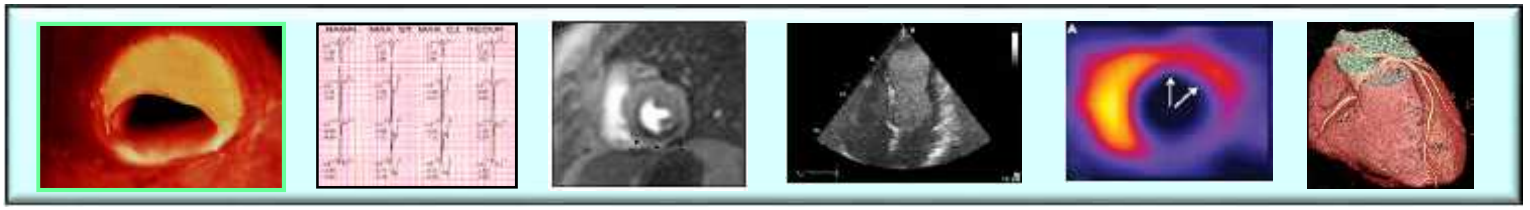
Lípidos y enfermedad coronaria



Francisco Javier Chorro Gascó
Departamento de Medicina. Universidad de Valencia.
Servicio de Cardiología. Hospital Clínico Universitario de Valencia. INCLIVA.

Junio 2015

RIESGO CARDIOVASCULAR

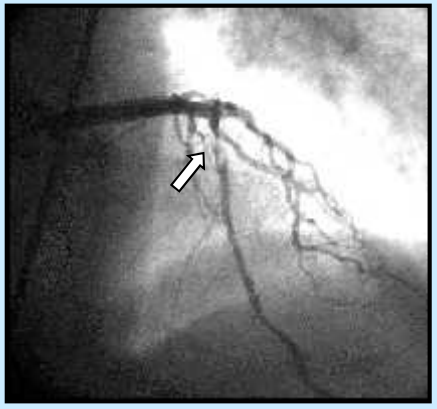
Factores de riesgo clásicos

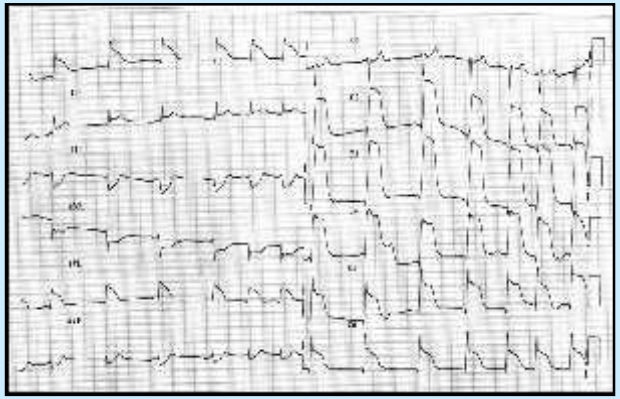
Biomarcadores en sangre

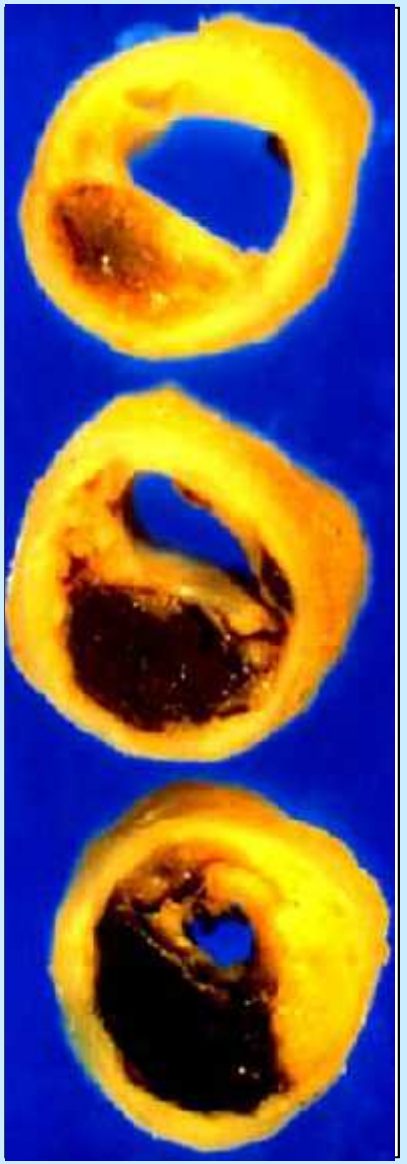
Marcadores genéticos

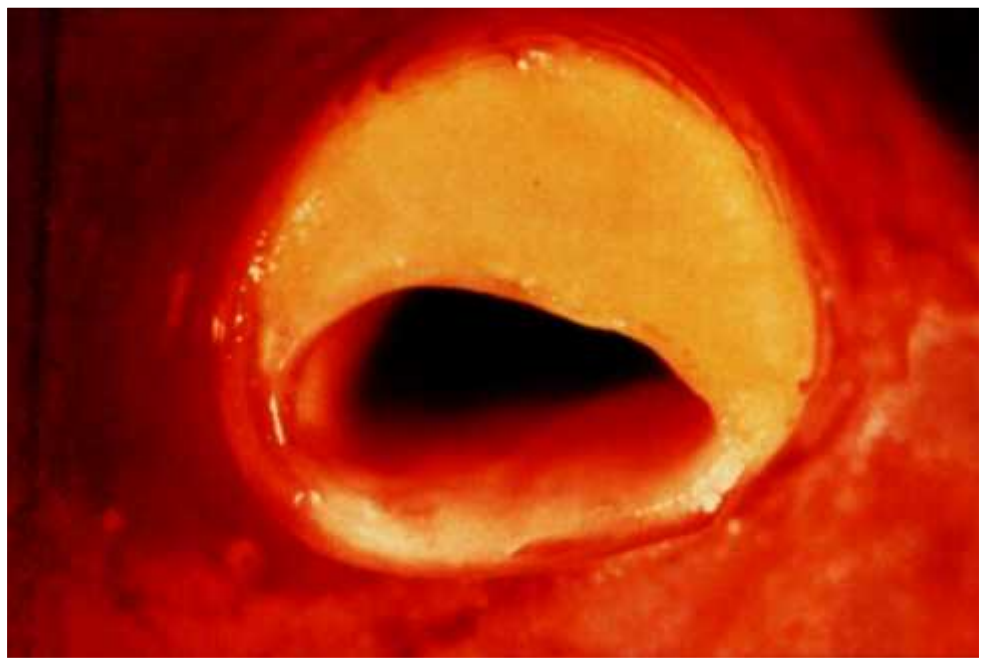
Técnicas diagnósticas

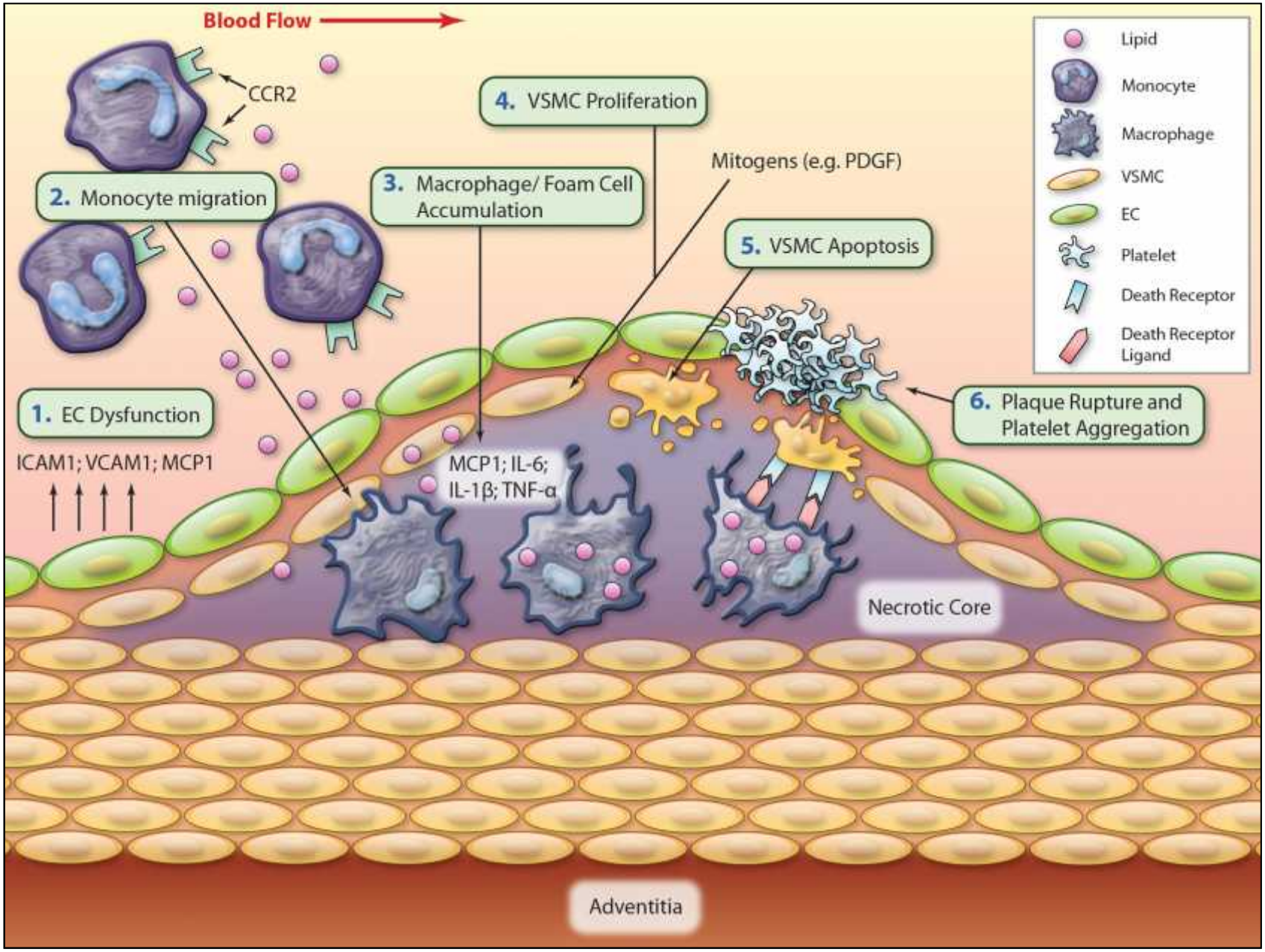
Manifestaciones clínicas










Blood Flow
CCR2
2. Monocyte migration
1. EC Dysfunction
ICAM1; VCAM1; MCP1
3. Macrophage/ Foam Cell Accumulation
MCP1; IL-6; IL-1β; TNF-α
4. VSMC Proliferation
Mitogens (e.g. PDGF)
5. VSMC Apoptosis
6. Plaque Rupture and Platelet Aggregation
Necrotic Core
Adventitia
Lipid
Monocyte
Macrophage
VSMC
EC
Platelet
Death Receptor
Death Receptor Ligand

ATEROSCLEROSIS

FACTORES DE RIESGO

Aumento de LDL
Disminución de HDL
HTA
Diabetes
Tabaquismo
PCR
Síndrome metabólico
Lp(a)
Homocisteína
LDL densa
Lp-PLA2
ApoB/ApoA
Historia familiar
Vida sedentaria
Obesidad
Estrés
.
.
.
(Se han comunicado más de 200 factores de riesgo)

Grosor íntima-media Carótidas (ECO)

Ateromas aórticos y Carótideos (RMN)

Calcio coronario (TAC)

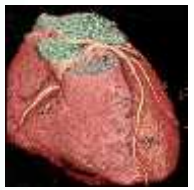
Índice brazo-tobillo

Reactividad vascular (ECO-Dopl.)

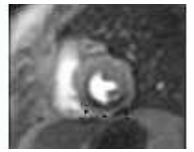
Distensibilidad vascular (Tonometría radial)

Reactividad microvascular (tonometría en dedos)

ESTRUCTURA (ANATOMÍA)

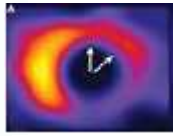


TAC multic.

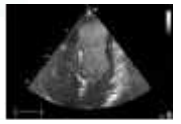


RMN coro.

Prueba esf.



SPECT.



ECO estr.

FUNCIÓN ARTERIAL / ISQUEMIA

COLESTEROL Y CORONARIOPATIAS	
1910	Colesterol en las placas ateroscleróticas
1913	Dieta con contenido alto de colesterol causa aterosclerosis en conejos
1919	Se describen los “ataques cardiacos” en humanos
1933	Se demuestra la inhibición de la síntesis de colesterol cuando aumenta la ingesta de colesterol
1938	Se describe la hipercolesterolemia familiar
1950	Se dilucida la la via de síntesis del colesterol
1951	Las dietas con contenido alto de grasas elevan el colesterol plasmático
1953	Se introduce el concepto de factor de riesgo
1955	Se identifica al LDL como factor de riesgo
1973	Se descubre el receptor de LDL
1976	Se descubren los inhibidores de la HMG CoA reductasa (estatinas)
1981	Las estatinas aumentan los receptores de LDL in vivo
1987	Se aprueba la primera estatina para huso humano
1994	Las estatinas disminuyen los ataques cardiacos y prolongan la vida
1997	Se elucida la via SREBP
2006	PCSK9: Destructor de los receptores LDL

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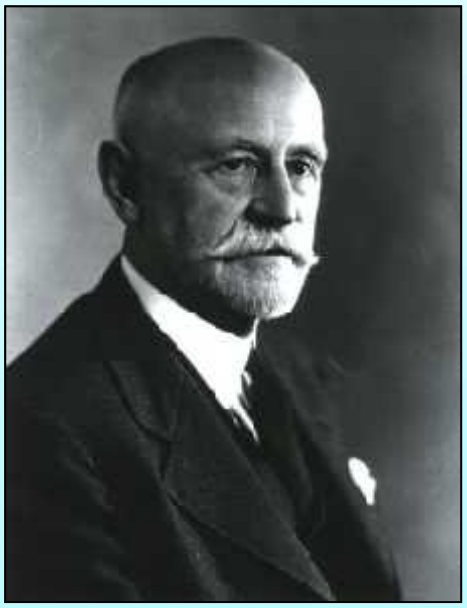
Adolf Windaus

Rudolf Schoenheimer

J. Herrick



N. Anitschkow

COLESTEROL Y CORONARIOPATIAS	
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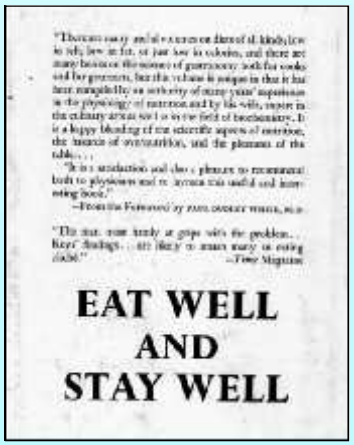
Carl Müller

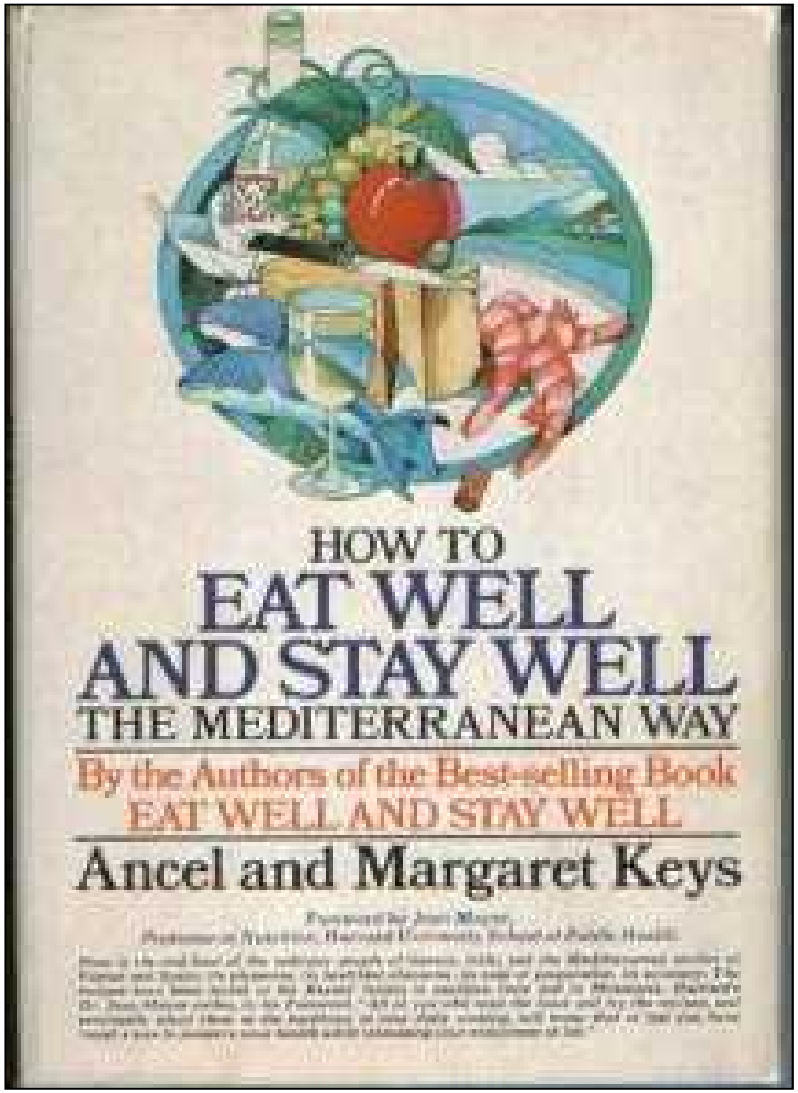
PD White. A Keys

A y M Keys



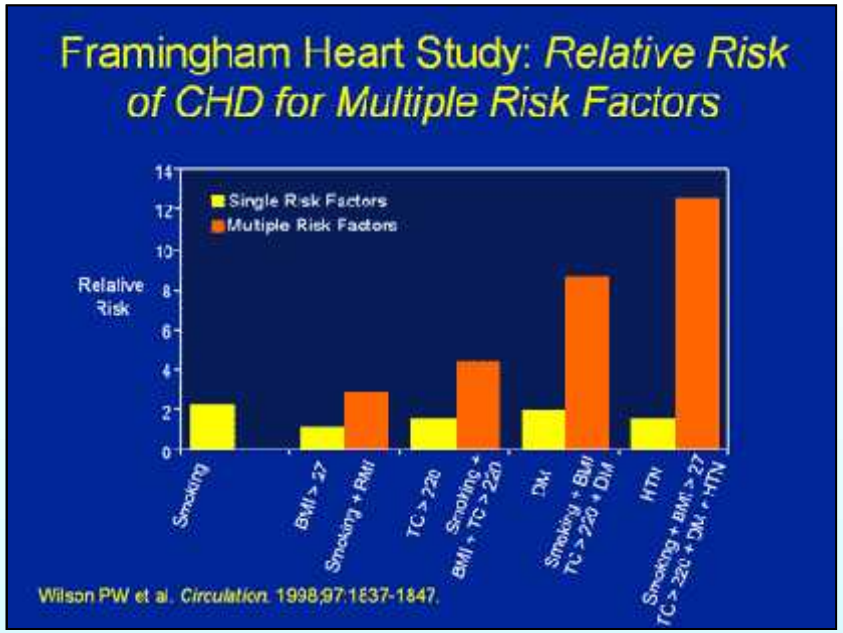
K Bloch y F Lynen

FACTORES DE RIESGO C.V.



FACTORES DE RIESGO C.V.

- Estudio Framingham: papel de la HTA, hipercolesterolemia, diabetes, tabaquismo…)
- Estudio de los 7 paises (Ancel y Margaret Keys)
- Ensayos clínicos que demuestran la disminución de la mortalidad CV al controlar los FR



W. Kannel

COLESTEROL Y CORONARIOPATIAS	
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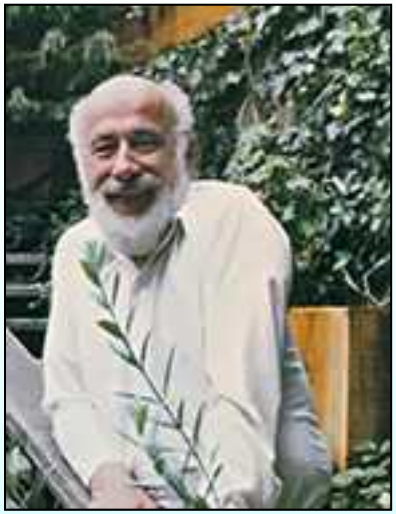
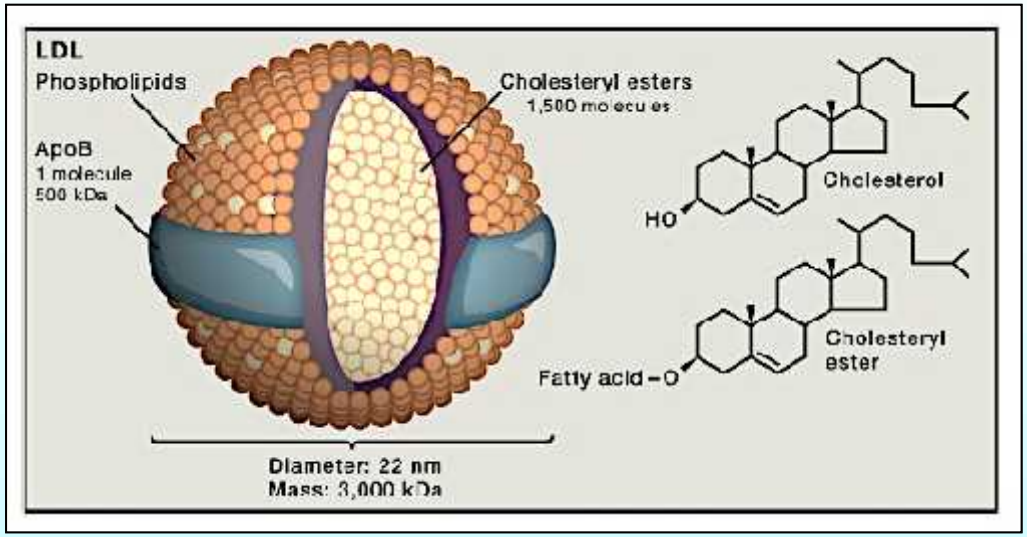
J Gofman



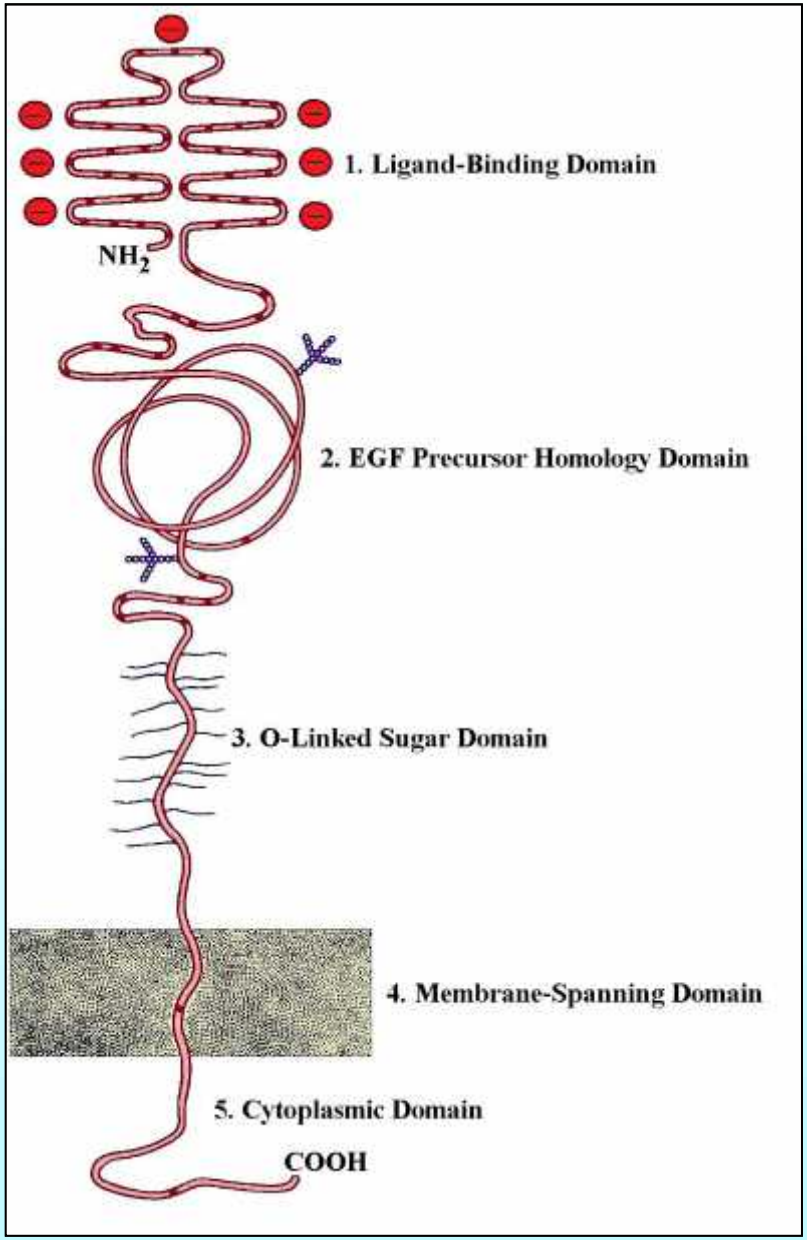
P Kovanen

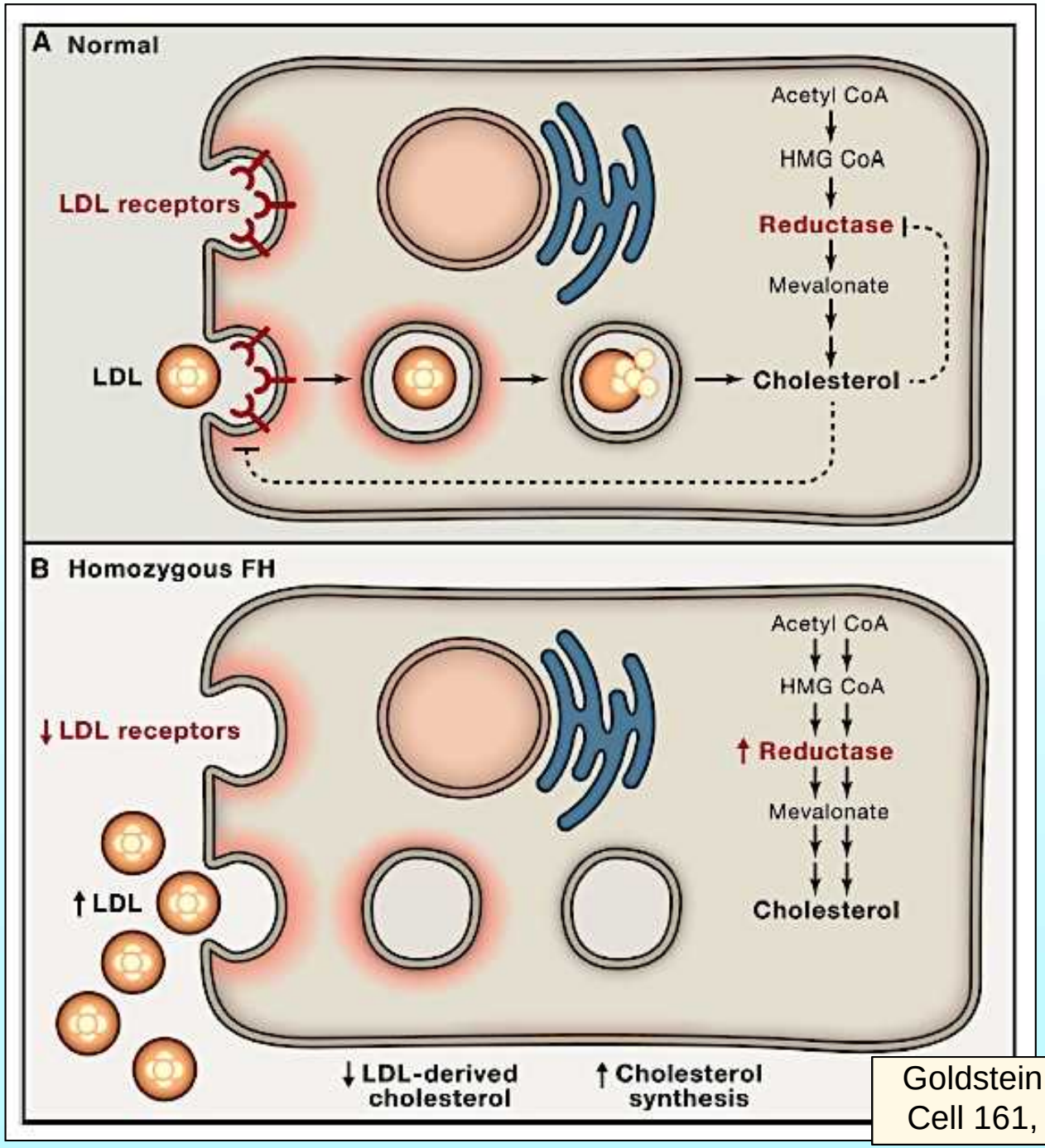
A Endo

JL Goldstein, MS Brown



Goldstein JL, Brown MS. Cell 161, 2015:161-171.





Goldstein JL, Brown MS.
Cell 161, 2015:161-171.

METABOLISMO LIPÍDICO

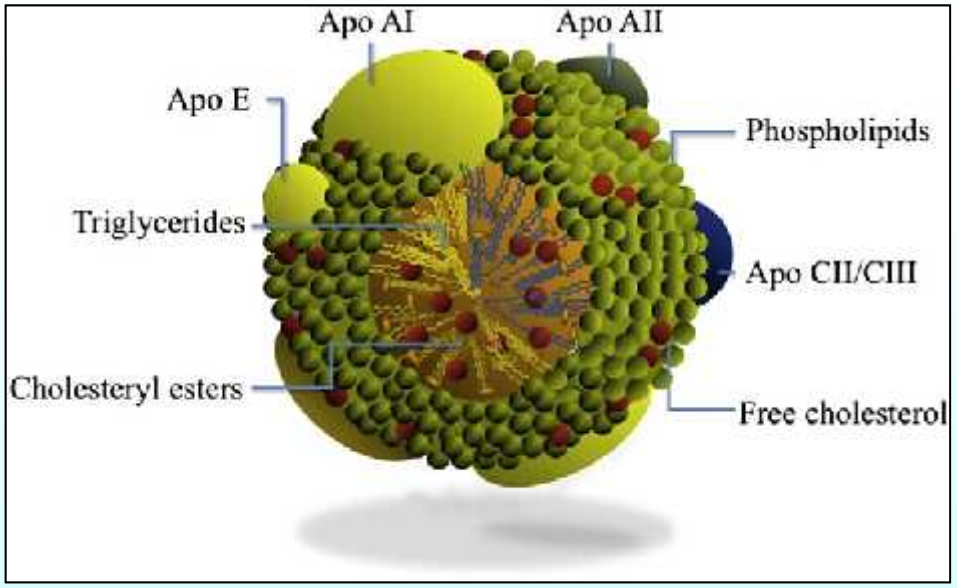
METABOLISMO LIPÍDICO:

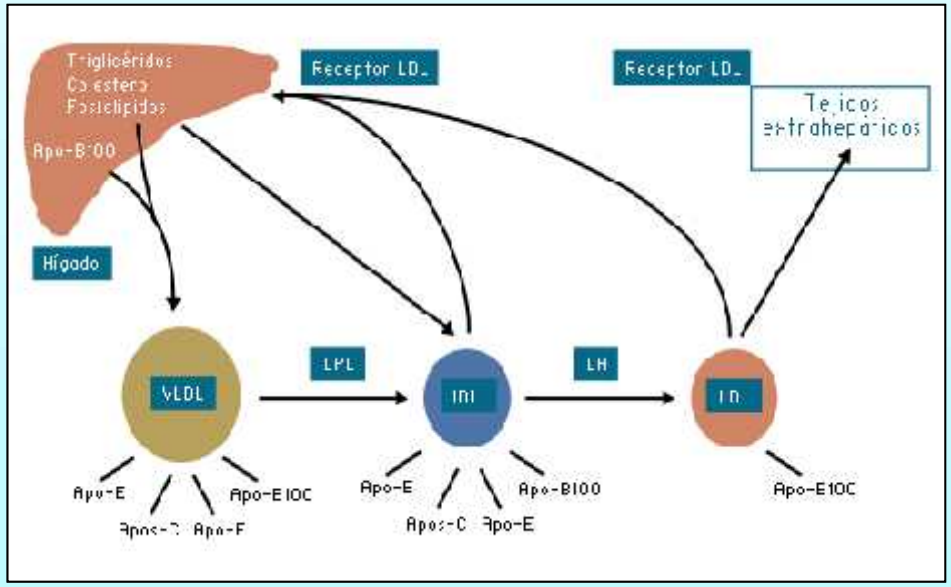
- TRANSPORTE PLASMÁTICO:
  - Quilomicrones, VLDL, IDL, LDL

- METABOLISMO EXÓGENO:
  - Quilomicrones, LPL, remanentes.

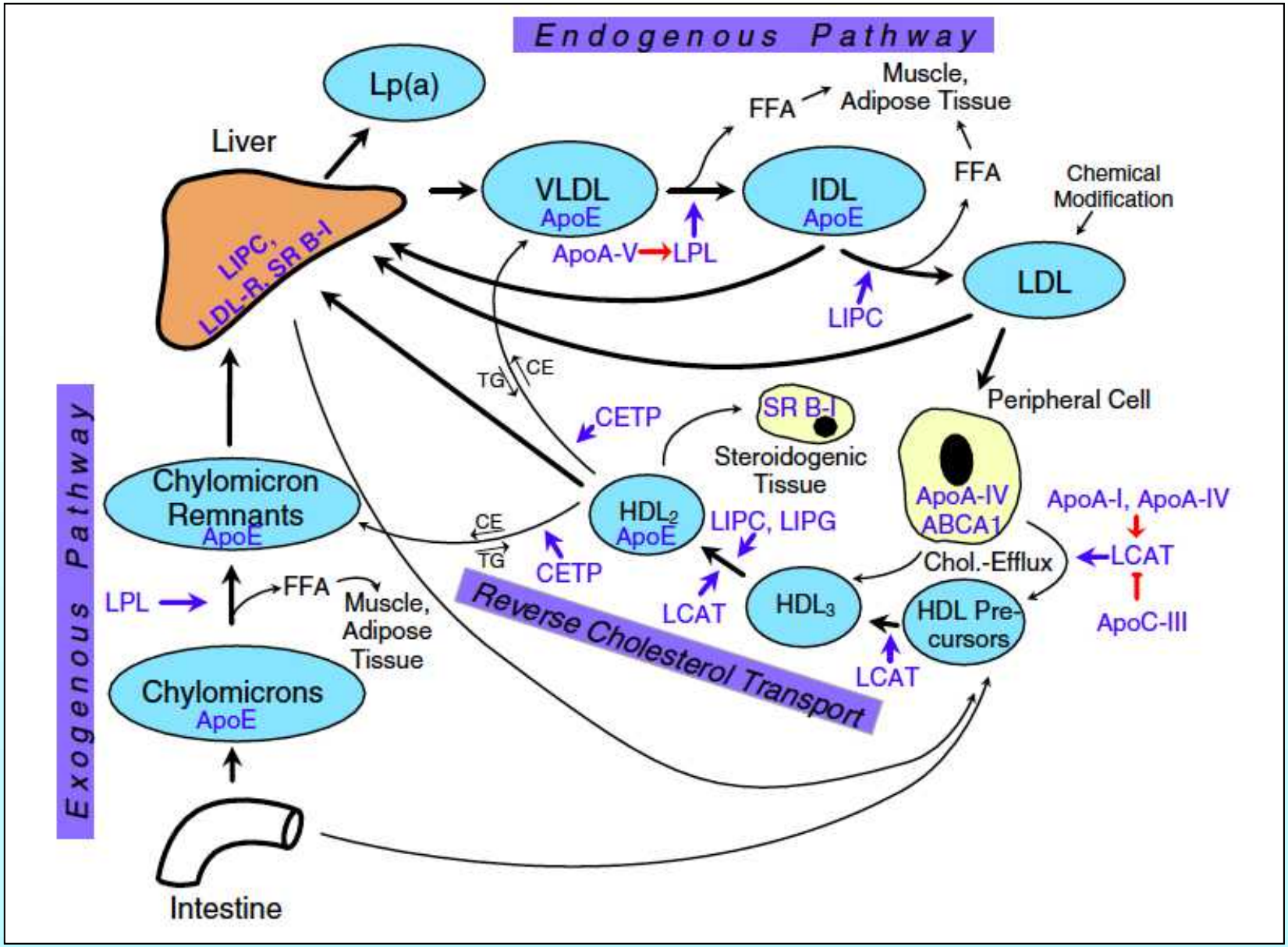
- METABOLISMO ENDÓGENO
  - LDL, Lisosomas, Espacio subendotelial

- TRANSPORTE INVERSO
  - HDL

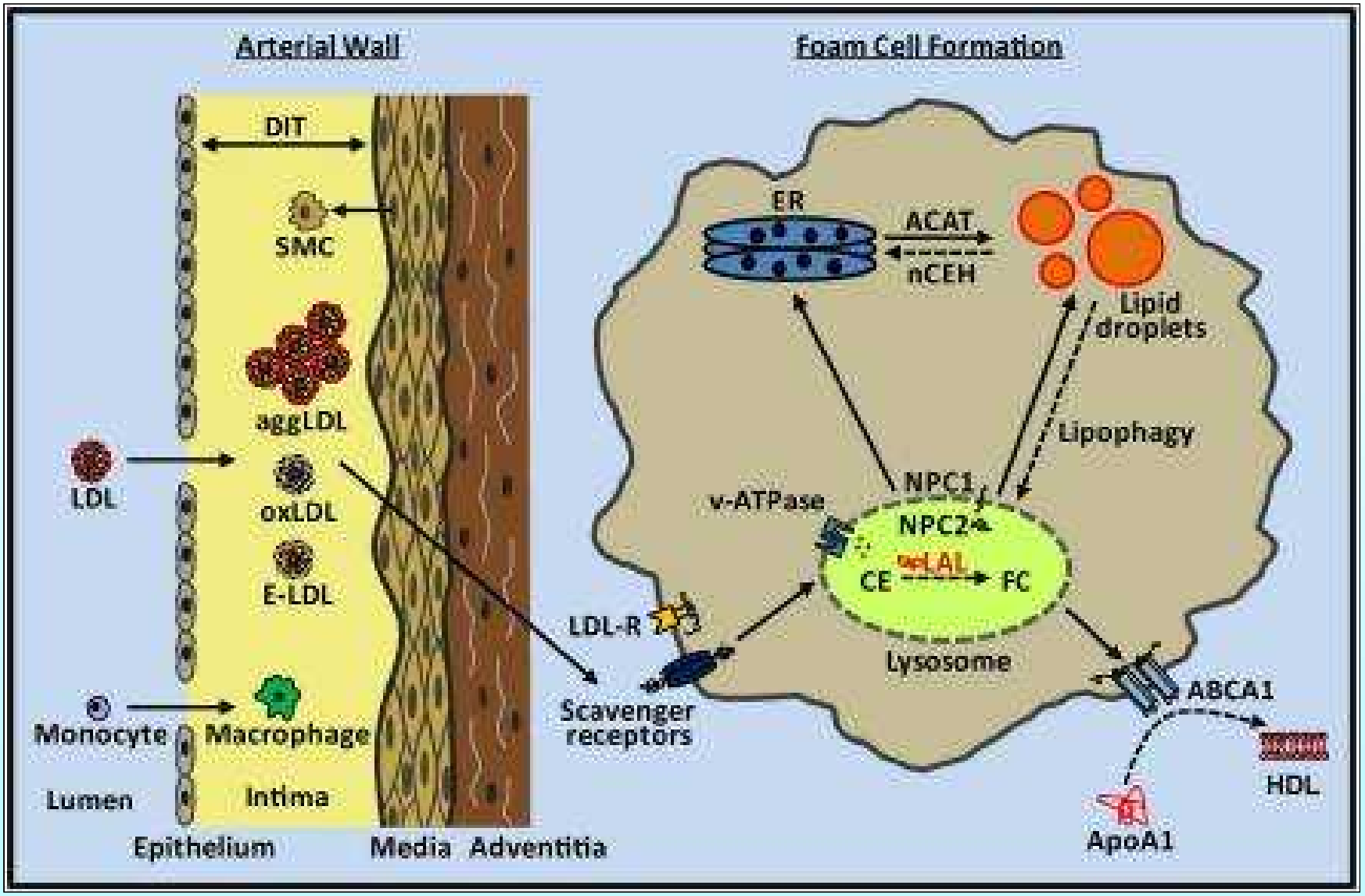




METABOLISMO LIPÍDICO

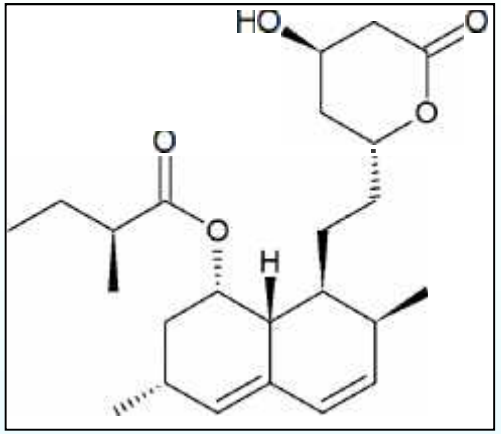


SUBENDOTELIO



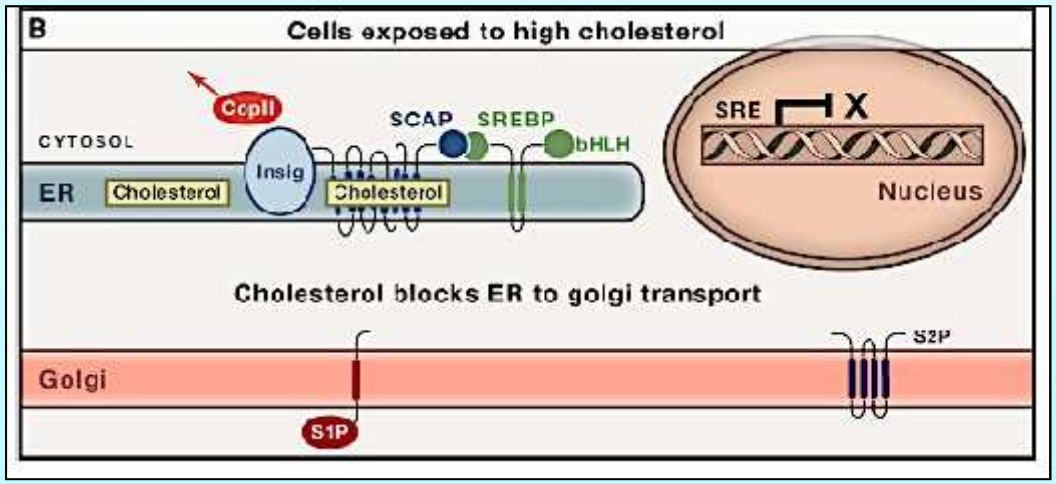
COLESTEROL Y CORONARIOPATIAS	
1987	Se aprueba la primera estatina para uso humano (lovastatina)
1994	Las estatinas disminuyen los ataques cardiacos y prolongan la vida
1997	Se elucida la via SREBP “sterol regulatory element-binding protein -2” (regulación de la transcripción)

Brody, Byrne

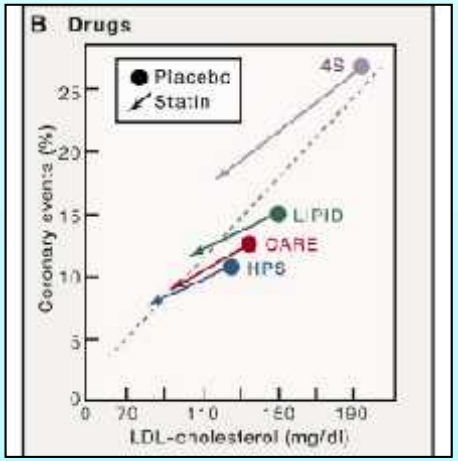


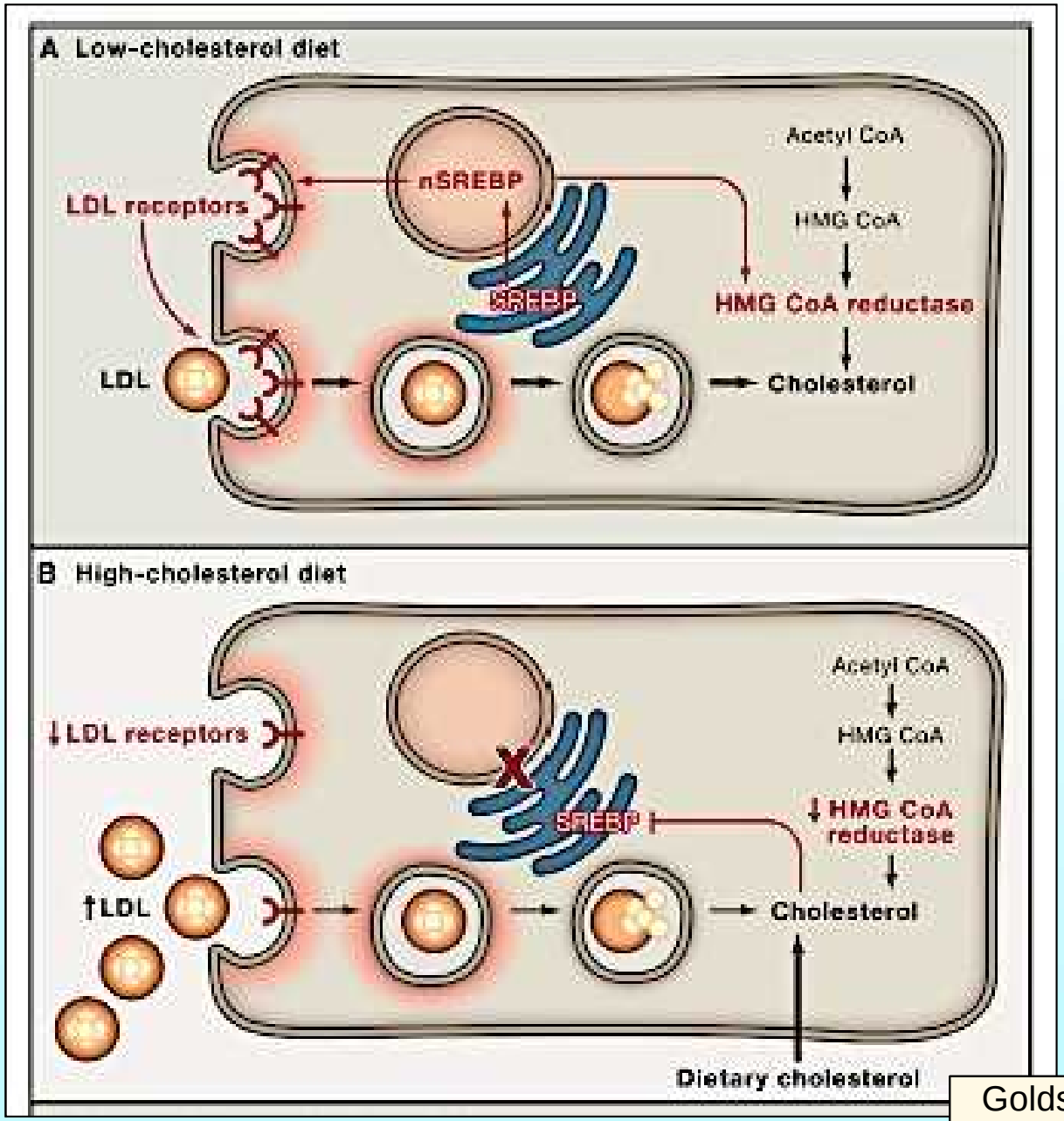
Estudio 4S (simvastatina)

Goldstein , Brown



Lancet. 1994 Nov 19;344(8934):1383-9. **Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)**.





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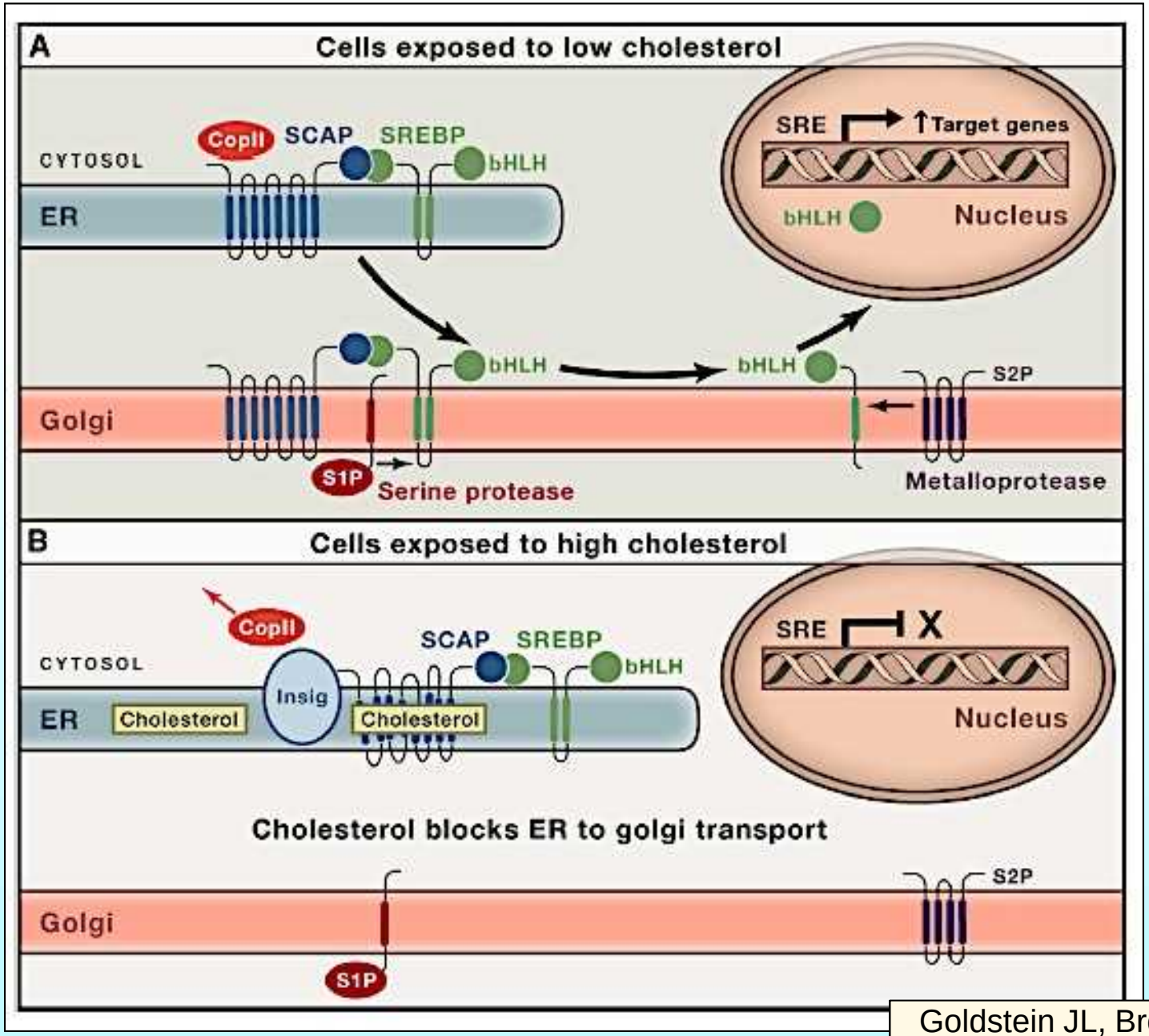

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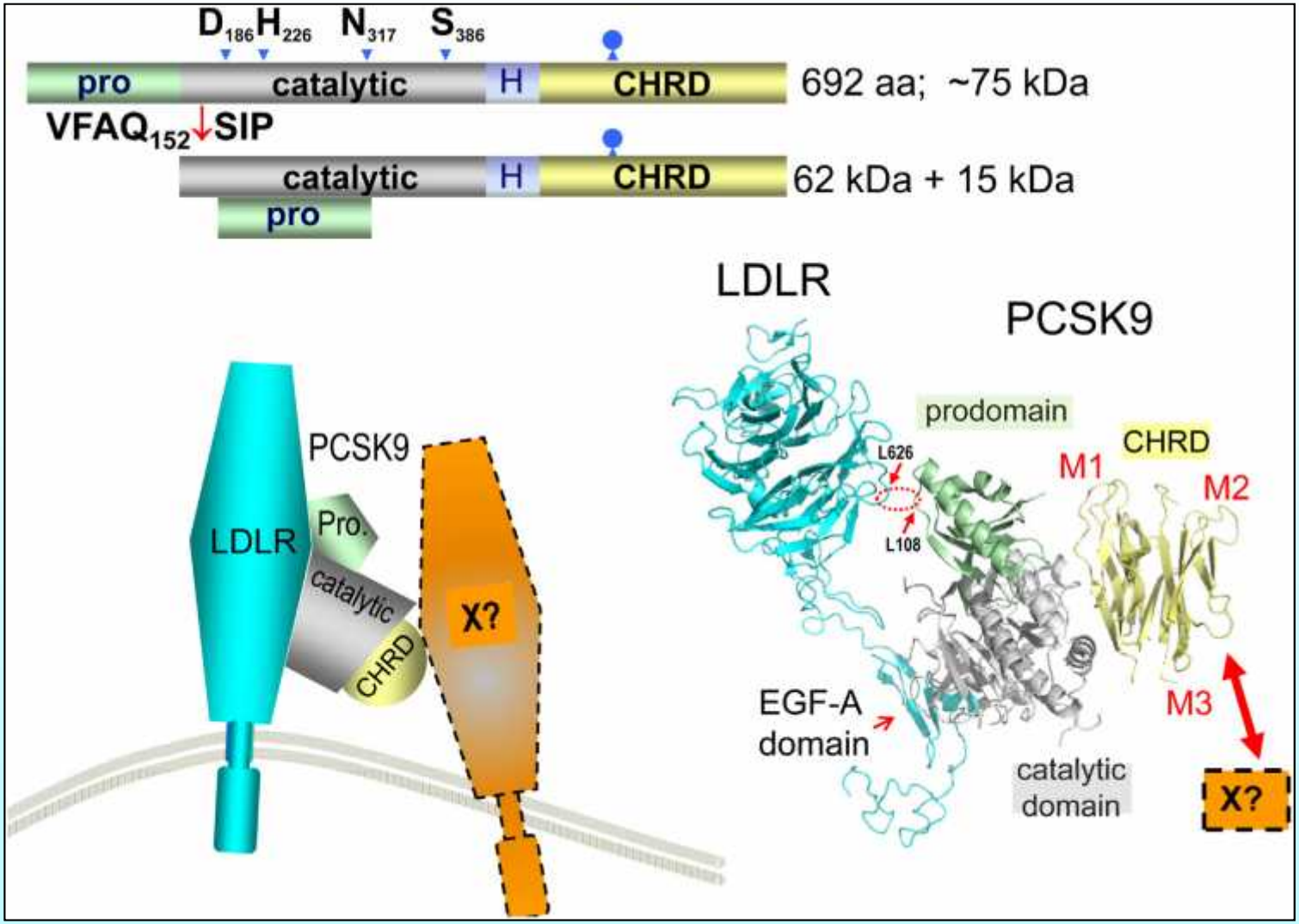
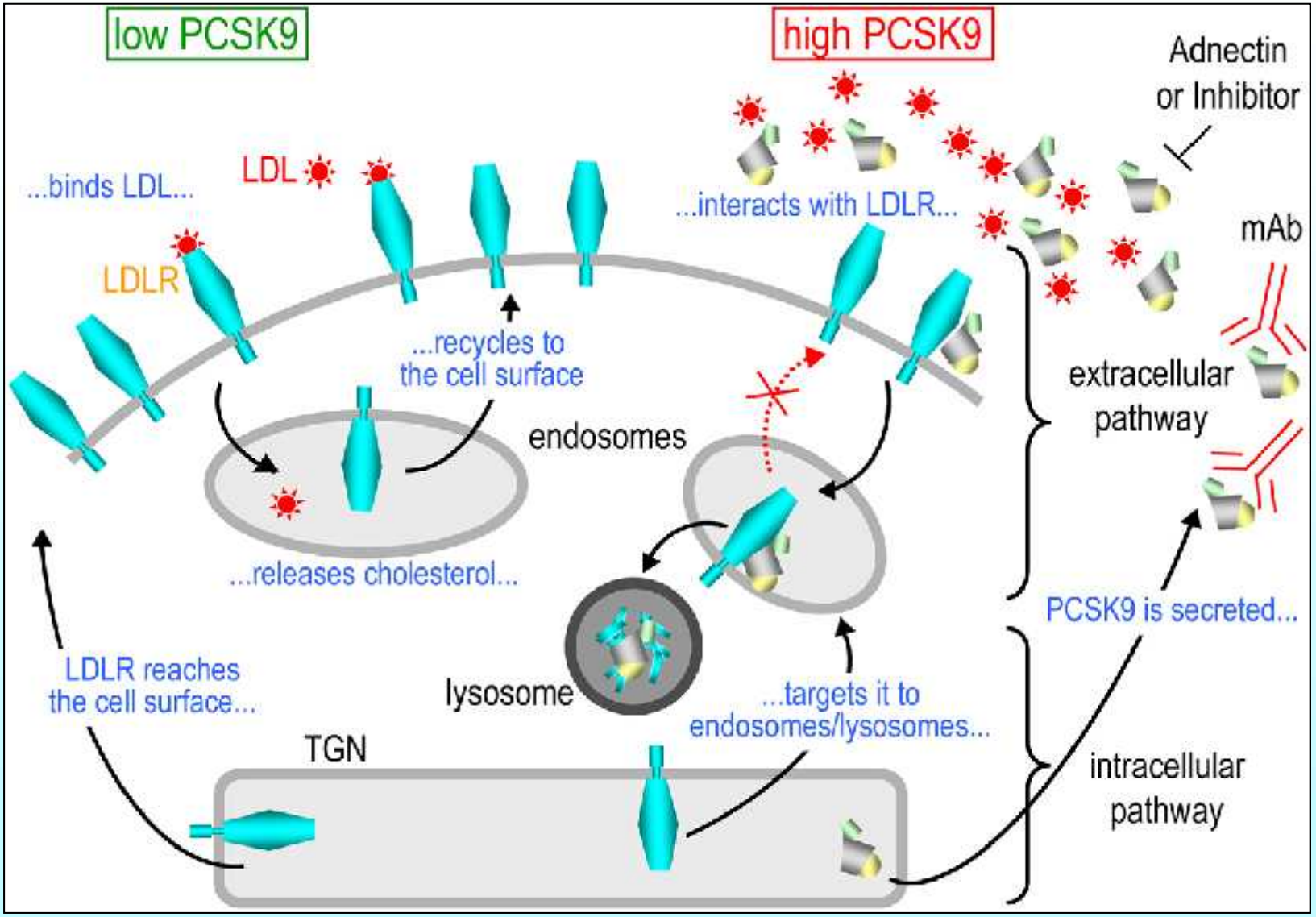
COLESTEROL Y CORONARIOPATIAS

2006	PCSK9 (Proprotein convertase subtilisin/kexin type-9): Destructor de los receptores LDL



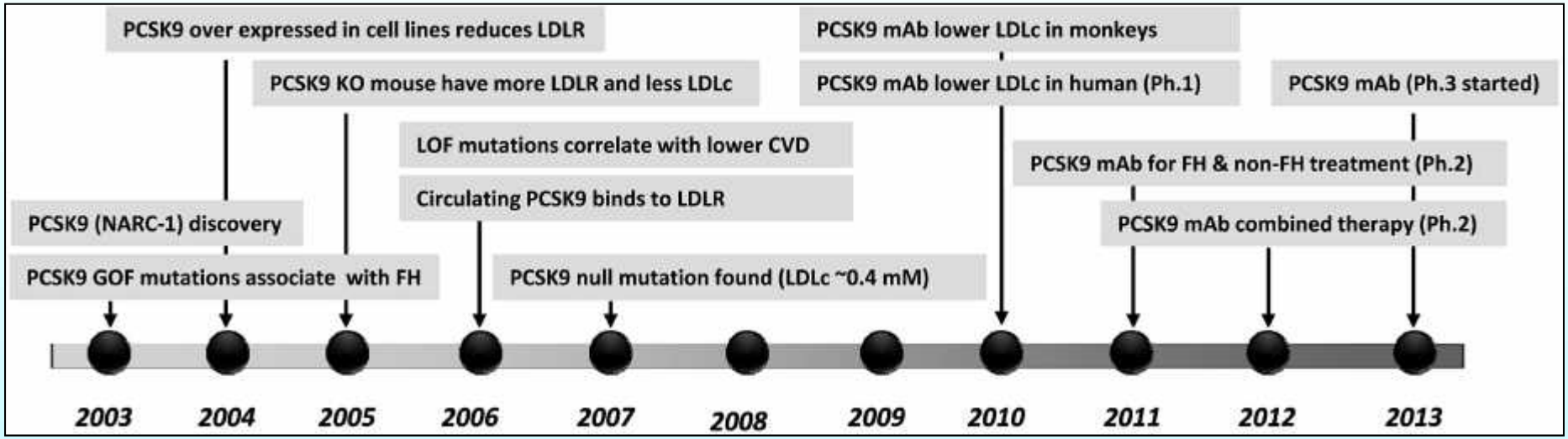
Seidah NG, et al. Circ Res 2014;114:1022

PCSK9



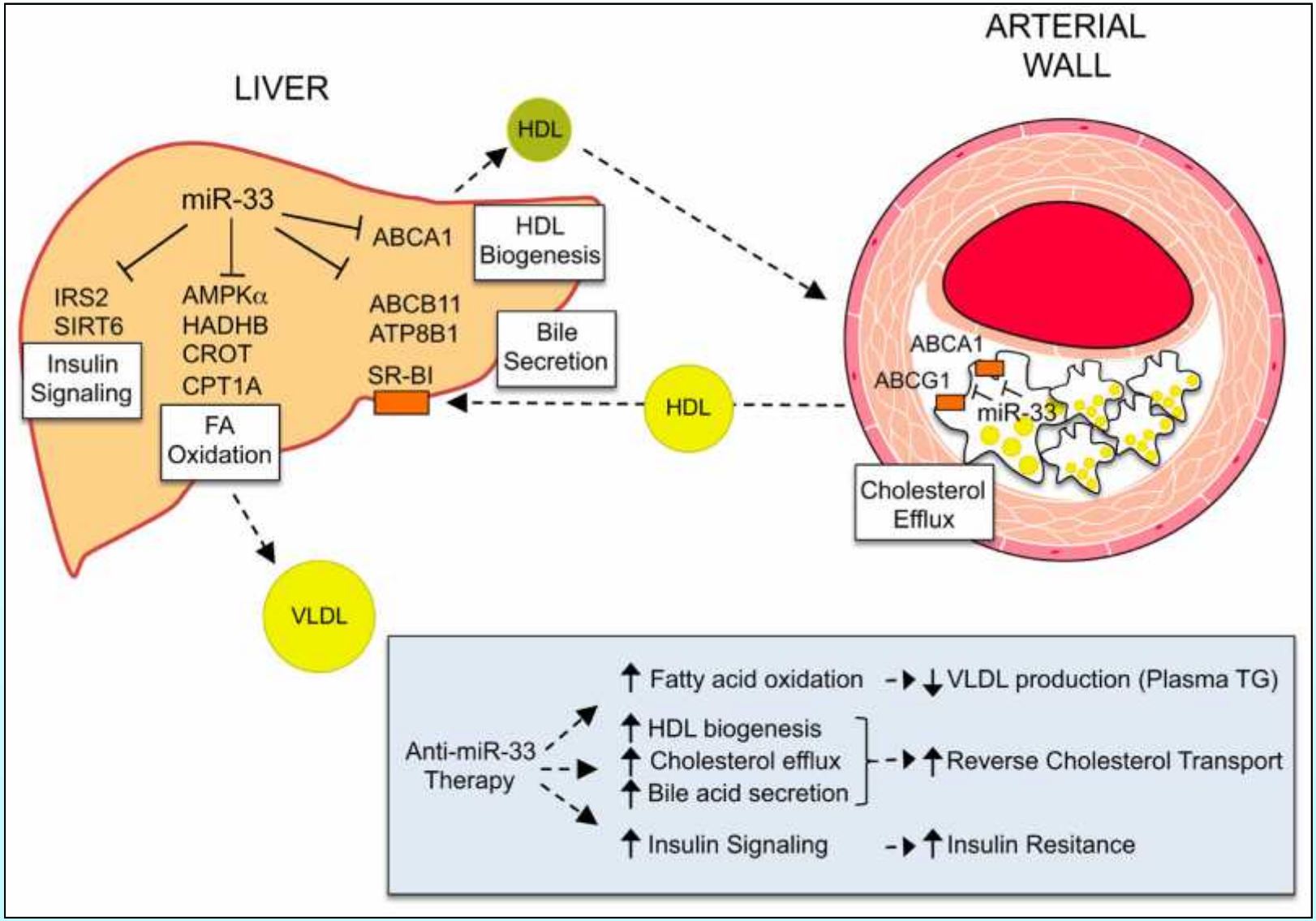
Seidah NG, et al. Circ Res 2014;114:1022

PCSK9



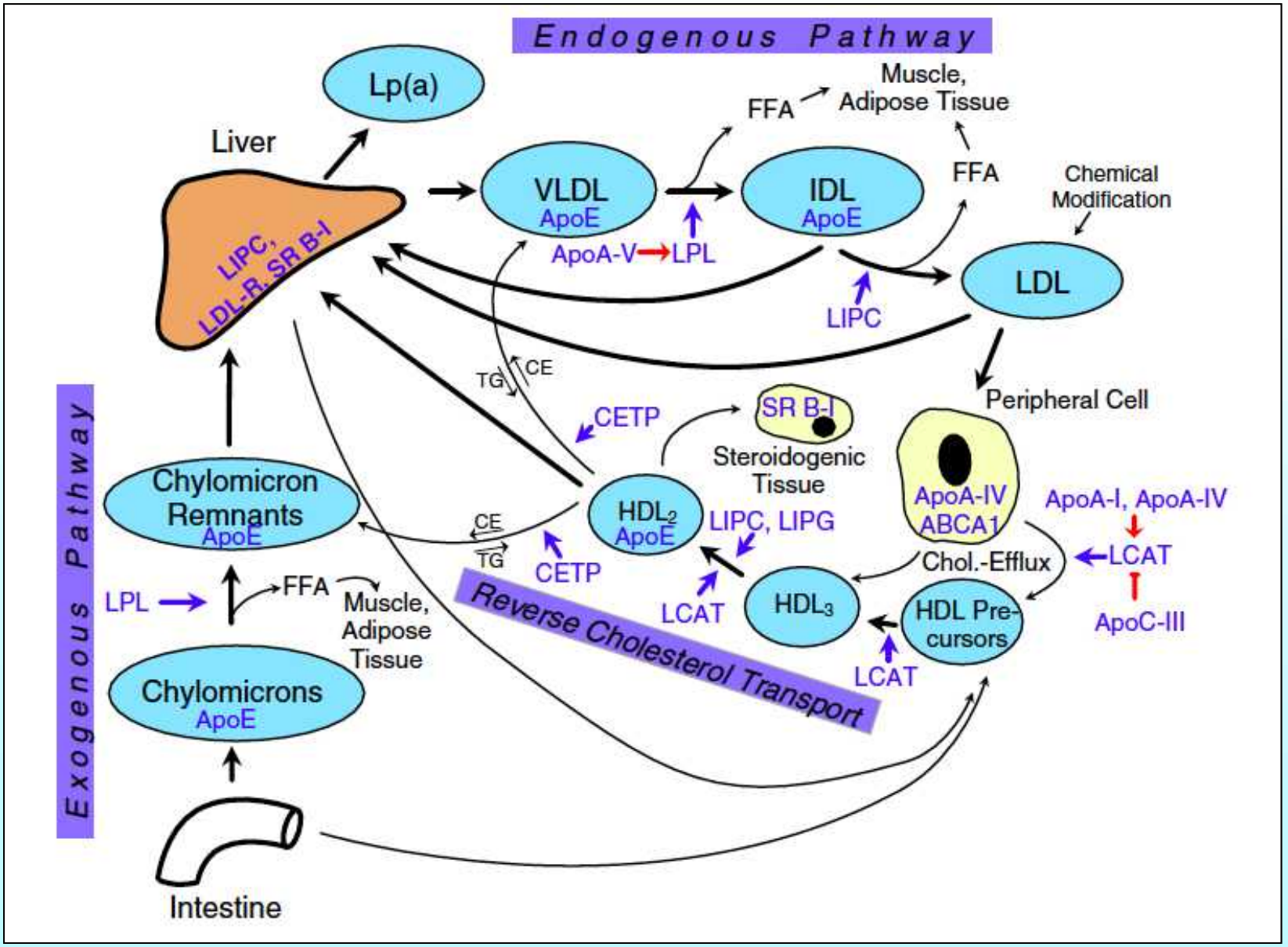
Seidah NG, et al. Circ Res 2014;114:1022

miRNA



Norata DG et al. Atherosclerosis. 2013; 227: 209.

METABOLISMO LIPÍDICO



HDL

HDL: FUNCIONES ANTI-ATEROGÉNICAS:

-**TRANSPORTE INVERSO DEL COLESTEROL:**

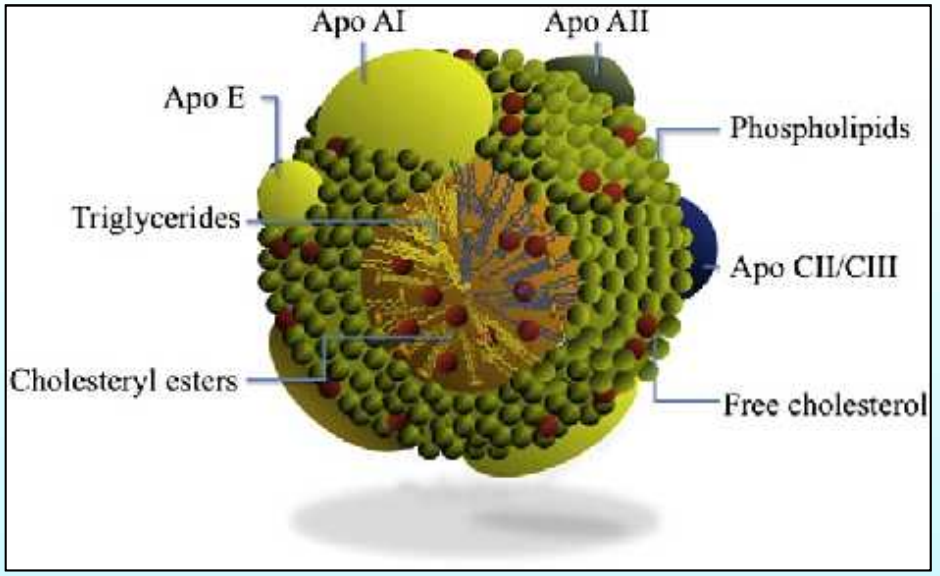
- Disminución del colesterol en la pared arterial

- **ANTIOXIDANTES:**
  - Disminuye la oxidación de las LDL

- **ANTIINFLAMATORIAS**
  - Disminuye el reclutamiento / adhesión / infiltración de los leucocitos

- **ANTITROMBÓTICAS/PRO-FIBRINOLÍTICAS:**
  - Disminuye la trombosis aguda

- **ESTABILIZACIÓN DEL ENDOTELIO:**
  - Mejora la vasodilatación arterial



Perez Mendez O, et al. Clinica Chimica Acta 429 (2014) 111–122.

HDL

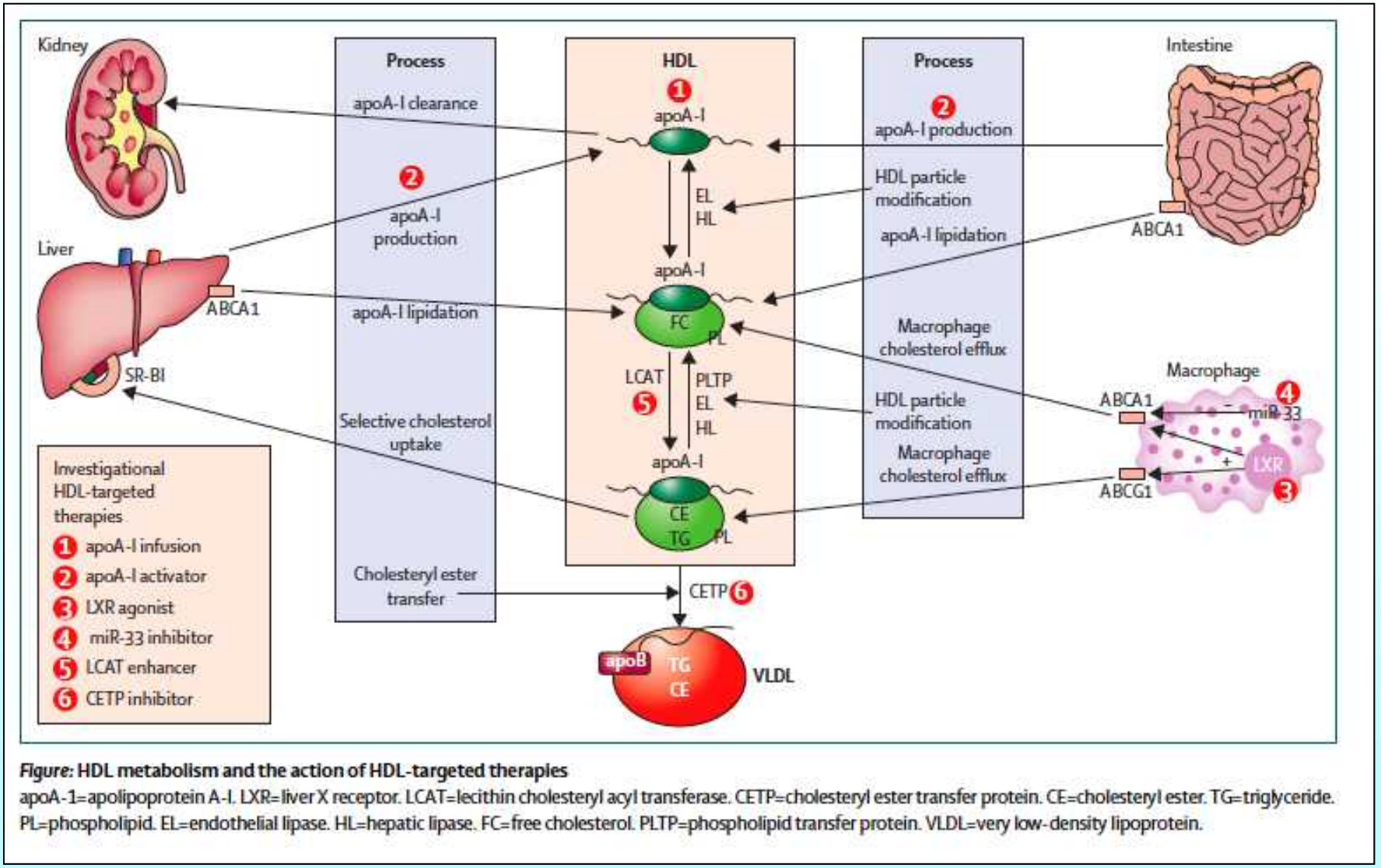


Figure: **HDL metabolism and the action of HDL-targeted therapies**
apoA-1=apolipoprotein A-I. LXR=liver X receptor. LCAT=lecithin cholesteryl acyl transferase. CETP=cholesteryl ester transfer protein. CE=cholesteryl ester. TG=triglyceride. PL=phospholipid. EL=endothelial lipase. HL=hepatic lipase. FC=free cholesterol. PLTP=phospholipid transfer protein. VLDL=very low-density lipoprotein.

Rader DJ, Hovingh GK. www.thelancet.com 384, august 16, 2014.

Review

Medical Principles and Practice

Cholesterol: The Good, the Bad, and the Ugly – Therapeutic Targets for the Treatment of Dyslipidemia

Nabil A. Elshourbagy Harold V. Meyers Sherin S. Abdel Meguid

Shire Biomedical Corporation, Wayne, Pa., USA

Abstract

Maintaining cholesterol and triglyceride (TG) levels within healthy limits is critical for decreasing the risk of heart disease. Dyslipidemia refers to the abnormal levels of lipids in the blood, including low high-density lipoprotein cholesterol (HDL-C), also known as good cholesterol, high low-density lipoprotein cholesterol (LDL-C), also known as bad choles-

Drug class	Drug	Company	Status	Effect
apoAI variant	MDCO-216	The Medicines Company	Phase I/II	Raise HDL
apoAI	CER-001	Cerenis Therapeutics	Phase II	Raise HDL
MTTP inhibitor	Lomitapide	Aegerion Pharmaceuticals	Marketed	Lower LDL
apoB mRNA antisense	Mipomersen	Genzyme	Marketed	Lower LDL
PCSK9 antagonist (monoclonal antibody)	REGN727/SAR236553	Regeneron/Sanofi	Phase III	Lower LDL
PCSK9 antagonist (monoclonal antibody)	AMG-145	Amgen	Phase III	Lower LDL
PCSK9 antagonist (monoclonal antibody)	LGT209	Novartis	Phase II	Lower LDL
PCSK9 antagonist (monoclonal antibody)	RN316	Pfizer	Phase II	Lower LDL
PCSK9 antagonist (monoclonal antibody)	1D05	Merck	Development	Lower LDL

in raising HDL-C, where we discuss three apoAI-based drugs under development. These are its mutated dimer (apoAI-Milano), a complex with phospholipids, and a mimetic peptide. Atherosclerosis, mainly because of dyslipidemia, is a leading cause of cardiovascular disease. Regarding the title of this article, the 'good' refers to HDL-C, the 'bad' refers to LDL-C, and the 'ugly' refers to atherosclerosis.

Review

Medical Principles and Practice

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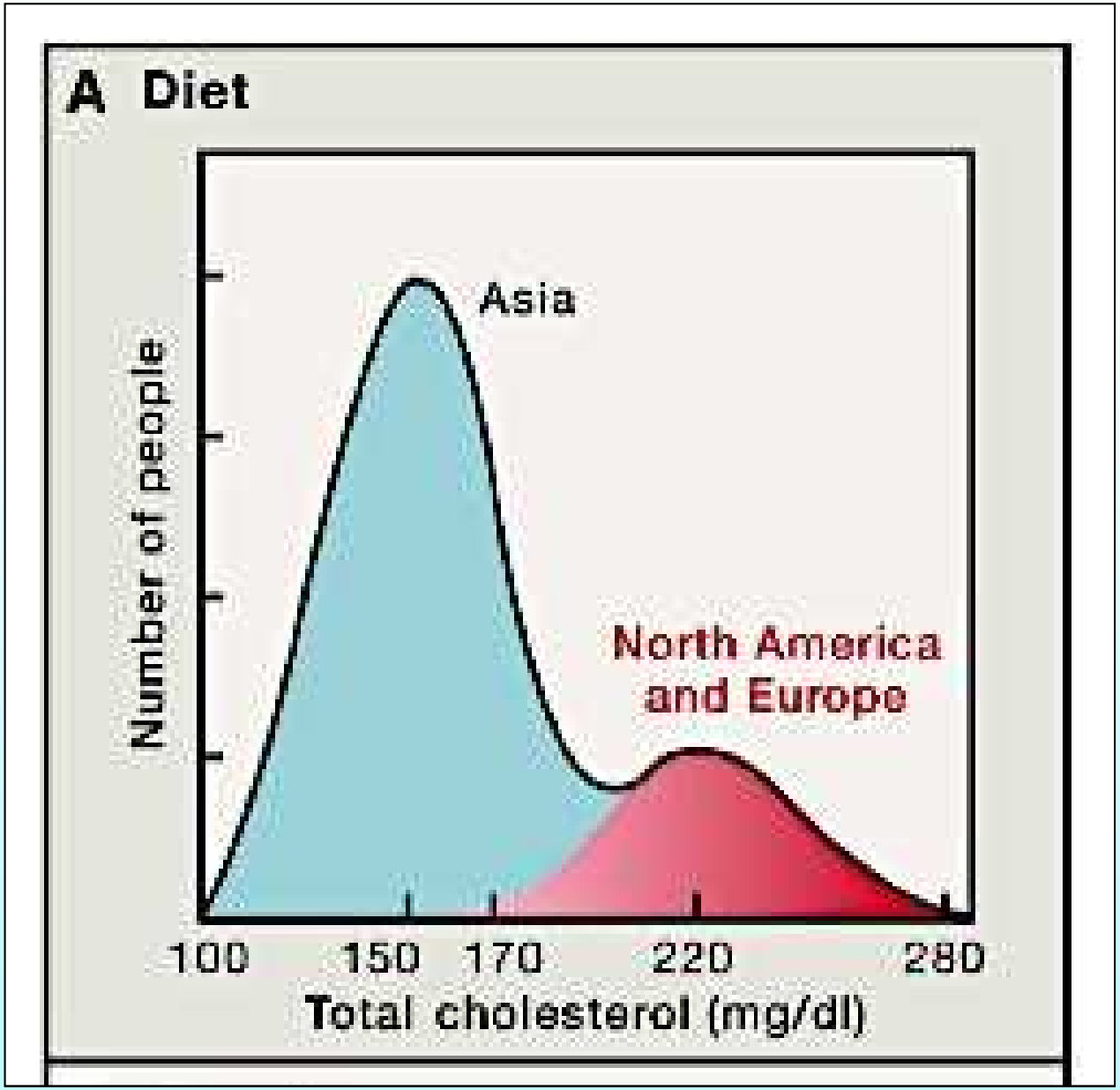


Goldstein JL, Brown MS.
Cell 161, 2015:161-171.

RIESGO CARDIOVASCULAR

Prevención primaria de la enfermedad cardiovascular

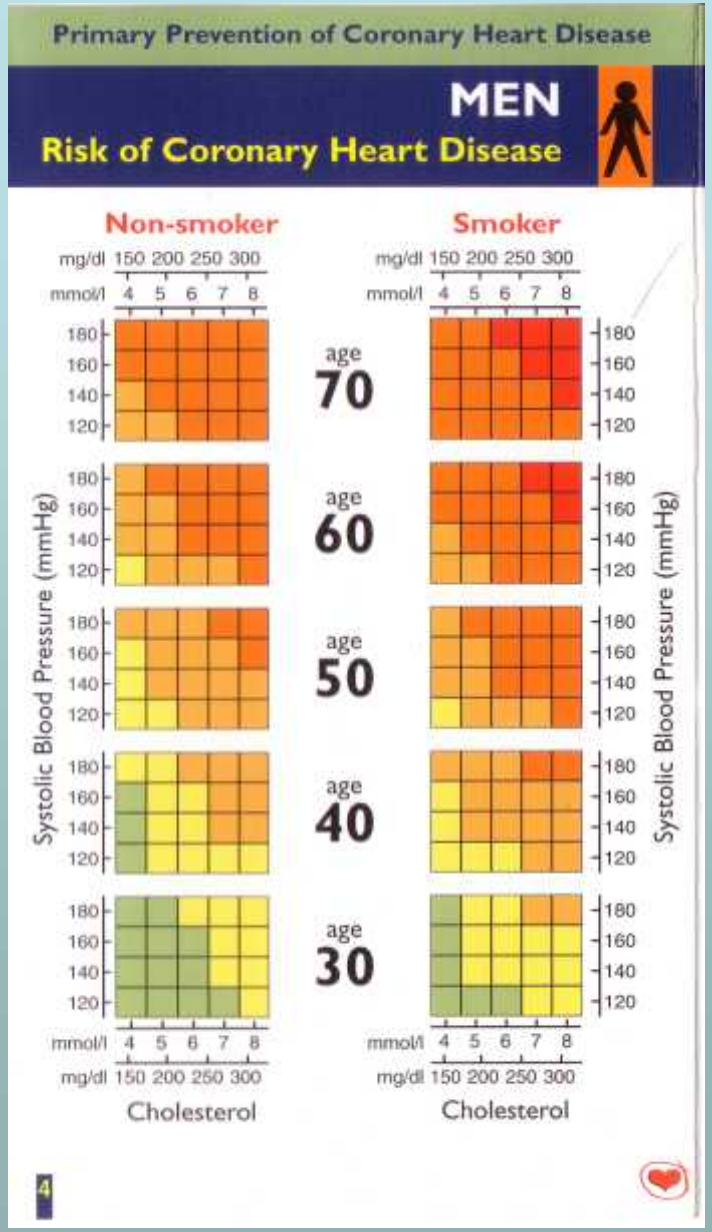
Estilos de vida

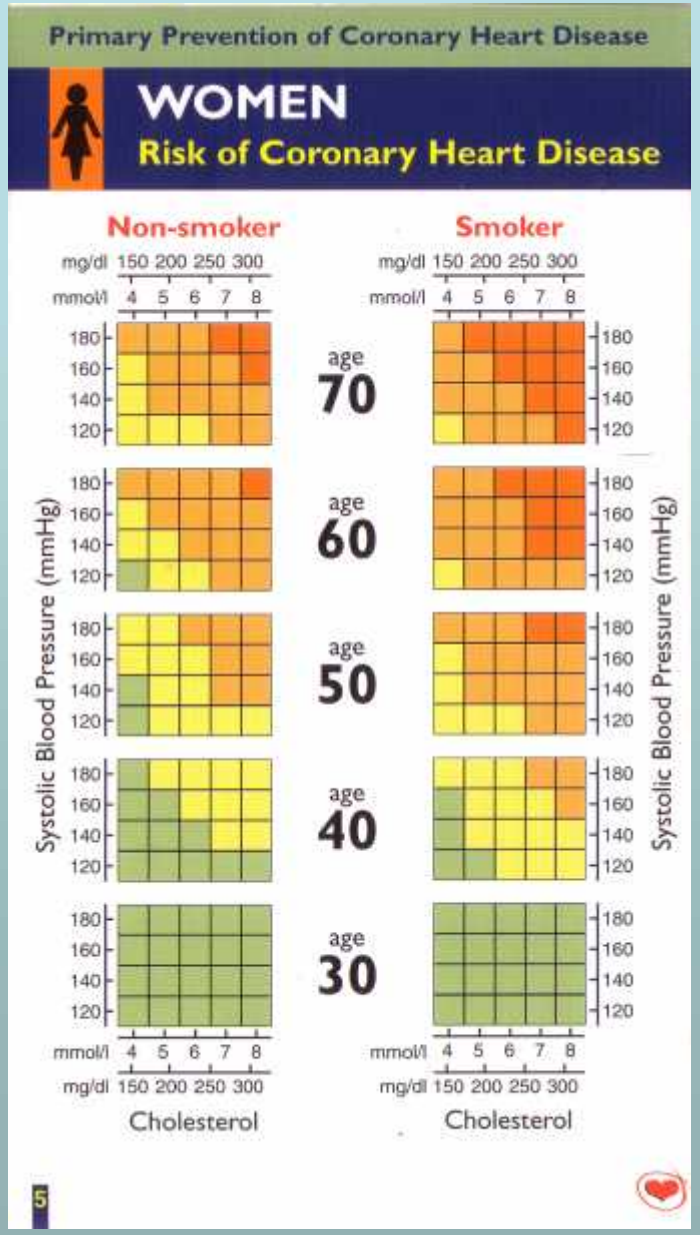
No fumar

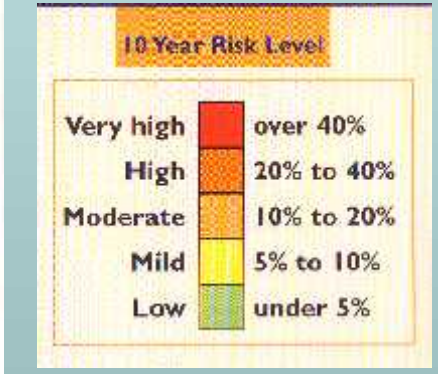
- **Reducir** el consumo alimentario total de grasas, especialmente grasas saturadas y colesterol.
- **Aumentar** el consumo alimentario de grasas insaturadas procedentes de verduras y del pescado.
- **Aumentar** el consumo alimentario de fruta fresca, cereales y verduras.
- **Reducir** las calorías para alcanzar el peso ideal.

Realizar actividad física

RIESGO CARDIOVASCULAR







Drug class	Drug	Company	Status	Effect
apoAI variant	MDCO-216	The Medicines Company	Phase I/II	Raise HDL
apoAI	CER-001	Cerenis Therapeutics	Phase II	Raise HDL
MTTP inhibitor	Lomitapide	Aegerion Pharmaceuticals	Marketed	Lower LDL
apoB mRNA antisense	Mipomersen	Genzyme	Marketed	Lower LDL
PCSK9 antagonist (monoclonal antibody)	REGN727/SAR236553	Regeneron/Sanofi	Phase III	Lower LDL
PCSK9 antagonist (monoclonal antibody)	AMG-145	Amgen	Phase III	Lower LDL
PCSK9 antagonist (monoclonal antibody)	LGT209	Novartis	Phase II	Lower LDL
PCSK9 antagonist (monoclonal antibody)	RN316	Pfizer	Phase II	Lower LDL
PCSK9 antagonist (monoclonal antibody)	1D05	Merck	Development	Lower LDL