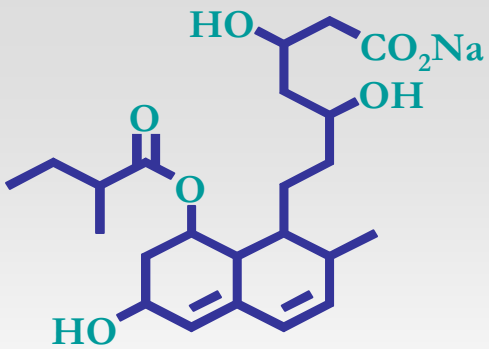
Jose Maria Mostaza

Hospital Carlos III

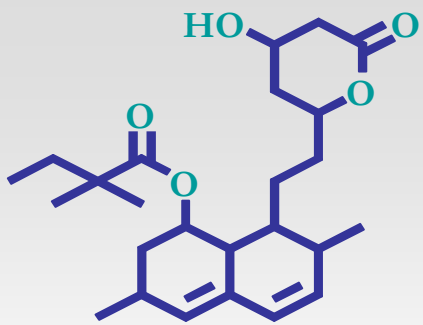
Madrid

NUEVOS FÁRMACOS EN DISLIPEMIAS ¿QUÉ PODEMOS ESPERAR?

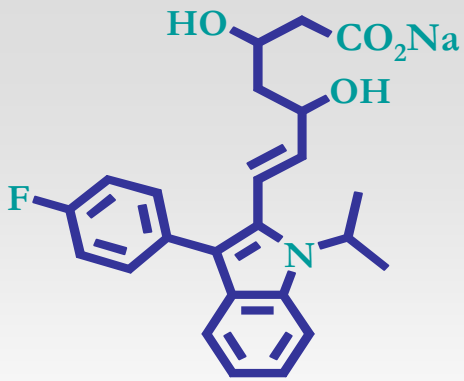
Estatinas



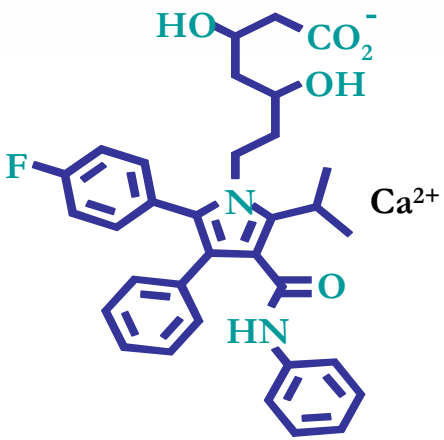
Pravastatina



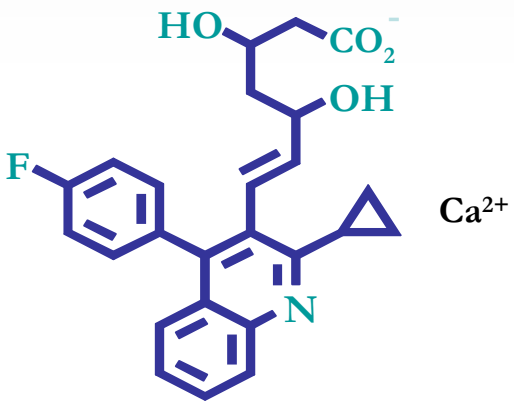
Simvastatina



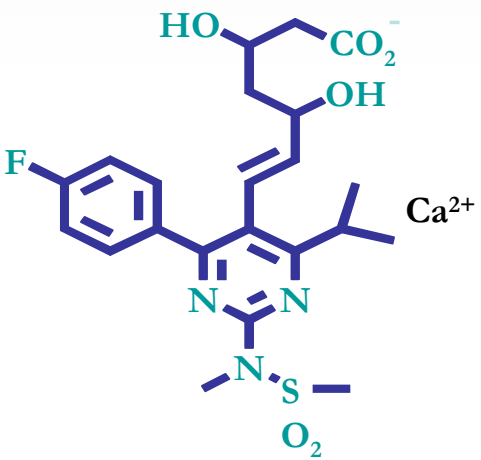
Fluvastatina



Atorvastatina

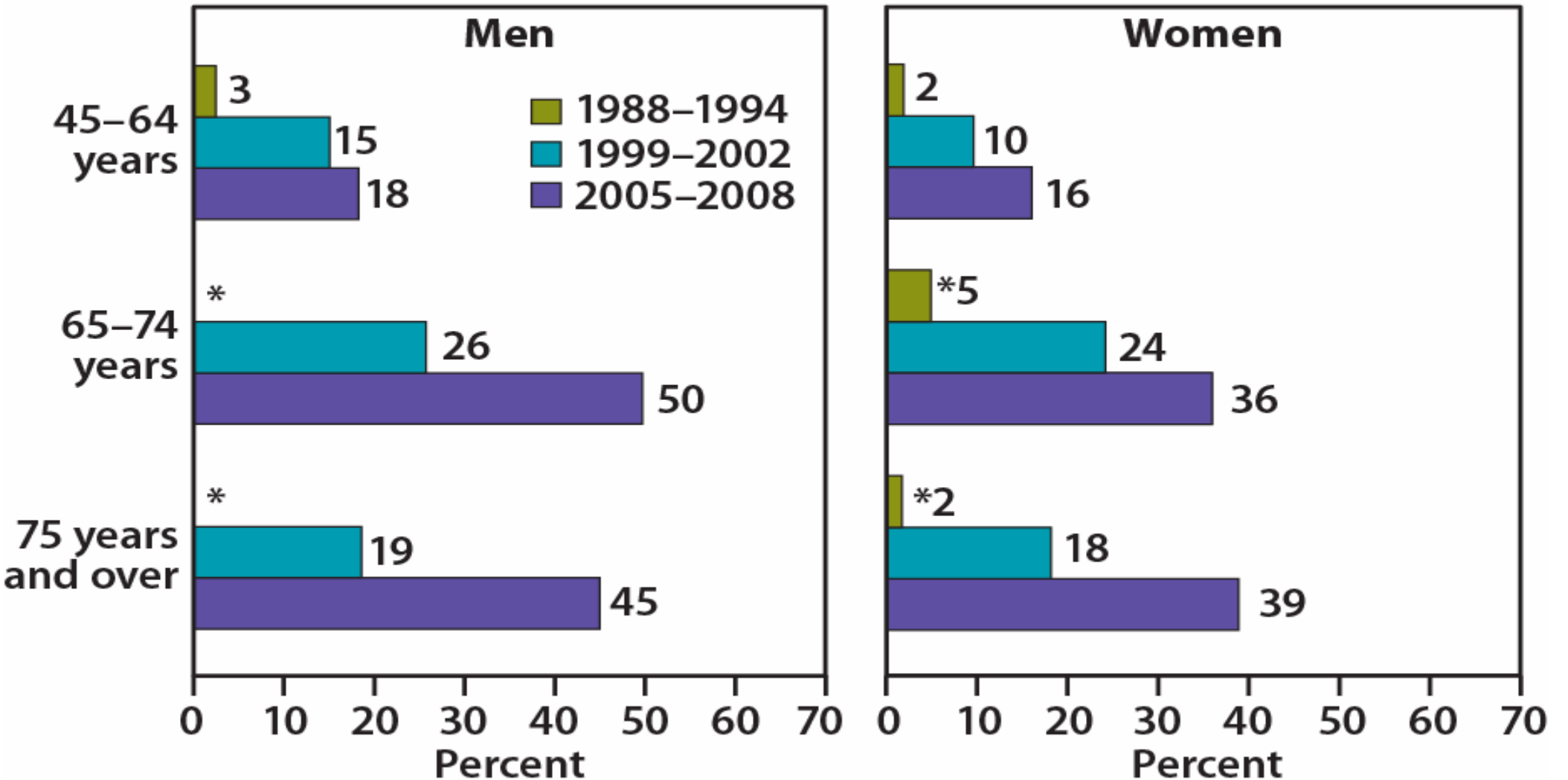


Pitavastatina



Rosuvastatina

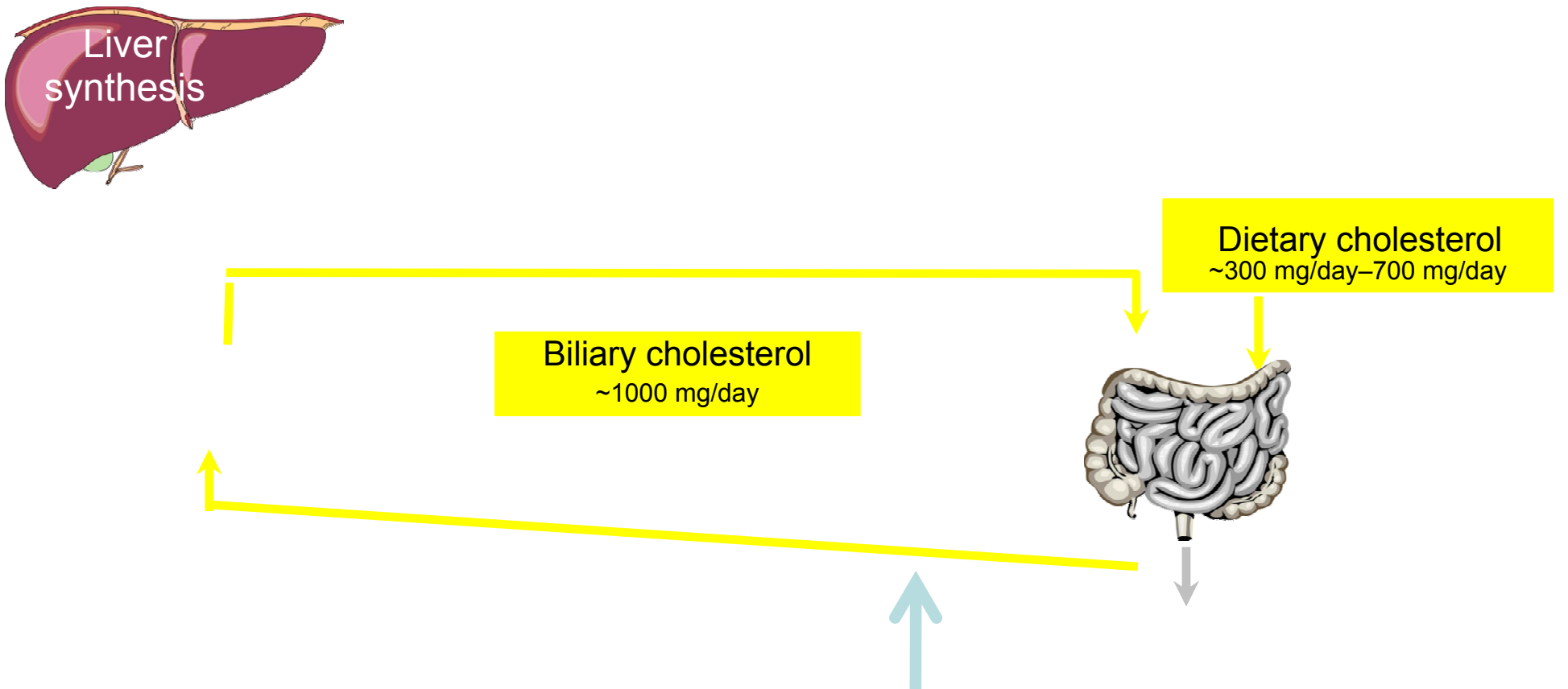
Statin drug use in the past 30 days



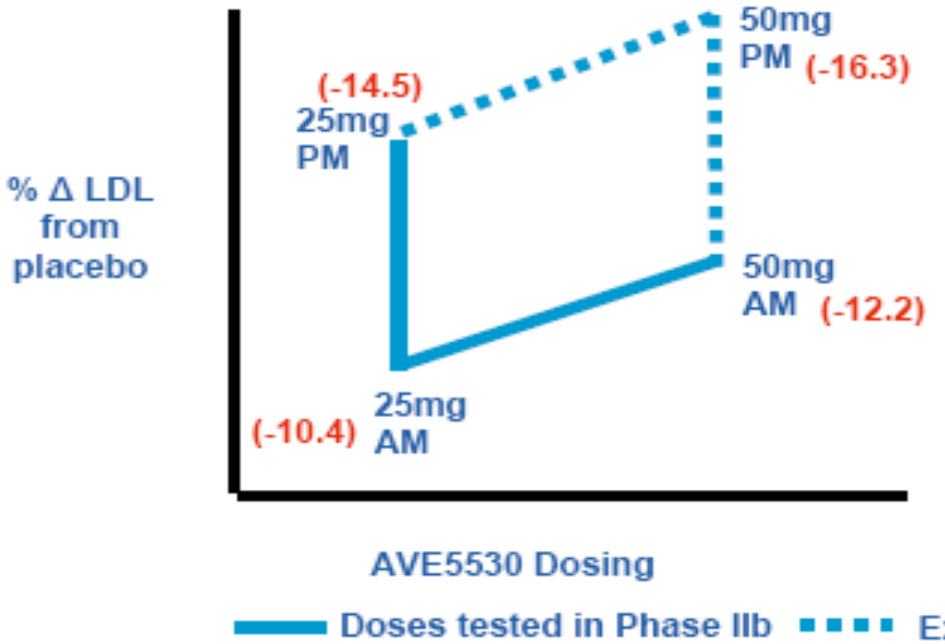
*Estimates are considered unreliable. Data preceded by an asterisk have a relative standard error (RSE) of 20%–30%. Data not shown have an RSE of greater than 30%.

SOURCE: CDC/NCHS, *Health, United States, 2010*, Figure 17. Data from the National Health and Nutrition Examination Survey.

Inhibición de la absorción intestinal de colesterol



AVE5530 (cholesterol absorption inhibitor for hypercholesterolemia): Phase II results



Phase IIb Study Design

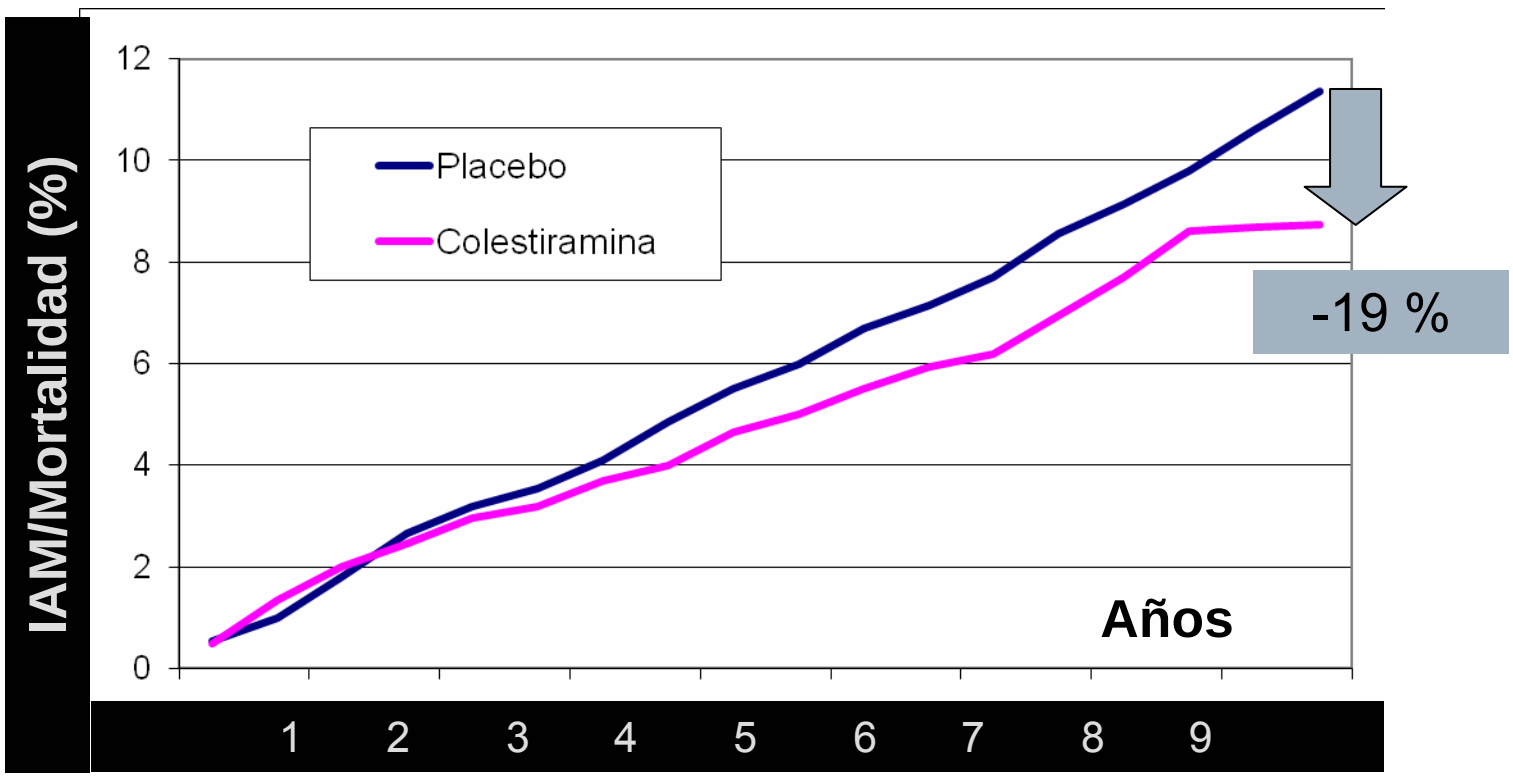
- patients with mild to moderate primary hypercholesterolemia
- randomized, double-blind,
- parallel-group, placebo-controlled
- ezetimibe-calibrated, multicenter
- 4 weeks treatment duration

% Δ LDL from placebo	Pbo (N=28)	Ezetimibe (N=25)	5mg am (N=31)	25mg am (N=37)	25mg pm (N=26)	50mg am (N=29)	100mg am (N=26)
	-	-19.5	-4.8	-10.4	-14.5	-12.2	-12.0
P value	-	<0.0001	0.1650	0.0019	<0.0001	0.0002	0.0001

sanofi aventis

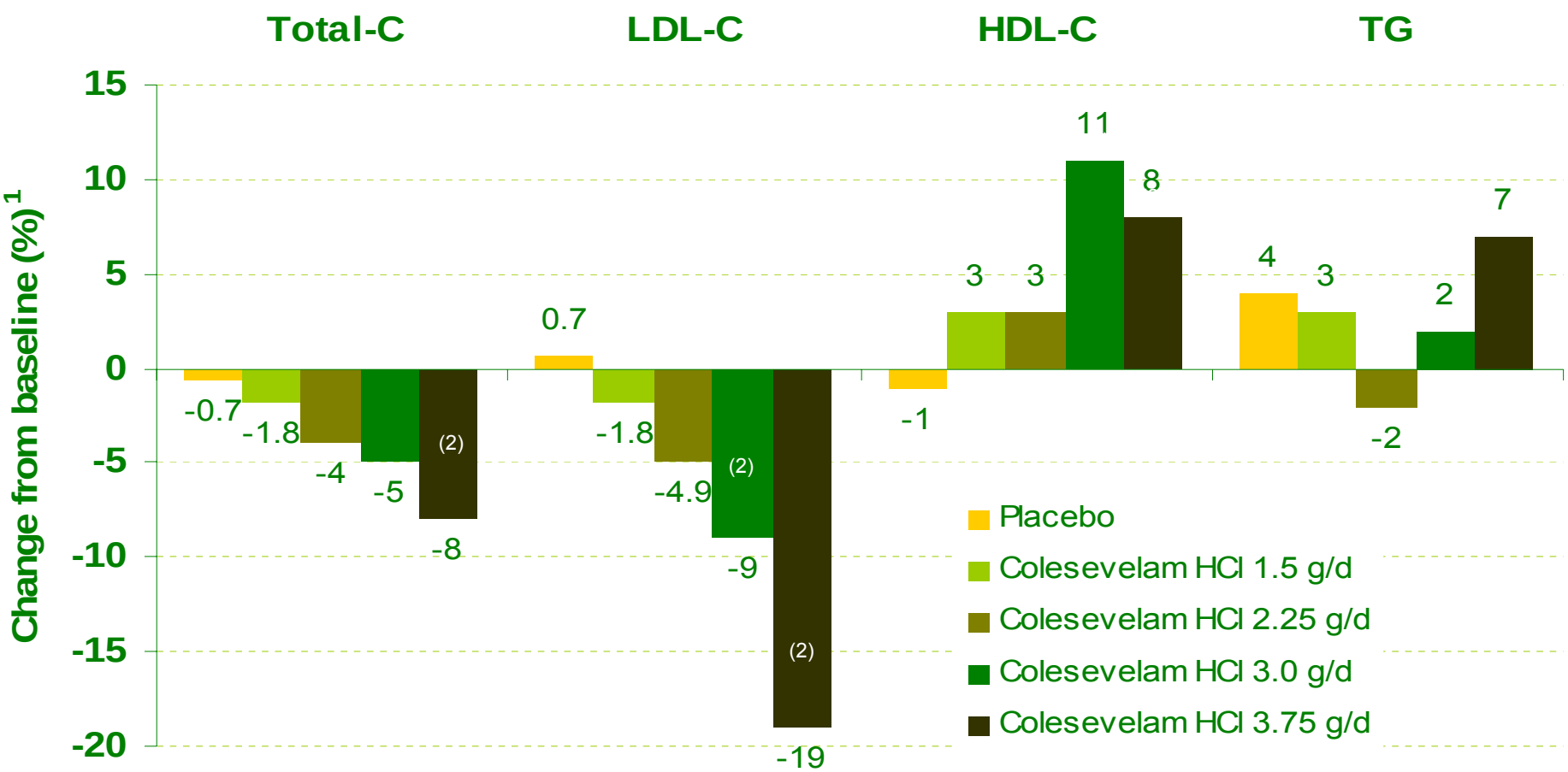
Lipid Research Clinics Coronary Primary Prevention Trial

Reducción del colesterol total del 8,5% y del C-LDL del 12,6% con Colestiramina (24 g/d) vs. Placebo



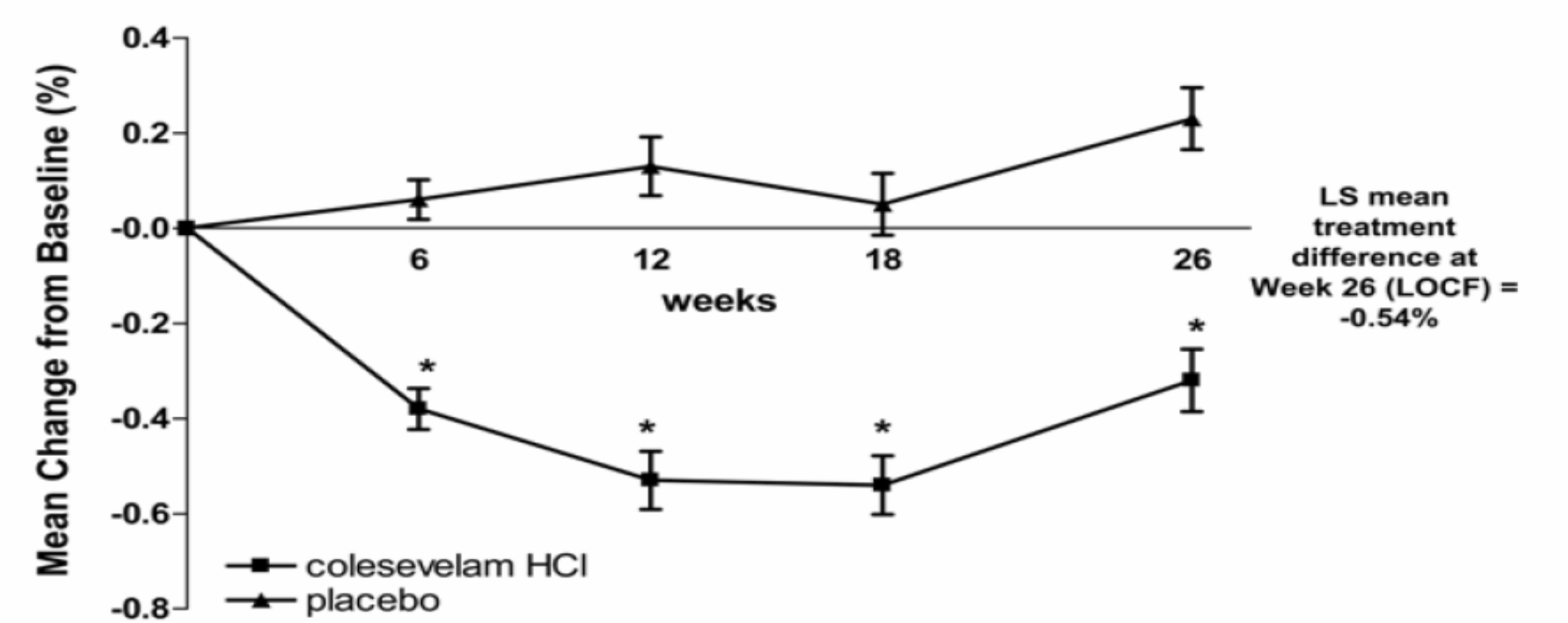
LRC-CPPT, J Am. Med Assoc. 1984; 251: 351 - 64

Eficacia del colesevelam en monoterapia



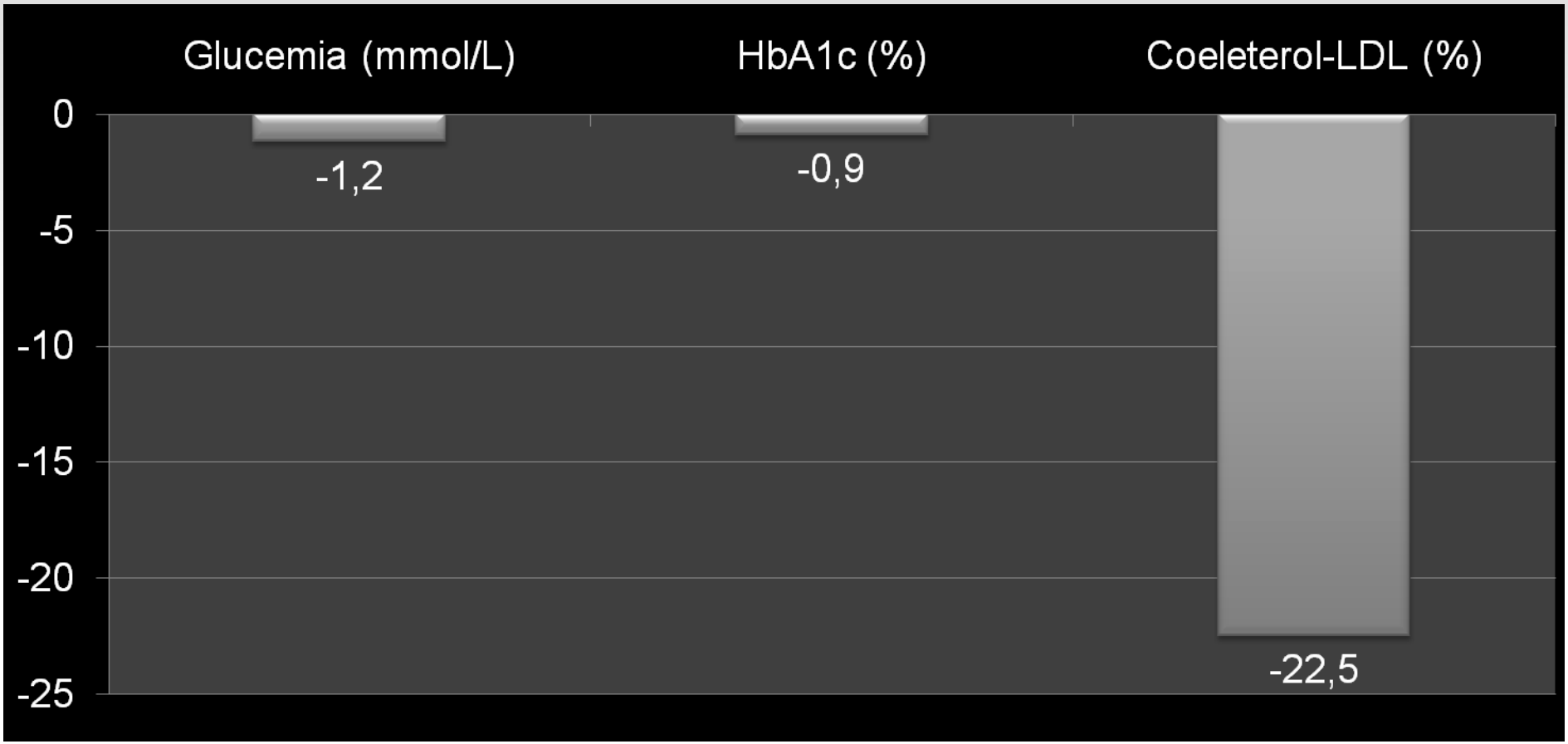
1. LDLC-C, Total-C and HDL-C values are expressed as mean; TG values are expressed as median; **2.** P<0.05 vs. placebo;
Source. Davidson et *al*. Arch Intern Med 1999: 159.

Cambios en la HbA1C en diabéticos tipo 2 con colesevelam

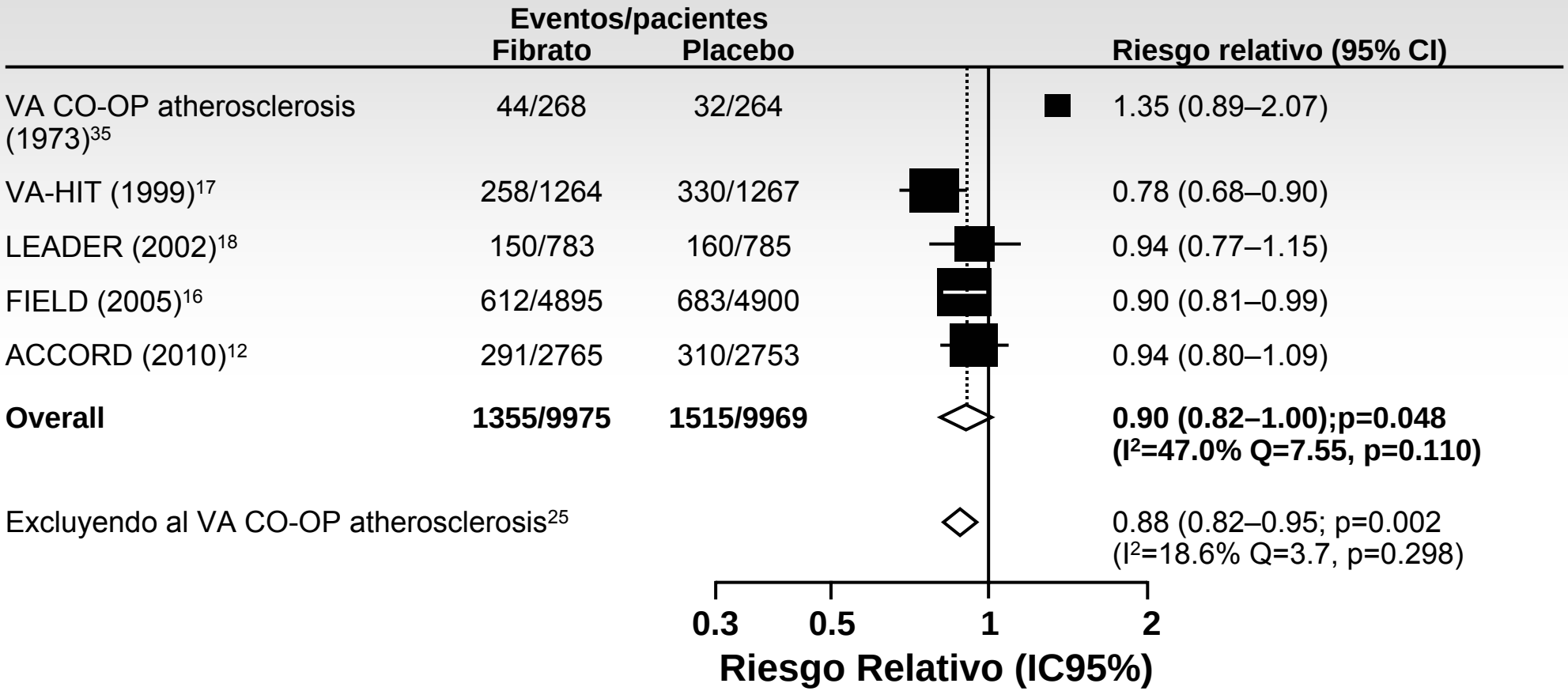


Colestilan (Mitsubishi) MCI-196

Eficacia en pacientes diabéticos con HbA1C > 7%

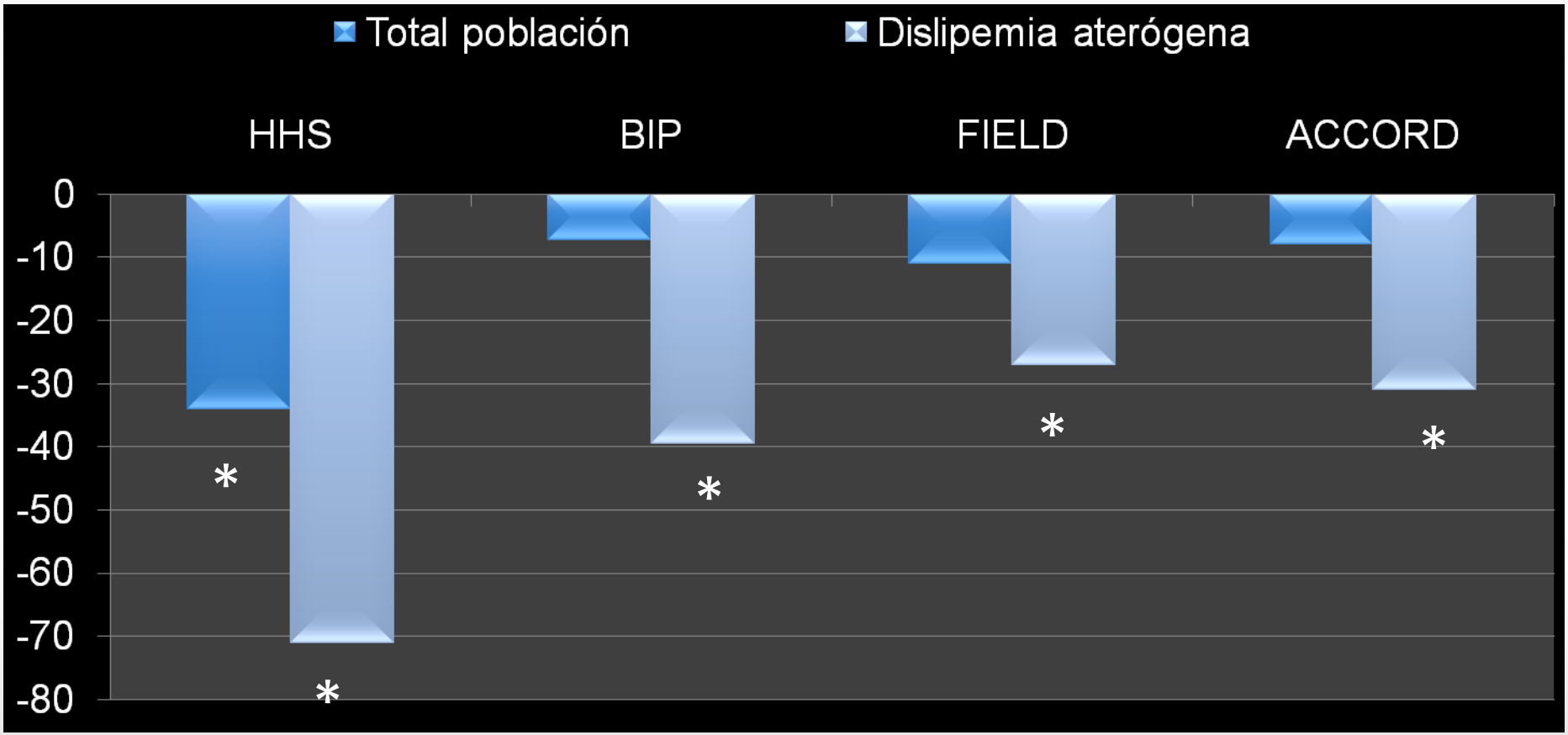


Resultados de estudios con fibratos



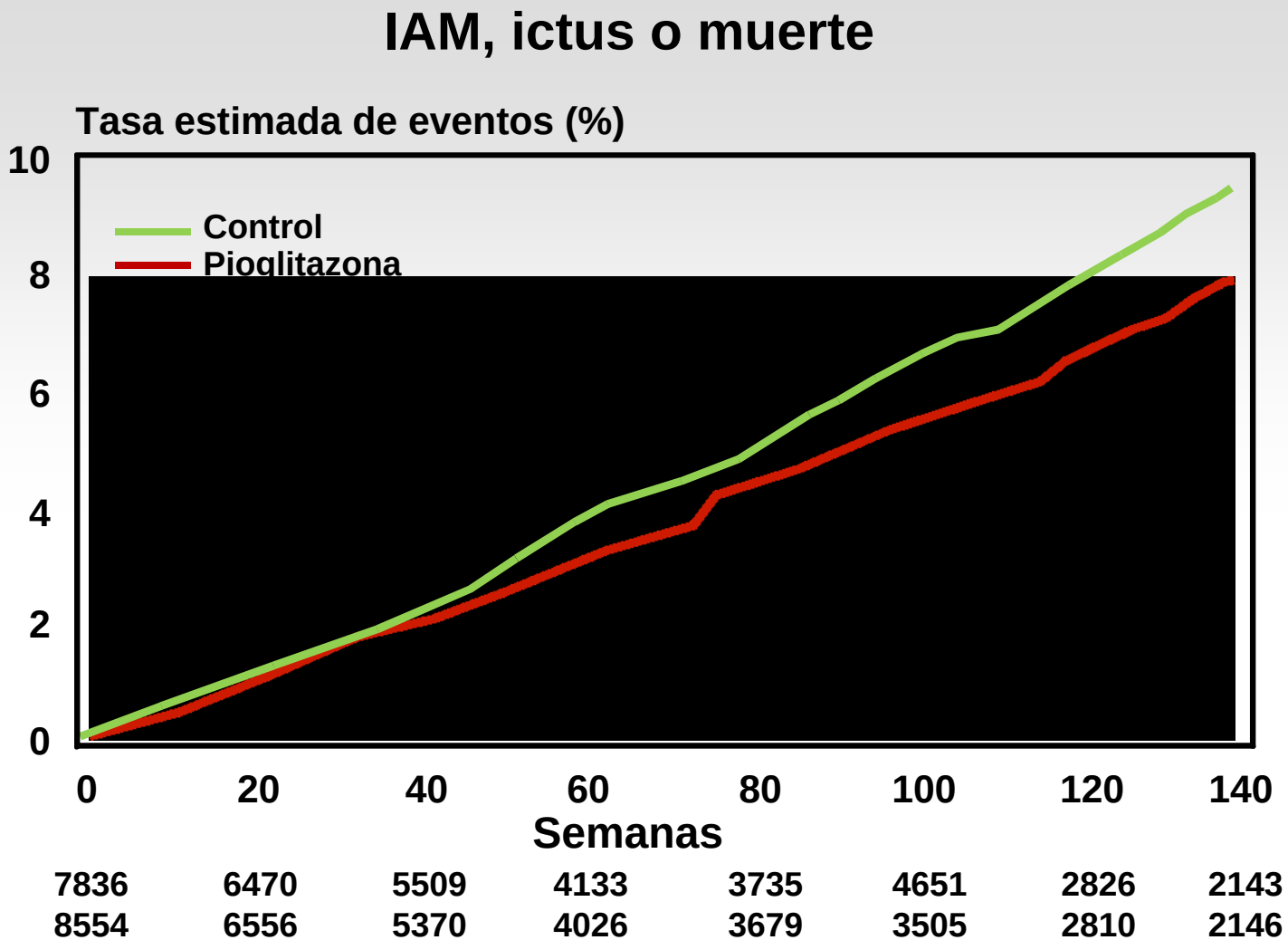
Min Jun, Celine Foote, Jicheng Lv, Bruce Neal, Anushka Patel, Stephen J Nicholls, Diederick E Grobbee, Alan Cass, John Chalmers, Vlado Perkovic. Lancet 2010; 375: 1875–84

*Reducción del objetivo 1º en diversos estudios con fibratos, en el total de la población y en el grupo con dislipemia aterógena**



*HHS: Tgs > 200 mg/dl y C-LDL/C-HDL > 5; BIP Tgs>200 mg/dL; FIELD Tgs > 204 y HDL < 42 mg/dl: ACCORD Tgs > 204 y HDL < 34 mg/dl

Pioglitazona meta-analisis



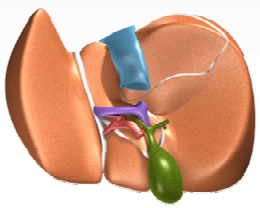
No en riesgo:								
Control	7836	6470	5509	4133	3735	4651	2826	2143
Pioglitazona	8554	6556	5370	4026	3679	3505	2810	2146

Lincoff et al. JAMA 2007; 298:1180–1188

Efectos de la activación dual PPAR α/γ

Receptores nucleares que funcionan como factores de transcripción regulando la expresión de genes

α



Corazón, hígado, músculo, vasos

↑Captación de Acidos Grasos

↑Oxidación de Acidos grasos

↑Apo AI, HDL

↓VLDL-TG

Acciones Anti-inflamatorias

γ

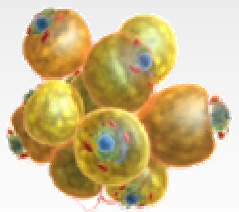
↑Sensibilidad a la insulina

↑Función de la célula beta

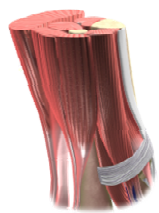
↑ Captación de Acidos Grasos

↑Secreción de adiponectina

Acciones anti-inflamatorias



Adipocitos



Músculo

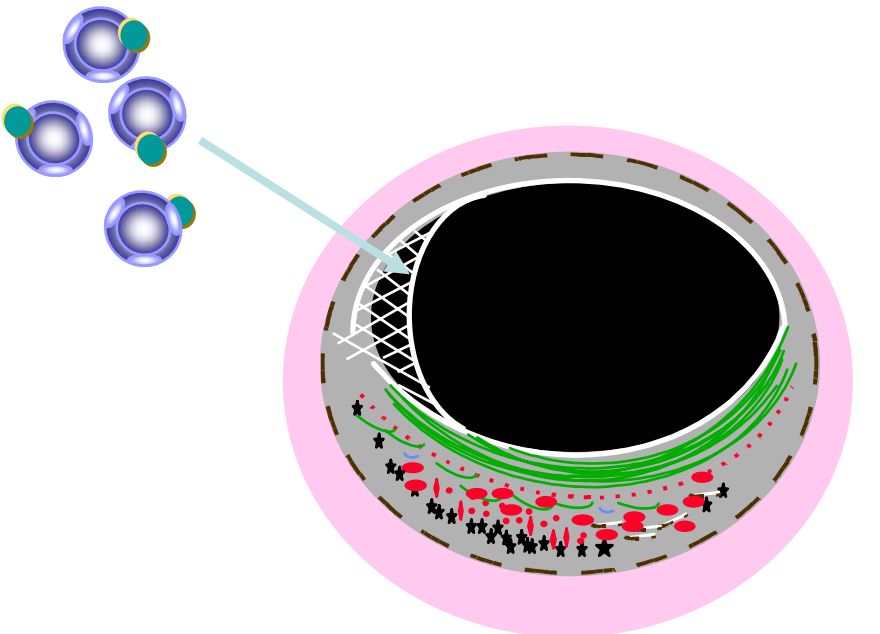
α Efecto principal la mejoría del perfil lipídico

γ Efecto principal la mejoría de la sensibilidad a la insulina

Posicionamiento de nuevos hipolipemiantes

- **En el medio/largo plazo siempre asociados a estatinas debiendo demostrar que:**
  - **Producen descensos aditivos de la morbi-mortalidad ó**
  - **Demostrar que tienen un hueco como fármacos "compasivos" en:**
    - **Personas con intolerancia a estatinas**
    - **Personas con niveles tan altos de colesterol-LDL que precisen nuevas asociaciones (Hipercolesterolemia familiar)**

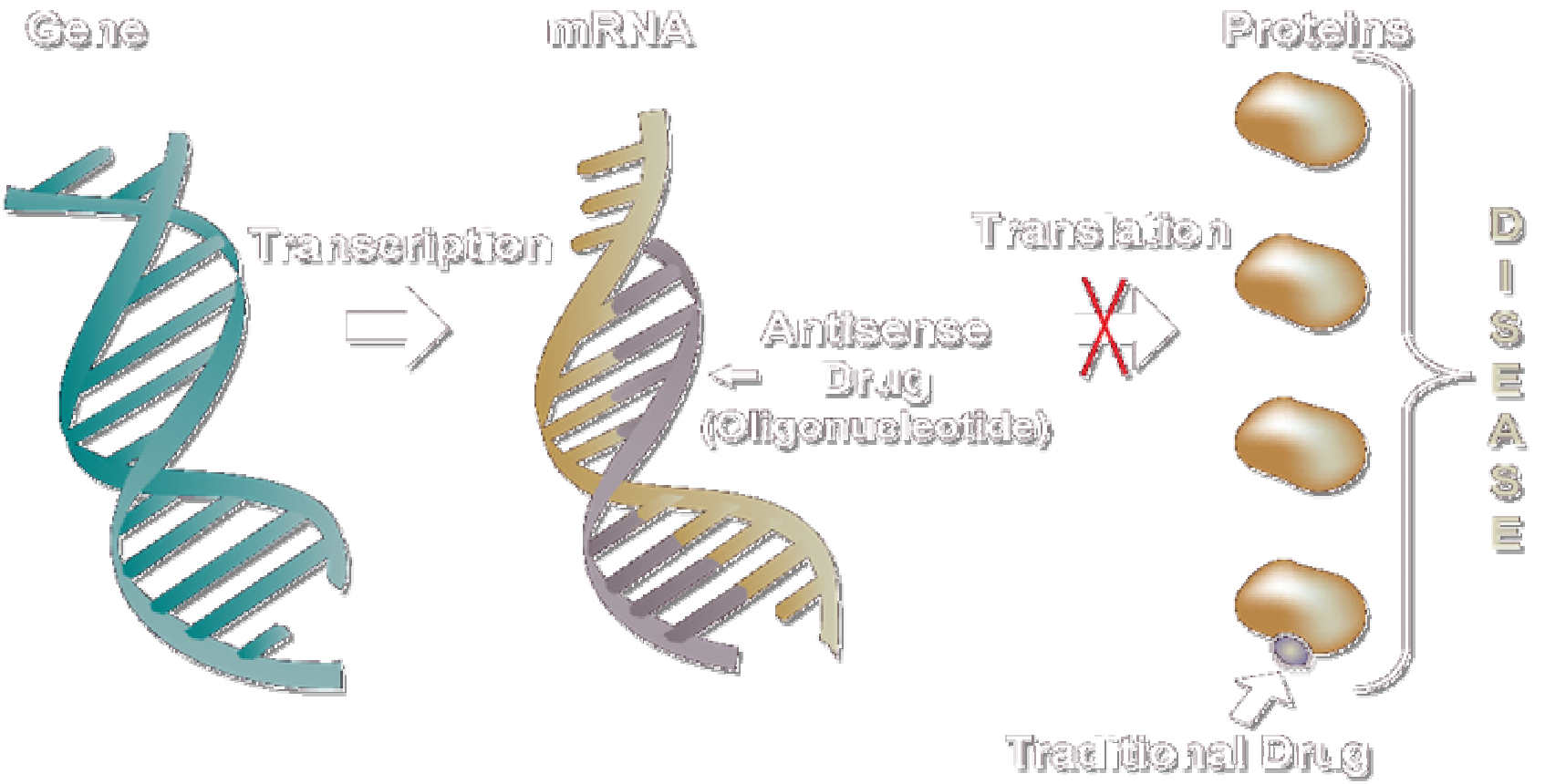
Metabolismo de las LDL



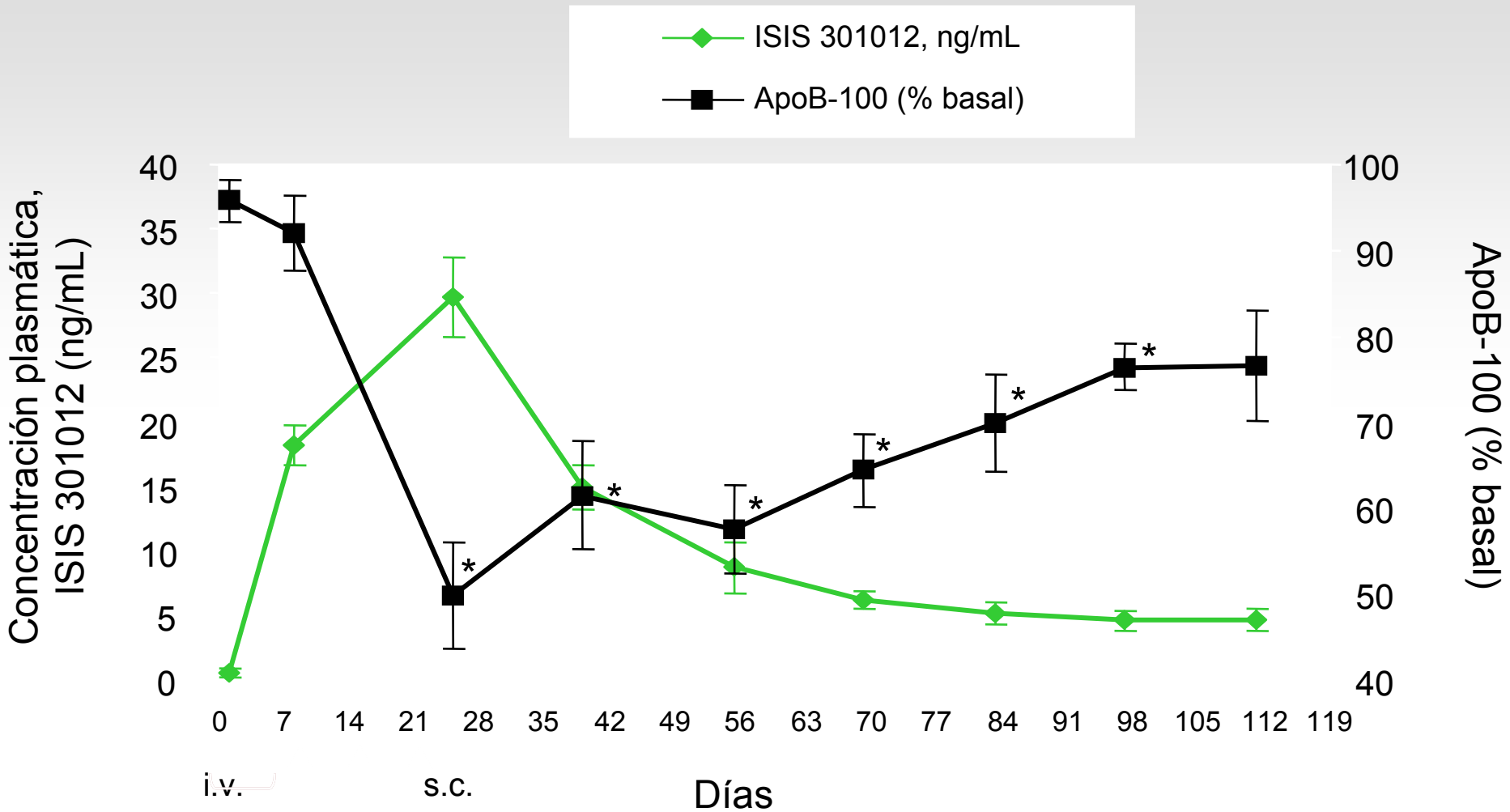
Descender mas el colesterol-LDL

- **Oligonucleótidos antisentido Apo B mRNA**
- **Fármacos tiromiméticos**
- **Inhibidores de la PCSK9**

Oligonucleótidos antisentido



Mipomersem ISIS 301012 – Fase 1

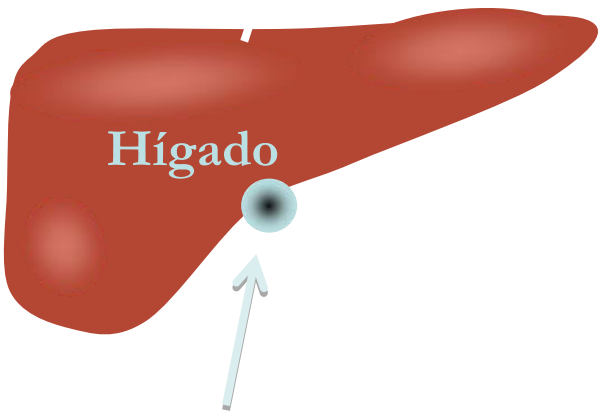


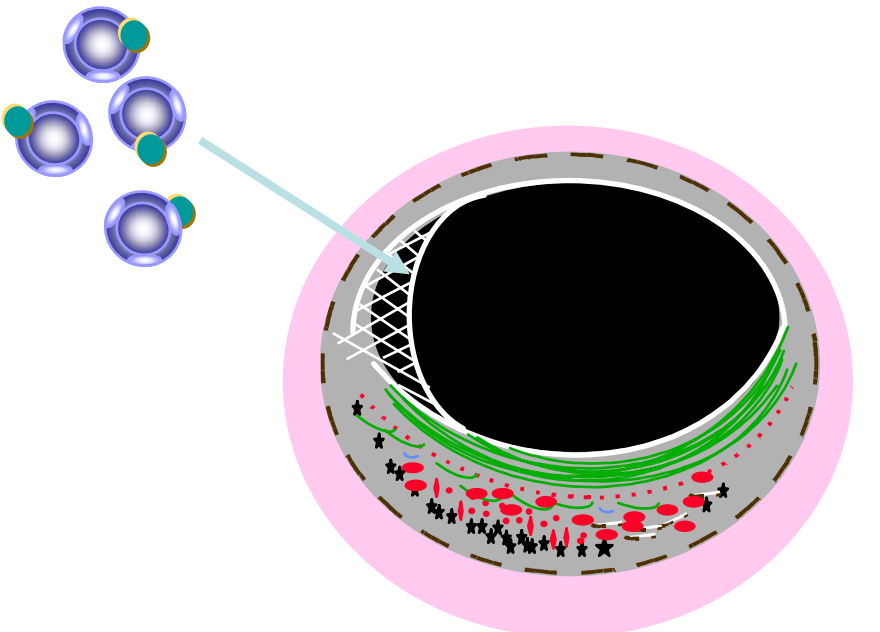
Cambios en lípidos, lipoproteínas y apo B con mipomersen en estudios publicados

Lipid parameter	Mipomersen 200 mg per week				Mipomersen 300 mg per week	
	Total cholesterol <300 mg/dl[61] (*n* = 8); trial period 4 weeks	Concomitant statin therapy[63] (*n* = 10); trial period 13 weeks	Heterozygous FH[65] (*n* = 11); trial period 6 weeks	Homozygous FH[66] (*n* = 34); trial period 26 weeks	Concomitant statin therapy[63] (*n* = 8); trial period 5 weeks	Heterozygous FH[65] (*n* = 9); trial period 6 weeks
Apo B	–50.2 ± 17.3	–35.7 ± 14.1	–23 ± 19	–26.8% (–32.7 to –20.8)	–54.4 ± 19.2	–33 ± 22
LDL-C	–30.6 ± 15.9	–35.8 ± 16.4	–21 ± 23	–24.7% (–31.6 to –17.7)	–51.8 ± 14.3	–34 ± 18
VLDL-C	NR	–11.0 ± 21.6	–14 ± 28	–17.4% (–37.5 to –3.5)	–27.4 ± 87.5	–6 ± 61
Non-HDL-C	NR	–28.5 ± 17.5	–21 ± 19	–24.5% (–31.2 to –17.8)	–52.0 ± 14.9	–31 ± 20
HDL-C	NR	–1.1 ± 8.5	–1 ± 13	15.1% (3.2 to 27.1)	2.9 ± 17.3	6 ± 11
Total cholesterol	NR	–21.8 ± 12.9	–16 ± 15	–21.2% (–27.4 to –15.0)	–38.5 ± 12.5	–25 ± 17
Triglycerides	NR	–14.6	–23 (–48 to 48)	–17.4% (–36.0 to –4.2)	–40.5	–22 (–62 to 137)
Lp(a)	NR	NR	–17 ± 19	–31.1% (–39.1 to –23.1)	NR	–24 ± 26

Brautbar, A. & Ballantyne, C. M. (2011) Pharmacological strategies for lowering LDL cholesterol: statins and beyond *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2011.2

Metabolismo de las LDL





Descender mas el colesterol-LDL

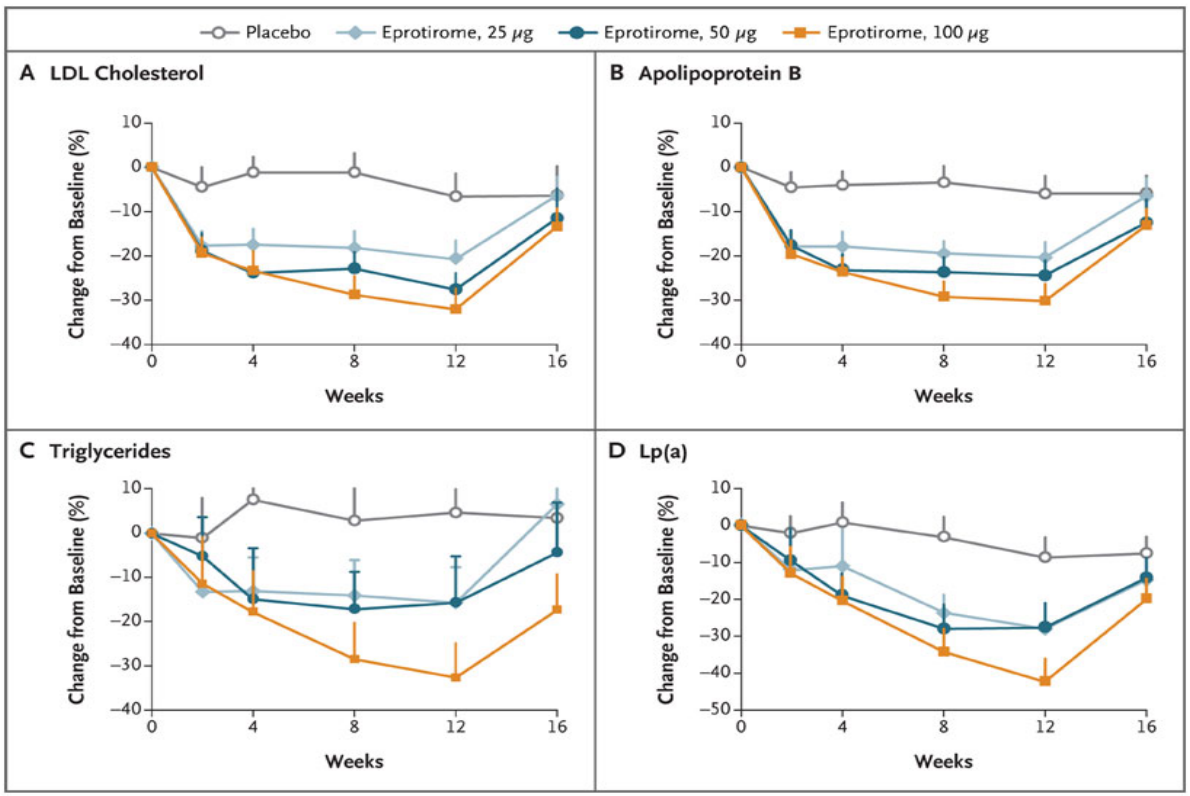
- **Oligonucleótidos antisentido Apo B mRNA**
- **Fármacos tiromiméticos**
- **Inhibidores de la PCSK9**

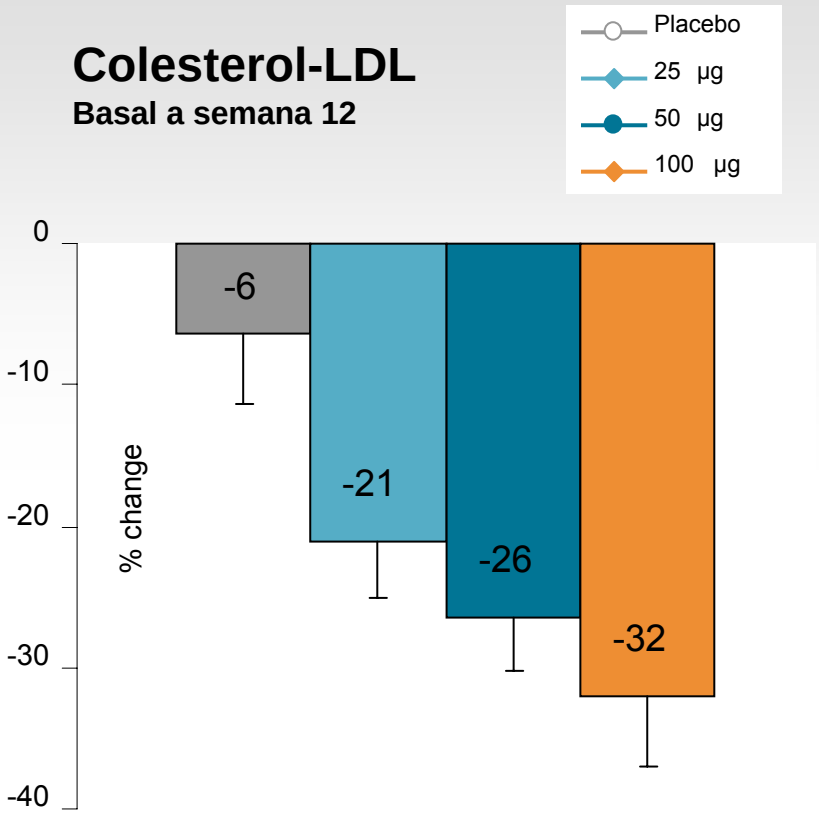
The Coronary Drug Project

Findings Leading to Further Modifications of Its Protocol With Respect to Dextrothyroxine

The Coronary Drug Project Research Group

Monoterapia con Eprotirome: Efecto sobre el C-LDL





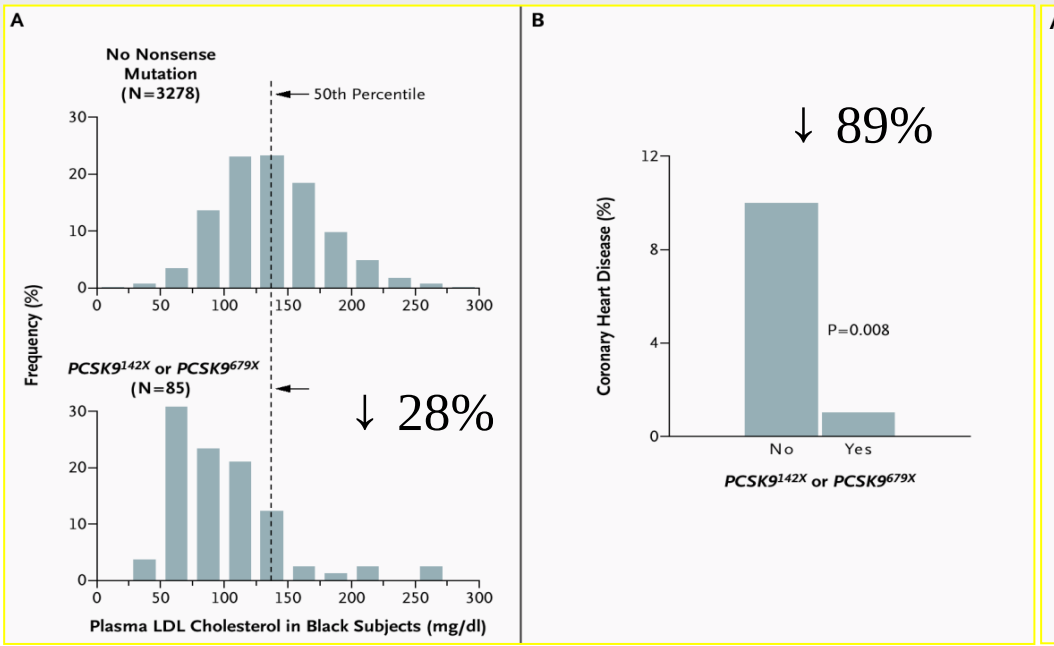
Ladenson PW et al. N Engl J Med 2010; 362: 906-16.

Descender mas el colesterol-LDL

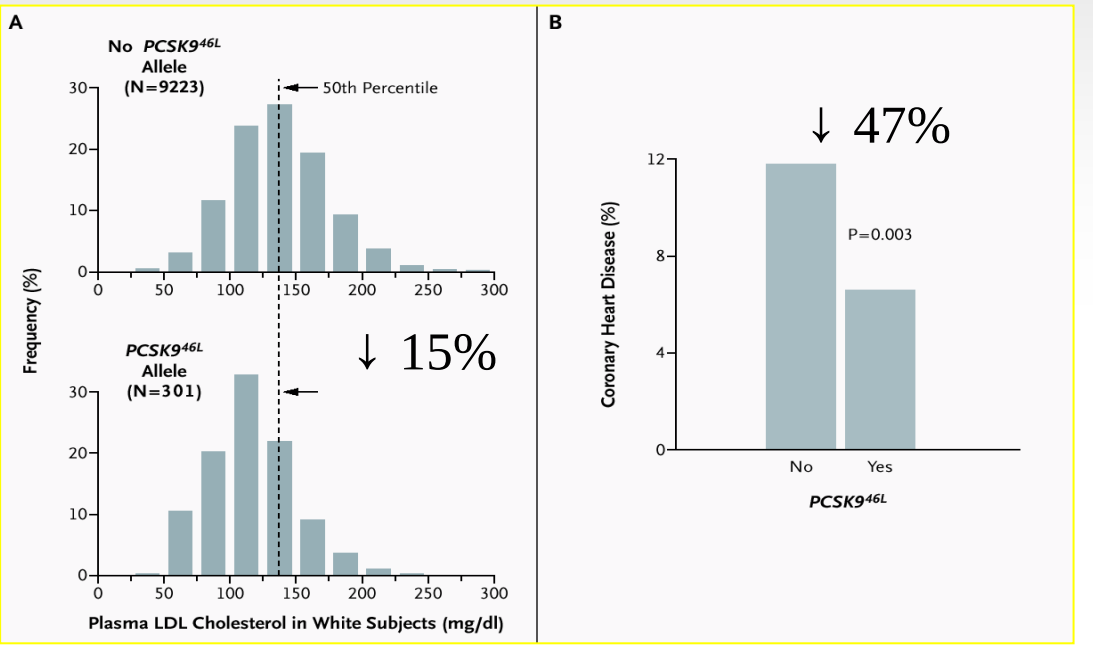
- **Oligonucleótidos antisentido Apo B mRNA**
- **Fármacos tiromiméticos**
- **Inhibidores de la PCSK9**

Distribución de colesterol-LDL e incidencia de enfermedad coronaria en función de la presencia o ausencia de mutaciones en el gen PCSK9 142X o PCSK9 679X

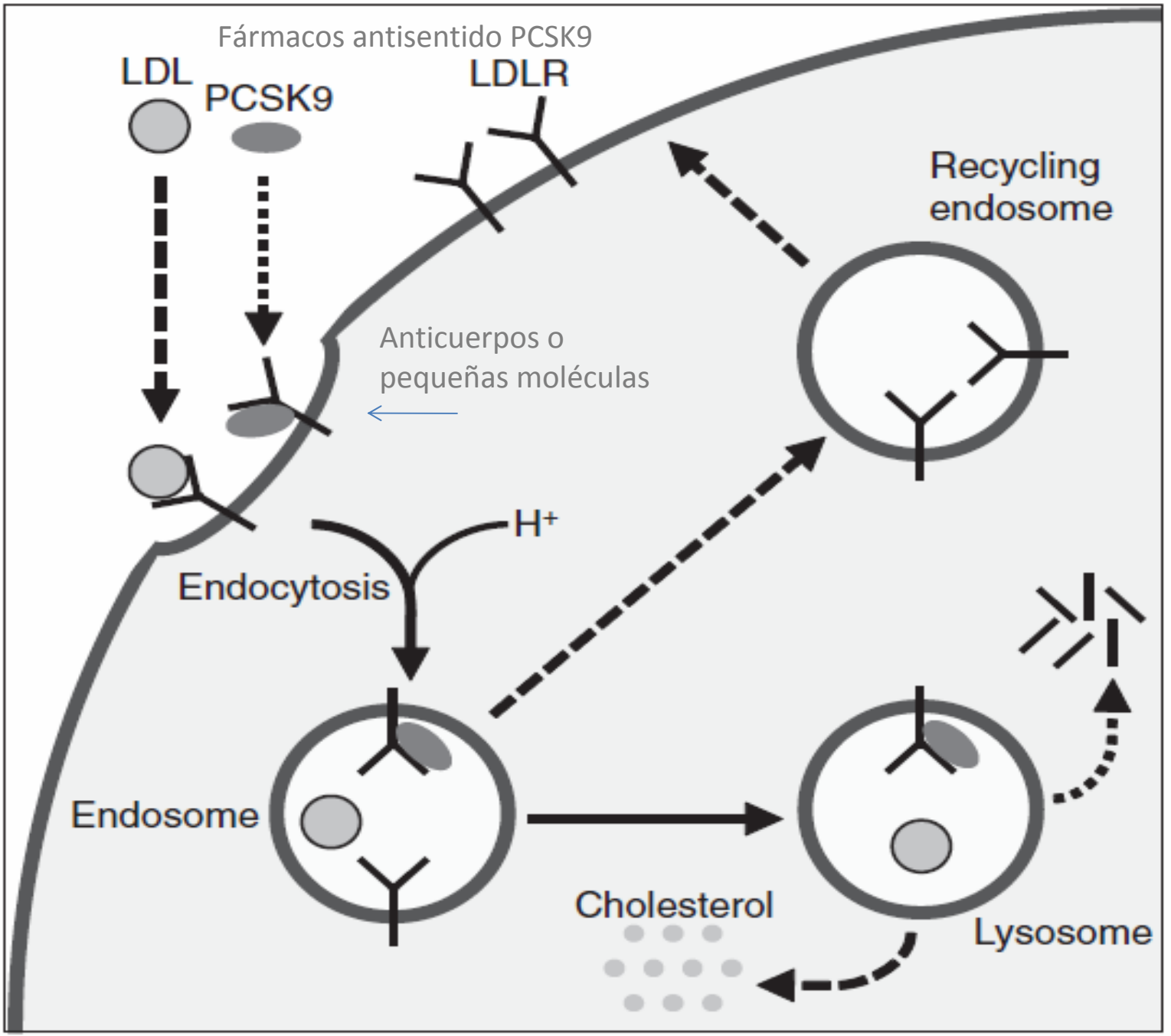
Negros



Blancos



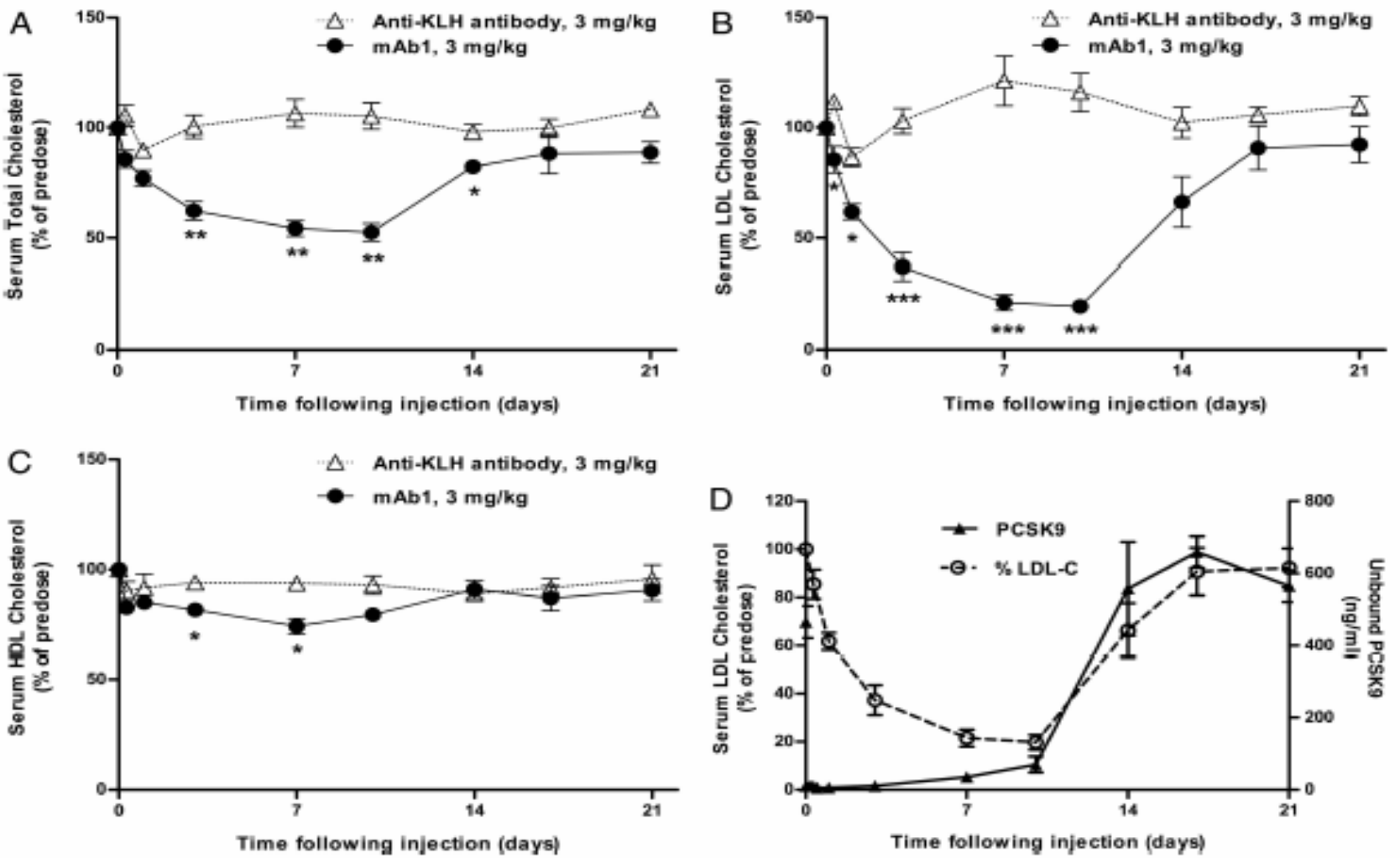
Jonathan C.Cohen, et al, N Engl J Med 2006;354:1264-72



BMS / ISIS
Teknira-Alnylam
Amgen

Duff C.J. et al. Expert Opin. Ther. Targets (2011) 15(2):157-168

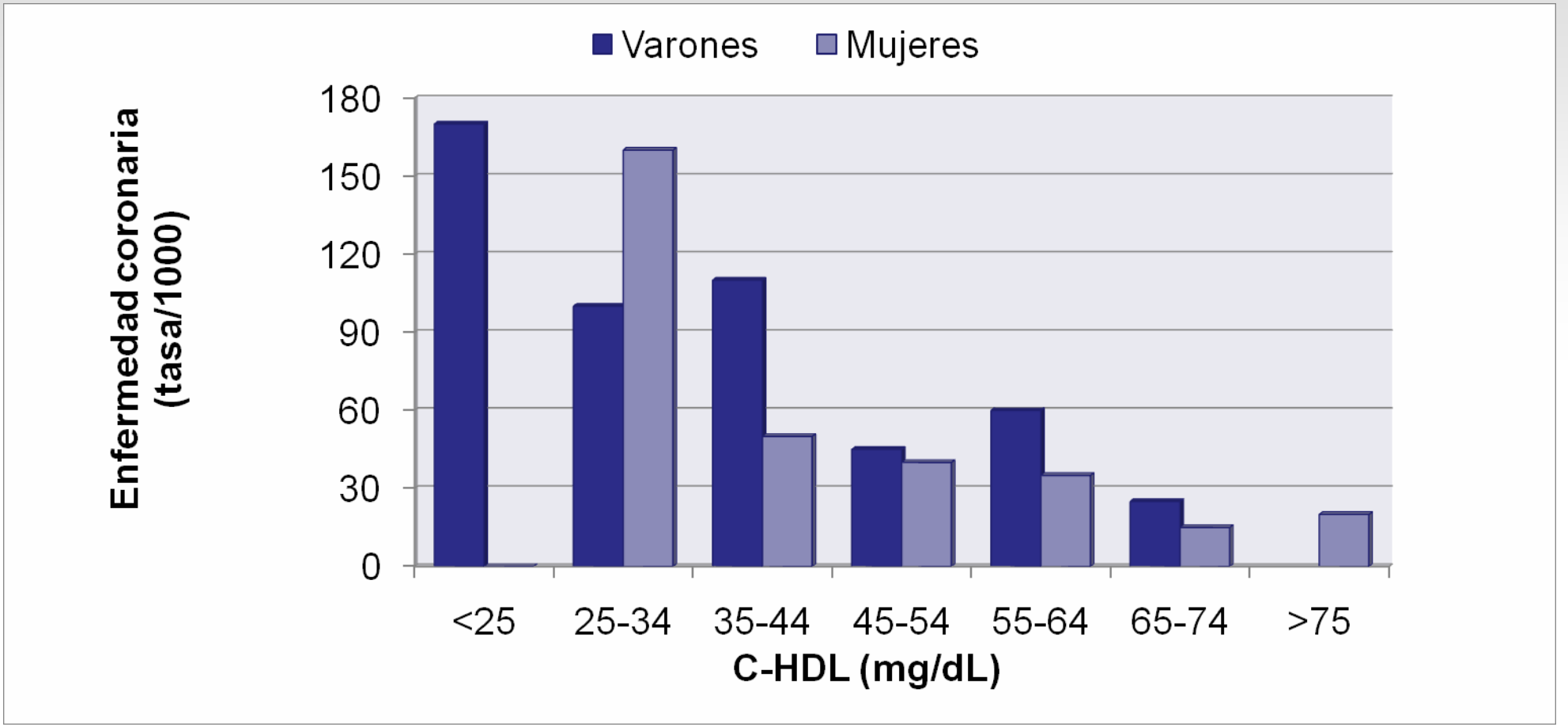
A PCSK9 neutralizing antibody reduces serum cholesterol in mice and nonhuman primates



In monkeys, a single injection of mAb1 reduces serum LDL-C by 80%, and a significant decrease is maintained for 10 days.

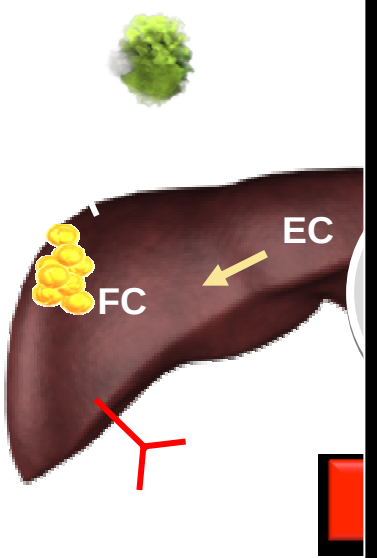
Chan JC et al. PNAS 2009 vol. 106: 9820–25

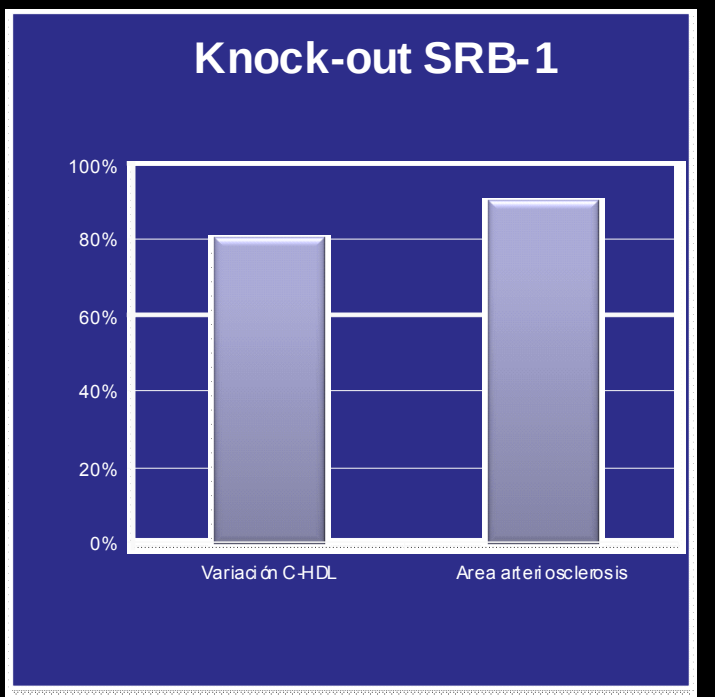
Colesterol-HDL y enfermedad coronaria

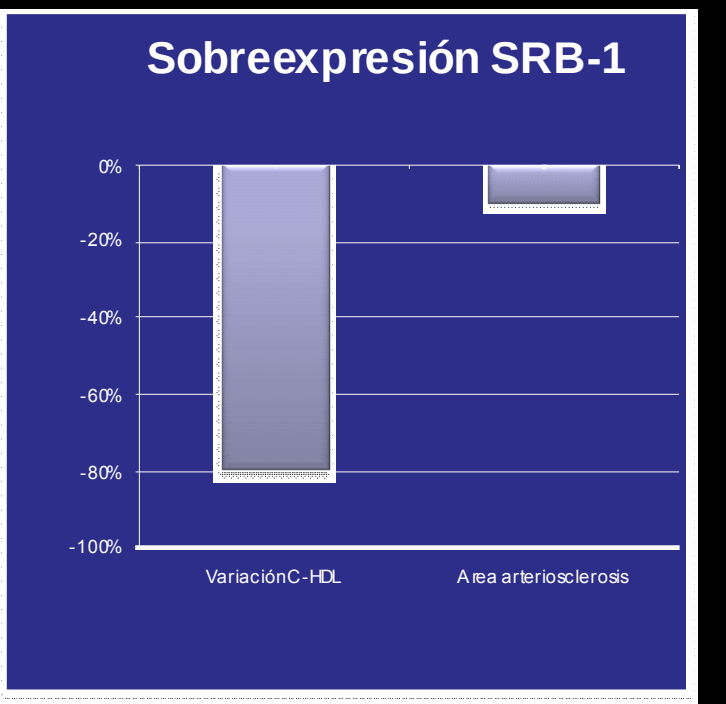


Castelli WP. Am j Cardiol 1989;63(suppl 1):12-19

Cambios en el C-HDL y en la arteriosclerosis aórtica tras modificar la actividad SBR-1



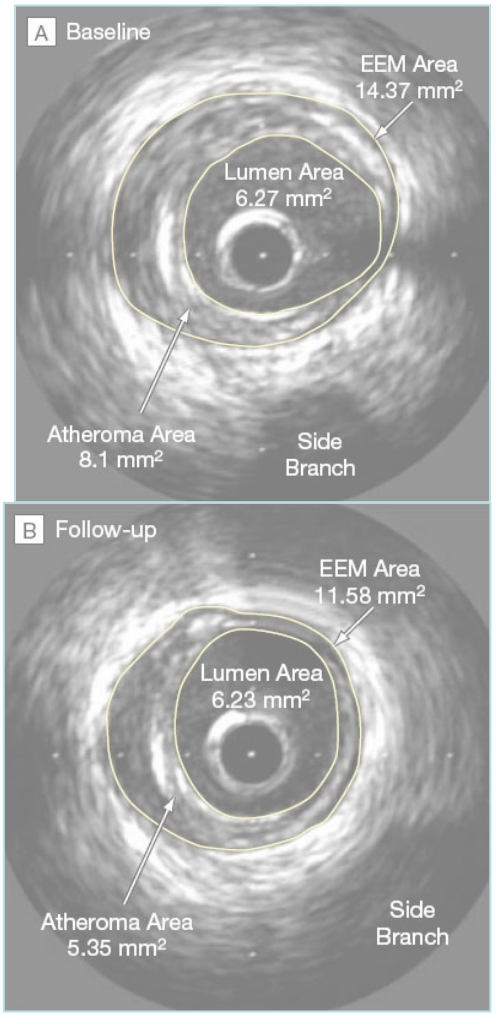




Elevar el colesterol-HDL

- **Inyección de apoA artificial**
- **Aumento de la síntesis de Apo A-1**
- **Inhibidores de la CETP**

Eficacia de la ApoA-I Milano recombinante sobre la arteriosclerosis coronaria



ETC-216: ApoA-I Milano/Fosfolípidos

Dosis de ETC-216

A First-in-Man, Randomized, Placebo-Controlled Study to Evaluate the Safety and Feasibility of Autologous Delipidated High-Density Lipoprotein Plasma Infusions in Patients With Acute Coronary Syndrome

Ron Waksman, MD,* Rebecca Torguson, MPH,* Kenneth M. Kent, MD, PHD,*
Augusto D. Pichard, MD,* William O. Suddath, MD,* Lowell F. Satler, MD,* Brenda D. Martin, RN,*
Timothy J. Perlman, BSME,† Jo-Ann B. Maltais, PHD,† Neil J. Weissman, MD,*
Peter J. Fitzgerald, MD,‡ H. Bryan Brewer, JR, MD*†

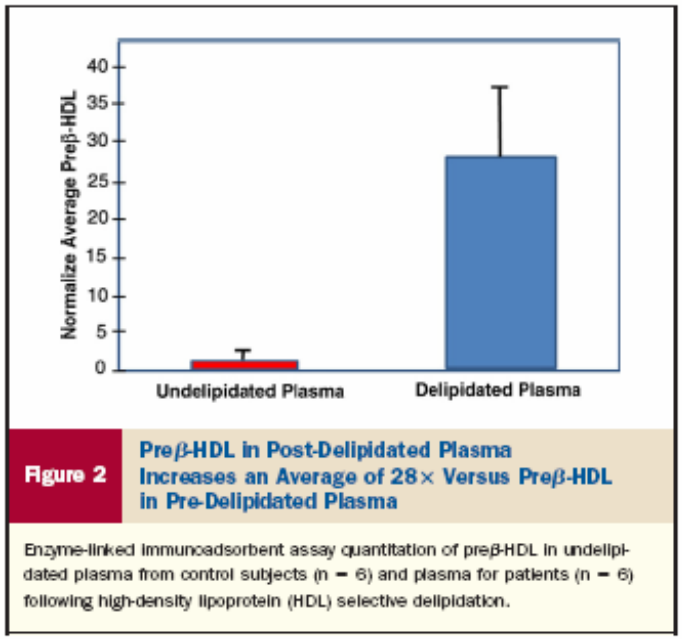


Figure 2 Preβ-HDL in Post-Delipidated Plasma Increases an Average of 28× Versus Preβ-HDL in Pre-Delipidated Plasma

Enzyme-linked immunoadsorbent assay quantitation of preβ-HDL in undelipidated plasma from control subjects (n = 6) and plasma for patients (n = 6) following high-density lipoprotein (HDL) selective delipidation.

Table 6 Comparison of the Changes in IVUS Parameters in Lipid Sciences Selective Delipidation Trial, ApoA-I Milano Trial, and REVERSAL Trial

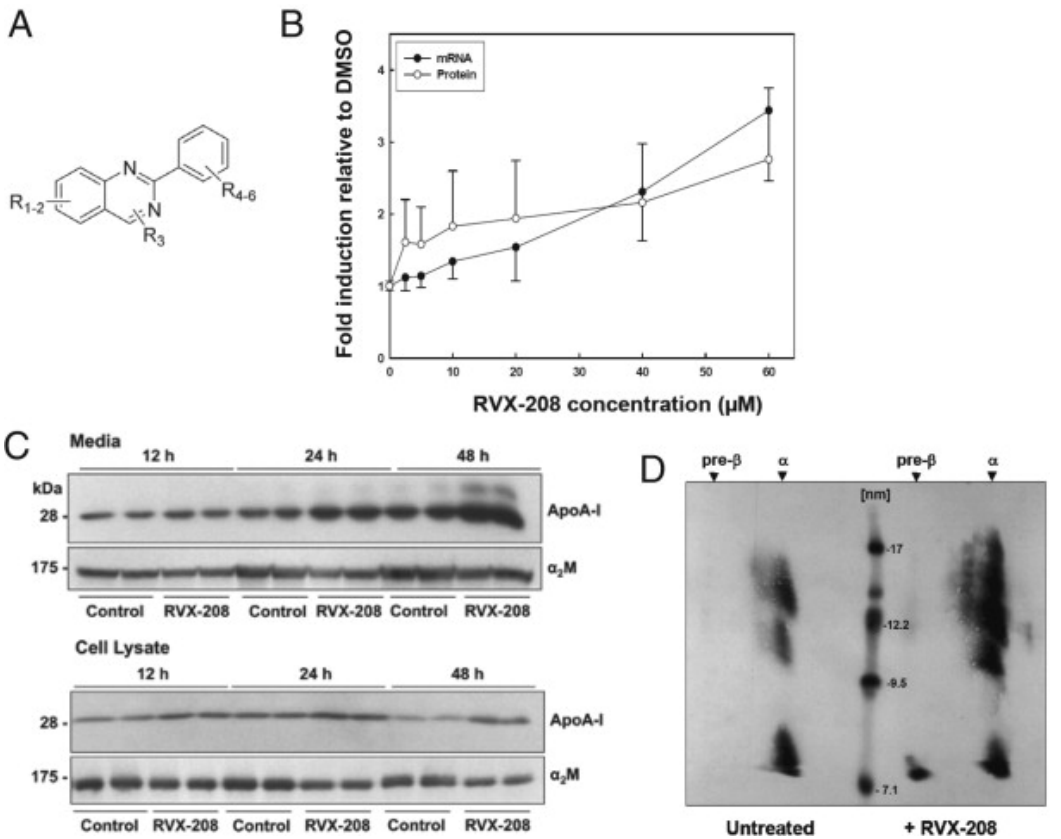
Variable	Selective HDL Delipidation Trial (7 Weeks; n = 14)	ApoA-I Milano Trial* (5 Weeks; n = 36)	REVERSAL Trial† (18 Months; n = 253)
Change in total atheroma volume (mm^3)	−12.18 ± 36.75	−14.10 ± 39.50	−0.04 ± 31.80
Change in % atheroma-plaque burden	−1.0 ± 4.0	−1.1 ± 3.2	−0.6 ± 5.1
Change in 10-mm most diseased segment (mm^3)	−6.24 ± 17.94	−7.20 ± 12.60	−4.2 ± 12.8

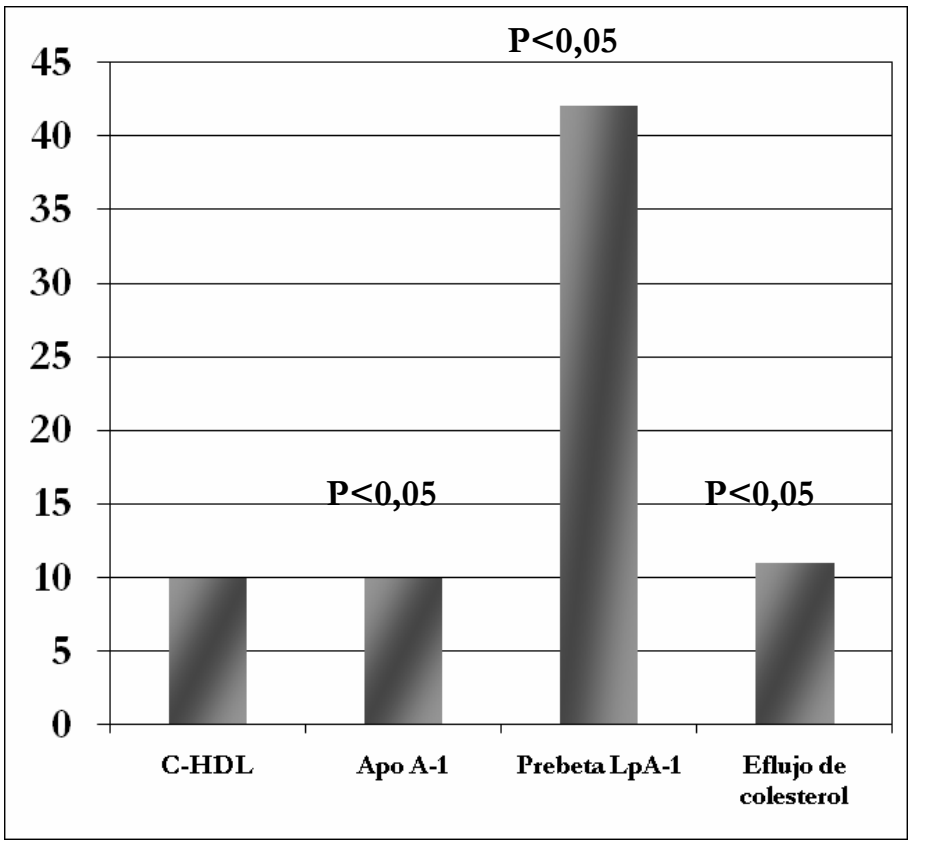
JACC 2010;55:2727-35.

Elevar el colesterol-HDL

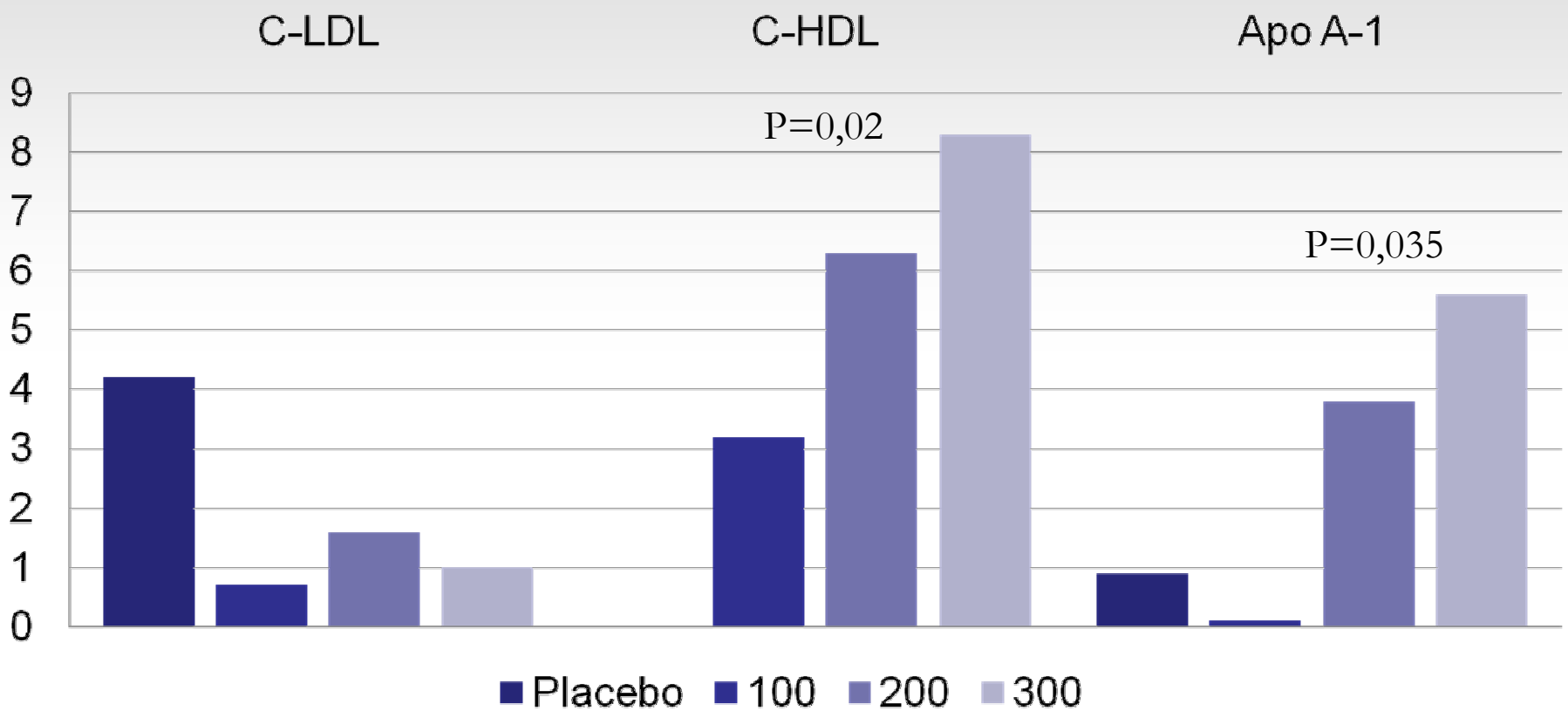
- **Inyección de apoA artificial**
- **Aumento de la síntesis de Apo A-1**
- **Inhibidores de la CETP**

RVX-208: Cambios en células hepáticas en cultivo y en humanos



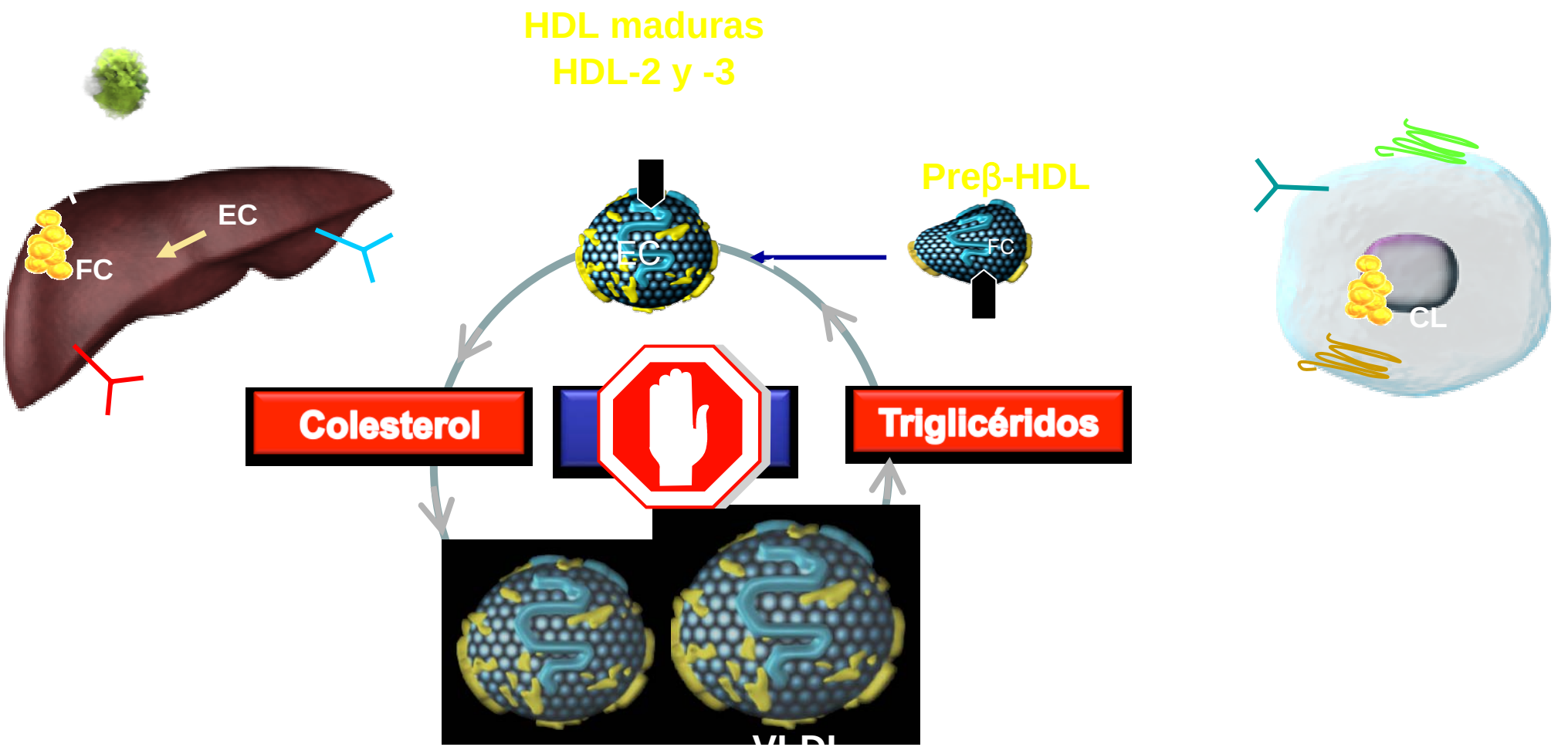


Cambios lipídicos con RVX-208



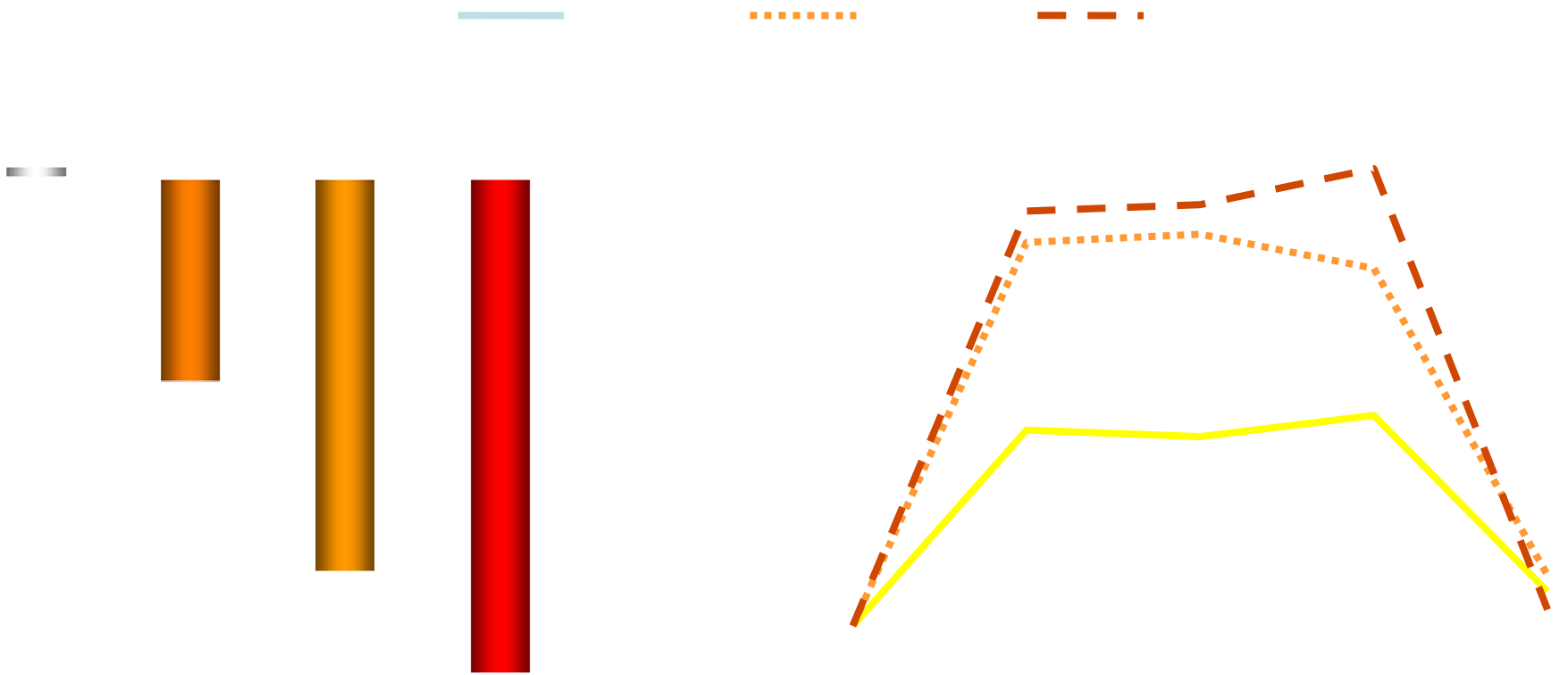
Elevar el colesterol-HDL

- **Inyección de apoA artificial**
- **Aumento de la síntesis de Apo A-1**
- **Inhibidores de la CETP**

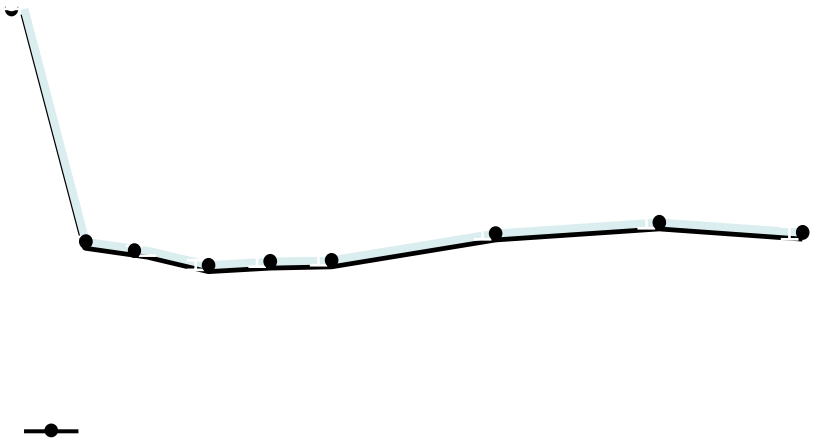

HDL maduras
HDL-2 y -3
EC
FC
EC
Preβ-HDL
FC
CL
Colesterol
Triglicéridos

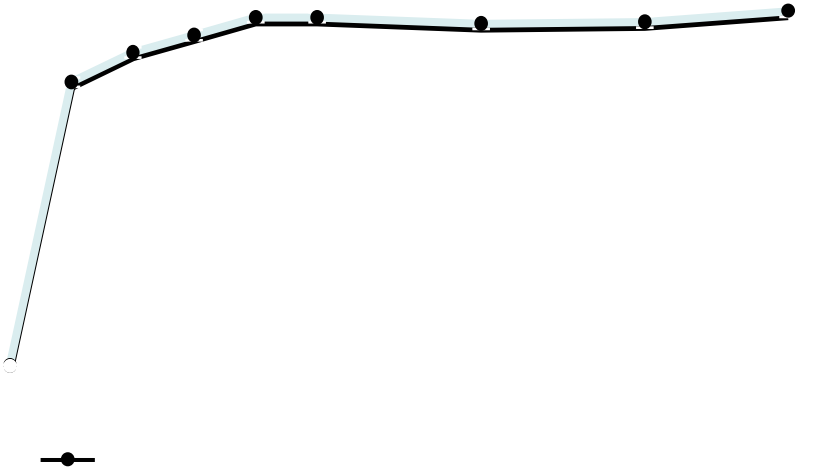
	Dalcetrapib[1]	Torcetrapib[2]	Anacetrapib[3]
Peso molecular	389.60	600.40	637.51
Lipofilicidad	cLogP ~7	cLogP ~9	cLogP ~9

Dalcetrapib Estudios fase IIa



Anacetrapib: Efectos sobre el C-LDL y C-HDL

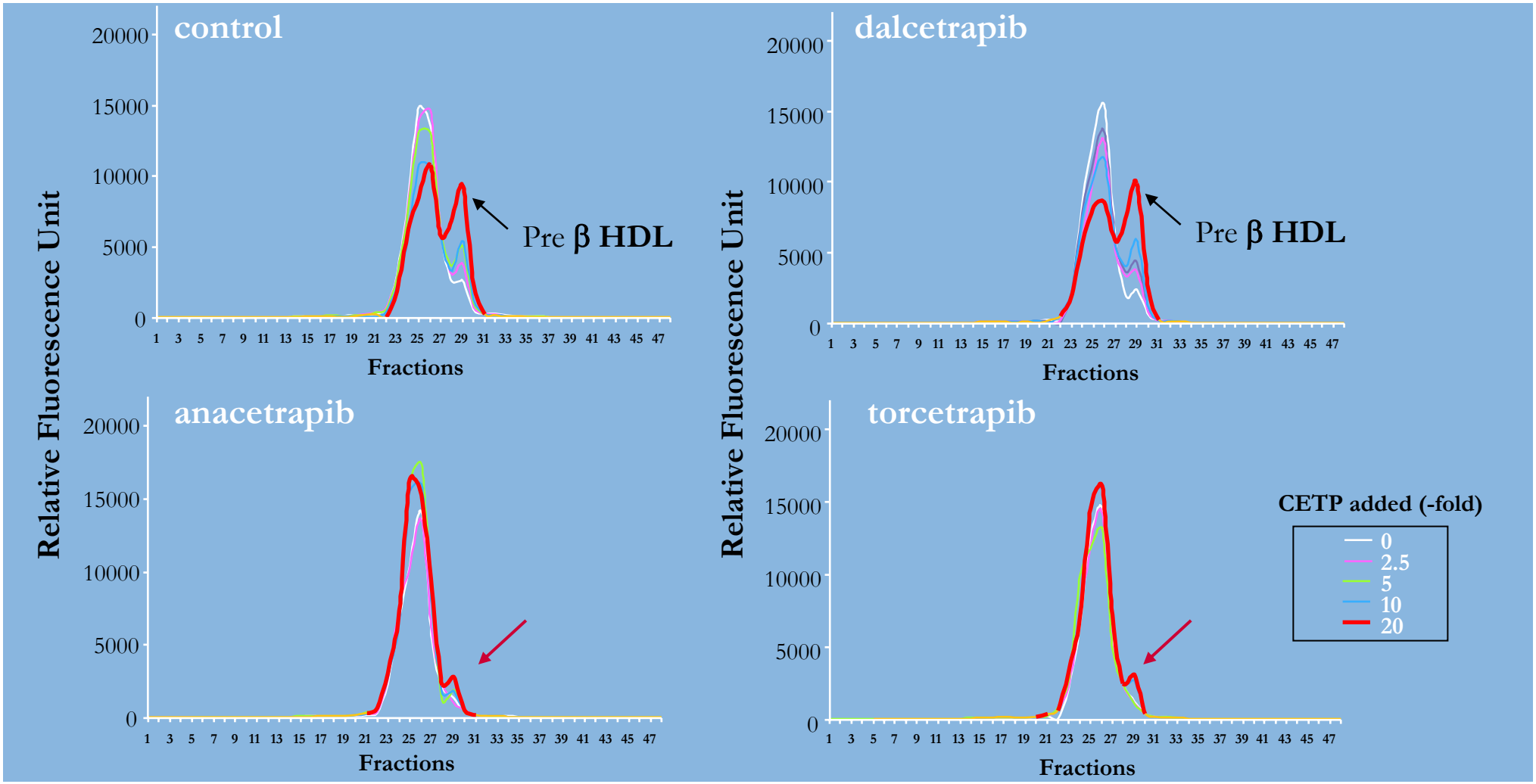




Anacetrapib n =

Placebo n =

CETP-induced pre-β-HDL formation *in vitro*



- 30,000 patients with occlusive arterial disease in North America, Europe and Asia
- Background LDL-lowering with atorvastatin
- Randomized to anacetrapib 100 mg vs. placebo
- Scheduled follow-up: 4 years
- Primary outcome: Coronary death, myocardial infarction or coronary revascularization

www.revealtrial.org

dal-HEART Program

dalcetrapib HDL Evaluation, Atherosclerosis & Reverse cholesterol Transport

The **dal**-HEART Program tests a novel hypothesis – that raising HDL through CETP inhibition will attenuate cardiovascular risk

Double blind, randomized, placebo-controlled studies

dal-OUTCOMES[1]

15,600 *patients recently hospitalized for ACS*

To evaluate the effect of dalcetrapib on CV outcomes

dal-VESSEL[2]

450 *patients with CHD or CHD risk equivalent*

To evaluate the effect of dalcetrapib on endothelial function and blood pressure, measured by FMD and ABPM

dal-PLAQUE[3]

130 *patients with CHD*

To evaluate the effect of dalcetrapib on inflammation, plaque size and burden, measured by PET/CT and MRI

dal-PLAQUE 2[4]

900 *patients with CAD*

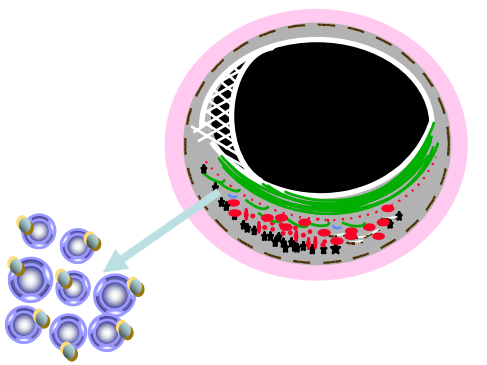
To evaluate the effect of dalcetrapib on atherosclerotic disease progression, assessed by IVUS and carotid B-mode ultrasound

[1]http://clinicaltrials.gov/ct2/show/NCT00658515 Accessed April 21st 2009;
[2]http://clinicaltrials.gov/ct2/show/NCT00655538; Accessed April 21st 2009;
[3]hhttp://clinicaltrials.gov/ct2/show/NCT00655473 accessed 21st April 2009; [4]http://www.clinicaltrials.gov/ct2/show/NCT01059682

La elevación de las HDL ¿Cuál es su futuro?

Enfermedad coronaria y capacidad del plasma para extraer colesterol

	OR para el desarrollo de enfermedad coronaria



Adverse events with mipomersen added to conventional LDL-cholesterol-lowering therapy

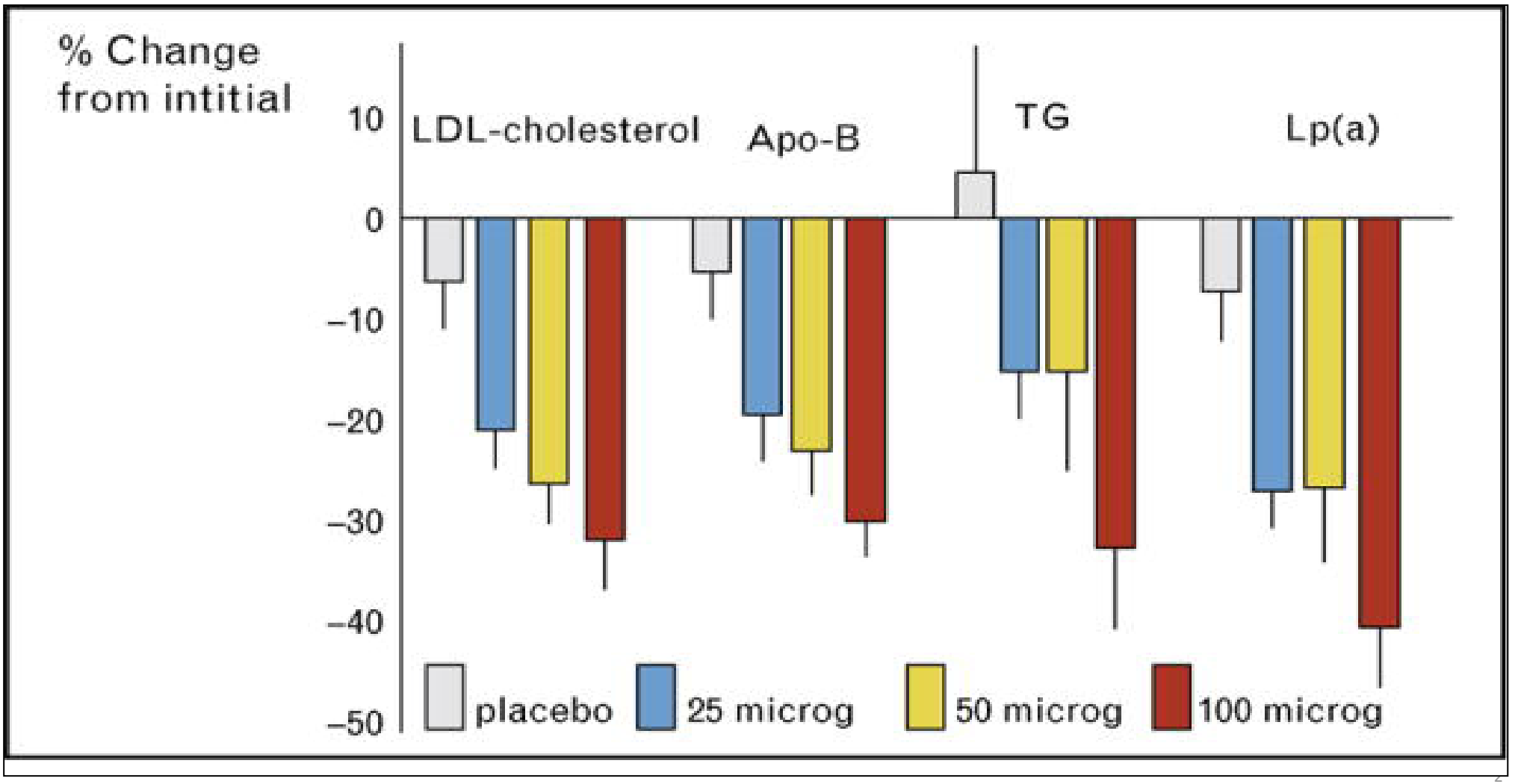
Table 3 | Adverse events with mipomersen added to conventional LDL-cholesterol-lowering therapy

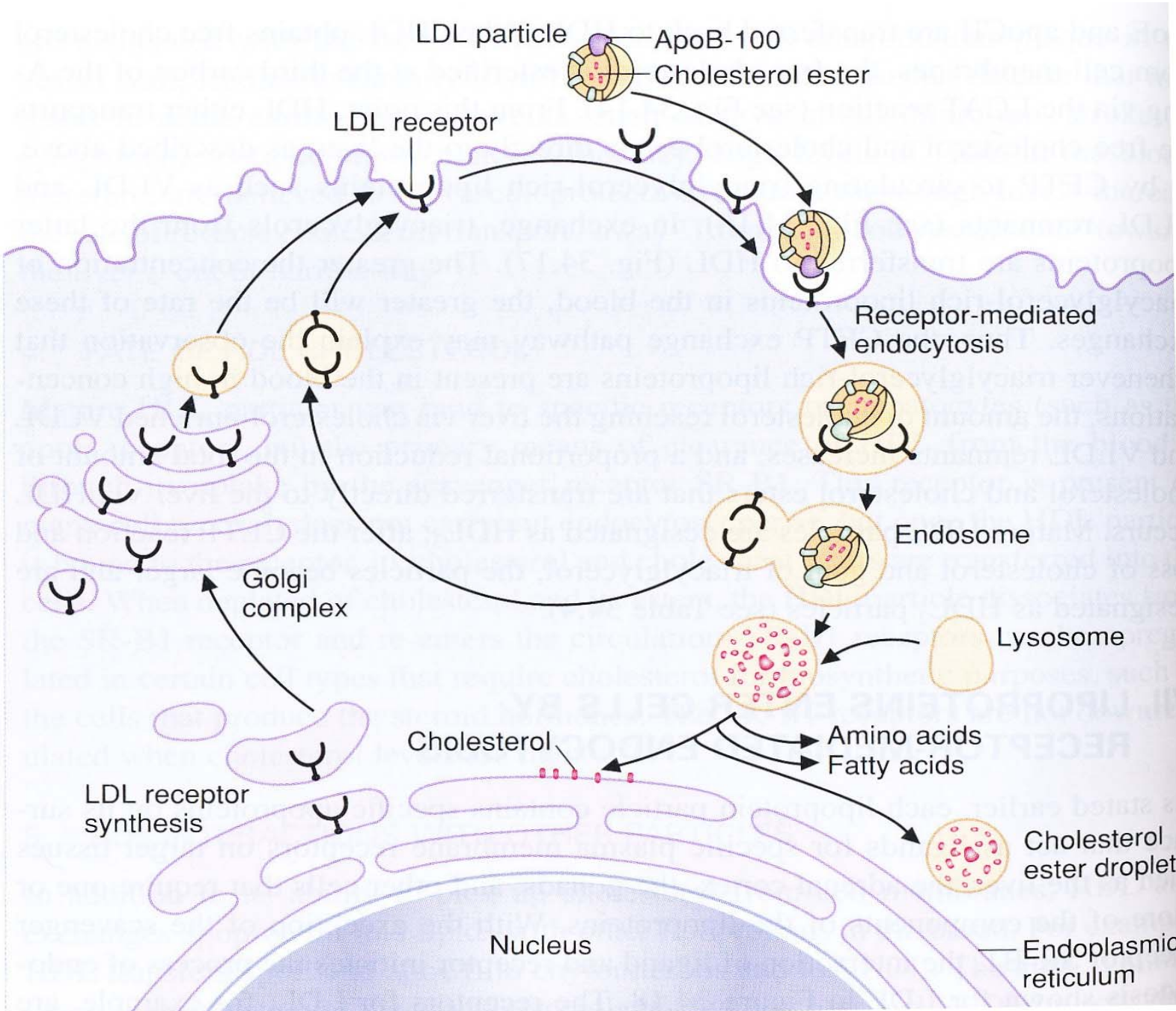
Adverse events*	Total cholesterol <300 mg/dl[61] (*n* = 29)	Concomitant statin therapy[63] (*n* = 59)	Heterozygous FH[65] (*n* = 36)	Homozygous FH[66] (*n* = 34)
Injection site reaction	21 (72)	53 (90)	35 (97)	26 (76)
Headache	5 (17)	18 (31)	8 (22)	5 (15)
Influenza-like symptoms	NR	15 (25)	NR	10 (29)
Nasopharyngitis	3 (10)	10 (17)	7 (19)	NR
Myalgia	NR	NR	6 (17)	NR
Fatigue	5 (17)	11 (19)	4 (11)	4 (12)
Nausea	3 (10)	NR	6 (17)	6 (18)
Urinary-tract infection	NR	6 (10)	5 (14)	NR
Diarrhea	NR	NR	4 (11)	NR
Back pain	NR	10 (17)	4 (11)	NR
Muscle stiffness	NR	NR	4 (11)	NR
Arthralgia	NR	NR	4 (11)	NR
Hepatic enzyme elevation‡	1 (3)	10 (17)	4 (11)	4 (12)

*Values represent number of events and (% of patients). ‡Alanine aminotransferase >3 times upper limit of normal. Abbreviations: FH, familial hypercholesterolemia; NR, not reported.

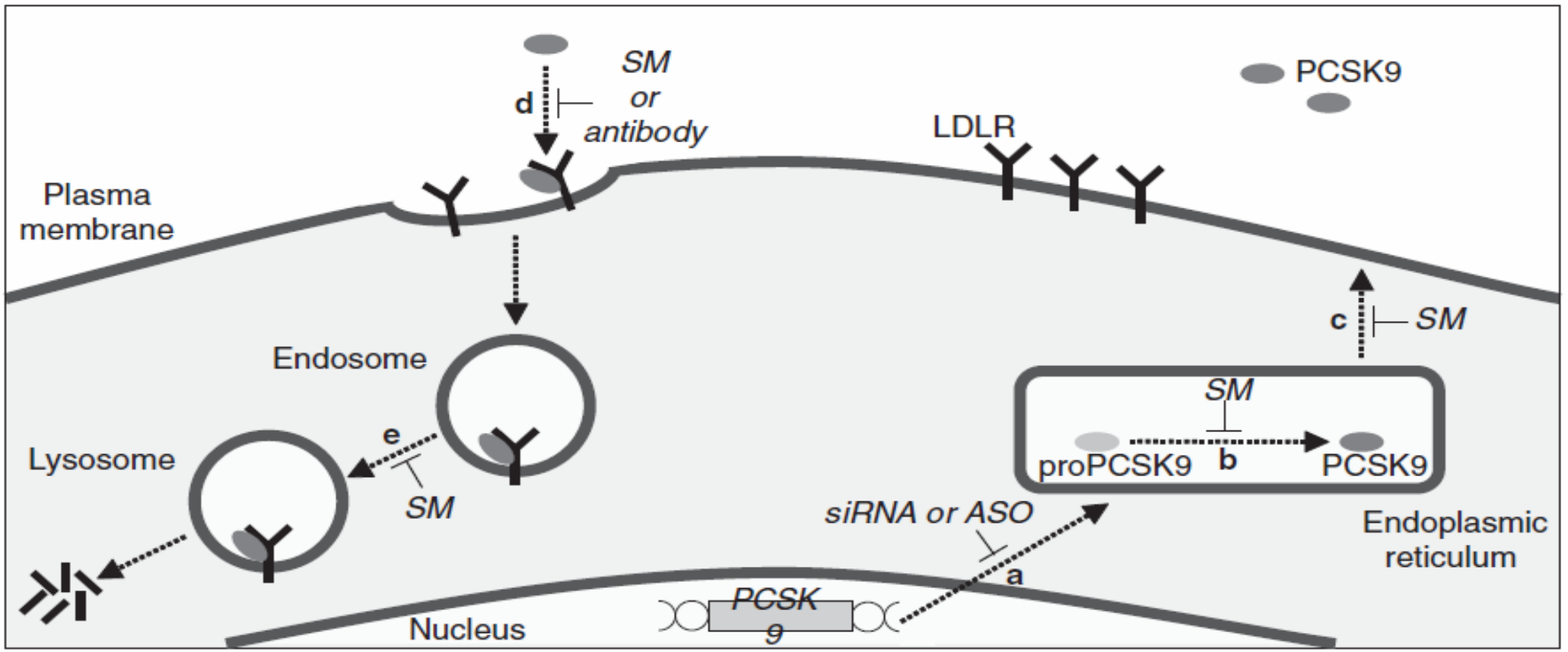
Brautbar, A. & Ballantyne, C. M. (2011) Pharmacological strategies for lowering LDL cholesterol: statins and beyond *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2011.2

Figure 3


% Change from intitial
10
0
−10
−20
−30
−40
−50
LDL-cholesterol
Apo-B
TG
Lp(a)
placebo
25 microg
50 microg
100 microg

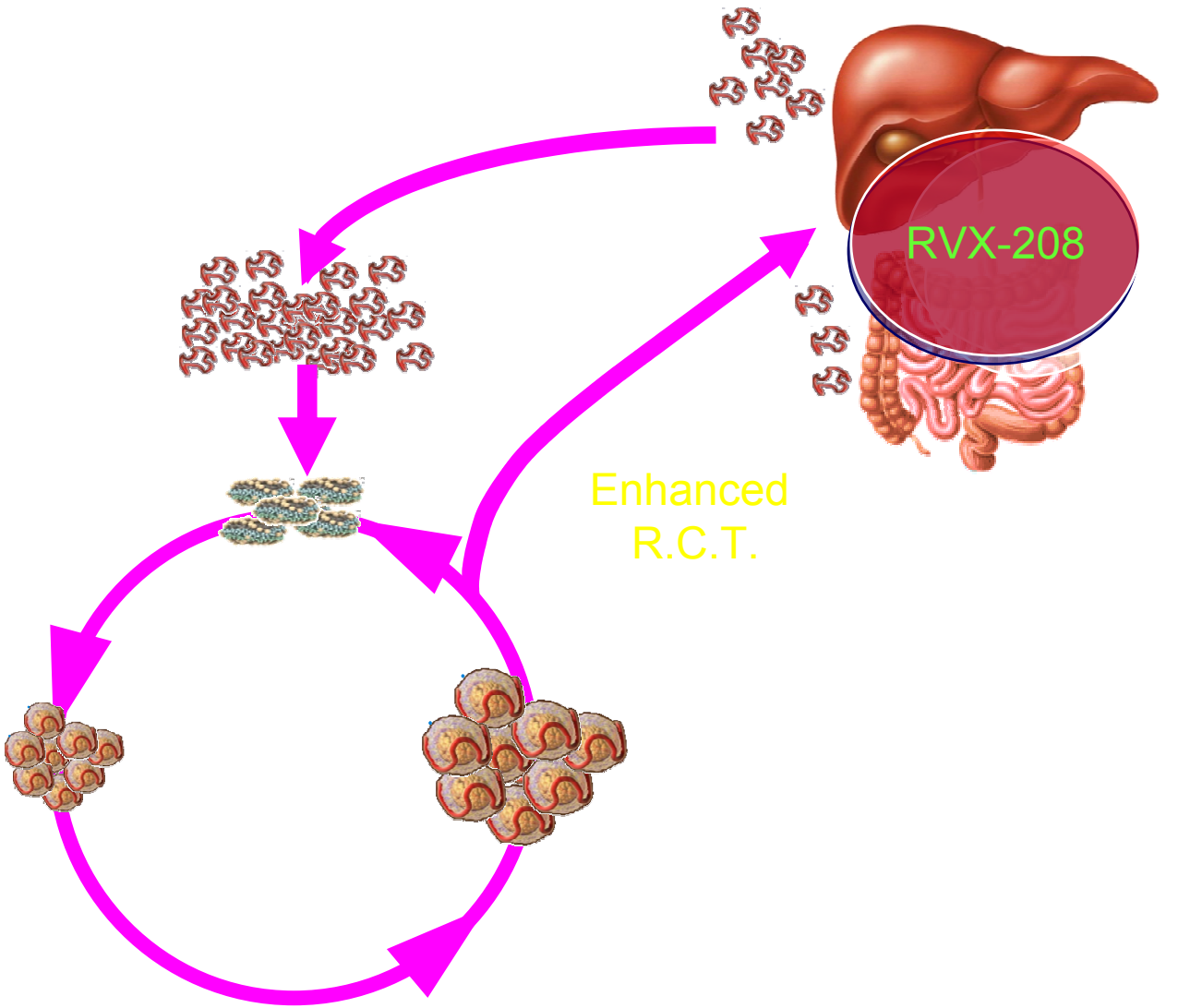

LDL particle
ApoB-100
Cholesterol ester
LDL receptor
Receptor-mediated endocytosis
Endosome
Lysosome
Golgi complex
Cholesterol
Amino acids
Fatty acids
LDL receptor synthesis
Cholesterol ester droplet
Nucleus
Endoplasmic reticulum

PCSK9: an emerging target for treatment of hypercholesterolemia



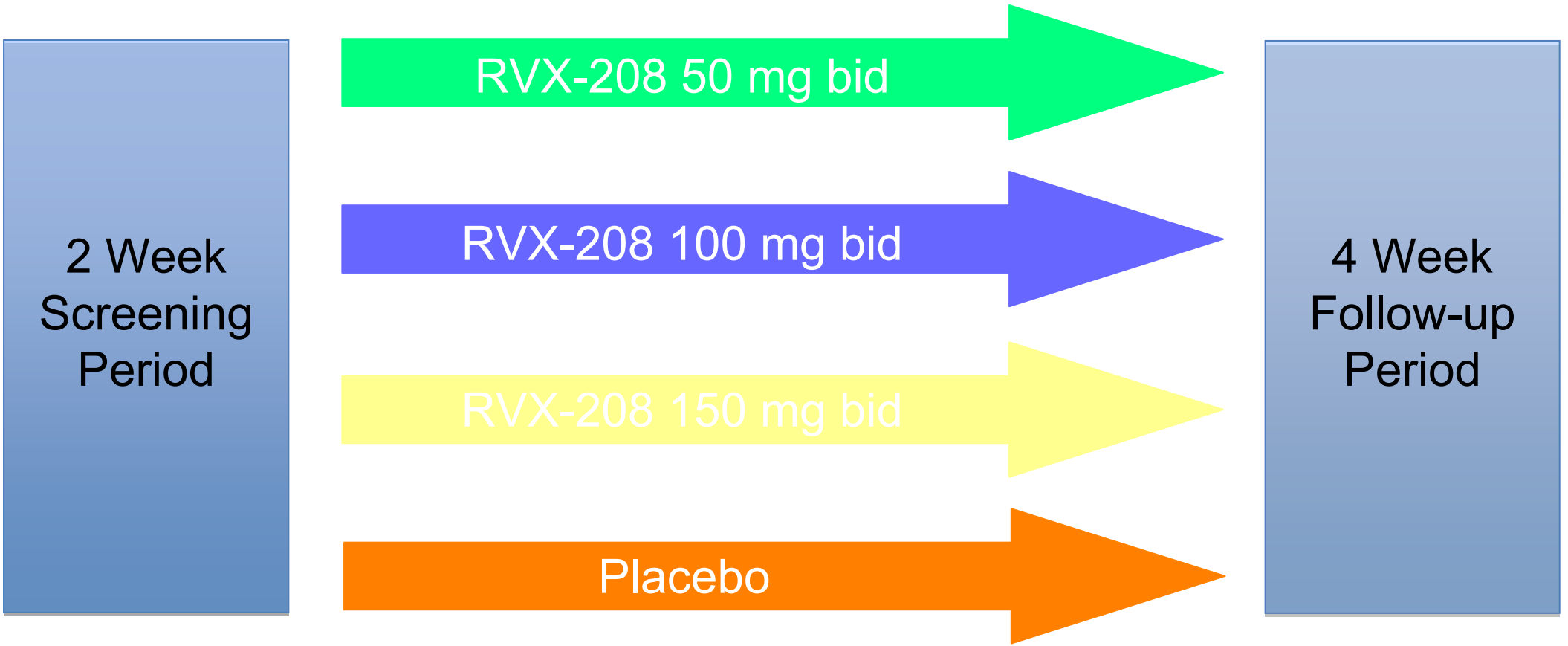
Duff C.J. et al. Expert Opin. Ther. Targets (2011) 15(2):157-168

RVX-208 increases ApoA-I production, thus triggering HDL synthesis, especially pre-beta HDL known for its potent cholesterol efflux activity.



ASSERT Study Design

299 Statin-Treated Patients with Stable Coronary Artery Disease at 35 sites in the US



2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease: Executive Summary

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery

Developed in Collaboration With the American Academy of Neurology and Society of Cardiovascular Computed Tomography

6. Recommendations for Control of Hyperlipidemia

CLASS I

1. Treatment with a statin medication is recommended for all patients with extracranial carotid or vertebral atherosclerosis to reduce low-density lipoprotein (LDL) cholesterol below 100 mg/dL (4,13,14). *(Level of Evidence: B)*

CLASS IIa

1. Treatment with a statin medication is reasonable for all patients with extracranial carotid or vertebral atherosclerosis who sustain ischemic stroke to reduce LDL-cholesterol to a level near or below 70 mg/dL (13). *(Level of Evidence: B)*
2. If treatment with a statin (including trials of higher-dose statins and higher-potency statins) does not achieve the goal selected for a patient, intensifying LDL-lowering drug therapy with an additional drug from among those with evidence of improving outcomes (i.e., bile acid sequestrants or niacin) can be effective (15–18). *(Level of Evidence: B)*
3. For patients who do not tolerate statins, LDL-lowering therapy with bile acid sequestrants and/or niacin is reasonable (15,17,19). *(Level of Evidence: B)*

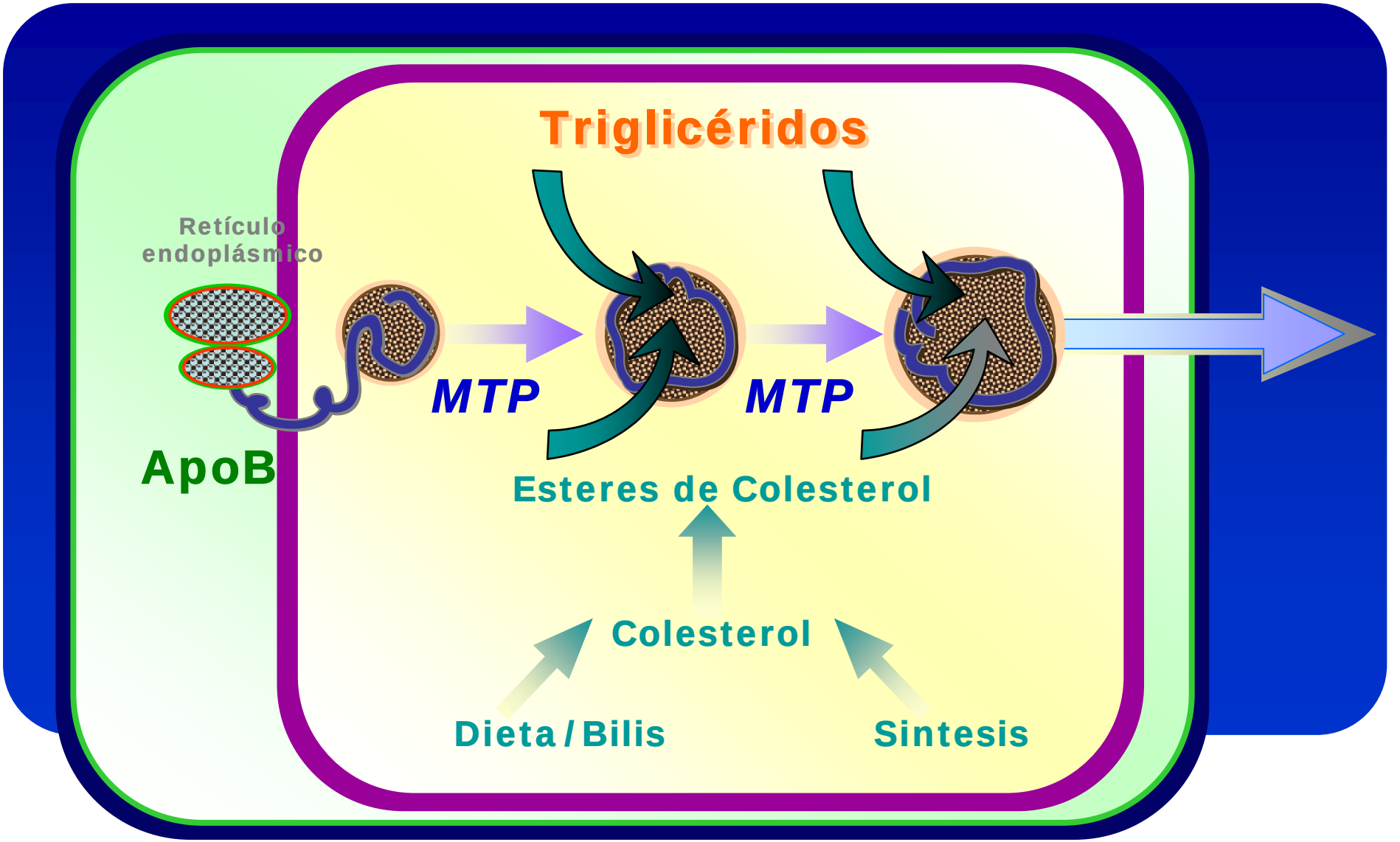
IMP R O V E I O T

- **IMPROVE-IT:**






Ensamblaje y secreción de las VLDL



La depleción celular de colesterol aumenta la expresión de receptores de LDL