TRATAMIENTO DE LA HIPERCOLESTEROLEMIA Y COMPLICACIONES

Real Academia de la Medicina de la Comunidad Valenciana
Colegio Oficial de Médicos de Alicante
Alicante 13.03.2014

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Reducción de mortalidad coronaria atribuible al tratamiento vs prevención

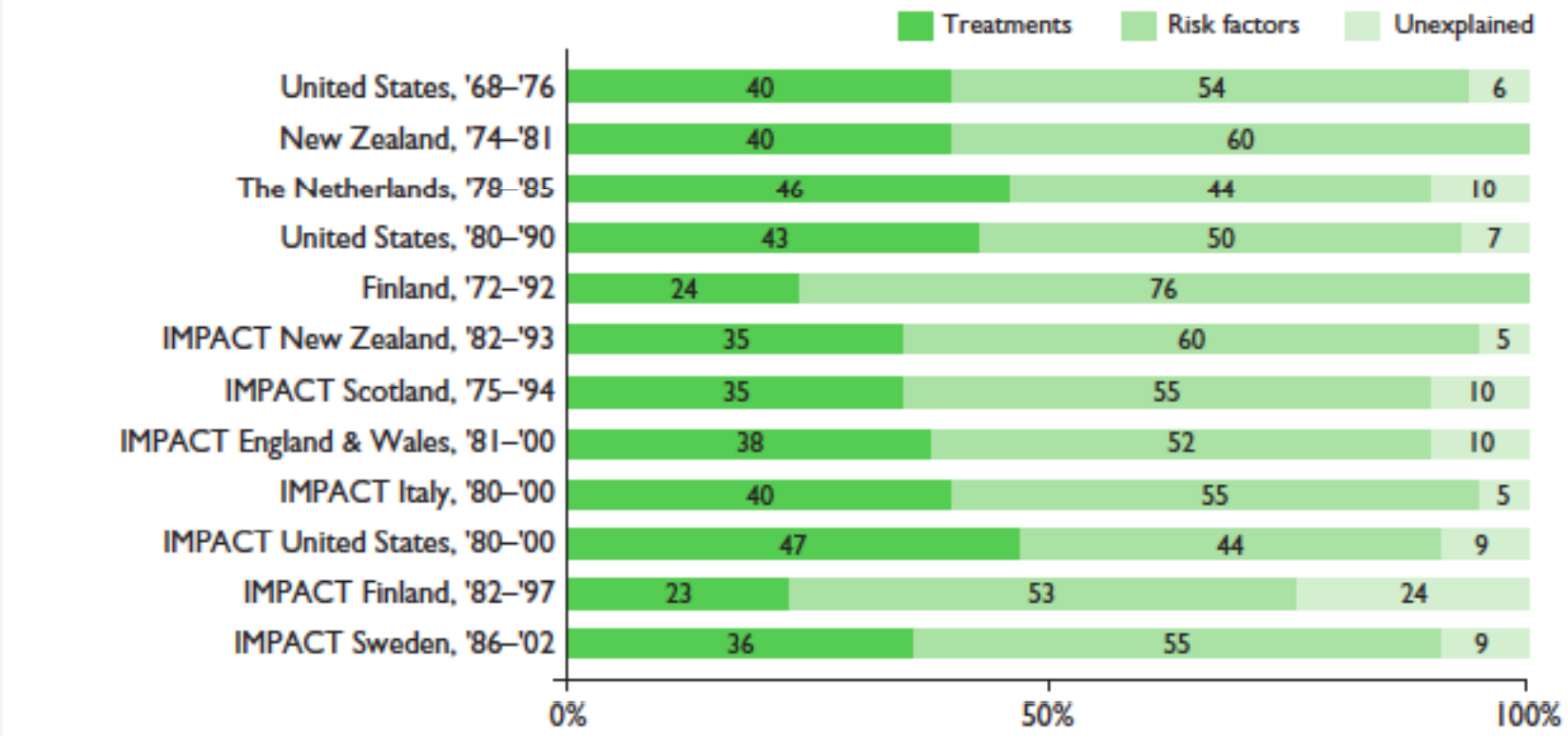
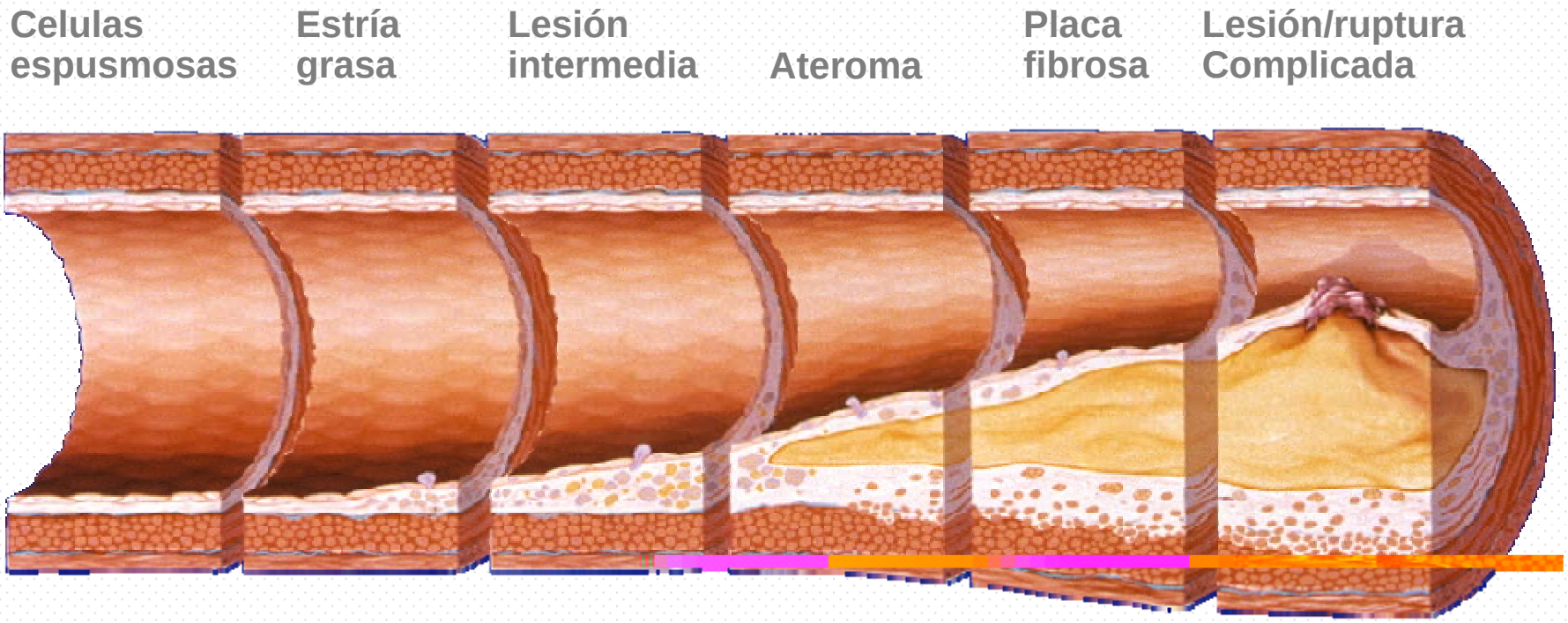


Figure 1 Percentage of the decrease in deaths from coronary heart disease attributed to treatments and risk factor changes in different populations (adapted from Di Chiara *et al*[31])

Desarrollo de la placa.

"De la disfunción endotelial a la ruptura"



¿ A QUIEN TRATAR ?

European Heart Journal
doi:10.1093/eurheartj/ehs092

European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)

Recommendations regarding risk estimation

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Total risk estimation using multiple risk factors (such as SCORE) is recommended for asymptomatic adults without evidence of CVD.	I	C	Strong	36
High-risk individuals can be detected on the basis of established CVD, diabetes mellitus, moderate to severe renal disease, very high levels of individual risk factors, or a high SCORE risk, and are a high priority for intensive advice about all risk factors.	I	C	Strong	36,37

CVD = cardiovascular disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

European Heart Journal
doi:10.1093/eurheartj/ehs092

European G… r disease prevention i… 2012)

Recommendations regarding other diseases with increased risk for cardiovascular disease

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
In patients with chronic kidney disease, risk factors have to be attended to in the same way as for very high-risk persons.	I	C	Strong	165, 166
All persons with obstructive sleep apnoea should undergo medical assessment, including risk stratification and risk management.	IIa	A	Strong	167, 168
All men with erectile dysfunction should undergo medical assessment, including risk stratification and risk management.	IIa	B	Strong	169

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

European Heart Journal
doi:10.1093/eurheartj/ehs092

European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)

Recommendations for genetic testing

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
DNA-based tests for common genetic polymorphisms do not presently add significantly to diagnosis, risk prediction, or patient management and cannot be recommended.	III	B	Strong	71
The added value of genotyping, as an alternative or in addition to phenotyping, for a better management of risk and early prevention in relatives, cannot be recommended.	III	B	Strong	72

Recommendations for thrombotic biomarkers

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Homocysteine may be measured as part of a refined risk assessment in patients with an unusual or moderate CVD risk profile.	IIb	B	Weak	120
Homocysteine should not be measured to monitor CVD risk prevention.	III	B	Strong	128
LpPLA2 may be measured as part of a refined risk assessment in patients at high risk of a recurrent acute atherothrombotic event.	IIb	B	Weak	129

CVD, cardiovascular disease; LpPLA2 = lipoprotein-associated phospholipase.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

European Heart Jour
doi:10.1093/eurheartj

JOINT ESC GUIDELINES

European G … prevention i … ar disease … n 2012)

Recommendations for inflammatory biomarkers

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
High-sensitivity CRP may be measured as part of refined risk assessment in patients with an unusual or moderate CVD risk profile.	IIb	B	Weak	125
High-sensitivity CRP should not be measured in asymptomatic low-risk individuals and high-risk patients to assess 10-year risk of CVD.	III	B	Strong	126
Fibrinogen may be measured as part of refined risk assessment in patients with an unusual or moderate CVD risk profile.	IIb	B	Weak	127
Fibrinogen should not be measured in asymptomatic low-risk individuals and high-risk patients to assess 10-year risk of CVD.	III	B	Strong	127

CRP = C-reactive protein; CVD, cardiovascular disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

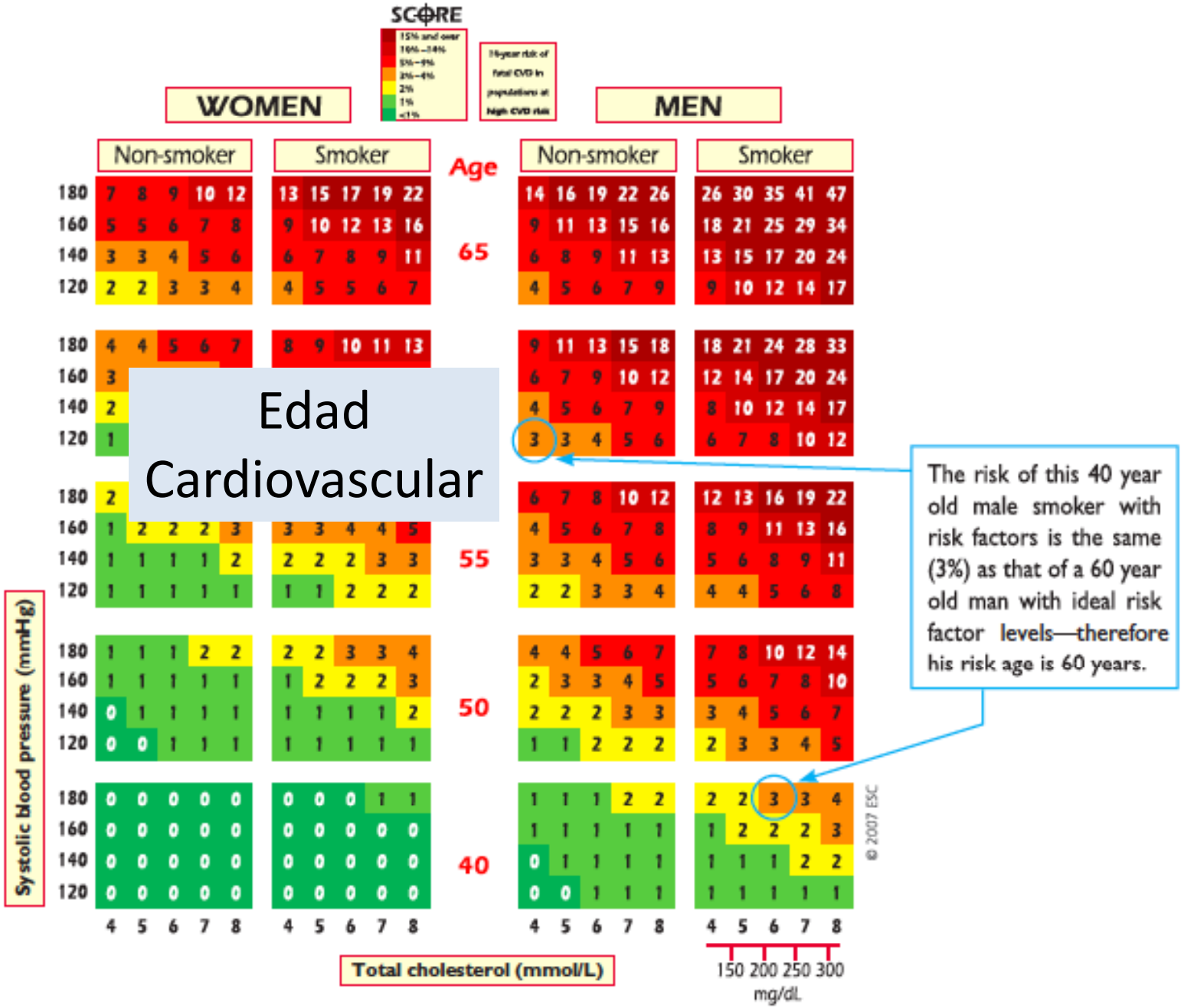


Figure 6 Illustration of the risk–age concept.

¿ COMO TRATAR ?

DISLIPEMIA

European Heart Journal (2011) **32**, 1769–1818
doi:10.1093/eurheartj/ehr158

ESC/EAS GUIDELINES

ESC/EAS Guidelines for the management of dyslipidaemias

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

DISLIPEMIA

Importante evaluar el riesgo cardiovascular global del paciente teniendo en cuenta todos los factores (no sólo las tablas de score).

Table 3 Intervention strategies as a function of total CV risk and LDL-C level

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.5 mmol/L	100 to <155 mg/dL 2.5 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	>190 mg/dL >4.9 mmol/L
<1	No lipid intervention	No lipid intervention	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
>5 to <10, or high risk	Lifestyle intervention, consider drug*	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high risk	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

European Heart Journal
doi:10.1093/eurheartj/ehs092

European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)

- Parámetros a medir: CT, LDL, TG y HDL.
- Objetivo principal: LDL.
  - Pacientes de muy alto riesgo: <70 mg/dl (nivel de evidencia IA) .
  - Pacientes de alto riesgo: <100 mg/dl (IIaA).
  - Pacientes de riesgo moderado: <115 mg/dl (IIaC).

Reducción al menos del 50% de los niveles basales.

- Relevancia de medidas higiénico-dietéticas:
  - Mejoría de los parámetros lipídicos.
  - Beneficios sobre PA y glucemia.
  - Mejoras en calidad de vida y percepción de la enfermedad.

Table 14 Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class[a]	Level[b]	Ref[c]
Prescribe statin up to the highest recommended dose, or highest tolerable dose to reach the target level.	I	A	15, 16, 17
In the case of statin intolerance, bile acid sequestrants or nicotinic acid should be considered	IIa	B	108, 120
A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid, may also be considered in the case of statin intolerance.	IIb	C	-
If target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered.	IIb	C	-

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

- Las estatinas son los fármacos que mejor se han relacionado con la disminución de colesterol total y LDL.

- Por cada ↓ de 40 mg/dl de LDL se consigue una reducción del 22% de la morbimortalidad.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Niacin in Patients with Low HDL Cholesterol

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Niacin at 56 Years of Age — Time for an Early Retirement?

Robert P. Giugliano, M.D., S.M.

No. at Risk					
Placebo plus statin	1696	1581	1381	910	436
Niacin plus statin	1718	1606	1366	903	428

Figure 1. Kaplan–Meier Curve for the Primary End Point.

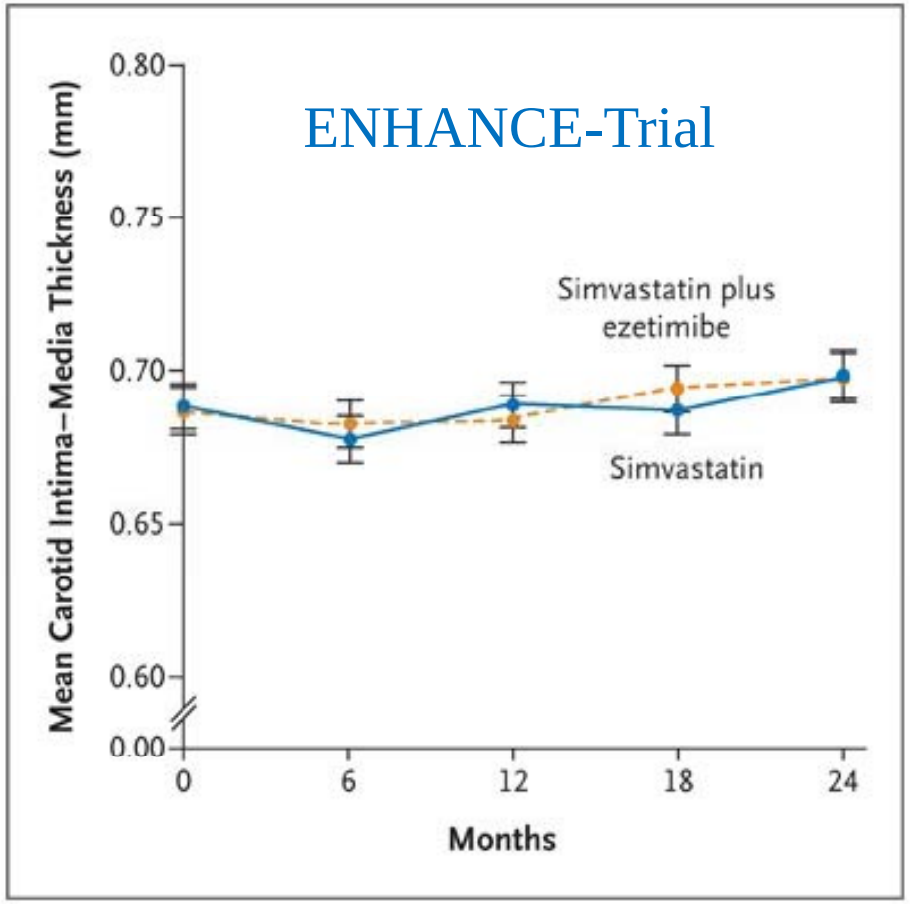
N Engl J Med. 2011 Nov 15.

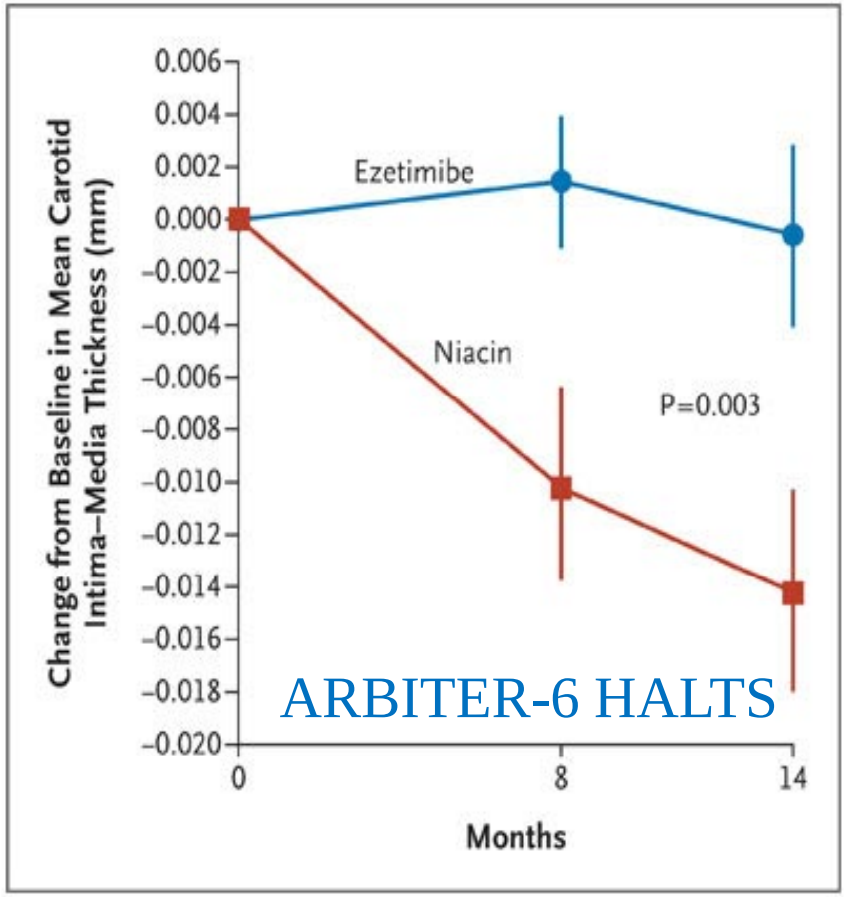
Acerca del Estudio HPS2-THRIVE

la adición de la combinación de ácido nicotínico de liberación modificada y laropiprant al tratamiento con estatinas ***no produjo una reducción adicional significativa*** del riesgo de la combinación de muertes coronarias, fallos cardiacos no mortales, ictus o revascularizaciones en comparación con el tratamiento solamente con estatinas. Además, hubo un ***aumento estadísticamente significativo en la incidencia de algunos tipos de acontecimientos adversos graves no mortales*** en el grupo que recibió ácido nicotínico de liberación modificada y laropiprant.

MSD recomienda que los médicos ***dejen de recetar TREDAPTIVE***. MSD también recomienda que a su debido tiempo, los médicos revisen los planes de tratamiento de los pacientes que están tomando TREDAPTIVE para ***suspender el tratamiento con TREDAPTIVE***

Intima-Media Thickness of the Carotid Artery during 24 and 14 Months of Therapy

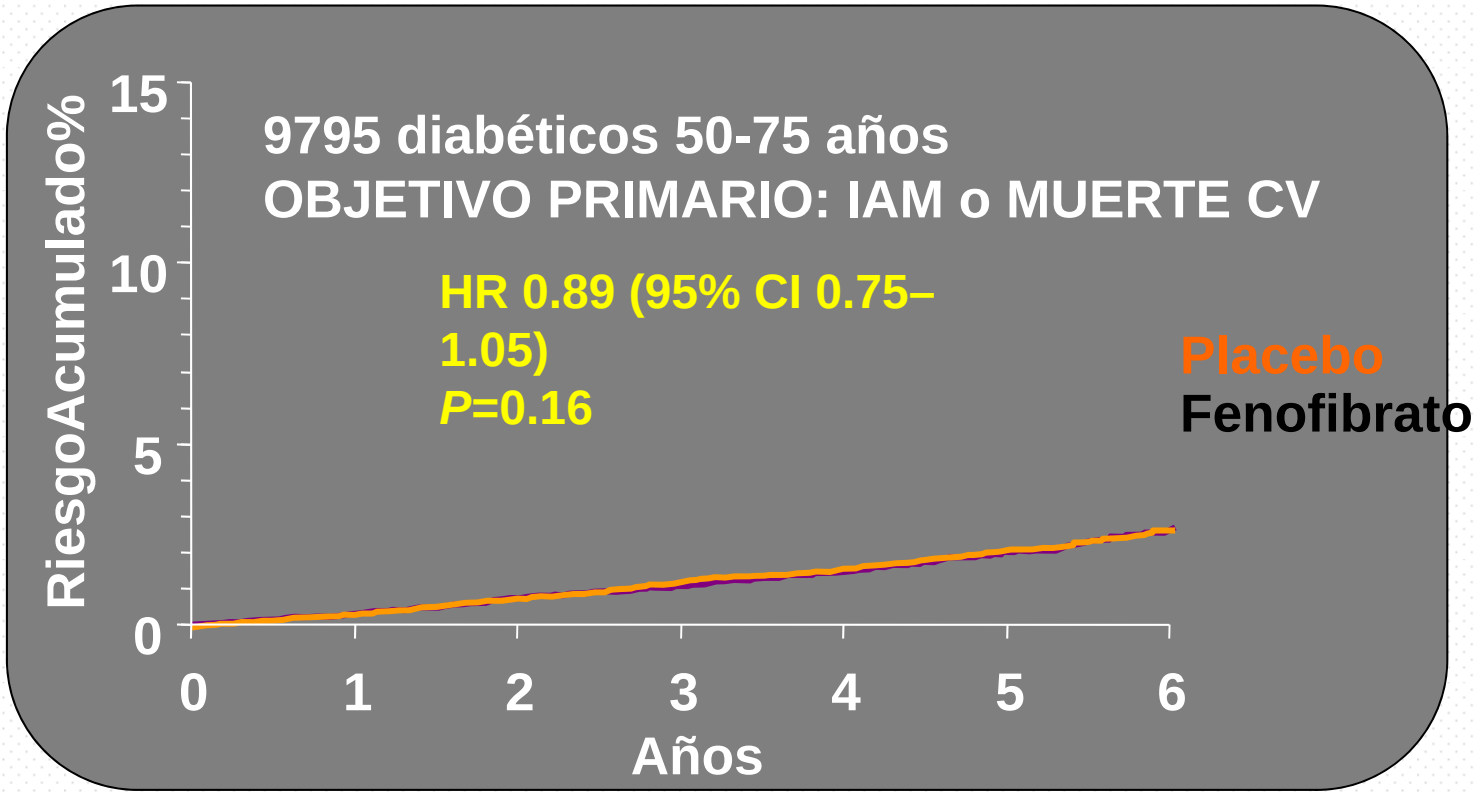




Kastelein J et al. N Engl J Med 2008;358:1431-1443

Taylor A et al. N Engl J Med 2009;361:2113-2122

Fibratos: Estudio FIELD



FIELD, Lancet. 2005;366:1849–1861.

COMBINACIONES: ESTATINA + FIBRATO

The NEW ENGLAND JOURNAL of MEDICINE

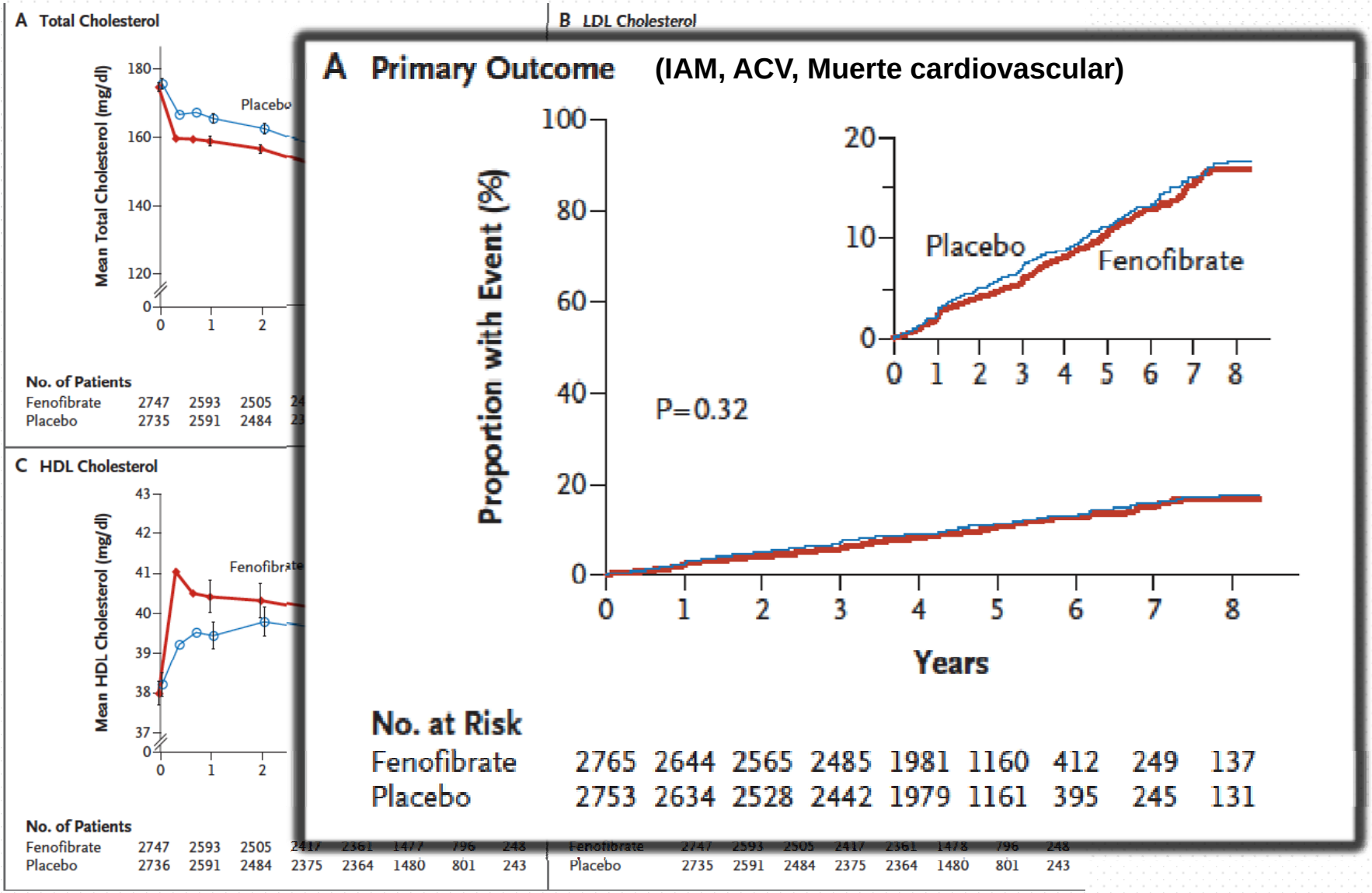
ORIGINAL ARTICLE

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

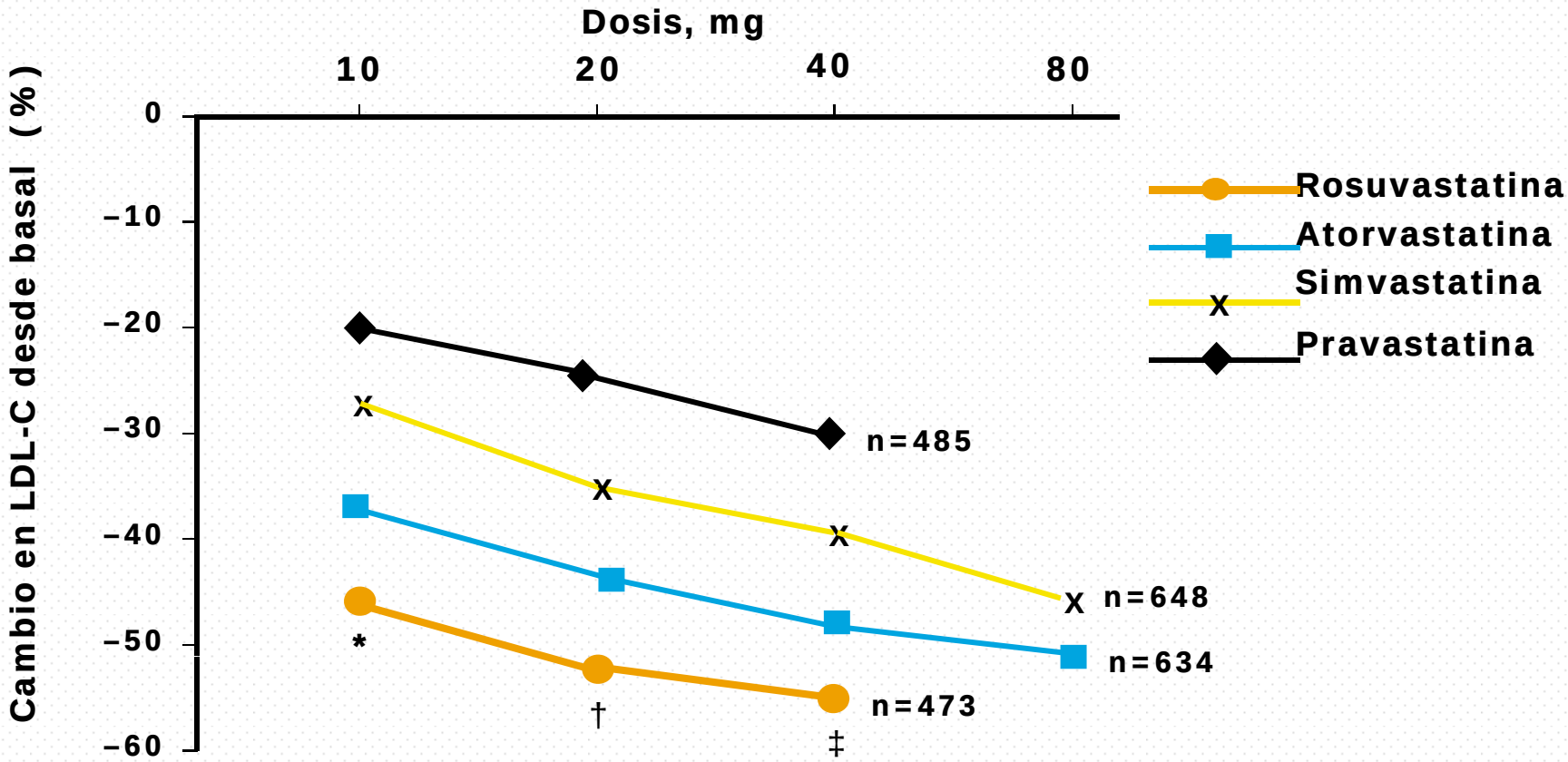
The ACCORD Study Group*

- 5518 pacientes con DM2, (36,5% con enfermedad CV previa).
- LDL 60-180 mg/dl y HDL < 50 mg/dl (varones)/ 55 mg/dl (mujeres)
- Simvastatina vs Simvastatina + Fenofibrato
- Seguimiento medio 4,7 años

RESULTADOS


A Total Cholesterol
Mean Total Cholesterol (mg/dl)
Placebo
No. of Patients
Fenofibrate 2747 2593 2505
Placebo 2735 2591 2484
B LDL Cholesterol
C HDL Cholesterol
Mean HDL Cholesterol (mg/dl)
Fenofibrate
No. of Patients
Fenofibrate 2747 2593 2505 2417 2361 1477 796 248
Placebo 2736 2591 2484 2375 2364 1480 801 243
A Primary Outcome (IAM, ACV, Muerte cardiovascular)
Proportion with Event (%)
P=0.32
Placebo
Fenofibrate
Years
No. at Risk
Fenofibrate 2765 2644 2565 2485 1981 1160 412 249 137
Placebo 2753 2634 2528 2442 1979 1161 395 245 131

Estudio STELLAR . LDL-C



*p<0.002 vs atorvastatin 10 mg; simvastatin 10, 20, 40 mg; pravastatin 10, 20, 40 mg
†p<0.002 vs atorvastatin 20, 40 mg; simvastatin 20, 40, 80 mg; pravastatin 20, 40 mg
‡p<0.002 vs atorvastatin 40 mg; simvastatin 40, 80 mg; pravastatin 40 mg

Jones P et al. Am J Cardiol 2003;92:152–160

ESTATINAS Y DIABETES

Lancet 2010; 375: 735–42

Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

Naveed Sattar, David Preiss, Heather M Murray, Paul Welsh, Brendan M Buckley, Anton J M de Craen, Sreenivasa Rao Kondapally Seshasai, John J McMurray, Dilys J Freeman, J Wouter Jukema, Peter W Macfarlane, Chris J Packard, David J Stott, Rudi G Westendorp, James Shepherd, Barry R Davis, Sara L Pressel, Roberto Marchioli, Rosa Maria Marfisi, Aldo P Maggioni, Luigi Tavazzi, Gianni Tognoni, John Kjekshus, Terje R Pedersen, Thomas J Cook, Antonio M Gotto, Michael B Clearfield, John R Downs, Haruo Nakamura, Yasuo Ohashi, Kyoichi Mizuno, Kausik K Ray, Ian Ford

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http://dx.doi.org/10.1016/j.jacc.2012.05.019

Cardiometabolic Risk

Statins, Risk of Diabetes, and Implications on Outcomes in the General Population

Journal of the American College of Cardiology
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http://dx.doi.org/10.1016/j.jacc.2012.09.042

Cardiovascular Event Reduction Versus New-Onset Diabetes During Atorvastatin Therapy

Effect of Baseline Risk Factors for Diabetes

David D. Waters, MD,* Jennifer E. Ho, MD,† S. Matthijs Boekholdt, MD, PHD,‡ David A. DeMicco, DPHARM,§ John J. P. Kastelein, MD, PHD,‡ Michael Messig, PHD,§ Andrei Breazna, PHD,§ Terje R. Pedersen, MD, PHD‖

San Francisco, California; Framingham, Massachusetts; Amsterdam, the Netherlands; New York, New York; and Oslo, Norway

Riesgo de nueva diabetes

1) HTA
2) Glucemia >100 mg/dl
3) IMC >30 kg/m2
4) Triglicéridos >150 mg/dl

Waters DD, et al. J Am Coll Cardiol 2013;61:148-52

CONCLUSIONES

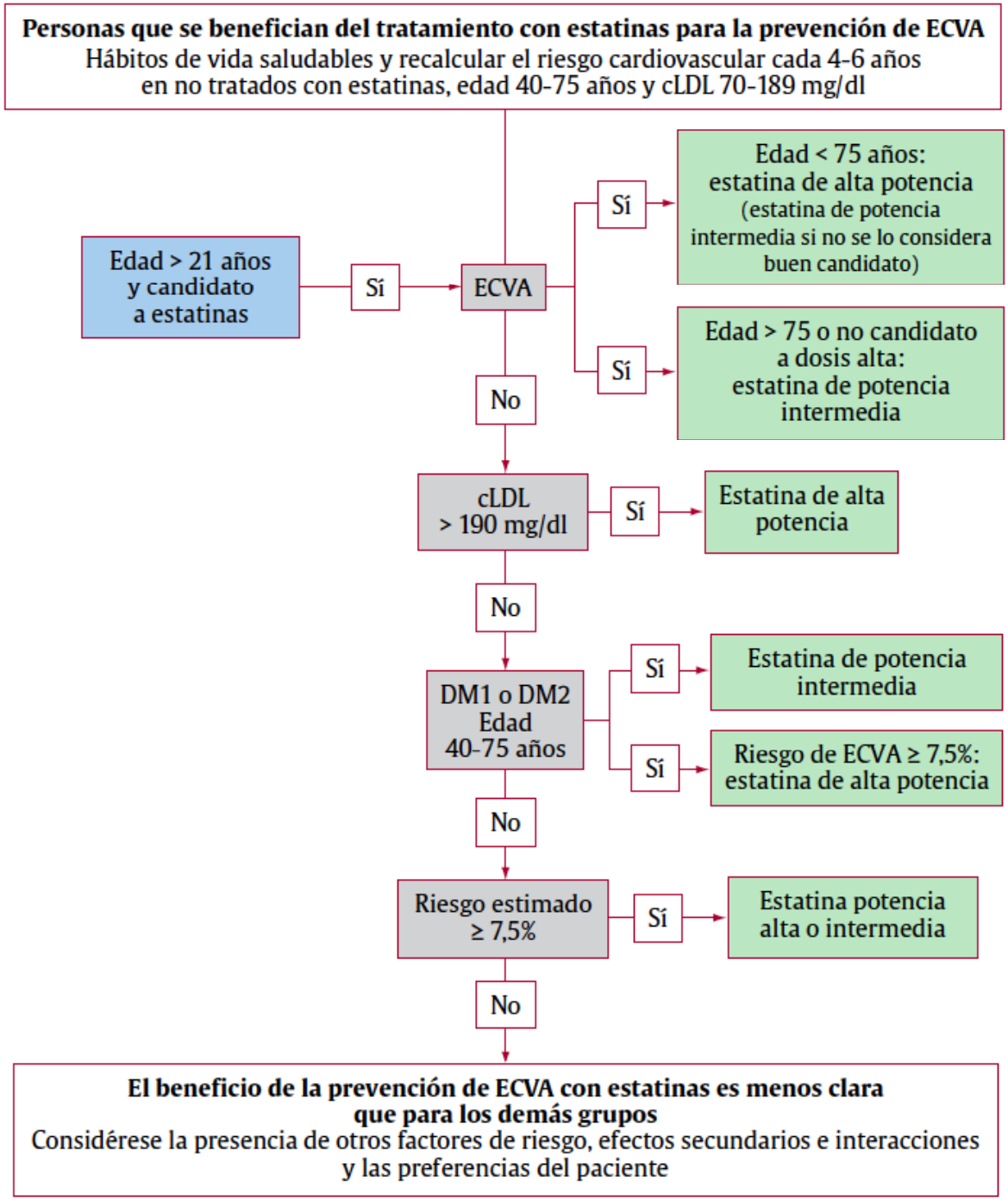
En los pacientes con bajo riesgo de desarrollar DM, la dosis alta de ATOR no aumentó la incidencia de DM y si redujo la aparición de complicaciones cardiovasculares.

En los pacientes de alto riesgo, la dosis máxima de ATOR si aumentó el riesgo de nueva DM en un 24% pero redujo en un 18% la aparición de complicaciones CV.

Waters DD, et al. J Am Coll Cardiol 2013;61:148-52

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

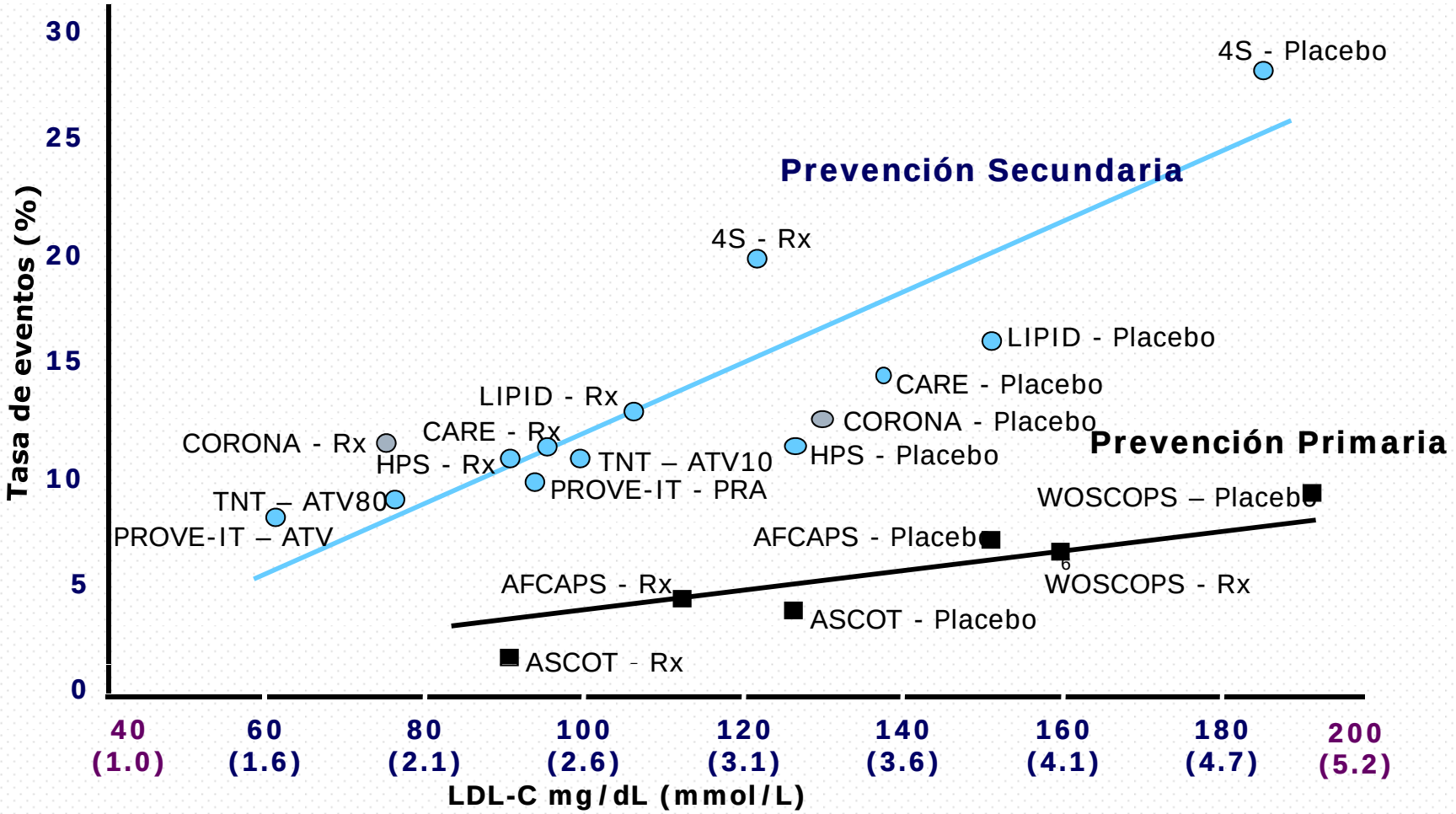
Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease


Personas que se benefician del tratamiento con estatinas para la prevención de ECVA
Hábitos de vida saludables y recalcular el riesgo cardiovascular cada 4-6 años
en no tratados con estatinas, edad 40-75 años y cLDL 70-189 mg/dl
Edad > 21 años y candidato a estatinas
Sí
ECVA
Sí
Edad < 75 años: estatina de alta potencia (estatina de potencia intermedia si no se lo considera buen candidato)
Sí
Edad > 75 o no candidato a dosis alta: estatina de potencia intermedia
No
cLDL > 190 mg/dl
Sí
Estatina de alta potencia
No
DM1 o DM2 Edad 40-75 años
Sí
Estatina de potencia intermedia
Sí
Riesgo de ECVA ≥ 7,5%: estatina de alta potencia
No
Riesgo estimado ≥ 7,5%
Sí
Estatina potencia alta o intermedia
No
El beneficio de la prevención de ECVA con estatinas es menos clara que para los demás grupos
Considérese la presencia de otros factores de riesgo, efectos secundarios e interacciones y las preferencias del paciente

Tratamiento intensivo	Potencia intermedia	Potencia baja
Reducción de cLDL ≥ 50%	Reducción de cLDL 30-50%	Reducción de cLDL < 30%
Atorvastatina (40) 80 mg Rosuvastatina 20-40 mg	Atorvastatina 10 (20) mg Rosuvastatina (5) 10 mg Simvastatina 20-40 mg Pravastatina 40 (80) mg Lovastatina 40 mg Fluvastatina 40-80 mg Pitavastatina 2-4 mg	Simvastatina 10 mg Pravastatina 10-20 mg Lovastatina 20 mg Fluvastatina 20-40 mg Pitavastatina 1 mg

cLDL: colesterol unido a lipoproteínas de baja densidad.
Los valores entre paréntesis cuentan con datos indirectos de estudios clínicos.

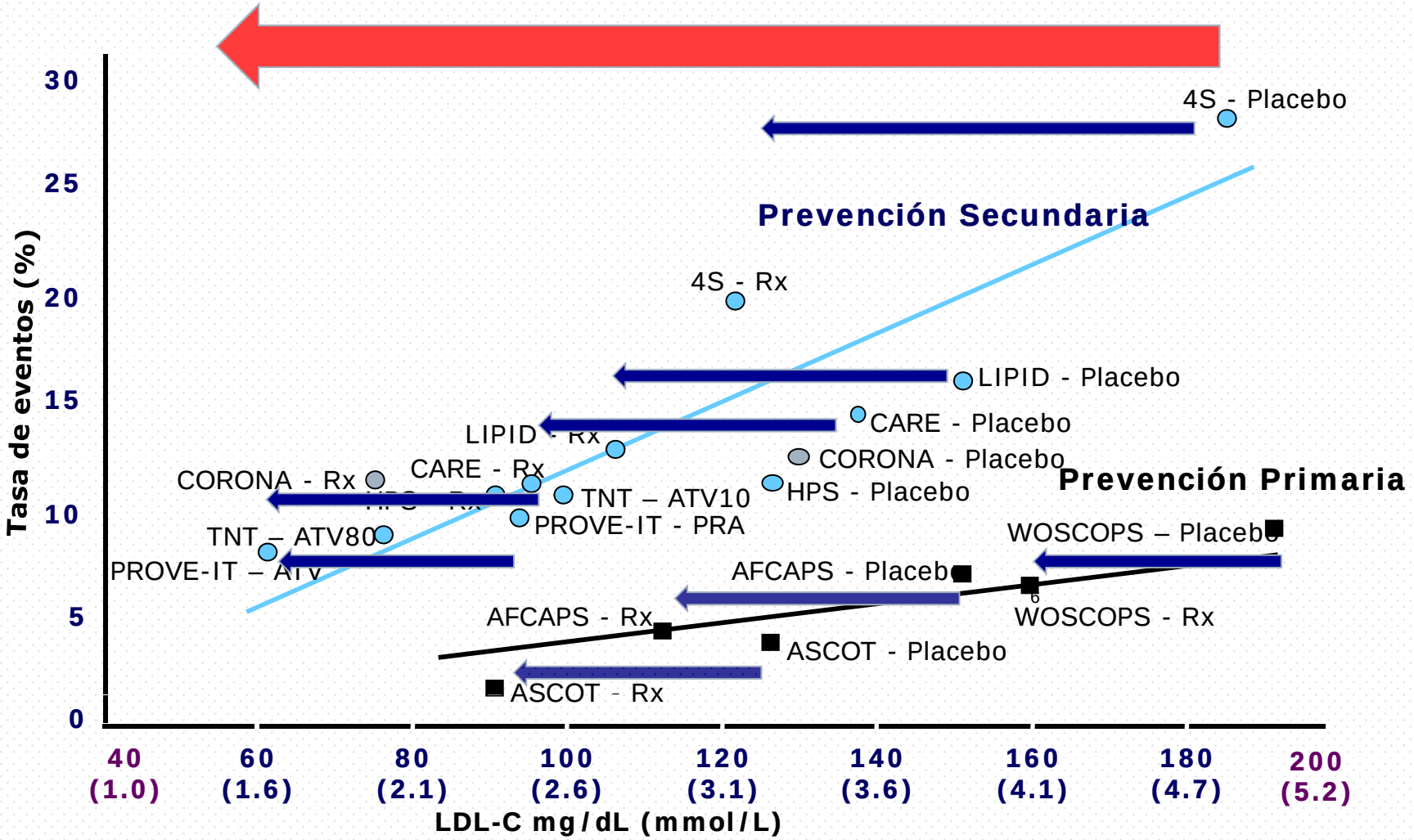
Nivel de LDL-C y eventos CV



Adapted from Rosensen RS. *Exp Opin Emerg Drugs* 2004;**9**(2):269-279

LaRosa JC *et al. N Engl J Med* 2005;**352**:1425-1435

Nivel de LDL-C y eventos CV



Adapted from Rosensen RS. *Exp Opin Emerg Drugs* 2004;**9**(2):269-279

LaRosa JC *et al. N Engl J Med* 2005;**352**:1425-1435

Los pacientes que recibían estatinas, a pesar de ya tener un LDL bajo, tenían mejores tasas de eventos cardiacos mayores.

- Pacientes post-IAM con LDL <70 mg/dl.

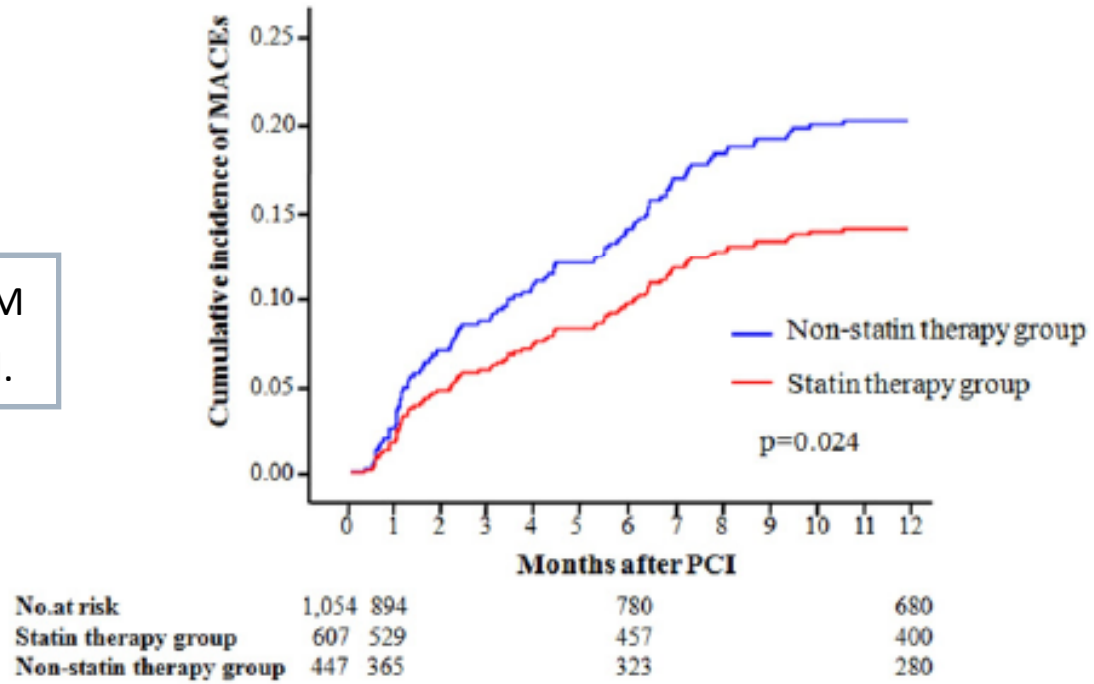


Figure 1 **Estimates of the Rate of the Primary Endpoint Events**

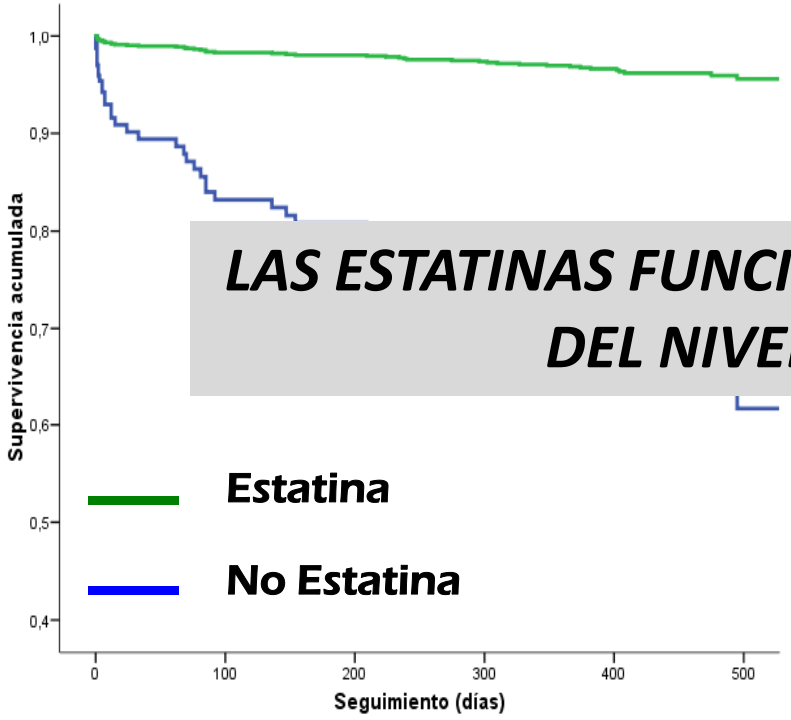
The primary endpoint was the composite of death, recurrent myocardial infarction, and coronary revascularization. MACE = major adverse cardiac event(s); PCI = percutaneous coronary intervention.

HK Lee et al. Benefit of early statin therapy in patients with acute myocardial infarction who have extremely low low-density lipoprotein cholesterol. J Am Coll Cardiol 2011;58:1664-1671.

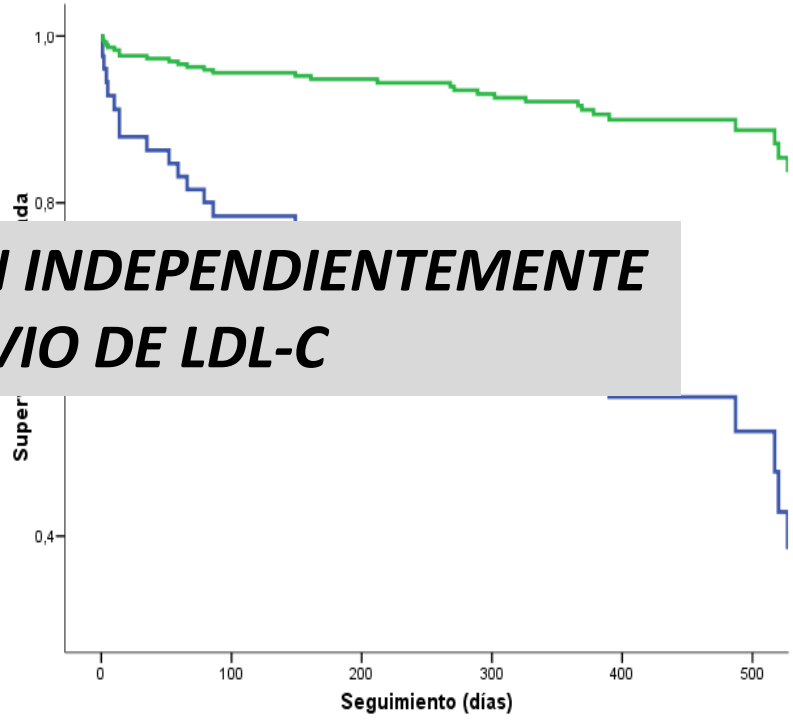
Beneficio de las estatinas en todos los pacientes tras un SCA

Mortalidad por cualquier causa

cLDL >70 mg/dl



cLDL <70 mg/dl



LAS ESTATINAS FUNCIONAN INDEPENDIENTEMENTE DEL NIVEL PREVIO DE LDL-C

Cordero A, et al.Rev Esp Cardiol 2013

HDL: principal determinante del SCA

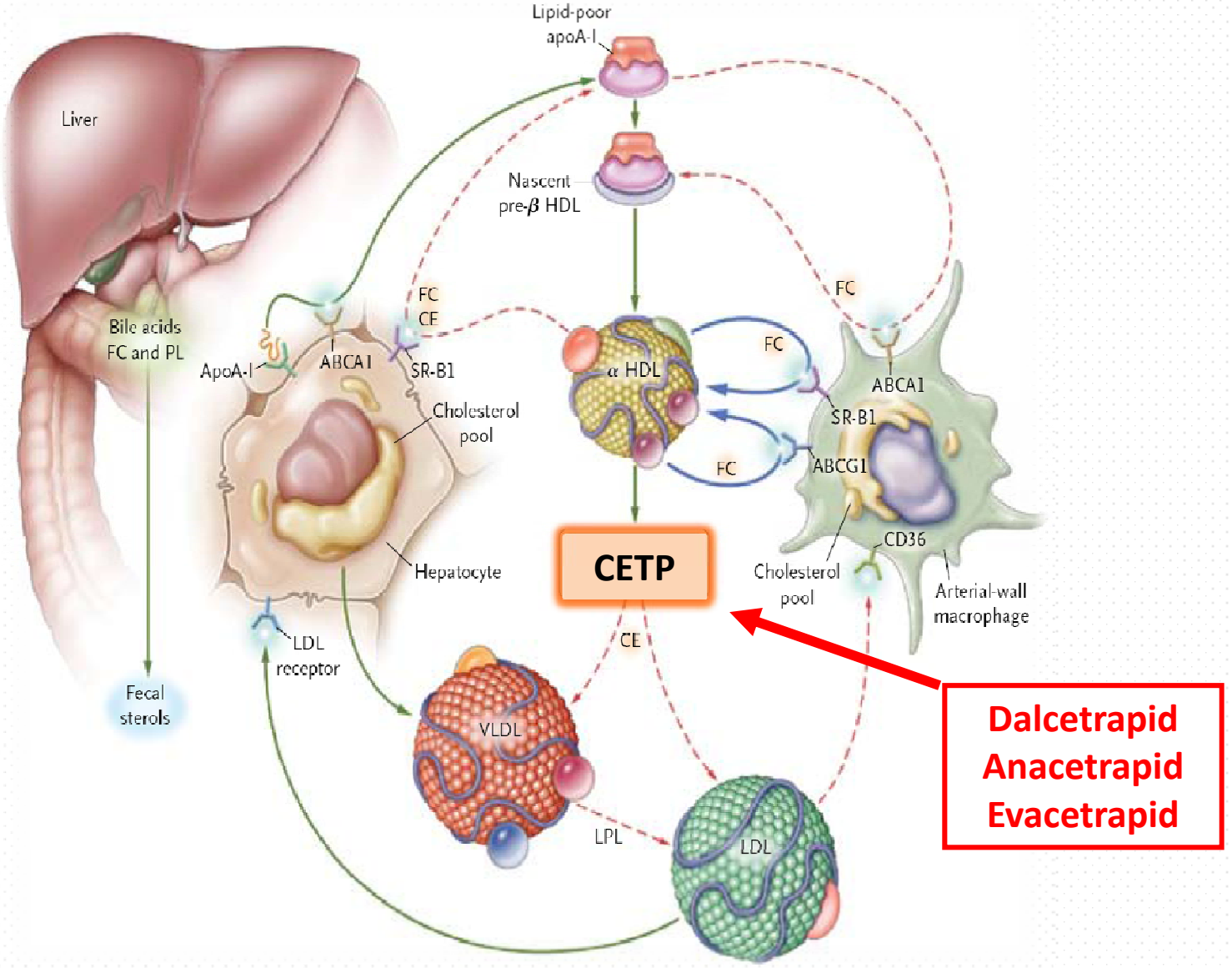
Determinantes bioquímicos de SCA vs. DT no *isquémico*

Variables	OR	IC 95%	p
Sexo femenino	0,36	0,23 - 0,57	<0,01
Fibrilación auricular	0,27	0,14 - 0,52	<0,01
Edad	1,05	1,03 - 1,06	<0,01
Tabaquismo activo	1,73	1,00 - 2,99	0,05
Diabetes	1,75	1,10 - 2,80	0,02
Glucemia >100 mg/dl	1,89	1,22 - 2,94	<0,01
HDL < 40 mg/dl	2,99	1,95 - 4,59	<0,01

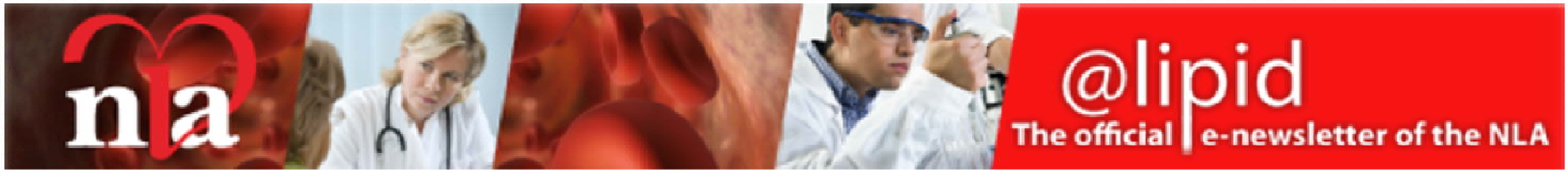
Cordero A, Bertomeu V, et al. Rev Esp Cardiol; 2012:65:319-25

¿ FUTURO ?

2. ↑ HDL-c: Inhibición de CETP



2. ↑ HDL-c: Inhibición de CETP

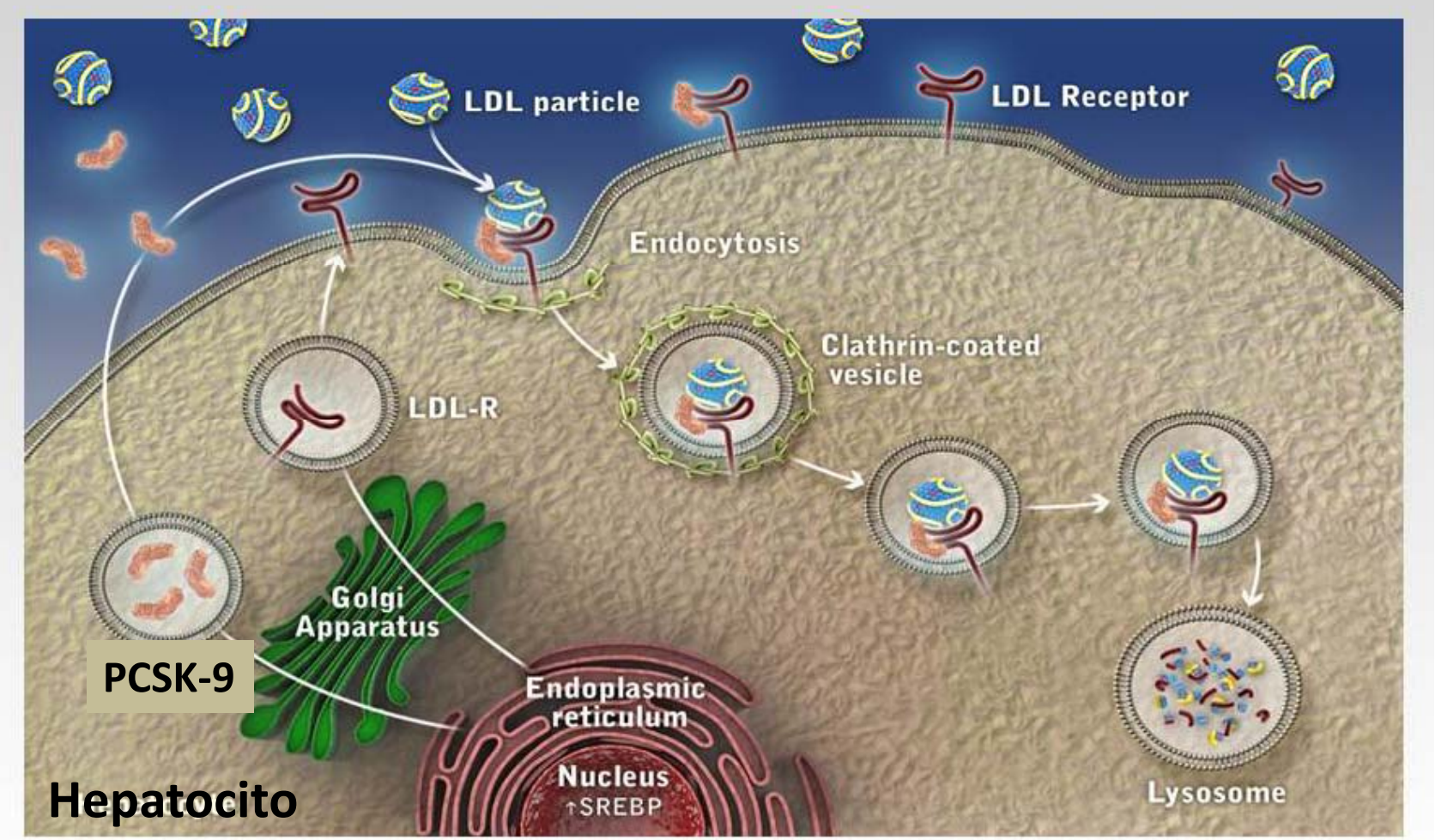


Joint Statement by EAS, IAS and the NLA on CETP Inhibition and HDL

On May 6, the decision was made to halt a late-stage trial of dalcetrapib, an experimental cholesterol drug intended to boost high density lipoprotein-cholesterol (HDL-C). A late-stage study, the dal-OUTCOMES Phase III trial, showed that dalcetrapib was not working effectively. The below statement provides the joint response from the European Atherosclerosis Society (EAS), International Atherosclerosis Society (IAS) and the National Lipid Association (NLA).

The development of dalcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, was terminated on May 6, 2012 by Hoffman-La Roche (Genentech) after its Phase III dal-OUTCOMES trial in acute coronary syndrome patients failed to demonstrate a significant reduction in cardiovascular adverse events.[1] In contrast to the earlier CETP inhibitor, torcetrapib, no safety concerns were reported.

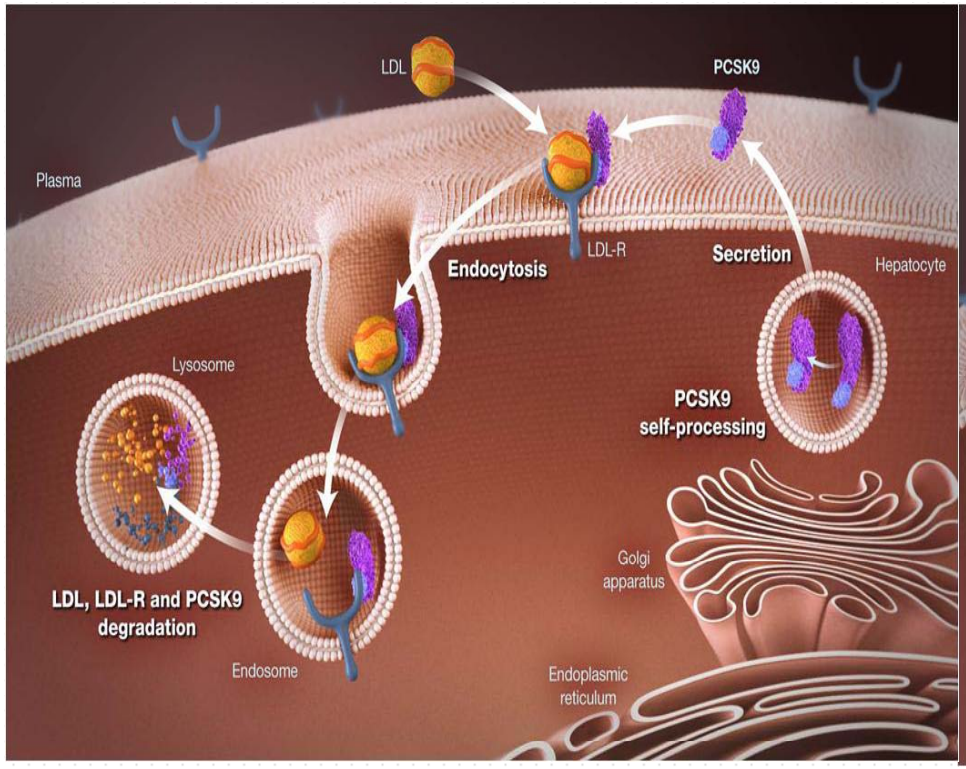
6. ↓LDL-c: Inhib. degradación LDL-R



McKenney J, et al. ACC 2012

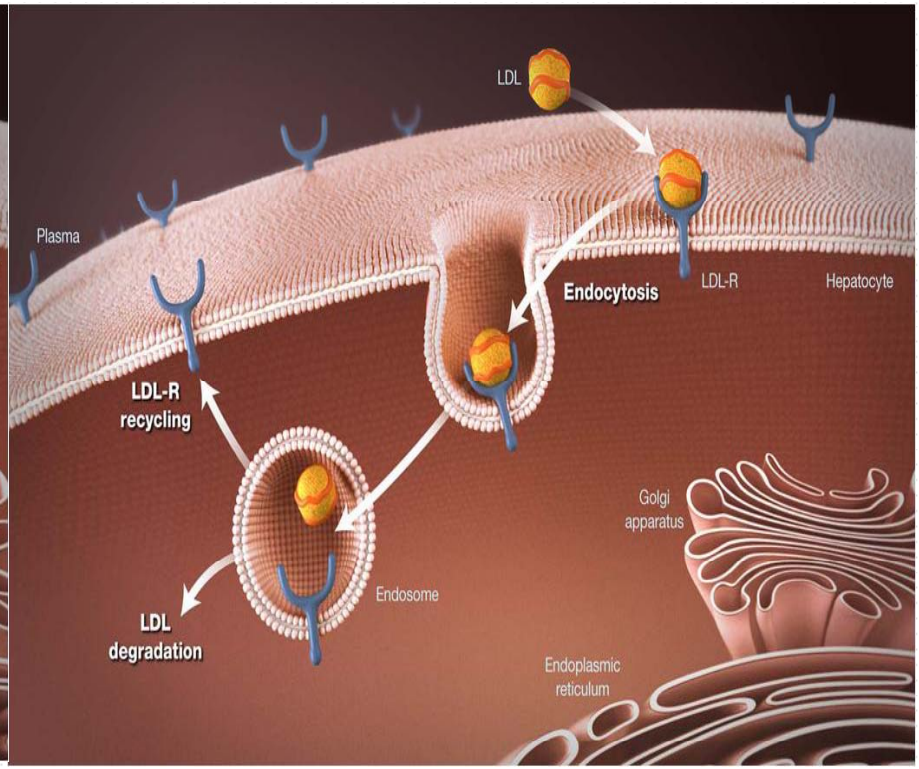
6. ↓LDL-c: Inhib. Degradación LDL-R

Presencia de PCSK9



- Menos LDL-Receptor
- LDL-C sérico alto

Ausencia de PCSK9



- Más LDL-Receptor
- LDL-C sérico bajo

Abifadel M, et al. Nature Genet 2003; 34:154-156

6. ↓LDL-c: Inhib. Degradación LDL-R

Cambio en LDL-c en 12 semanas

Intervention	Baseline LDL-C (mg/dL)	% Change LDL-C*
Placebo	130.2	-5.1 (3.1)
SAR236553 50 mg every 2 weeks	123.2	-39.6 (3.2)†
SAR236553 100 mg every 2 weeks	127.0	-64.2 (3.1)†
SAR236553 150 mg every 2 weeks	123.9	-72.4 (3.2)†
SAR236553 200 mg every 4 weeks	128.2	-43.2 (3.3)†
SAR236553 300 mg every 4 weeks	131.6	-47.7 (3.2)†

*Least squares mean (SE), using last observation carried forward method
†$P < .0001$ for % change SAR236553 vs placebo

Stein EA, et al. NEJM 2012;366:1108-18

6. ↓LDL-c: Inhib. Degradación LDL-R

Fármacos en desarrollo

Company	Name of Agent	Stage of Development	Comments
Monoclonal antibodies			
Merck	1D05-IgG	In development	Rhesus monkeys, results presented 2009 AHA
Sanofi/Regeneron	SAR236553/ REGN727 IgG	Phase 2 complete	Results presented 2012 ACC
Pfizer-Rinat	RN316 IgG	Phase 1	
Amgen	mAb1-IgG	In development	Cynomolgus monkeys
Antisense oligonucleotides			
Santaris	SPC5001	In development	
Alnylam	ALN-PCS	In development	Cynomolgus monkeys
BMS-ISIS	BMS-844421	Phase 1	
Adenectin			
BMS-Adnexus	BMS-962476	Preclinical	

McKenney J, et al. ACC 2012

European Heart Journal (2011) 32, 2143–2152
doi:10.1093/eurheartj/ehr080

CLINICAL RESEARCH
Prevention

Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: the EURIKA study

- Ensayo que pretende estudiar el grado de control sobre los FRCV en prevención primaria.
- Realizado en países de toda Europa con datos principalmente extraídos de médicos de atención primaria.
- Resultados:
  - Edad media: 63,2 años. Hombres 48,4%.
  - HTA 72,7%; DM 26,8%; DLP 57,7 %; obesidad 43,6%.
  - Sedentarismo 19,8%.
  - Objetivos:
    - PA <140/90 mmHg (DM: <130/80 mmHg).
    - Colesterol total <190 mg/dl; LDL < 115 mg/dl (DM: <175 mg/dl y <100 mg/dl, respectivamente).
    - HbA1c <6.5%; glucosa en ayunas <110 mg/dl.
    - IMC <30 kg/m2; perímetro cintura <102 cm en hombres y <88 cm en mujeres.

ESTUDIO EURIKA

- Resultados:

FRCV	PACIENTES TRATADOS (%)	OBJETIVO ALCANZADO (% PACIENTES)	
HTA	94,2		
DM2	87,2		
DLP	74,4		
Obesidad	92,2 (cumplen medidas higiénico-dietéticas)		
		Ambas	3,2

ESTUDIO EURIKA

- Resultados:

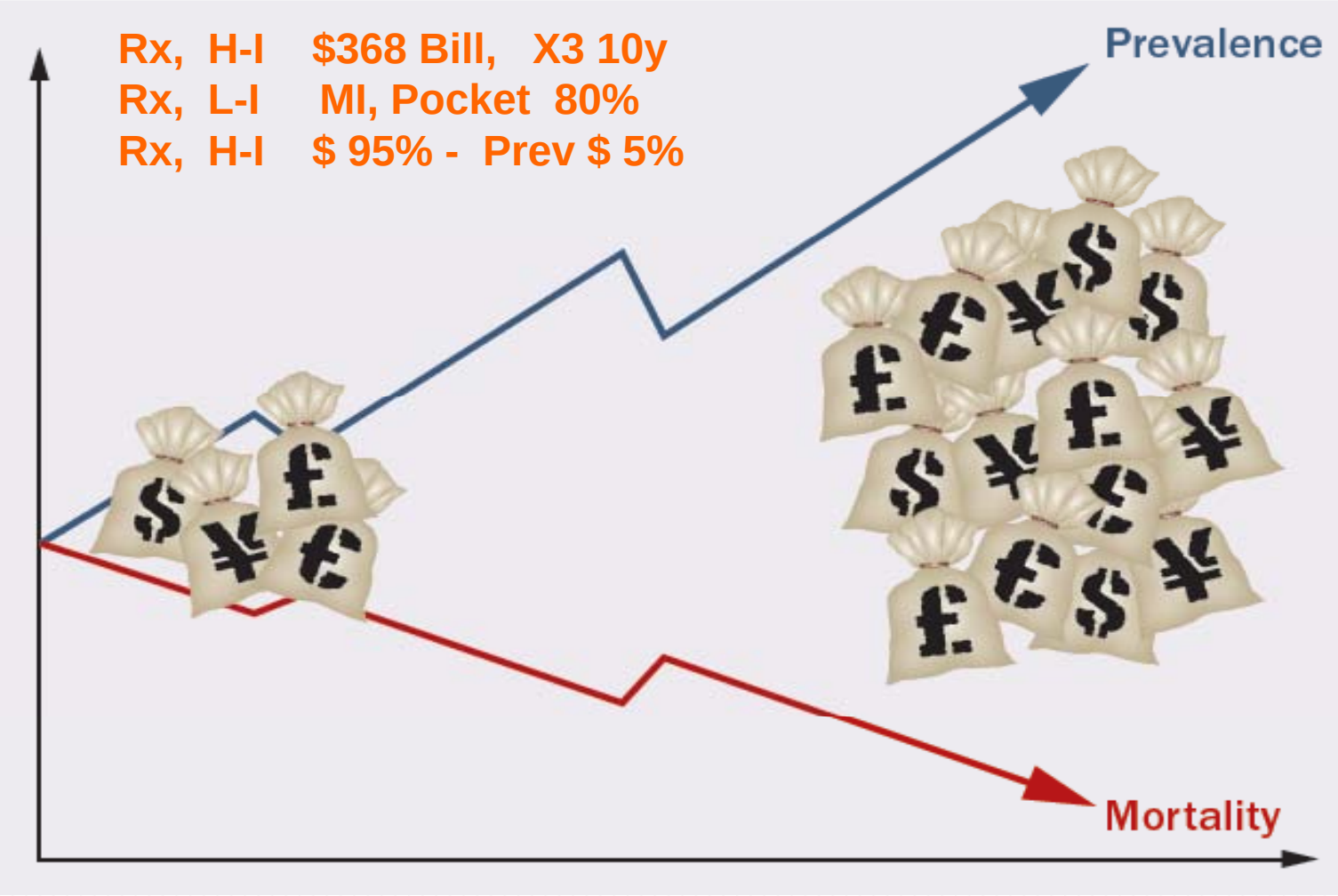
FRCV	PACIENTES TRATADOS (%)	OBJETIVO ALCANZADO (% PACIENTES)	
HTA	94,2	38,8	
DM2	87,2	HbA1c	36,7
		Glucosa en ayunas	20
		Ambas	7,2
DLP	74,4	Colesterol total	43,3
		Colesterol total + LDL	41,2
Obesidad	92,2 (cumplen medidas higiénico-dietéticas)	IMC	24,7
		Perímetro cintura	6,8
		Ambas	3,2

European Heart Journal
doi:10.1093/eurheartj/ehs092

European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)

Recommendations for behavioural change

Recommendations	Class[a]	Level[b]	GRADE	Ref[c]
Established cognitive-behavioural strategies (e.g. motivational interviewing) to facilitate lifestyle change are recommended.	I	A	Strong	195, 196
Specialized healthcare professionals (e.g. nurses, dieticians, psychologists, etc.) should be involved whenever necessary and feasible.	IIa	A	Strong	185, 197, 198
In individuals at very high CVD risk, multimodal interventions, integrating education on healthy lifestyle and medical resources, exercise training, stress management, and counselling on psychosocial risk factors, are recommended.	I	A	Strong	195, 197, 199, 200



V Fuster et. al. Nat Rev. Cardiol. 2009;6:669.