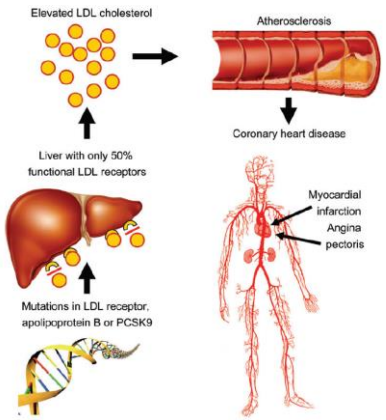
Sademi
Sociedad Andaluza de Medicina Interna

XXXII Congreso de la Sociedad Andaluza de Medicina Interna (SADEMI)



"Nuevas dianas terapéuticas en el tratamiento de la hiperlipemia: Inhibidores PCSK9"

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INDICE

- El escenario pasado-actual:

  la era de las estatina-ezetimibe

- El escenario actual-futuro:

  la era de los Inhibidores de PCSK9

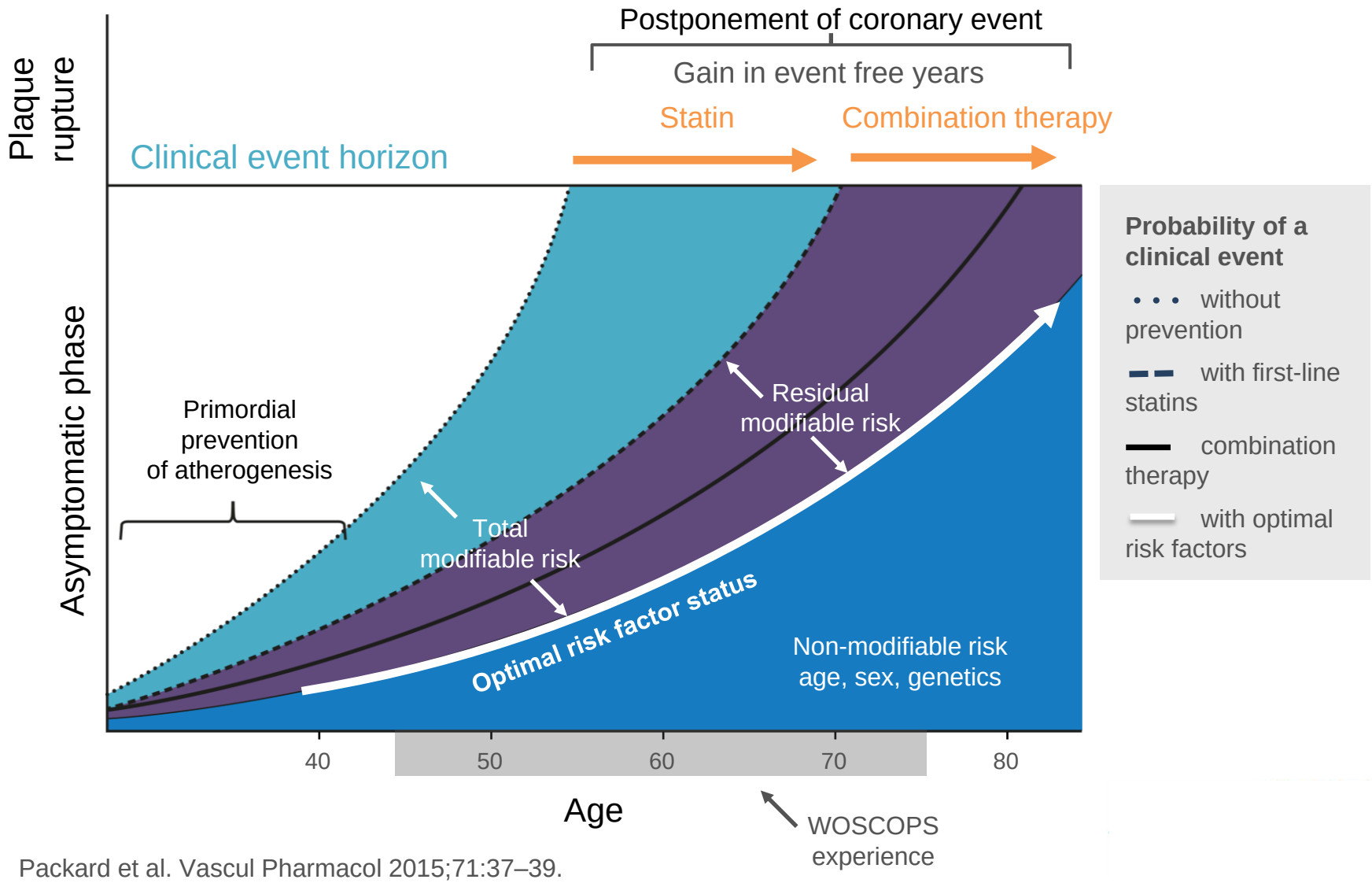
Enfermedad Cardiovascular

1. Es suficiente la reducción de episodios CCV tras tratamiento actual.

2. Podemos obtener beneficios adicionales tras el tratamiento actual.

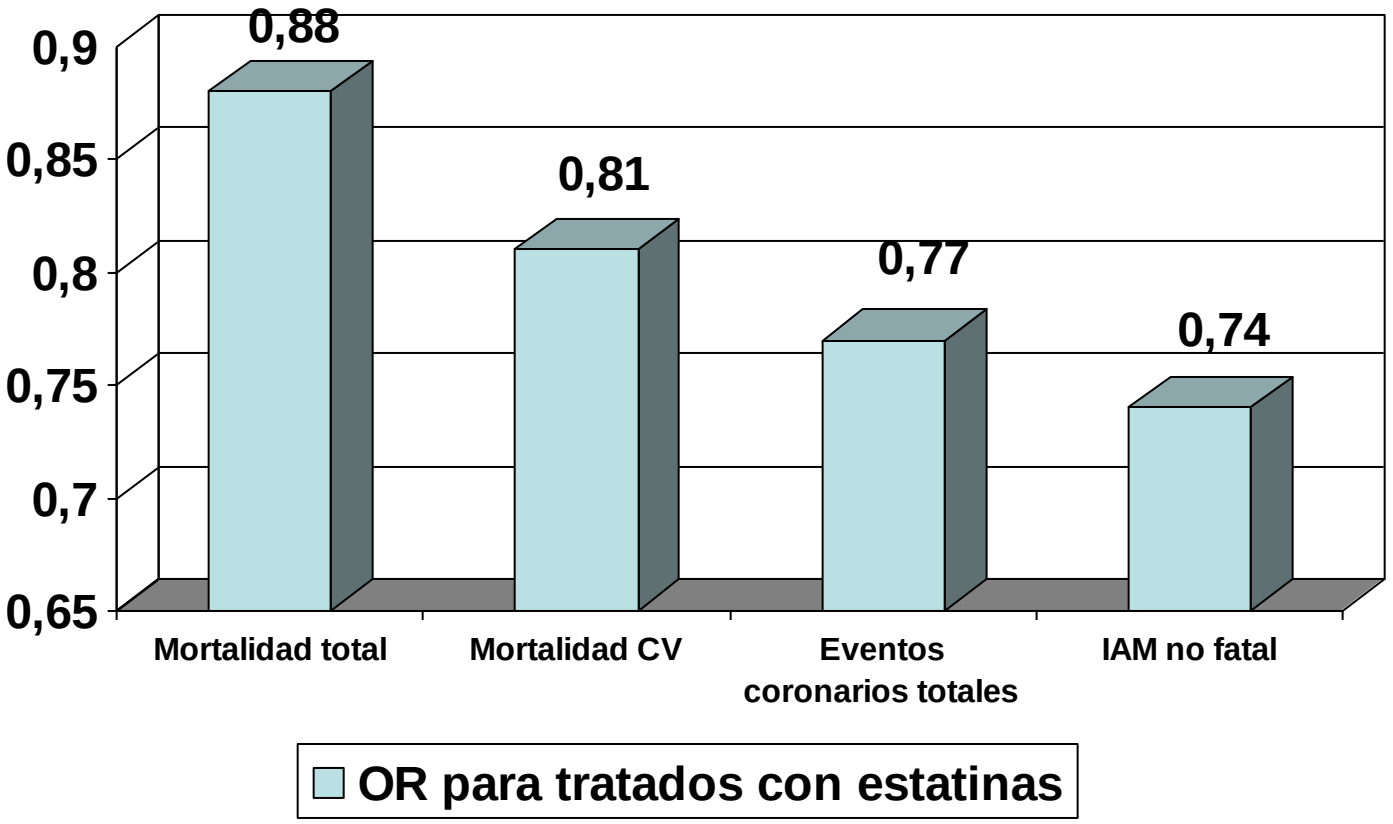
3. Nuevas dianas terapéuticas

Not all CVD risk is modifiable



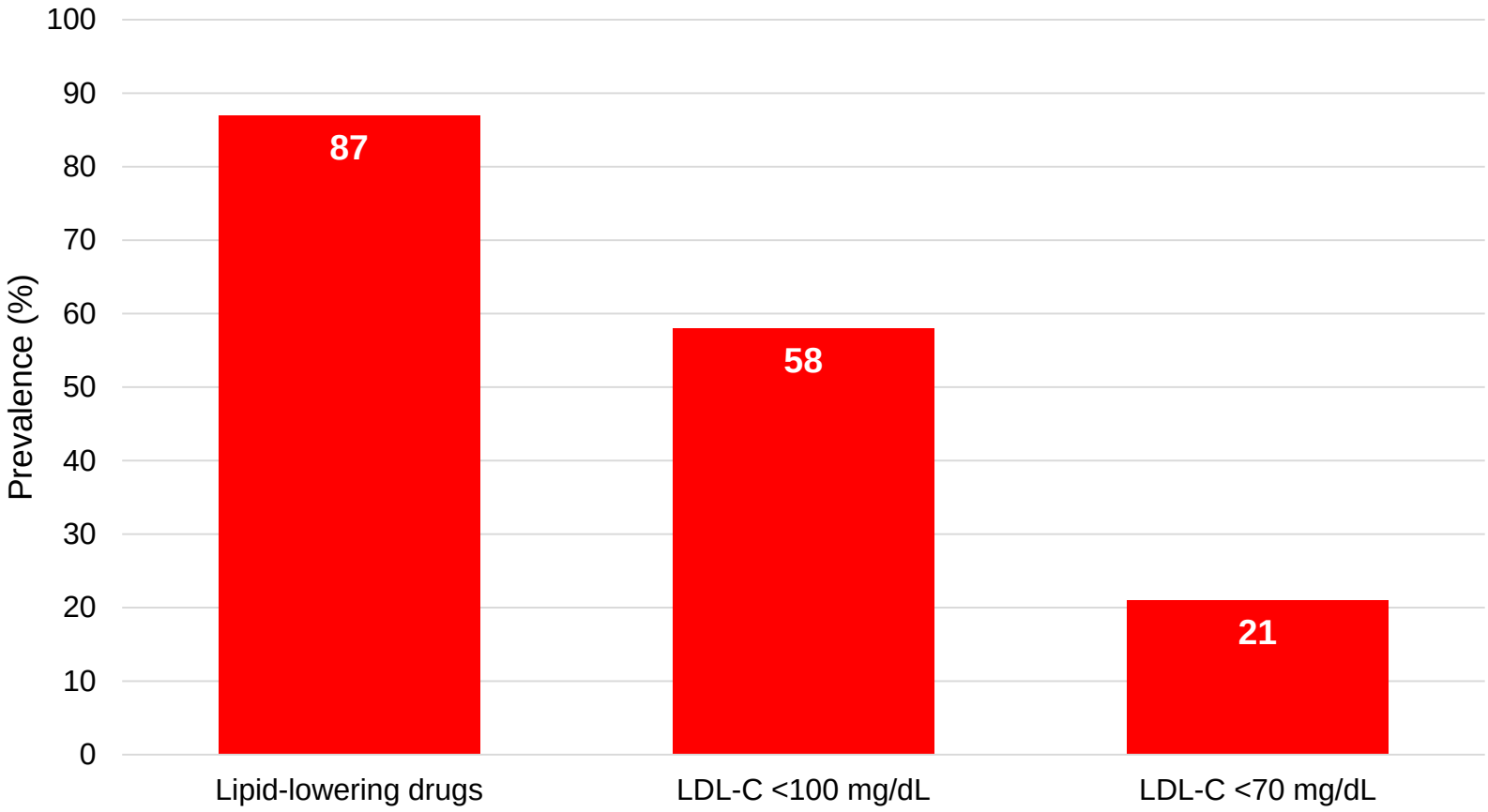
Packard et al. Vascul Pharmacol 2015;71:37–39.

No menos de ¾ partes de los pacientes tratados con estatinas mueren por accidentes coronarios (Lancet, 2005)



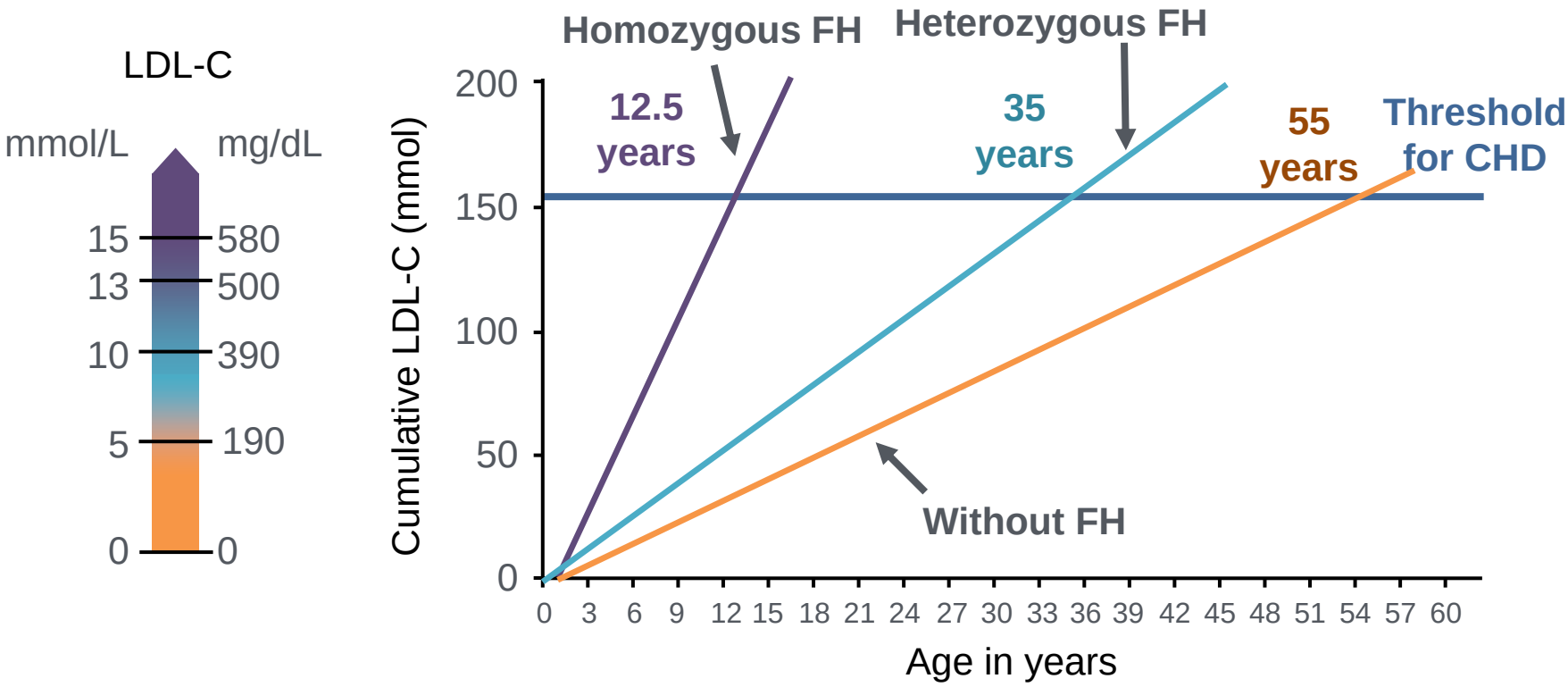
Only 1 in 5 MI patients achieve LDL-C target <70 mg/dL despite high statin prescription rate and good adherence

EUROASPIRE IV: 7998 patients <80 years old with established CHD*



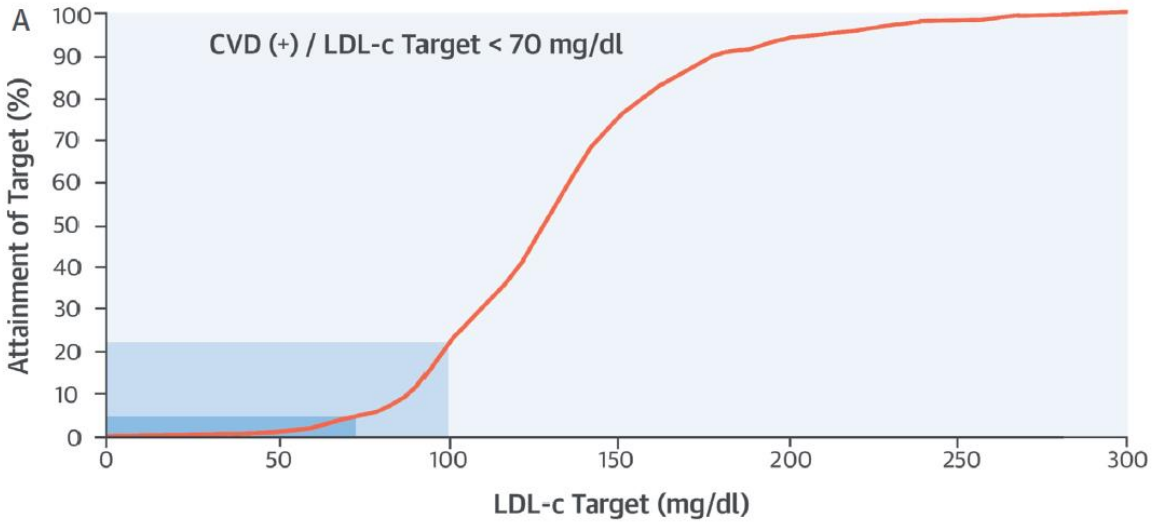
*25% women, mean age 64 years, one third <60 years old, 2012–2013.
CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.
http://www.escardio.org/about/press-releases/esc13-Amsterdam/Pages/euroaspire-iv-success-challenges-secondary-prevention-CVD-Europe.aspx. [Accessed 23 October 2015].

Familial hypercholesterolaemia patients reach LDL-C threshold levels for CHD at an early age



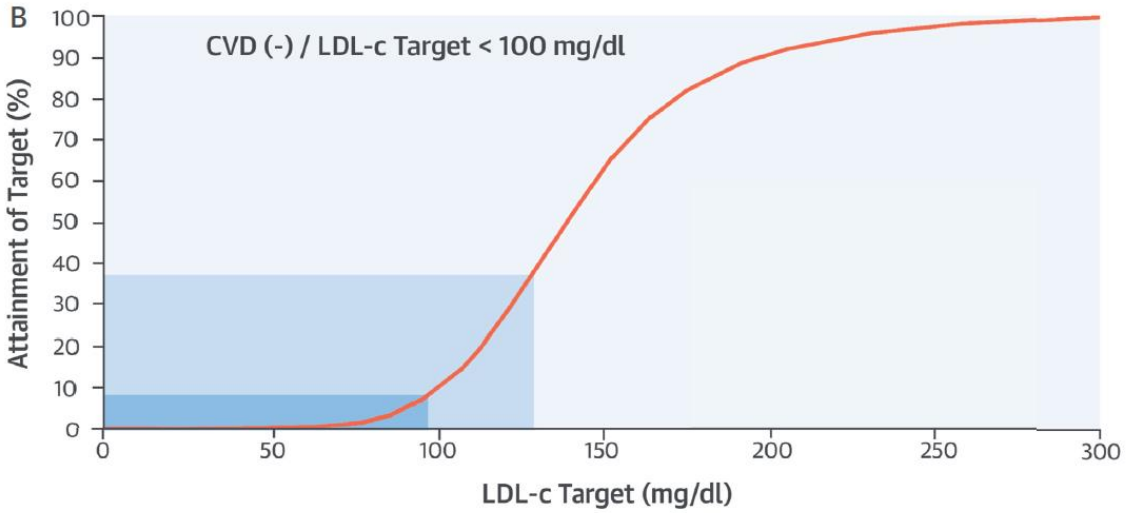
Cuchel et al. Eur Heart J 2014;35:2146–2157.
Nordestgaard et al. Eur Heart J 2013;34:3478–3490.

Consecución de objetivos de LDL-c en pacientes con HFHe



Porcentaje de pacientes **con** evento CV previo que alcanzan objetivos de LDL-c

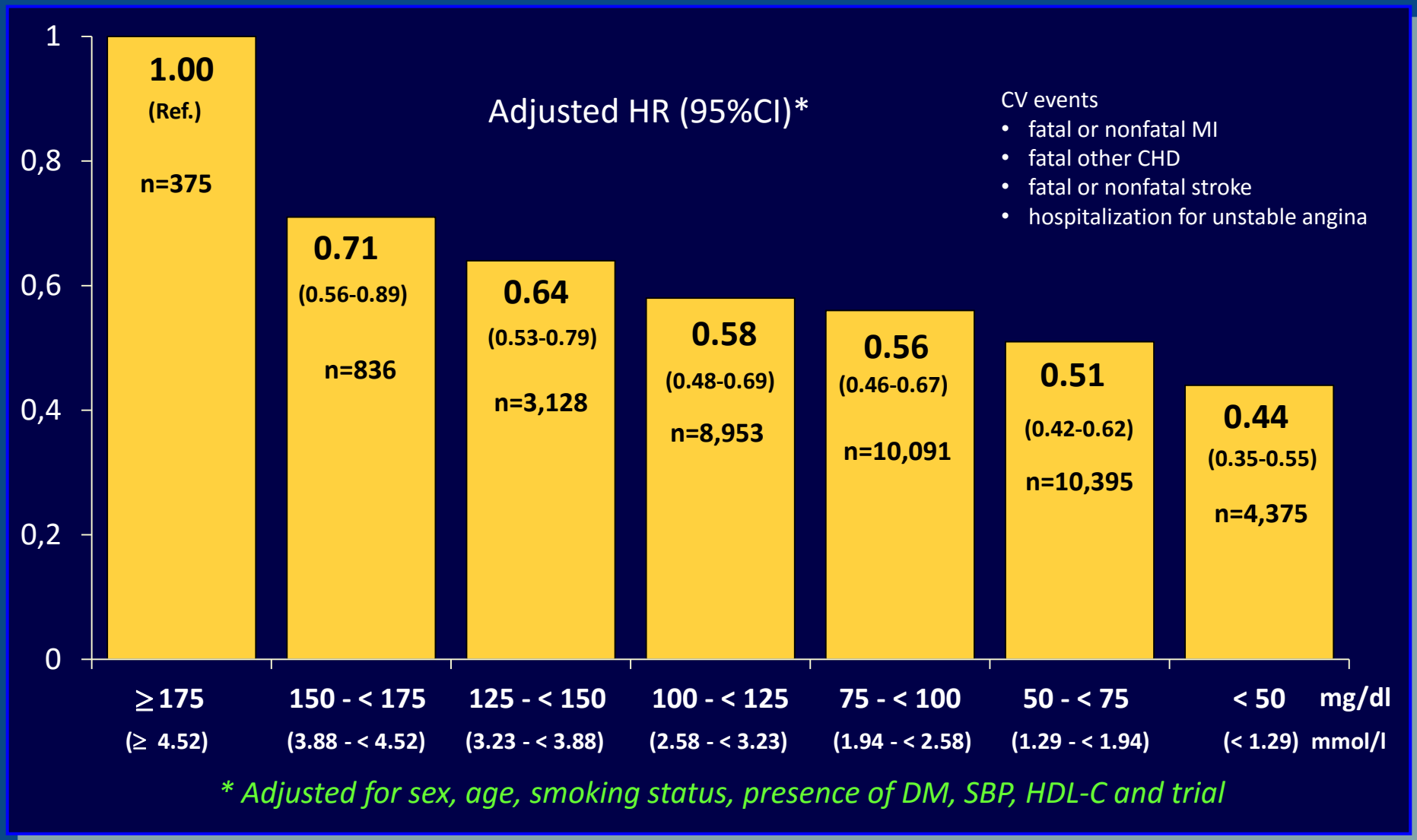
Porcentaje de pacientes **sin** evento CV previo que alcanzan objetivos de LDL-c



Perez de Isla, L. et al. J Am Coll Cardiol. 2016; 67(11):1278–85

Risk for Major CV Events by Achieved On-trial LDL-C Levels

Metanalysis of individual patient data from 8 RCT (N=38,153)
Conventional lipids and apolipoproteins were determined at baseline and at 1 year follow-up



CV=Cardiovascular LDL-C=Low-Density Lipoprotein Cholesterol

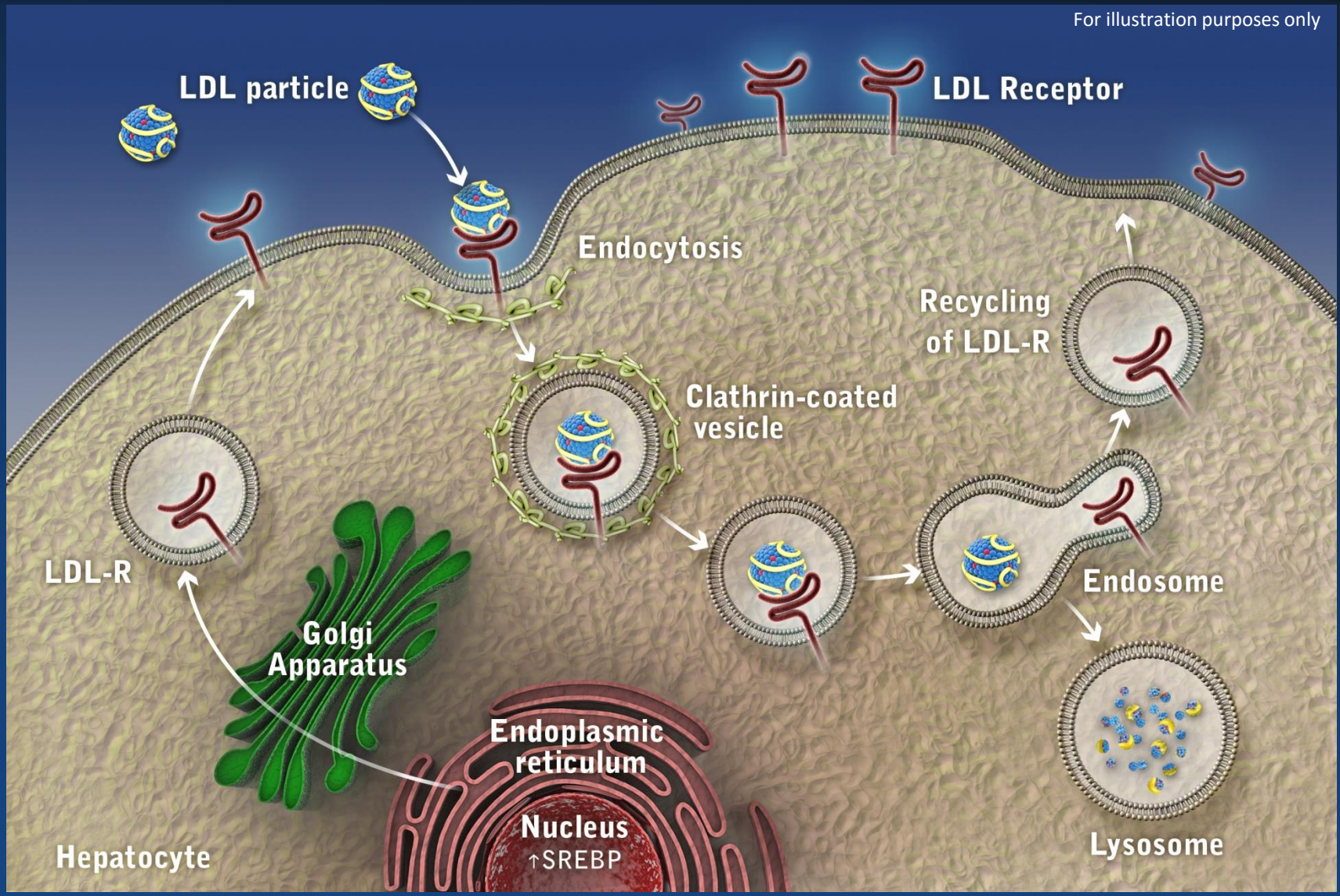
Boekholdt et al. *JACC* 2014; 64: 485-494

EDITORIAL

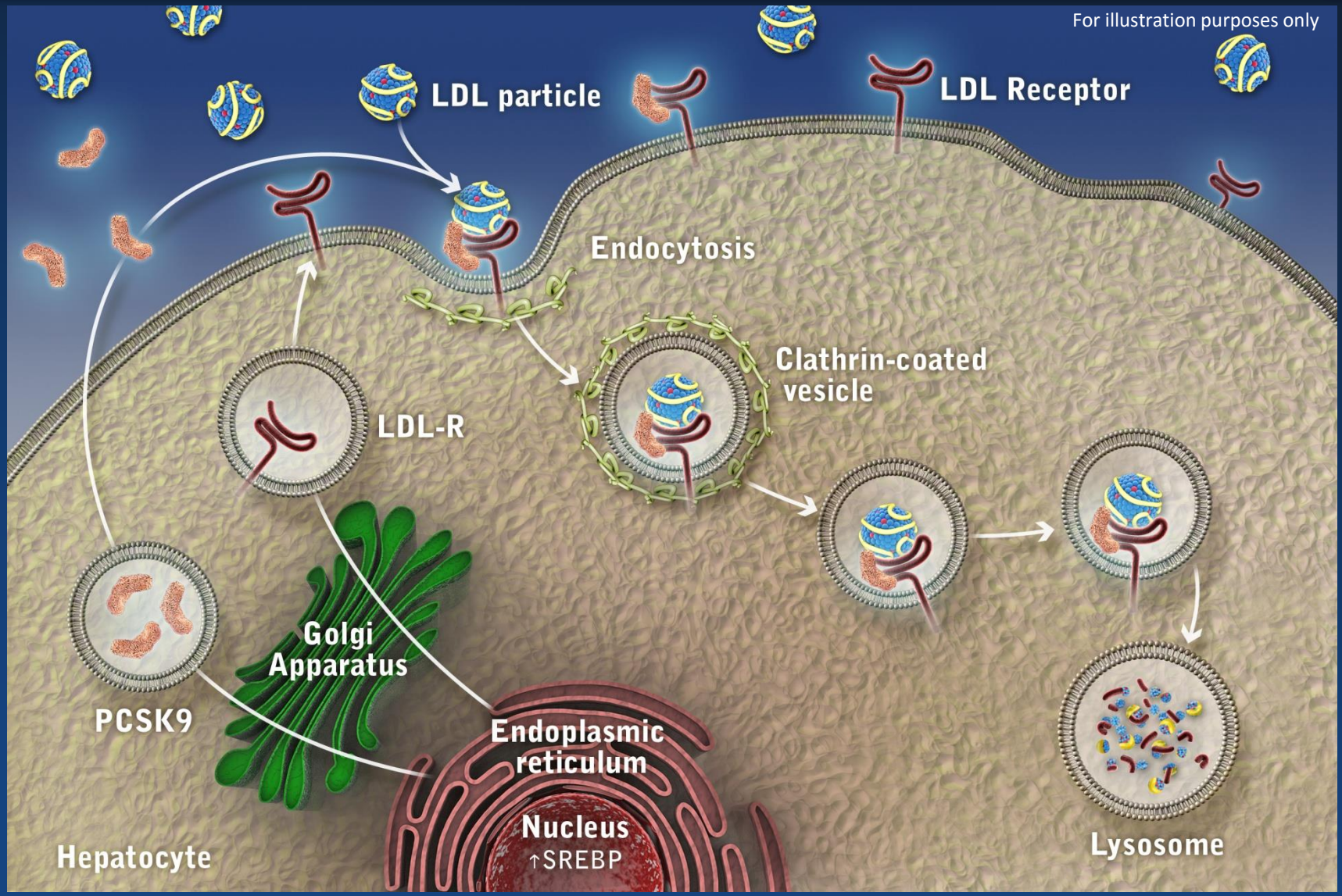
Annals of Internal Medicine

PCSK9 Inhibitors: A New Era in Lipid-Lowering Treatment?

LDL Receptor Function and Life Cycle

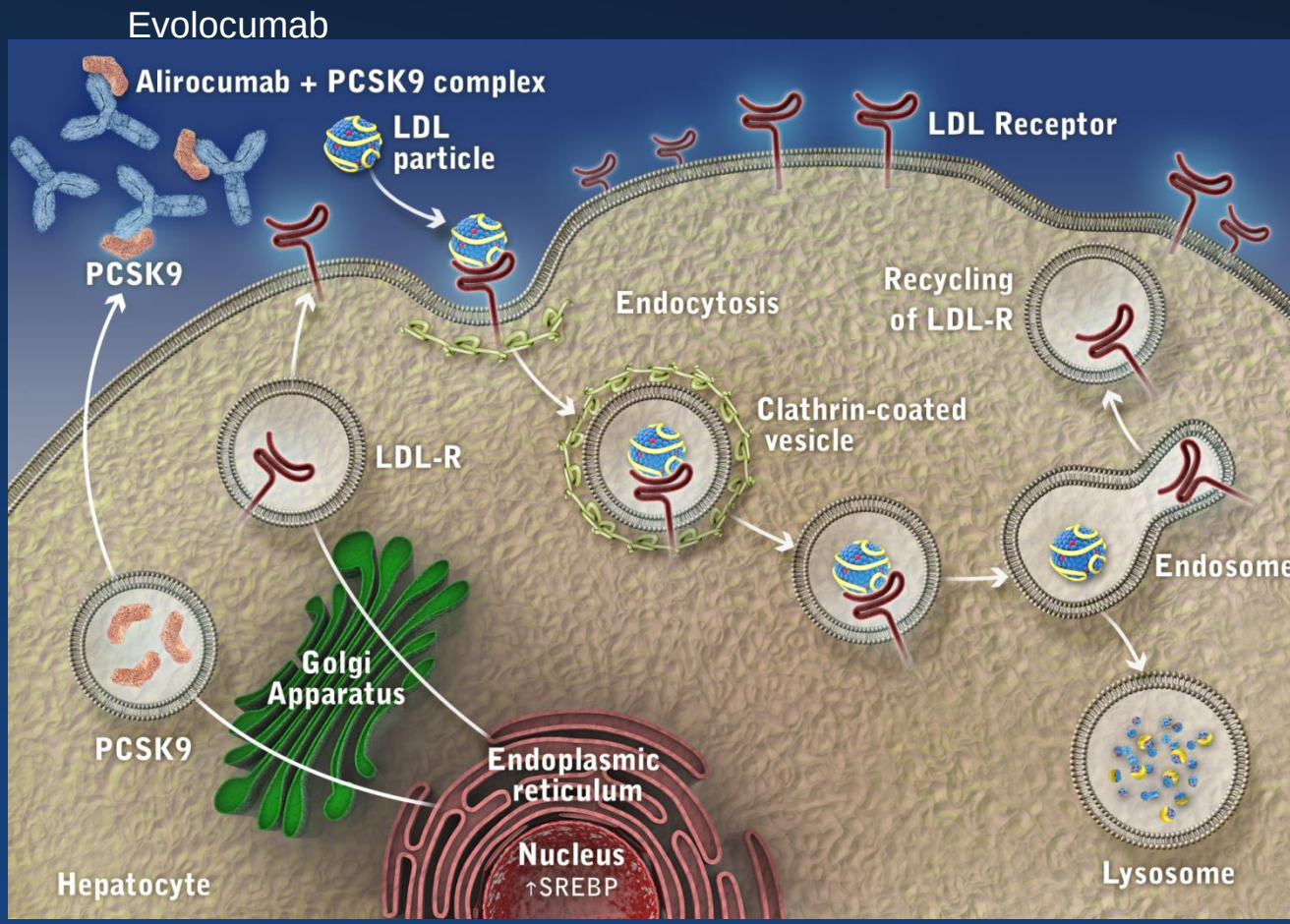


The Role of PCSK9 in the Regulation of LDL Receptor Expression

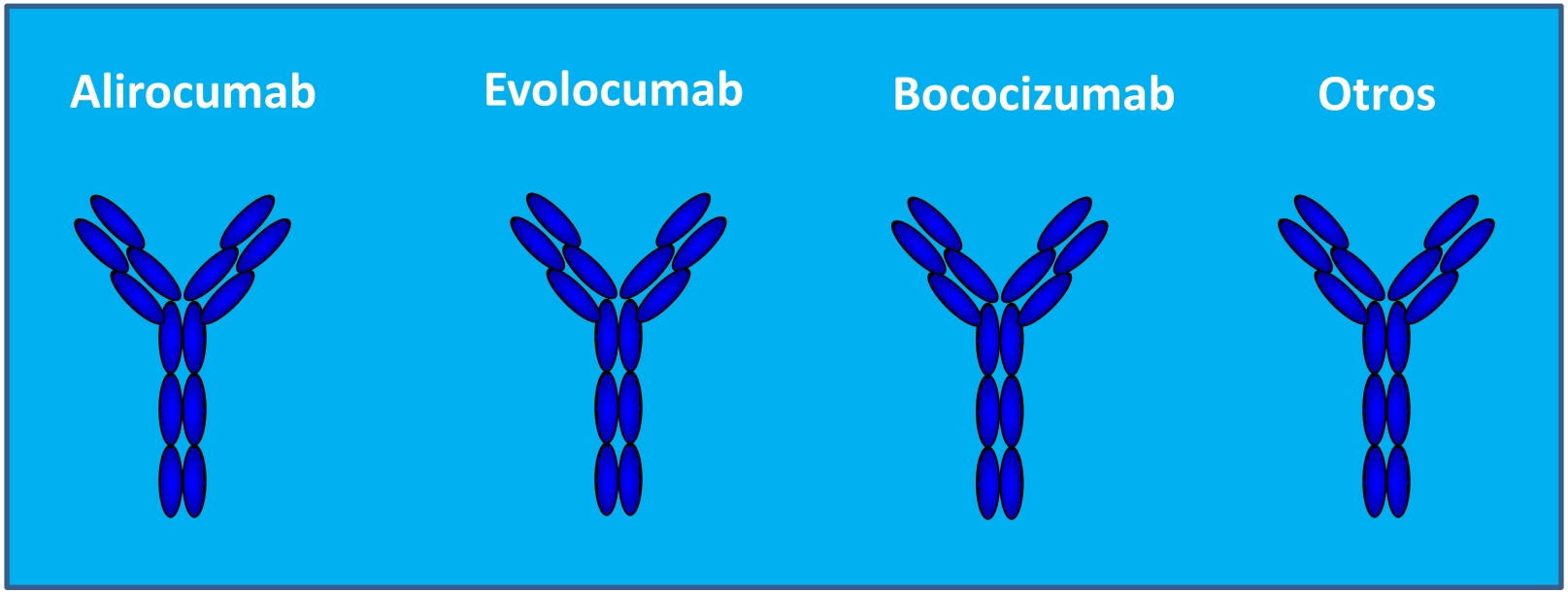


Impact of Alirocumab and Evolocumab on LDL Receptor Expression

- **Alirocumab and Evolocumab are a highly specific, fully human monoclonal antibody to PCSK9 currently in Phase 3 development for the treatment of hypercholesterolemia**



Anticuerpos ANTI-PCSK9

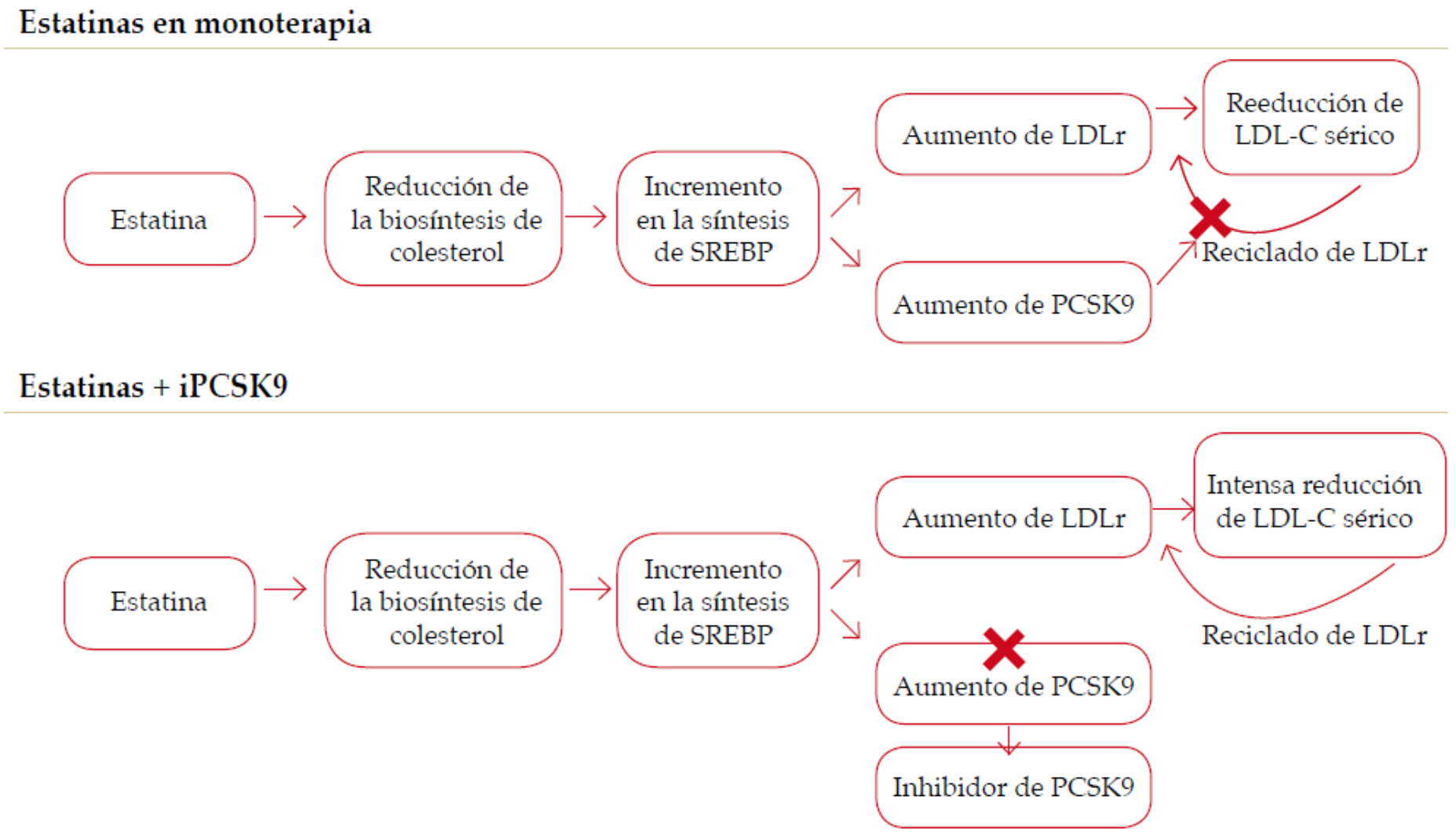


Dosis de 75 mg y 150 mg para inyección cada 14 días

Dosis de 140 mg para inyección/14 días

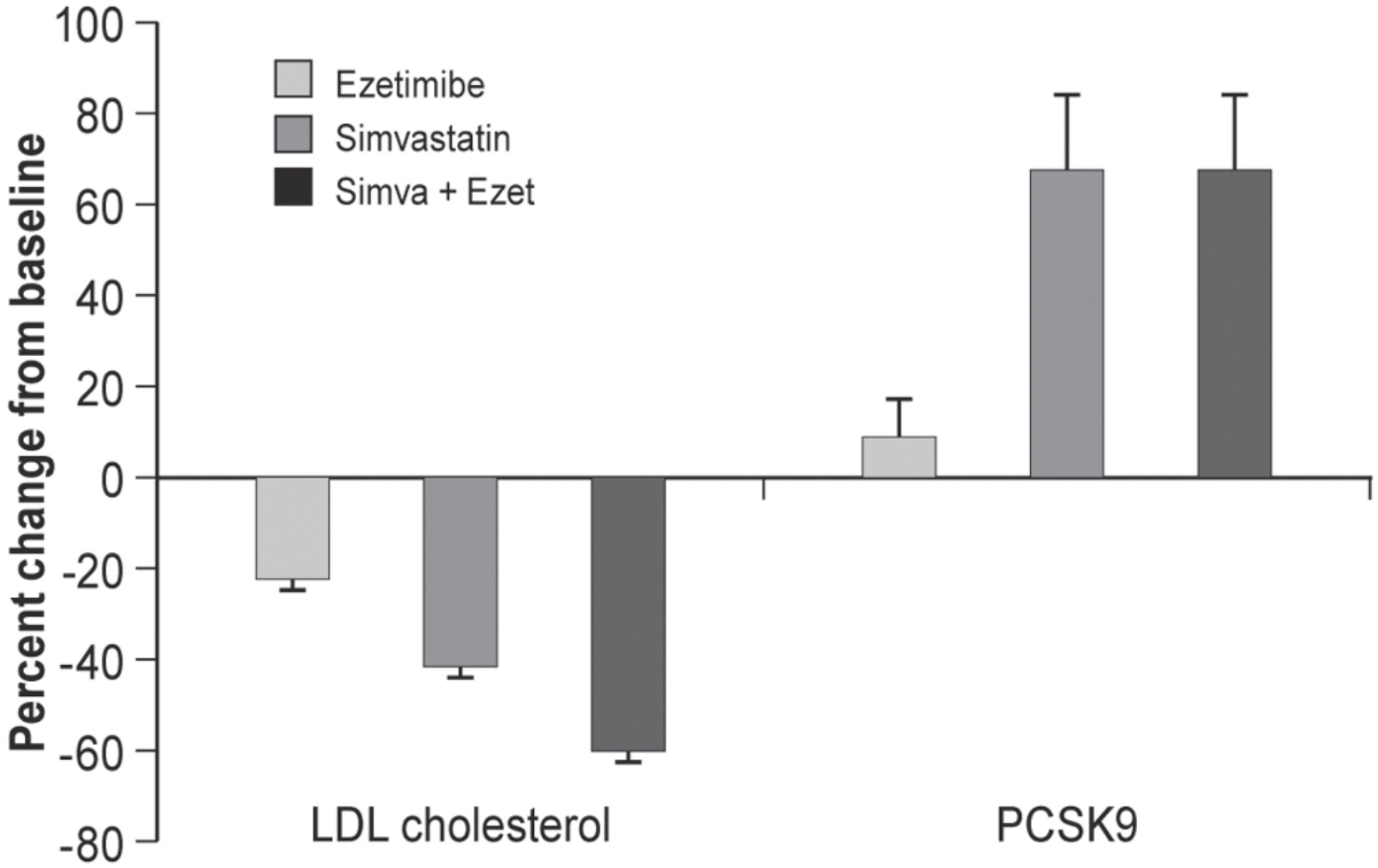
Dosis de 420 mg para inyección cada 28 días

PCSK9 Function and Regulation



(Clinica Chimica Acta 437 (2014) 66–71)

PCSK9 Regulation by statins and ezetimibe



Change in LDL cholesterol and PCSK9 from baseline according to treatment groups

(Atherosclerosis Supplements 17 C (2015) 23–26)

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

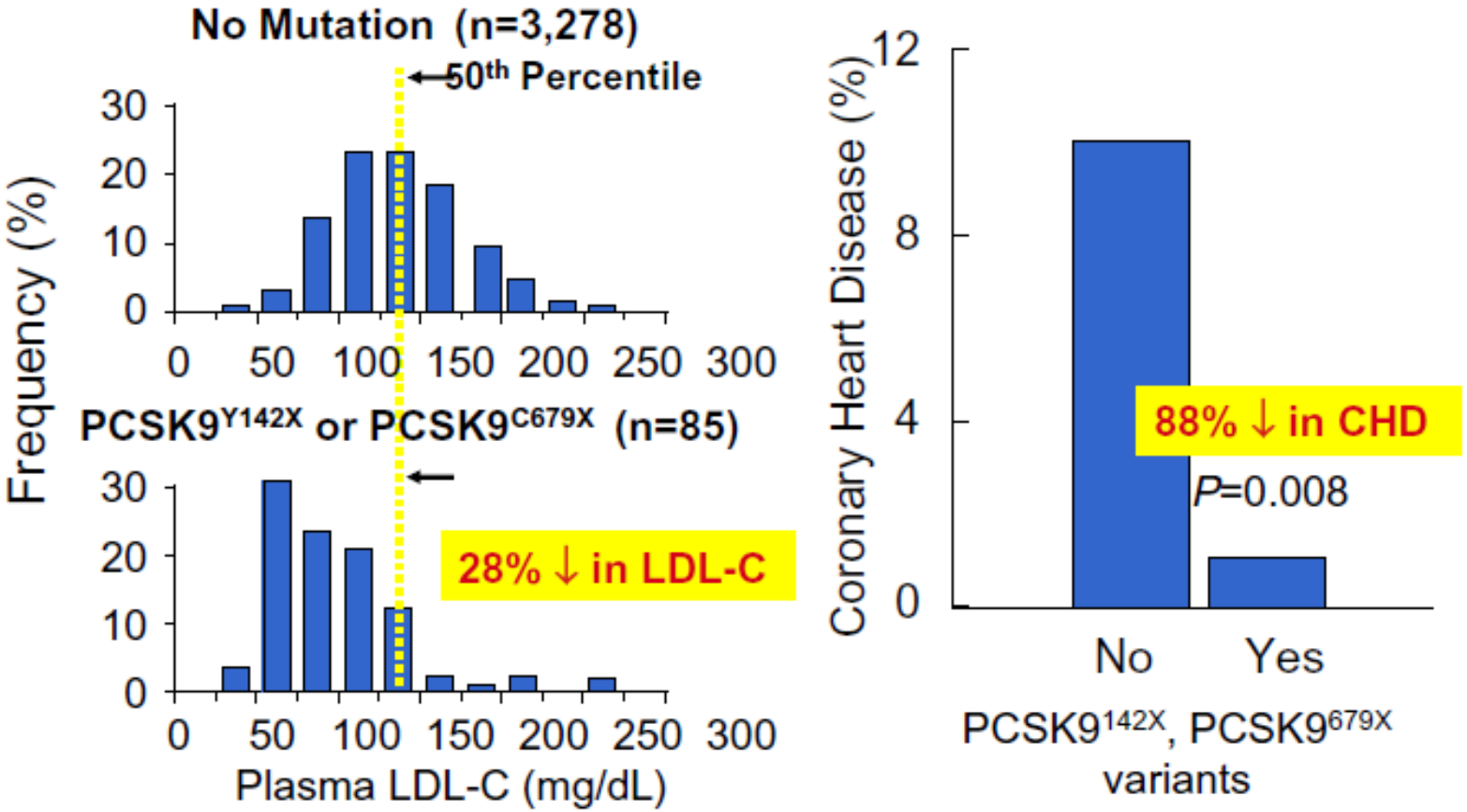
Variable	Noncarriers	Carriers			P Value†
		PCSK9^{142X}	*PCSK9*^{679X}	*PCSK9*^{142X} *or* *PCSK9*^{679X}	
Mutation status — no. of subjects (%)	3278 (97.4)	26 (0.8)	60 (1.8)	85 (2.6)‡	
Age — yr§	53±6	54±6	53±6	54±6	0.61
Male sex — %	37	42	27	31	0.22
Body-mass index	29.6±6.1	28.7±4.4	29.7±5.5	29.5±5.2	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

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

Cardiovascular Events in PCSK9 Variants: Loss of function

Table 1 Summary of the effects of PCSK9 variants

Type of variant	Example	Effect on LDL-C levels	Effect on cardiovascular risk
Gain of function	E670G	↑	Increased risk
Loss of function	C679X (African Americans) R46L (Caucasians)	↓	Cardioprotective



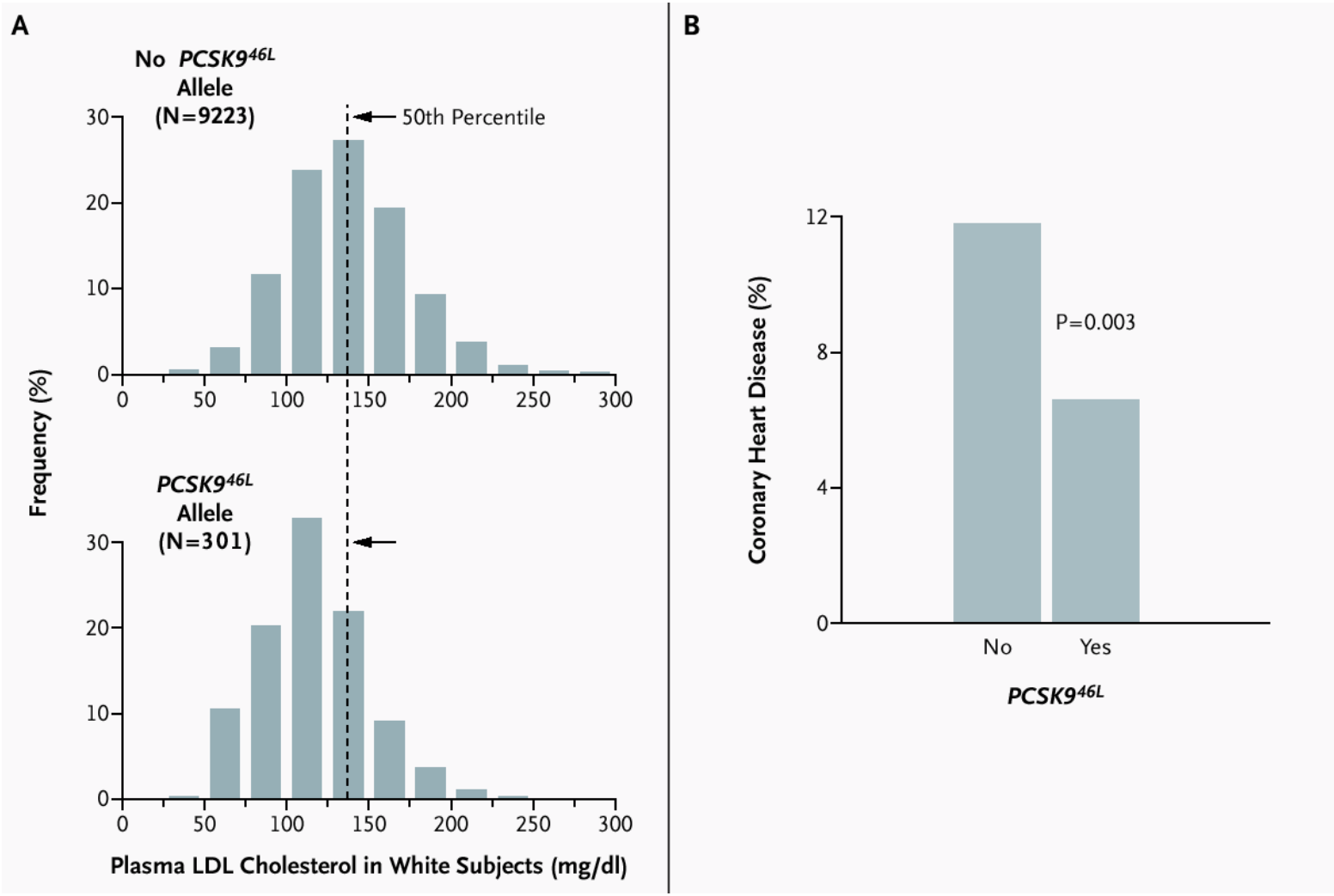
(N Engl J Med 2006;354:1264–72.)

The R46L-Encoding Allele of *PCSK9* and Cardiovascular Risk Factors among 9524 White Subjects in the Study*

Variable	Noncarriers	Carriers of *PCSK9*^{46L}	P Value†
Mutation status — no. of subjects (%)	9223 (96.8)	301 (3.2)	
Age — yr‡	54±6	54±6	0.56
Male sex — %	45	46	0.84
Body-mass index	26.9±4.9	26.8±4.5	0.51
Total cholesterol — mg/dl	214±40	194±37	<0.001
Triglycerides — mg/dl	133±87	135±89	0.79
LDL cholesterol — mg/dl	137±37	116±33	<0.001
HDL cholesterol — mg/dl	51±17	52±17	0.64
Hypertension — %§	25.0	24.6	0.87
Diabetes — %¶	8.0	7.3	0.68
Smoking — %‖	24.6	25.2	0.80
Carotid-artery intima–media thickness — mm	0.73±0.18	0.71±0.16	0.005
Coronary heart disease — no. of subjects	1089	19	0.003
Stroke — no. of subjects (%)	267 (2.9)	9 (3.0)	0.92
Death — no. of subjects (%)	988 (10.7)	25 (8.3)	0.18

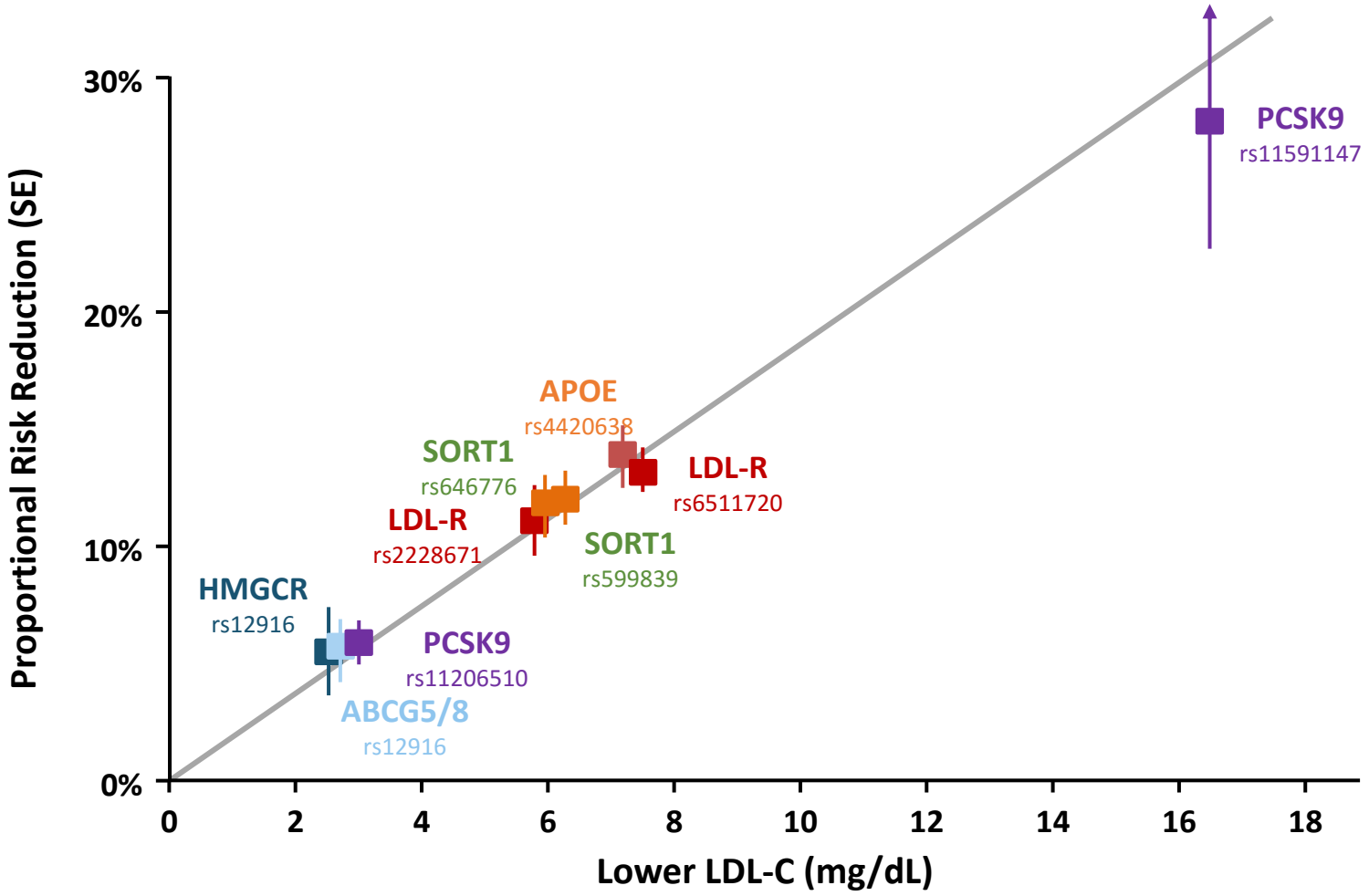
Jonathan C.Cohen, et al, N Engl J Med 2006;354:1264-72

Distribution of Plasma LDL Cholesterol Levels (A)and Incidence of Coronary Events (Panel B) among White Subjects, According to the Presence or Absence of a *PCSK9* ^{46L} Allele

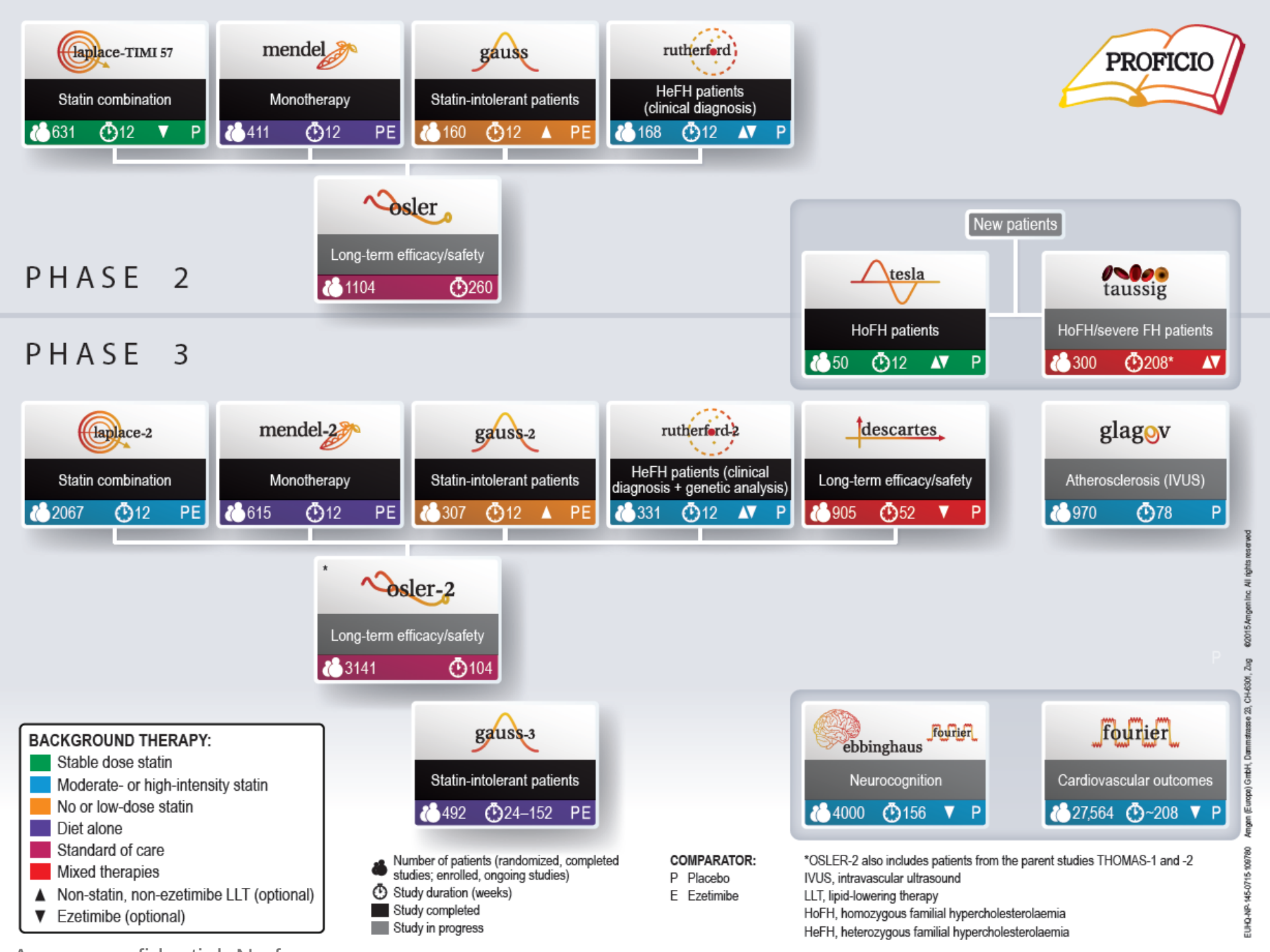


Jonathan C.Cohen, et al, N Engl J Med 2006;354:1264-72

Lower risk of CV events via multiple genetic variants affecting LDL-C



CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; SE, standard error.
Ference BA, et al. J Am Coll Cardiol 2012;60:2631–9.



Overview of ODYSSEY Phase 3 clinical trial program

12 global phase 3 trials
Including more than 23,500 patients across more than 2,000 study centers

HeFH population

Add-on to max tolerated statin (± other LMT)

ODYSSEY FH I (EFC12492) N=471
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100mg/dL
18 months

ODYSSEY FH II (CL1112) N=250
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100mg/dL
18 months

ODYSSEY HIGH FH (EFC12732) N=105
LDL-C ≥ 160 mg/dL
18 months

ODYSSEY LONG TERM (LTS11717) N=2,100
LDL-C ≥ 70 mg/dL
18 months

HC in high CV risk population

Add-on to max tolerated statin (± other LMT)

ODYSSEY COMBO I (EFC11568) N=306
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
12 months

***ODYSSEY COMBO II (EFC11569)** N=660
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
24 months

ODYSSEY OUTCOMES (EFC11570)
N=18,000
LDL-C ≥ 70 mg/dL

Additional populations

ODYSSEY MONO (EFC11716) N=100
Patients on no background LMTs
LDL-C ≥ 100 mg/dL
6 months

ODYSSEY ALTERNATIVE (CL1119) N=250
Patients with defined statin intolerance
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
6 months

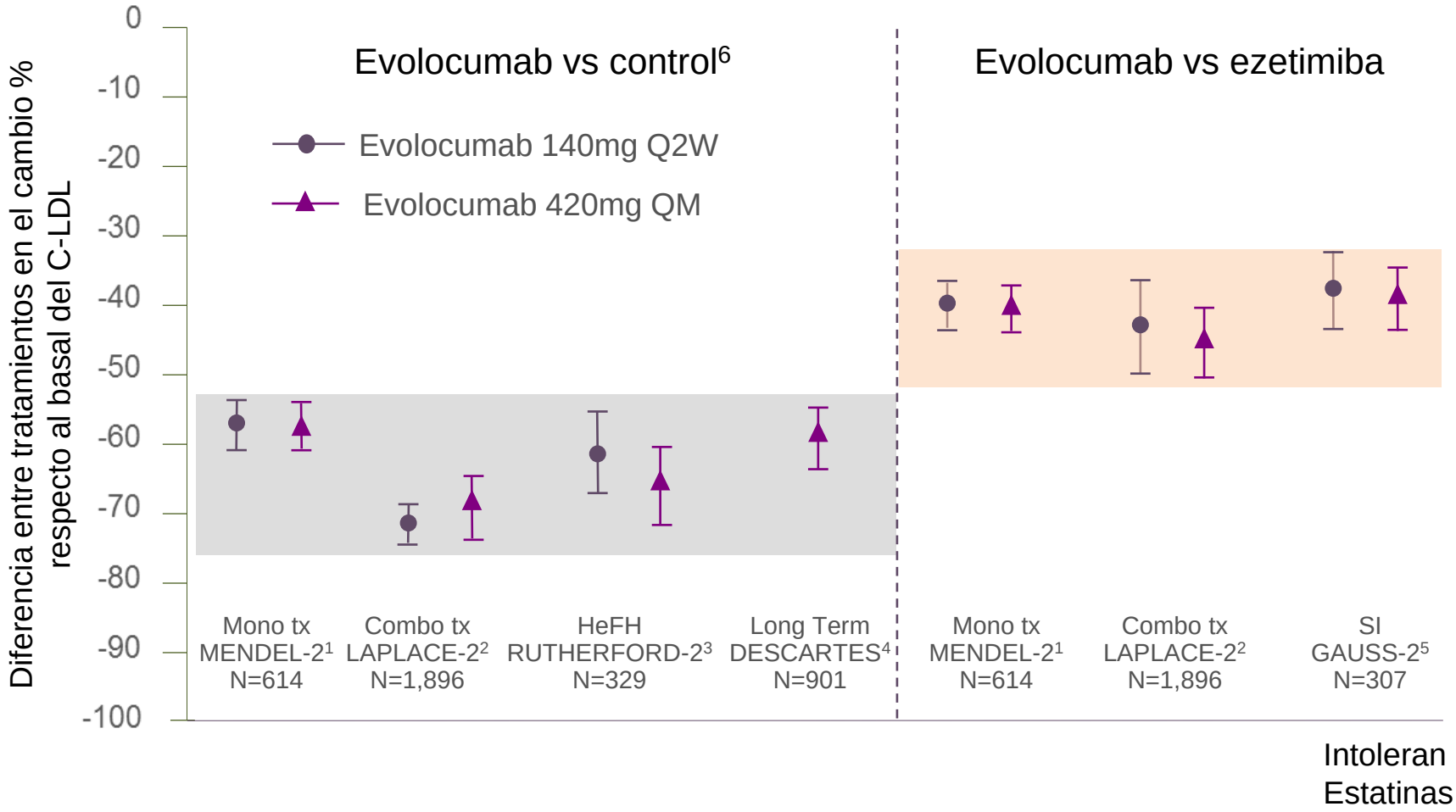
ODYSSEY CHOICE (CL1308) N=700
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
12 months

ODYSSEY OPTIONS I (CL1110) N=350
Patients not at goal on moderate dose atorvastatin
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
6 months

ODYSSEY OPTIONS II (CL1118) N=300
Patients not at goal on moderate dose rosuvastatin
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
6 months

HC = hypercholesterolemia; LMT = lipid-modifying therapy
*For ODYSSEY COMBO II other LMT not allowed at entry

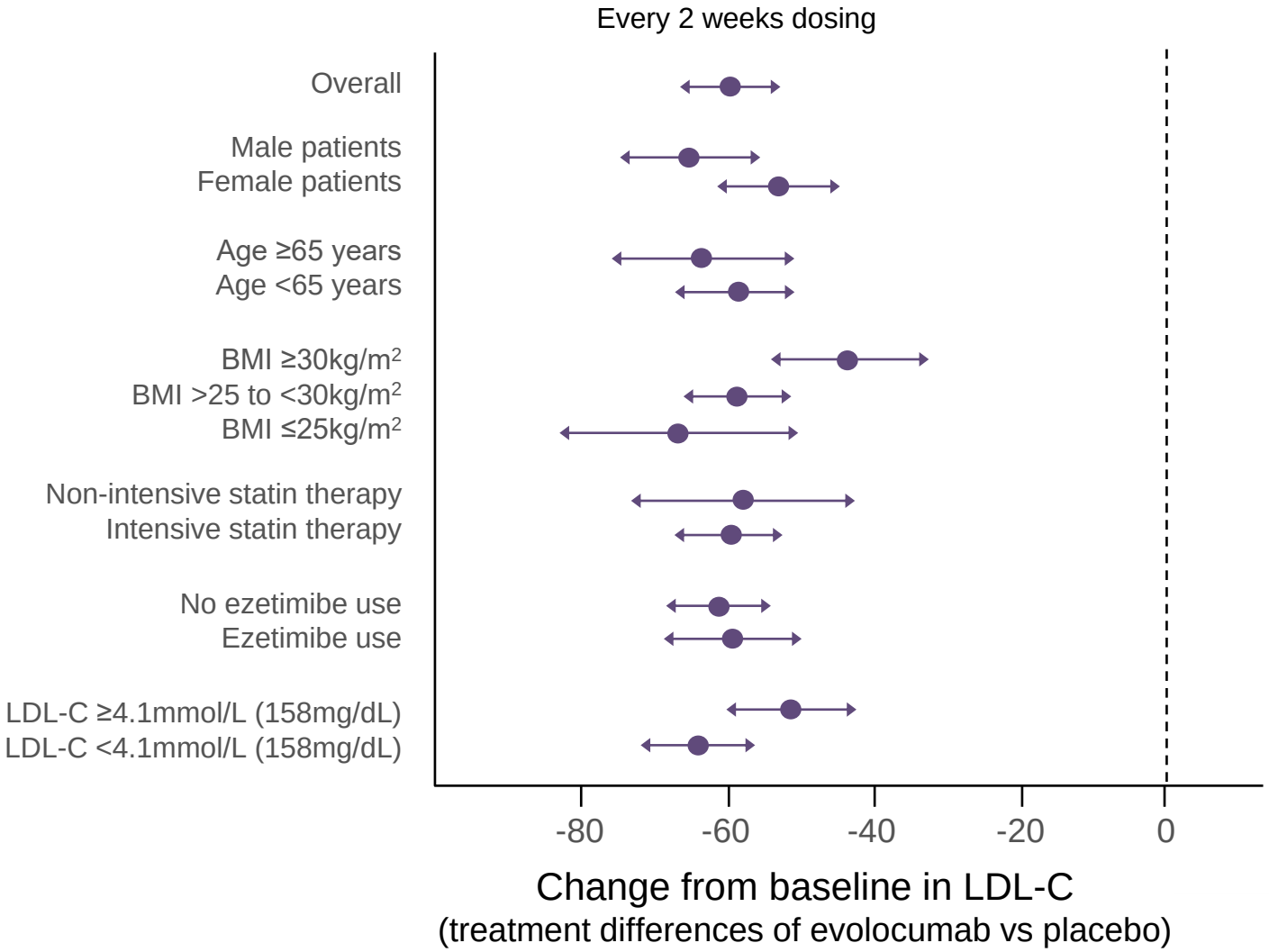
Reducción de C-LDL entre el 55-75% sostenida a largo plazo



Los resultados muestran las medias a las semanas 10 y 12 , excepto en el estudio DESCARTES (semana 52).

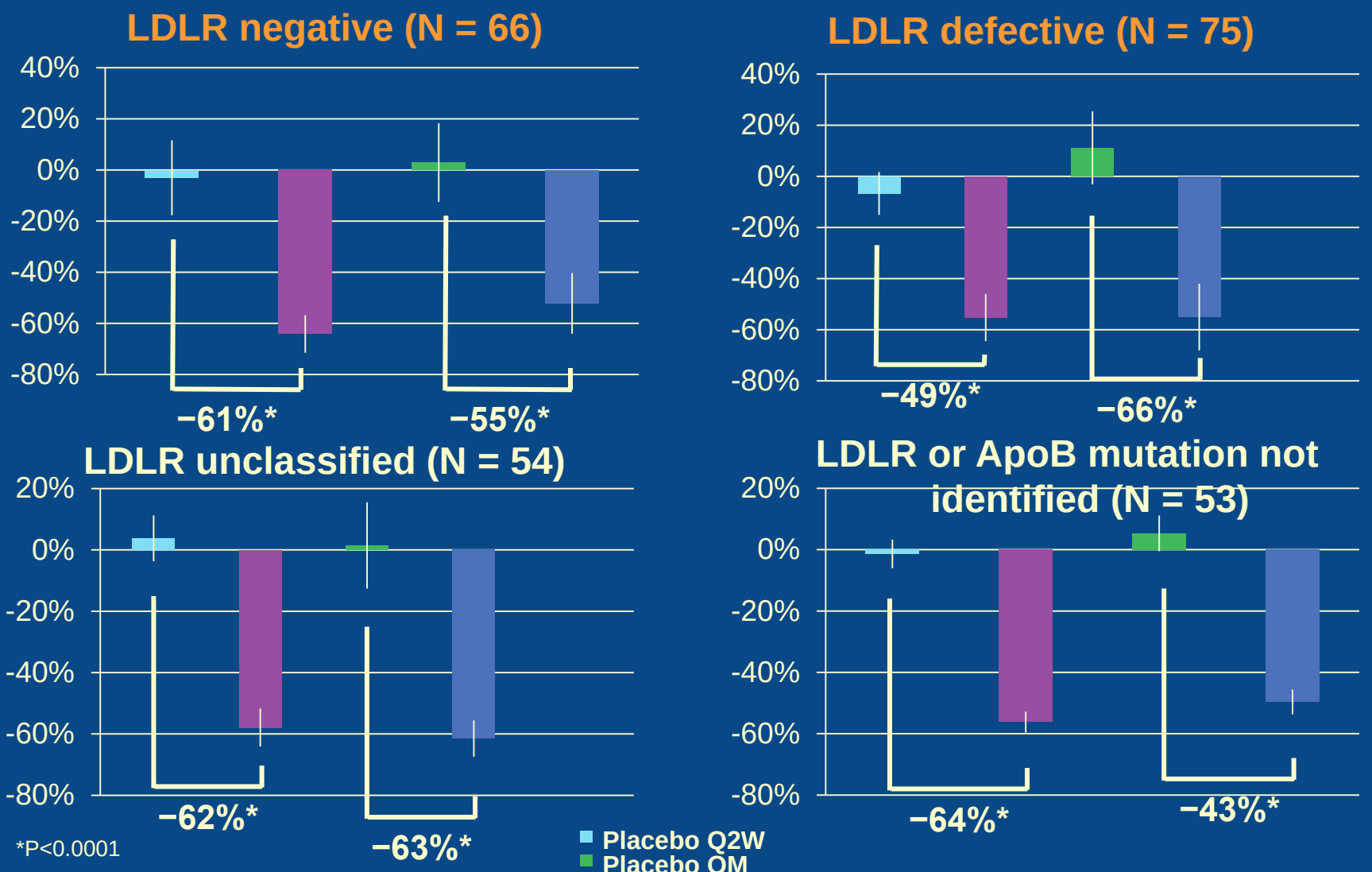
1. Koren et al. J Am Coll Cardiol 2014;63:2531–2540. 2. Robinson et al. JAMA 2014;311:1870–1882. 3. Raal et al. Lancet 2015;385:331–340. 4. Blom et al. N Engl J Med 2014;370:1809–1819. 5. Stroes et al. J Am Coll Cardiol 2014;63:2541–2548. 6. Najam et al. Clin Lipidol 2015;10:481–498.

Evolocumab significantly reduces LDL-C irrespective of baseline characteristics



Raal et al. Lancet 2015;385:331–340.

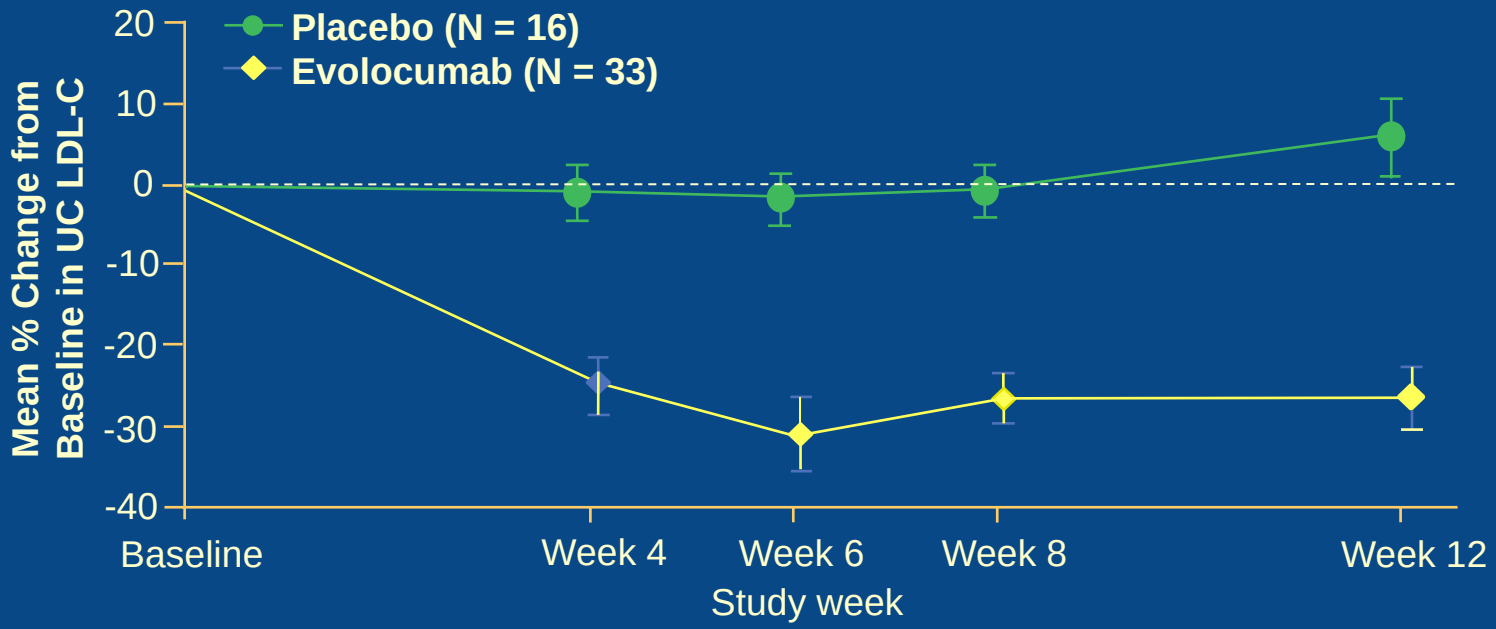
RUTHERFORD-2:
% Change in LDL-C (Week 12) Based on Genetic Subgroup



*P<0.0001

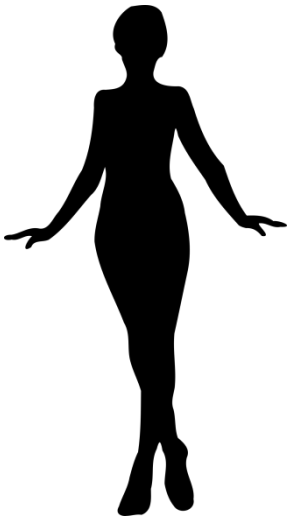
Raal FJ, et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4 and supplementary material.

TESLA: Homozygous Familial Hypercholesterolemia
Mean % Change in UC LDL-C from Baseline over Time



Number of patients analysed at each visit					
Placebo	16	16	15	16	15
Evocolumab	33	32	28	32	29

Raal FJ, et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61374–X.



Mujer de 54 años.

AF: Padre fallecido por IAM y con HF, además primos hermanos por rama paterna con HF. Dos hijos con HF.

AP: HFHe diagnosticada en 1991. Cardiopatía isquémica con revascularización del tronco de la CI y de la CD con 47 años (2009). Pielonefritis aguda izqda (2013).

EF: No xantomas, xantelasmas ni arco corneal

Analítica: CT: 305 mg/dl, HDL: 60 mg/dl, LDL: 205 mg/dl, Tg: 201 mg/dl. Lp (a) 204 mg/dl.

- Rosuvastatina 40 mg/d
- Ezetimibe 10 mg/d
- Colesevelam 2.5 g/d

HIPERCOLESTEROLEMIA FAMILIAR HETEROCIGOTA
Mutación del rececptor LDL M079

2003: Atorva 80mg + Ezetimibe 10mg → 2009: A los 47 años → IAM. Cambio a Rosu 40mg + Ezet 10mg + Ac nicotinico + Colesevelam → 2010: Dx genético → 2012: LDL aféresis

	Pre LDL aféresis	Tras LDL aféresis
Colesterol Total	342	155
HDL-C	55	32
LDL-C	247	90
Triglicéridos	197	214
Lp (a)	204	49

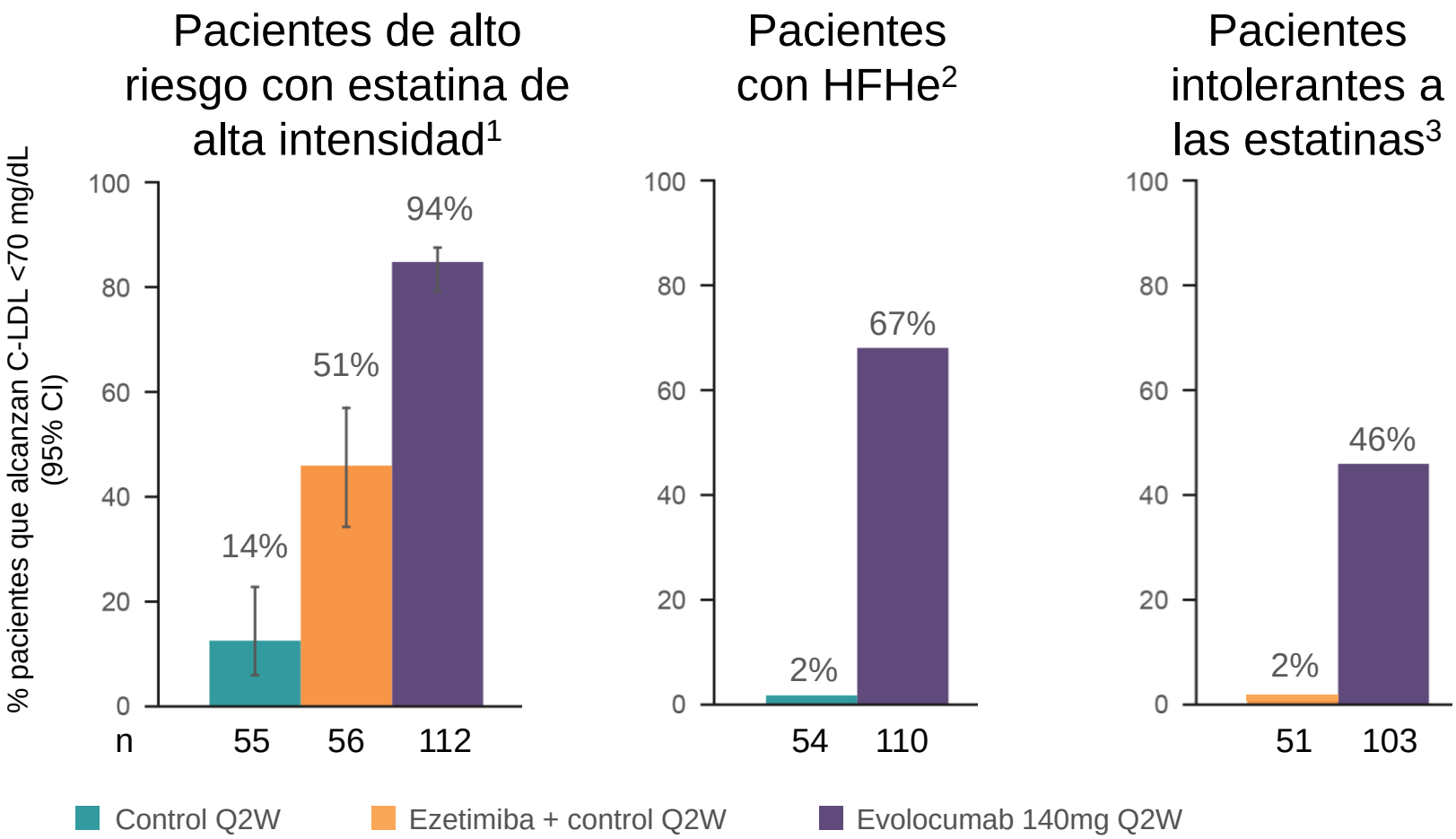
HIPERCOLESTEROLEMIA FAMILIAR HETEROCIGOTA
Mutación del rececptor LDL M079

2003: Atorva 80mg + Ezetimibe 10mg → 2009: A los 47 años → IAM. Cambio a Rosu 40mg + Ezet 10mg + Ac nicotinico + Colesevelam → 2010: Dx genético → 2012: LDL aféresis →

2014: PCSK9 (Evolocumab 420 mg/2 sem) y se suspende LDL aféresis por cifras de LDL < 1mg/dl → 2016: CT: 100 mg/dl, HDL 47 mg/dl, LDL 21mg/dl, Tg: 161 mg/dl. Lp(a): 173mg/dl

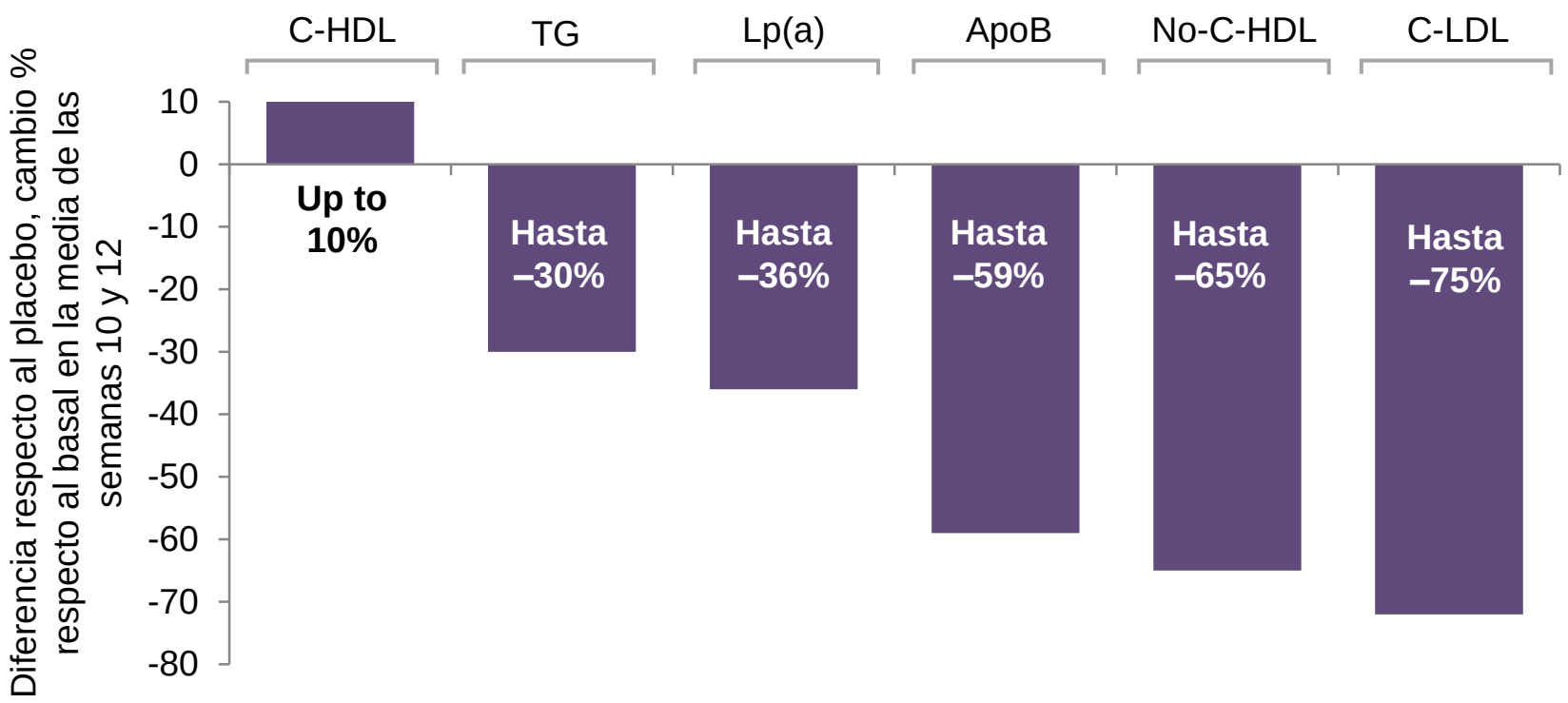
	Pre LDL aféresis	Tras LDL aféresis	LDL aféresis + Evolocumab 420/2sem	Sin aféresis y Evolocumab 420 mg/2 sem
Colesterol Total	342	155	97	100
HDL-C	55	32	51	47
LDL-C	247	90	8	21
Triglicéridos	197	214	188	161
Lp (a)	204	49	36	38

Un 80-85% de los pacientes tratados con Evolocumab reducen el C-LDL ≥ 50% y hasta un 94% logran un C-LDL < 70 mg/dl



1. Robinson et al. JAMA 2014;311:1870–1882. 2. Raal et al. Lancet 2015;385:331–340.
3. Stroes et al. J Am Coll Cardiol 2014;63:2541–2548.

Evolocumab reduce marcadamente otros parámetros lipídicos y aumenta el C-HDL

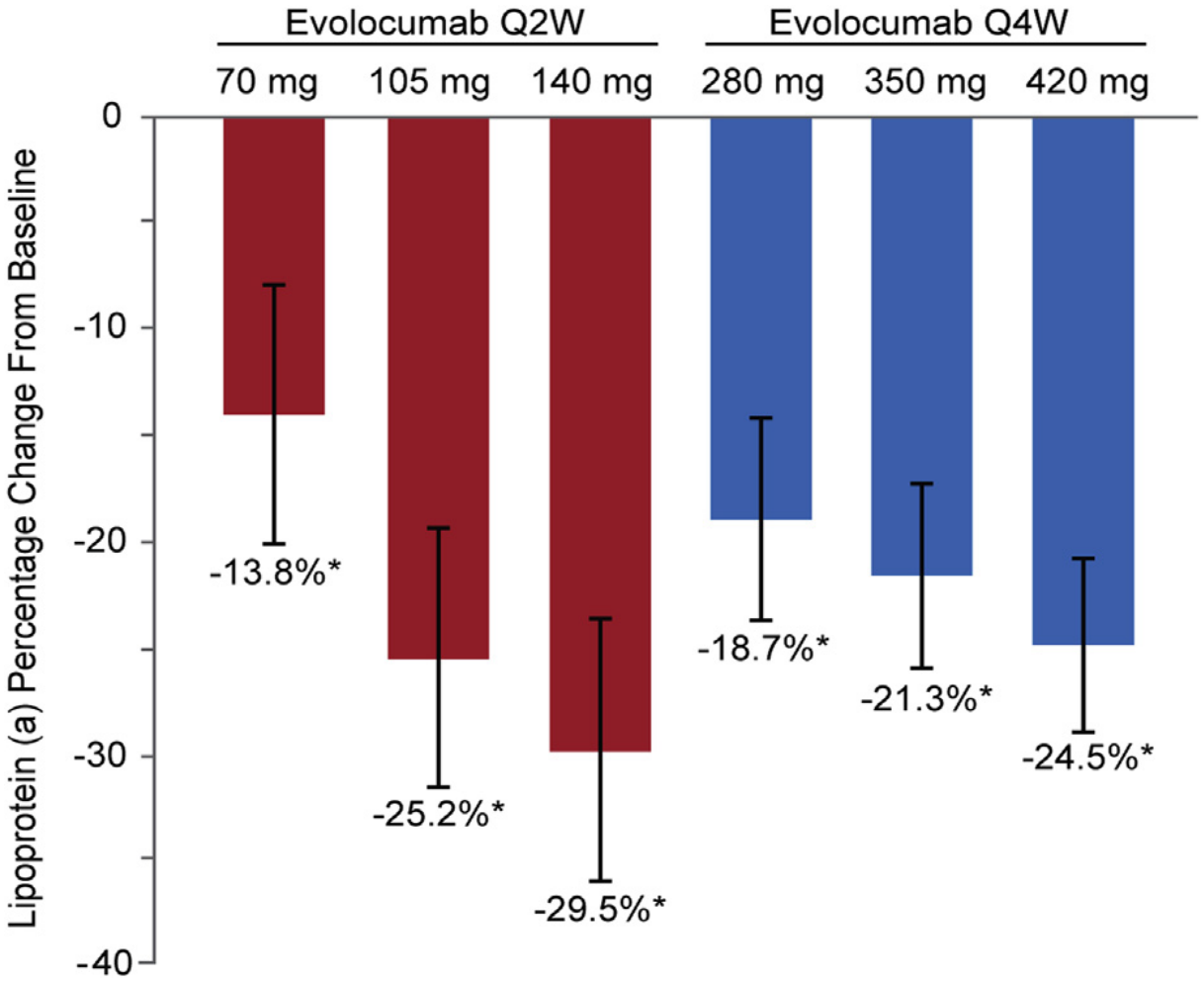


P<0.001 cuando comparado con el placebo

El rango de datos incluye los resultados observados en los dos brazos de evolocumab Q2W y QM

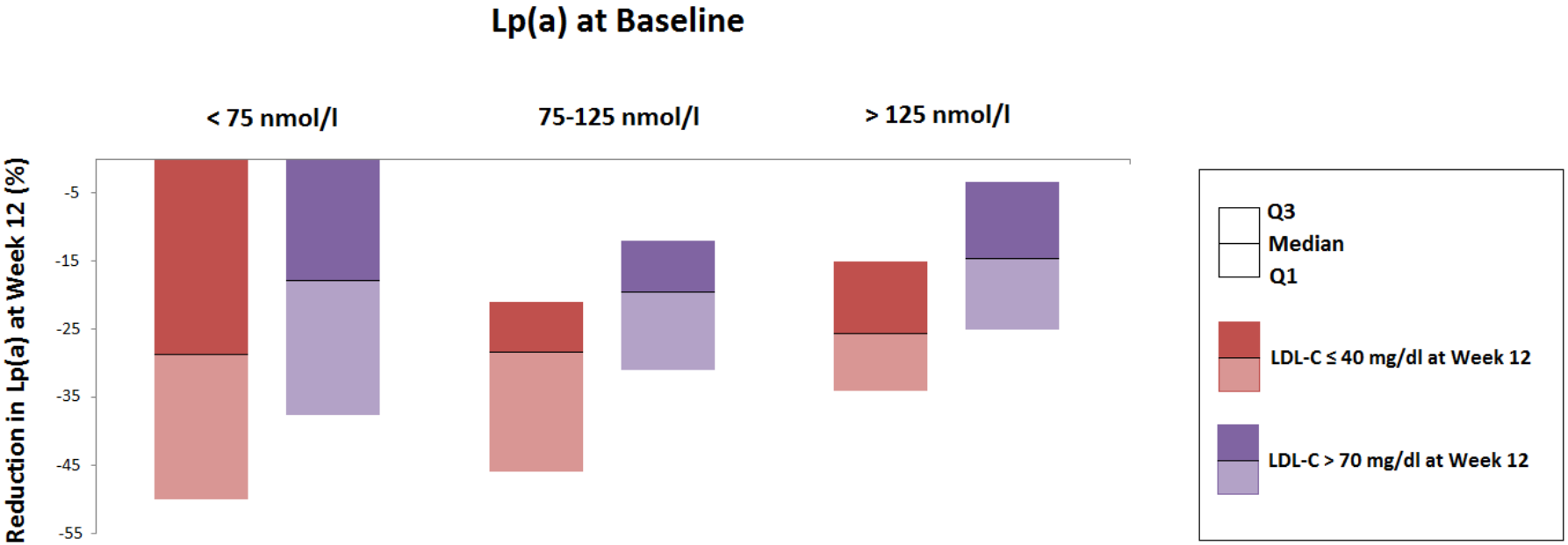
Robinson et al. JAMA 2014;311:1870–1882

Lipoprotein(a) Mean Percentage Change (95% CI) From Baseline at Week 12



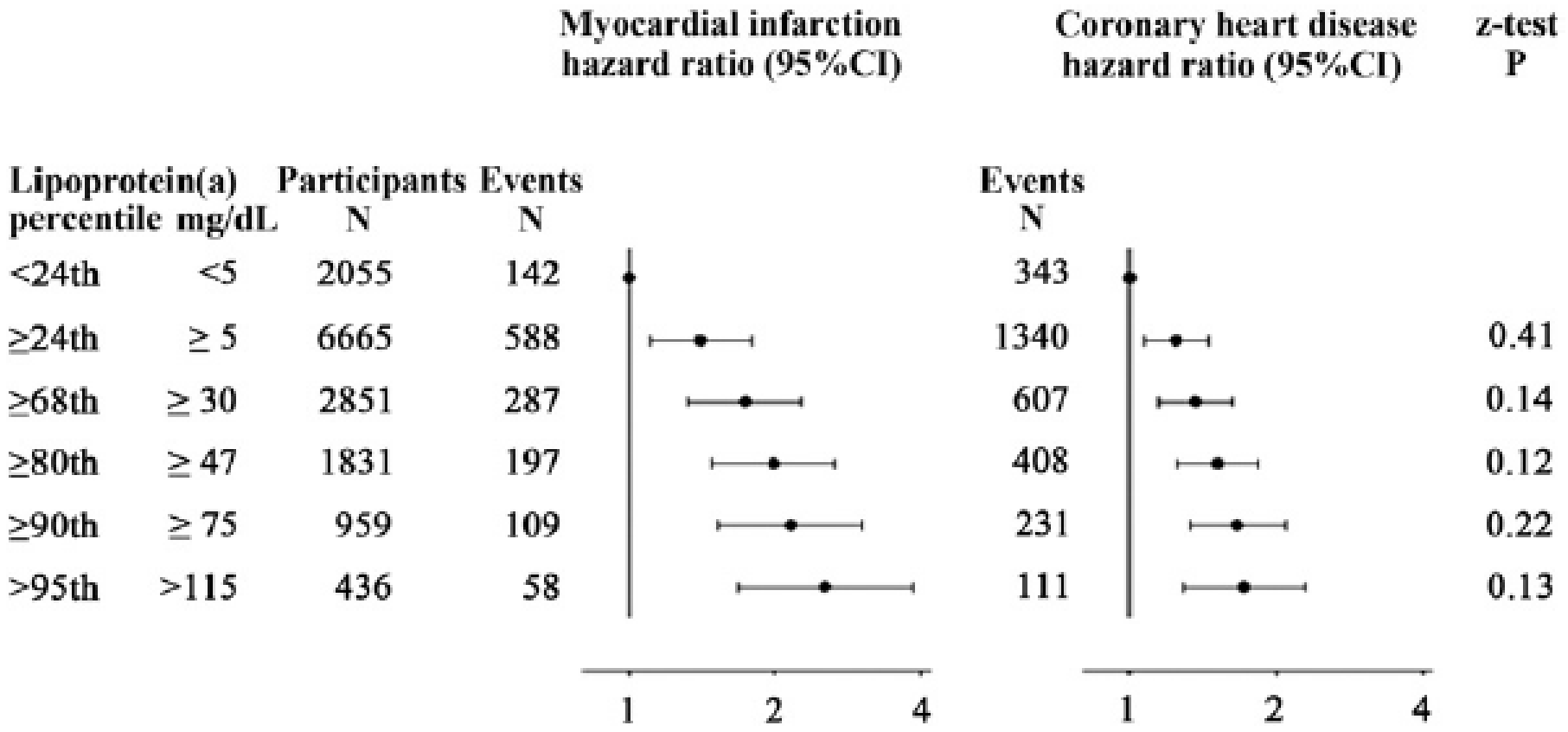
(J Am Coll Cardiol 2014;63:1278–88)

Percent reductions in Lp(a) at parent study Week 12 by baseline Lp(a) and achieved LDL-C



Raal FJ et al. PCSK9 inhibition-mediated reduction in Lp(a) with evolocumab: an analysis of 10 clinical trials and the LDL receptor's role. *J Lipid Res*. 2016 Apr 21

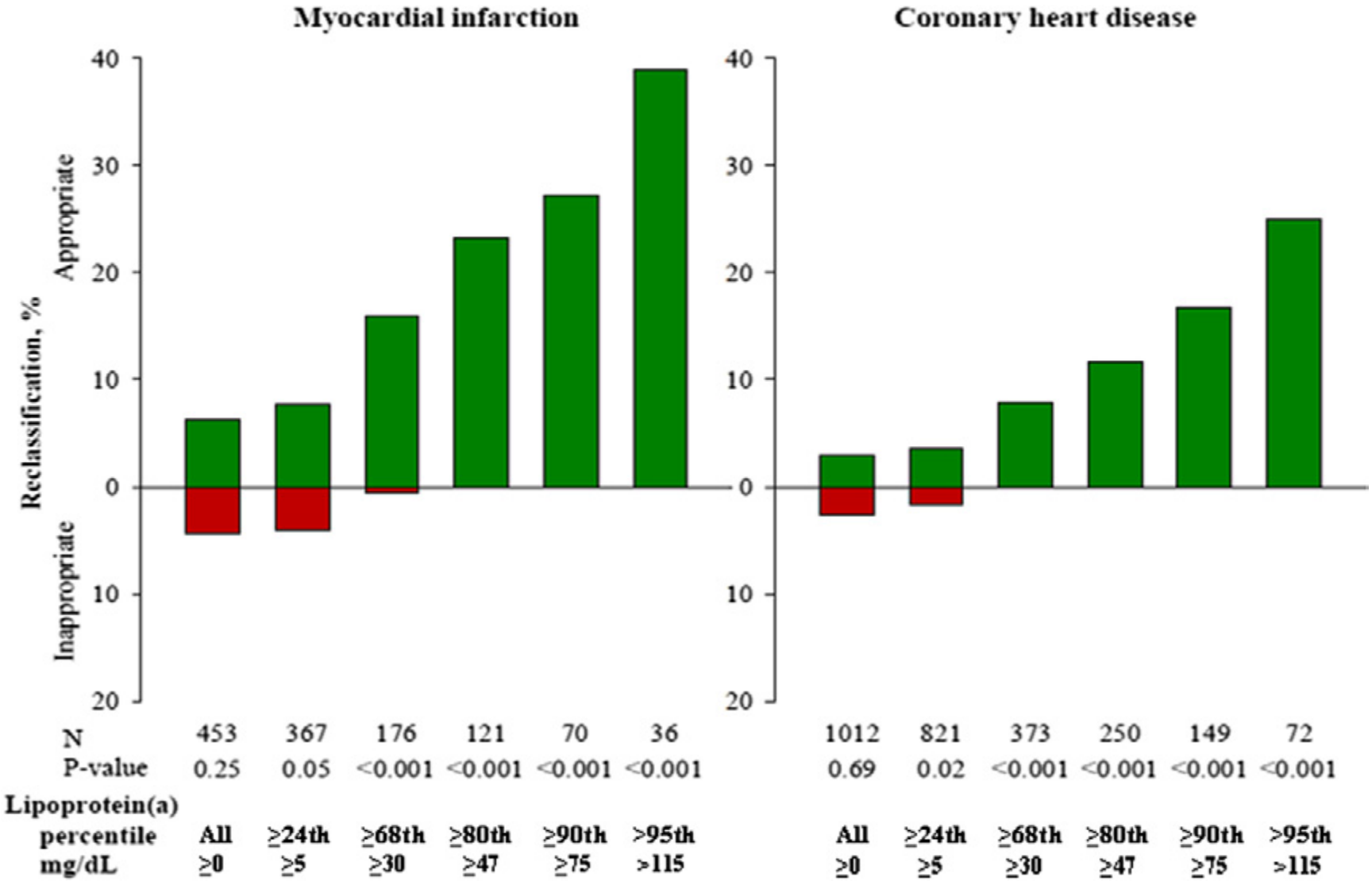
Extreme Lipoprotein(a) Levels and Improved Cardiovascular Risk Prediction



They followed 8,720 Danish participants in a general population study from 1991 to 1994 through 2011 without losses to follow-up. During this period, 730 and 1,683 first-time MI and CHD events occurred.

(J Am Coll Cardiol 2013;61:1146–56)

Extreme Lp(a) Levels and Improved Cardiovascular Risk Prediction: Reclassification as a Function of Elevated Lp(a) Levels



(J Am Coll Cardiol 2013;61:1146–56)

Lipoprotein(a) in Familial Hypercholesterolemia: The SAFEHEART study

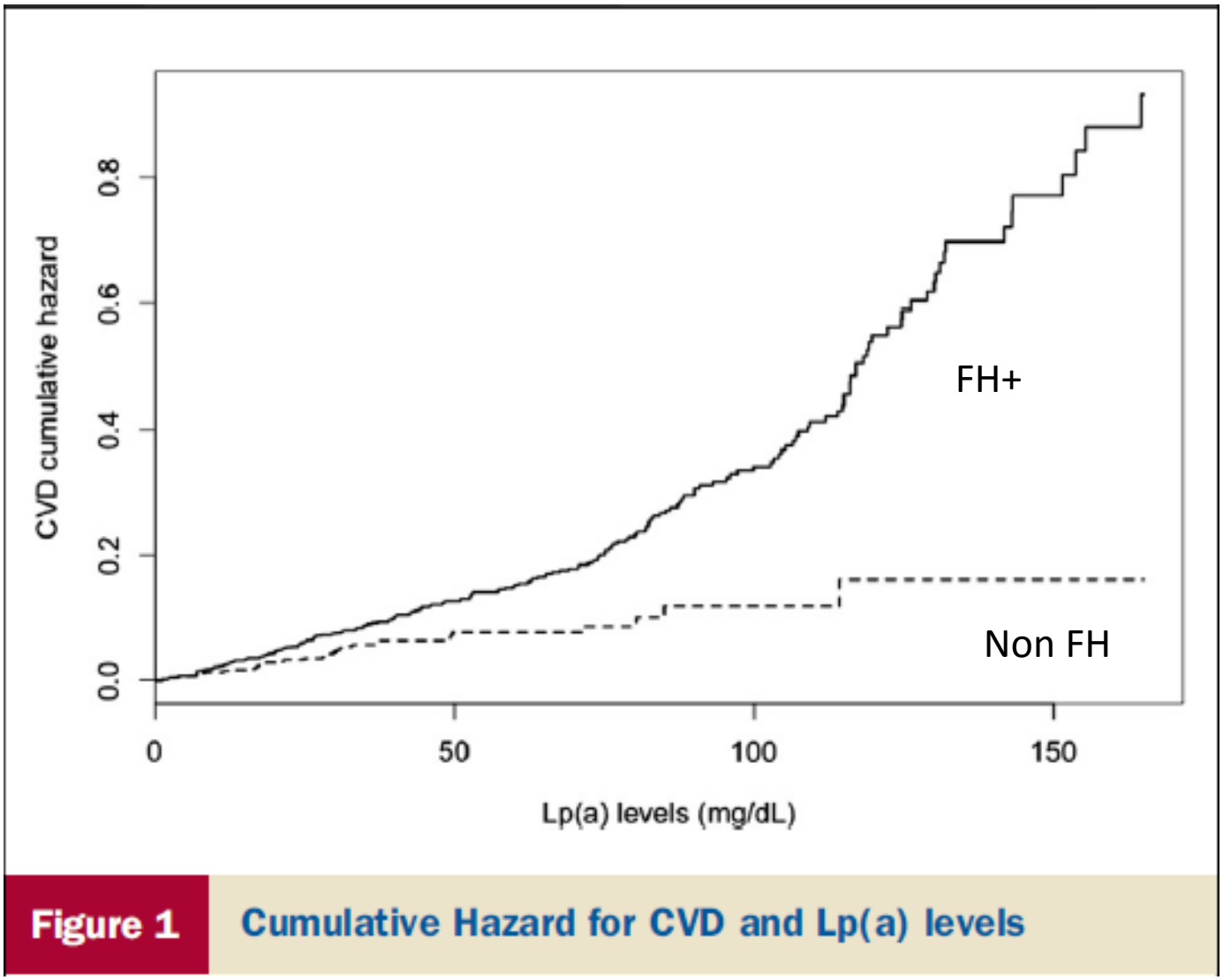
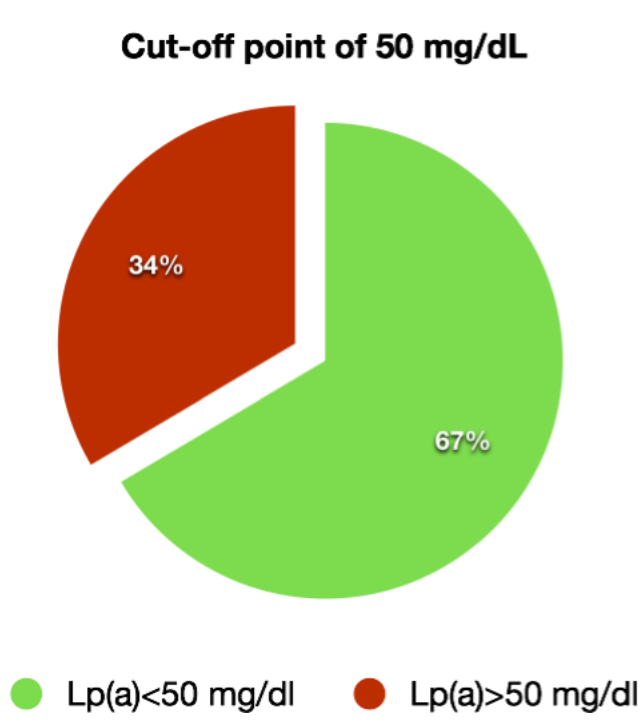
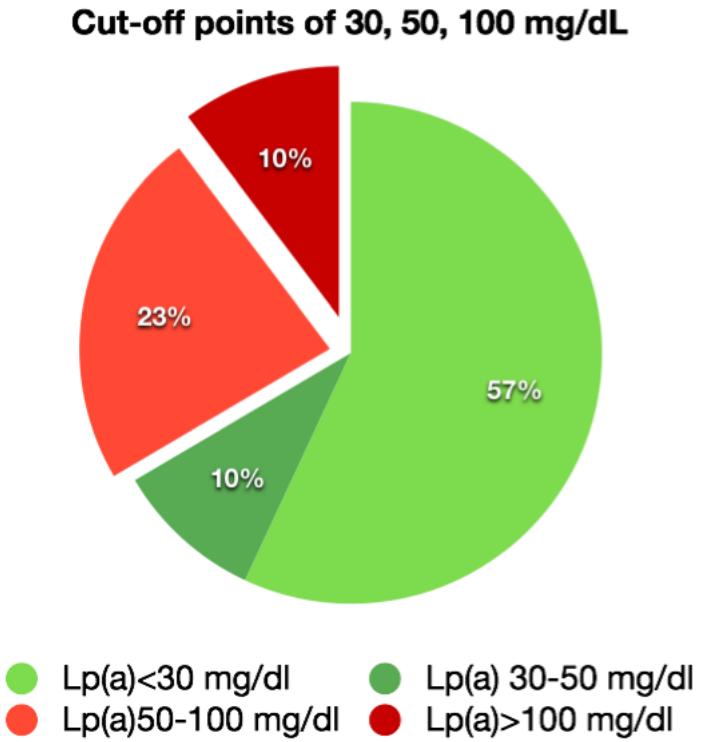


Figure 1 Cumulative Hazard for CVD and Lp(a) levels

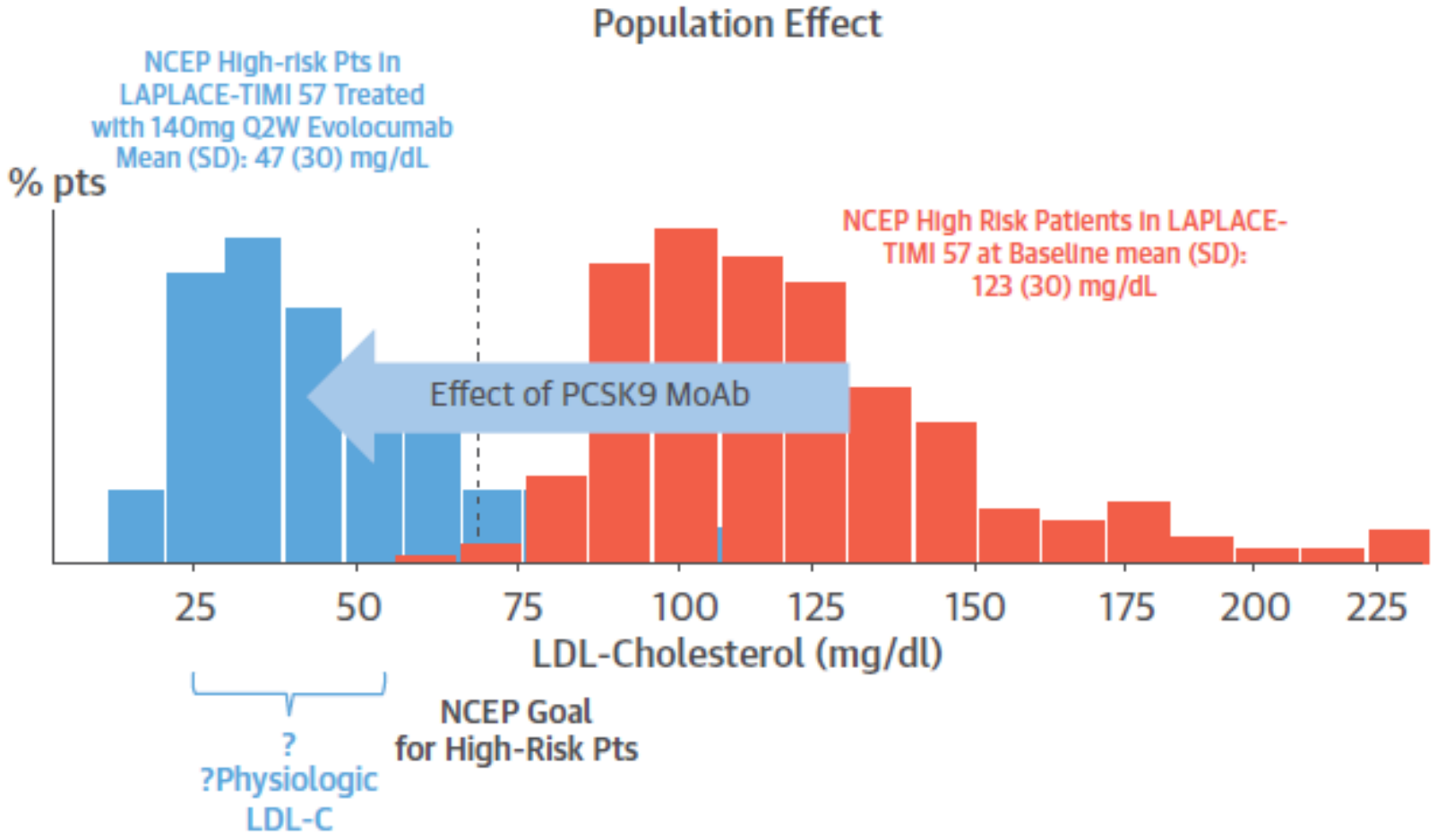
Alonso R, et al JACC Vol. 63, No. 19, 2014:1982–9 .

% Patients according to Lp(a) levels





Shift in Distribution of LDL-C in a Population of High-Risk Individuals WithUse of PCSK9 Inhibitor

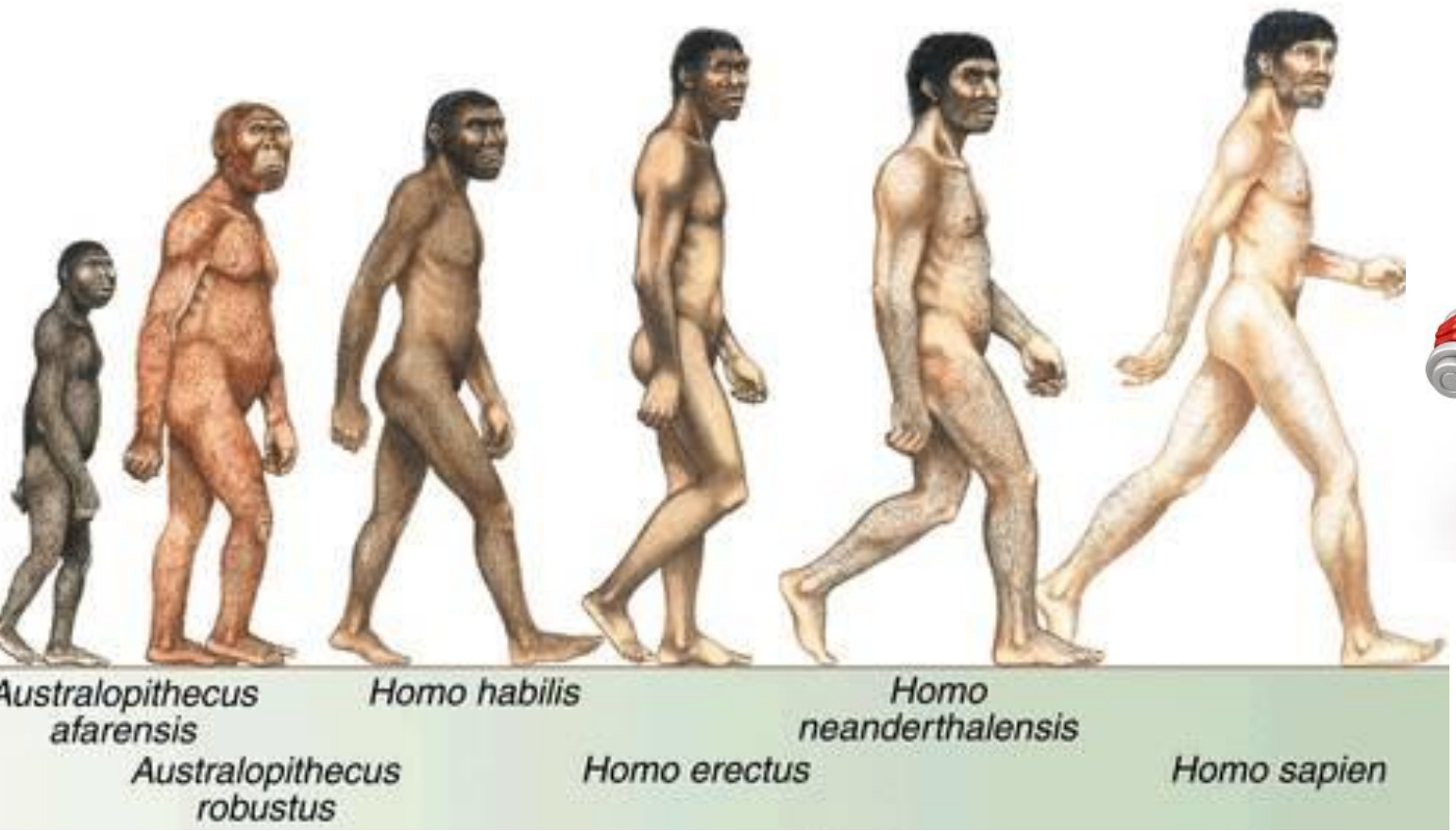


(J Am Coll Cardiol 2015;65:2638–51)

Adverse Events by Achieved LDL-C

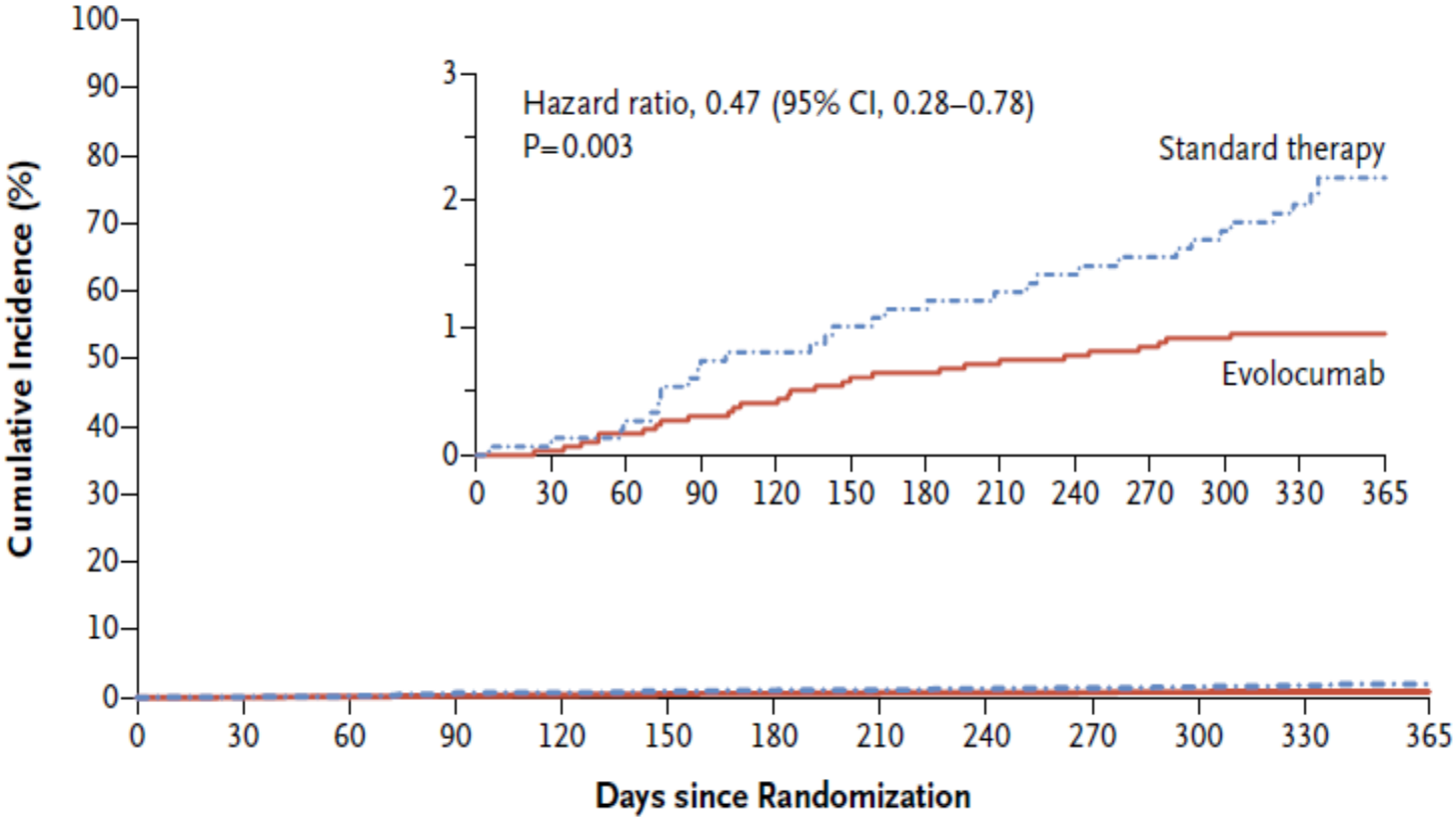
	Evolocumab subjects stratified by minimum achieved LDL-C				All EvoMab (n=2976)	Stnd of Care Alone (n=1489)
	<25 mg/dL (n=773)	25 to <40 mg/dL (n=759)	<40 mg/dL (n=1532)	≥40 mg/dL (n=1426)		
Adverse Events (%)						
Any	**70.0**	68.1	69.1	70.1	69.2	**64.8**
Serious	**7.6**	6.9	7.2	7.8	7.5	**7.5**
Muscle-related	**4.9**	7.1	6.0	6.9	6.4	**6.0**
Neurocognitive	**0.5**	1.2	0.8	1.0	0.9	**0.3**
Lab results (%)						
ALT/AST >3×ULN	**0.9**	0.8	0.8	1.3	1.0	**1.2**
CK >5×ULN	**0.4**	0.9	0.7	0.5	0.6	**1.2**

La evolución del tratamiento hipolipemiante



Epidemiologia → LRC → LDL-R → Estatinas → PCSK9 → ????

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

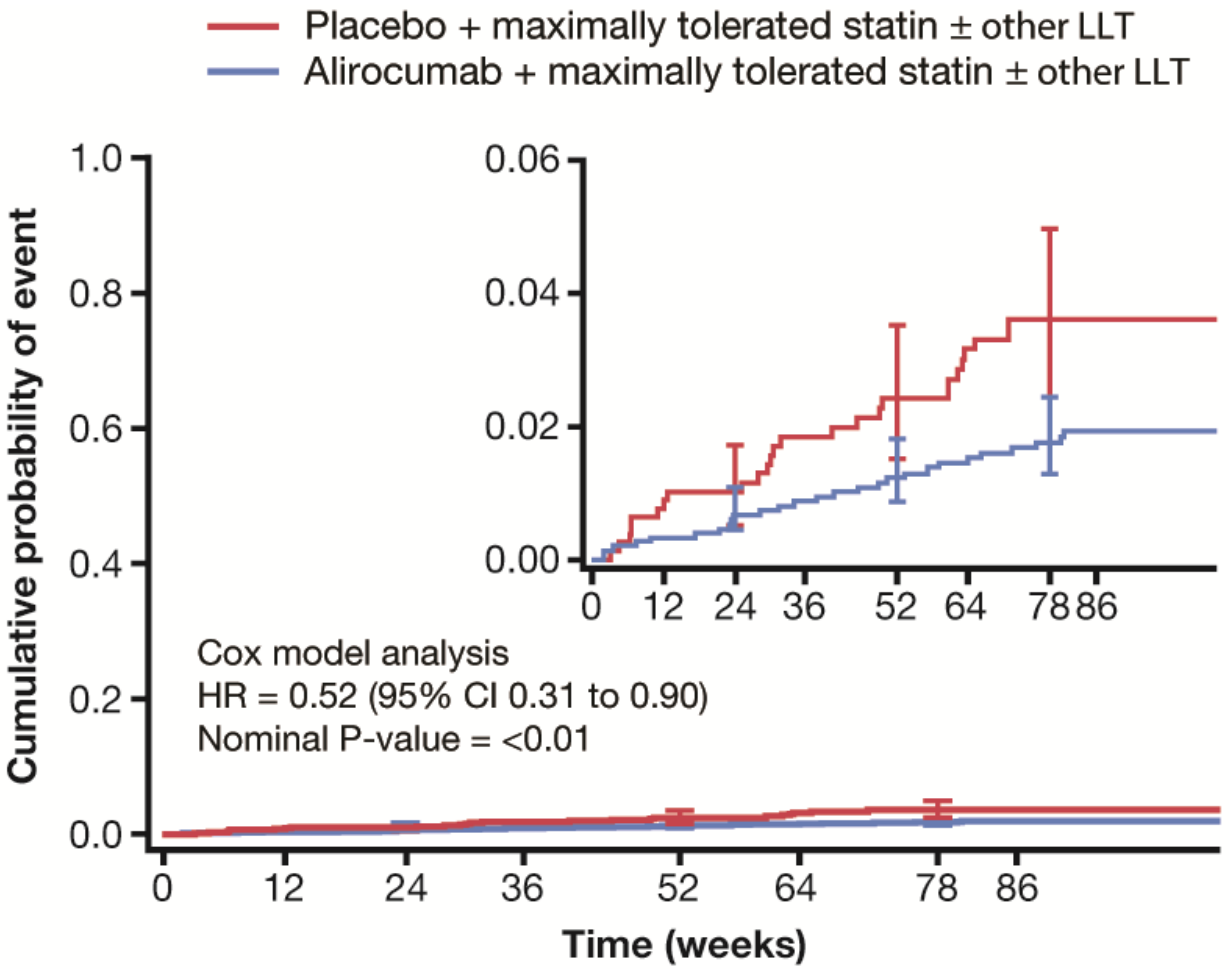


No. at Risk

Standard therapy	1489	1486	1481	1473	1467	1463	1458	1454	1447	1438	1428	1361	407
Evolocumab	2976	2970	2962	2949	2938	2930	2920	2910	2901	2885	2871	2778	843

N Engl J Med 2015;372:1500-9.

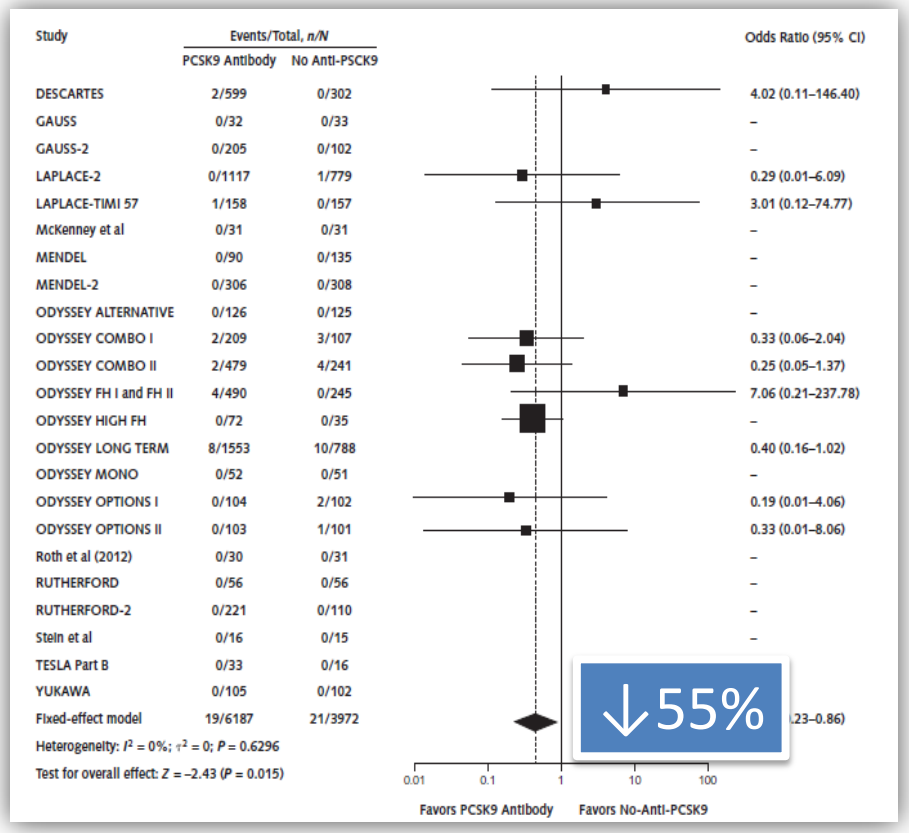
Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

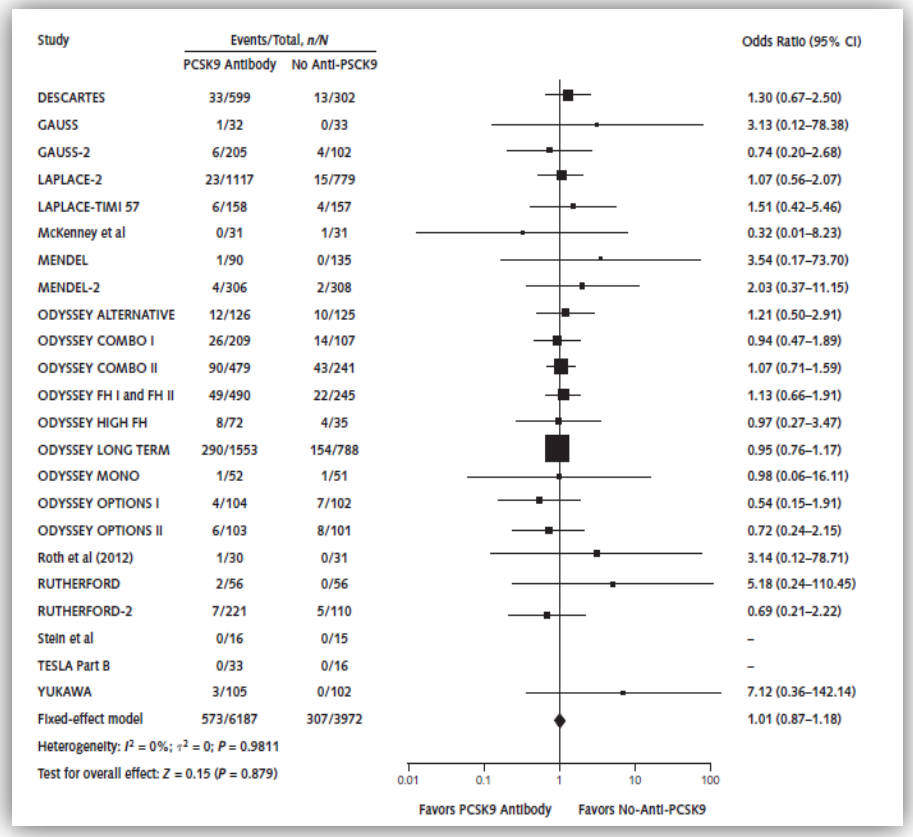


N Engl J Med 2015;372:1489-99.

Meta-análisis de eficacia y seguridad de PCSK-9

10.159 pacientes C-LDL ↓ 47,5%





Mortalidad por cualquier causa

Efectos adversos graves

Navarese, EP et al. *Ann Intern Med.* 2015;163:40-51

Meta-análisis de eficacia y seguridad de PCSK-9

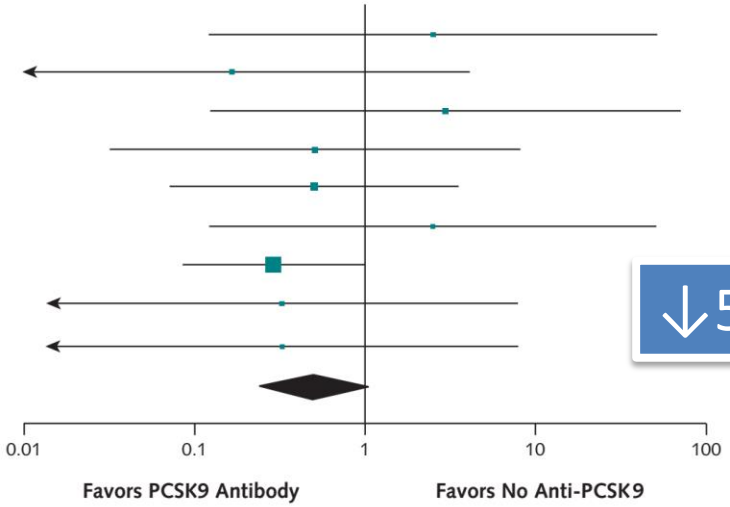
10.159 pacientes C-LDL ↓ 47,5%

Mortalidad Cardiovascular

Study or Subgroup	log(Rate Ratio)	SE	Weight, %	Rate Ratio (95% CI)*
DESCARTES	0.925	1.549	6.5	2.52 (0.12–52.51)
LAPLACE-2	–1.793	1.633	5.9	0.17 (0.01–4.09)
LAPLACE-TIMI 57	1.092	1.633	5.9	2.98 (0.12–73.16)
ODYSSEY COMBO I	–0.67	1.414	7.8	0.51 (0.03–8.18)
ODYSSEY COMBO II	–0.687	1	15.7	0.50 (0.07–3.57)
ODYSSEY FH I and FH II	0.916	1.549	6.5	2.50 (0.12–52.4)
ODYSSEY LONG TERM	–1.238	0.627	39.9	0.29 (0.08–0.99)
ODYSSEY OPTIONS I	–1.118	1.633	5.9	0.33 (0.01–8.03)
ODYSSEY OPTIONS II	–1.118	1.633	5.9	0.33 (0.01–8.03)
Total (95% CI)			100.00	0.49 (0.23–1.07)

Heterogeneity: chi square = 4.71 ($P = 0.79$); $I^2 = 0\%$

Test for overall effect: $Z = 1.78$ ($P = 0.07$)

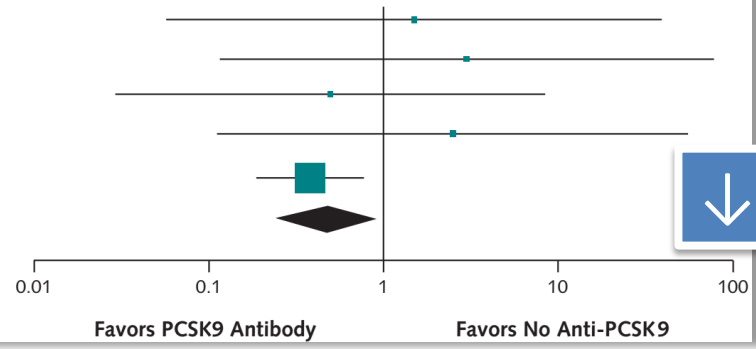


↓51%

Study or Subgroup	log(Rate Ratio)	SE	Weight, %	Rate Ratio (95% CI)*
DESCARTES	0.414	1.633	3.9	1.51 (0.06–37.14)
ODYSSEY ALTERNATIVE	1.091	1.633	3.9	2.98 (0.12–73.08)
ODYSSEY COMBO I	–0.67	1.414	5.2	0.51 (0.03–8.18)
ODYSSEY FH I and FH II	0.916	1.549	4.4	2.50 (0.12–52.04)
ODYSSEY LONG TERM	–0.93	0.356	82.6	0.39 (0.20–0.79)
Total (95% CI)			100.00	0.49 (0.26–0.93)

Heterogeneity: chi square = 3.17 ($P = 0.53$); $I^2 = 0\%$

Test for overall effect: $Z = 2.18$ ($P = 0.03$)

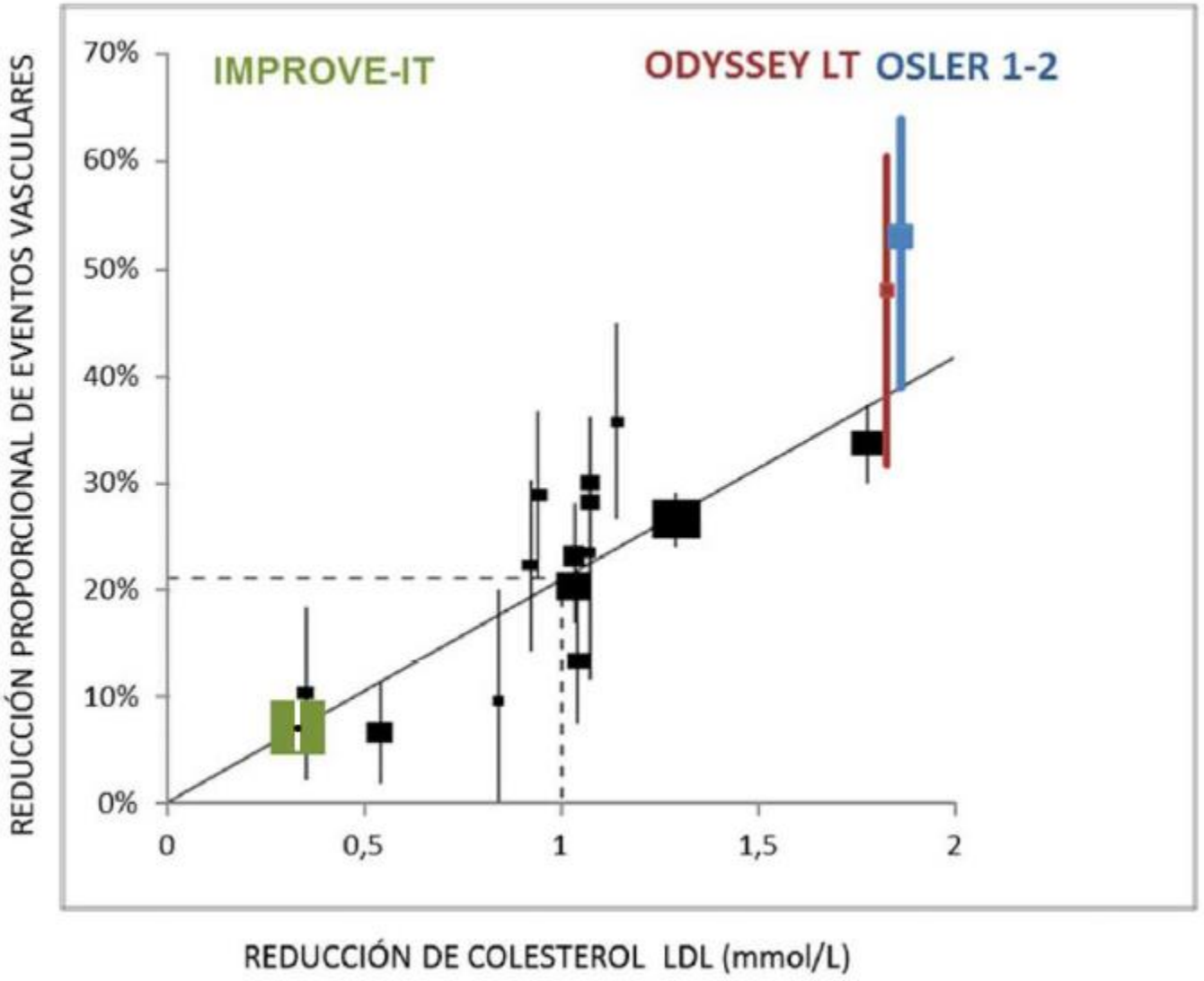


↓51%

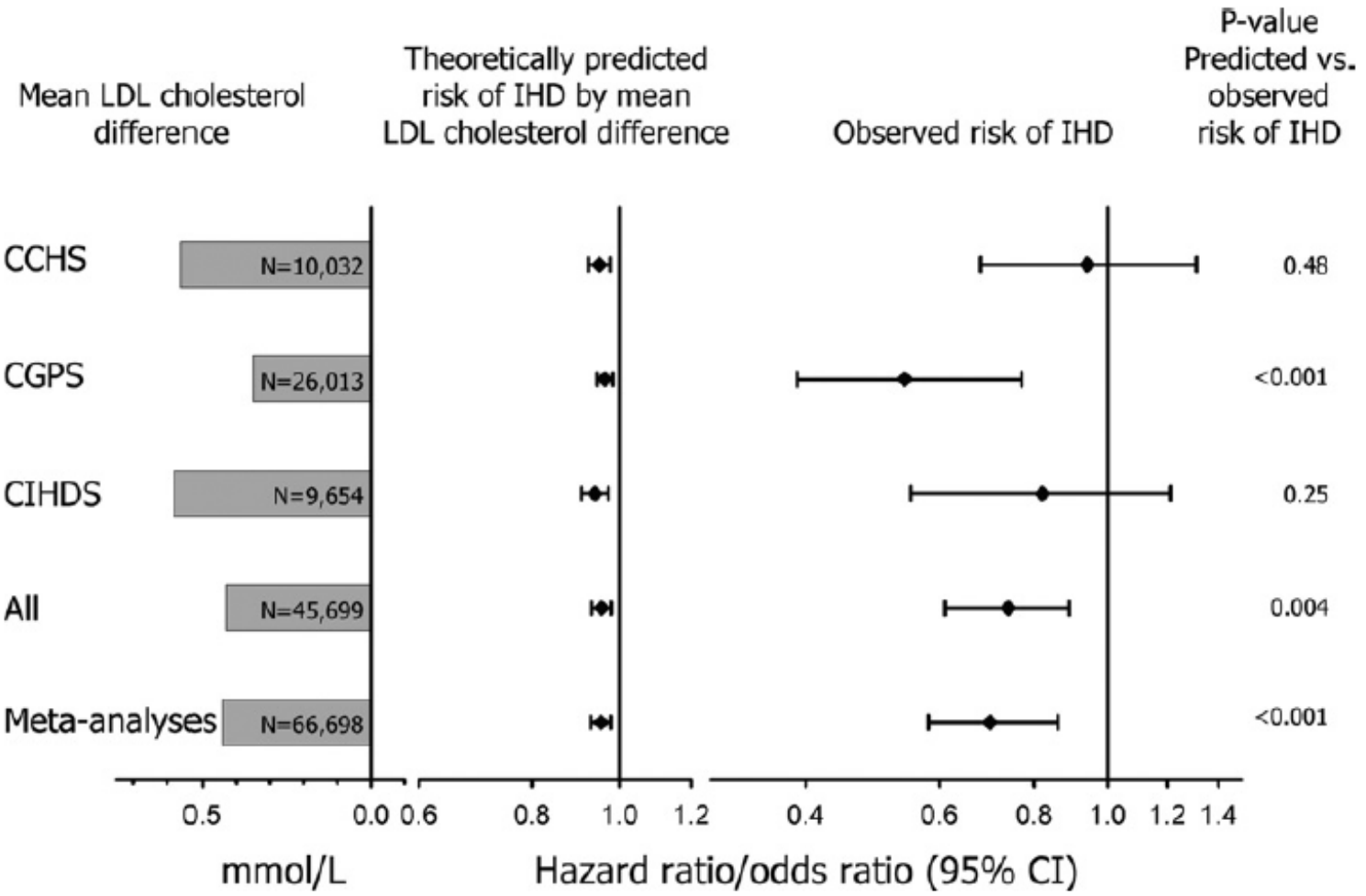
IAM

Navarese, EP et al. *Ann Intern Med.* 2015;163:40-51

Relación entre la reducción de la incidencia de eventos vasculares graves y la reducción de LDL-c en los ensayos clínicos con estatinas



PCSK9 R46L, LDL-c Levels, and Risk of Ischemic Heart Disease



The 30% reduction in risk of IHD observed was larger than predicted by the reduction in LDL-C alone. This could be because genotype is a better predictor of lifelong exposure to LDL-C than LDL-C measured in adult life.

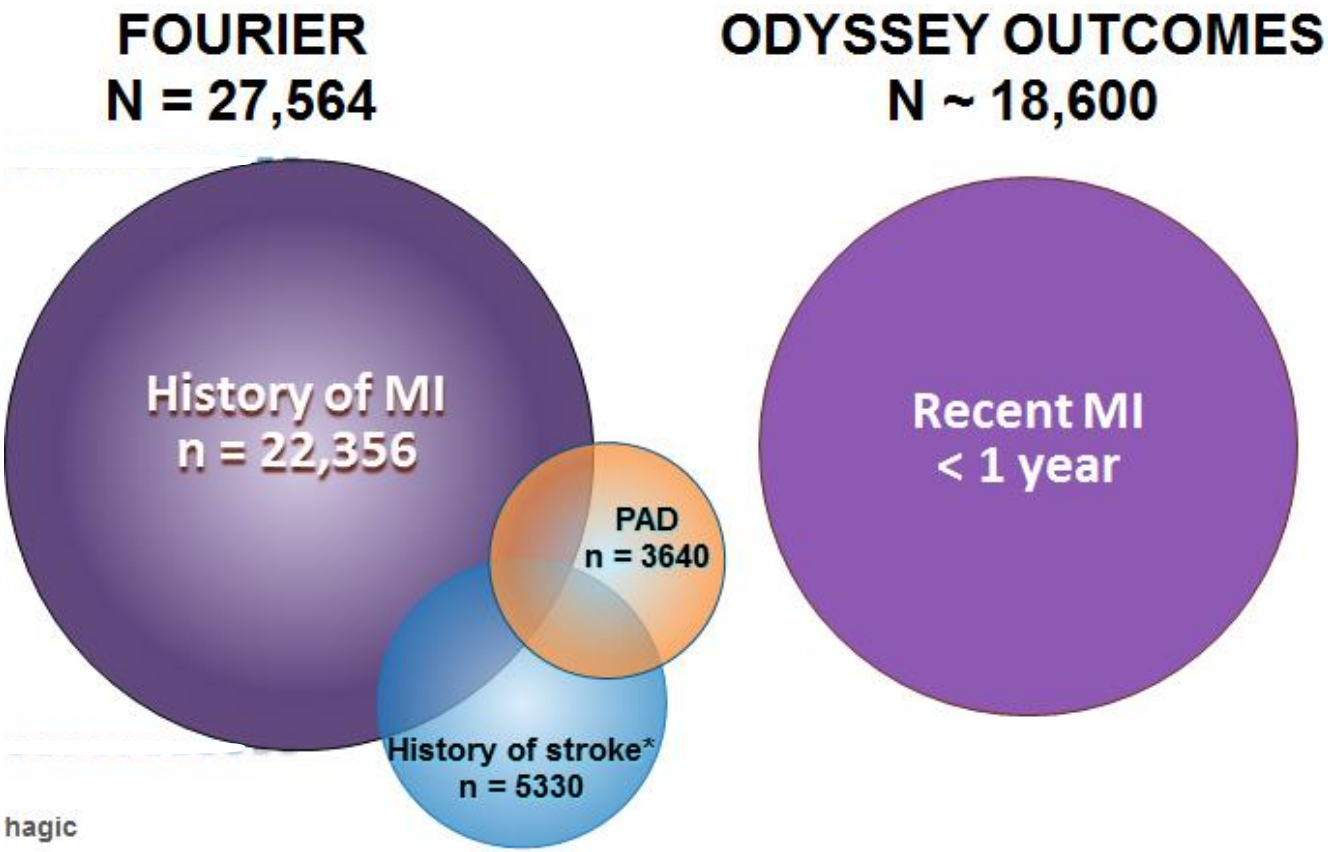
(J Am Coll Cardiol 2010;55:2833–42).

Indicaciones de los Inhibidores de PCSK9

CONDICIÓN CLÍNICA	NIVEL DE C-LDL (tras tratamiento con máxima dosis de estatina tolerada + ezetimiba)	COMENTARIOS
HFHe	> 130	
HFHe bajo riesgo	> 160	Edad <40 años; sin factores de riesgo; Lp(a) < 50 mg/dL; no ECV isquémica familiar…)
HFHe + ECV ateromatosa	> 100	
HFHo		Al menos un alelo defectuoso. Evolocumab.
ECV ateromatosa estable	> 130	Incluye cardíaca, cerebral y periférica oclusiva.
ECV ateromatosa clínicamente inestable; progresiva y/o recidivante; síndrome coronario agudo	> 100	De cualquier localización: cardíaca, cerebral y periférica oclusiva
ECV ateromatosa + diabetes o Lp(a) > 100 mg/L	> 100	
Diabetes + 2 factores de riesgo o albuminuria o FGe < 45 ml/min/1.73m²	> 130	No incluida en indicaciones oficiales de uso
Pacientes intolerantes a estatinas		Todas las condiciones anteriores + prevención primaria con C-LDL > 190 mg/dL

HFHe = Hipercolesterolemia familiar heterocigota; HFHo = Hipercolesterolemia familiar homocigota
ECV = Enfermedad cardiovascular; FGe = Filtrado glomerular estimado

Estudios de eventos cardiovasculares con anti PCSK9



*ictus no hemorrágico

1. Sabatine MS, et al. Am Heart J 2016;173:94–101.
2. Schwartz GG, et al. Am Heart J 2014;168:682–9.