Tratamiento de la hipercolesterolemia: terapia combinada.

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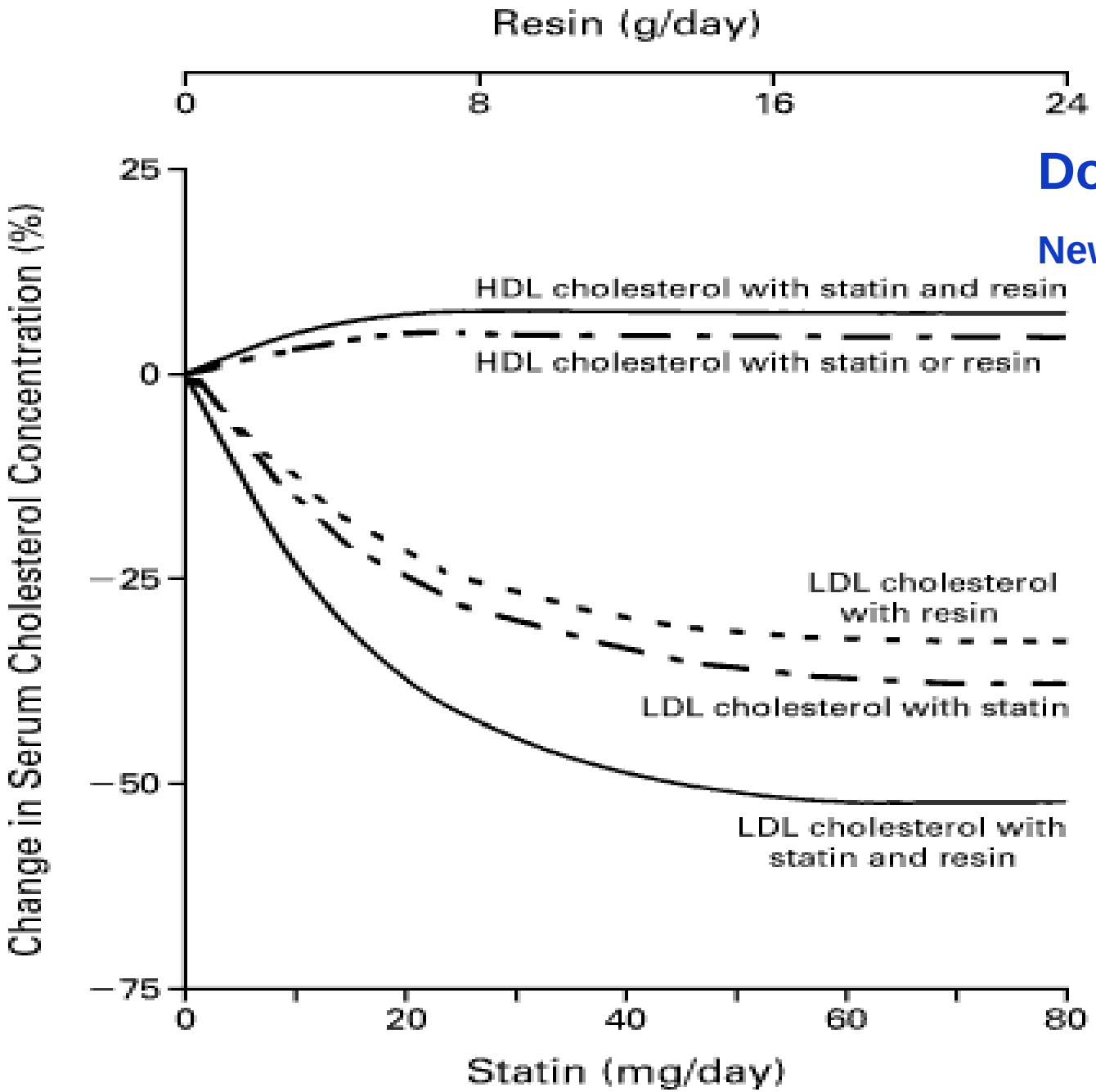
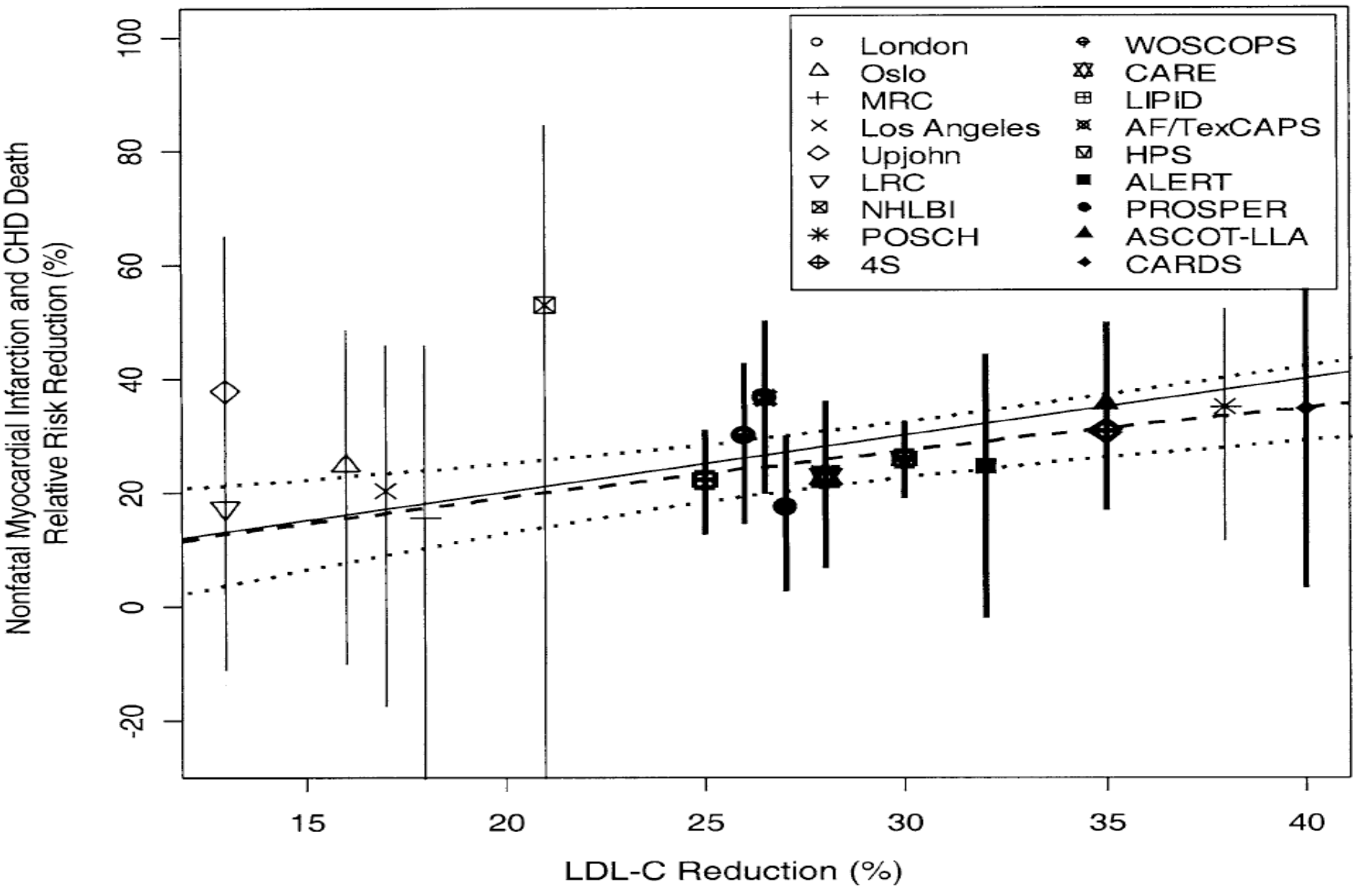
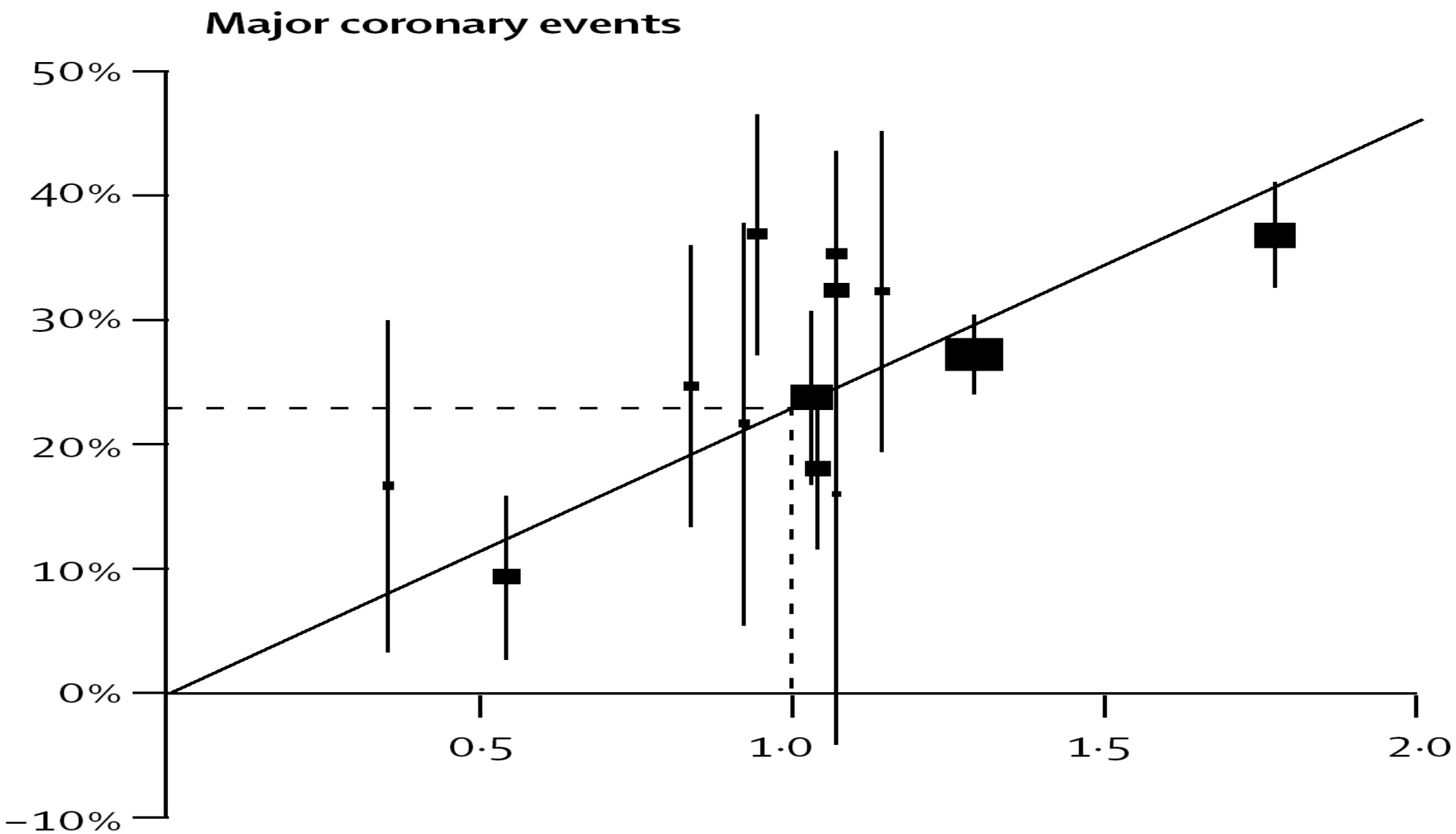


Dose response of statins.

New Eng J Med. 1999; 341: 498-511.

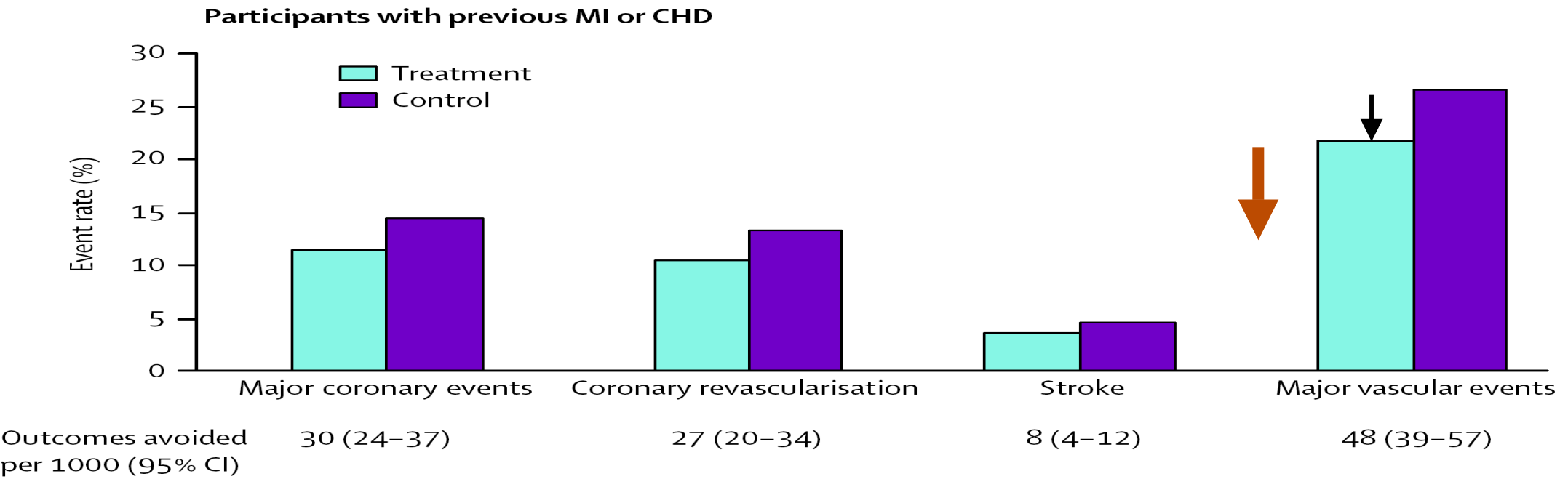
Pleiotropic Effects of Statins: Benefit Beyond Cholesterol Reduction. Robinson J. JACC 2005

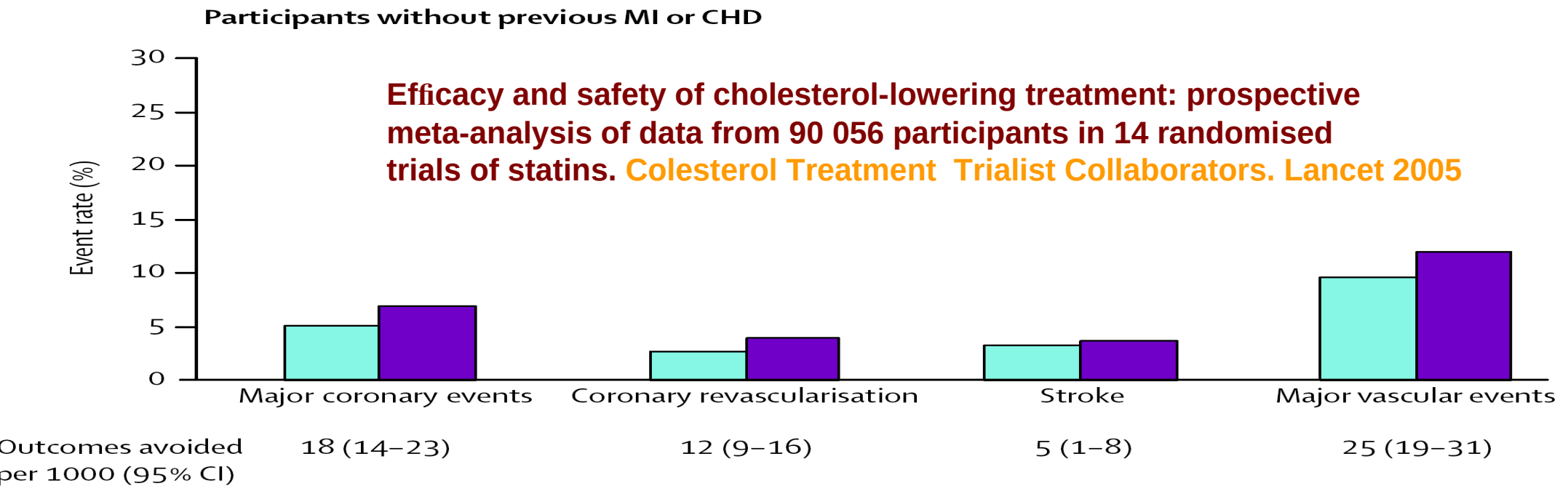




Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins.

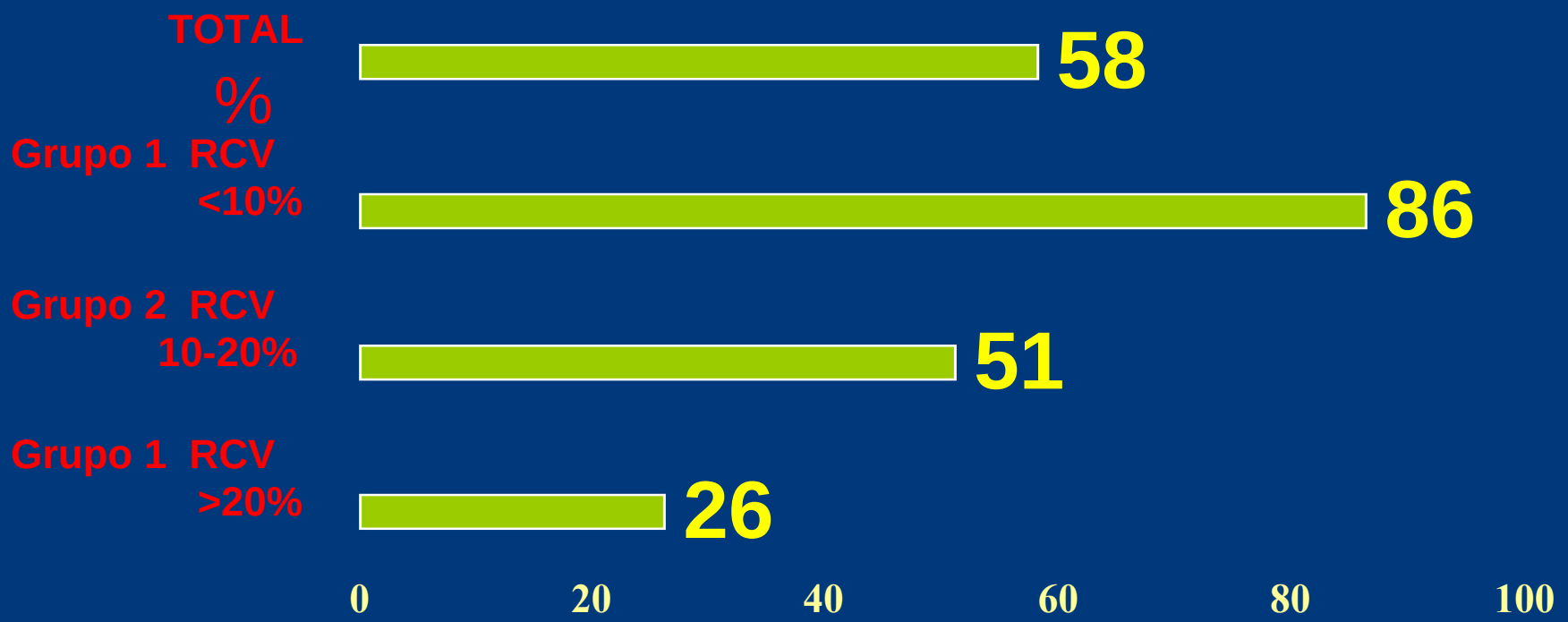
Colesterol Treatment Trialist Collaborators. Lancet 2005.





Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Colesterol Treatment Trialist Collaborators. Lancet 2005

Pacientes que cumplen los objetivos de C-LDL (NCEP-ATP III) (1811 pacientes)



Med Clin (Barc) 2003;121:527-31

Meta-Analysis of Cardiovascular Outcomes Trials Comparing Intensive Versus Moderate Statin Therapy.

Cannon C et al. J Am Coll Cardiol 2006.

Table 1. Trial Design and Baseline Characteristics of the Four Trials Included in the Meta-Analysis

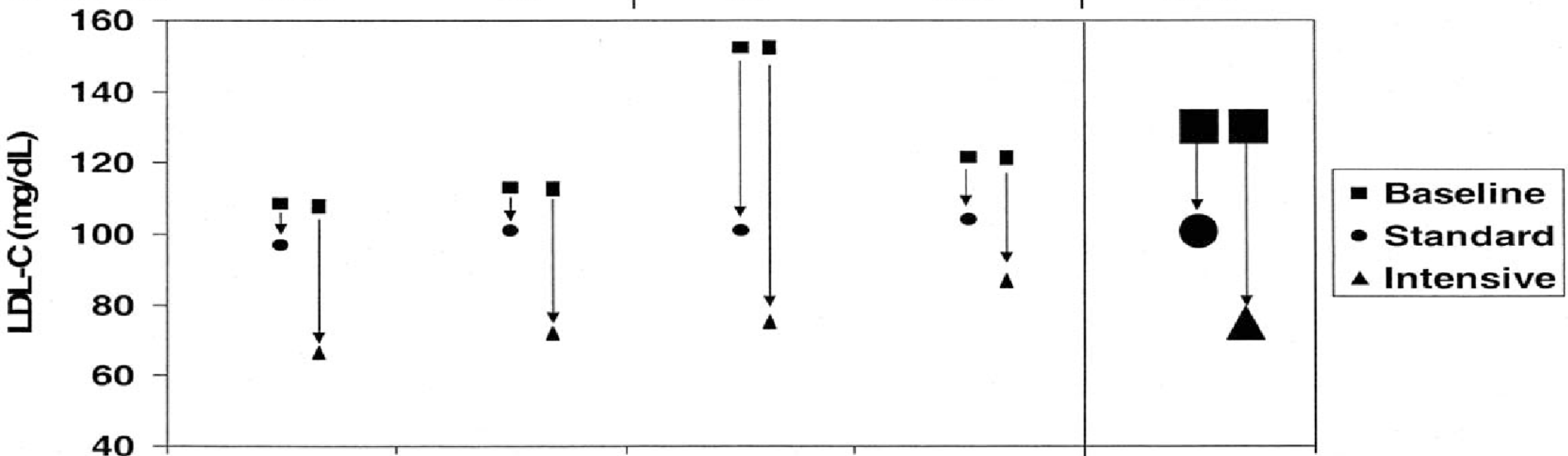
	PROVE IT–TIMI-22 (2)	A-to-Z (4)	TNT (3)	IDEAL (5)
n	4,162	4,497	10,001	8,888
Population	Post-ACS	Post-ACS	Stable CAD	Stable CAD
Treatment arms	40 mg pravastatin vs. 80 mg atorvastatin	Placebo (4 months) then 20 mg simvastatin vs. 40 mg simvastatin (1 month) then 80 mg simvastatin	10 mg atorvastatin vs. 80 mg atorvastatin	20 mg simvastatin vs. 80 mg atorvastatin
Duration	24 months (mean)	721 days (median)	4.9 yrs (median)	4.8 yrs (median)
Run-in	None	None	10 mg atorvastatin (8 weeks) per guidelines	None
Primary end point	Death, MI, UA requiring hospitalization, revascularization (>30 days), stroke	CV death, MI, readmission for ACS, stroke	CHD death, Non–procedure-related MI, resuscitation after cardiac arrest, stroke	CHD death, MI, cardiac arrest with resuscitation

A to Z = Aggrastat to Zocor trial; ACS = acute coronary syndrome; CAD = coronary artery disease; CHD = congenital heart disease; CV = cardiovascular; IDEAL = Incremental Decrease in End Points Through Aggressive Lipid-Lowering trial; MI = myocardial infarction; PROVE IT–TIMI-22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction trial; TNT = Treating to New Targets trial; UA = unstable angina.

Meta-Analysis of Cardiovascular Outcomes Trials Comparing Intensive Versus Moderate Statin Therapy.

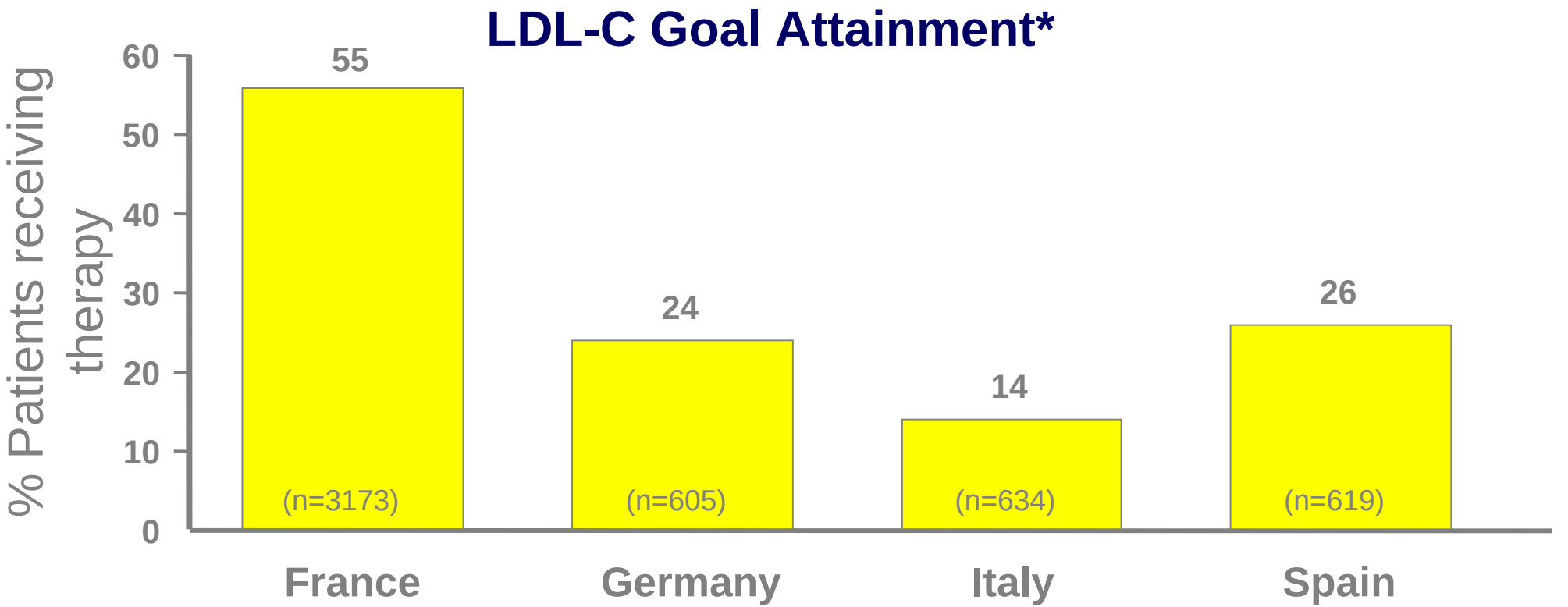
Cannon C et al. J Am Coll Cardiol 2006.

Patients	ACS		Stable CAD		Pooled
n	4162	4497	10001	8888	27548
Prior Statin Use	25.2%	0%	0%	75.5%	28.2%



	PROVE IT-TIMI 22	A-to-Z	TNT	IDEAL	Pooled*
Baseline	108	113	152	122	130
Standard	97	101	101	104	101
Intensive	65	69	77	81	75

Cholesterol Goal Attainment in the Real World: The REALITY Study



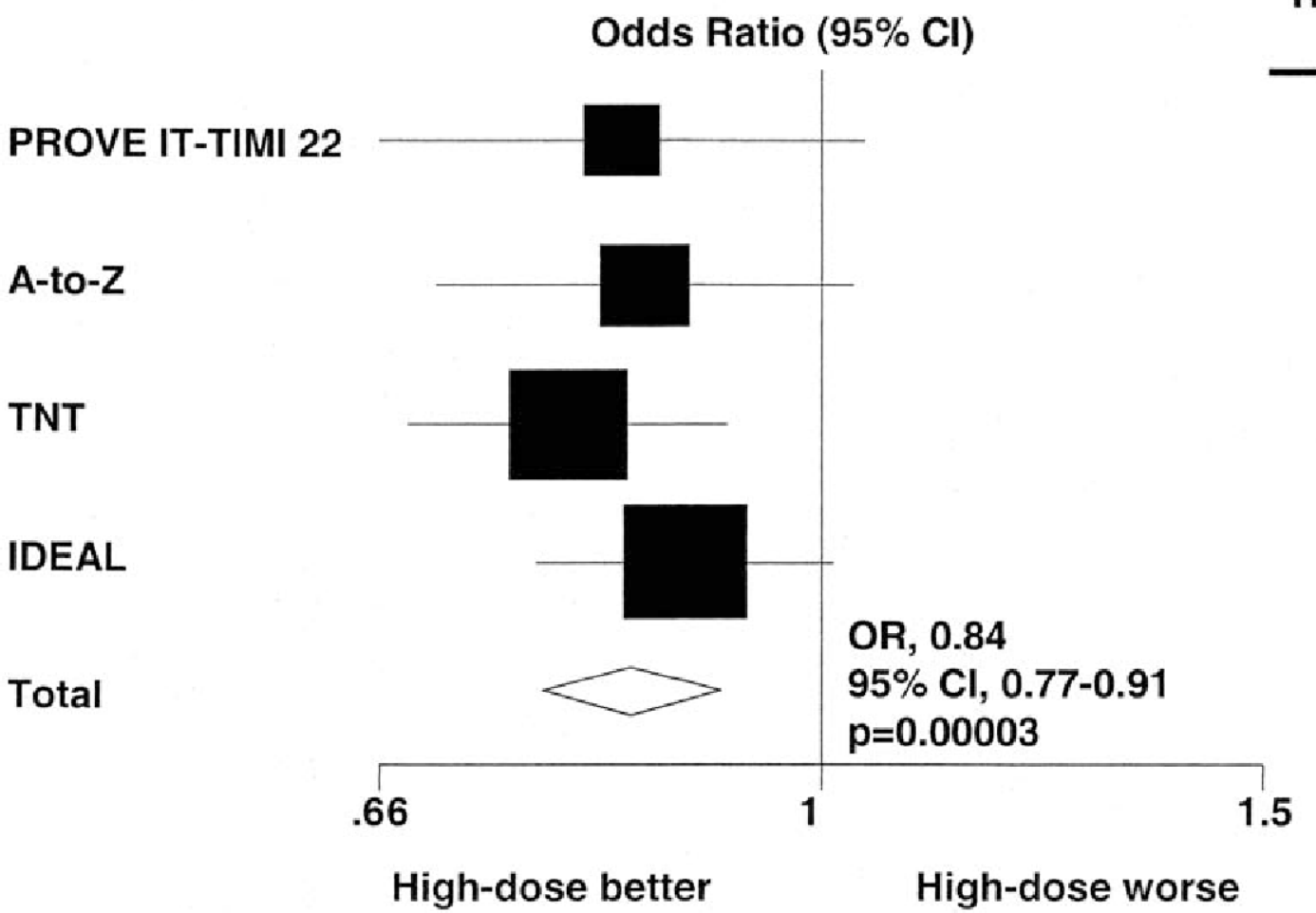
*LDL-C goal of <100 mg/dl (<2.6 mmol/L) per NCEP Adult Treatment Panel III (ATP III) guidelines

Adapted from Van Ganse E et al *Curr Med Res Opin* 2005;21(9):1389–1399.

Meta-Analysis of Cardiovascular Outcomes Trials Comparing Intensive Versus Moderate Statin Therapy.

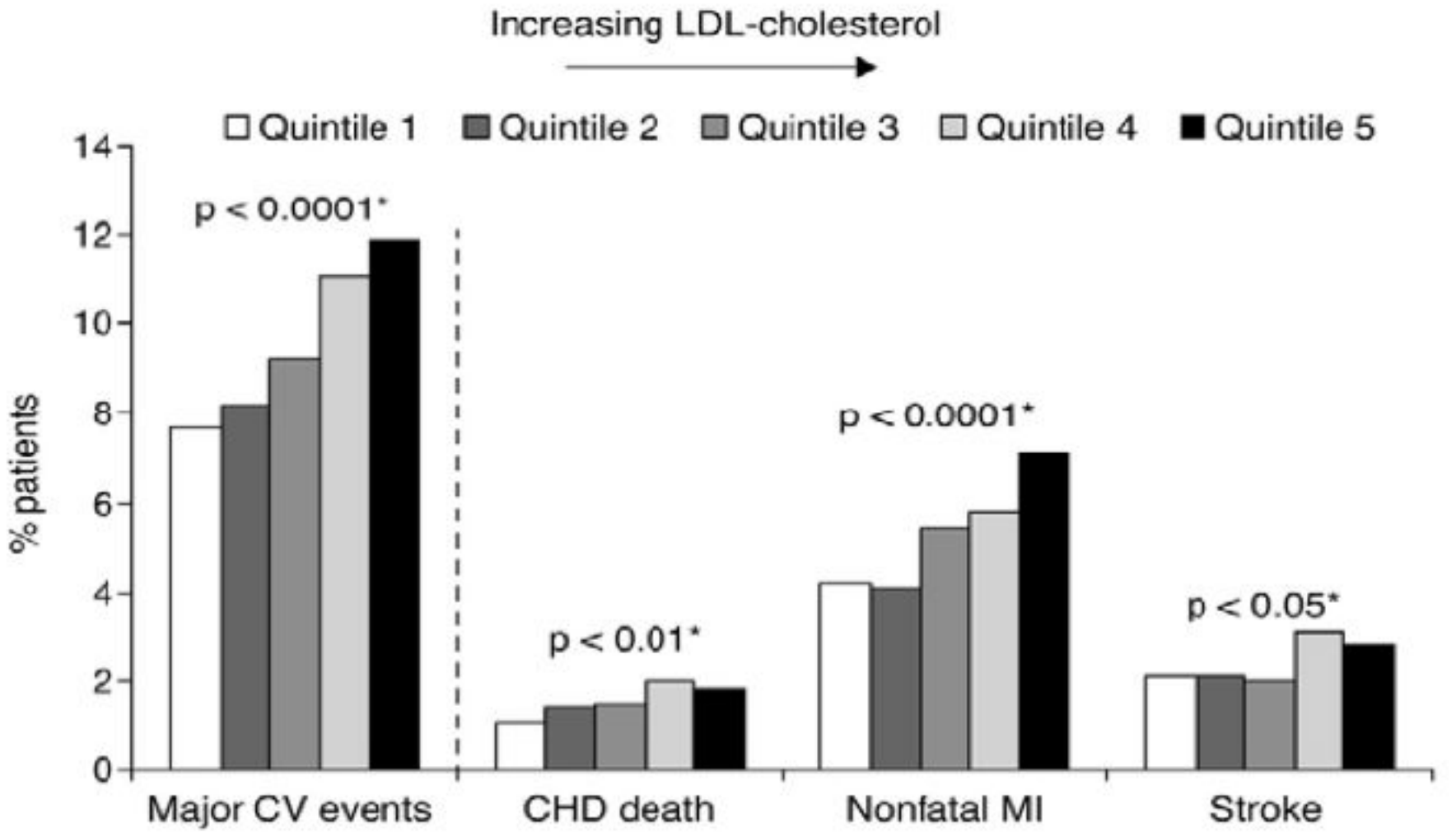
Cannon C et al. J Am Coll Cardiol 2006.

Coronary death or MI.



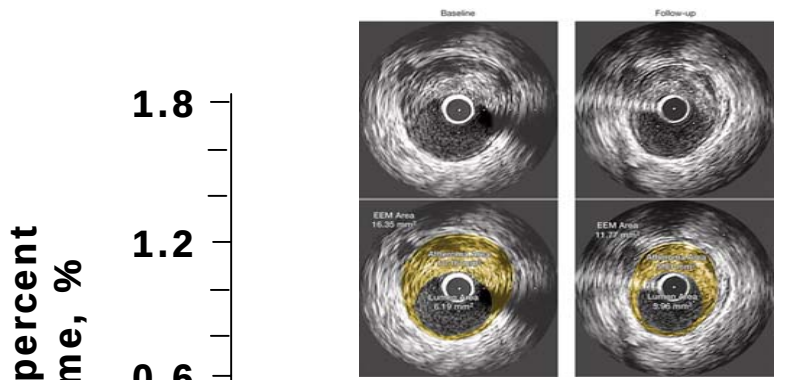
	Odds Reduction	Event Rates No./Total (%) High Dose	Event Rates No./Total (%) Std Dose
PROVE IT-TIMI 22	-17%	147/2099 (7.0)	172/2063 (8.3)
A-to-Z	-15%	205/2265 (9.1)	235/2232 (10.5)
TNT	-21%	334/4995 (6.7)	418/5006 (8.3)
IDEAL	-12%	411/4439 (9.3)	463/4449 (10.4)
Total	-16%	1097/13798 (8.0)	1288/13750 (9.4)

Safety and Efficacy of Atorvastatin-Induced Very Low-Density Lipoprotein Cholesterol Levels in Patients With Coronary Heart Disease (a Post Hoc Analysis of the Treating to New Targets [TNT] Study). La Rosa et al. Am J Cardiol 2007;100:747.



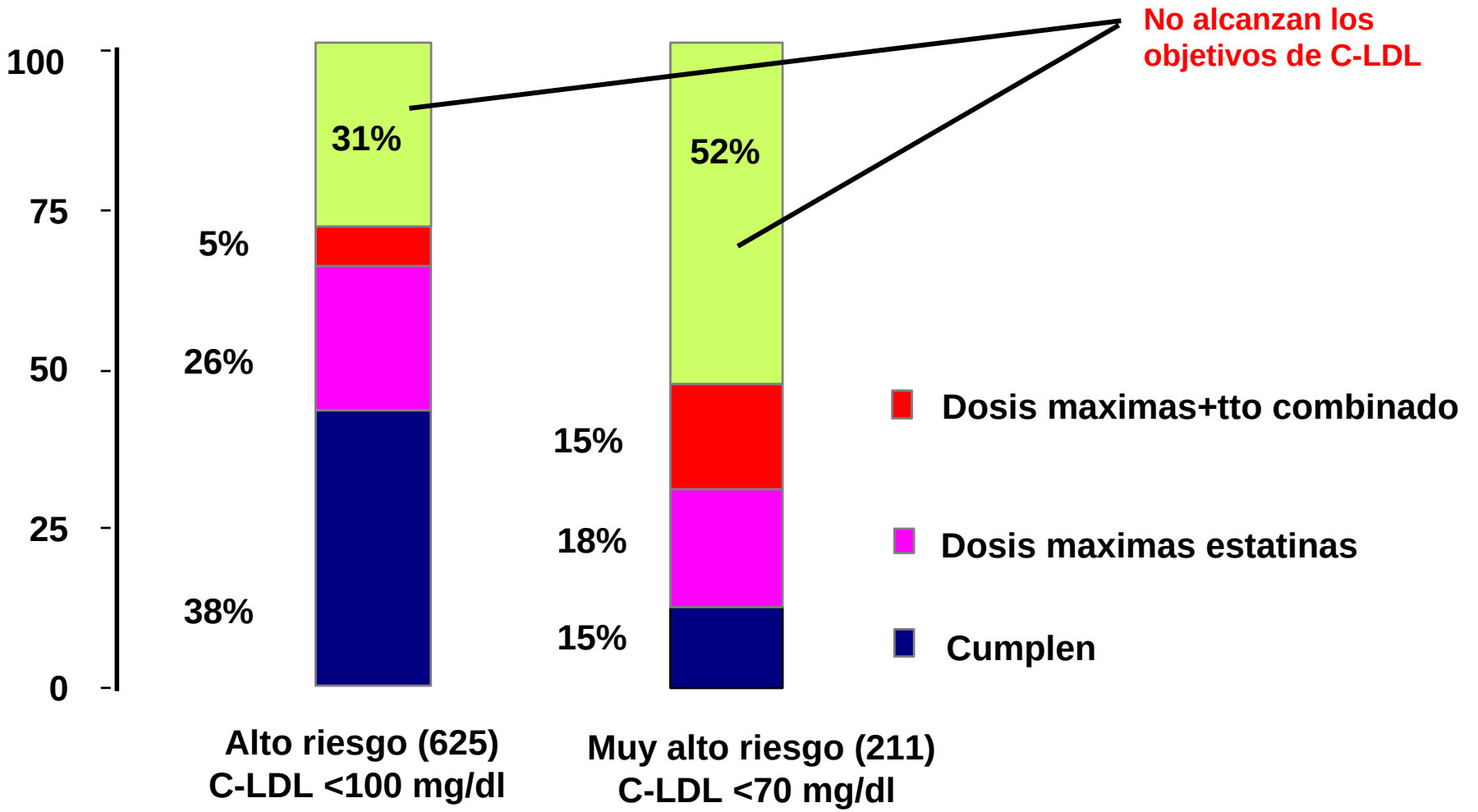
*p-value for trend across LDL-C

Relationship between mean LDL-C levels and median change in percent atheroma volume for several intravascular ultrasound trials



Nissen SE, et al. *JAMA* 2006

Objetivos del tratamiento hipolipemiante en pacientes de alto riesgo, y muy alto riesgo cardiovascular. ¿Un reto posible?.



Rev Clin Esp 2006;206:417

ASTEROID:Lipid results (mean values)

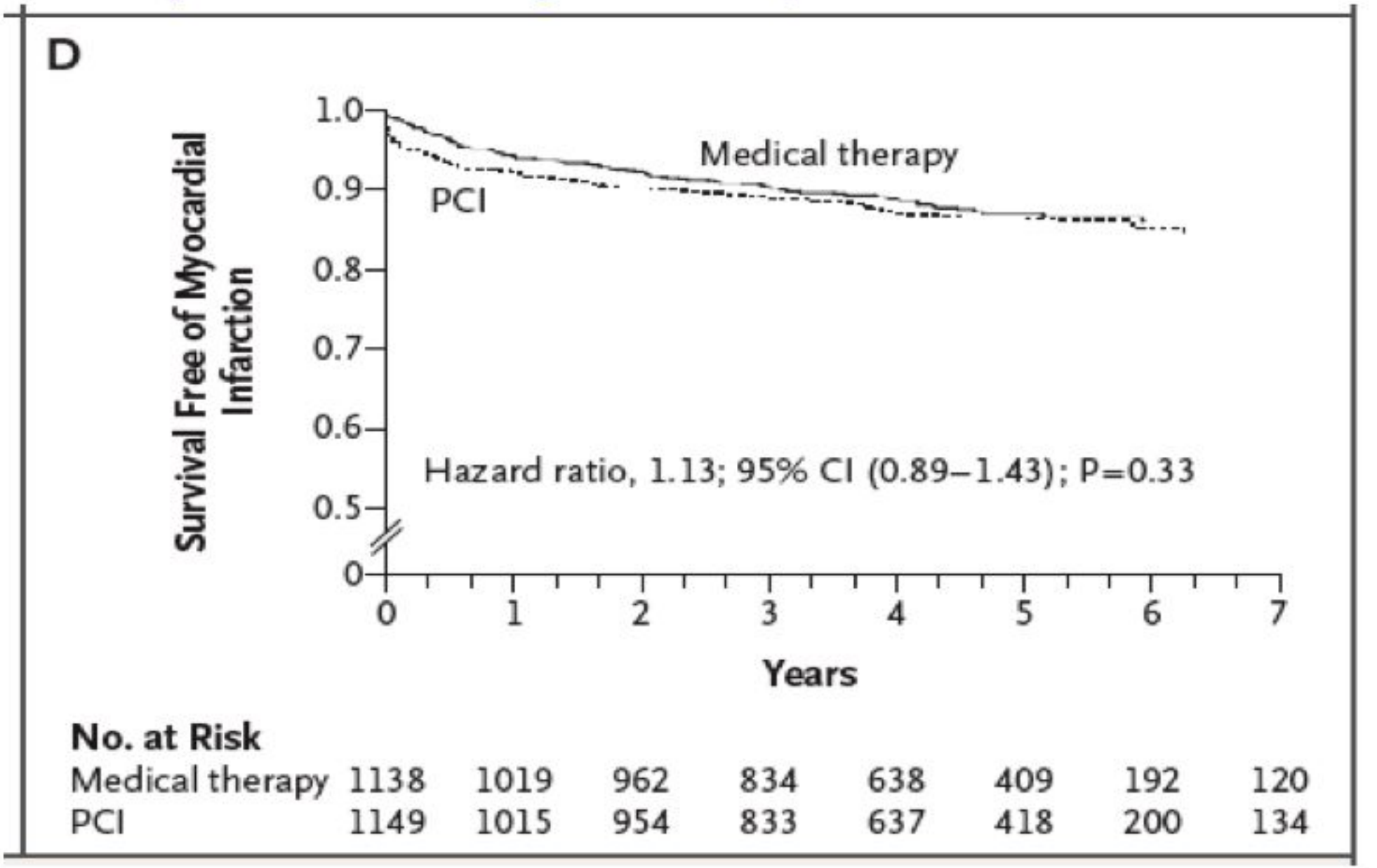
	Baseline	After 24 months of treatment	% change*
Total cholesterol (mg/dL)	204	133.8	–33.8
LDL-C (mg/dL)	130.4	60.8	–53.2
HDL-C (mg/dL)	43.1	49.0	+14.7
Triglycerides (mg/dL)	152.2	121.2	-14.5
LDL-C/HDL-C ratio	3.2	1.3	–58.5

*p<0.001 for all comparisons between baseline and during treatment

- Average decrease in volume (p=0.001)

Nissen SE, et al. *JAMA* 2006;295:1556.

Optimal Medical Therapy with or without PCI for Stable Coronary Disease. Courage trial. N Engl J Med 2007;356:1503-16.



No. at Risk

Medical therapy	1138	1019	962	834	638	409	192	120
PCI	1149	1015	954	833	637	418	200	134

Optimal Medical Therapy with or without PCI for Stable Coronary Disease. Courage trial. N Engl J Med 2007;356:1503-16.

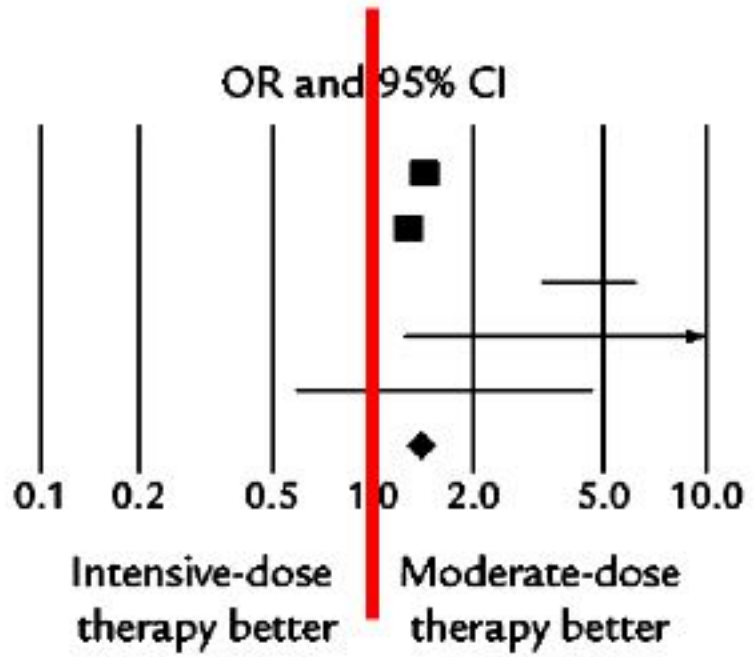
Table 2. Clinical Status, Risk and Lifestyle Factors, and Use of Medication.*

Variable	PCI Group (N=1149)				Medical-Therapy Group (N=1138)			
	Baseline	1 Yr	3 Yr	5 Yr	Baseline	1 Yr	3 Yr	5 Yr
	median ±SE							
Clinical status								
No. evaluated	1148	1031	820	423	1137	1010	824	406
Blood pressure — mm Hg								
Systolic	131±0.77	126±0.64	125±0.68	124±0.81	130±0.66	124±0.73	123±0.78	122±0.92
Diastolic	74±0.33	72±0.35	70±0.52	70±0.81	74±0.33	70±0.43	70±0.52	70±0.65
Cholesterol — mg/dl								
Total	172±1.37	156±1.17	148±1.13	143±1.74	177±1.41	150±1.10	145±1.30	140±1.64
HDL	39±0.39	42±0.39	43±0.47	41±0.67	39±0.37	41±0.42	42±0.49	41±0.75
LDL	100±1.17	84±0.97	76±0.85	71±1.83	102±1.22	81±0.86	74±0.92	72±1.21
Triglycerides — mg/dl	143±2.96	129±2.74	124±2.79	123±4.13	149±3.03	133±2.90	126±2.84	131±4.70

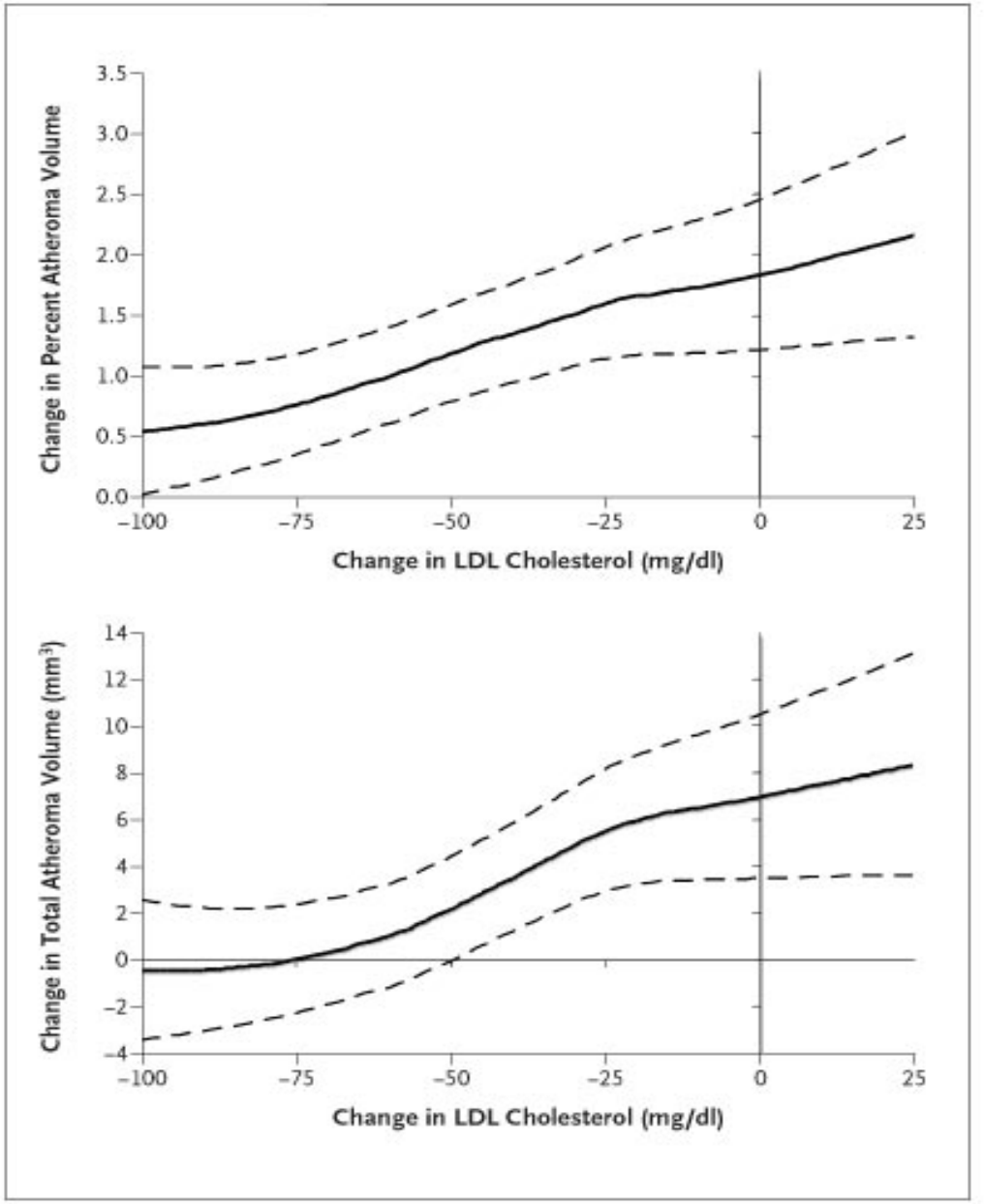
Terapia combinada 8% 49% 8% 54%

Meta-Analysis of Drug-Induced Adverse Events Associated with Intensive-Dose Statin Therapy

Drug-Induced AEs	OR	95% CI	*Z*	*P*
Any AE	1.437	1.329–1.553	9.131	<0.001
Any AE requiring statin discontinuation	1.282	1.182–1.390	6.008	<0.001
LFT abnormalities (AST/ALT ≥3 × ULN)	4.484	3.265–6.159	9.268	<0.001
CK ≥10 × ULN	9.972	1.276–77.919	2.192	0.028
Rhabdomyolysis	1.661	0.604–4.570	0.983	0.326
Overall	1.413	1.337–1.493	12.287	<0.001



Silva M et al. Clinical Therapeutics 2007; 2:253



Nissen, S. E. et al. N Engl J Med 2005;352:29-38

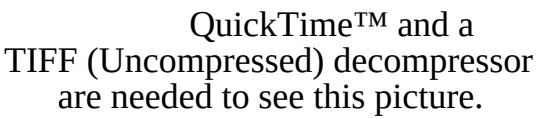
LDL-C target in five years

Prediction

- **An LDL-C of 50 mg/dL in a high-risk population**
- **An LDL-C of 75 mg/dL in a lower-risk population**

Valentin Fuster

Lancet 2006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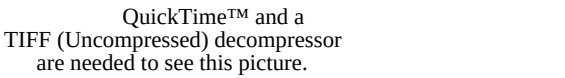
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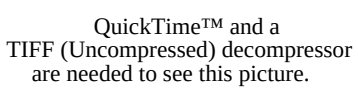
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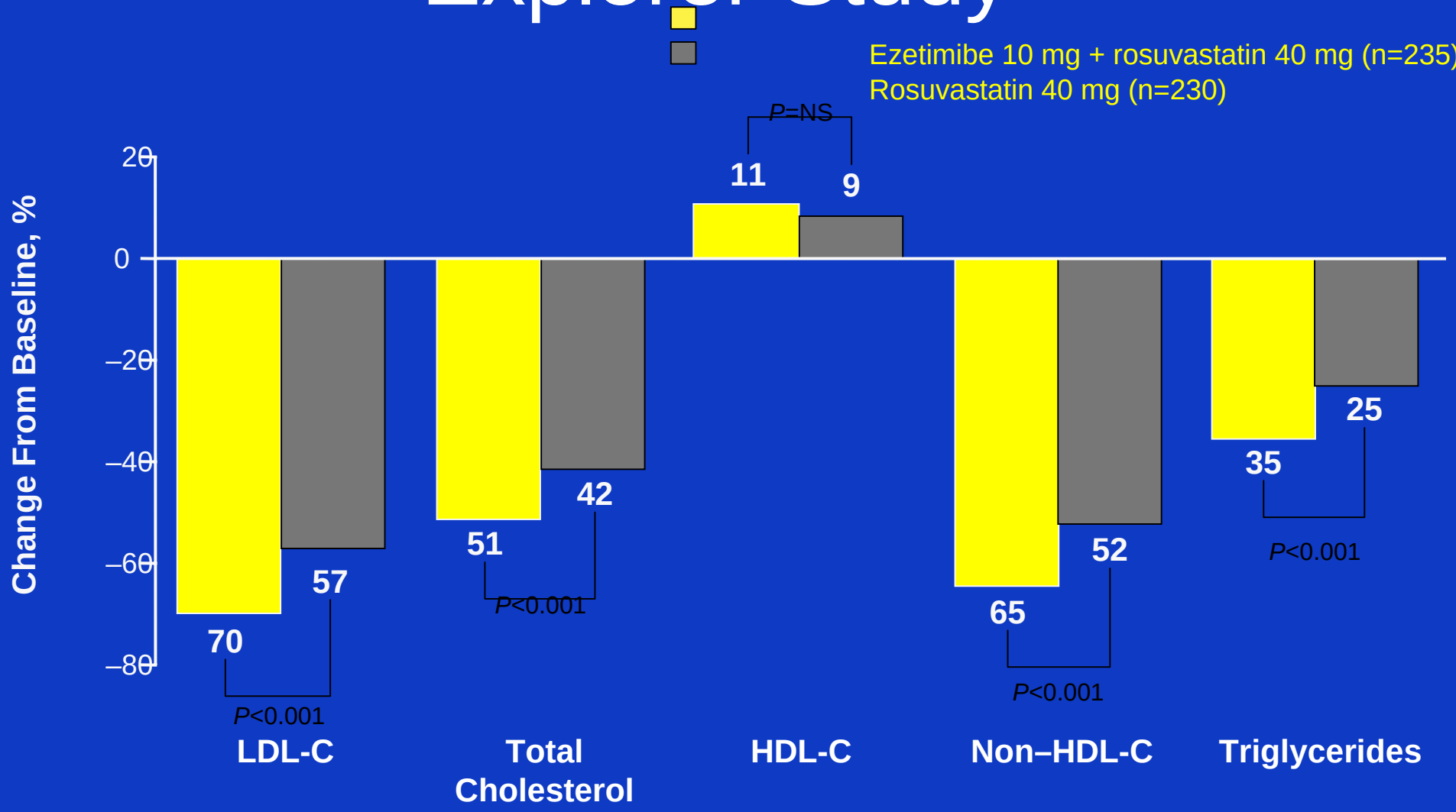
Terapia combinada:

la norma en pacientes

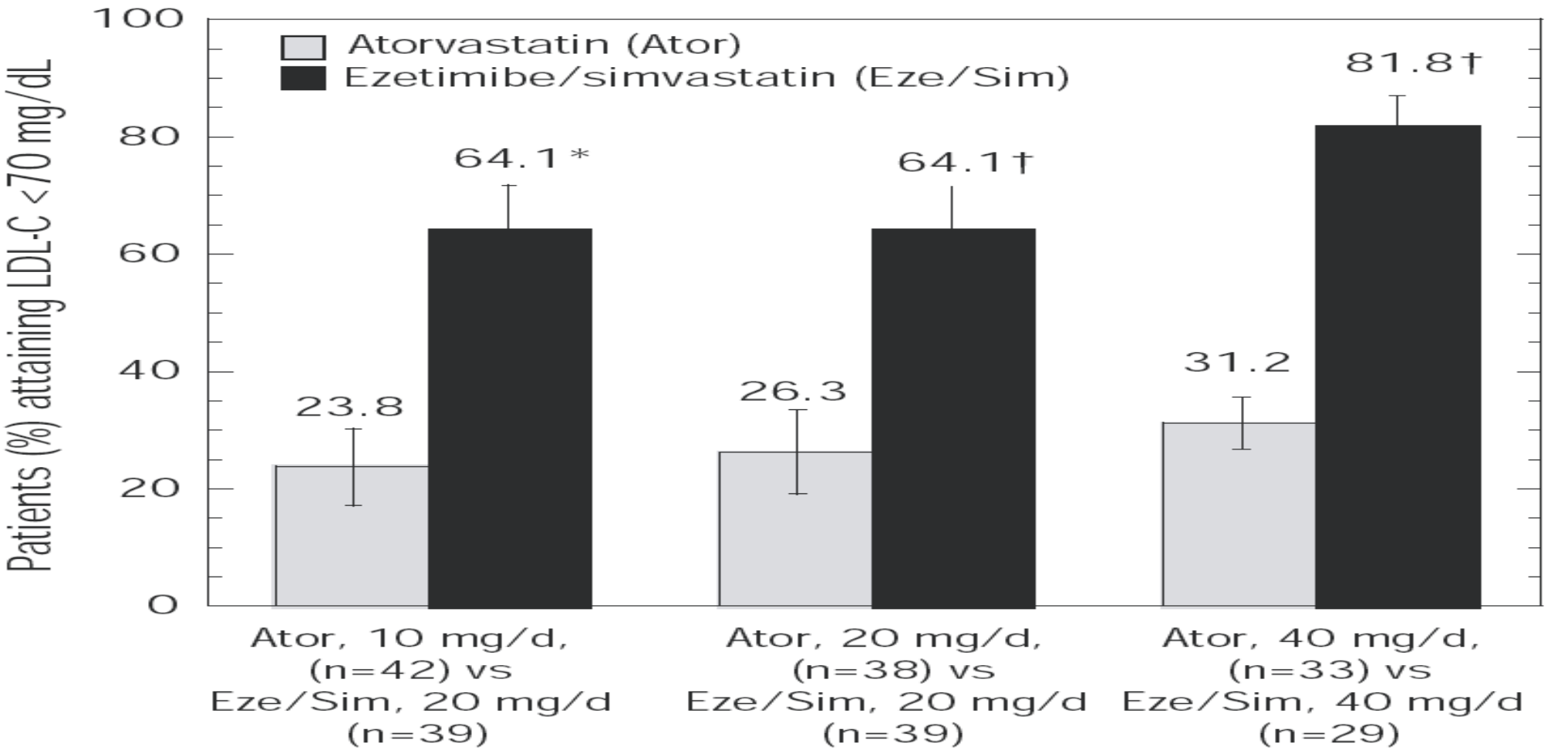
de alto riesgo.

Effects on LDL-C and Other Lipids. Explorer Study

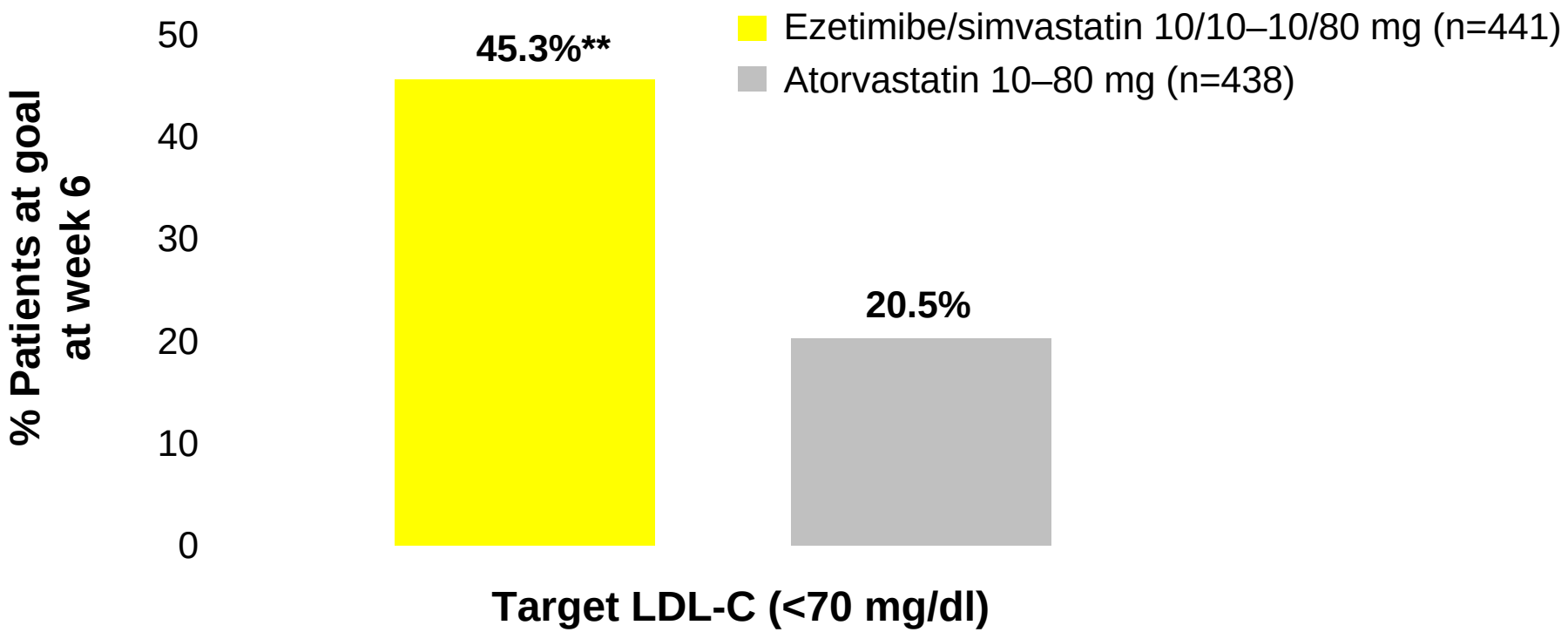


Adapted from Ballantyne CM, et al. *Am J Cardiol*. 2007;99:673–680.

Ezetimibe/Simvastatin vs Atorvastatin in Patients With Type 2 Diabetes Mellitus and Hypercholesterolemia: The VYTAL Study. Mayo Clin Proc 2006



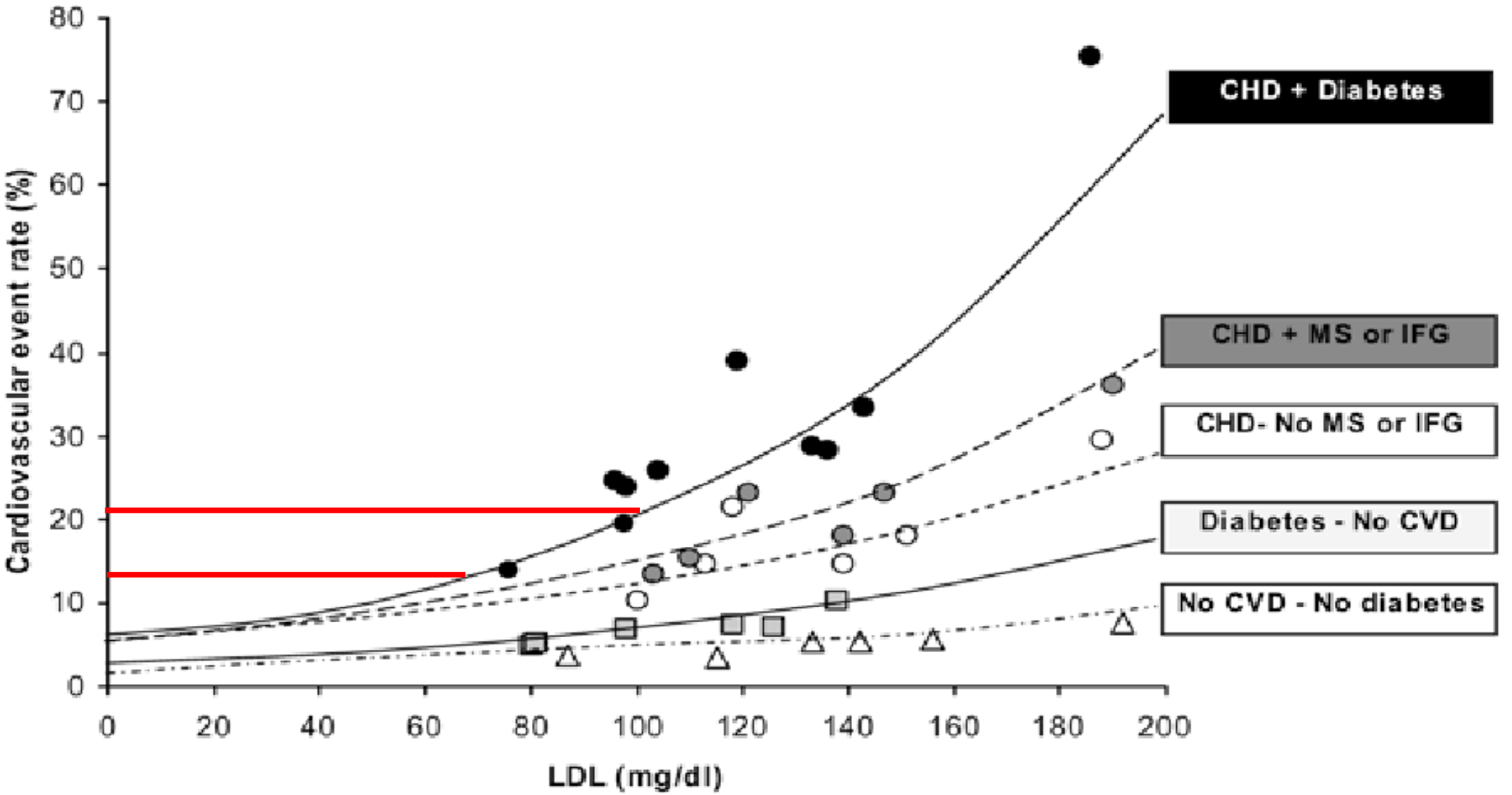
Superior Goal Attainment (LDL-C <70 mg/dl) in High-Risk Patients*



*Patients with CHD or CHD risk equivalent
**p<0.001 vs. atorvastatin

Adapted from Ballantyne CM et al *Am Heart J* 2005;149:464–473.

Identifying Patients for Aggressive Cholesterol Lowering: The Risk Curve Concept. *Robinson, Am J Cardiol 2006*



Conclusiones

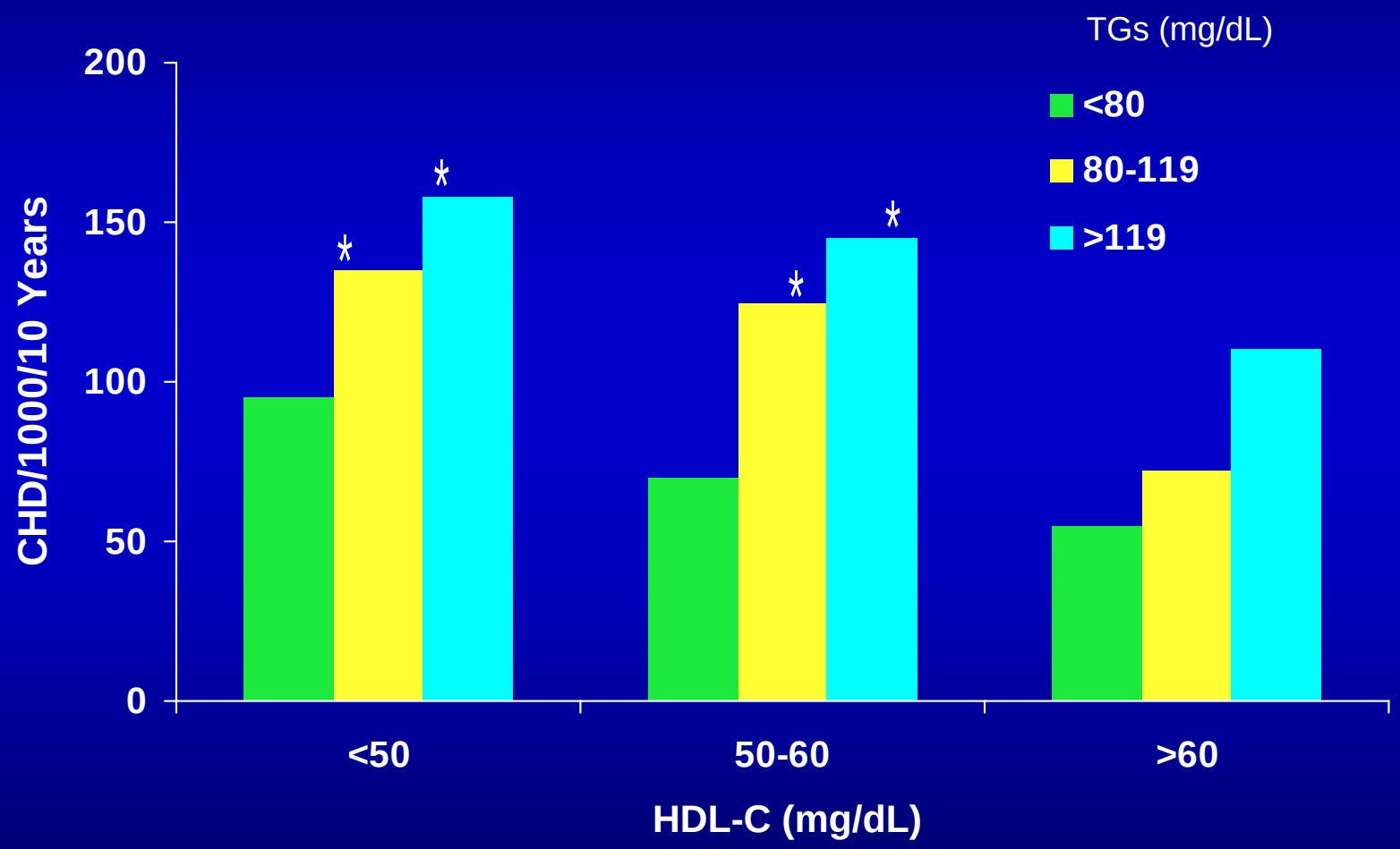
1. Los objetivos de C-LDL <70 mg/dl se asocian a una disminución significativa de eventos cardiovasculares, disminuciones del 50% en cualquier caso parecen detener o estabilizar las lesiones arterioesclerosa.

2. Lo importante es descender el colesterol independientemente del medio terapéutico utilizado

3. Los objetivos de C-LDL son dificiles de alcanzar usando solo estatinas.

4. La terapia combinada con ezetimiba+estatina debe ser la pauta habitual en el manejo de pacientes de alto riesgo.

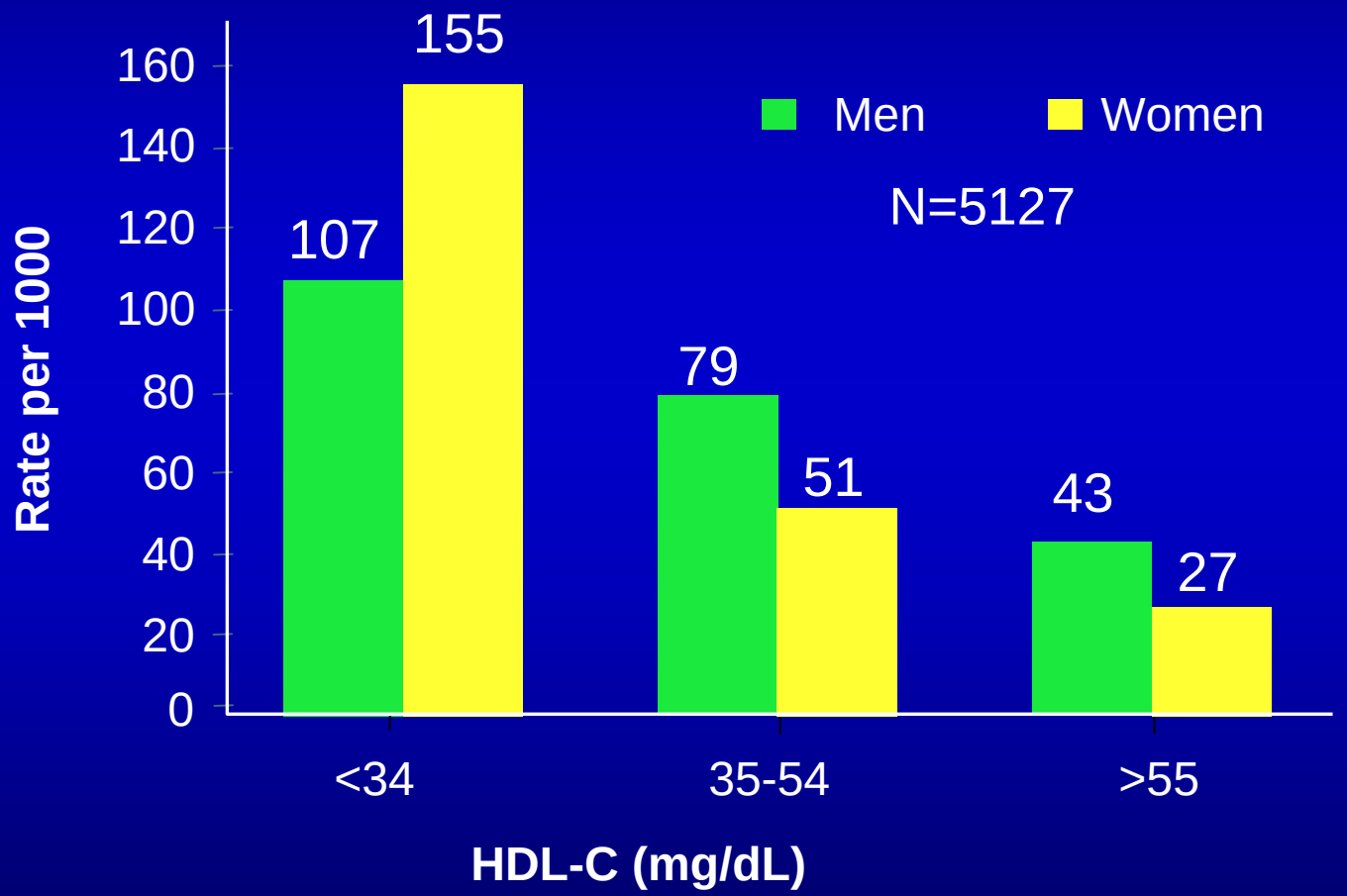
CHD Incidence by HDL-C and TG Levels



* $P < 0.05$

Castelli WP. Am J Cardiol. 1992;70:3H-9H.

Rate of CVD by HDL-C Level
The Framingham Heart Study



Kannel WB. Am J Cardiol. 1983;52:9B-12B.

Estudios de morbi-mortalidad en marcha con ezetimiba y simvastatina

	SHARP Study of Heart and Renal Protection	ENHANCE	SEAS Simvastatin + Ezetimibe in Aortic Stenosis	IMPROVE-IT
Nombre completo	Study of Heart and Renal Protection	Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression	Simvastatin + Ezetimibe in Aortic Stenosis	Improved Reduction of Outcomes: VYTORIN (INEGY) Efficacy International Trial
Tratamientos	Ezetimiba 10 mg/día + simvastatina 20 mg/día frente a placebo*	Ezetimiba 10 mg/día + simvastatina 80 mg/día frente a simvastatina 80 mg/día	Ezetimiba 10 mg/día + simvastatina 40 mg/día frente a placebo	Ezetimiba 10 mg/día + simvastatina 40 mg/día frente a simvastatina 40 mg/día
Participantes	Aprox. 9.000 pacientes (≥40 años de edad) con nefropatía crónica (creatinina ≥1,5 md/dl en mujeres; ≥2 mg/dl en varones) o sometidos a diálisis	725 pacientes (de 30 a 70 años) con hipercolesterolemia familiar heterocigota	1.400 pacientes (de 45 a 85 años) con estenosis moderada asintomática de la válvula aórtica (velocidad Doppler de 2,5–4,0 m/s), C-LDL <230 mg/dl, TG ≤400 mg/dl	Aprox. 10.000 pacientes con síndromes coronarios agudos
Criterio de valoración principal	Momento de aparición de episodios vasculares importantes (IM, ictus, revascularización, muerte cardíaca)	Variación media durante el estudio del grosor de la íntima-media de la carótida por ecografía	Compuesto episodios cardiovasculares mayores: valvuloplastia aórtica o episodios cardiovasculares importantes (p. ej. IM no mortal, revascularización)	Combinación de muerte, IM, nueva hospitalización por SCA o revascularización
Duración prevista	4 años	2 años	Mediana de duración de 4 años	Al menos 2 años de seguimiento

Tomado de Baigent C, Landry M. Study of Heart and Renal Protection (SHARP). *Kidney International* 2003;63:(Suppl 84):S207-S210. Kastelein JP et al for the ENHANCE Investigators. The ENHANCE Trial: [Abstract 1513]. Presentado en el XIIIth International Symposium on Atherosclerosis (ISA), Kyoto, Japan, September 28 - October 2, 2003. http://www.congre.co.jp/isa/18 Rossebo A et al for the SEAS Steering Committee. Design of the simvastatin and Ezetimibe in aortic stenosis (SEAS) Study. [Abstract & Póster #3P-0870]. Presentado en el XIIIth International Symposium on Atherosclerosis (ISA), Kyoto, Japan, September 28 - October 2, 2003. http://www.congre.co.jp/isa; IMPROVE-IT http://www.medicalnewstoday.com/medicalnews.php?newsid=17578

HDL Cholesterol, Very Low Levels of LDL Cholesterol, and Cardiovascular Events.

Barter P et al. NEJM 2007;357:1301-10

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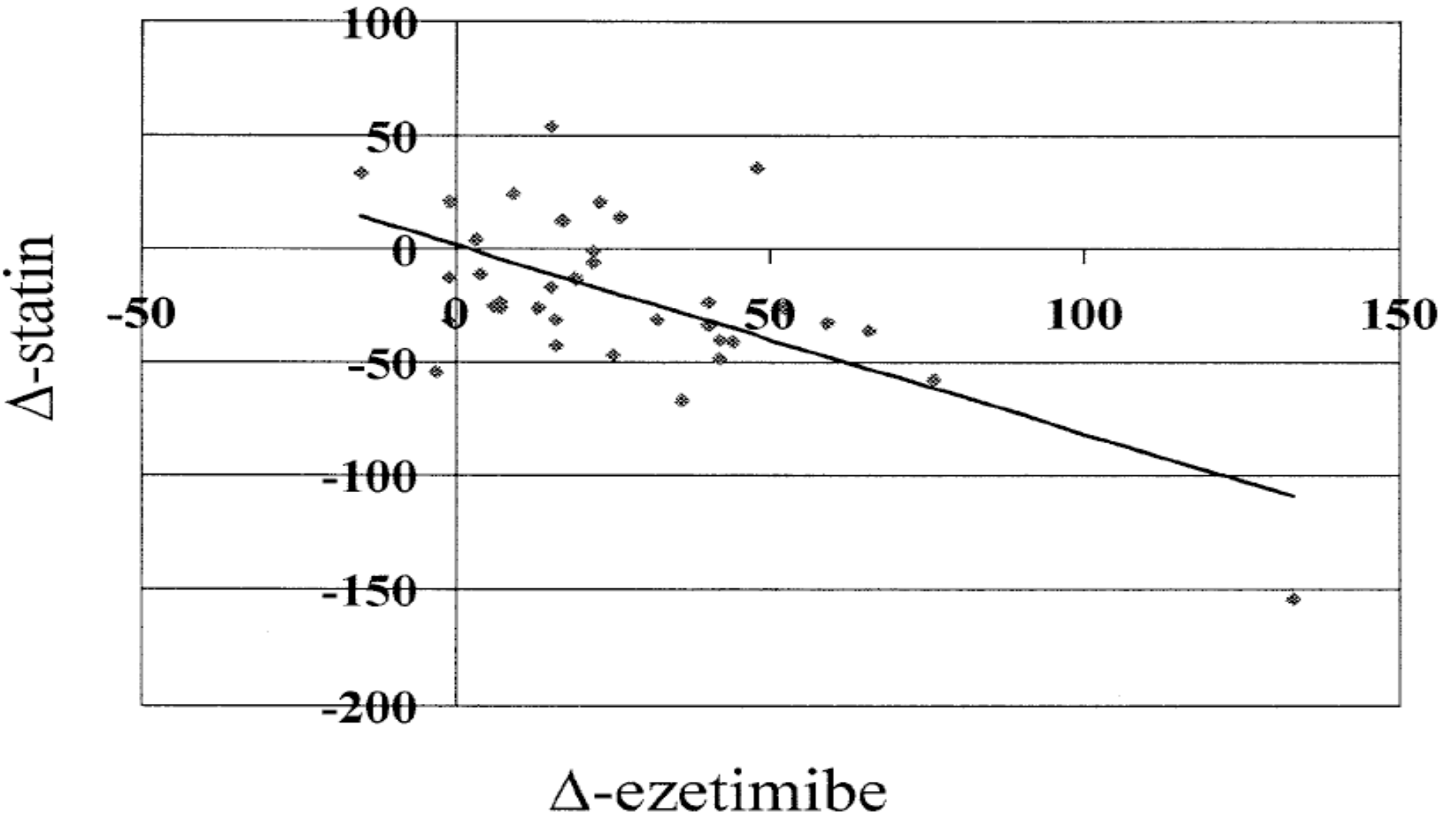
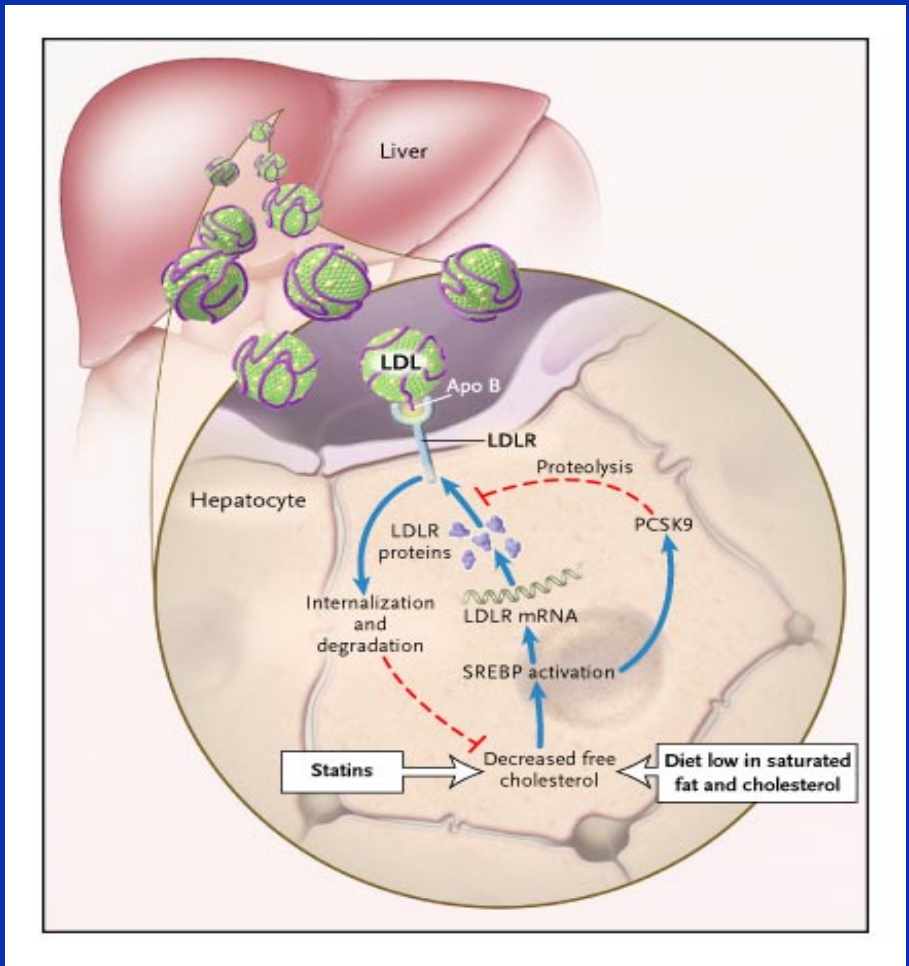
QuickTime™ and a
TIFF (Uncompressed) decompressor

Initial LDL response to statin therapy predicts subsequent LDL response to the addition of ezetamibe . Am J Cardiol 2004; 93:779-80

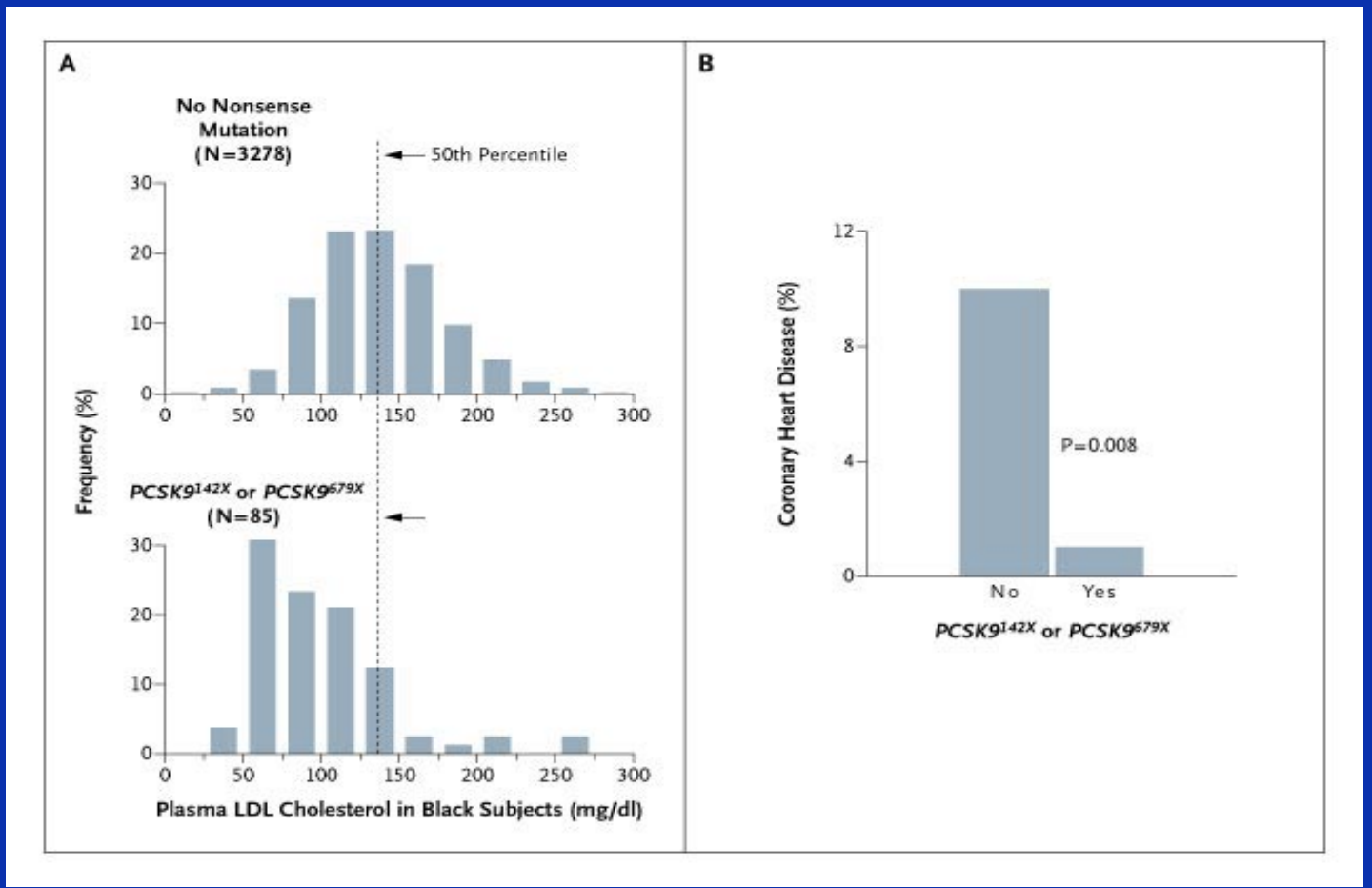


The Role and Regulation of the LDL Receptor



Tall, A. R. N Engl J Med 2006;354:1310-1312

Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Heart Disease (Panel B) among Black Subjects, According to the Presence or Absence of a PCSK9^{142X} or PCSK9^{679X} Allele



Cohen, J. et al. N Engl J Med 2006;354:1264-1272

Effects of ezetimibe and/or simvastatin on LDL receptor protein expression and on LDL receptor and HMG-CoA reductase gene expression: A randomized trial in healthy men.

Gouni-Berthold et al. Atherosclerosis (2007).