SEMI
LA VISIÓN GLOBAL DE LA PERSONA ENFERMA

XXXIV
Congreso Nacional de la Sociedad Española de Medicina Interna (SEMI)

21-23
Noviembre 2013
Palacio de Ferias y Congresos de Málaga
Málaga

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

CONTROVERSIAS Y NOVEDADES EN DISLIPEMIAS: Nuevas evidencias en el tratamiento de la dislipemia en pacientes de alto riesgo cardiovascular.

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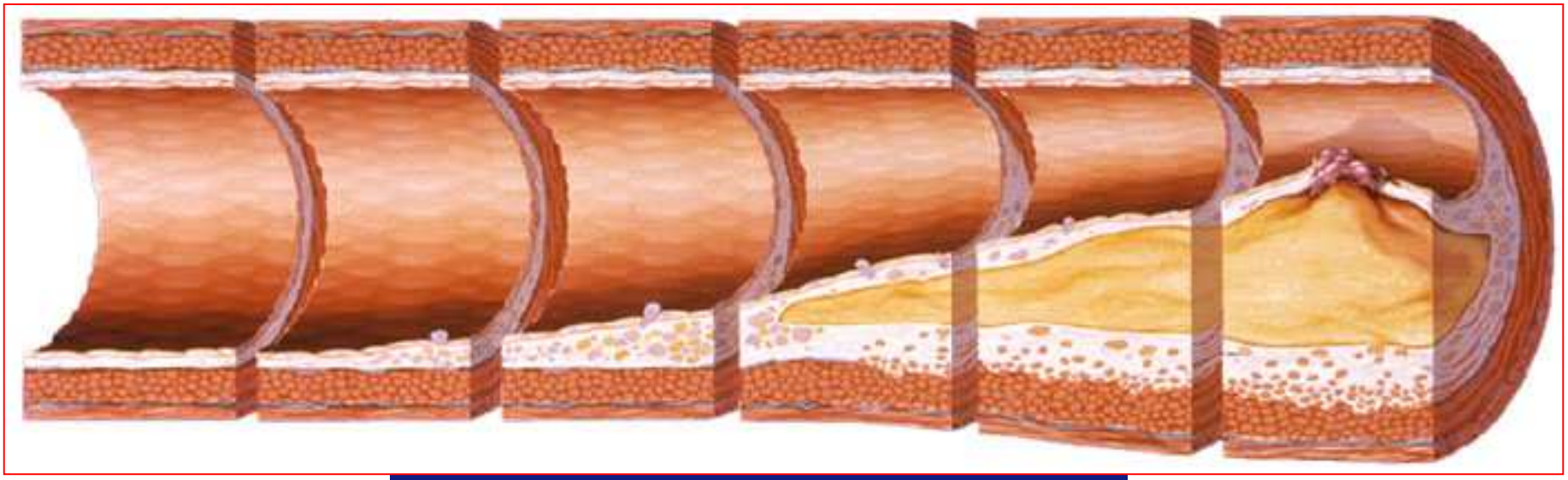
Hospital Universitario Reina Sofía.

Aterosclerosis: un proceso progresivo y sistémico

La escena del crimen

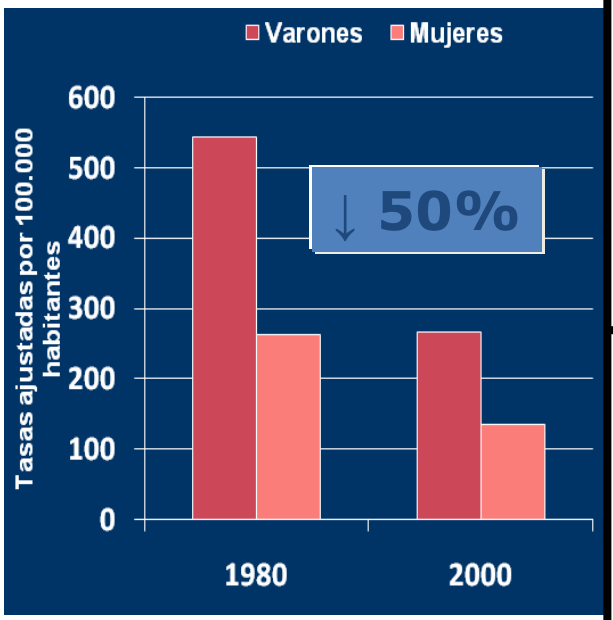


Disfunción Endotelial

Primera-Segunda década	Tercera década	Cuarta década	
Acumulación lipídica		Cls.musculares y colágena	Trombosis, Hematoma

Adaptado de Stary HC et al. *Circulation*. 1995;92:1355-1374.

Muertes coronarias en USA prevenidas o pospuestas 1980-2000 (% sobre la reducción total)



9%

Desconocida

44%

Control FRCV en Prevención 1ª

Tabaco	↓ 11,7 %
PAS	↓ 20,1 %
Colesterol	↓ 24,2 %
Actividad física	↓ 5,1 %
IMC	↑ 7,6 %
Diabetes	↑ 9,8 %

47%

Tratamiento enf. coronaria establecida

RCP	↓ 2,5 %
Trombolisis	↓ 0,7 %
Revascularización	↓ 7,1 %
Fármacos	↓ 36 %

Ford ES et al. N Engl J Med 2007; 356: 2388-98.

Manejo de la dislipemia
Los primeros 50 años

1950s

- **Inicio de la lipidología**
- **Datos epidemiológicos disponibles sobre la aterosclerosis**

1960s

- **Debate sobre la hipótesis lipídica**
- **Opciones de tratamiento existentes (fibratos, resinas, ácido nicotínico) de eficacia limitada**

1970s

- **Identificado el receptor del c-LDL**
- **Caracterización de la HMG-CoA reductasa y primer desarrollo de inhibidores**

1980s

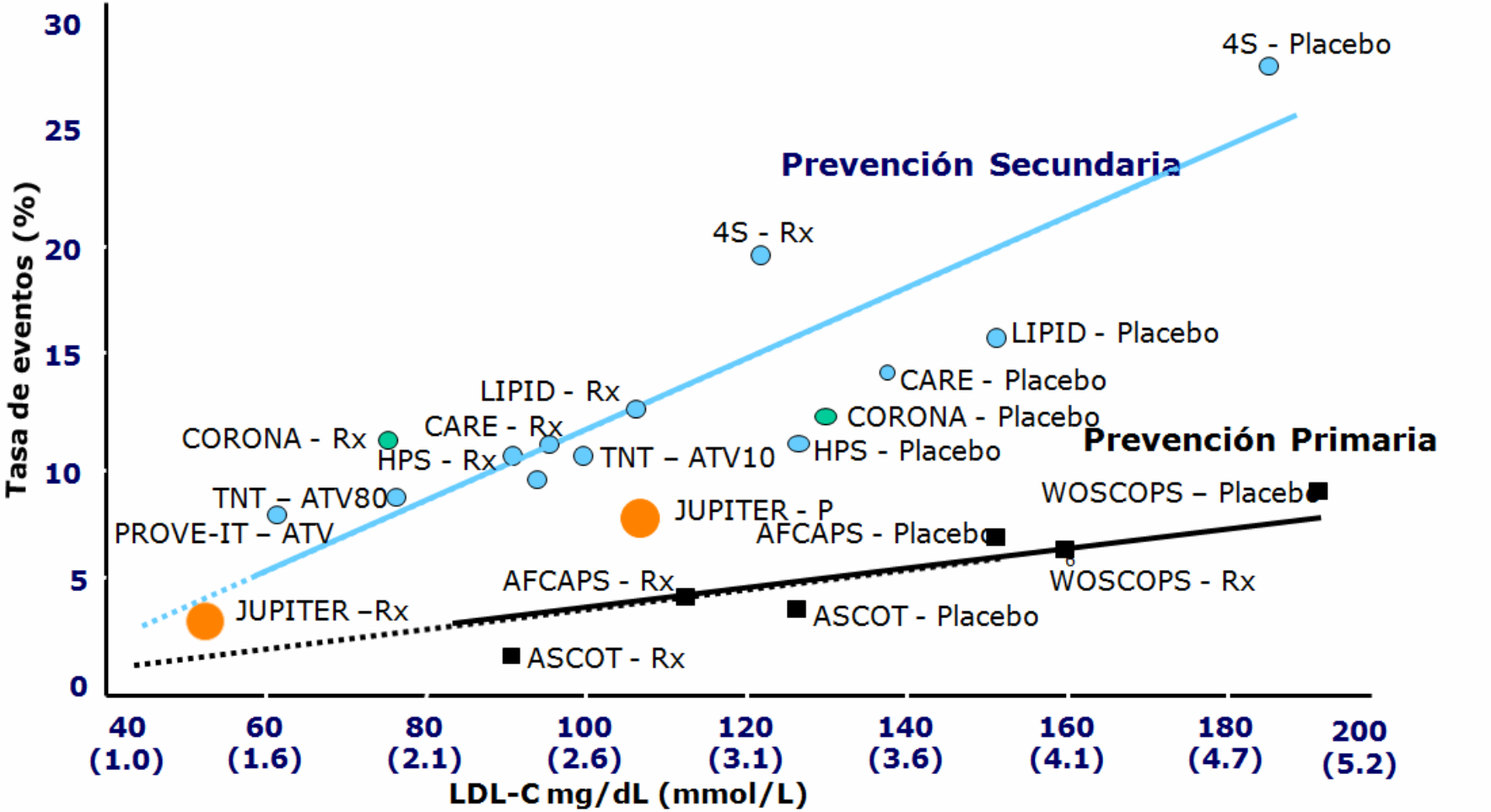
- **Se introducen las estatinas (lovastatina y simvastatina)**

1990s

- **Los principales estudios de estatinas confirman la hipótesis de lípidos y transforman la práctica médica**
- **c-LDL como diana principal del tratamiento**

2000s ¿Qué más se puede hacer?

Relación entre el C-LDL y la incidencia de episodios de enfermedad cardiovascular



Atv = atorvastatina; Pra = pravastatina; Sim = simvastatina; PROVE-IT = Pravastatin or AtorVastatin Evaluation and Infection Therapy; IDEAL = Incremental Decrease in Endpoints through Aggressive Lipid Lowering; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; AFCAPS = Air Force Coronary Atherosclerosis Prevention Study; WOSCOPS = West of Scotland Coronary Prevention Study

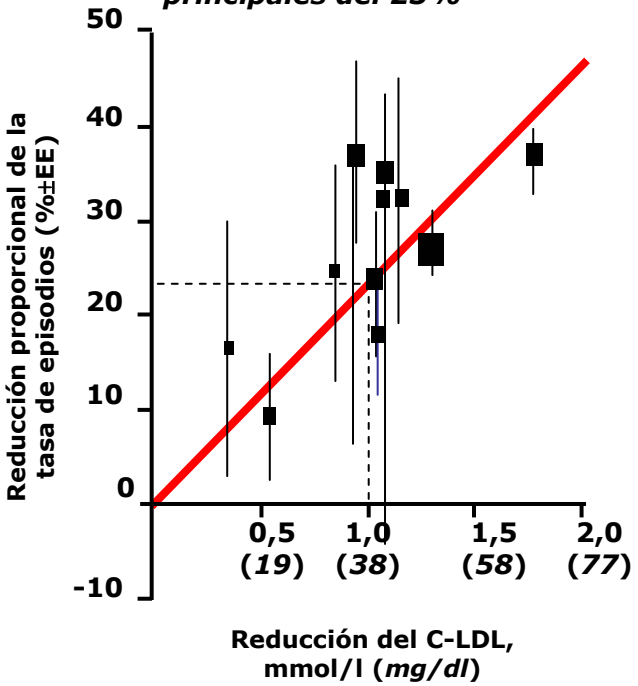
Rosenson RS. *Expert Opin Emerg Drugs*. 2004;9:269–279; LaRosa JC, et al. *N Engl J Med.* 2005;352:1425–1435; Pedersen TR, et al. JAMA. 2005;294:2437–2445.

Relación entre la reducción proporcional de episodios y la disminución media del C-LDL al cabo de 1 año

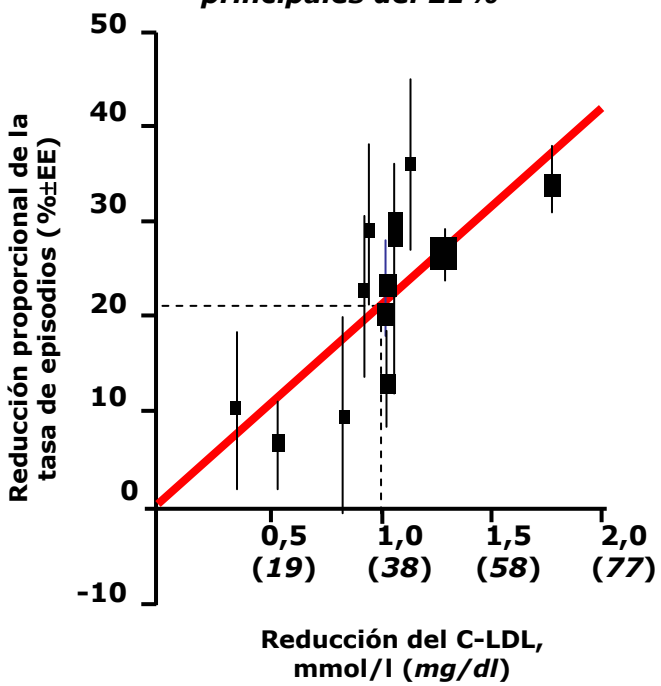
Metanálisis prospectivo de los datos de 90.056 pacientes procedentes de 14 ensayos de estatinas

Una reducción del C-LDL de 1 mmol/l (39 mg/dl) se tradujo en...

... una reducción de los episodios coronarios principales del 23%



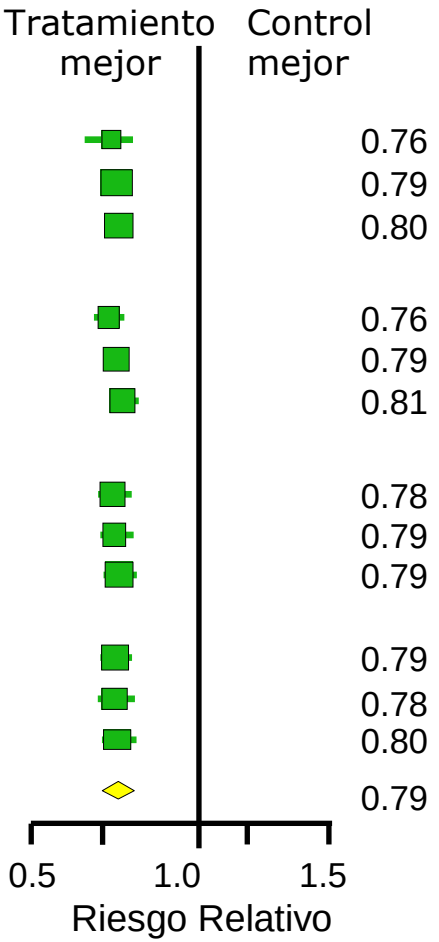
... una reducción de los episodios vasculares principales del 21%



CTT Collaborators. *Lancet* 2005;366:1267–1278.

Estatinas: beneficio independiente de los niveles lipídicos

Grupos	Eventos (%)		
	Tratamiento (45,054)	Control (45,002)	
Total-C (mg/dL)			
≤201	13.5	16.6	0.76
>201–251	13.9	17.4	0.79
>251	15.2	19.7	0.80
LDL-C (mg/dL)			
≤135	13.4	16.7	0.76
>135–174	14.2	17.6	0.79
>174	15.8	20.4	0.81
HDL-C (mg/dL)			
≤35	18.2	22.7	0.78
>35–43	14.3	18.2	0.79
>43	11.4	14.2	0.79
TG (mg/dL)			
≤124	13.4	16.8	0.79
>124–177	13.8	18.0	0.78
>177	15.3	18.8	0.80
Totall	14.1	17.8	0.79



CHD muerte, IAM, Ictus, Revascularización coronaria

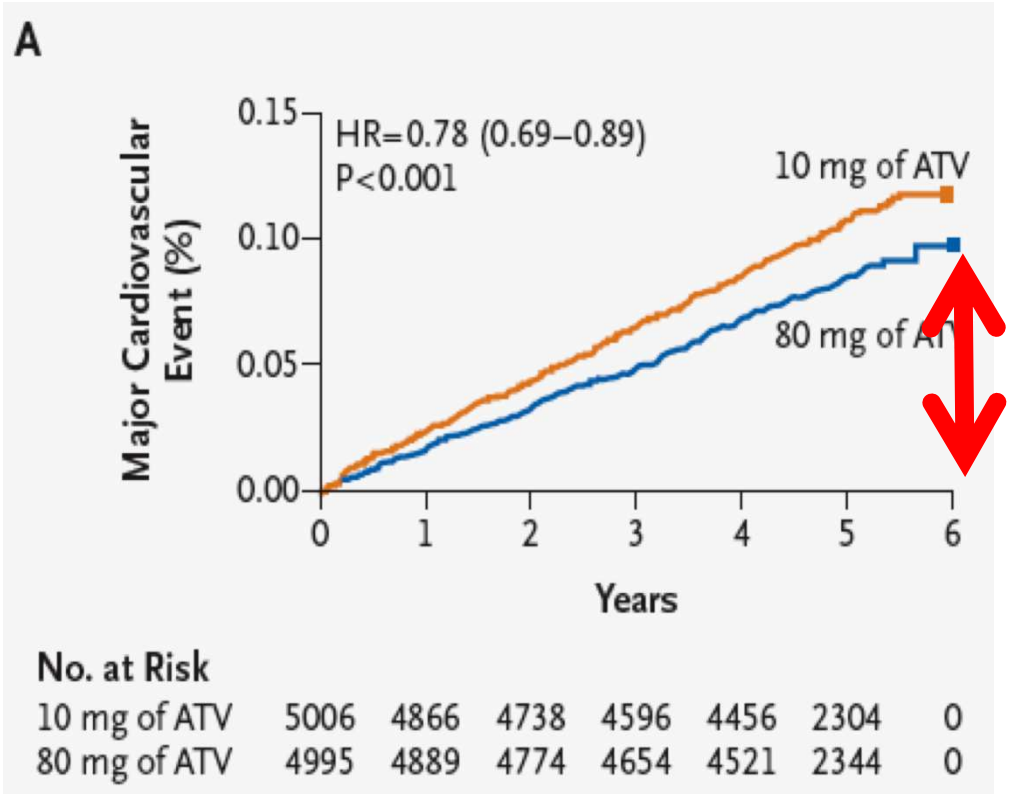
CTT Collaborators. Lancet. 2005;366:1267-78

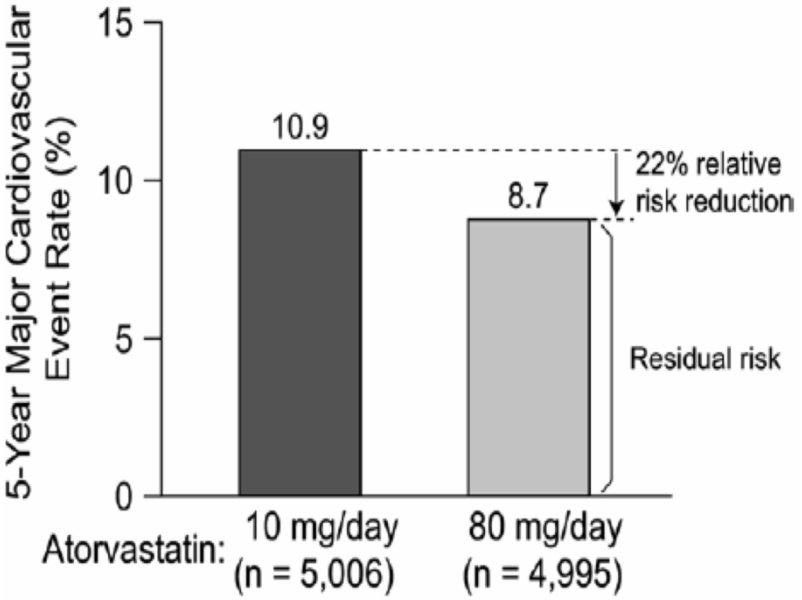
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

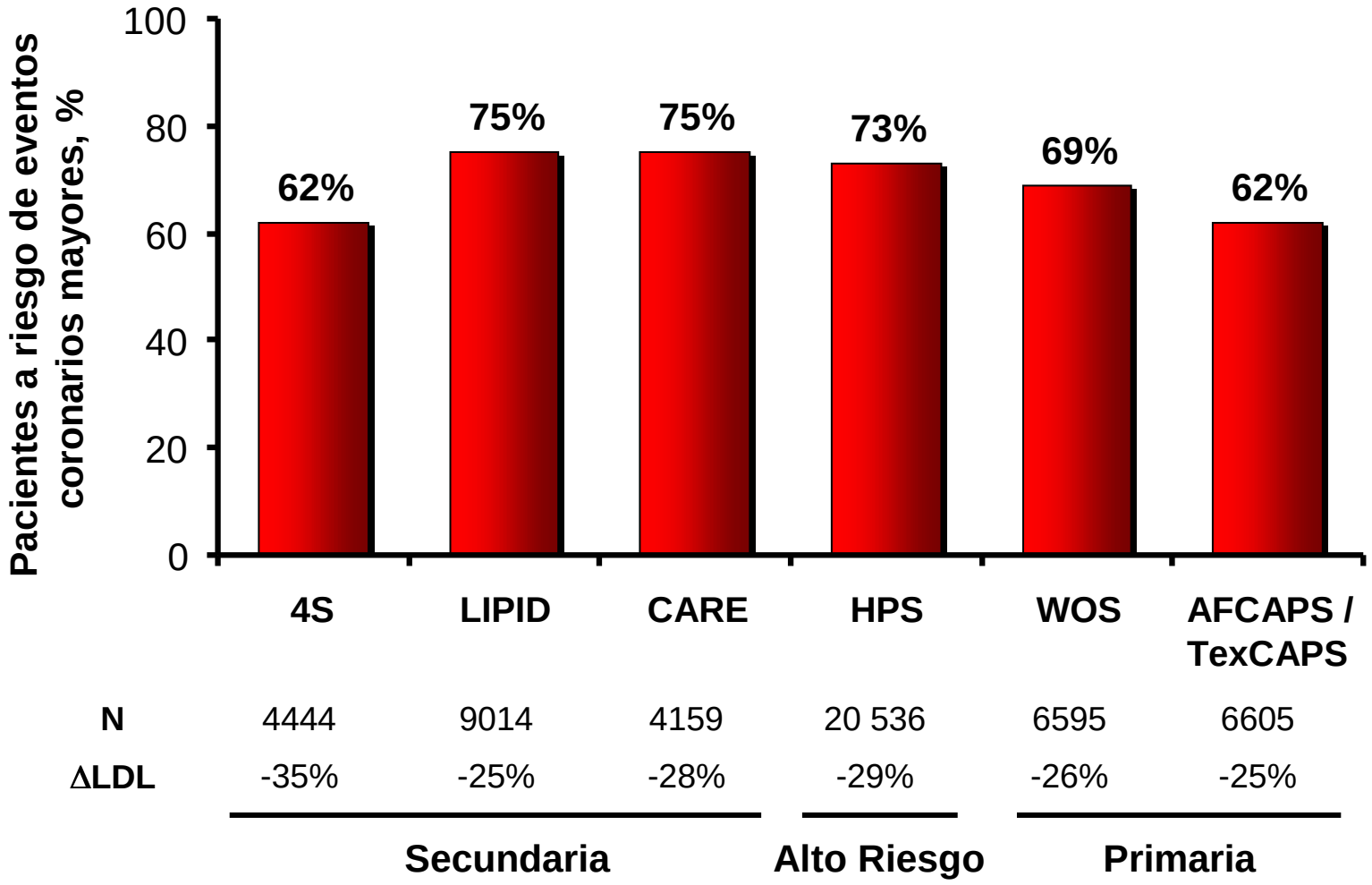
Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease

John C. LaRosa, M.D., Scott M. Grundy, M.D., Ph.D., David D. Waters, M.D., Charles Shear, Ph.D., Philip Barter, M.D., Ph.D., Jean-Charles Fruchart, Pharm.D., Ph.D., Antonio M. Gotto, M.D., D.Phil., Heiner Greten, M.D., John J.P. Kastelein, M.D., James Shepherd, M.D., and Nanette K. Wenger, M.D., for the Treating to New Targets (TNT) Investigators*



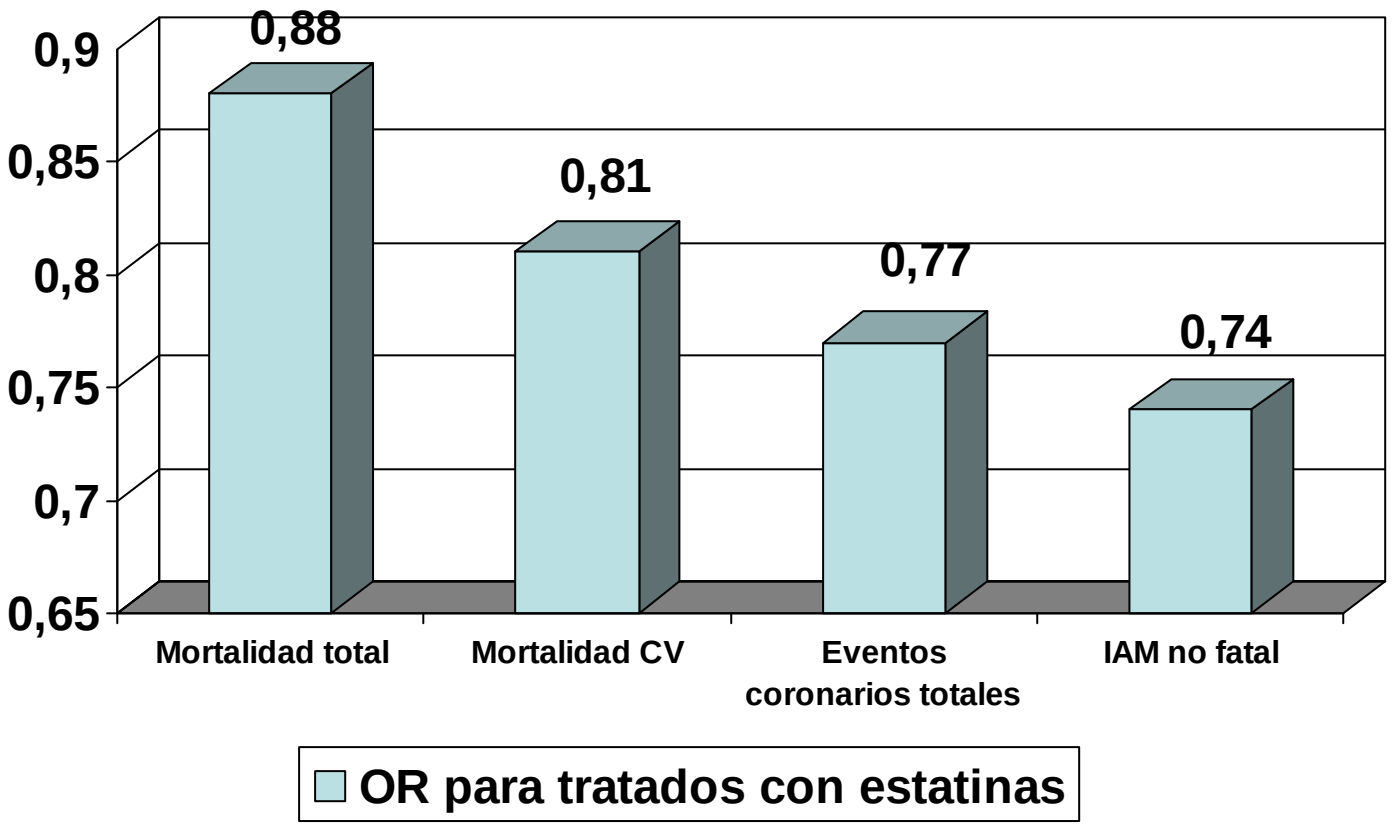


Riesgo Residual Cardiovascular en ensayos con estatinas a dosis estándar

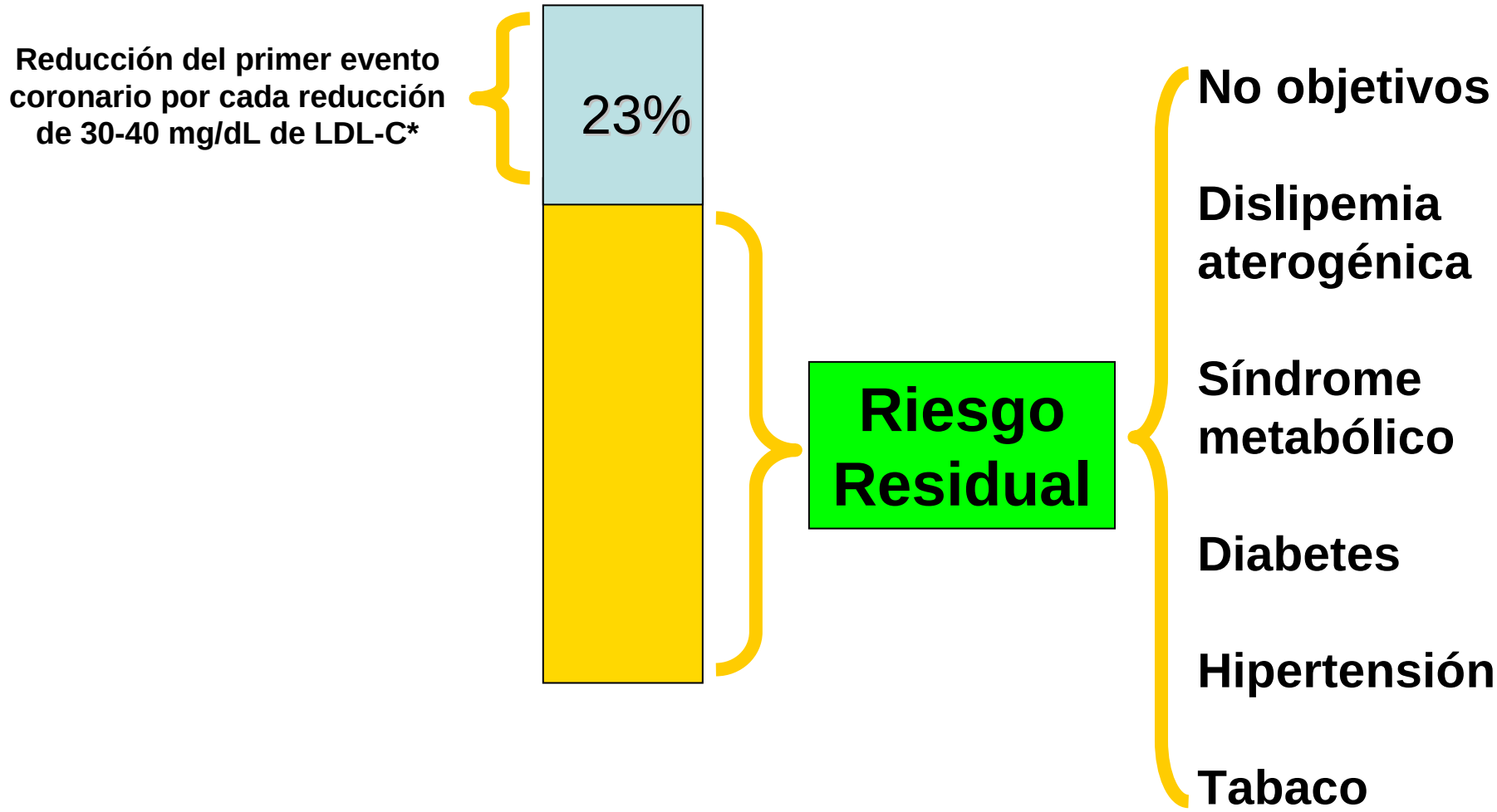


Adaptado de Libby PJ, et al. *J Am Coll Cardiol*, 2005:46:1225-1228.

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



Riesgo Residual de enfermedad cardiovascular: algunos factores susceptibles de tratamiento



*Cholesterol Treatment Trialists' (CTT) Collaborators. Lancet. 2005;366:1267-1278.

EL RIESGO RESIDUAL

- **Con LDL bajo**
  - Otros FR Lipídicos
    - HDL-C, Triglicéridos (Dislipemia aterógena)
    - Síndrome Metabólico
    - Lp (a)
    - Tamaño LDL
  - FR no lipídicos
    - Inflamación, oxidación, coagulación
    - Diabetes
    - Hipertensión
    - Tabaquismo
- Por no conseguir objetivos LDL

Pacientes con riesgo lipídico “no-LDL dependiente”

In Framingham, Lowest HDL-C Associated with Greater CHD Risk than Highest LDL-C

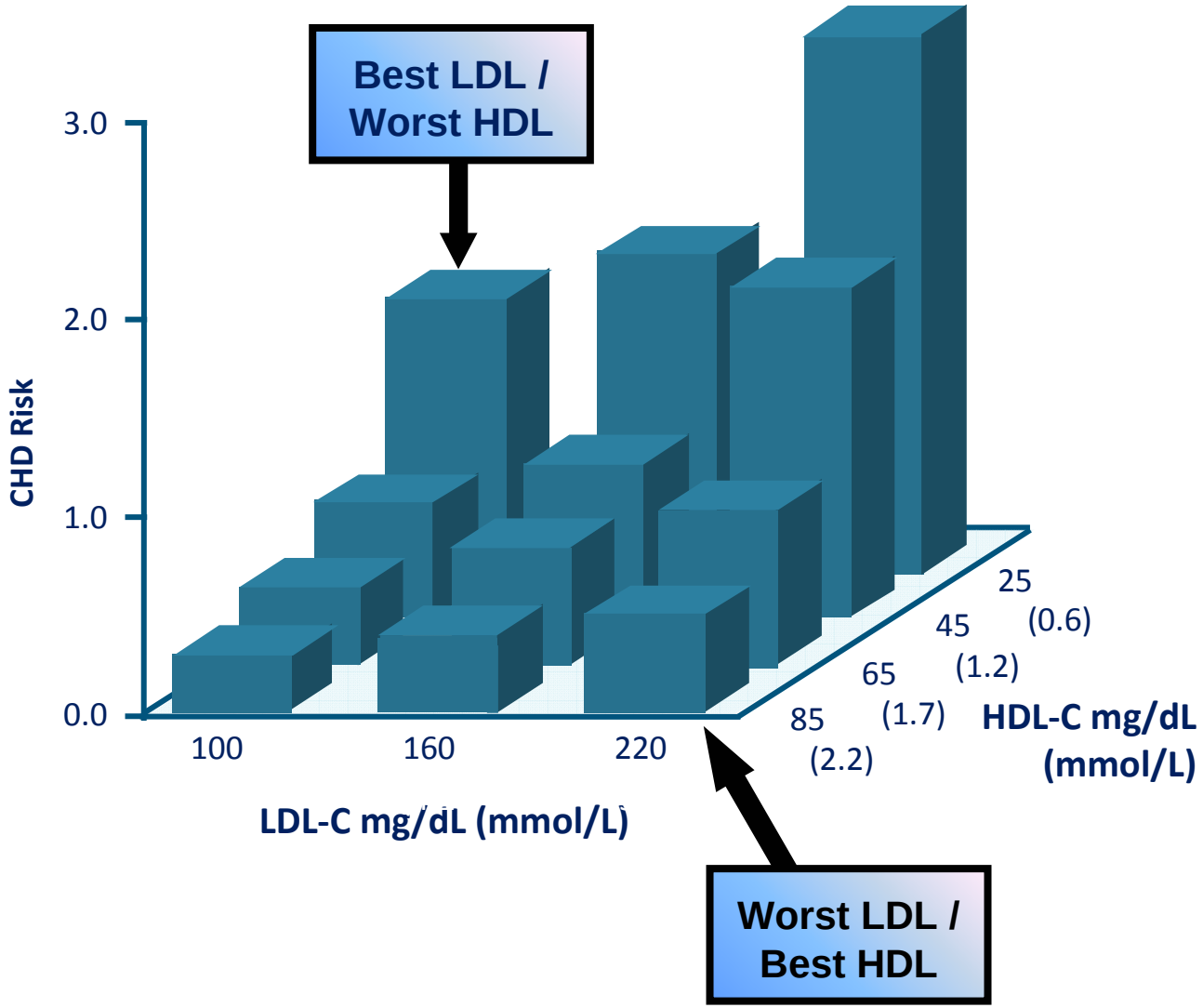
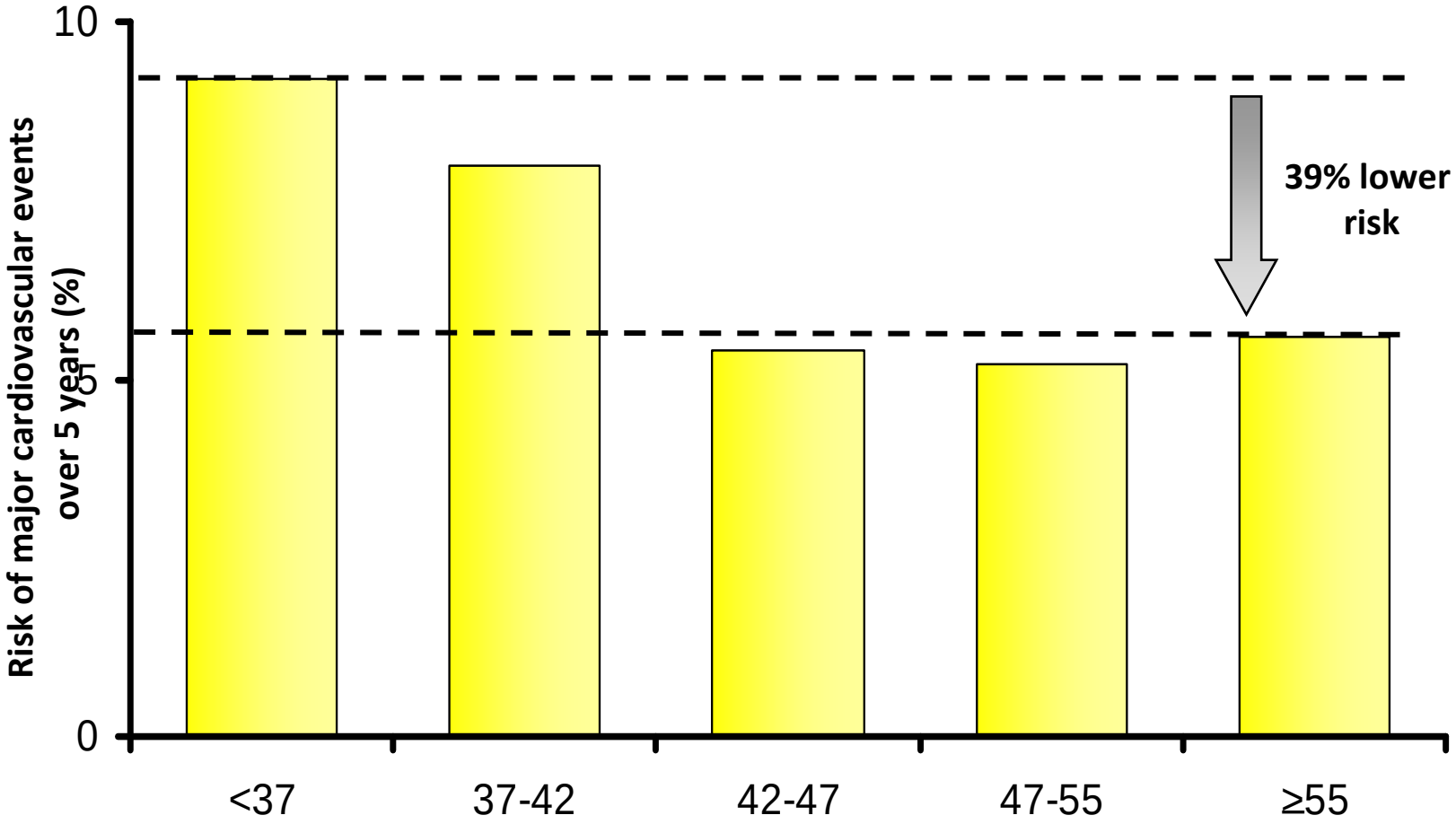


Chart adapted from Gordon T, Castelli WP, Hjortland MC, et al. *Am J Med*. 1977;62:707-714.

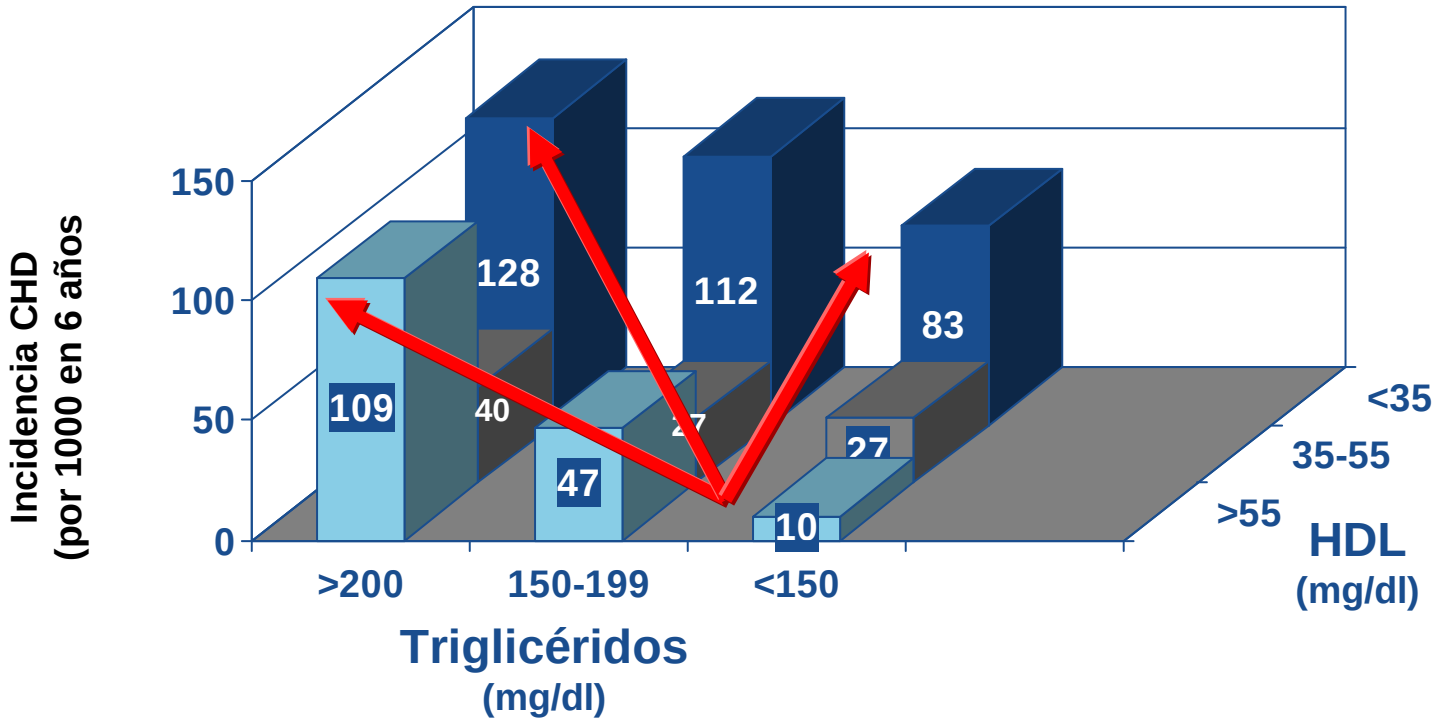
High HDL-C decreases cardiovascular risk at low LDL-C (<70 mg/dL) – TNT study



Barter P et al. N Engl J Med 2007;357:1301-10.

Incidencia de eventos coronarios según niveles de TG y de HDL

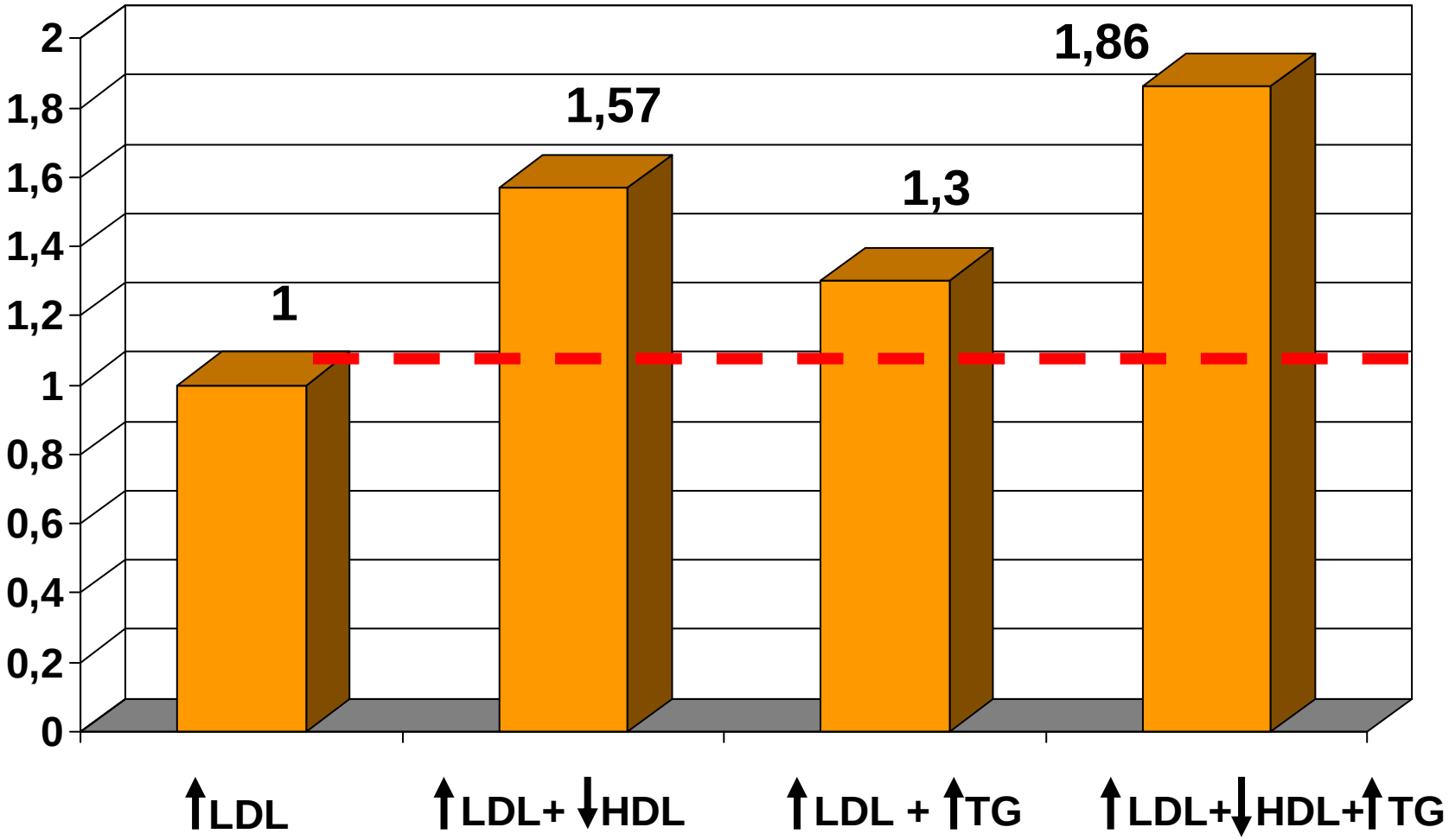
Estudio PROCAM



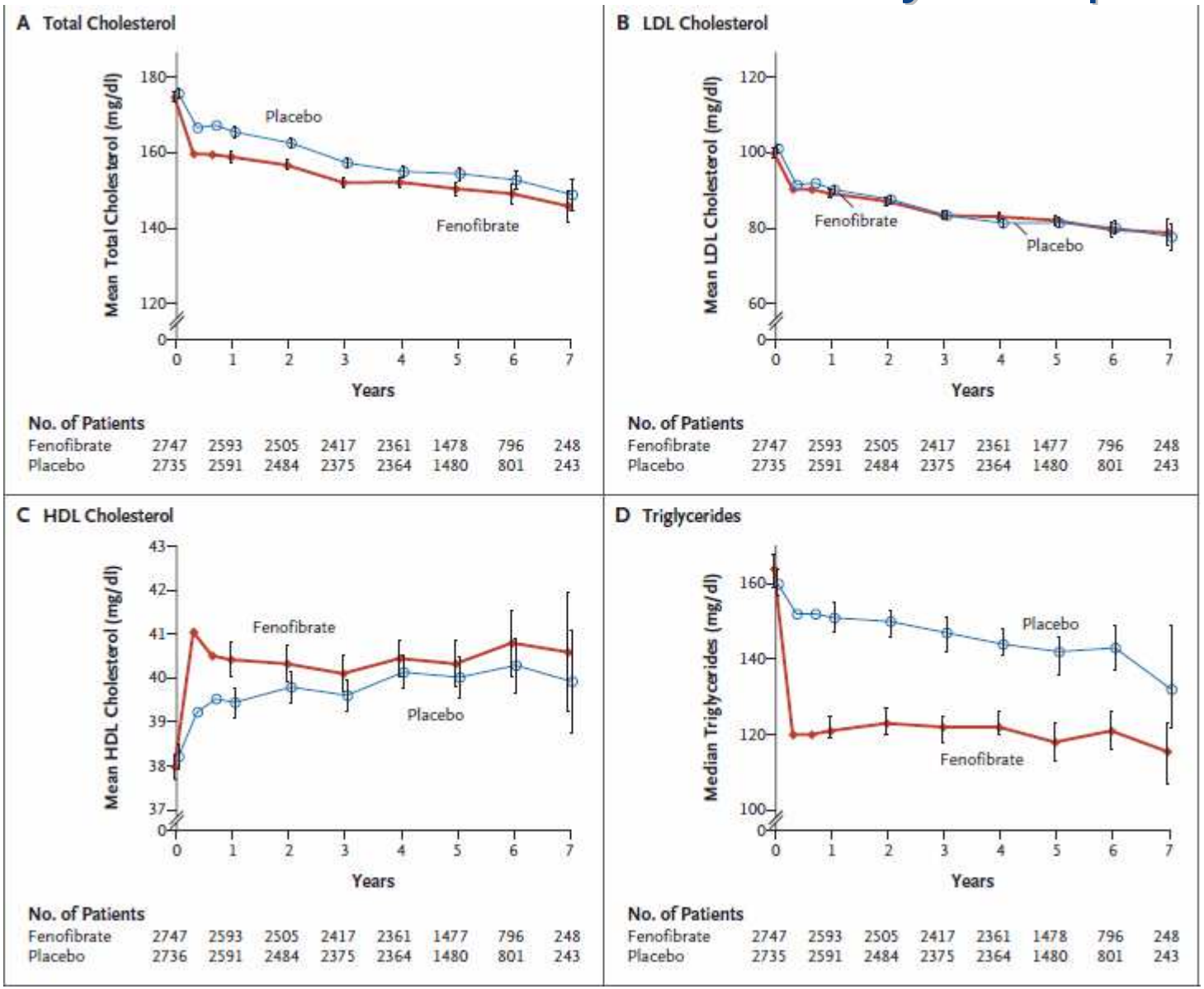
Incidencia de enfermedad coronaria por 1000 sujetos en un periodo de 6 años

Assman G et al. Atherosclerosis 124 Suppl (1996) S11-S20

Exceso de riesgo atribuible a TG y HDL
(estudio PREV-ICTUS)

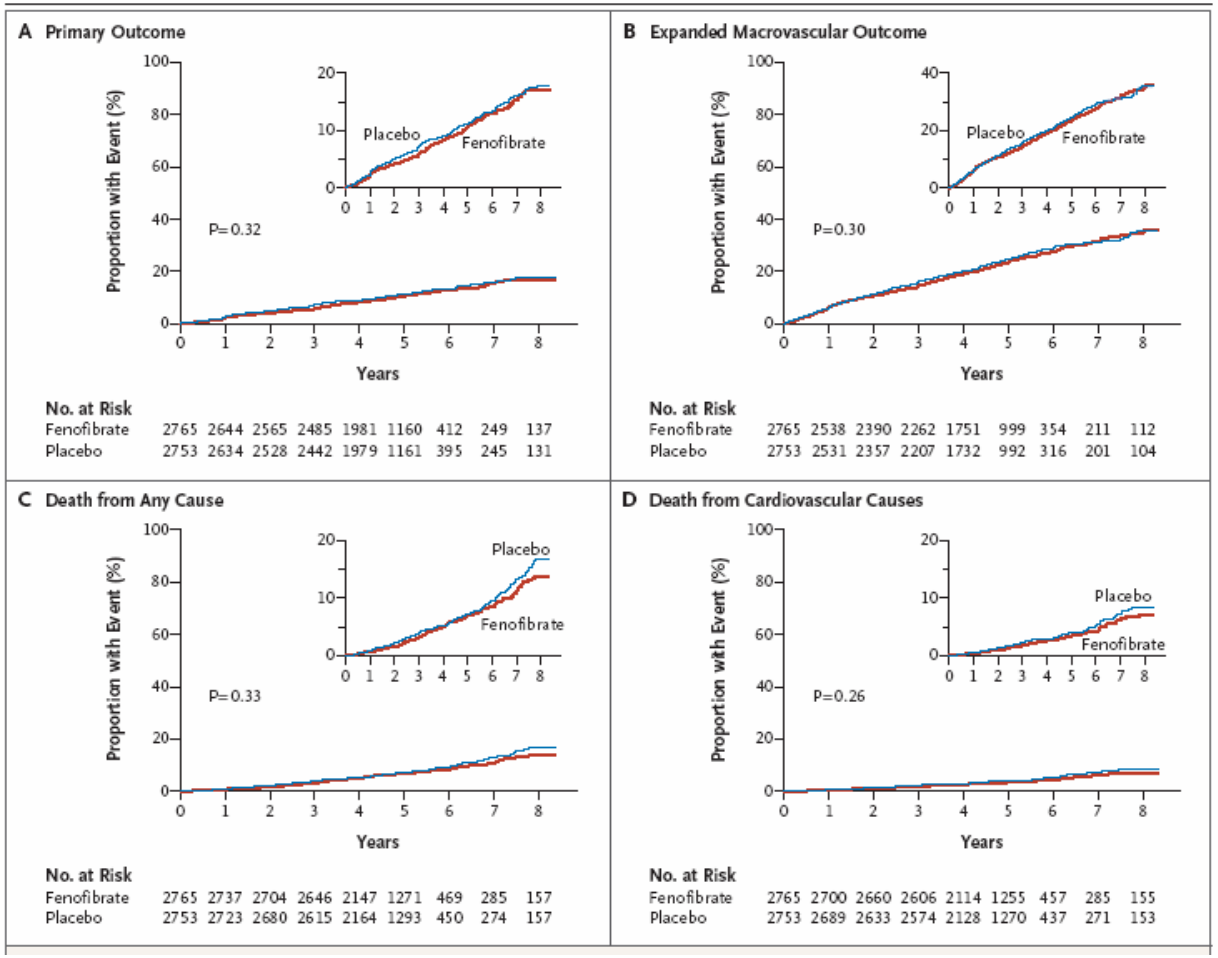


Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. The ACCORD Study Group

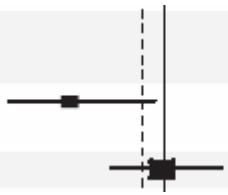


N Engl J Med 2010;362:1563-74.

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. The ACCORD Study Group

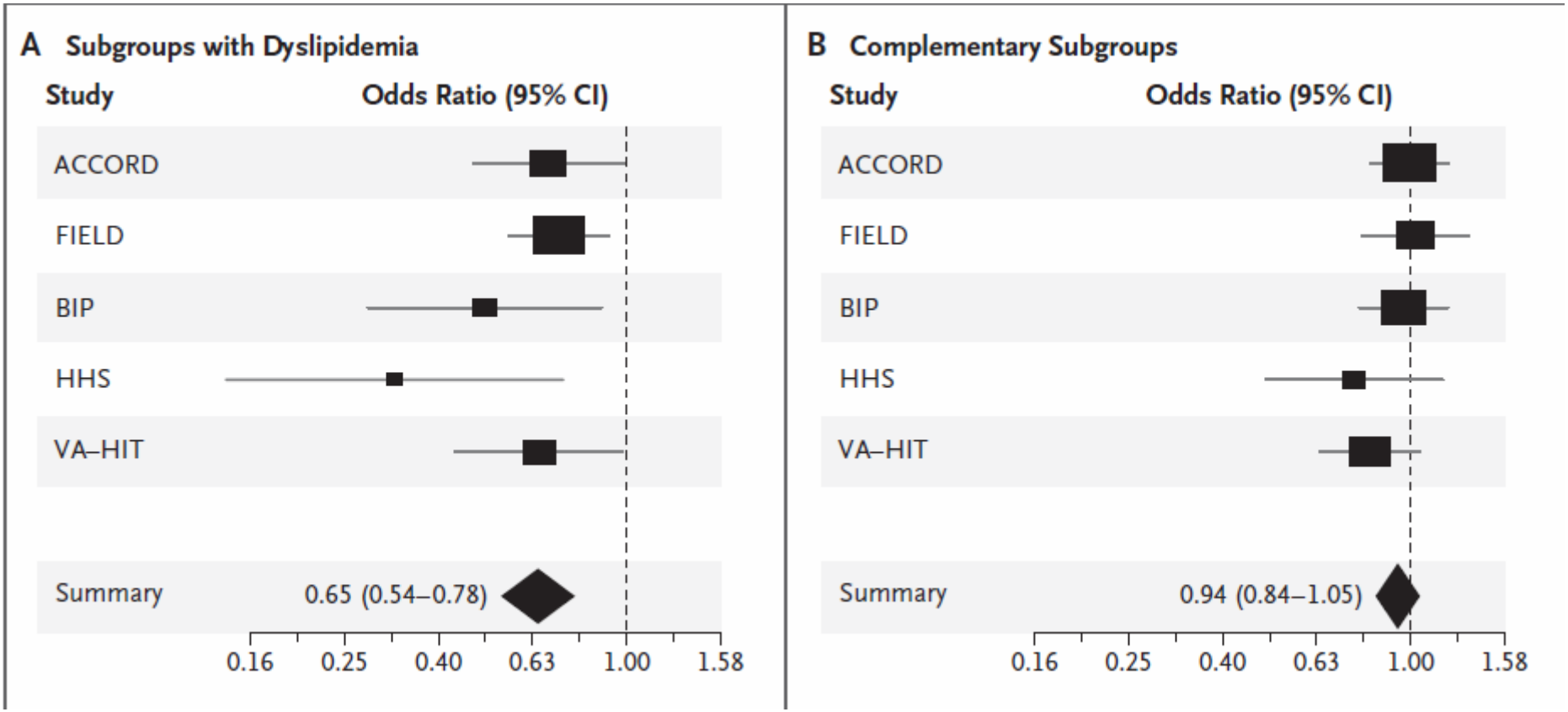


Triglyceride–HDL cholesterol combination			0.06
Triglyceride ≥204 mg/dl and HDL ≤34 mg/dl	12.37 (485)	17.32 (456)	
All others	10.11 (2264)	10.11 (2284)	



N Engl J Med 2010;362:1563-74.

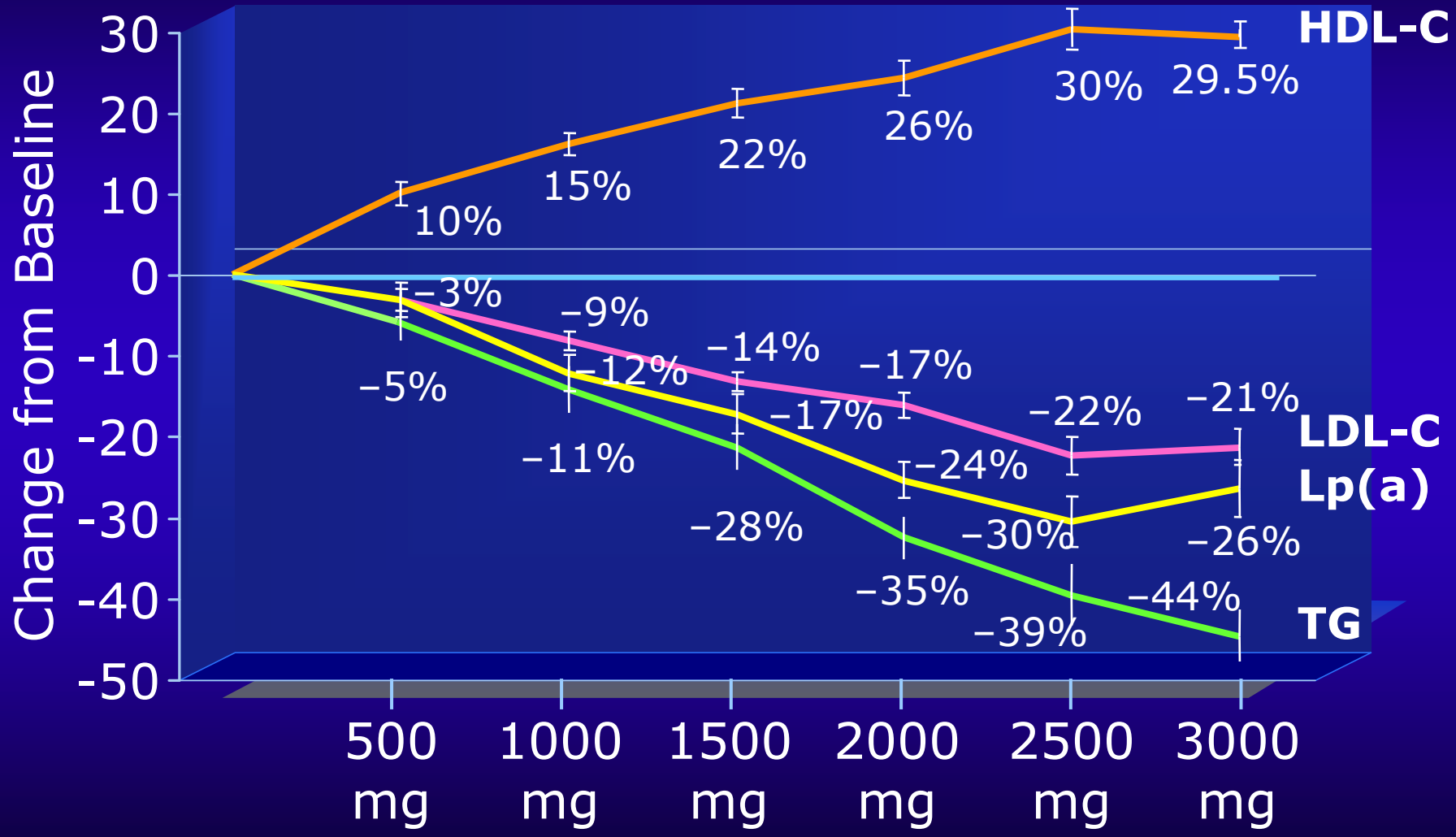
Combination Lipid Therapy in Type 2 Diabetes



The subgroup with dyslipidemia defined according to criteria prespecified in the ACCORD Lipid trial:
triglyceride level of ≥204 mg/dL and an HDL-c level ≤34 mg/dL

N Engl J Med 2010; 363:692-4

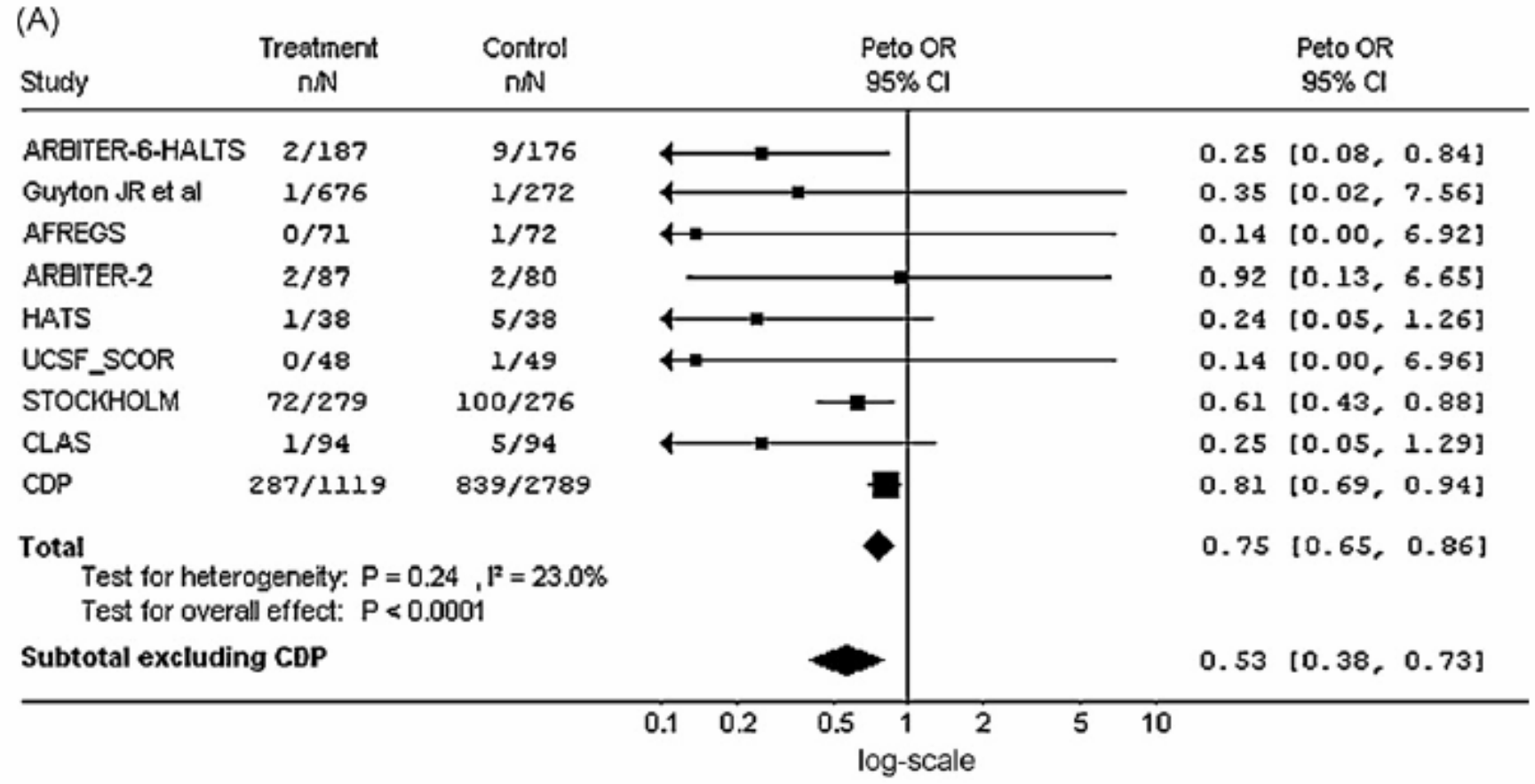
Efficacy of Extended-Release Niacin



Goldberg A et al. *Am J Cardiol* 2000;85:1100-1105.

Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis

Major Cardiovascular events



Atherosclerosis 210 (2010) 353–361

Trials of Combined LDL-C Lowering and HDL-C Raising

Study	Sponsor	Rx vs. Control	N total*	$ total (mil)*	Median Follow	Finish Year*
AIM-HIGH	NIH & Kos	**Nia + Sim vs. Sim**	3300	42 M	4.0 years	**Q3–'10**
HPS-THRIVE	Merck, USA	**Nia + Sim + FI† vs. Sim**	20000	????	4+ years	**Q4–'12**

* Approximate

Drug Codes: Feno = fenofibrate, St = statin, Tor = torcetrapib, Ator = atorvastatin, Sim = simvastatin, Nia = extended release niacin

†FI = flush inhibitor (PgD2 receptor blocker).

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy: AIM-HIGH study

Table 2. Lipid Values at Baseline and during Follow-up.*

Variable	Placebo plus Statin (N=1696)				Extended-Release Niacin plus Statin (N=1718)			
	Baseline (N=1696)	Year 1 (N=1554)	Year 2 (N=1326)	Year 3 (N=873)	Baseline (N=1718)	Year 1 (N=1561)	Year 2 (N=1329)	Year 3 (N=865)
LDL cholesterol								
Mean (mg/dl)	75.8±24.3	70.4±18.9	69.5±19.9	68.3±19.3	76.2±25.7	66.4±19.9	65.0±20.5	65.2±21.8
Median (mg/dl)	74	69	68	67	74	64	62	62
Interquartile range (mg/dl)	60–87	59–79	57–78	56–78	59–87	54–75	52–74	51–74
Median change from baseline (%)		−4.3	−5.5	−7.6		−10.0	−12.0	−13.6
Triglycerides								
Median (mg/dl)	162	155	153	152	164	121	122	120
Interquartile range (mg/dl)	128–218	118–208	117–210	114–204	127–218	86–170	85–170	84–172
Median change from baseline (%)		−5.0	−8.1	−9.9		−28.2	−28.6	−30.8
HDL cholesterol								
Mean (mg/dl)	35.3±5.9†	38.4±7.6	38.7±7.4	39.1±7.7	34.8±5.9	43.6±10.9	43.9±10.6	44.1±11.3
Median (mg/dl)	35	38	38	38	35	42	42	42
Interquartile range (mg/dl)	31–39	34–43	34–43	34–44	31–39	36–49	37–50	36–50
Median change from baseline (%)		9.1	9.8	11.8		23.3	25.0	25.0
Non-HDL cholesterol (mg/dl)								
Mean	111.9±28.3	105.0±24.9	Not analyzed	102.3±23.7	112.6±30.5	94.3±27.2	Not analyzed	92.8±28.6
Median	108	102		99	108	90		90
Interquartile range	93–126	89–117		87–114	93–127	78–107		74–105

N Engl J Med 2011;365:2255-67.

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy: AIM-HIGH study

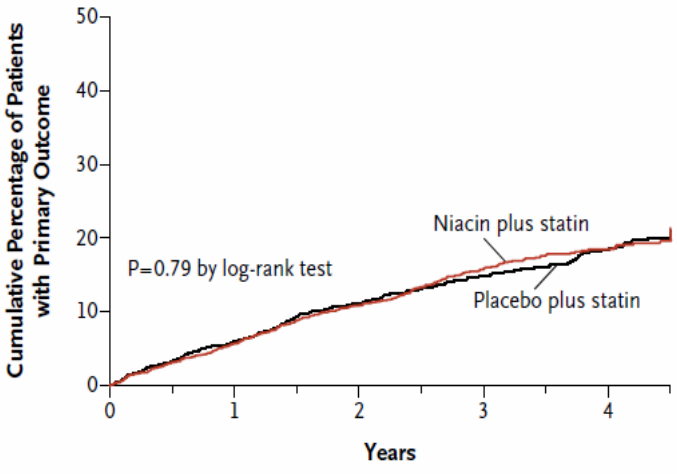


Table 4. Primary, Secondary, and Tertiary End Points.

End Point	Placebo plus Statin (N=1696)	Extended-Release Niacin plus Statin (N=1718)	Hazard Ratio with Niacin (95% CI)	P Value*
	number of patients (percent)			
Primary end point: death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization	274 (16.2)	282 (16.4)	1.02 (0.87–1.21)	0.80
Individual primary-end-point events				
Death from coronary heart disease	26 (1.5)	20 (1.2)		
Nonfatal myocardial infarction	80 (4.7)	92 (5.4)		
Ischemic stroke	15 (0.9)	27 (1.6)		
Hospitalization for acute coronary syndrome	67 (4.0)	63 (3.7)		
Symptom-driven coronary or cerebral revascularization	86 (5.1)	80 (4.7)		
Secondary end points				
Death from coronary heart disease, nonfatal myocardial infarction, high-risk acute coronary syndrome, or ischemic stroke	158 (9.3)	171 (10.0)	1.08 (0.87–1.34)	0.49
Death from coronary heart disease, nonfatal myocardial infarction, or ischemic stroke	138 (8.1)	156 (9.1)	1.13 (0.90–1.42)	0.30
All deaths from cardiovascular causes	38 (2.2)	45 (2.6)	1.17 (0.76–1.80)	0.47
Tertiary end points†				
Death from coronary heart disease	34 (2.0)	38 (2.2)	1.10 (0.69–1.75)	0.68
Death from any cause	82 (4.8)	96 (5.6)	1.16 (0.87–1.56)	0.32
Nonfatal myocardial infarction	93 (5.5)	104 (6.1)	1.11 (0.84–1.47)	0.46
Hospitalizations for acute coronary syndrome	82 (4.8)	72 (4.2)	0.87 (0.63–1.19)	0.38
Symptom-driven coronary or cerebral revascularizations	168 (9.9)	167 (9.7)	0.99 (0.80–1.22)	0.90
Ischemic stroke‡	18 (1.1)	29 (1.7)	1.61 (0.89–2.90)	0.11
Ischemic stroke or stroke of uncertain origin	18 (1.1)	30 (1.7)	1.67 (0.93–2.99)	0.09

N Engl J Med 2011;365:2255-67.

Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)

MERCK

News Release

Media Contacts: Pamela Eisele (908) 423-5042

Skip Irvine (267) 305-5397

Investor Contact: Carol Ferguson (908) 423-4465

Merck Announces HPS2-THRIVE Study of TREDAPTIVE™ (Extended Release Niacin/Laropiprant) Did Not Achieve Primary Endpoint

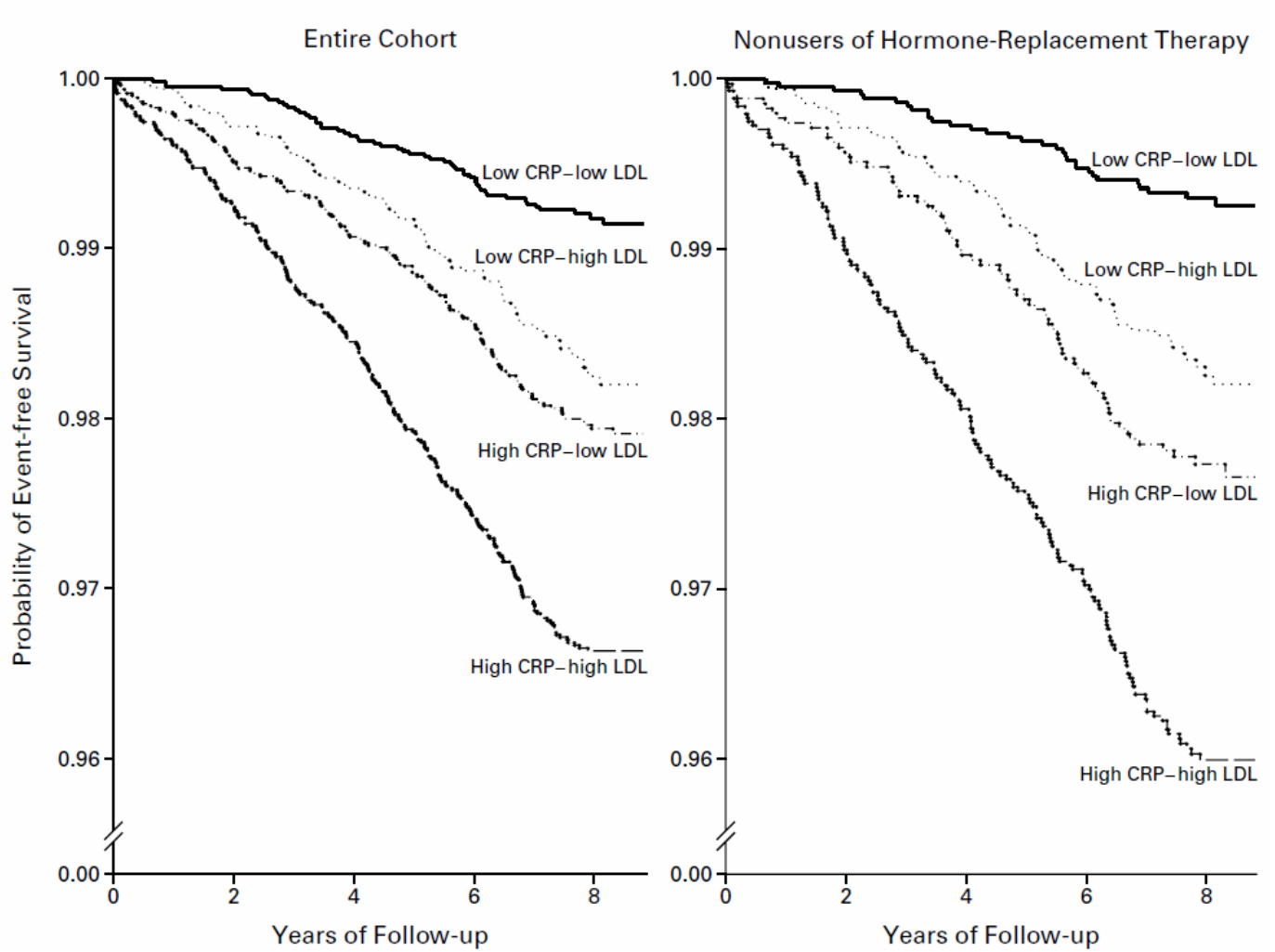
- La variable principal: muerte coronaria, infarto no mortal, ictus o revascularización coronaria se produjo en el 15,0% de los pacientes del grupo de control y el 14,5% de los pacientes en el grupo de niacina / laropiprant, NS.
- Aumento significativo del riesgo de eventos adversos con niacina / laropiprant, 30 eventos adversos por cada 1.000 pacientes tratados.
- En el brazo de niacina, hubo un aumento de riesgo del 3,7% de complicaciones de la diabetes y del 1,8% de aparición de diabetes.
- El tratamiento con niacina se asoció a un 1,4% más de riesgo de infección y un 0,7% de sangrado

(ACC, 2013)

EL RIESGO RESIDUAL

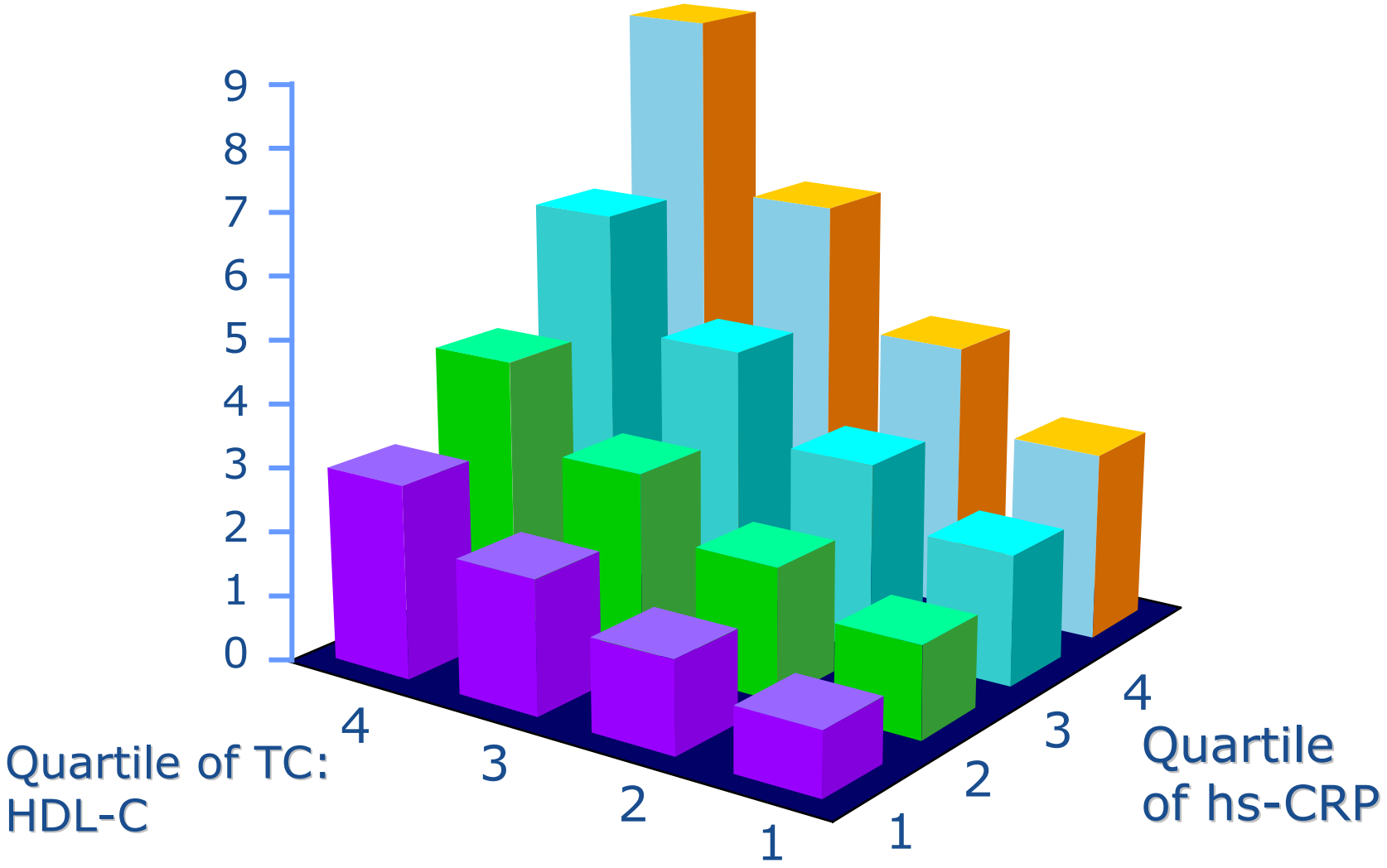
- **Con LDL bajo**
  - Otros FR Lipídicos
    - HDL-C, Triglicéridos, Lp (a)
    - Apo A1 y apo B
    - Tamaño LDL
  - FR no lipídicos
    - Inflamación ←
    - Coagulación
    - Oxidación
    - Metabólicos
- Por no conseguir objetivos LDL

Cumulative Incidence of Recurrent MI or Death from Coronary Causes, According to the Levels of Both LDL Cholesterol and CRP The Women's Health Study



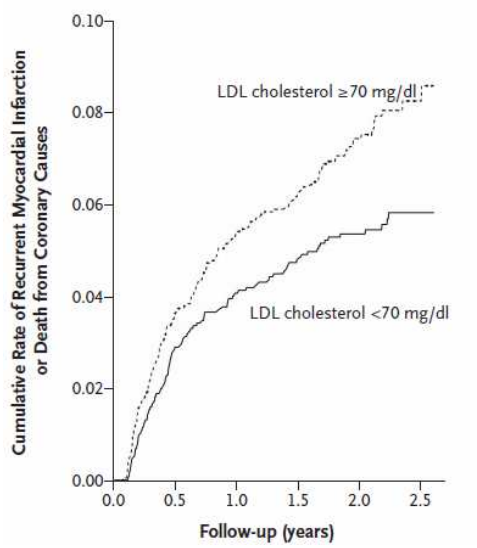
(Ridker PM, *et al. N Engl J Med* 2002,347:1557–1565.

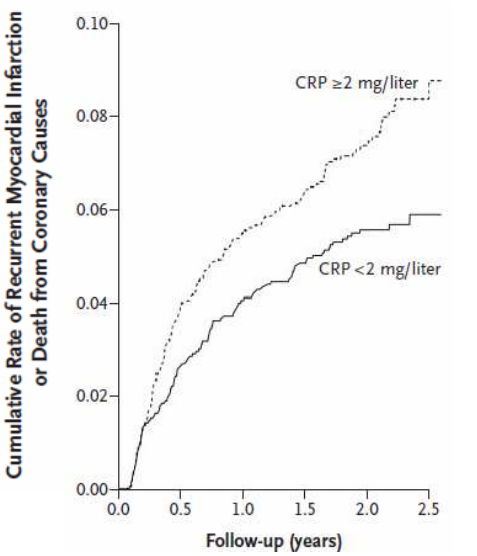
hs-CRP, Lipids, and Risk of Future Coronary Events: *Women's Health Study*

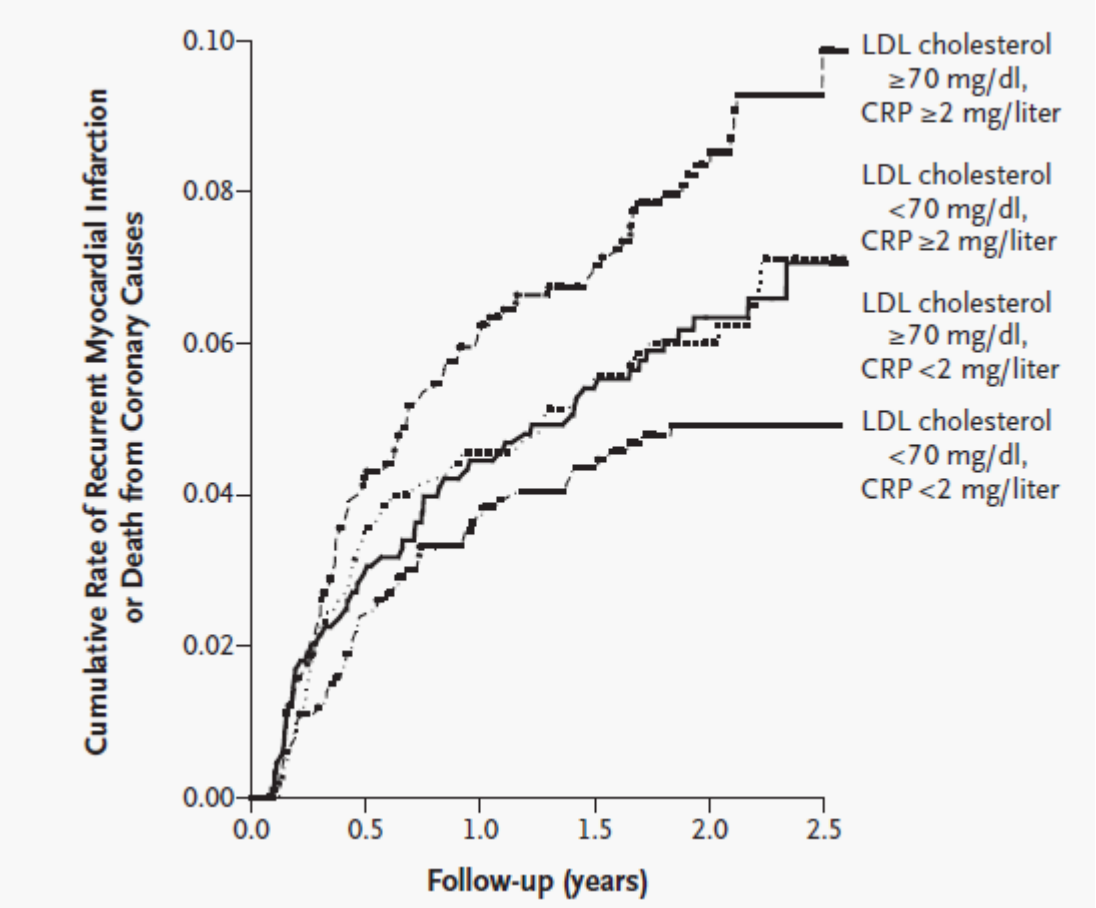


Ridker PM et al. *N Engl J Med* 2000;342:836-843.

Cumulative Incidence of Recurrent MI or Death from Coronary Causes, According to the Achieved Levels of Both LDL Cholesterol and CRP

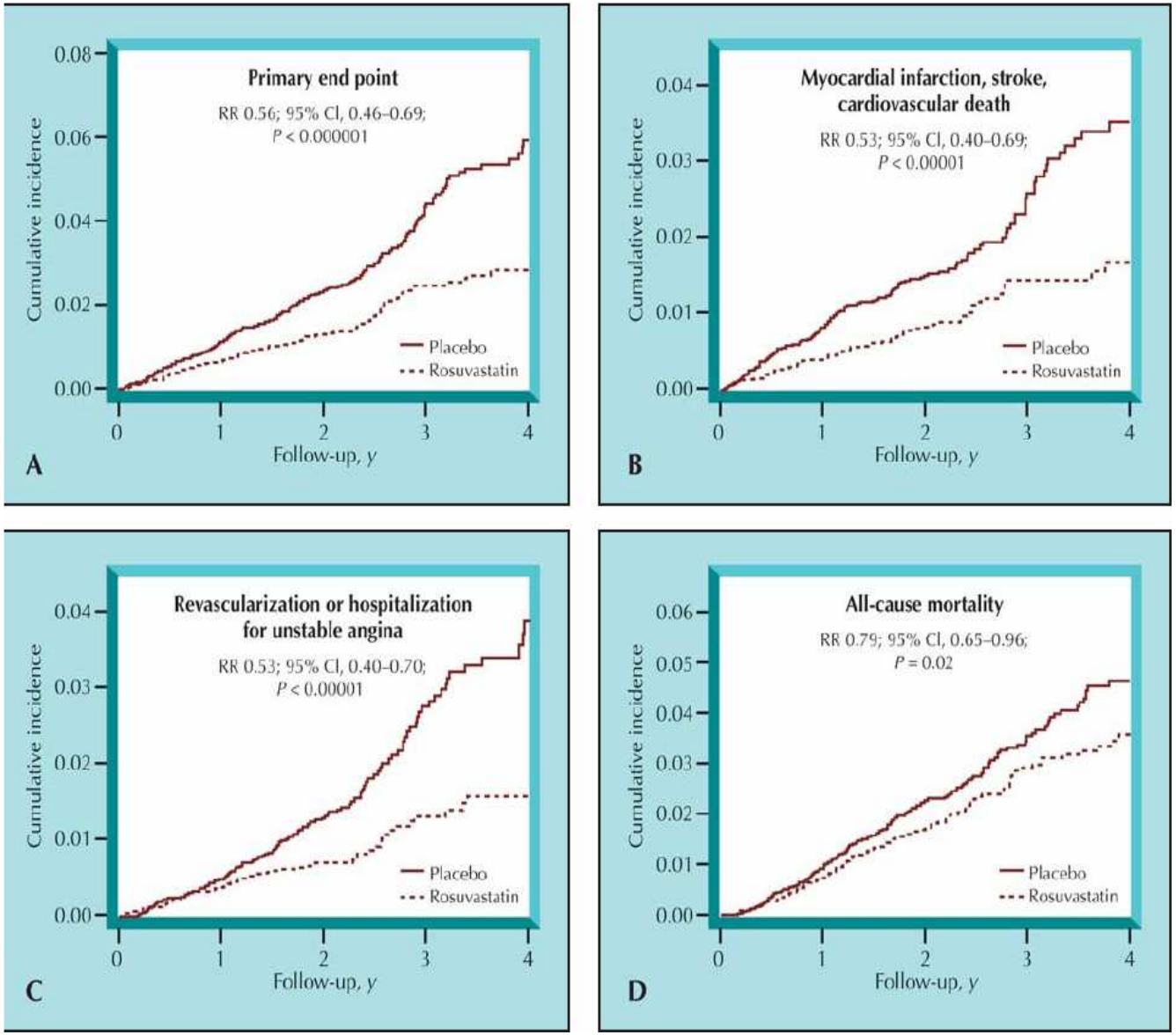






(N Engl J Med 2005;352:20-8.)

EFECTOS CARDIOVASCULARES: ESTUDIO JUPITER



44% reduction in primary end point of all vascular events

54% reduction in myocardial infarction

48% reduction in stroke

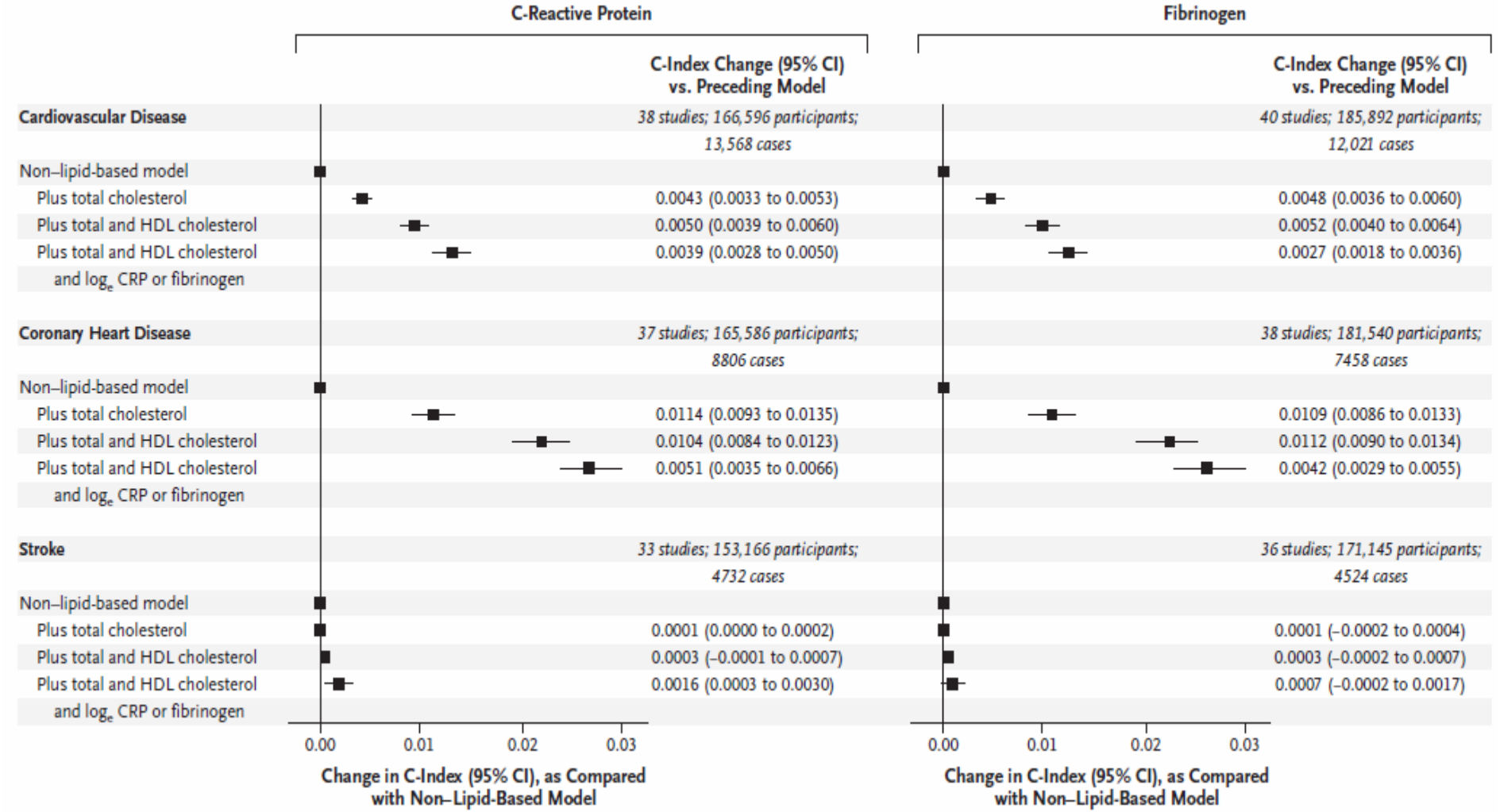
46% reduction in need for arterial revascularization

20% reduction in all-cause mortality.

79% reduction in LDL < 70 and CRP < 2

Ridker PM, et al. for the JUPITER Study Group: *N Engl J Med 2008, 359:2195–2207.*

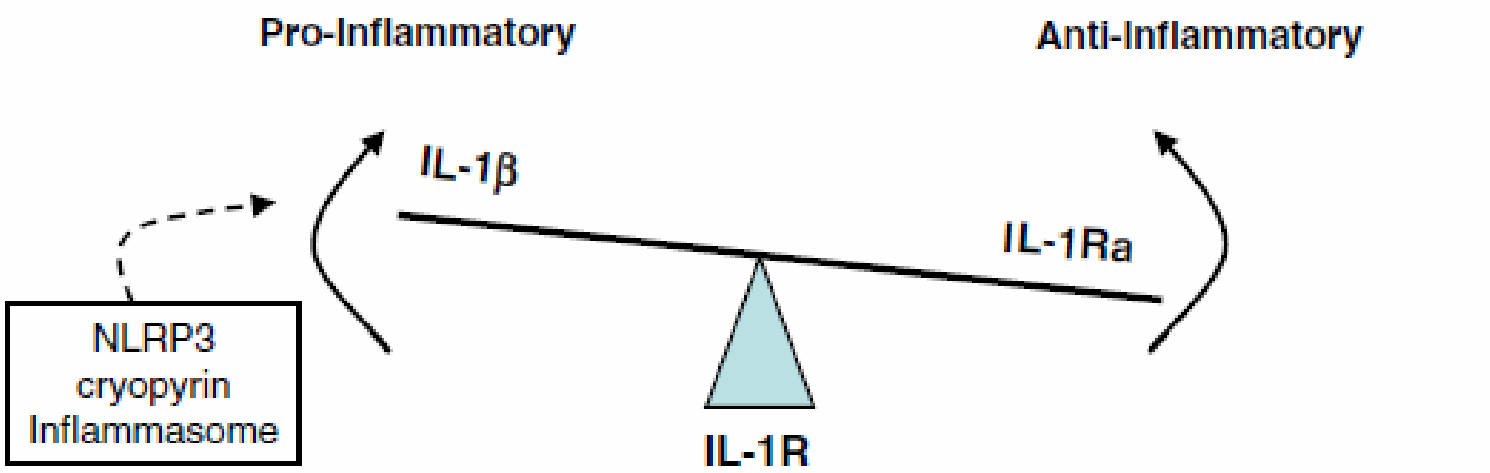
Changes in the Prediction Index after the Addition of Lipids and C-Reactive Protein or Fibrinogen to a Non–Lipid-Based Model (52 studies: 246,669 Pts.)



1 extra CVD outcome would be prevented over a period of 10 years for every 440 people in whom CRP levels were assessed as a result of the initiation of statin therapy in about 23 additional people

(The Emerging Risk Factors Collaboration N Engl J Med 2012; 367:1310-1320*)*

IL-1β system and its contributions to human disease

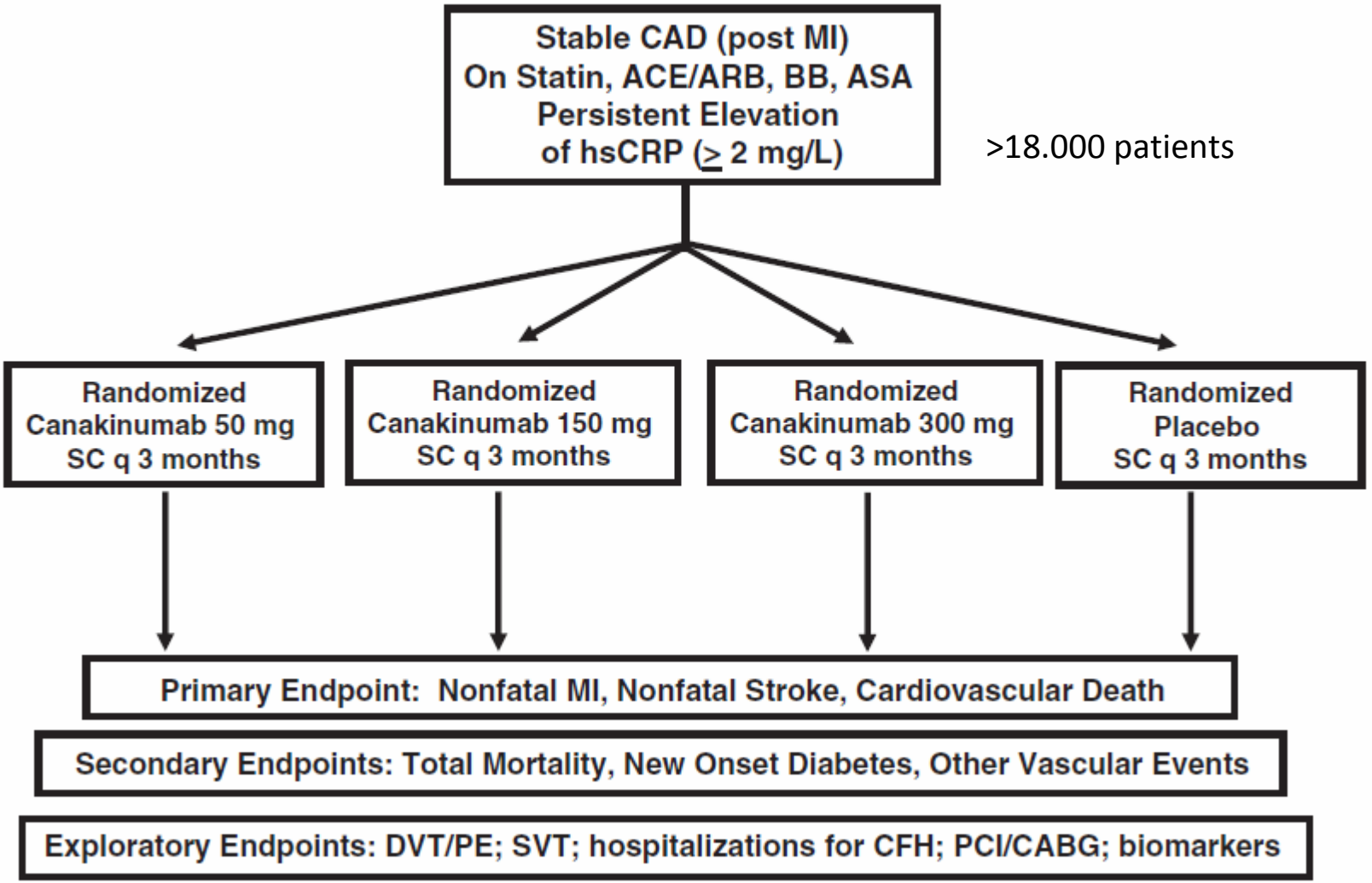


Severe Imbalance	(Inflammasome mutations) CAPS, MWS, NOMID
Moderate Imbalance	Psoriasis, contact hypersensitivity syndromes Gout, inflammatory arthritis, Crohn's, Ulcerative colitis Autoimmune Disorders, thyroiditis
Mild Imbalance	Atherosclerosis, Diabetes

IL-1β system and its contributions to atherosclerosis

1. Inducing **tissue factor-like procoagulant activity** in human vascular endothelial cells suggesting a role of IL-1b in modulating thrombogenicity of the blood vascular wall interface.
2. **Decreased atherosclerosis in mice deficient in IL-1b** or the type I IL-1 receptor and increased atherogenesis in mice exposed to excess IL-1b
3. **Cholesterol crystals activate the NLRP3 inflammasome** leading to increased IL-1b production.
4. **IL-1b** and IL-1ra were found in **greater concentrations in atherosclerotic human coronary arteries** compared with normal coronary arteries
5. IL-1ra levels were shown to be **higher among those with acute coronary syndrome.**
6. IL-1ra plasma levels were shown to be **independent predictors of major adverse cardiac events.**

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)



>18.000 patients

Design of the CANTOS.

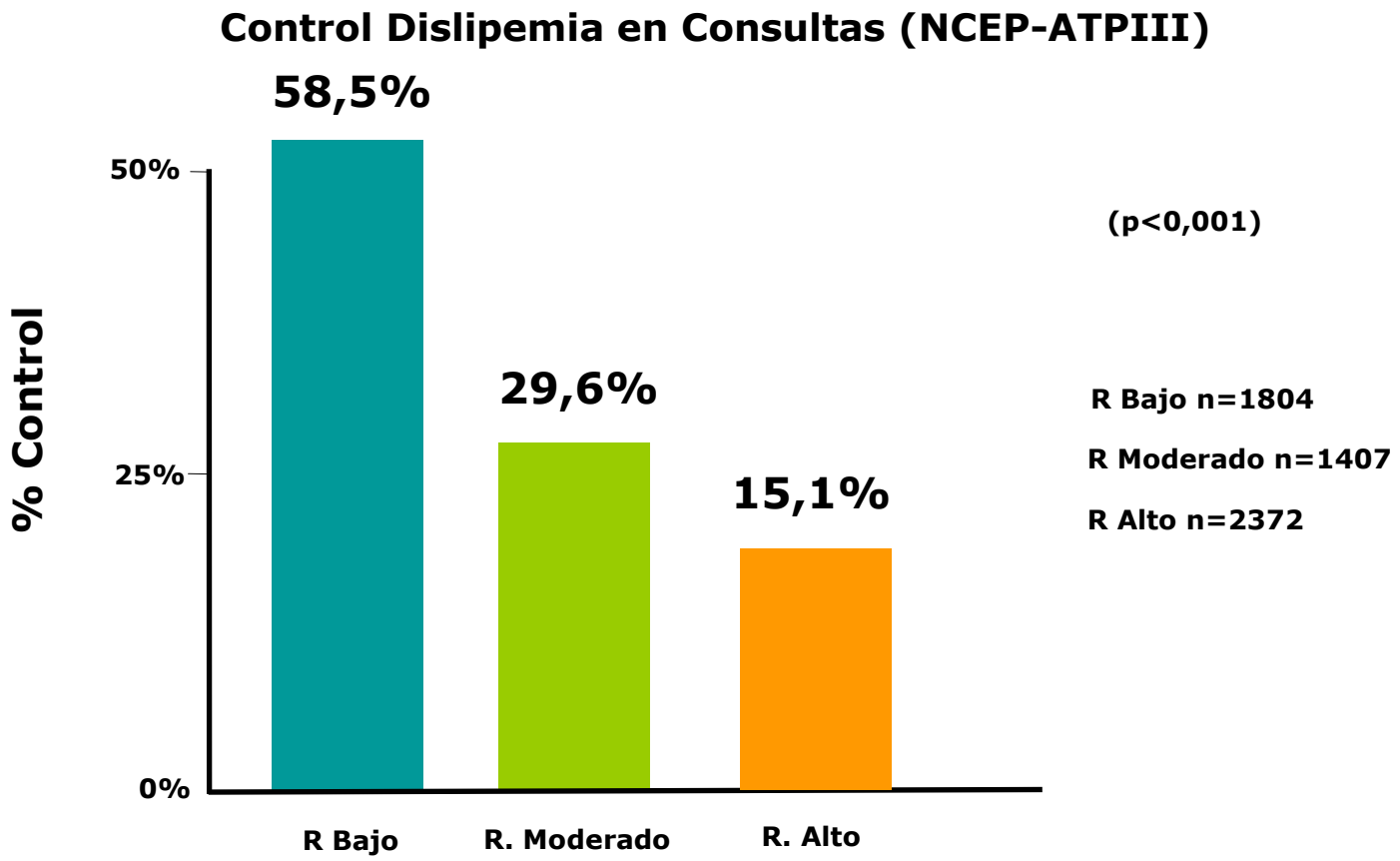
(Ridker PM et al, Am Heart J 2011;162:597-605.)

EL RIESGO RESIDUAL

- **Con LDL bajo**
  - ► Otros FR Lipídicos
    - – HDL-C, Triglicéridos (Dislipemia aterógena)
    - – Síndrome Metabólico
    - – Lp (a)
    - – Tamaño LDL
  - ► FR no lipídicos
    - – Inflamación, oxidación, coagulación
    - – Diabetes
    - – Hipertensión
    - – Tabaquismo
- Por no conseguir objetivos LDL ←

Estudio HISPALIPID:

Control de la dislipemia en los distintos Grupos de Riesgo

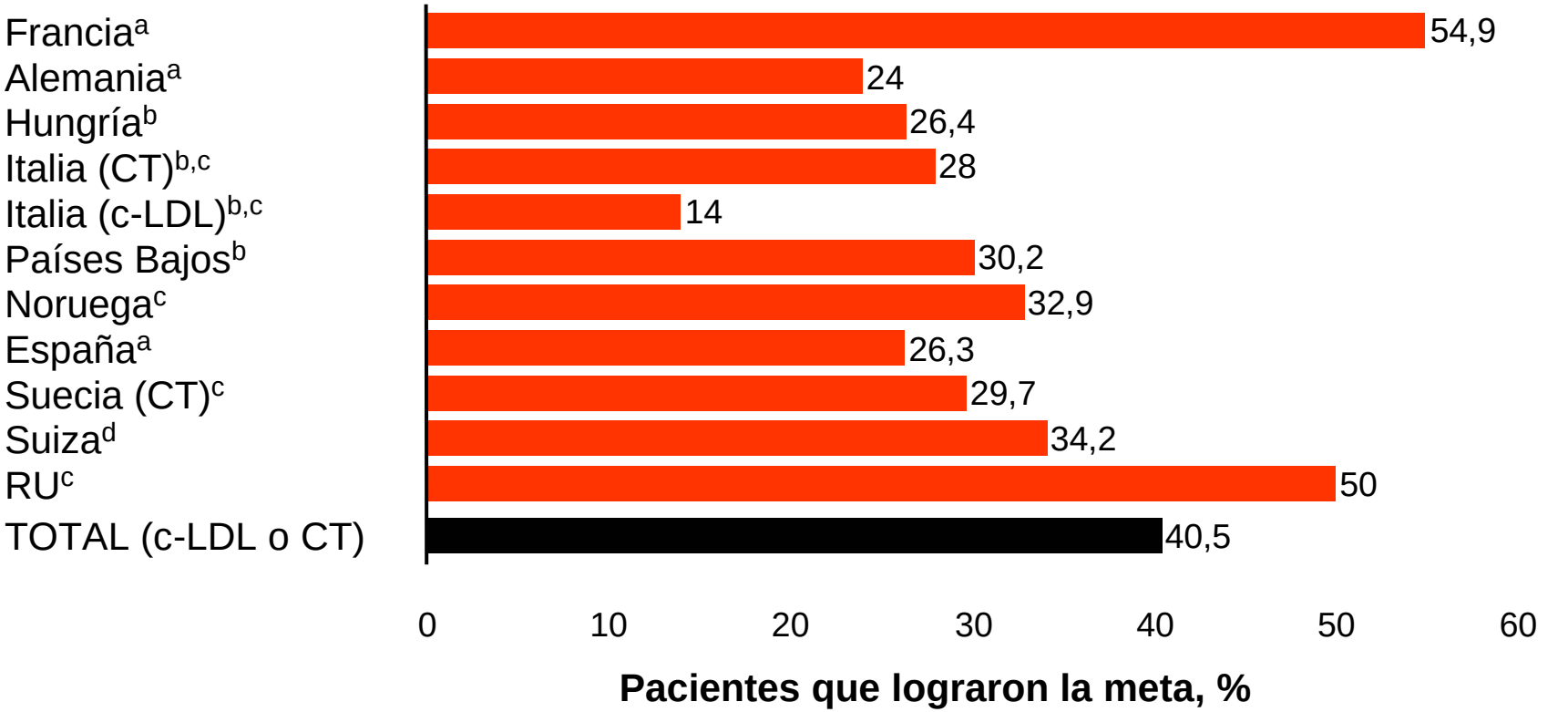


El control objetivo de la dislipemia en España es bajo en los pacientes de factores de riesgo más elevedos

Tomado de Banegas et al. The gap between dyslipidemia control perceived by physicians and objective control patterns in Spain. *Atherosclerosis* 2006(188): 420-424

Proporción de pacientes europeos en tratamiento hipolipemiante que lograron los objetivos de lípidos

Return on Expenditure Achieved for Lipid Therapy (REALITY) Study

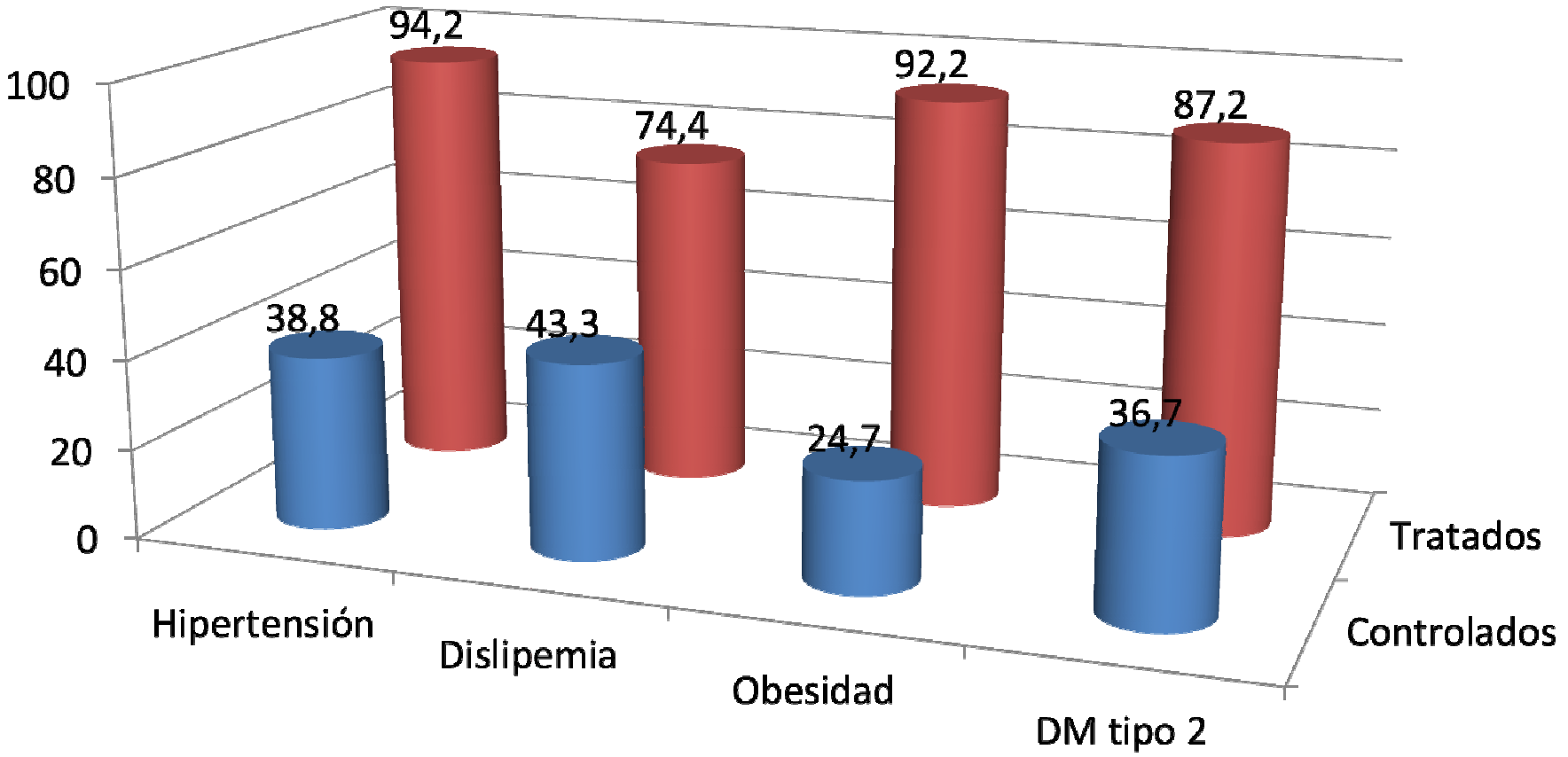


[a]Programa Nacional de Educación sobre el Colesterol (NCEP) ATP III (c-LDL< 100 mg/dl con CC/ equivalente de riesgo de CC); [b]CT < 200 mg/dl; [c] c-LDL <116 mg/dl, CT <193 mg/dl); [d]Determinado por el médico tratante o de acuerdo con NCEP ATP III CT= colesterol total; c-LDL= colesterol de lipoproteínas de baja densidad; CC= cardiopatía coronaria

Adaptado de Van Ganse E y cols. *Curr Med Res Opin.* 2005;21:1389–1399.

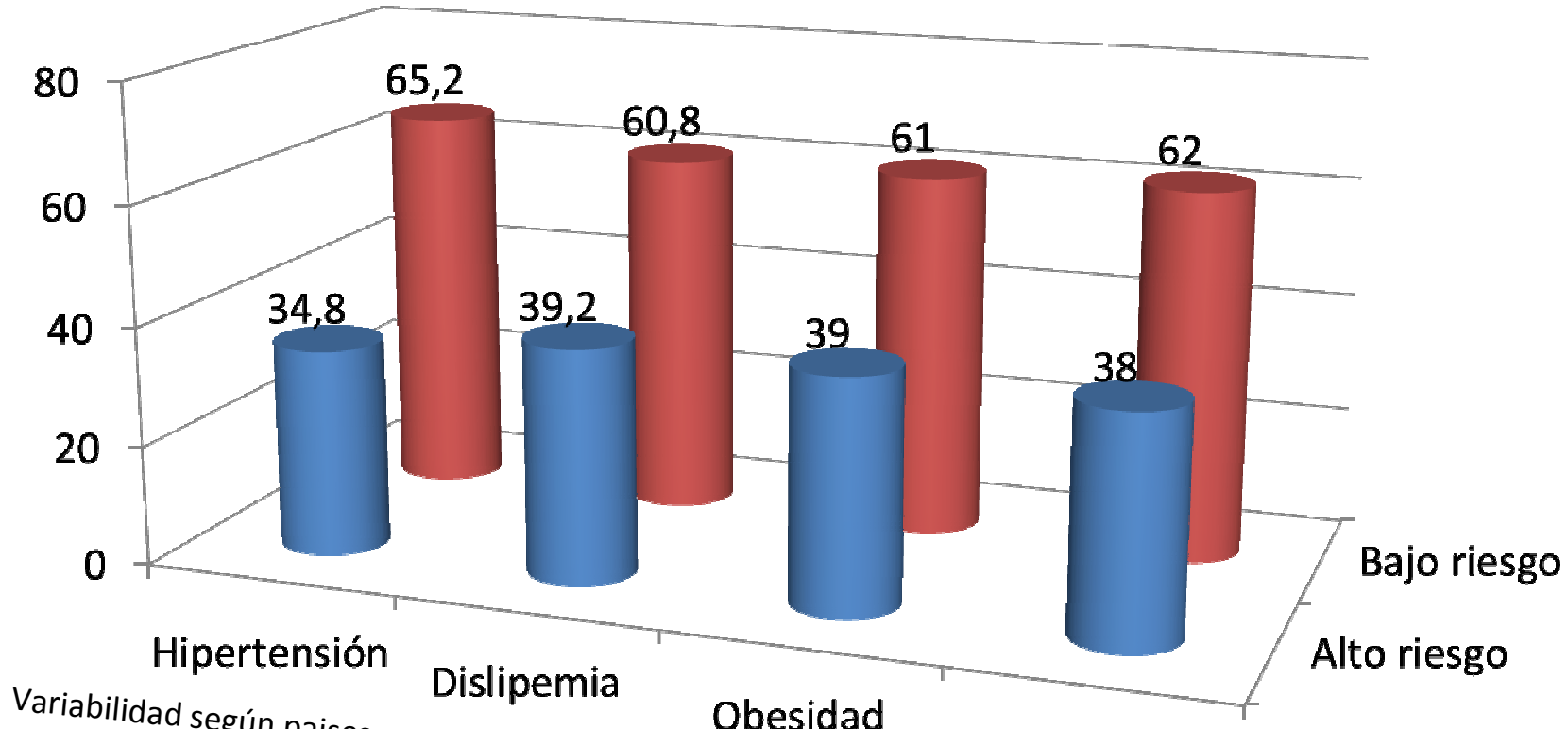
Individuos (%) bajo tratamiento y control de distintos factores de riesgo

Estudio EURIKA (Eur Heart J doi:10.1093/eurheartj/ehr080)



Individuos (%) tratados y controlados según riesgo individual

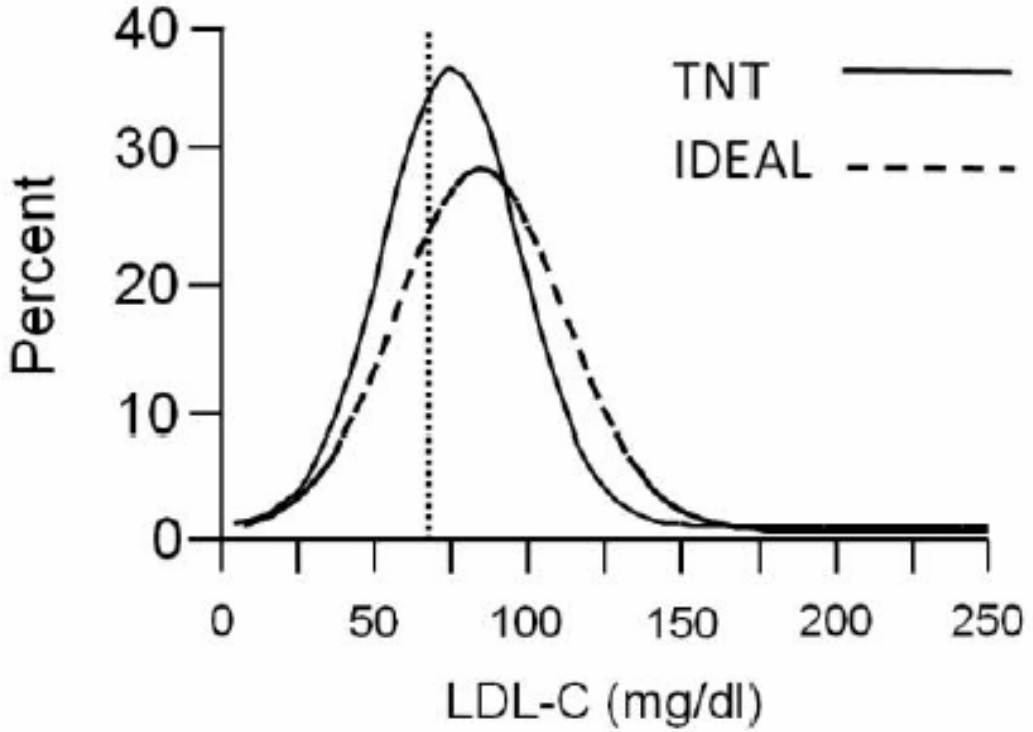
Estudio EURIKA (Eur Heart J)



Variabilidad según paises:

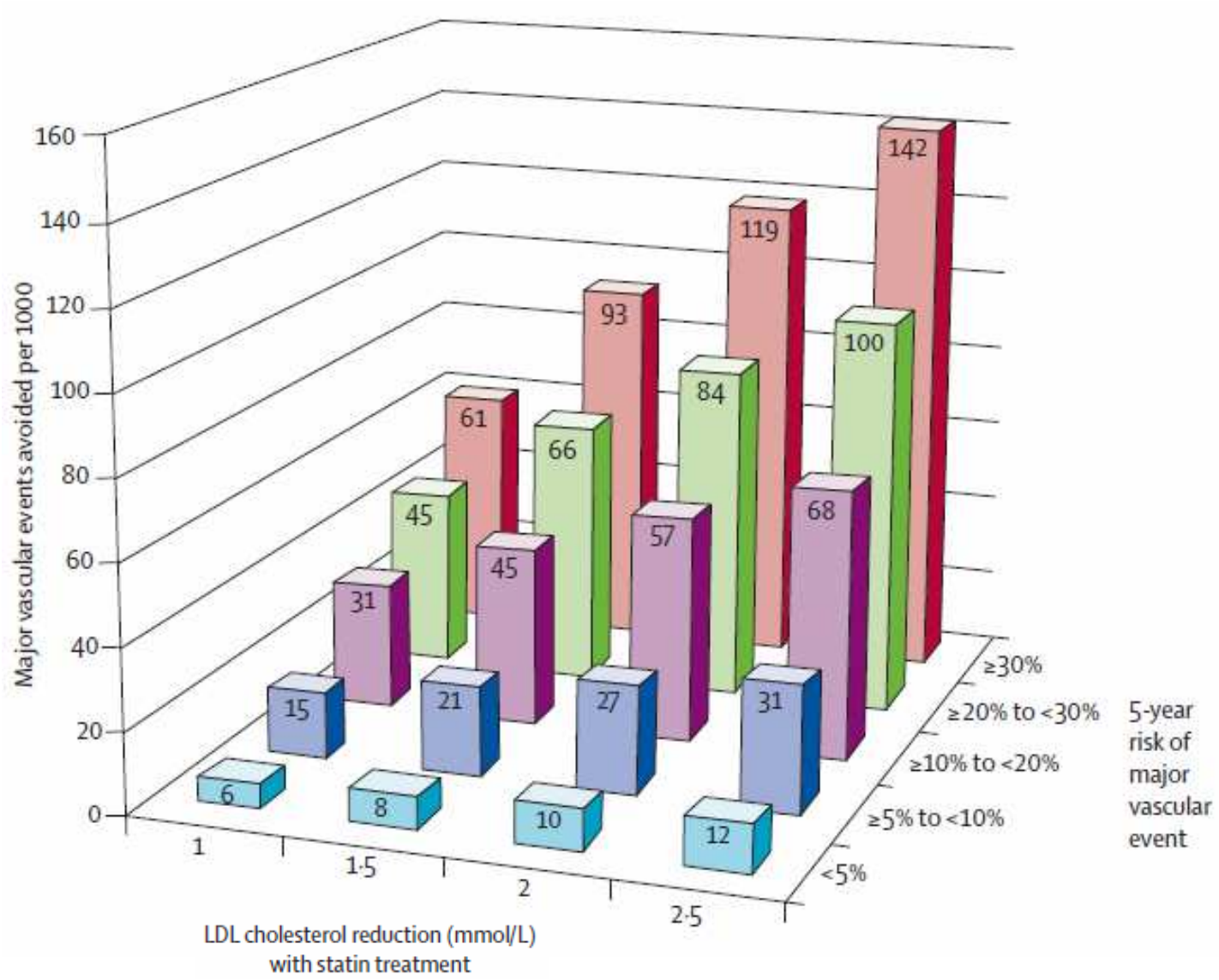
	Hipertensión	Dislipemia	Obesidad	DM tipo 2
Alto riesgo	20,3-45,0	19,6-57,5	24,1-59,3	40,6-80,4
Bajo riesgo	50,0-79,7	46,2-80,4	40,6-80,4	40,7-75,9

Distribution of on-treatment LDL-C levels for patients on high-dose atorvastatin (80 mg/day) in TNT and IDEAL studies



LaRosa JC, et al N Engl J Med. 2005;352:1425-35.

Predicted 5-year benefits of LDL cholesterol reductions with statin treatment at different levels of risk



Cholesterol Treatment Trialists' (CTT) Collaborators Lancet 2012; 380: 581–90

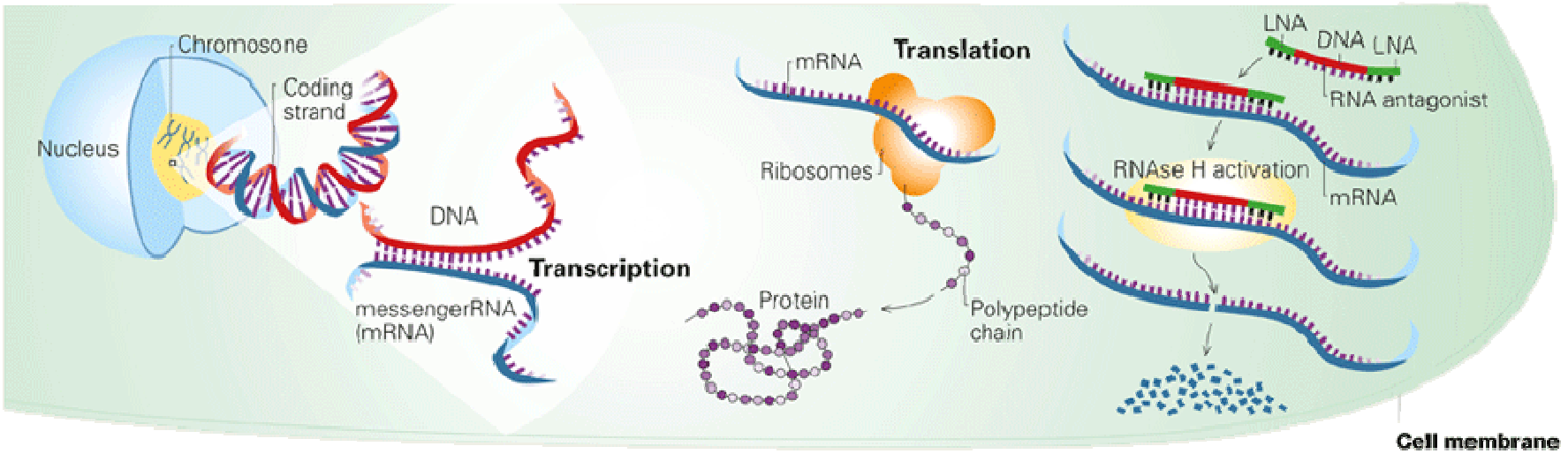
Nuevas dianas terapeuticas para reducir los niveles de LDL-c

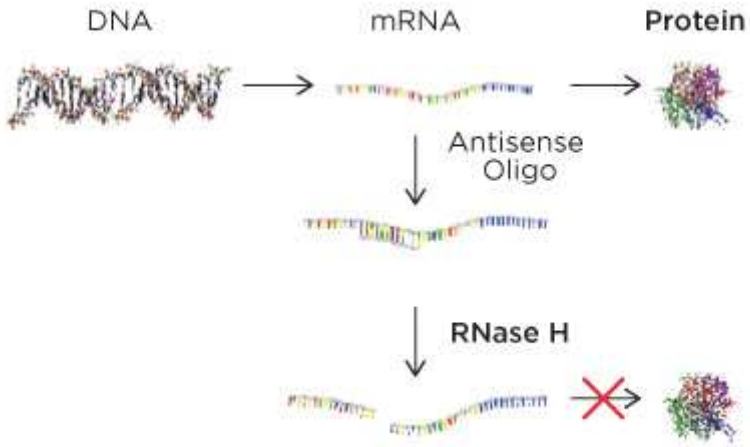
1. Anticuerpos
2. Terapia génica: Oligonucleotidos antisentido

DIANAS TERAPEUTICAS:

1. PCSK9
2. APOLIPOPROTEINA B
3. MTP

Antisense oligonucleotides potently reduce apolipoprotein B mRNA





(Nucleic Acids Res 2010; 38:7100–7111)

Mipomersen: an antisense oligonucleotide, that inhibits the apoB-100 synthesis in the liver

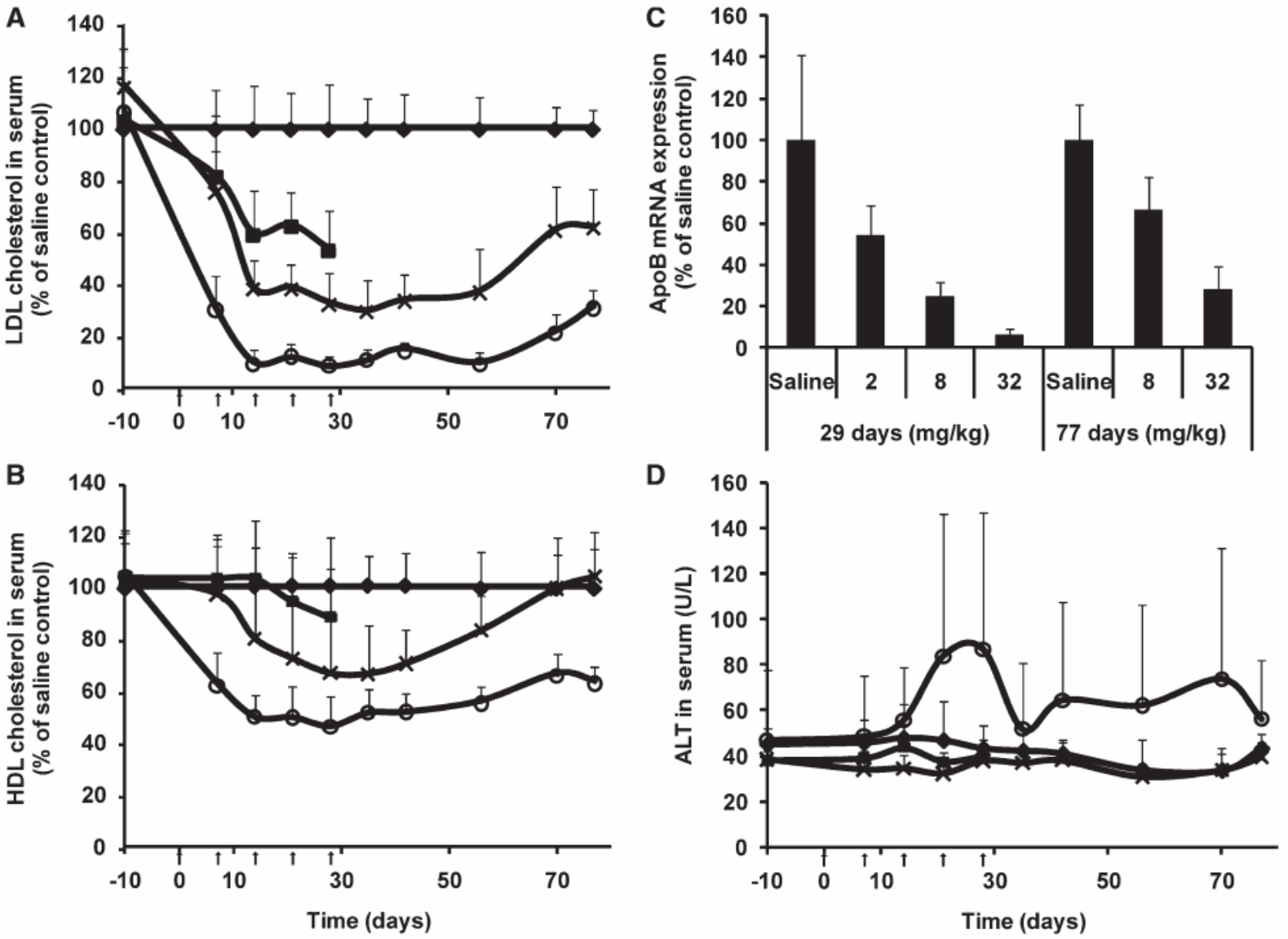
Table 1. Efficacy results of mipomersen phase III trials

	ISIS 301012-CS5 (NCT00607373) [15]		MIPO3500108 (NCT00794664) [16▪]		ISIS 301012-CS7 (NCT00706849) [18▪]		ISIS 301012-CS12 (NCT00770146) [19▪▪]	
	Placebo ($n=17$)	HoFH ($n=34$)	Placebo ($n=18$)	Severe HC ($n=39$)	Placebo ($n=41$)	HeFH with CAD ($n=83$)	Placebo ($n=52$)	HC high-risk CAD ($n=105$)
Baseline LDL-C levels (mmol/l)	10.4	11.4	6.5	7.2	3.7	4.0	3.2	3.2
LDL-C change (%)	−3	−25	13	−36	5	−28	−5	−37 ←
Baseline non-HDL-C levels (mmol/l)	10.9	12.0	7.2	7.9	4.3	4.5	3.7	3.7
Non-HDL-C change (%)	−3	−25	14	−34	4	−25	−1	−39
Baseline apoB levels (g/l)	2.6	2.8	1.8	2.0	1.3	3.4	1.1	1.1
ApoB change (%)	−3	−27	11	−36	7	−26	−2	−41 ←
Baseline lipoprotein(a) levels (g/l)	0.6	0.6	0.3	0.6	0.5	0.4	0.5	0.5
Lp(a) change (%)	−7	−32	−2	−33	0	−21	2.3	−24 ←

Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia

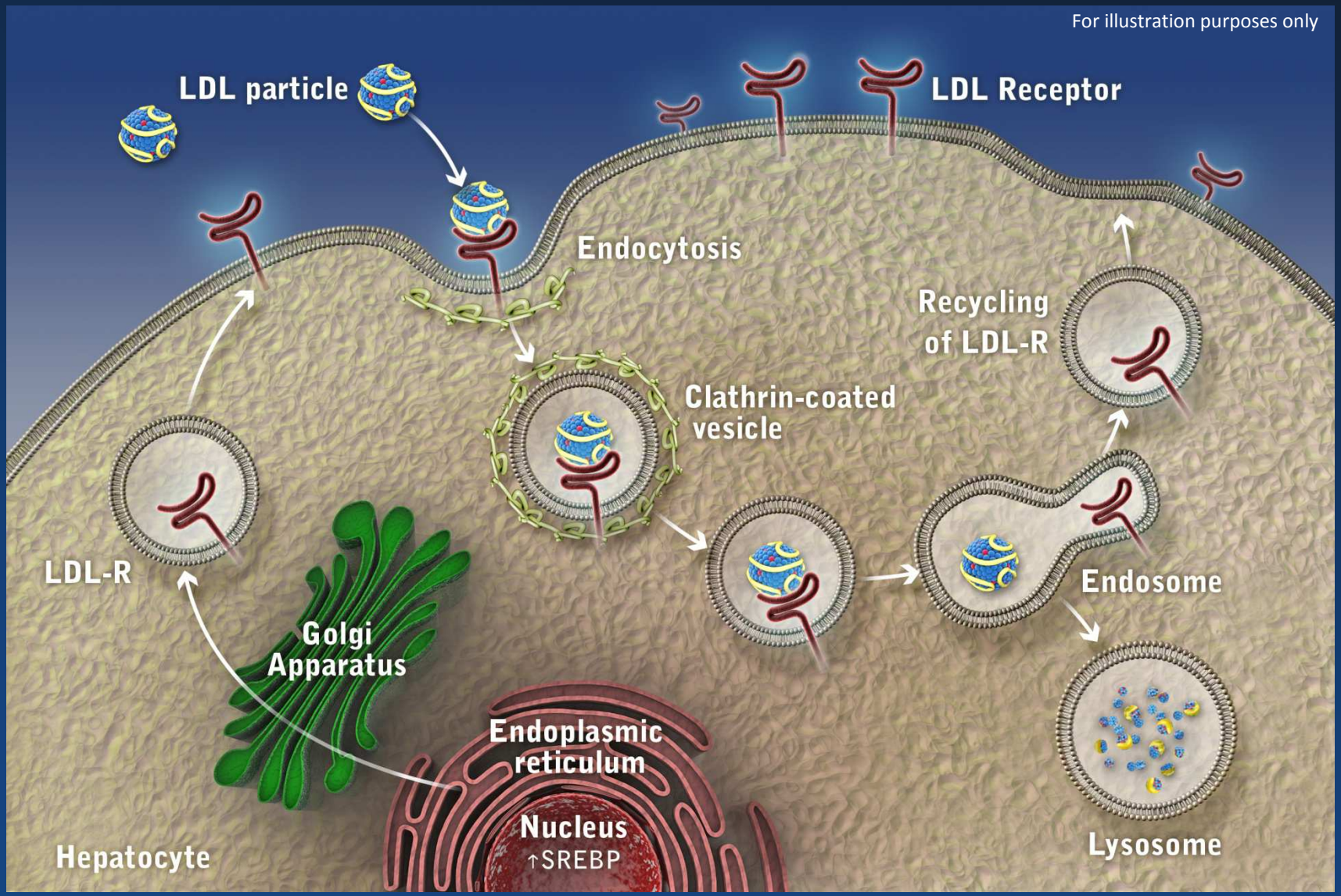
(Curr Opin Lipidol 2013, 24:301–306; Lancet 2010; 375:998–1006)

Short locked antisense oligonucleotides potently reduce apolipoprotein B mRNA and serum cholesterol in mice and non-human primates

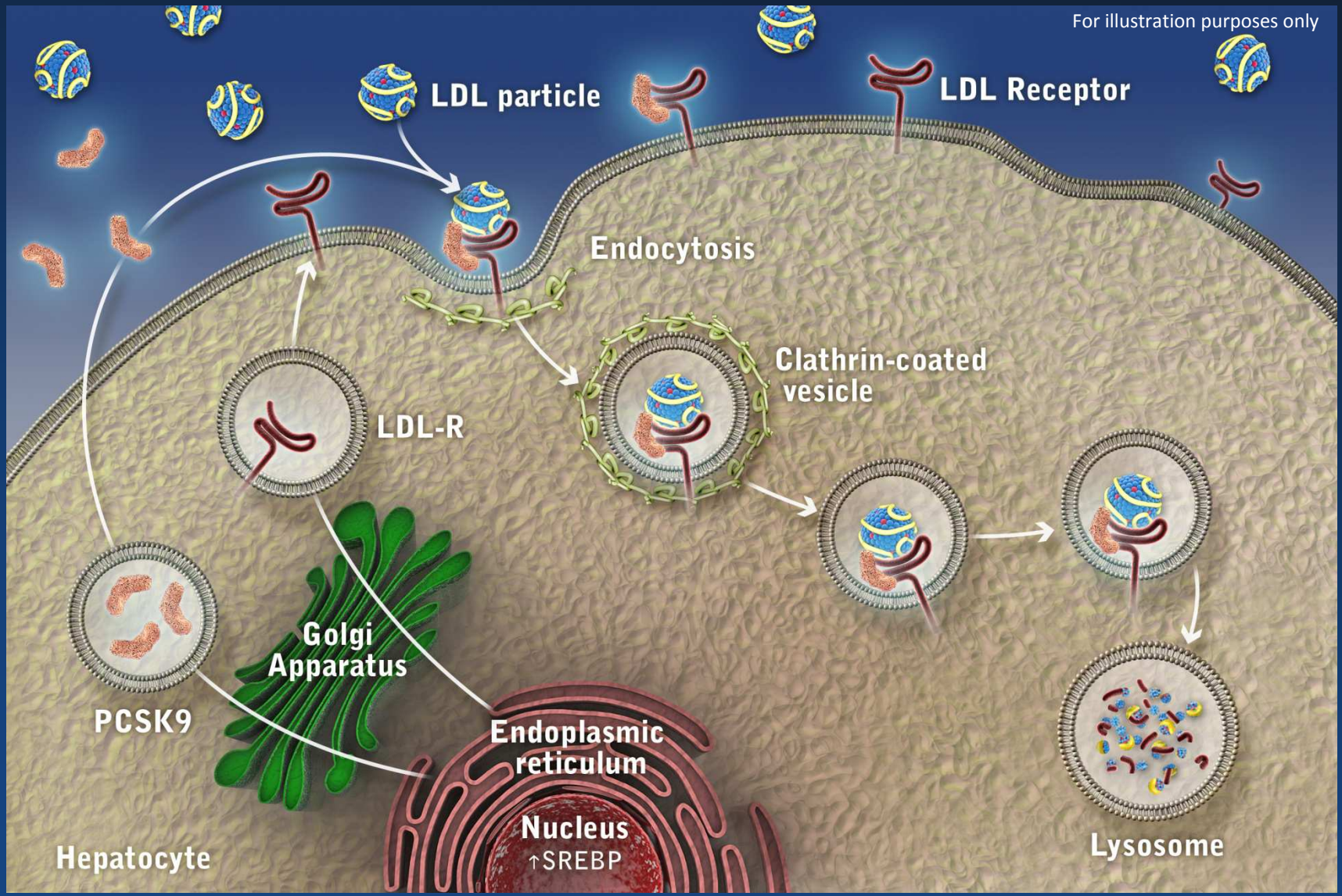


(Nucleic Acids Res 2010; 38:7100–7111)

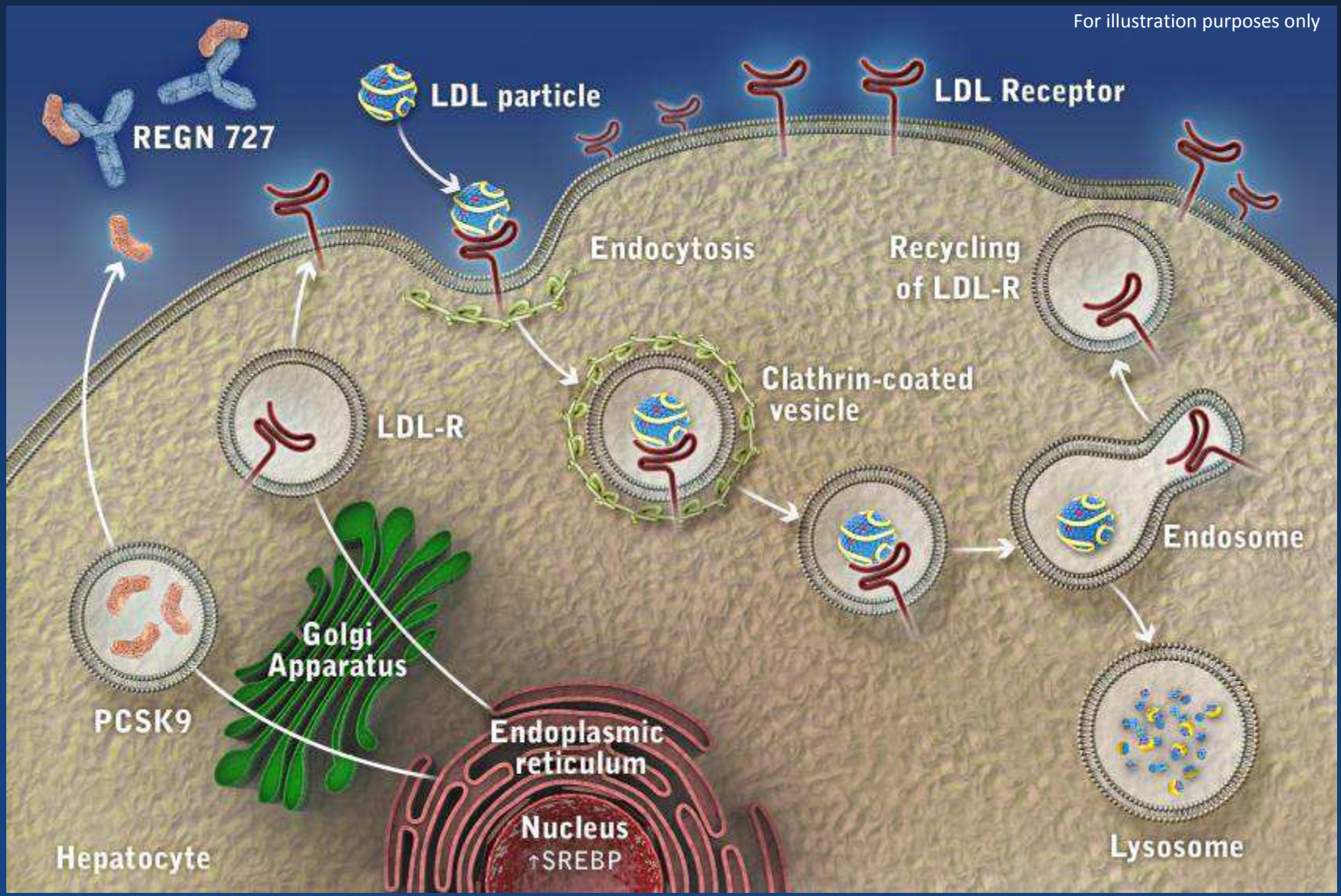
LDL Receptor Function and Life Cycle



The Role of PCSK9 in the Regulation of LDL Receptor Expression



Impact of an PCSK9 mAb on LDL Receptor Expression

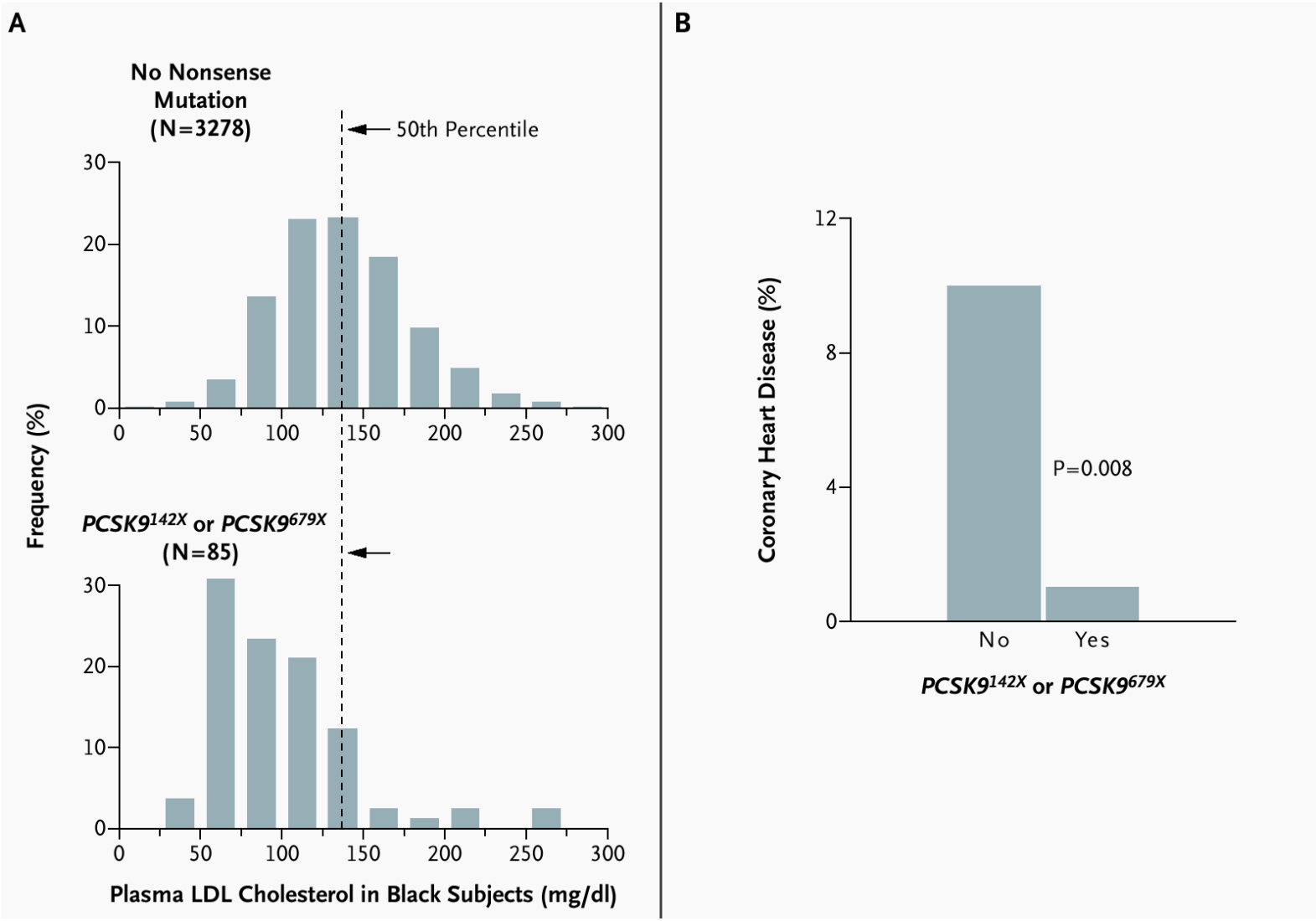


Nonsense Mutations in *PCSK9* and Cardiovascular Risk Factors among 3363 Black Participants in the Study

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

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



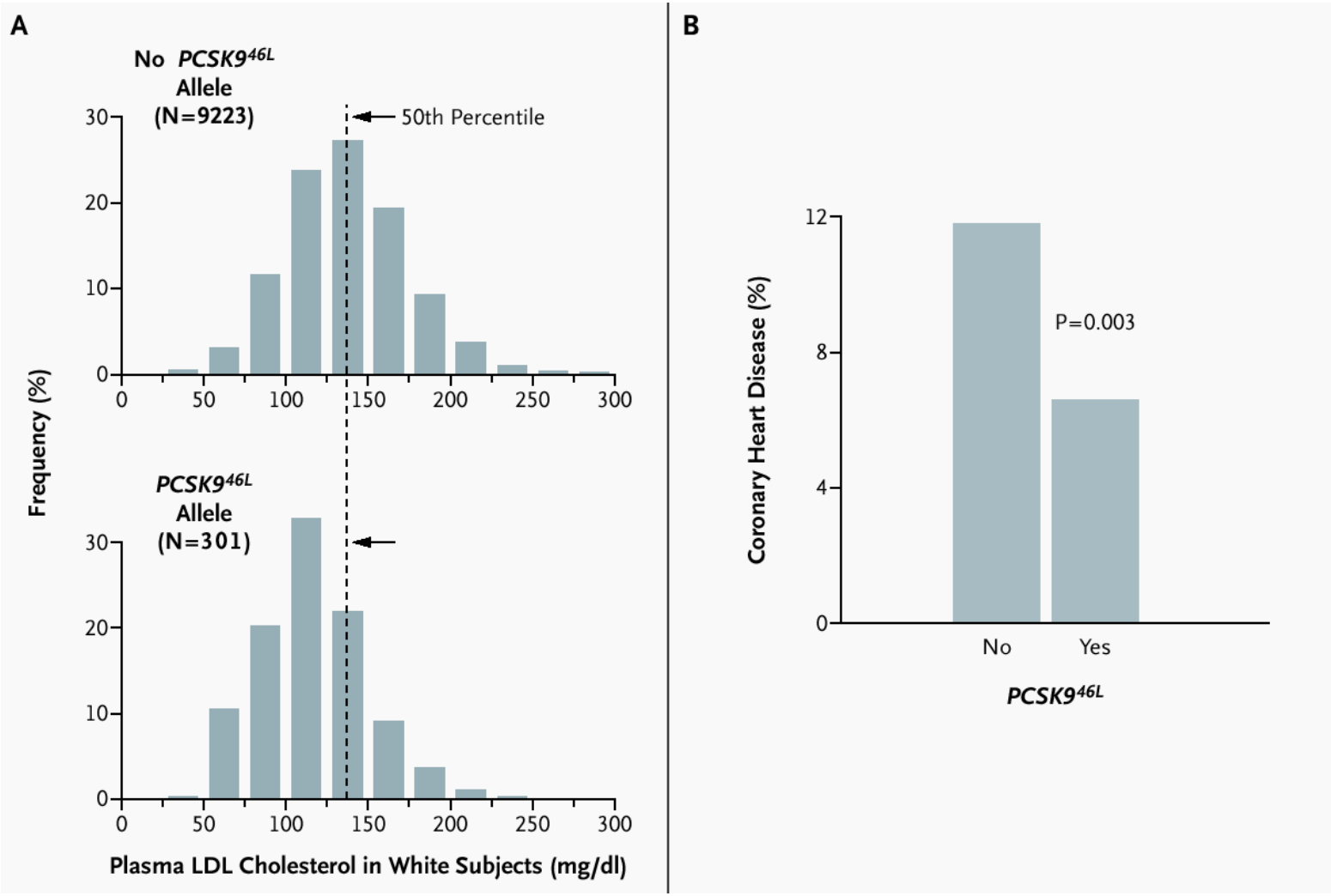
Jonathan C.Cohen, et al, N Engl J Med 2006;354:1264-72

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

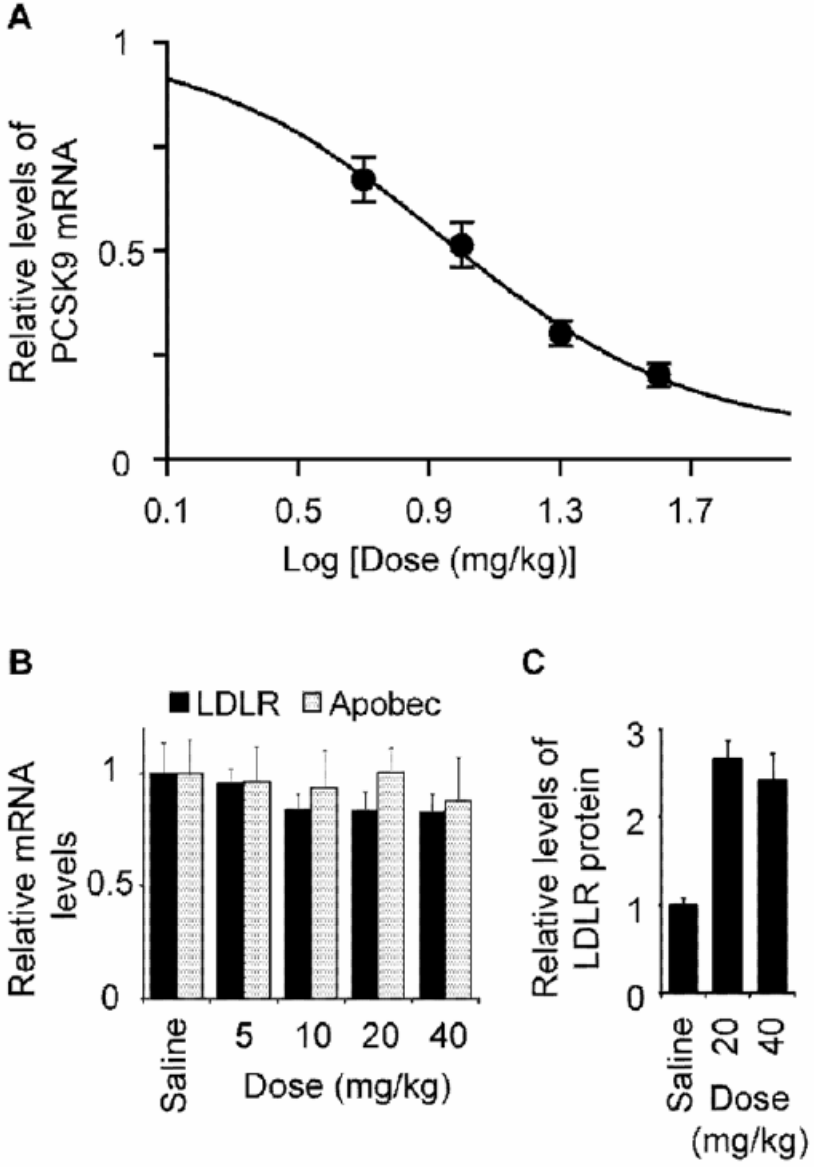
Jonathan C.Cohen, et al, N Engl J Med 2006;354:1264-72

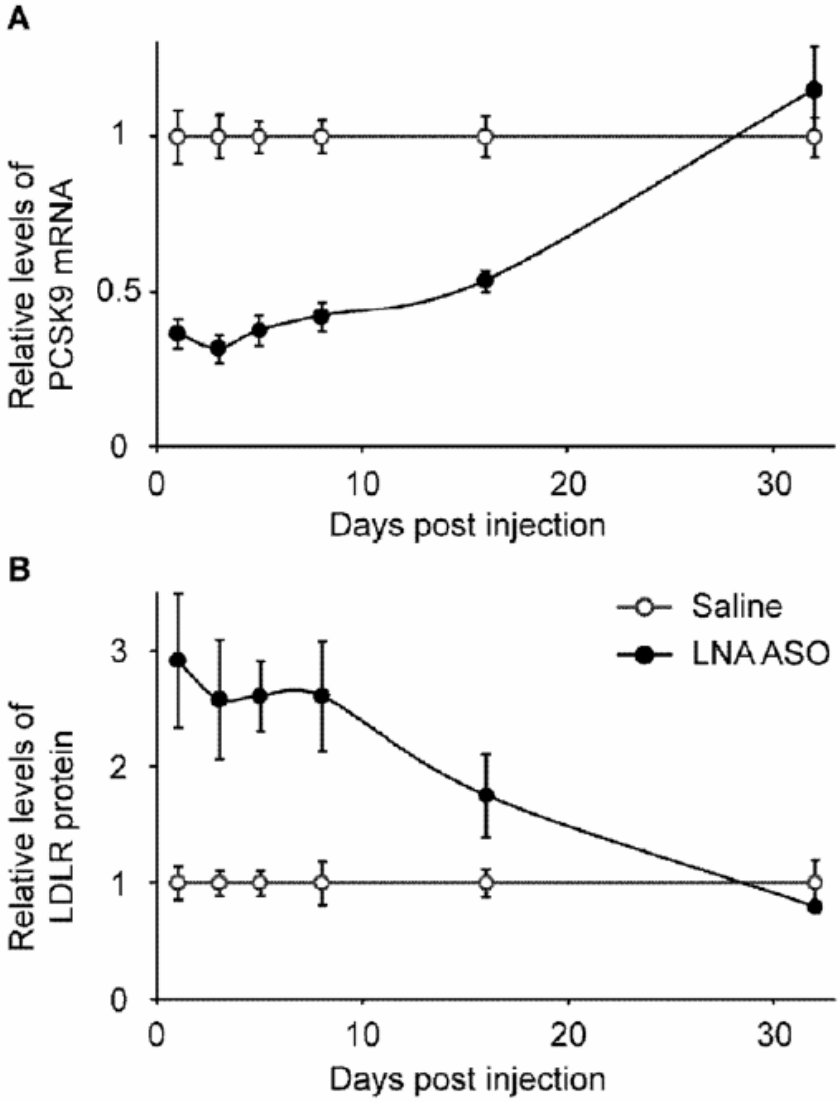
Distribution of Plasma LDL Cholesterol Levels (A)and Incidence of Coronary Events (Panel B) among White Subjects, According to the Presence or Absence of a *PCSK9 46L* Allele



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

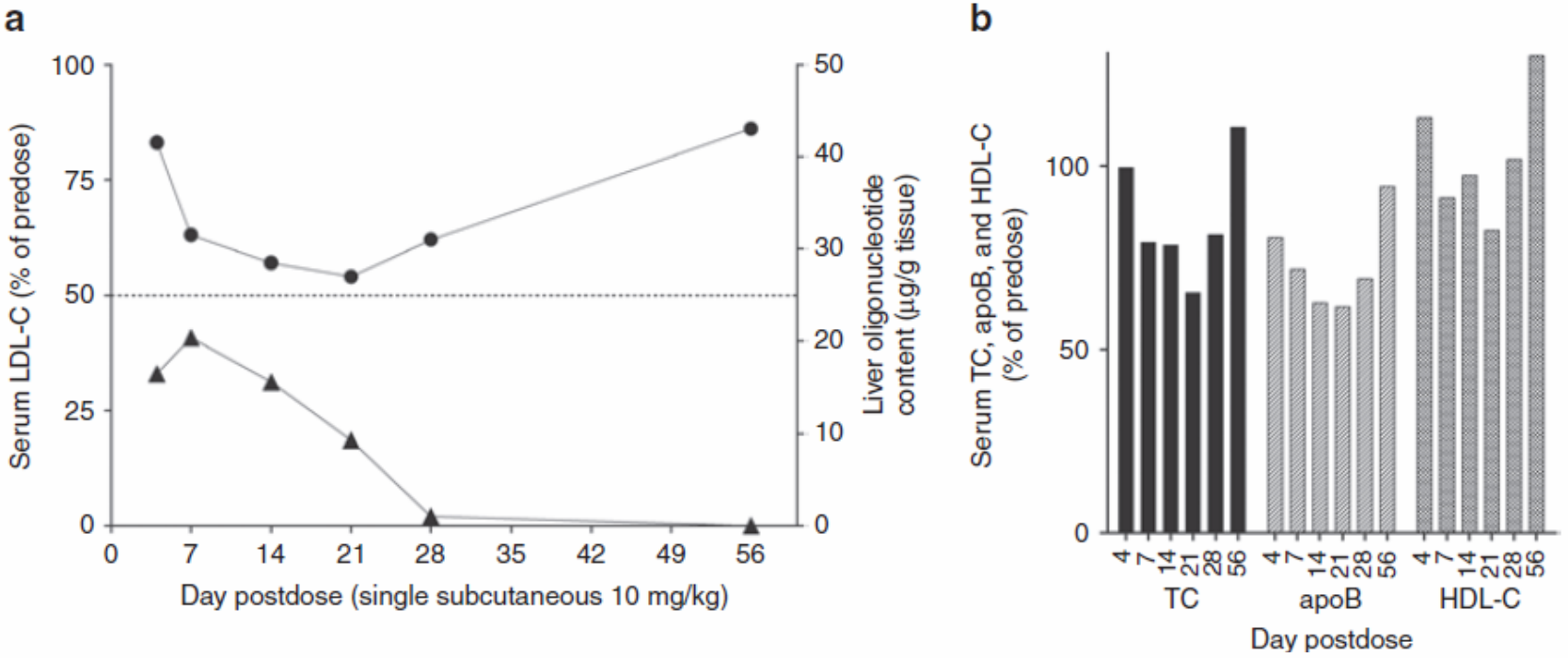
A Locked Nucleic Acid Antisense Oligonucleotide (LNA) Silences PCSK9 and Enhances LDLR Expression In Vitro and In Vivo

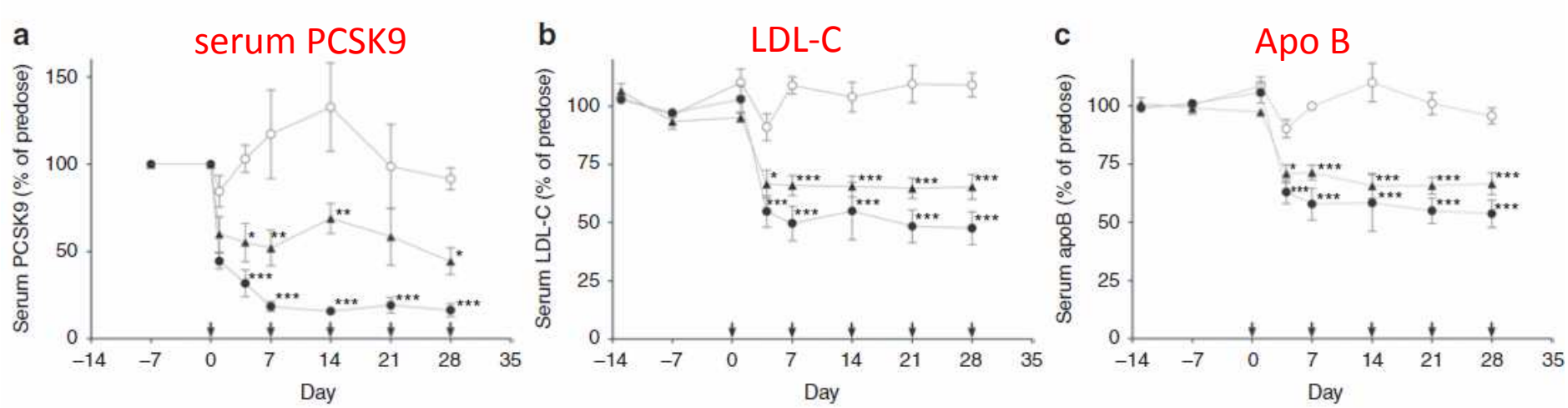




(PLoS One 2010; 5:e10682.)

PCSK9 LNA Antisense Oligonucleotides Induce Sustained Reduction of LDL Cholesterol in Nonhuman Primates

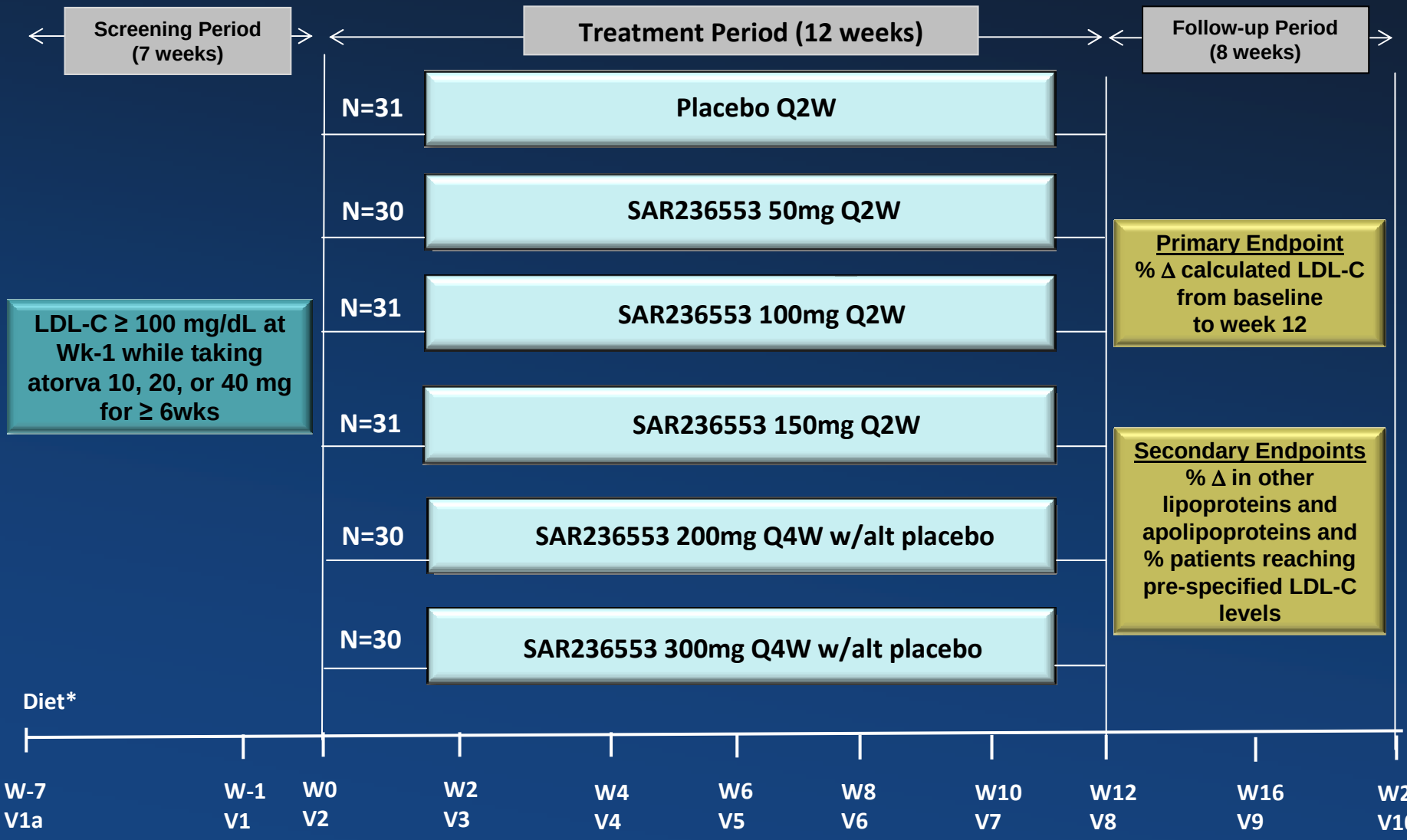




(Mol Ther 2012; 20:376–381)

Subcutaneous 20 mg/kg dose, followed by a 5 mg/kg subcutaneous dose at day 7, 14, 21, and 28

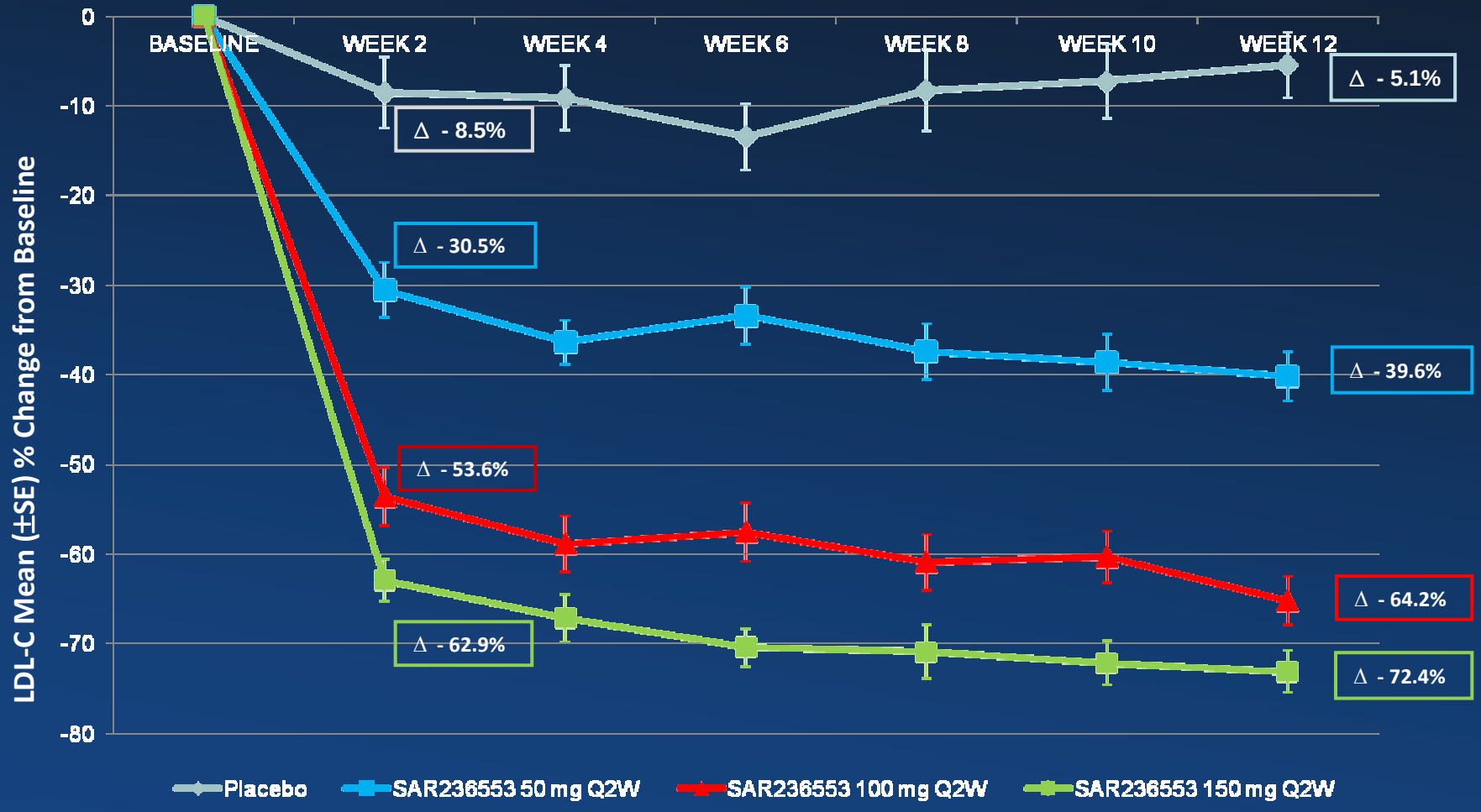
Study Design



*NCEP ATP-III TLC or equivalent diet

McKenney JM et al. *J Am Coll Cardiol.* 2012;59:2344–2353

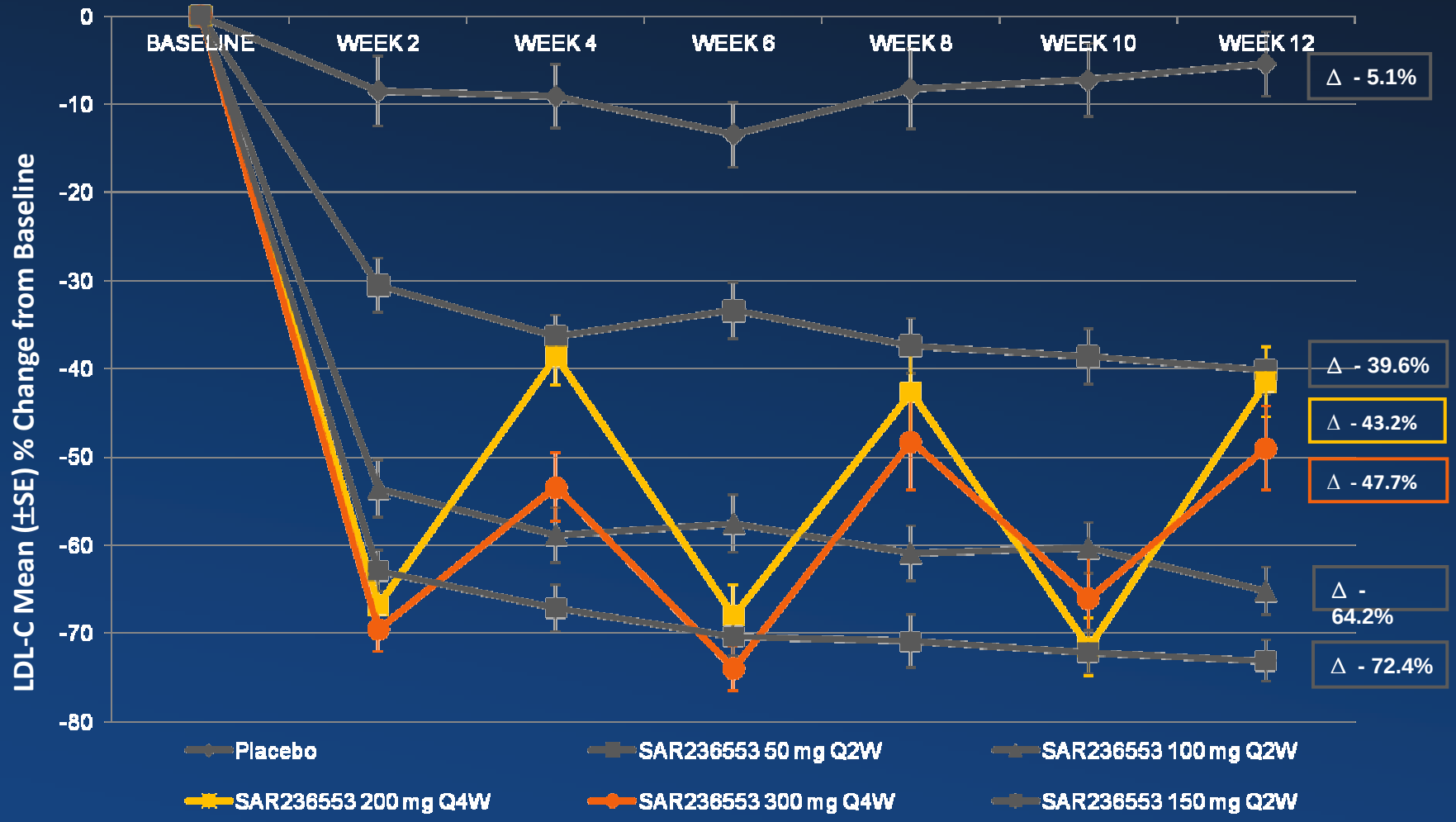
Change in Calculated LDL-C at 2 Weekly Intervals from Baseline to Week 12



A Randomized, Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of a Monoclonal Antibody to PCSK9, in Patients with Primary Hypercholesterolemia

McKenney JM et al. *J Am Coll Cardiol.* 2012;59:2344–2353

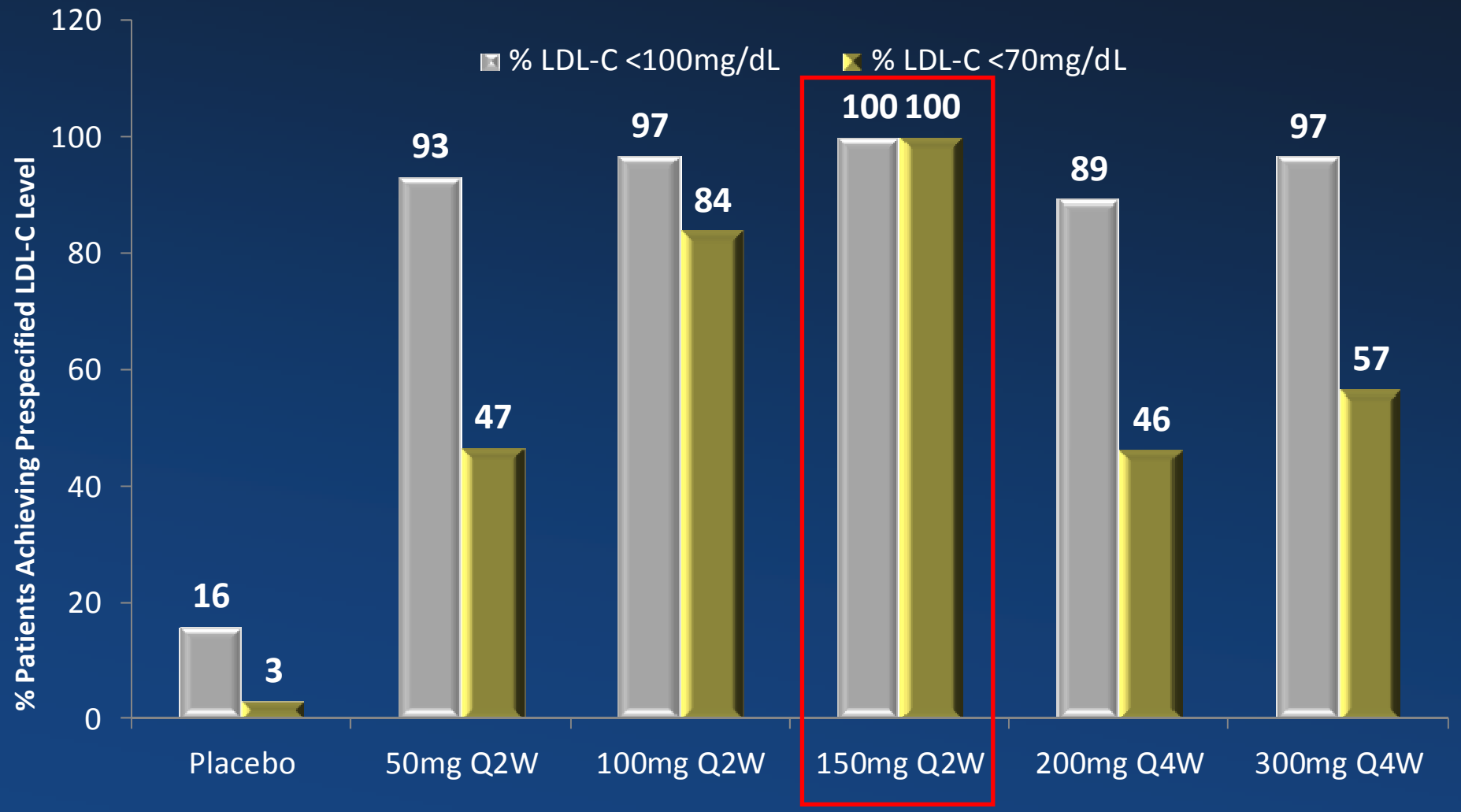
Change in Calculated LDL-C at 2 Weekly Intervals from Baseline to Week 12



Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.

McKenney JM et al. *J Am Coll Cardiol.* 2012;59:2344–2353

Attainment of Prespecified LDL-C Levels at Week 12 (mITT Population)



McKenney JM et al. *J Am Coll Cardiol.* 2012;59:2344–2353

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

Intervention	% Change Apo B	% Change Non–HDL-C	% Change Lp (a)
Placebo	2.2	–2.2	0.0
SAR236553 50mg Q2W	–27.3*	–33.6*	–13.3†
SAR236553 100mg Q2W	–48.1*	–55.6*	–26.1*
SAR236553 150mg Q2W	–56.1*	–62.5*	–28.6*
SAR236553 200mg Q4W	–28.7*	–37.4*	–16.7†
SAR236553 300mg Q4W	–33.1*	–40.7*	–7.9†

*P<0.0001 for % change SAR236553 vs. placebo
†P=0.05 for % change SAR236553 vs. placebo
P values are not adjusted for multiplicity (descriptive only)

McKenney JM et al. *J Am Coll Cardiol.* 2012;59:2344–2353

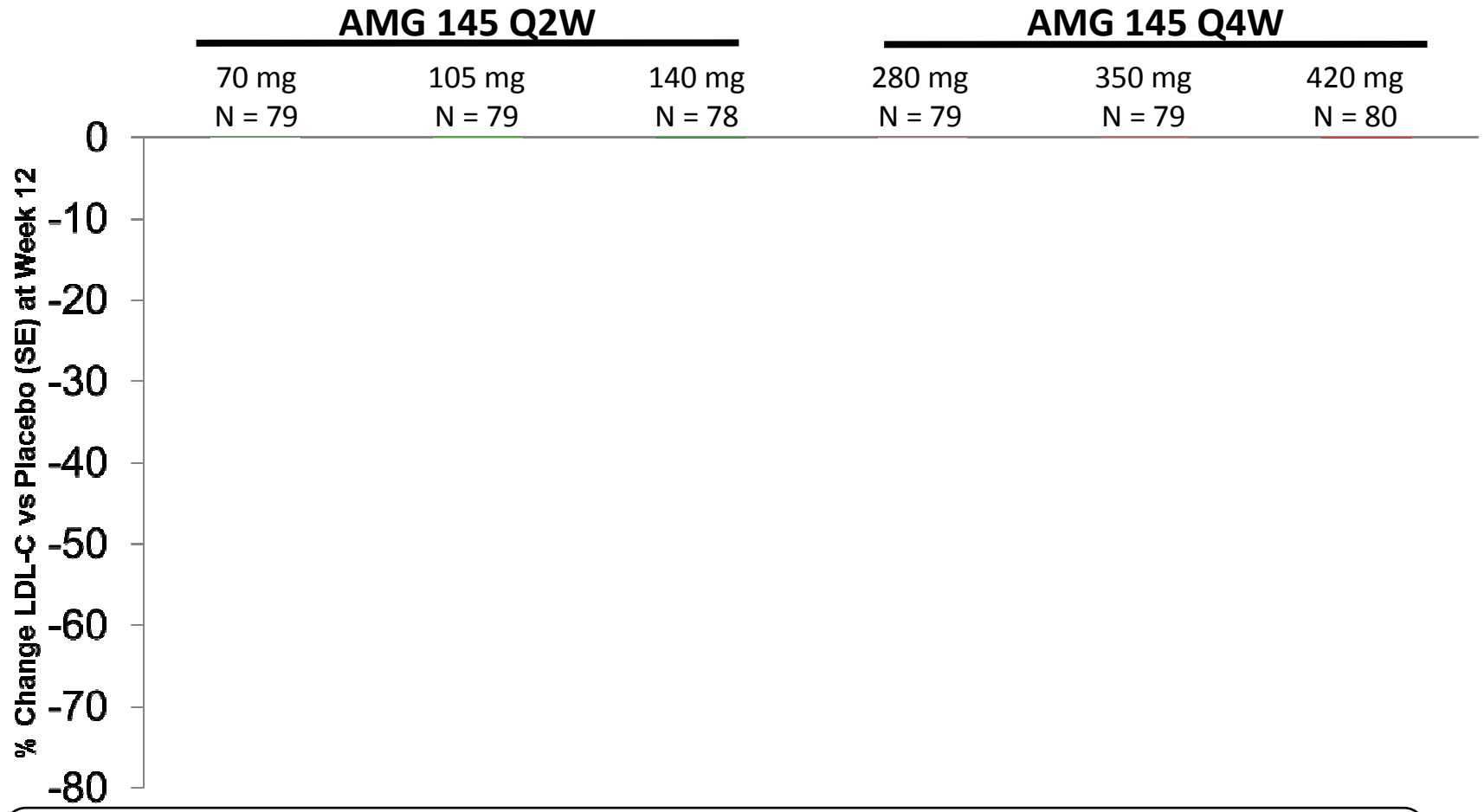
THE LANCET

Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging phase 2 study

*Robert P Giugliano, Nihar R Desai, Payal Kohli, William J Rogers, Ransi Somaratne, Fannie Huang, Thomas Liu, Satishkumar Mohanavelu, Elaine B Hoffman, Shannon T McDonald, Timothy E Abrahamsen, Scott M Wasserman, Robert Scott, Marc S Sabatine, for the LAPLACE-TIMI 57 Investigators**

***Lancet* 2012:380**

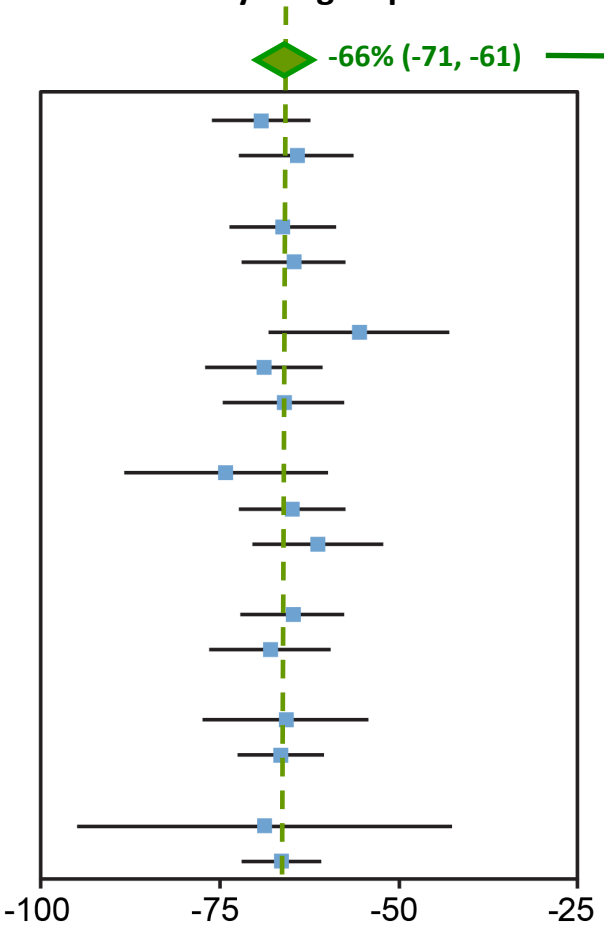
Primary Endpoint:
AMG 145 Reduced LDL-C at 12 wks



Giugliano R, et al Lancet 2012:380

% Reduction in LDL with Top 2 AMG 145 Doses: Major Subgroups

140 mg Q2W dose of AMG 145 reduced LDL at 12 weeks ranging from 56-74% in key subgroups

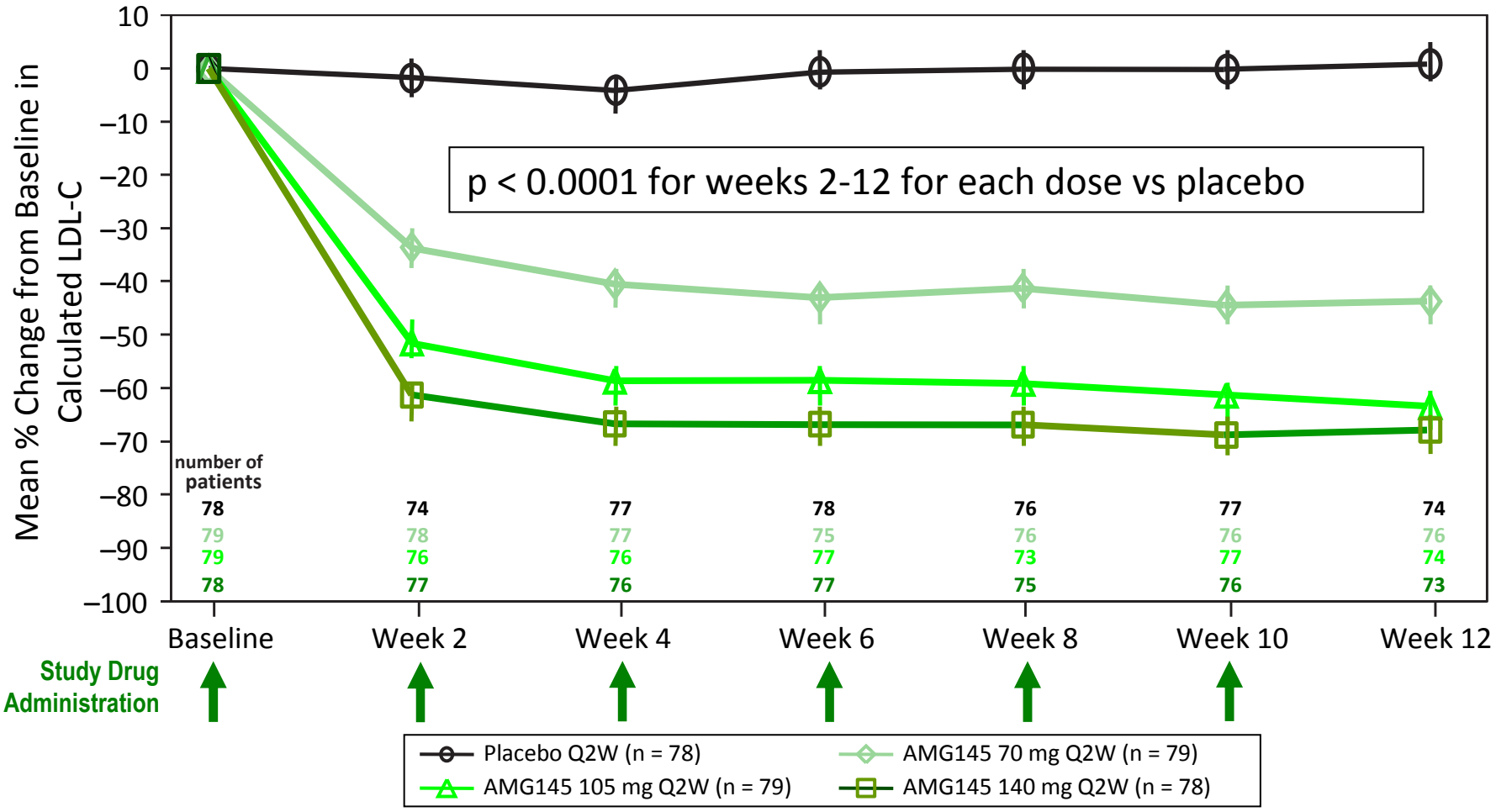


Baseline Characteristics	
All patients	-66% (-71, -61)
Men	
Women	
Age < 65 Years	
Age ≥ 65 Years	
BMI < 25 Kg/M2	
BMI 25-30 Kg/M2	
BMI ≥ 30 Kg/M2	
Baseline UC LDL-C < 100 mg/dL	
Baseline UC LDL-C 100-130 mg/dL	
Baseline UC LDL-C ≥ 130 mg/dL	
Baseline PCSK9 < median	
Baseline PCSK9 ≥ median	
Intensive statin regimen	
Non-intensive statin regimen	
Concomitant ezetimibe	
No concomitant ezetimibe	

UC = Ultra centrifugation

Giugliano R, et al Lancet 2012:380

AMG 145 Q2W Dose Response:
% Change in LDL-C Through 12 Wks



Giugliano R, et al Lancet 2012:380

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

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER)

This study is currently recruiting participants.

Verified November 2013 by Amgen

ClinicalTrials.gov Identifier:
NCT01764633

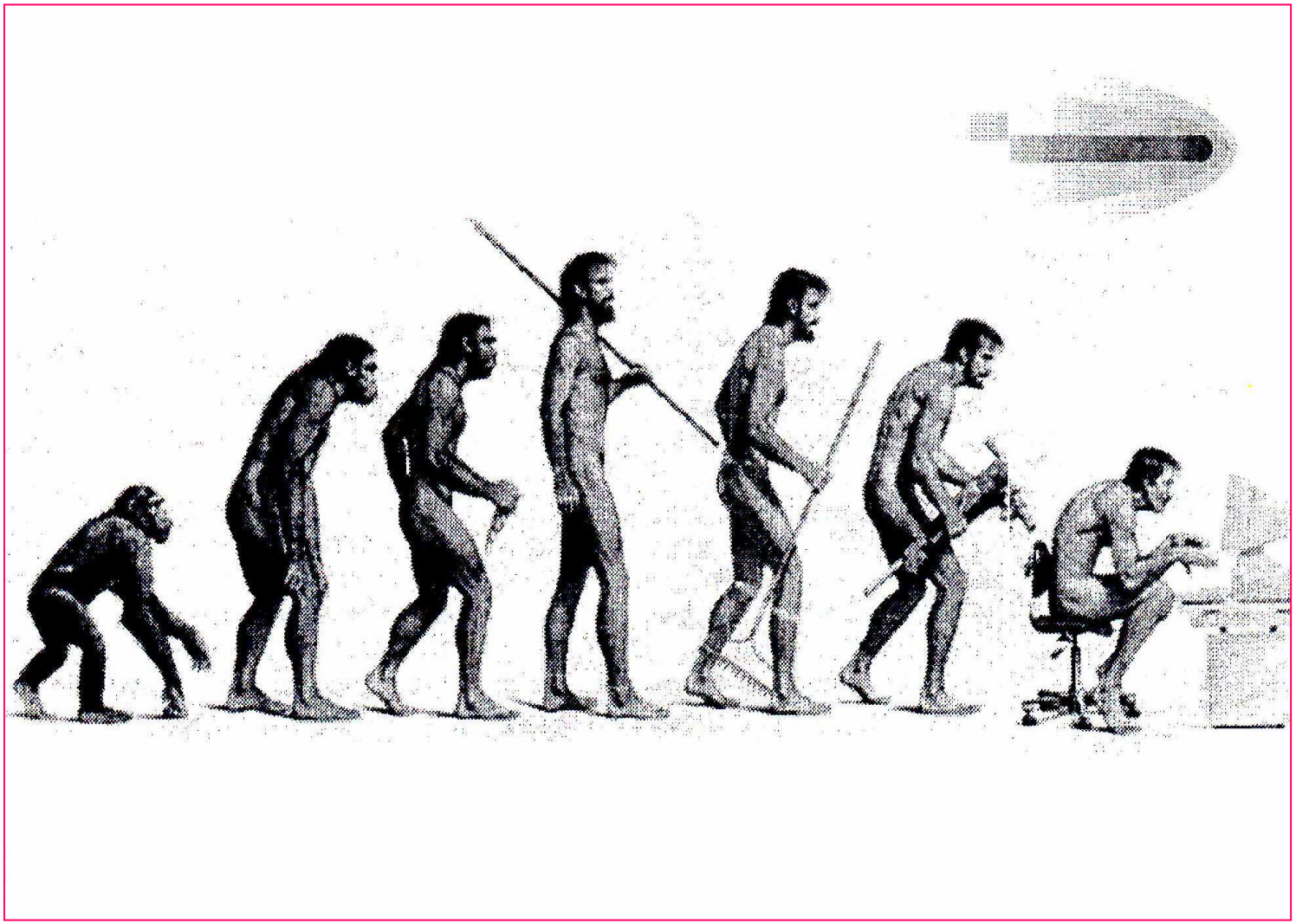
The primary endpoint is the time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization, whichever occurs first.

Estimated Enrollment:	22500
Study Start Date:	January 2013
Estimated Study Completion Date:	February 2018
Estimated Primary Completion Date:	December 2017 (Final data collection date for primary outcome measure)

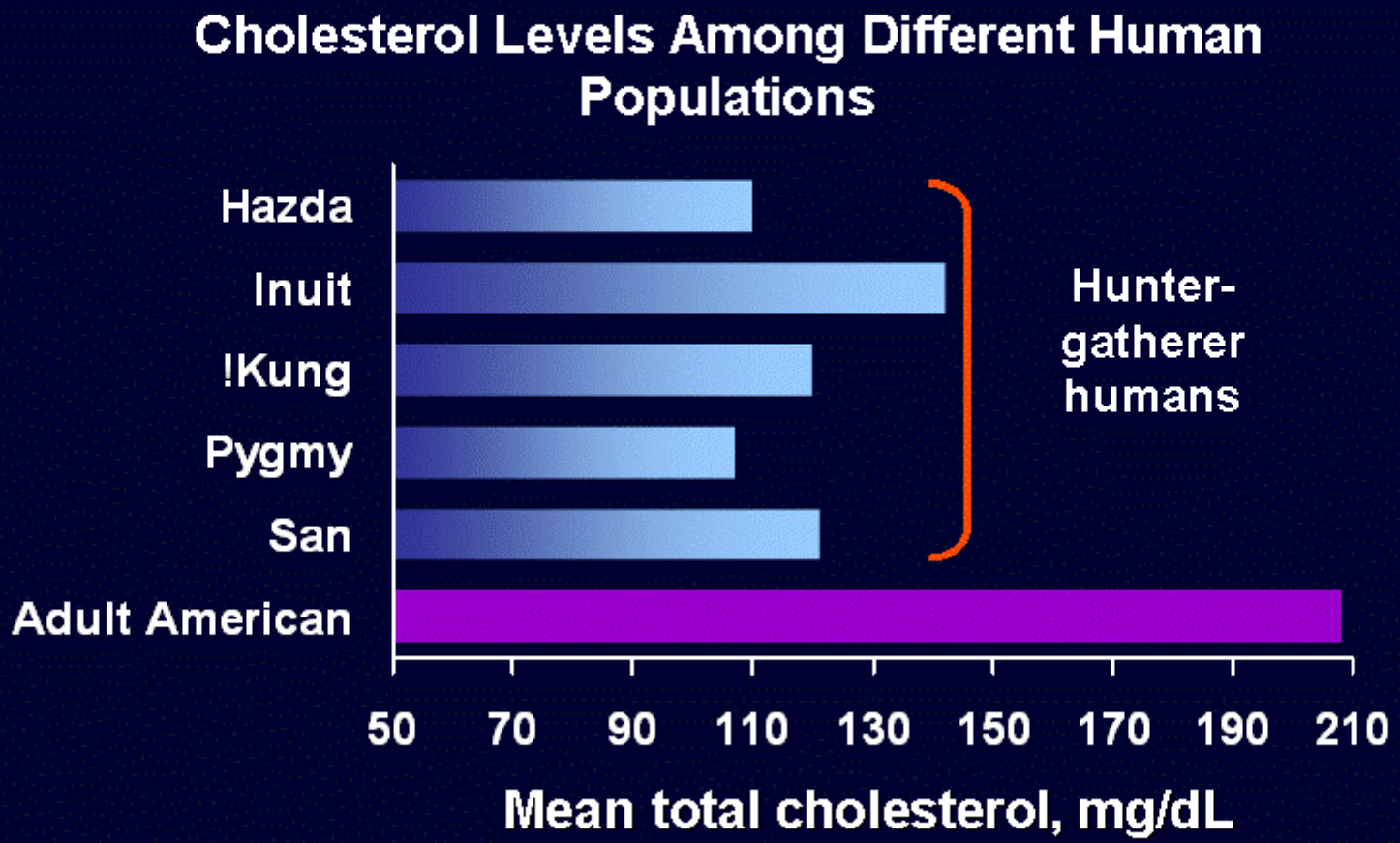
Inclusion Criteria:

- Male or female ≥ 40 to ≤ 85 years of age
- History of clinically evident cardiovascular disease at high risk for a recurrent event
- Fasting LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L)) or non-HDL-C ≥ 100 mg/dL (> 2.6 mmol/L)
- Fasting triglycerides ≤ 400 mg/dL (4.5 mmol/L)

The human evolution
What was the LDL-C of our ancestry?



What Is Desirable Cholesterol?



Adapted from O'Keefe JH Jr et al. *J Am Coll Cardiol*. 2004;43:2142–2146.