Manejo Global de la Dislipemia

Estudio HPS-2. El Futuro que Viene

1

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Dislipemia-2012

- Las Guías de Dislipemia/Prevención 2011/12
- El Concepto de Riesgo Residual
- HPS-2. La evidencia que viene
- El Futuro

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)

Developed with the special contribution of: European Association for Cardiovascular Prevention & Rehabilitation†

Atherrosclerosis 2011, June 28
doi:10.1016/j.atherosclerosis.2011.06.012

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

ESC/EAS Guidelines for the management of dyslipidaemias

Aspectos relevantes y novedosos

1. El tratamiento de la dislipidemia debe considerarse dentro de la **prevención integral** de la enfermedad cardiovascular.
2. Se recomienda el baremo **SCORE** para valorar el RCV.
3. Objetivos terapéuticos: se consideran objetivos de c-LDL de **forma estricta** (no opcional) para pacientes de moderado, alto y muy alto riesgo cardiovascular.
4. Fármacos hipolipemiantes: **estatinas**.

Atherosclerosis 2011, June 28
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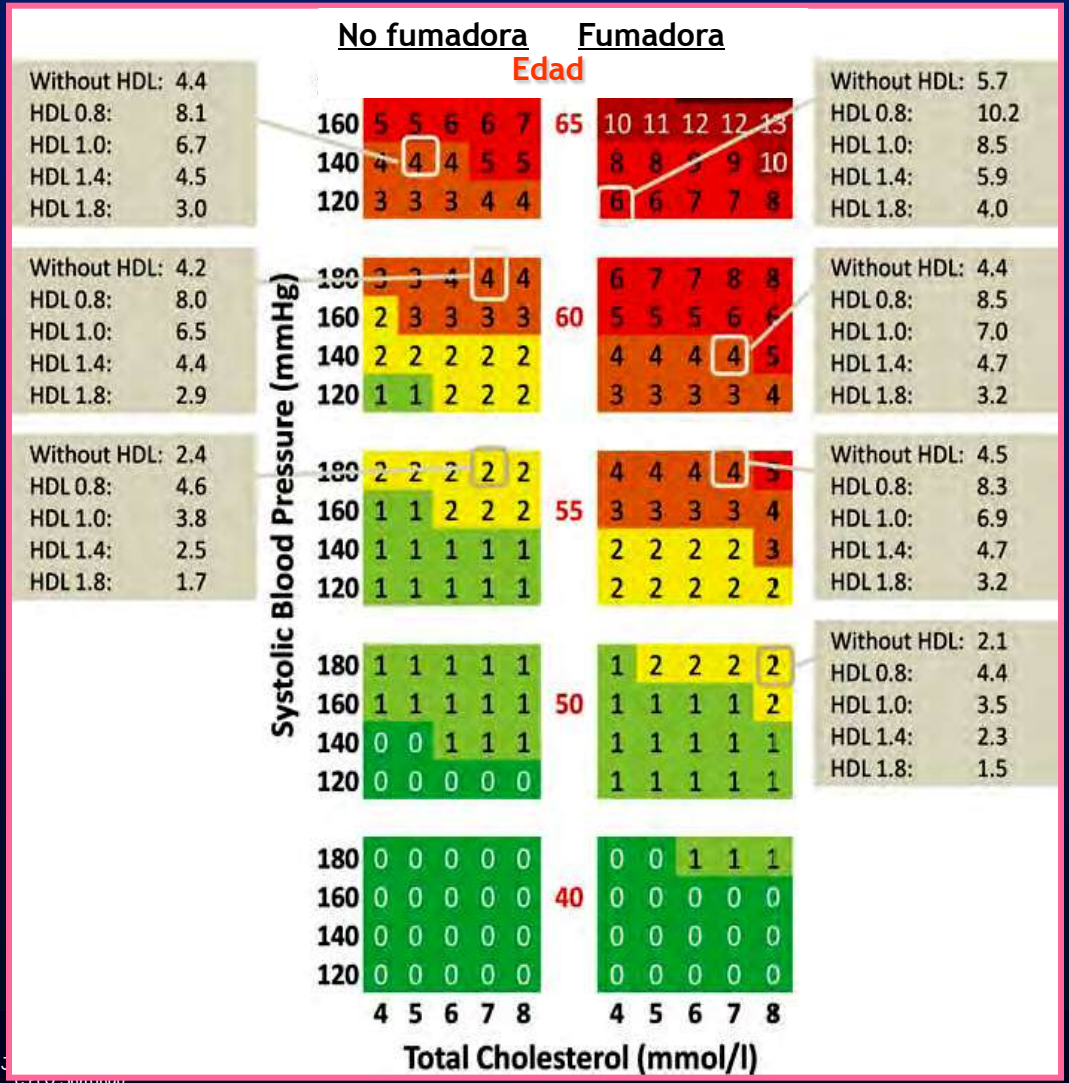
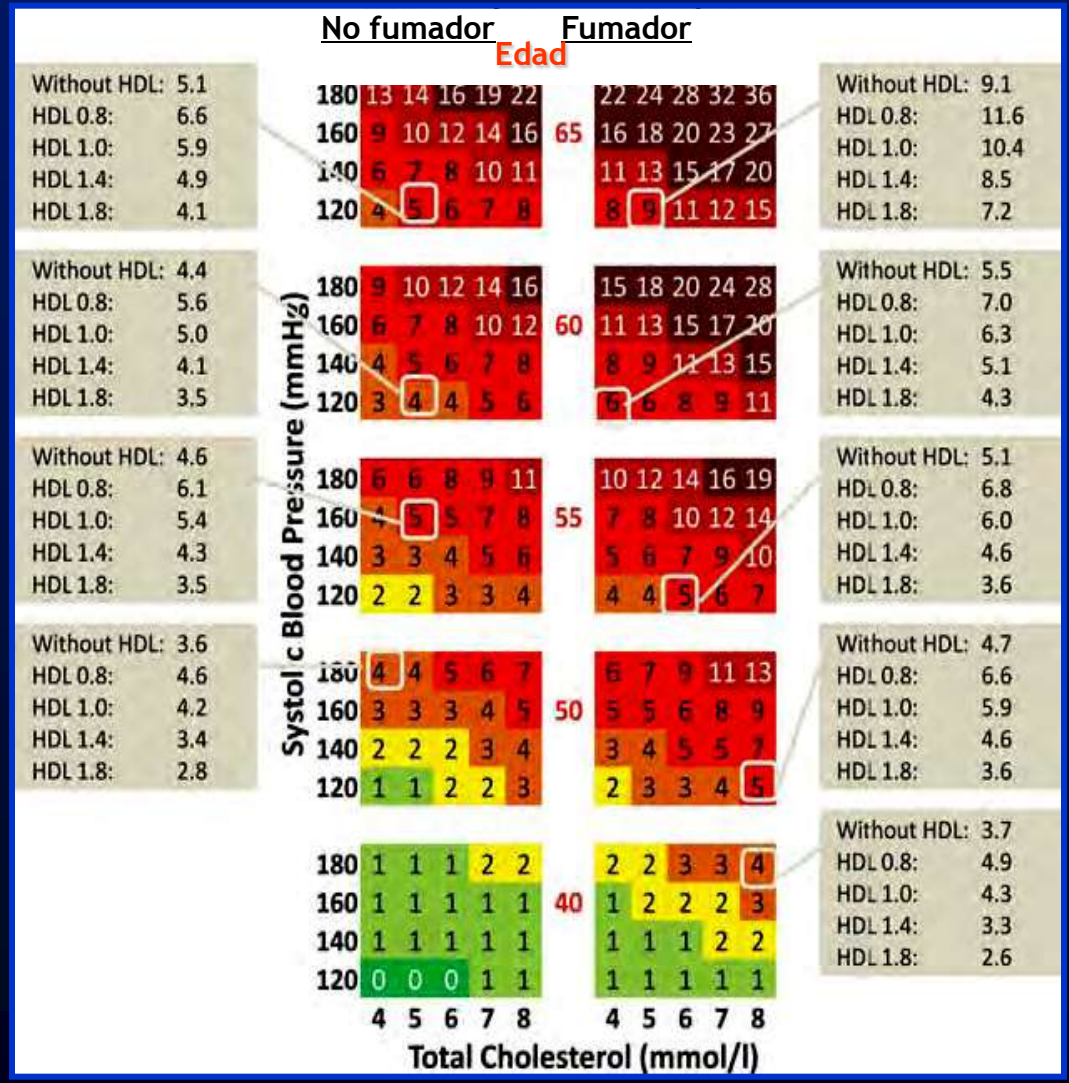
Dislipidemias y riesgo global

Tablas SCORE con inclusión del c-HDL





Riesgo CV global

Directrices ESC/EAS, 2011

Riesgo muy alto

- Enfermedad cardiovascular documentada (clínica o imagen)
- *Diabetes de tipo 2*
- *Diabetes de tipo 1 con lesión orgánica*
- IRC (FGe < 60 ml/min/1,73 m^2)
- Riesgo calculado SCORE > 10%

Riesgo alto

- Un FR francamente patológico
- Riesgo calculado SCORE entre 5% y 10%

Riesgo moderado

- Riesgo calculado SCORE entre 1% y 5% (refinar con otros)

Riesgo bajo

- Riesgo calculado SCORE < 1%

Objetivos terapéuticos c-LDL

Pacientes	Objetivo c-LDL	Clase	Nivel
Pacientes con riesgo "muy alto"	< 70 mg/dL (<1,8 mmol/l) y/o reducción del c-LDL > 50% cuando no pueda alcanzarse el objetivo	I	A[1,2,3]
Pacientes con riesgo "alto"	< 100 mg/dL (<2,5 mmol/l)	IIa	A[1,4,5]
Pacientes de riesgo "moderado"	< 115 mg/dL (< 3 mmol/l)	IIa	C

1. **Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials.** Lancet. 2010; 376:1670-81.
2. Pedersen TR, Faergeman O, Kastelein JJ, et al; **Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial.** JAMA. 2005; 294:2437-45.
3. LaRosa JC, Grundy SM, Waters DD, et al; **Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease.** N Engl J Med. 2005; 352:1425-35.
4. Brugts JJ, Yetgin T, Hoeks SE, et al. **The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials.** BMJ. 2009; 338:b2376.
5. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. **Primary prevention of cardiovascular mortality and events with statin treatments. A network metaanálisis involving more than 65,000 patients.** J Am Coll Cardiol. 2008; 52:1769-81.

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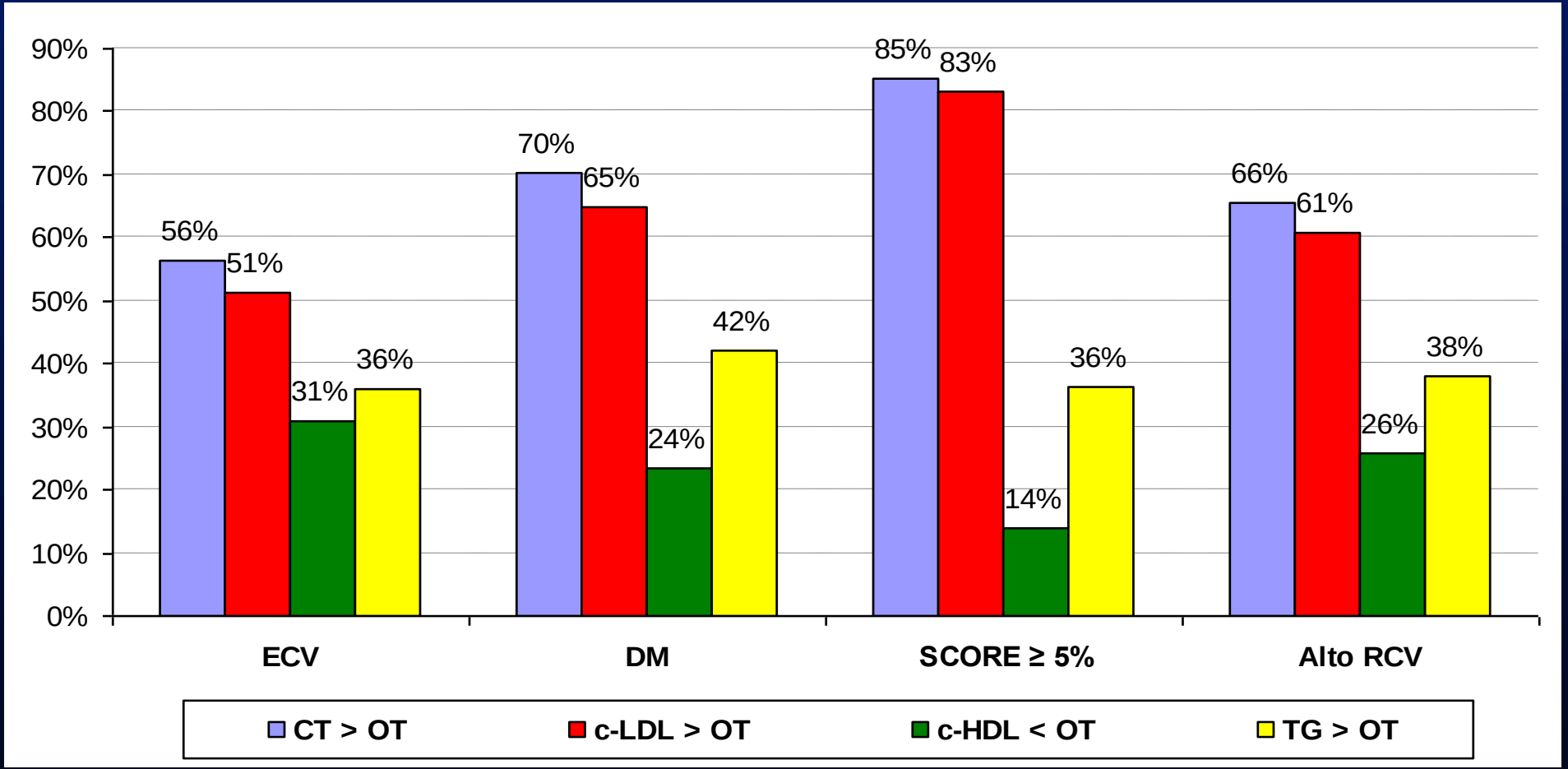
Alto RCV:
Sin control de objetivos terapéuticos

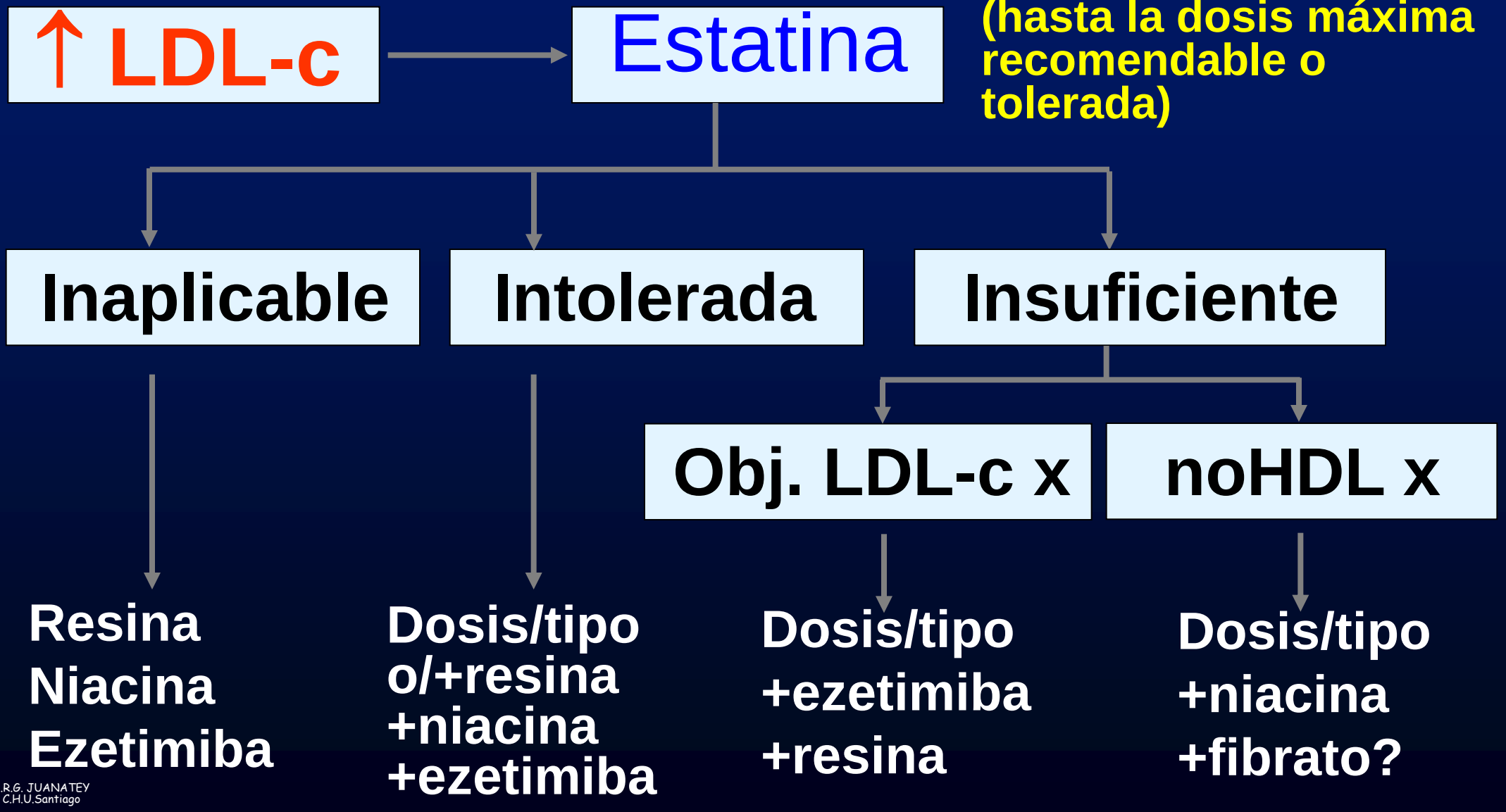
España
n: 3.617

Pacientes en España tratados con estatinas
(68,8% MAP; 31,2% Med Interna, Cardiología, Endocrinología)



González-Juanatey J.R, Millán J, Alegría E, Guijarro C, Lozano J.V y Vitale G. Prevalencia y características de la dislipemia en pacientes en prevención primaria y secundaria tratados con estatinas en España. Estudio DYSIS-España. Rev Esp Cardiol 2011; 64(4):286-294

Para disminuir el LDL-c
Terapia hipolipemiante



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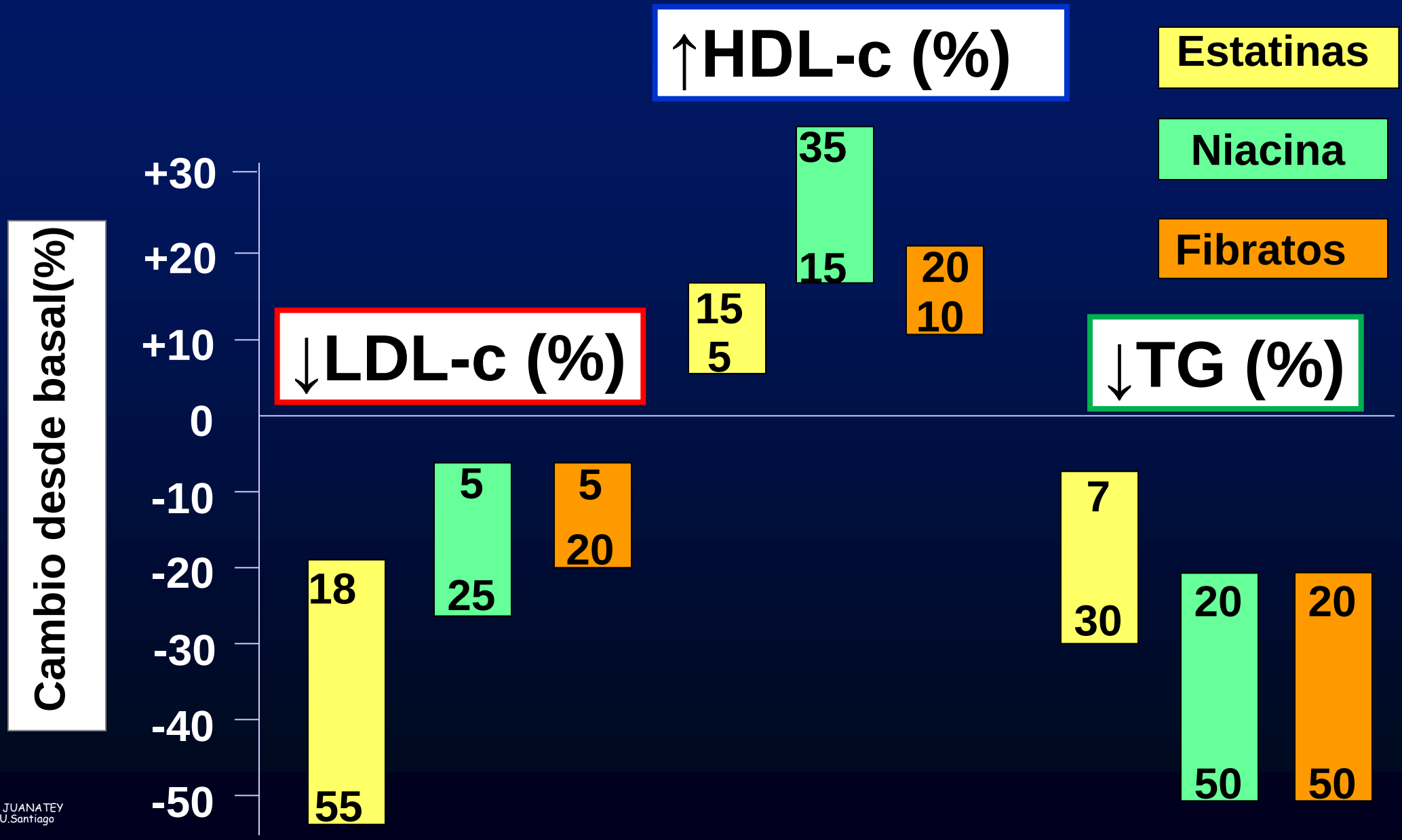
Hipolipemiantes: efectos



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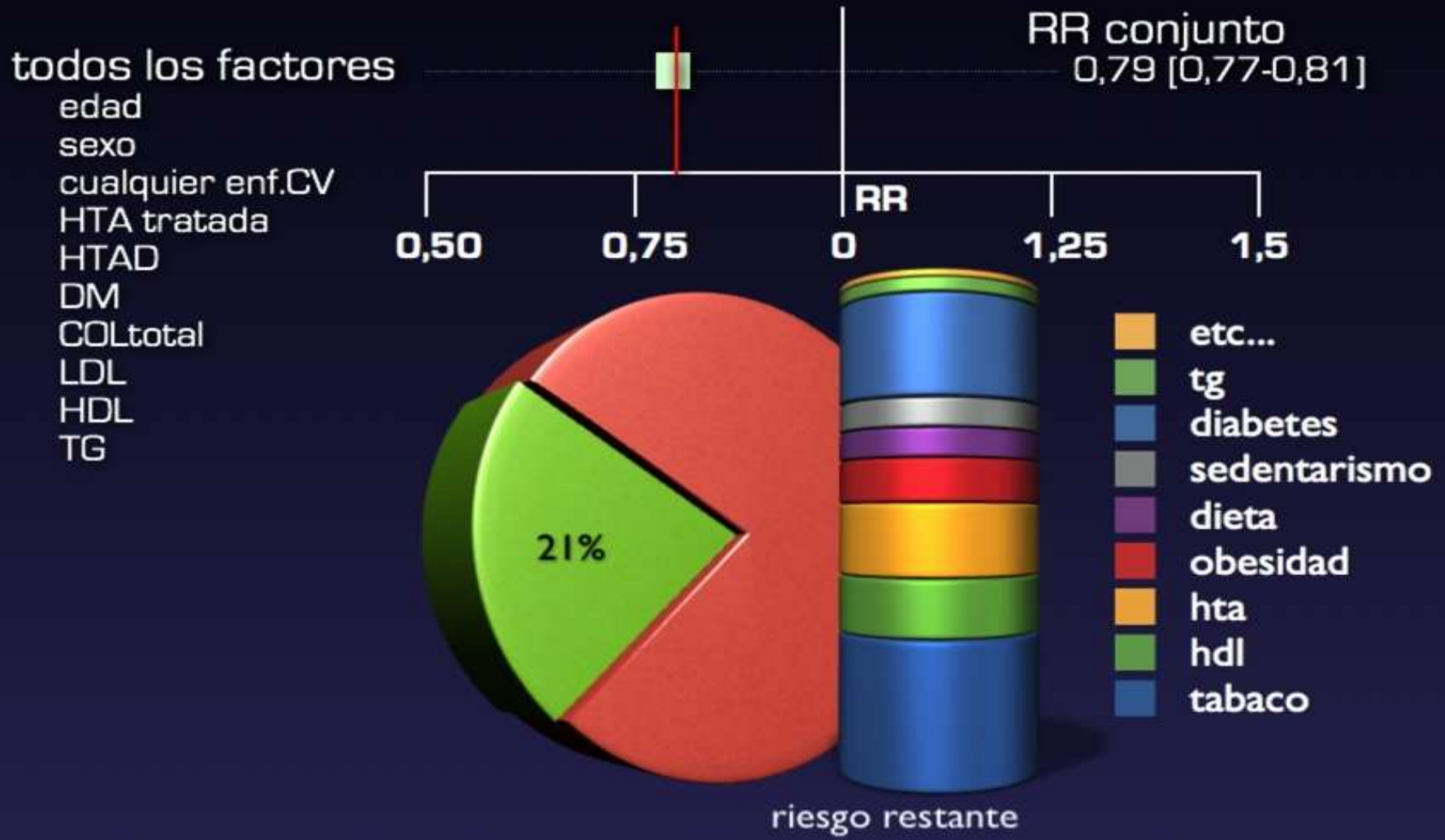
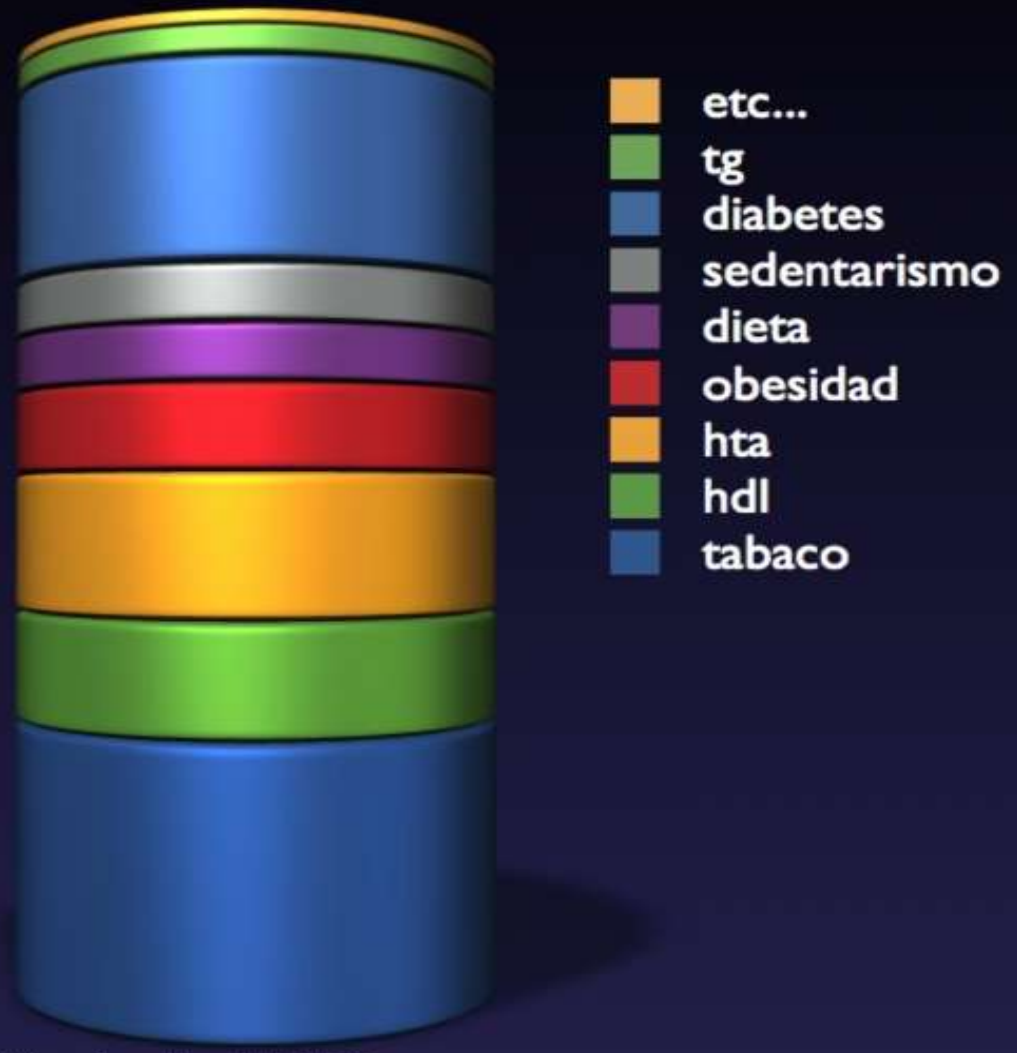
el riesgo más allá del LDL

- tratar el LDL protege del riesgo CV



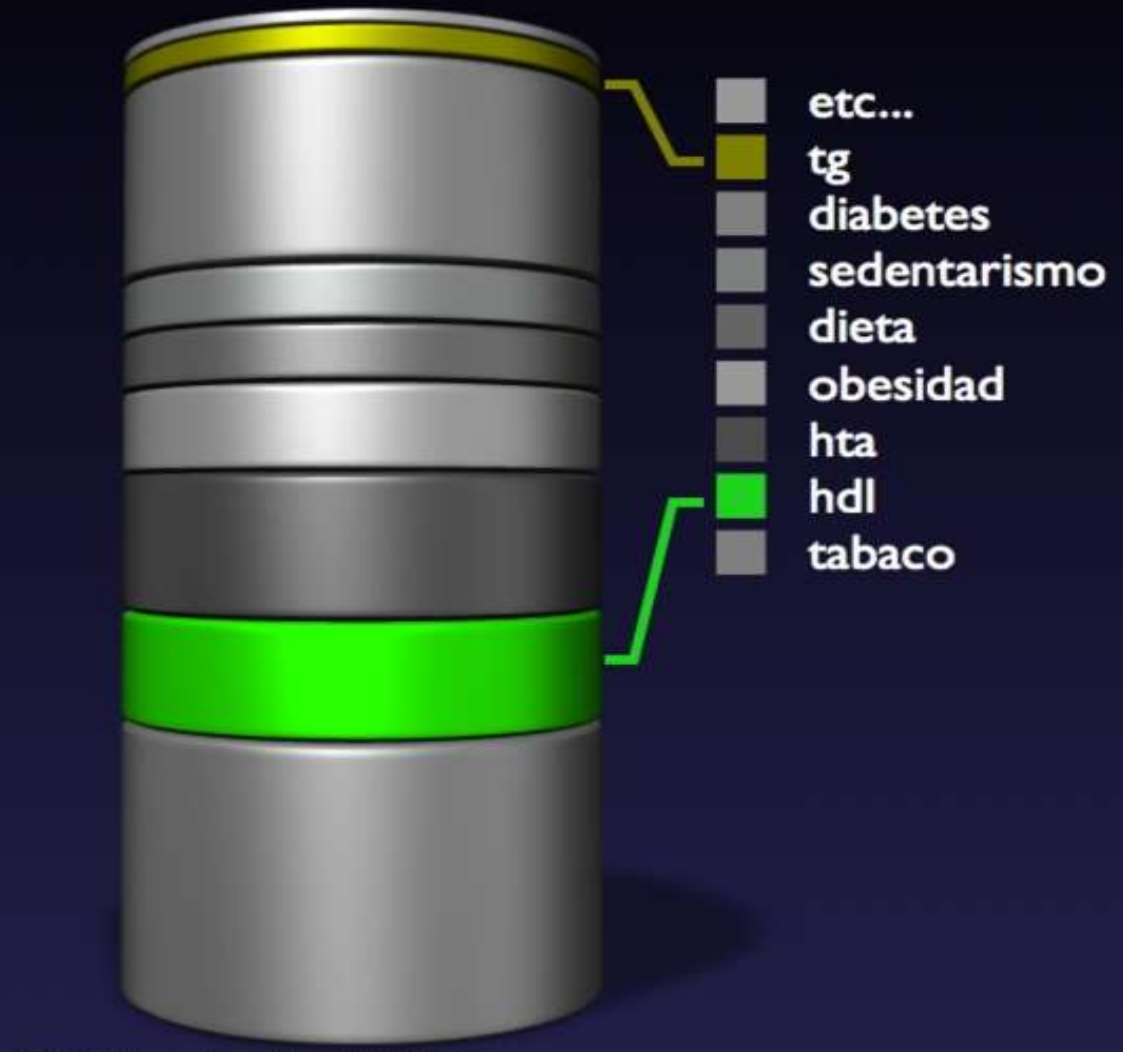
Baigent C, Keech A, Kearney PM, Blackwell L, et al, Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78

el riesgo más allá del LDL



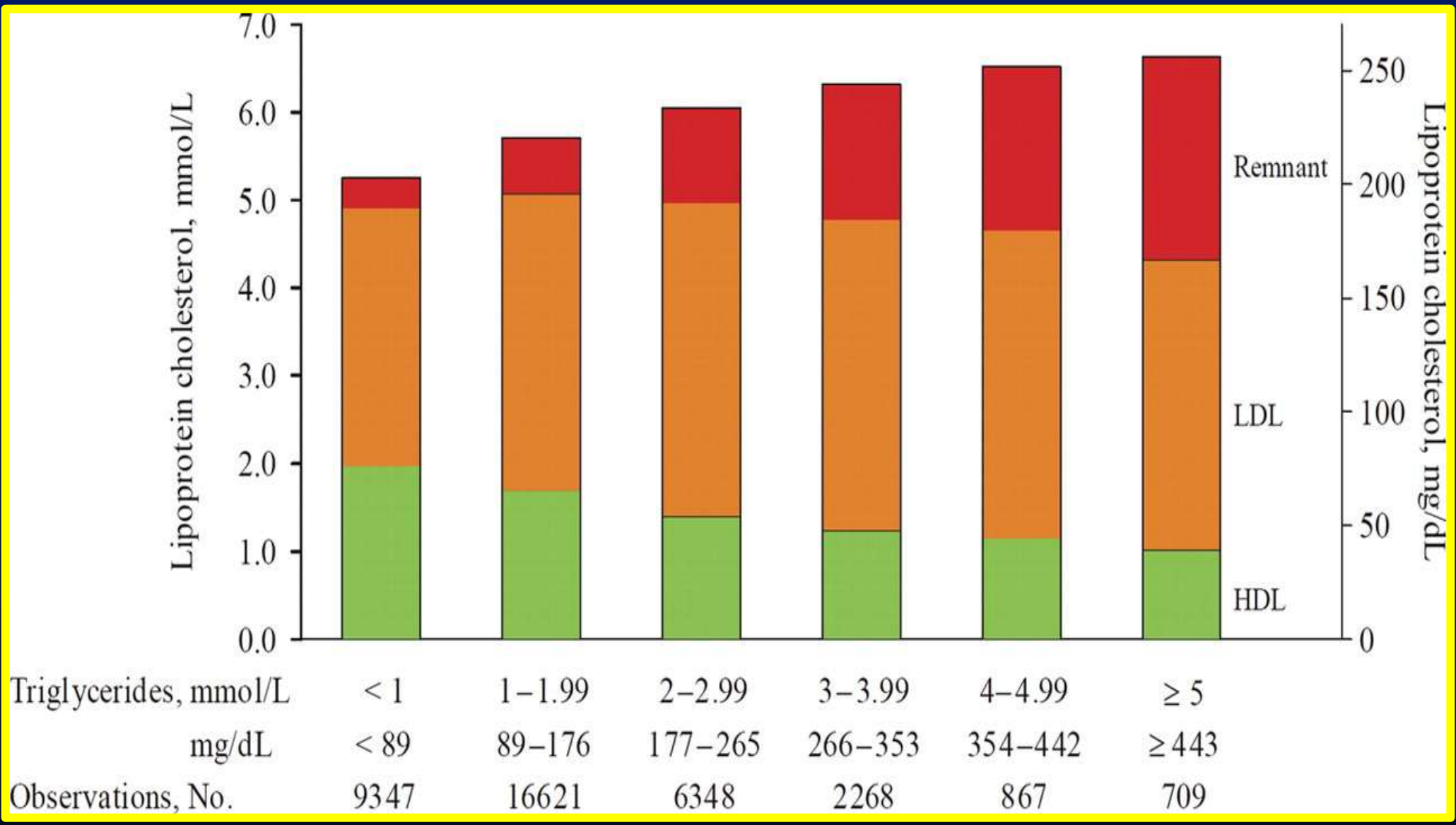
FRCV más alla del LDL

el riesgo más allá del LDL



FRCV más alla del LDL

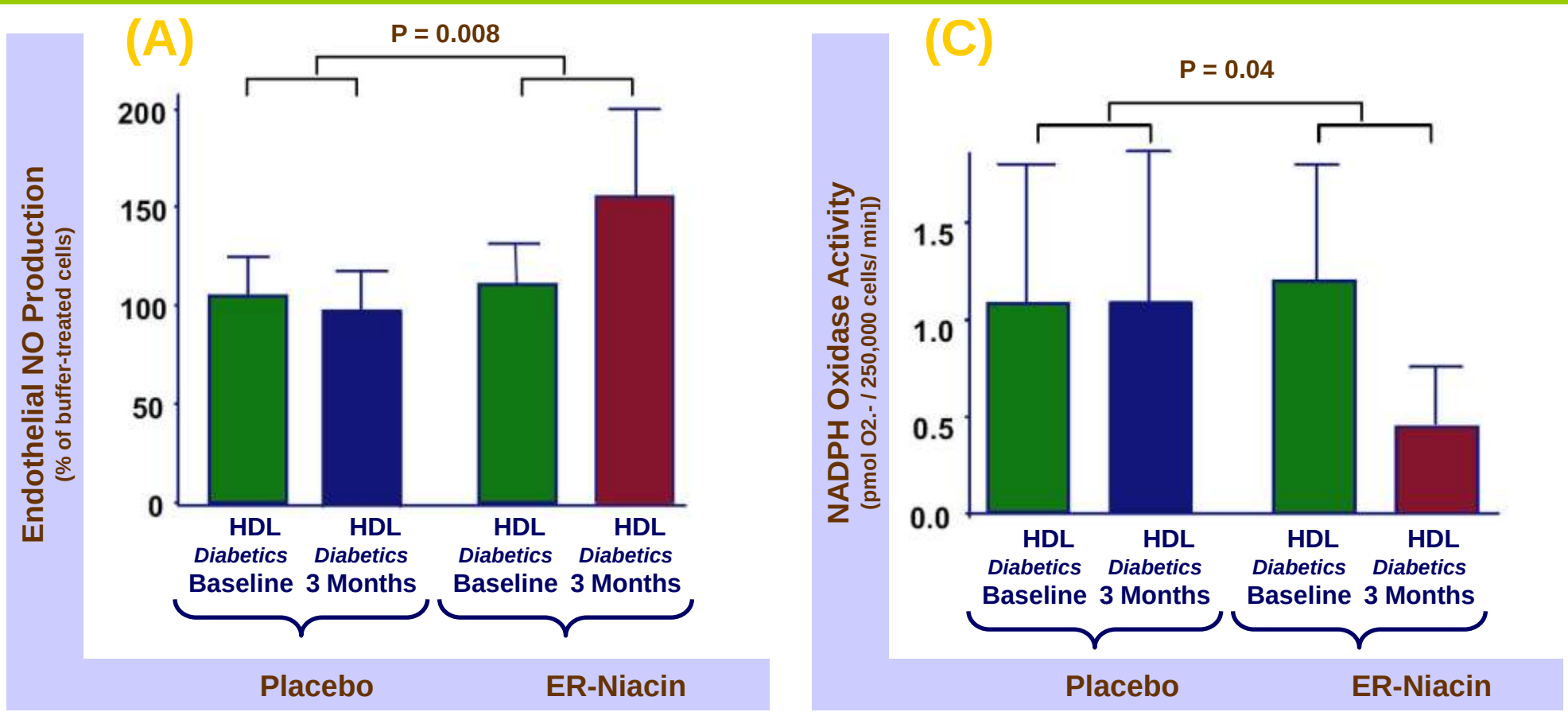
CT, Triglicéridos, LDL y HDL



Chapman M J et al. Eur Heart J 2011; 32:1345-61

Endothelial-Vasoprotective Effects of High-Density Lipoprotein Are Impaired in Patients With Type 2 Diabetes Mellitus but Are *Improved After Extended-Release Niacin Therapy*

Effect of ER niacin therapy or placebo on endothelial-protective properties of HDL in diabetic patients



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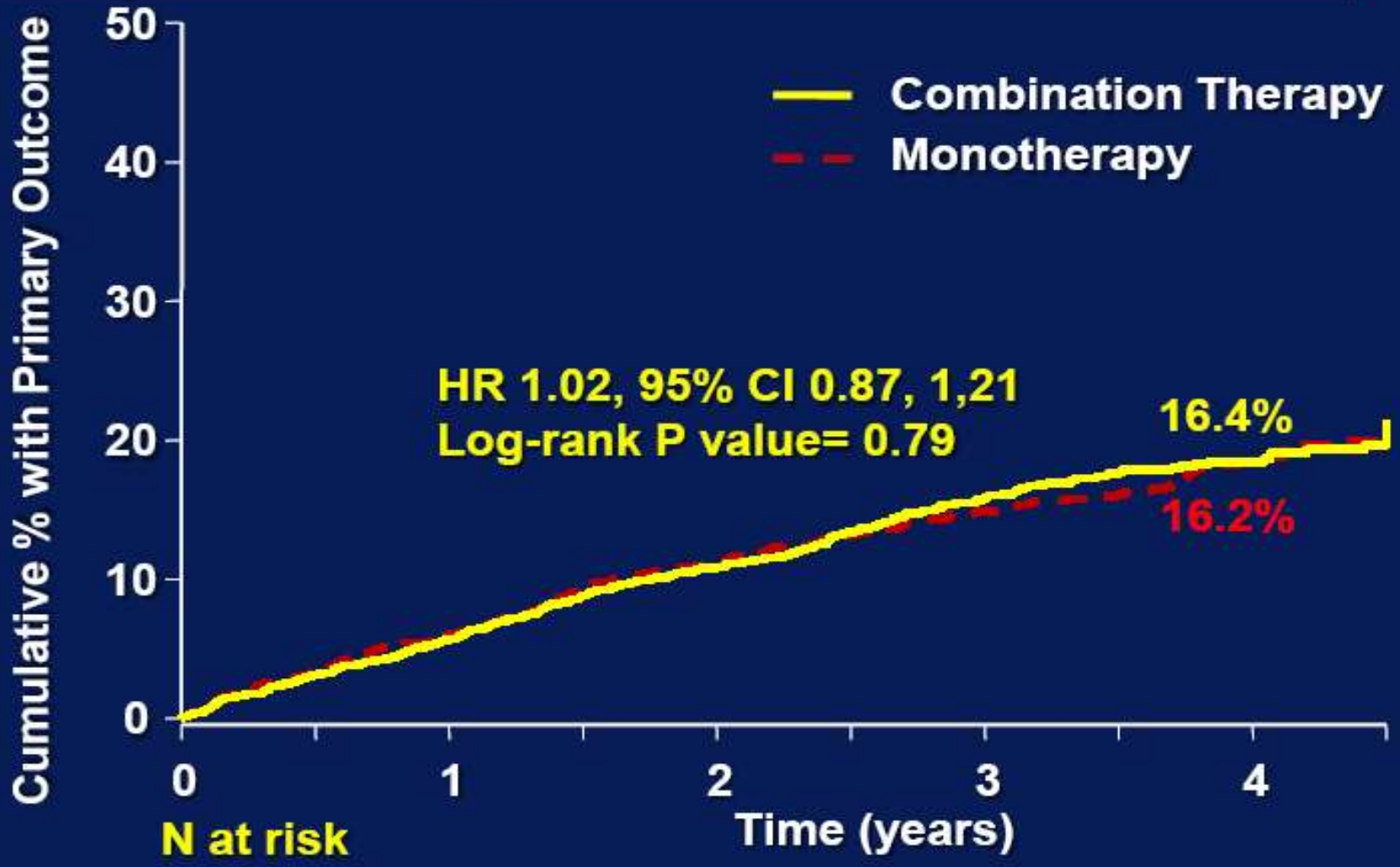
Sorrentino SA et al. Circulation. 2010;121:110-122

AIM-HIGH (AHA 2011) Primary Outcome



N at risk					
Monotherapy	1696	1581	1381	910	436
Combination Therapy	1718	1606	1366	903	428

Dislipemia y Síndrome metabólico

Transporte reverso de colesterol: TORCETRAPID

NEJM 2004;350:1491-94

Ácido nicotínico y aterosclerosis: Efecto positivo en resultados clínicos

Ensayos clínicos aleatorizados y controlados del ácido nicotínico y efecto sobre el c-HDL y los resultados clínicos

Estudios con imagen	Agentes faramacológico	Pacientes en tratamiento, n/N (%)	Duración del seguimiento en años	Resultados[a]
CDP	Ácido nicotínico	1119/8341 (13,4)	6	Descenso (27%) de los IM no mortales
CDP seguimiento	Ácido nicotínico	1119/8341 (13,4)	15	Descenso (11%) de la mortalidad

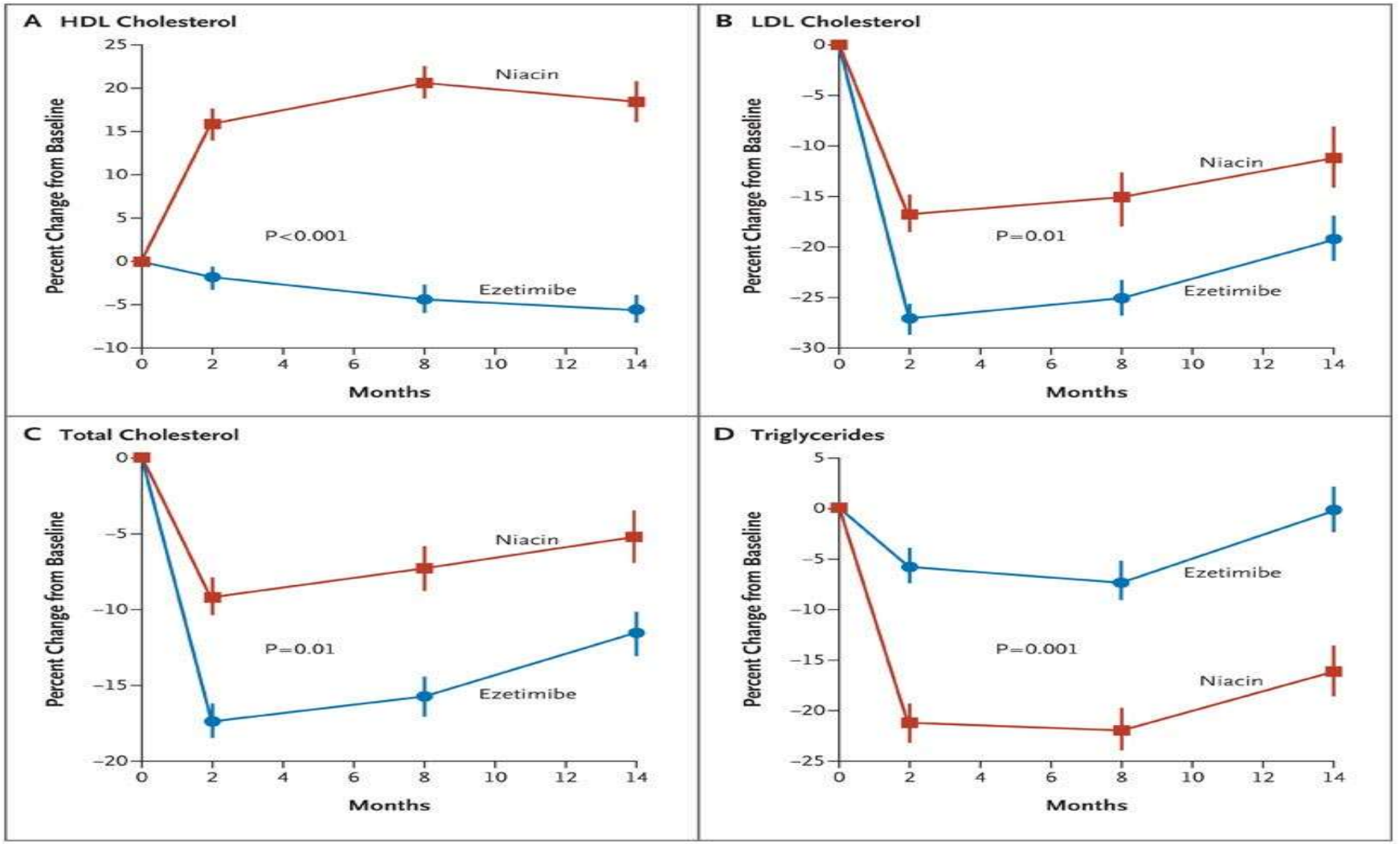
CDP = Coronary Drug Project;;IM = infarto de miocardio.

[a]Muerte se refiere a la mortalidad por cualquier causa.

Adaptado de Singh IM et al. JAMA. 2007;298:786–798; Coronary Drug Project Research Group. JAMA. 1975;231:360–381; Canner PL et al. J Am Coll Cardiol. 1986;8:1245–1255.

ARBITER 6-HALTS

- Cambios lipídicos



Taylor A et al. N Engl J Med 2009;10.1056/NEJMoa0907569

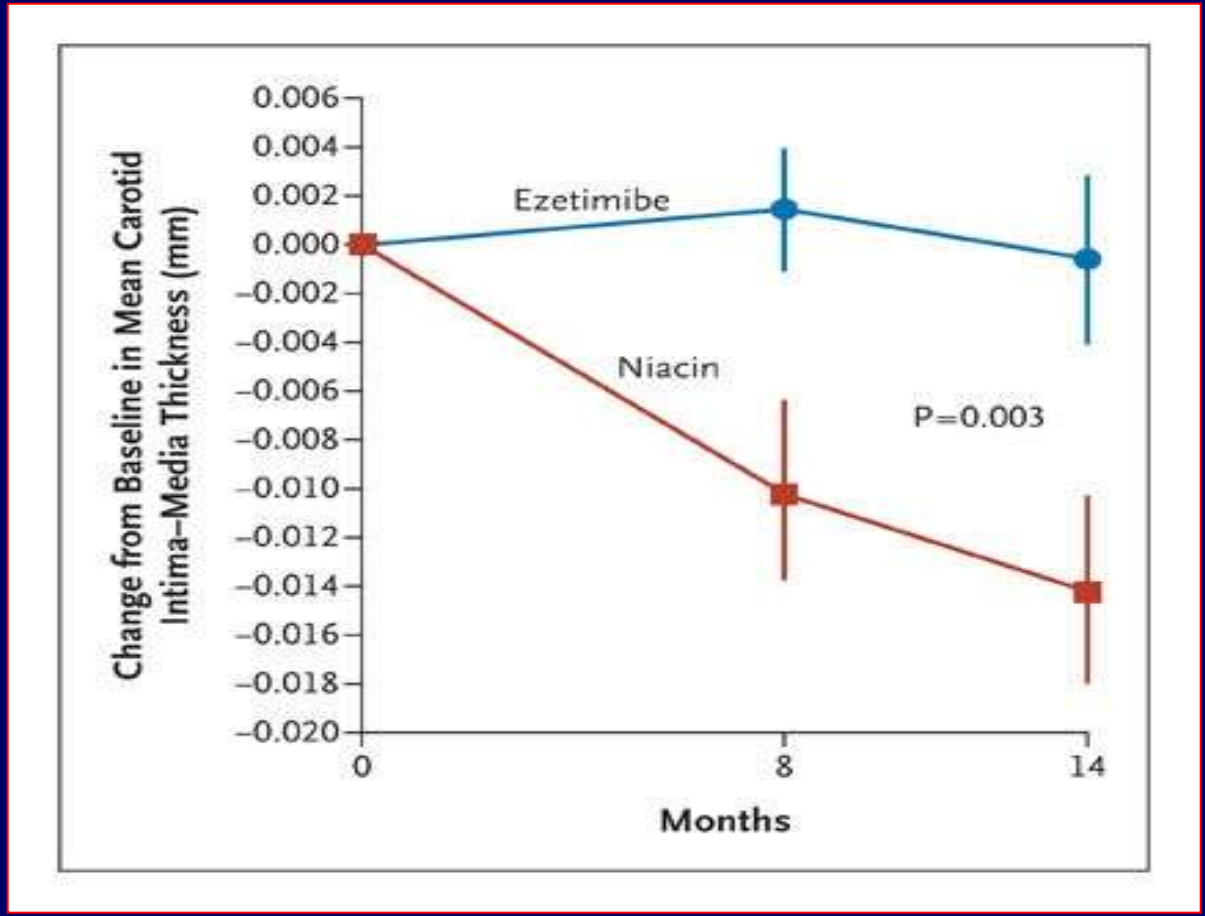
ARBITER 6 - HALTS

- Resultados. Objetivo Primario
  - Cambio en Espesor Íntima-Media Carotídea

208 pacientes de Alto Riesgo CV (111 ezetimibe y 97 niacina; asociadas a estatinas)

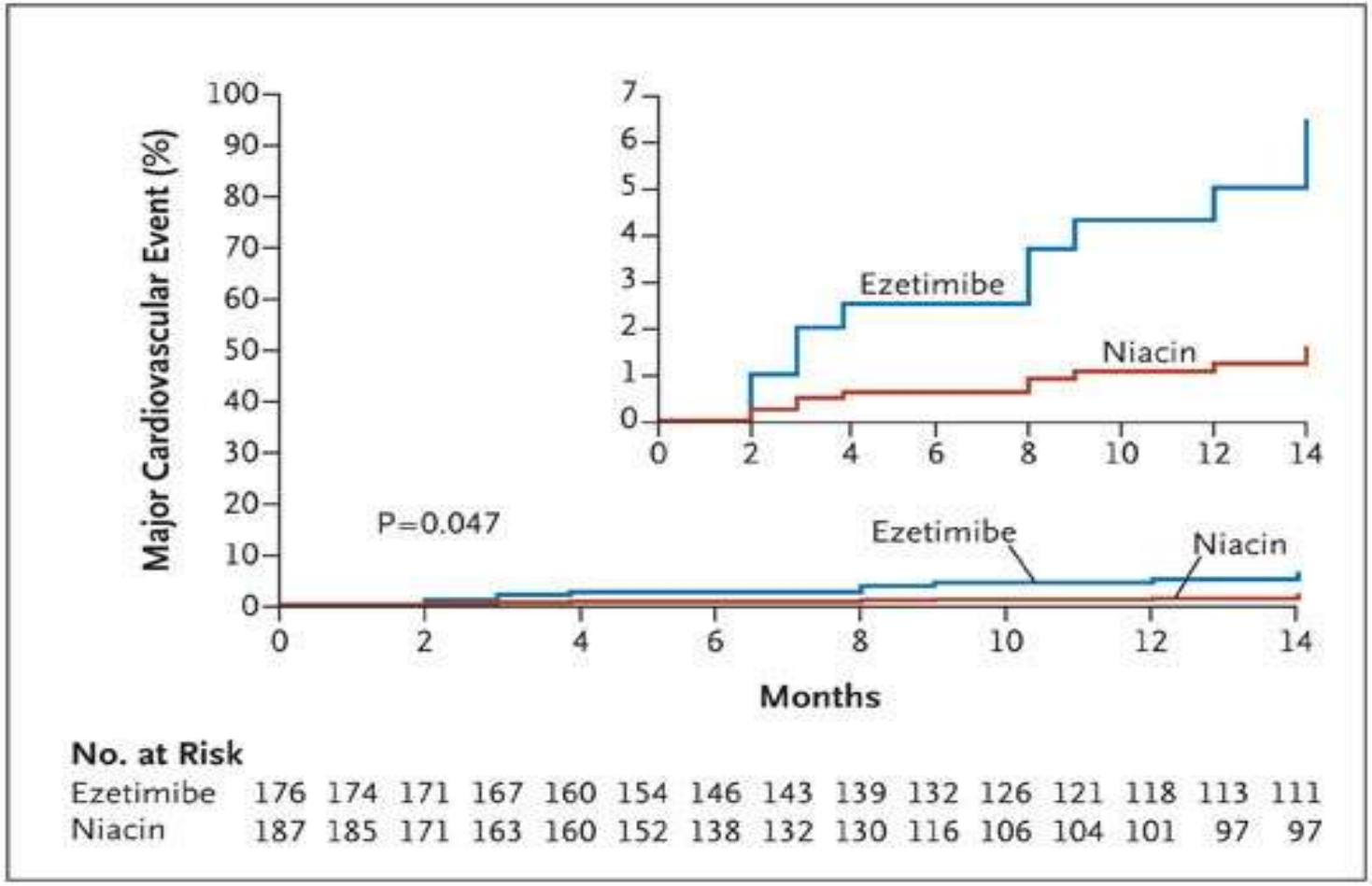
A los 14 meses: 18.4% incremento HDL (50 mg/dL) en Niacina y 19.% descenso LDL (66 mg/dL) en Ezetimibe

Complicaciones CV mayores: 5.5% vs 1.2% (Ez vs Nc)



Taylor A et al. N Engl J Med 2009;10.1056/NEJMoa0907569

ARBITER 6-HALTS. Kaplan-Meier Estimates of the Incidence of a Major Cardiovascular Event among the 363 Study Patients, According to Treatment Group

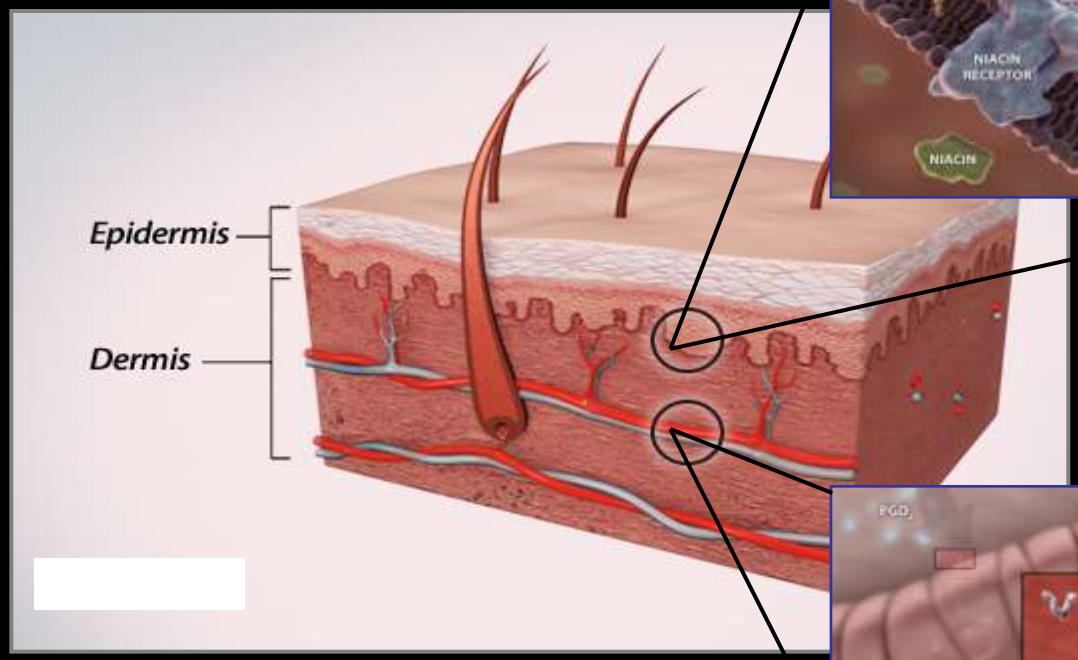


Taylor A et al. N Engl J Med 2009;10.1056/NEJMoa0907569

The NEW ENGLAND JOURNAL of MEDICINE

¿Porqué Niacina LP/Laropiprant?

La vía de rubefacción inducida por niacina tiene dos sitios independientes de acción



Representación artística.

1. Células epidérmicas de Langerhans
   - Se une la niacina al receptor GPR109A
   - Se produce y libera PGD_2.

2. Vasos sanguíneos dérmicos
   - PGD_2 se une a DP1
   - se produce vasodilatación

3. Vasos sanguíneos dérmicos
   - **LAROPIPRANT** compite con la PGD_2 y se une al receptor DP1
   - **Se reduce el efecto vasodilatador**

PGD_2 = prostaglandina D_2; DP1 = receptor de la prostaglandina D_2 1.

Benyó Z y cols. *Mol Pharmacol*. 2006;70:1844–1849; Morrow JD y cols. *J Invest Dermatol*. 1992;98:812–815; Cheng K y cols. *Proc Natl Acad Sci USA*. 2006;103:6682–6687; Pike NB y cols. *J Clin Invest*. 2005;115:3400–3403.

Study Design

AIM2-THRIVE
Treatment of HDL to Reduce the Incidence of Vascular Events

High Risk Patients (MI, Peripheral/Cerebrovascular Disease, or Diabetes + Vascular Disease)

Unblinded Active Run-In

ERN/LRPT 1g/20mg for 4 wks then ERN/LRPT 2g/40mg for 4 wks

(On top of Simva 40mg +/- ezetimibe)

ERN/LRPT 2g/40mg

(On top of Simva 40mg +/- ezetimibe)

Simva 40 mg

(+/- ezetimibe)

n= ~25*,000*
2,300 events
4 Year Median Follow-up

Composite of non-fatal MI or coronary death; fatal or non-fatal stroke; or any revascularization procedure (including coronary or non-coronary angioplasty or grafting)

Key Inclusion Criteria

AIM-HIGH
HPS2-THRIVE
Treatment of HDL to Reduce the Incidence of Vascular Events

- History of MI, or
- Cerebrovascular disease, or
- Peripheral artery disease, or
- Diabetes mellitus with any of the above or with evidence of CHD (i.e. stable or unstable angina, revascularization, or acute coronary syndrome)
- Study does *NOT pre-specify any blood lipid thresholds* in order to determine eligibility

Study Efficacy Endpoints

- **Primary Endpoint - Major vascular events**
  - Composite of non-fatal MI or coronary death; fatal or non-fatal stroke; or any revascularization procedure (including coronary or non-coronary angioplasty or grafting)
- **Secondary Endpoints**
  - Separate components of the primary endpoint
    - Major coronary events (non-fatal MI or coronary death)
    - Total stroke (fatal or non-fatal)
    - Revasularizations
  - Mortality – overall and within particular categories of causes of death
  - MVE in patients with and without:
    - Coronary heart disease
    - Peripheral artery disease
    - Cerebrovascular disease
    - Diabetes mellitus

Study Safety Endpoints

AIM-HIGH
HPS2-THRIVE
Treatment of HDL to Reduce the Incidence of Vascular Events

- Serious Adverse Events
- Myopathy (muscle symptoms with CK > 10xULN) and rhabdomyolysis
- Confirmed elevation of liver transaminases: aspartate or alanine transaminase (AST or ALT) >3xULN on 2 occasions within about one week
- Non-viral drug-related hepatitis
- Discontinuation of study treatment overall and by various causes, including known adverse effects of niacin (such as flushing and gastrointestinal symptoms)

Statistical Methods

AIM-HIGH HPS2-THRIVE
Treatment of HDL to Reduce the Incidence of Vascular Events

- Intent-to-Treat (ITT) population used to analyze all safety and efficacy data
  - Include all subjects receiving randomized treatment assignment
- ~25,000 subjects will be randomized, with the trial continuing until accrual of approximately 2,300 primary endpoint events
- Assumptions: ER niacin/laropiprant 2g/40mg (On top of Simva 40mg +/- ezetimibe) expected to
  - Result in a ~15% reduction in hazard in primary endpoint event at 4 years vs. simvastatin 40 mg (+/- ezetimibe)
- 85% power to detect the expected reduction in CV events, assuming 2,300 events and anticipated rate of loss of subjects to follow-up

HPS2-THRIVE and AIM-HIGH - Design Comparison

Aspect	ERN/L - HPS2-THRIVE	Niaspan - AIM HIGH
Study Size	25,000	3,300
Patient Population	High Risk; No Lipid Requirements	High Risk; Dyslipidemic
Study Design - niacin	4 weeks at 1 gram, then advanced to 2g for remainder of study	2g titrated in 500mg increments over 4 weeks, can be back-titrated if necessary for tolerability
Study Design - statin	Both arms simva 40 +/-ezetimibe to target LDL-C <80mg/dL	Initiated on simva 40 but titrated throughout study (raise/lower simva dose and/or add ezetimibe) to maintain LDL >=40mg/dL and <=80mg/dL
Primary Endpoint	Composite CHD Death, Non-Fatal MI, Stroke, Revasc	Composite CHD Death, Non-Fatal MI, Non-hemorrhagic Stroke, Hospitalization ACS, Revascularizations
Estimated Risk Reduction	15%	25%
Planned/Actual Follow Up	4 years / TBD	3.5 years / 32 months
Estimated Completion	June 2012	September 2012
Patent Expiry	2023	3Q2013

de qué estamos pendientes…

- EZE…
  - IMPROVE-IT (2013)
  - SHARP
- NIA…
  - AIM-HIGH (2011)
  - HPS2-THRIVE (2013)

O'Riordan M. ARBITER 6-HALTS: Final results from complete study population published. The Heart 2010 abril 14, en: www.theheart.org

Para disminuir el LDL-c
Terapia hipolipemiante

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