XI REUNIÓN DE RIESGO VASCULAR

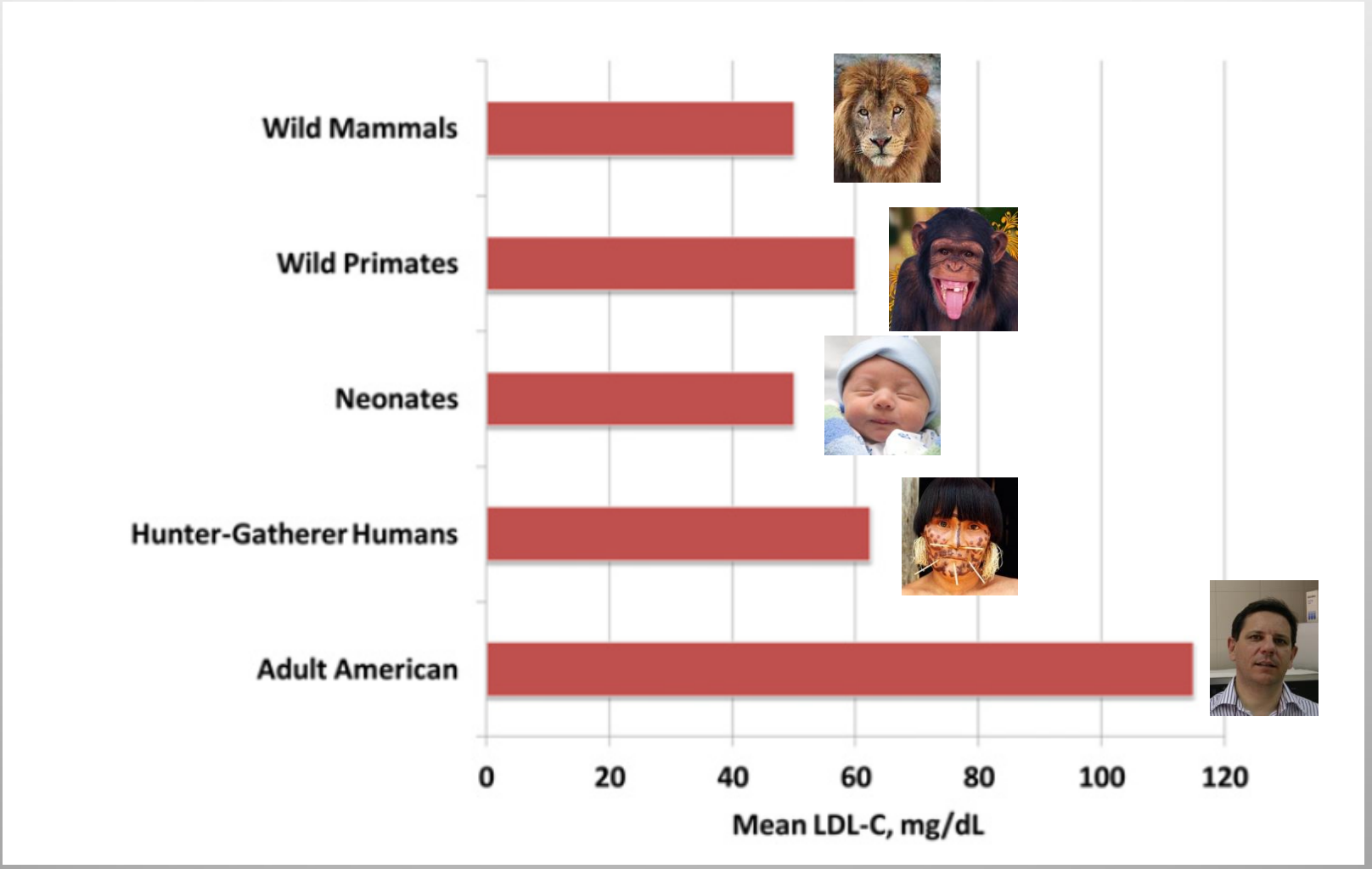
23-24 de Abril 2015

Hotel Holiday Inn-Madrid

¿Existen evidencias para bajar el colesterol por debajo de las recomendaciones actuales?

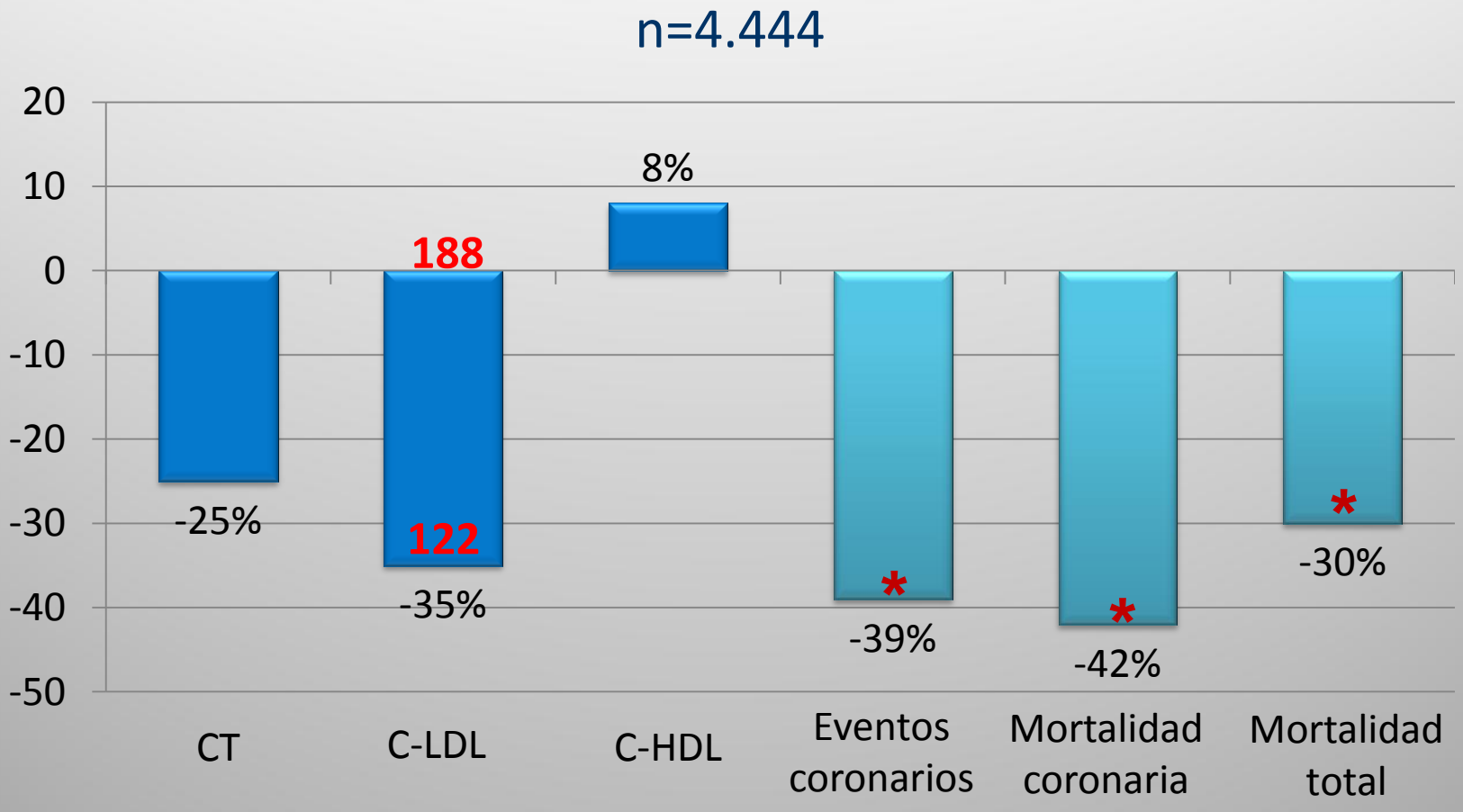
Carlos Lahoz

Niveles de cLDL en animales y humanos



Martin SS. Med Clin North Am. 2012;96:13-26.

Scandinavian Simvastatin Survival Study (4S).



Scandinavian Simvastatin Survival Study Group. *Lancet* 1994;344:1383-9.

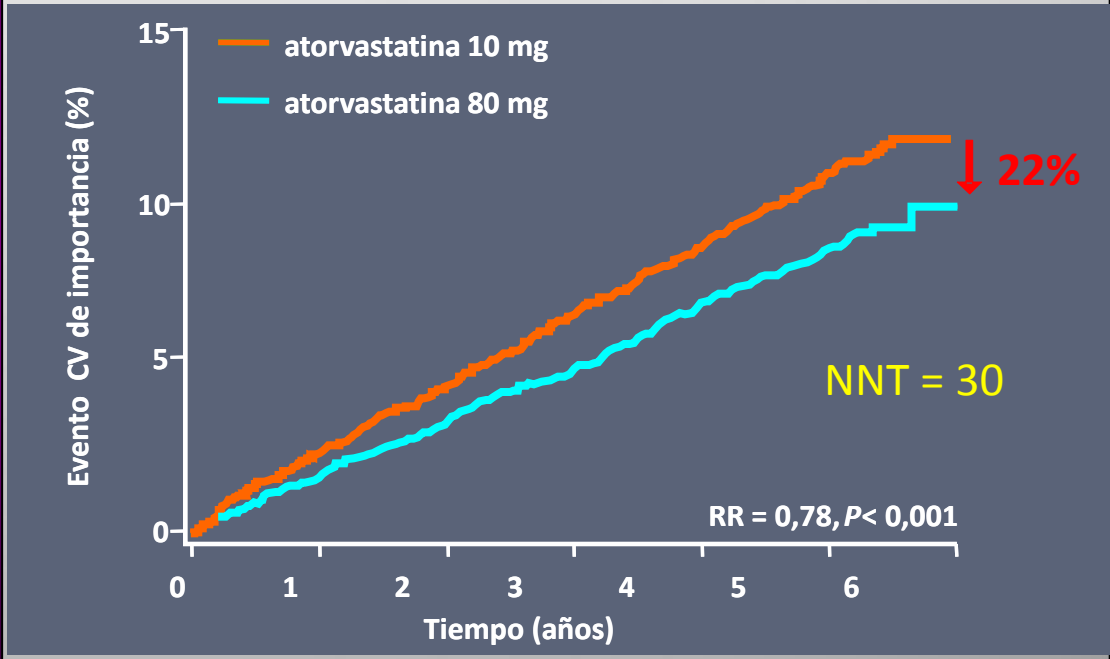
TNT: Treating new targets

n = 10.001
Enf. Coron. estable y LDL<250
Seguimiento 5 años

Tto	A10	A80
LDL basal (mg/dl)	152	
LDL final (mg/dl)	101	76
Eventos (%)	10,9	8,7

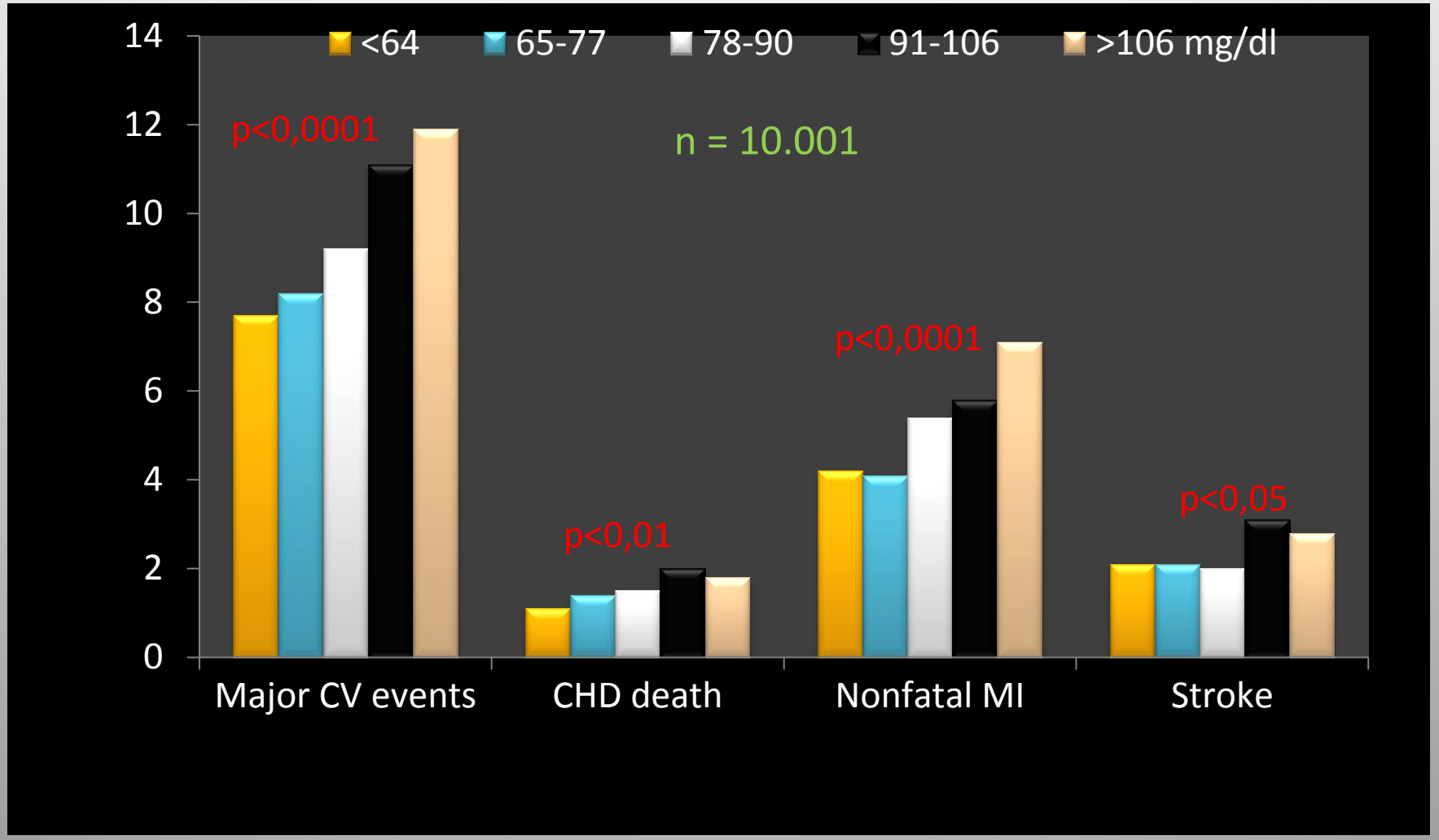
-22% p<0,001

Variable de resultado
Mortalidad por CI, IAM no fatal, resucitación, Ictus fatal o no.



La Rosa JC. N Engl J Med 2005;352:1425-1.435.

TNT: Eventos CV según niveles de cLDL alcanzados y eventos CV



LaRosa JC. Am J Cardiol 2007;100:747–752

TNT: Efectos adversos según niveles de cLDL alcanzados

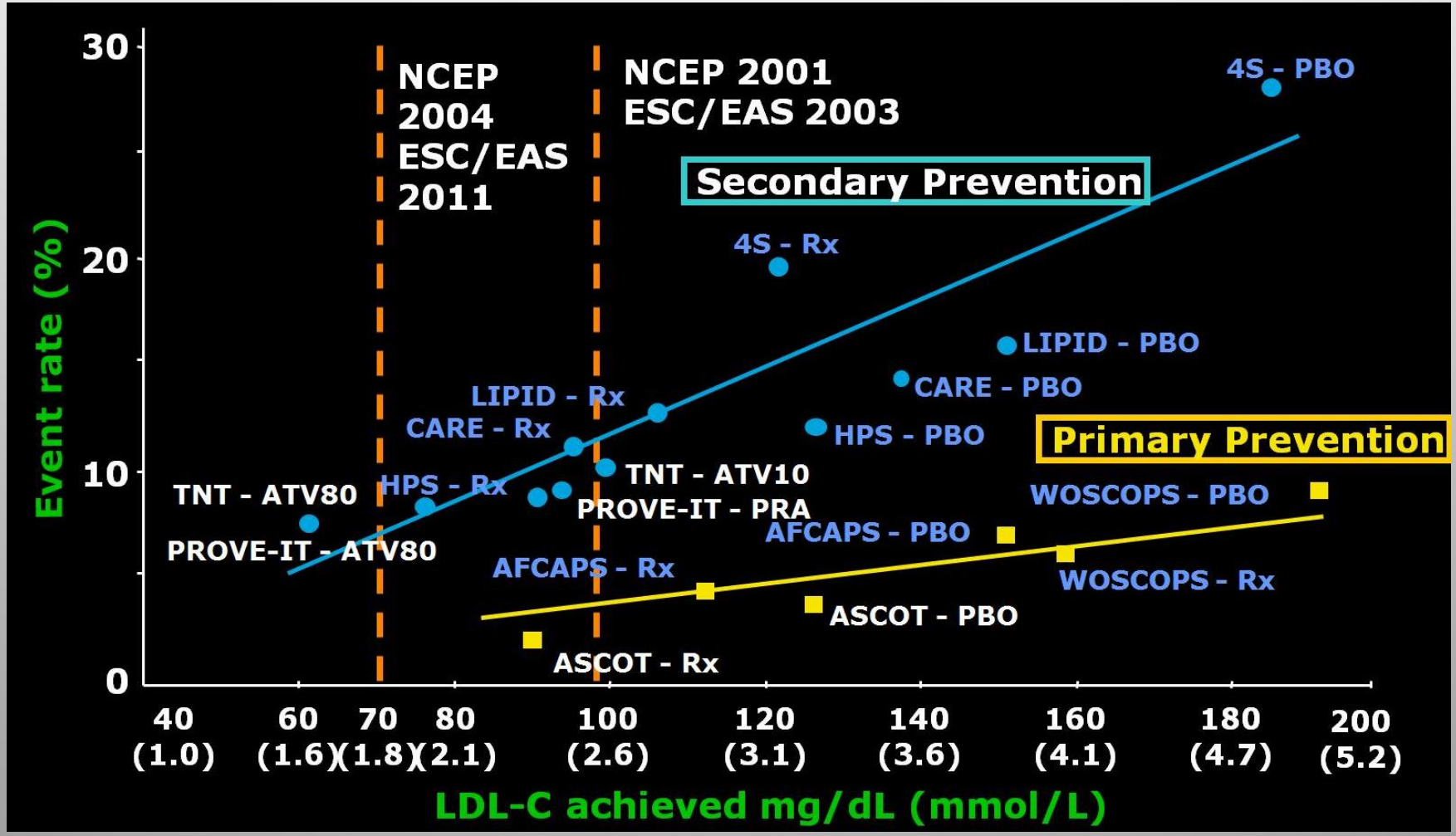
n = 10.001

Adverse event profiles across quintiles

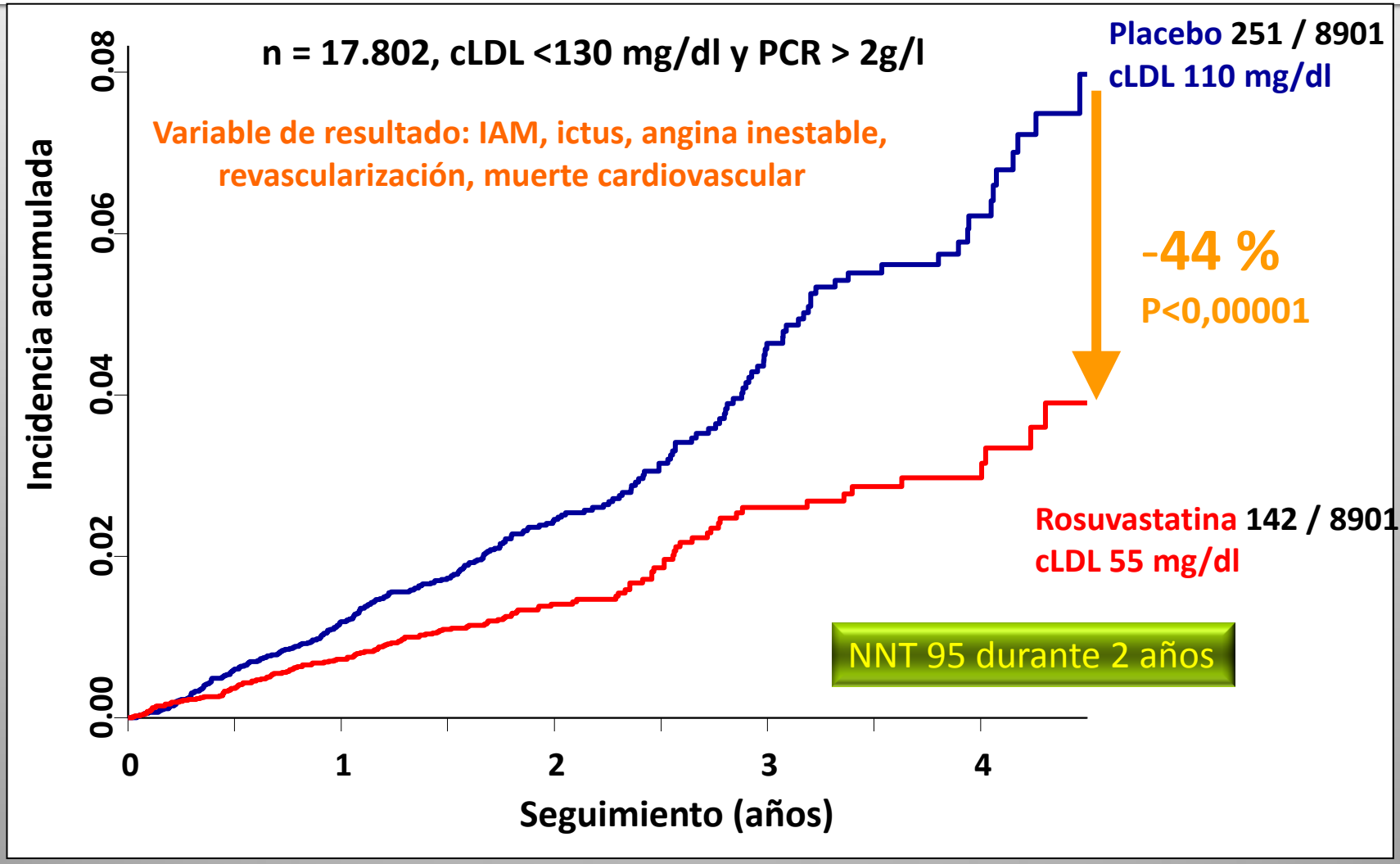
	LDL Cholesterol Quintile (mg/dl)				
	1 <64	2 64–<77	3 77–<90	4 90–<106	5 ≥106
Variable	(1,722/114)*	(1,403/529)*	(968/1,019)*	(515/1,515)*	(266/1,718)*
Patients experiencing adverse events					
All	96.1%	95.3%	95.7%	96.3%	95.1%
Treatment associated	7.6%	6.6%	5.9%	6.2%	7.8%
Withdrawals because of adverse events					
All	8.8%	8.6%	7.6%	7.9%	10.5%
Treatment associated	6.6%	5.5%	5.0%	5.2%	7.2%
Treatment-associated myalgia	4.6%	4.4%	4.7%	4.7%	5.2%
Persistent† CK >10 × ULN	0%	0%	0%	0%	0%
Persistent† ALT/AST >3 × ULN	1.1%	0.8%	0.9%	0.4%	0.5%

LaRosa JC. Am J Cardiol 2007;100:747–752

Eventos CV según cLDL alcanzado

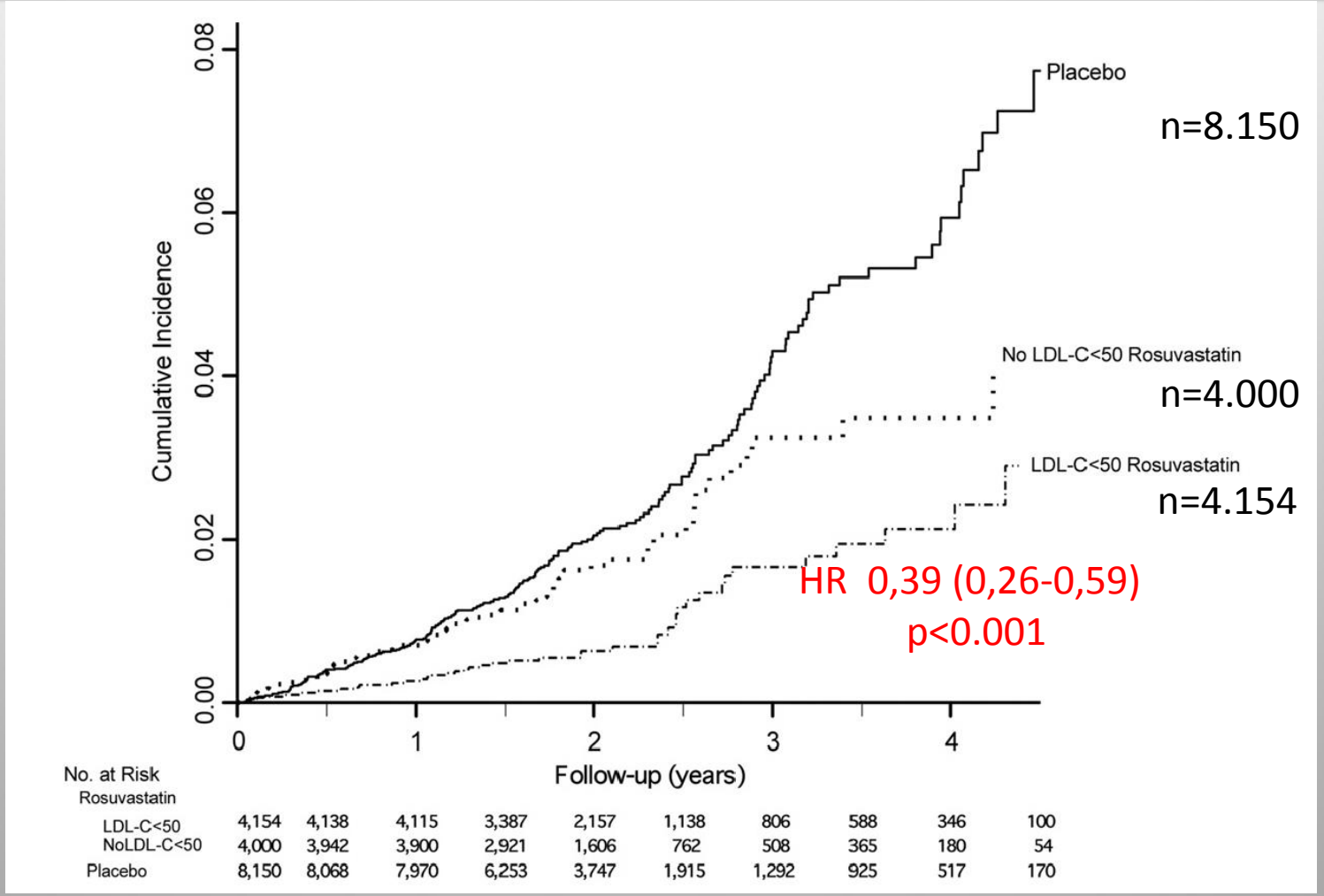


JUPITER: descenso de LDL en sujetos con PCR elevada y cLDL bajo



Ridker PM. N Engl J Med 2008;359:2195-207.

JUPITER: Eventos CV según cLDL alcanzado



Hsia J. J Am Coll Cardiol 2011;57:1.666-75.

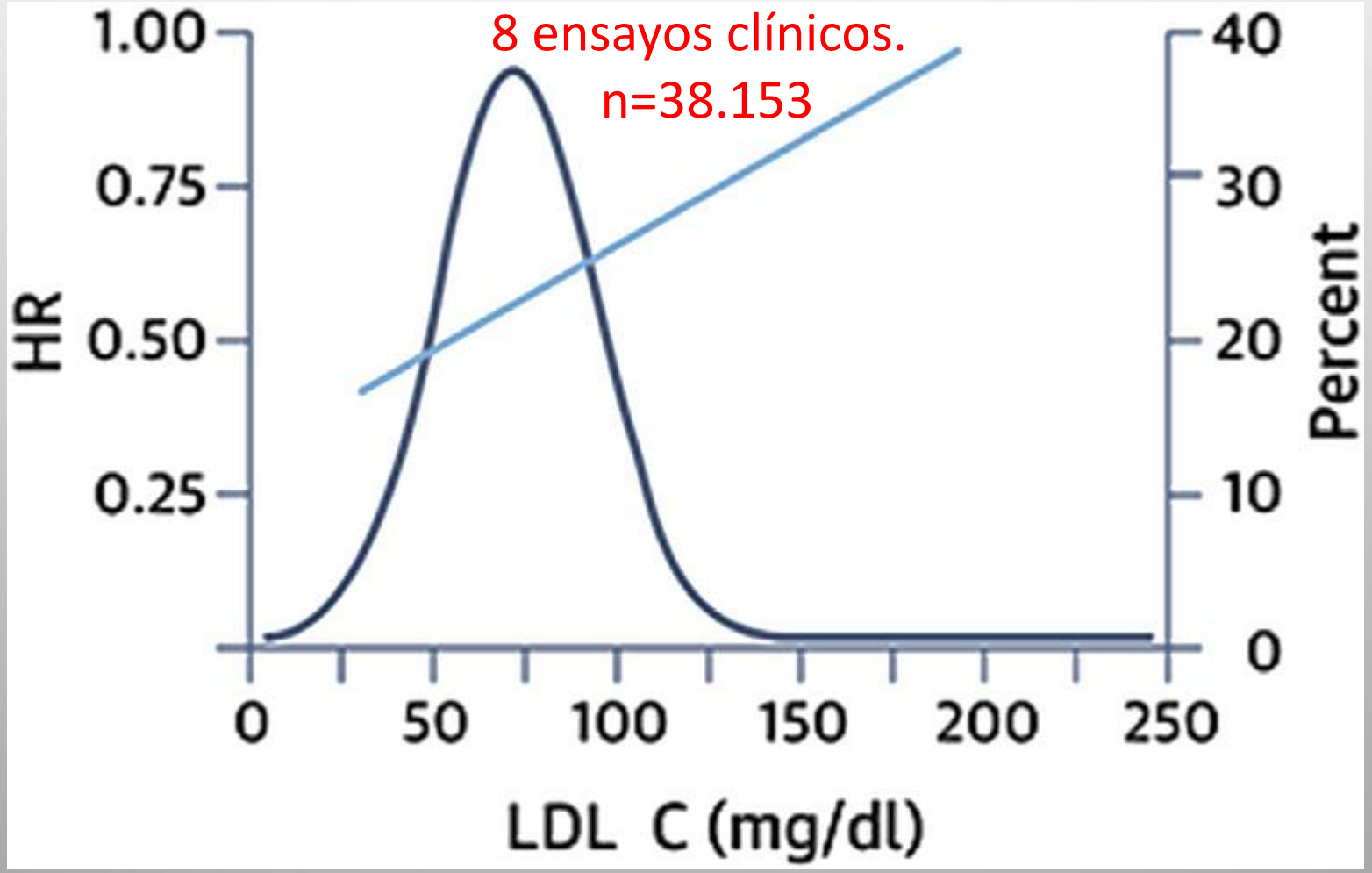
Efectos adversos con cLDL<30 mg/dl en sujetos tratados con rosuvastatina

JUPITER n = 16.304

Adverse Event	LDL-cholesterol (mg/dL) <30 (N=767) N (Incidence rate*)	LDL-cholesterol (mg/dL) ≥30 (N=7387) N (Incidence rate*)	Adjusted† Relative Risk (LDL-cholesterol (mg/dL) < vs. ≥ 30)	Placebo (N=8150) N (Incidence rate*)	Adjusted† Relative Risk (LDL-cholesterol (mg/dL) <30 vs. Placebo)
Any	620 (103.0)	5930 (106.5)	1.10 (1.01-1.21)‡	6509 (103.1)	1.06 (0.98-1.16)
Musculoskeletal Disorders	306 (23.6)	2874 (24.4)	1.08 (0.95-1.23)	2930 (21.7)	1.14 (1.00-1.29)‡
Hepatobiliary Disorders	30 (1.7)	149 (0.9)	1.77 (1.15-2.73)¶	177 (1.0)	2.01 (1.33-3.05)¶
Nervous system disorders	136 (8.3)	1212 (8.3)	1.13 (0.93-1.38)	1431 (8.8)	1.02 (0.85-1.23)
Psychiatric Disorders	69 (4.0)	534 (3.4)	1.40 (1.06-1.85)¶	619 (3.6)	1.20 (0.92-1.57)
Insomnia	27 (1.5)	195 (1.2)	1.59 (1.03-2.48)‡	205 (1.1)	1.55 (1.01-2.38)‡
Depression	19 (1.0)	167 (1.0)	1.14 (0.68-1.92)	217 (1.2)	0.86 (0.52-1.41)
Anxiety	17 (0.9)	114 (0.7)	1.42 (0.80-2.50)	158 (0.9)	1.21 (0.71-2.06)
Diabetes	47 (2.6)	209 (1.3)	1.56 (1.09-2.23)‡	209 (1.2)	1.90 (1.34-2.68)§
Cancer	19 (1.0)	240 (1.5)	0.76 (0.46-1.25)	269 (1.5)	0.65 (0.40-1.06)
Renal and Urinary	107 (6.4)	676 (4.3)	1.51 (1.21-1.90)§	782 (4.5)	1.37 (1.10-1.70)¶

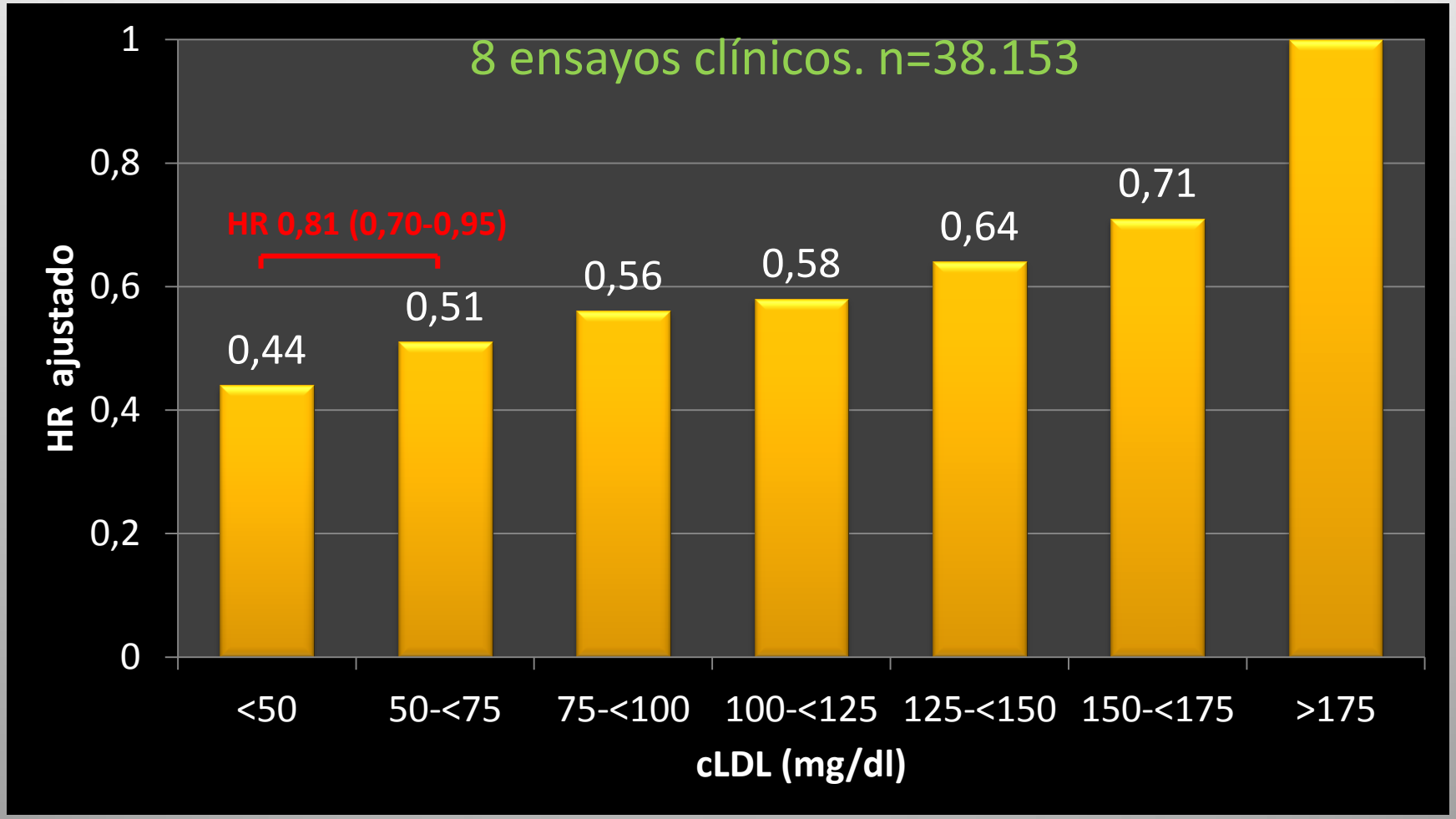
Everett BM. Am J Cardiol 2014;114:1.682-89.

Niveles de cLDL alcanzado con estatinas y riesgo de eventos CV mayores



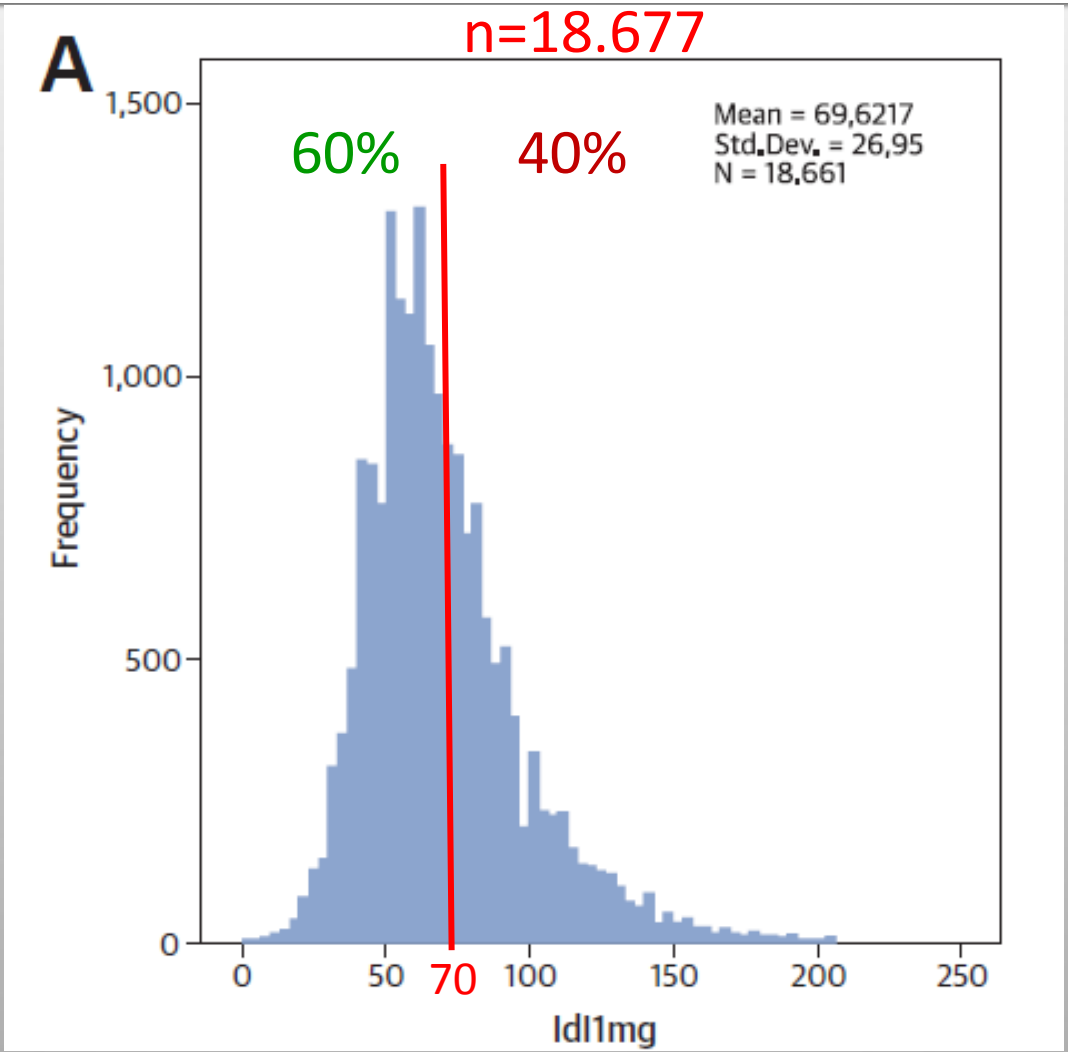
Boekholdt SM. JACC 2014;64:485-94.

Disminución del riesgo de evento CV mayor según cLDL alcanzado



Boekholdt SM. JACC 2014;64:485-94.

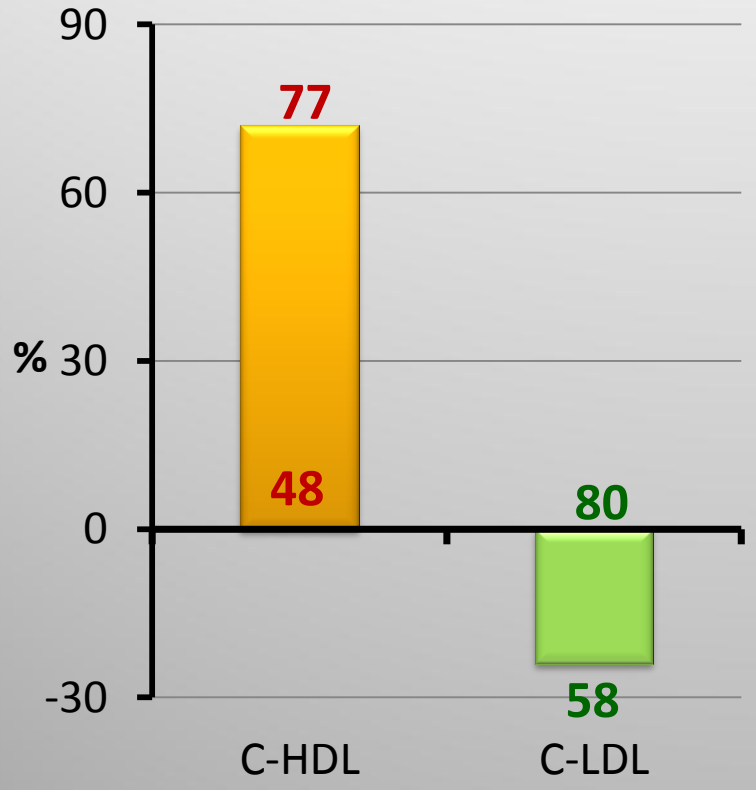
Niveles de cLDL alcanzados con estatinas a dosis altas

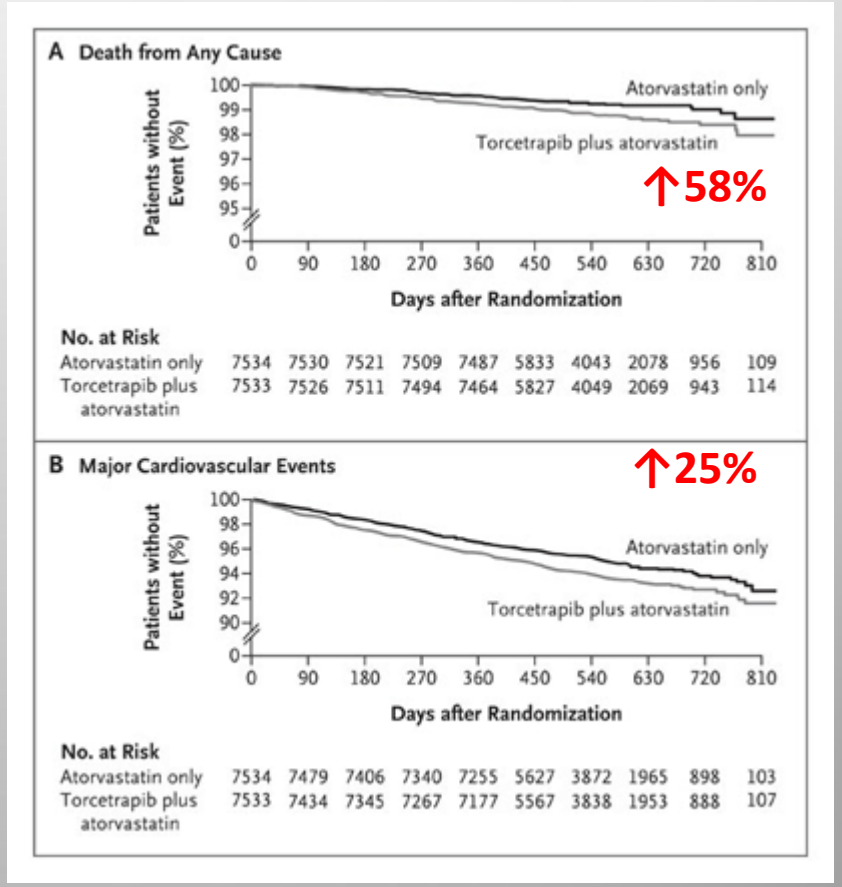


Boekholdt SM. JACC 2015;64:485-94.

Torcetrapib, HDL y eventos cardiovasculares

n=15.067

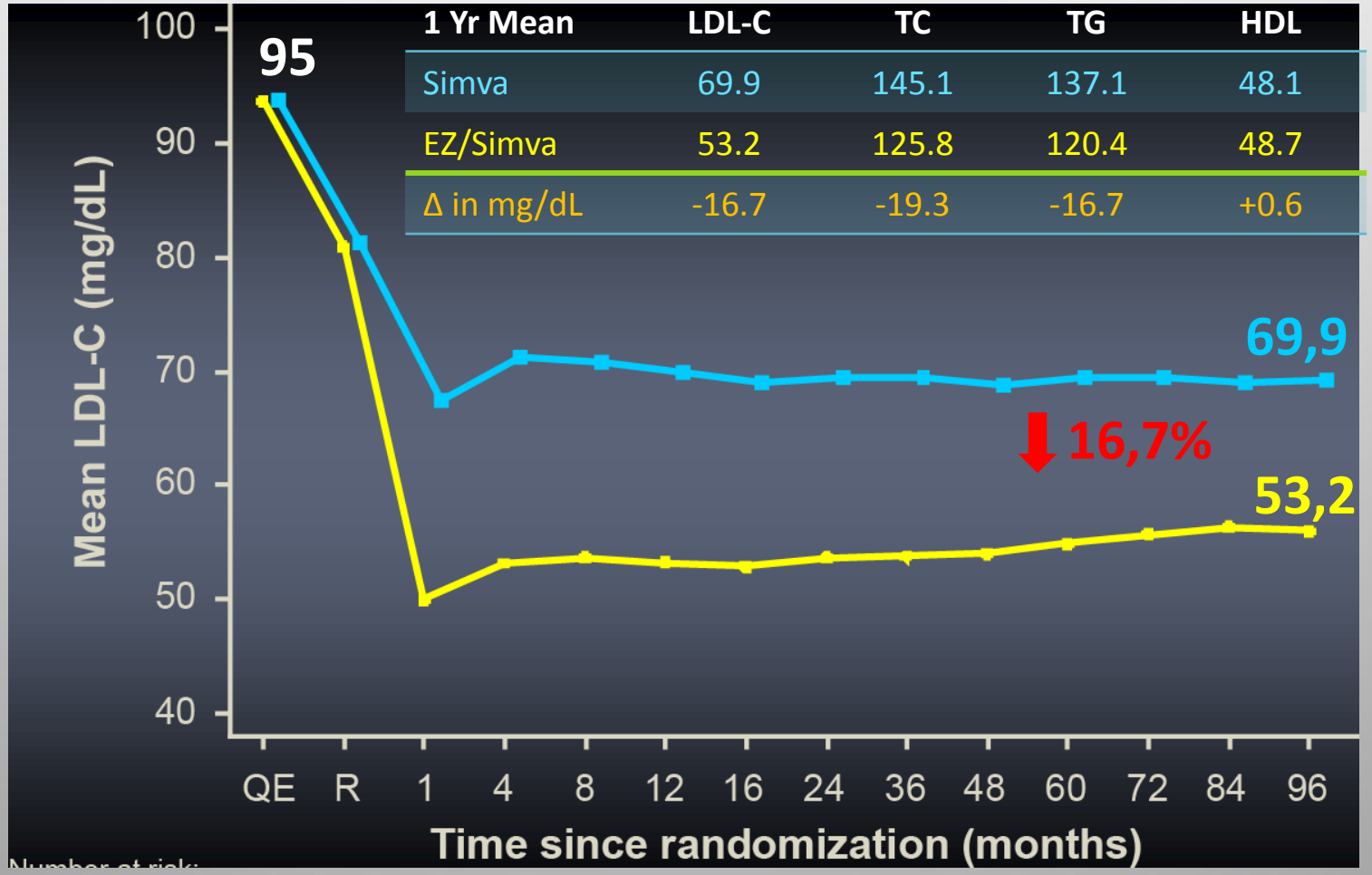




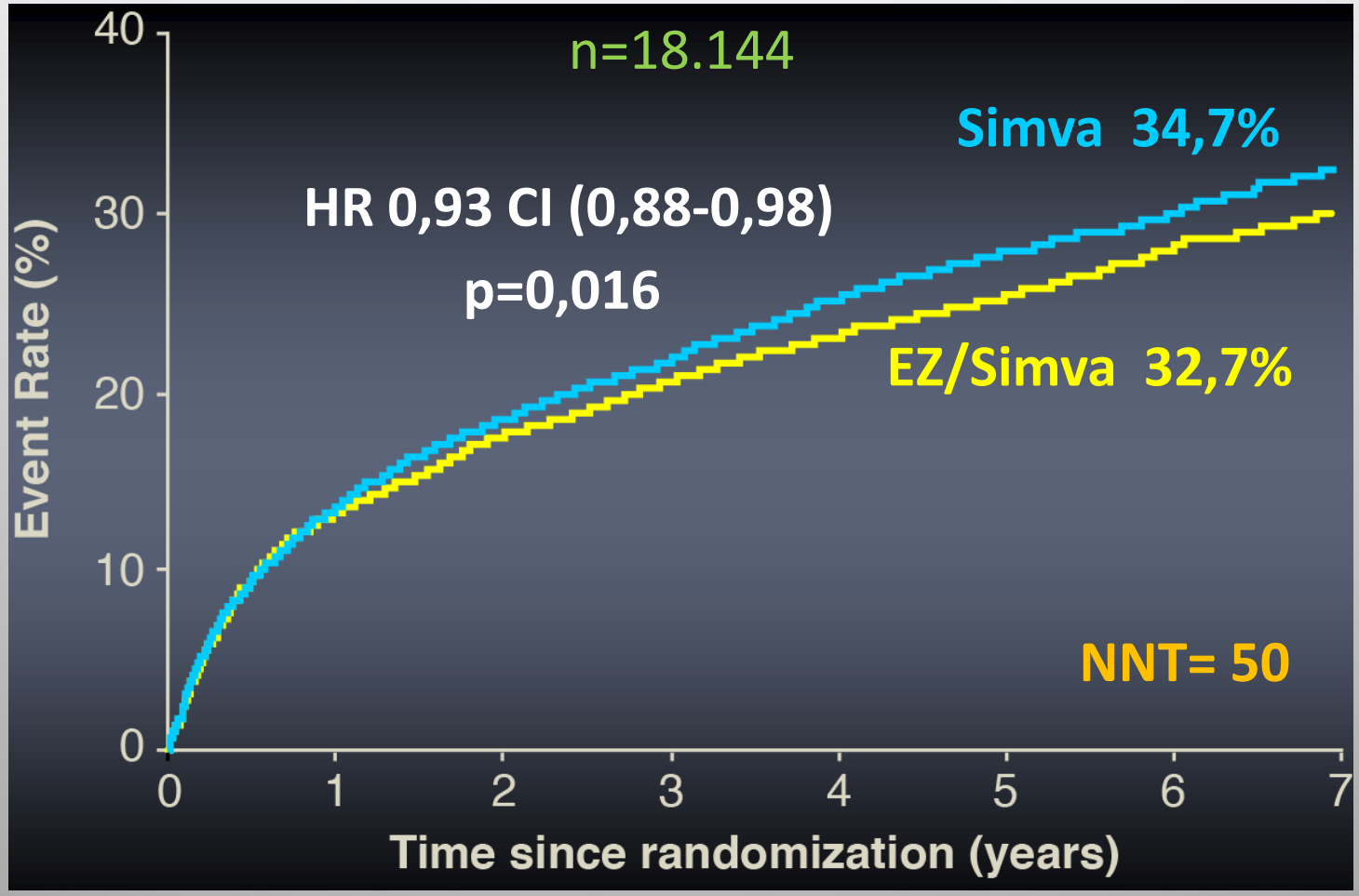
Barter PJ. N Engl J Med 2007; 357:2019-22.

IMPROVE-IT: Cambios lipídicos

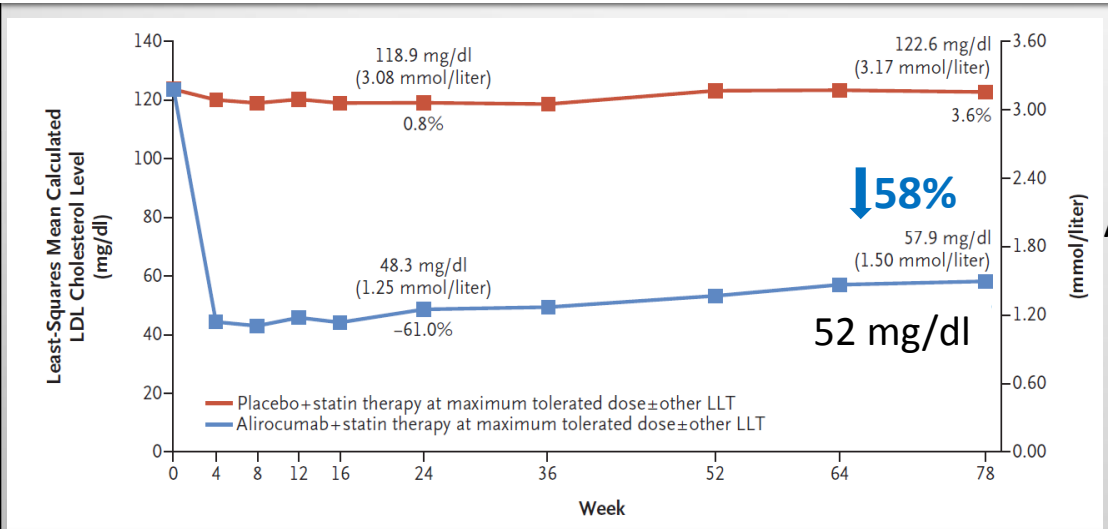
n=18.144



IMPROVE-IT: Resultados



Descenso de cLDL con anti PCSK9



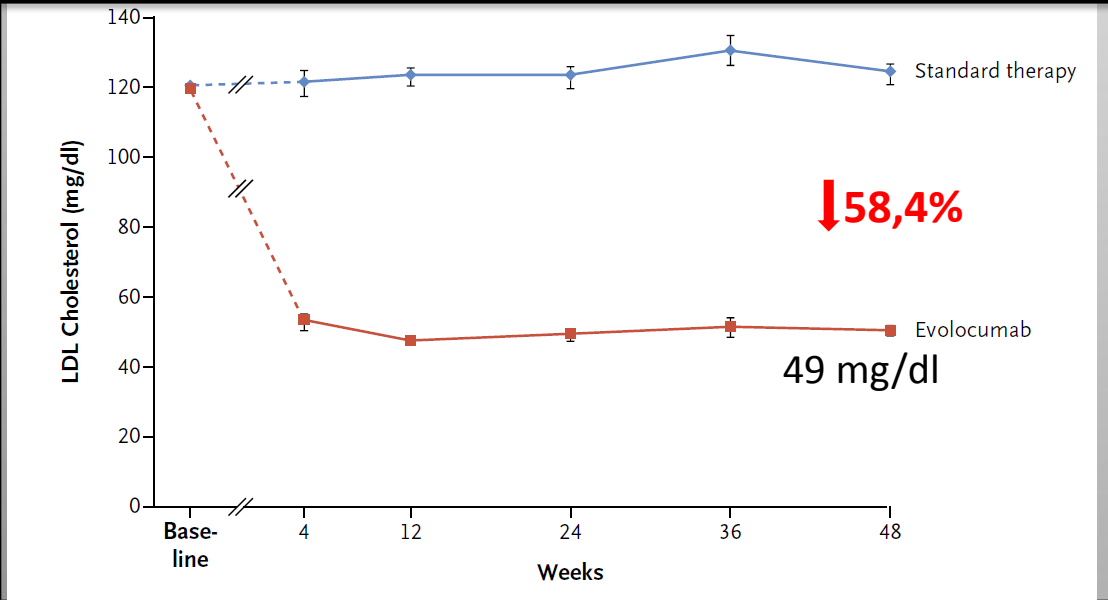
ODISSEY LONG TERM

n=2.314, 2:1

Alirocumab 150 mg/2sem. versus placebo

70 semanas

Robinson JG. NEJM 2015; 372:1489-99.



OSLER

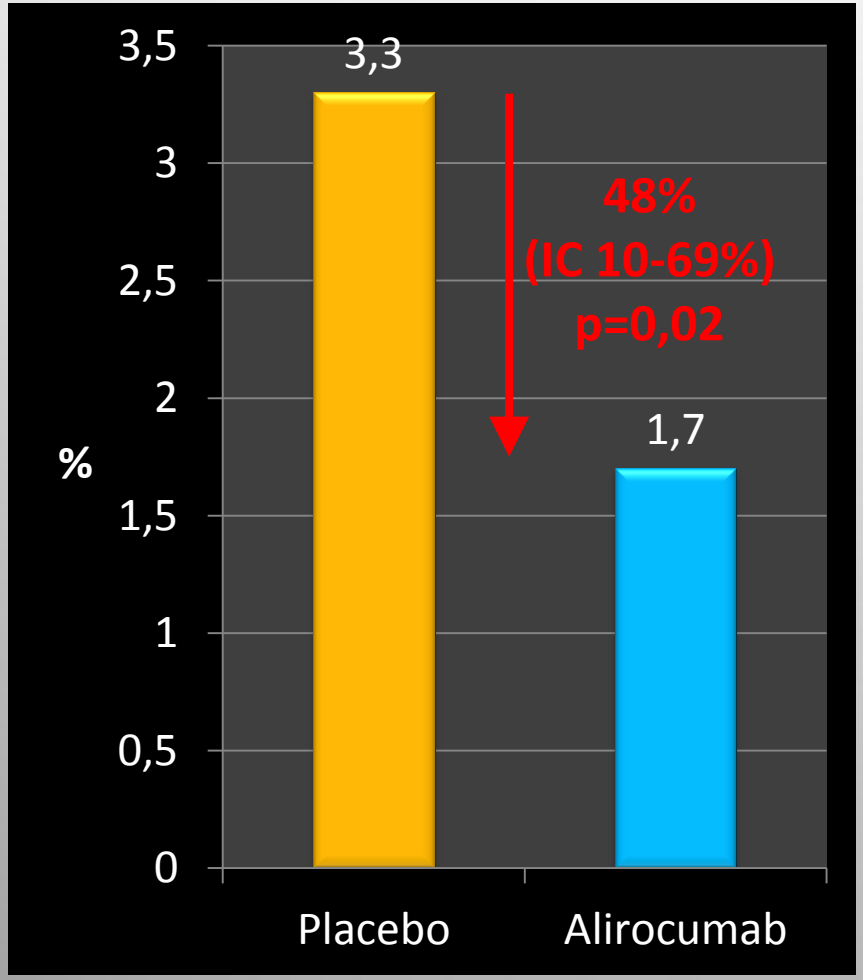
n=4.465, 2:1

Evolocumab 140 mg/2sem. o 420mg/mes. versus placebo

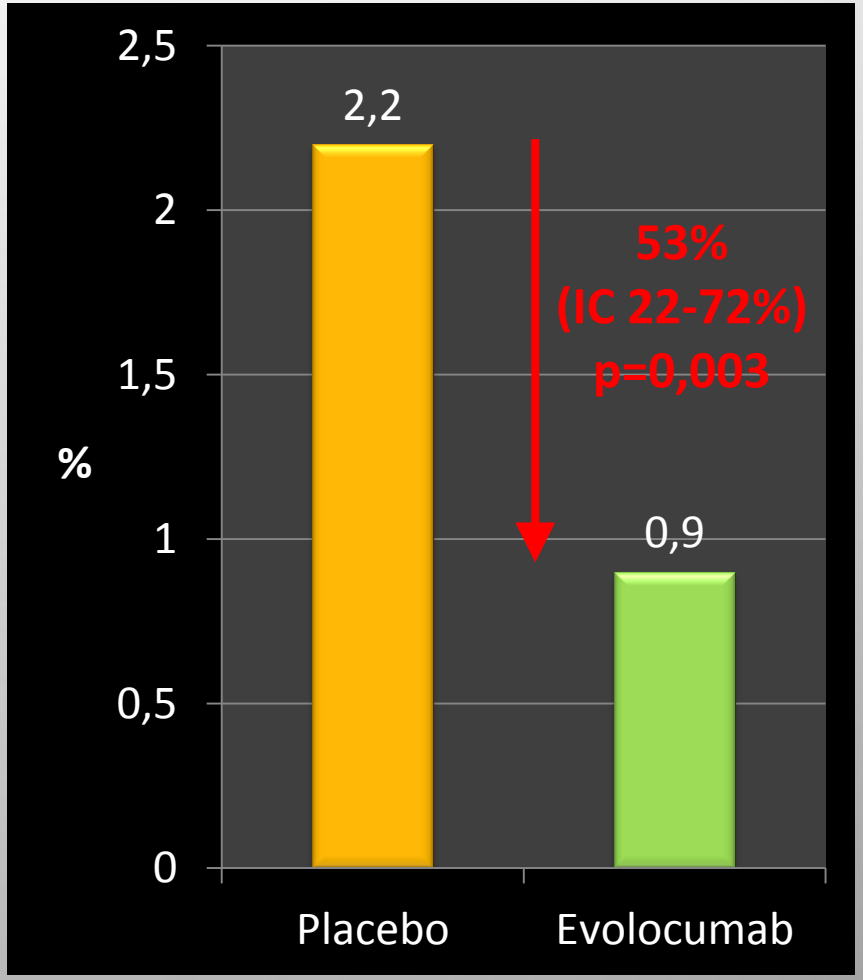
11 meses

Sabatine MS. NEJM 2015; 372:150-9.

Reducción de eventos CV mayores con anti PCSK9



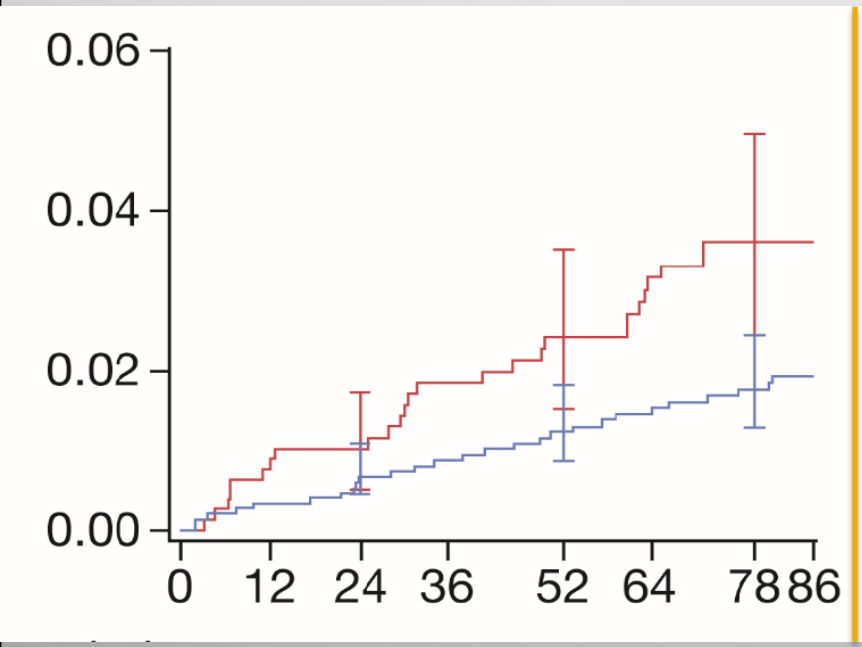
Robinson JG. NEJM 2015;372:1489-99.



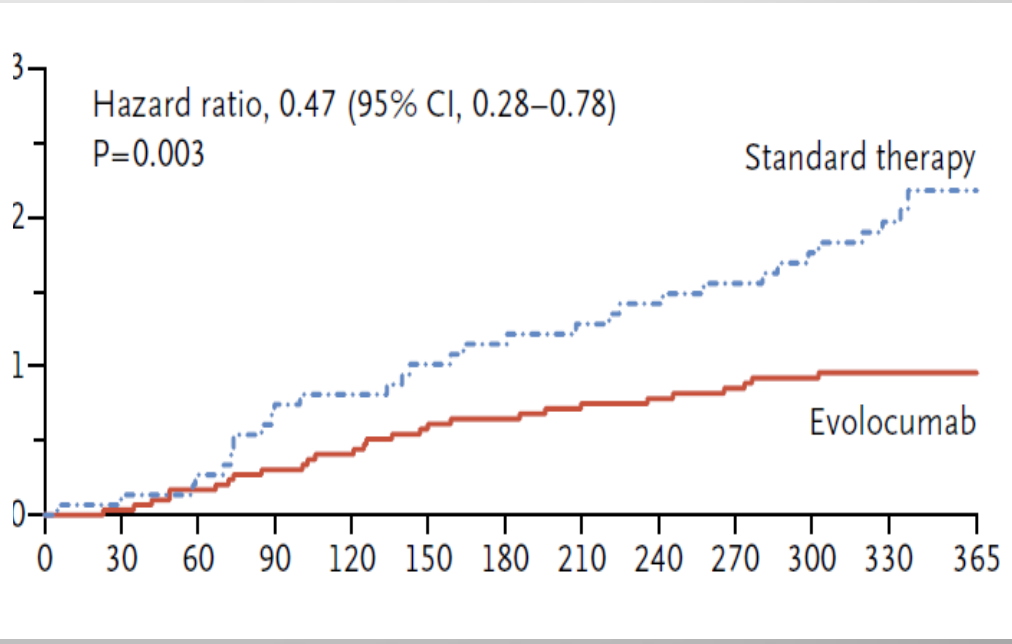
Sabatine MS. NEJM 2015;372;1500-9.

Reducción de eventos CV mayores

n=2.314, 70 semanas



n=4.465. 11 meses



Robinson JG. NEJM 2015;372:1.489-99.
Sabatine MS. NEJM 2015;372:1.500-9.

Eventos adversos con anti PCSK9

Event	Alirocumab (N=1550)	Placebo (N=788)	P Value†
Summary of adverse events — no. of patients (%)			
Any adverse event	1255 (81.0)	650 (82.5)	0.40
Serious adverse event	290 (18.7)	154 (19.5)	0.66
Other adverse events of interest			
General allergic reaction — no. of patients (%)	156 (10.1)	75 (9.5)	0.71
Local injection-site reaction — no. of patients (%)	91 (5.9)	33 (4.2)	0.10
Myalgia — no. of patients (%)	84 (5.4)	23 (2.9)	0.006
Neurologic event — no. of patients (%)§	65 (4.2)	35 (4.4)	0.83
Neurocognitive disorder — no. of patients (%)¶	18 (1.2)	4 (0.5)	0.17
Amnesia	5 (0.3)	0	0.17
Memory impairment	4 (0.3)	1 (0.1)	0.67
Confusional state	4 (0.3)	1 (0.1)	0.67
Ophthalmologic event — no. of patients (%)‖	45 (2.9)	15 (1.9)	0.65
Hemolytic anemia — no. of patients	0	0	NC
Diabetes in patients with no history of diabetes — no. of patients/total no. (%)**	18/994 (1.8)	10/509 (2.0)	0.84
Laboratory values of interest — no. of patients/total no. (%)			
Alanine aminotransferase >3× ULN	28/1533 (1.8)	16/779 (2.1)	0.75
Aspartate aminotransferase >3× ULN	22/1533 (1.4)	18/779 (2.3)	0.13
Creatine kinase >3× ULN	56/1507 (3.7)	38/771 (4.9)	0.18

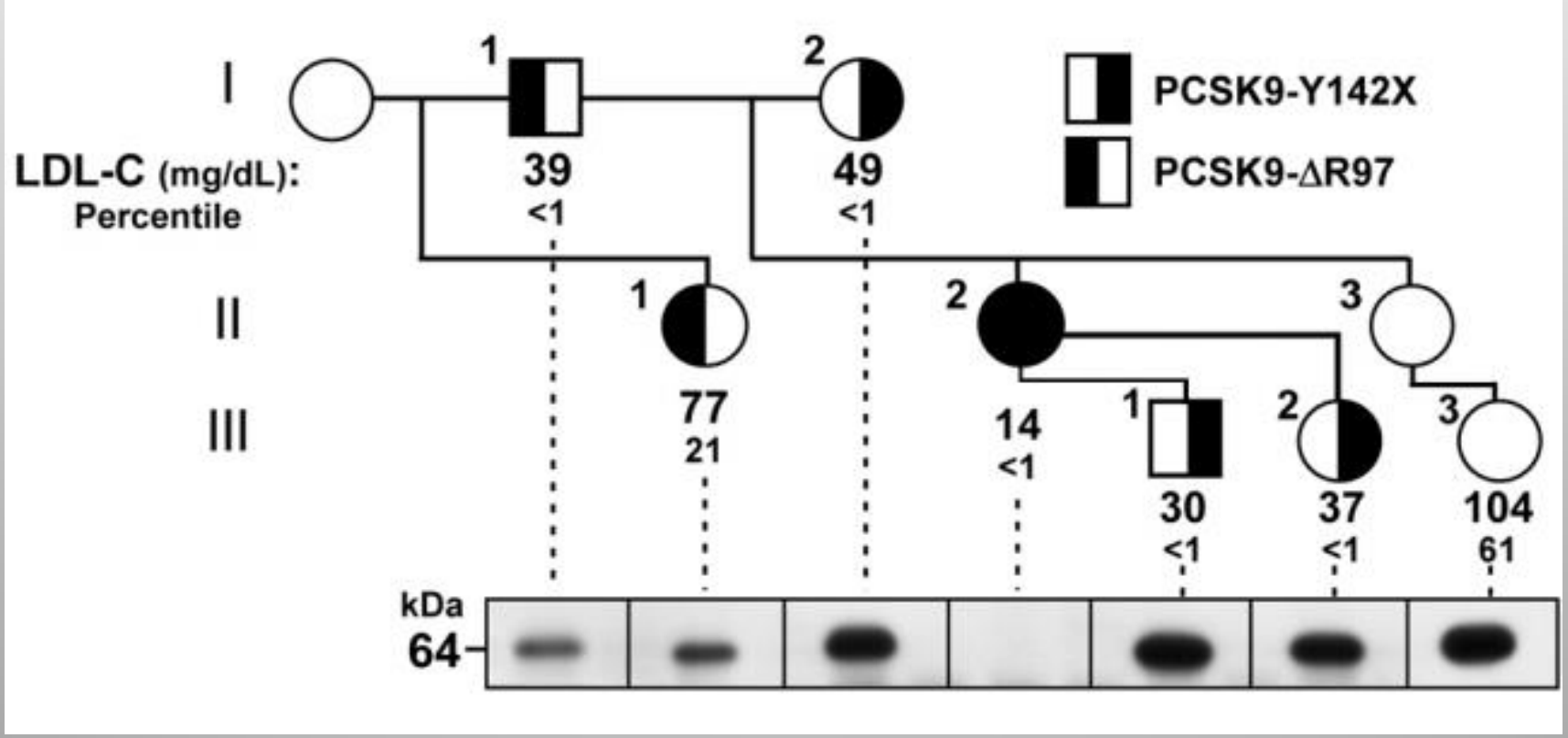
Robinson JG. NEJM 2015;372:1489-99.

Eventos adevrsos con anti PCSK9 según niveles de cLDL alcanzados

Subject incidence, n (%)	Evolocumab subjects stratified by minimum post-baseline (achieved) LDL cholesterol				All evolocumab subjects (N =2976)
	<25 mg/dL (N =773)	25 to <40 mg/dL (N = 759)	<40 mg/dL (N = 1532)	≥40 mg/dL (N= 1426)	
Adverse event	541 (70.0)	517 (68.1)	1058 (69.1)	1000 (70.1)	2060 (69.2)
Serious adverse event	59 (7.6)	52 (6.9)	111 (7.2)	111 (7.8)	222 (7.5)
Muscle-related adverse event	38 (4.9)	54 (7.1)	92 (6.0)	98 (6.9)	190 (6.4)
CK >5× ULN	3 (0.4)	7 (0.9)	10 (0.7)	7 (0.5)	17 (0.6)
ALT/AST >3× ULN	7 (0.9)	6 (0.8)	13 (0.8)	18 (1.3)	31 (1.0)
Neurocognitive adverse event	4 (0.5)	9 (1.2)	13 (0.8)	14 (1.0)	27 (0.9)

Sabatine MS. NEJM 2015;372:1500-9.

Niveles muy bajos de cLDL por mutación en el gen de la PCSK-9



Zhao Z. Am. J. Hum. Genet. 2006;79:514–523.

Conclusiones

- La disminución del cLDL por debajo de los niveles recomendados:
  - Consigue una mayor y significativa reducción de los eventos cardiovasculares.
  - Es segura, al menos en el medio plazo.
- En un futuro próximo habrá que redefinir las recomendaciones ¿Hasta donde?¿A quien? basándose en criterios de eficiencia y seguridad

¡¡Muchas Gracias !!