

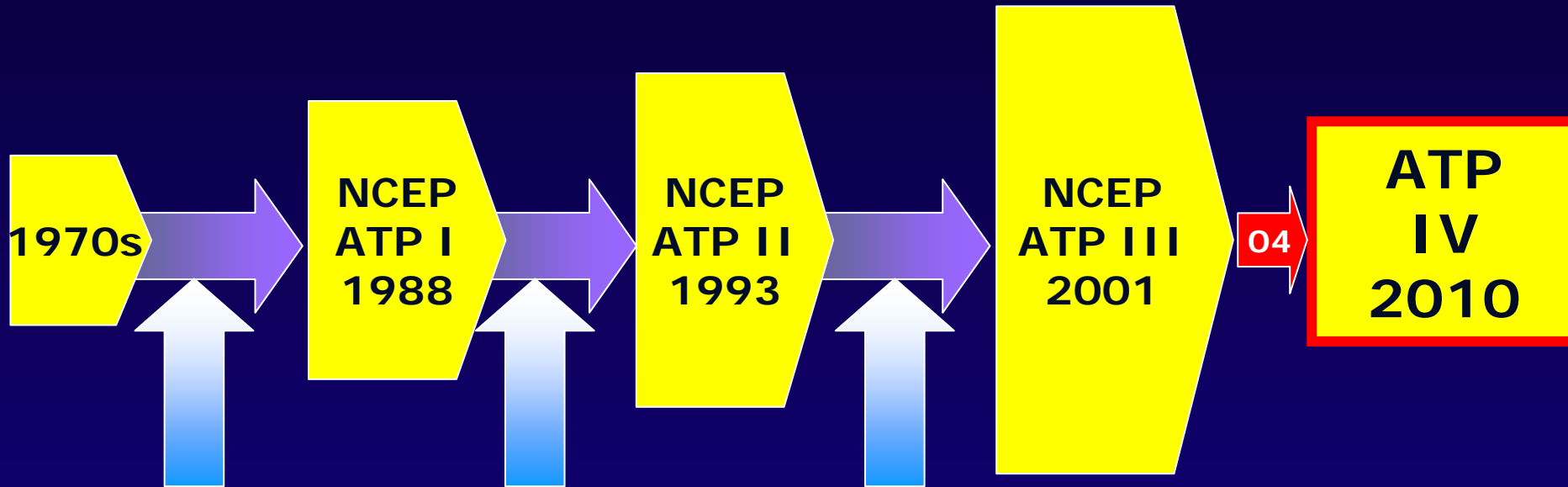
Guías en DLP: que dicen hoy, y en el futuro?



**CENTRO DE LIPIDOS
Y PREVENCION
DE ATEROESCLEROSIS**

Universidad Austral y F.L.E.N.I

Evolucion de las guias terapeuticas



Framingham
MRFIT
LFC-CPPT
Coronary
Drug Project
Helsinki

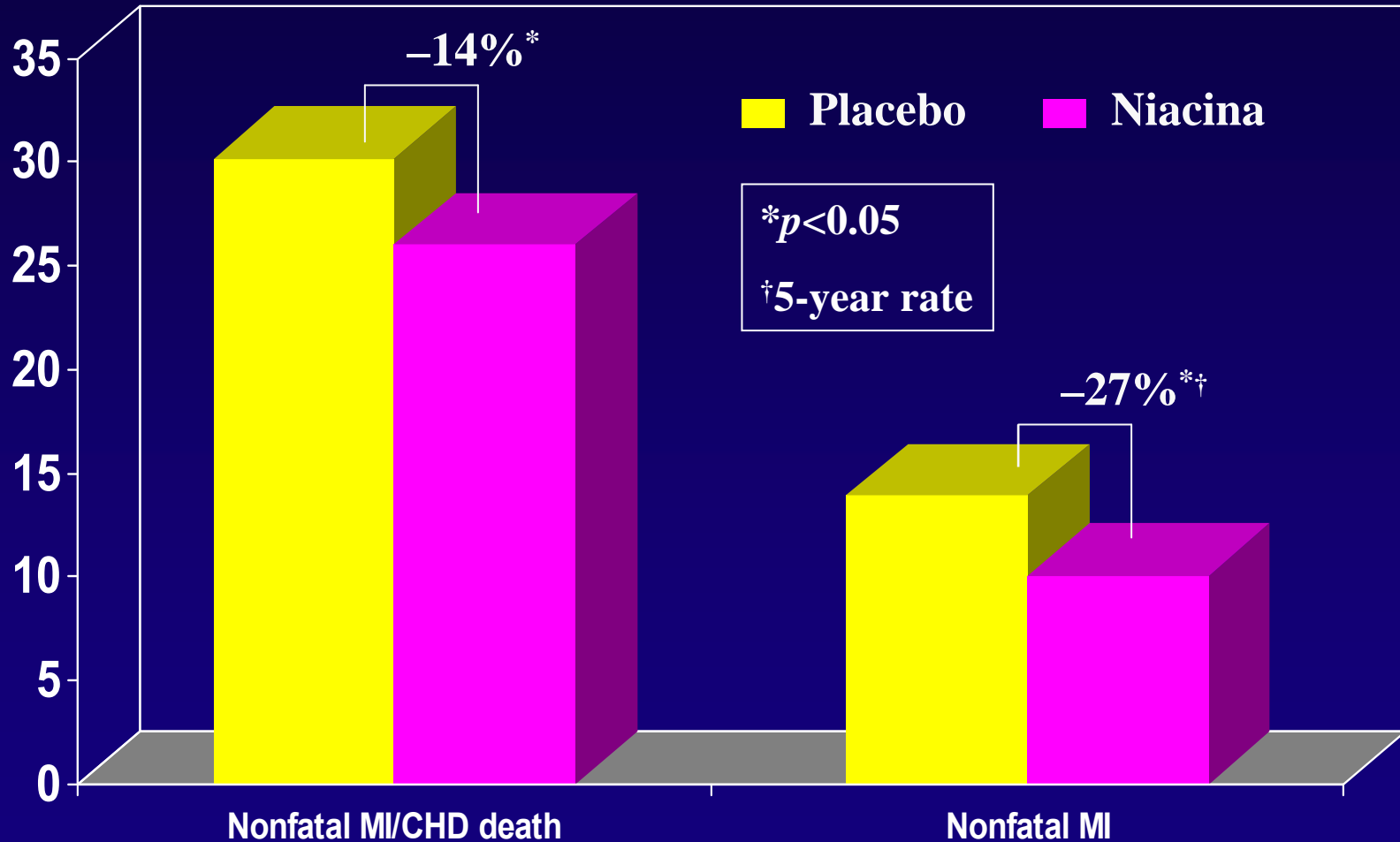
Angiograficos
(FATS, POSCH,
SCOR, STARS,
Omish, MARS)
Meta-Analisis
(Holme,
Rossouw)

WOSCOPS,
4S,CARE,
LIPID,
AFCAPS,
VAHIT,
Otros

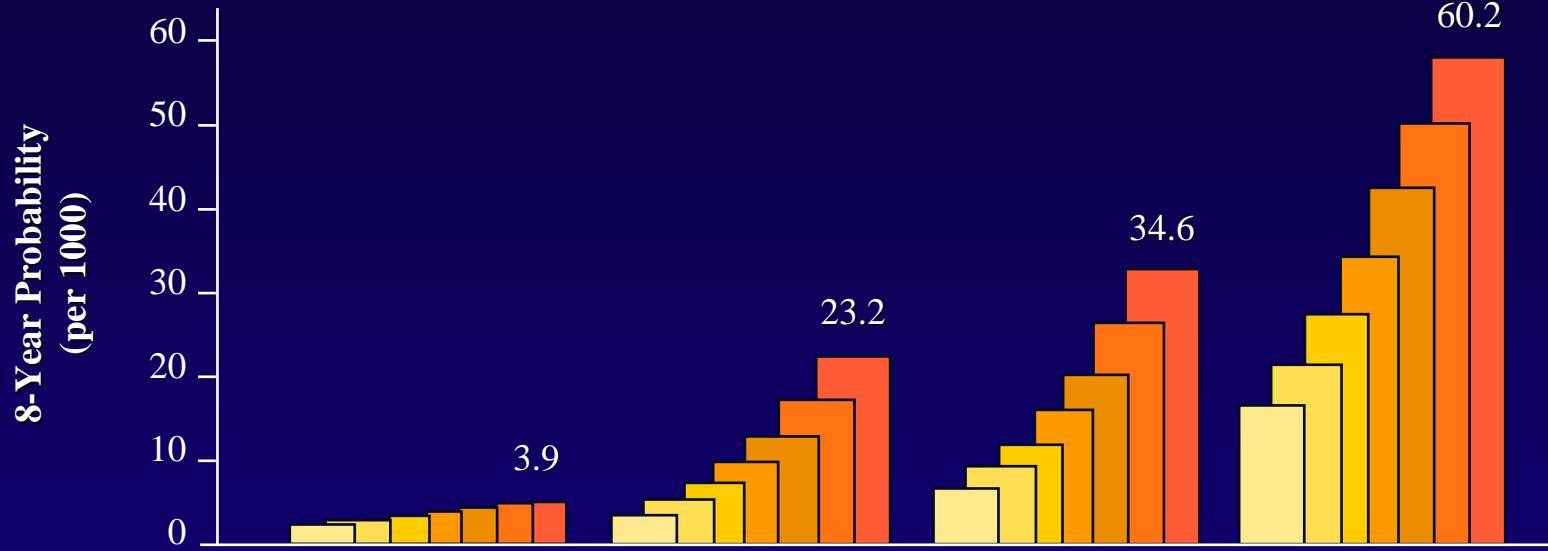
Improve It
TNT, IDEAL
A to Z
HPS
PROSPER
ASCOT
MIRACL
Jupiter

Coronary Drug Project

Eventos clínicos en el seguimiento

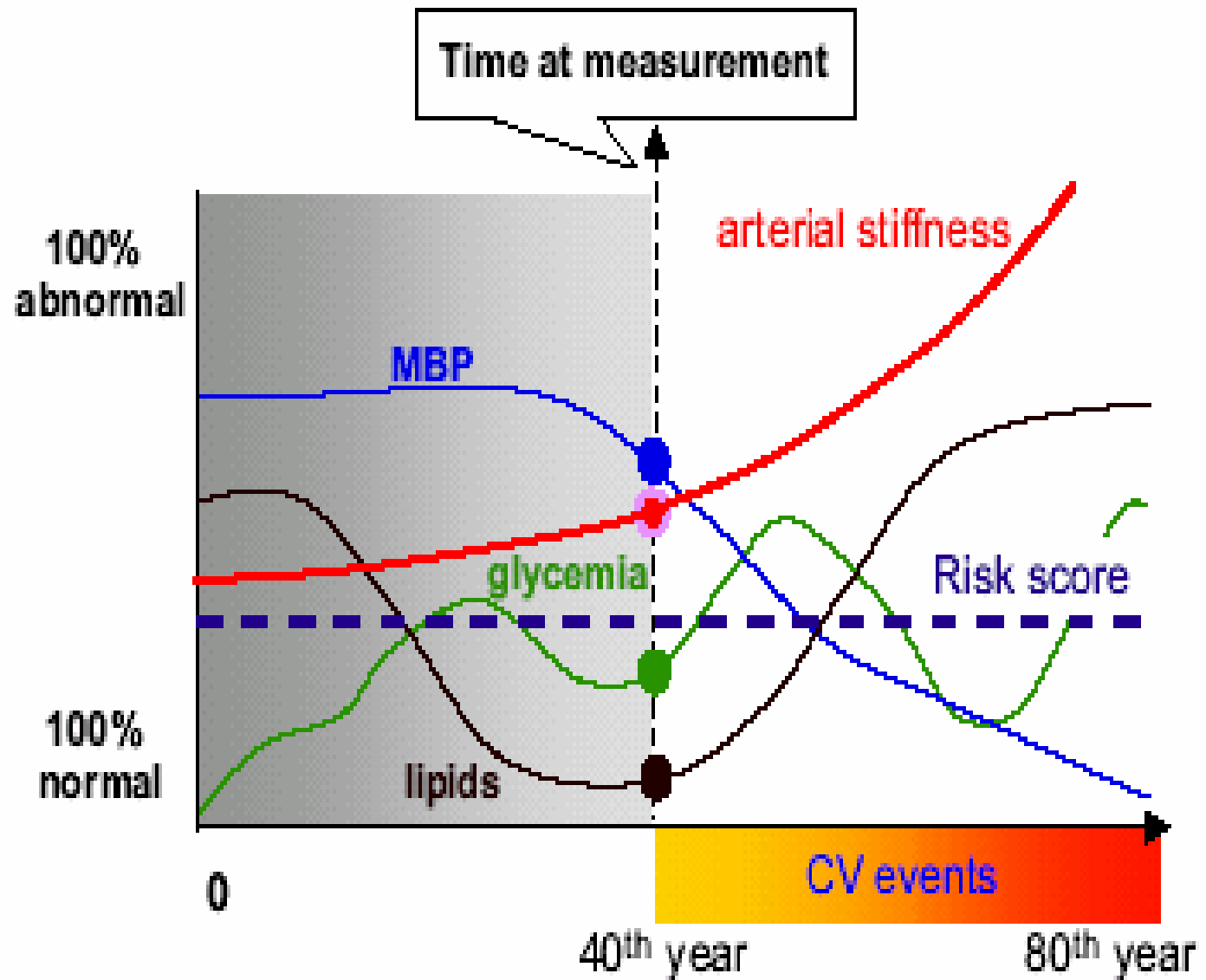


Riesgo de Eventos Coronarios según la cantidad de Factores de Riesgo presentes: Framingham



Colesterol, mg/dL	185↔335		185↔335		185↔335		185↔335	
Intol. Glucosa	0	+	+	+	+	+	+	+
Sistólica, mm Hg	105	105	195	195	195	195	195	195
Cigarrillo	0	0	0	+	+	+	+	+
HVI en ECG	0	0	0	0	0	0	0	+

Exposicion a FR-CV: tiempo y consecuencias



Estimado de Riesgo a 10 años para Hombres (Framingham)

1

Age, y	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

3

Systolic BP mm Hg	If Untreated	If Treated
< 120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

5

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

4

HDL, mg/dl	Points
≥ 60	-1
50-59	0
40-49	1
<40	2

6

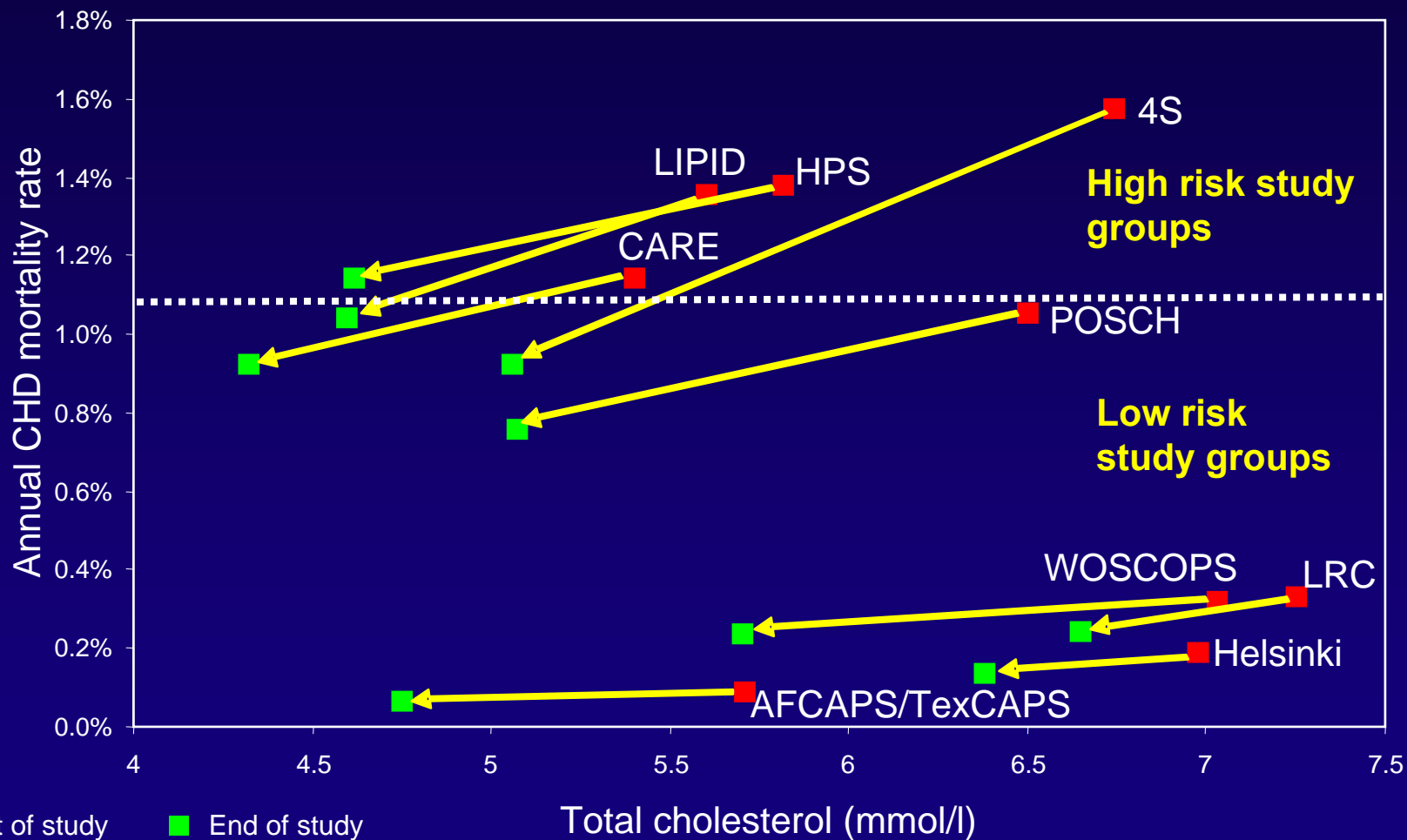
Point Total	10-Year Risk%
< 0	< 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥ 17	≥ 30

2

Total Cholesterol	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
< 160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥ 280	11	8	5	3	1

Reduccion de la mortalidad CV segun RCV

High risk study groups



SPECIAL ARTICLE

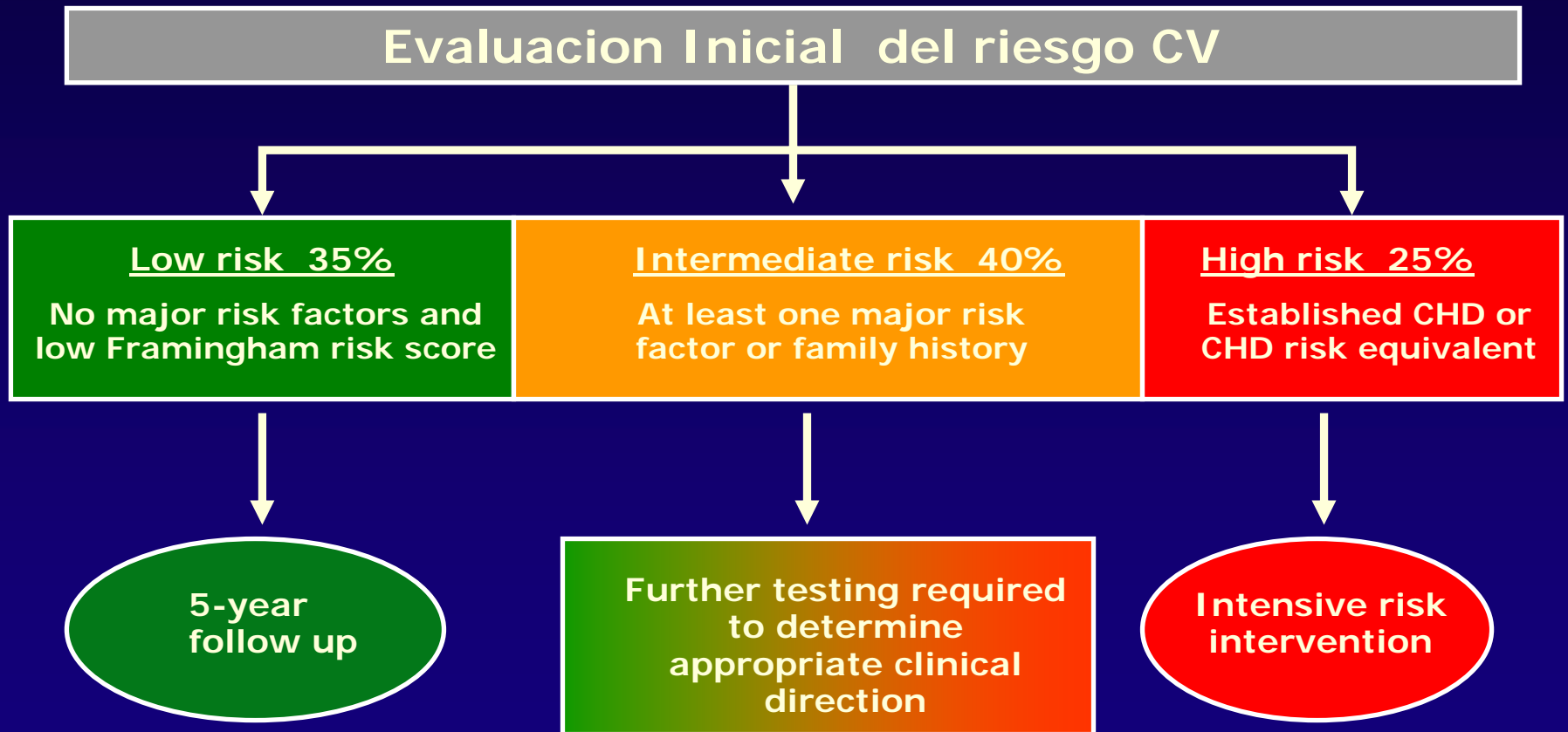
2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations

Jacques Genest MD¹, Ruth McPherson MD PhD², Jiri Frohlich MD³, Todd Anderson MD⁴, Norm Campbell MD⁴, André Carpentier MD⁵, Patrick Couture MD⁶, Robert Dufour MD⁷, George Fodor MD², Gordon A Francis MD³, Steven Grover MD¹, Milan Gupta MD⁸, Robert A Hegele MD⁹, David C Lau MD¹⁰, Lawrence Leiter MD¹¹, Gary F Lewis MD¹², Eva Lonn MD¹³, GB John Mancini MD¹⁴, Dominic Ng MD PhD¹¹, Glen J Pearson PharmD¹⁵, Allan Sniderman MD¹⁶, James A Stone MD PhD¹⁰, Ehud Ur MD¹⁴

TARGETS OF THERAPY

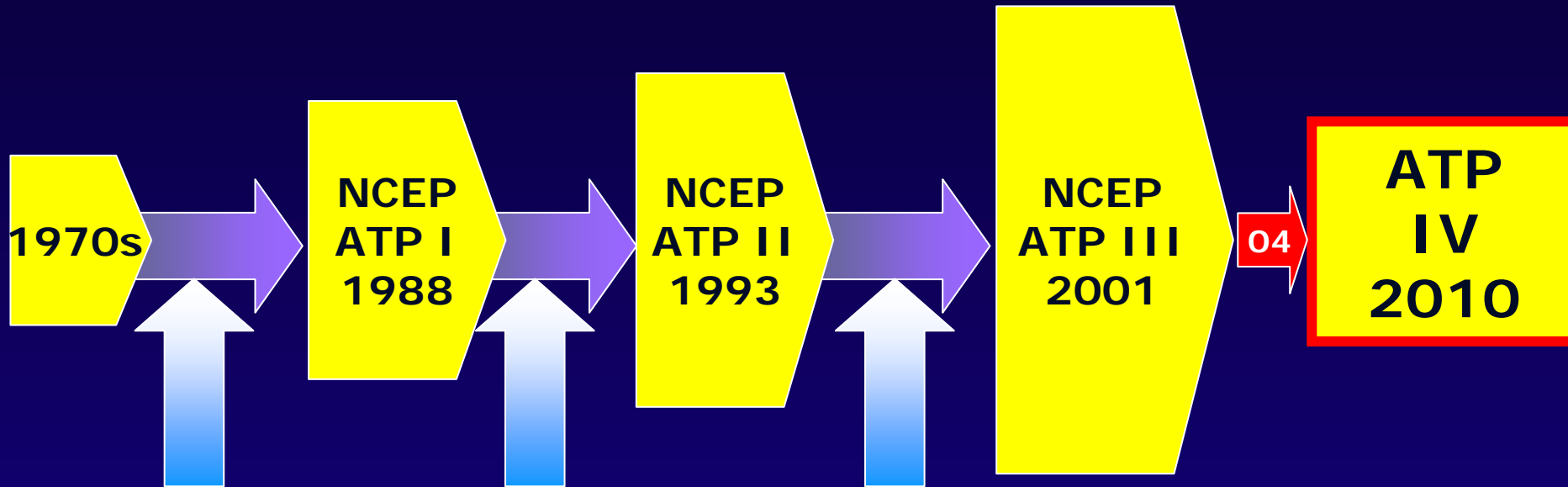
Risk level	Primary target: LDL-C	Class, level
<p>High</p> <p>CAD, PVD, atherosclerosis</p> <p>Most patients with diabetes</p> <p>FRS $\geq 20\%$</p> <p>RRS $\geq 20\%$</p>	<p>< 2 mmol/L</p> <p>or</p> <p>$\geq 50\%$ ↓ LDL-C</p> <p>apoB < 0.80 g/L</p>	<p>Class I, level A</p>
<p>Moderate</p> <p>FRS 10% to 19%</p> <p>LDL-C > 3.5 mmol/L</p> <p>TC/HDL-C > 5.0</p> <p>hs-CRP > 2 mg/L in men</p> <p>> 50 years and women</p> <p>> 60 years of age</p> <p>Family history and hs-CRP modulate risk</p>	<p>< 2 mmol/L*</p> <p>or</p> <p>$\geq 50\%$ ↓ LDL-C</p> <p>apoB < 0.80 g/L</p>	<p>Class IIa, level A</p>
<p>Low</p> <p>FRS $< 10\%$</p>	<p>$\geq 50\%$ ↓ LDL-C</p>	<p>Class IIa, level A</p>

Redefiniendo la evaluacion del riesgo cardiaco en pacientes asintomaticos



Non invasive assessment

Evolucion de las guias terapeuticas



Framingham
MRFIT
LFC-CPPT
Coronary
Drug Project
Helsinki

Angiograficos
(FATS, POSCH,
SCOR, STARS,
Omish, MARS)
Meta-Analisis
(Holme,
Rossouw)

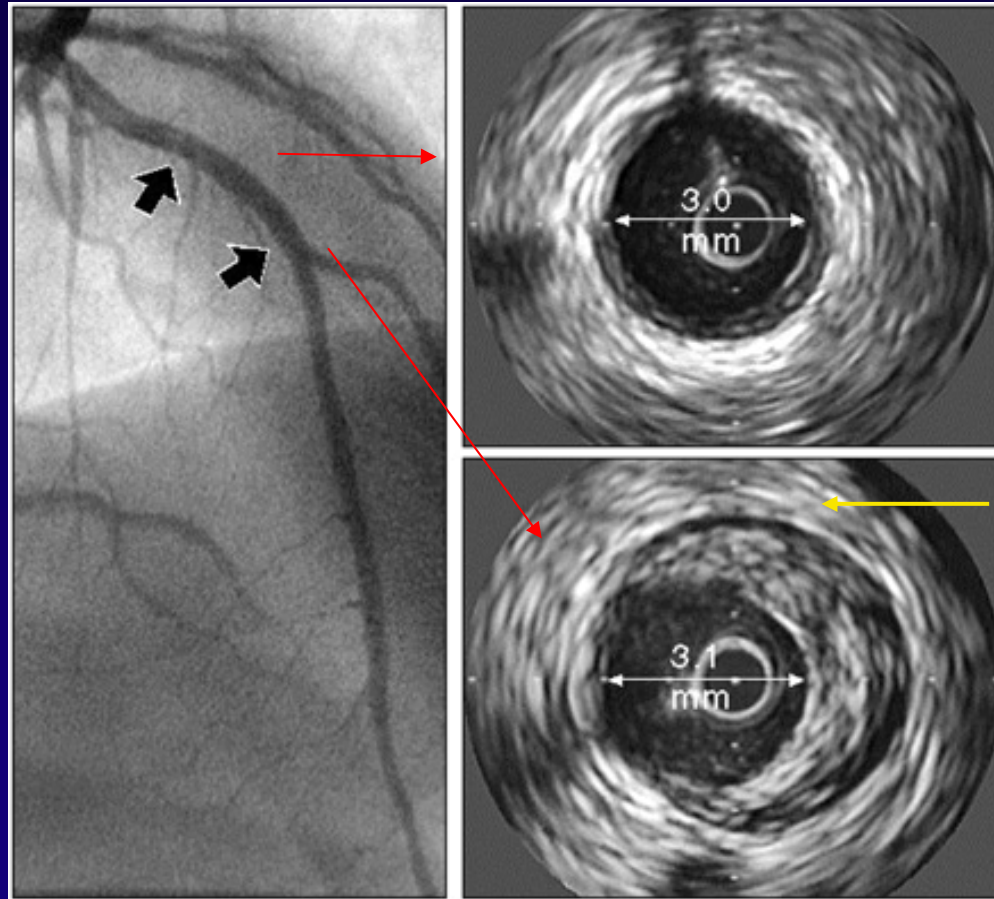
WOSCOPS,
4S,CARE,
LIPID,
AFCAPS,
VAHIT,
Otros

Improve It
TNT, IDEAL
A to Z
HPS
PROSPER
ASCOT
MIRACL
Jupiter

Placa aterosclerotica en imagenes por IVUS, comp. angio convencional

Angiogram

IVUS



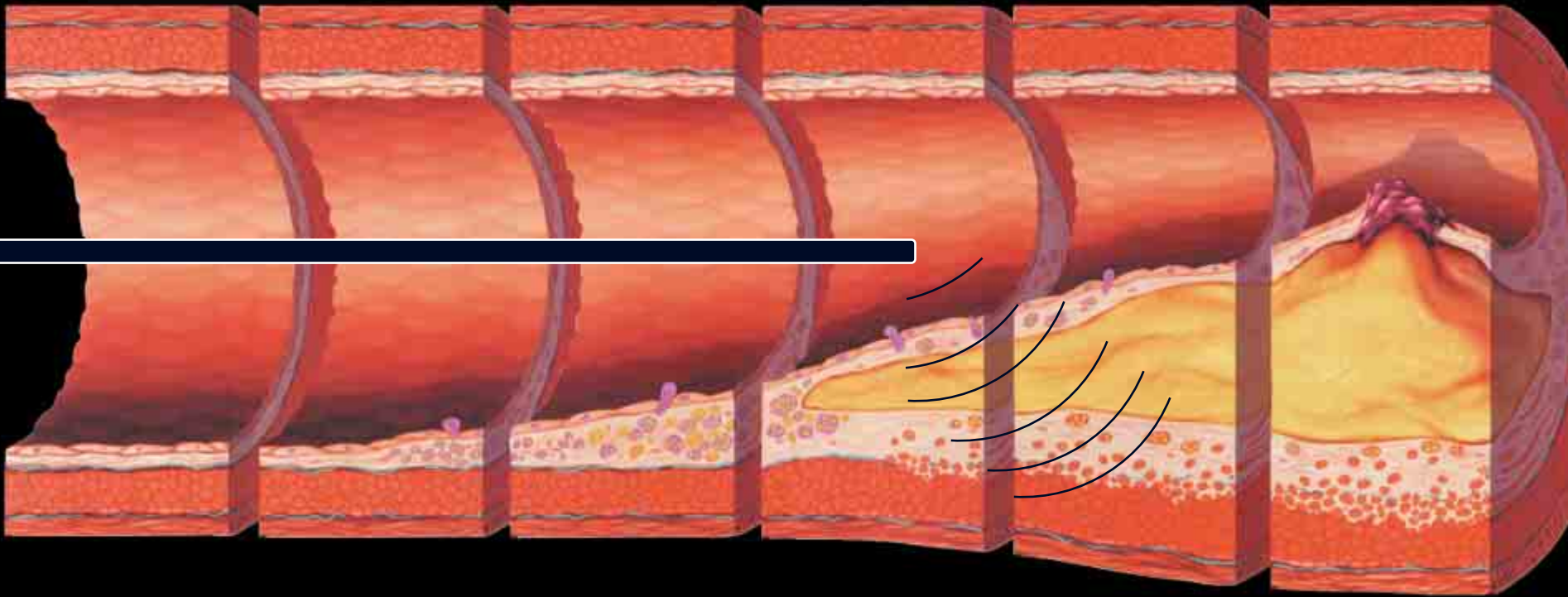
Ateroma

F

Fatty
streak

Atheroma

Complicated
lesion/rupture

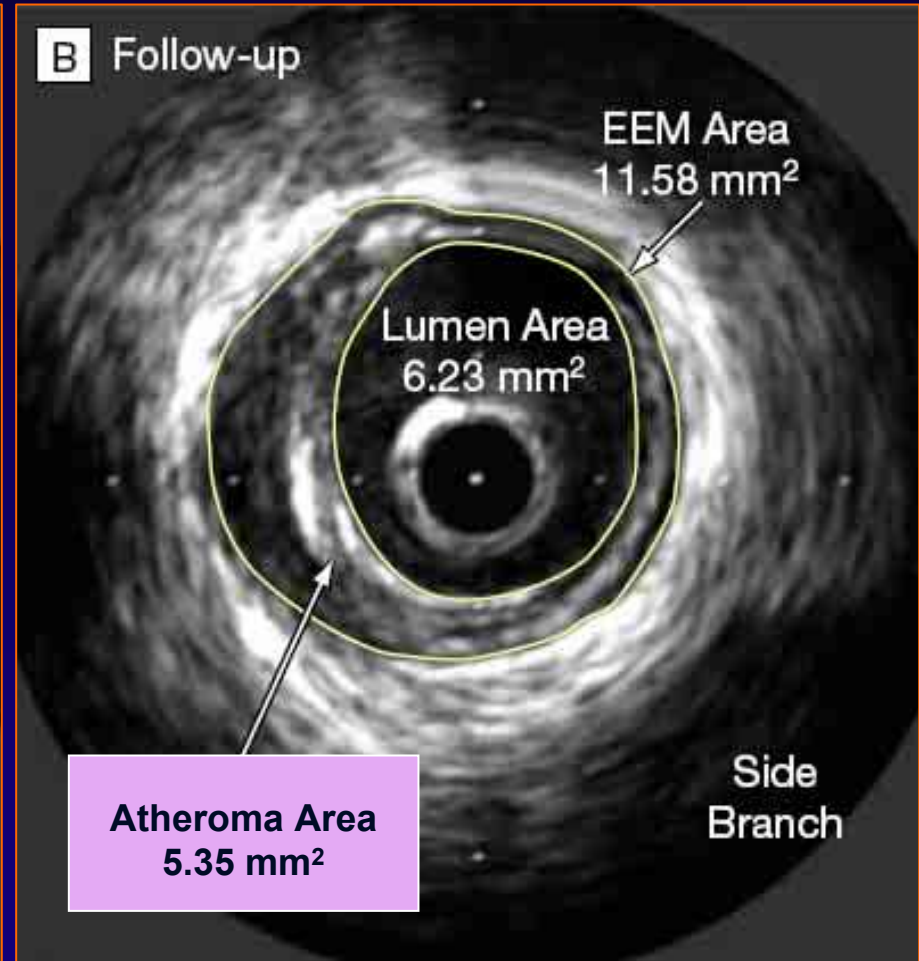
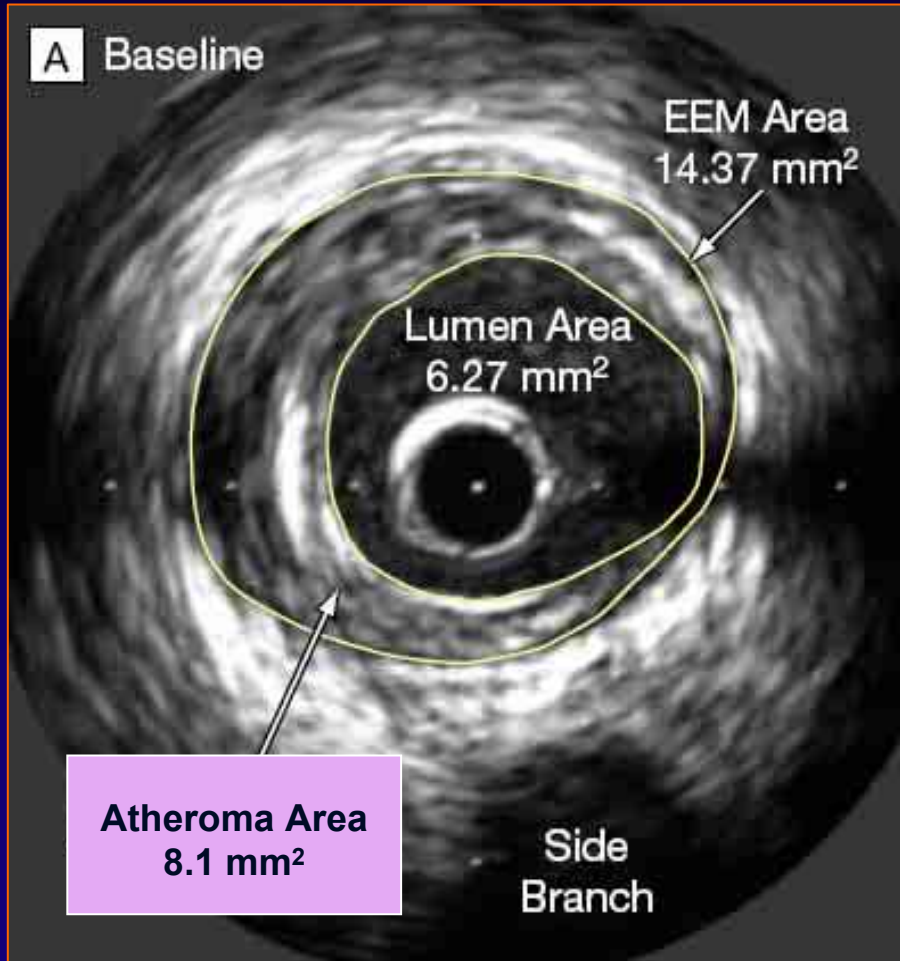


From first decade

From third decade

From fourth decade

Regresion de ateroma/ humanos Apo A-I Milano / Fosfolipidos

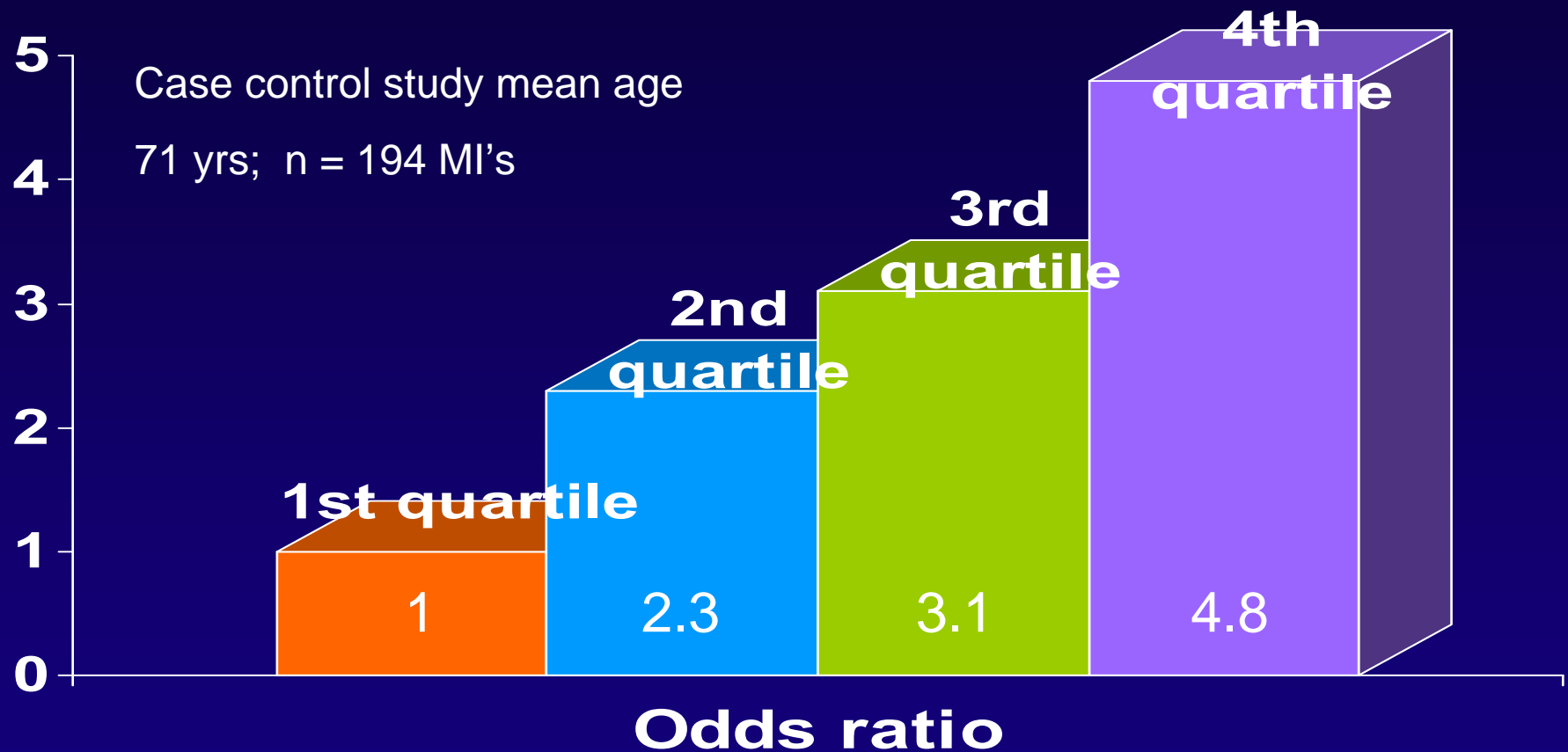


ETC-216 : Apo A-I_{Milano} / Phospholipids

TARGETS OF THERAPY

Risk level	Primary target: LDL-C	Class, level
High CAD, PVD, atherosclerosis Most patients with diabetes FRS $\geq 20\%$ RRS $\geq 20\%$	< 2 mmol/L or $\geq 50\%$ \downarrow LDL-C apoB < 0.80 g/L	Class I, level A
Moderate FRS 10% to 19% LDL-C > 3.5 mmol/L TC/HDL-C > 5.0 hs-CRP > 2 mg/L in men >50 years and women >60 years of age Family history and hs-CRP modulate risk	< 2 mmol/L* or $\geq 50\%$ \downarrow LDL-C apoB < 0.80 g/L	Class IIa, level A
Low FRS $< 10\%$	$\geq 50\%$ \downarrow LDL-C	Class IIa, level A

El Rotterdam study: grosor intima-media combinado y riesgo de Infarto de Miocardio

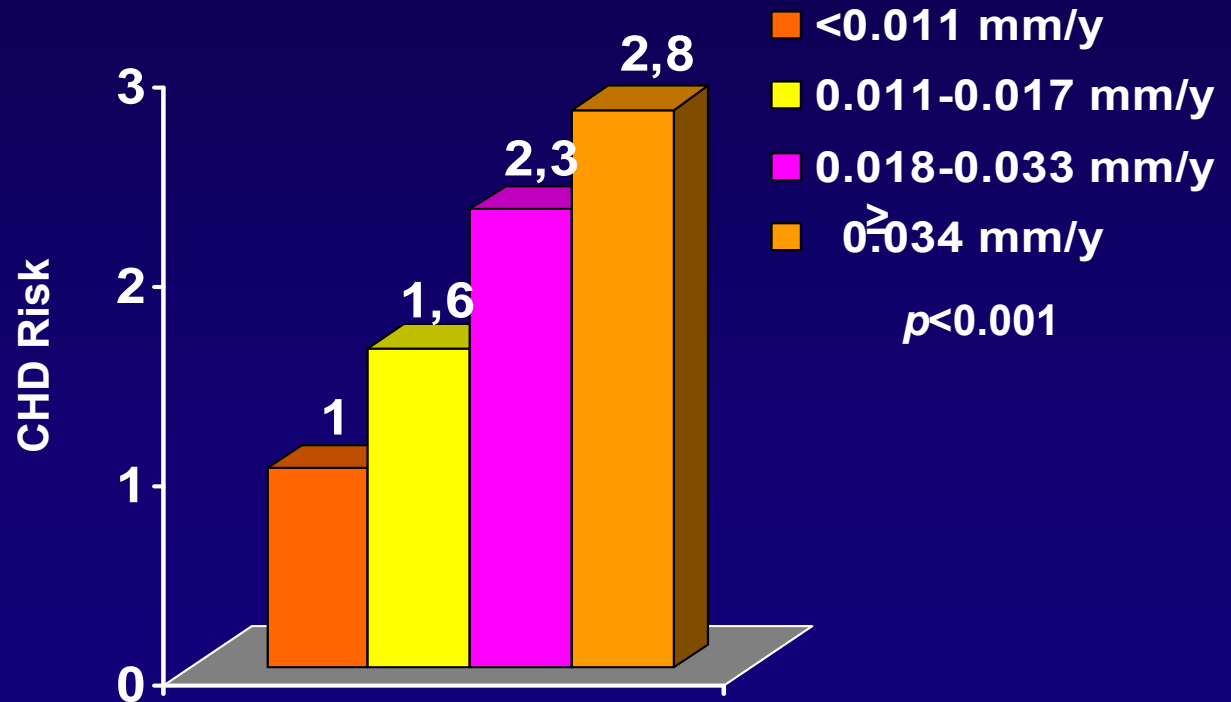


Adjusted for age, gender, BMI, BP, Total Chol, HDL, smoking & DM

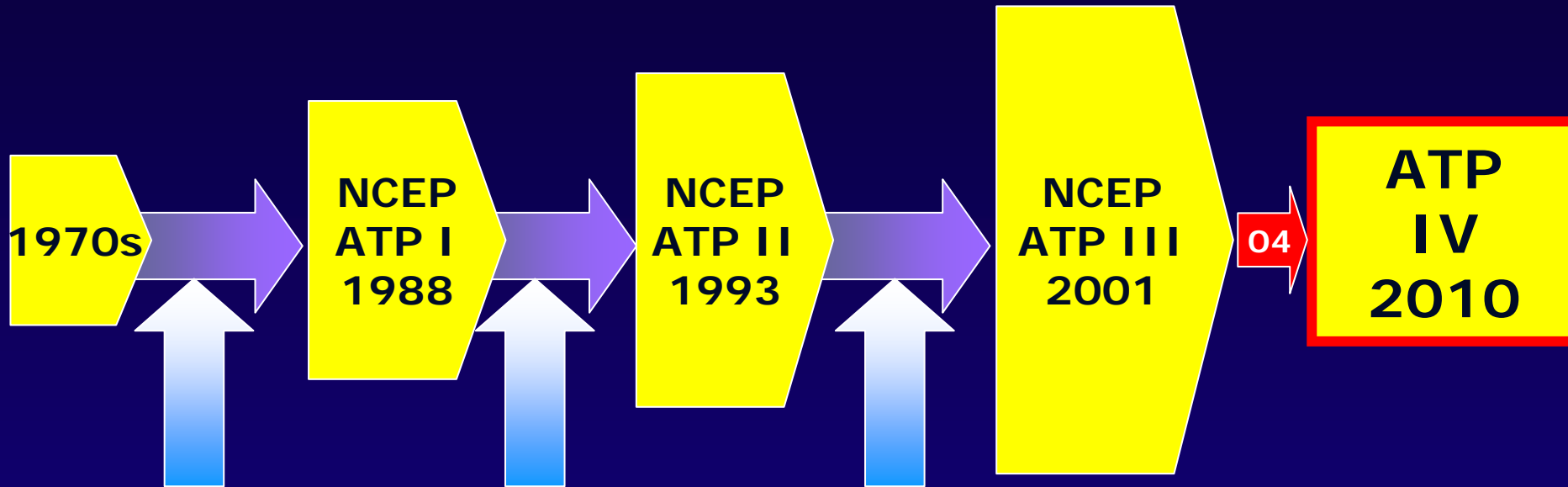
El CLAS study: la progresion del grosor mio intimal predice eventos futuros

Colestipol/Niacina vs. Placebo

146 hombres
(40 a 59 a)
con CRM previa



Evolucion de las guias terapeuticas



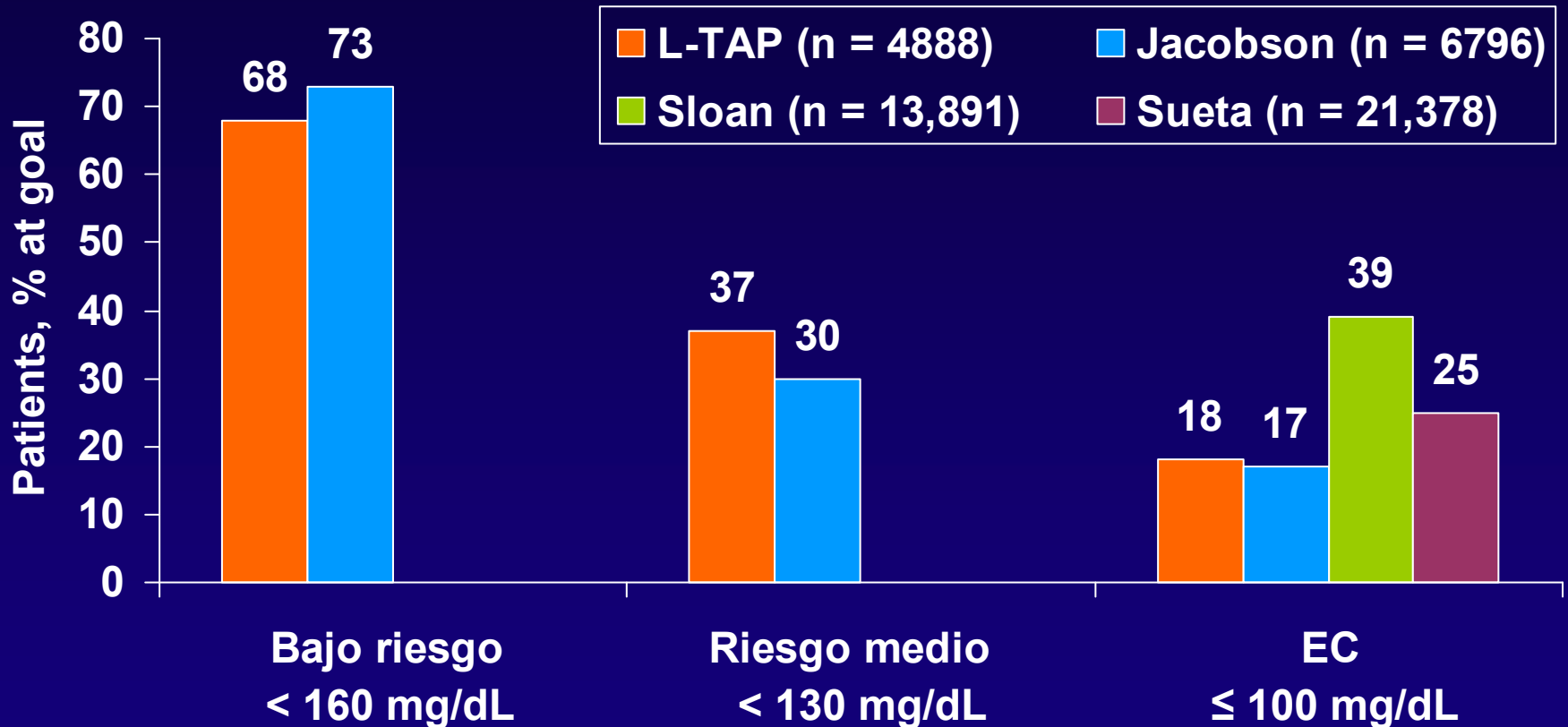
Framingham
MRFIT
LFC-CPPT
Coronary
Drug Project
Helsinki

Angiograficos
(FATS, POSCH,
SCOR, STARS,
Omish, MARS)
Meta-Analisis
(Holme,
Rossouw)

WOSCOPS,
4S,CARE,
LIPID,
AFCAPS,
VAHIT,
Otros

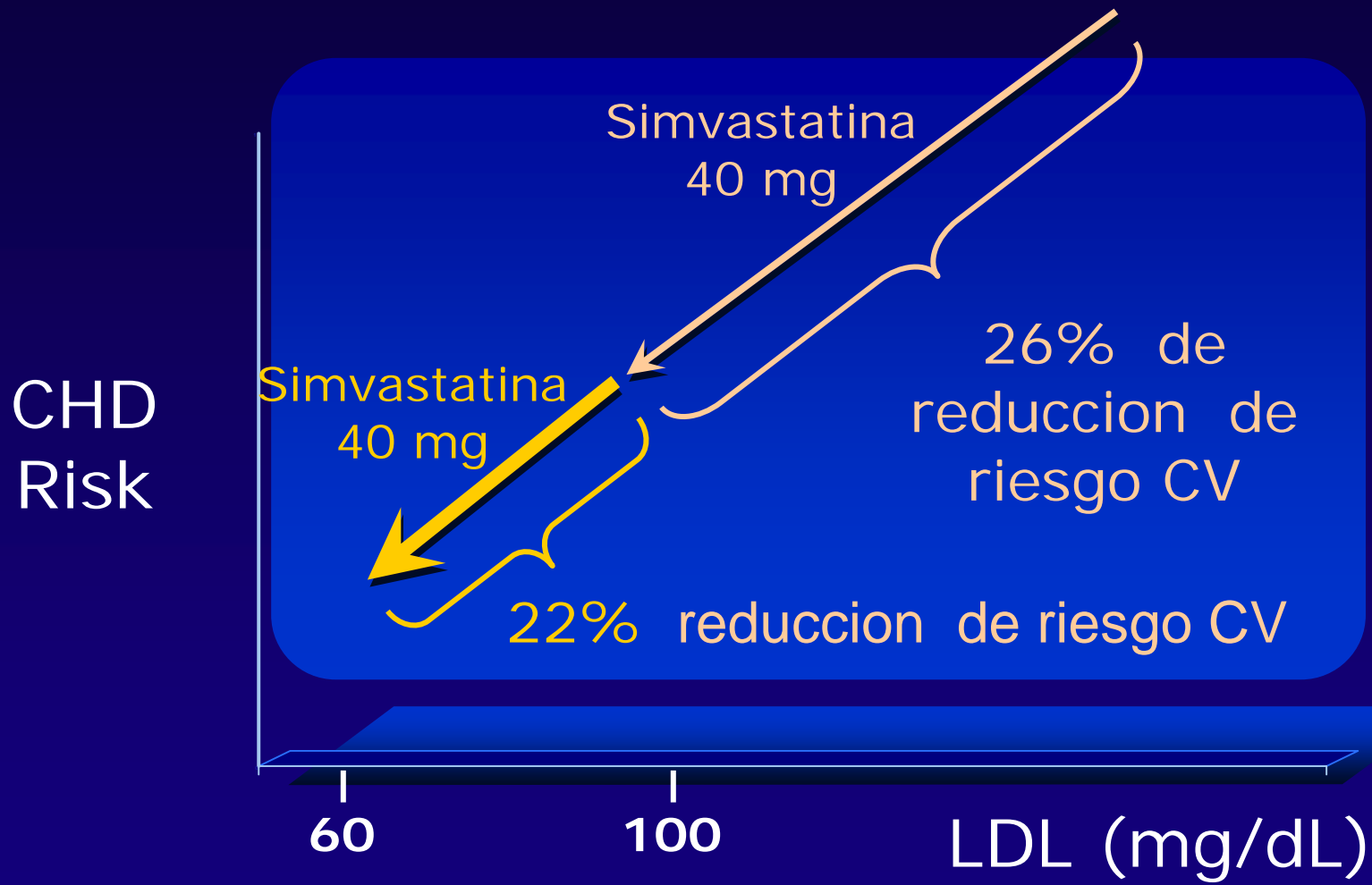
Improve It
TNT, IDEAL
A to Z
HPS
PROSPER
ASCOT
MIRACL
Jupiter

Cumplimiento de objetivos de LDL ATP II: Pocos pacientes los alcanzan: Por que ??



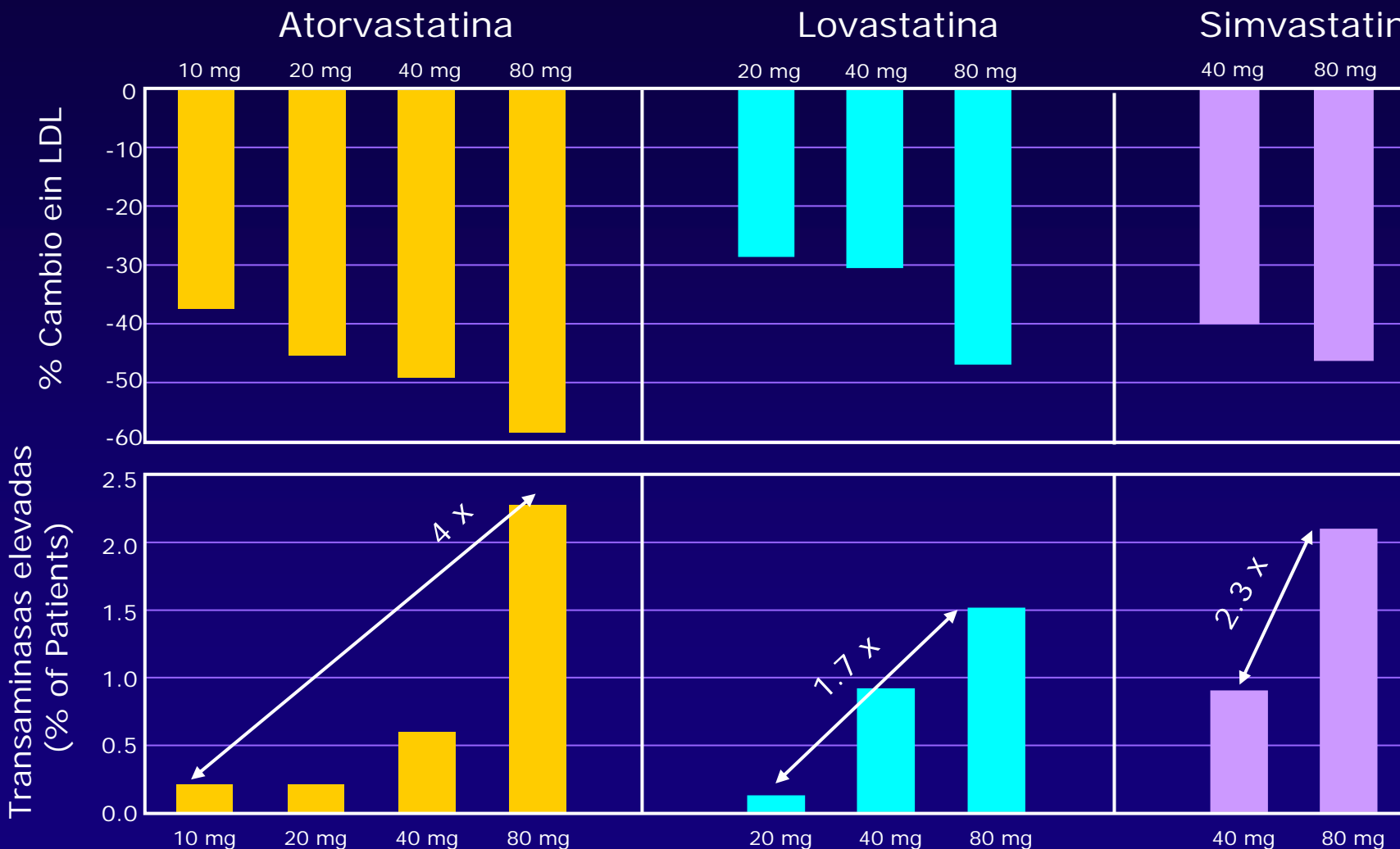
Pearson TA, et al. *Arch Intern Med.* 2000;160:459-467;
Jacobson TA, et al. *Arch Intern Med.* 2000;160:1361-1369;
Sloan KL, et al. *Am J Cardiol.* 2001;88:1143-1146;
Sueta CA, et al. *Am J Cardiol.* 1999;83:1303-1307.

Heart Protection Study: LDL y riesgo CV



Heart Protection Study Collaborative Group. *Lancet* 2002;360:7-22.

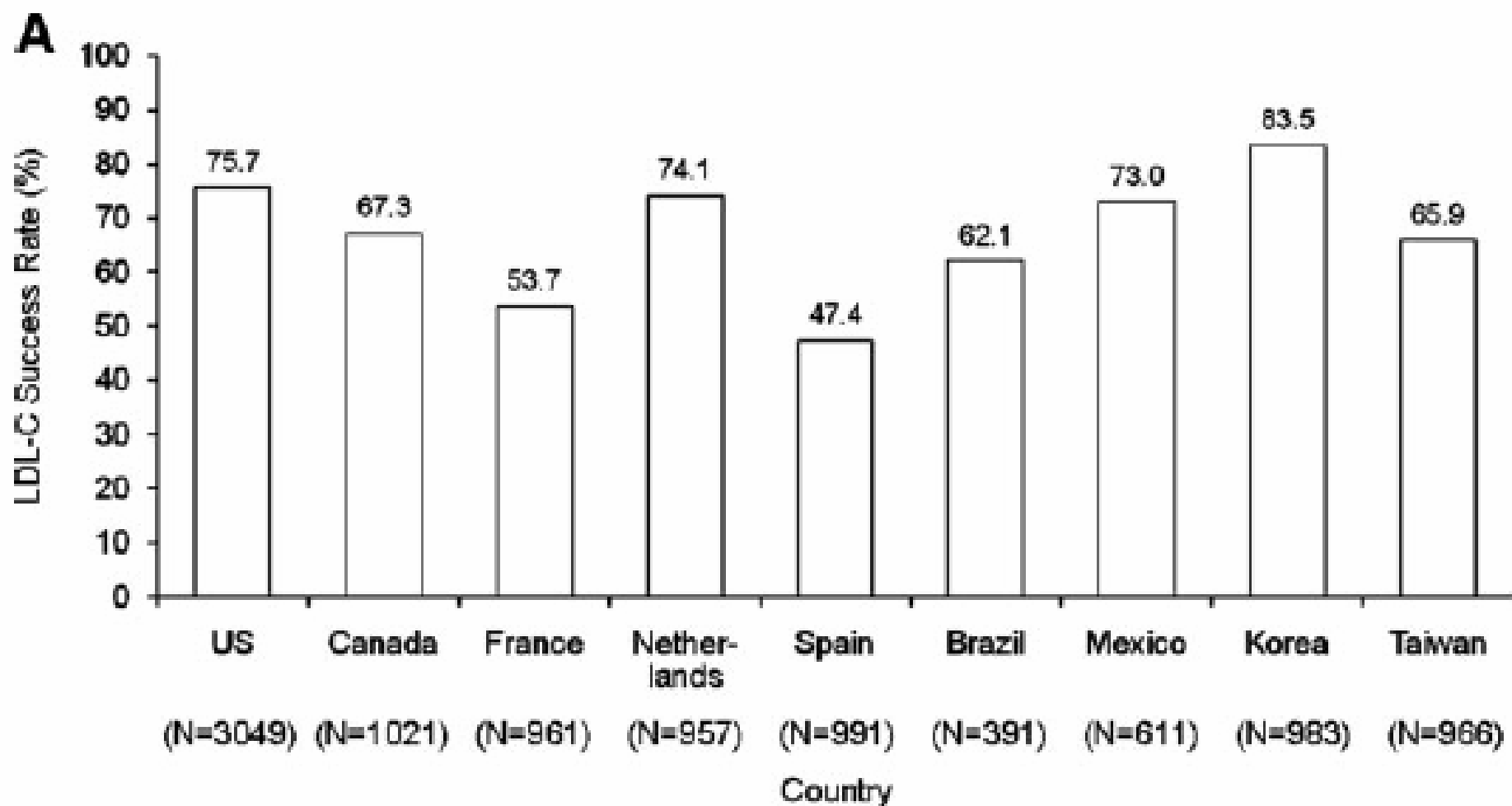
Riesgo Beneficio al Titular Estatinas



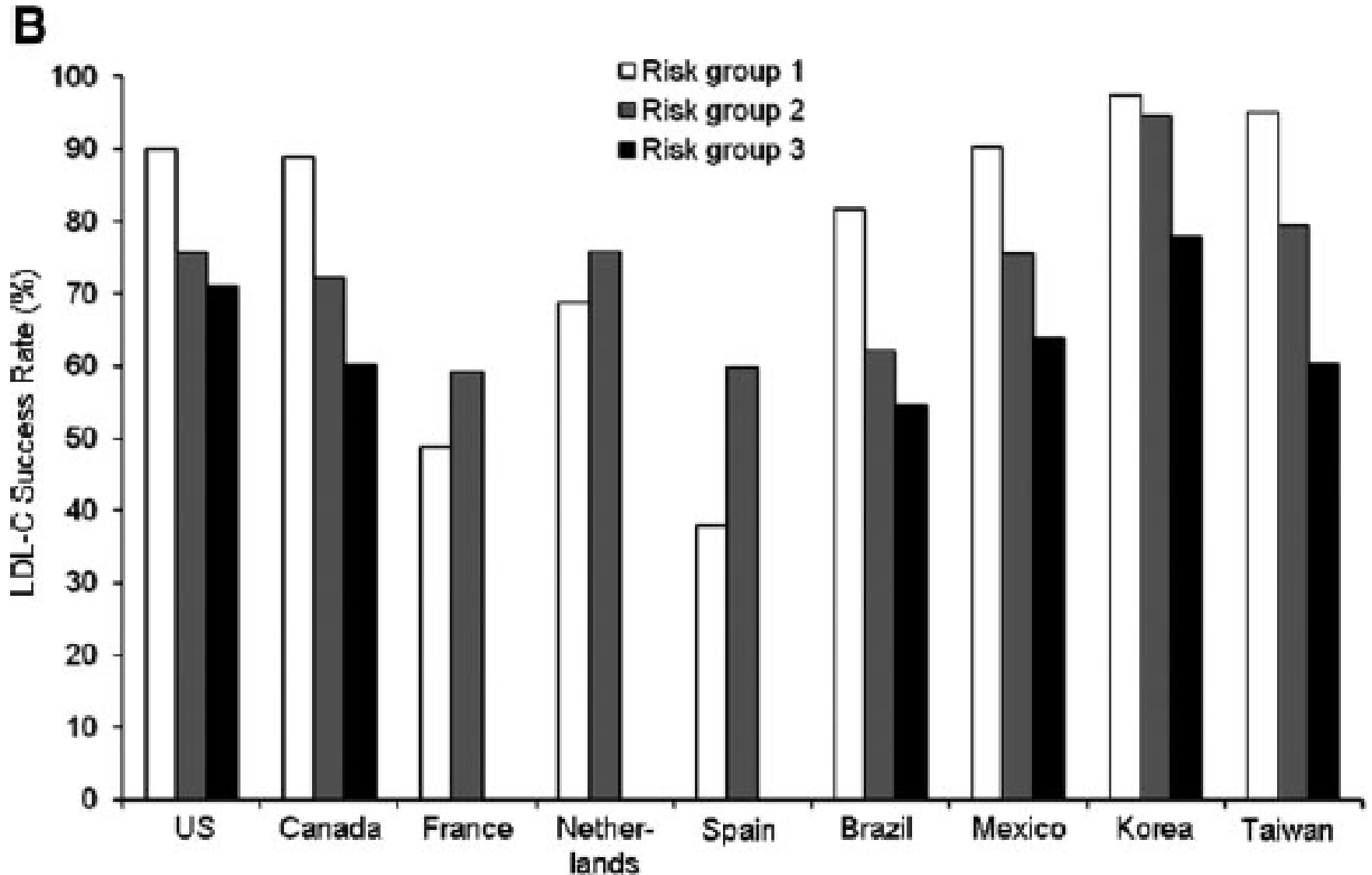
Data from prescribing information for atorvastatin, lovastatin, simvastatin. This does not represent data from a comparative study.

LTAP 2: Cumplimiento de las Metas y paises

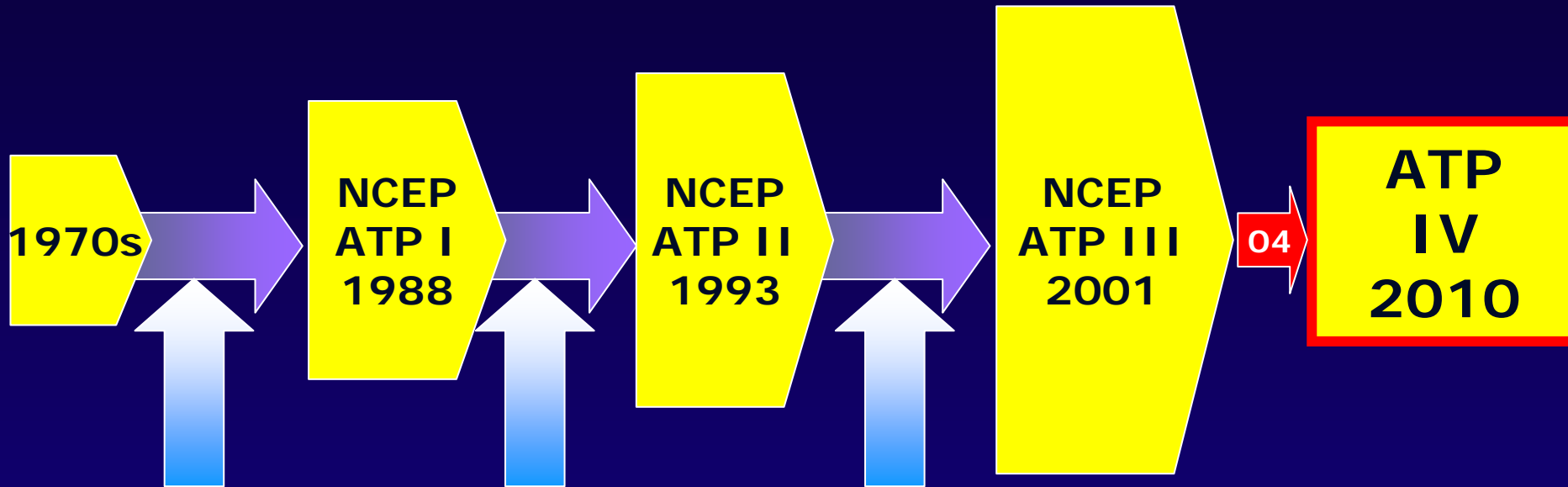
32 *Circulation* July 7, 2009



LTAP 2: Cumplimiento de las Metas y riesgo



Evolucion de las guias terapeuticas



Framingham
MRFIT
LFC-CPPT
Coronary
Drug Project
Helsinki

Angiograficos
(FATS, POSCH,
SCOR, STARS,
Omish, MARS)
Meta-Analisis
(Holme,
Rossouw)

WOSCOPS,
4S,CARE,
LIPID,
AFCAPS,
VAHIT,
Otros

Improve It
TNT, IDEAL
A to Z
HPS
PROSPER
ASCOT
MIRACL
Jupiter

MIRACL– uso temprano de una estatina

Primary efficacy measure*

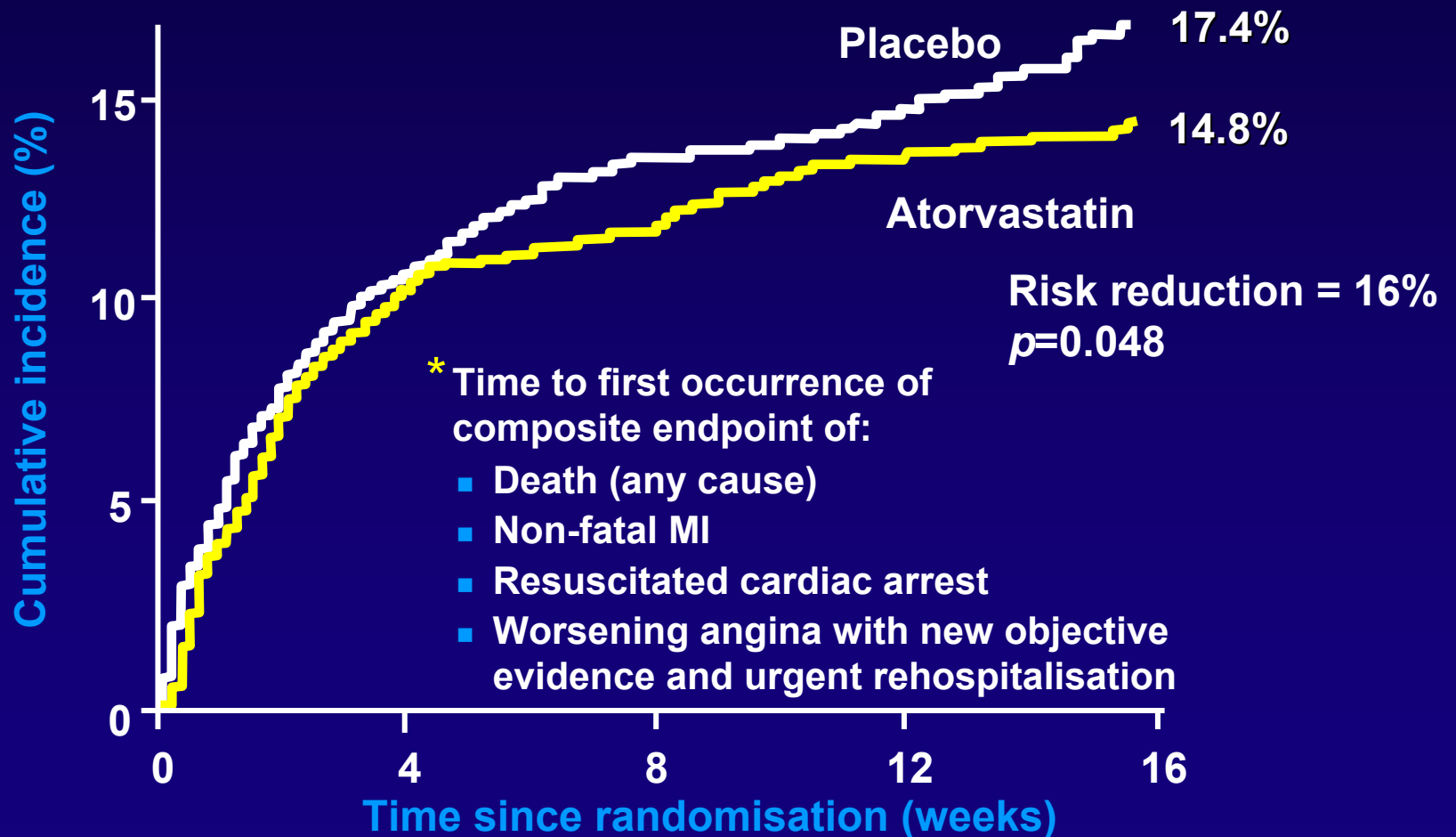
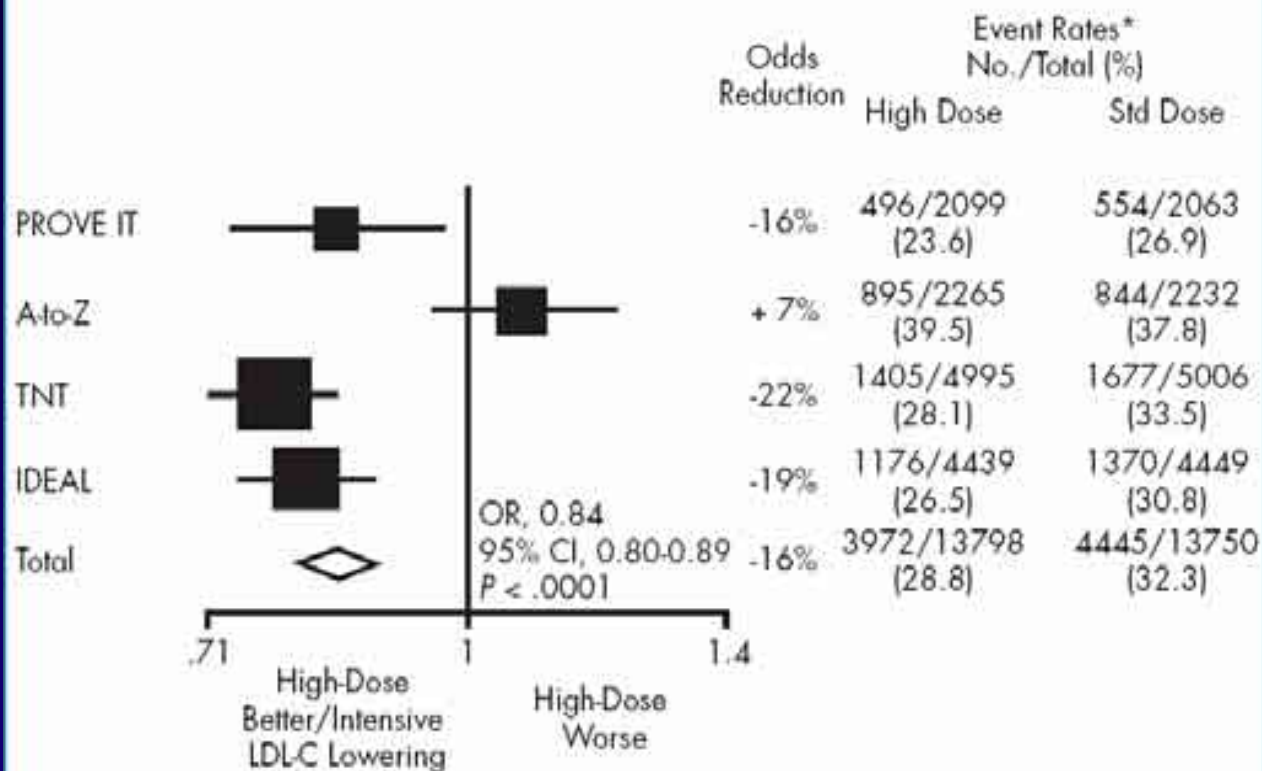


Figure 2. Intensive LDL-C Lowering Reduces Risk of Coronary Death or any CV Event*

More Intensive LDL-C Lowering With High-Dose Therapy†



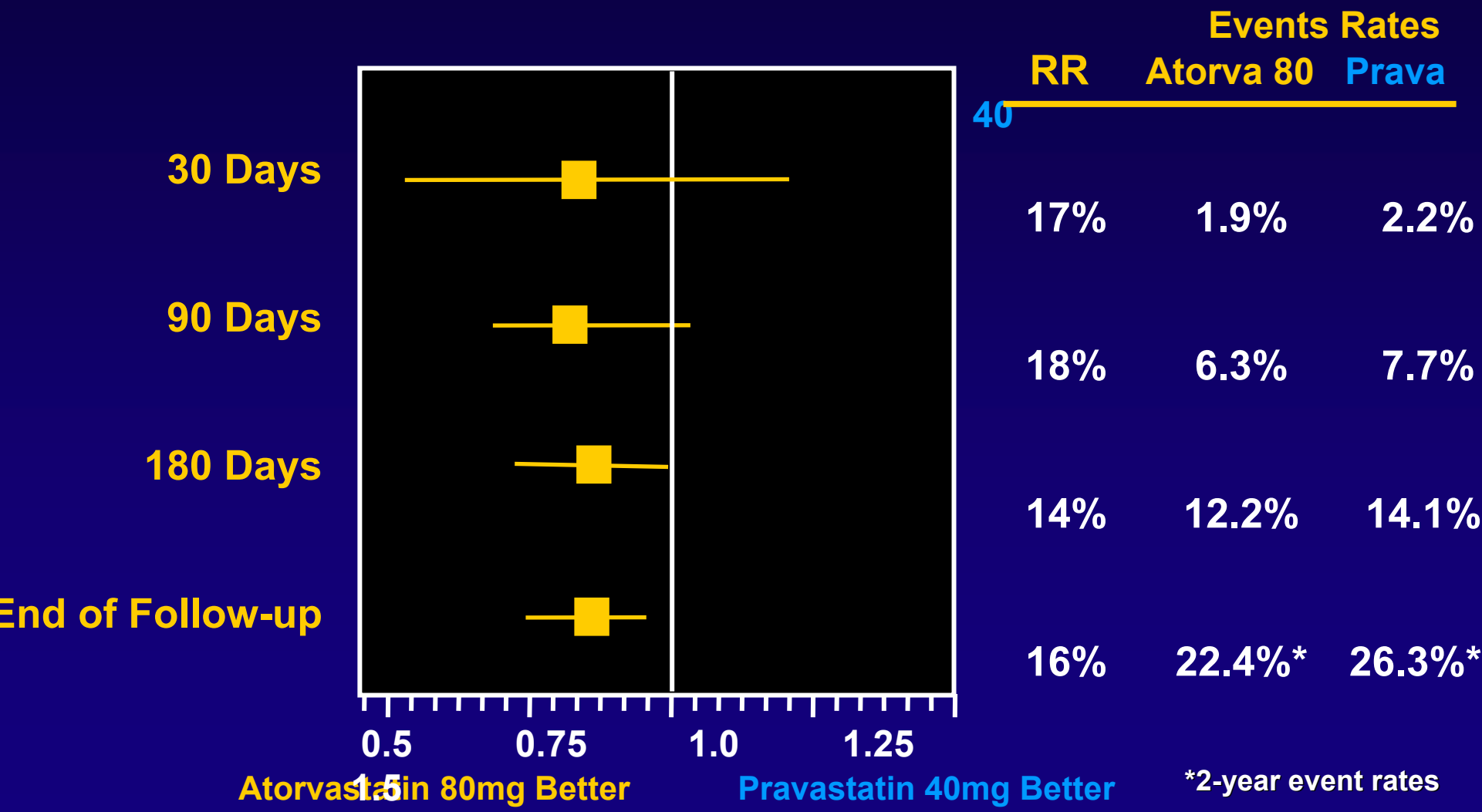
*Coronary death or any cardiovascular event (myocardial infarction, stroke, hospitalisation for unstable angina, revascularisation).

†Mean LDL-C: high-dose therapy, 1.9 mmol/L; standard-dose therapy, 2.6 mmol/L.

Ato-Z: Aggrastat to Zocor; IDEAL: Incremental Decrease in Events Through Aggressive Lipid Lowering; PROVE IT: Pravastatin and Atorvastatin Evaluation and Infection Therapy; TNT: Treating to New Targets.

Adapted from: Cannon CP et al. *J Am Coll Cardiol.* 2006;48:438-445.

PROVE IT - TIMI 22: puntos finales y tiempo



TNT Study Design: Treating to New Targets

Patient Population

- 35-75 y.o.
- Major coronary event in prior 5 years
- LDL 130-250 mg/dl
- TG <600 mg/dl
- 250 centers in 14 countries

Open Run-in

atorvastatin
10 mg

8,600
Patients

LDL < 130 mg

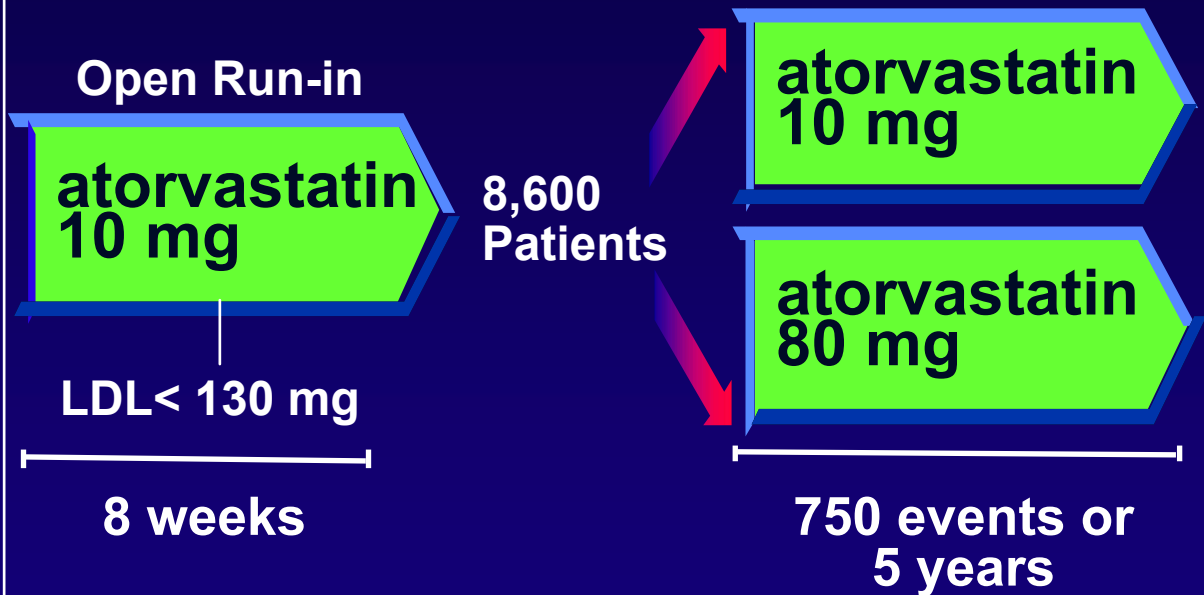
8 weeks

Double-Blind

atorvastatin
10 mg

atorvastatin
80 mg

750 events or
5 years



SPARCL Study Design: Stroke Prevention by Aggressive Reduction of Cholesterol Levels

Patient Population

- Stroke/TIA 1-6 months prior
- LDL 100-190 mg/dl
- Exclusions:
 - Age <18 years
 - Hx of CAD
 - Endarterectomy in prior month
 - Subarachnoid hemorrhage
- Many Neurologists



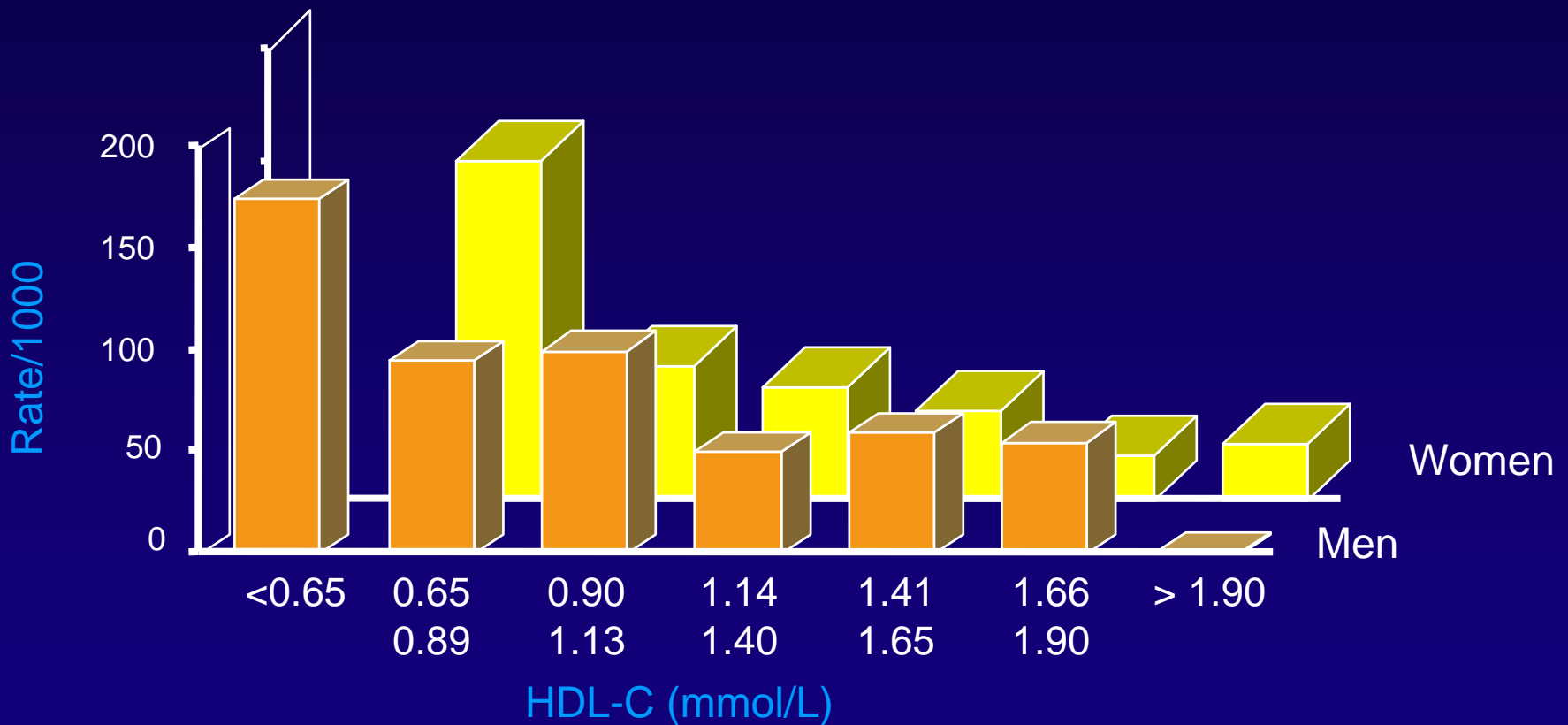
Primary Endpoint

- Time to first fatal or non-fatal stroke

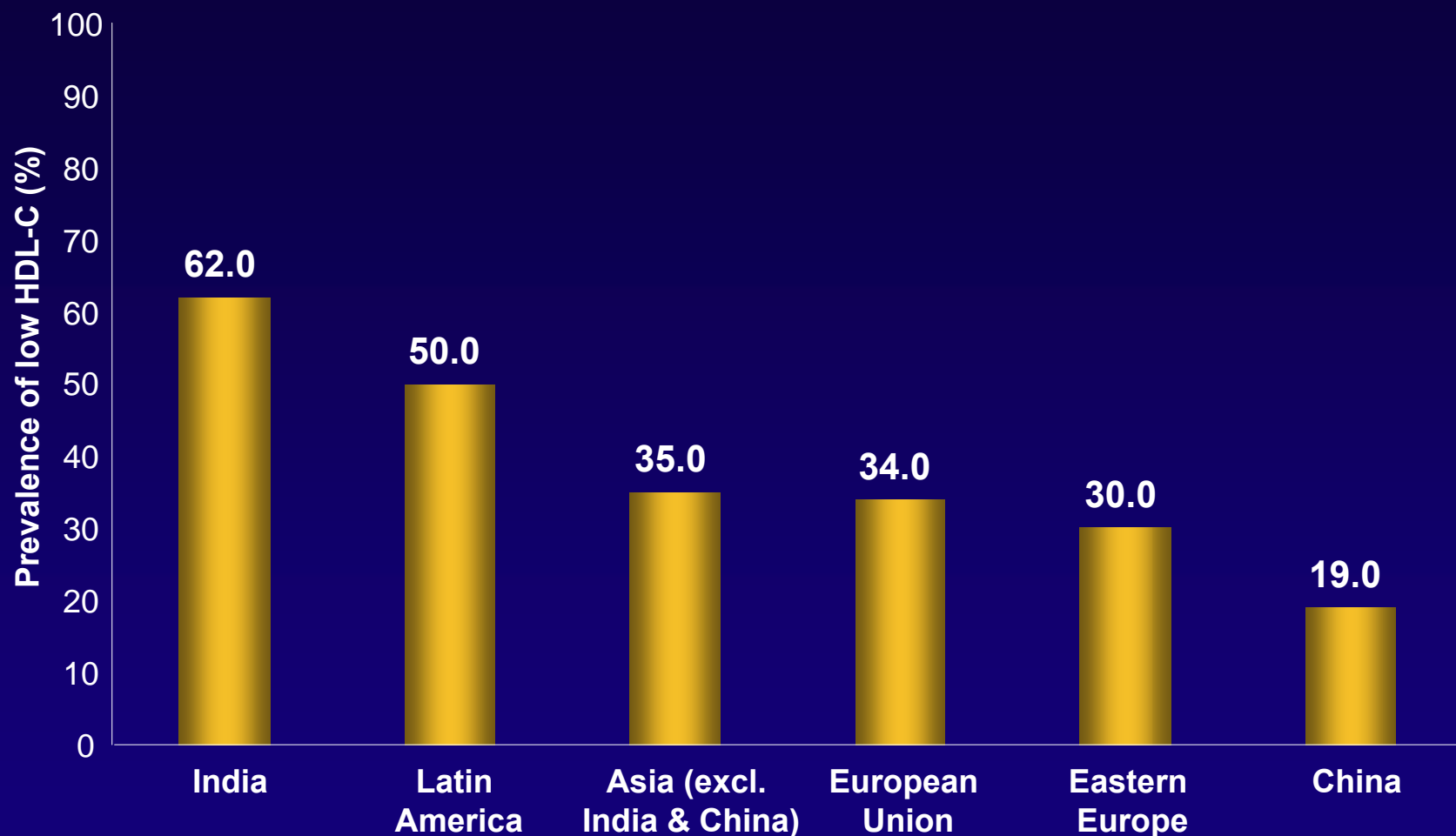
as

investigators

HDL y Tasas de Enfermedad Coronaria en el Framingham Heart Study

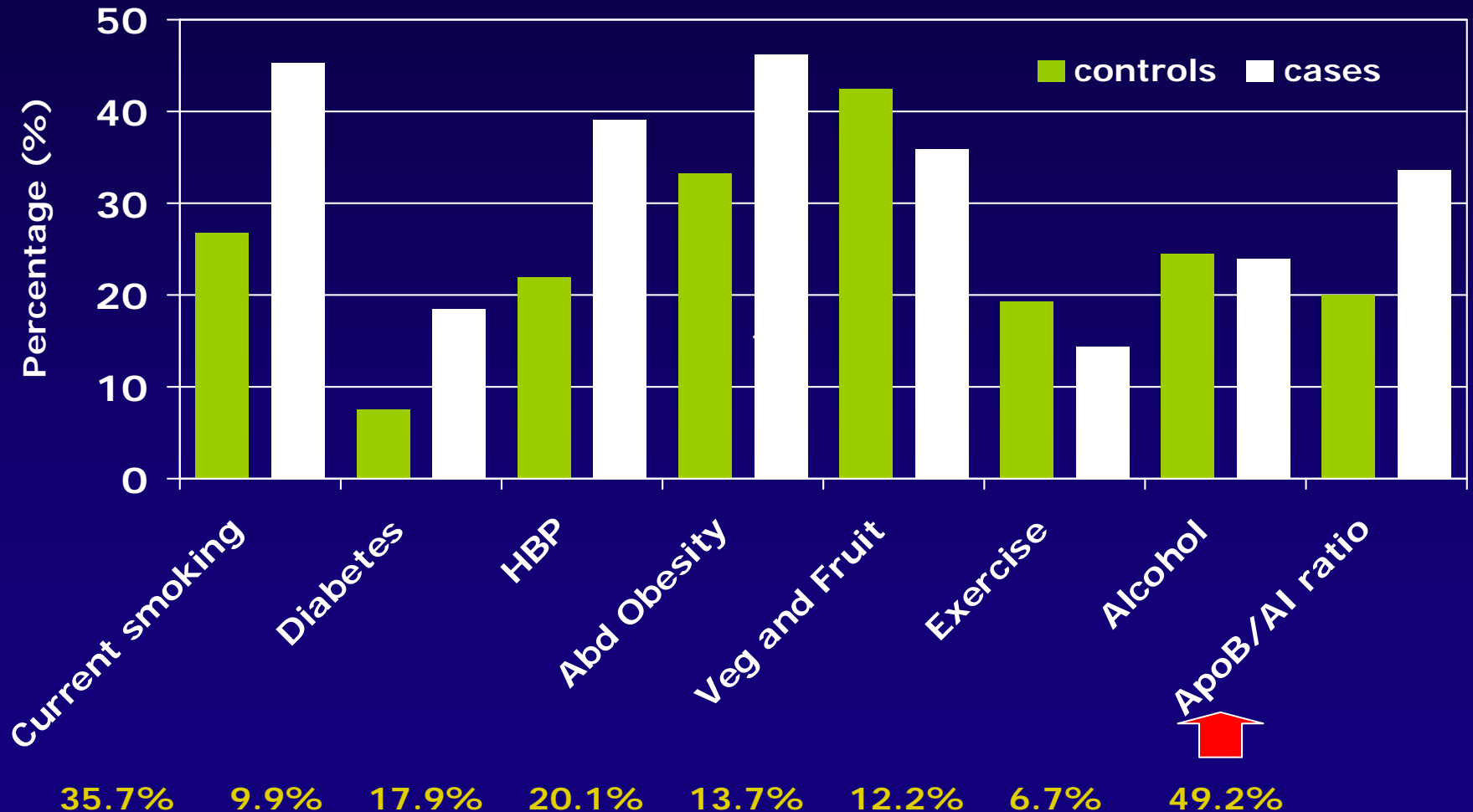


Prevalencia de HDL bajo en el mundo



Interheart: Factores de Riesgo IAM

Odds Ratio: 2.87 2.37 1.91 1.62 0.7 0.86 0.91 3.25



Population attributable risk

Yusuf S, et al. Lancet 2004;364:937-952

Regresion de lesiones de Aterosclerosis

Progresion

Regresion

Monocito

LDL

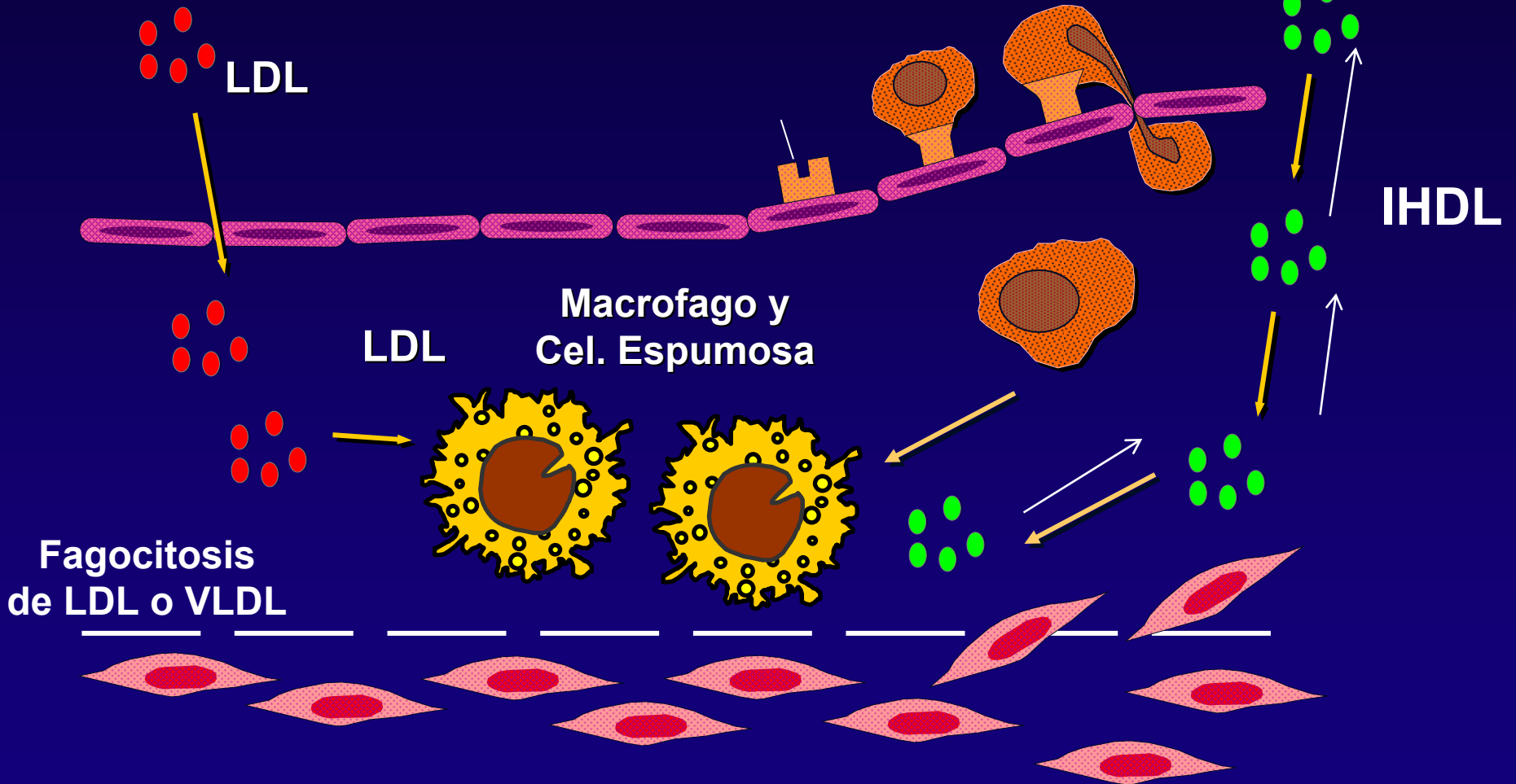
IHDL

LDL

Macrofago y
Cel. Espumosa

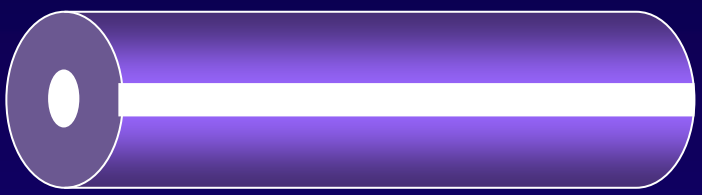
Fagocitosis
de LDL o VLDL

Media



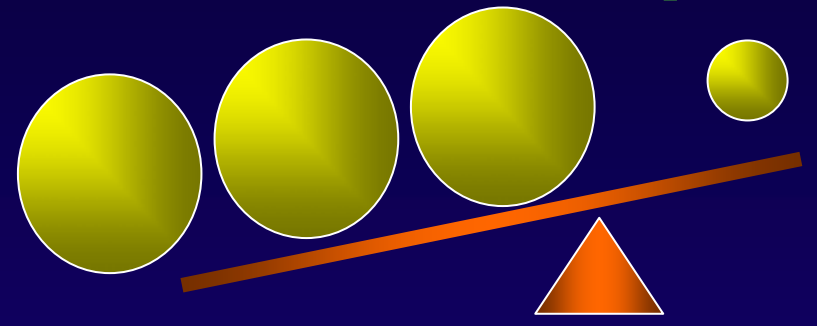
El Balance Aterogenico: Apo B / Apo A

Balance con predominio Aterogenico



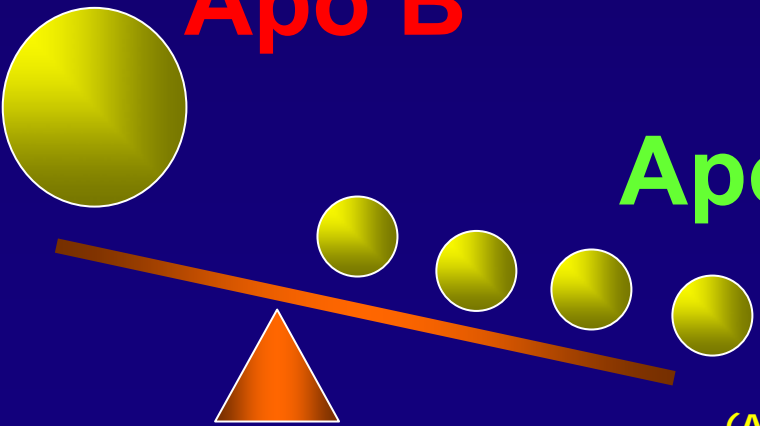
Apo B

Apo A



Apo B

Apo A

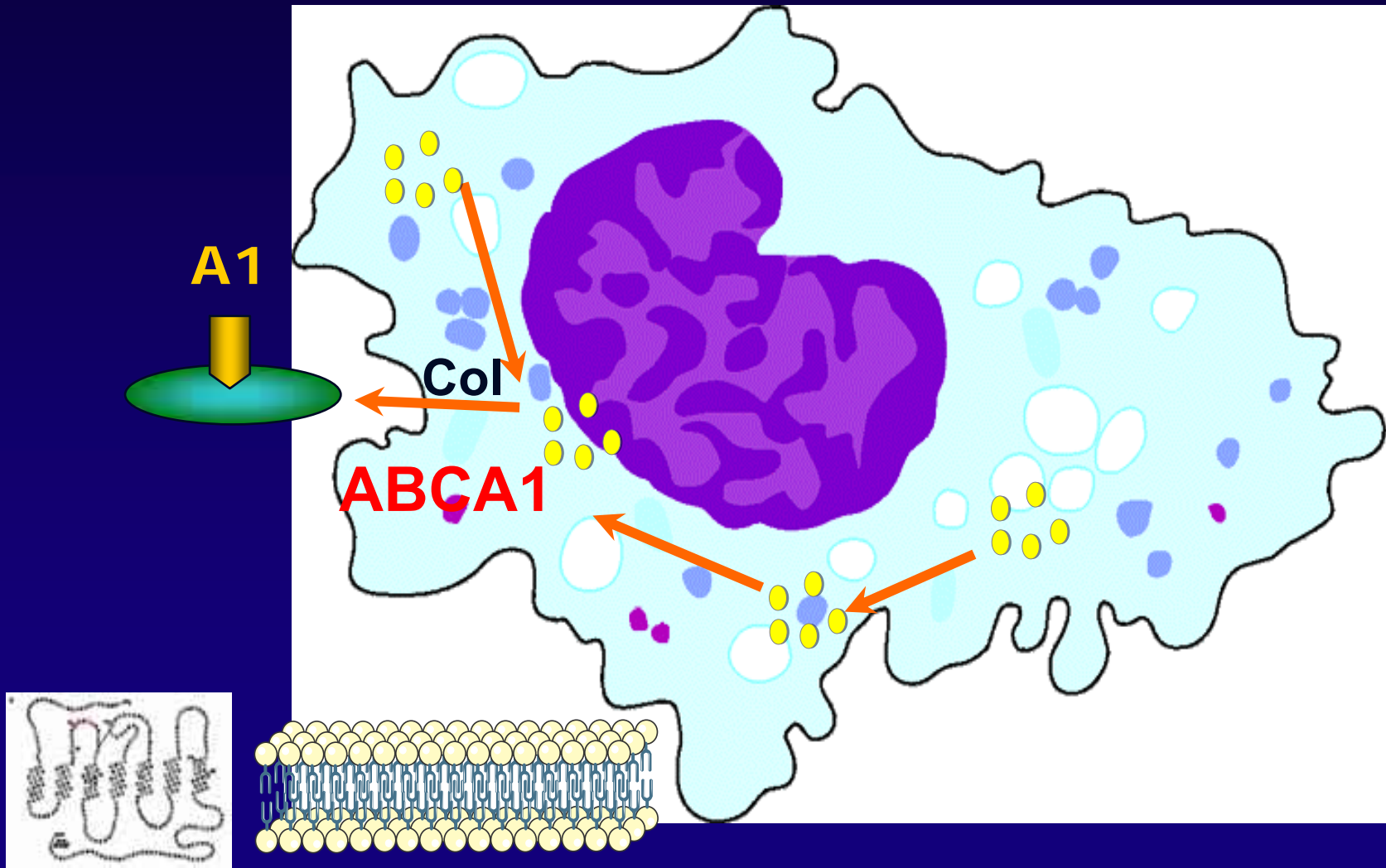


Balance con predominio de Regresion

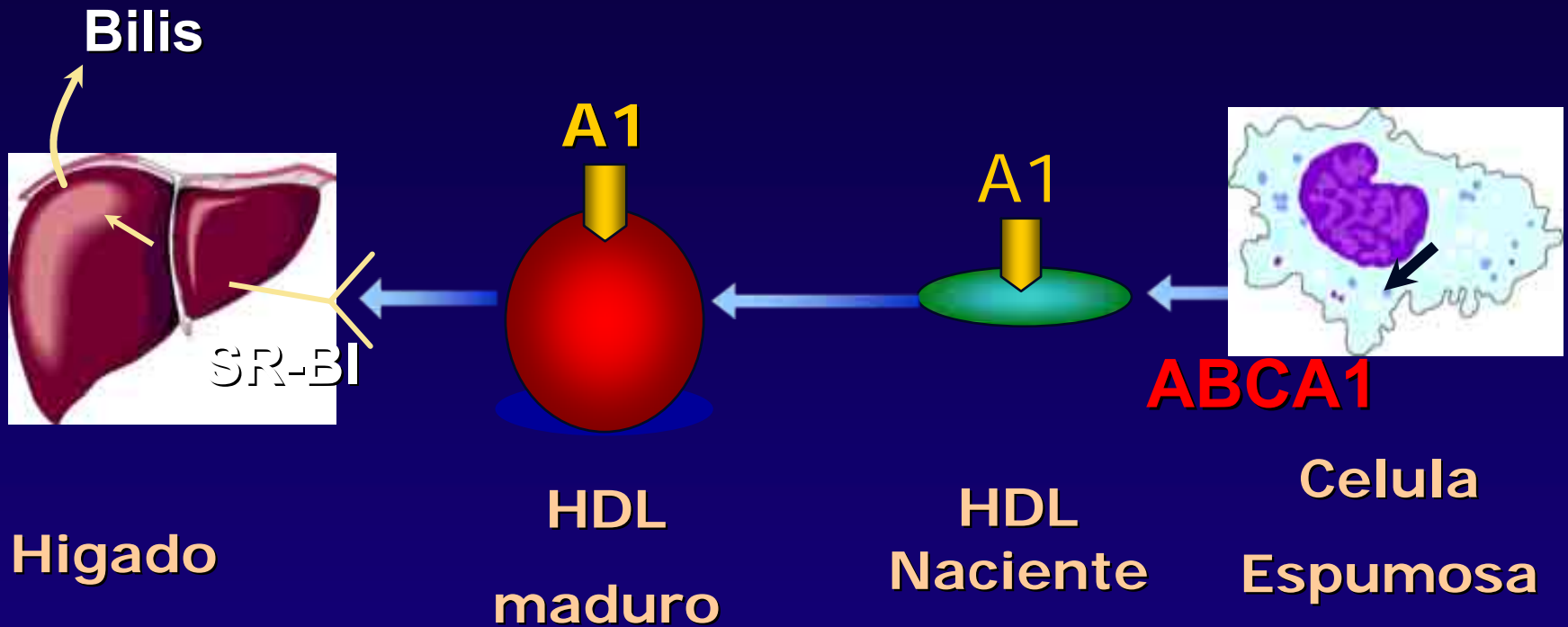


(Amoris e Interheart)

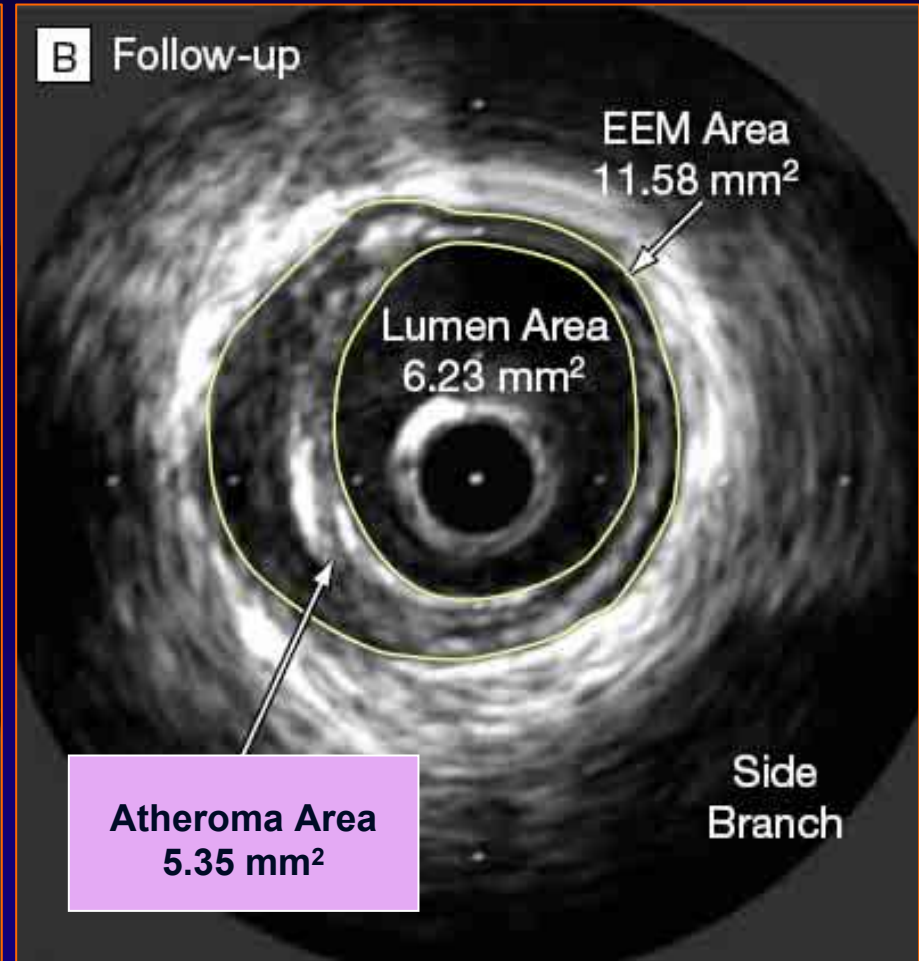
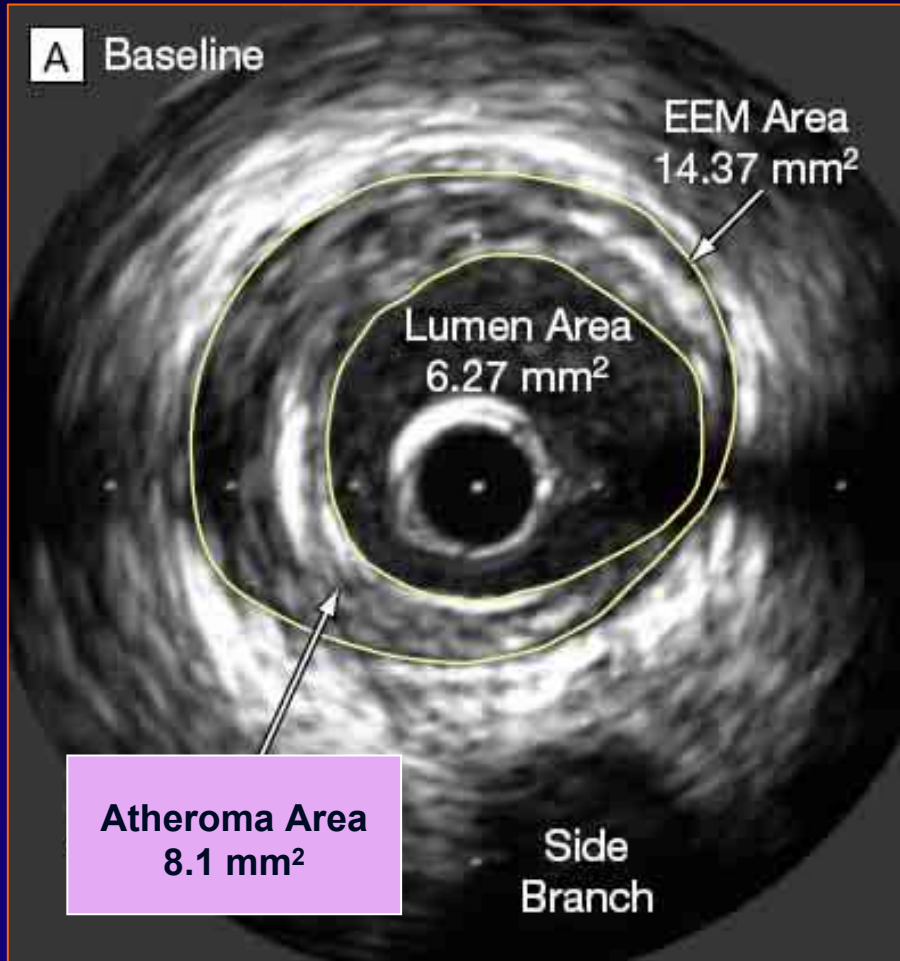
Transporte de Colesterol de la célula espumosa al HDL mediado x ABC A1



HDL y Transporte Reverso de Colesterol

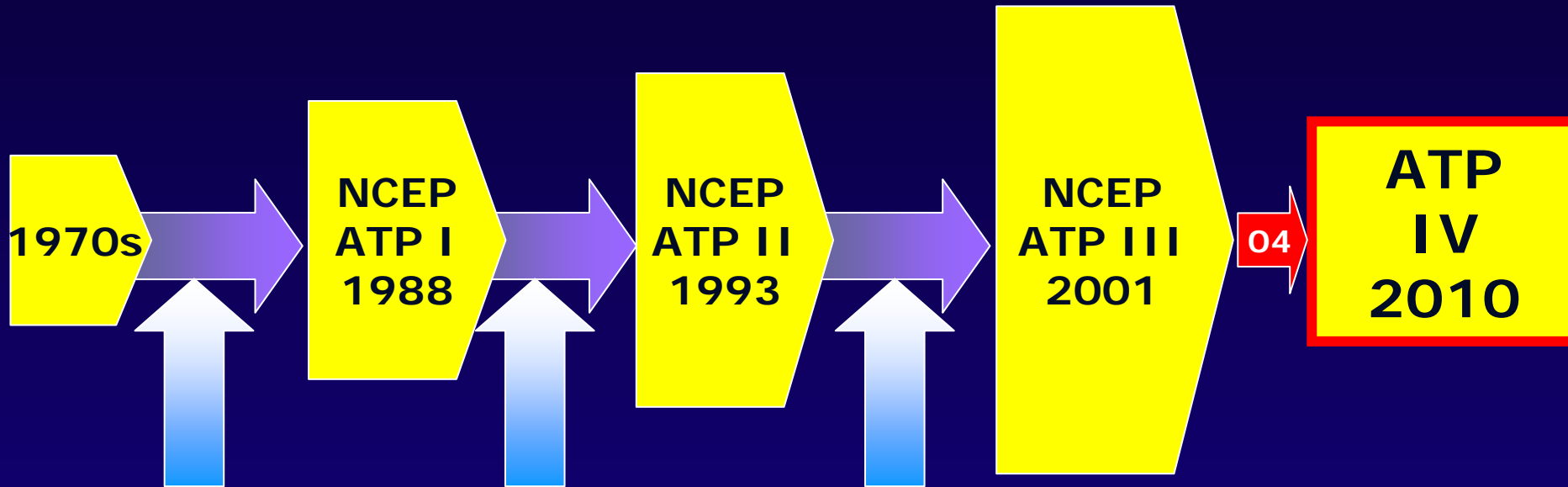


Regresion de ateroma/ humanos Apo A-I Milano / Fosfolipidos



ETC-216 : Apo A-I_{Milano} / Phospholipids

Evolucion de las guias terapeuticas



Framingham
MRFIT
LFC-CPPT
Coronary
Drug Project
Helsinki

Angiograficos
(FATS, POSCH,
SCOR, STARS,
Omish, MARS)
Meta-Analisis
(Holme,
Rossouw)

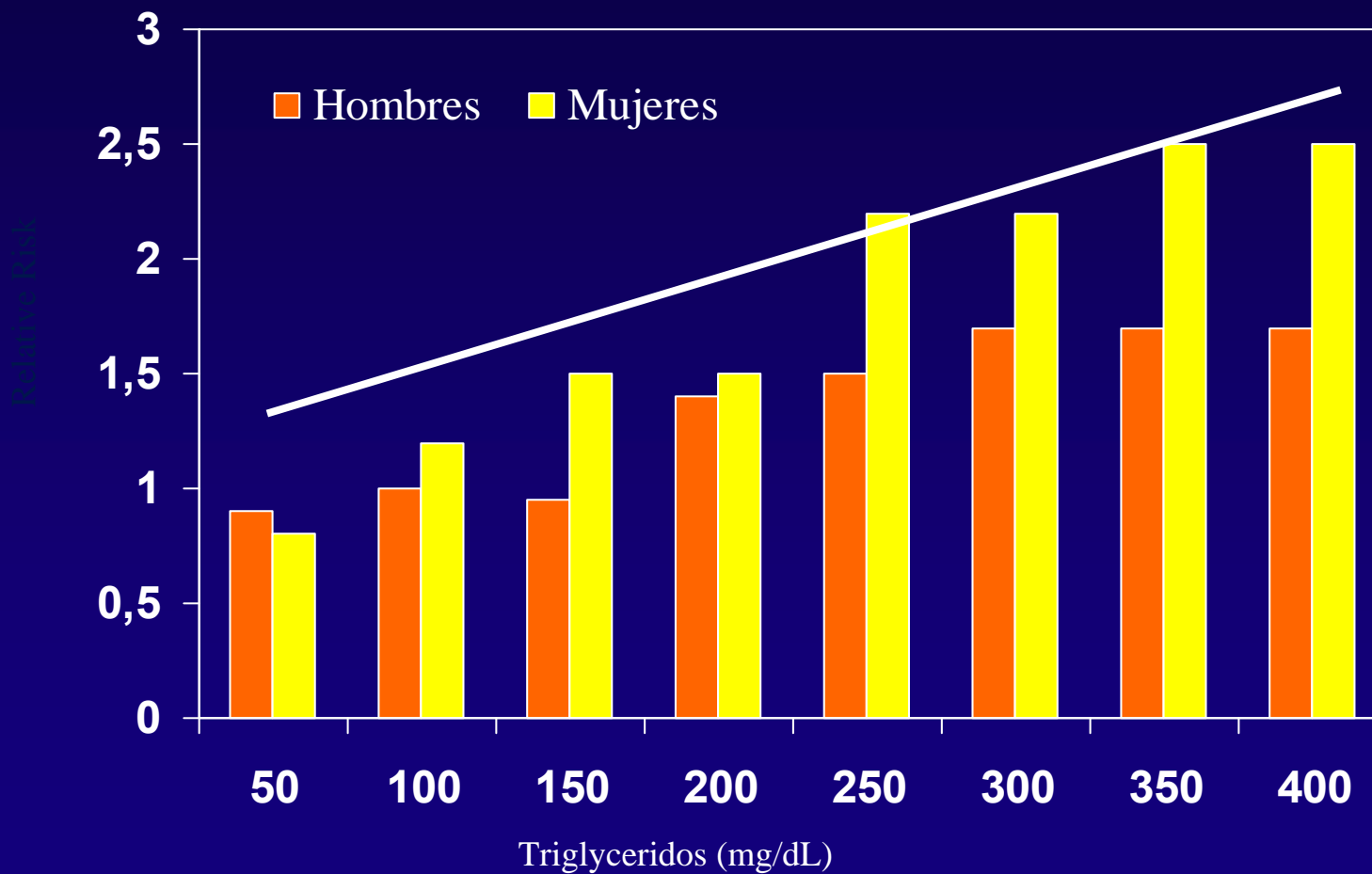
WOSCOPS,
4S,CARE,
LIPID,
AFCAPS,
VAHIT,
Otros

Improve It
TNT, IDEAL
A to Z
HPS
PROSPER
ASCOT
MIRACL
Jupiter

Riesgo de EC segun Trigliceridos

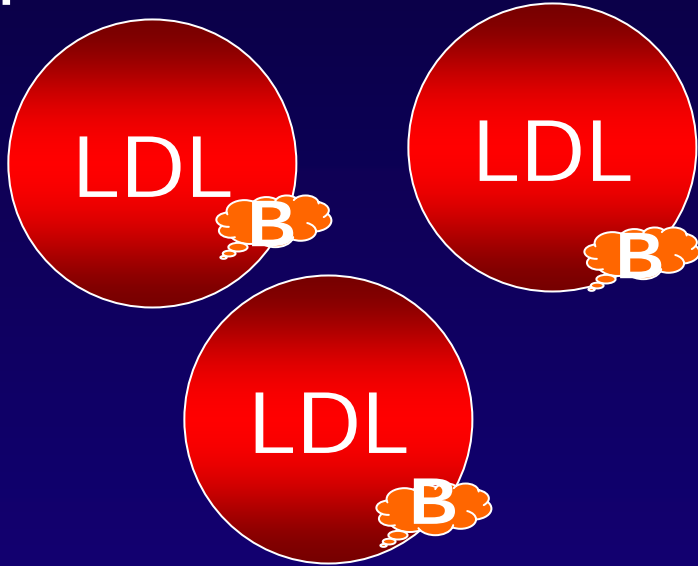
(Framingham Heart Study)

N=5127



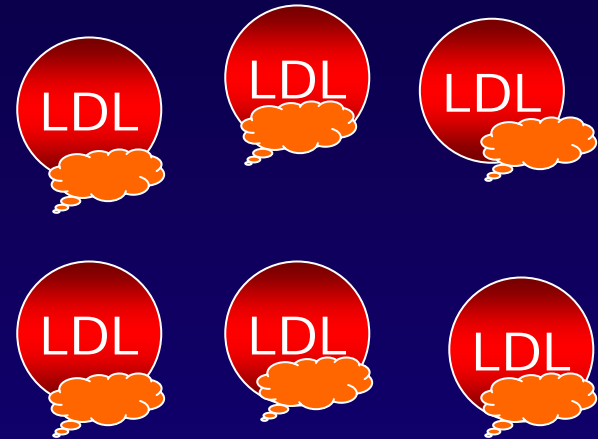
Apo B y las LDL pequeñas y densas

patron a



LDL 116 mg/dL
apo B **80** mg/dL

patron b



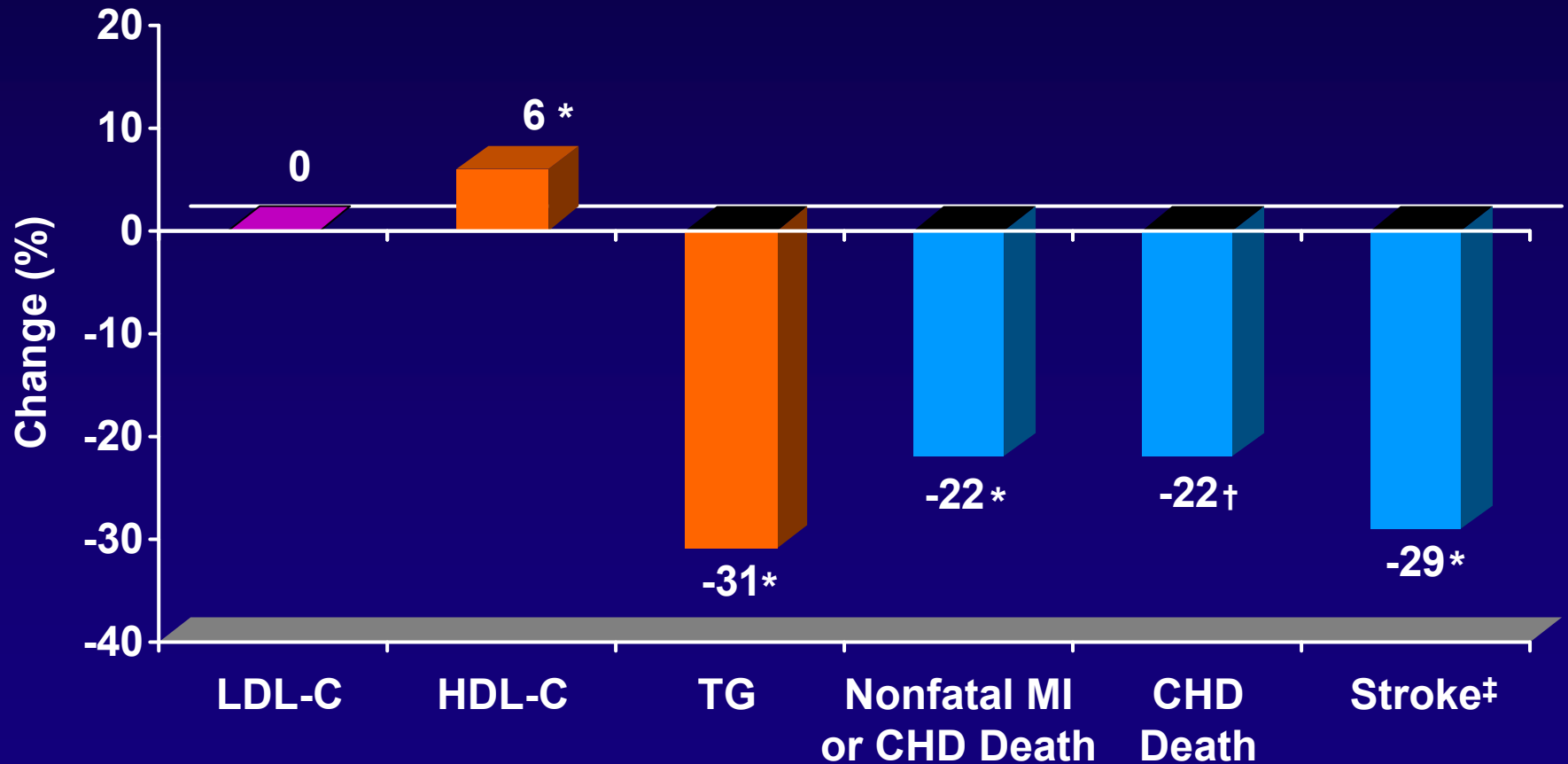
LDL 116 mg/dL
apo B **160** g/L

VA-HIT: HDL Intervention Trial

* $P \leq 0.05$

† $P = 0.07$

Lipidos y Eventos



OMS: Prime : sobrevida con diferentes drogas

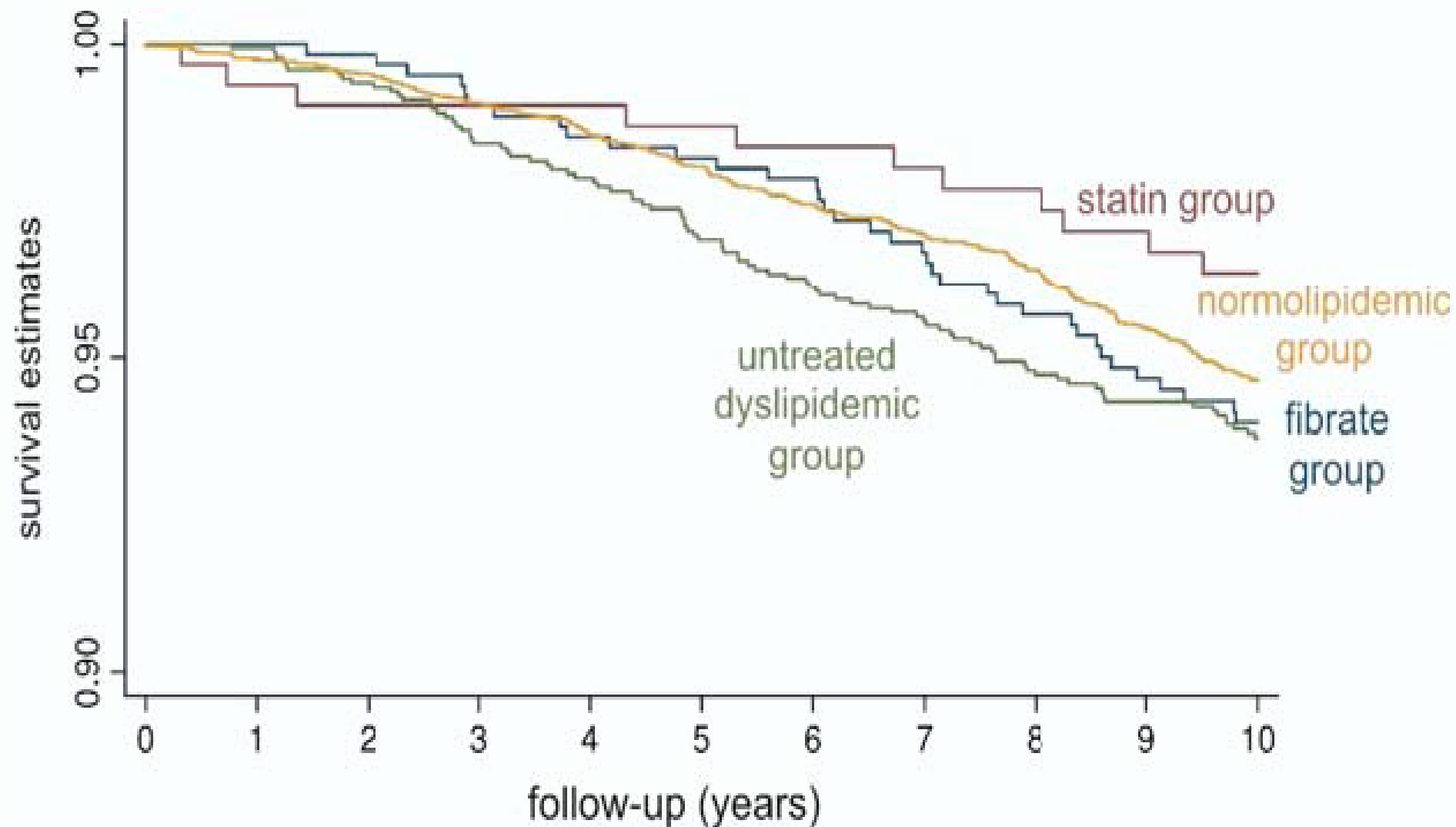


Table 7 | Numbers needed to harm (NNH) or numbers needed to treat (NNT) and numbers of extra or prevented cases for each outcome over five years in patients aged 35-74 free of cardiovascular disease at baseline with QRISK2 score of $\geq 20\%$ or $\geq 15\%$

Variables	Adjusted hazard ratio† for statin use (95% CI)	High risk patients (QRISK2 score $\geq 20\%$)			Medium risk patients (QRISK2 score $\geq 15\%$)		
		5 year risk of outcome in patients unexposed to statins	NNH or NNT (95% CI)	Estimated No of extra (or prevented) cases per 10 000 patients treated (95% CI)	5 year risk of outcome in patients unexposed to statins	NNH or NNT (95% CI)	Estimated No of extra (or prevented) cases per 10 000 patients treated (95% CI)
Women							
Potential benefits:							
Cardiovascular disease*	0.76 (0.67 to 0.86)	0.1184	-37 (-64 to -27)	-271 (-374 to -157)	0.0989	-44 (-76 to -32)	-228 (-315 to -132)
Oesophageal cancer	0.68 (0.52 to 0.88)	0.0025	-1266 (-3460 to -850)	-8 (-12 to -3)	0.0021	-1483 (-4053 to -996)	-7 (-10 to -3)
Potential harms:							
Acute renal failure	1.56 (1.31 to 1.86)	0.0041	434 (284 to 783)	23 (13 to 35)	0.0030	593 (388 to 1070)	17 (9 to 26)
Cataract	1.3 (1.26 to 1.35)	0.1089	33 (28 to 38)	307 (260 to 355)	0.0882	40 (34 to 47)	252 (213 to 292)
Liver dysfunction	1.53 (1.41 to 1.66)	0.0140	136 (109 to 175)	74 (57 to 91)	0.0123	154 (125 to 199)	65 (50 to 80)
Myopathy	2.97 (2.36 to 3.74)	0.0020	259 (186 to 375)	39 (27 to 54)	0.0016	313 (225 to 453)	32 (22 to 44)
Men							
Potential benefits:							
Cardiovascular disease*	0.76 (0.67 to 0.86)	0.1326	-33 (-57 to -24)	-301 (-417 to -174)	0.1156	-38 (-65 to -27)	-265 (-366 to -153)
Oesophageal cancer	0.78 (0.66 to 0.91)	0.0042	-1082 (-2807 to -711)	-9 (-14 to -4)	0.0037	-1236 (-3207 to -812)	-8 (-12 to -3)
Potential harms:							
Acute renal failure	1.61 (1.39 to 1.87)	0.0047	346 (245 to 539)	29 (19 to 41)	0.0037	447 (316 to 696)	22 (14 to 32)
Cataract	1.32 (1.26 to 1.37)	0.0630	52 (44 to 63)	191 (158 to 225)	0.0495	66 (56 to 80)	151 (125 to 178)
Liver dysfunction	1.53 (1.42 to 1.66)	0.0133	142 (115 to 180)	71 (56 to 87)	0.0122	155 (126 to 197)	64 (51 to 79)
Myopathy	6.15 (5.19 to 7.3)	0.0021	91 (74 to 112)	110 (90 to 134)	0.0018	106 (87 to 130)	95 (77 to 116)

Negative numbers indicate numbers needed to treat or cases prevented. Positive numbers indicate numbers needed to harm or extra cases.

*Odds ratios based on meta-analysis by Bruggs et al.²

†Adjusted hazard ratios for all statins combined adjusted for same variables as in tables 4 and 5 (see web extra).

statins were of similar magnitude and all less than 1, but few patients were prescribed rosuvastatin to draw firm

El estudio Courage

The NEW ENGLAND JOURNAL of MEDICINE

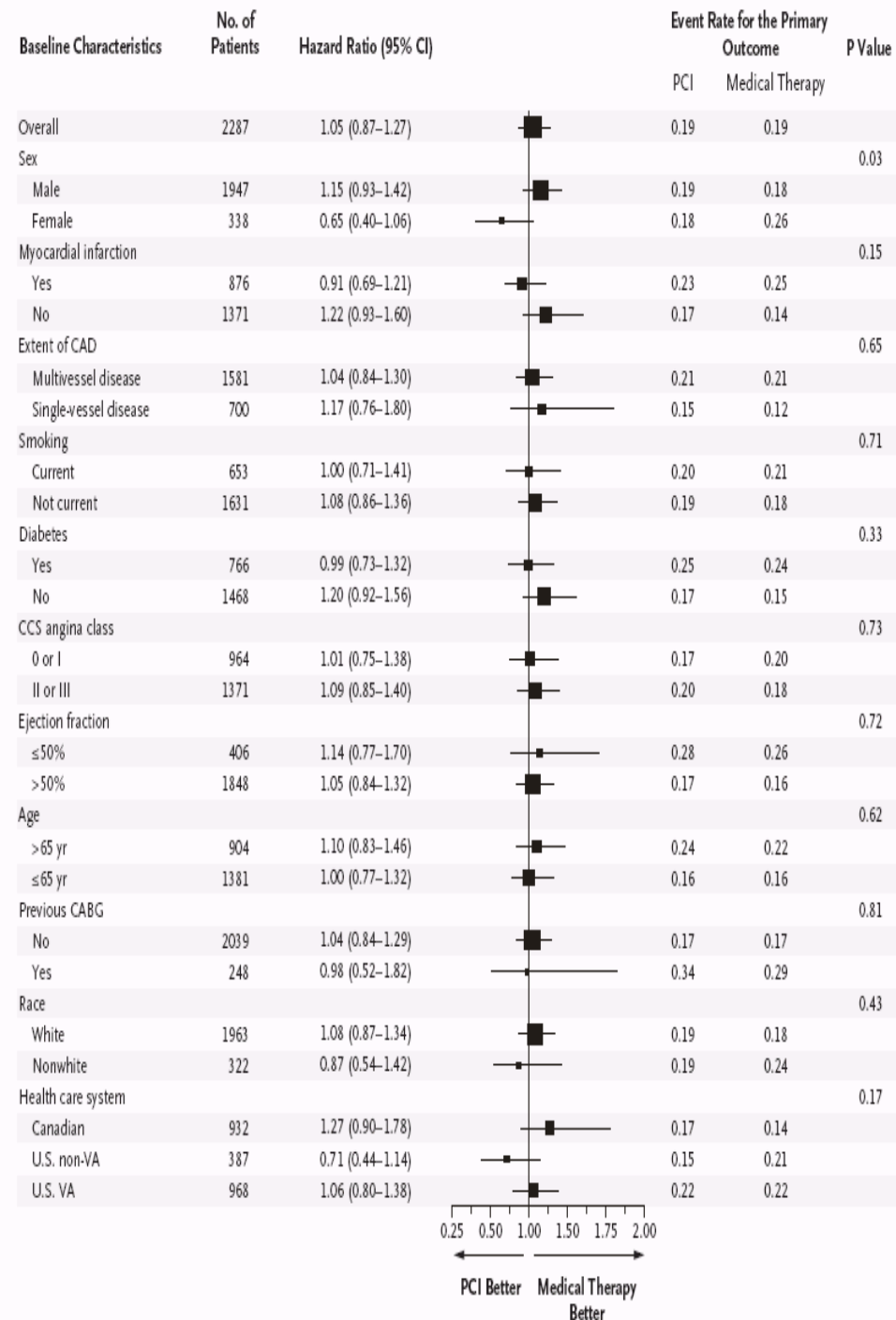
ESTABLISHED IN 1812

APRIL 12, 2007

VOL. 356 NO. 15

Optimal Medical Therapy with or without PCI for Stable Coronary Disease

William E. Boden, M.D., Robert A. O'Rourke, M.D., Koon K. Teo, M.B., B.Ch., Ph.D., Pamela M. Hartigan, Ph.D., David J. Maron, M.D., William J. Kostuk, M.D., Merrill Knudtson, M.D., Marcin Dada, M.D., Paul Casperson, Ph.D., Crystal L. Harris, Pharm.D., Bernard R. Chaitman, M.D., Leslee Shaw, Ph.D., Gilbert Gosselin, M.D., Shah Nawaz, M.D., Lawrence M. Title, M.D., Gerald Gau, M.D., Alvin S. Blaustein, M.D., David C. Booth, M.D., Eric R. Bates, M.D., John A. Spertus, M.D., M.P.H., Daniel S. Berman, M.D., G.B. John Mancini, M.D., and William S. Weintraub, M.D., for the COURAGE Trial Research Group*

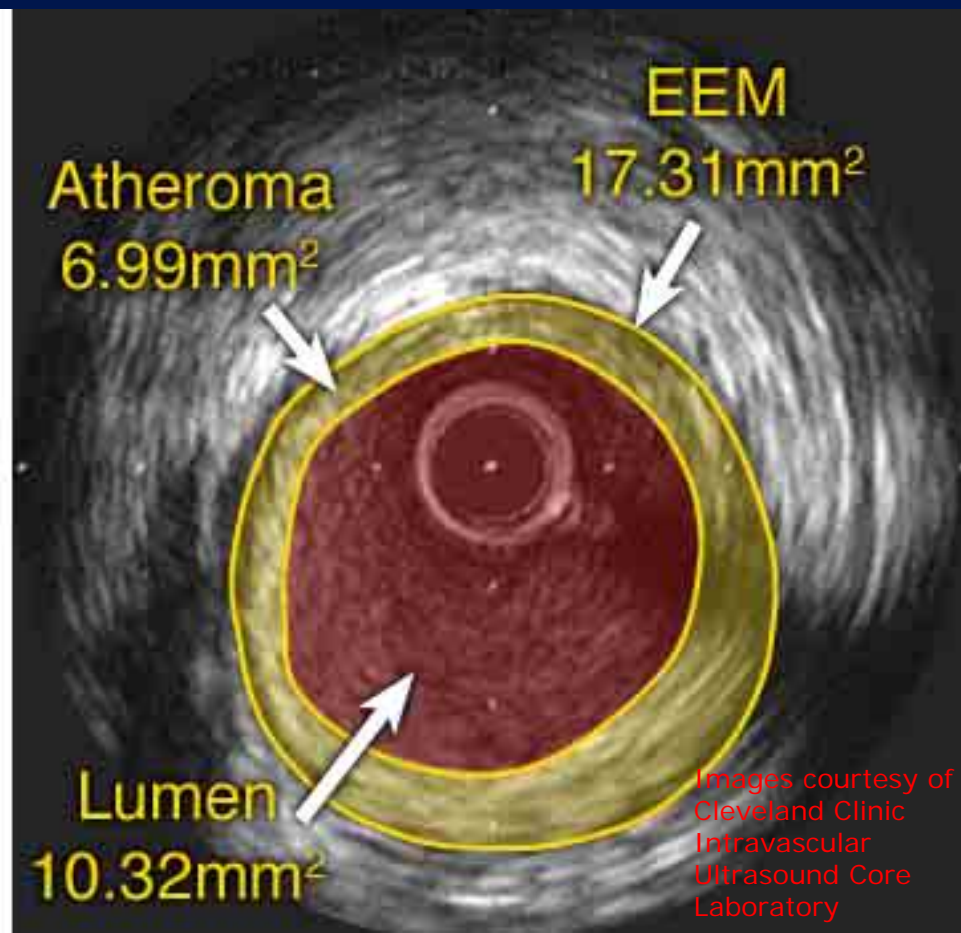
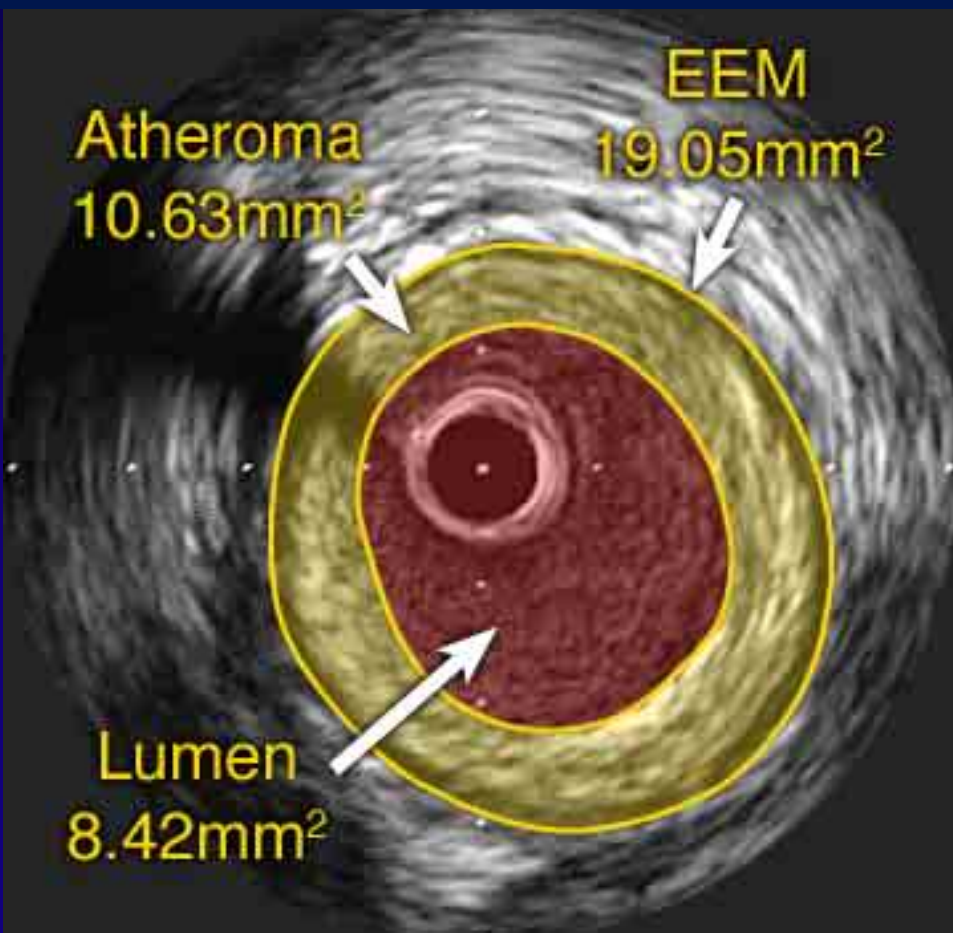


Evidencias Post ATP III: Como seguimos ?

- ATP III: Riesgo x Framingham
- Tratamiento dirigido a todos los FR-CV ?
- Aterosclerosis Subclinica y marcadores ?
- Costos, genericos ?
- Nuevos scores de riesgo
- Casos especiales, HDL
- Regresion en carotidas
- Nuevos FRCV

Cambios en la Placa aterosclerótica en las imágenes por US-IV

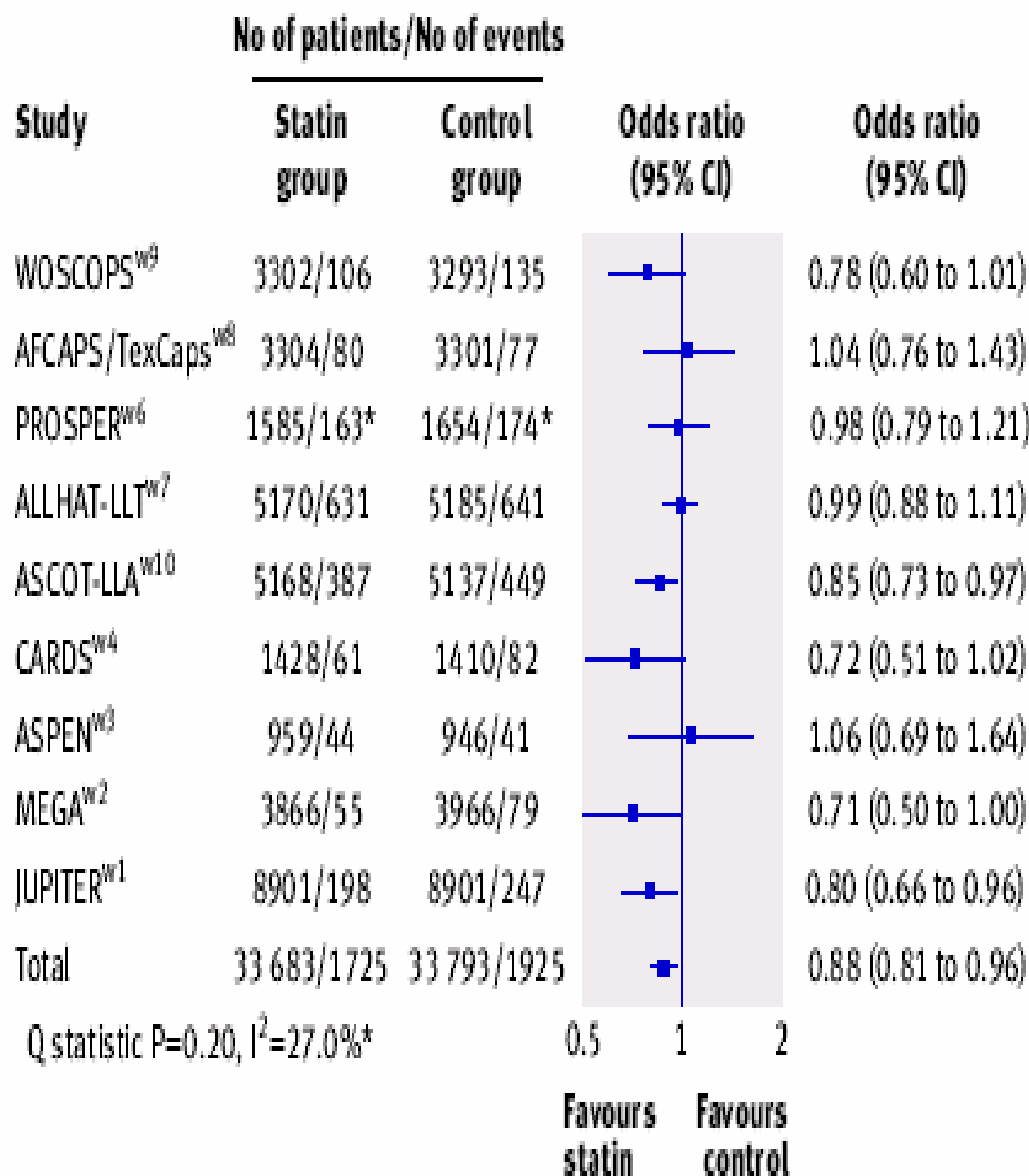
Inicial y los de 2 años de Intervención



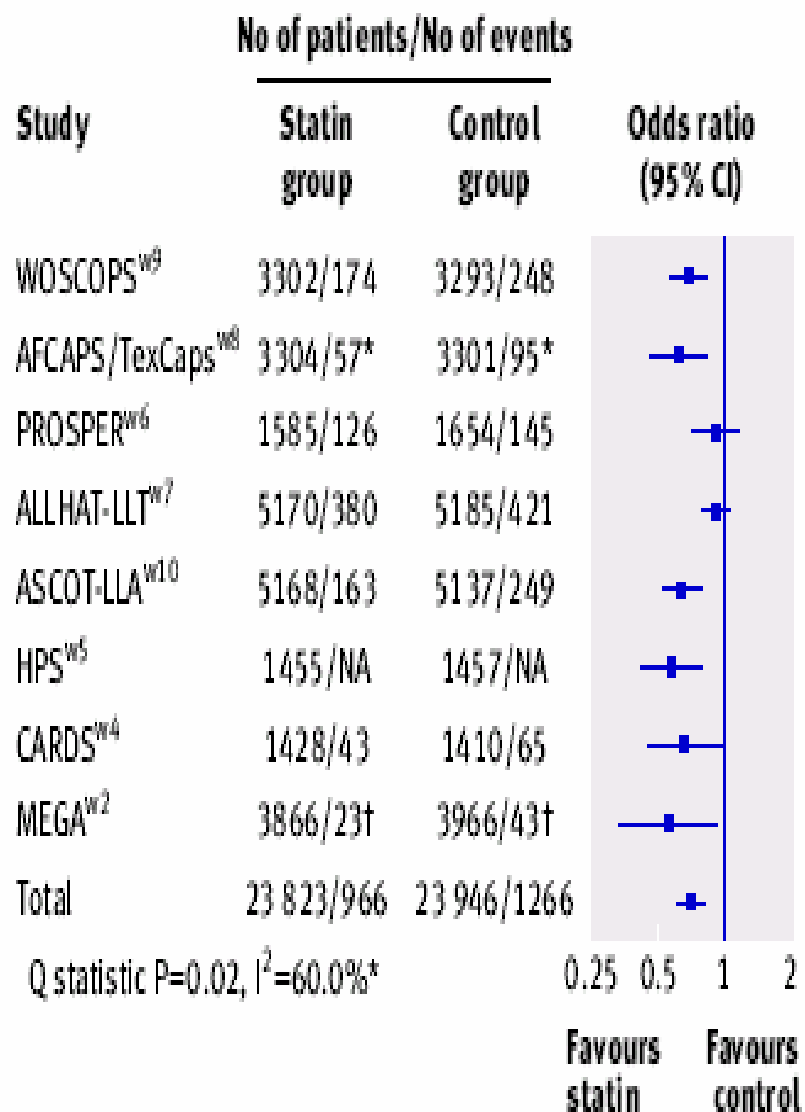
Images courtesy of
Cleveland Clinic
Intravascular
Ultrasound Core
Laboratory

Characteristic	WOSCOPS 1995 ^{w9}	AFCAPS/ TexCAPS 1998 ^{w8}	PROSPER* 2002 ^{w6}	ALLHAT-LLT 2002 ^{w7}	ASCOT-LLA 2003 ^{w10}	HPS* 2003 ^{w5}	CARDS 2004 ^{w4}	ASPEN* 2006 ^{w3}	MEGA 2006 ^{w2}	JUPITER 2008 ^{w1}
Target population	Men with hypercholesterolaemia (no history of myocardial infarction)	People with average or below average cholesterol levels (without atherosclerotic cardiovascular disease)	Elderly people with cardiovascular risk factors	People with hypertension, moderate hypercholesterolaemia, and at least one coronary heart disease risk factor	People with hypertension, average or lower cholesterol levels, and at least three other risk factors	People with diabetes	People with diabetes and low density lipoprotein cholesterol (no history of cardiovascular disease)	People with diabetes and low density lipoprotein cholesterol levels below guideline targets	People with hypercholesterolaemia and no history of coronary heart disease or stroke	People without vascular disease, low density lipoprotein cholesterol <130 mg/dl, and high sensitivity C reactive protein > 2.0 mg/l
Design	Randomised double blind placebo controlled trial	Randomised double blind placebo controlled trial	Randomised double blind placebo controlled trial	Randomised controlled trial (control=usual care)	Randomised double blind placebo controlled trial	Randomised double blind placebo controlled trial	Randomised double blind placebo controlled trial	Randomised double blind placebo controlled trial	Randomised double blind placebo controlled trial (control=diet)	Randomised double blind placebo controlled trial
No of participants (statin/control)	6595 (3302/3293)	6605 (3304/3301)	3239 (1585/1654)	10355 (5170/5185)	10305 (5168/5137)	2912 (1455/1457)	2838 (1428/1410)	1905 (959/946)	7832 (3866/3966)	17802 (8901/8901)
Mean follow-up (years)	4.9	5.2	3.2	4.8	5.5†	4.8	3.9†	4.0†	5.3	1.9†

All cause mortality

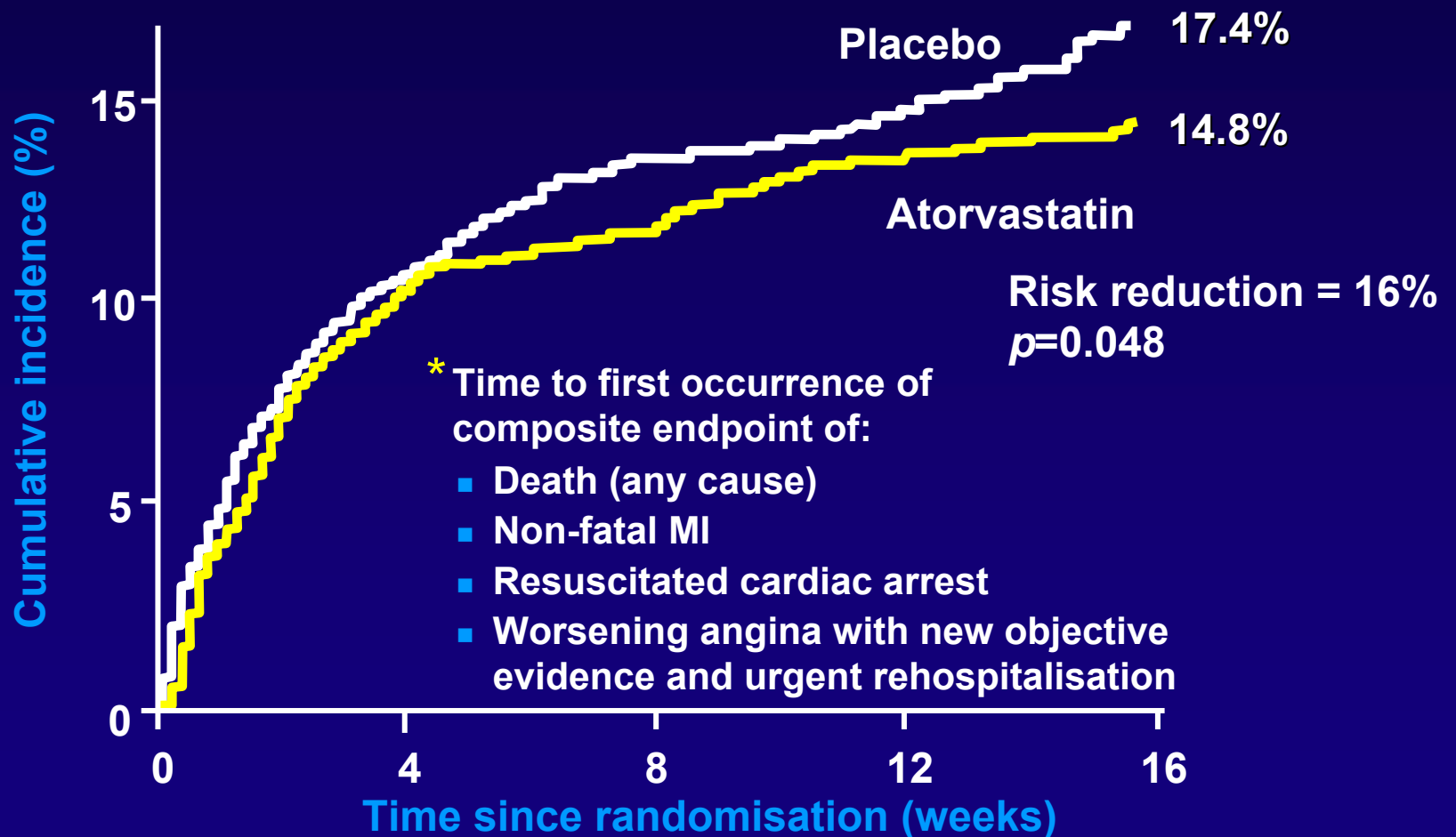


Major coronary events

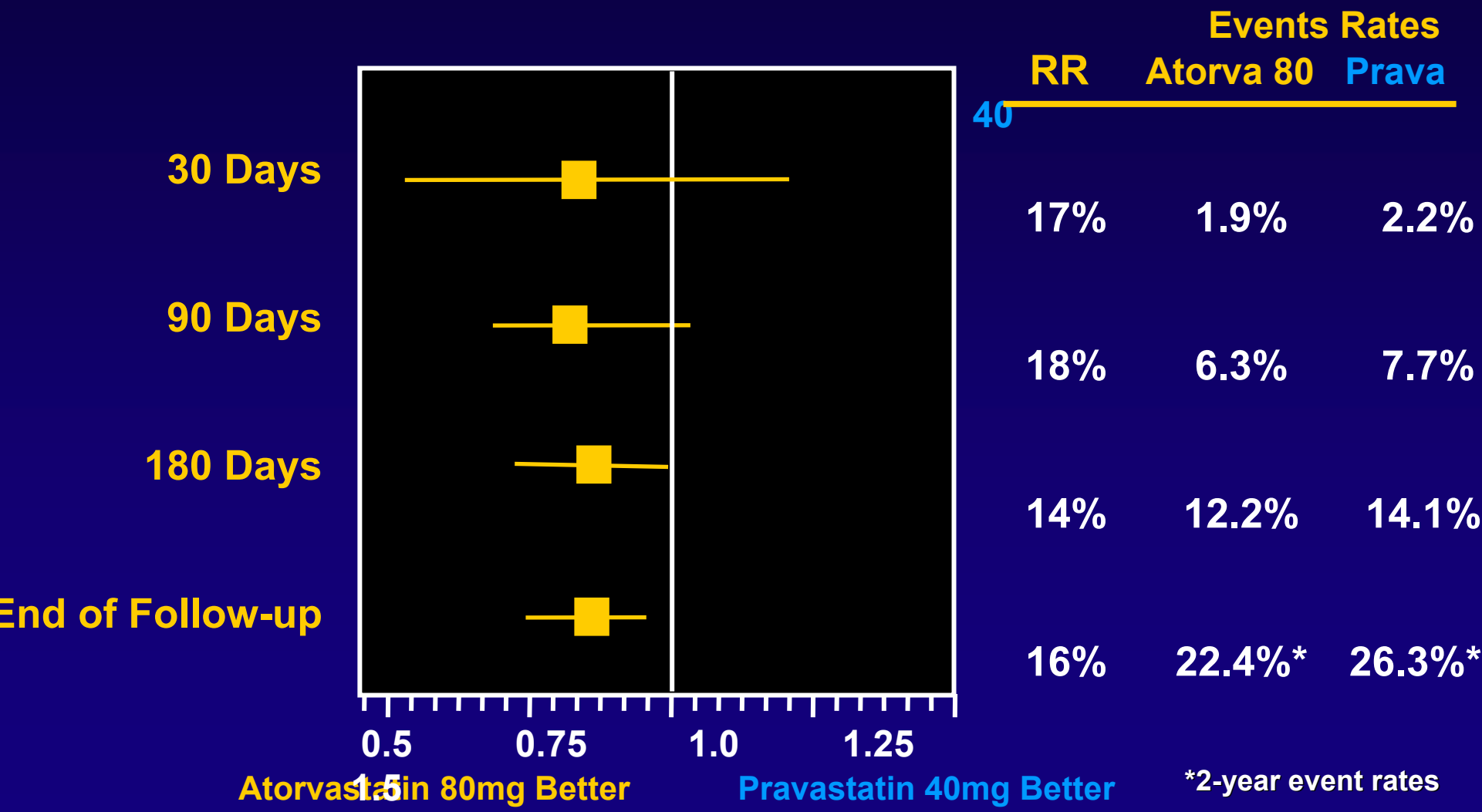


MIRACL– uso temprano de una estatina

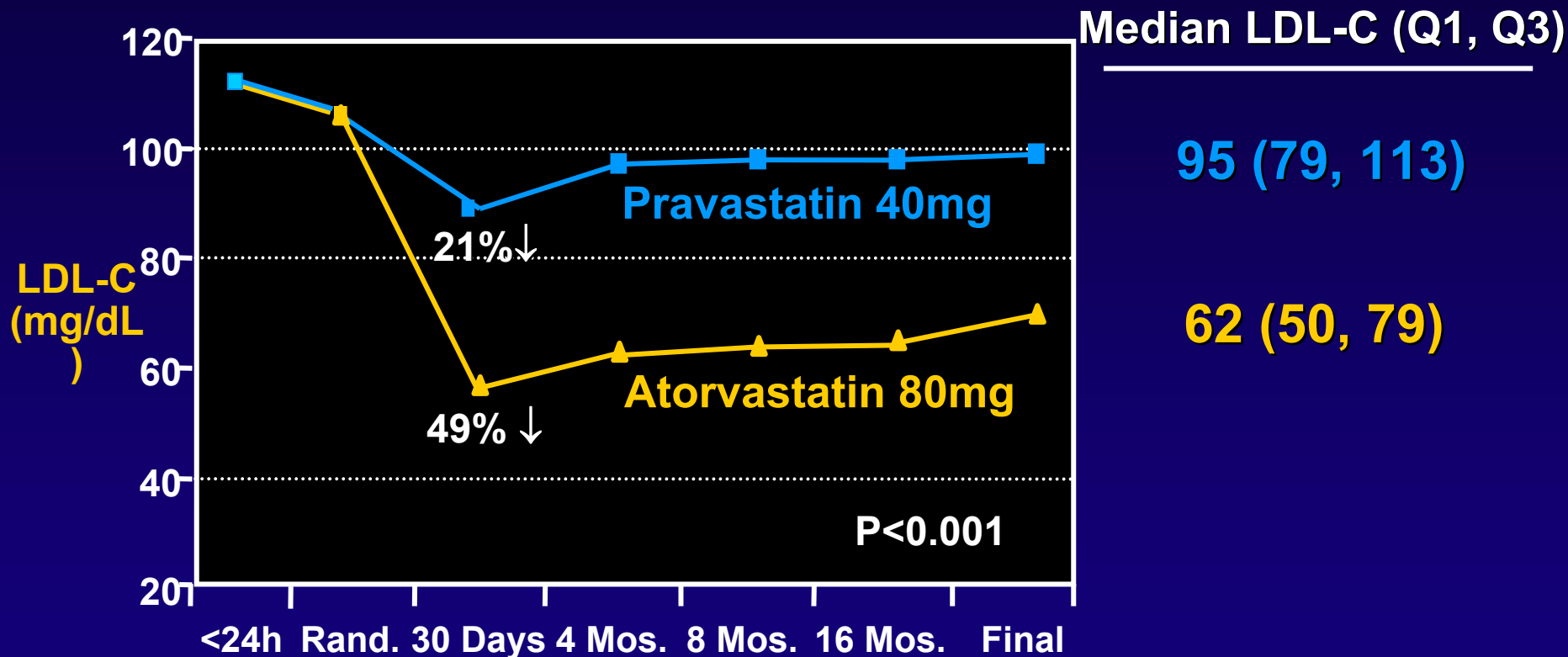
Primary efficacy measure*



PROVE IT - TIMI 22: puntos finales y tiempo



Changes from (Post-ACS) Baseline in Median LDL-C



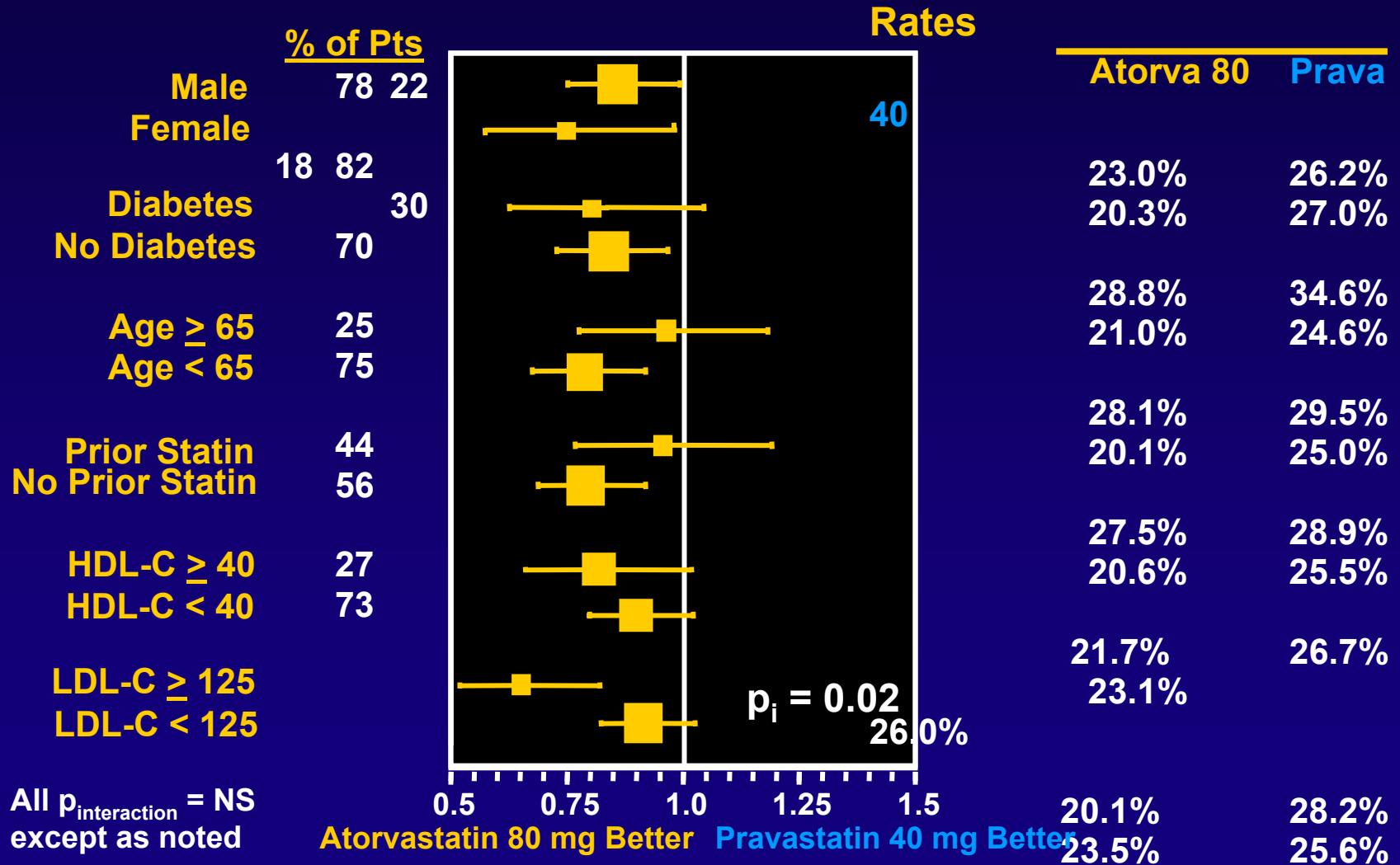
Note: Changes in LDL-C may differ from prior trials:

- 25% of patients on statins prior to ACS event
- ACS response lowers LDL-C from true baseline



Subgroups: Reduction in All-Cause Mortality or Major CV Events

2 Year Event



All $p_{interaction} = NS$
except as noted

TNT Study Design: Treating to New Targets

Patient Population

- 35-75 y.o.
- Major coronary event in prior 5 years
- LDL 130-250 mg/dl
- TG <600 mg/dl
- 250 centers in 14 countries

Open Run-in

atorvastatin
10 mg

8,600
Patients

LDL < 130 mg

8 weeks

Double-Blind

atorvastatin
10 mg

atorvastatin
80 mg

750 events or
5 years

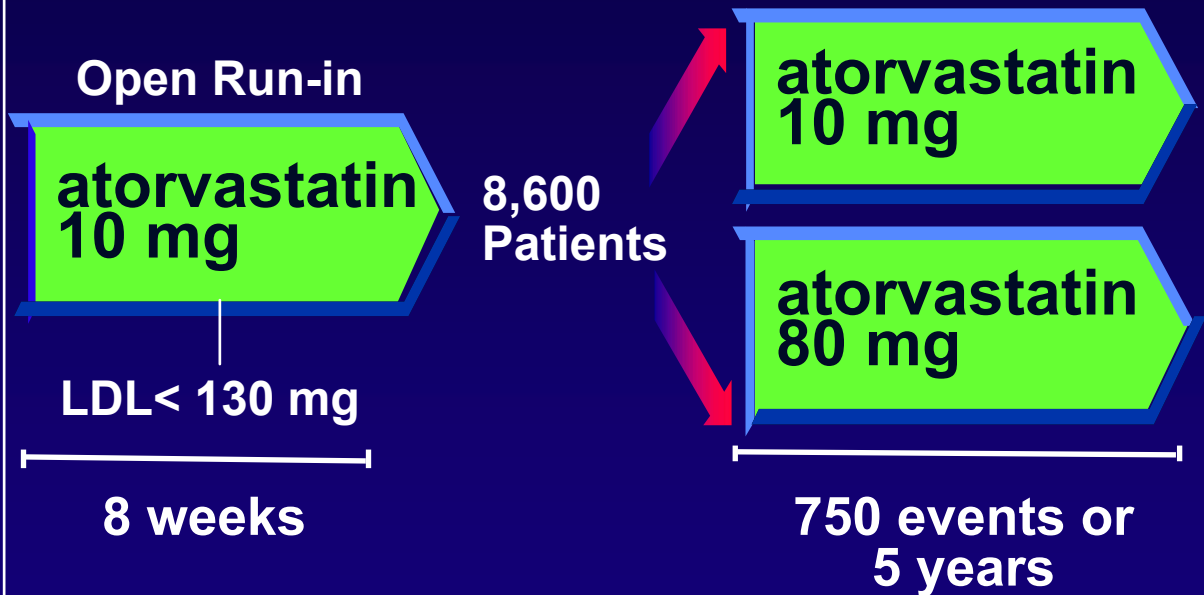
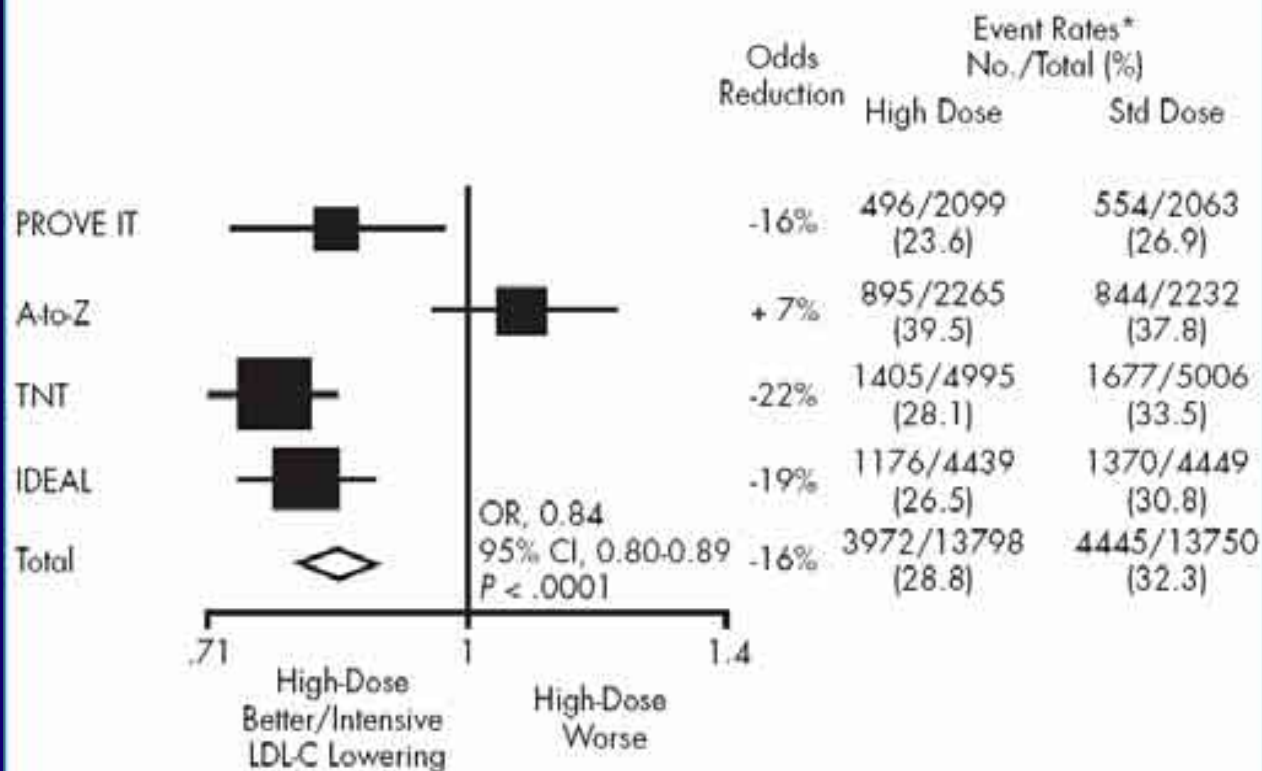


Figure 2. Intensive LDL-C Lowering Reduces Risk of Coronary Death or any CV Event*

More Intensive LDL-C Lowering With High-Dose Therapy†



*Coronary death or any cardiovascular event (myocardial infarction, stroke, hospitalisation for unstable angina, revascularisation).

†Mean LDL-C: high-dose therapy, 1.9 mmol/L; standard-dose therapy, 2.6 mmol/L.

Ato-Z: Aggrastat to Zocor; IDEAL: Incremental Decrease in Events Through Aggressive Lipid Lowering; PROVE IT: Pravastatin and Atorvastatin Evaluation and Infection Therapy; TNT: Treating to New Targets.

Adapted from: Cannon CP et al. *J Am Coll Cardiol.* 2006;48:438-445.

SPARCL Study Design: Stroke Prevention by Aggressive Reduction of Cholesterol Levels

Patient Population

- Stroke/TIA 1-6 months prior
- LDL 100-190 mg/dl
- Exclusions:
 - Age <18 years
 - Hx of CAD
 - Endarterectomy in prior month
 - Subarachnoid hemorrhage
- Many Neurologists



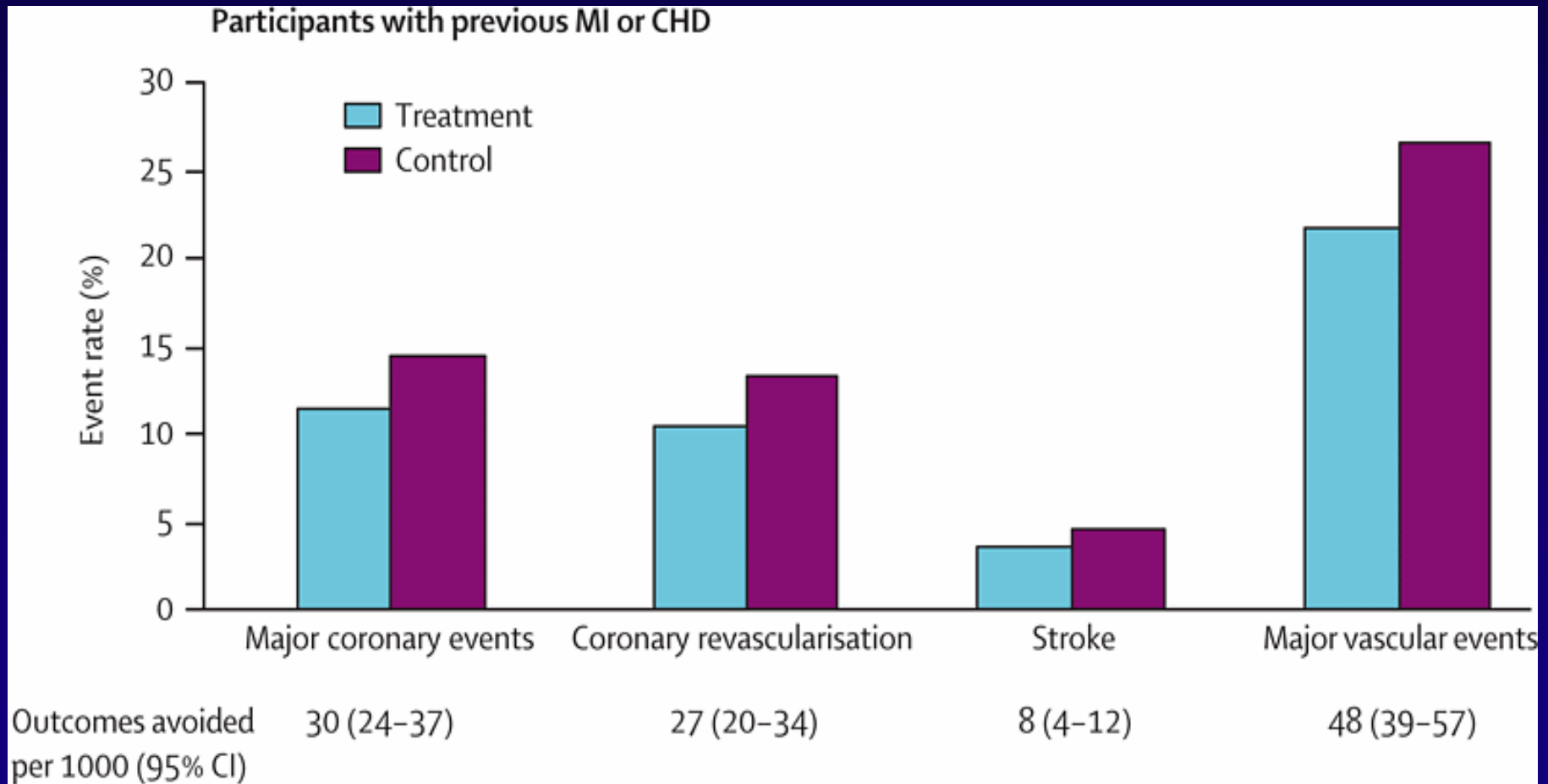
Primary Endpoint

- Time to first fatal or non-fatal stroke

as

investigators

Cholesterol Trialists' Collaboration: Beneficio en puntos finales vasculares a 5 años por mmol/l LDL reducido

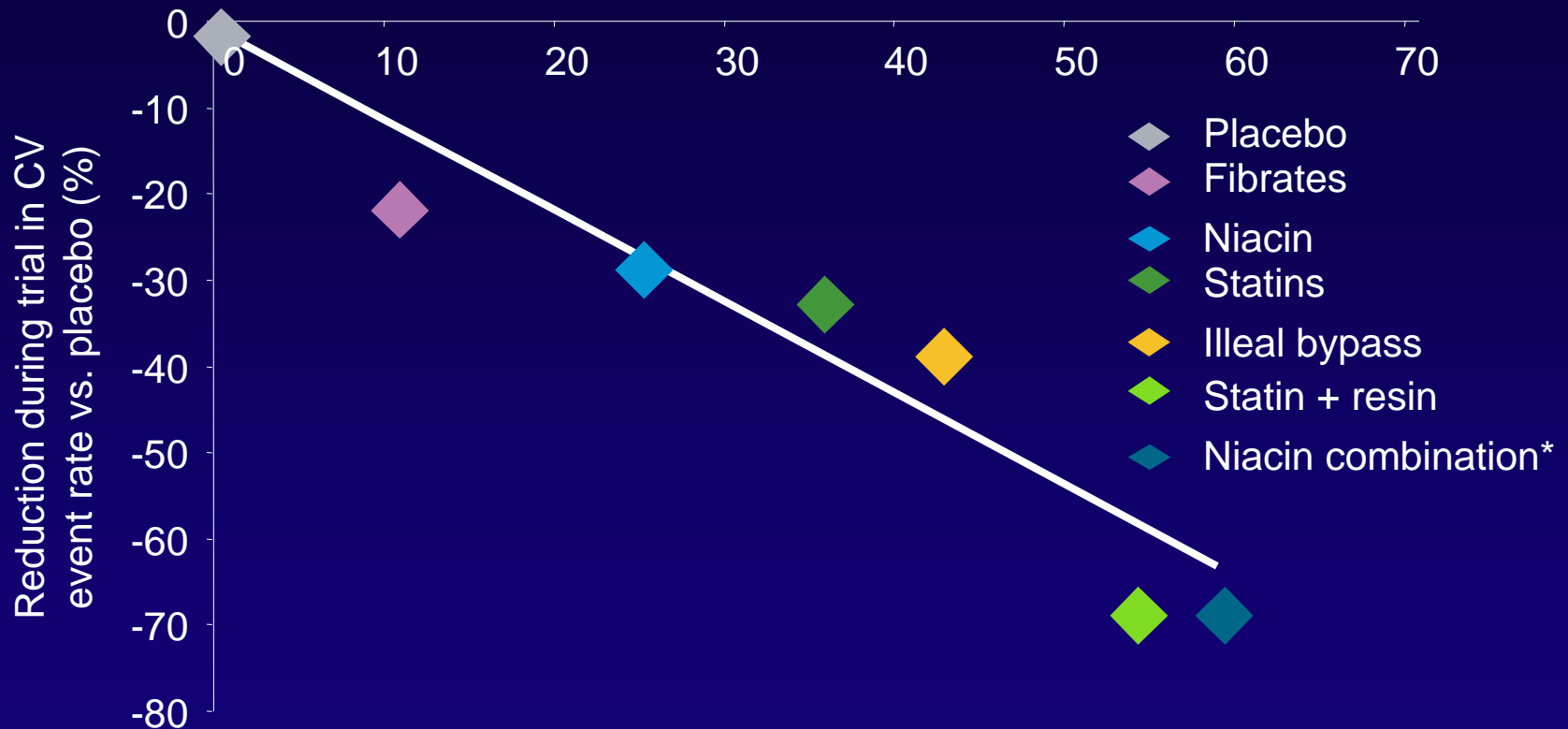


Evidencias Post ATP III: Como seguimos ?

■ Diabetes ?

■ Fibratos ?

Efecto de clases de drogas en los eventos



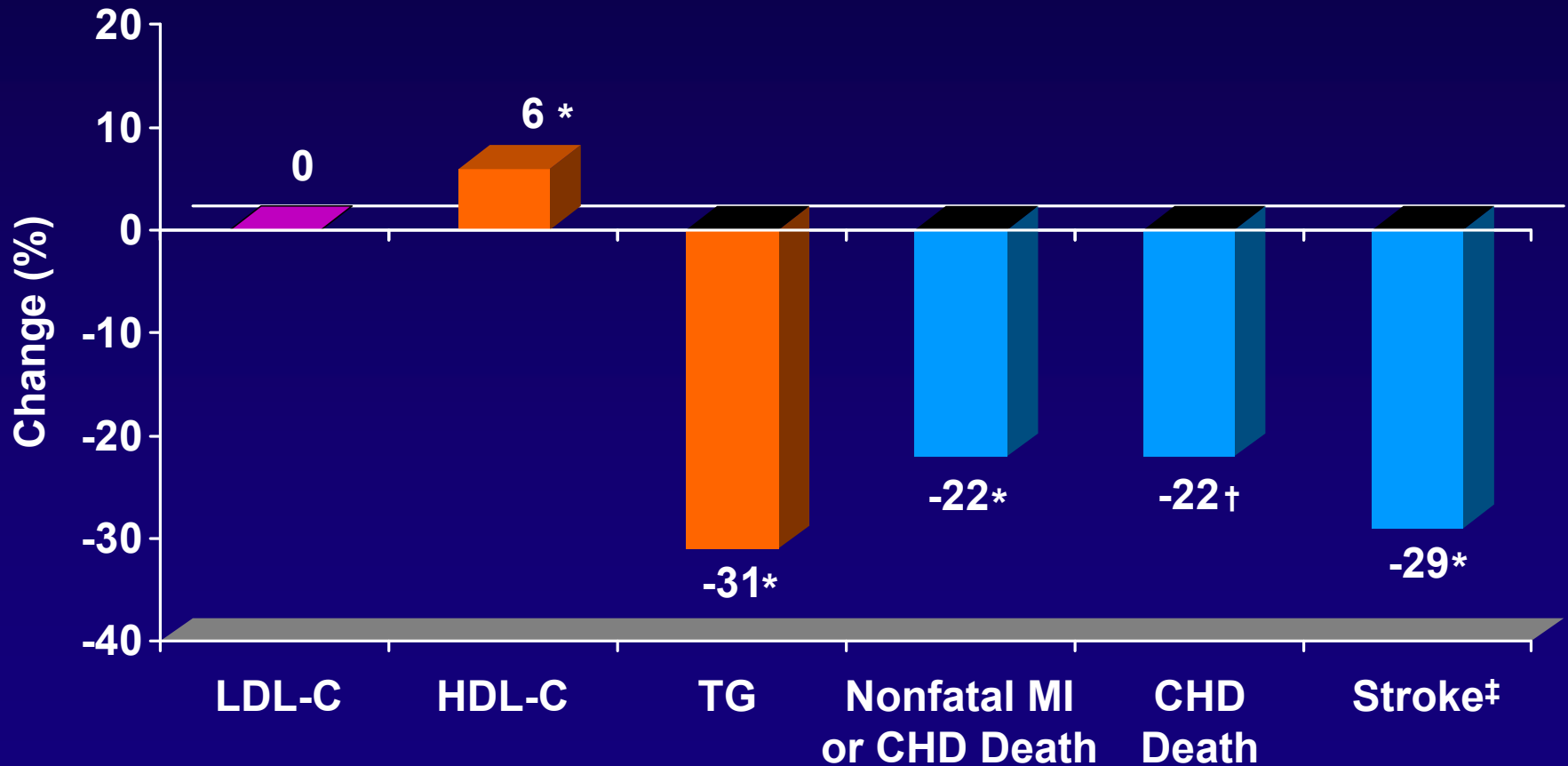
Percentage change in HDL-C - percentage change in LDL-C in Rx [placebo adjusted] (%)

VA-HIT: HDL Intervention Trial

* $P \leq 0.05$

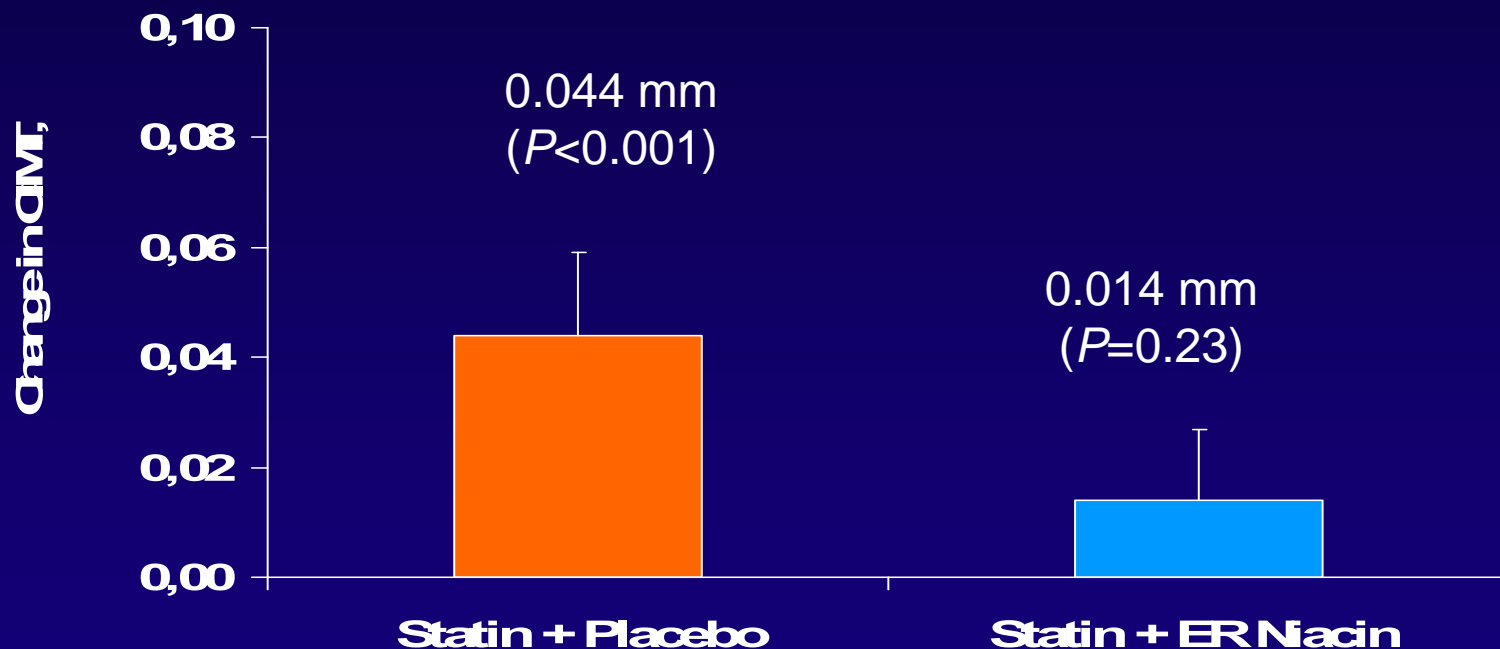
† $P = 0.07$

Lipidos y Eventos



ARBITER 2: Combinacion de Nicotnico con estatina fue superior a estatina sola en efecto sobre IMT

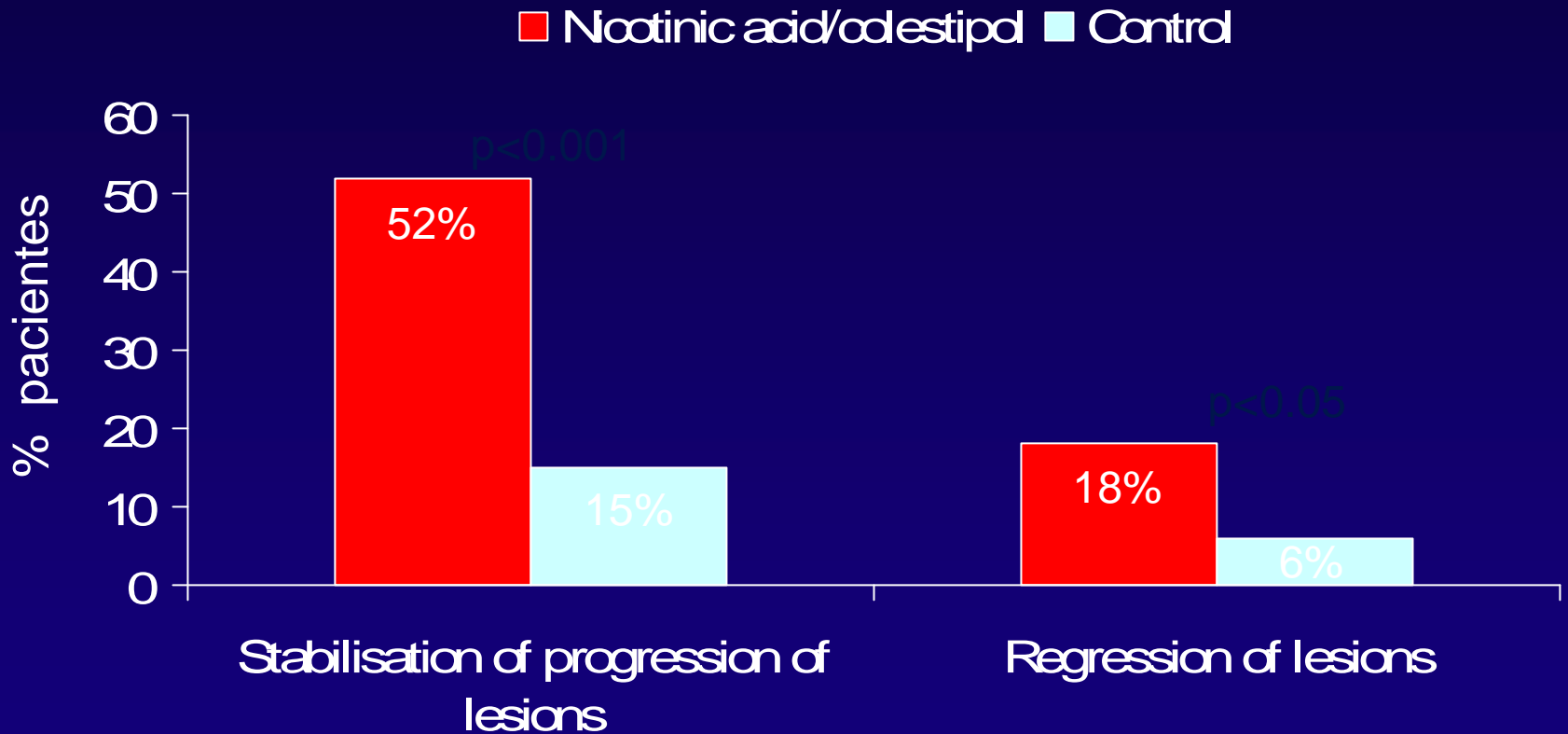
N=167



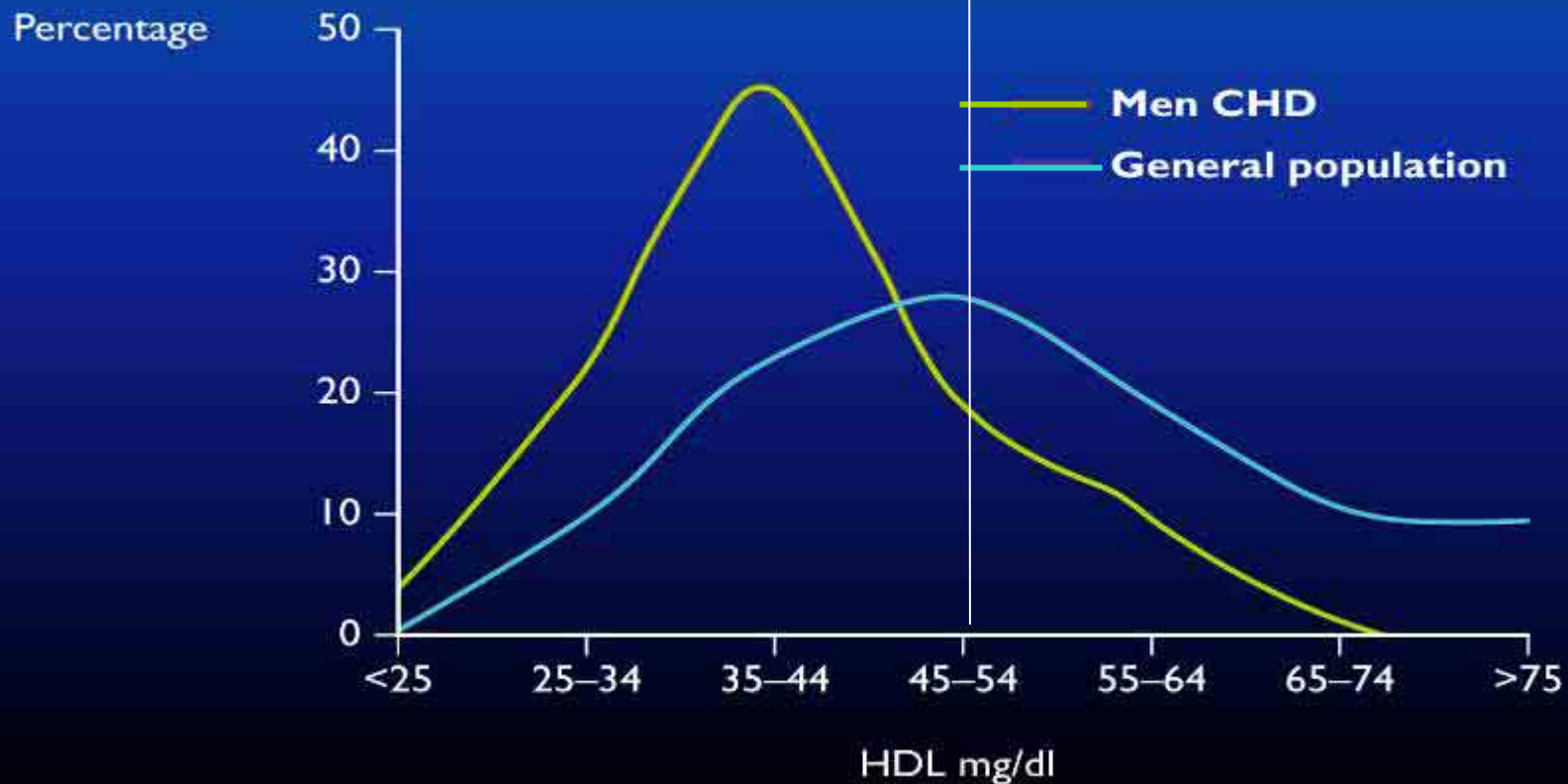
ARBITER 2=Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; ER=extended release; CIMT=carotid intima-media thickness; SEM=standard error of mean

Reprinted with permission from Taylor AJ et al. *Circulation*. 2004;110:3512–3517.

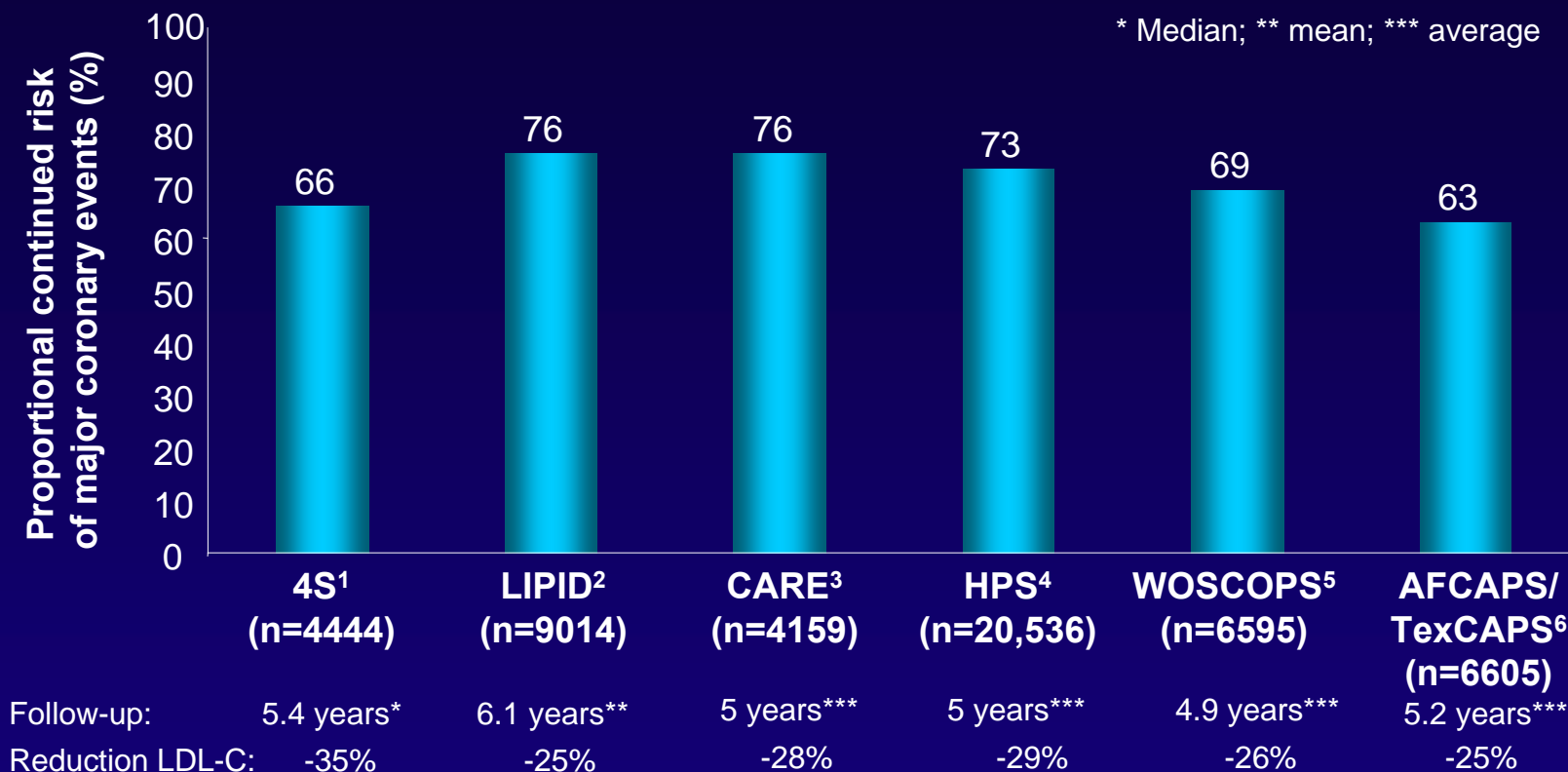
(CLAS): Cholesterol Lowering Atherosclerosis Study: Estab/ Regresion de la Aterosclerosis



70% de hombres con EC tienen HDL bajo ≤ 44 mg/dL (Framingham Male Offspring 35-54)



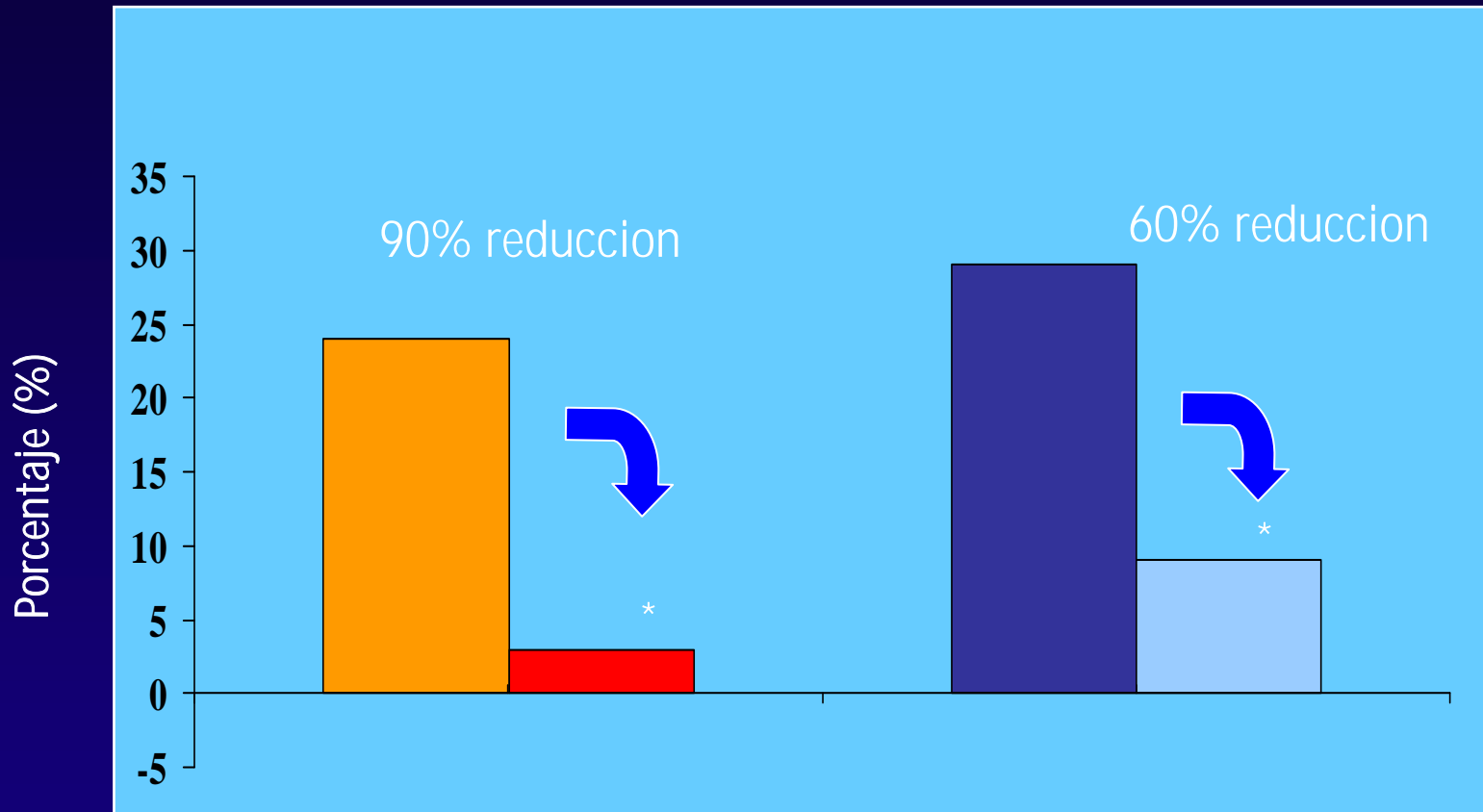
2/3 de los eventos CV continúan ocurriendo con estatinas



1. Scandinavian Simvastatin Survival Study Group. *Lancet* 1994;344:1383-1389.
2. LIPID Study Group. *N Engl J Med* 1998;339:1349-1357.
3. Sacks FM et al. *N Engl J Med* 1996;335:1001-1009.
4. MRC/BHF Heart Protection Study Collaborative Group. *Lancet* 2002;360:7-22.
5. Shepherd J et al. *N Engl J Med* 1995;333:1301-1307.
6. Downs JR et al. *JAMA* 1998;279:1615-1622.

HDL Atherosclerosis Treatment Study

o HATS: Eventos Coronarios Mayores



Placebo



Placebo ± vitaminas



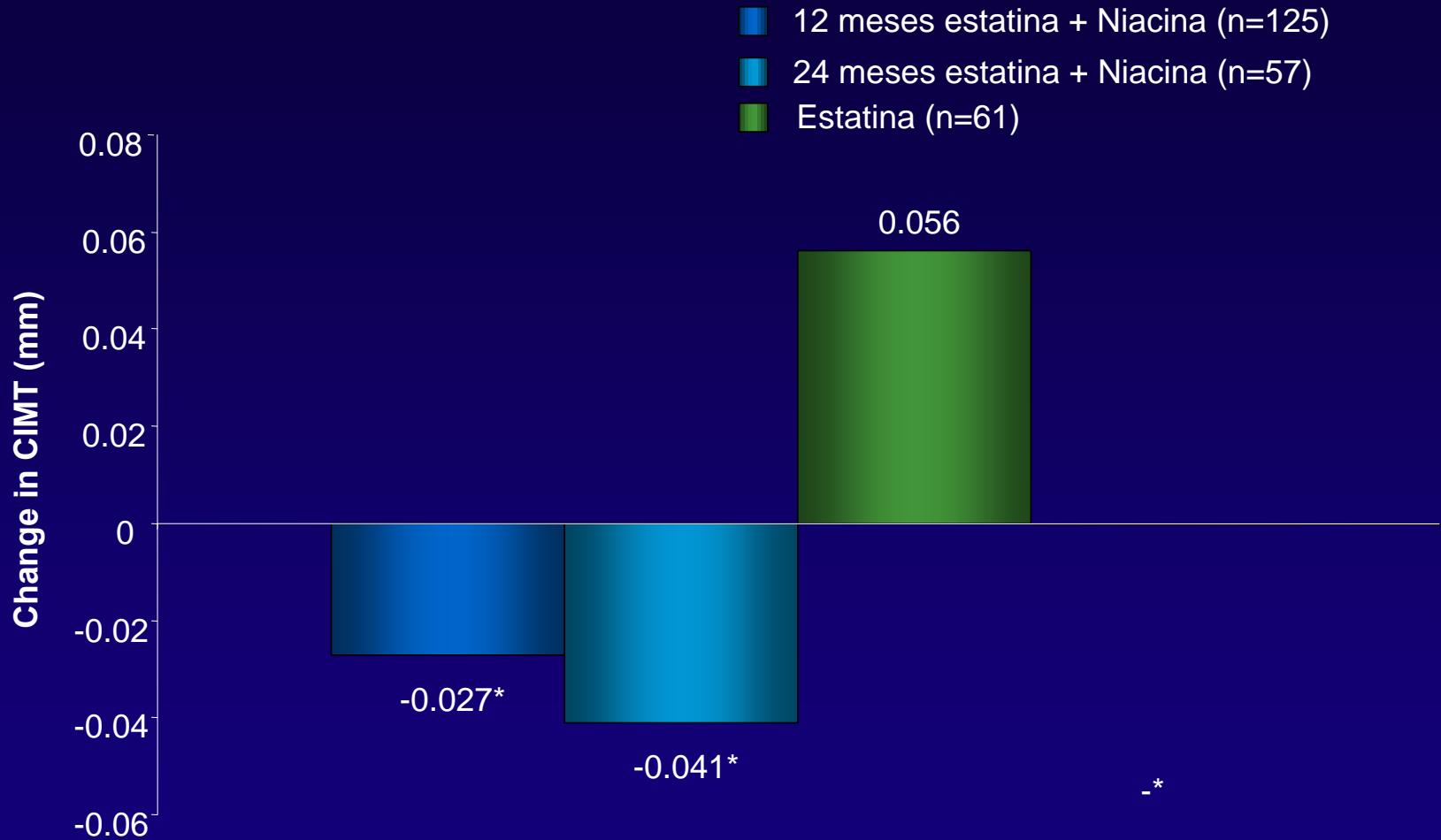
Niacina/simvastatin



Niacina/simvastatina ± vitaminas

* p<0.01

ARBITER, la combinacion estatina + niacina : Regresion de aterosclerosis versus estatina



1. Taylor AJ et al. *Curr Med Res Opin* 2006;22:2243-2250.

*p<0.001 versus statin monotherapy

Table 1 | Characteristics of included trials

Characteristic	WOSCOPS 1995 ⁴⁹	AFCAPS/ TexCAPS 1998 ⁴⁸	PROSPER ^a 2002 ⁴⁶	ALLHAT-LLT 2002 ⁴⁷	ASCOT-LLA 2003 ⁴⁵	HPS ^a 2003 ⁴⁵	CARDS 2004 ⁴⁴	AS-PEN ^a 2006 ⁴³	MEGA 2006 ⁴²	JUPITER 2008 ⁴¹
Target population	Men with hypercholesterolaemia (no history of myocardial infarction)	People with average or below average cholesterol levels (without atherosclerotic cardiovascular disease)	Elderly people with cardiovascular risk factors	People with hypertension, moderate hypercholesterolaemia, and at least one coronary heart disease risk factor	People with hypertension, average or lower cholesterol levels, and at least three other risk factors	People with diabetes	People with diabetes and low density lipoprotein cholesterol (no history of cardiovascular disease)	People with diabetes and low density lipoprotein cholesterol levels below guideline targets	People with hypercholesterolaemia and no history of coronary heart disease or stroke	People without vascular disease, low density lipoprotein cholesterol <130 mg/dL, and high sensitivity C reactive protein > 2.0 mg/l
Design	Randomised double blind placebo controlled trial	Randomised double blind placebo controlled trial	Randomised double blind placebo controlled trial	Randomised controlled trial (control=usual care)	Randomised double blind placebo controlled trial	Randomised double blind placebo controlled trial	Randomised double blind placebo controlled trial	Randomised double blind placebo controlled trial	Randomised double blind placebo controlled trial (control=die)	Randomised double blind placebo controlled trial
No of participants (statin/control)	6595 (3302/3293)	6605 (3304/3301)	3239 (1585/1654)	10355 (5170/5185)	10305 (5168/5137)	2912 (1455/1457)	2838 (1428/1410)	1905 (959/946)	7832 (3866/3966)	17802 (8901/8901)
Mean follow up (years)	4.9	5.2	3.2	4.8	5.5†	4.8	3.9†	4.0†	5.3	1.9†
Drug	Pravastatin	Lovastatin	Pravastatin	Pravastatin	Atorvastatin	Simvastatin	Atorvastatin	Atorvastatin	Pravastatin	Rosuvastatin
Dose (mg/day)	40	20-40	40	20-40	10	40	10	10	10-20	20
Mean age (range) (years)	55.3 (45-64)	58 (45-73)	75 (70-82)	66.4 (51-81)	63.1 (40-79)	NA (40-80)	61.5 (40-75)	60.5 (40-75)	58.3 (40-70)	66† (60-71)
Women (%)	0	15	58‡	49	18.9	NA	32	38	68.4	37.9
With diabetes (%)	1	3.8	12.2†	34.4	24.3	100	100	100	21	0
Current smoker (%)	44	13	33.4†	23.3	33.2	NA	22	12	21	16
Hypertension (%)	16	22	71.6†	89.9	80.3	NA	84	52	42	0
Mean body mass index	26	26.8	27‡	29.9	28.6	NA	28.7	28.9	23.8	28.4†
Mean systolic blood pressure (mm Hg)	136	138	156.6‡	145	164.2	NA	144	133	132	134†
Mean diastolic blood pressure (mm Hg)	84	78	85.2‡	84	95	NA	83	77.1	78.4	80†
Baseline lipid levels (mmol/l) (% change):										
Total cholesterol	7.0 (-20.0)	5.7 (-19.3)	5.7 (NA)	5.9 (-9.6)	5.5 (-18.2)	NA	5.4 (-21.8)	5.0 (-19.8)	6.3 (-11.0)	4.8 (NA)
Low density lipoprotein cholesterol	5.0 (-26.0)	3.9 (-26.5)	3.8 (NA)	3.8 (-16.7)	3.4 (-27.6)	NA	3.0 (-33.9)	3.0 (-30.5)	4.0 (-18.0)	2.8 (NA)
High density lipoprotein cholesterol	1.1 (5.0)	1.0 (4.8)	1.3 (NA)	1.2 (0.9)	1.3 (1.5)	NA	1.4 (4.0)	1.2 (1.9)	1.5 (5.0)	1.3 (NA)
Triglycerides	1.8 (-12.0)	1.7 (-12.7)	1.5 (NA)	1.7 (0.0)	1.7 (-12.6)	NA	2.0 (-15.9)	1.6 (-4.7)	1.4 (-7.0)	1.3 (NA)

Estrategias Actuales en Prevencion Primaria

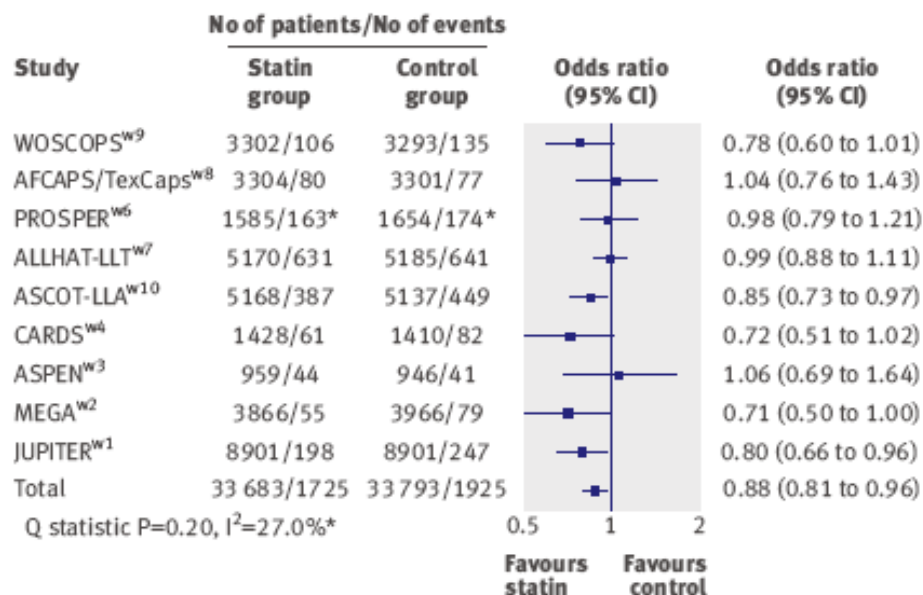
BMJ

RESEARCH

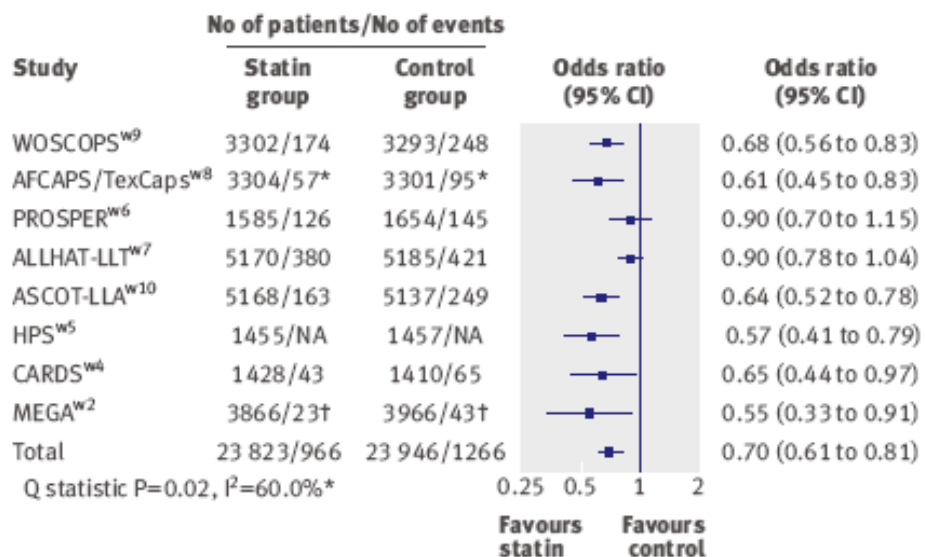
The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials

J J Brugts, doctor,¹ T Yetgin, doctor,¹ S E Hoeks, epidemiologist,¹ A M Gotto, professor, doctor,² J Shepherd, professor, doctor,³ R G J Westendorp, professor, doctor,⁴ A J M de Craen, epidemiologist,⁴ R H Knopp, professor, doctor,⁵ H Nakamura, professor, doctor,⁶ P Ridker, professor, doctor,⁷ R van Domburg, epidemiologist,¹ J W Deckers, doctor¹

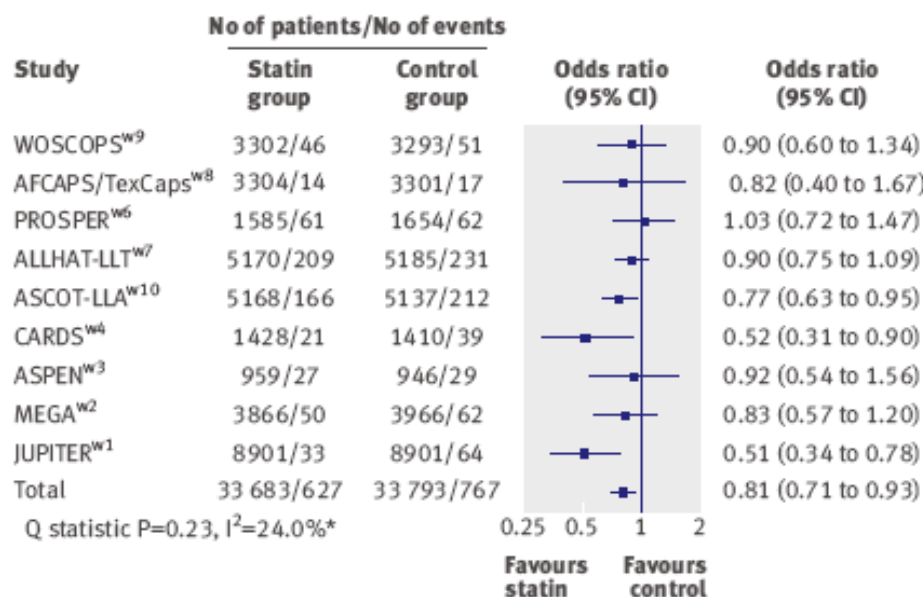
All cause mortality



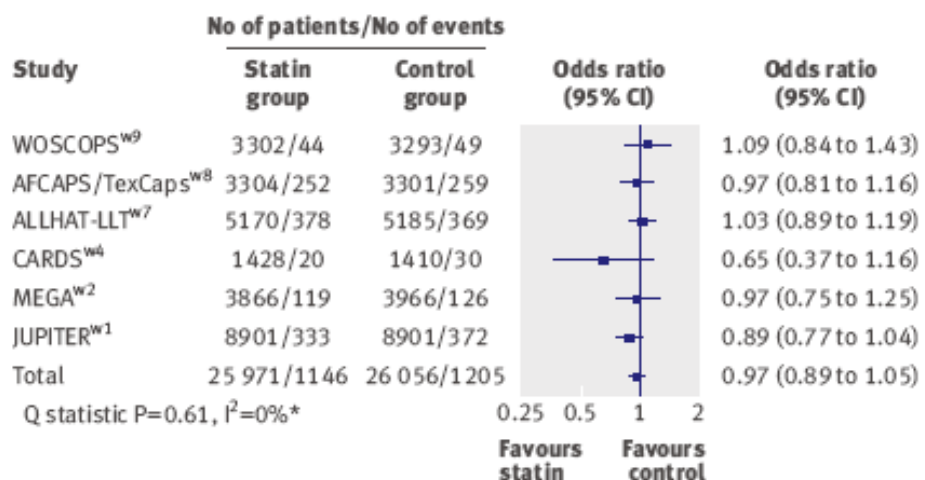
Major coronary events



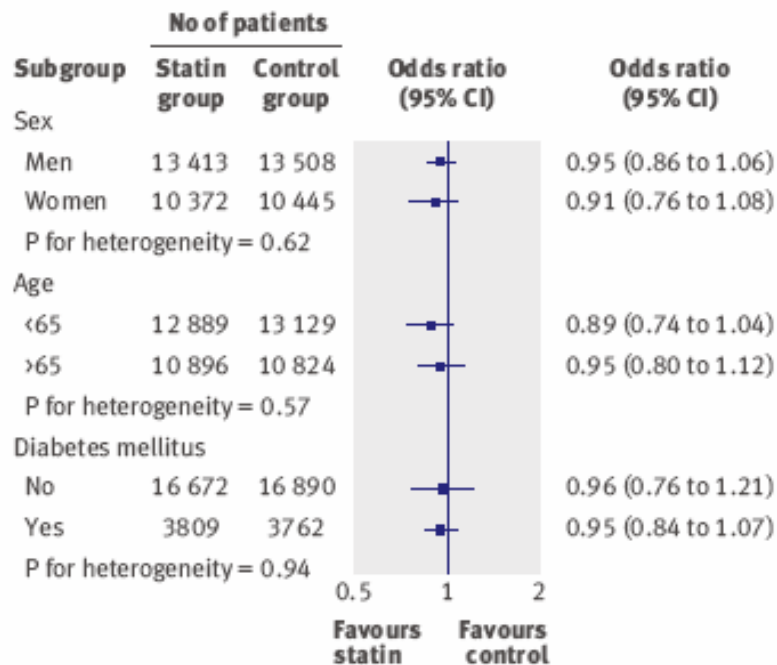
Major cerebrovascular events



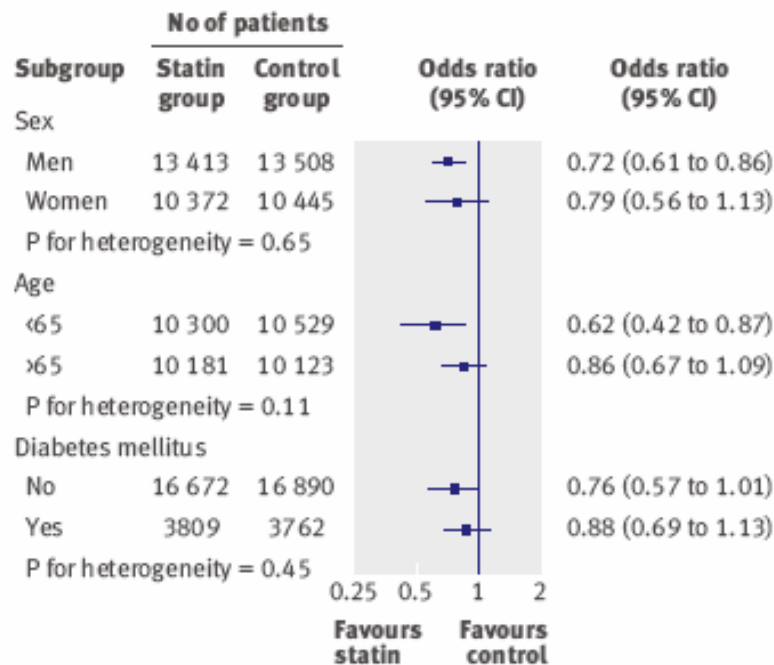
Cancer



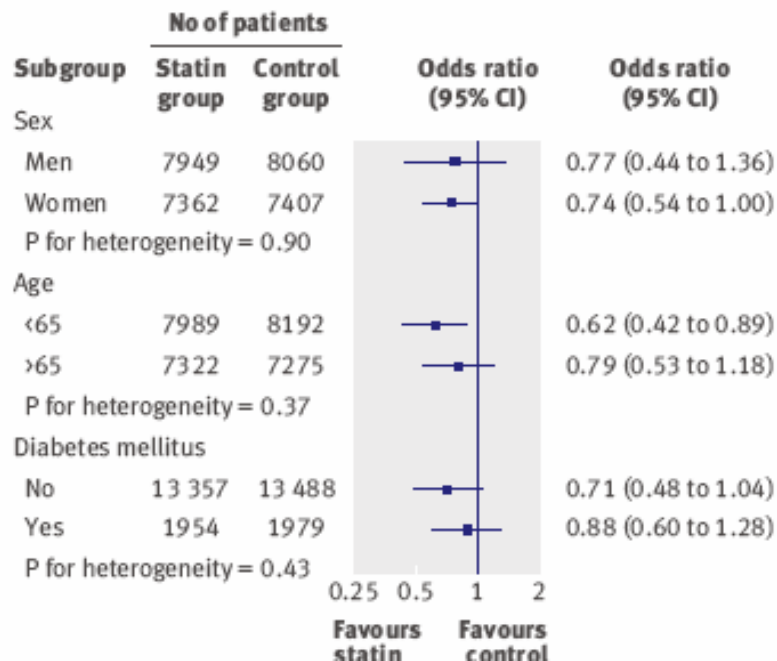
All cause mortality



Major coronary events



Major cerebrovascular events



Cancer

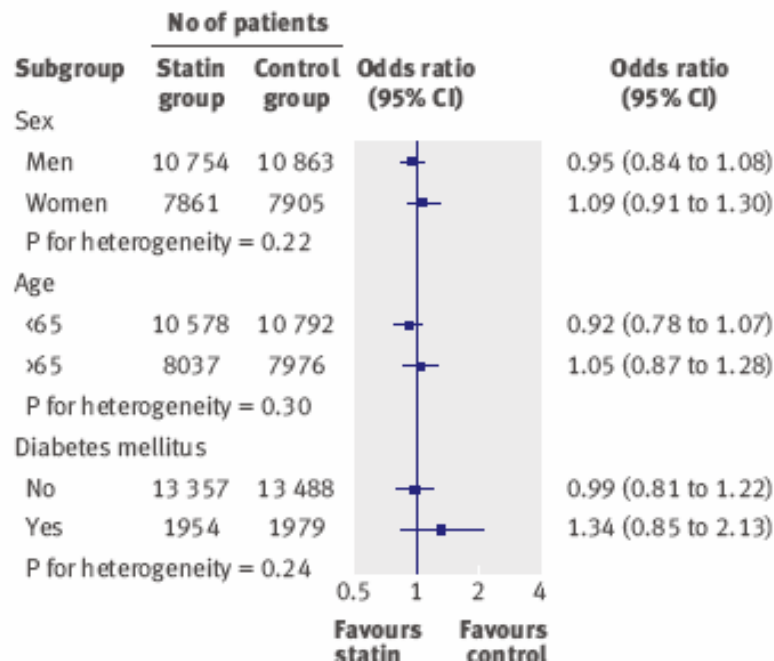
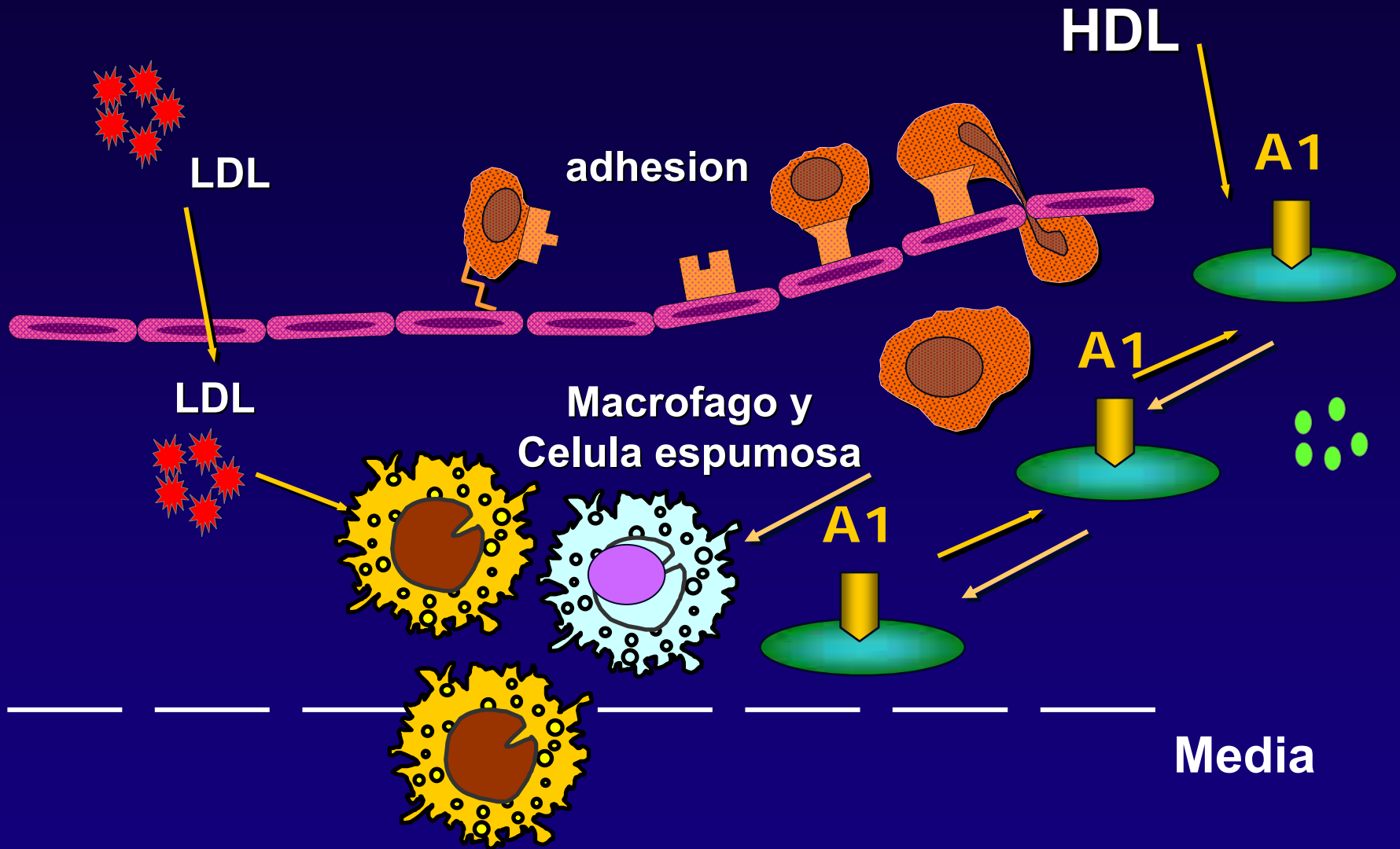


Table 2. Clinical Features of the Patients According to Risk Category

	All Patients	Low Risk	Moderate Risk	High Risk/CHD
Patients, n	9955	2066	1959	5930
Age, y	62±12	57±14	61±11	64±11
Women, n (%)	4513 (46)	1254 (62)	905 (46)	2354 (40)
BMI, kg/m ²	28.6±6.9	27.3±10.2	28.9±5.4	28.9±5.8
Waist circumference, cm	96.8±16.8	91.8±16.4	97.0±15.7	98.5±16.9
Risk factors, n (%)				
Age >45 y for men, >55 y for women	8830 (89)	1434 (69)	1833 (94)	5563 (94)
Diabetes mellitus	3088 (31)	0	0	3088 (52)
Hypertension	6349 (64)	584 (28)	1541 (79)	4224 (71)
Current smokers	1358 (14)	134 (7)	411 (21)	813 (14)
Low HDL-C	790 (8)	18 (1)	201 (10)	571 (10)
No. of risk factors	2.1±1.2	0.6±0.6	2.4±0.6	2.5±1.1
Metabolic syndrome, n (%)	4274 (43)	492 (24)	917 (47)	2865 (48)
Lipid lowering therapy, n (%)				
Statin	7450 (75)	1225 (60)	1368 (70)	4857 (82)
Other	835 (8)	193 (10)	180 (9)	462 (8)
Dietary counseling, n (%)	6569 (68)	1535 (78)	1341 (70)	3693 (64)
Lipid measurements, mg/dL				
LDL-C	100±37	119±37	109±37	91±33
HDL-C	53±15	62±16	49±12	50±14
Non-HDL-C	130±41	146±41	142±41	121±38
Triglycerides	152±86	136±79	167±95	152±84
Triglycerides/HDL-C	3.3±2.8	2.5±2.0	3.8±3.3	3.4±2.7
hs-CRP, mg/L	1.5 (0.7–3.3)	1.3 (0.6–2.8)	1.6 (0.8–3.6)	1.6 (0.8–3.4)
Fasting blood glucose, mg/dL	115±39	99±22	103±19	125±45

Atherosclerosis: Evolucion de las Lesiones



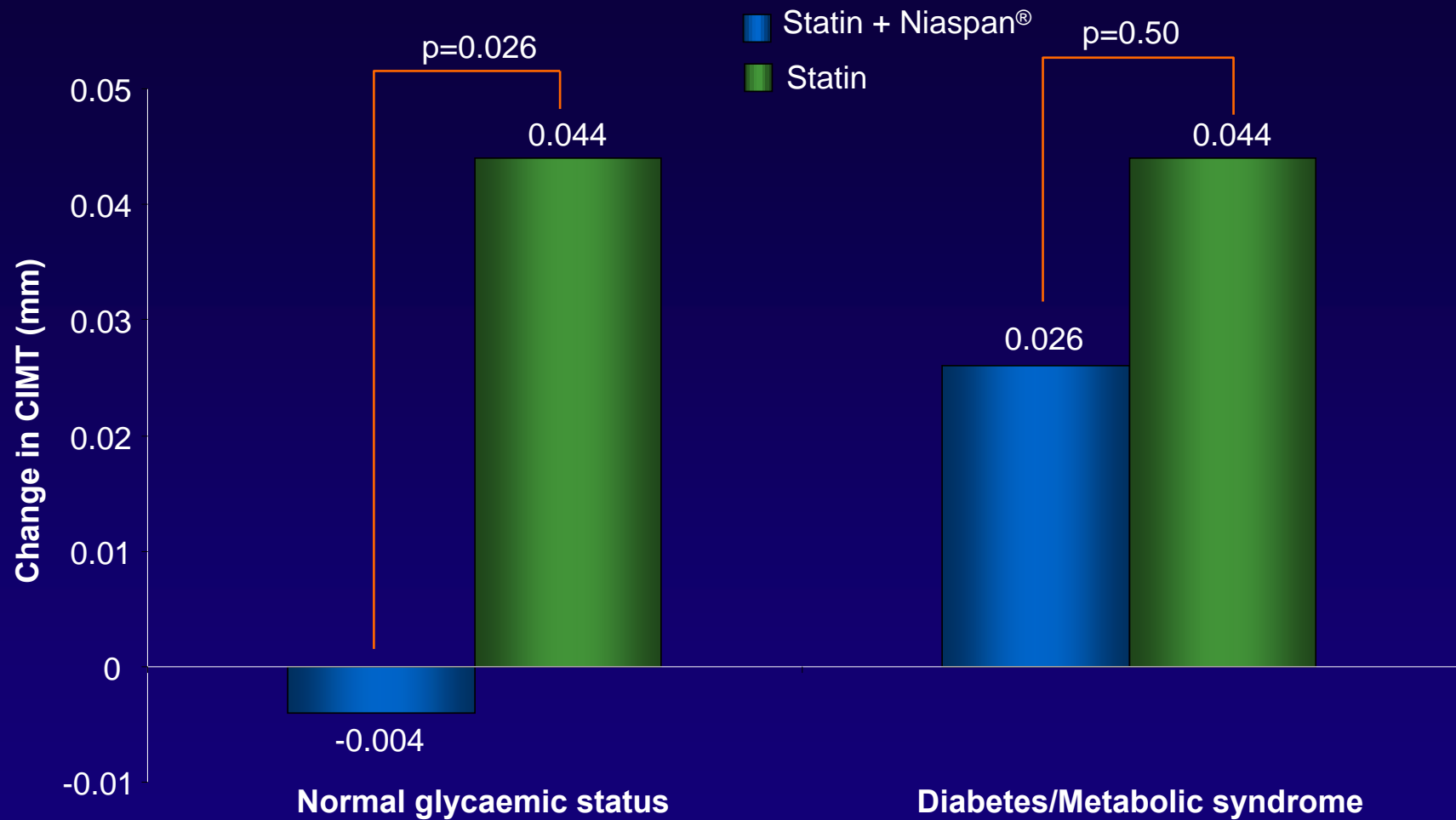
Target lipid levels

Risk level	Initiate treatment if:	Primary targets	
		LDL-C	Alternate
High CAD, PVD, atherosclerosis* Most patients with diabetes FRS $\geq 20\%$ RRS $\geq 20\%$	Consider treatment in all patients	< 2 mmol/L or $\geq 50\%$ \downarrow LDL-C Class I, level A	apoB < 0.80 g/L Class I, level A
Moderate FRS 10%–19%	LDL-C > 3.5 mmol/L TC/HDL-C > 5.0 hs-CRP > 2 mg/L Men > 50 years Women > 60 years Family history and hs-CRP modulates risk (RRS)	< 2 mmol/L or $\geq 50\%$ \downarrow LDL-C Class IIa, level A	apoB < 0.80 g/L Class IIa, level A
Low FRS $< 10\%$	LDL-C ≥ 5.0 mmol/L	$\geq 50\%$ \downarrow LDL-C Class IIa, level A	

*Coronary artery disease, peripheral vascular disease, cerebrovascular disease, aortic disease, and aortic aneurysm

	All Patients	United States	Canada	France	Netherlands	Spain	Brazil	Mexico	Korea	Taiwan
Patients, n	9955	3049	1021	961	957	991	391	611	983	966
Age, y	62±12	62±12	63±11	63±12	62±11	61±12	61±12	58±12	61±10	62±12
Women, n (%)	4513 (46)	1407 (46)	335 (33)	403 (42)	387 (40)	487 (49)	237 (62)	294 (49)	497 (51)	464 (48)
BMI, kg/m ²	28.6±6.9	30.4±6.5	29.8±13.9	27.2±4.7	28.7±5.1	28.7±4.7	28.0±4.7	28.6±4.4	25.3±3.4	26.3±3.8
Waist circumference, cm	96.8±16.8	100.6±17.3	100.1±15.8	95.3±18.5	101.1±20.2	96.1±15.4	96.6±11.6	96.5±13.2	88.0±9.8	88.7±14.5
Known CHD, n (%)	2993 (30)	928 (30)	368 (36)	192 (20)	241 (25)	140 (14)	124 (32)	186 (30)	531 (54)	283 (29)
Risk factors, n (%)										
Age >45 y for men, >55 y for women	8830 (89)	2677 (88)	938 (92)	848 (88)	874 (91)	853 (86)	349 (89)	493 (81)	913 (93)	875 (91)
Diabetes mellitus	3088 (31)	972 (32)	300 (29)	212 (22)	318 (33)	274 (28)	115 (29)	198 (32)	200 (20)	495 (51)
Hypertension	6349 (64)	2026 (66)	626 (61)	533 (56)	511 (53)	550 (56)	325 (83)	404 (66)	675 (69)	694 (72)
Current smokers	1358 (14)	362 (12)	160 (16)	137 (14)	210 (22)	155 (16)	18 (5)	60 (10)	122 (12)	132 (14)
Low HDL-C	790 (8)	327 (11)	120 (12)	24 (3)	62 (7)	36 (4)	12 (3)	43 (7)	84 (9)	79 (8)
No. of risk factors	2.1±1.2	2.3±1.2	2.3±1.2	1.6±1.2	2.3±1.2	1.7±1.2	2.1±1.0	1.9±1.1	2.0±0.9	2.3±1.2
Metabolic syndrome, (%)	4274 (43)	1405 (46)	514 (50)	311 (32)	515 (53)	416 (41)	145 (37)	269 (44)	308 (31)	391 (40)
Lipid-lowering therapy, (%)										
Statins	7450 (75)	2297 (75)	839 (82)	325 (34)	773 (81)	753 (76)	223 (58)	465 (77)	966 (98)	803 (83)
Other	835 (8)	314 (10)	61 (6)	170 (18)	69 (7)	70 (7)	9 (2)	39 (7)	16 (2)	85 (9)
Dietary counseling, (%)	6569 (68)	2178 (74)	709 (71)	814 (89)	545 (58)	950 (98)	344 (90)	534 (89)	8 (1)	481 (50)
Risk category, (%)										
Low	2066 (21)	595 (20)	157 (15)	349 (36)	133 (14)	374 (38)	82 (21)	163 (27)	111 (11)	102 (11)
Moderate	1959 (20)	681 (22)	207 (20)	162 (17)	177 (18)	215 (21)	100 (26)	110 (18)	205 (21)	102 (11)
High/CHD	5930 (59)	1773 (58)	657 (65)	453 (47)	655 (68)	416 (41)	209 (53)	338 (55)	667 (68)	762 (78)
Lipid measurements, mg/dL										
LDL-C	100±37	98±36	94±34	113±37	97±33	119±38	113±46	98±40	84±27	98±31
HDL-C	53±15	51±15	49±13	60±16	52±15	57±15	54±14	51±13	50±12	52±14
Non-HDL-C	130±41	129±42	124±39	140±41	126±36	146±40	142±49	136±47	111±29	127±35
Triglycerides	152±86	158±101	154±96	138±71	149±69	138±67	145±67	189±106	139±61	148±71
Triglycerides/HDL-C	3.3±2.8	3.6±3.3	3.6±3.4	2.6±1.9	3.2±2.0	2.7±1.9	3.0±1.9	4.2±3.0	3.1±2.5	3.2±2.1
hs-CRP, mg/L	1.5 (0.7–3.3)	1.9 (0.9–4.2)	1.6 (0.8–3.4)	1.7 (0.8–3.5)	1.6 (0.8–3.2)	1.7 (0.8–3.6)	1.6 (0.8–3.4)	NA	0.7 (0.4–0.14)	1.2 (0.7–2.6)
Fasting blood glucose, mg/dL	115±39	115±40	116±32	107±31	122±42	116±38	110±41	114±50	106±27	124±45

Niaspan[®]/statin therapy is less effective in patients with metabolic syndrome



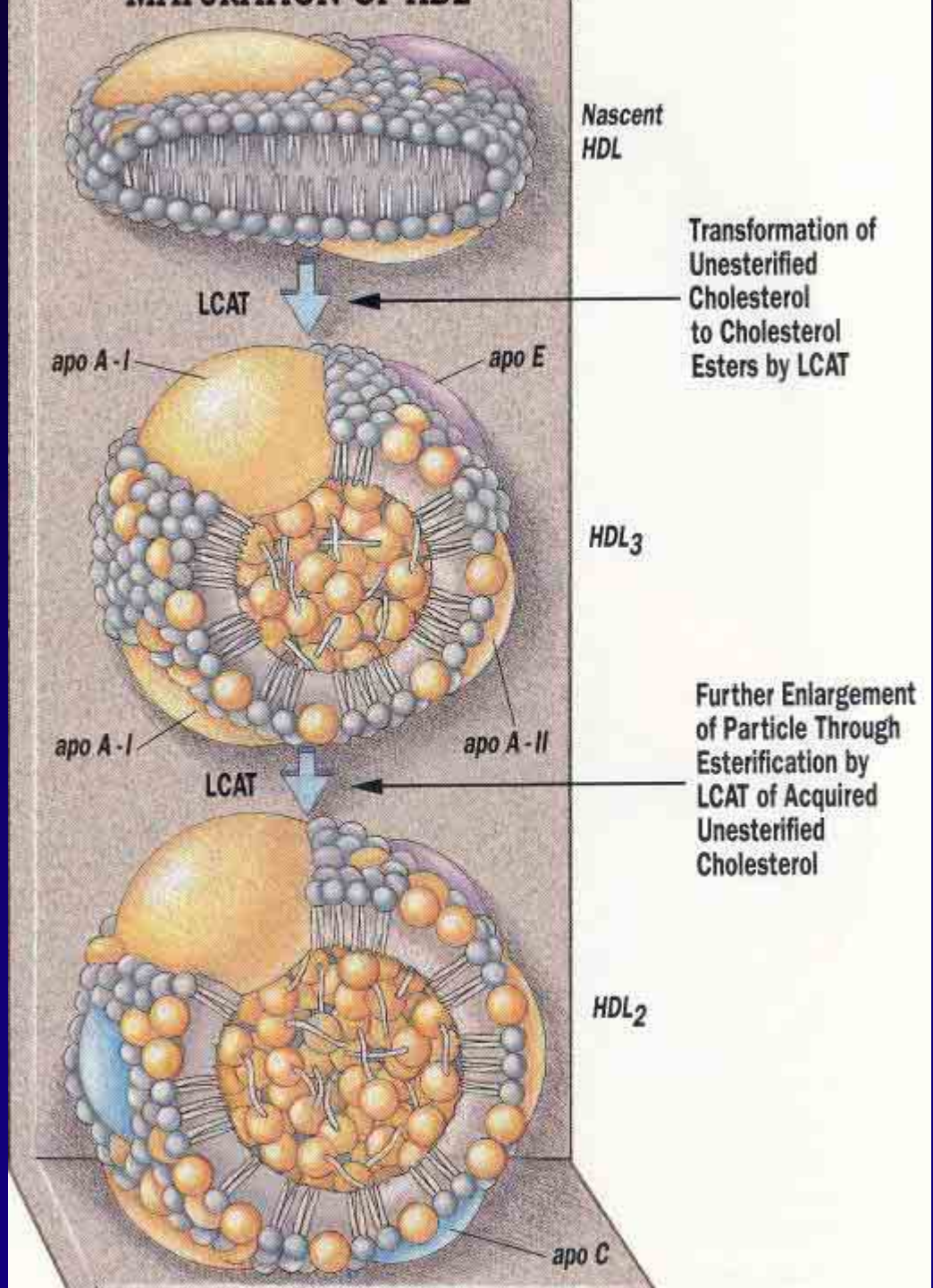
1. Taylor AJ et al. *Circulation* 2004;110:3512-3517.

HDL y su metabolismo

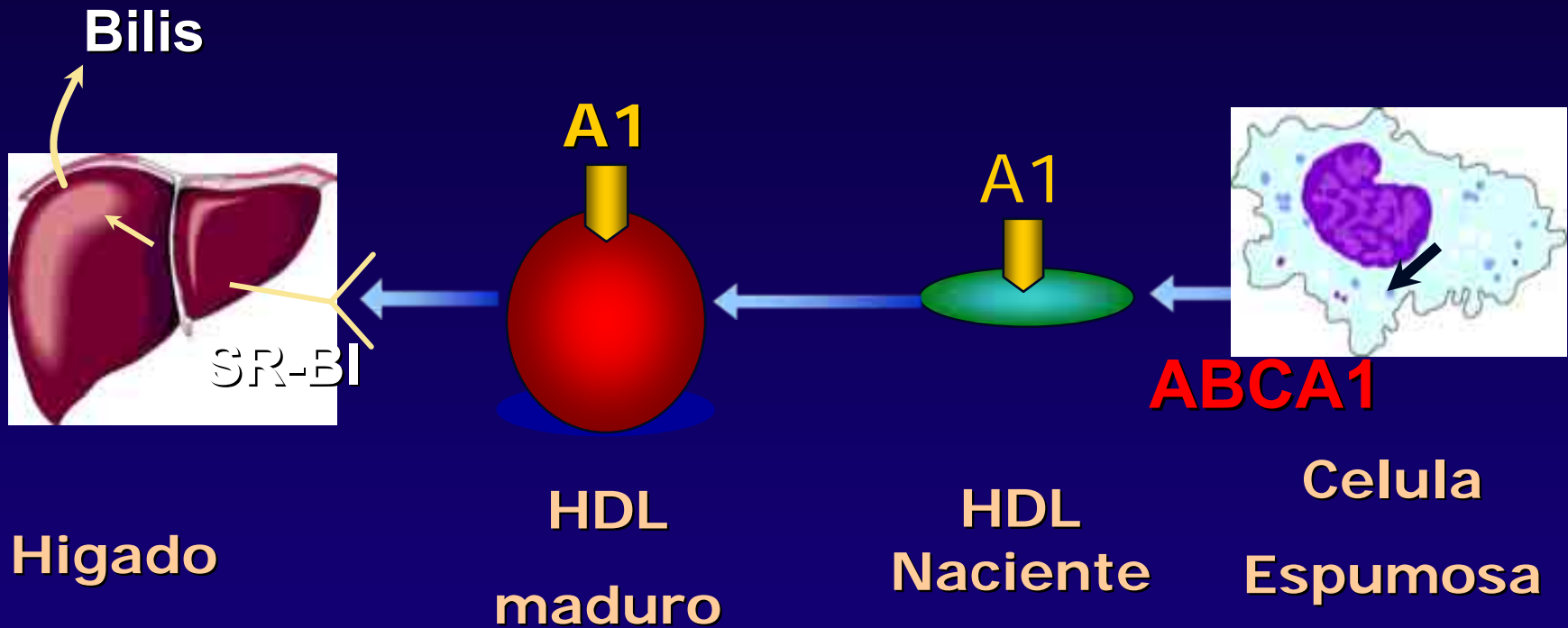
HDL secretado es discoidal

Adquiere colesterol de, madura a forma esferica)

Cholesterol and Atherosclerosis, Grundy)



HDL y Transporte Reverso de Colesterol



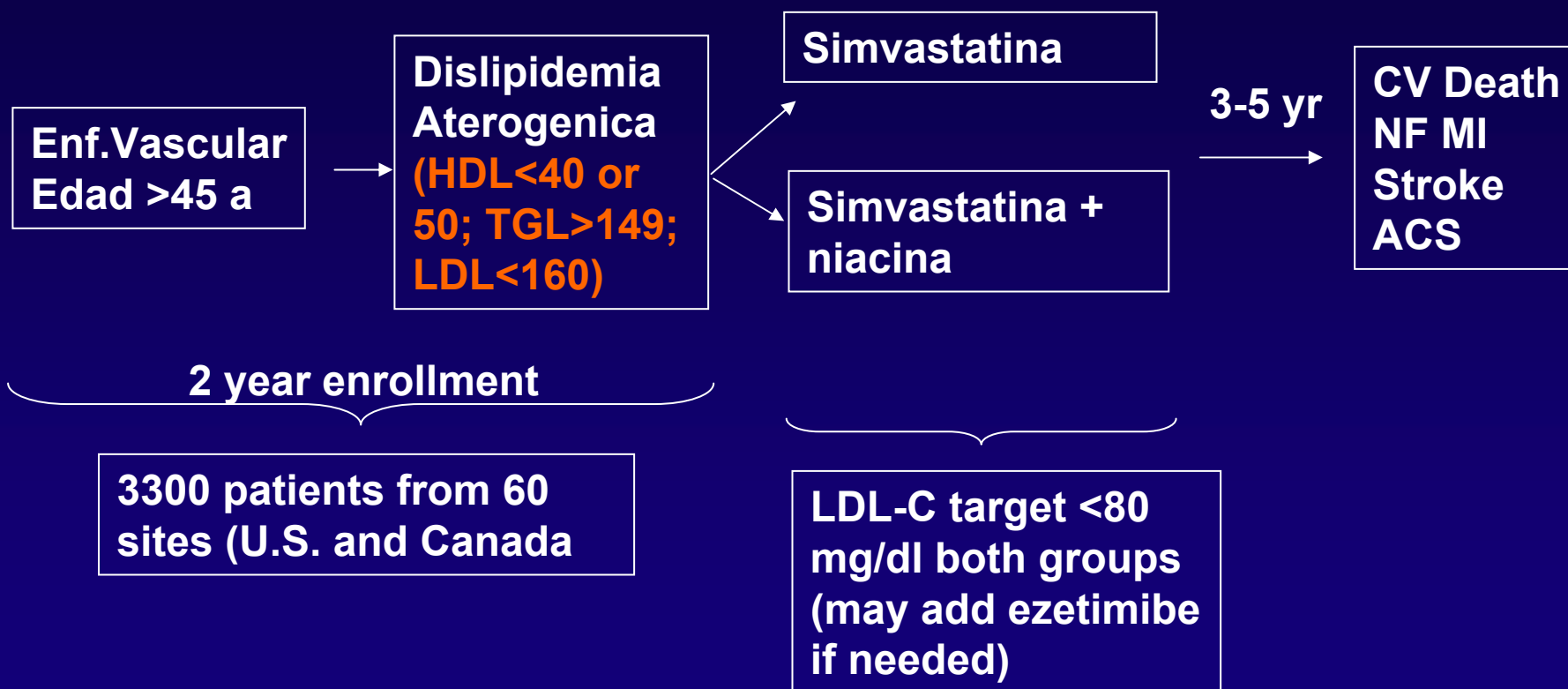
TARGETS OF THERAPY

Risk level	Primary target: LDL-C	Class, level
High CAD, PVD, atherosclerosis Most patients with diabetes FRS $\geq 20\%$ RRS $\geq 20\%$	< 2 mmol/L or $\geq 50\%$ \downarrow LDL-C apoB < 0.80 g/L	Class I, level A
Moderate FRS 10% to 19% LDL-C > 3.5 mmol/L TC/HDL-C > 5.0 hs-CRP > 2 mg/L in men >50 years and women >60 years of age Family history and hs-CRP modulate risk	< 2 mmol/L* or $\geq 50\%$ \downarrow LDL-C apoB < 0.80 g/L	Class IIa, level A
Low FRS $< 10\%$	$\geq 50\%$ \downarrow LDL-C	Class IIa, level A

Prevencion primaria: que es hoy, que sera manana?

- Antes de un Evento
- Riesgo x Framingham
- Tratamiento dirigido a los FR-CV
- Aterosclerosis Subclinica y marcadores no evaluados
- Nuevos scores de riesgo
- Casos especiales, HDL
- Regresion en carotidas
- Nuevos FRCV
- Estudios en mod. riesgo

AIM-HIGH: diseño del estudio

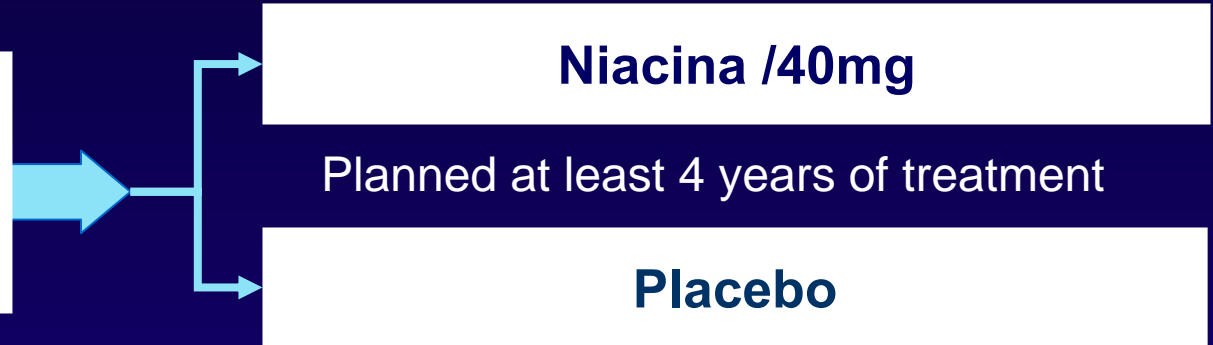


Study Start Date: September 2005

Study Completion Date: approximately December 2010

HPS 2-THRIVE (Heart Protection Study 2 Treating HDL to Reduce Vascular Events)

All patients receive either simvastatin 40mg or ezetimibe/simvastatin 10/40 mg

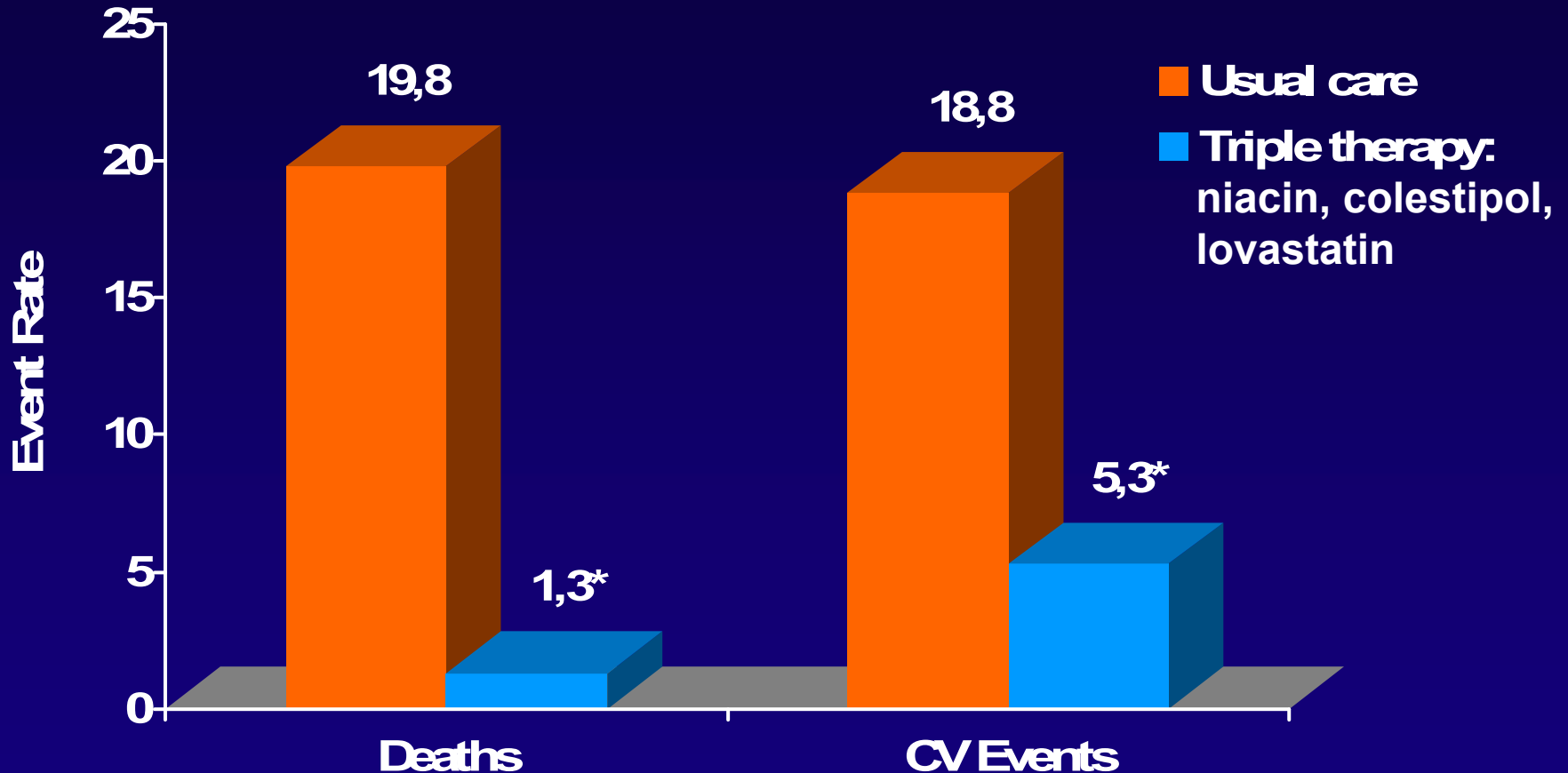


Patient Population	Subjects	Primary End Point
<ul style="list-style-type: none"> ■ Age 50-80 • History of MI or cerebrovascular atherosclerotic disease or PAD or Diabetes mellitus with any of the above or with other evidence of symptomatic CHD 	<ul style="list-style-type: none"> ■ 20,000 ■ UK (n=7500), Scandinavia (n=5000) and China (n=7500) 	<ul style="list-style-type: none"> ■ Major vascular events during the scheduled treatment period (non-fatal MI or coronary death, non-fatal or fatal stroke, or revascularisation)

- Study start: January 2007
- Expected completion: January 2013

FATS: Familial Atherosclerosis Treatment Study

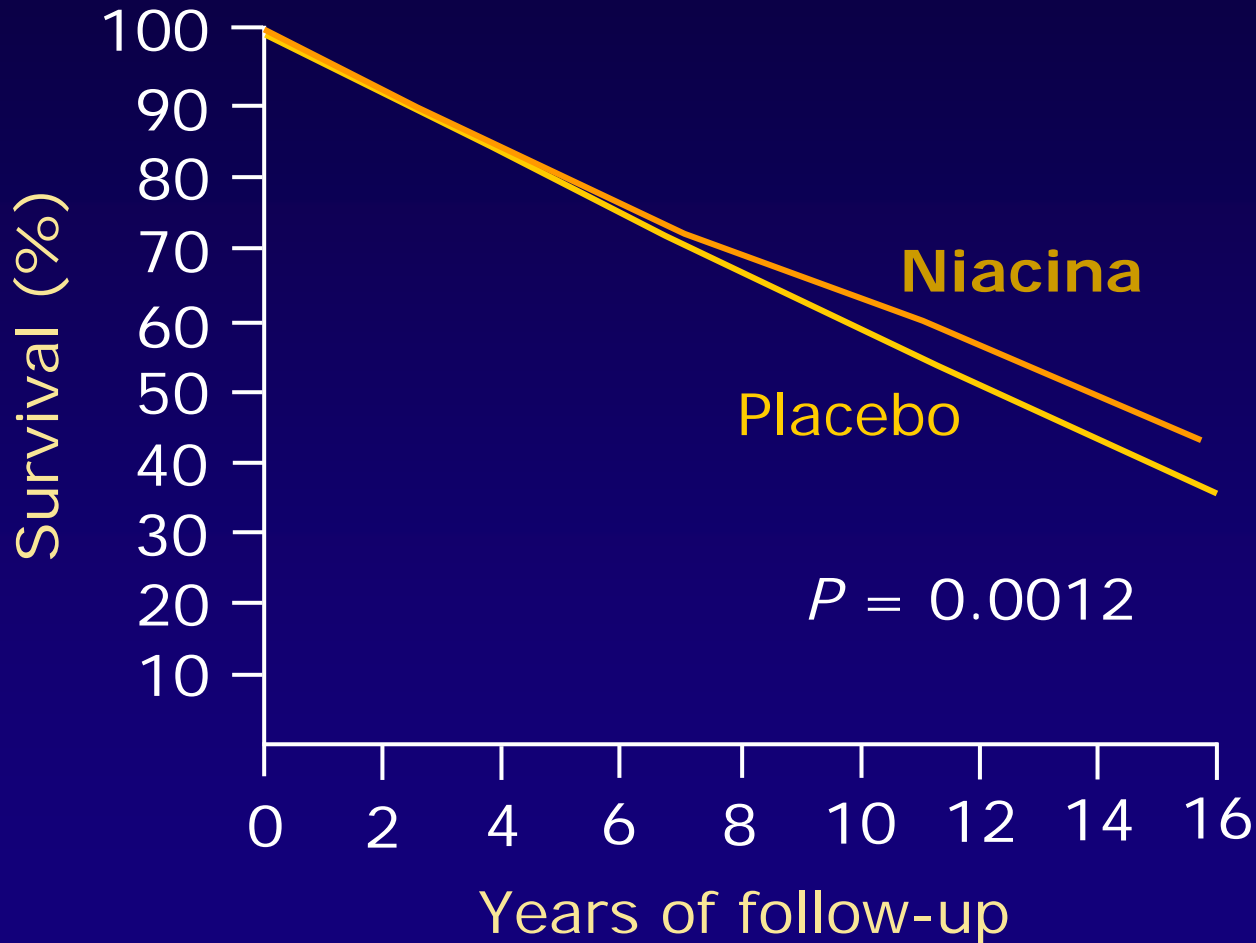
Resultados eventos a 10-a de seguimiento

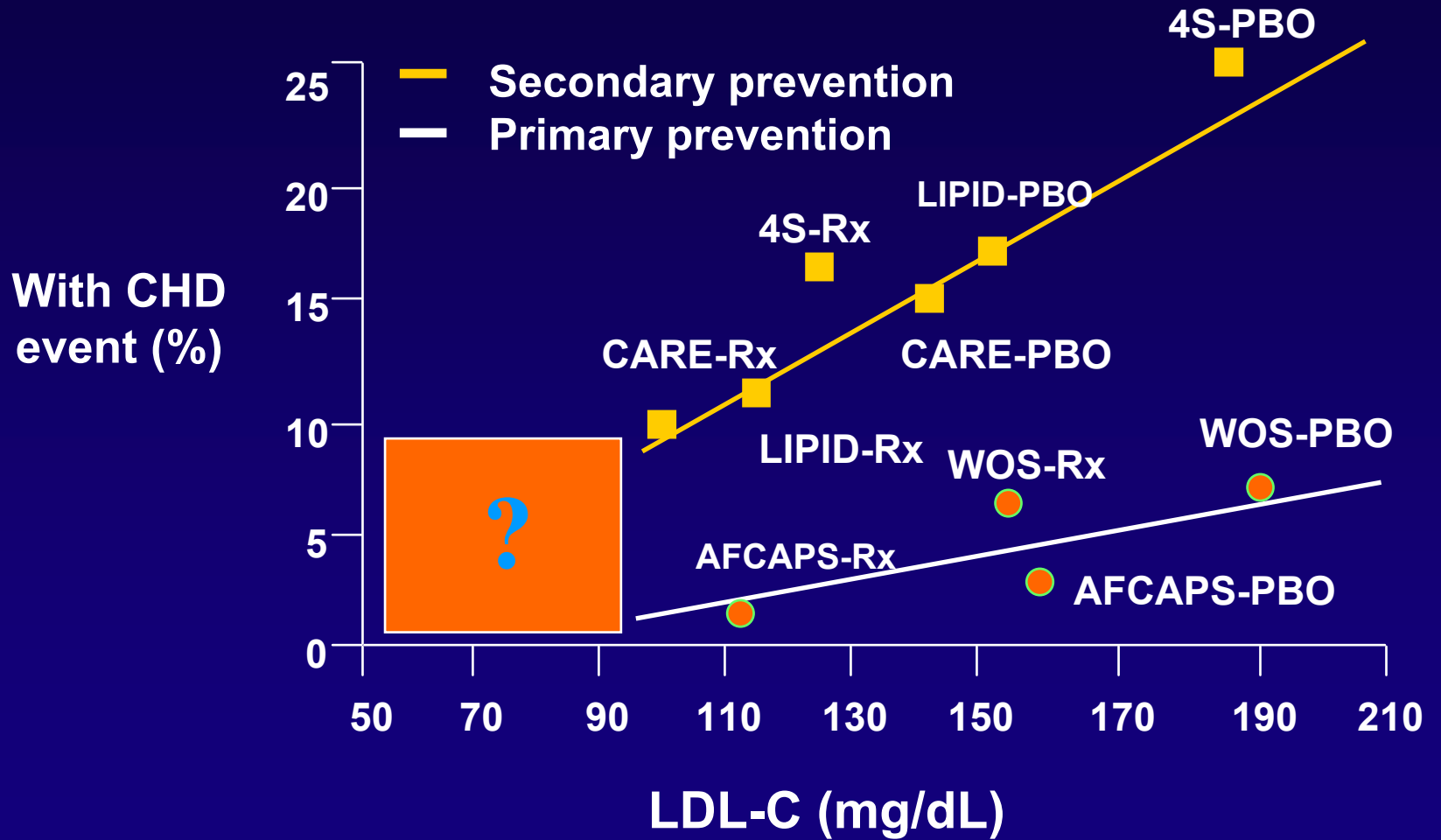


* $P < 0.05$ Usual Care N = 110 Vs Combination N = 75

Brown BG et al. *Circulation*. 1998;98(suppl I):I-635. Abstr 3341

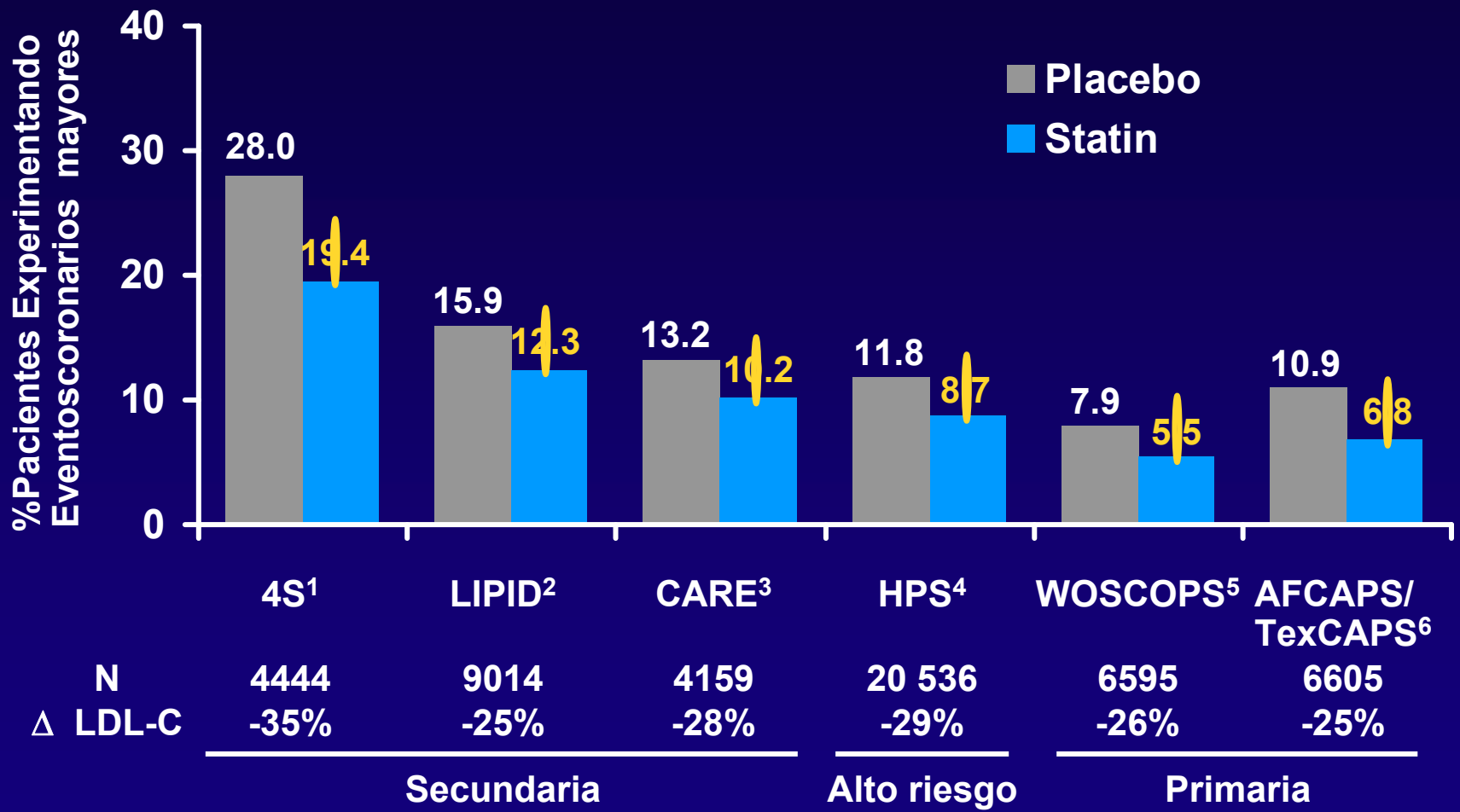
Coronary Drug Project: Beneficio de Mortalidad a largo plazo de Niacina





Riesgo Cardiovascular Residual y Estatinas

Eventos Cardiovasculares versus placebo



¹ 4S Group. *Lancet*. 1994; 344:1383-1389.

² LIPID Study Group. *N Engl J Med*. 1998; 339:1349-1357.

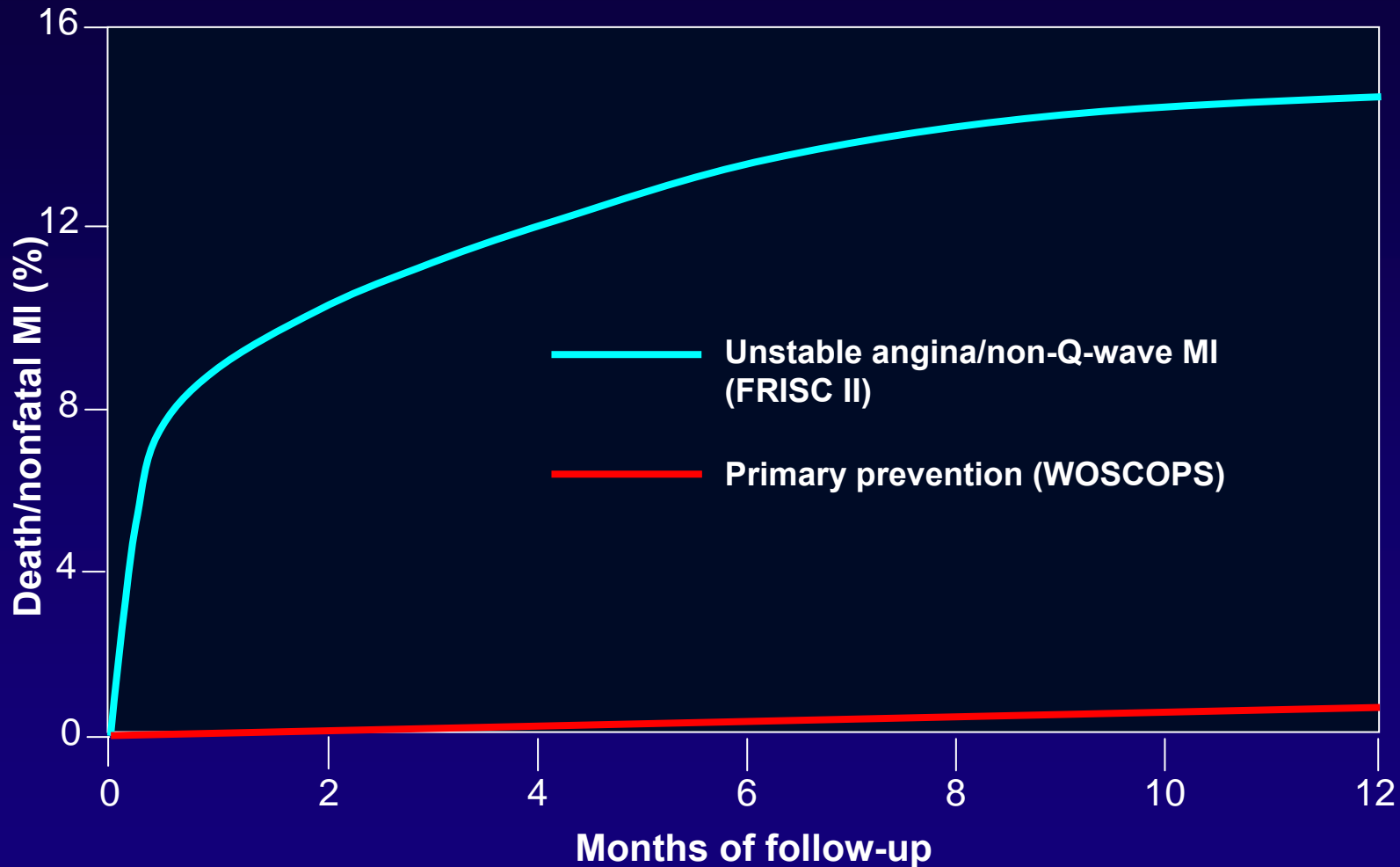
³ Sacks FM, et al. *N Engl J Med*. 1996; 335:1001-1009.

⁴ HPS Collaborative Group. *Lancet*. 2002; 360:7-22.

⁵ Shepherd J, et al. *N Engl J Med*. 1995; 333:1301-1307.

⁶ Downs JR, et al. *JAMA*. 1998; 279:1615-1622.

Riesgo y eventos en los estudios de prevencion 1^a y enfermedad coronaria estable e inestable



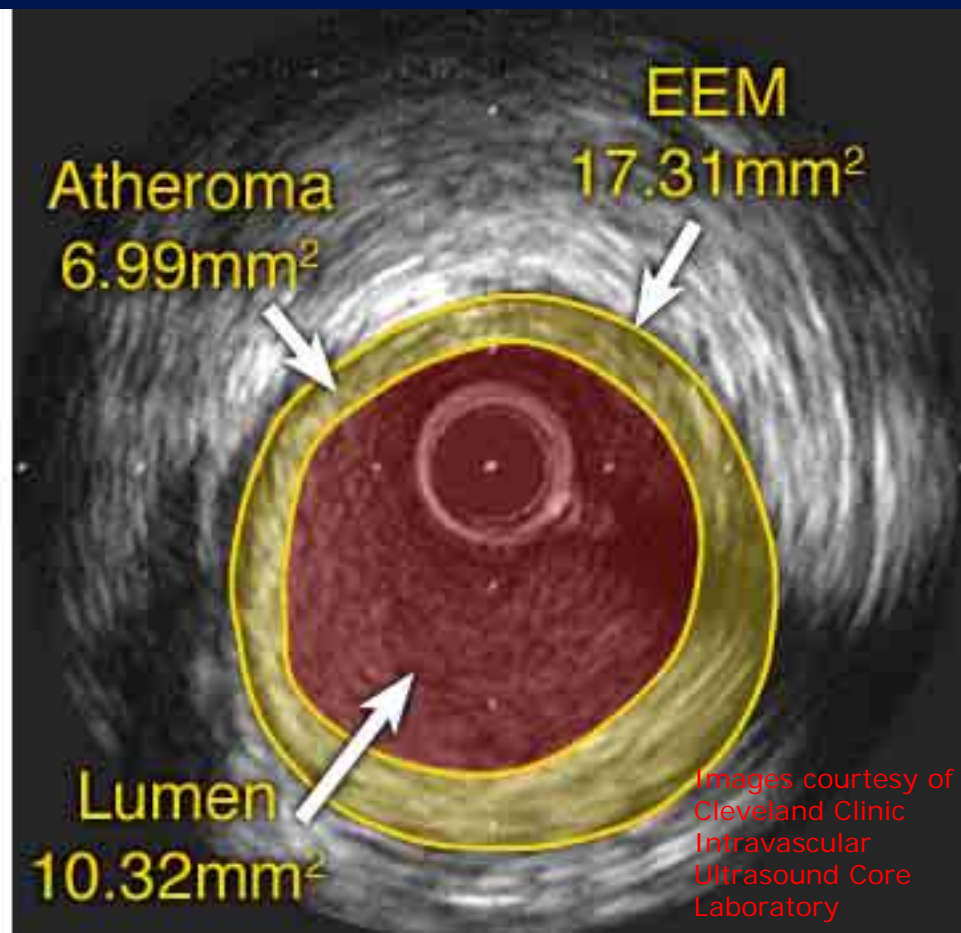
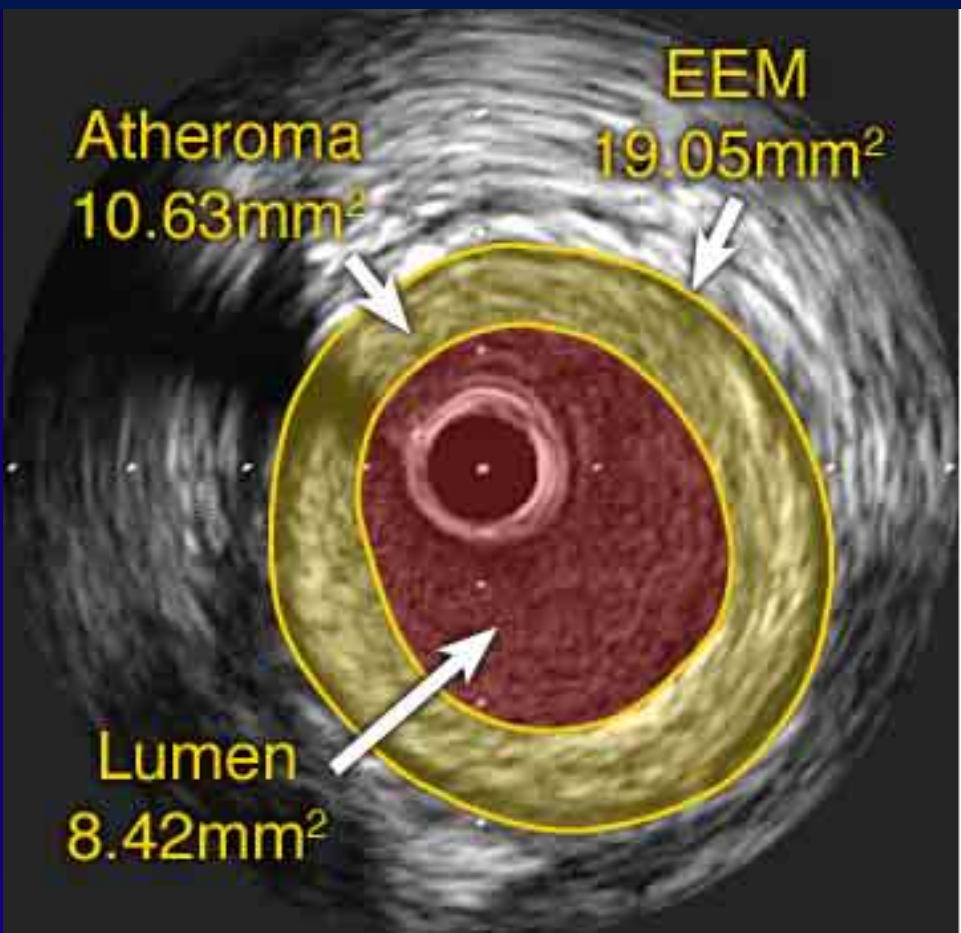
Wallentin L *et al. Lancet* 2000;**356**:9–16.

Juul-Moller S *et al. Lancet* 1992;**340**:1421–1425.

Shepherd J *et al. N Engl J Med* 1995;**333**:1301–1307.

Cambios en la Placa aterosclerótica en las imágenes por US-IV

Inicial y los de 2 años de Intervención



Images courtesy of
Cleveland Clinic
Intravascular
Ultrasound Core
Laboratory

Evidencias Post ATP III: Como seguimos ?

- ATP III: Riesgo x Framingham
- Tratamiento dirigido a todos los FR-CV ?
- Aterosclerosis Subclinica y marcadores ?
- Costos, genericos ?
- Nuevos scores de riesgo
- Casos especiales, HDL
- Regresion en carotidas
- Nuevos FRCV

Exposicion a FR-CV: tiempo y consecuencias

