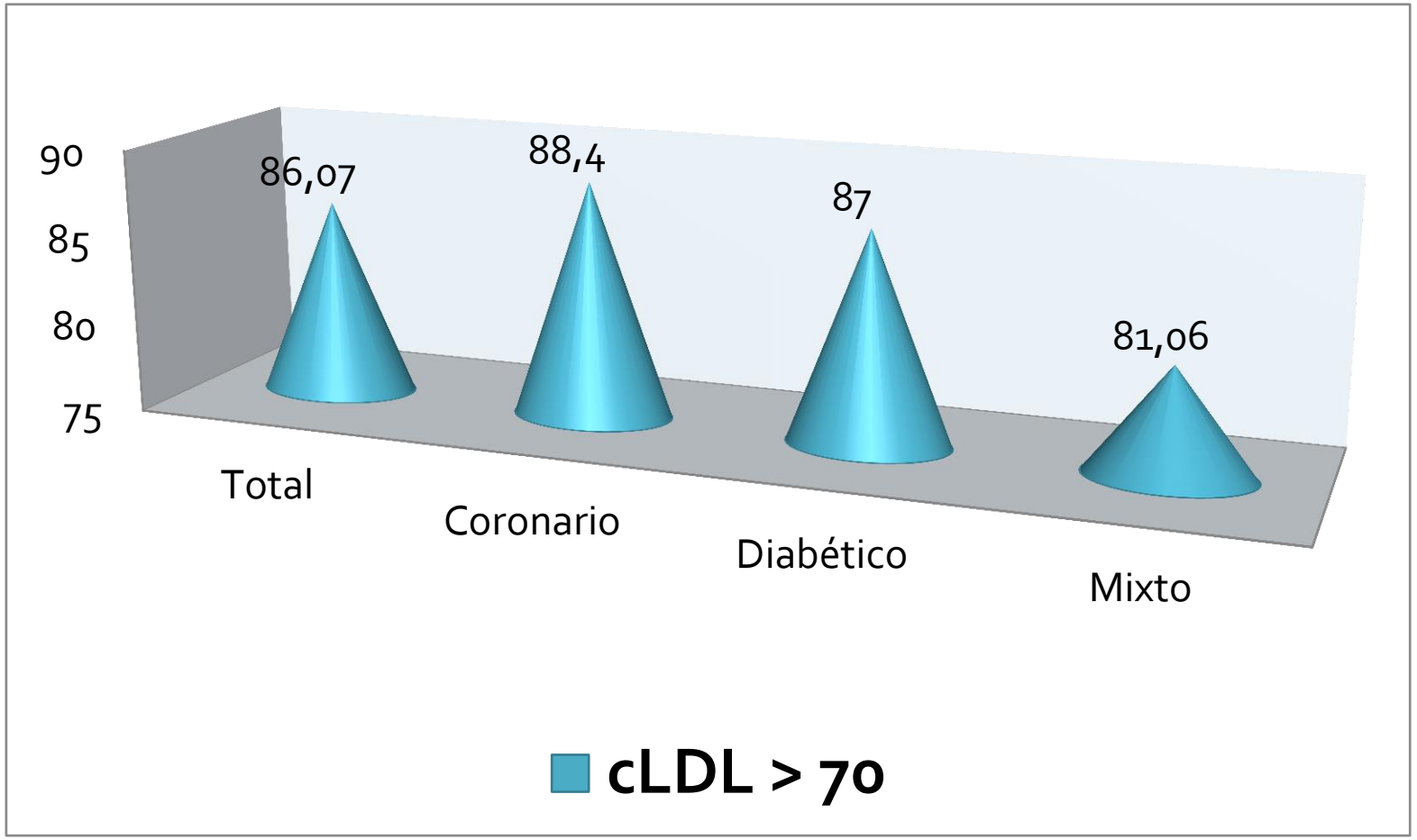
50 Congreso Sociedad Andaluza de Cardiología
"Congreso Andaluz de las Enfermedades Cardiovasculares"
14 – 16 mayo 2015
Hotel Abades Nevada Palace
Granada
SOCIEDAD ANDALUZA DE CARDIOLOGÍA

Nuevas evidencias de la terapia combinada en el tratamiento del LDL en pacientes de muy alto riesgo cardiovascular

Dr. Leopoldo Pérez de Isla
Hospital Clínico San Carlos
Madrid. España.

Nivel de Riesgo	Objetivo cLDL
RCV Muy alto: Enfermedad CV establecida Diabéticos (con lesión de órgano diana o un FRCV asociado) Enfermedad Renal Crónica (F.G. <60 ml/min/1,73m²) SCORE > 10%	< 70 mg/dl (1,8mmol/l) (o reducción del 50% del cLDL)
RCV Alto: Diabéticos (sin lesión de órgano diana o un FRCV asociado) SCORE 5-10%	< 100 mg/dl (2,5mmol/l)
RCV Moderado: SCORE < 1-5%	< 115 mg/dl (4,0mmol/l)
RCV Bajo: SCORE < 1%	Control de otros FRCV

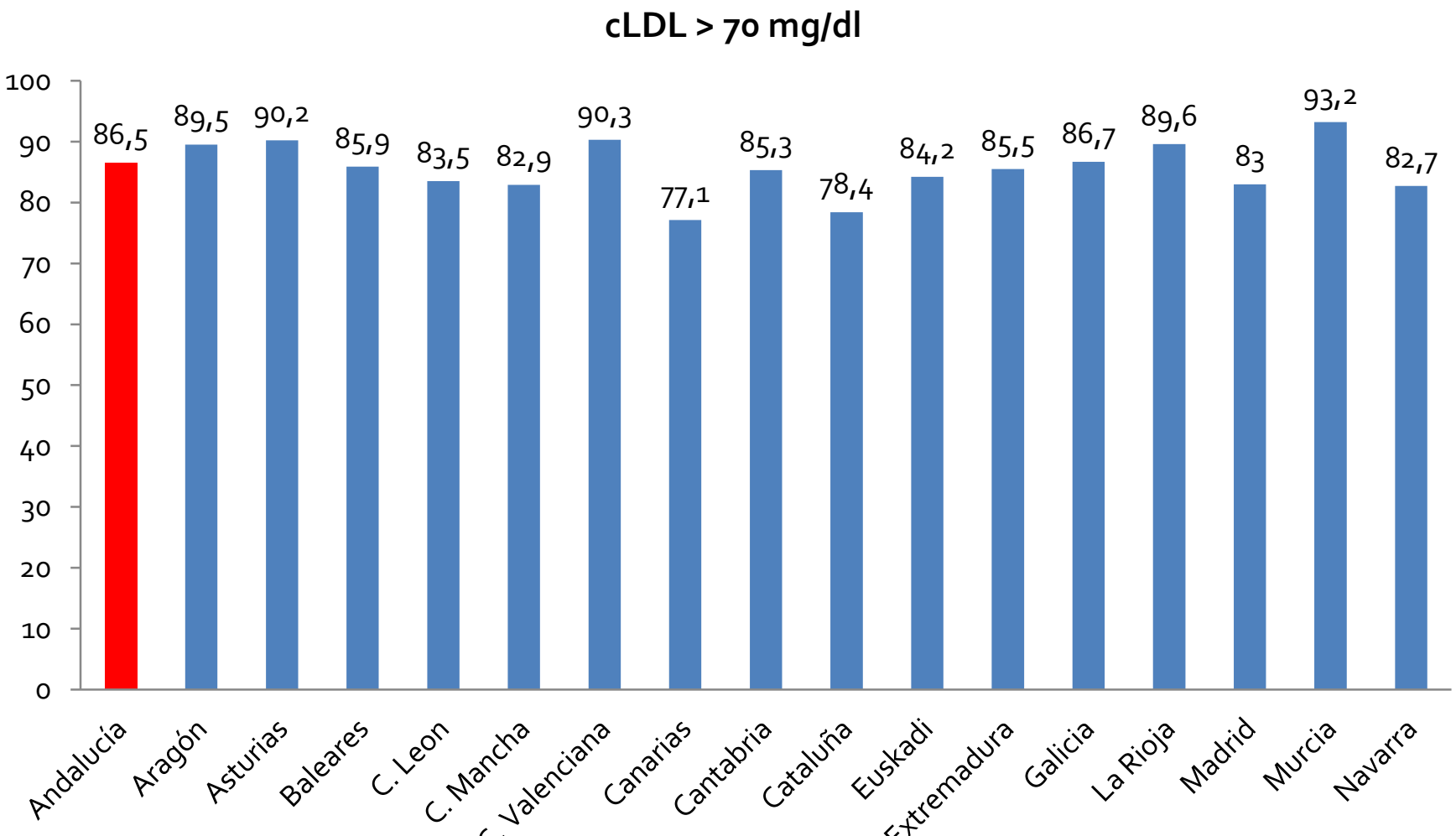
Control de la concentración de cLDL



Pérez de Isla L et al. Rev Clin Esp. 2012 Nov;212(10):475-81

Falta de control de cLDL (> 70 mg/dl) por CCAA

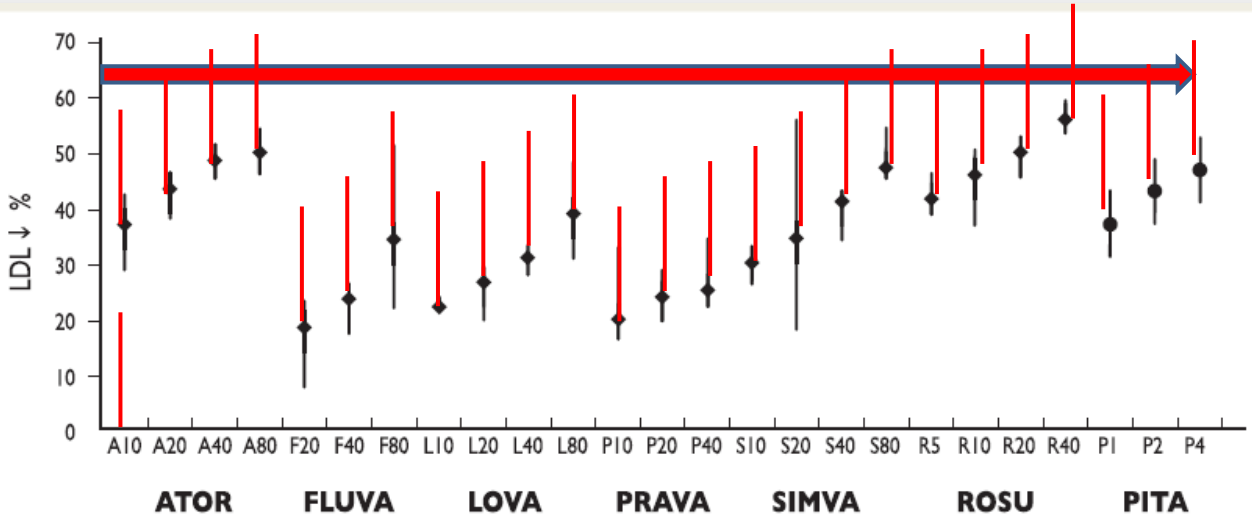
Todos los Pacientes



Ezetimibe

Ezetimibe

Eficacia Añadida Por Ezetimibe



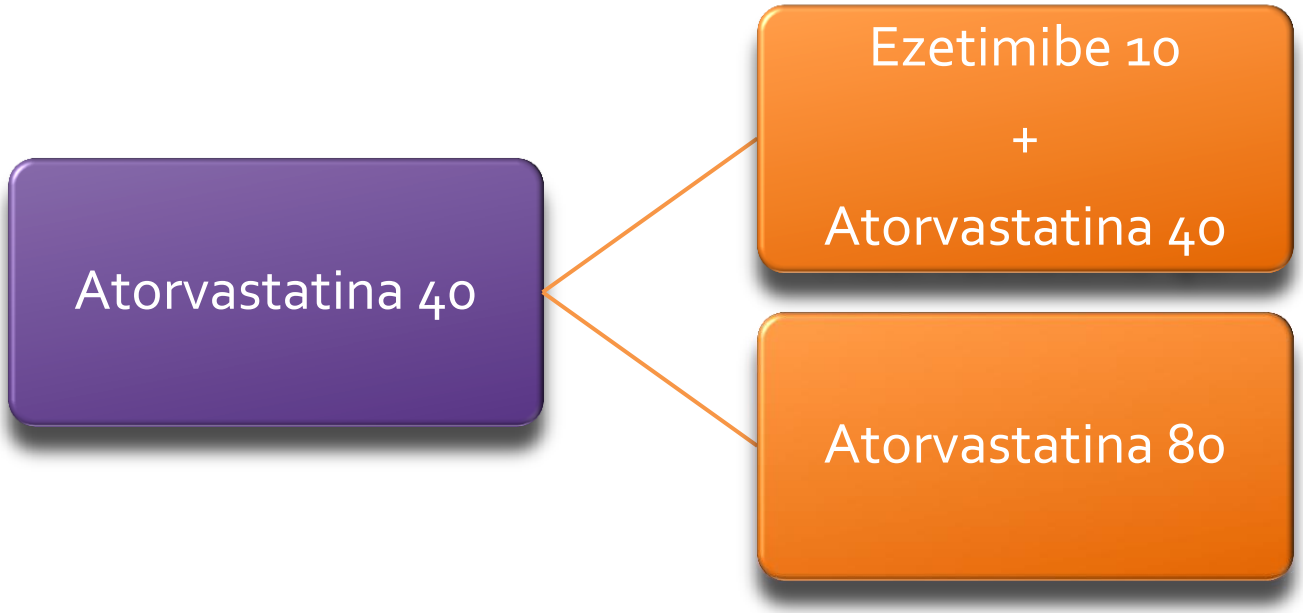
Weng TC, *et al. J Clin Pharm Ther* . 2010;35:139-151

Mukhtar RY, *et Al. Int J Clin Pract* . 2005;59(2):239-252

Figure A systematic review and meta-analysis on the therapeutic equivalence of statins.

Ezetimibe

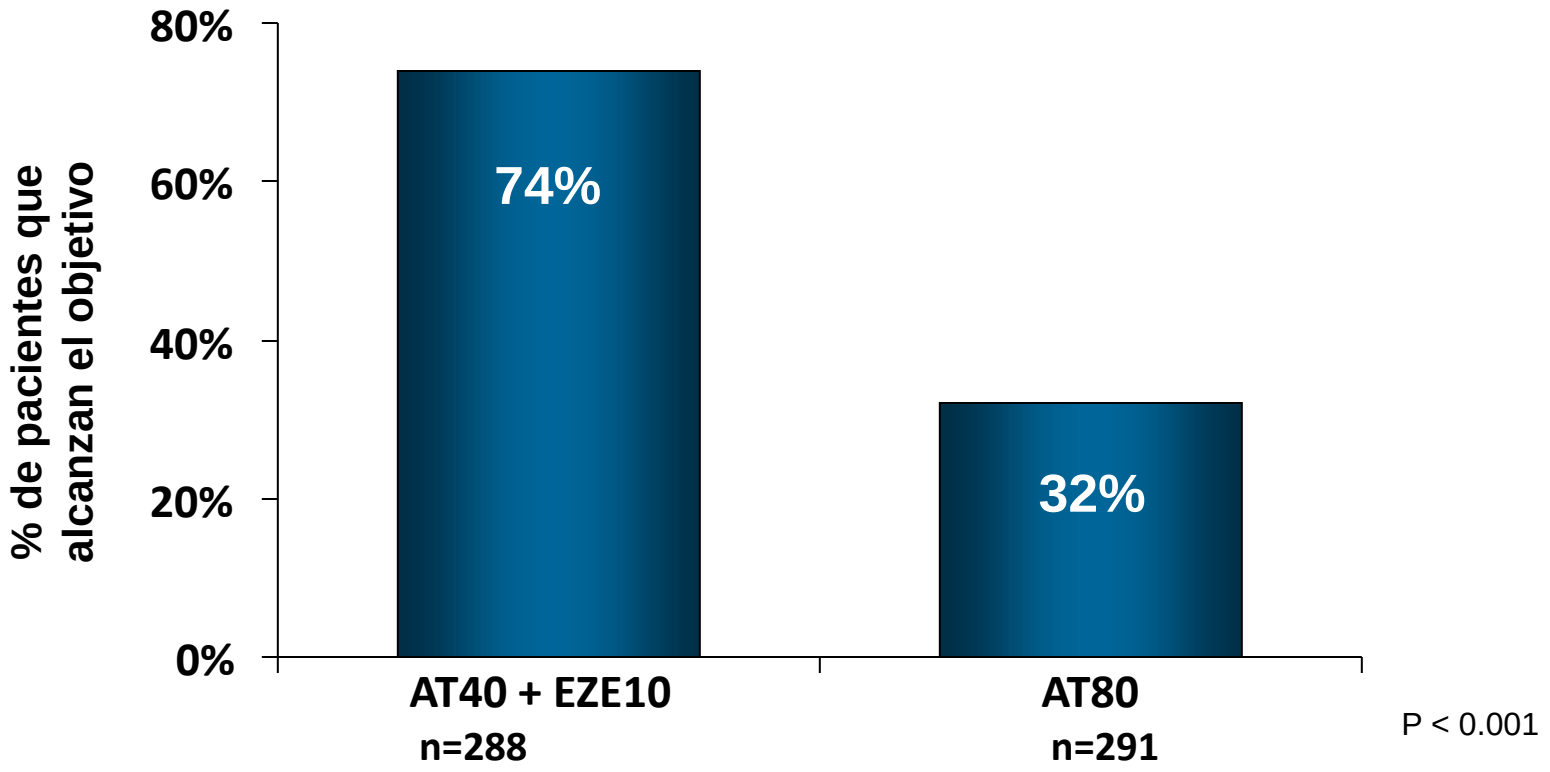
EZ PATH Trial



Ezetimibe

ESTUDIO EZ PATH

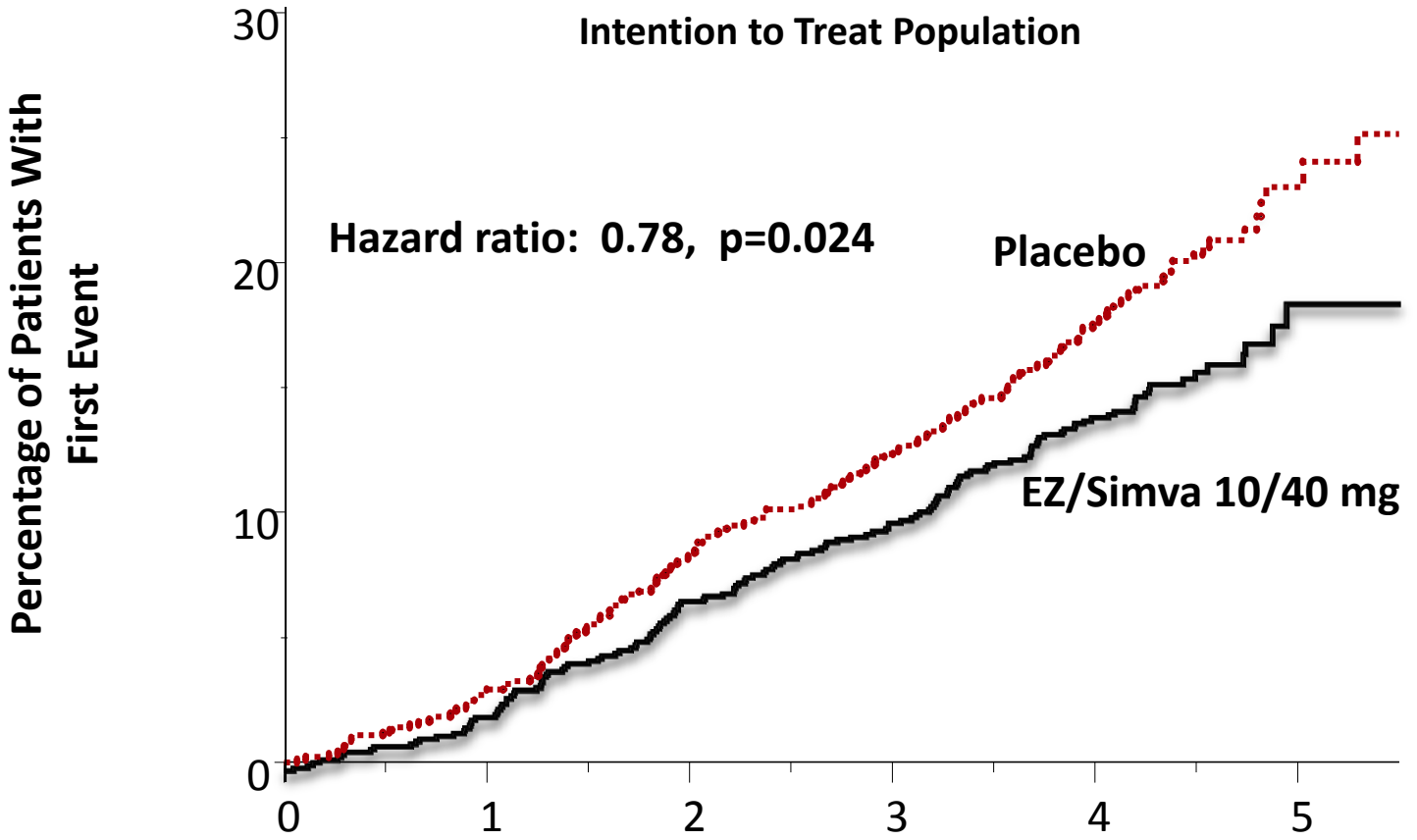
Pacientes en objetivo terapéutico



Ezetimibe

Un nuevo HITO en Medicina Cardiovascular

End-point 2º: Eventos CV isquémicos

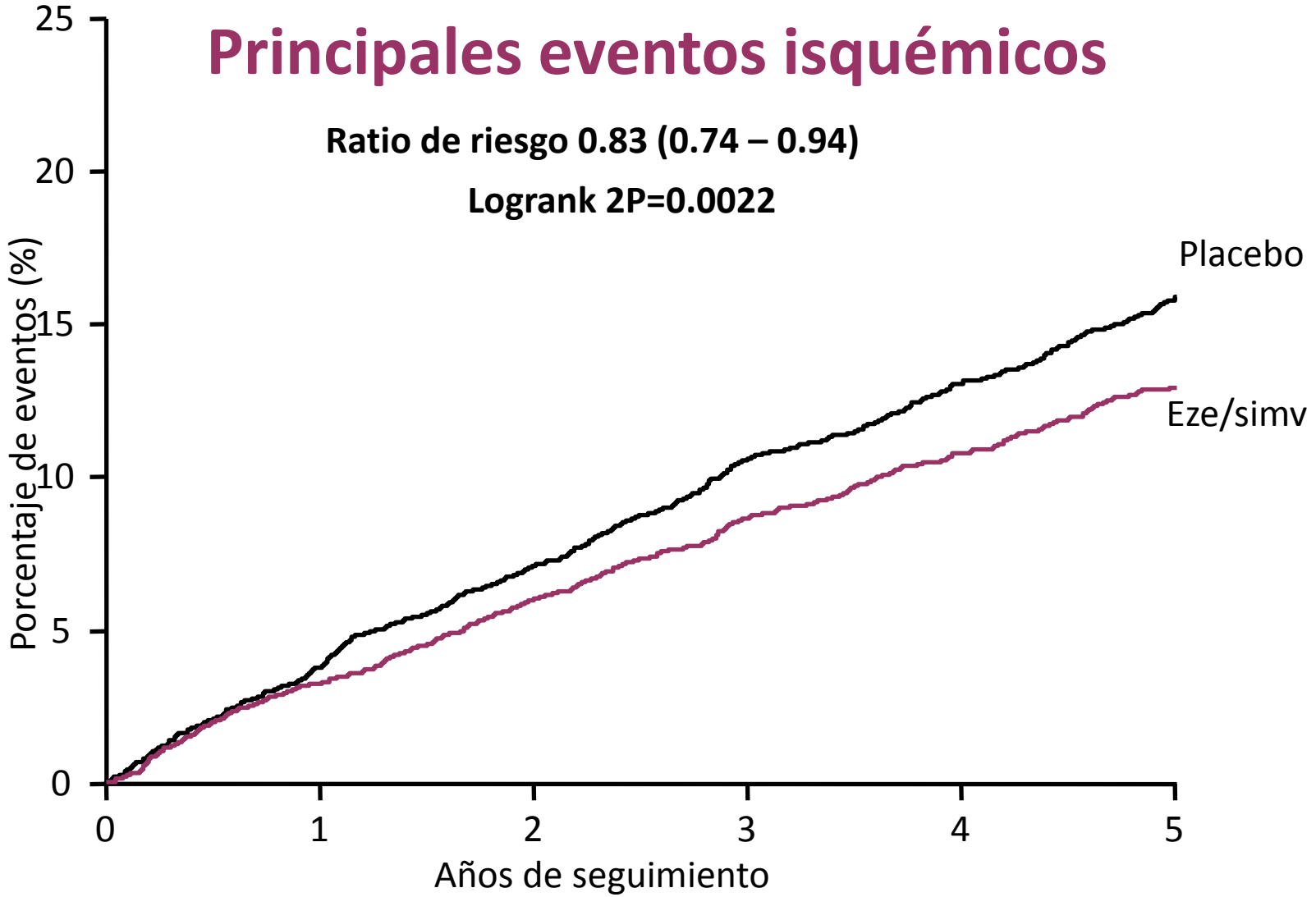


No. at risk					
EZ/Simva 10/40 mg	917	867	823	769	76
Placebo	898	838	788	729	76

N Engl J Med 2008;359:1343-56.

SHARP

SHARP
Principales eventos isquémicos



IMPROVE-IT

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome

Objetivo

IMPROVE-IT: **Evaluar la eficacia de ezetimibe+simva vs. simva:**

- **¿La reducción del LDL con ezetimibe reduce los eventos?**
- **C-LDL ¿Cuanto más bajo mejor?**
- **Seguridad de ezetimibe**

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

Pacientes

IMPROVE-IT

Criterios de inclusión:

- Hospitalización por SCA < 10 días
- ≥ 50 años y ≥ 1 característica de alto riesgo:
  - Nuevo cambio ST, troponina +, DM, IAM previo, enfermedad vascular periférica, enfermedad cerebrovascular previa, CABG previo > 3 years, enfermedad multivaso

- **C-LDL 50-125 mg/dL**
  - **(50–100 mg/dL si tratamiento hipolipemiante)**

Diseño

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

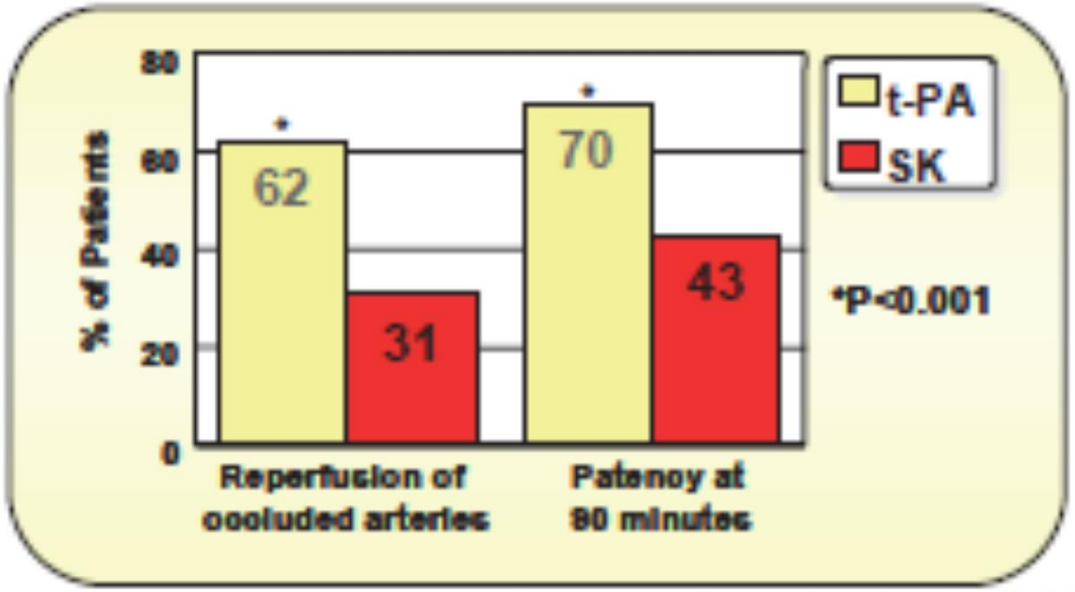
90% power to detect ~9% difference

Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

TIMI 1



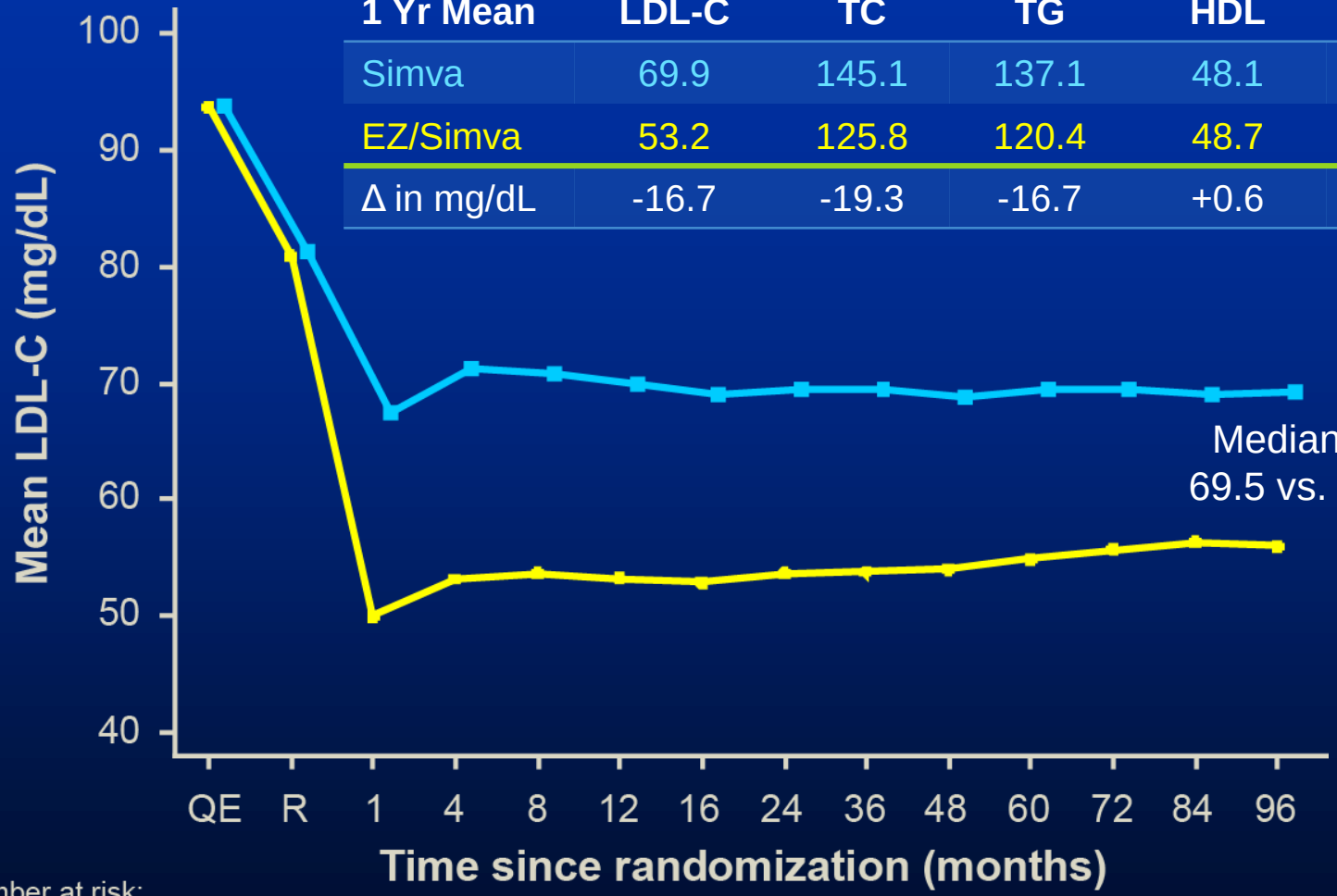
TIMI Study Group, N Engl J Med 1985; 312:932-36

The TIMI 1 trial enrolled 290 patients with acute MI and randomized them to tPA or SK. Patients treated with tPA (yellow bars) had improved reperfusion and vessel patency at 90 minutes.

Lípidos

IMPROVE-IT

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



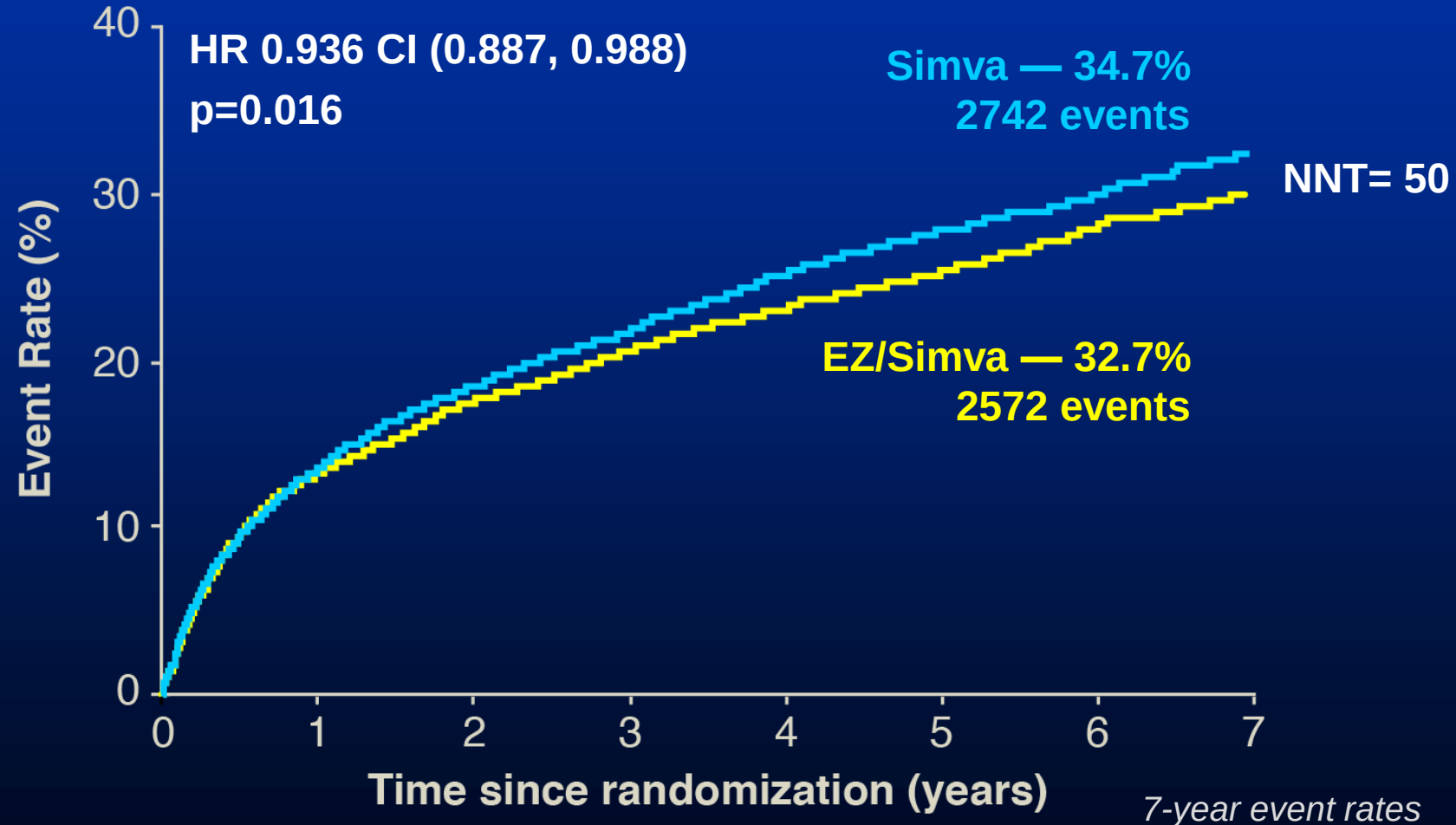
Median Time avg
69.5 vs. 53.7 mg/dL

Number at risk:

EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

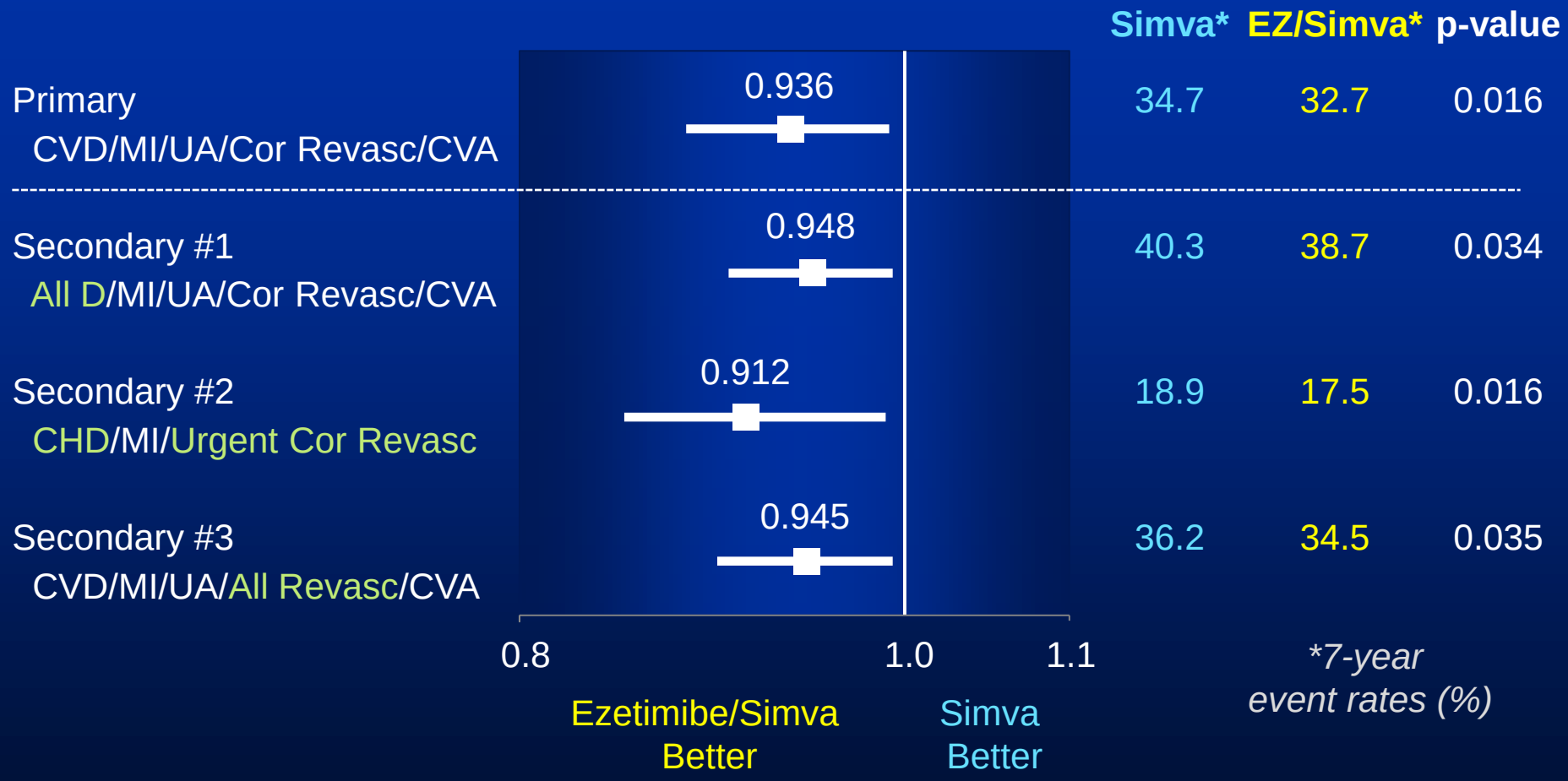
End-point primario — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



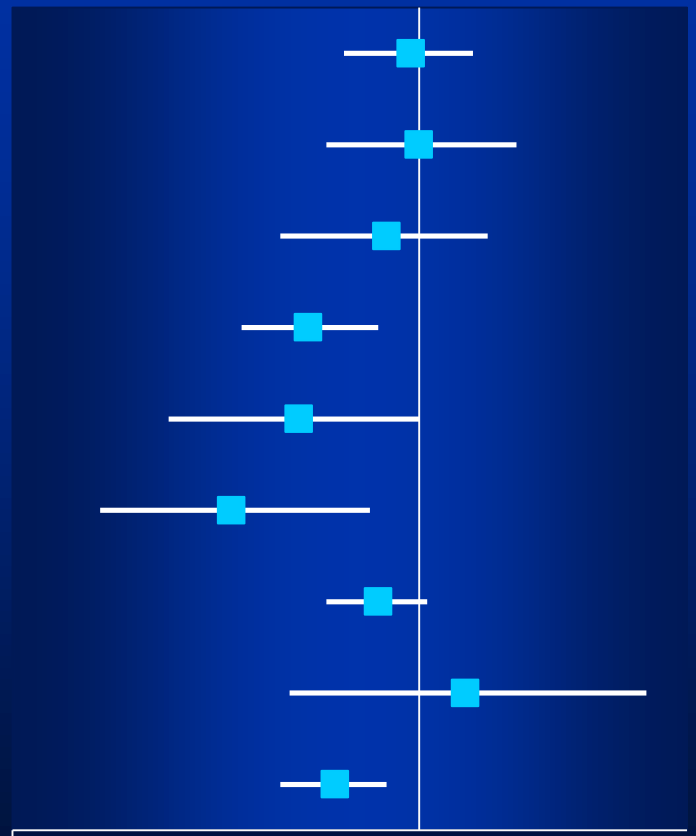
7-year event rates

End point secundarios — ITT



UA, documented unstable angina requiring rehospitalization; Cor Revasc, coronary revascularization (≥30 days after randomization); All D, all-cause death; CHD, coronary heart disease death; All Revasc, coronary and non-coronary revascularization (≥30 days)

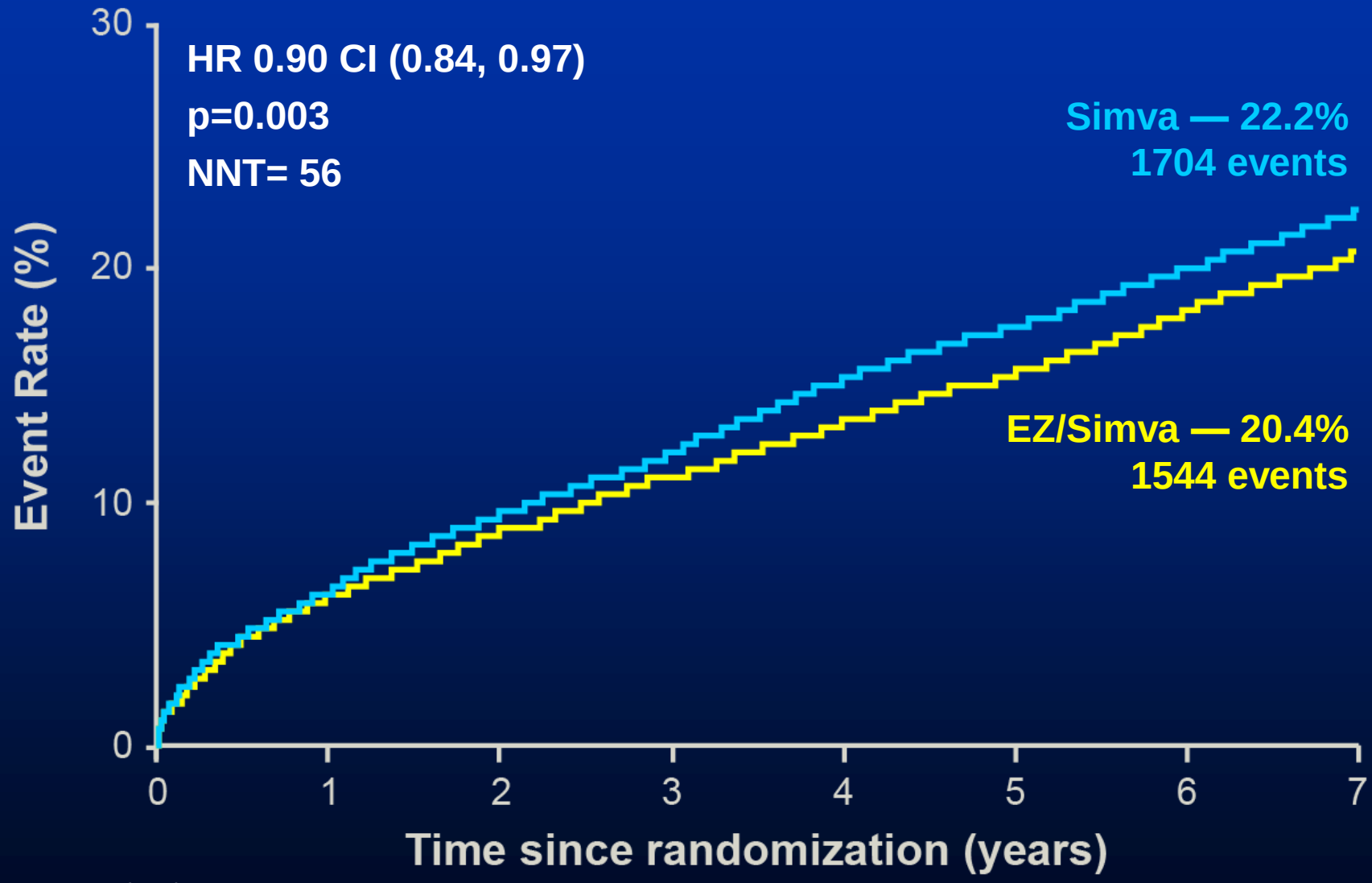
Endpoints individuales



	HR	Simva*	EZ/Simva*	p-value
All-cause death	0.99	15.3	15.4	0.782
CVD	1.00	6.8	6.9	0.997
CHD	0.96	5.8	5.7	0.499
MI	0.87	14.8	13.1	0.002
Stroke	0.86	4.8	4.2	0.052
Ischemic stroke	0.79	4.1	3.4	0.008
Cor revasc ≥ 30d	0.95	23.4	21.8	0.107
UA	1.06	1.9	2.1	0.618
CVD/MI/stroke	0.90	22.2	20.4	0.003

**7-year event rates (%)*

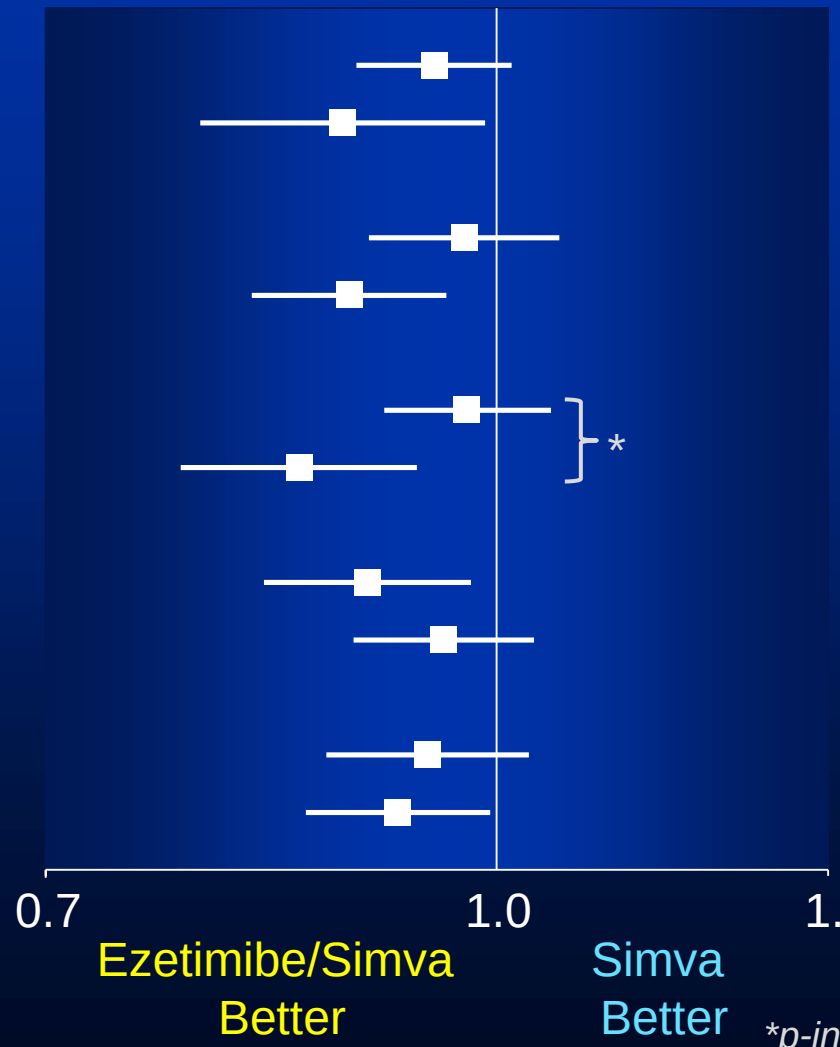
Muerte CV, IM no mortal o ictus no mortal



7-year event rates

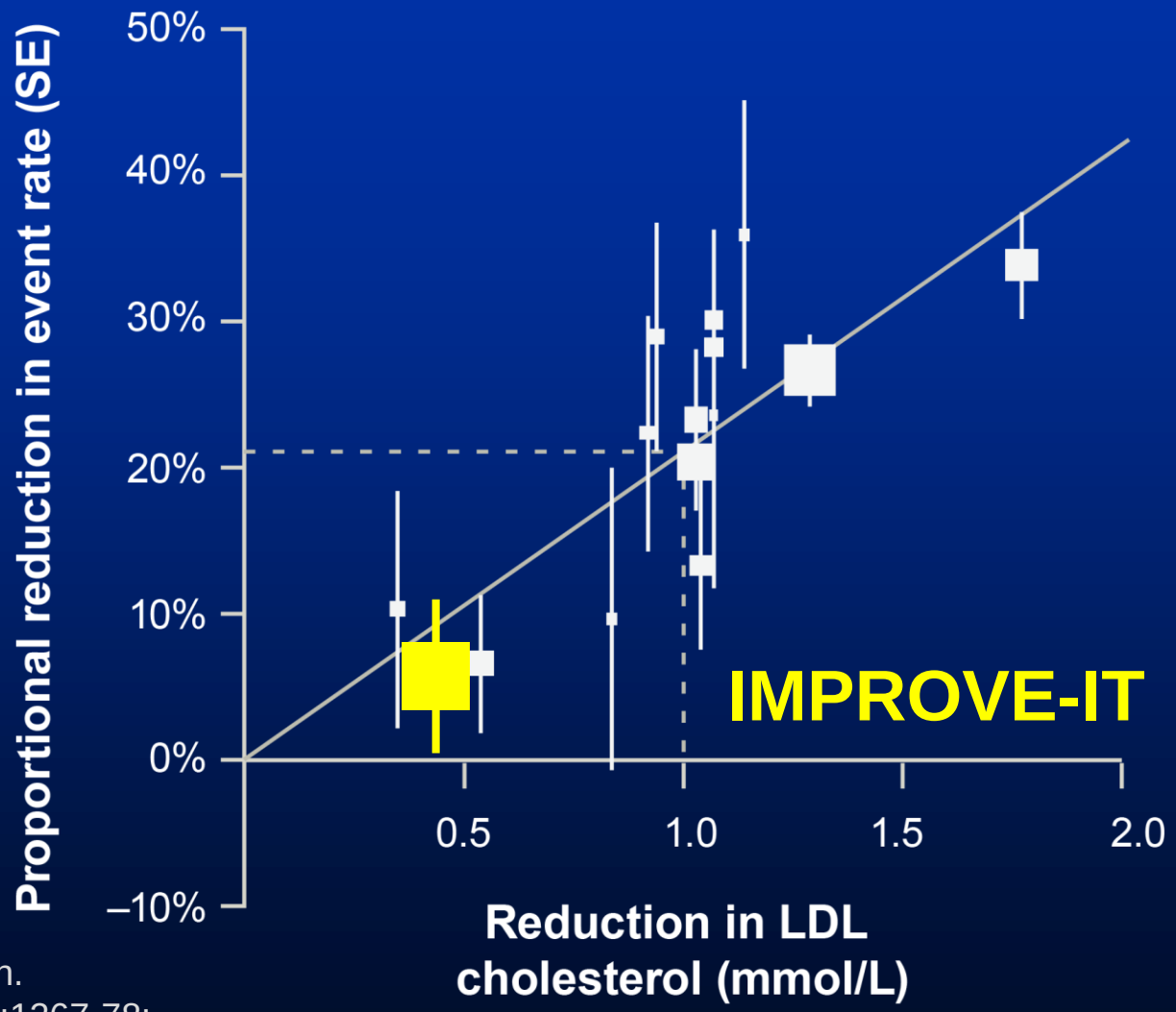
Análisis de subgrupos

	Simva†	EZ/Simva†
Male	34.9	33.3
Female	34.0	31.0
Age < 65 years	30.8	29.9
Age ≥ 65 years	39.9	36.4
No diabetes	30.8	30.2
Diabetes	45.5	40.0
Prior LLT	43.4	40.7
No prior LLT	30.0	28.6
LDL-C > 95 mg/dl	31.2	29.6
LDL-C ≤ 95 mg/dl	38.4	36.0



†*7-year event rates*

**p-interaction = 0.023, otherwise > 0.05*



CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376:1670-81.

Seguridad

No statistically significant differences in cancer or muscle- or gallbladder-related events

	Simva n=9077 %	EZ/Simva n=9067 %	p
ALT and/or AST≥3x ULN	2.3	2.5	0.43
Cholecystectomy	1.5	1.5	0.96
Gallbladder-related AEs	3.5	3.1	0.10
Rhabdomyolysis*	0.2	0.1	0.37
Myopathy*	0.1	0.2	0.32
Rhabdo, myopathy, myalgia with CK elevation*	0.6	0.6	0.64
Cancer* (7-yr KM %)	10.2	10.2	0.57

** Adjudicated by Clinical Events Committee*

% = n/N for the trial duration

Implicaciones IMPROVE-IT

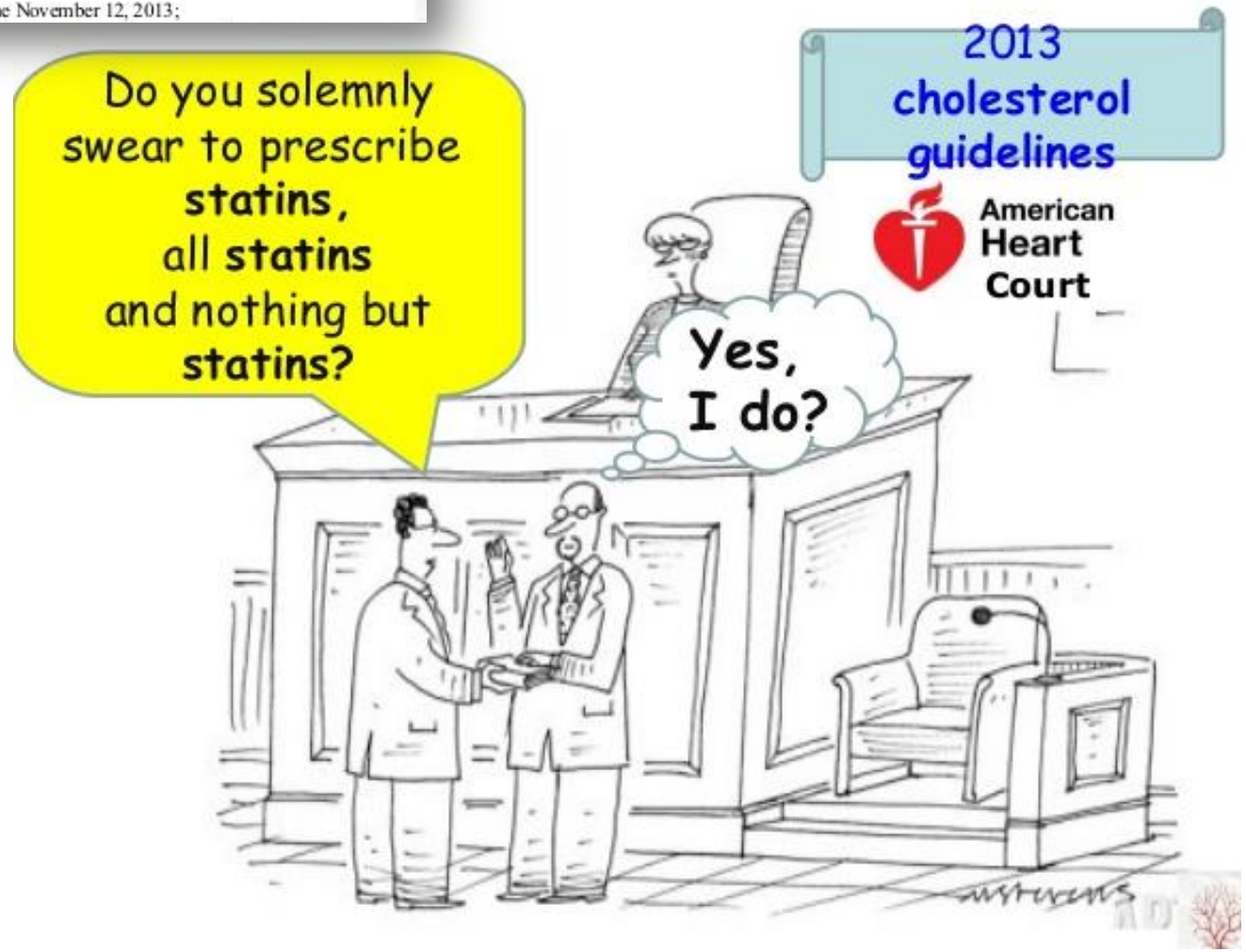
Circulation

American Heart Association

2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Robert H. Eckel, John M. Jakicic, Jamy D. Ard, Van S. Hubbard, Janet M. de Jesus, I-Min Lee, Alice H. Lichtenstein, Catherine M. Loria, Barbara E. Millen, Nancy Houston Miller, Cathy A. Nonas, Frank M. Sacks, Sidney C. Smith, Jr, Laura P. Svetkey, Thomas W. Wadden and Susan Z. Yanovski

Circulation. published online November 12, 2013;

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Circulation. published online November 12, 2013;

Implicaciones IMPROVE-IT

- Reconocen que un tratamiento más intenso con estatinas puede reducir más el riesgo CV más que uno moderado o de baja intensidad
- Admiten el empleo de no-estatinas evaluando el riesgo/beneficio
- SOLO la evidencia basada en ensayos clínicos debe ser empleada para establecer recomendaciones…

Deberían ser modificadas

IMPROVE-IT: 'Modest' Benefit When Adding Ezetimibe to Statins in Post-ACS Patients

Michael O'Riordan | November 21, 2014

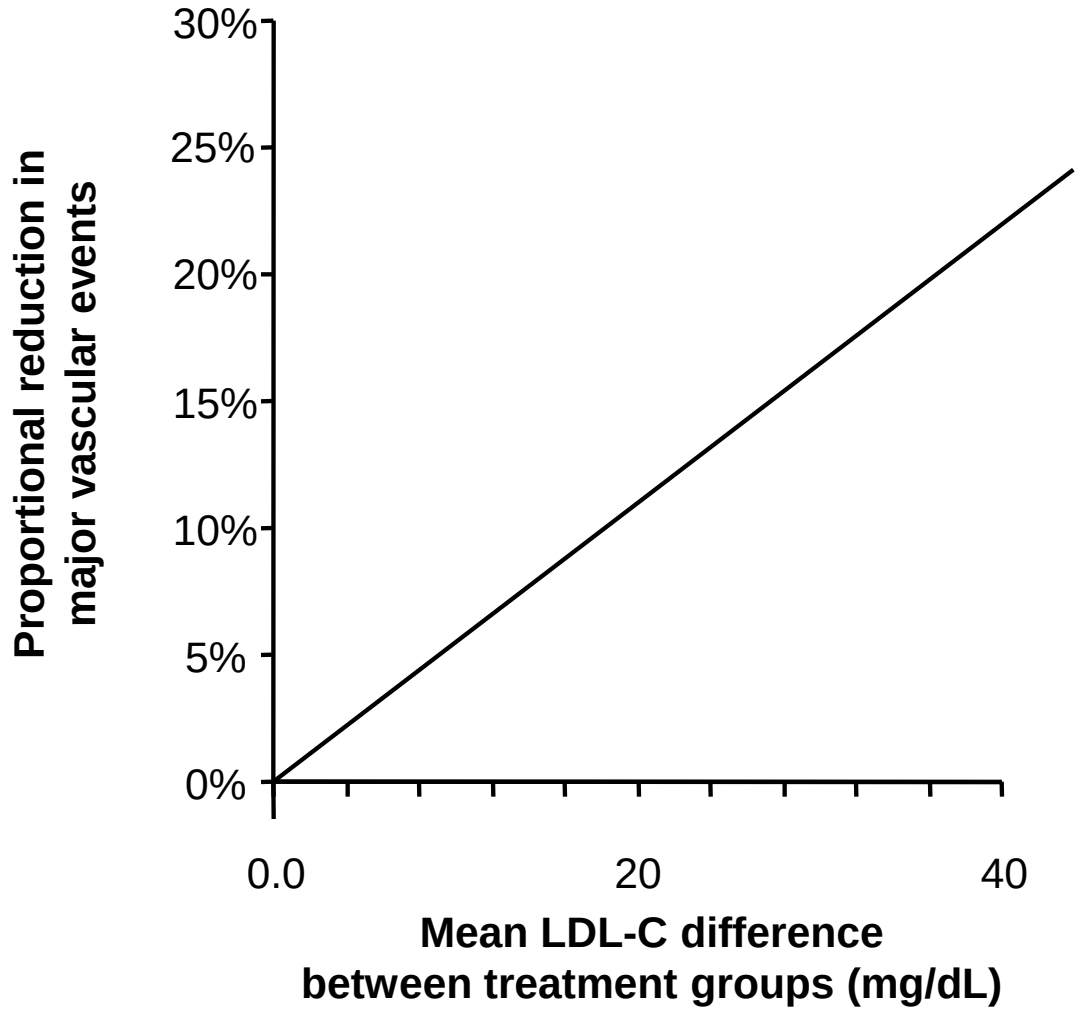
CHICAGO, IL (***updated***) — More than 9 years since the IMPROVE-IT study was launched, physicians now have their answer when it comes to using ezetimibe (*Zetia*, Merck/Schering-Plough) in clinical practice. The large-scale, long-delayed, and controversial study of ezetimibe in post–acute-coronary-syndrome (ACS) patients showed a "modest" benefit in reducing cardiovascular events when ezetimibe was added to simvastatin in this population.

Over a period of 7 years, the addition of ezetimibe to simvastatin 40 mg reduced the primary end point—a composite of cardiovascular death, MI, unstable angina requiring rehospitalization, coronary revascularization, or stroke—by 6.4% when compared with patients who received simvastatin alone (*P* =0.016). The absolute reduction in risk over 7 years was 2.0%, with 32.7% in the ezetimibe/simvastatin arm experiencing a primary end point compared with 34.7% in the simvastatin arm.

In terms of individual components of the primary end point, the reduction was driven by a statistically significant reduction in the risk of MI and ischemic stroke. Overall, there was a significant 10% reduction in the risk of cardiovascular death, nonfatal MI, or nonfatal stroke. All-cause mortality was not affected by treatment.

Dr Christopher Cannon (Brigham and Women's Hospital, Boston, MA), one of the lead investigators, said this is the "first trial demonstrating an incremental clinical benefit when adding a nonstatin, cholesterol-lowering agent to a statin."

The study, however, also supports the "lower–is-better" cholesterol premise, said Cannon. At baseline, the mean LDL-cholesterol level among the ACS patients was 95 mg/dL in both treatment arms. With simvastatin 40 mg, LDL-cholesterol levels were reduced to 69.9

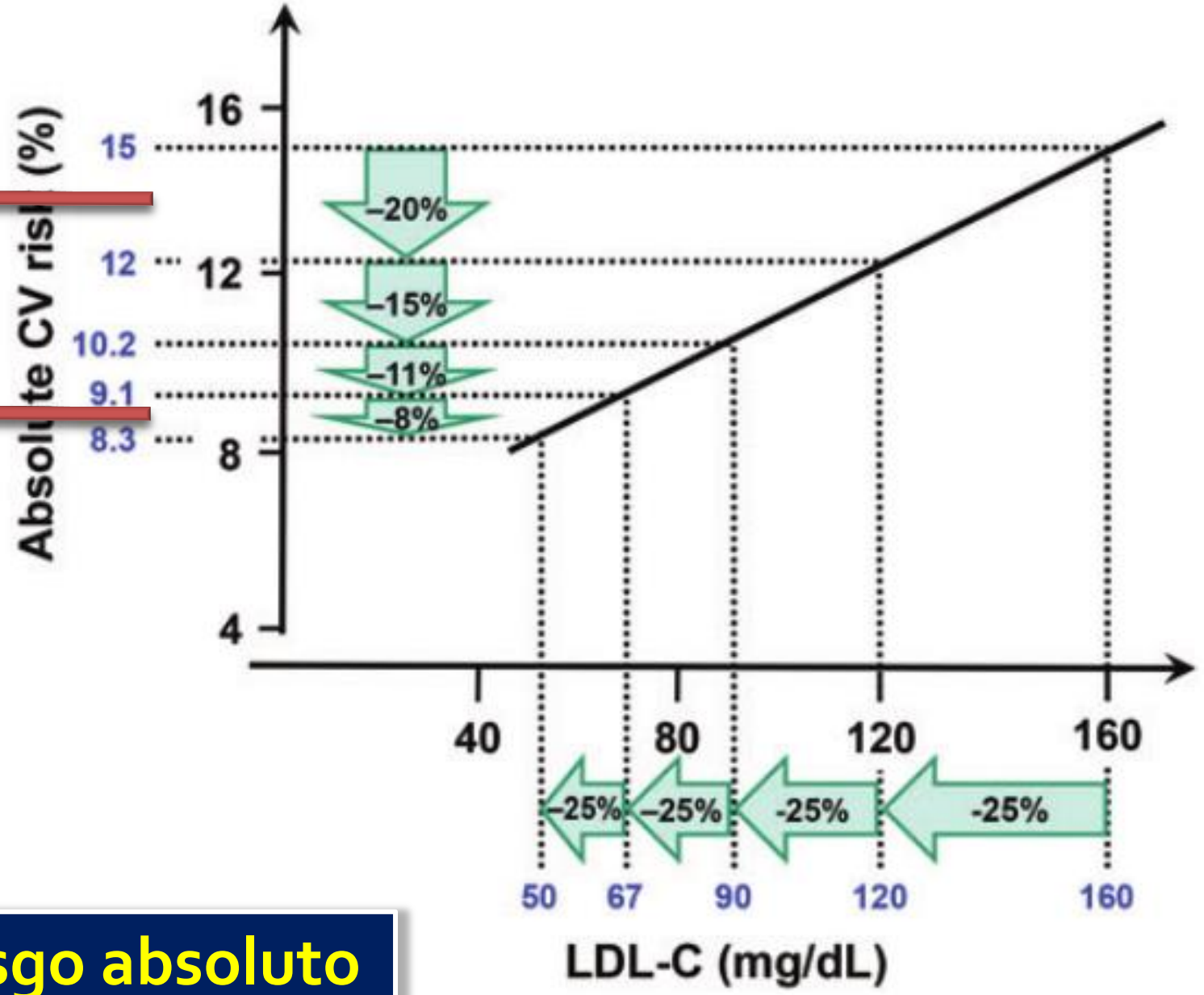


- *Una reducción de 39 mg/dl. de colesterol LDL lleva a una reducción de un 23% de eventos CV*

Cholesterol Treatment Trialists' Collaboration. *Lancet*. 2010;376:1670-1681.

NNT = 33

NNT = 125



NNT = 1 / reducción riesgo absoluto

Nuevas evidencias….

Risk Stratification for Cardiovascular Events in the IMPROVE-IT Trial

E.A. Bohula May, J.A. White, M.A. Blazing, R.P. Giugliano, T.A. Musliner, A.M. Tershakovec, A. McCagg, D.L. Bhatt, C.P. Cannon, R.M. Califf & E. Braunwald

on behalf of the IMPROVE-IT Investigators

REACH Registry Risk Score

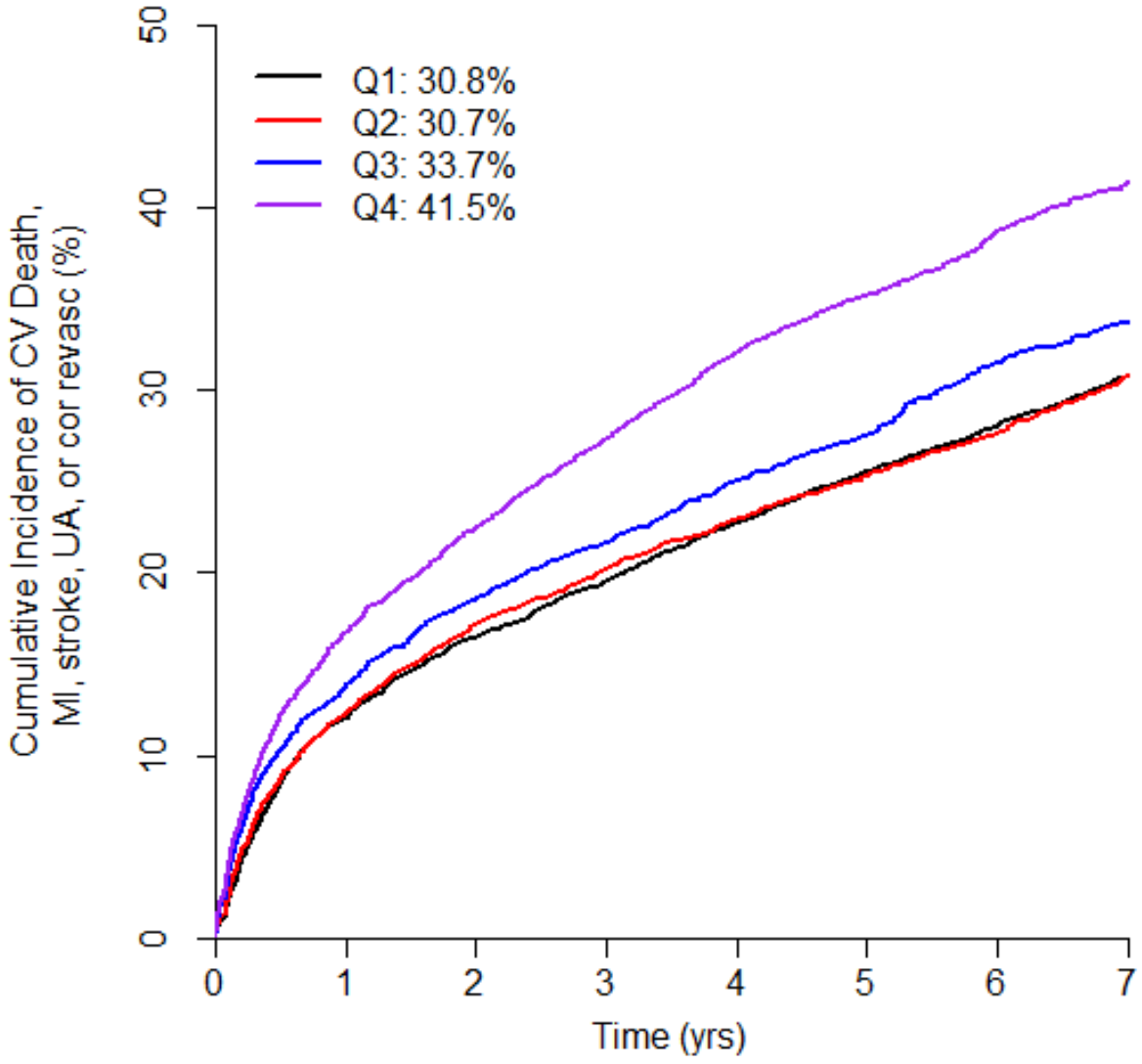
- The REduction of Atherothrombosis for Continued Health (REACH) score
  - Predice segundos eventos CV a 20 meses (CV death, MI, stroke & CV hospitalization) en pacientes estables

Variable	Points	Variable	Points
Male	1	BMI<20kg/m²	2
Age, 25-85 yr	1/every 4 yr	CV event in the past yr	2
Smoking	2	CHF	3
Diabetes	2	Atrial Fibrillation	2
Number vascular beds		Statin therapy	-2
One	2	ASA therapy	-1
Two	4	E. Europe or Middle East	2
Three	6	Japan or Australia	-2

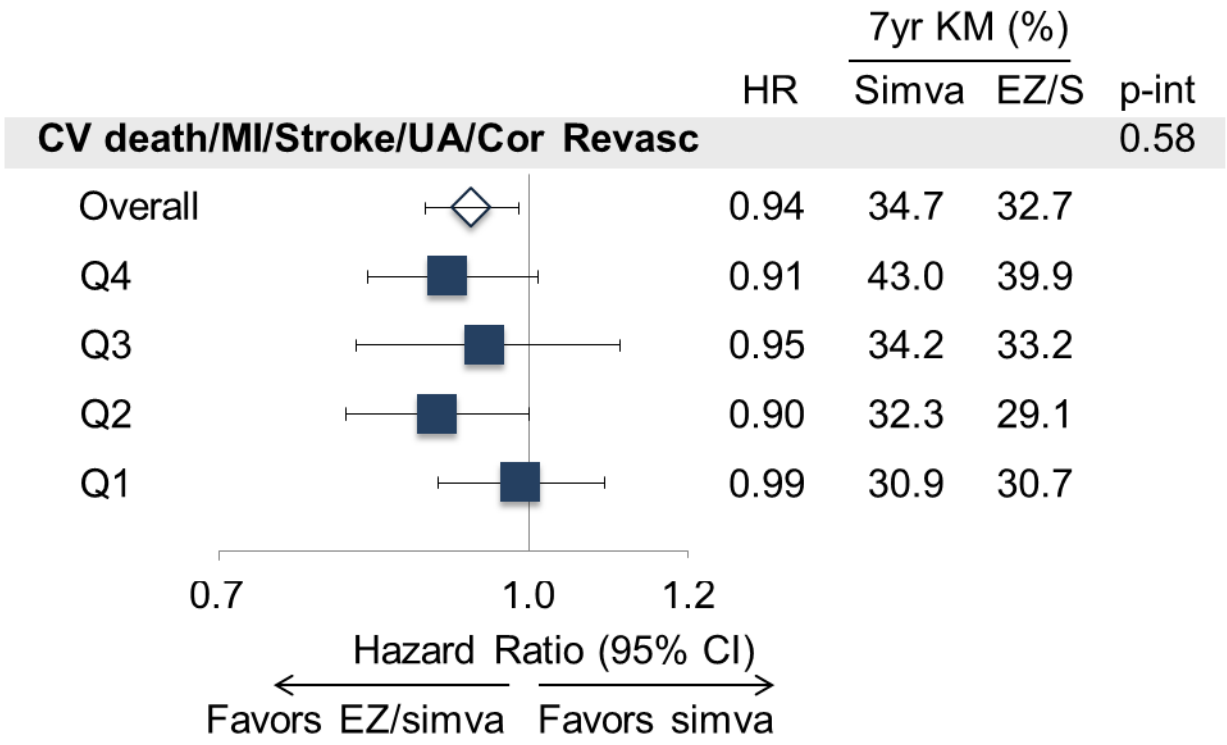
Hipótesis

- **El Score REACH puede:**
  - **Identificar el grupo de mayor riesgo de eventos CV**
  - **Definir un grupo que se beneficie más de la combinación ezetimibe/simvastatina**

Predicción de riesgo por cuartiles



Análisis de subgrupos



Conclusiones

- **En este análisis pre-especificado el score REACH:**
  - **Predice eventos CV en pacientes post-SCA (no sólo estables).**
  - **Ezetimibe es igual de eficaz en pacientes con diferentes niveles de riesgo**

Baseline LDL-C and Clinical Outcomes With Addition of Ezetimibe to Statins in 18,144 Patients Post ACS: An Analysis From IMPROVE IT†

RP Giugliano[1], CP Cannon[1], MA Blazing[2], JA White[2], SA Murphy[1], AM Tershakovec[3], TA Musliner[3], RM Califf[2], E Braunwald[1]

[1]Brigham and Women's Hospital, Boston, MA,
[2]Duke Clinical Research Institute, Durham, NC, and
[3]Merck & Co., Inc., Kenilworth, NJ, USA

†Moderated Poster Session: Acute Coronary Syndromes Moderated Poster Theater, Poster Hall B1; Poster #01477; Saturday March 14th 10:45AM PDT

Background

- PROVE IT-TIMI 22: menos beneficio de atrova 80 vs prava 40 tras SCA cuanto más bajo es el LDL-c
- Ezetimibe ha demostrado su eficacia en el IMPROVE-IT
- No conocemos el beneficio de ezetimibe en función del LDL-c basal

Preliminary Results – Presented at ACC 2015 by R Giugliano

Objetivo

- Evaluar el beneficio clínico de EZETIMIBE-SIMVASTATINA en función del LDL-c en el ingreso

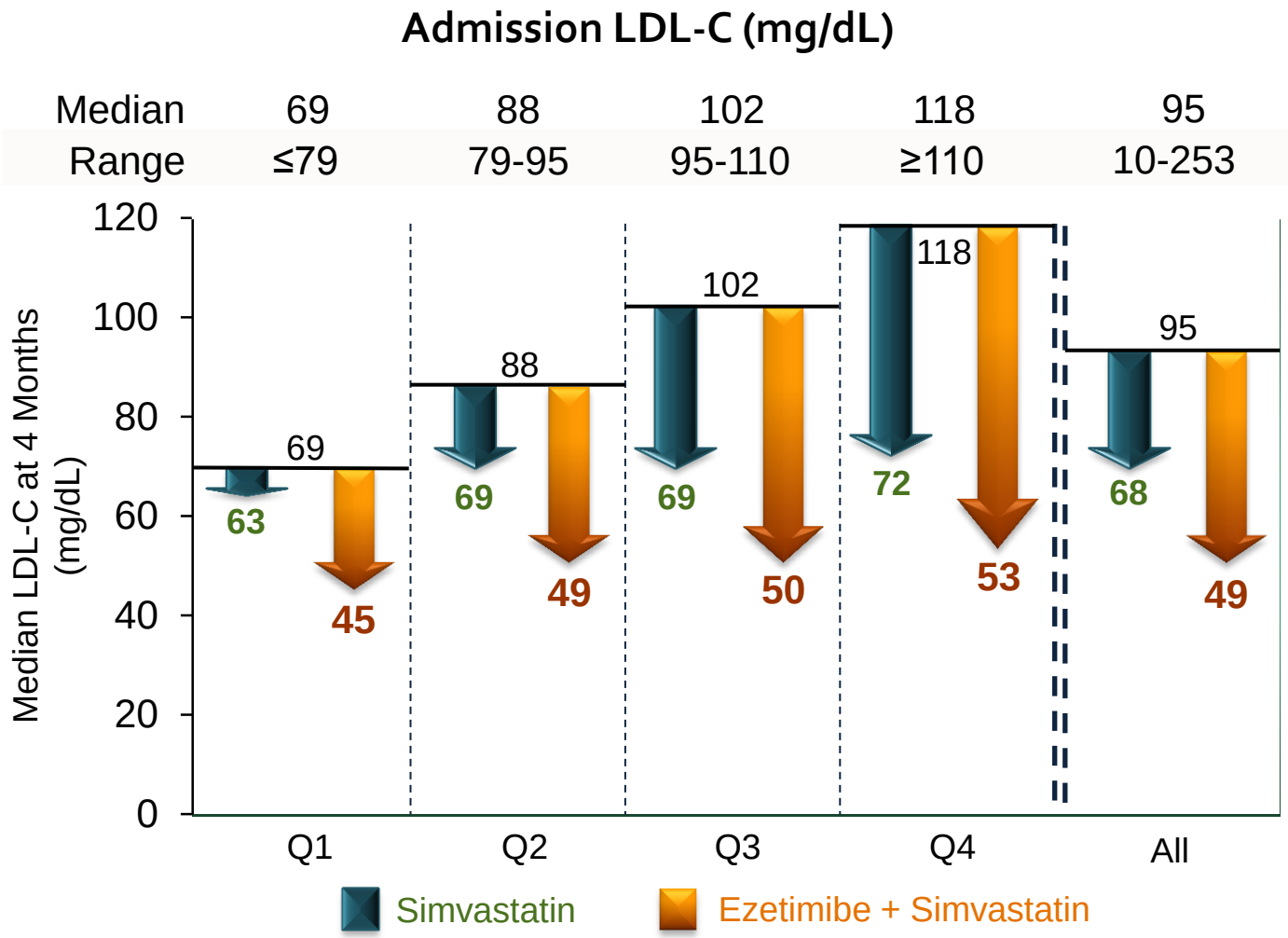
Preliminary Results – Presented at ACC 2015 by R Giugliano

Baseline Characteristics by LDL-C Quartiles at Admission

	All Pts	Q1	Q2	Q3	Q4	
# of Pts	**17,999**	**4542**	**4583**	**4429**	**4450**	**P**
Median Baseline LDL-C	**95**	**69**	**88**	**102**	**118**	**Value**
Age (yr, median)	63	65	64	62	61	<0.001
Weight (kg, median)	81	82	81	81	82	0.41
Male sex (%)	76	77	75	76	76	0.35
Caucasian (%)	84	83	83	84	85	0.066
Hypertension (%)	61	71	64	58	52	<0.001
Diabetes mellitus (%)	27	37	30	23	18	<0.001
Smoking (%)	33	26	31	36	39	<0.001
Prior lipid-lowering Rx (%)	36	67	48	21	4.9	<0.001
Prior MI (%)	21	36	25	15	8.6	<0.001
Prior PCI (%)	20	34	24	13	6.9	<0.001
Prior CABG (%)	9.3	17	12	5.1	3.4	<0.001
Hx of CHF (%)	4.4	7.5	4.6	2.9	2.3	<0.001
Hx of PAD (%)	5.5	7.4	6.3	4.9	3.4	<0.001
STEMI at admission (%)	29	20	27	32	36	<0.001
Killip Class ≥ II (%)	8.5	9.0	8.9	8.1	7.9	0.15
In-hospital PCI (%)	70	63	69	73	75	<0.001

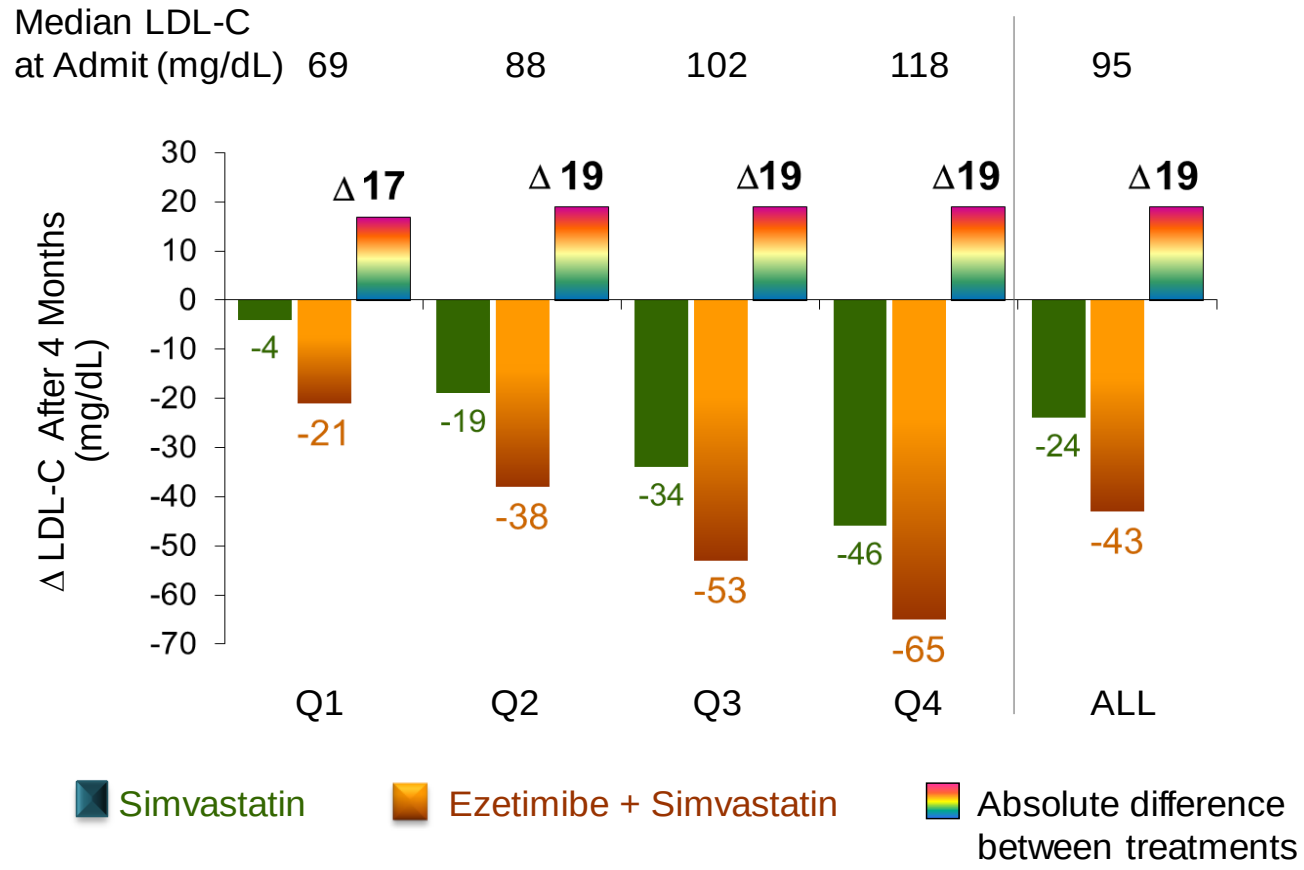
Preliminary Results – Presented at ACC 2015 by R Giugliano

LDL-C at Admission and after 4 Months of Therapy by Quartiles of Admission LDL-C



Preliminary Results – Presented at ACC 2015 by R Giugliano

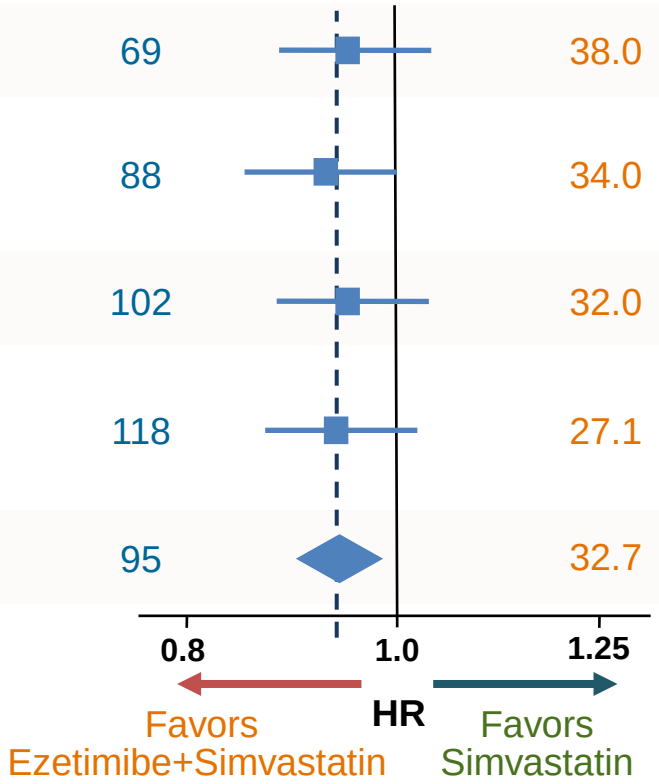
Absolute Change in LDL-C from Baseline to 4 Months by Treatment and Quartiles of Admission LDL-C



Preliminary Results – Presented at ACC 2015 by R Giugliano

Hazard Ratios for the Primary Endpoint by Quartiles of LDL-C at Admission

Quartile	Median LDL-c (mg/dL)	Primary Endpoint	EZ/S (%)	Simvastatin (%)	HR	P Value	Adj P_{int}
1	69		38.0	39.0	0.95	0.33	0.85
2	88		34.0	37.1	0.91	0.068	0.58
3	102		32.0	33.0	0.95	0.38	0.70
4	118		27.1	29.4	0.93	0.24	Ref
Overall	95		32.7	34.7	0.936	0.017	



Adj P_{int}= 0.77 for Rx* LDL in quartiles

Adj P_{trend} = 0.76

Preliminary Results – Presented at ACC 2015 by R Giugliano

Secondary Composite Endpoints by LDL-C Quartile at Admission

	Secondary Endpoint: Hazard Ratio (95% CI)		
Quartile of LDL-C (mg/dL) at admission	All D/MI/UA/ Cor Revasc/ CVA	CHD/MI/Urgent Cor Revasc	CVD/MI/UA/All Revasc/CVA
Quartile 1	0.99 (0.90,1.09)	0.96 (0.84, 1.09)	0.95 (0.86, 1.05)
Quartile 2	0.90 (0.82, 0.99)	0.84 (0.72, 0.97)	0.93 (0.84, 1.03)
Quartile 3	0.97 (0.88, 1.08)	0.93 (0.79, 1.09)	0.95 (0.85, 1.06)
Quartile 4	0.92 (0.83, 1.03)	0.92 (0.78, 1.09)	0.95 (0.85, 1.07)
Adjusted P_{Int}	P=0.35	P=0.44	P=0.90
Adjusted P_{Irend}	P=0.99	P=0.65	P=0.78

Preliminary Results – Presented at ACC 2015 by R Giugliano

Conclusiones

- Mayor nivel de LDL-c basal = mayor reducción de LDL-c a los 4 meses, tanto en monoterapia como en combinación
- Beneficios de EZETIMIBE similares en los diferentes cuartiles
- Ezetimibe es beneficioso independientemente del LDL-c basal

Preliminary Results – Presented at ACC 2015 by R Giugliano

Reduction in Total (**First and Recurrent**) Cardiovascular Events with Ezetimibe/Simvastatin compared with Simvastatin Alone post ACS in the IMPROVE-IT Trial

Sabina A. Murphy, Christopher Cannon, Robert Giugliano, Michael Blazing, Thomas Musliner, Andrew Tershakovec, Jennifer White, Kelly Im, Naveen Deenadayalu, Haral Darius, Witold Ruzyllo, Andrew Tonkin, Uma Kher, Robert Califf, Eugene Braunwald

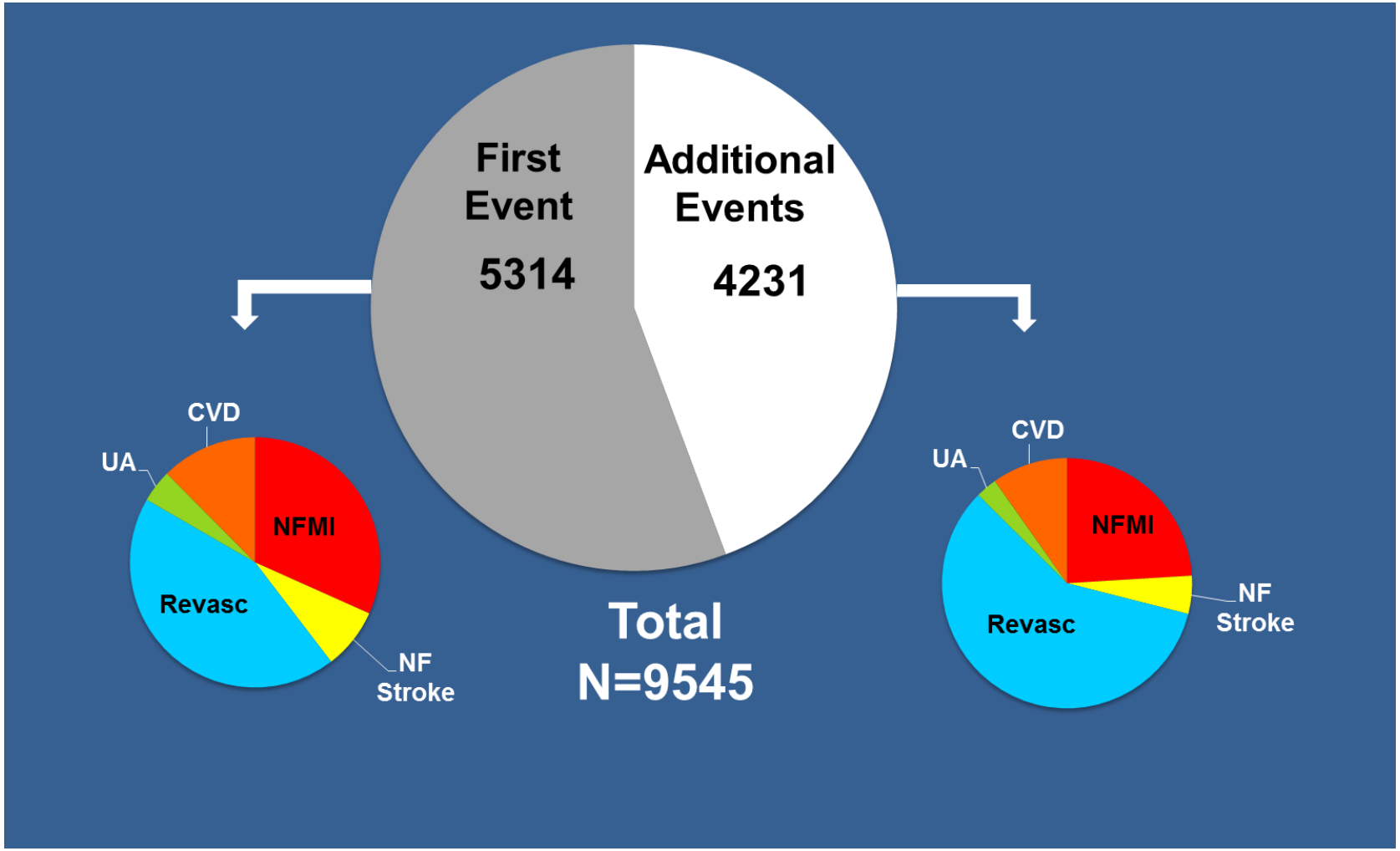
On behalf of the IMPROVE IT Investigators

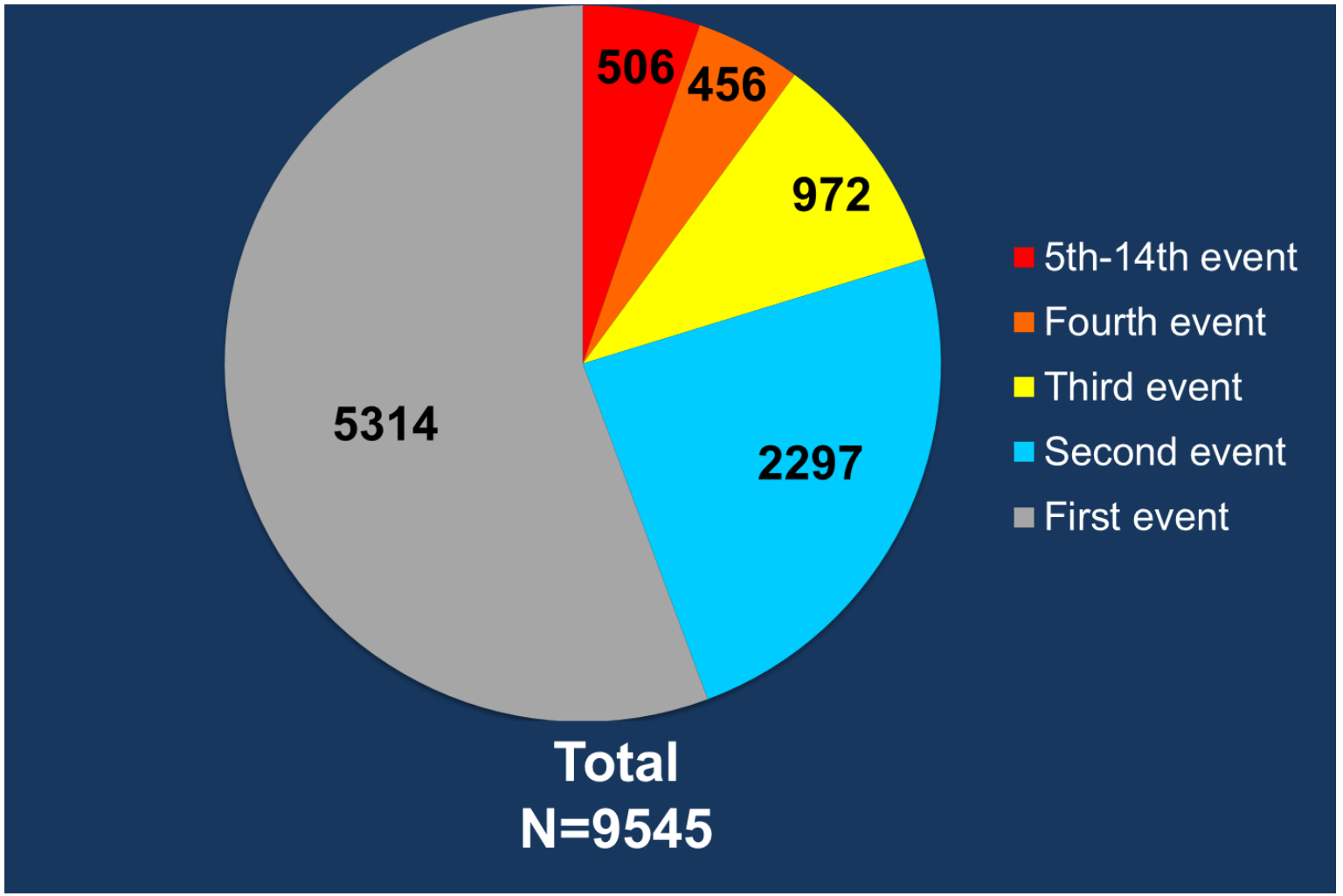
Background:

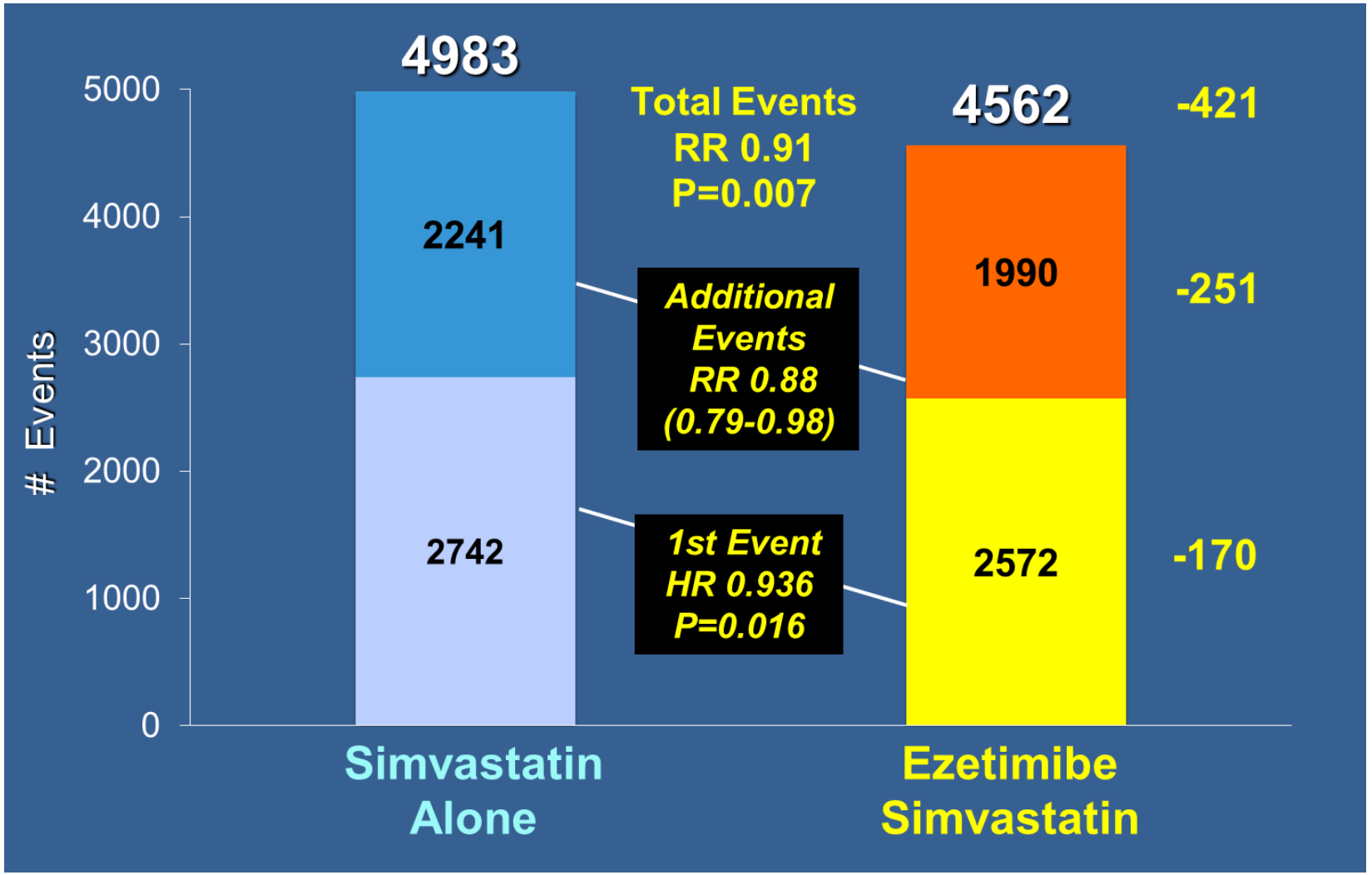
- Ensayos clínicos de seguimiento a largo palzo suelen analizar solo el primer evento
- Pero todos los eventos, PRIMERO y TOTALES son importantes

Hipótesis

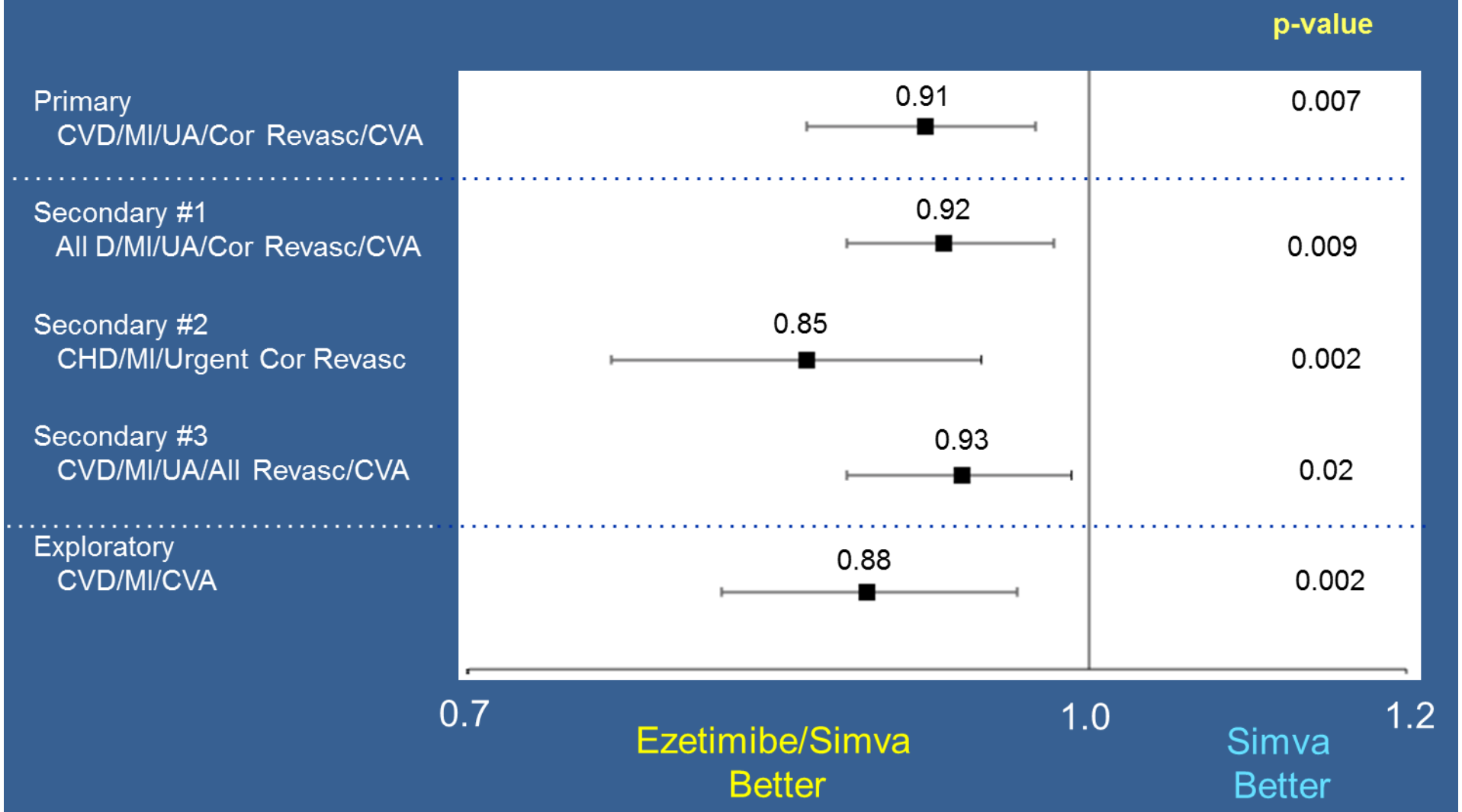
- **Ezetimibe/simvastatina reduce los primeros eventos y los totales en la población IMPROVE-IT**


First Event
5314
Additional Events
4231
Total
N=9545
CVD
UA
NFMI
Revasc
NF Stroke
CVD
UA
NFMI
Revasc
NF Stroke

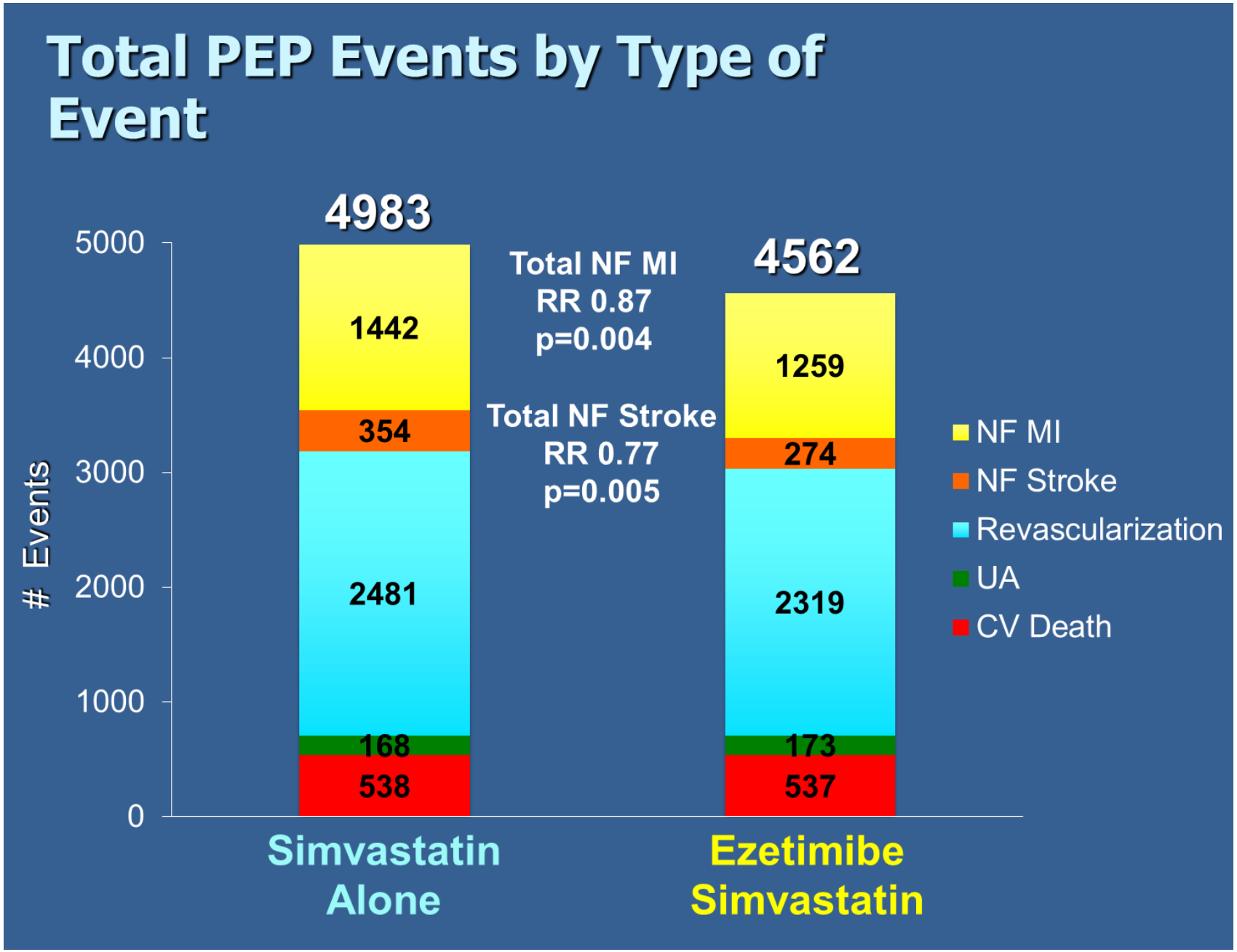

506
456
972
2297
5314
5th-14th event
Fourth event
Third event
Second event
First event
Total
N=9545


4983
5000
4000
3000
2000
1000
0
Events
2241
2742
Total Events
RR 0.91
P=0.007
Additional Events
RR 0.88
(0.79-0.98)
1st Event
HR 0.936
P=0.016
4562
1990
2572
-421
-251
-170
Simvastatin Alone
Ezetimibe Simvastatin

Primary and 3 Prespecified Secondary Endpoints — Total Events



Total PEP Events by Type of Event



Conclusiones

- Ezetimibe/simvastatina reduce los eventos TOTALES
- Al tomar en consideración los eventos totales, el beneficio de la coadministración es aún mayor
- Beneficio de mantener EZETIMIBE-SIMVASTATINA tras un evento recurrente

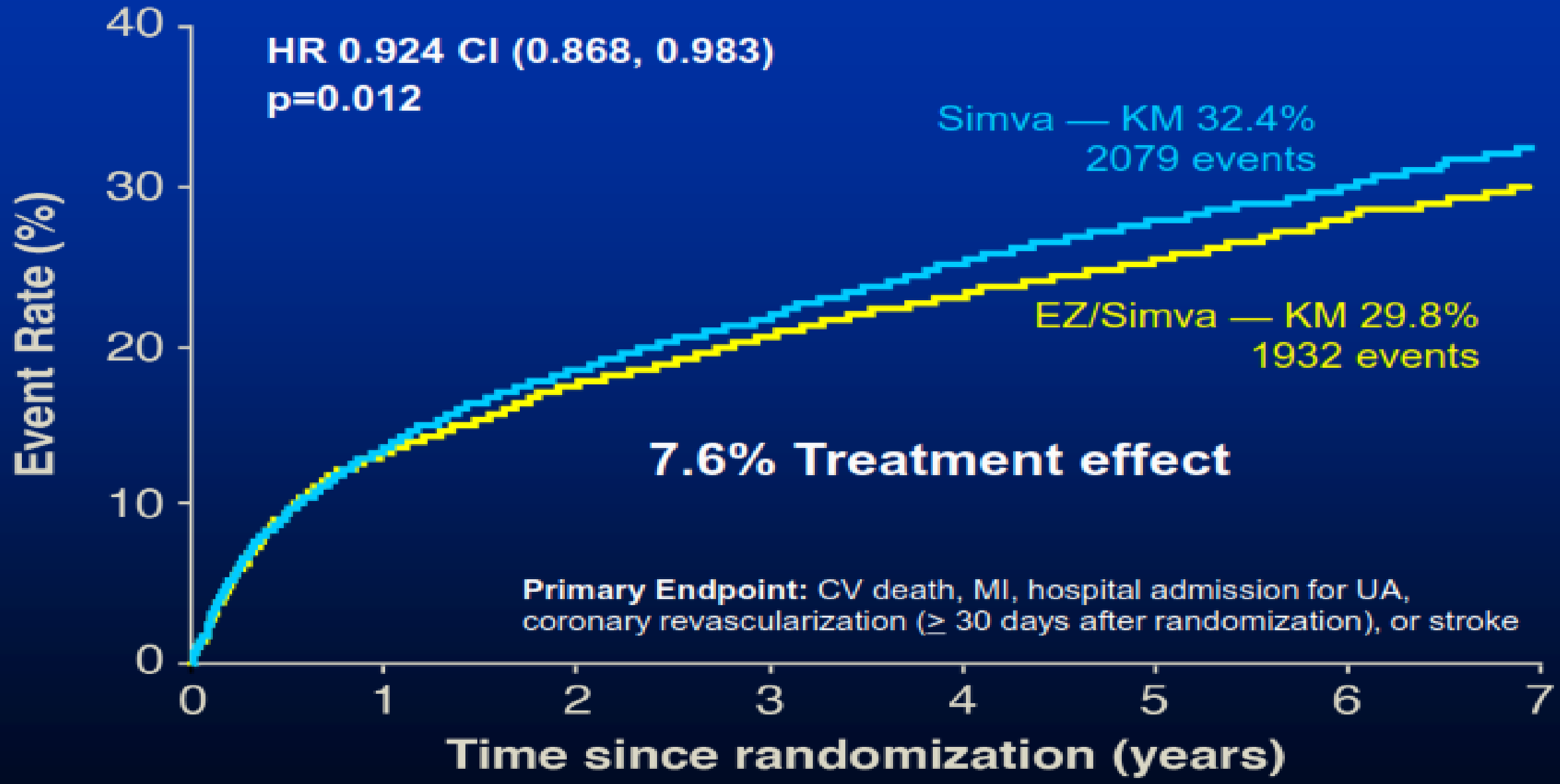
IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

On-Treatment Analysis

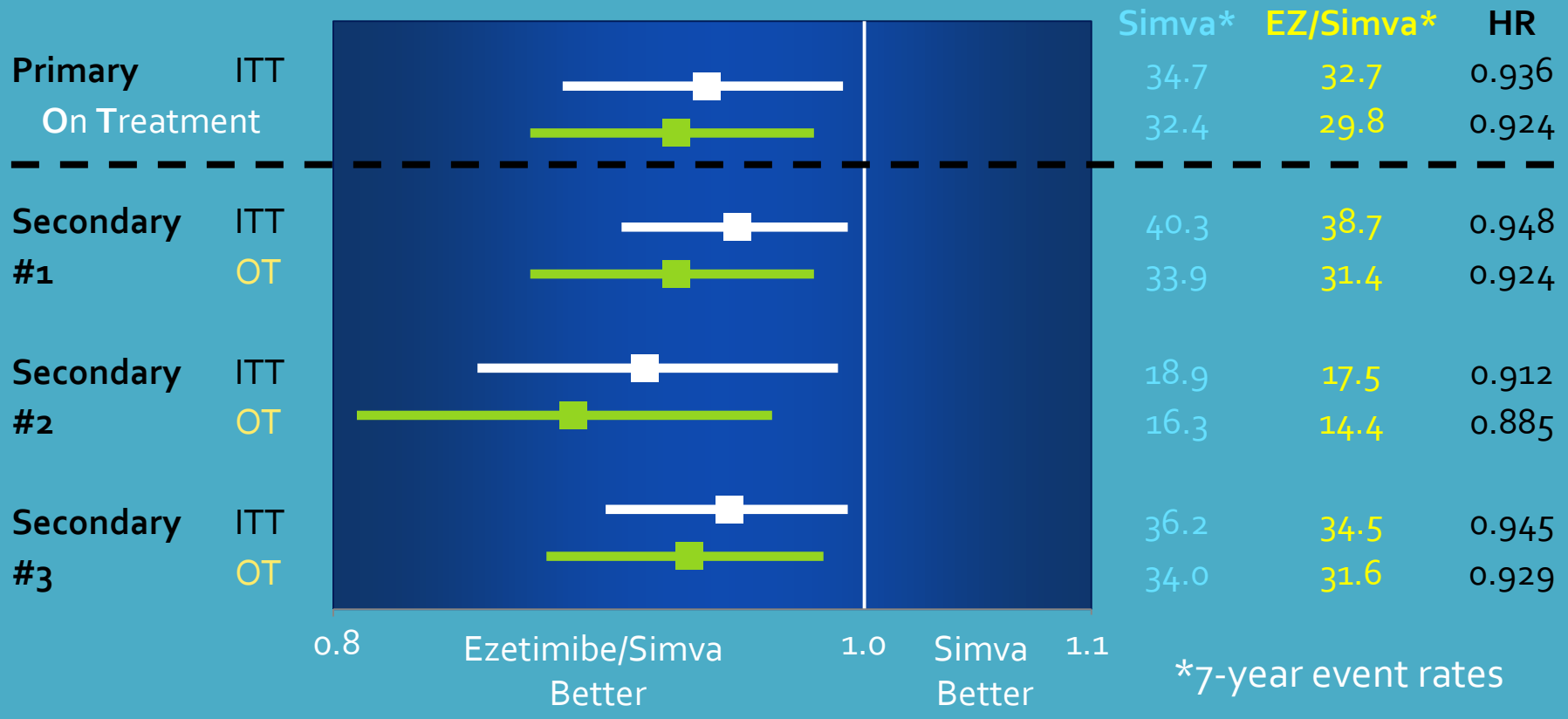
A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome

Primary Endpoint On-Treatment

IMPROVE-IT



Primary and 3 Prespecified Secondary Endpoints ITT & OT



1 = All-cause death, major coronary event, or stroke post randomization

2 = CHD death, non-fatal MI, or urgent CABG or PCI (>30 days) after randomization

3 = CV death, non-fatal MI, documented UA requiring rehospitalization, all revascularization (>30 days) after randomization, or non fatal stroke

Safety — OT Population Muscle and Gallbladder

No statistically significant differences in muscle- or gallbladder-related events

	Simva n=8855	EZ/Simva n=8851	P
ALT and/or AST >3xULN, consecutive	2.2%	2.3%	0.540
Cholecystectomy	1.2%	1.0%	0.279
Gallbladder-related AEs	2.8%	2.4%	0.068
Rhabdomyolysis*	0.2%	0.1%	0.273
Myopathy*	0.1%	0.1%	0.393
Rhabdo, myopathy, myalgia with CK elevation*	0.6%	0.5%	0.428

** Adjudicated events*

Total patient years follow up for primary endpoint= 60,298

Conclusiones

- Resultados “On-treatment” apoyan aún más el beneficio de la combinación EZETIMIBE-SIMVASTATINA
- La reducción es similar a la hallada en el estudio CTT (calidad de la reducción de LDL-c por ezetimibe de la misma calidad que estatinas)

Conclusiones

Implicaciones IMPROVE-IT

Gracias!!!!!!

leopisla@hotmail.com