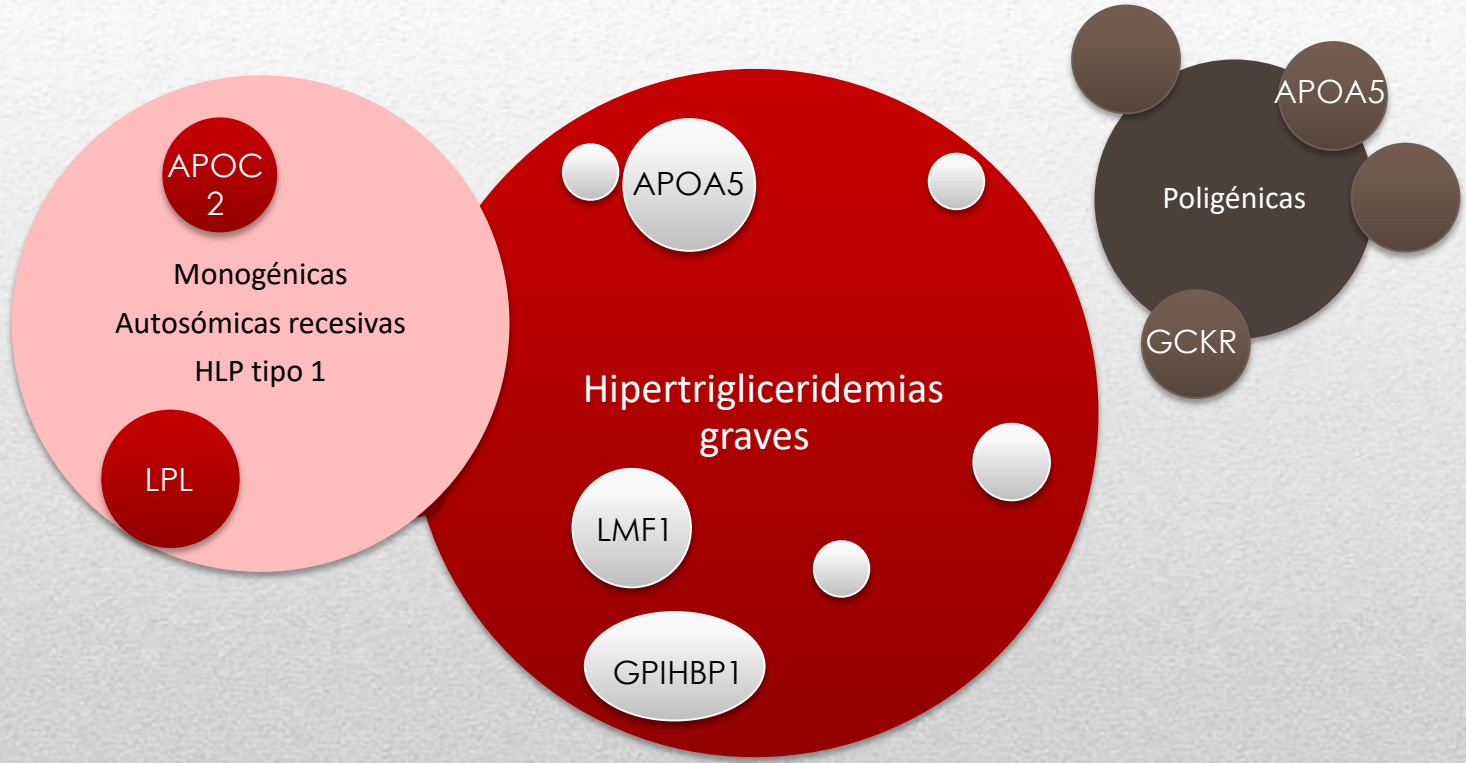
TG = 2.500-5000 mg/dl

…jido adiposo, el corazón y el músculo esquelético.
…ino… 4 dominios:

GPIHBP1 se une a LPL y QM

…bico.

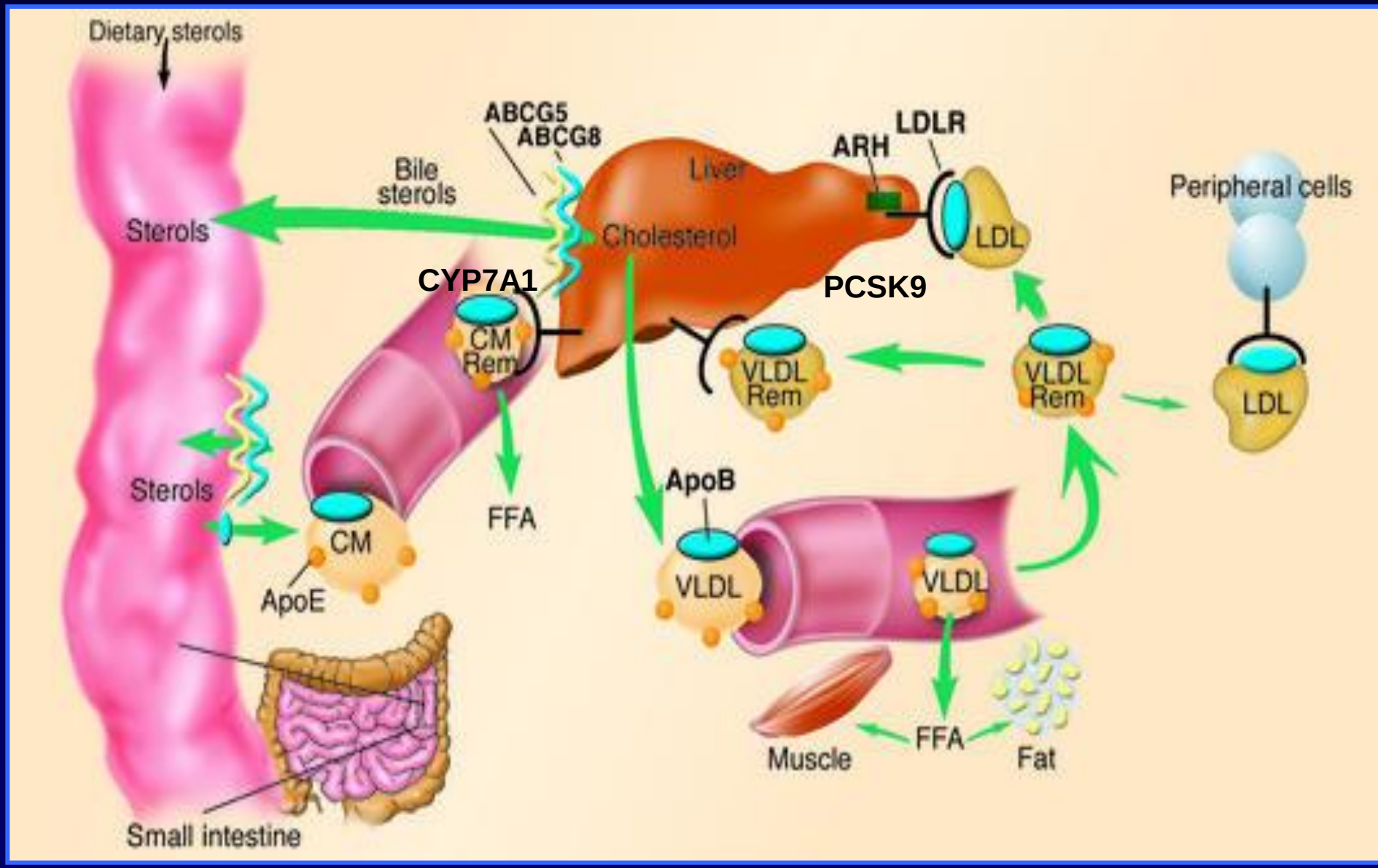

CM docking and
TG hydrolysis
apoB48
TG, CE
apoA-V
apoE
LpL
Negative charge
Negative charge
GPIHBP1 dimer
Release of apoB48 remnants rich in LpL, apoE, and CE
Putative transfer of LpL
Transfer of NEFA
Capillary lumen
Microvascular endothelium
CAV1
CAV1
NEFA
CD36
Nucleus
Transendothelial transport of LpL
Transendothelial transport of NEFAs
Syndecan
VLDL receptor
Glypican
LpL secretion
LpL secretion
Adipocyte
HSPG-mediated endocytosis and destruction of LpL
Uptake for energy storage
Uptake for combustion
Striated muscle cell


APOC 2
Monogénicas
Autosómicas recesivas
HLP tipo 1
LPL
APOA5
Hipertrigliceridemias graves
LMF1
GPIHBP1
APOA5
Poligénicas
GCKR

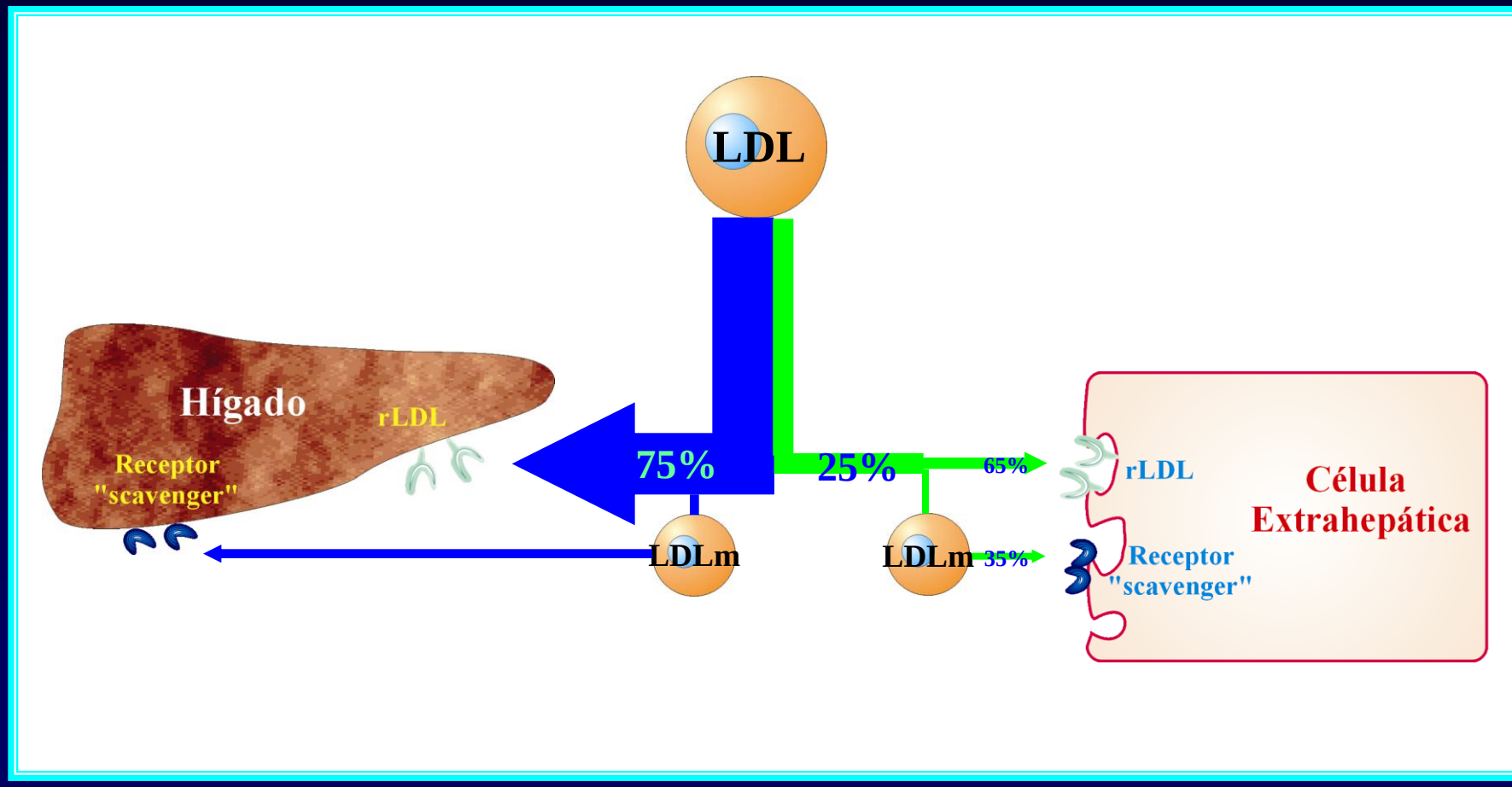
HIPERTRIGLICERIDEMIAS PRIMARIAS

- Aumento de la producción hepática
  - Cromosoma 1: Hiperlipemia Familiar combinada (USF1 ?)
  - Hipertrigliceridemia familiar (?, USF1)
- Defectos catabolismo partículas ricas en TG
  - Periféricos
    - Deficiencia de Lipoprotein lipasa
    - Deficiencia de apo C-II
    - Deficiencia de apoAV
    - Deficiencia de LMF1
    - Deficiencia de GPIHBP1
  - Hepáticos
    - Deficiencia de Lipasa hepática
- Disminución captación hepática remanentes
  - Defectos ligando:
    - Mutaciones apoE(2/2): Hiperlipoproteinemia tipo III
  - Defectos receptor LRP (?)

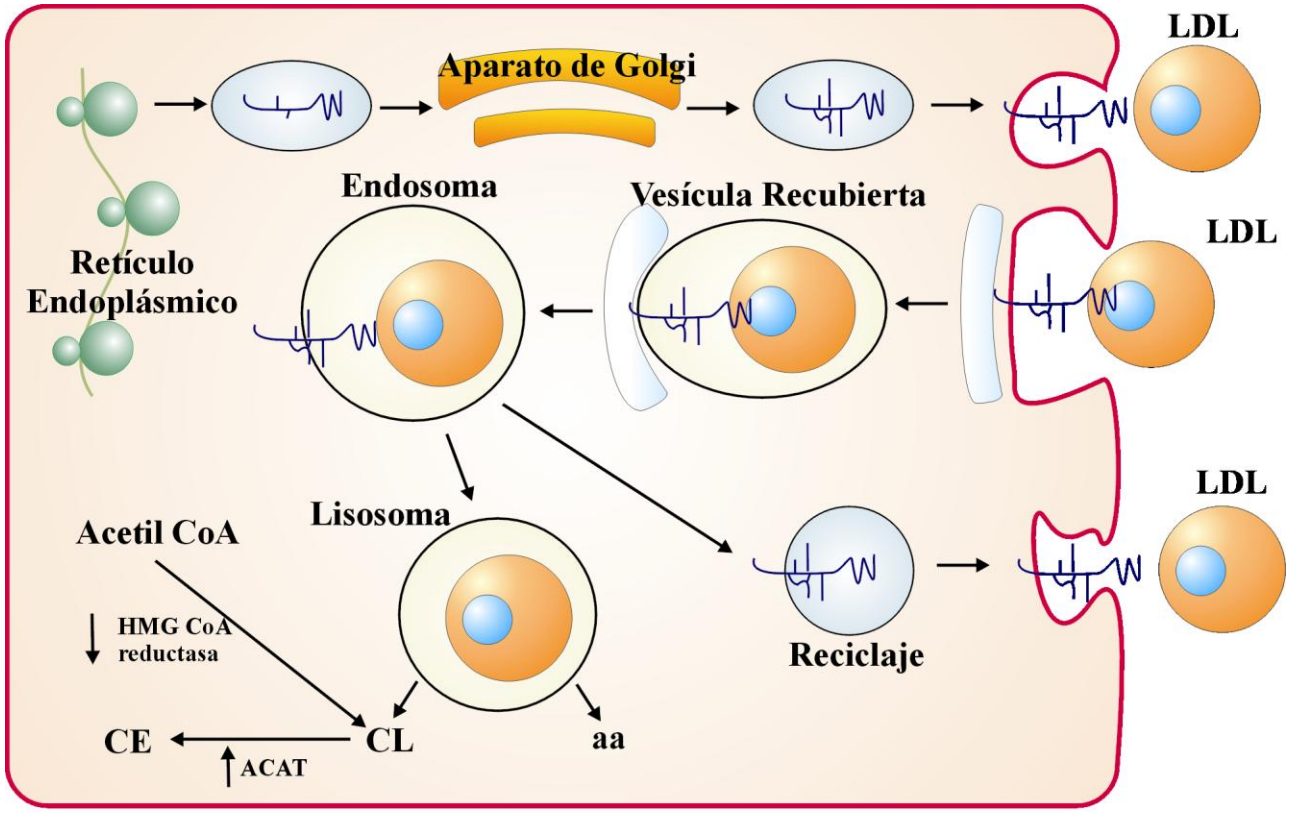
Metabolismo lipídico



RETIRADA DE LAS LDL



PROCESO DE ENDOCITOSIS MEDIADO POR EL RECEPTOR LDL



Metabolismo de las LDL

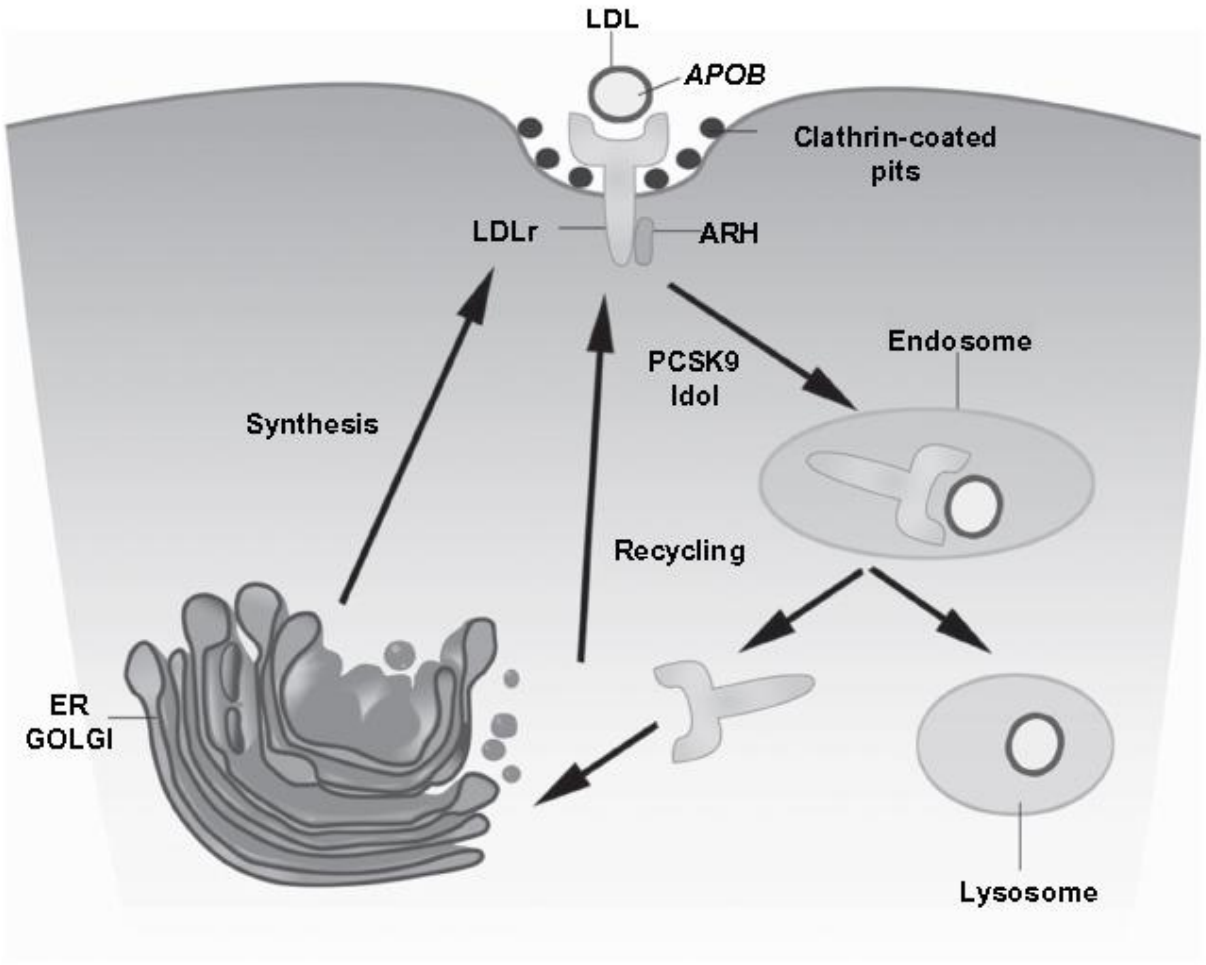
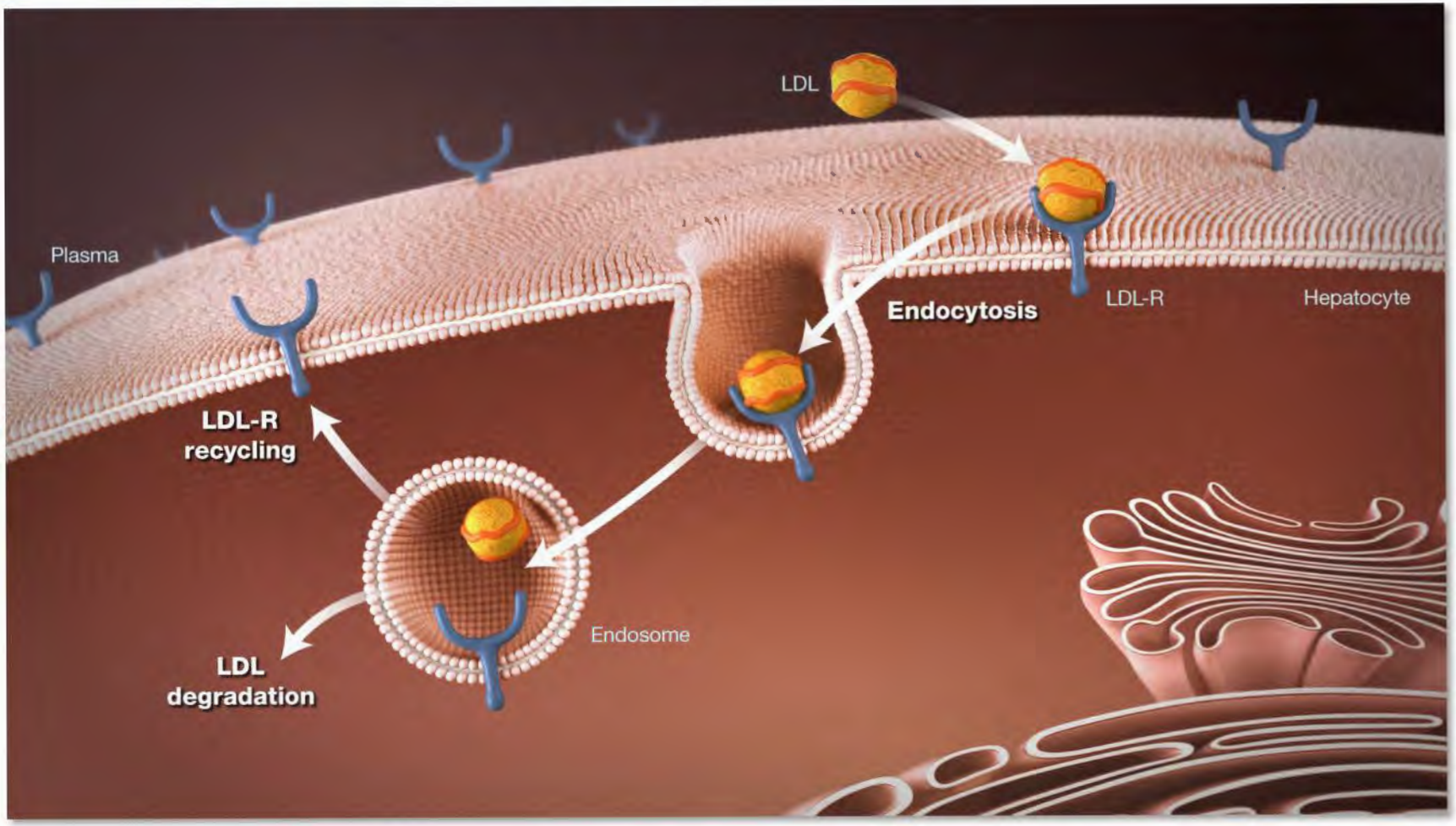


Figure 1 The LDL receptor pathway.

Hepatic LDL-Rs Play a Key Role in Regulating Plasma LDL-C Levels



1. Brown MS, Goldstein JL. *Proc Natl Acad Sci* U S A. 1979;76:3330-3337.
2. Steinberg D, Witztum JL. *Proc Natl Acad Sci* U S A. 2009;106:9546-9547.
3. Goldstein JL, Brown MS. *Arterioscler Thromb Vasc Biol*. 2009;29:431-438.

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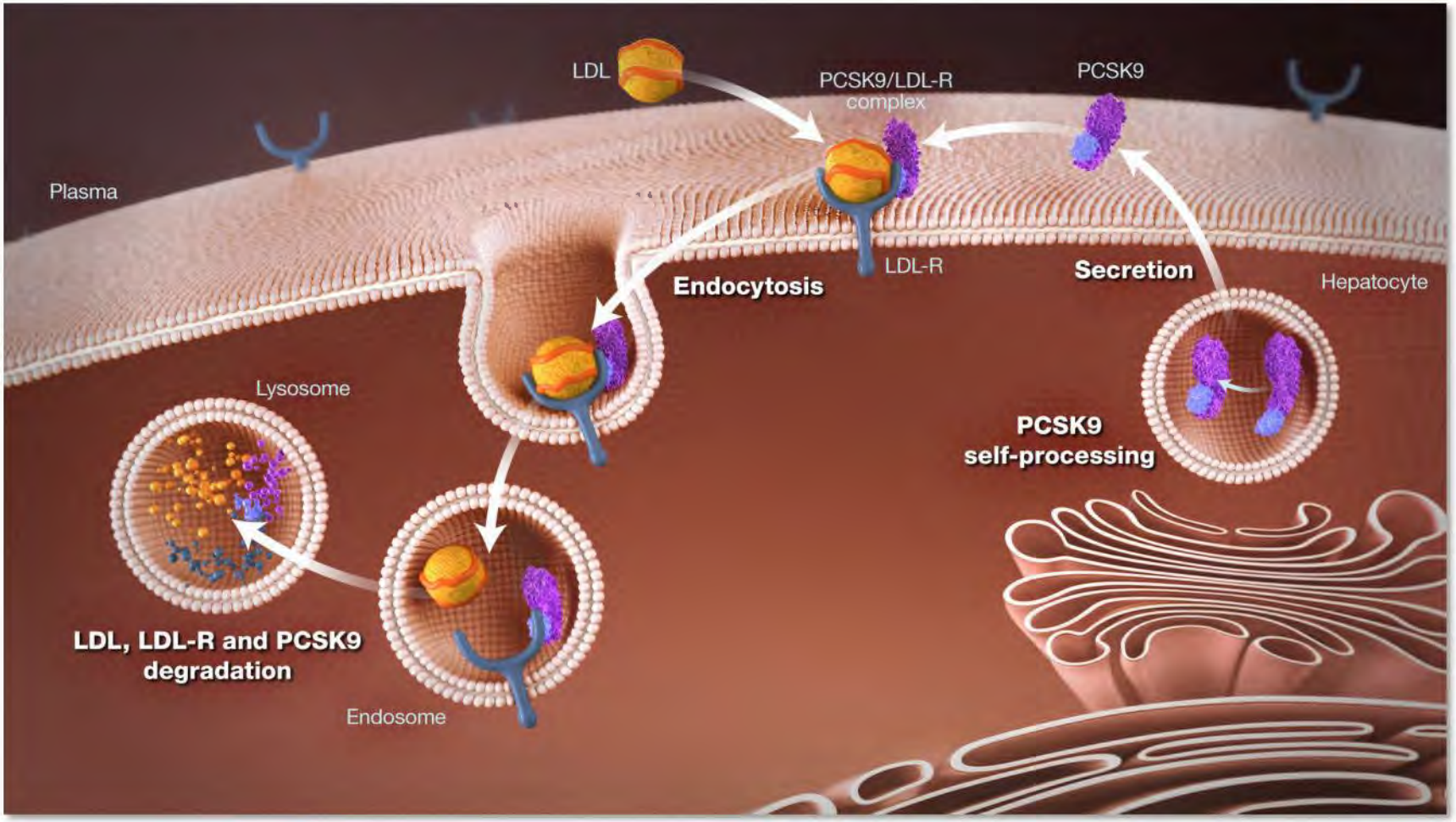
PCSK9 Regulates the Surface Expression of Hepatic LDL-Rs



1. Qian YW, Schmidt RJ, Zhang Y, et al. *J Lipid Res.* 2007;48:1488-1498.
2. Horton JD, Cohen JC, Hobbs HH. *J Lipid Res.* 2009;50(suppl):S172-S177

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THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

N ENGL J MED 354;12 WWW.NEJM.ORG MARCH 23, 2006

Table 1. Nonsense Mutations in *PCSK9* and Cardiovascular Risk Factors among 3363 Black Participants in the Study.*

Variable	Noncarriers	Carriers			P Value†
		PCSK9^{R46X}	*PCSK9*^{G670X}	*PCSK9*^{R46X} or *PCSK9*^{G670X}	
Mutation status — no. of subjects (%)	3278 (97.4)	26 (0.8)	60 (1.8)	85 (2.6)‡	
Age — yr§	53±6	54±6	53±6	54±6	0.61
Male sex — %	37	42	27	31	0.22
Body-mass index	29.6±6.1	28.7±4.4	29.7±5.5	29.5±5.2	0.88
Total cholesterol — mg/dl	215±44	177±44	172±45	173±44	<0.001
Triglycerides — mg/dl	113±81	97±38	94±39	94±38	0.04
LDL cholesterol — mg/dl	138±42	103±39	100±45	100±43	<0.001
HDL cholesterol — mg/dl	55±17	55±14	54±17	55±16	0.72
Hypertension — %¶	55	42	36	37	0.001
Diabetes — %‖	18	12	13	13	0.26
Smoking — %**	30	38	23	27	0.62
Carotid-artery intima–media thickness — mm	0.73±0.16	0.72±0.17	0.69±0.11	0.70±0.13	0.04
Coronary heart disease — no. of subjects	319	0	1	1	0.008
Stroke — no. of subjects (%)	217 (6.6)	3 (11.5)	3 (5.0)	6 (7.1)	0.87
Death — no. of subjects (%)	580 (17.7)	4 (15.4)	8 (13.3)	12 (14.1)	0.39

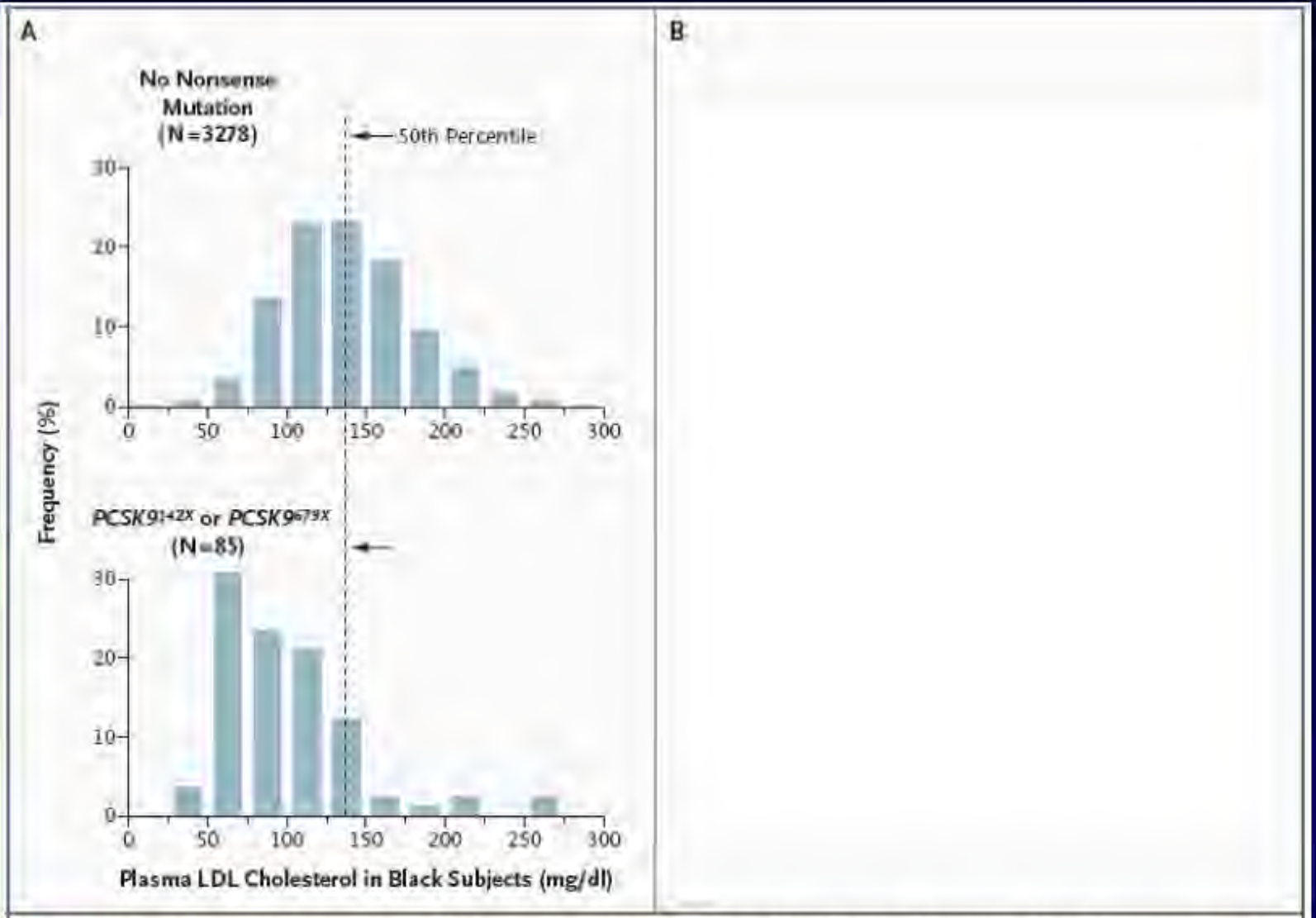


Figure 1. Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Heart Disease (Panel B) among Black Subjects, According to the Presence or Absence of a *PCSK9*^{Y142X} or *PCSK9*^{C679X} Allele.

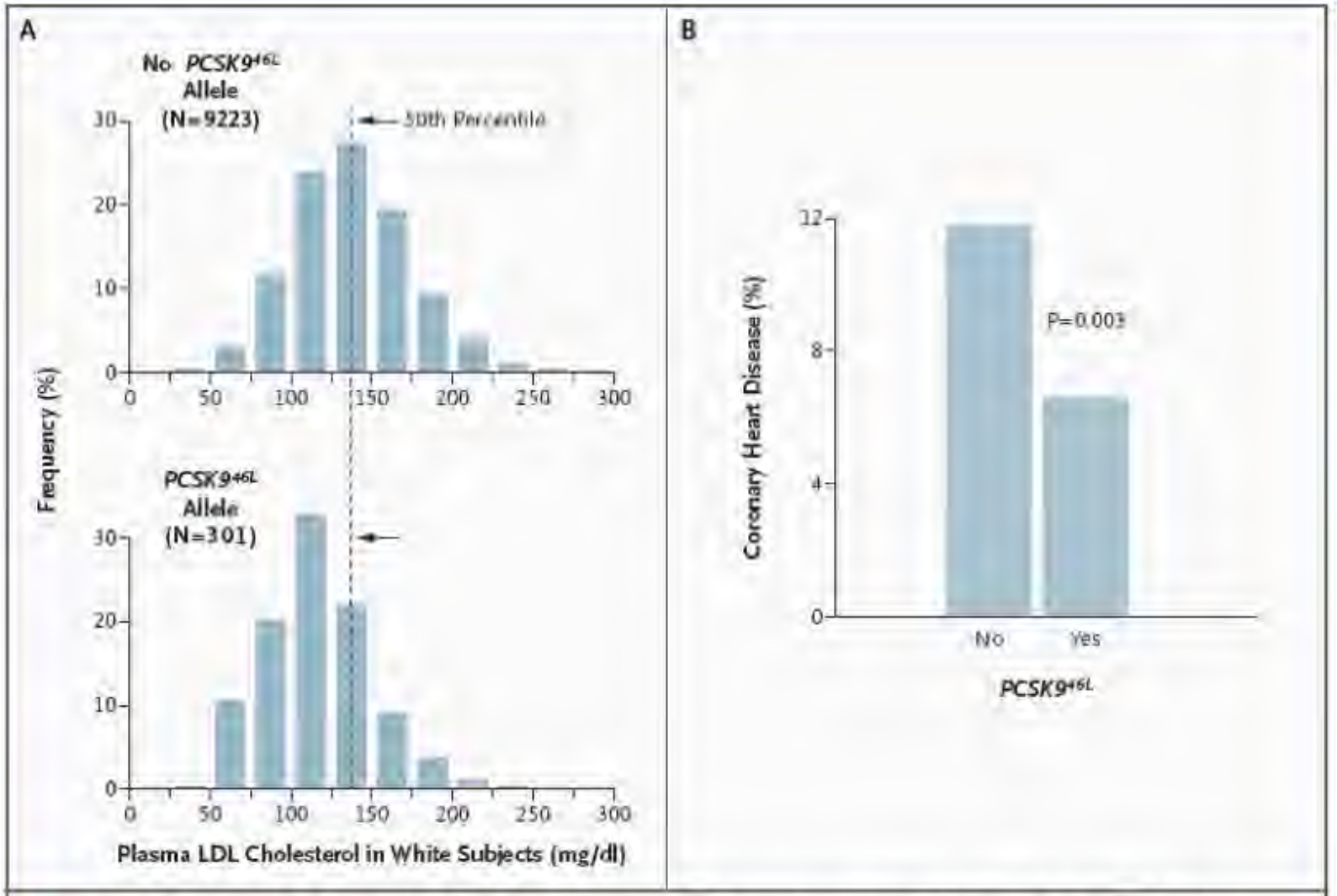
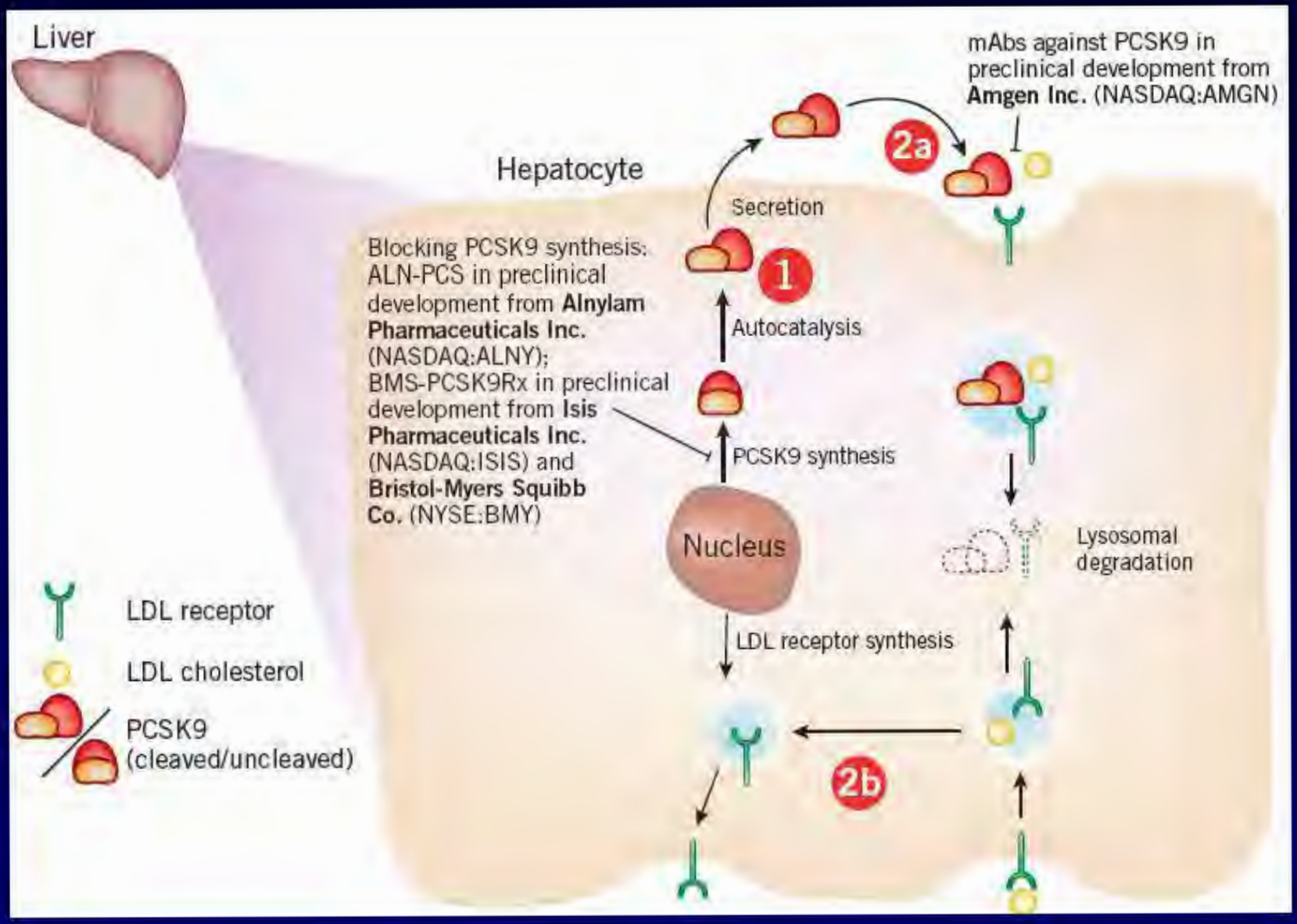
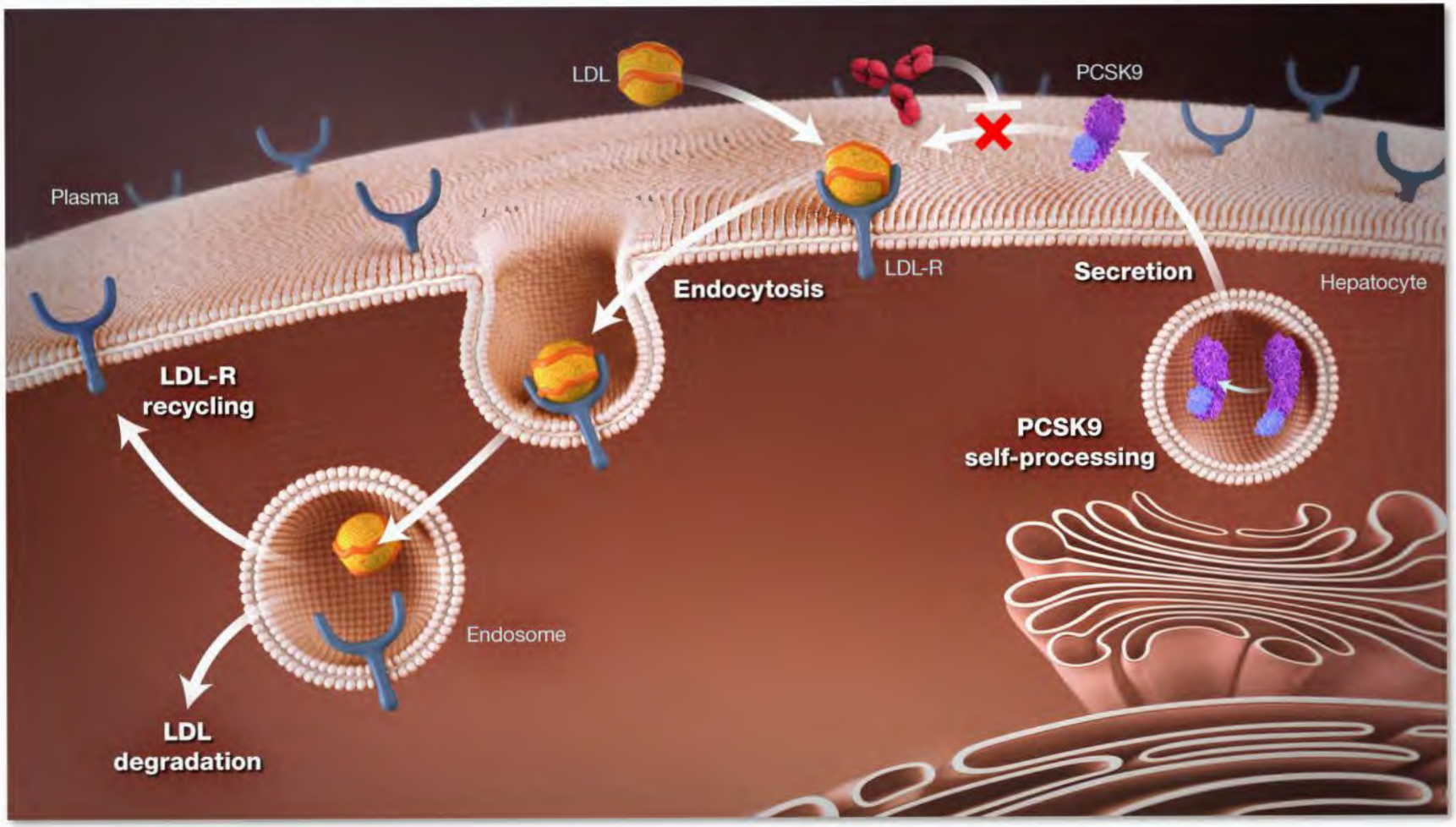


Figure 2. Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Events (Panel B) among White Subjects, According to the Presence or Absence of a *PCSK9*[46L] Allele.


Liver
Hepatocyte
mAbs against PCSK9 in preclinical development from **Amgen Inc.** (NASDAQ:AMGN)
2a
Secretion
1
Autocatalysis
Blocking PCSK9 synthesis:
ALN-PCS in preclinical development from **Alnylam Pharmaceuticals Inc.** (NASDAQ:ALNY);
BMS-PCSK9Rx in preclinical development from **Isis Pharmaceuticals Inc.** (NASDAQ:ISIS) and **Bristol-Myers Squibb Co.** (NYSE:BMY)
PCSK9 synthesis
Nucleus
Lysosomal degradation
LDL receptor synthesis
2b
LDL receptor
LDL cholesterol
PCSK9 (cleaved/uncleaved)

Anti-PCSK9 Monoclonal Antibodies (mABs) Block PCSK9/LDL-R Interaction and May Lower LDL-C Levels



1. Chan JC, Piper DE, Cao Q, et al. *Proc Natl Acad Sci U S A.* 2009;106:9820-9825.

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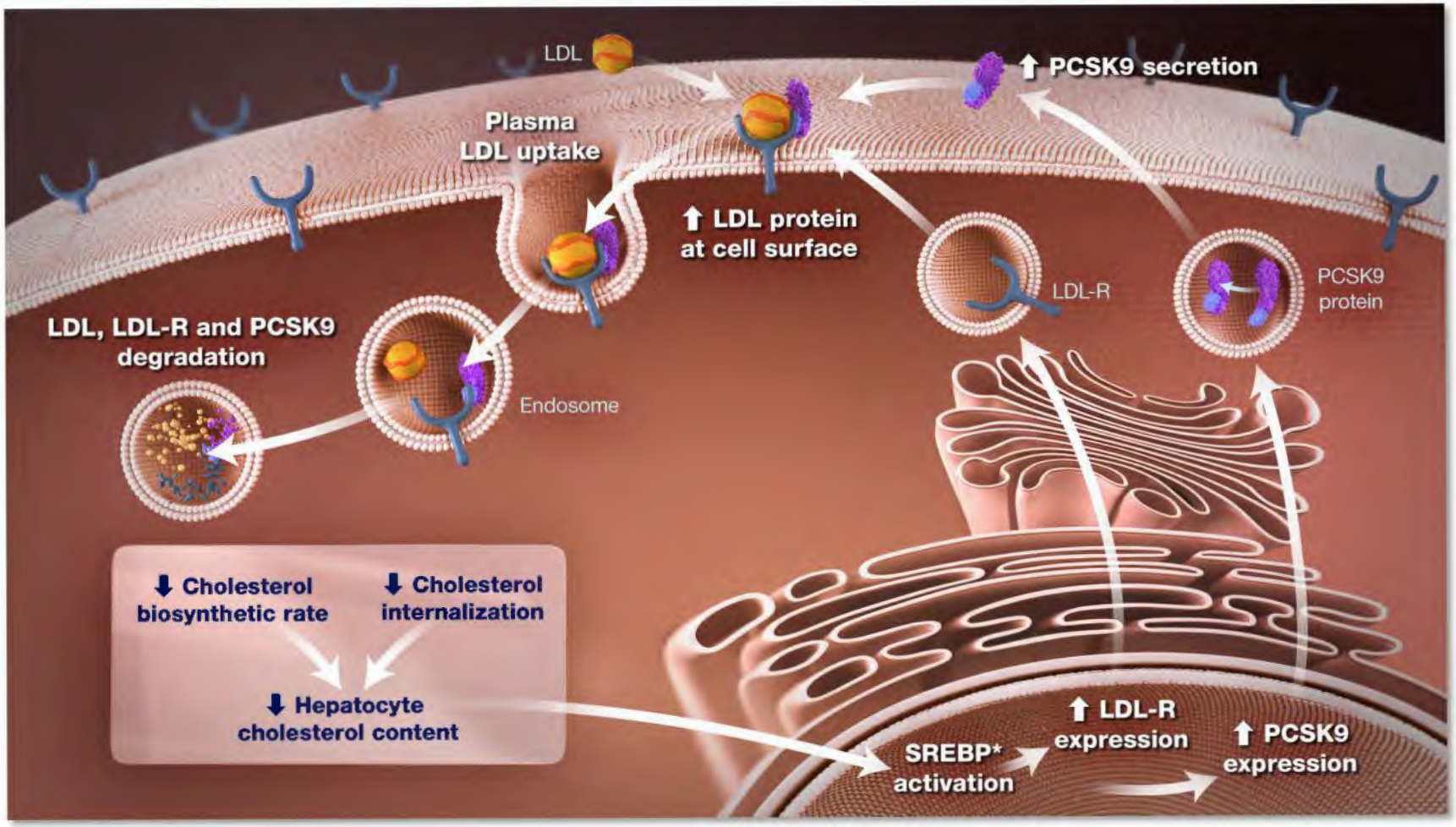
LDL-R and PCSK9 Expression Are Both Upregulated When Intercellular Cholesterol Levels Are Low



*[SREBP] = sterol regulatory element-binding protein

1. Goldstein JL, Brown MS. *Arterioscler Thromb Vasc Biol.* 2009;29:431-438.
2. Dubuc G, Chamberland A, Wassef H, et al. *Arterioscler Thromb Vasc Biol.* 2004;24:1454-1459.

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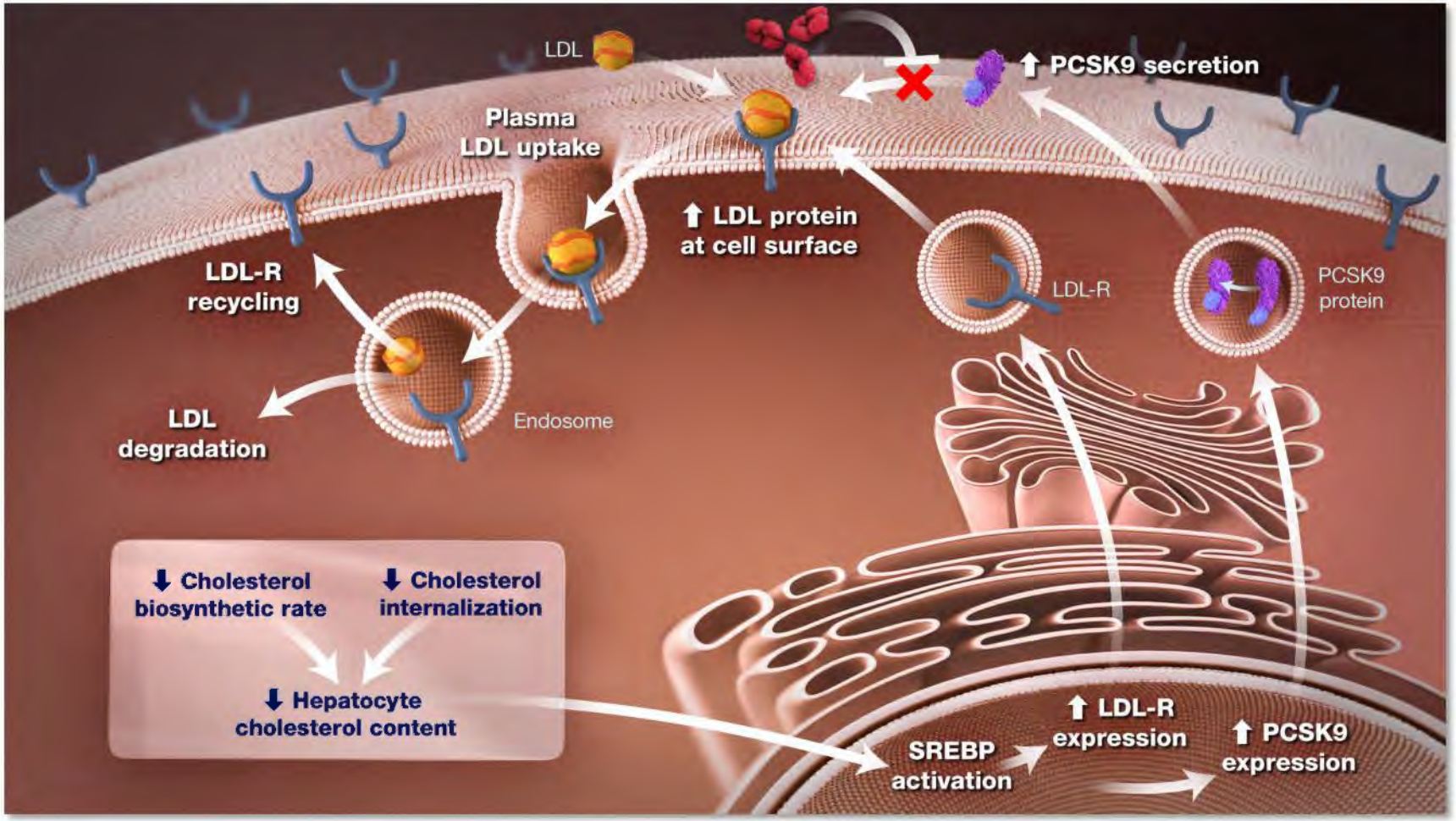
Anti-PCSK9 mAbs May Further Lower LDL-C Levels Under These Conditions



1. Chan JC, Piper DE, Cao Q, et al. *Proc Natl Acad Sci* U.S A. 2009;106:9820-9825.

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Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol

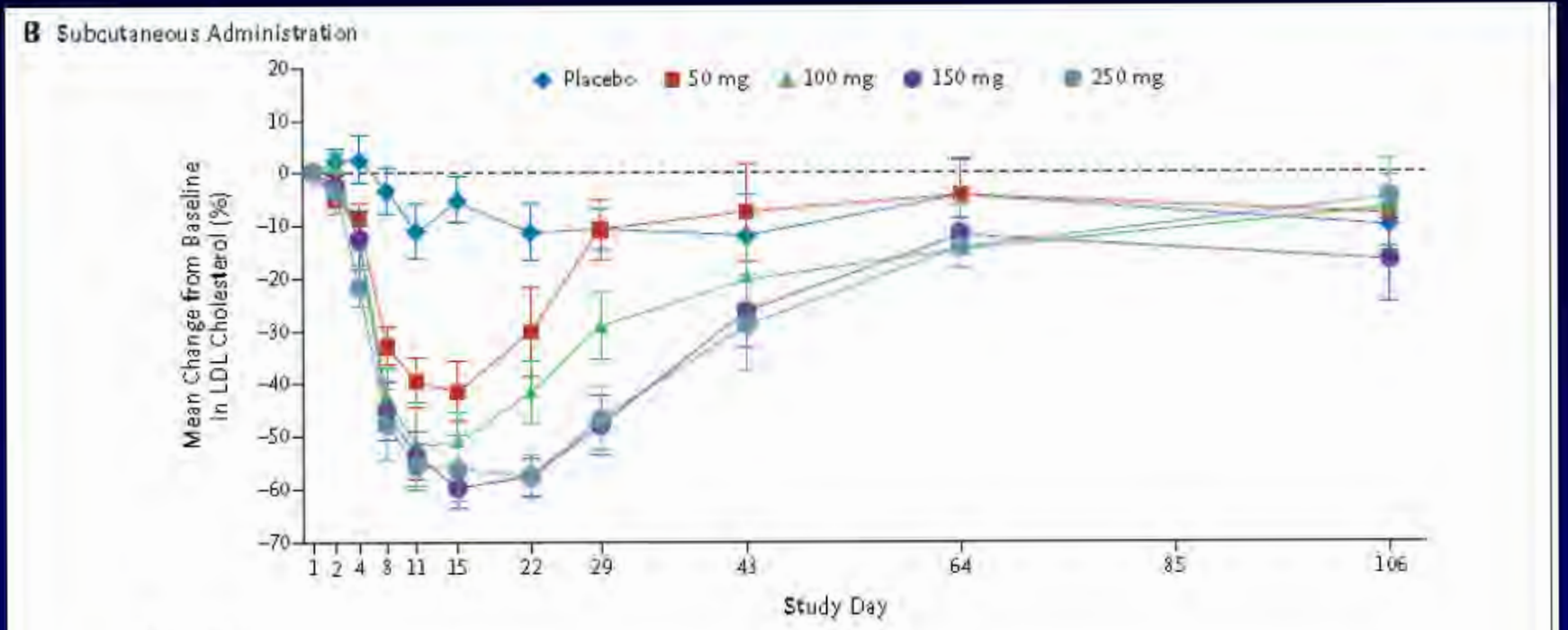


Figure 1. Mean Percent Change from Baseline in LDL Cholesterol Values among Healthy Volunteers in Single-Dose Studies.

HIPERCOLESTEROLEMIAS LDL

- Aumento de la absorción intestinal
  - Primarias:
    - ABCG5/G8 : sitosterolemia
    - Mutaciones: ABCG5/G8 (?)
    - Mutaciones: NPC1L1 (?)
  - Secundarias
    - Dietas ricas en colesterol
- Aumento de la producción hepática
  - Primarias
    - Cromosoma 1: Hiperlipemia Familiar combinada (USF1 ?)
    - Ligados a Lp(a): Hiper-Lp(a)
  - Secundarias
    - Obesidad, dietas ricas en grasa saturada
    - Síndrome nefrótico
- Disminución captación hepática
  - Primarias
    - Defectos ligando: ApoB 100 defectuosa familiar
    - Defectos receptor LDL: Gen receptor LDL: Hipercolesterolemia Familiar
    - Mutaciones en PCSK9 con ganancia de función
  - Secundarias
    - Hipotiroidismo
    - Fármacos: ciclosporina
- Defectos eliminación colesterol bilis
  - Primarias
    - ABCG5/G8 (?)
    - Deficiencia de Cholesterol 7 alpha-hydroxylasa (CYP7A1)
  - Secundarias
    - Colestasis

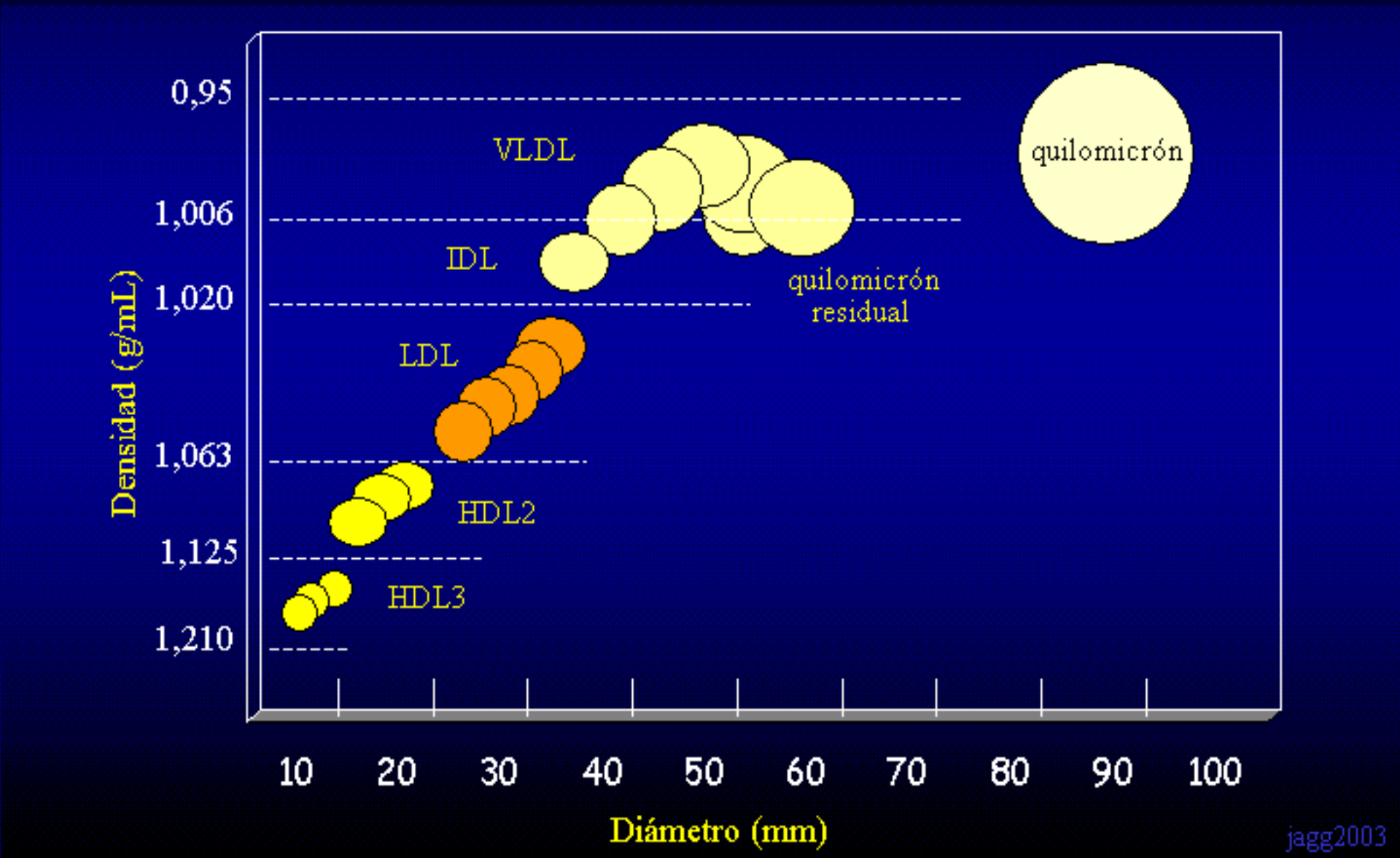
GENETIC HYPERCHOLESTEROLEMIAS

- **Monogenic (1/500)**
  - **Autosomal dominant**
    - **Familial Hypercholesterolemia (*LDLR*): 60-80%**
    - **Familial Defective ApoB-100 (*APOB*): 1-5%**
    - **FH 3 (*PCSK9*): 0-3%**
    - **Unknown 20-40%**
  - **Autosomal recessive (<1/1.000.000)**
    - **Autosomal recessive hypercholesterolemia (*LDLRAP1*)**
    - **Sitosterolemia (ABCG5/ABCG8)**
- **Complex diseases (1/50)**
  - **Familial combined hyperlipidemia (?)**
- **Polygenic (1/25)**
  - **APOE, APOB, LDLR, PSCK9,…**

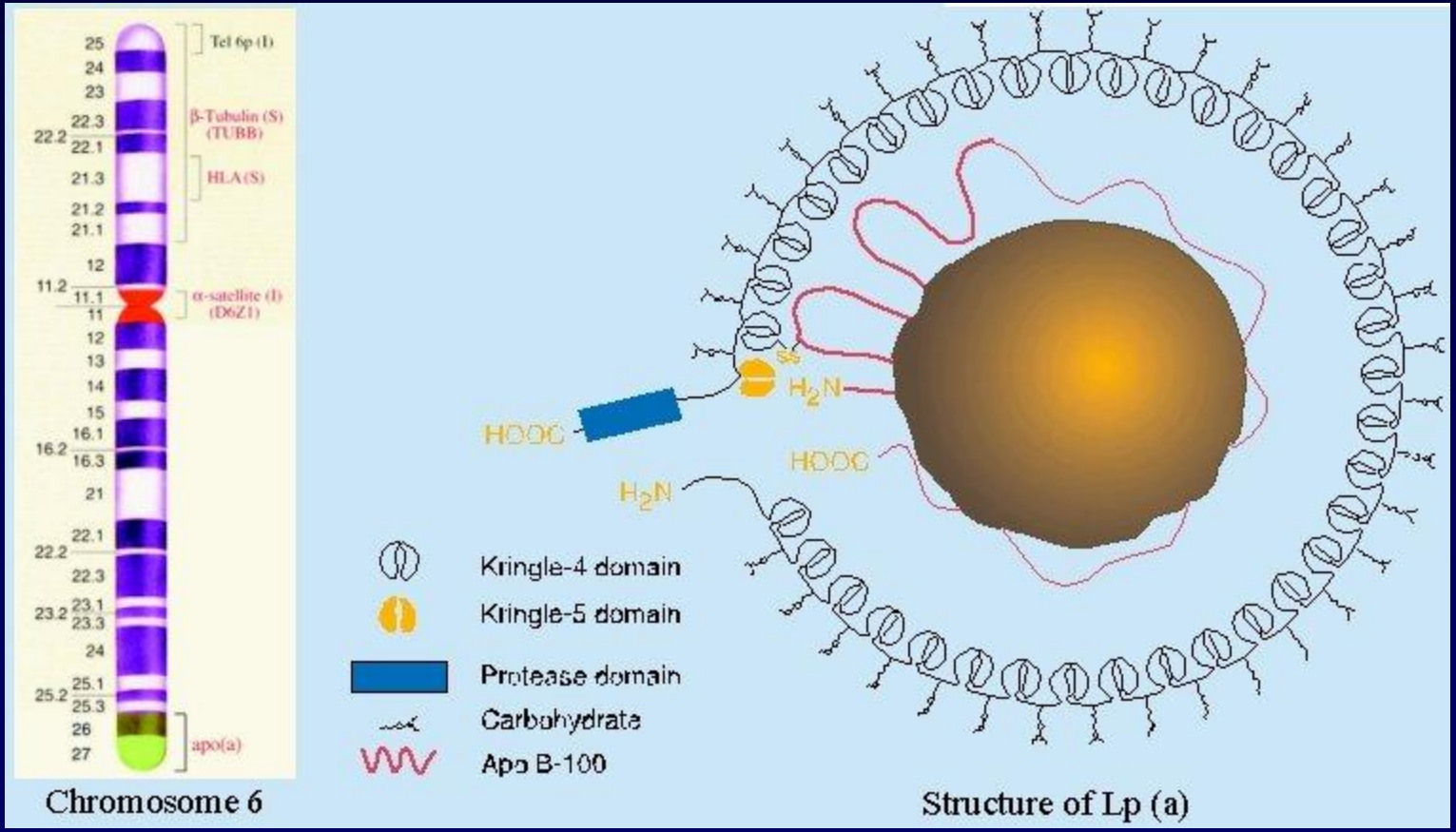
Retos terapéuticos más allá del colesterol LDL

- Lipoproteína(a), lp(a)
- Apolipoproteína B, (apoB)
- Colesterol no-HDL, (c-no-HDL)

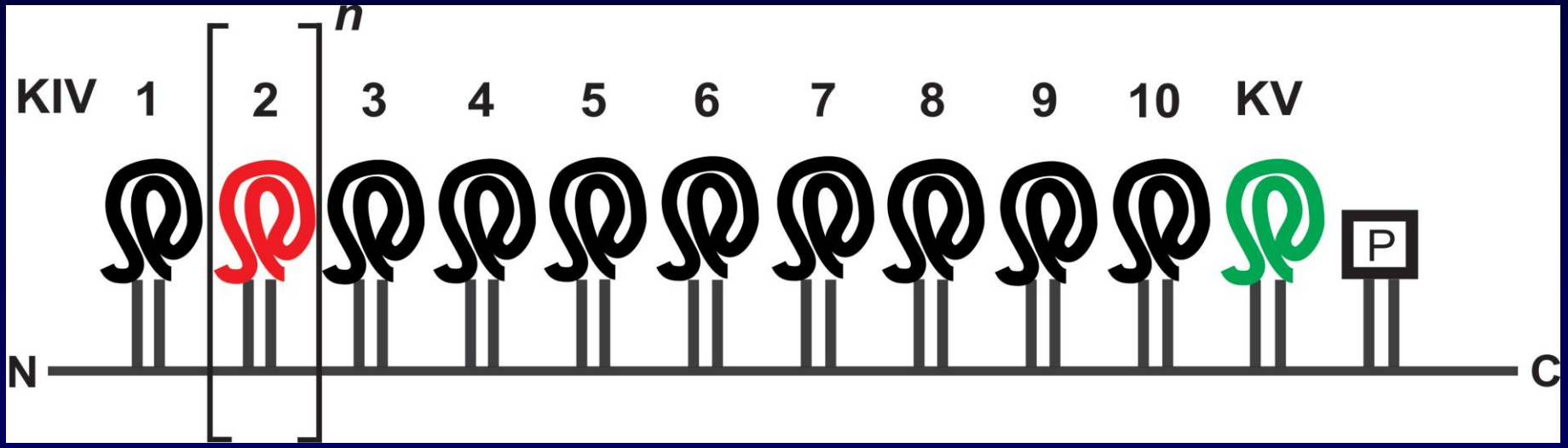
Tamaño de las lipoproteínas



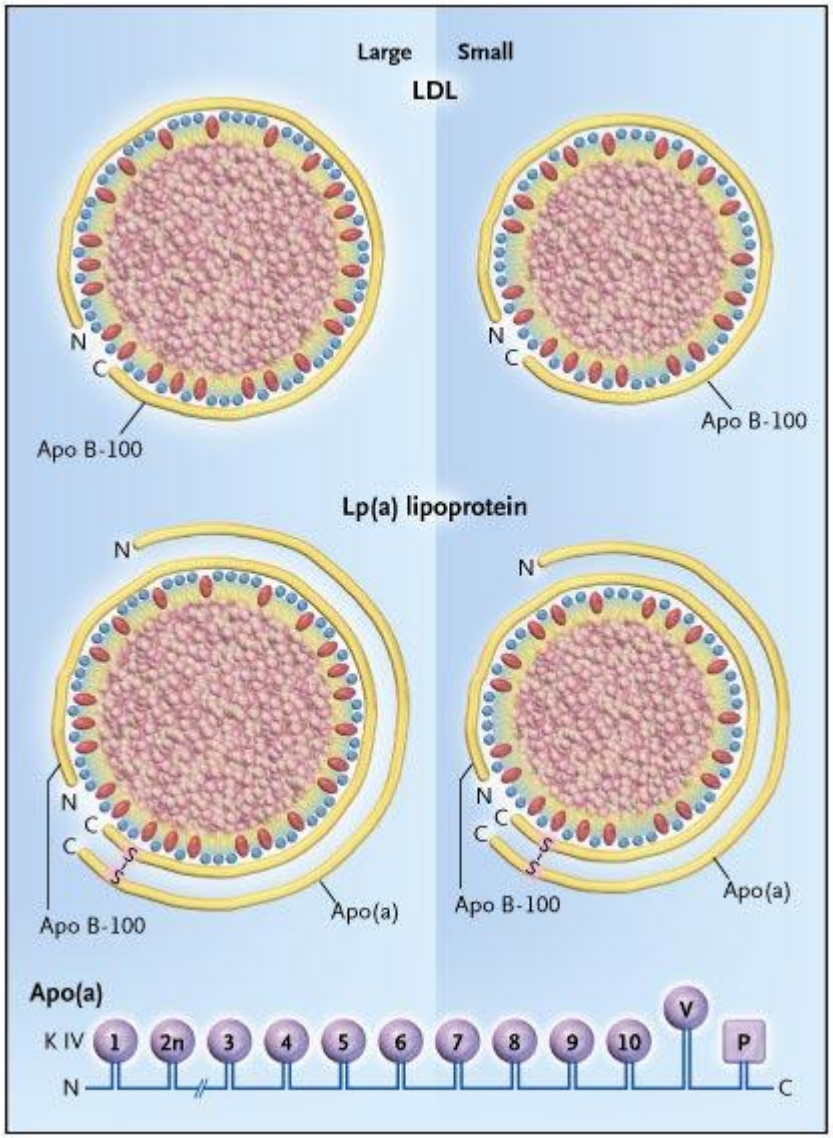
Lipoproteína (a) Lp(a)



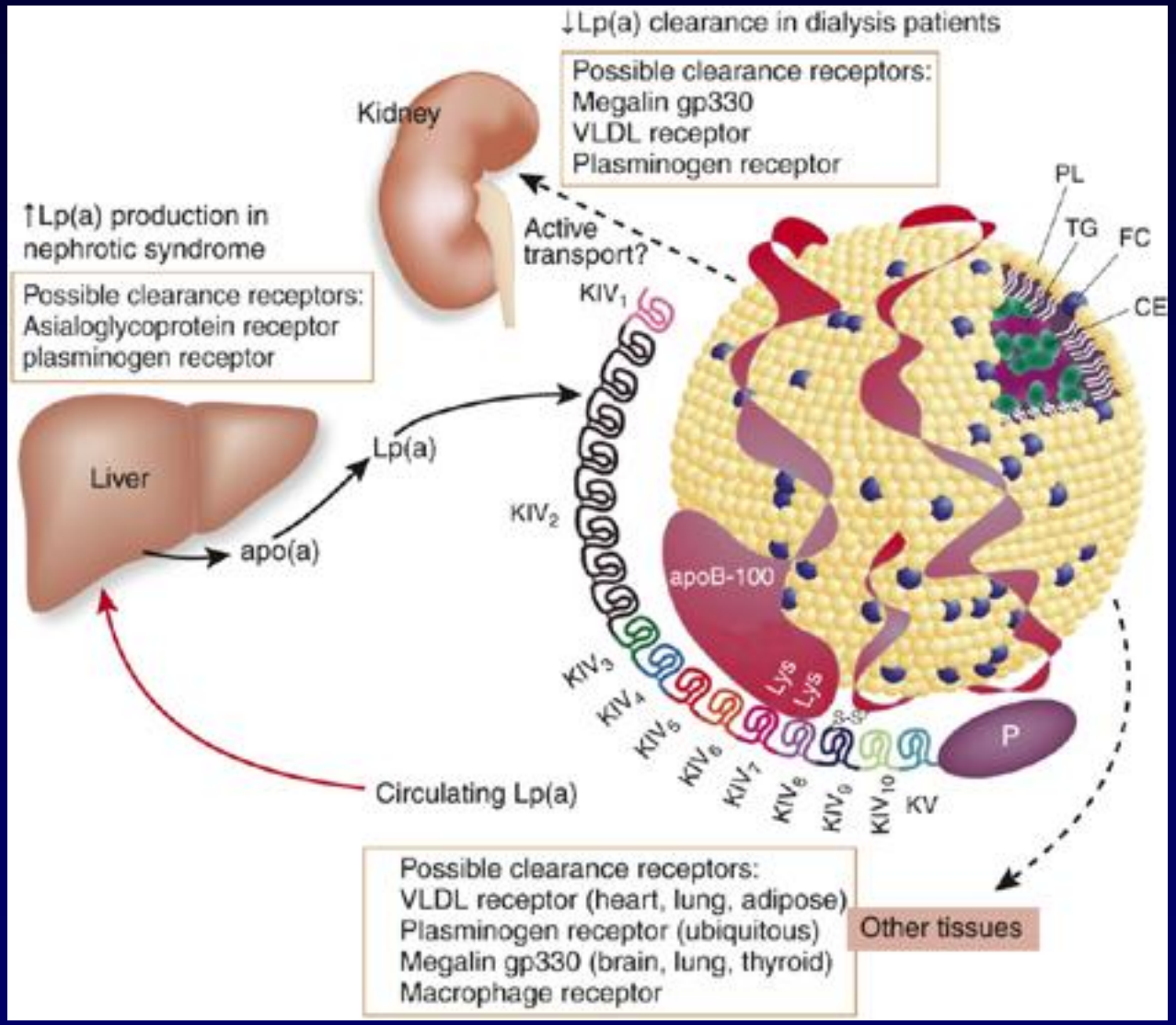
Apo(a)



Partículas LDL y Lp(a)



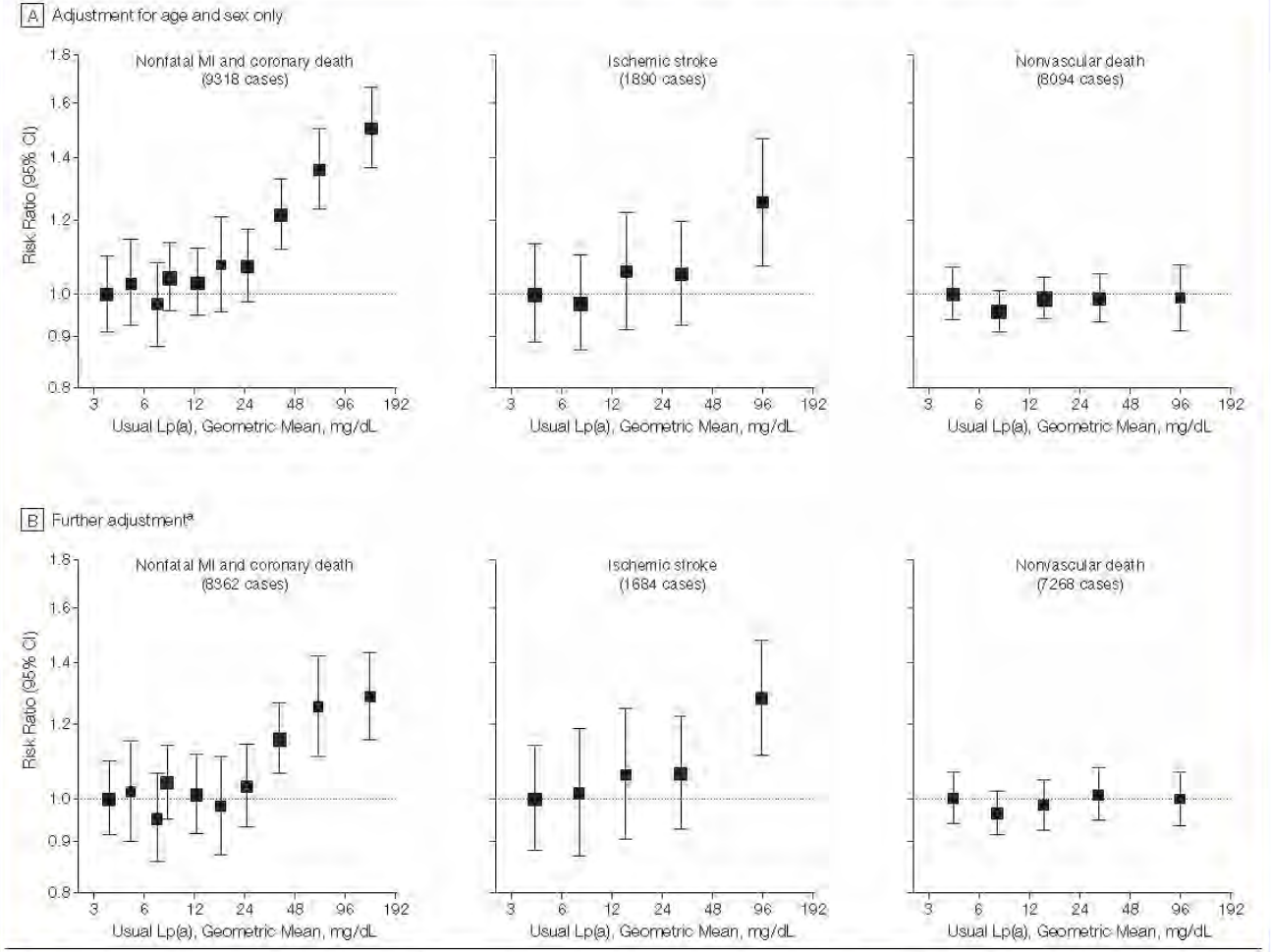
Metabolismo de Lp(a)



Lipoprotein(a) Concentration and the Risk of Coronary Heart Disease, Stroke, and Nonvascular Mortality

JAMA. 2009;302(4):412-423

Figure 2. Risk Ratios for Coronary Heart Disease, Ischemic Stroke, or Nonvascular Death by Quantile of Usual Lp(a) Level



Lp(a) indicates lipoprotein(a); MI, myocardial infarction. Sizes of data markers are proportional to the inverse of the variance of the risk ratios. Confidence intervals (CIs) were calculated using a floating absolute risk technique. Studies involving fewer than 10 cases of any outcome were excluded from the analysis of that outcome.

[a]Further adjustment for usual levels of systolic blood pressure, smoking status, history of diabetes, body mass index, and total cholesterol. The x- and y-axes are shown on a log scale. Lowest quantiles are referents.

Lipoprotein(a) levels, apo(a) isoform size, and coronary heart disease risk in the Framingham Offspring Study

TABLE 4. Hazard ratios for incident CHD in FOS men by baseline Lp(a) levels (upper tertile vs. lower tertile) or apo(a) isoform size (lower tertile vs. upper tertile)

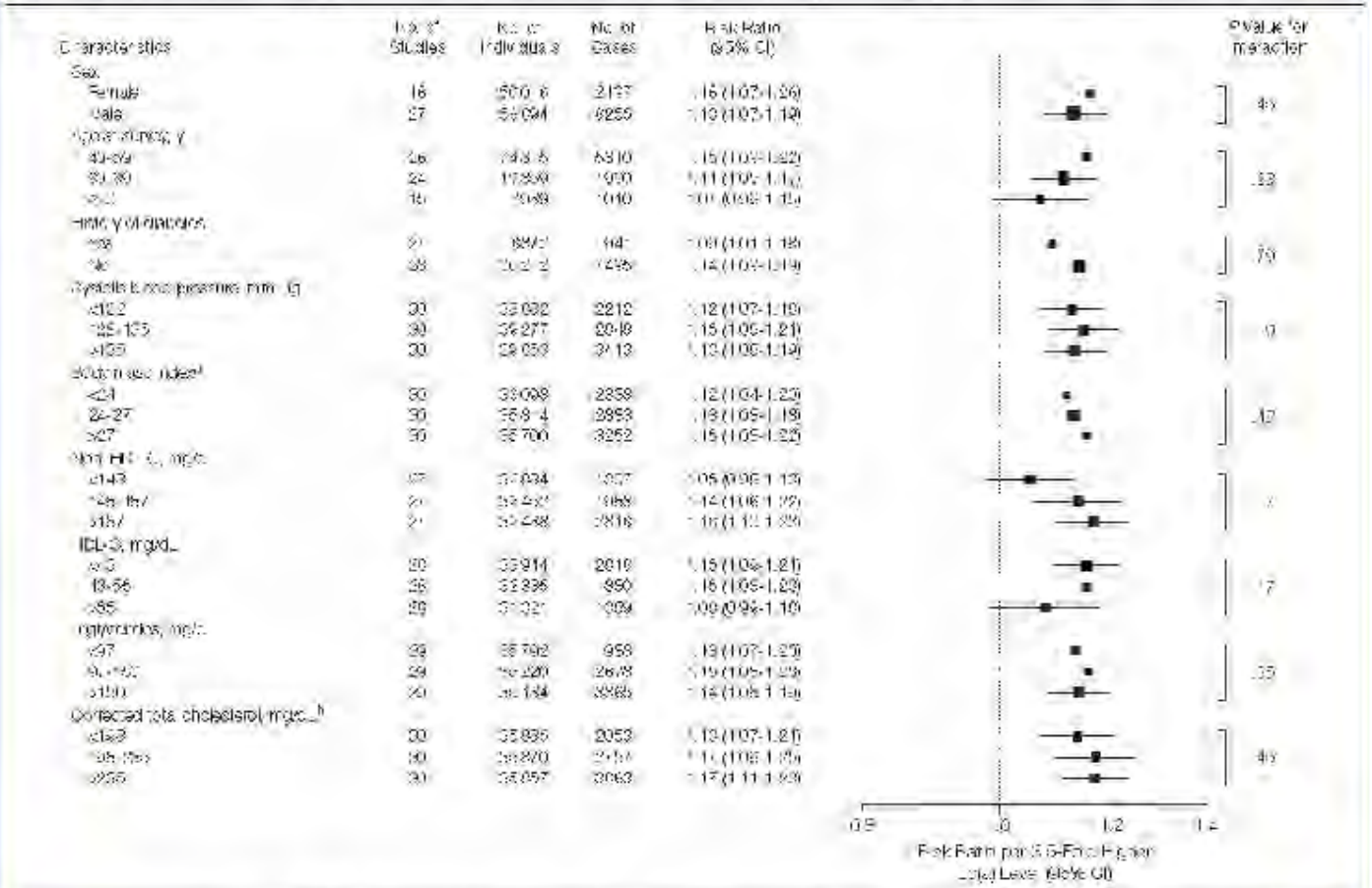
	HR	CI	P	HR	CI	P
Model	Lp(a) (NWRL)			Lp(a) (Wako)		
1	2.23	1.33–1.74	0.003	2.36	1.36–4.09	0.003
2	2.48	1.46–4.21	0.0008	2.69	1.51–4.78	0.0008
3	2.57	1.50–4.40	0.0006	2.69	1.51–4.81	0.0008
4	2.36	1.37–4.07	0.002	2.52	1.40–4.53	0.003
5	2.45	1.20–4.99	0.013	2.74	1.35–5.58	0.004
			Predominant apo(a) isoform			
1	1.70	1.04–2.77	0.03	1.70	1.04–2.77	0.03
2	1.76	1.07–2.88	0.03	1.76	1.07–2.88	0.03
3	1.78	1.09–2.93	0.03	1.78	1.09–2.93	0.03
4	1.68	1.02–2.77	0.04	1.68	1.02–2.77	0.04
6	1.15	0.59–2.25	0.67	1.08	0.54–2.12	0.83

Model 1 covariate: age; Model 2 covariates: age, BMI, smoking, hypertension, and diabetes; Model 3 covariates: age, BMI, smoking, hypertension, diabetes, TC, log-TG, and HDL-C; Model 4 covariates: age, BMI, smoking, hypertension, diabetes, TC, log-TG, HDL-C, and use of cholesterol-lowering medications and/or niacin; Model 5 covariates as in Model 4, plus predominant apo(a) isoform size; Model 6 covariates as in Model 4, plus Lp(a) levels.

Lipoprotein(a) Concentration and the Risk of Coronary Heart Disease, Stroke, and Nonvascular Mortality

JAMA. 2009;302(4):412-423

Figure 4. Risk Ratios for Coronary Heart Disease per 3.5-Fold (1 SD) Higher Usual Lp(a) Level, by Age and Thirds of Individual Characteristics



Lp(a) = lipoprotein(a); HDL-C, high-density lipoprotein cholesterol; SD, standard deviation. Sizes of data markers are proportional to the inverse of the variance of the risk ratios. Risk ratios are adjusted for age, usual levels of body mass index, blood pressure, smoking status, history of diabetes, body mass index, and total cholesterol and are stratified where appropriate by sex and study group. Strata with fewer than 5 cases per stratum were excluded from analyses.

[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.

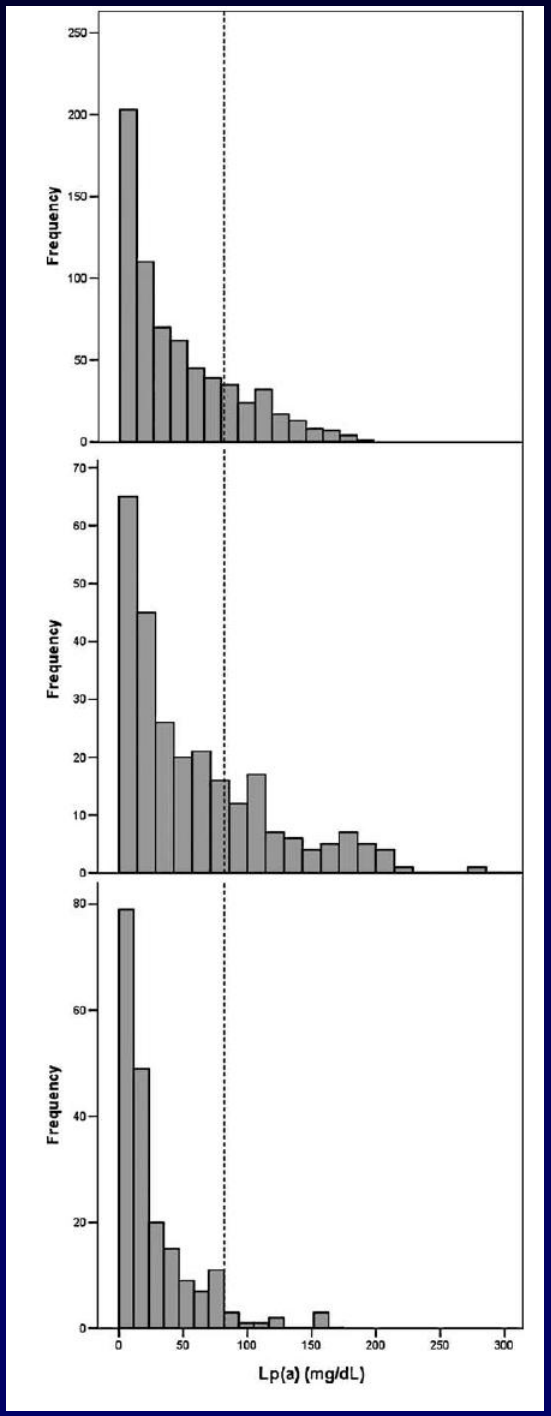
[b] Correction for the cholesterol content of Lp(a) was made by subtracting estimated Lp(a) cholesterol values from total cholesterol. Lp(a) cholesterol was estimated from Lp(a) total mass using the following equation: [Lp(a)–cholesterol (mg/dL)] = [0.15 × Lp(a) (mg/dL)] − 1.2.[24]

Uso clínico de la determinación de Lp(a)

- Sujetos con enfermedad cardiovascular prematura sin factores de riesgo llamativos
- Familiares de primer grado de sujetos con hiper Lp(a) y enfermedad cardiovascular prematura
- Historia familiar de muerte súbita prematura
- Diagnóstico de hipercolesterolemias primarias

Cálculo del colesterol unido a Lp(a)
Fórmula de Dahlen

Lp(a)-adjusted LDL cholesterol was calculated as recommended by Dahlen (Dahlen 1990; Dahlen 1992) as follows (in mg/dl): total cholesterol − triglycerides/5 − HDL cholesterol − 0.3×Lp(a).



Distribución de Lp(a)

Conclusions: HyperLp(a) is responsible for ADH in approximately 6% of nonLDLR/nonAPOB subjects.

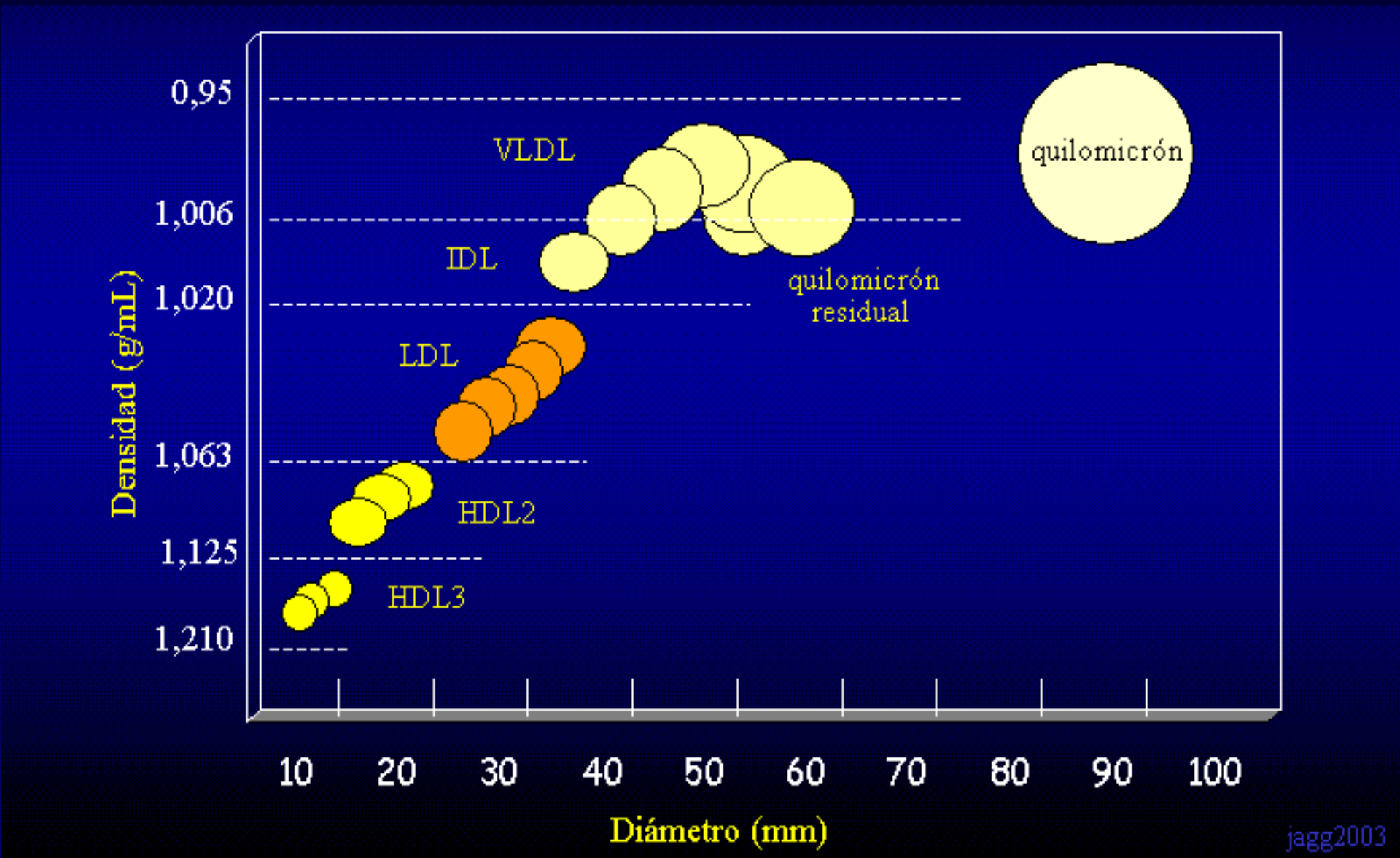
J Inherit Metab Dis (2007) 30:970–977

E. Meriño-Ibarra · E. Jarauta · A. Cenarro · D. Recalde · Á. L. García-Otín · F. Civeira (✉)
Lipid Unit and Molecular Research Laboratory, Hospital Universitario Miguel Servet, Instituto Aragonés de Ciencias de la Salud, Avda Isabel La Católica 1–3, 50009 Zaragoza, Spain
e-mail: civeira@unizar.es

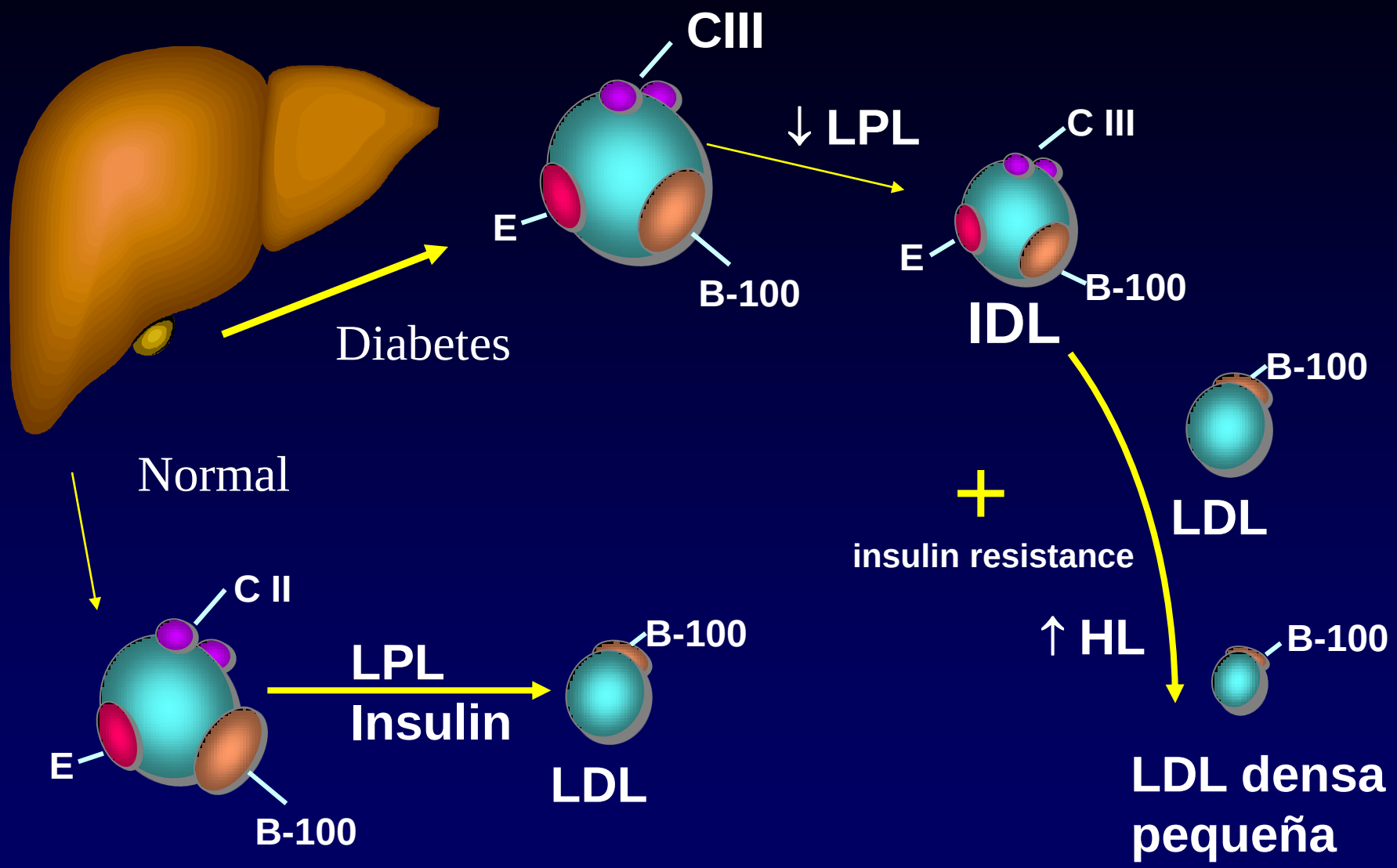
Retos terapéuticos más allá del colesterol LDL

- Lipoproteína(a), lp(a)
- Apolipoproteína B, (apoB)
- Colesterol no-HDL, (c-no-HDL)

Tamaño de las lipoproteínas



Metabolismo de LDL en Diabetes



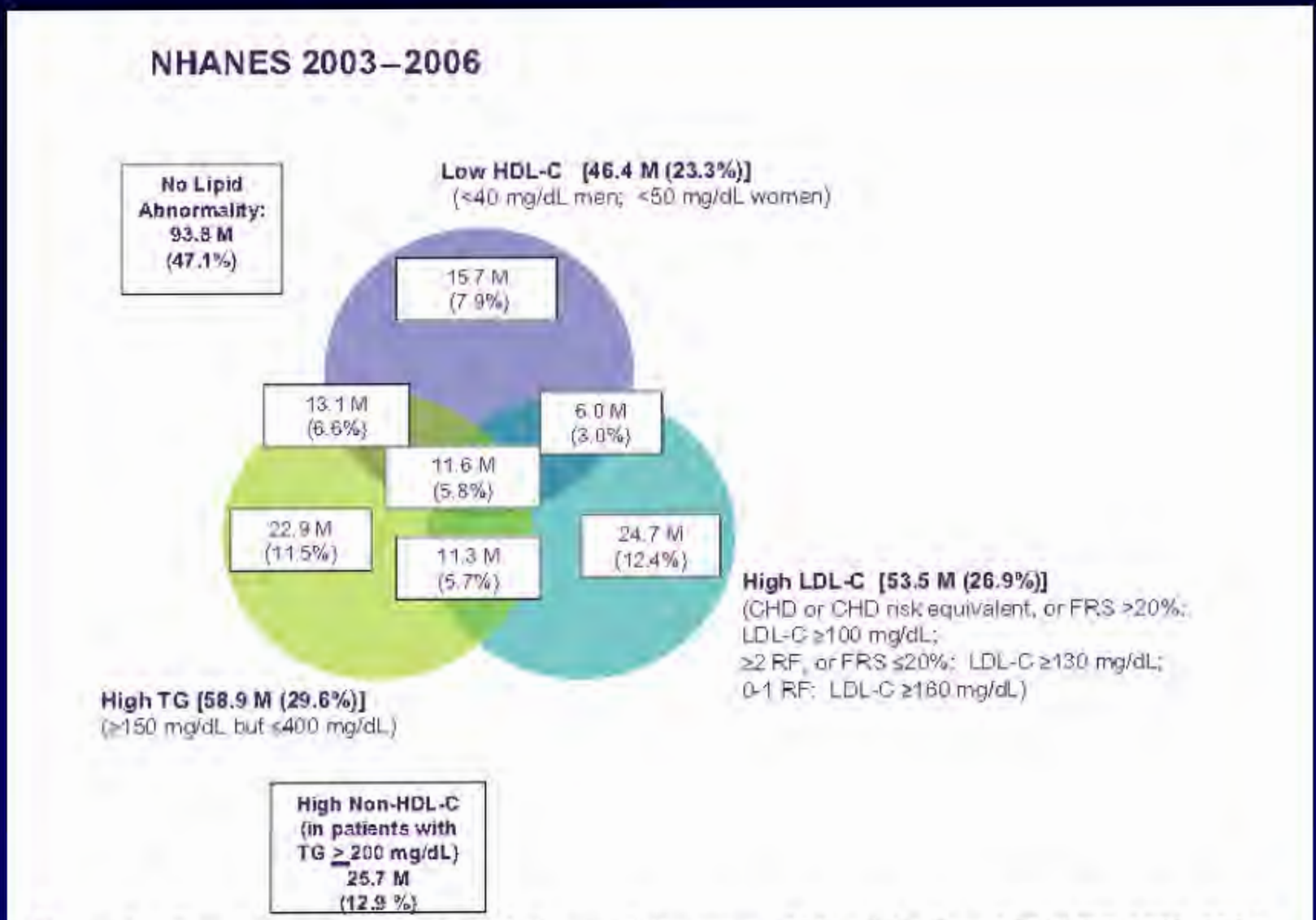


Figure 1 Prevalence of standard lipid abnormalities among U.S. adults from NHANES 2003–2006.

IMPORTANCIA LDL PEQUEÑAS Y DENSAS

- Se asocian con hipertrigliceridemia, aumentos de LDL-c y HDL-c bajo
- Favorecen permeabilidad endotelial
- Mayor captación arterial
- Mayor captación por macrófagos
- Mayor susceptibilidad a oxidación
- Menor afinidad por LDLR

Utilidad clínica de apo B

- Medida del número de lipoproteínas aterogénicas
- Elevada especialmente en presencia de LDL pequeñas y densas
- Mejor predictor de acontecimientos cardiovasculares que el cLDL en sujetos con hiperlipemias mixtas y diabetes

Major Lipids, Apolipoproteins, and Risk of Vascular Disease

The Emerging Risk Factors Collaboration*

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

Figure 3. Hazard Ratios for Coronary Heart Disease Across Fifths of Usual Lipids or Apolipoproteins

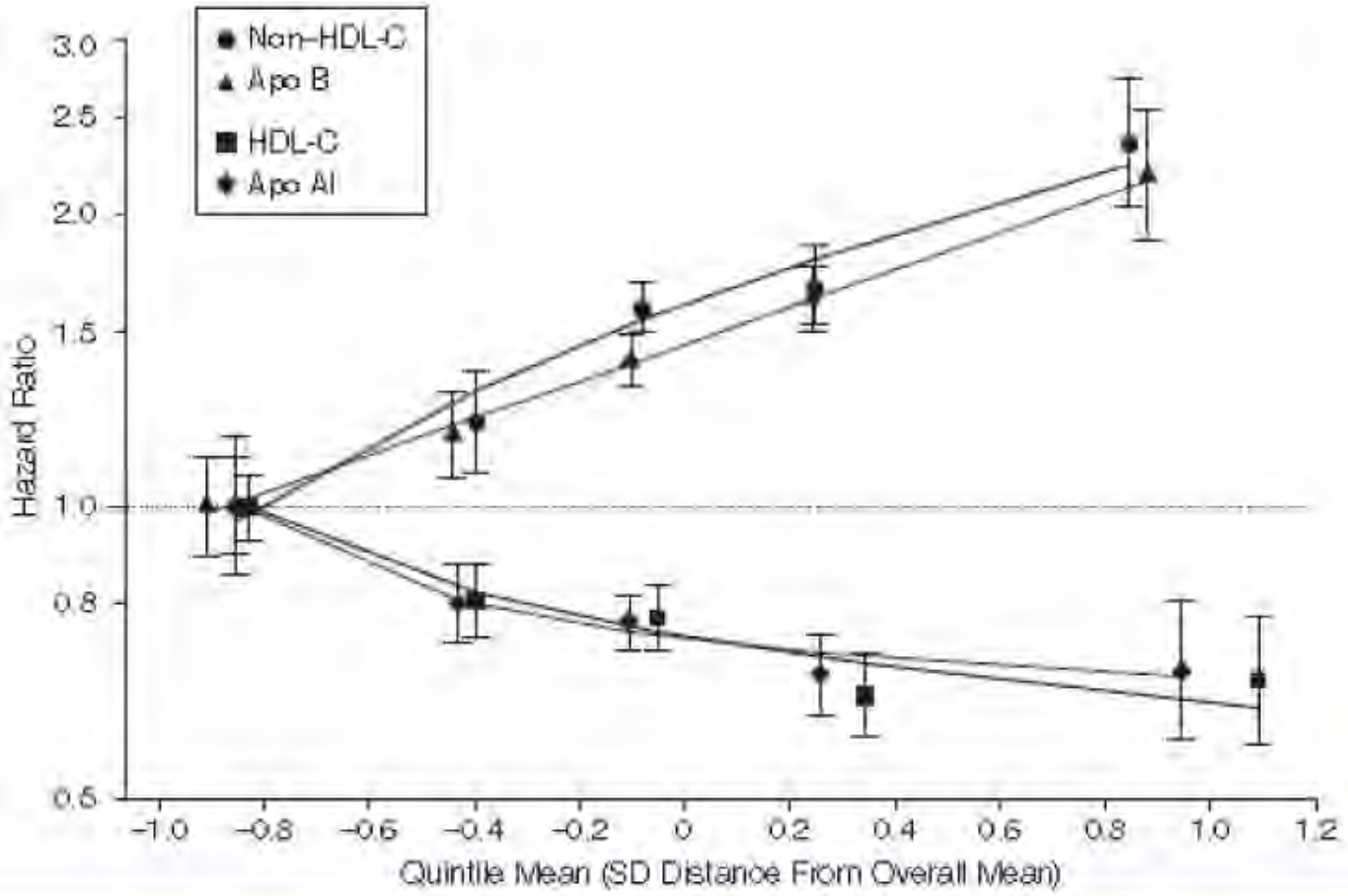


Table 3. Comparison of Lipid Levels in Predicting CVD Mortality in Men and Women*

	Coefficient (SE)	RR (95% CI)†	χ^2 for Addition to Model‡
Men			
Non–HDL-C§	0.17 (0.03)	1.19 (1.13-1.26)	24.3
LDL-C§	0.11 (0.05)	1.11 (1.02-1.22)	5.0
TC§	0.15 (0.03)	1.16 (1.08-1.23)	14.4
HDL-C‖	–0.26 (0.06)	0.77 (0.69-0.86)	23.2
Women			
Non–HDL-C§	0.14 (0.04)	1.15 (1.06-1.25)	8.3
LDL-C§	0.08 (0.06)	1.08 (0.96-1.22)	1.8
TC§	0.09 (0.05)	1.10 (0.99-1.22)	2.8
HDL-C‖	–0.26 (0.06)	0.77 (0.69-0.88)	18.5

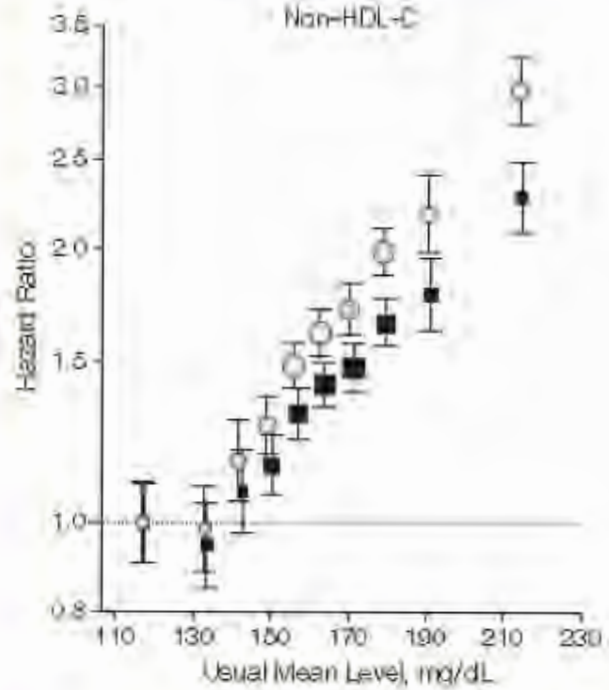
Lipid Research Program Prevalence Study. Arch Inter Med 2001; 161:1413

Major Lipids, Apolipoproteins, and Risk of Vascular Disease

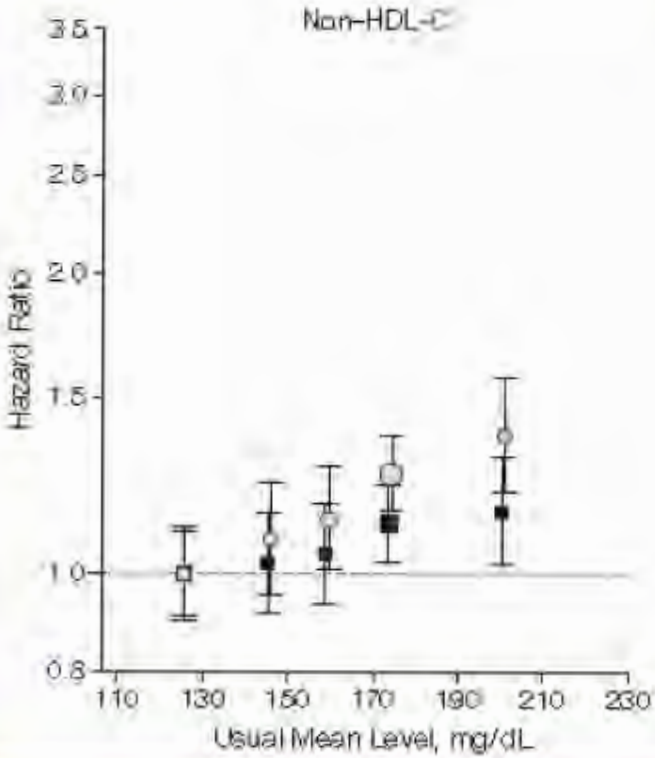
The Emerging Risk Factors Collaboration*

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

Coronary heart disease



Ischemic stroke



Atherosclerosis 217S (2011) S1–S44

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Review

ESC/EAS Guidelines for the management of dyslipidaemias

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)☆,☆☆

European Heart Journal Advance Access published May 3, 2012

European Heart Journal
doi:10.1093/eurheartj/ehs092

JOINT ESC GUIDELINES

European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)

The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts)

Recommendations for lipid analyses for characterization of dyslipidaemias before treatment.

Recommendations	Class[a]	Level[b]
LDL-C is recommended to be used as the primary lipid analysis.	I	C
TG adds information to risk and is indicated for diagnosis and choice of treatment.	I	C
HDL-C is recommended to be analysed before initiation of treatment.	I	C
Non-HDL-C should be recommended for further characterization of combined hyperlipidaemias and dyslipidaemia in diabetes, the MetS or CKD.	IIa	C
Apo B should be recommended for further characterization of combined hyperlipidaemias and dyslipidaemia in diabetes, the MetS or CKD.	IIa	C
Lp(a) should be recommended in selected cases at high risk and in subjects with a family history of premature CVD.	IIa	C
TC may be considered but is usually not enough for the characterization of dyslipidaemia before initiation of treatment.	IIb	C

Table 1 Suggested Treatment Goals in Patients With CMR and Lipoprotein Abnormalities

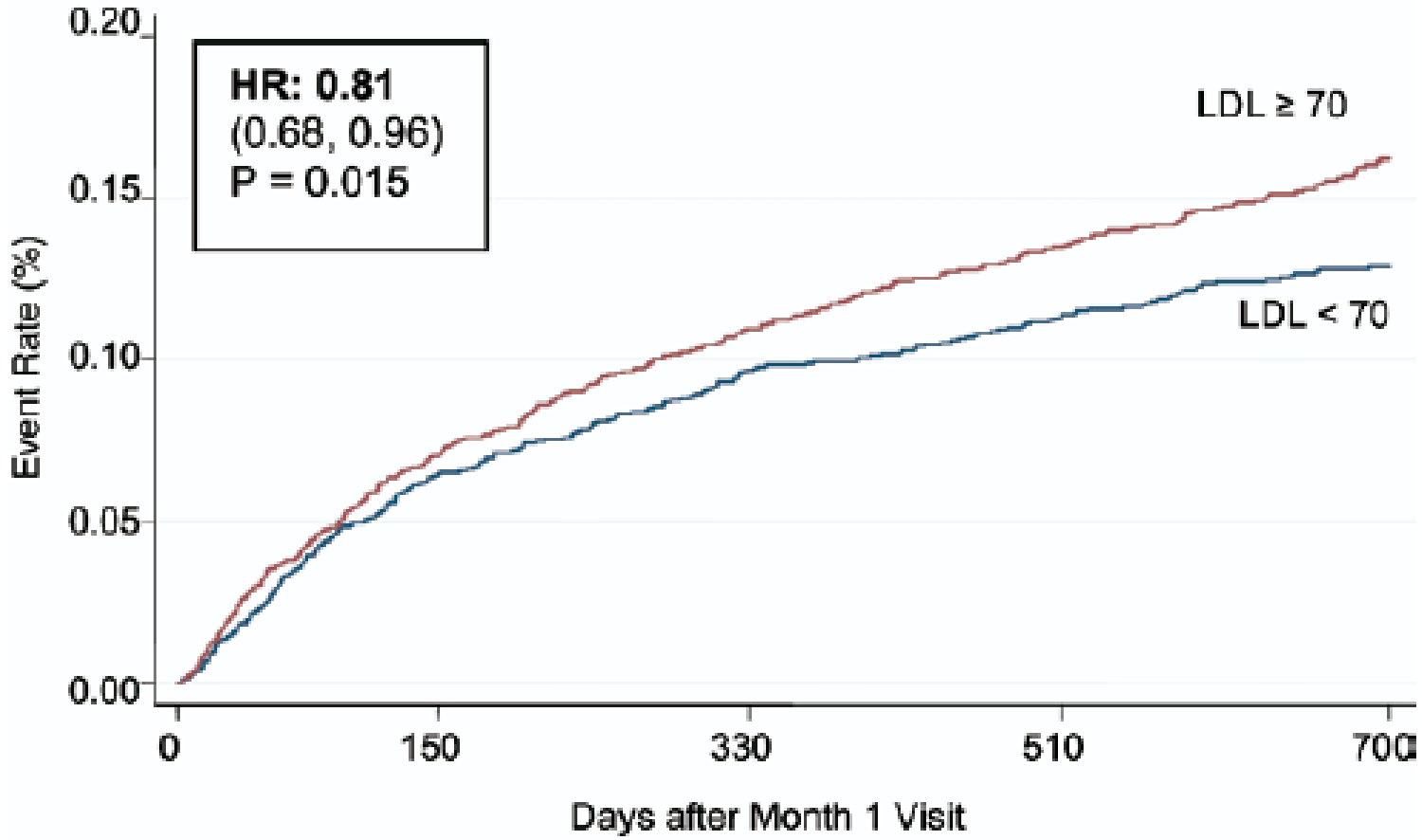
	LDL-C (mg/dl)	Non–HDL-C (mg/dl)	ApoB (mg/dl)
CHD patients or diabetic patients with 1 or more additional major CHD risk factor	<70	<100	<80
1) High-risk patients without diabetes or CHD but 2 or more major CHD risk factors; or 2) diabetic patients without other major CHD risk factors	<100	<130	<90

Other major risk factors include smoking, hypertension, and family history of premature CHD. Adapted from Brunzell et al. (21).

apoB = apolipoprotein B; CHD = coronary heart disease; CMR = cardiometabolic risk; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology JACC, 2011;58:464

ESTUDIO PROVE-IT

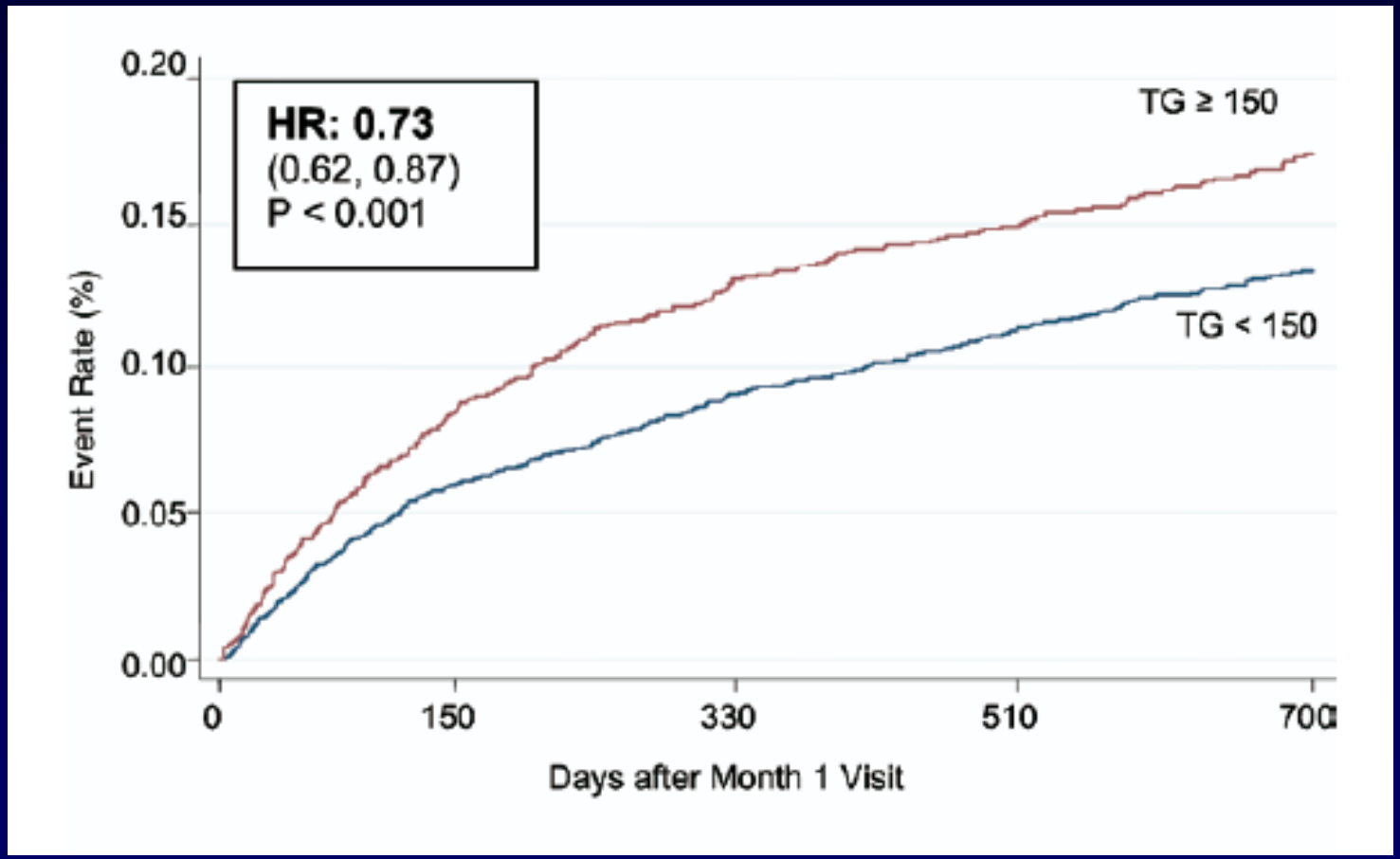


JACC Vol. 51, No. 7, 2008
February 19, 2008:724–30

Miller *et al.*
Impact of Triglycerides After ACS

Estudio PROVE IT

Eventos coronarios de acuerdo a triglicéridos durante el ensayo



JACC Vol. 51, No. 7, 2008
February 19, 2008:724–30

Miller *et al.*
Impact of Triglycerides After ACS

Estudios IDEAL y TNT

Table 1. On-Treatment Values of Lipids, Apolipoproteins, and Their Ratios in Both Treatment Groups of TNT and IDEAL

	TNT		IDEAL	
	Atorvastatin 10 mg (n=4665)	Atorvastatin 80 mg (n=4654)	Simvastatin 20–40 mg (n=4369)	Atorvastatin 80 mg (n=4330)
Total cholesterol, mg/dL*	178.1 (28.5)	147.5 (29.5)	176.1 (29.9)	147.9 (34.1)
LDL cholesterol, mg/dL	101.0 (22.3)	75.3 (22.6)	102.2 (25.2)	79.5 (28.0)
HDL cholesterol, mg/dL	46.2 (10.9)	46.1 (11.2)	47.1 (12.7)	45.7 (12.5)
Non-HDL cholesterol, mg/dL†	131.9 (27.9)	101.4 (28.0)	129.0 (29.5)	102.2 (32.2)
Triglycerides, mg/dL	156.0 (86.5)	131.3 (76.8)	139.4 (83.8)	116.6 (66.3)
Apolipoprotein B, mg/dL	113 (22)	91 (21)	107 (27)	84 (28)
Total/HDL cholesterol	4.0 (1.0)	3.3 (0.9)	4.0 (1.2)	3.4 (1.1)
LDL/HDL cholesterol	2.3 (0.7)	1.7 (0.6)	2.3 (0.8)	1.9 (0.8)
Apolipoprotein B/A-I	0.8 (0.2)	0.7 (0.2)	0.8 (0.2)	0.6 (0.2)

On-Statin Prediction of Cardiovascular Events

Circulation **June 10, 2008**

Estudios IDEAL y TNT

Table 1. On-Treatment Values of Lipids, Apolipoproteins, and Their Ratios in Both Treatment Groups of TNT and IDEAL

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	Atorvastatin 10 mg (n=4665)	Atorvastatin 80 mg (n=4654)	Simvastatin 20–40 mg (n=4369)	Atorvastatin 80 mg (n=4330)
Total cholesterol, mg/dL*	178.1 (28.5)	147.5 (29.5)	176.1 (29.9)	147.9 (34.1)
LDL cholesterol, mg/dL	101.0 (22.3)	75.3 (22.6)	102.2 (25.2)	79.5 (28.0)
HDL cholesterol, mg/dL	46.2 (10.9)	46.1 (11.2)	47.1 (12.7)	45.7 (12.5)
Non-HDL cholesterol, mg/dL†	131.9 (27.9)	101.4 (28.0)	129.0 (29.5)	102.2 (32.2)
Triglycerides, mg/dL	156.0 (86.5)	131.3 (76.8)	139.4 (83.8)	116.6 (66.3)
Apolipoprotein B, mg/dL	113 (22)	91 (21)	107 (27)	84 (28)
Total/HDL cholesterol	4.0 (1.0)	3.3 (0.9)	4.0 (1.2)	3.4 (1.1)
LDL/HDL cholesterol	2.3 (0.7)	1.7 (0.6)	2.3 (0.8)	1.9 (0.8)
Apolipoprotein B/A-I	0.8 (0.2)	0.7 (0.2)	0.8 (0.2)	0.6 (0.2)

On-Statin Prediction of Cardiovascular Events

Circulation **June 10, 2008**

Estudios IDEAL y TNT

Table 3. Direct Pairwise Comparisons of the Relationships With MCVEs for On-Treatment Levels of LDL Cholesterol, Non-HDL Cholesterol, Apolipoprotein B, or Their Ratios in TNT and IDEAL

	Hazard Ratio*	95% CI	*P*
Comparisons of single measures			
LDL cholesterol	0.90	0.82–0.99	0.04
Non-HDL cholesterol†	1.31	1.19–1.44	<0.001
LDL cholesterol	0.95	0.87–1.05	0.33
Apolipoprotein B	1.24	1.13–1.36	<0.001
Non-HDL cholesterol†	1.14	1.00–1.30	0.06
Apolipoprotein B	1.05	0.92–1.20	0.47

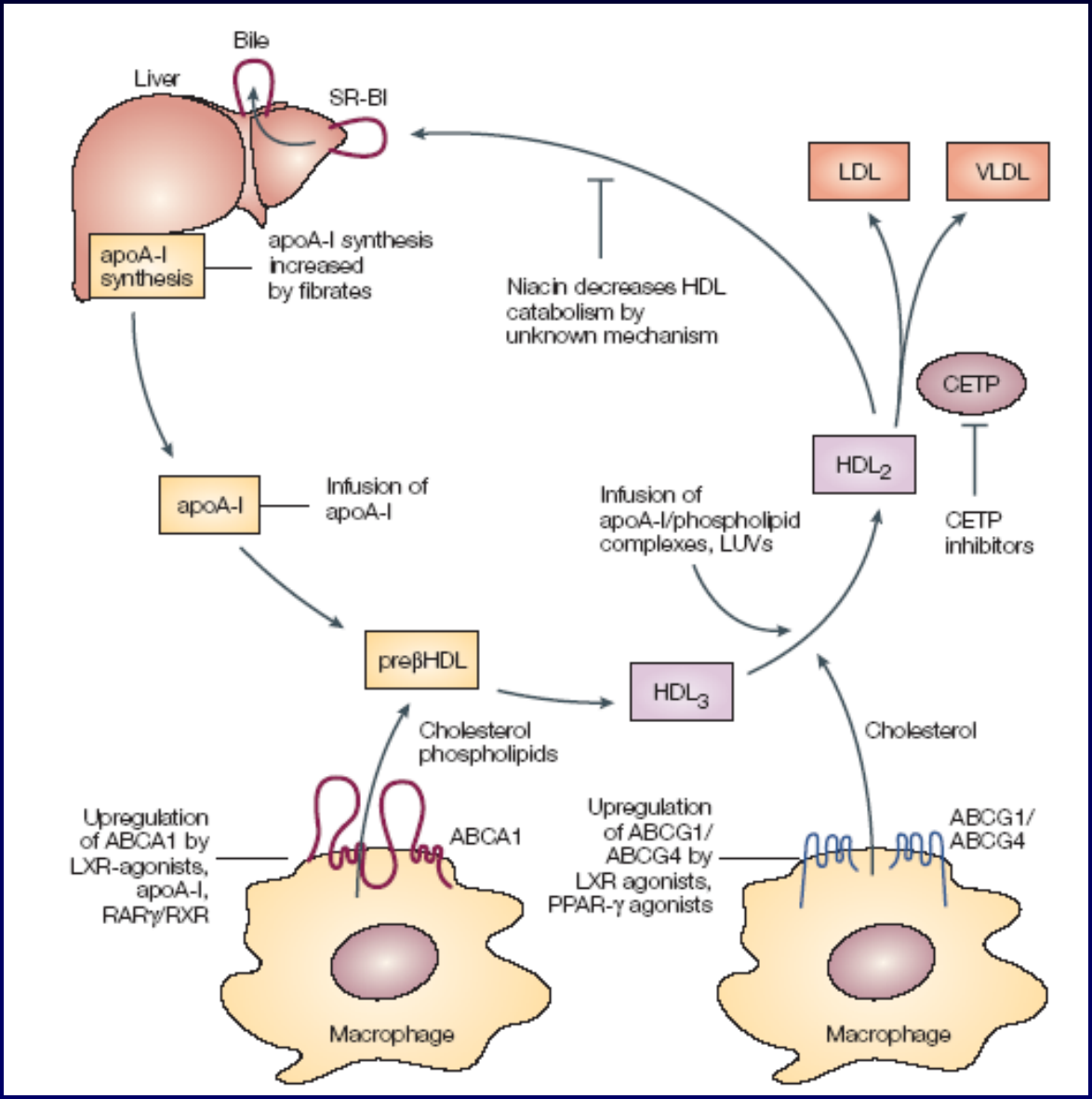
On-Statin Prediction of Cardiovascular Events

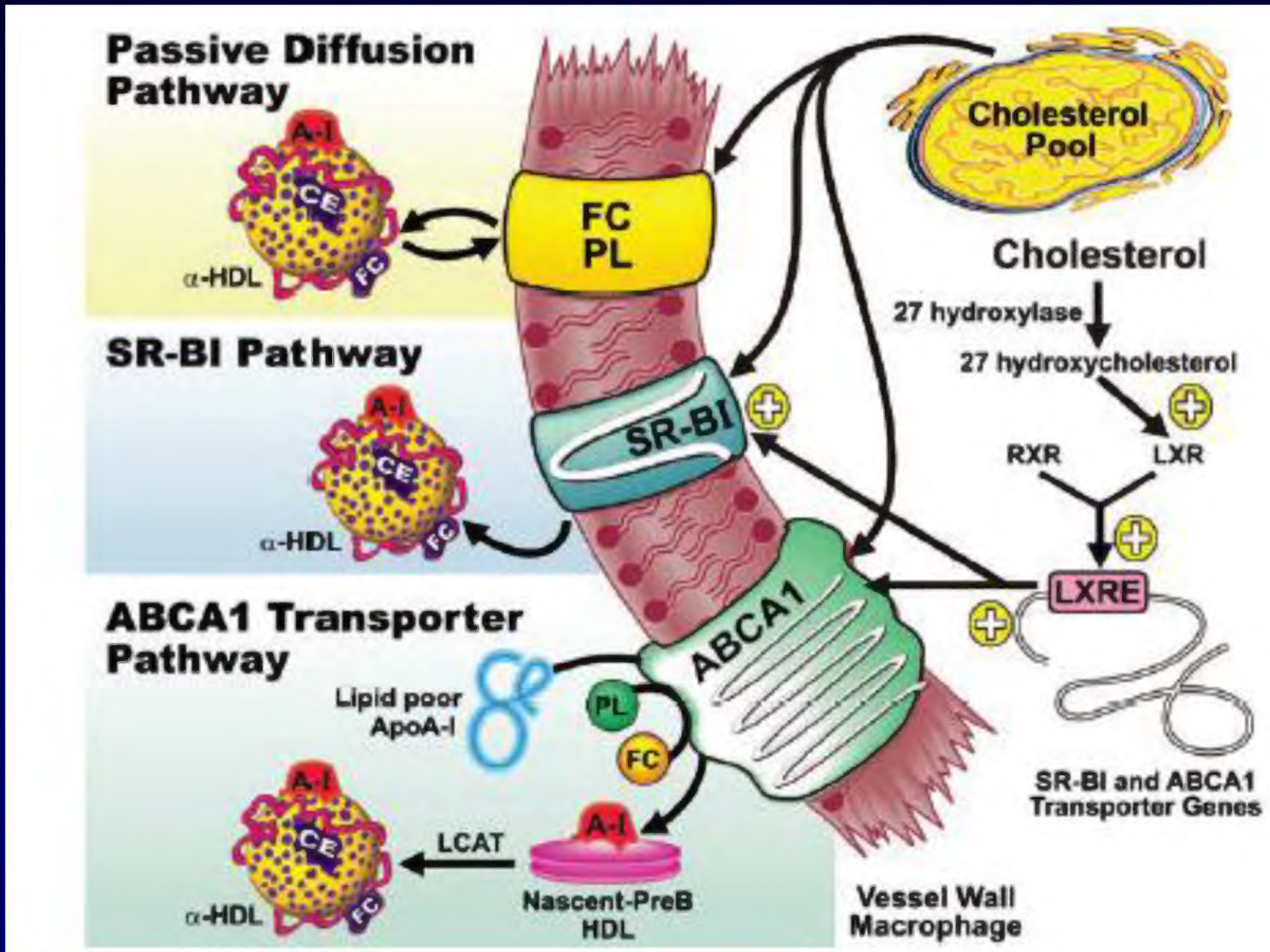
Circulation **June 10, 2008**

Table 7
Recommendations for lipid analyses as treatment target in the prevention of CVD [53].

Recommendations	Class[a]	Level[b]	Ref[c]
LDL-C is recommended as target for treatment.	I	A	15, 16, 17
TC should be considered as treatment target if other analyses are not available.	IIa	A	5, 15
TG should be analysed during the treatment of dyslipidaemias with high TG levels.	IIa	B	52
Non-HDL-C should be considered as a secondary target in combined hyperlipidaemias, diabetes, the MetS or CKD.	IIa	B	48
Apo B should be considered as a secondary treatment target.	IIa	B	48, 53
HDL-C is not recommended as a target for treatment.	III	C	-
The ratios apo B/apo A1 and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	C	-

TRANSPORTE REVERSO DE COLESTEROL

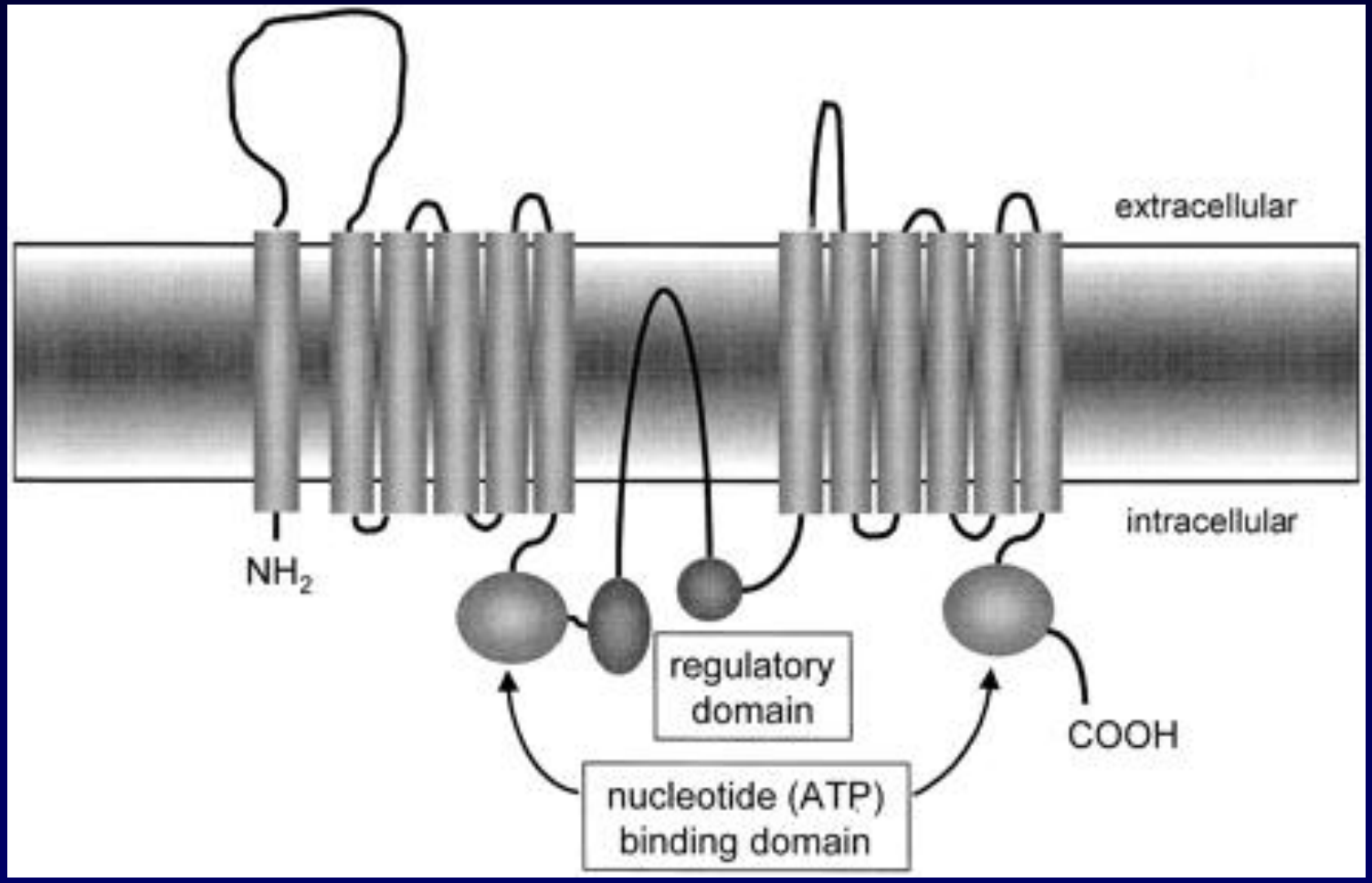



Passive Diffusion Pathway
A-I
CE
FC
α-HDL
FC
PL
Cholesterol Pool
Cholesterol
27 hydroxylase
27 hydroxycholesterol
SR-BI Pathway
SR-BI
RXR
LXR
LXRE
ABCA1 Transporter Pathway
ABCA1
Lipid poor ApoA-I
PL
FC
SR-BI and ABCA1 Transporter Genes
LCAT
Nascent-PreB HDL
Vessel Wall Macrophage

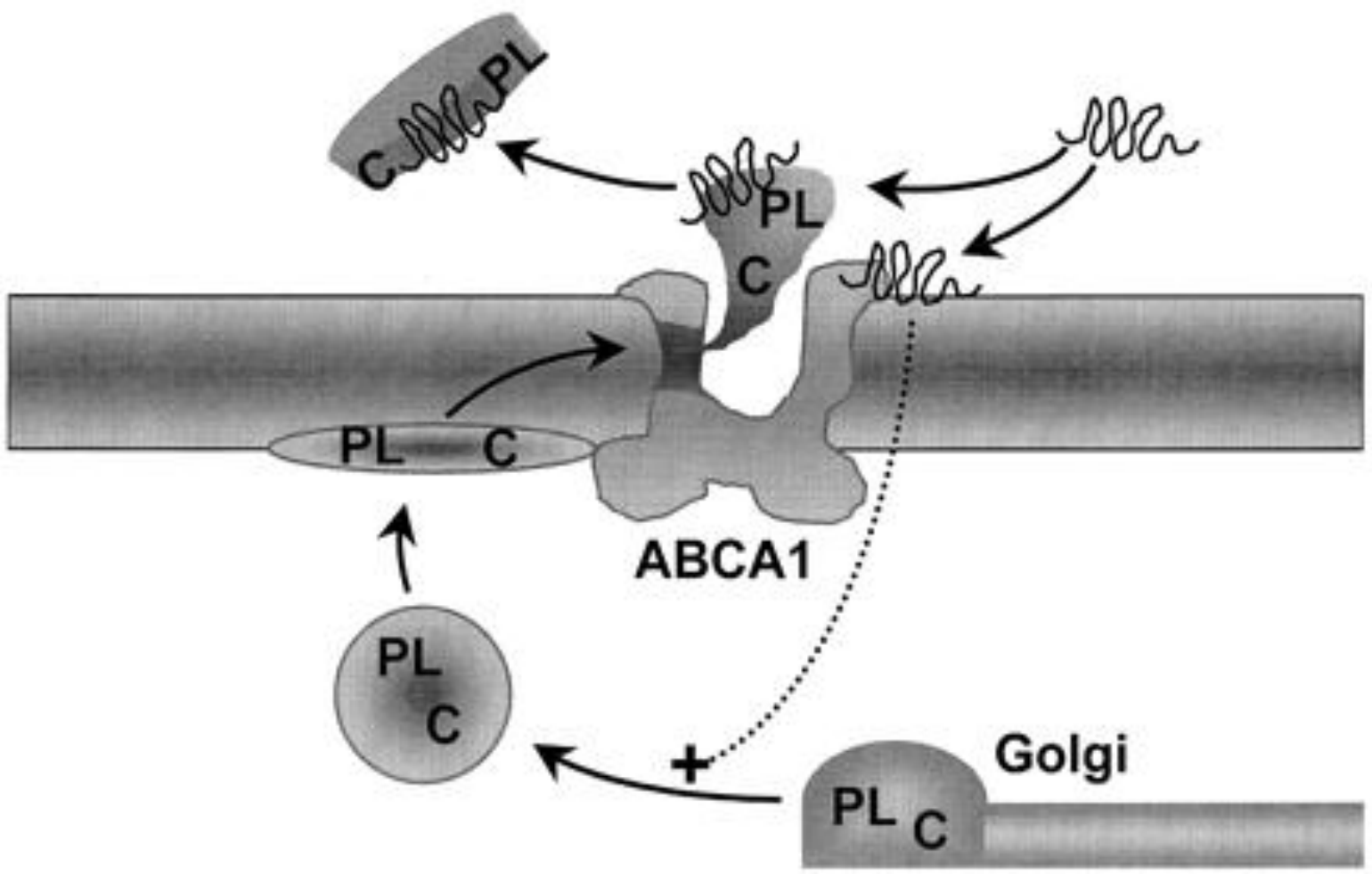
HIPOLIPEMIAS PRIMARIAS

DISLIPEMIA	Fenotipo	Transmisión	Genes	Frecuencia
Abetalipoproteinemia	ausencia apo B	Autosómica recesiva	MTTP	Rara
Hipobetalipoproteinemia Familiar	LDLc bajo	Autosómica dominante	apo B100	1/1000
Hipoalfalipoproteinemia Familiar	HDLc bajo	Autosómica variable	ABCA1, Apo A-I	rara
Enfermedad Tangier	HDLc bajo Tg altos	Autosómica recesiva	ABCA1	muy rara
Enfermedad de Ojos de Pescado	HDLc bajo Tg altos	Autosómica recesiva	LCAT	muy rara

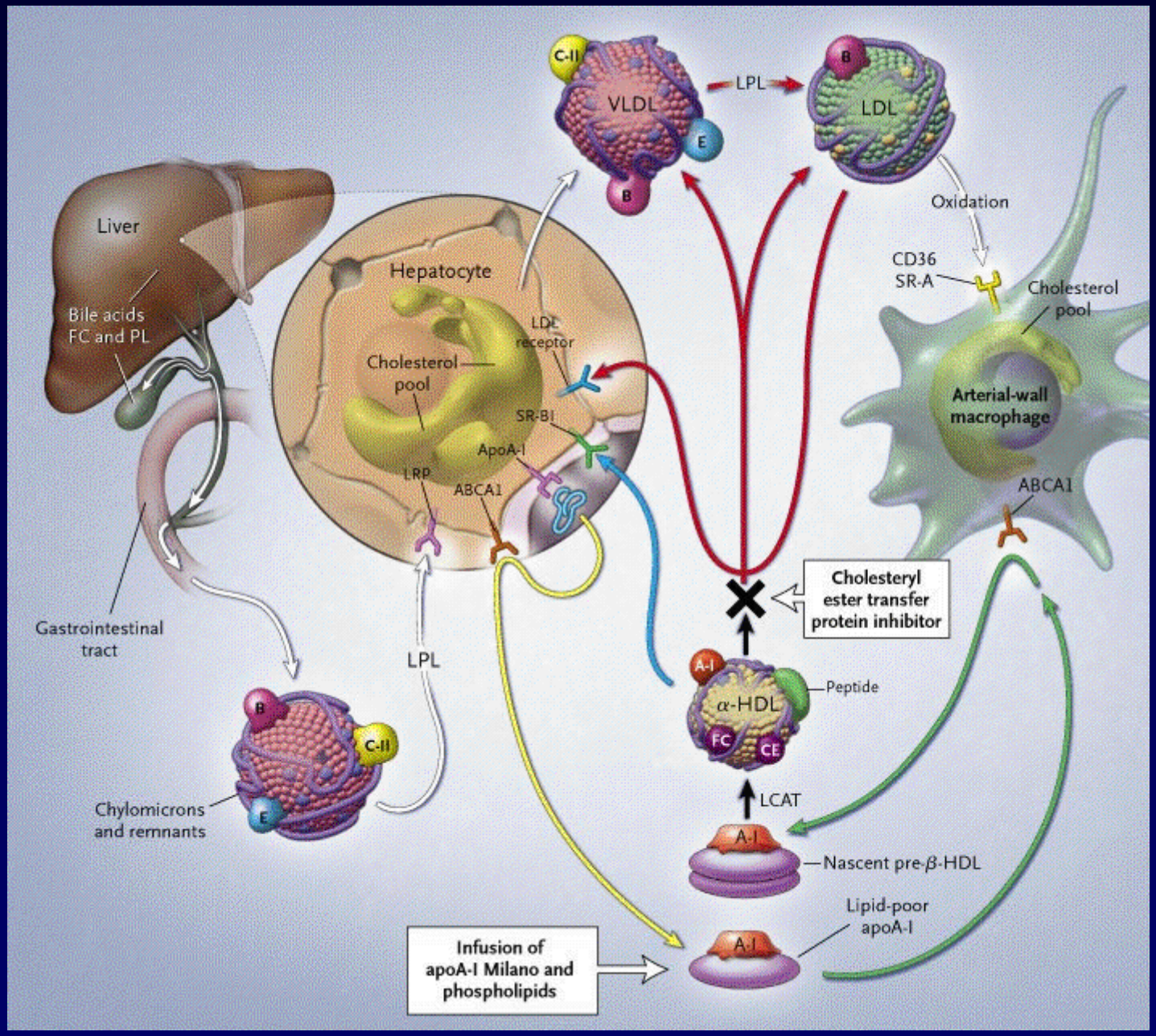
Esquema de la proteína “ATP-binding cassette A1” (ABCA1)



Esquema del funcionamiento de ABCA1

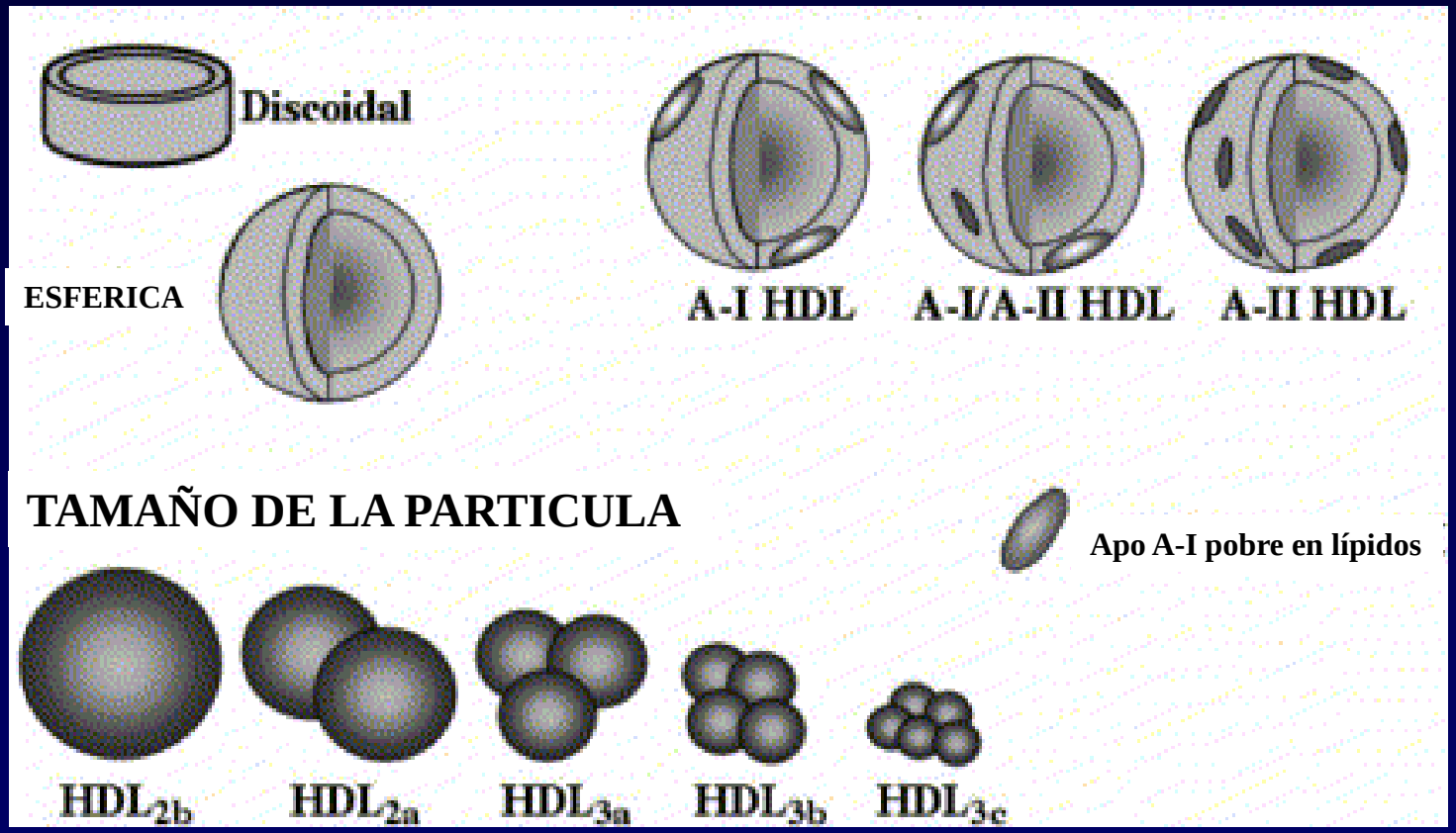


INHIBICION CETP

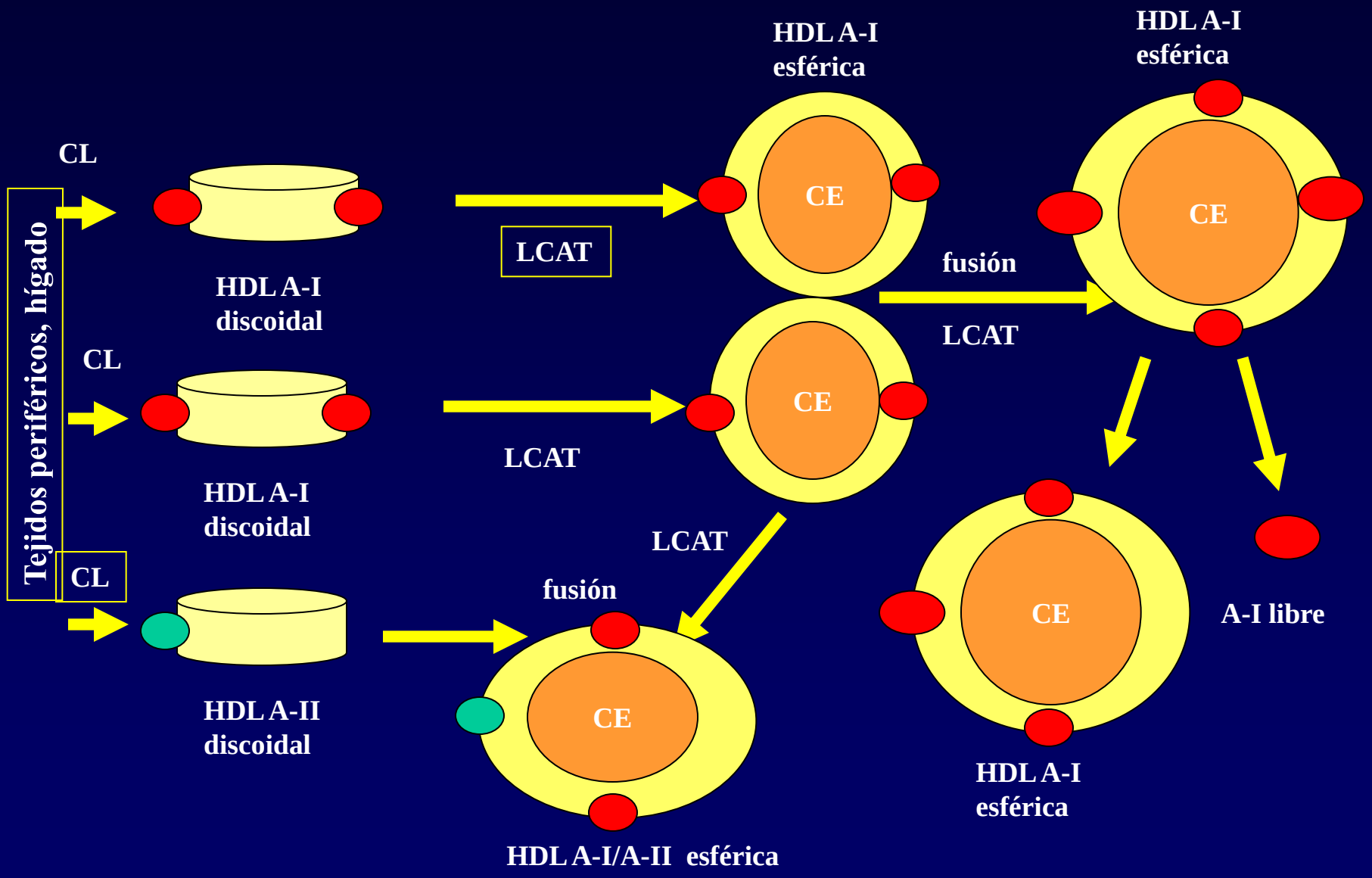


Heterogeneidad de las HDL

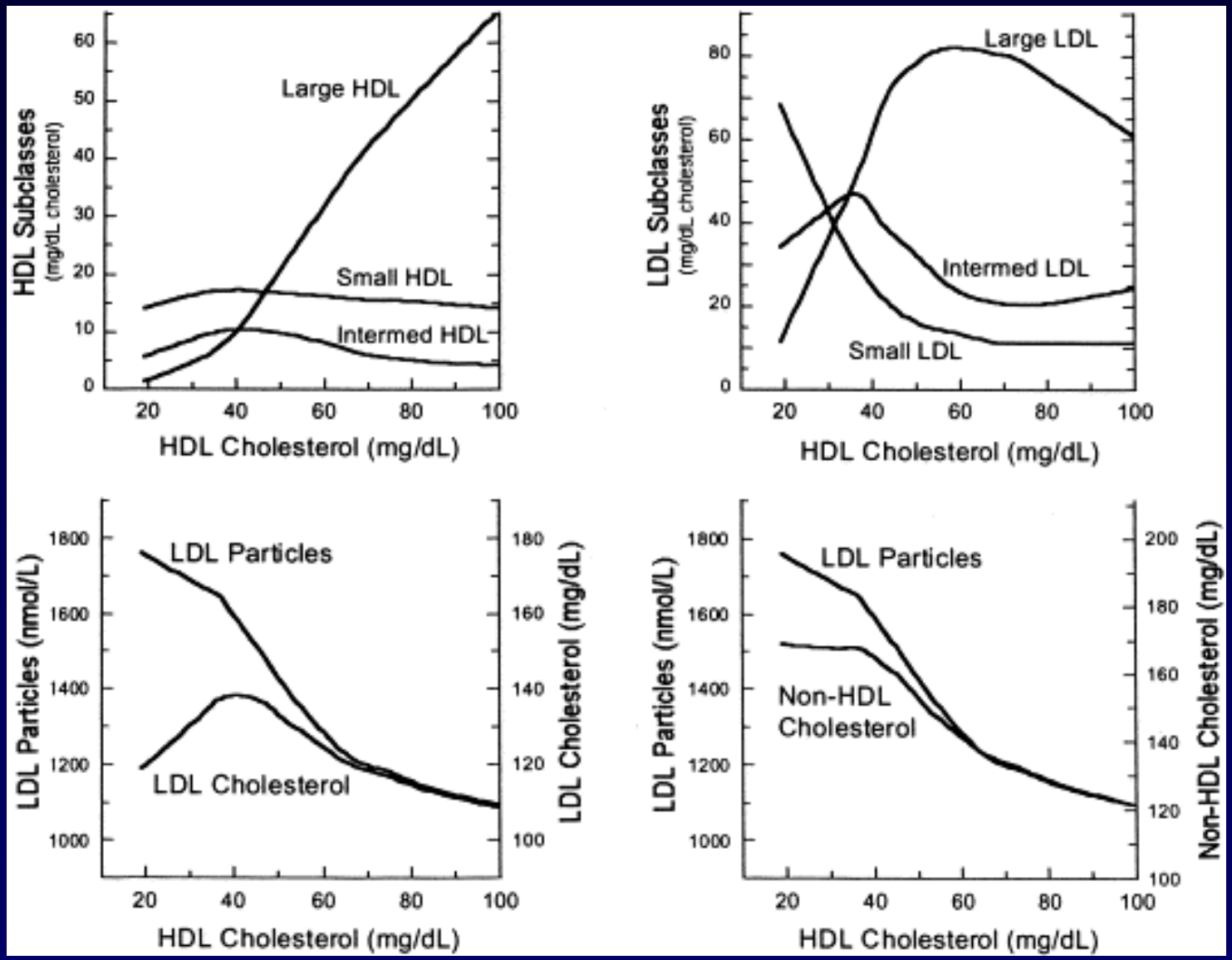
FORMA **COMPOSICION EN APOLIPOPROTEINAS**



Formación de la HDL A-I, y A-I/A-II



Relación entre la concentración de HDL-c y la heterogeneidad de LDL y HDL. Estudio Framingham



TRANSPORTE REVERSO DE COLESTEROL

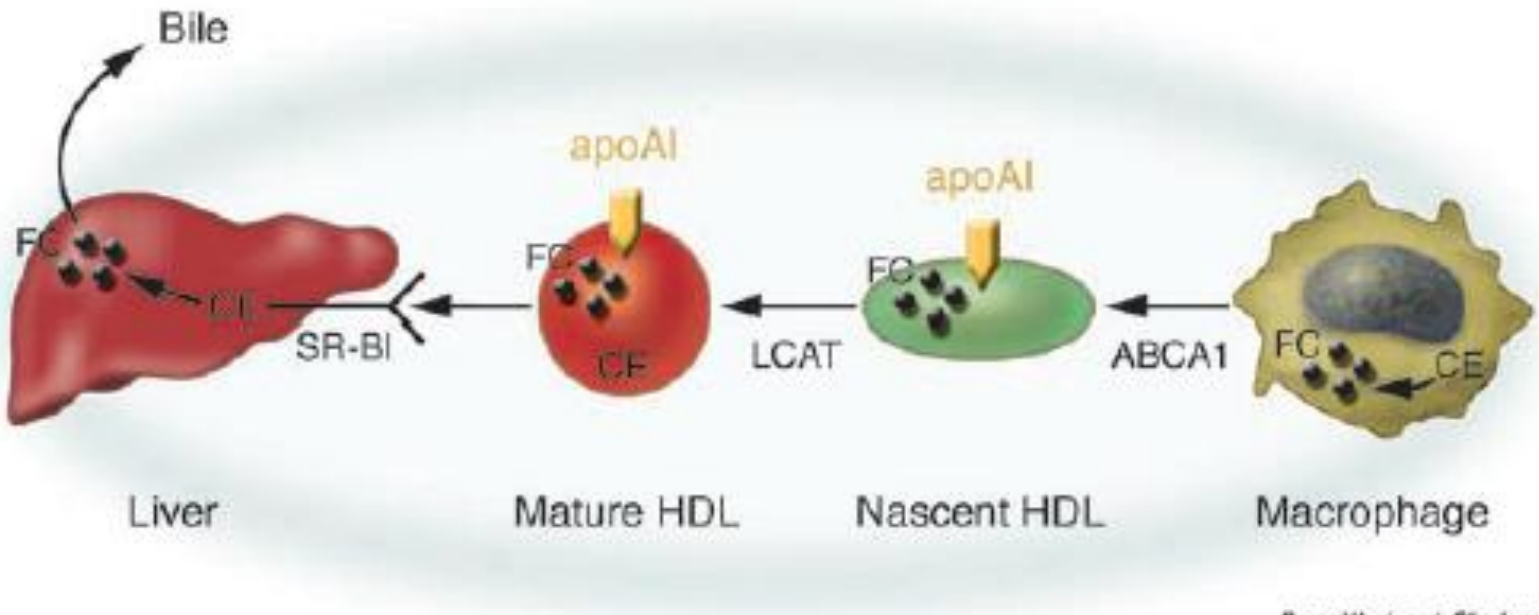


Figure 1

A schematic overview of the role of the ABCA1 protein in HDL metabolism and RCT. In RCT,

El eflujo de colesterol mediado por ABCA1 desde los macrófagos no es cuantitativamente importante en la concentración plasmática de cHDL

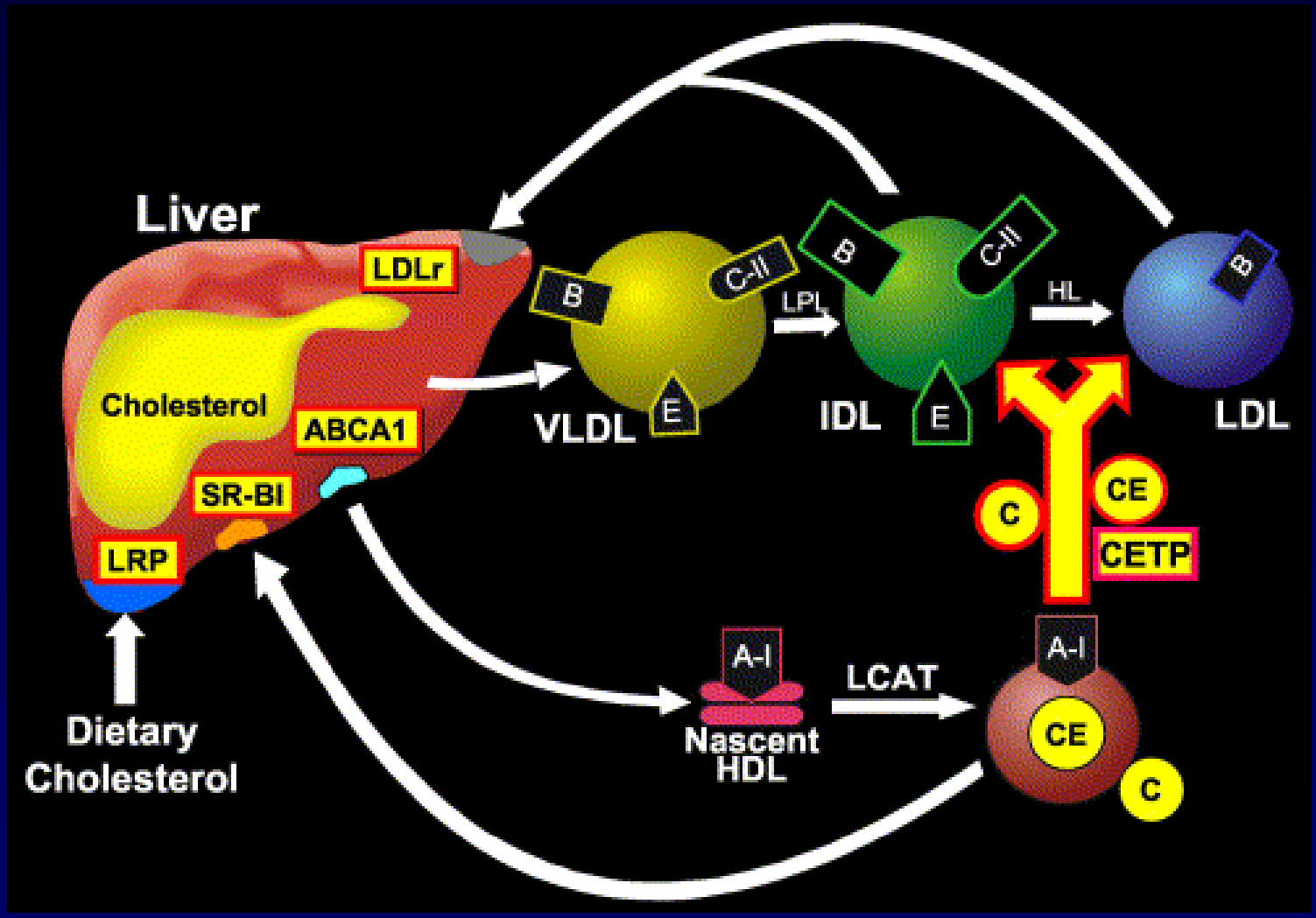
Table 1
Plasma cholesterol and apoAI levels in mice after bone marrow transplantation.

		Baseline			Week 2			Week 4		
Donor→recipient	*n*	TPC	HDL-c[A]	apoAI[B]	TPC	HDL-c	apoAI	TPC	HDL-c	apoAI
WT→*ABC1*$^{-/-}$	8	15.2 (2.6)	7.3 (1.8)	38.7 (9.0)	23.5 (7.2)	7.2 (4.8)	15.7[C] (2.3)	19.1 (9.1)	5.6 (1.0)	10.0[D] (2.8)
ABC1$^{-/-}$→*ABC1*$^{-/-}$	8	17.4 (3.6)	7.5 (1.3)	42.7 (9.1)	23.8 (7.4)	4.3 (3.6)	10.1 (2.6)	31.6 (8.3)	4.7 (1.0)	7.2 (1.0)
WT→WT	7	56.2 (12.2)	40.8 (11.2)	676.2 (176.1)	73.2 (4.0)	47.1 (2.0)	688.1 (152.1)	69.4 (7.4)	44.7 (7.3)	744.3 (112.5)
ABC1$^{-/-}$→WT	8	58.3 (7.2)	36.7 (2.5)	706.8 (118.8)	73.9 (11.9)	44.8 (3.8)	710.4 (159.5)	77.0 (12.0)	46.1 (5.0)	781.3 (87.4)

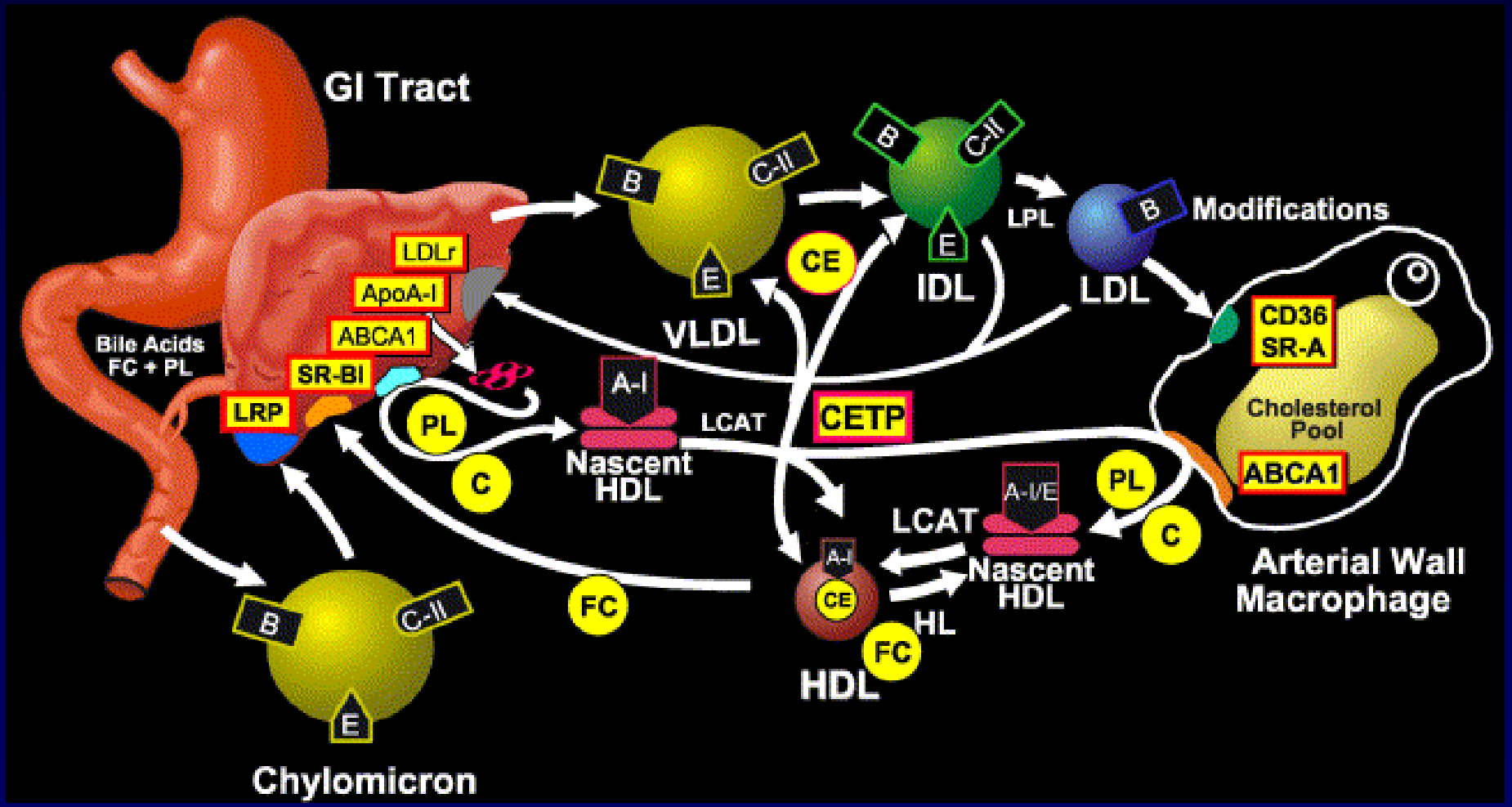
Plasma samples were obtained from each mouse on chow diet 1 day before (baseline) and 2, 4, and 6 weeks after the transpl
ing. Total and HDL cholesterol were determined enzymatically, and mouse apoAI was determined by an ELISA. SDs are shown i
[C]$P < 0.001$ compared with *ABC*$^{-/-}$→*ABC1*$^{-/-}$. [D]$P < 0.05$ compared with *ABC*$^{-/-}$→*ABC1*$^{-/-}$.

Haghpassand M, et al. J Clin Invest 2001;108:1317

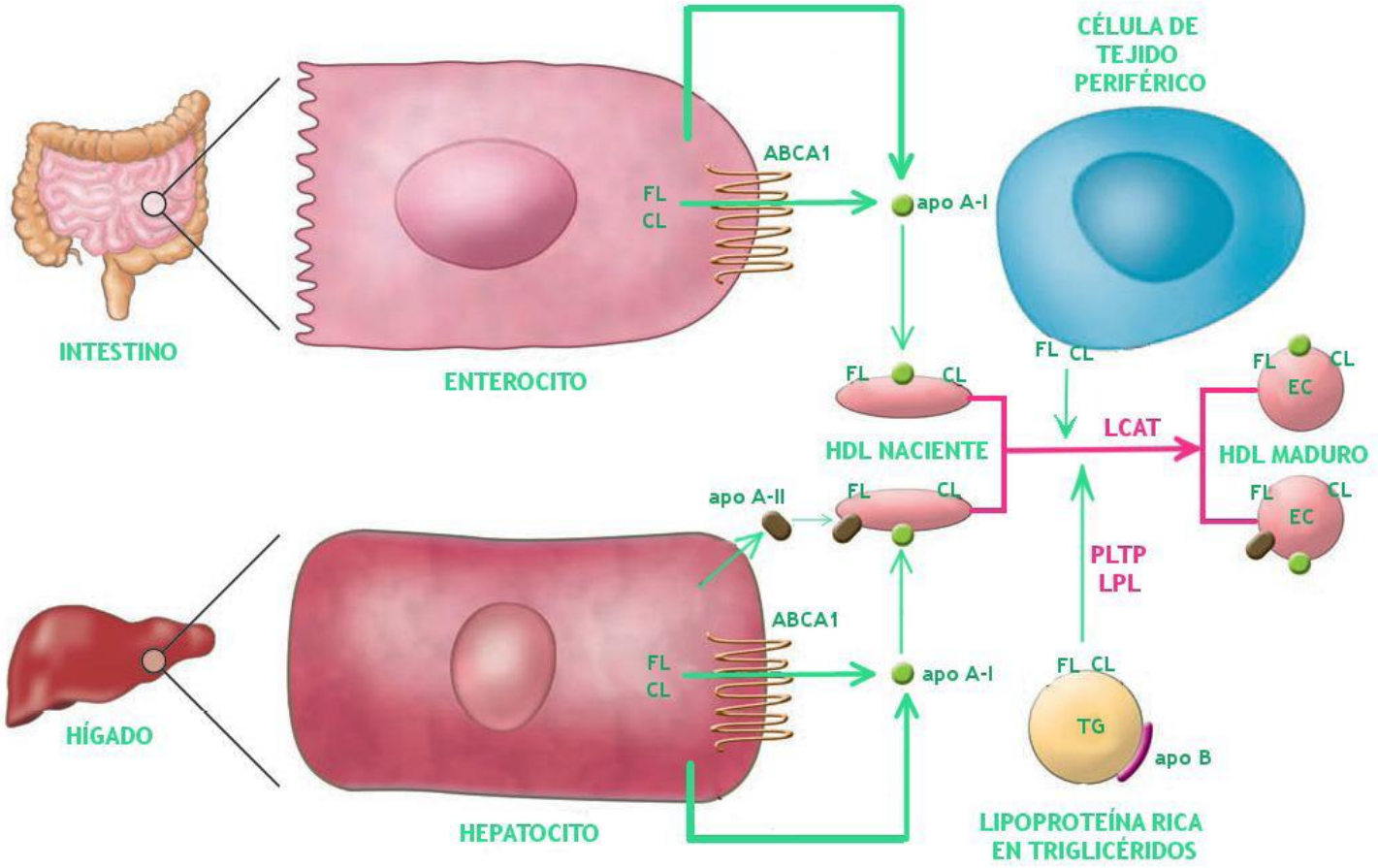
METABOLISMO DE HDL



METABOLISMO DE HDL

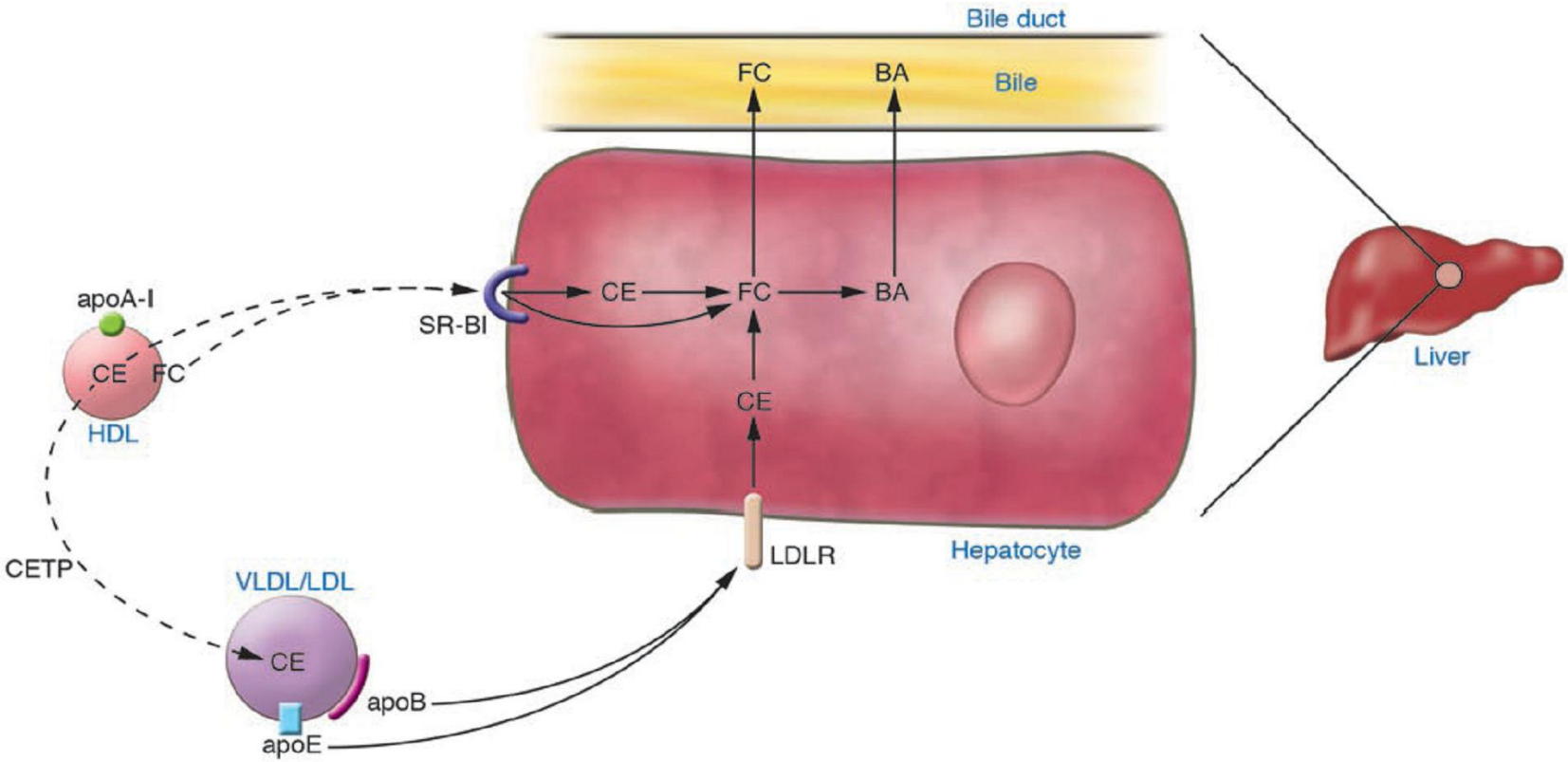


Síntesis y Metabolismo de la HDL



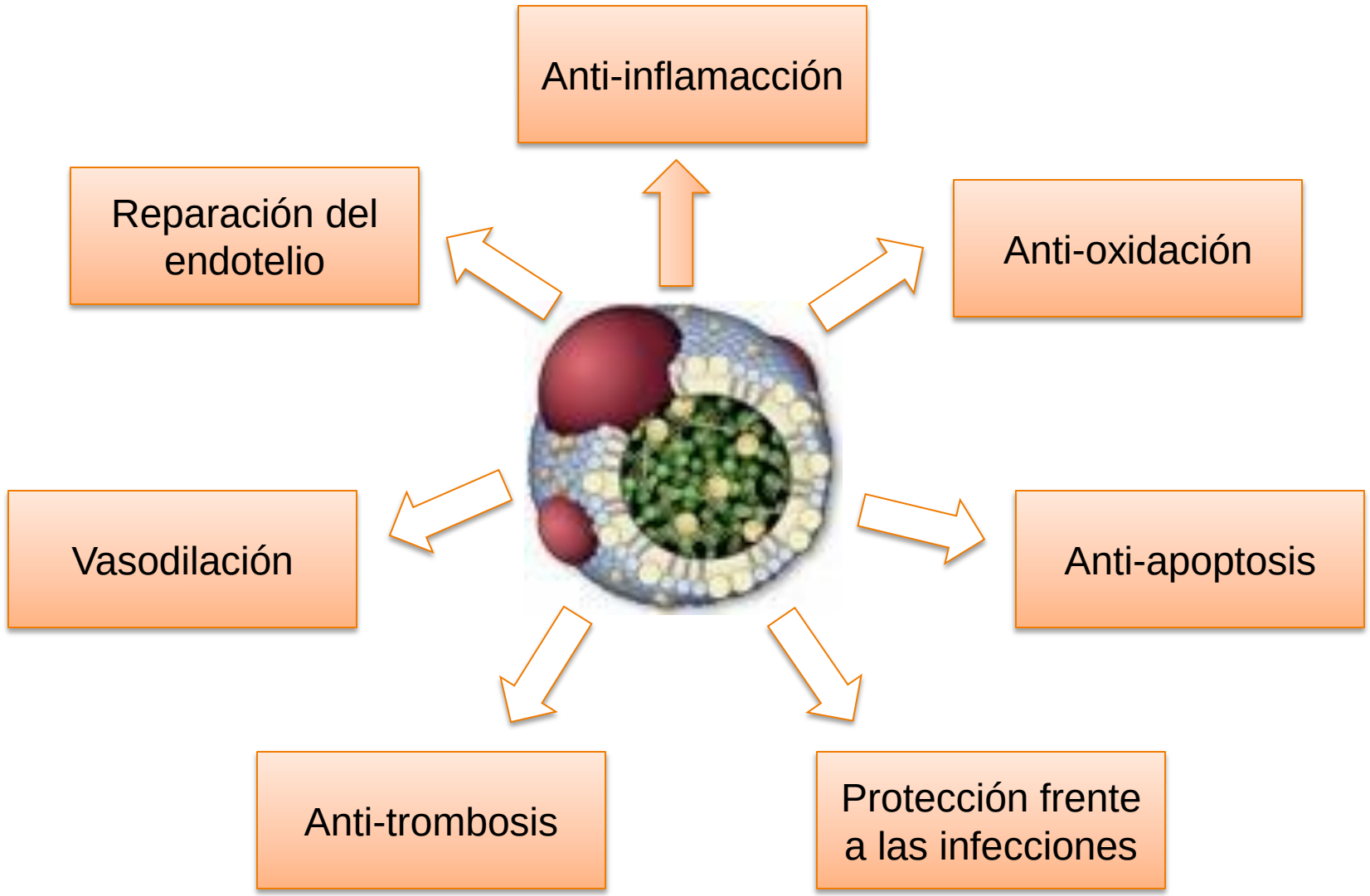
"Molecular regulation of HDL metabolism and function: implications for novel therapies". J. Clin. Invest. 2006

Catabolismo de la HDL



"Molecular regulation of HDL metabolism and function: implications for novel therapies". J. Clin. Invest. 2006

Funciones de las HDL



Shotgun proteomics implicates protease inhibition and complement activation in the antiinflammatory properties of HDL

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