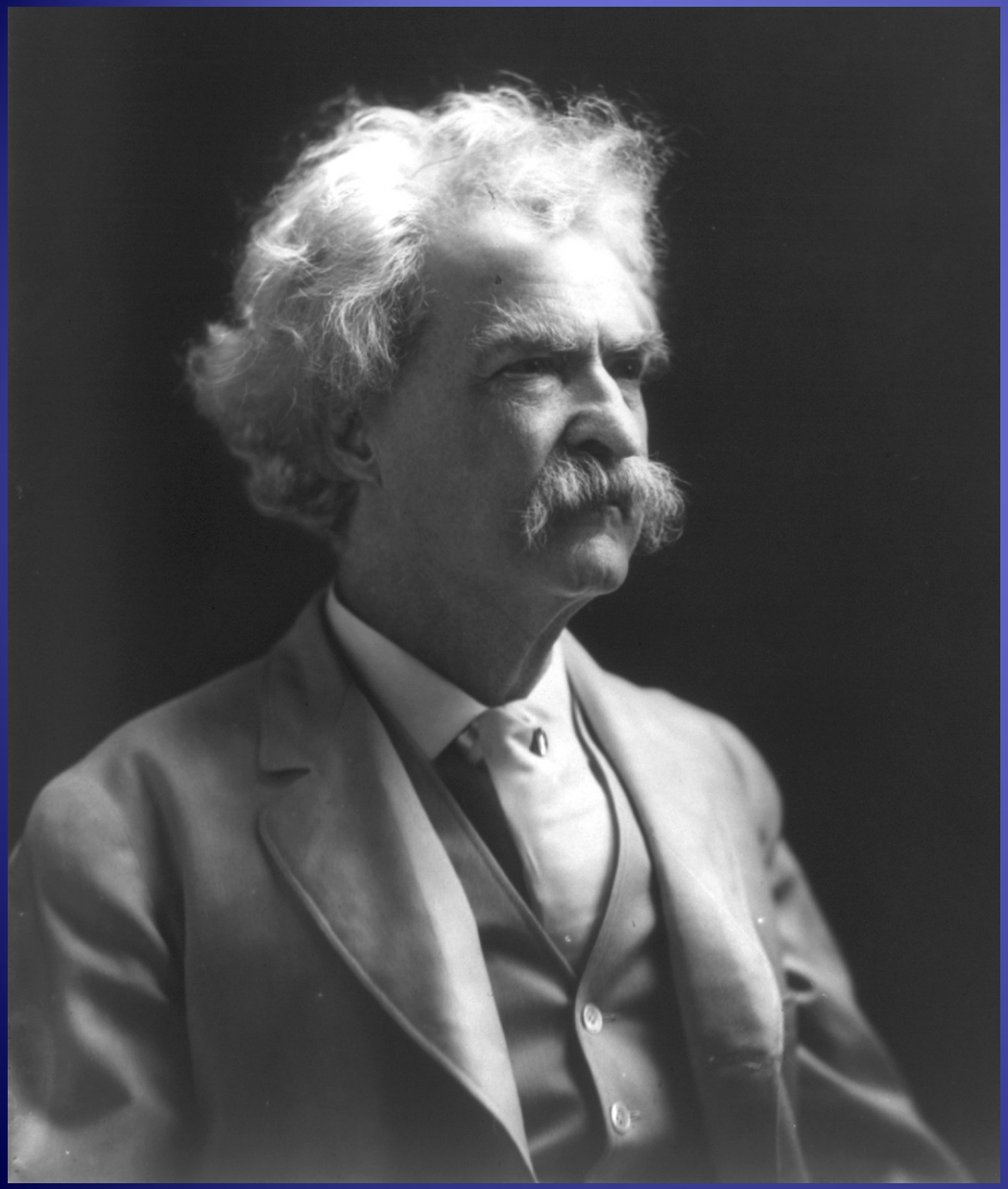
¿Hacia donde se dirige el tratamiento hipolipemiante?

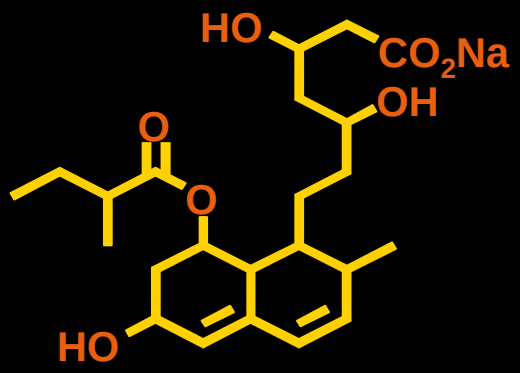
Jose M Mostaza
Unidad de Arteriosclerosis
Hospital Carlos III
Madrid



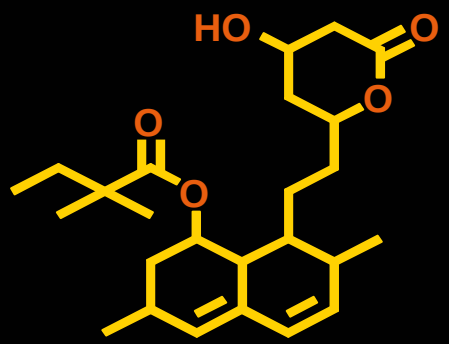
Hacer predicciones correctas es muy difícil, ...

particularmente sobre el futuro.
(Mark Twain)

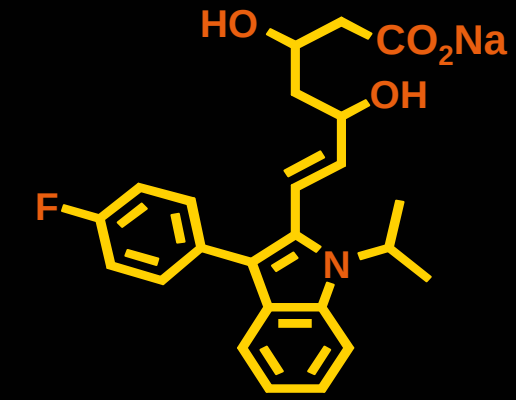
Estatinas



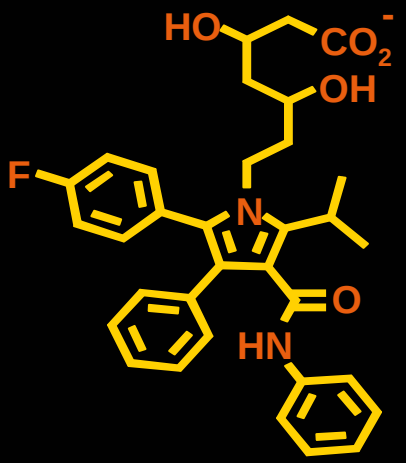
Pravastatina



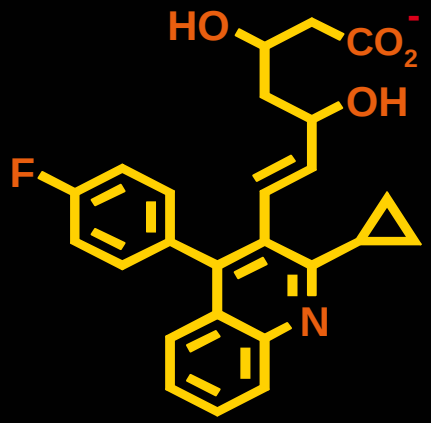
Simvastatina



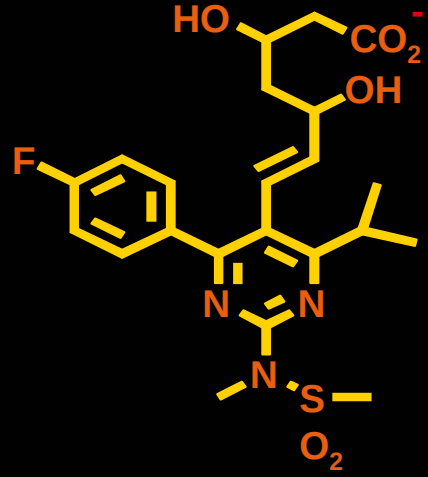
Fluvastatina



Atorvastatina

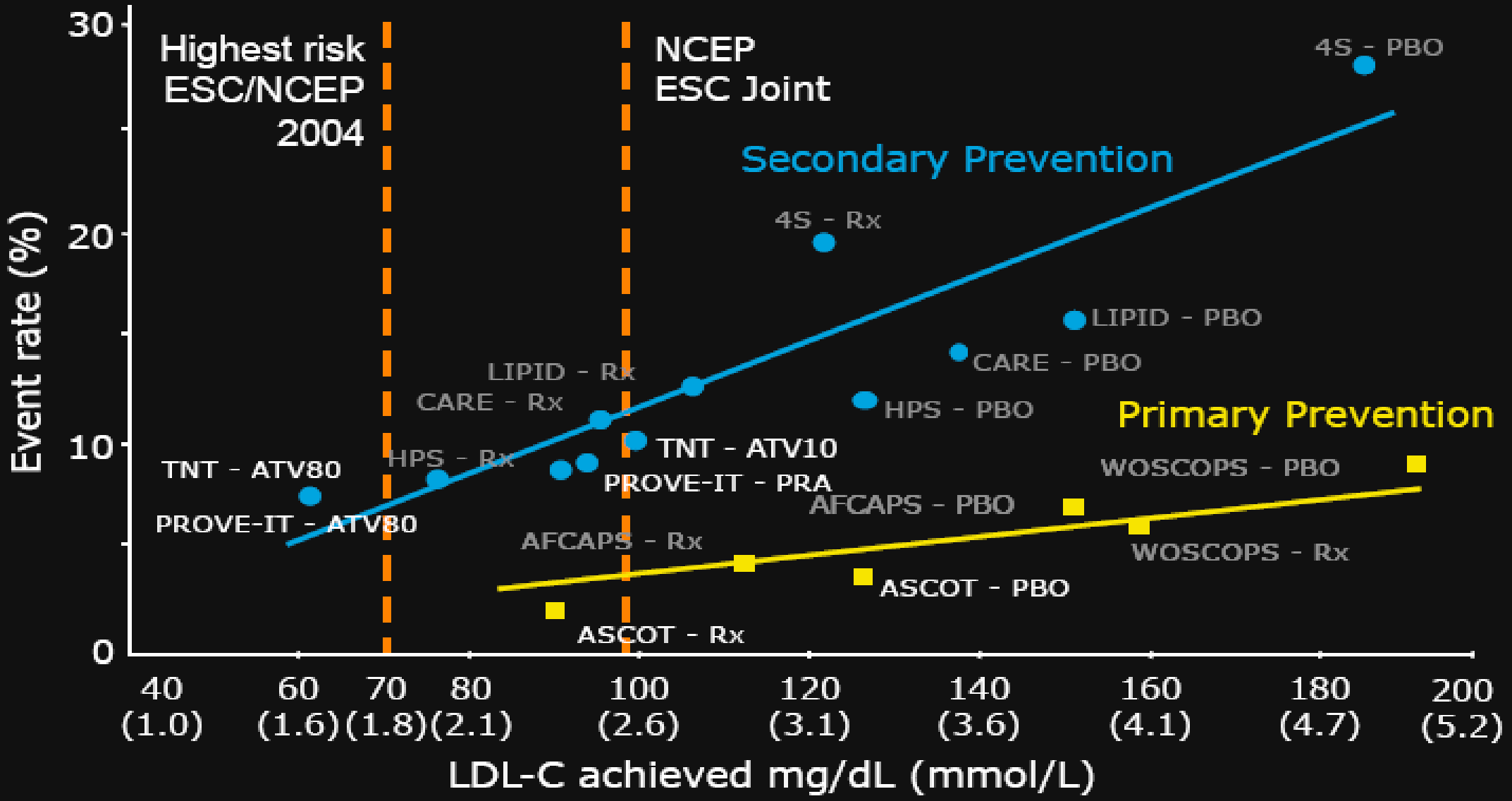


Pitavastatina



Rosuvastatina

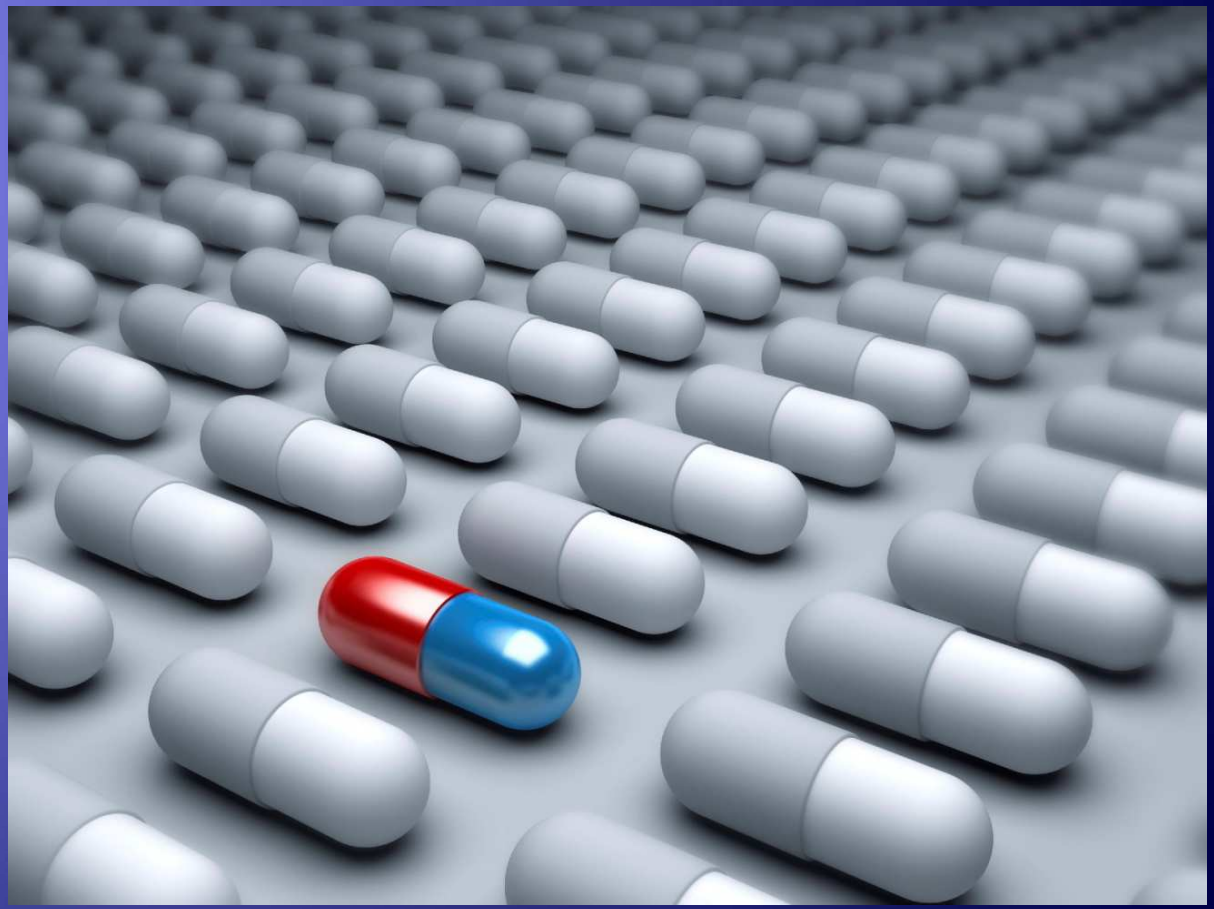
On-treatment LDL & CHD Events in Statin Trials



Adapted from Rosensen, Exp Opin Emerg Drugs 2004;9:269;
LaRosa J et al, N Engl J Med, 2005;352:1425

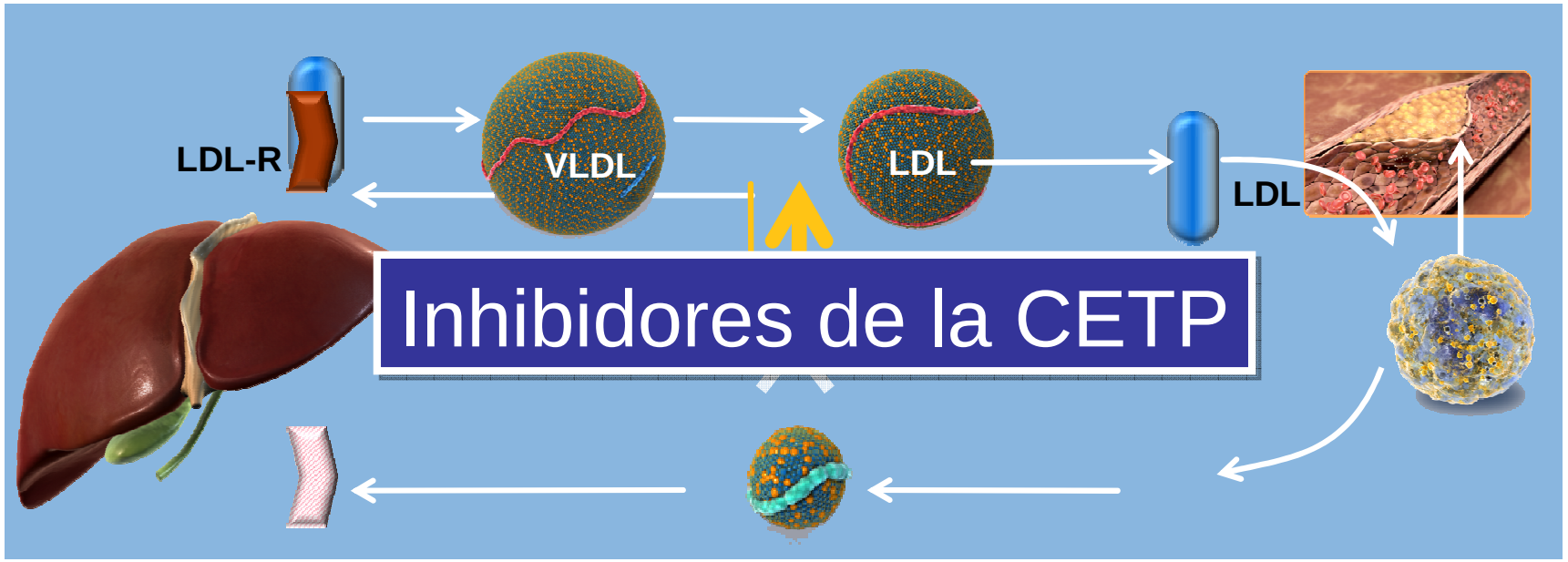
Fármacos disponibles para reducir el colesterol-LDL 2013

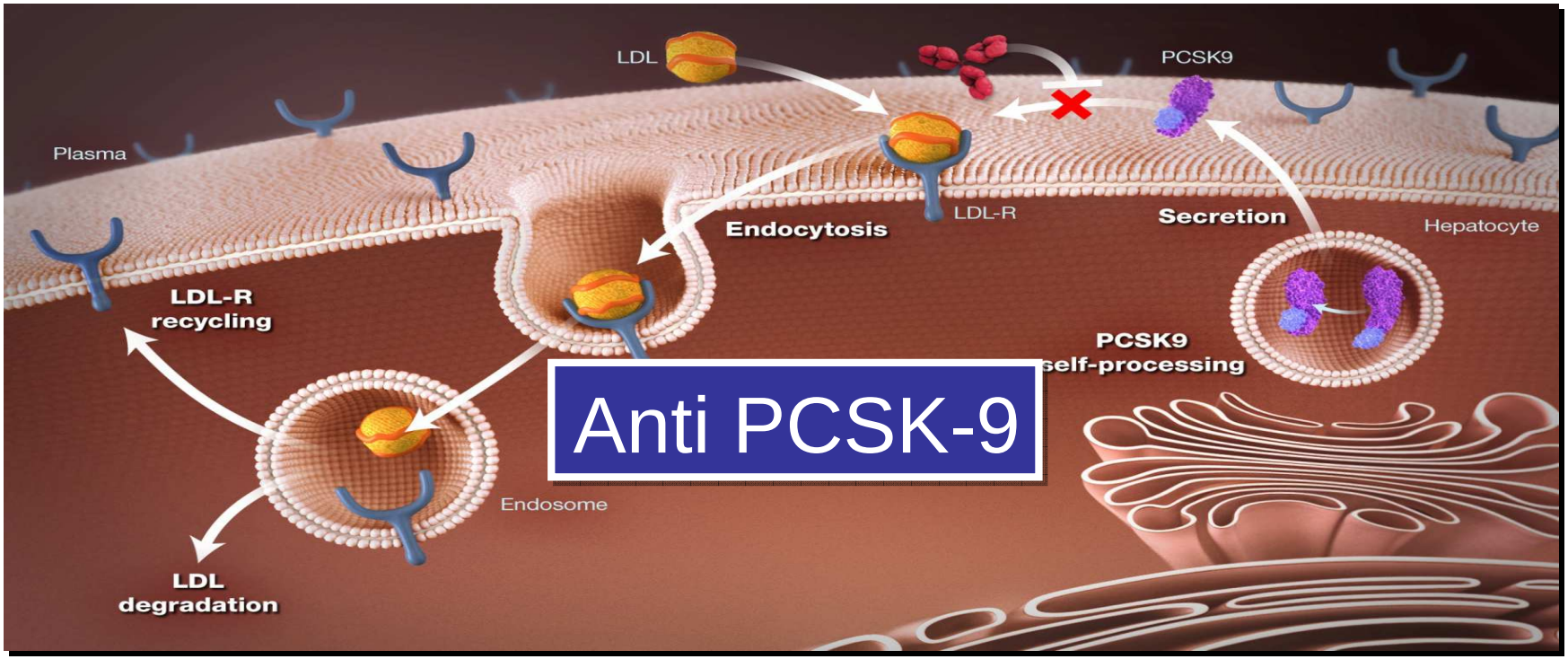
- Estatinas
- Ezetimibe
- Resinas



Pacientes con necesidades de nuevas opciones hipolipemiantes

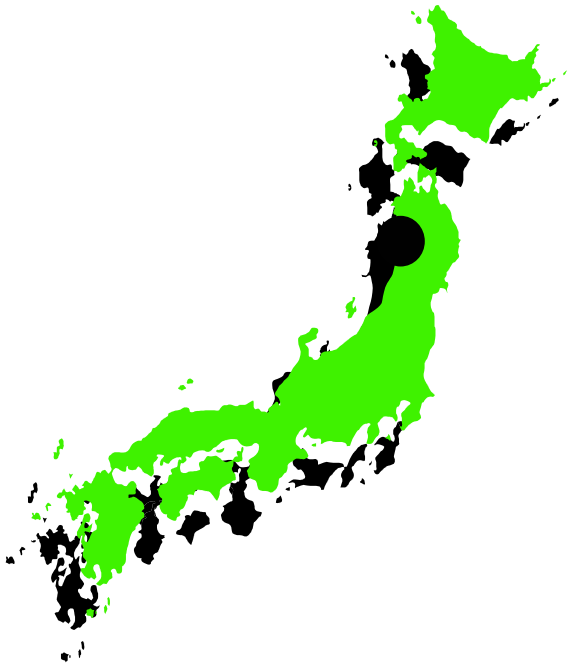
- **Pacientes que no alcanzan objetivos terapéuticos**:
  - -Pacientes de alto riesgo
  - -Hipercolesterolemia familiar
- **Intolerancia a estatinas**


LDL-R
VLDL
LDL
LDL
Inhibidores de la CETP


LDL
PCSK9
Plasma
LDL-R
Endocytosis
Secretion
Hepatocyte
LDL-R
recycling
PCSK9
self-processing
Anti PCSK-9
Endosome
LDL
degradation

Mutaciones de la CETP, lípidos y riesgo vascular en 5 familias japonesas

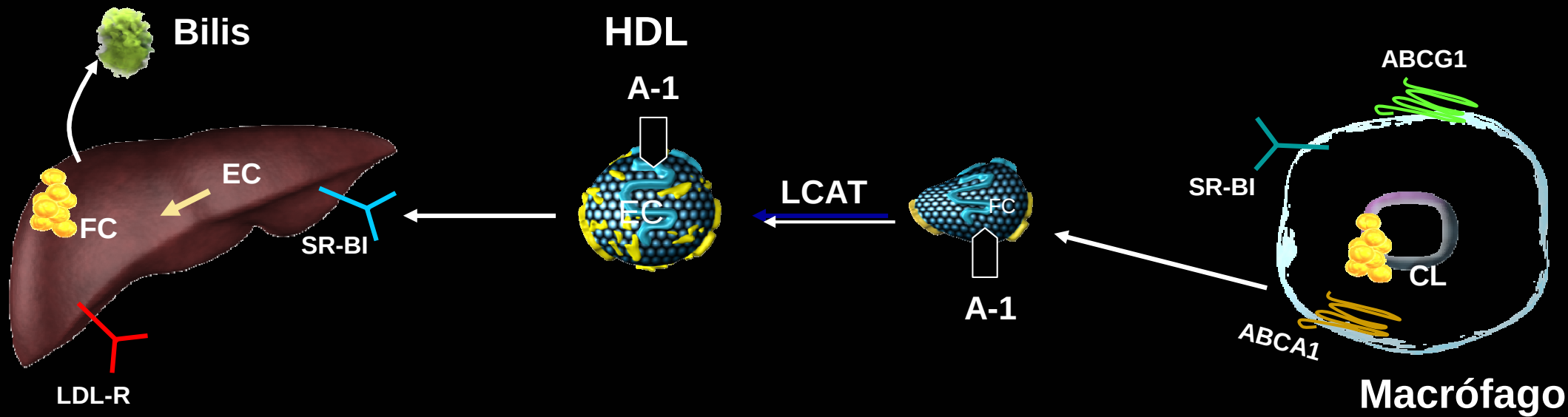
Grupo	Edad	C-HDL	C-LDL	CETP (μg/mL)
Homocigotos (10)	58 (51–68)	170 (↑ 209%)	80	0.0
Heterocigotos (20)	49 (19–100)	68 (↑ 25%)	115	1.4 (0.3)
No afectados (10)	48 (20–71)	55	76	2.3



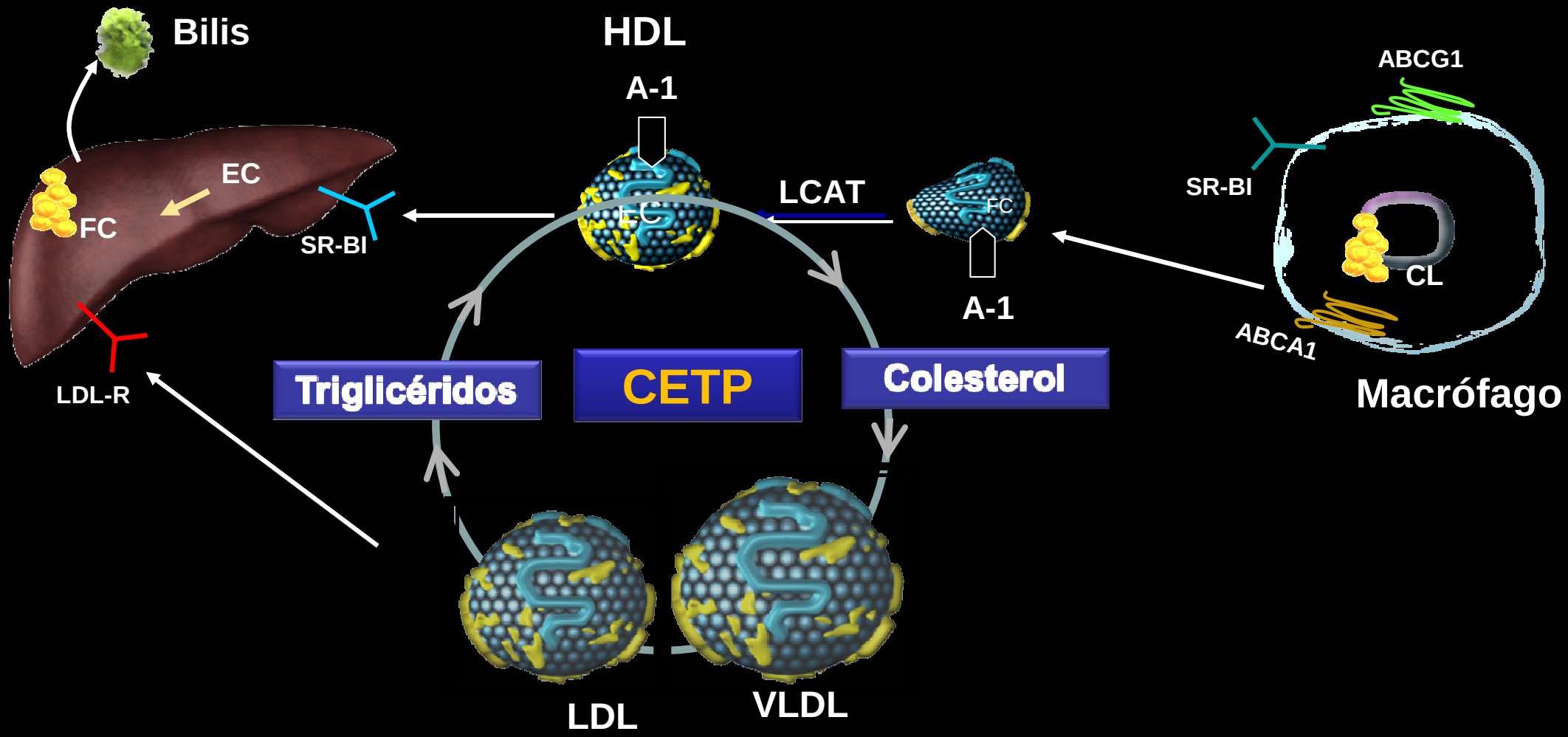
No evidencia de arteriosclerosis prematura en ninguno de los homocigotos. Tendencia a mayor longevidad en las familias afectas con 2 heterocigotos > 100 años

*Inazu et al. *N Engl J Med*. 1990;323:1234–1238

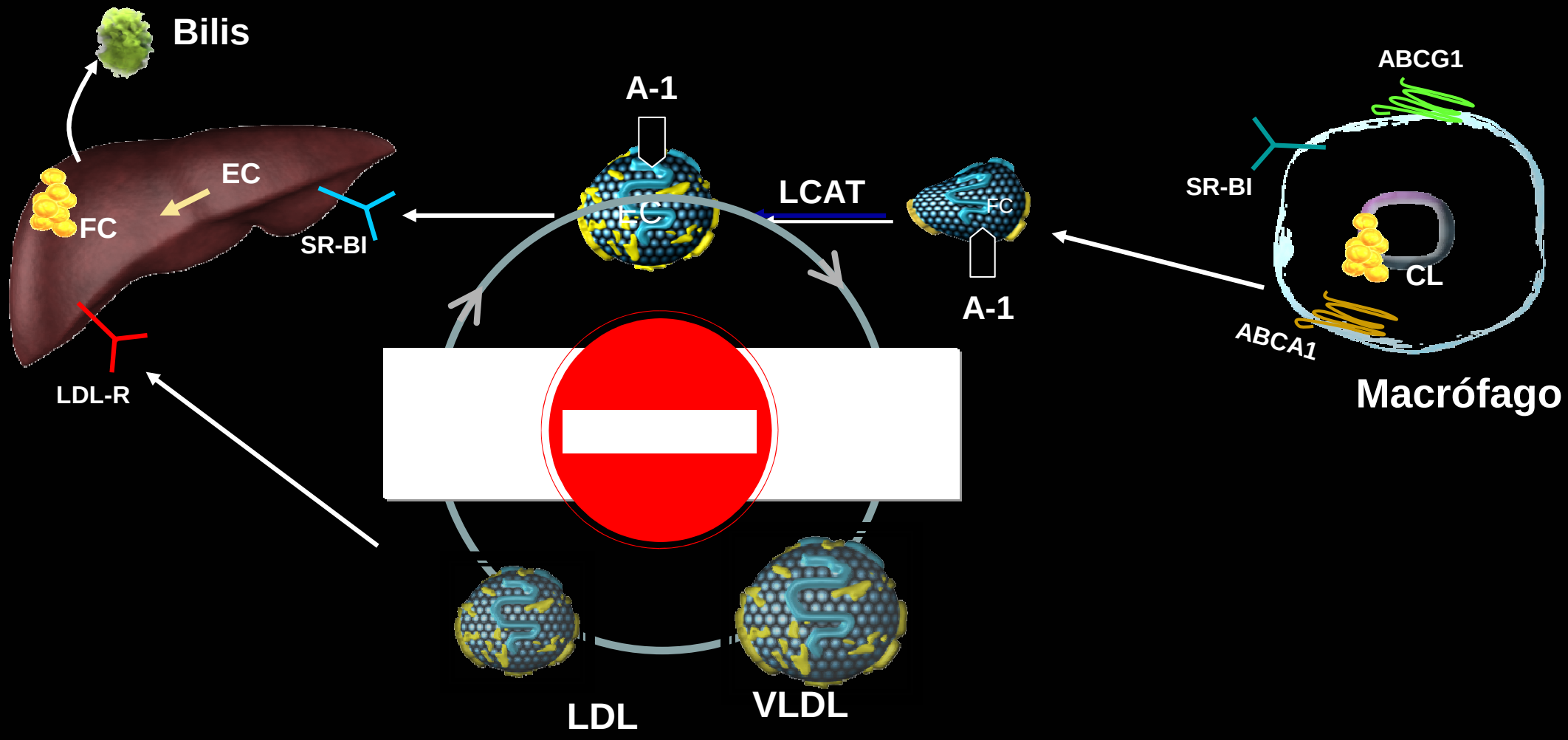
Transporte reverso de colesterol



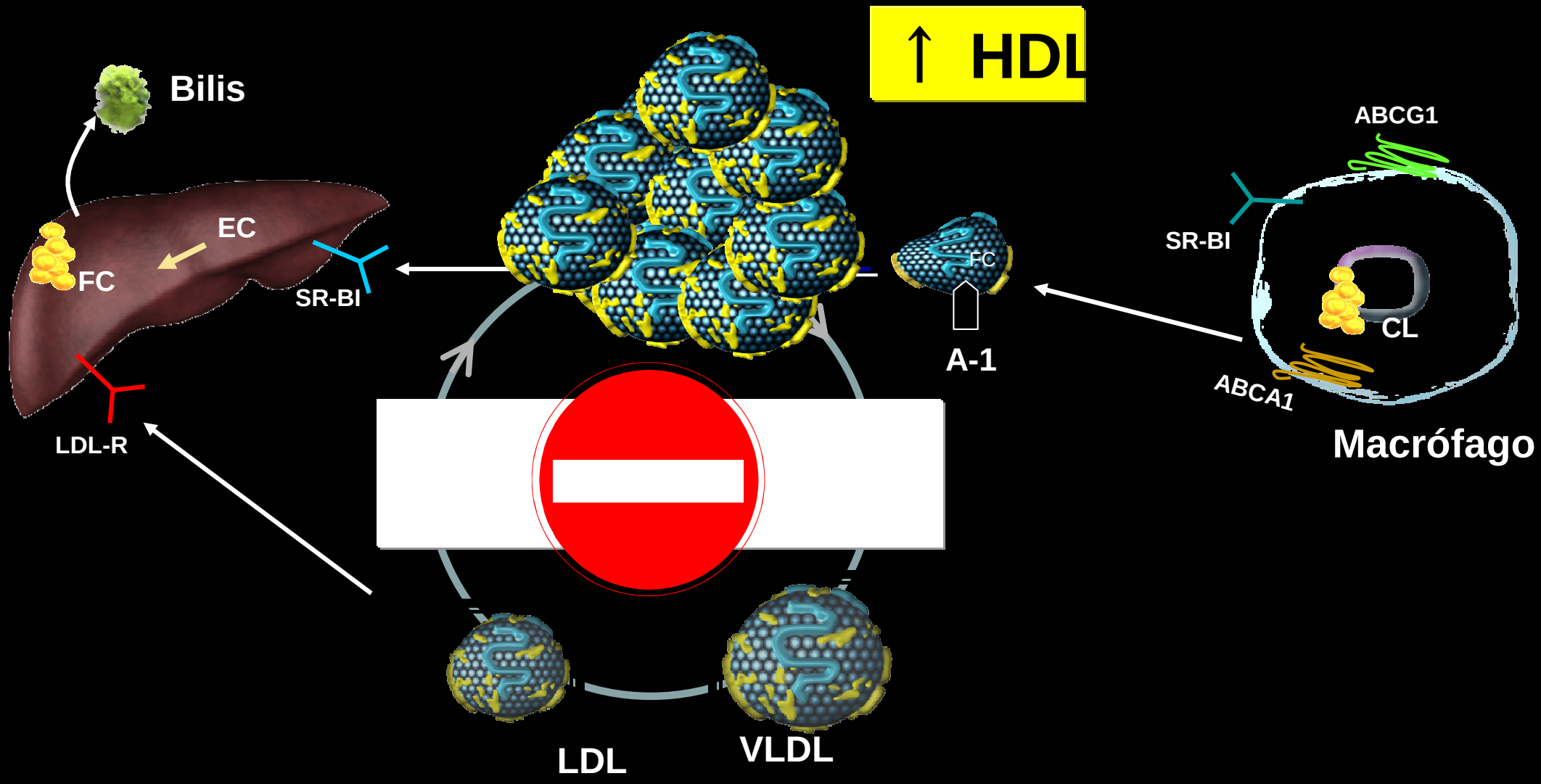
Transporte reverso de colesterol



Transporte reverso de colesterol



Transporte reverso de colesterol



Increased Coronary Heart Disease in Japanese-American Men with Mutation in the Cholesteryl Ester Transfer Protein Gene Despite Increased HDL Levels

Shaobin Zhong,* Dan S. Sharp,‡ John S. Grove,‖ Can Bruce, Katsuhiko Yano,§ J. David Curb,§ and Alan R. Tall*

**Division of Molecular Medicine, Department of Medicine, Columbia University, New York 10032; ‡National Heart, Lung and Blood Institute, Honolulu Heart Program, Honolulu, Hawaii 96817; §Honolulu Heart Program, Kuakini Medical Center, Honolulu, Hawaii; Division of Clinical Epidemiology, John A. Bruns School of Medicine University of Hawaii, Honolulu, Hawaii 96817; and ‖School of Public Health, University of Hawaii, Honolulu, Hawaii 96817*

The Journal of Clinical Investigation
Volume 97, Number 12, June 1996, 2917–2923

Genetic Cholesteryl Ester Transfer Protein Deficiency Is Extremely Frequent in the Omagari Area of Japan

Marked Hyperalphalipoproteinemia Caused by CETP Gene Mutation Is Not Associated With Longevity

Ken–ichi Hirano, Shizuya Yamashita, Norimichi Nakajima, Takeshi Arai, Takao Maruyama, Yu Yoshida, Masato Ishigami, Naohiko Sakai, Kaoru Kameda–Takemura, Yuji Matsuzawa

Arteriosclerosis, Thrombosis, and Vascular Biology.
1997;17:1053–1059
doi: 10.1161/01.ATV.17.6.1053

Efectos lipídicos de los inhibidores de la CETP

% Cambio frente al basal

Inhibidor de la CETP	Dosis (mg/día)	HDL-C (%)	LDL-C (%)	TG (%)
Torcetrapib	60	61	- 24	- 9
Anacetrapib	100	138	- 40	- 7
Evacetrapib	500	129	- 36	- 11
Dalcetrapib	600	31	- 2	- 3

Adapted from Cannon C et al. *JAMA.* 2011;306:2153-2155.
Nicholls SJ et al. *JAMA.* 2011;306:2099-2109.

Estudio Illuminate: Causas de muerte

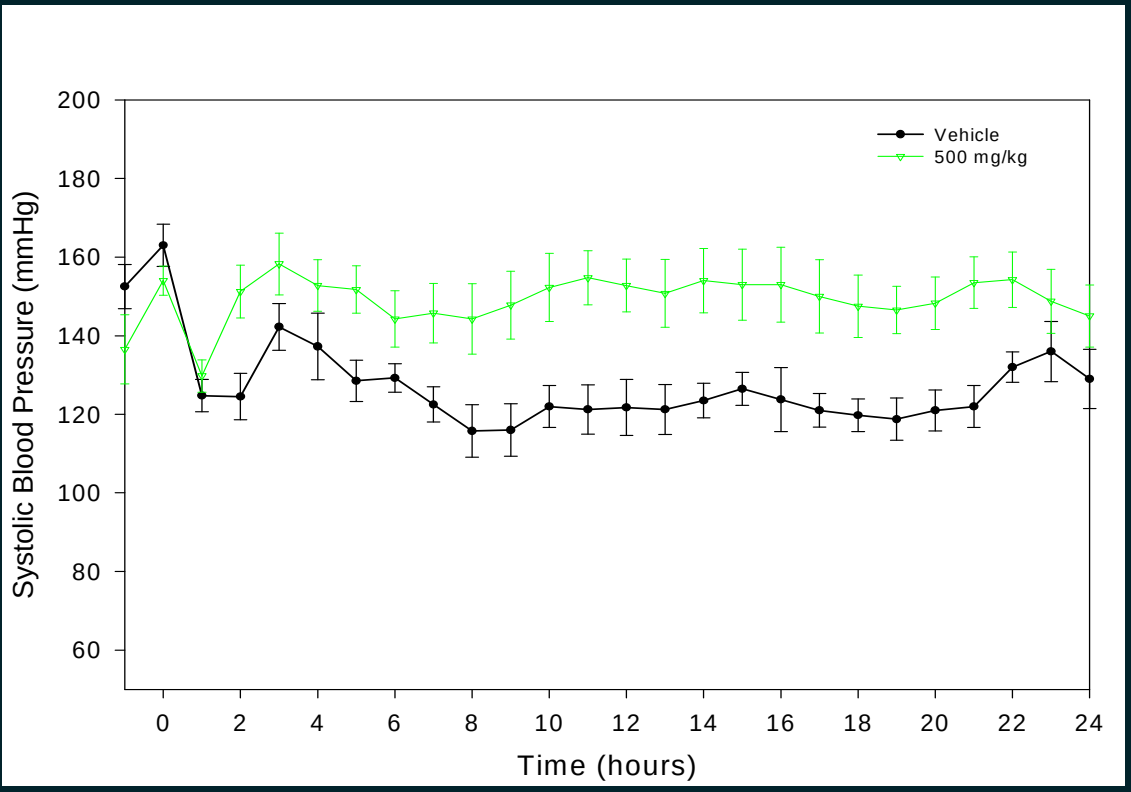
↑72% c-HDL y ↓ 25% c-LDL

	Placebo (n=59)	Torcetrapib (n=93)
Any cardiovascular death	**35**	**49**
Sudden cardiac death	25	26
Fatal MI - not procedure related	6	8
Fatal stroke	0	6
Other cardiac death	1	4
Fatal heart failure	1	2
Other vascular death/procedure related MI	2	3
Any non-cardiovascular	**20**	**40**
Cancer	**14**	**24**
Infection	**0**	**9**
Other non-cardiovascular	2	4
Trauma/suicide/homicide	4	3
Reason unknown	**4**	**4**

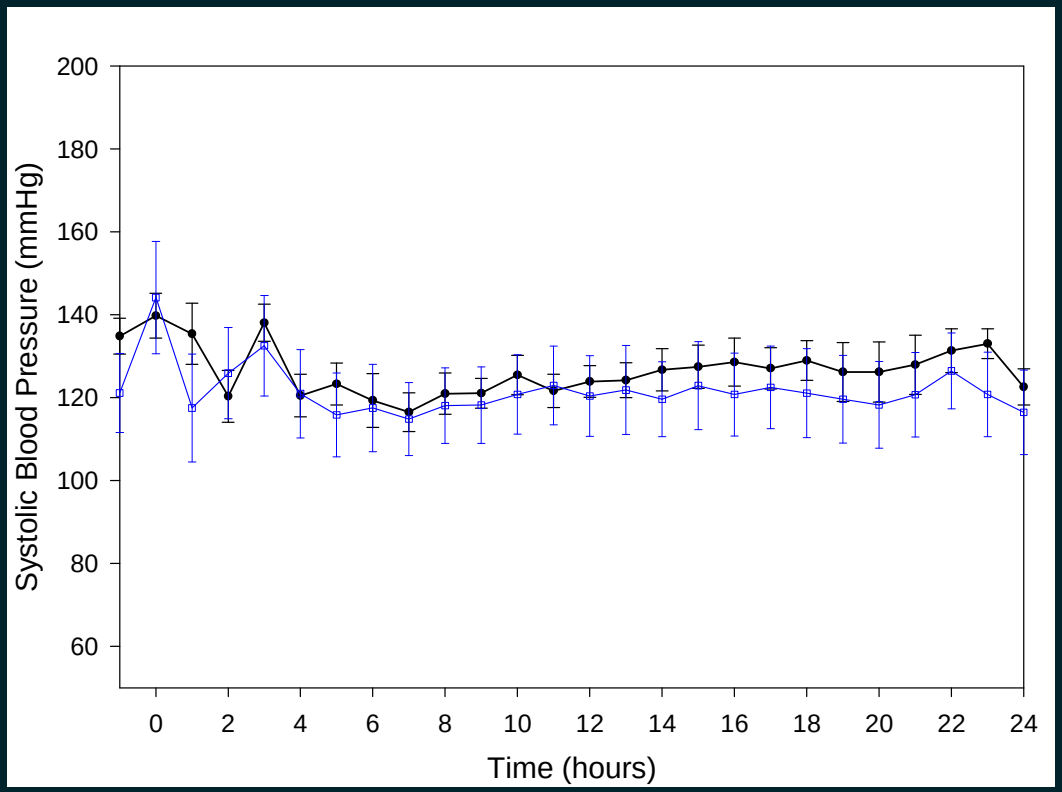
Barter P et al. N Engl J Med 2007;357:2109-22.

Effect of Torcetrapib and Anacetrapib on Blood Pressure in Rhesus Monkeys

Torcetrapib (500 mg/kg)

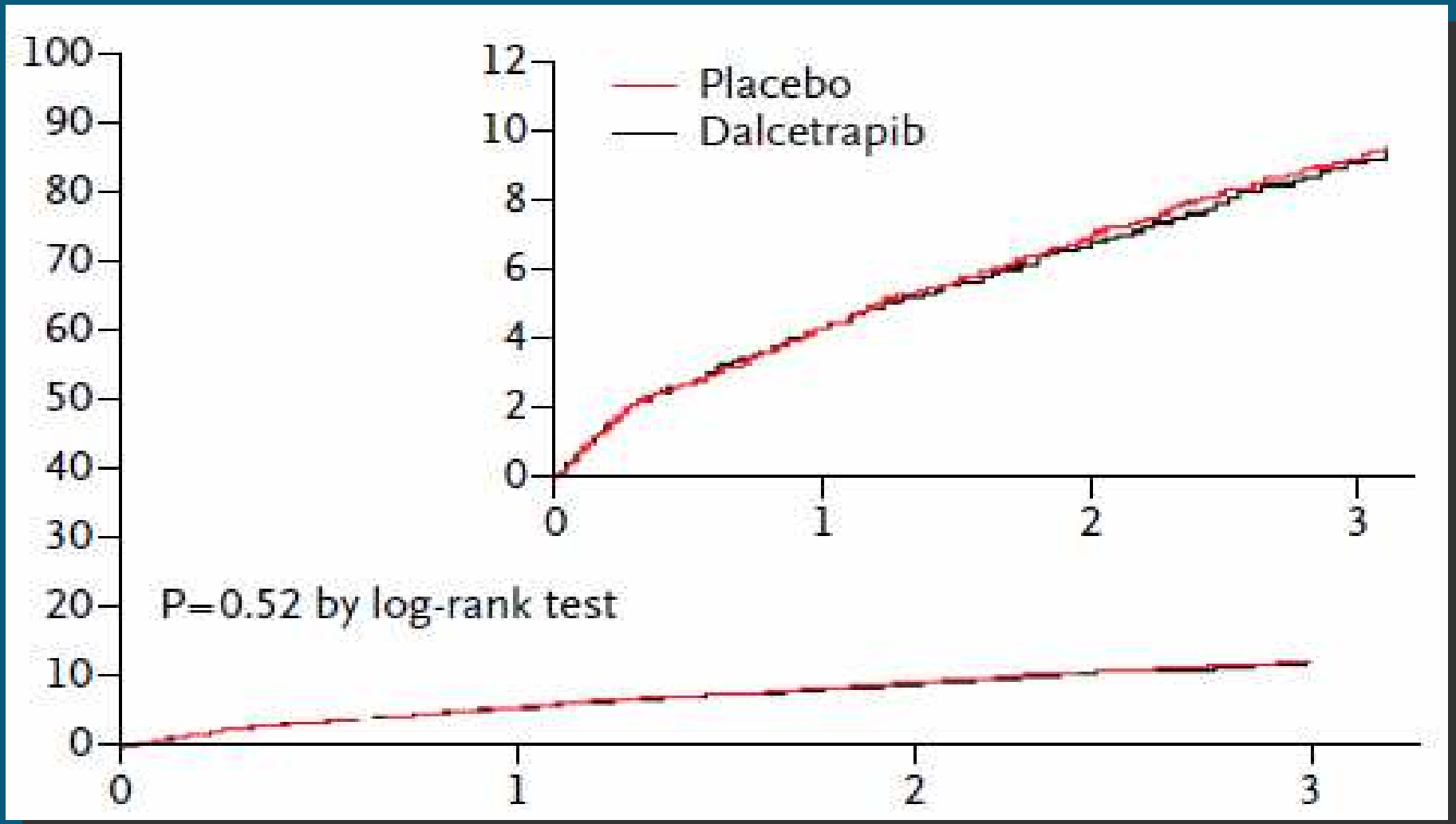


MK-0859 Anacetrapib (50 mg/kg)



Forrest et al. British Journal of Pharmacology (2008) 154, 1465–1473

dal-OUTCOMES Results: *No ↓ CVD*

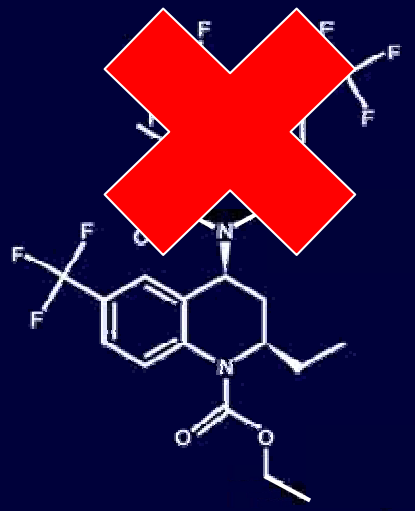


No. at risk				
Placebo	7933	7386	6551	1743
Dalcetrapib	7938	7372	6495	1736

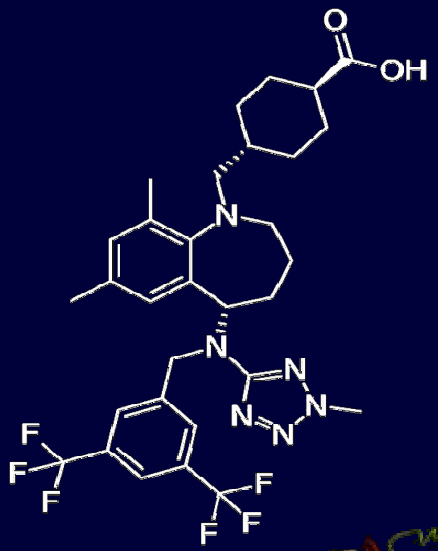
Schwartz GG et al. *N Engl J Med.* 2012 Nov 5. [Epub ahead of print].

CETP Inhibitors: 2 Down, 2 Remain

Torcetrapib

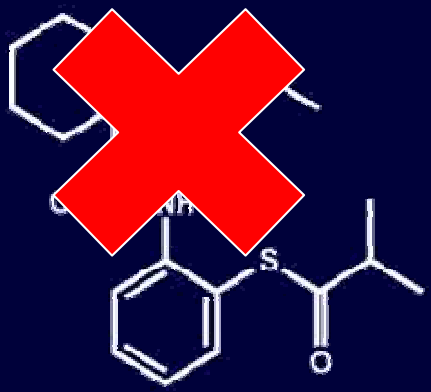


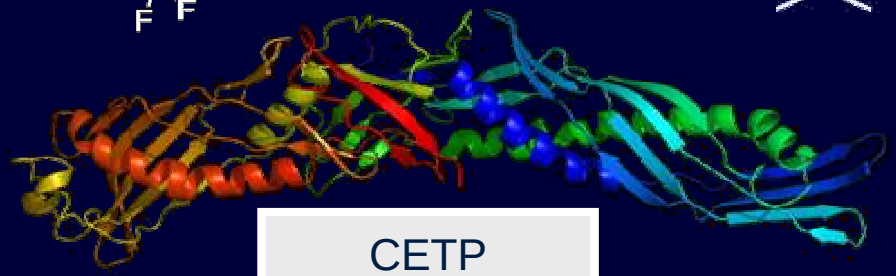
Evacetrapib



Anacetrapib

Dalcetrapib

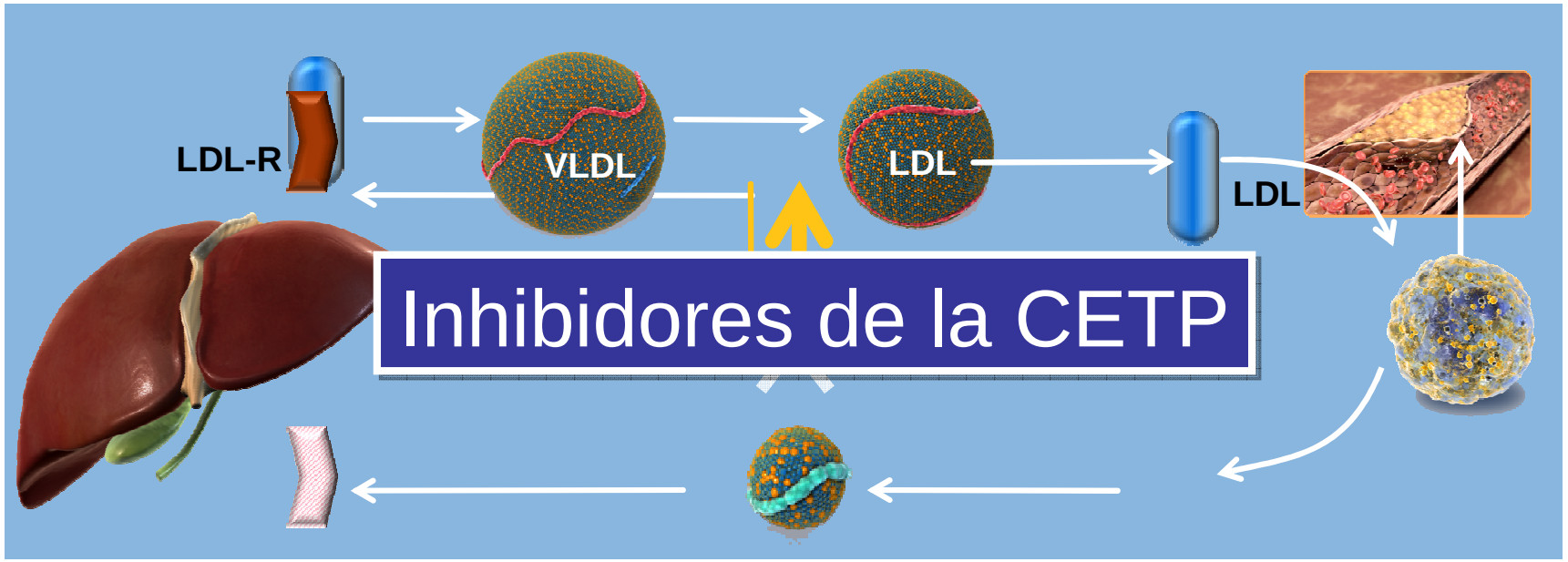


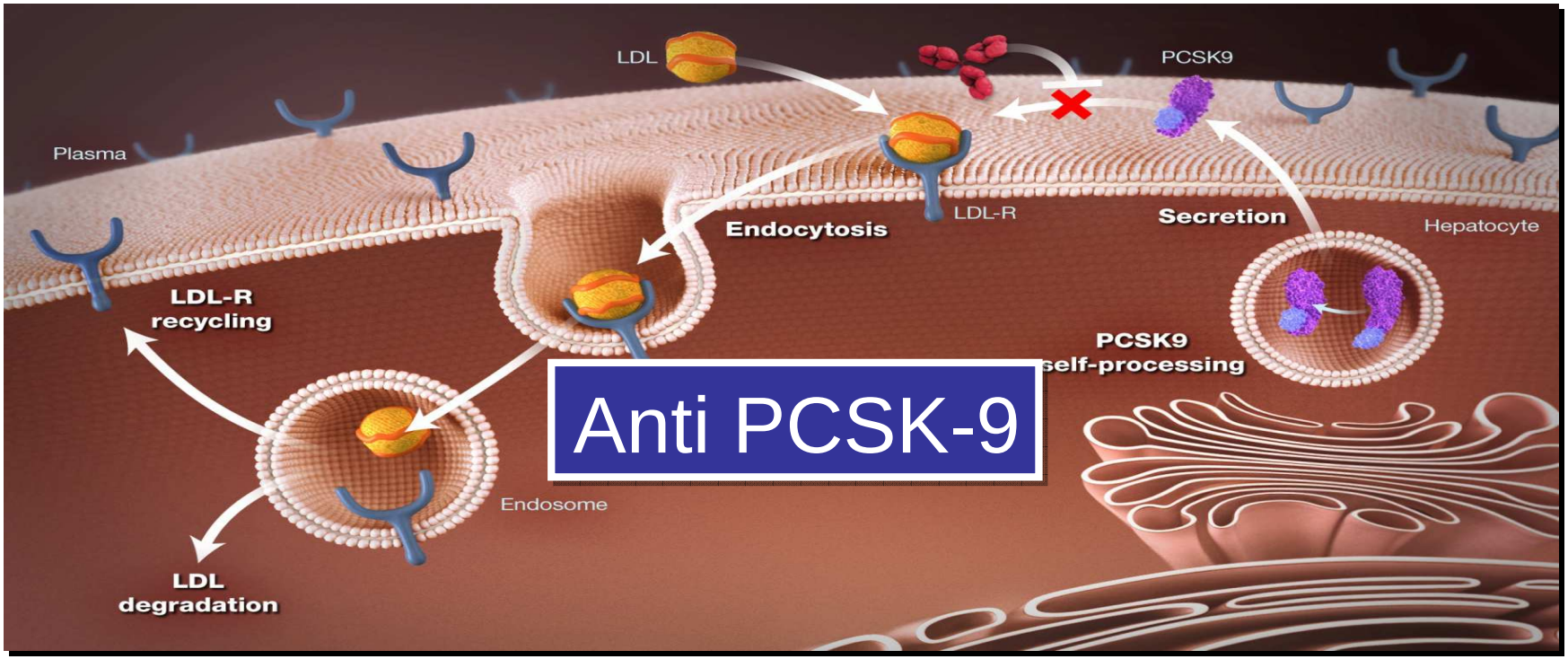


CETP

Barter et al. *N Engl J Med.* 2007;357(13):2109-2122.
http://www.ama-assn.org/ama1/pub/upload/mm/365/dalcetrapib.doc.
http://www.ama-assn.org/ama1/pub/upload/mm/365/torcetrapib.doc.
Qiu X et al. *Nat Struct Mol Biol.* 2007;14(2):106-113.
http://www.ama-assn.org/ama1/pub/upload/mm/365/anacetrapib.pdf.
http://www.roche.com/media/media_releases/med-cor-2012-05-07.htm.

*Dalcetrapib development stopped May 7, 2012 due to lack of efficacy in the Dal-Outcomes CVD endpoint trial.


LDL-R
VLDL
LDL
LDL
Inhibidores de la CETP


LDL
PCSK9
Plasma
LDL-R
Endocytosis
Secretion
Hepatocyte
LDL-R
recycling
PCSK9
self-processing
Anti PCSK-9
Endosome
LDL
degradation

Brief Communication

Nature Genetics **34**, 154 - 156 (2003)
Published online: 5 May 2003 | doi:10.1038/ng11

Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4],

March 2004, Volume 114, Issue 4, pp 349-353

A mutation in *PCSK9* causing autosomal -dominant hypercholesterolemia in a Utah pedigree

Kirsten M. Timms, Susanne Wagner, Mark E. Samuels, Kristian Forbey, Howard Goldfine, Srikanth

Mutations in the *PCSK9* gene in Norwegian subjects with autosomal dominant hypercholesterolemia

TP Leren*

Article first published online: 17 MAR 2004

DOI: 10.1111/j.0009-9163.2004.0238.x

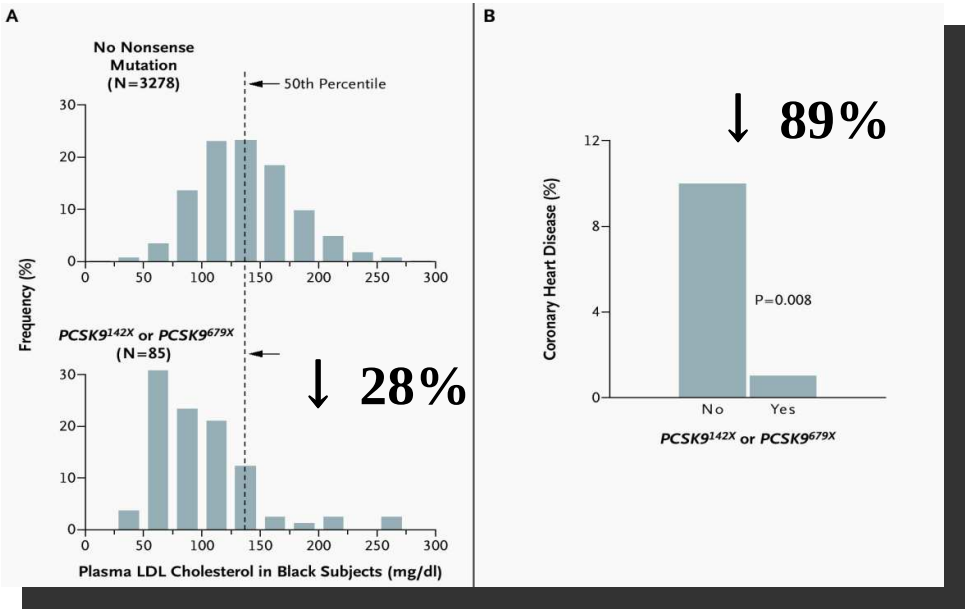
Issue

Clinical Genetics

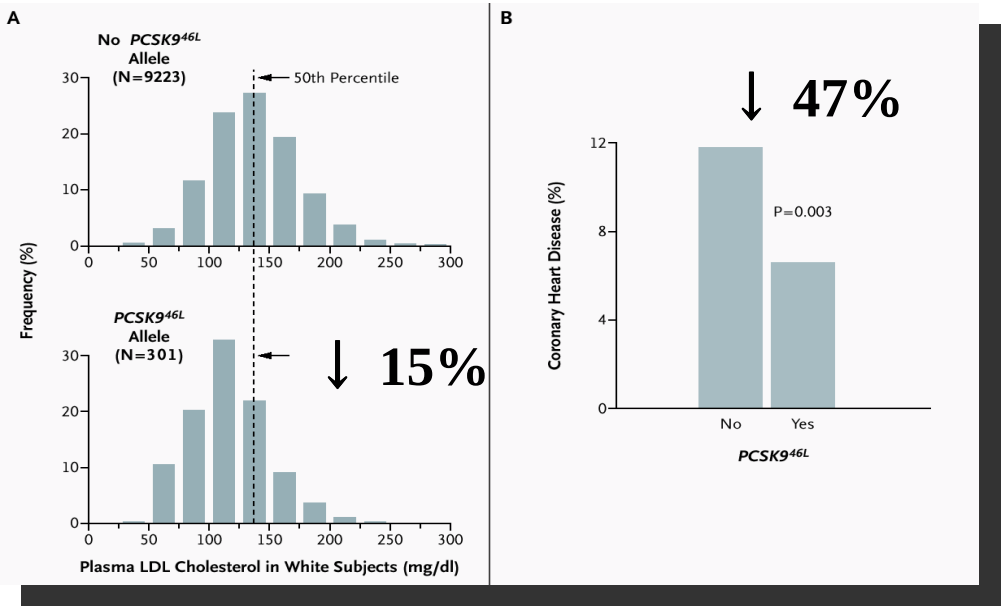
Volume 65, Issue 5, pages 419-422, May 2004

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

Población negra

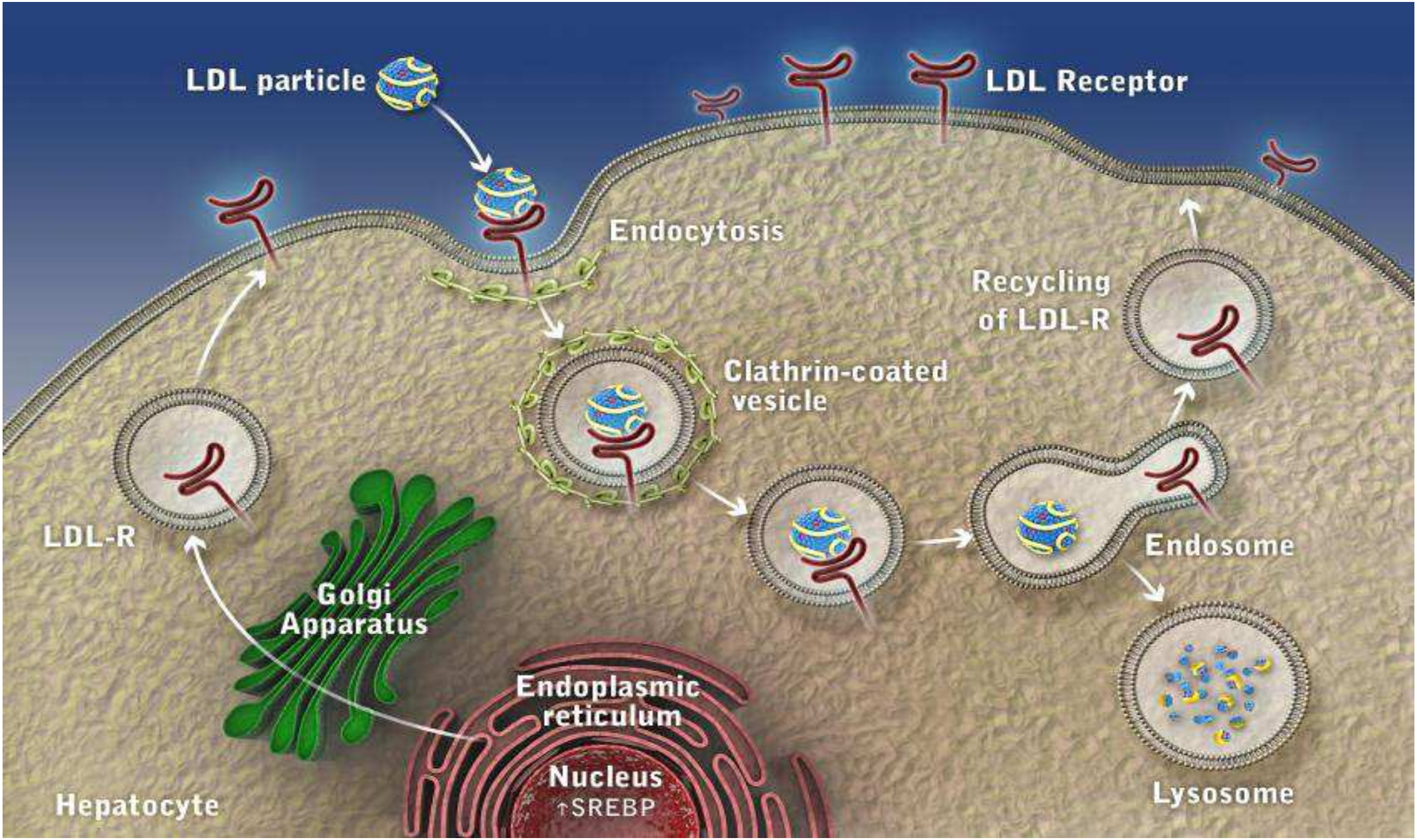


Población blanca

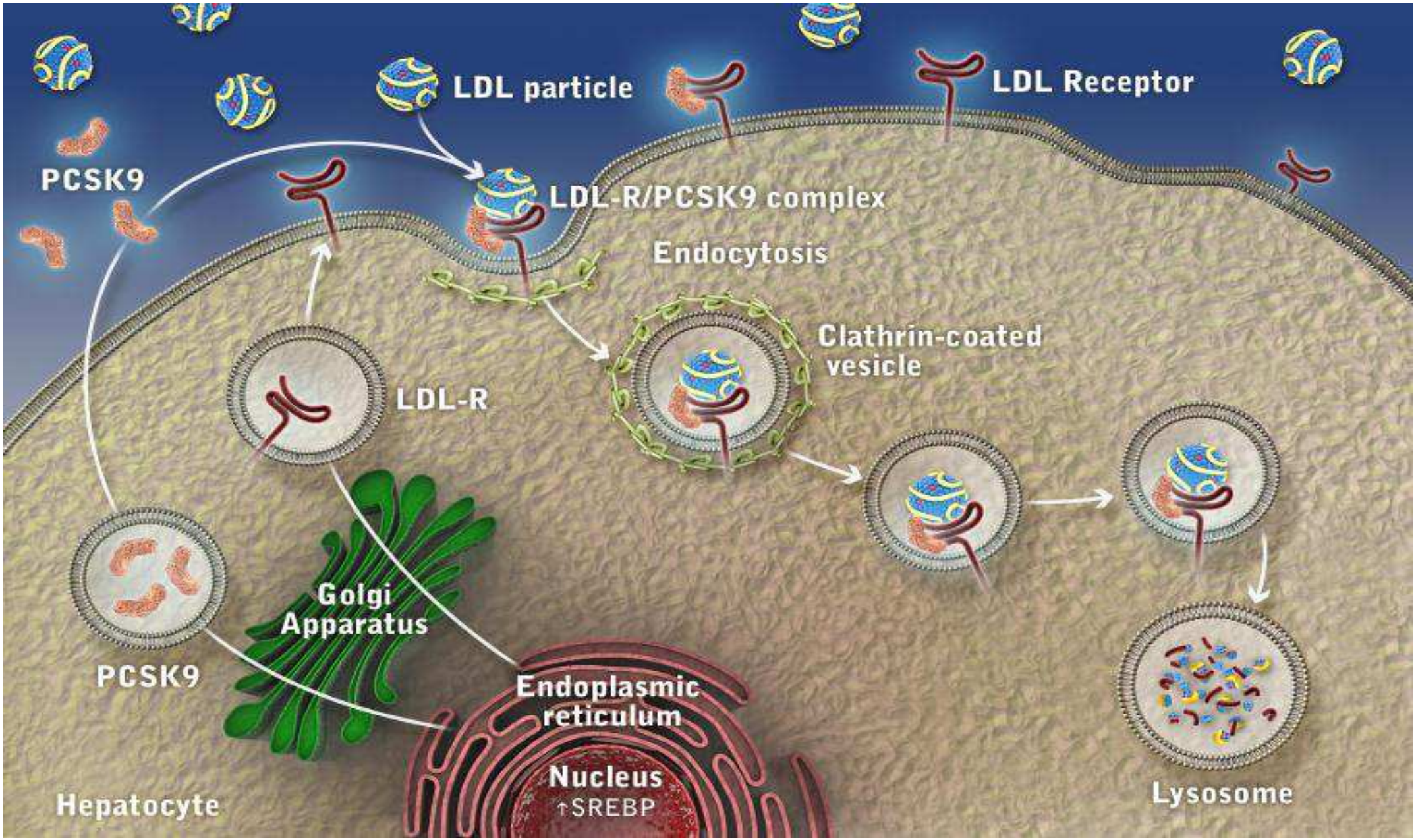


Jonathan C.Cohen, et al, N Engl J Med 2006;354:1264-72

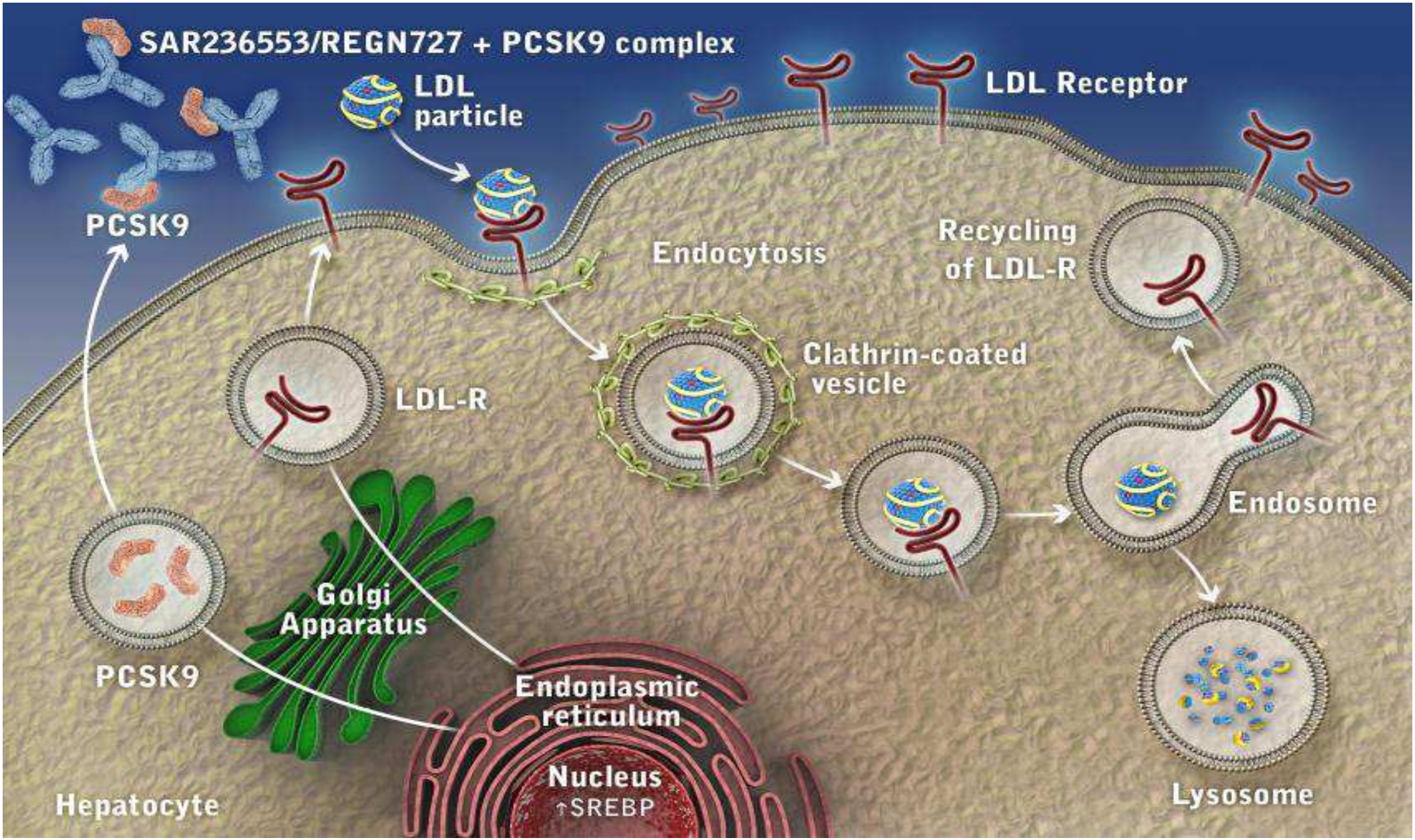
Función y reciclado del receptor de LDL



Regulación del receptor de LDL por la PCSK9



Bloqueo del PCSK-9 y expresión del receptor de LDL



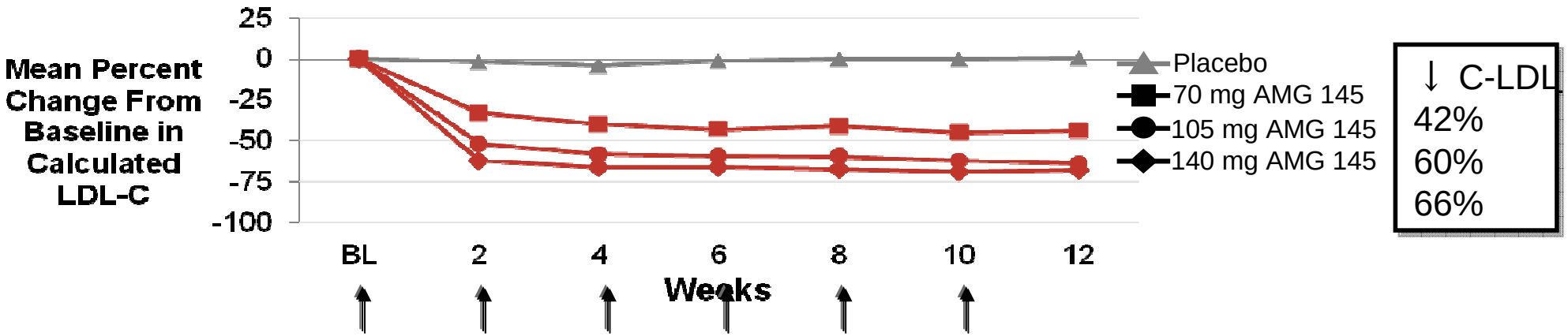
Eficacia del tratamiento con Anticuerpos Anti-PCSK9 para reducir el C-LDL

Intervention	Baseline LDL-C mg/dL	% Change LDL-C
Placebo	151	–10.7
REGN727 150 mg Q4W	167	–28.9
REGN727 200 mg Q4W	170	–31.5
REGN727 300 mg Q4W	140	–42.5
REGN727 150 mg Q2W	147	–67.9

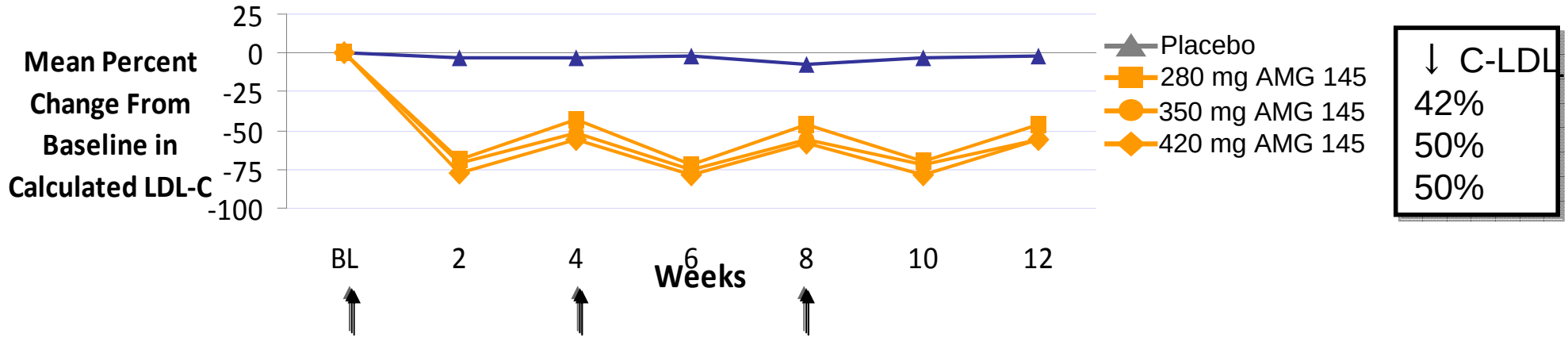
Stein EA et al. *Lancet.* 2012;380:29–36

Effects of AMG 145 on LDL-C Over 12 Weeks: LAPLACE Study

Q2W Dosing



Q4W Dosing

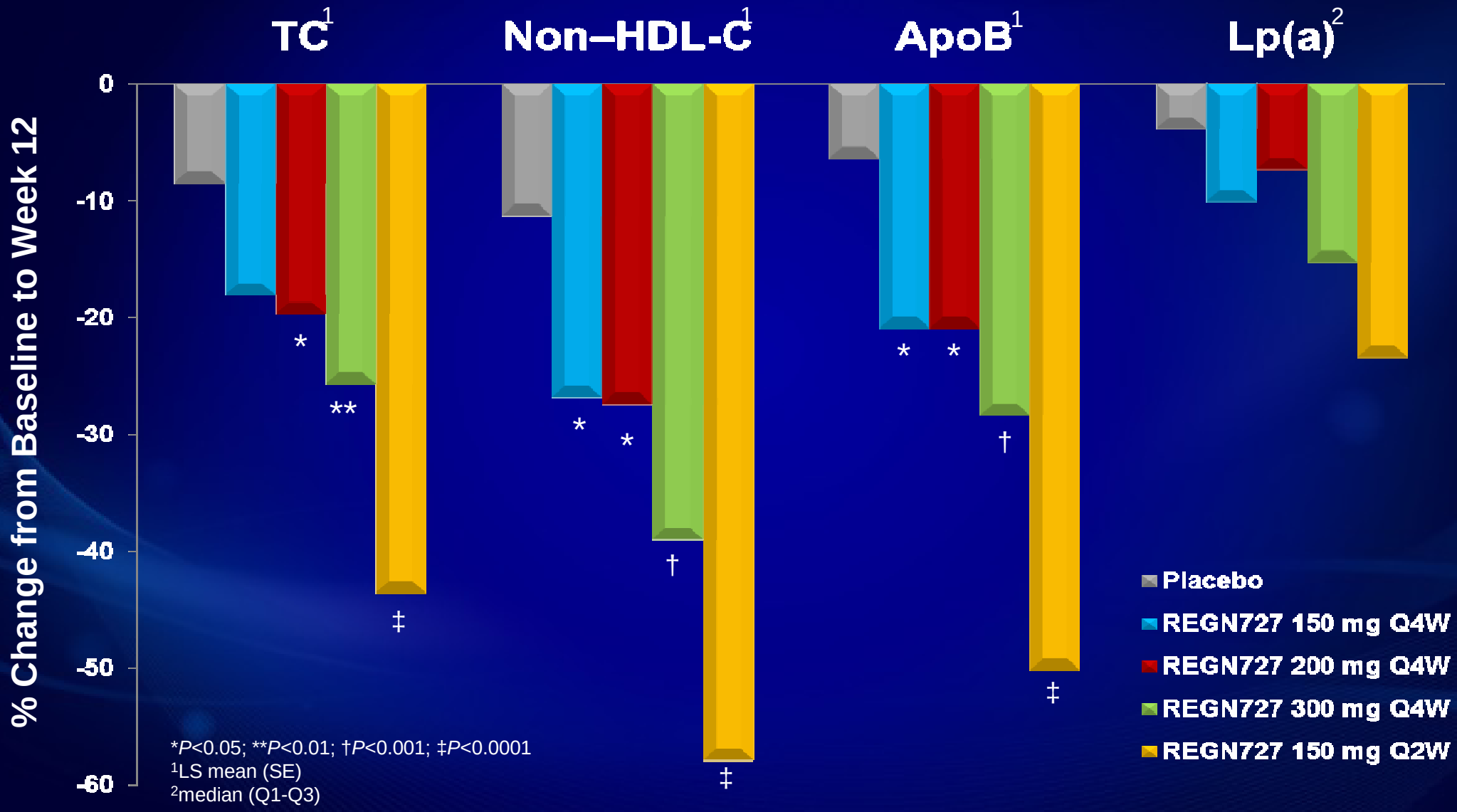


Mean observed values without imputation for missing data
BL = baseline

Guigliano RP, et al. *Lancet*. 2012. In press.

AMGEN
Cardiovascular

Changes in TC, non-HDL-C, Apo B and Lp(a) from Baseline to Week 12 by Treatment Group (mITT Population)



*P<0.05; **P<0.01; †P<0.001; ‡P<0.0001
[1]LS mean (SE)
[2]median (Q1-Q3)

Stein EA et al. *Lancet.* 2012;380:29–36

- √ Seguridad a largo plazo
- √ Eficacia a largo plazo
- √ Reducción de complicaciones cardiovasculares

Siempre evito hacer profecías anticipadas, porque es mucho mejor hacerlas después de que todo haya ocurrido

(W Churchill)