¿Qué factores de riesgo lipídicos debemos controlar? ¿En qué medida?.

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ATP III LDL cholesterol cutoffs for lifestyle interventions and drug therapy in different risk categories

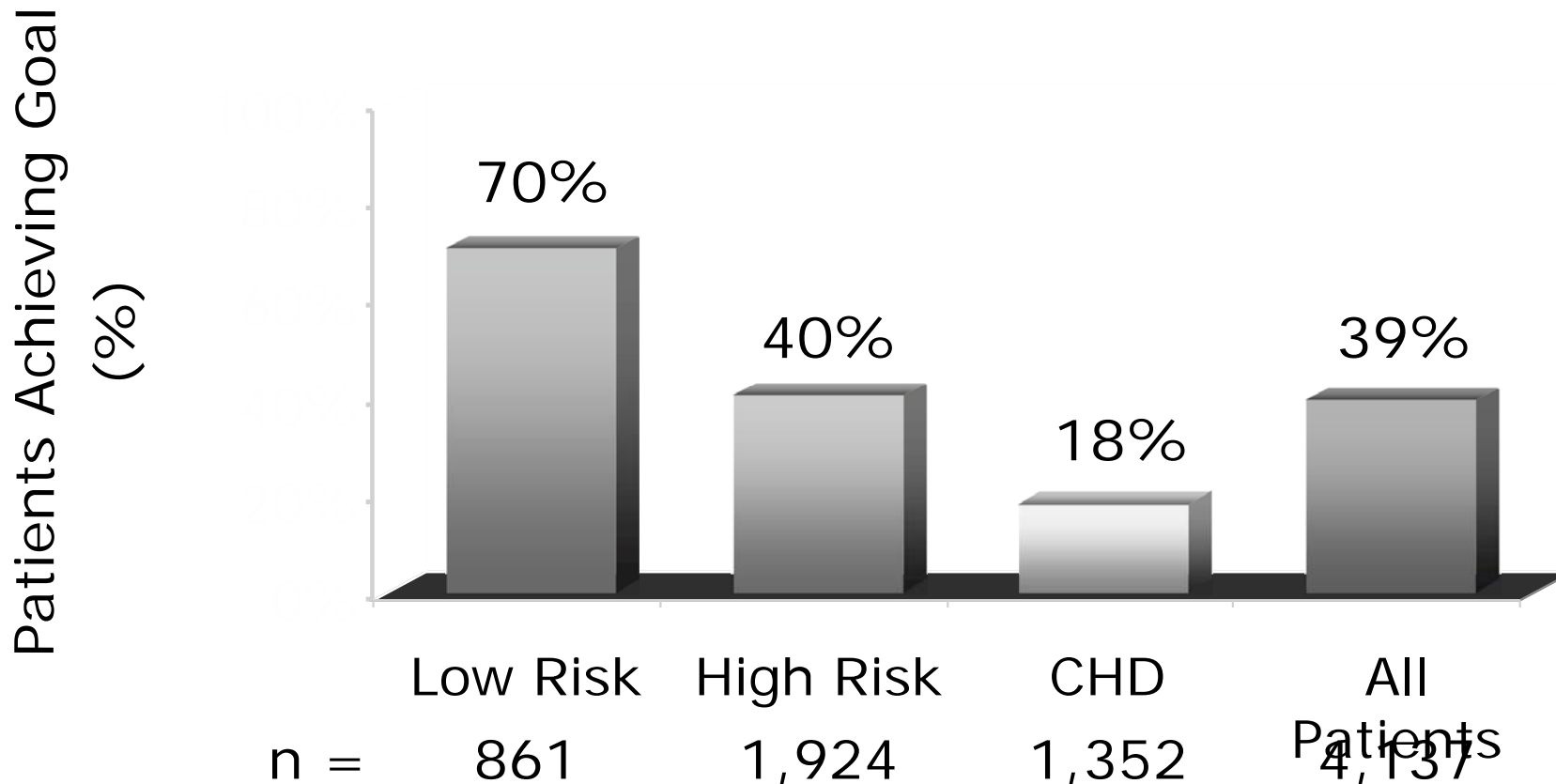| Risk category	LDL cholesterol goal	Initiate therapeutic lifestyle changes	Consider drug therapy
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL (with an optional goal of <70 mg/dL)	$\geq$100 mg/dL	$\geq$100 mg/dL (consider drug options if LDL-C <100 mg/dL)
Moderately high risk: two or more risk factors (10-year risk 10%-20%)	<130 mg/dL (with an optional goal of <100 mg/dL)	$\geq$130 mg/dL	$\geq$130 mg/dL (consider drug options if LDL-C 100-129 mg/dL)
Moderate risk: two or more risk factors (10-year risk <10%)	<130 mg/dL	$\geq$130 mg/dL	>160 mg/dL
Low risk: $\leq$1 risk factor	<160 mg/dL	$\geq$160 mg/dL	$\geq$190 mg/dL (consider drug options if LDL-C 160-189 mg/dL)

Grundy SM et al. *Circulation*; july 2004

¿Colesterol-LDL u otros marcadores lipídicos?.

¿estratificar objetivos lipídicos
o
estratificar riesgo vascular en los pacientes?

Inadequate Achievement of NCEP ATP III Treatment Goals, Especially among Patients at Highest Risk

Patients Achieving Goal (%)

70% — Low Risk
40% — High Risk
18% — CHD
39% — All Patients

n =	861	1,924	1,352	4,137
	Low Risk	High Risk	CHD	All Patients

Drug therapy included statins (fluvastatin, lovastatin, pravastatin, simvastatin), gemfibrozil, bile acid sequestrants, niacin, psyllium fiber, and combination drug therapy.

Adapted from Pearson TA et al. *Arch Intern Med* 2000;160;459-467.

Pacientes que cumplen objetivos de C-LDL
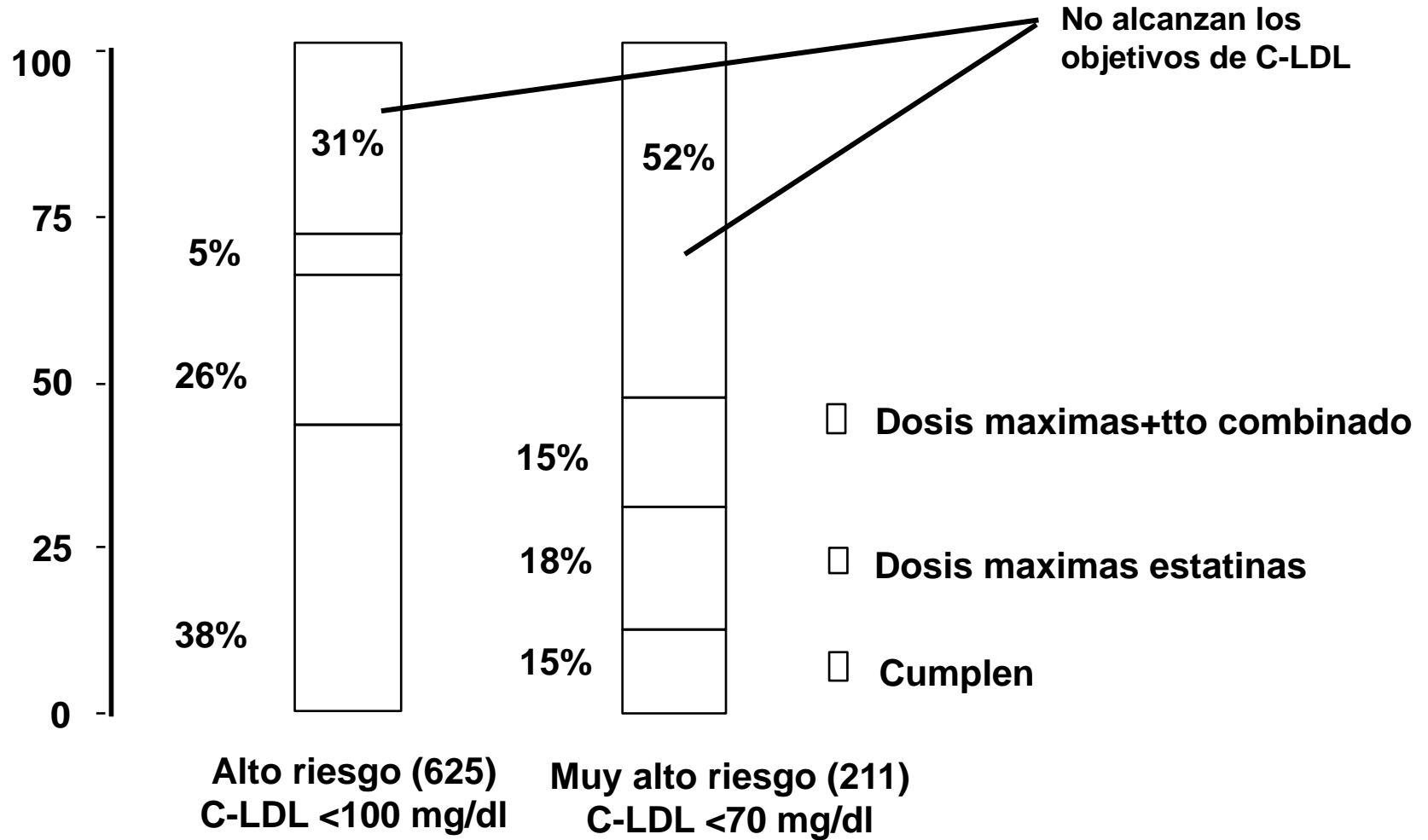## Acordes con su riesgo coronario.
Hospital de Sagunto (n=1811)
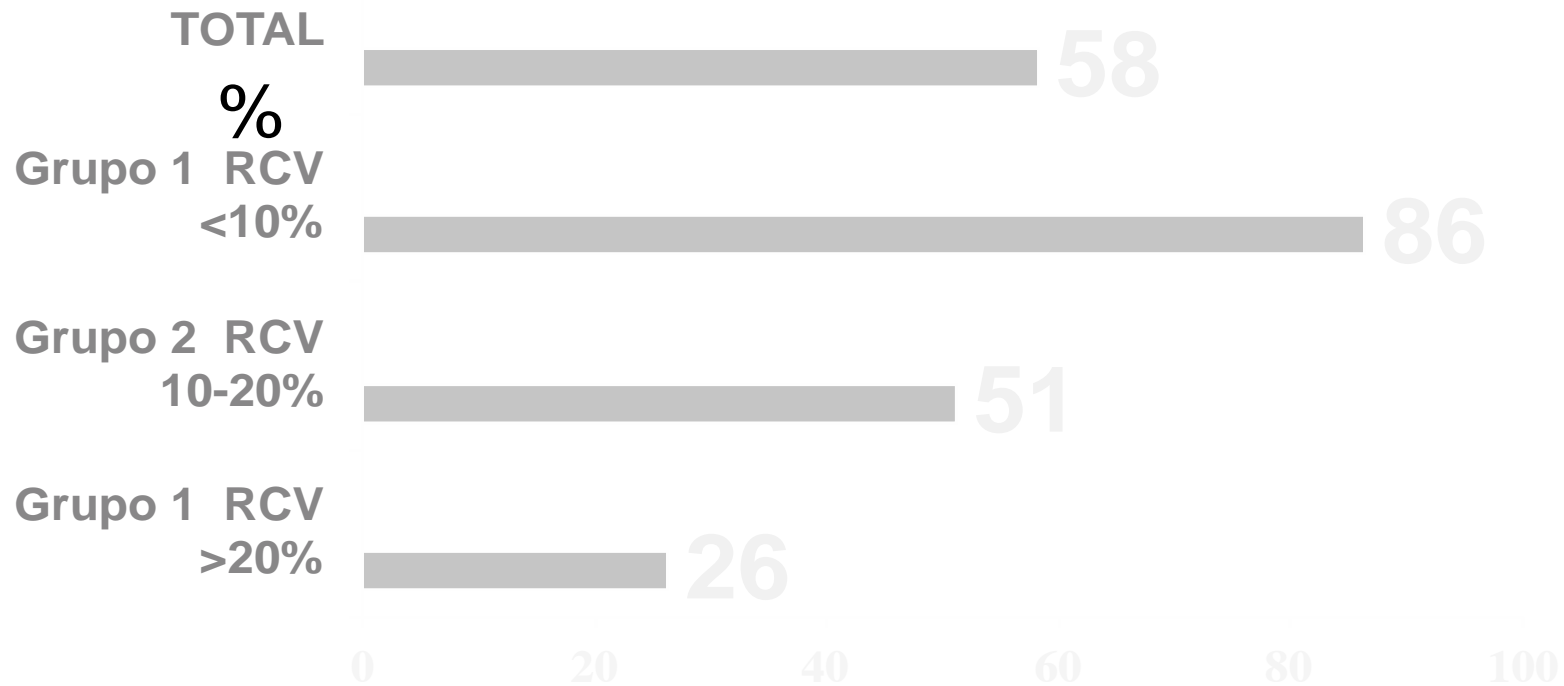
Table. Comparison Between L-TAP and L-TAP 2

	Overall	Low Risk (<1 Risk Factor)	Moderate Risk (≥2 Risk Factors)	High Risk (CHD, Other Atherosclerotic Disease, Diabetes)
LDL-C goal success rates, %				
L-TAP	38	68	37	18
L-TAP 2	73	86	74	67
Mean LDL-C in patients achieving goal, mg/dL				
L-TAP	...	129	109	87
L-TAP 2	...	108	92	73
Mean LDL-C in patients not achieving goal, mg/dL				
L-TAP	...	188	163	140
L-TAP 2	...	185	158	127

CHD indicates coronary heart disease; LDL-C, low-density lipoprotein cholesterol; and L-TAP, Lipid Treatment Assessment Project.

Editorial by Gotto A. Circulation 2009

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

No alcanzan los objetivos de C-LDL

Alto riesgo (625)
C-LDL <100 mg/dl

Muy alto riesgo (211)
C-LDL <70 mg/dl

31%
5%
26%
38%

52%
15%
18%
15%

☐ Dosis maximas+tto combinado

☐ Dosis maximas estatinas

☐ Cumplen

Rev Clin Esp 2006;206:417

Table 1. Lipid-lowering options for patients who have not achieved LDL-C and non–HDL-C goals on statin therapy

Drug	Changes from baseline, %			
	LDL-C	Non–HDL-C	Triglyceride	HDL-C
Double statin dose	-6	-6	-2 to -12	-2 to +2
Ezetimibe, 10 mg	-15	-12	-9	NS
Niacin, 2 g	-8 to -14	-15 to -30*	-24	+18 to +21
Bile acid–binding agents†	-12	-5 to +8	0 to +23	+1 to +7
Fenofibrate, 145 mg	-6 to +4	-3 to -18*	-15 to -20	+13
Gemfibrozil, 600 mg BID	+7	+2	-18	0

*Estimated by subtracting mean HDL-C from mean total cholesterol.
†These include colestipol, 2 scoops (6 g); cholestyramine, 2 scoops (8 g); and colesevelam, 6 tablets (3.75 g).
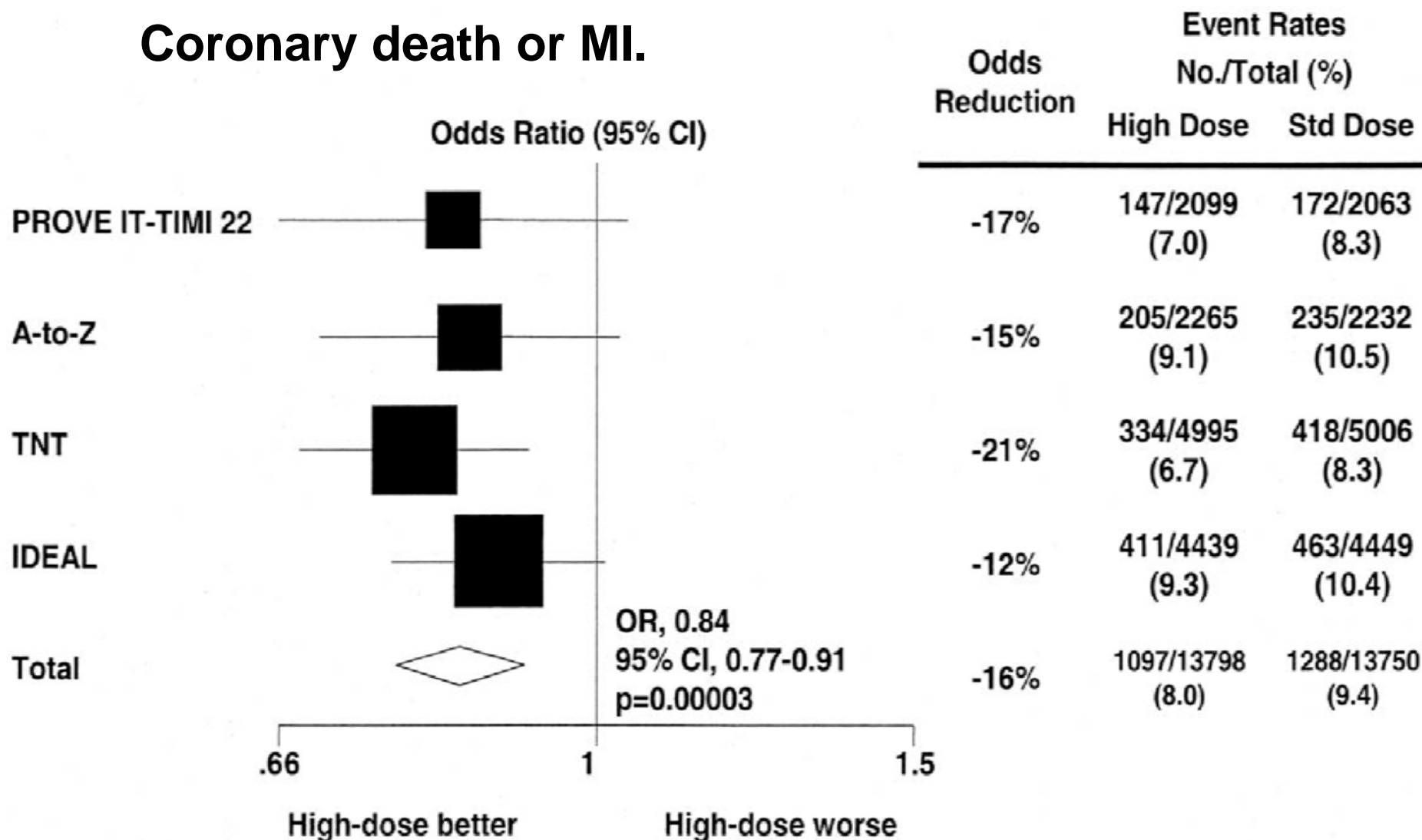BID—twice a day; HDL-C—high-density lipoprotein cholesterol; LDL-C—low-density lipoprotein cholesterol; NS—not significant.

Lipid Abnormalities and Cardiovascular Prevention 2008

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 Ratio (95% CI)	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	OR, 0.84 95% CI, 0.77-0.91 p=0.00003	-16%	1097/13798 (8.0)	1288/13750 (9.4)

.66   1   1.5

High-dose better   High-dose worse

Porcentaje de pacientes de alto riesgo y muy alto riesgo coronario que alcanzan el objetivo de C-LDL. (n=111)
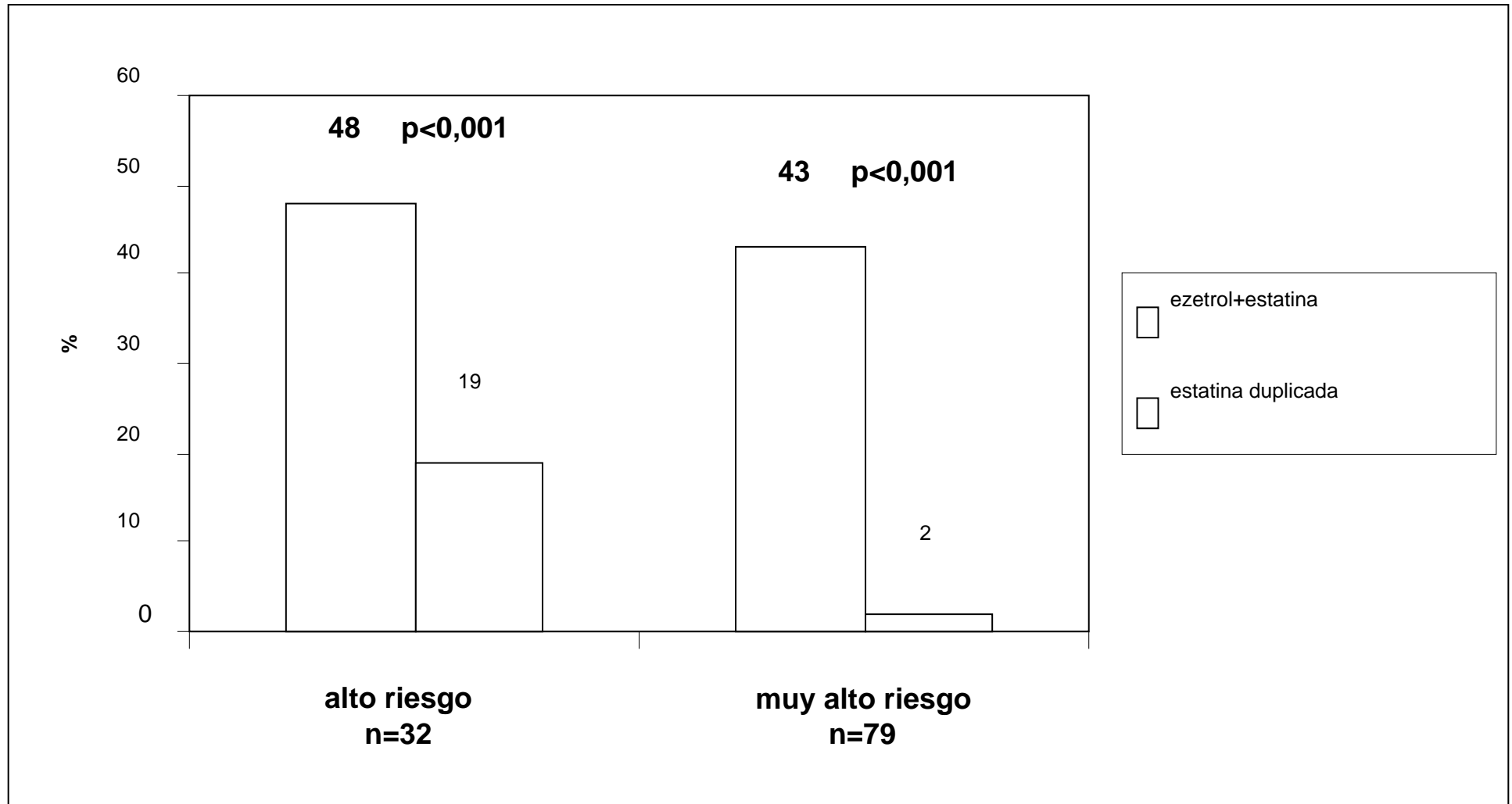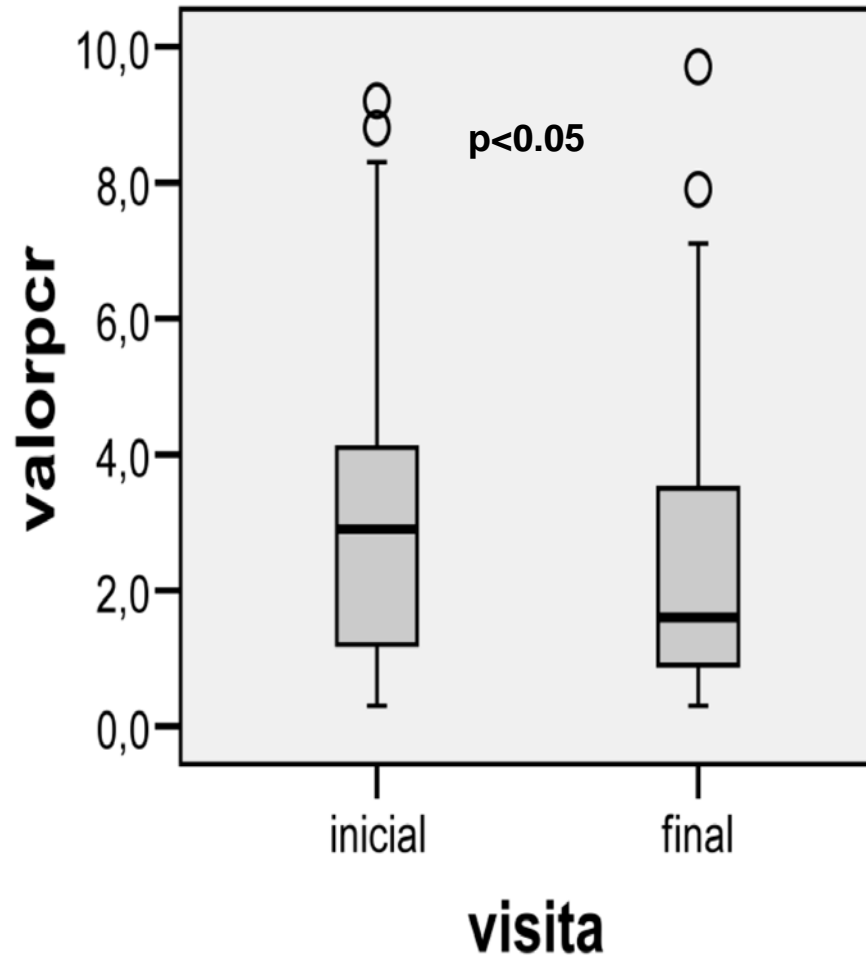
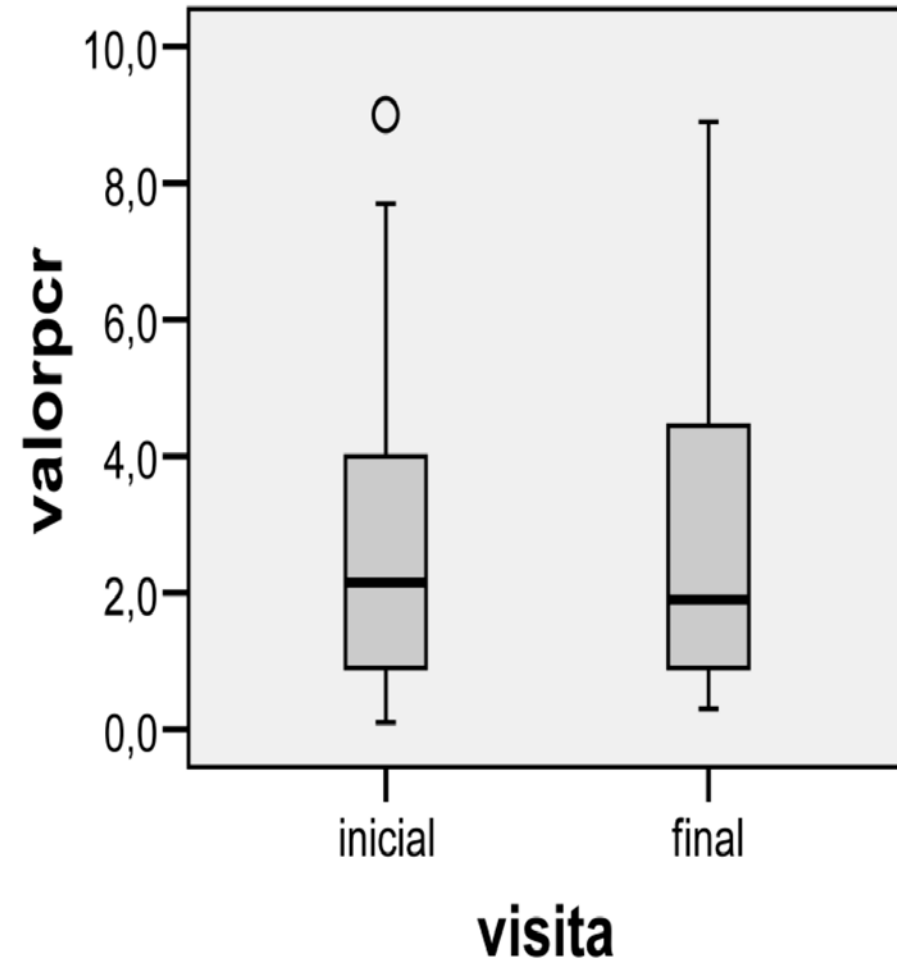# Porcentaje de pacientes con Diabetes Méllitus y Síndrome Metabólico que alcanzan el objetivo de C-LDL. (n=111)

Costa el al. Rev Clin Esp. 2009; 209(9):415-423
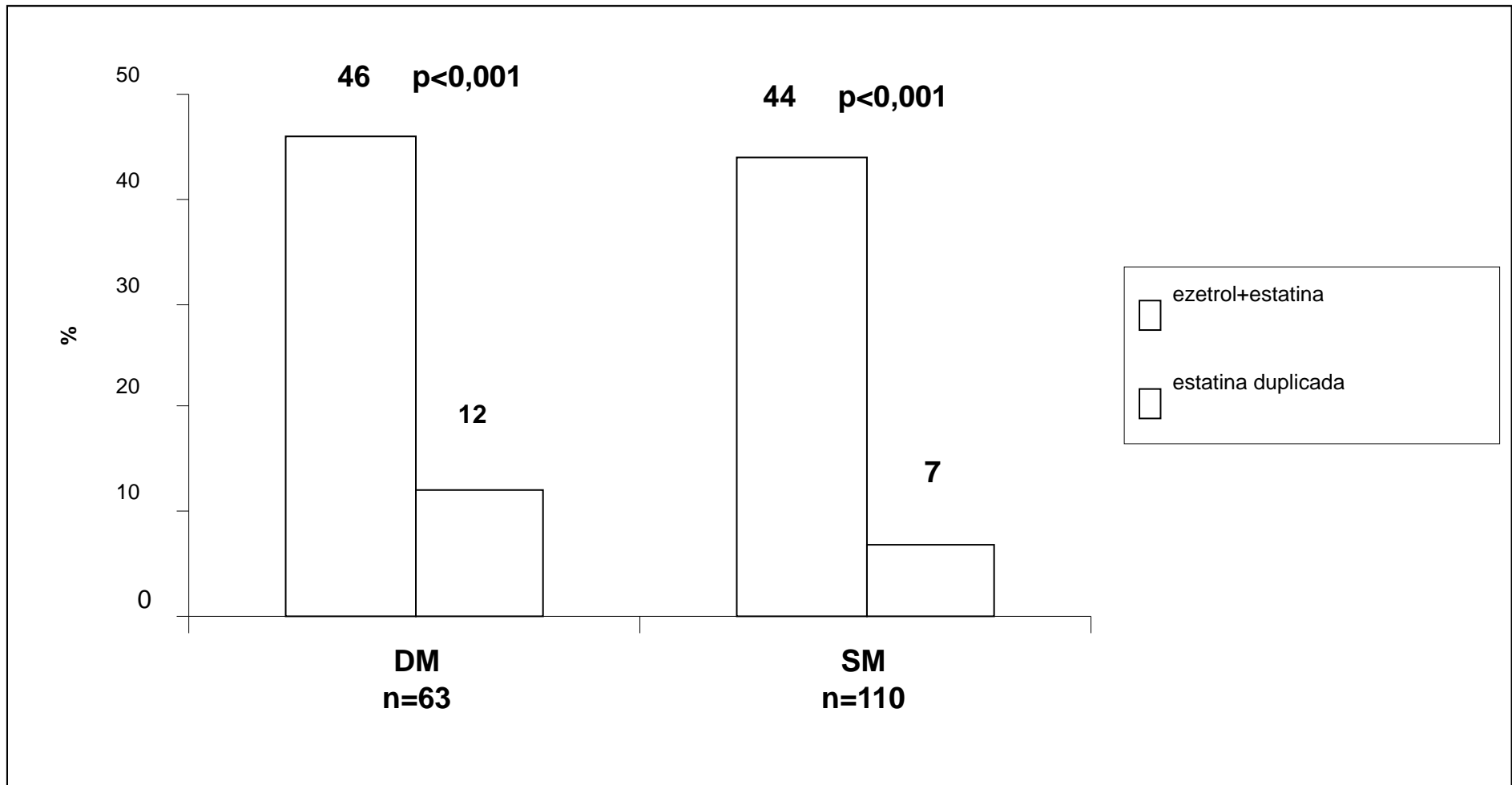
Cambios evolutivos de la PCR en pacientes de alto riesgo. (n=111)
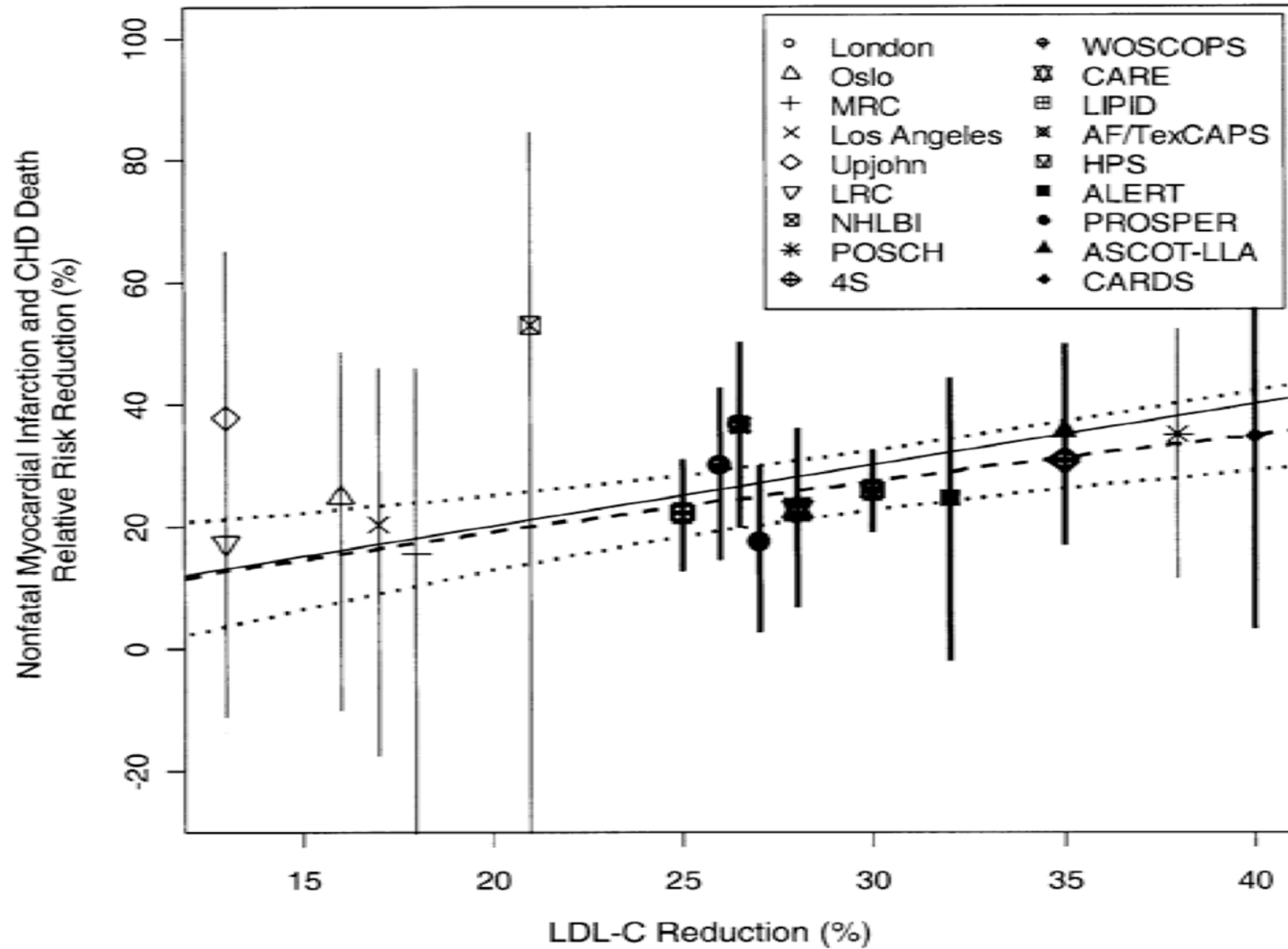
Lipid Management to Reduce Cardiovascular Risk. A New Strategy Is Required. *Superko et al. Circulation 2008.*
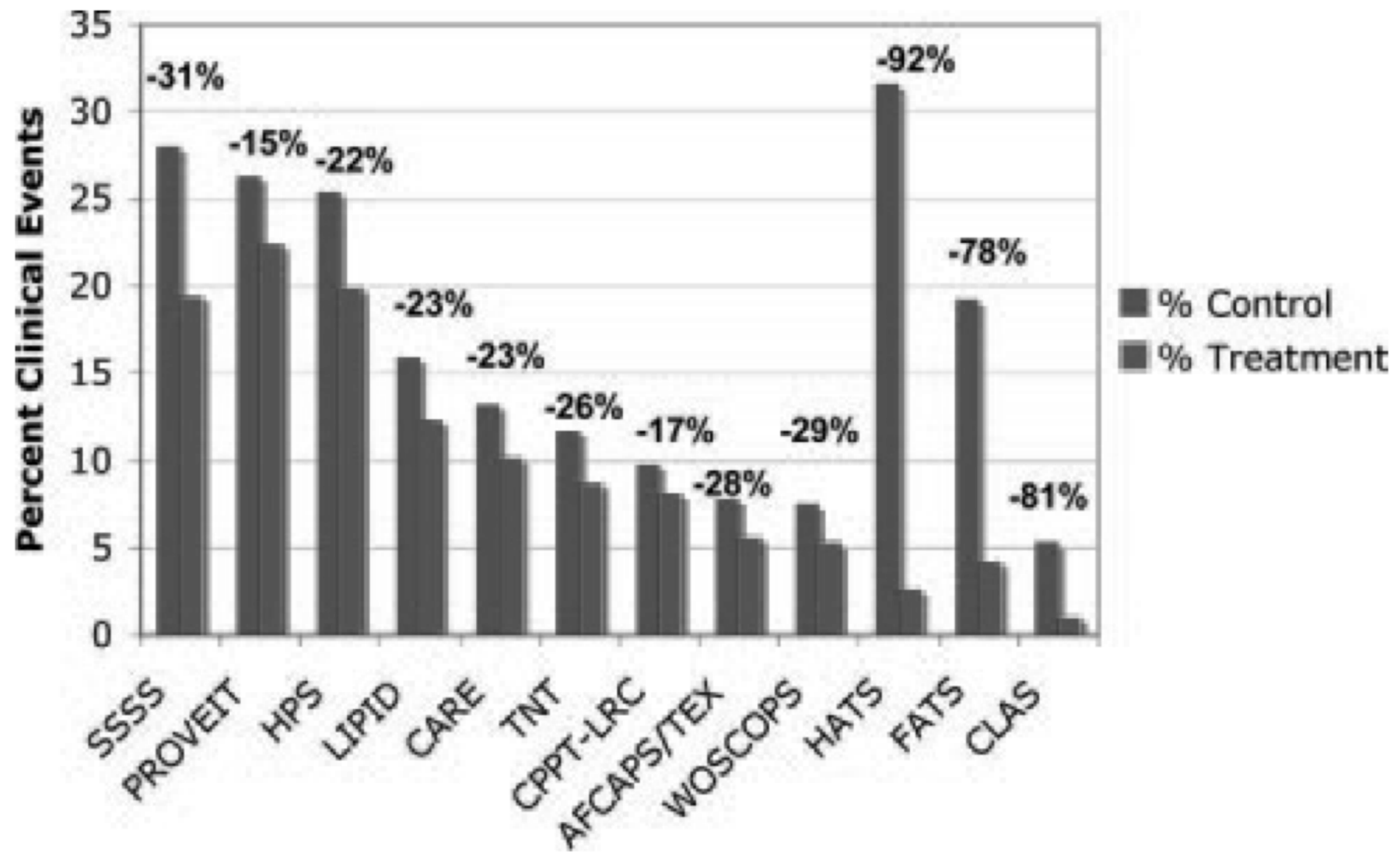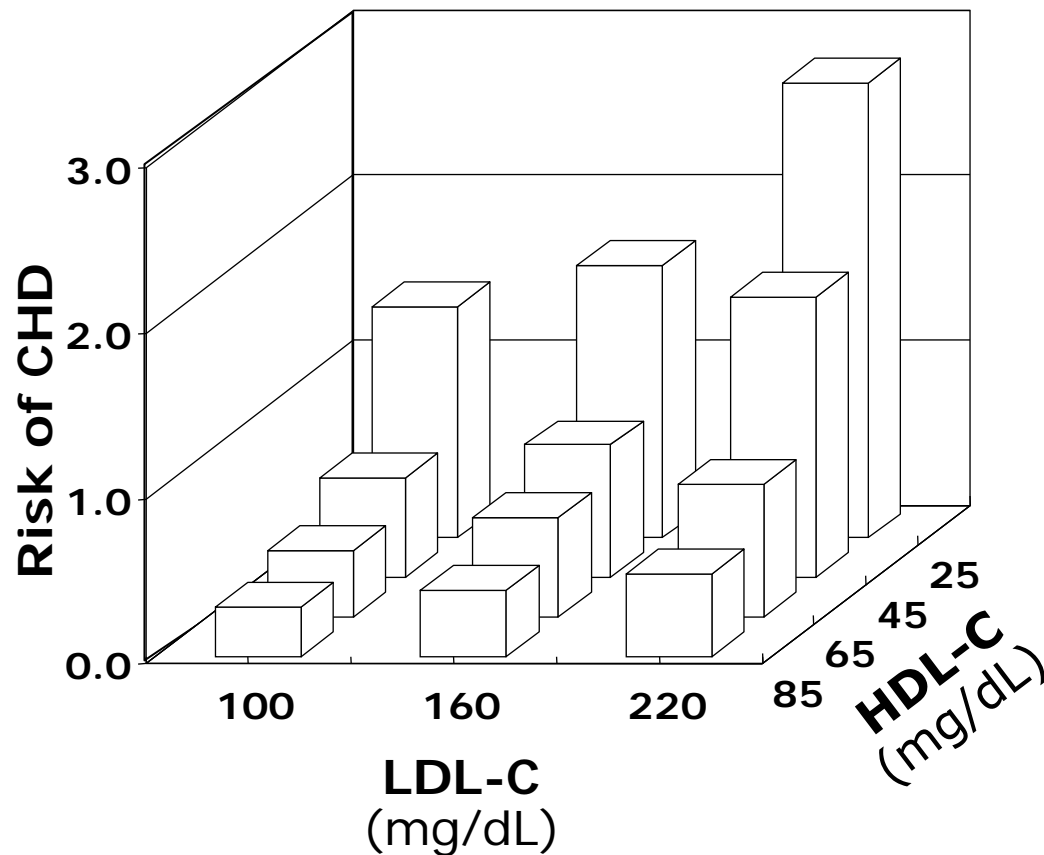
Pleiotropic Effects of Statins: Benefit Beyond Cholesterol Reduction. Robinson J. JACC 2005
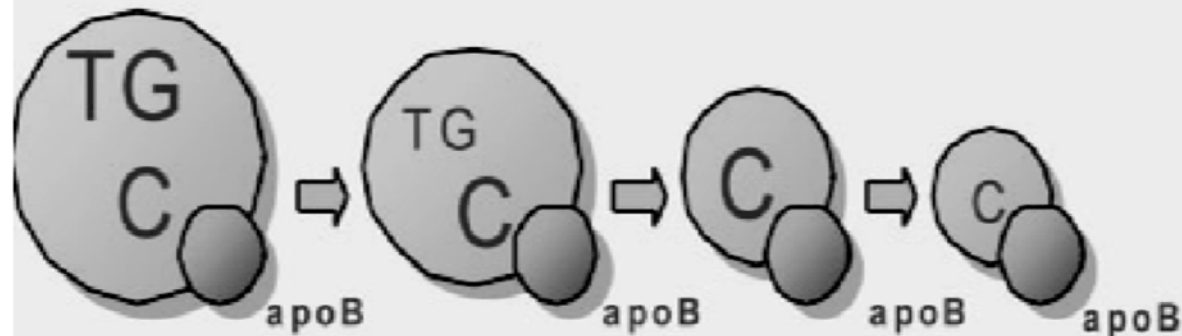
CV Risk: HDL-C and LDL-C Interaction

Data From Framingham Study

- For any level of LDL-C, HDL-C is inversely related to CHD risk

- Rule of 1's
  - For every 1% shift in HDL-C or LDL-C, event rates are ~1% lower

Gordon T et al. *Am J Med* 1977;62:707-714.
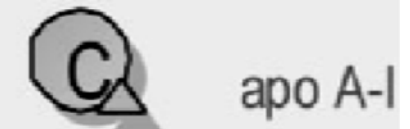
From the liver

Back to the liver

'Reverse cholesterol transport'

TG C apoB — VLDL

TG C apoB — IDL

C apoB — Large buoyant LDL

C apoB — Small dense LDL

C apo A-I — HDL

Atherogenic

Anti-atherogenic

INTER-HEART: Risk of acute MI associated with risk factors in the overall population

Risk factor	Odds ratio adjusted for age, sex, and smoking (99% CI)	Odds ratio adjusted for all (99% CI)
ApoB/ApoA-1 (fifth quintile compared with first)	3.87 (3.39-4.42)	3.25 (2.81-3.76)
Current smoking	2.95 (2.72-3.20)	2.87 (2.58-3.19)
Diabetes	3.08 (2.77-3.42)	2.37 (2.07-2.71)
Hypertension	2.48 (2.30-2.68)	1.91 (1.74-2.10)
Abdominal obesity	2.22 (2.03-2.42)	1.62 (1.45-1.80)
Psychosocial	2.51 (2.15-2.93)	2.67 (2.21-3.22)
Vegetable and fruits daily	0.70 (0.64-0.77)	0.70 (0.62-0.79)
Exercise	0.72 (0.65-0.79)	0.86 (0.76-0.97)
Alcohol intake	0.79 (0.73-0.86)	0.91 (0.82-1.02)
All combined	129.2 (90.2-185.0)	129.2 (90.2-185.0)

AMORIS: fatal myocardial infarction

Adjusted for age, gender TC and TG

Y-axis: Odds-Ratio (95% CI)

X-axis: apoB/apoA-1 (decile)
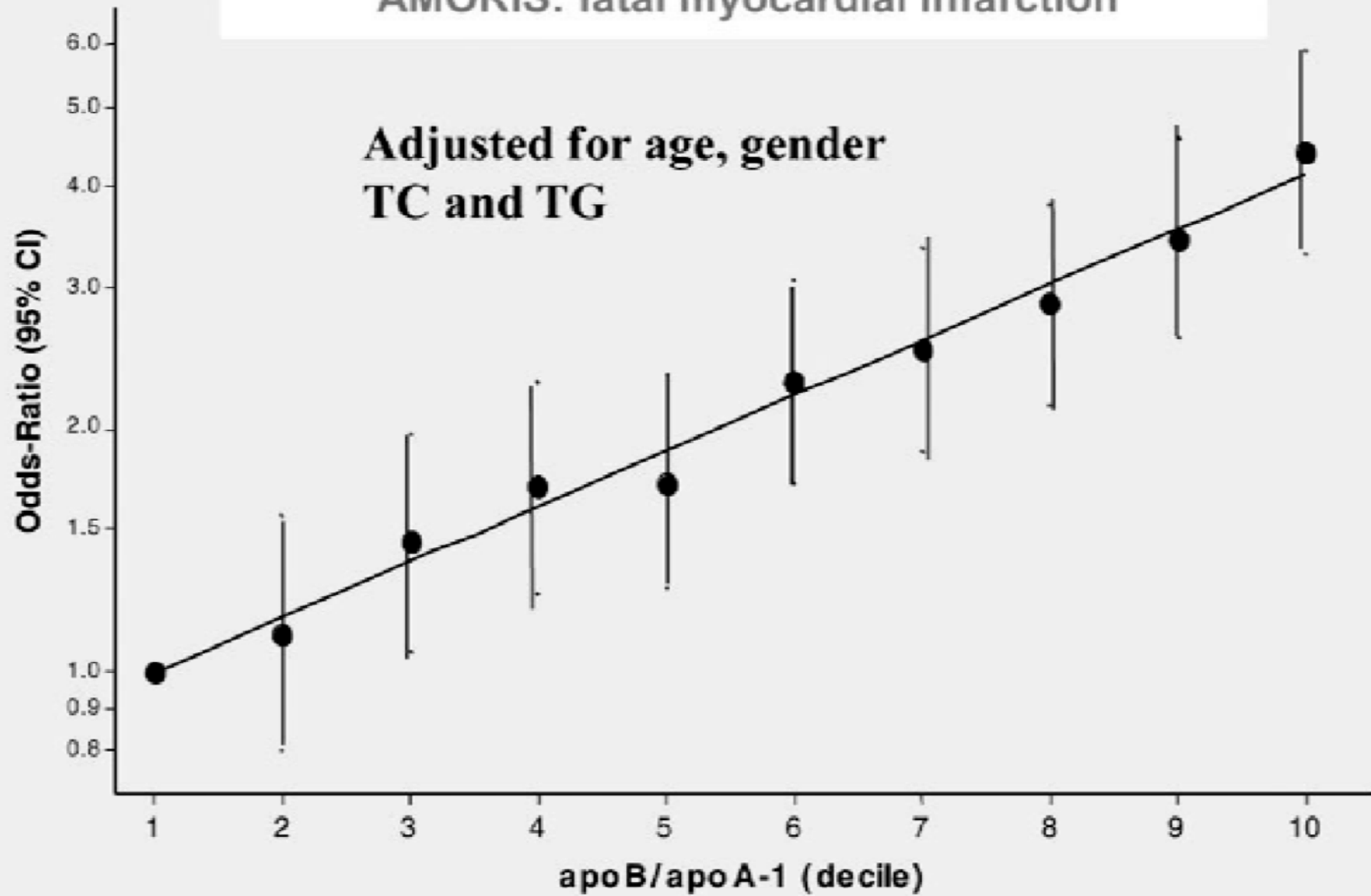
	1	2	3	4	5	6	7	8	9	10
Mean:	0.48	0.61	0.70	0.77	0.84	0.91	1.00	1.10	1.23	1.56
Cases:	61	78	123	146	155	236	265	298	372	479

The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy – a review of the evidence. Walldius G et al. *J Intern Med 2006;259:493*

AMORIS: Fatal MI
Men, $n = 1267$: adjusted for age, TC, and TG

P-values: * = <0.05, ** = <0.01, *** = <0.001, **** = <0.0001 (tested versus 1.00)
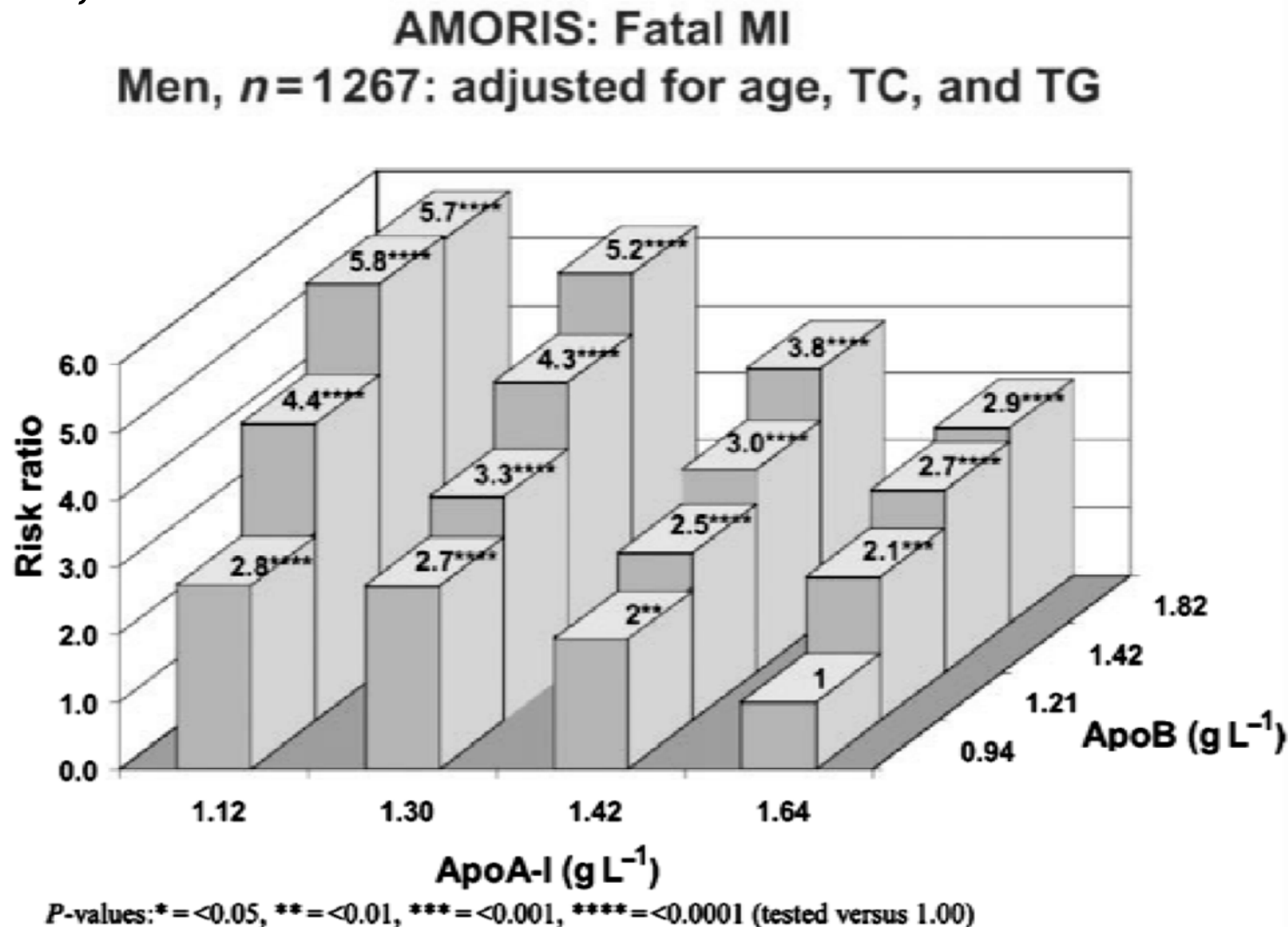
Risk of myocardial infarction in relation to the apoB/apoA-I ratio
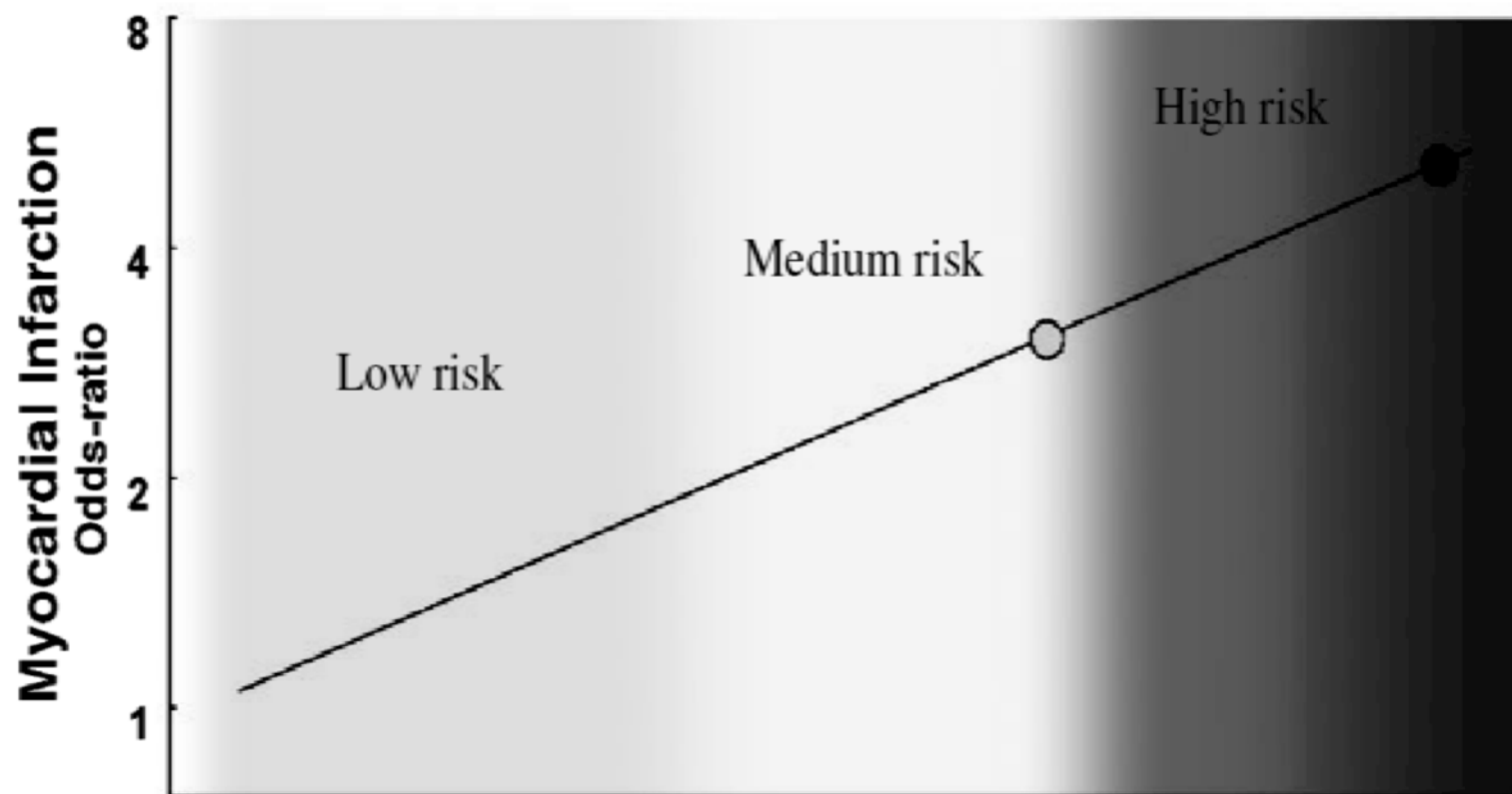
Based on results from

AMORIS; Walldius G et al. Lancet 2001;358:2026 and INTERHEART: Yusuf S et al. Lancet 2004:364:937.

Lipoprotein Management in Patients With Cardiometabolic Risk Consensus Conference Report From the American Diabetes Association and the American College of Cardiology Foundation. JAAC 2008

Table 1. Suggested Treatment Goals in Patients With CMR and Lipoprotein Abnormalities

	Goals		
	LDL Cholesterol (mg/dl)	Non-HDL Cholesterol (mg/dl)	ApoB (mg/dl)
Highest-risk patients, including those with 1) known CVD or 2) diabetes plus one or more additional major CVD risk factor	<70	<100	<80
High-risk patients, including those with 1) no diabetes or known clinical CVD but two or more additional major CVD risk factors or 2) diabetes but not other major CVD risk factors	<100	<130	<90

Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and family history of premature CAD.

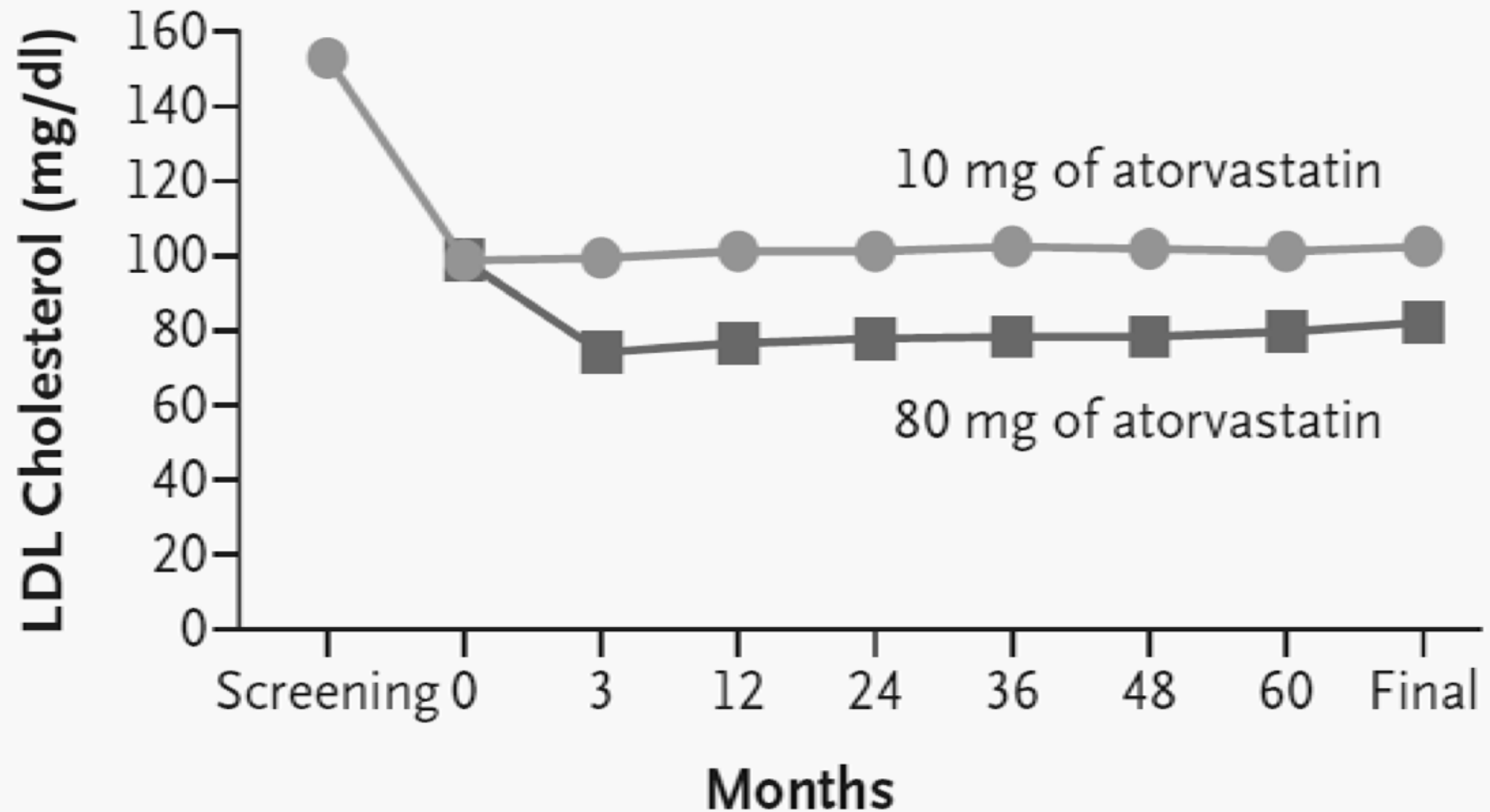# ¿Colesterol-LDL, C-HDL, C-no-HDL o apolipoproteinas?.

Meta-Analysis of the Relationship Between Non–High-Density Lipoprotein Cholesterol Reduction and Coronary Heart Disease Risk.

Robinson JG. JAAC 2009; 53:316
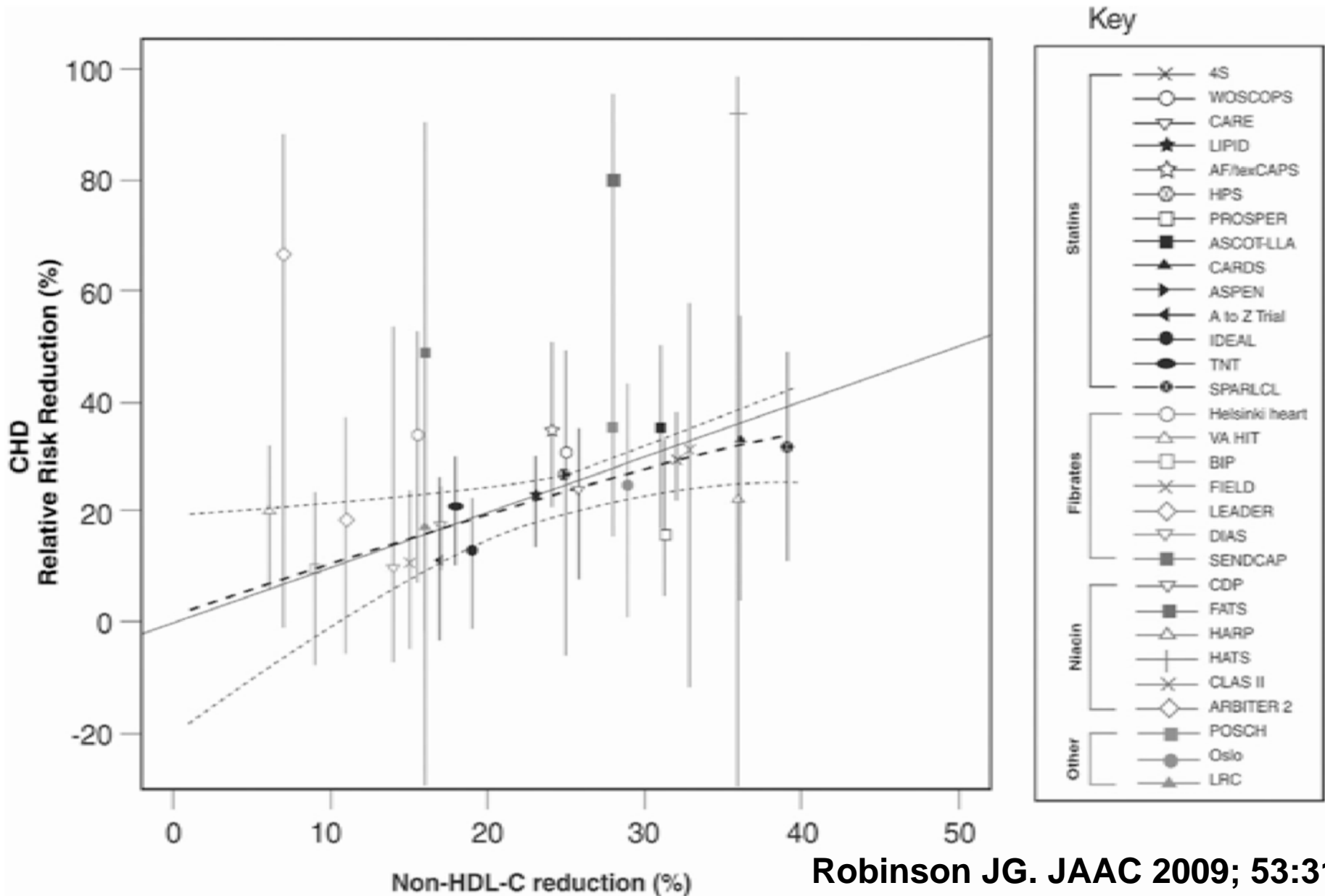
Treating to New Targets (TNT) Investigators.
LaRosa N Engl J Med 2005;352.

Lipids, Apolipoproteins, and Their Ratios in Relation to Cardiovascular Events With Statin Treatment.
Kastelein et al. Circulation 2008

Table 1.   On-Treatment Values of Lipids, Apolipoproteins, and Their Ratios in Both Treatment Groups of TNT and IDEAL

	TNT		IDEAL	
	Atorvastatin 10 mg (n=4665)	Atorvastatin 80 mg (n=4654)	Simvastatin 20–40 mg (n=4369)	Atorvastatin 80 mg (n=4330)
Total cholesterol, mg/dL*	178.1 (28.5)	147.5 (29.5)	176.1 (29.9)	147.9 (34.1)
LDL cholesterol, mg/dL	101.0 (22.3)	75.3 (22.6)	102.2 (25.2)	79.5 (28.0)
HDL cholesterol, mg/dL	46.2 (10.9)	46.1 (11.2)	47.1 (12.7)	45.7 (12.5)
Non-HDL cholesterol, mg/dL†	131.9 (27.9)	101.4 (28.0)	129.0 (29.5)	102.2 (32.2)
Triglycerides, mg/dL	156.0 (86.5)	131.3 (76.8)	139.4 (83.8)	116.6 (66.3)
Apolipoprotein B, mg/dL	113 (22)	91 (21)	107 (27)	84 (28)
Total/HDL cholesterol	4.0 (1.0)	3.3 (0.9)	4.0 (1.2)	3.4 (1.1)
LDL/HDL cholesterol	2.3 (0.7)	1.7 (0.6)	2.3 (0.8)	1.9 (0.8)
Apolipoprotein B/A-I	0.8 (0.2)	0.7 (0.2)	0.8 (0.2)	0.6 (0.2)

SI conversion factors: To convert the values for cholesterol to millimoles per liter, multiply by 0.0259. To convert the values for triglycerides to millimoles per liter, multiply by 0.0113.

*Values are expressed as mean (SD), derived from visits at 3, 6, or 12 months in IDEAL, or from visits at 12 months in TNT.

†Calculated as total cholesterol minus HDL cholesterol.

Lipids, Apolipoproteins, and Their Ratios in Relation to Cardiovascular Events With Statin Treatment. Kastelein et al. Circulation 2008

Table 2. Individual Relationships Between On-Treatment Levels of LDL Cholesterol, Non-HDL Cholesterol, Apolipoprotein B, or Their Ratios and MCVEs in TNT and IDEAL

	Hazard Ratio*	95% CI	P
LDL cholesterol	1.15	1.10–1.20	<0.001
Non-HDL cholesterol†	1.19	1.14–1.25	<0.001
Apolipoprotein B	1.19	1.14–1.24	<0.001
Total/HDL cholesterol	1.21	1.17–1.25	<0.001
LDL/HDL cholesterol	1.20	1.16–1.24	<0.001
Apolipoprotein B/A-I	1.24	1.20–1.29	<0.001

*Calculated by a Cox proportional hazard model with adjustment for the effects of study, age, and sex.

†Calculated as total cholesterol minus HDL cholesterol.

# Lipids, Apolipoproteins, and Their Ratios in Relation to Cardiovascular Events With Statin Treatment.
Kastelein et al. Circulation 2008

Table 3. Direct Pairwise Comparisons of the Relationships With MCVEs for On-Treatment Levels of LDL Cholesterol, Non-HDL Cholesterol, Apolipoprotein B, or Their Ratios in TNT and IDEAL

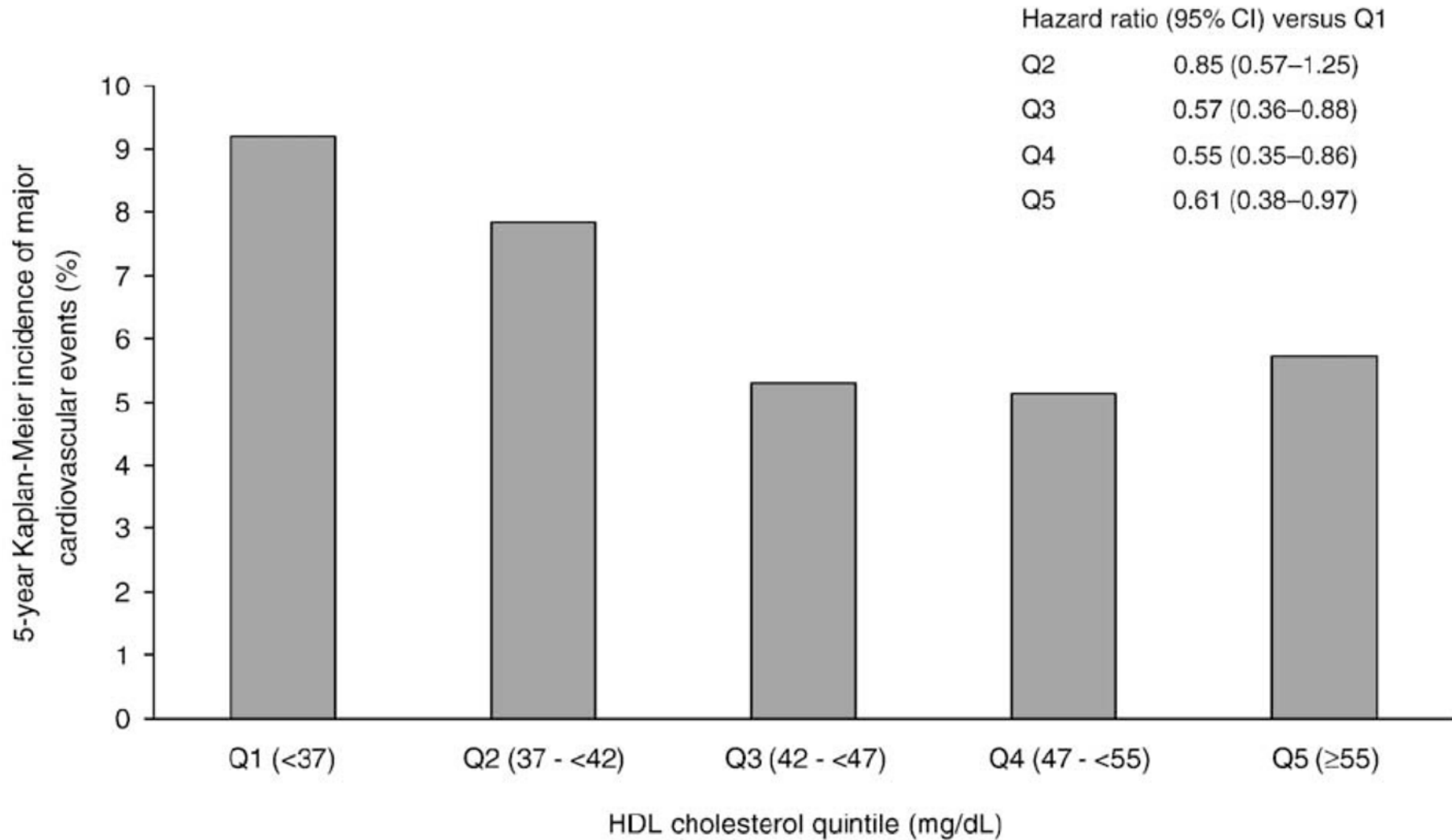|	Hazard Ratio*	95% CI	P
Comparisons of single measures			
LDL cholesterol	0.90	0.82–0.99	0.04
Non-HDL cholesterol†	1.31	1.19–1.44	<0.001
LDL cholesterol	0.95	0.87–1.05	0.33
Apolipoprotein B	1.24	1.13–1.36	<0.001
Non-HDL cholesterol†	1.14	1.00–1.30	0.06
Apolipoprotein B	1.05	0.92–1.20	0.47

¿Profundizamos mas en objetivos lipídicos?.

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.
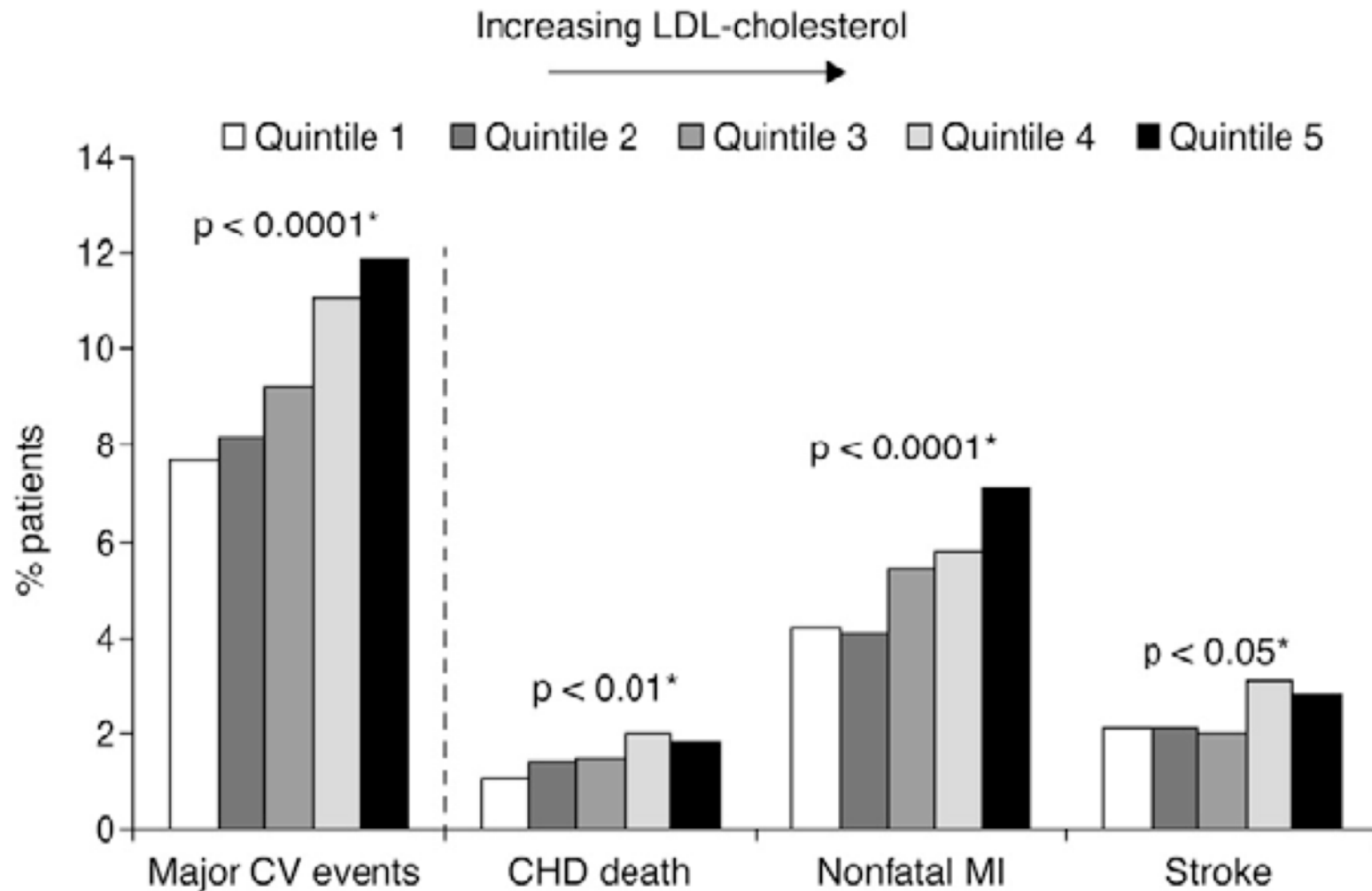
*p-value for trend across LDL-C

Multivariate analysis of major cardiovascular events by quintile of on-treatment HDL-C level.

Hazard ratio (95% CI) versus Q1

Q2	0.85 (0.57–1.25)
Q3	0.57 (0.36–0.88)
Q4	0.55 (0.35–0.86)
Q5	0.61 (0.38–0.97)

y-axis: 5-year Kaplan-Meier incidence of major cardiovascular events (%)

x-axis: HDL cholesterol quintile (mg/dL)

Q1 (<37) Q2 (37 - <42) Q3 (42 - <47) Q4 (47 - <55) Q5 (≥55)

Number of events/number of subjects

| 57/473 | 50/525 | 34/550 | 34/569 | 35/544 |

Meta-Analysis of Cardiovascular Outcomes Trials Comparing Intensive Versus Moderate Statin Therapy.
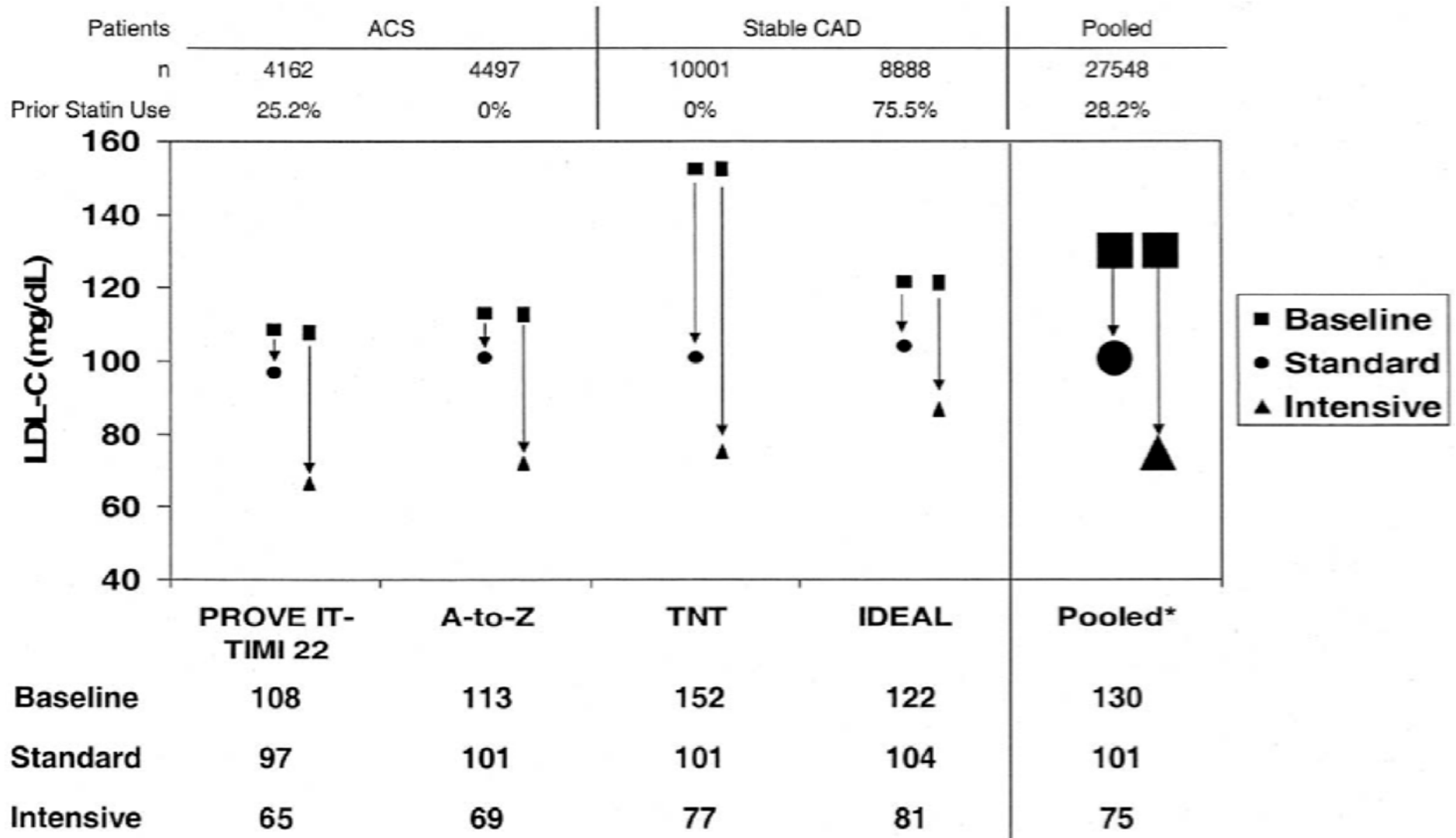**Cannon C et al. J Am Coll Cardiol 2006.**

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

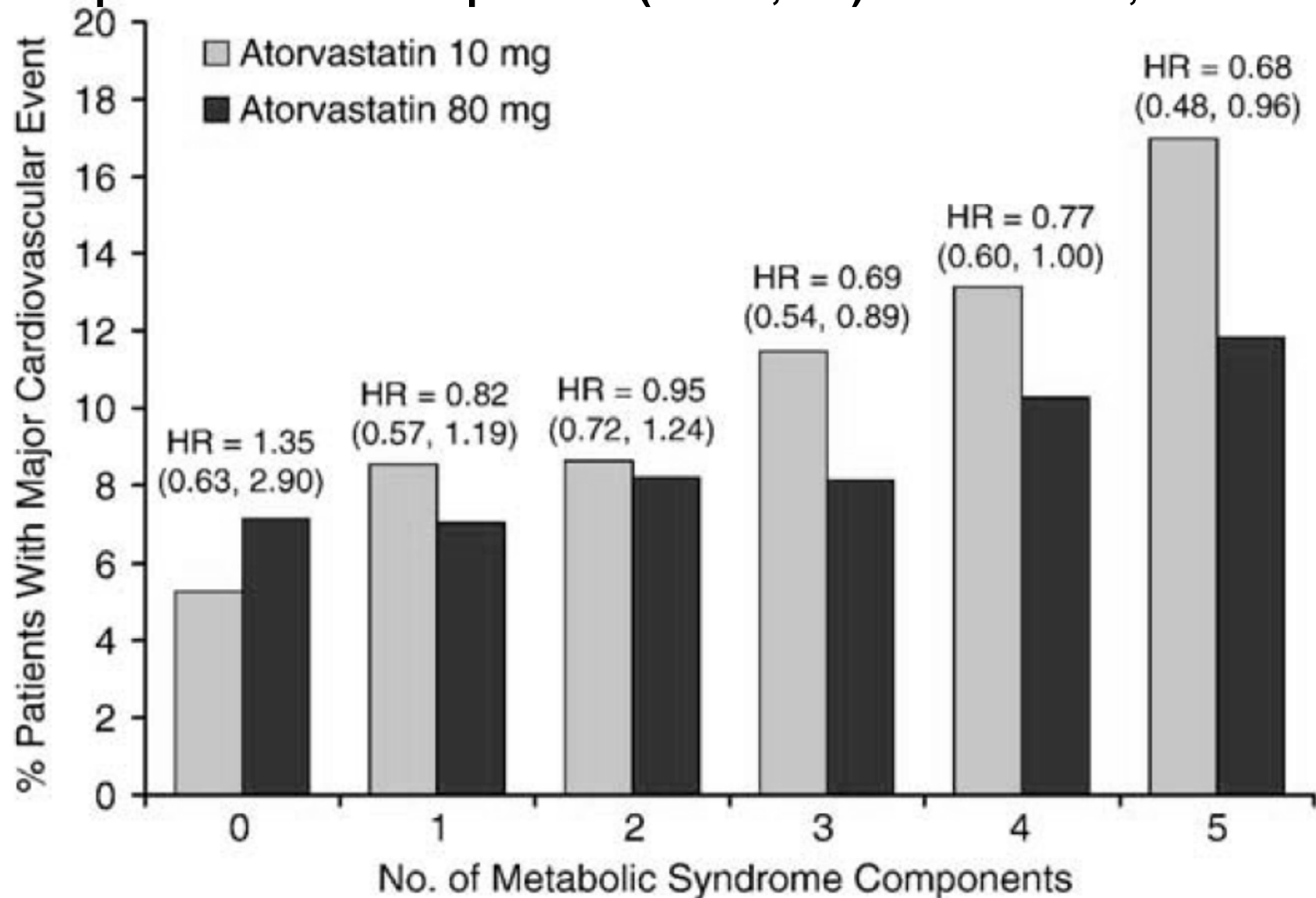Legend: ■ Baseline ● Standard ▲ Intensive

Y-axis: LDL-C (mg/dL)

¿Profundizamos mas en el riesgo?.

Number of major cardiovascular events by several risk components in all TNT patients (n = 10,001). Lancet 2006;368:919-28.
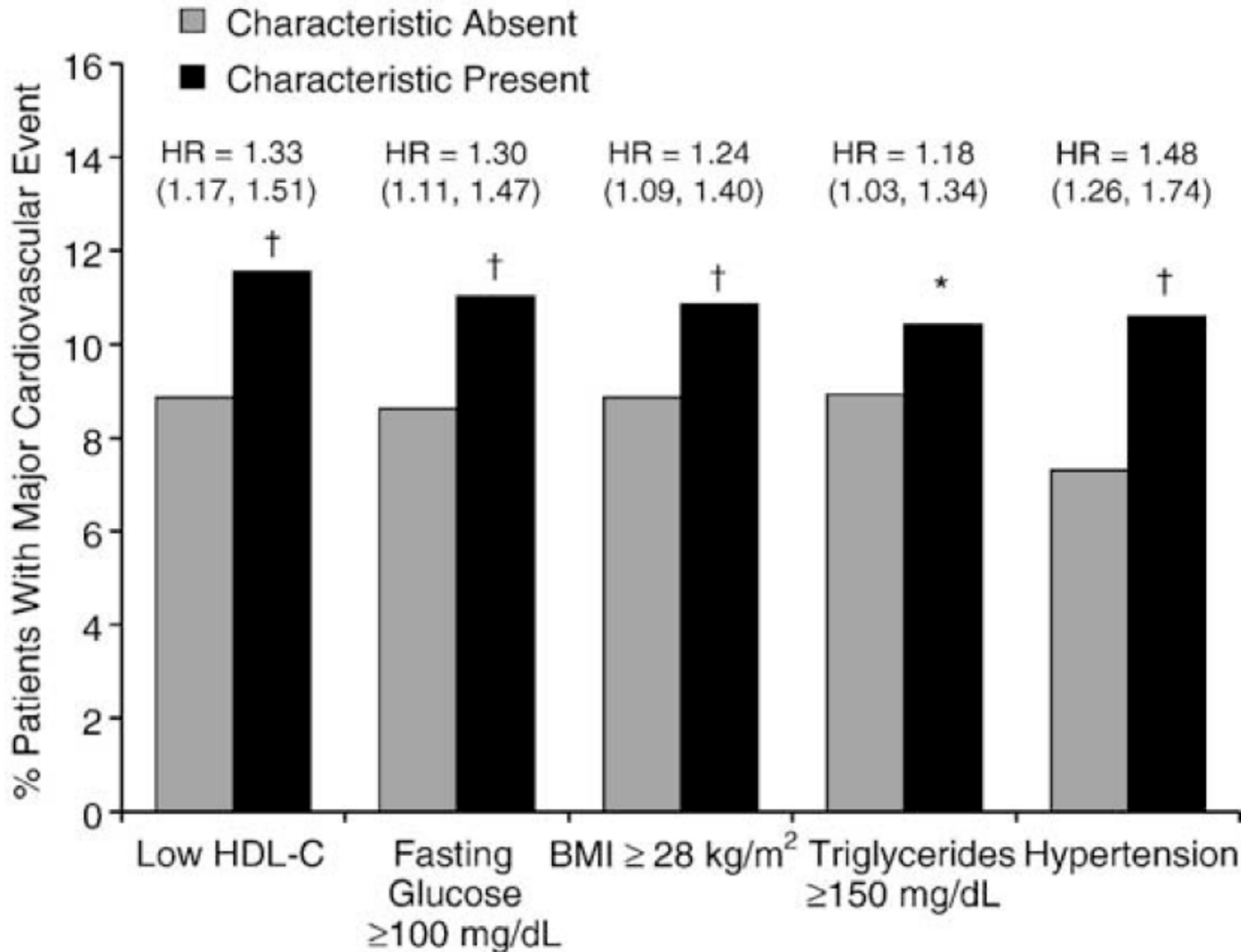
Number of major cardiovascular events by number of metabolic syndrome components in all TNT patients (n = 10,001). Lancet 2006;368:919-28.
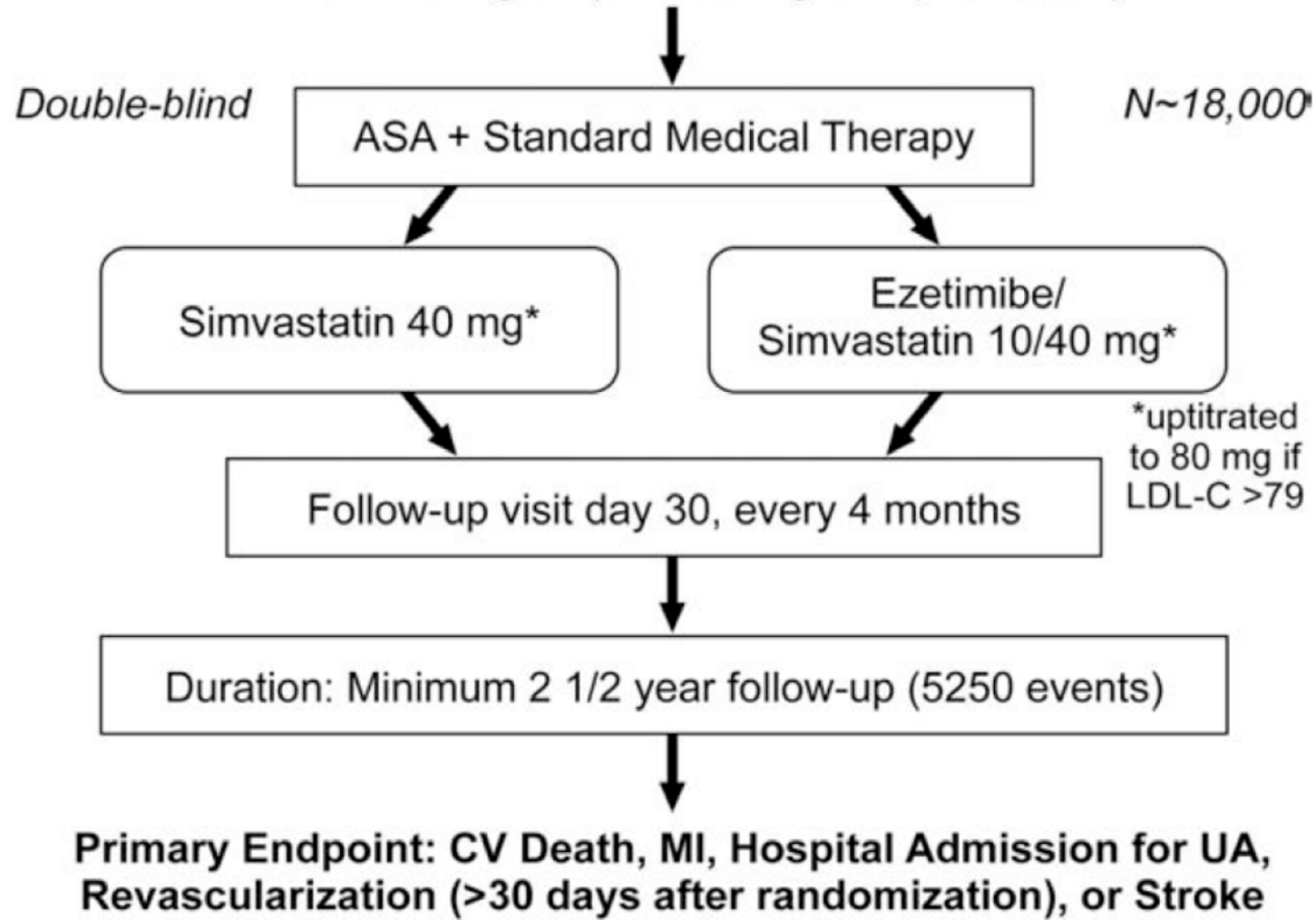
Chart legend:
- ☐ Atorvastatin 10 mg
- ■ Atorvastatin 80 mg

Y-axis: % Patients With Major Cardiovascular Event (0 to 20)

X-axis: No. of Metabolic Syndrome Components (0, 1, 2, 3, 4, 5)

Hazard ratios:
- 0: HR = 1.35 (0.63, 2.90)
- 1: HR = 0.82 (0.57, 1.19)
- 2: HR = 0.95 (0.72, 1.24)
- 3: HR = 0.69 (0.54, 0.89)
- 4: HR = 0.77 (0.60, 1.00)
- 5: HR = 0.68 (0.48, 0.96)

	0	1	2	3	4	5
Atorva10:	11/209	65/761	105/1216	147/1282	141/1073	79/465
Atorva80:	16/223	52/739	104/1269	109/1342	99/965	54/457

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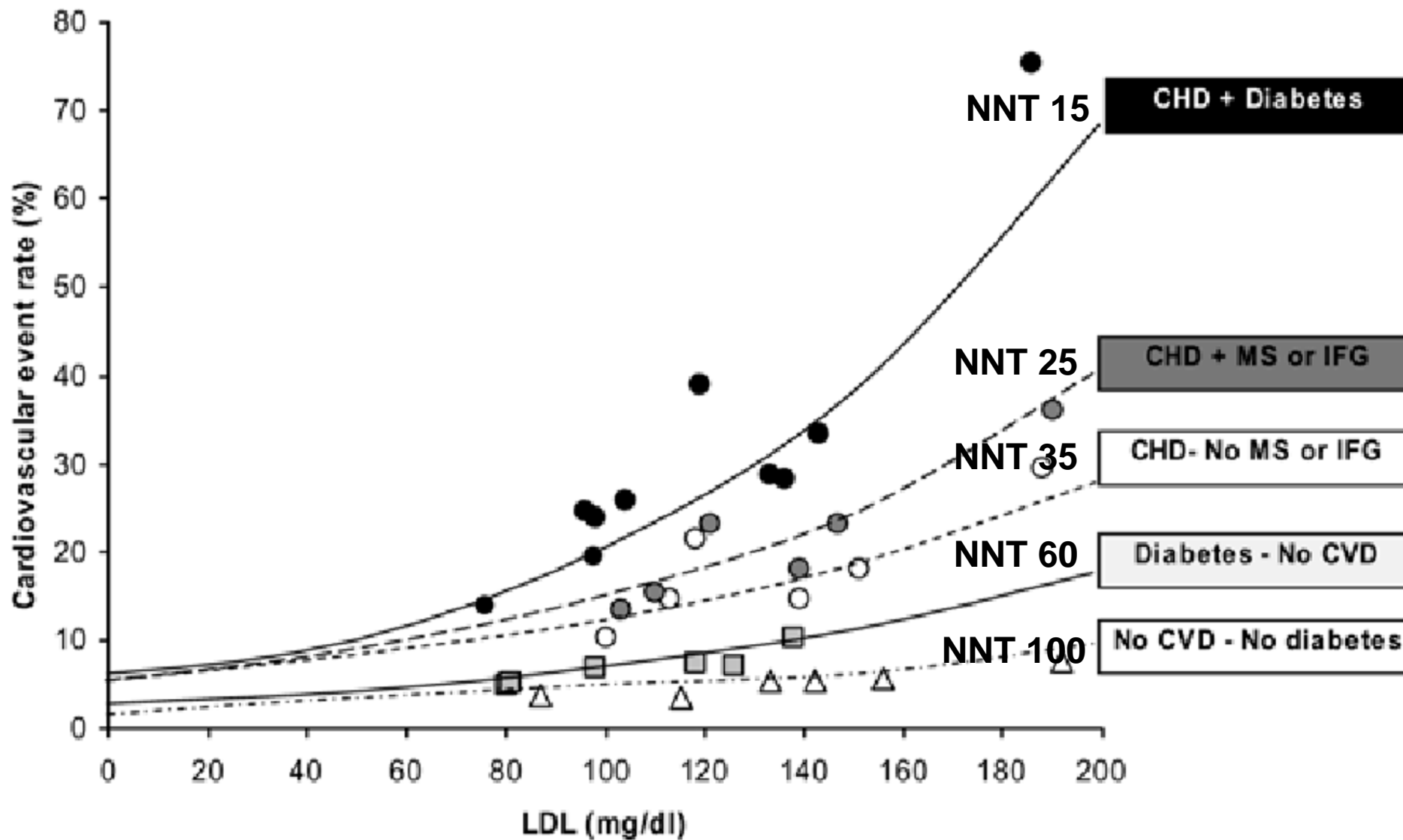
IMPROVE-IT

Patients stabilized post-ACS ≤ 10 days
LDL-C ≤125 mg/dL (or ≤100 mg/dL if prior statin)

Double-blind

N~18,000

ASA + Standard Medical Therapy

Simvastatin 40 mg*

Ezetimibe/
Simvastatin 10/40 mg*

*uptitrated
to 80 mg if
LDL-C >79

Follow-up visit day 30, every 4 months

Duration: Minimum 2 1/2 year follow-up (5250 events)

**Primary Endpoint: CV Death, MI, Hospital Admission for UA,
Revascularization (>30 days after randomization), or Stroke**

IMPROVE-IT study design.

October 2005- 2012

Estudio HPS2-THRIVE
(Treatment of HDL to Reduce the Incidence of Vascular Events)
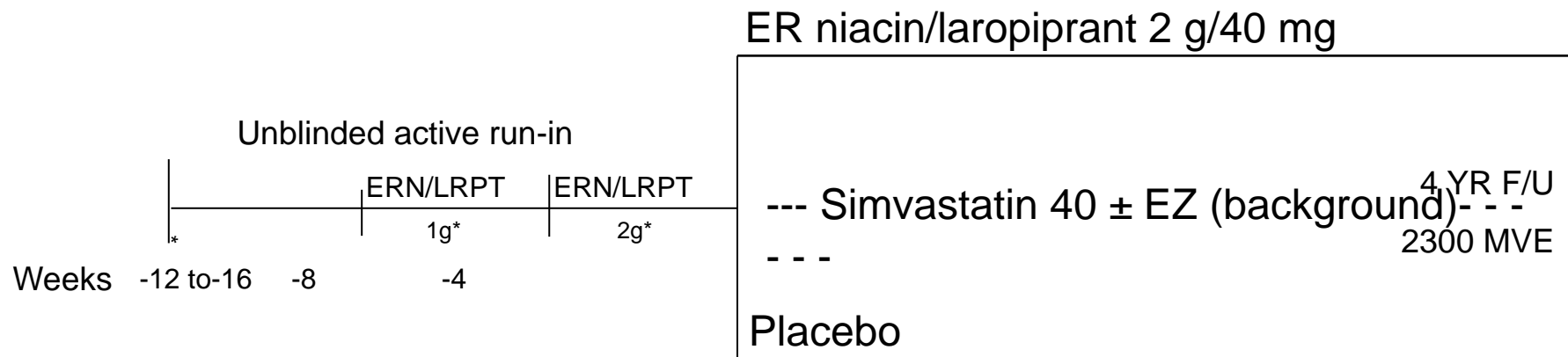
Población de pacientes:

25.000 pacientes *(7.000 diabéticos)* ateroscleróticos de alto riesgo con simvastatina 40 mg con o sin Ezetimiba 10mg + TREDAPTIVE o Placebo

Punto final primario:

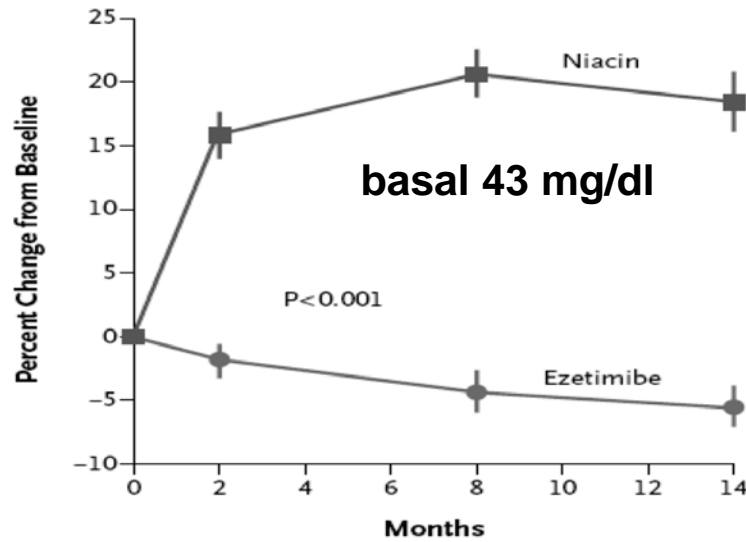Resultados (2013) de <u>Morbi-Mortalidad</u>
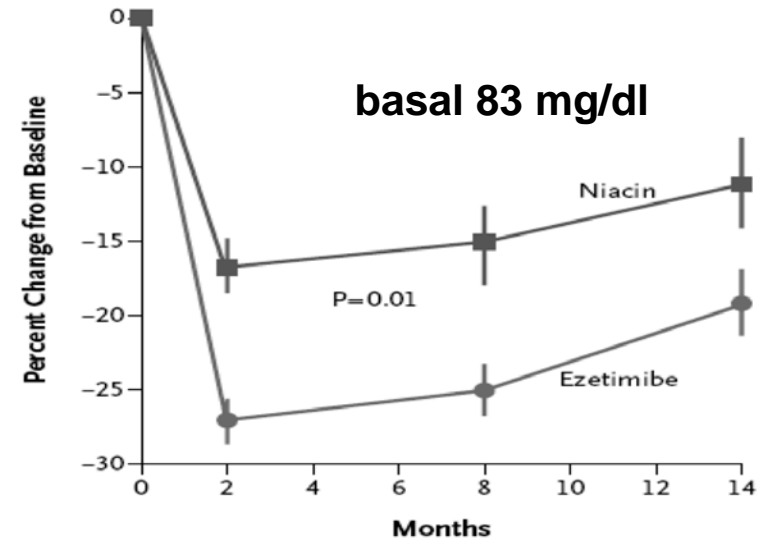
Enrolados:

20.000 pacientes

ER niacin/laropiprant 2 g/40 mg

Unblinded active run-in

| | ERN/LRPT | ERN/LRPT | | 4 YR F/U |
| | 1g* | 2g* | --- Simvastatin 40 ± EZ (background)- - - - - - | 2300 MVE |

Weeks   -12 to-16   -8   -4

Placebo

Extended-Release Niacin or Ezetimibe and Carotid Intima–Media Thickness. Taylor AJ. N Engl J Med 2009;361.

N=208 pacientes

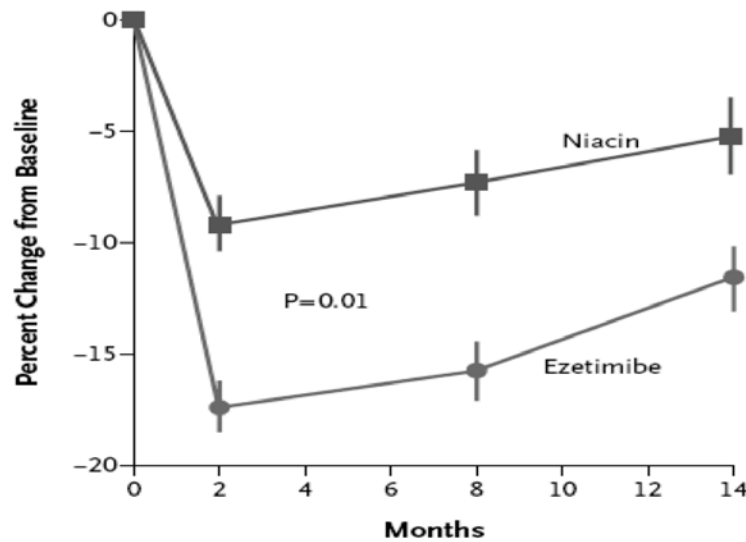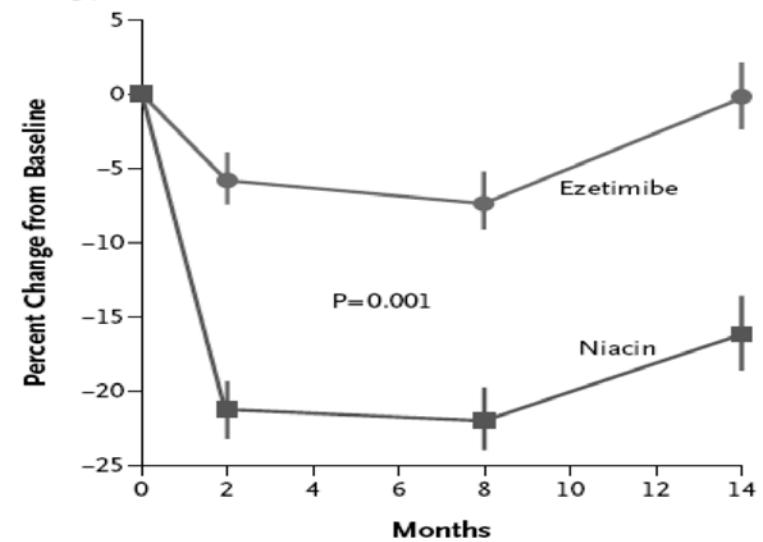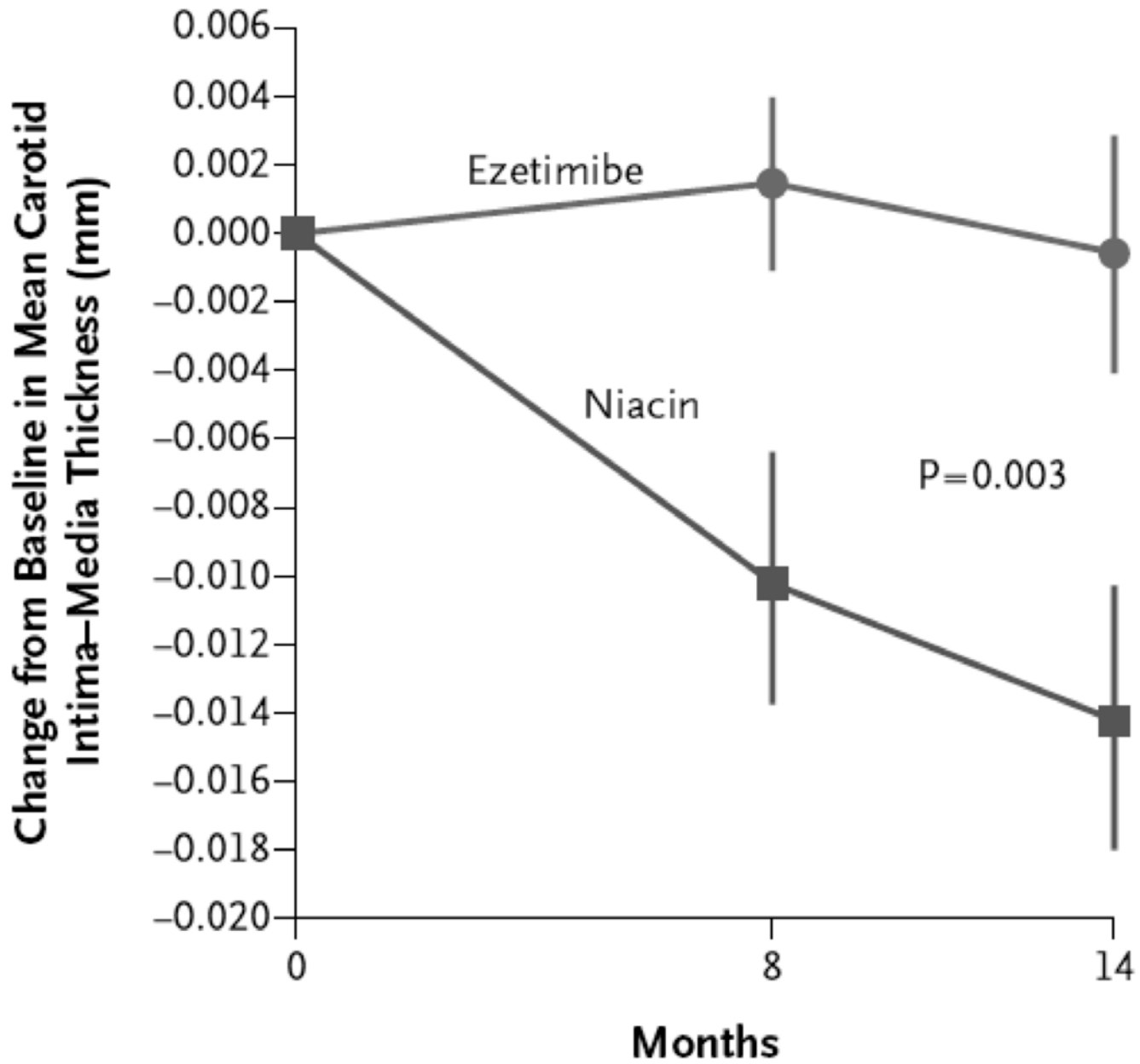A — HDL Cholesterol: basal 43 mg/dl — P<0.001 (Niacin, Ezetimibe)

B — LDL Cholesterol: basal 83 mg/dl — P=0.01 (Niacin, Ezetimibe)

C — Total Cholesterol: P=0.01 (Niacin, Ezetimibe)

D — Triglycerides: P=0.001 (Ezetimibe, Niacin)

Extended-Release Niacin or Ezetimibe and Carotid Intima–Media Thickness. Taylor AJ. N Engl J Med 2009;361.

NIA Plaque: Change in lipid parameters from baseline to 18 months

Lipid measure (mg/dL)	Statin + placebo, baseline	Statin + placebo, 18 mo	Statin + extended-release niacin, baseline	Statin + extended-release niacin, 18 mo	p (between groups)
Total cholesterol	166	152	174	150	0.65
LDL cholesterol	86	77	88	67	0.03
HDL cholesterol	55	49	55	58	<0.001
Triglycerides	123	93	115	84	0.02

….but failed to significantly alter atherosclerotic disease progression as measured by MRI.

Conclusiones

1. *Las estatinas, tras dieta y ejercicio, son fármacos de primera elección en la prevención de complicaciones coronarias y cardiovasculares. Son siempre obligatorias en prevención secundaria. El objetivo primario debe ser reducir el C-LDL, <u>medida mas eficaz cuanto mayor sea el riesgo del paciente.</u>*

2. *Aunque se usen estatinas a las dosis apropiadas es dificil alcanzar los objetivos de C-LDL en pacientes de alto riesgo en prevención secundaria. Utilizar terapia combinada es imprescindible en un gran número de pacientes (estatinas + ezetimiba o resinas o niacina) la mejor opción la darán los estudios clínicos en marcha.*

Table I. Baseline characteristics of the first 10,000 patients enrolled

Age (median [interquartile range]) in years	62 (55, 70)
Male (%)	77
Diabetes (%)	22
Prior MI (%)	17
Acute event	
STEMI (%)	47
NSTEMI (%)	37
UA (%)	16
Preenrollment coronary angiography	91
Preenrollment PCI after ACS event	76
Baseline LDL-C (median [interquartile range]) (mg/dL)	97 (81, 112)
No prior lipid-lowering therapy	104 (89, 116)
Prior lipid-lowering therapy	80 (68, 90)

Extended-Release Niacin or Ezetimibe and Carotid Intima–Media Thickness. Taylor AJ. N Engl J Med 2009;361.
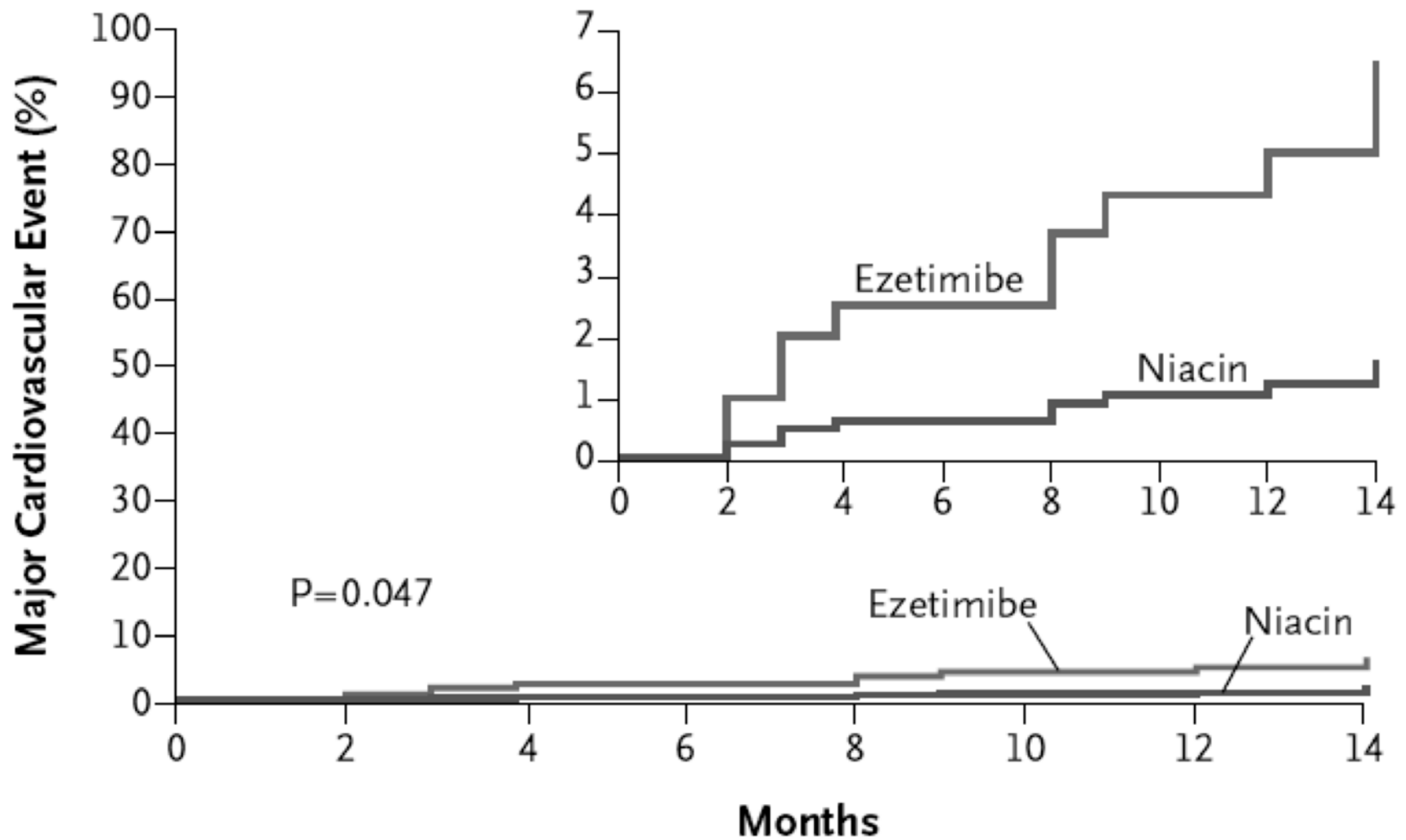
No. at Risk

Ezetimibe	176	174	171	167	160	154	146	143	139	132	126	121	118	113	111
Niacin	187	185	171	163	160	152	138	132	130	116	106	104	101	97	97