71° Congresso Nazionale

Recenti Acquisizioni sul Trattamento Ipolipemizzante nel Paziente con Sindrome Coronarica Acuta

Gaetano M. De Ferrari

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Domus De Maria (CA)
5-10 ottobre 2015

Conflitto di interessi:

Partecipazione a Steering Committee, relatore o consulente per:

Amgen, Boston Scientific, Menarini, MSD

Le Mie Aspettative

La Triste Realtà

74 Congresso Nazionale

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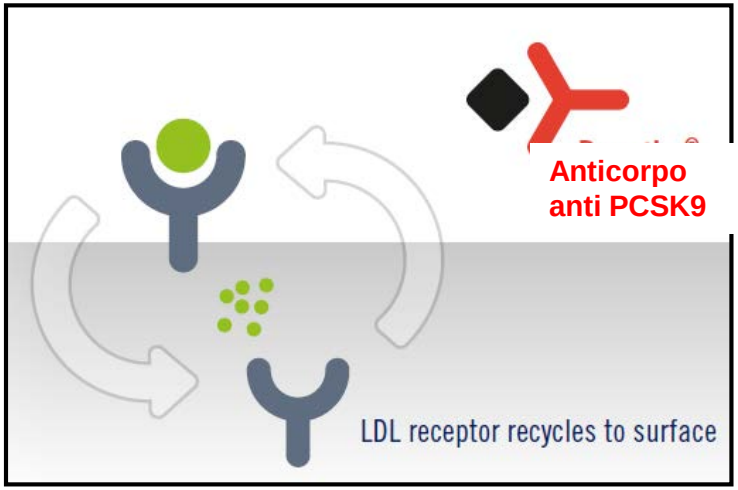
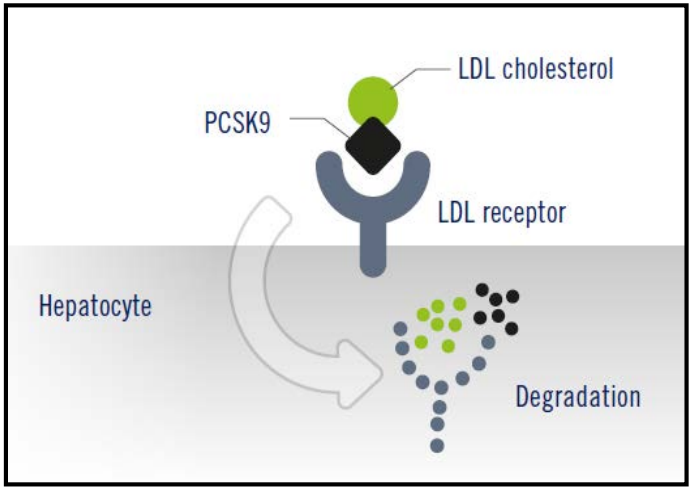
INIBIZIONE DI PCSK9 E RIDUZIONE DI C-LDL

- LDL binds to the LDL receptor and is internalised into the hepatocyte[1]
- LDL is degraded and the receptor recycles to the surface to clear more LDL-C[1]

- PCSK9 is a protein expressed by the liver that binds to LDL receptors and targets them for degradation by the lysosome[2]

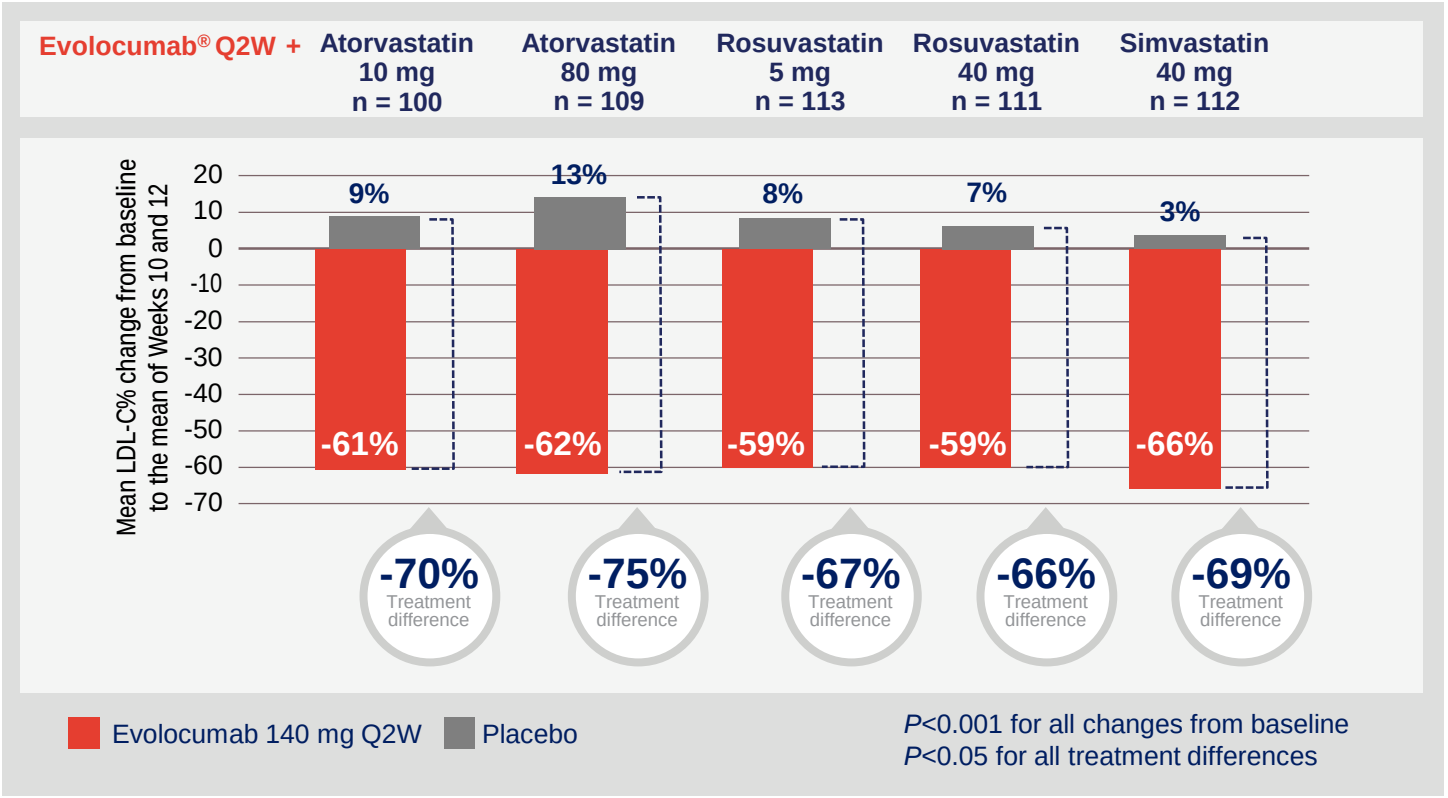




- Evolocumab lowers LDL-C levels by inhibiting PCSK9, which increases the number of LDL receptors in the hepatocyte surface, resulting in lower LDL-C plasma concentration

1. Seidah NG, et al. Circ Res 2014;114:1022–36.
2. Lagace TA. Curr Opin Lipidol 2014;25:387–93.

Evolocumab e LDL in Pazienti che Assumono Statine



- When added to statins, Evolocumab delivers intensive LDL-C reductions in patients with primary hypercholesterolaemia or mixed dyslipidaemia

Robinson JG, et al. JAMA. 2014;311:1870–82.

LDL-C, low-density lipoprotein cholesterol; Q2W, once every 2 weeks.

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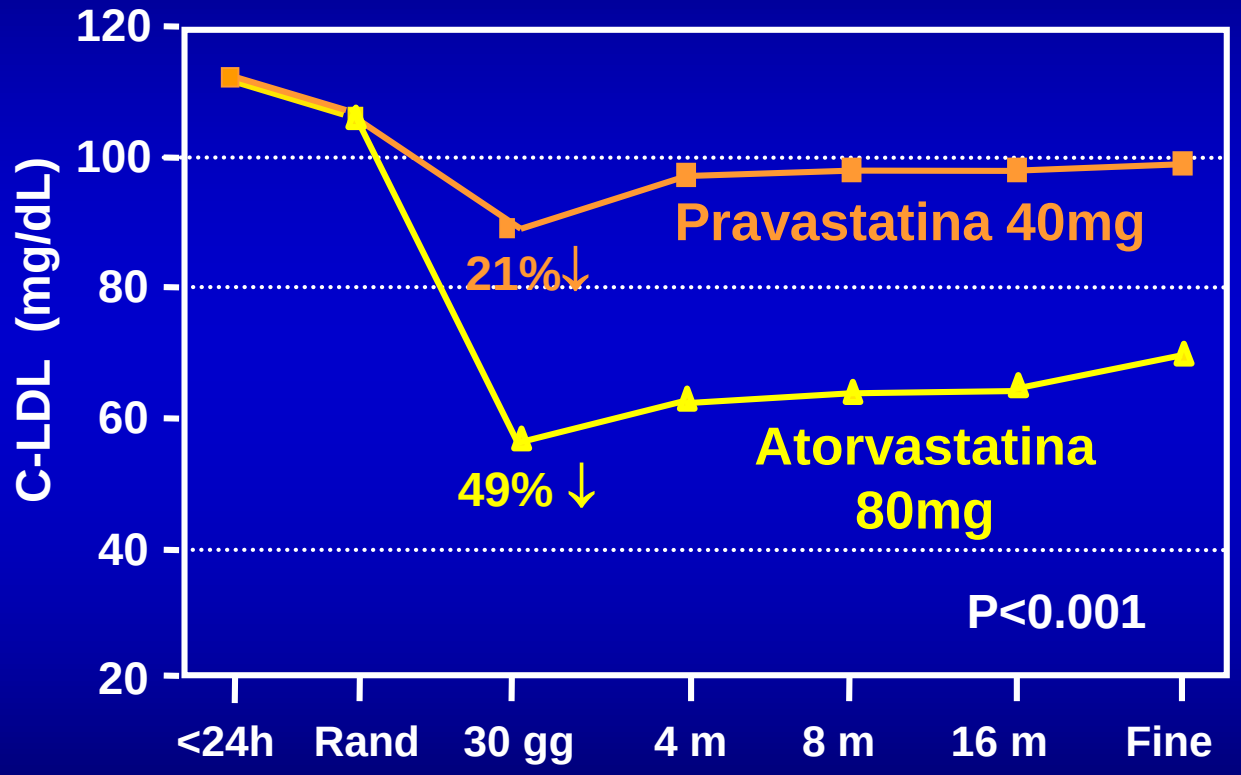
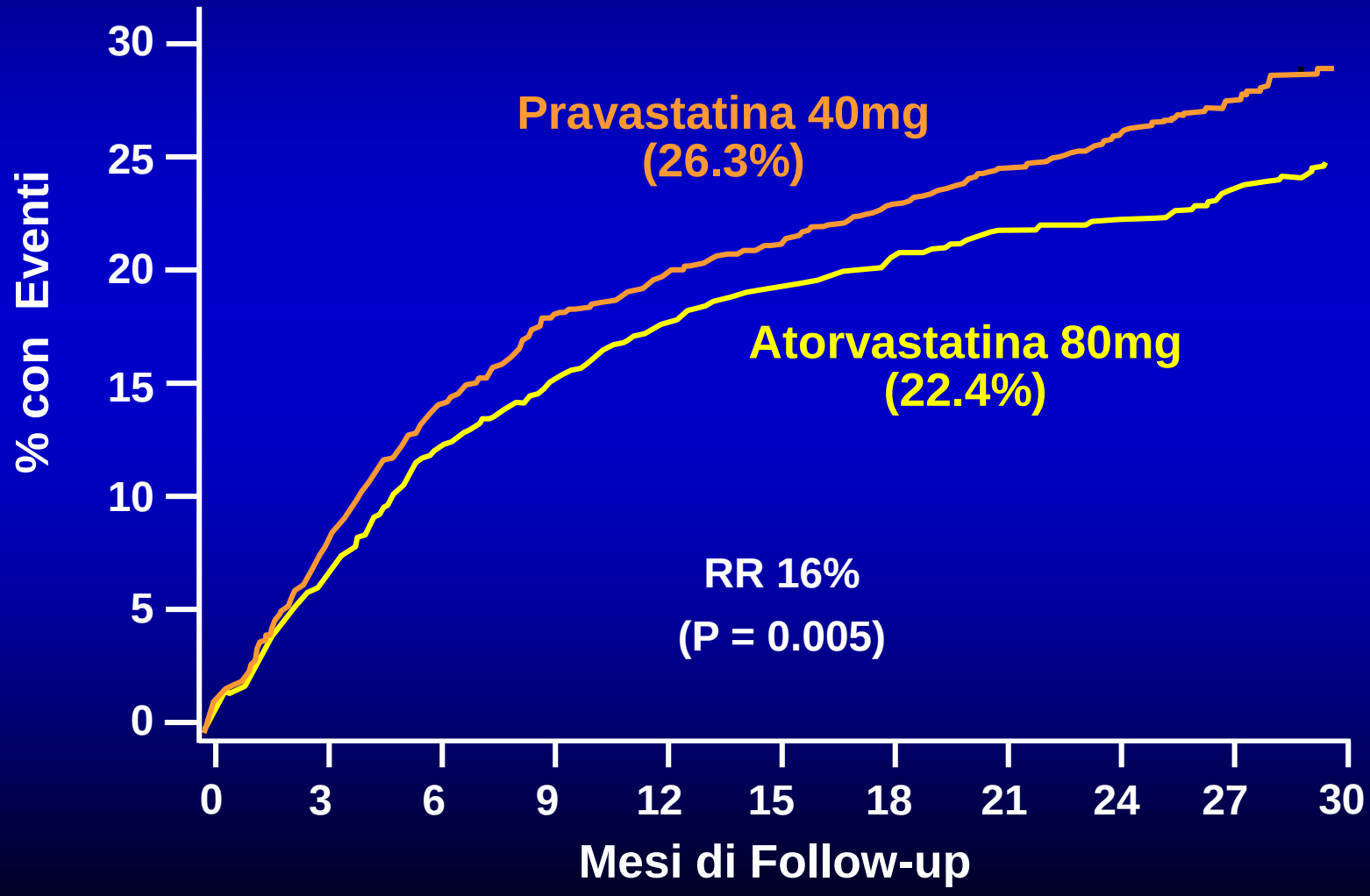
SI PARTE DALLE STATINE AD ALTA POTENZA

PROVE – IT: Variazioni di C-LDL Rispetto al Basale (dopo SCA)



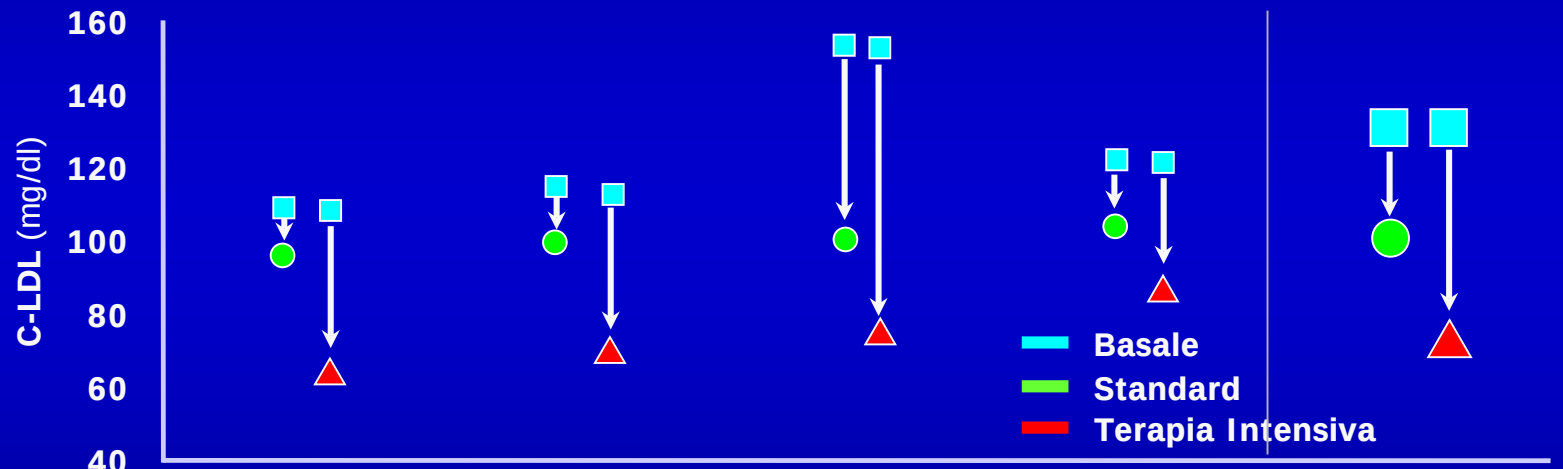
C-LDL Mediano (Q1, Q3)
95 (79, 113)
62 (50, 79)

PROVE – IT : Mortalità Totale ed Eventi CV Maggiori



Livelli di C-LDL negli Studi di Paragone tra Dose di Statine Alta e Standard

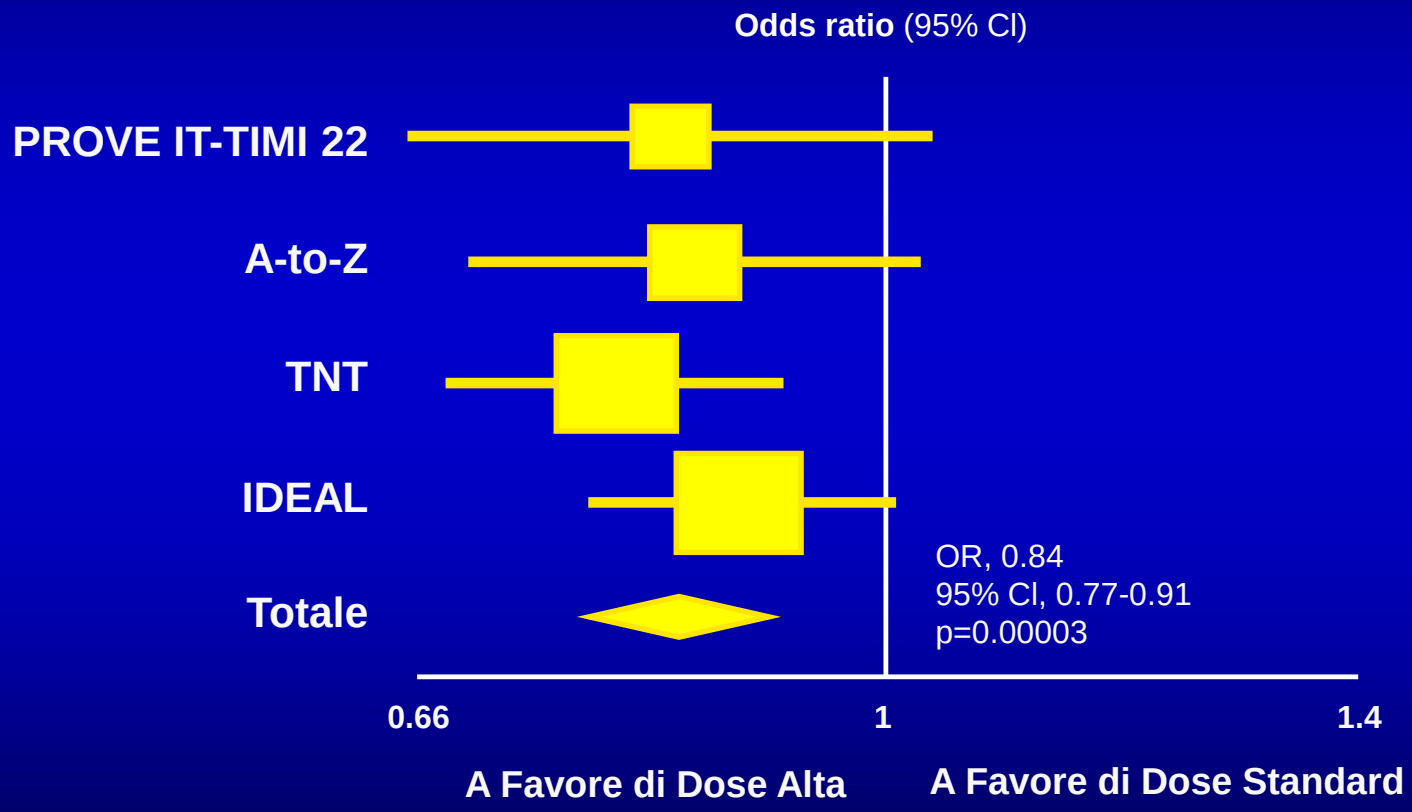
Pazienti	SCA		Coronaropatia Stabile		Dati Combinati
n	4162	4497	10001	8888	27548
Uso Pregresso Statine	25.2%	0%	0%	75.5%	28.2%



	PROVE IT-TIMI 22	A-to-Z	TNT	IDEAL	Dati Combinati
Basale	108	113	152	122	130
Standard	97	101	101	104	101
Terapia Intensiva	65	69	77	81	75

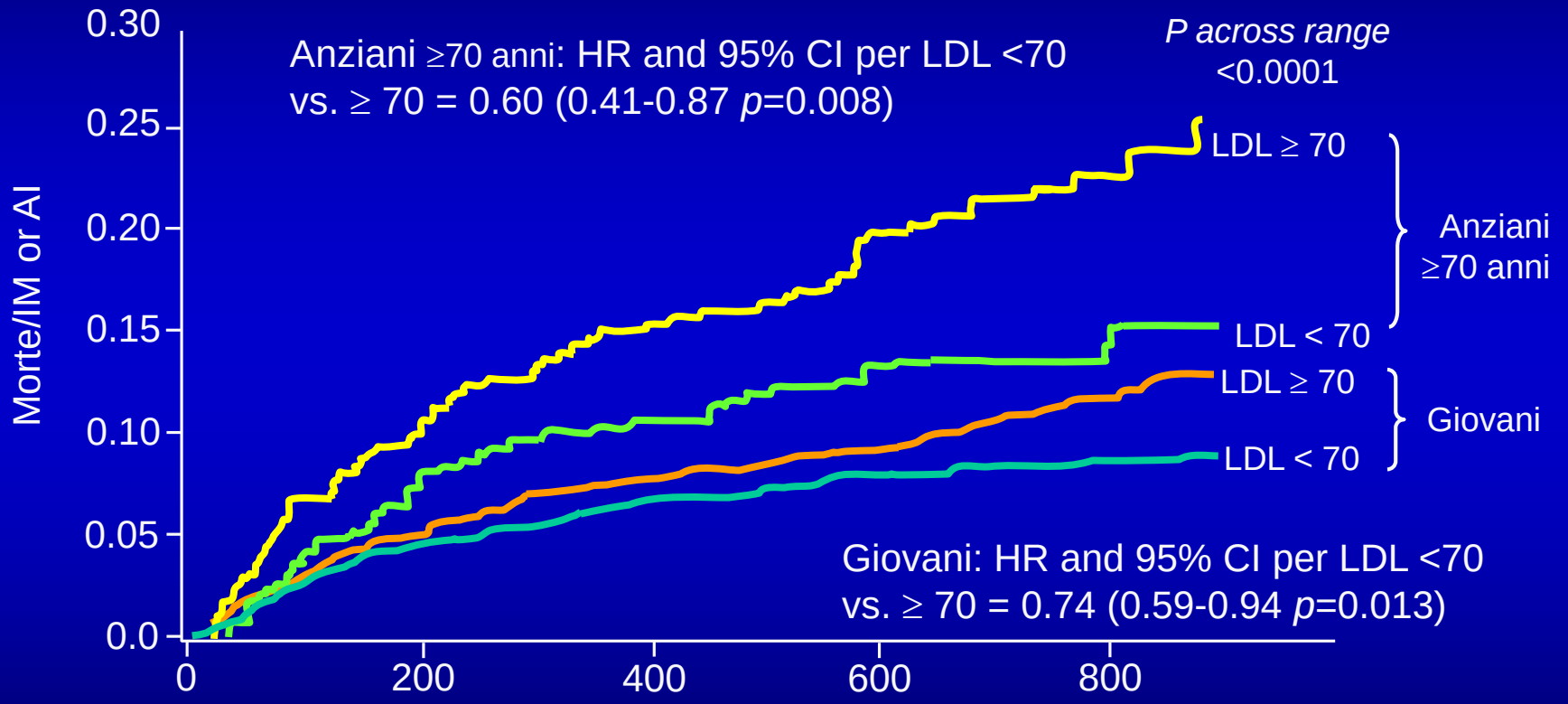
Cannon CP, et al. J Am Coll Cardiol 2006;48:438

Morte Coronarica o Infarto Miocardico
Benefici di un target LDL “ambizioso”



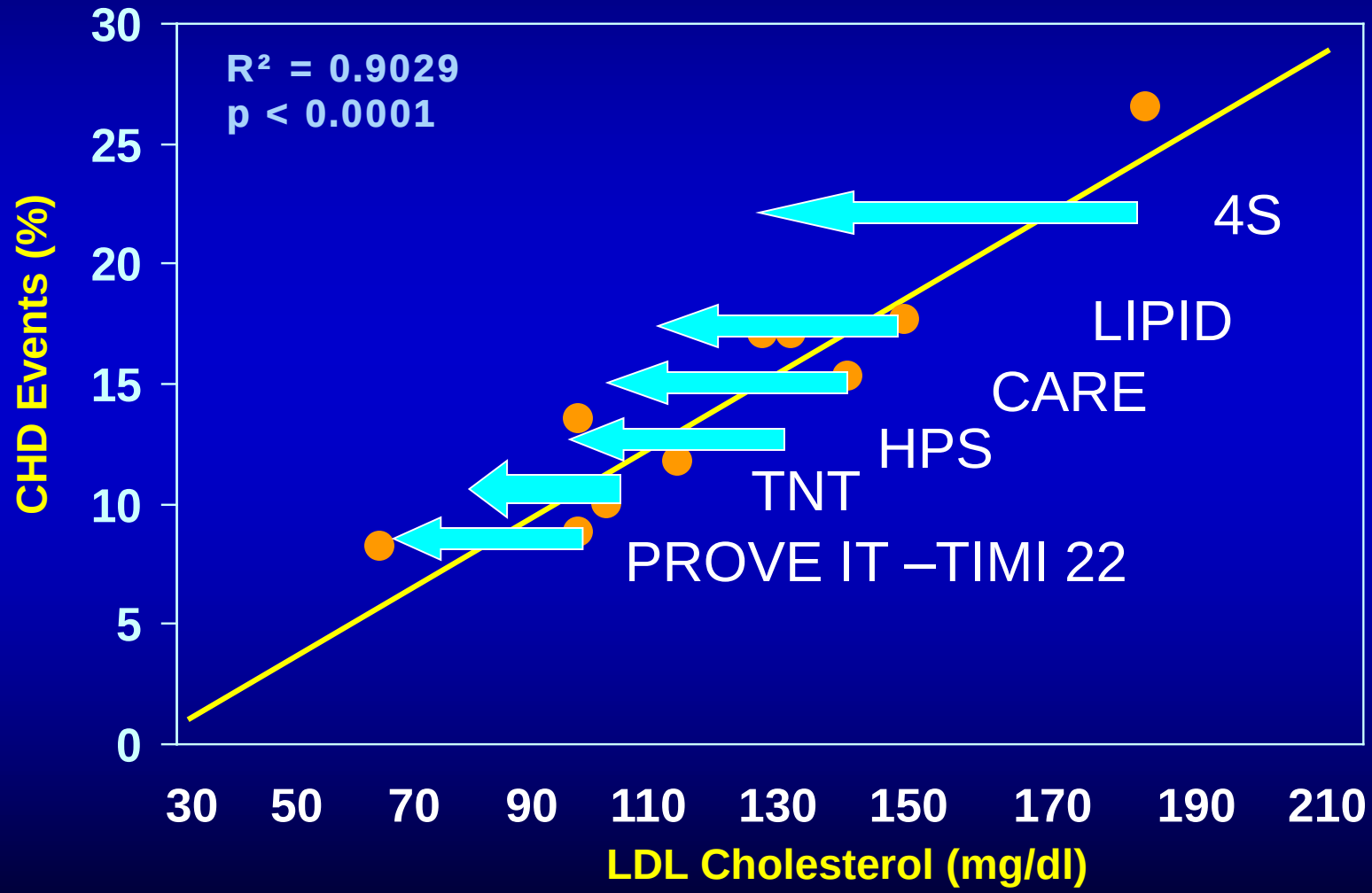
Cannon CP, et al. J Am Coll Cardiol 2006;48:438

Raggiungimento del Target nei Giovani ed Anziani sull'Incidenza di Morte/IMA/Angina Instabile



Ray KK, et al. Eur Heart J 2006 27:2310-2316

The Statin Decade: For LDL: "Lower is Better"



Adapted and Updated from O' Keefe, J. et al., *J Am Coll Cardiol* 2004;43:2142-6.

Livelli di C-LDL negli Studi di Paragone tra Dose di Statine Alta e Standard

Pazienti	SCA		Coronaropatia Stabile		Dati Combinati
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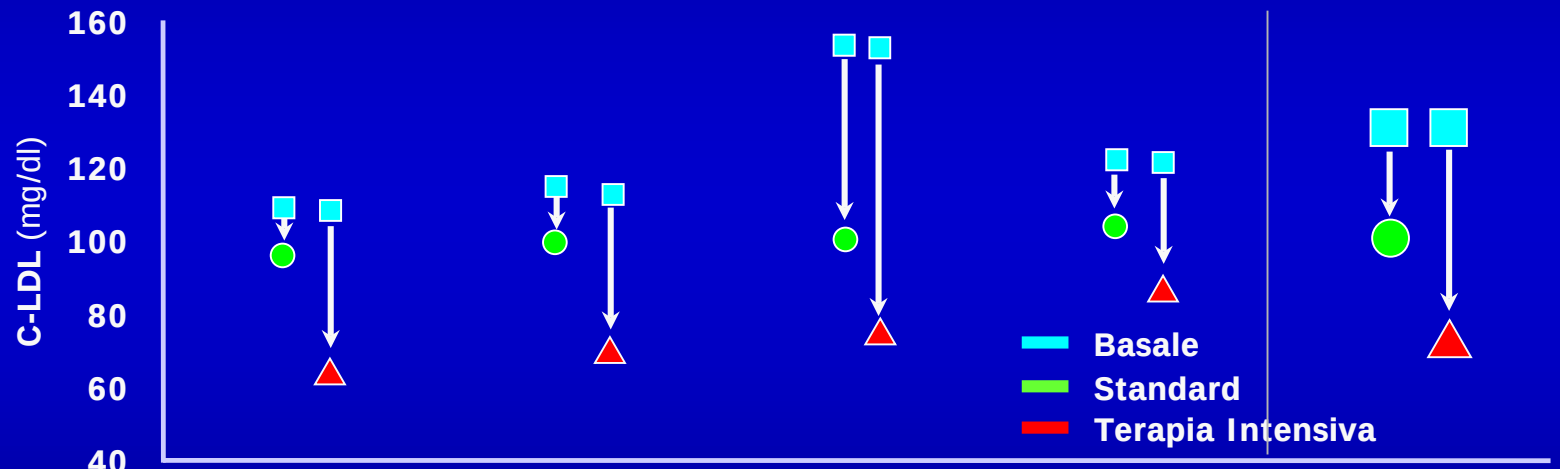

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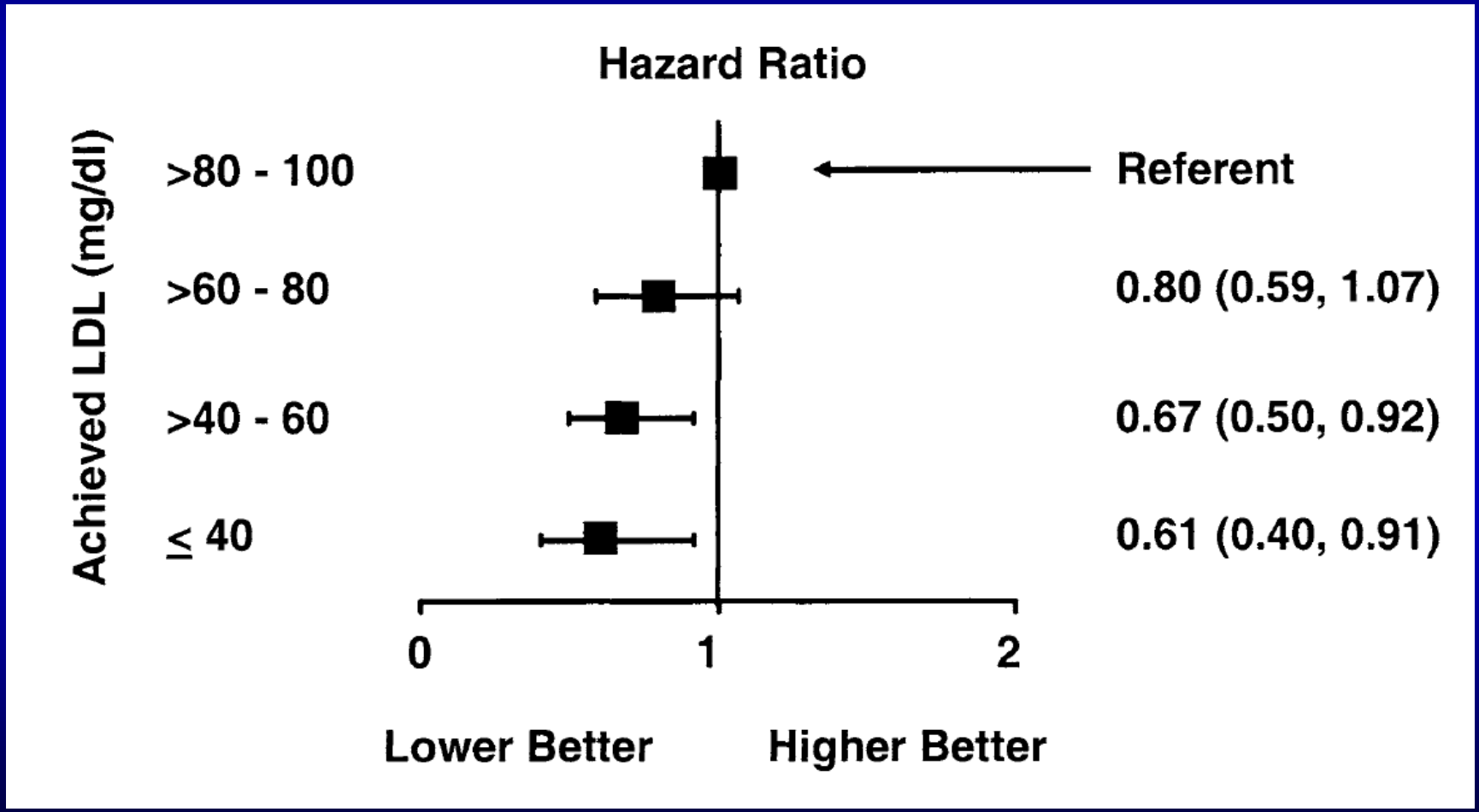
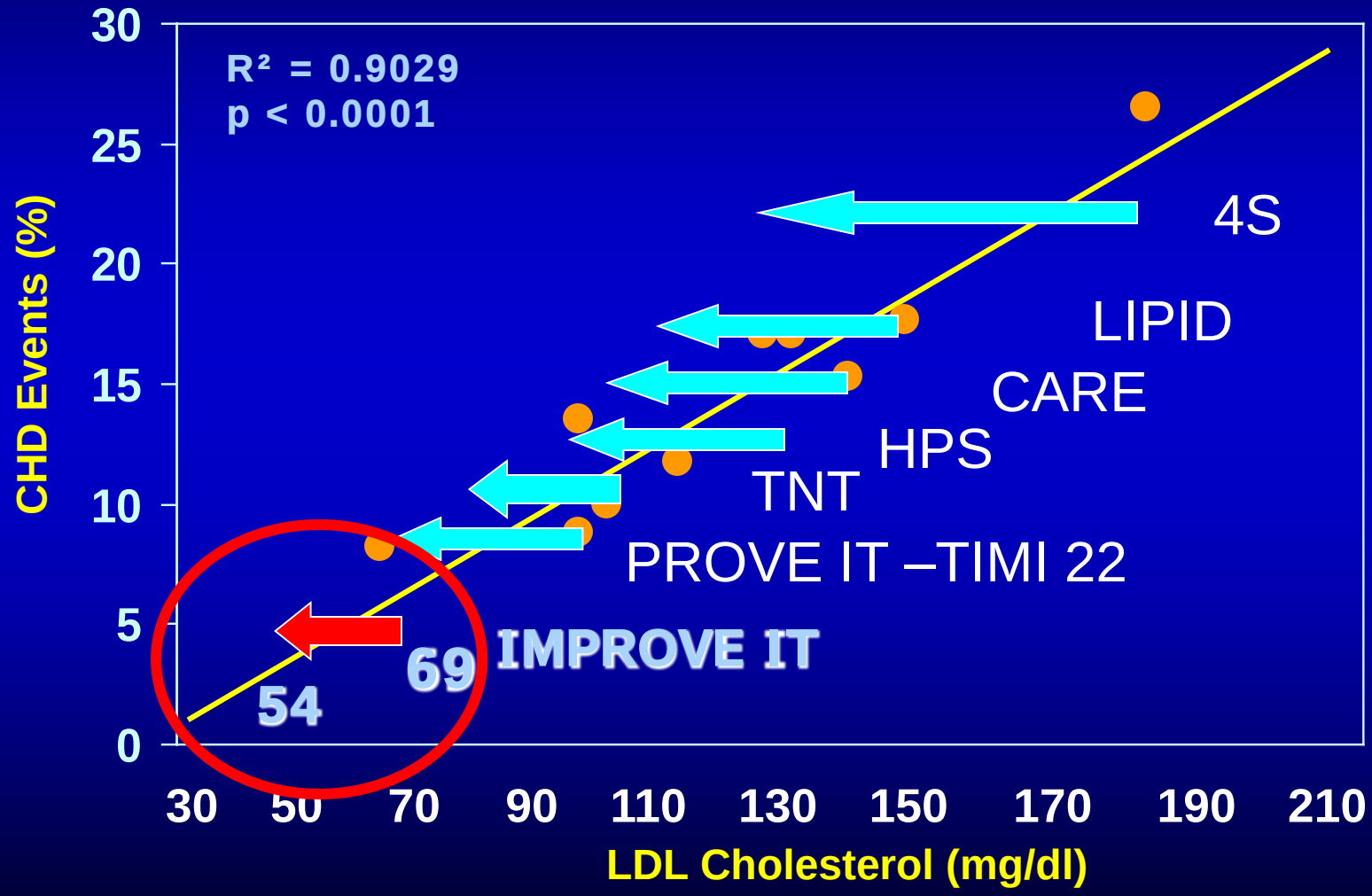
Cannon CP, et al. J Am Coll Cardiol 2006;48:438

Effetti di LDL molto basse nello studio PROVE-IT



Wiviott et al, JACC 2005

The Statin Decade: For LDL "Lower is Better"



Adapted and Updated from O' Keefe, J. et al., *J Am Coll Cardiol* 2004;43:2142-6.

Hic sunt leones

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*

N Engl J Med 2015;372:2387-97.

Background: Cholesterol Lowering

- Lowering LDL cholesterol (LDL-C) has been a mainstay of cardiovascular prevention
- Evidence mostly from statin trials which show reduction in morbidity and mortality
  - High-dose statins further reduce non-fatal CV events
- To date, no lipid-modifying therapy added to statins has been demonstrated to provide a clinical benefit
  - Fibrates, niacin, CETP inhibitors
- Recent ACC/AHA Guidelines have emphasized use of statin therapy
- Despite current therapies, patients remain at high risk

Ezetimibe: Background

- Ezetimibe inhibits Niemann-Pick C_1-like 1 (NPC_1L_1) protein
  - located primarily on the epithelial brush border of the GI tract
  - resulting in reduced cholesterol absorption
- When added to statin, produces ~20% further reduction in LDL-C
- Two recent human genetic analyses have correlated polymorphisms in NPC_1L_1 with lower levels of LDL-C and lower risk of CV events*

**MI Genetics Consortium Investigators NEJM 2014; online Nov 12; Ference BA et al AHA 2014*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inactivating Mutations in *NPC1L1* and Protection from Coronary Heart Disease

The Myocardial Infarction Genetics Consortium Investigators

ABSTRACT

BACKGROUND

Ezetimibe lowers plasma levels of low-density lipoprotein (LDL) cholesterol by inhibiting the activity of the Niemann–Pick C1-like 1 (NPC1L1) protein. However, whether such inhibition reduces the risk of coronary heart disease is not known. Human mutations that inactivate a gene encoding a drug target can mimic the action of an inhibitory drug and thus can be used to infer potential effects of that drug.

METHODS

We sequenced the exons of *NPC1L1* in 7364 patients with coronary heart disease and in 14,728 controls without such disease who were of European, African, or South Asian ancestry. We identified carriers of inactivating mutations (nonsense, splice-site, or frameshift mutations). In addition, we genotyped a specific inactivating mutation (p.Arg406X) in 22,590 patients with coronary heart disease and in 68,412 controls. We tested the association between the presence of an inactivating mutation and both plasma lipid levels and the risk of coronary heart disease.

Heterozygous carriers of *NPC1L1* inactivating mutations had a mean LDL cholesterol level that was 12 mg per deciliter (0.31 mmol per liter) lower than that in noncarriers ($P=0.04$). Carrier status was associated with a relative reduction of 53% in the risk of coronary heart disease (odds ratio for carriers, 0.47; 95% confidence interval, 0.25 to 0.87; $P=0.008$). In total, only 11 of 29,954 patients with coronary

CONCLUSIONS

Naturally occurring mutations that disrupt NPC1L1 function were found to be associated with reduced plasma LDL cholesterol levels and a reduced risk of coronary heart disease. (Funded by the National Institutes of Health and others.)

The authors are listed in the Appendix. Address reprint requests to Dr. Sekar Kathiresan at the Cardiovascular Research Center and Center for Human Genetic Research, Massachusetts General Hospital, 185 Cambridge St., CPZN 5.252, Boston, MA 02114, or at skathiresan@partners.org.

This article was published on November 12, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1405386

Goals

- **IMPROVE-IT: First large trial evaluating clinical efficacy of combination EZ/Simva vs. simvastatin (i.e., the addition of ezetimibe to statin therapy):**
  - **Does lowering LDL-C with the non-statin agent ezetimibe reduce cardiac events?**
  - **"Is (Even) Lower (Even) Better?" (estimated mean LDL-C ~50 vs. 65mg/dL)**
  - **Safety of ezetimibe**

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

Patient Population

- **Inclusion Criteria:**
  - Hospitalization for STEMI, NSTEMI/UA < 10 days
  - Age ≥ 50 years, and ≥ 1 high-risk feature:
    - New ST chg, + troponin, DM, prior MI, PAD, cerebrovasc,
      prior CABG > 3 years, multivessel CAD
  - LDL-C 50-125 mg/dL (50–100 mg/dL if prior lipid-lowering Rx)

- **Major Exclusion Criteria:**
  - CABG for treatment of qualifying ACS
  - Current statin Rx more potent than simva 40mg
  - Creat Cl < 30mL/min, active liver disease

Study Design

Patients stabilized post Acute Coronary Syndrome < 10 days
LDL ≤ 125 mg/dL (or ≤ 100 mg/dL if prior statin)

Double-blind

ASA + Standard Medical Therapy

N=18,144

Simvastatin 40 mg

Inegy 10/40 mg

Follow-Up Visit Day 30, Every 4 Months

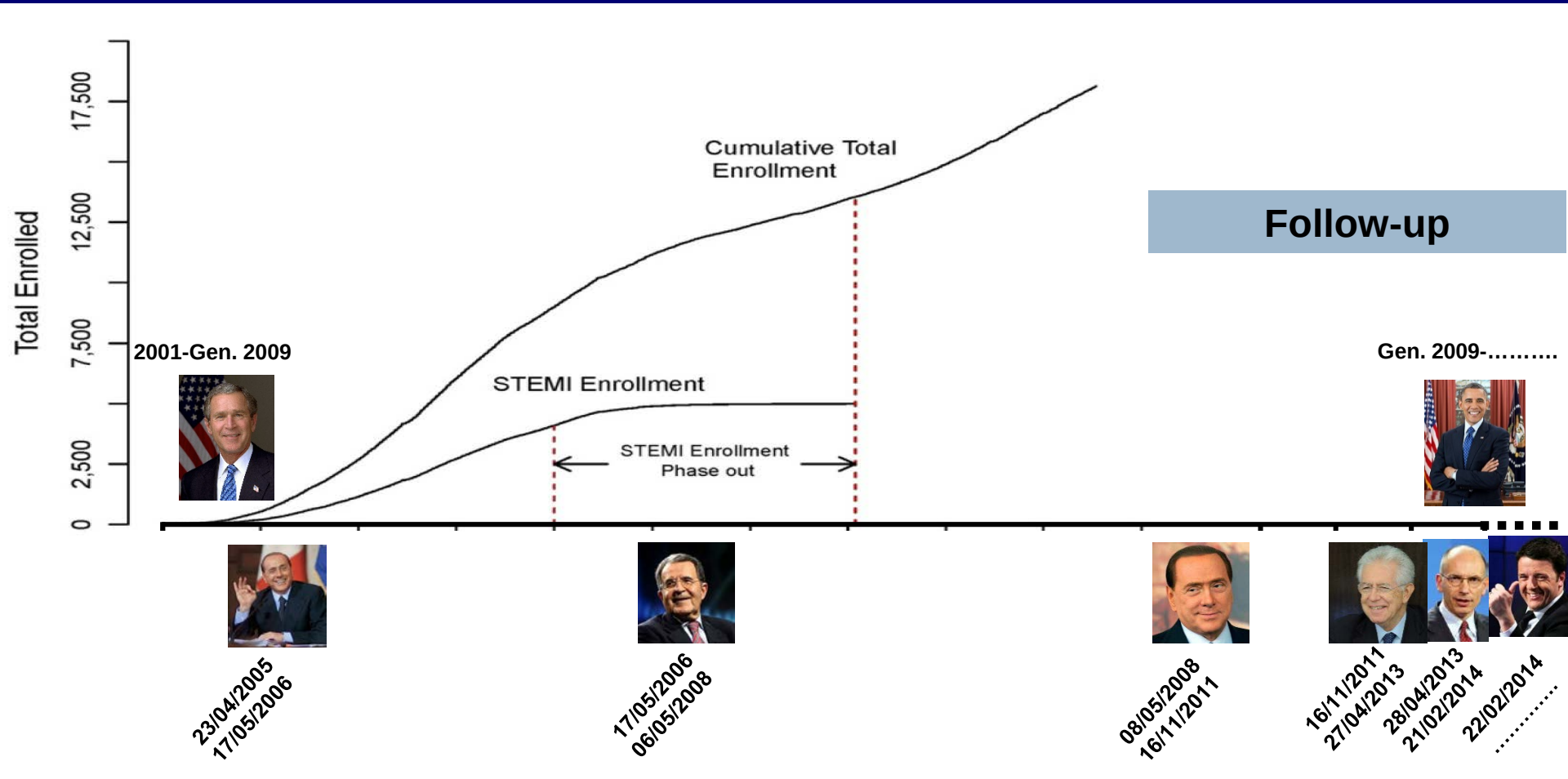
Until 5250 Primary Events

Primary Endpoint: CV Death, MI, Hospital Admission for UA, revascularization (> 30 days after randomization), or Stroke

Large CV Trials

Trial	Total N	# Endpoints	1° Endpoints
GUSTO-1	41,021	2848	Death
ALLHAT	33,357	2956	CHD Death/MI
ISIS-4	58,050	4319	Death
ISIS-3	41,299	4321	Death
COMMIT	45,852	4431	Death
HPS	20,536	4628	CHD Death/MI/Stroke/Revasc
		2835	Death
IMPROVE-IT	18,144	5314	CV Death, MI, UA, Stroke, Coronary revasc

Cronologia dello Studio IMPROVE-IT



Italian Investigators (69 sites, 593 patients)

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Napoli (20)

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Dr. M.Margheri
Margheri (RA) (13)

Prof. R.De Caterina
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Study Metrics

	Simva (N=9077)	EZ/Simva (N=9067)
Uptitration to Simva 80mg, %	27	6
Premature study drug D/C, %	42	42
Median follow-up, yrs	6.0	5.9
Withdraw consent w/o vital status, %/yr	0.6	0.6
Lost to follow-up, %/yr	0.10	0.09
Follow up for primary endpoint, %	91	91
Follow up for survival, %	97	97

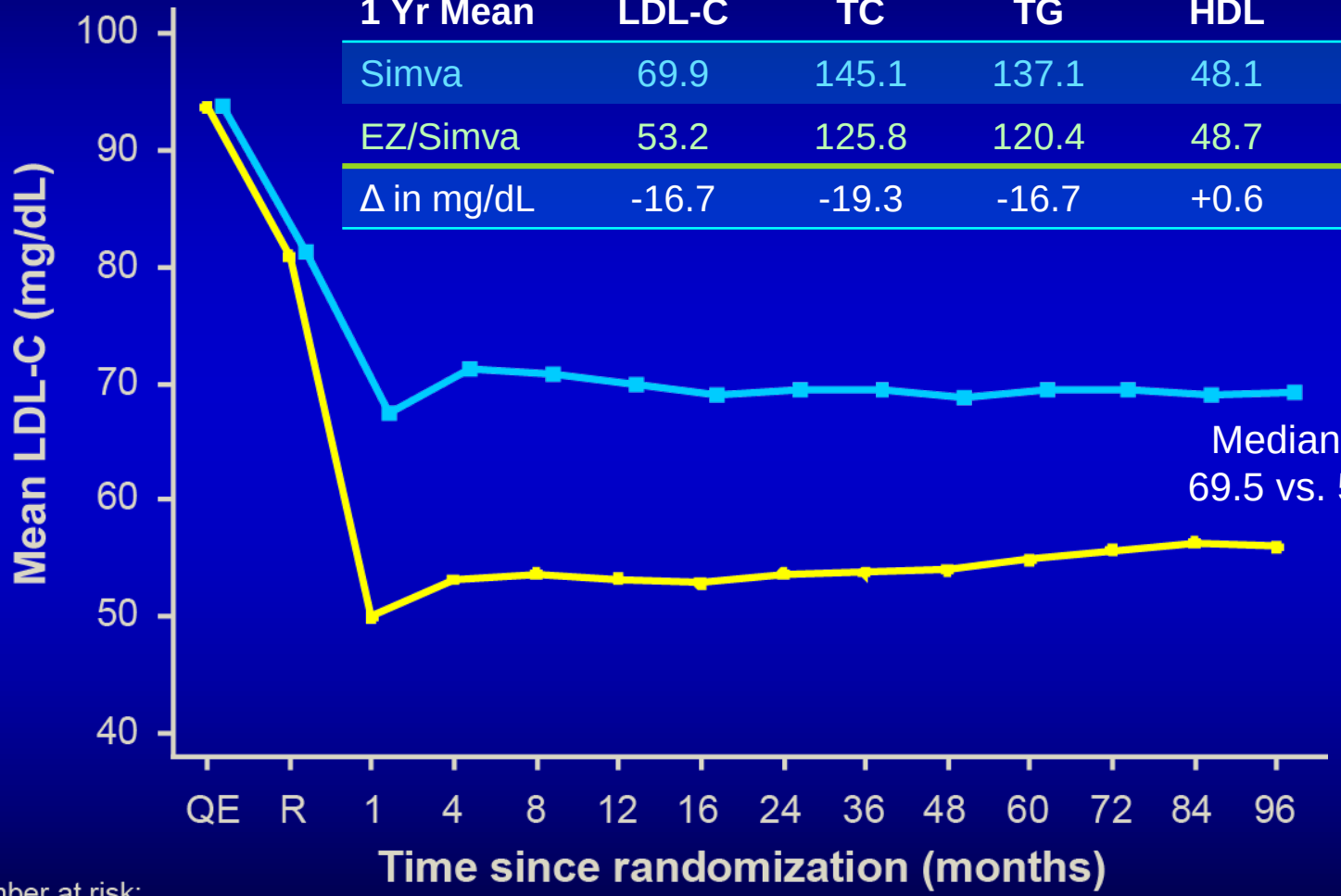
Total primary endpoint events = 5314
Total patient-years clinical follow-up = 97,822
Total patient-years follow-up for survival = 104,135

Baseline Characteristics

	Simvastatin (N=9077) %	EZ/Simva (N=9067) %
Age (years)	64	64
Female	24	25
Diabetes	27	27
MI prior to index ACS	21	21
STEMI / NSTEMI / UA	29 / 47 / 24	29 / 47 / 24
Days post ACS to rand (IQR)	5 (3, 8)	5 (3, 8)
Cath / PCI for ACS event	88 / 70	88 / 70
Prior lipid Rx	35	36
LDL-C at ACS event (mg/dL, IQR)	95 (79, 110)	95 (79,110)

LDL-C and Lipid Changes

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



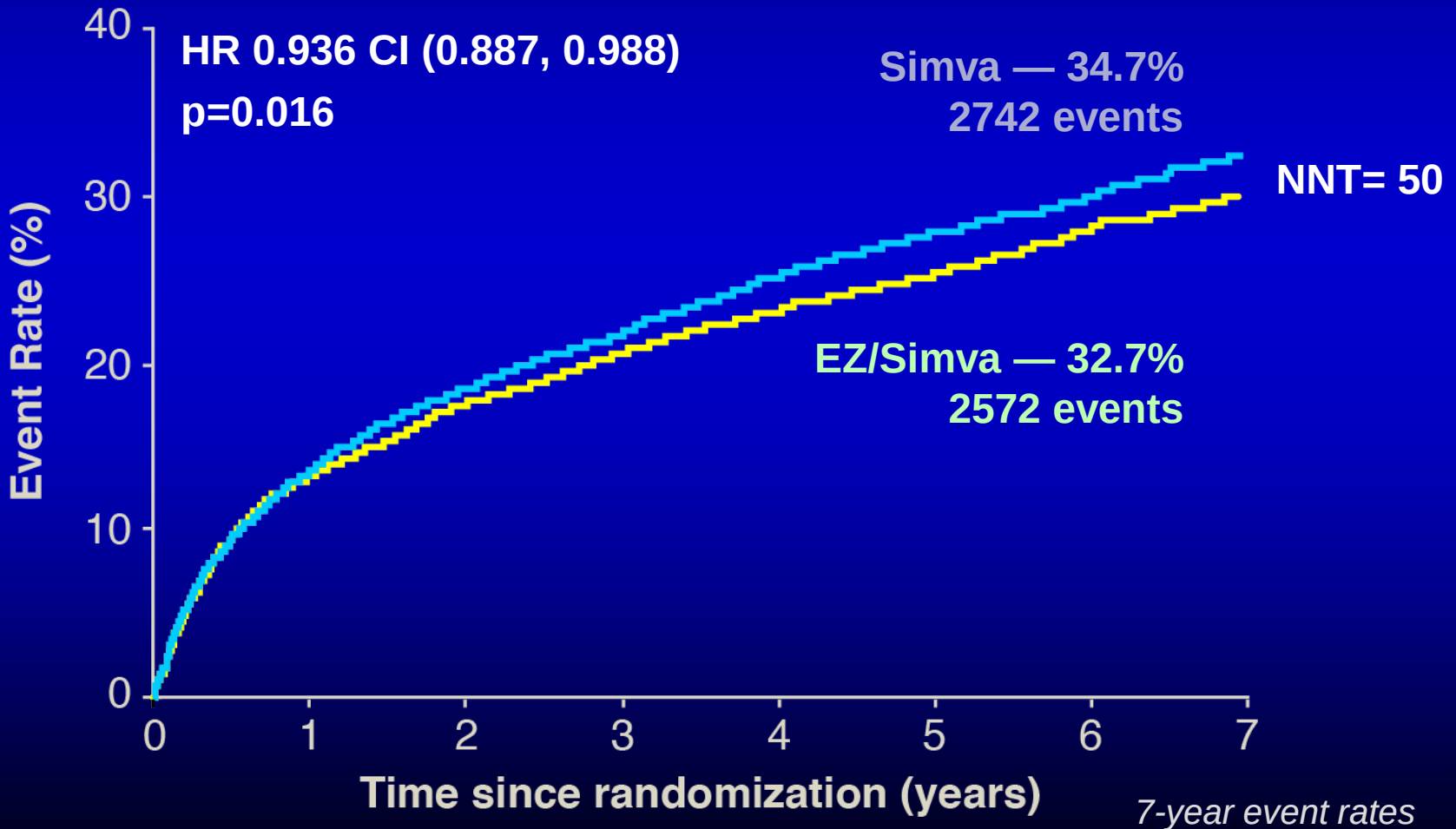
Median Time avg
69.5 vs. 53.7 mg/dL

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

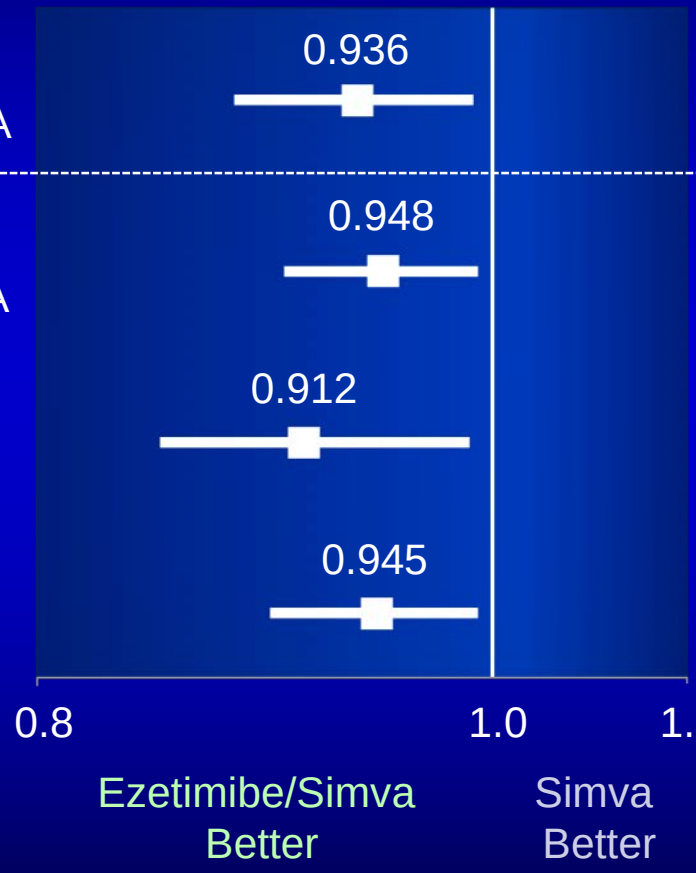
Primary Endpoint — ITT

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



7-year event rates

Primary and 3 Prespecified Secondary Endpoints — ITT

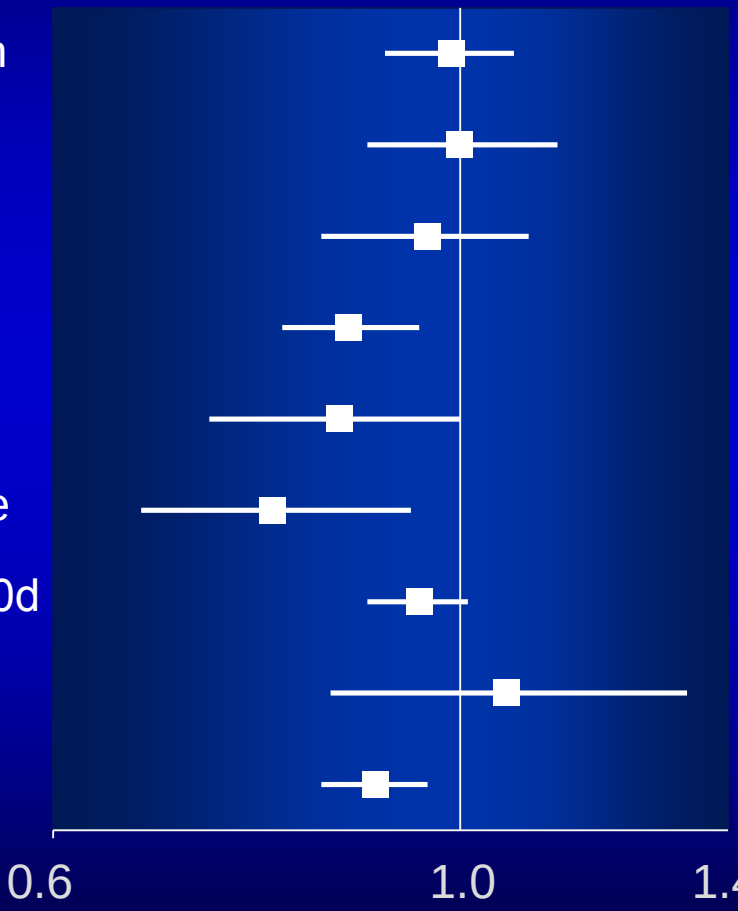


	Simva*	EZ/Simva*	p-value
Primary CVD/MI/UA/Cor Revasc/CVA	34.7	32.7	0.016
Secondary #1 All D/MI/UA/Cor Revasc/CVA	40.3	38.7	0.034
Secondary #2 CHD/MI/Urgent Cor Revasc	18.9	17.5	0.016
Secondary #3 CVD/MI/UA/All Revasc/CVA	36.2	34.5	0.035

**7-year event rates (%)*

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)

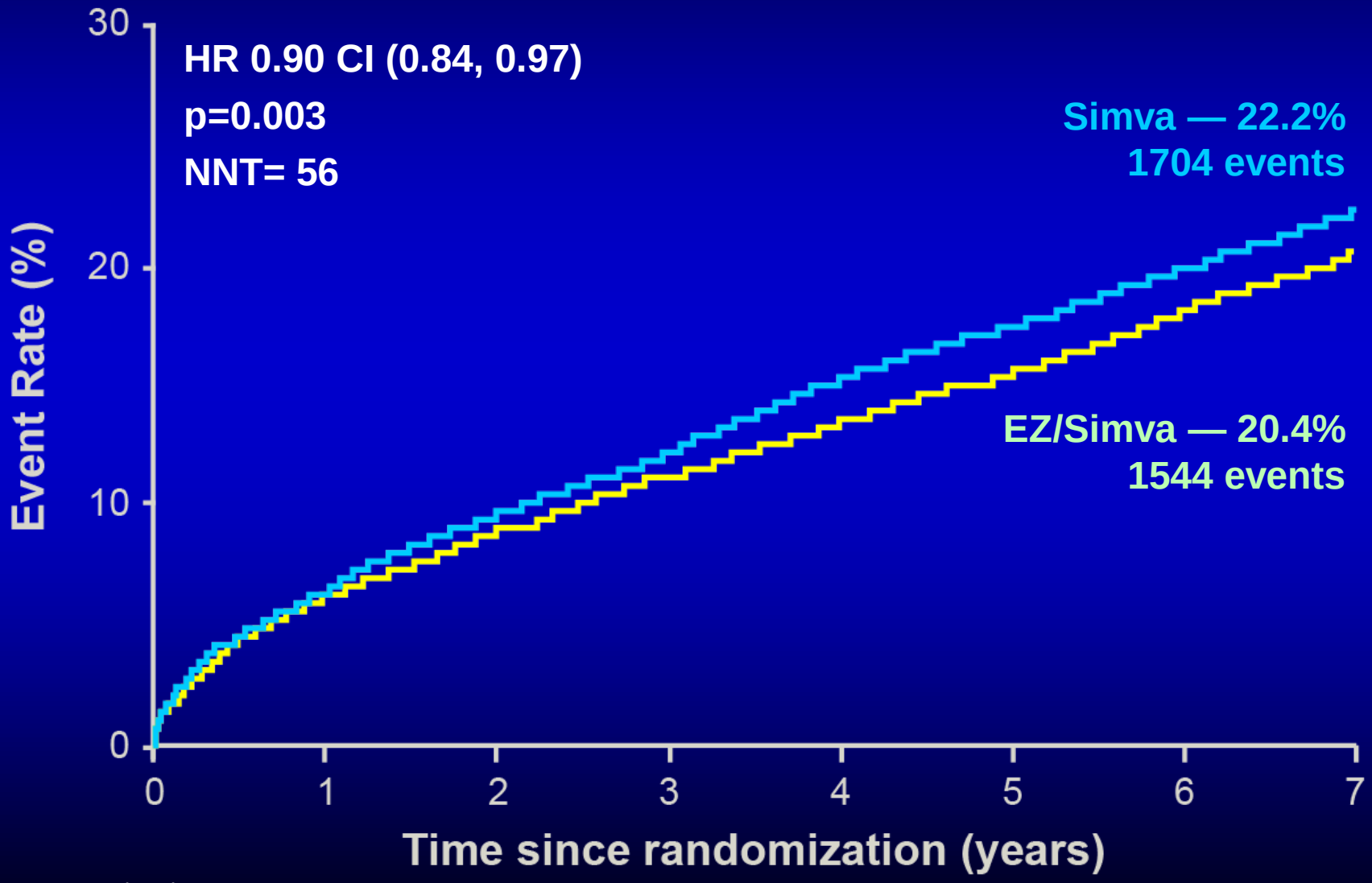
Individual Cardiovascular Endpoints and CVD/MI/Stroke



	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

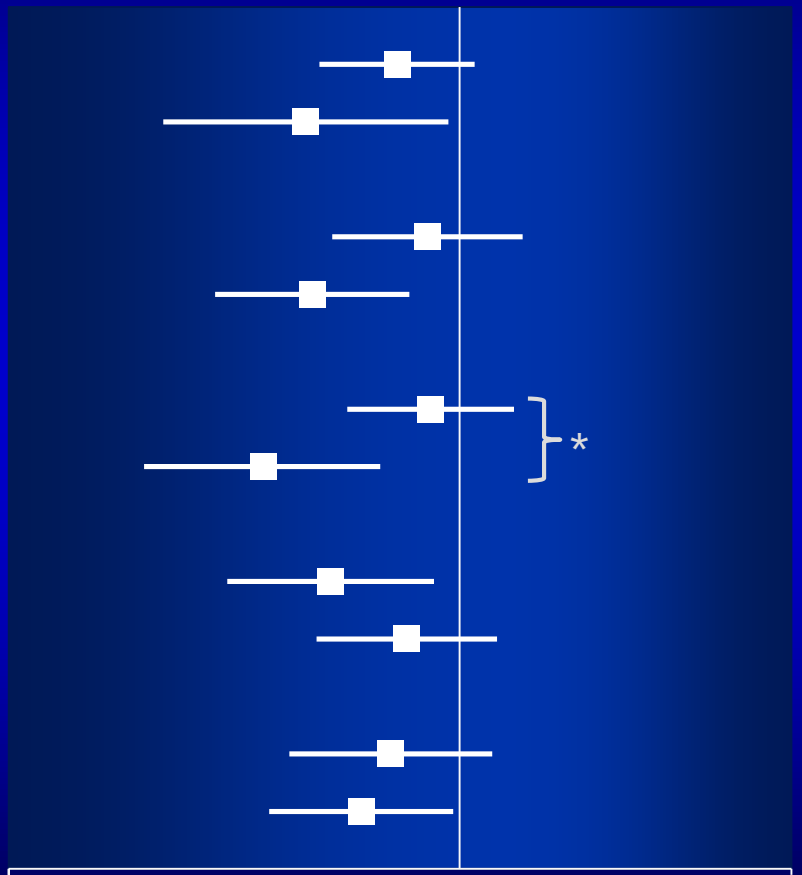
**7-years event rates (%)*

CV Death, Non-fatal MI or Non-fatal Stroke



7-year event rates

Major Pre-specified Subgroups

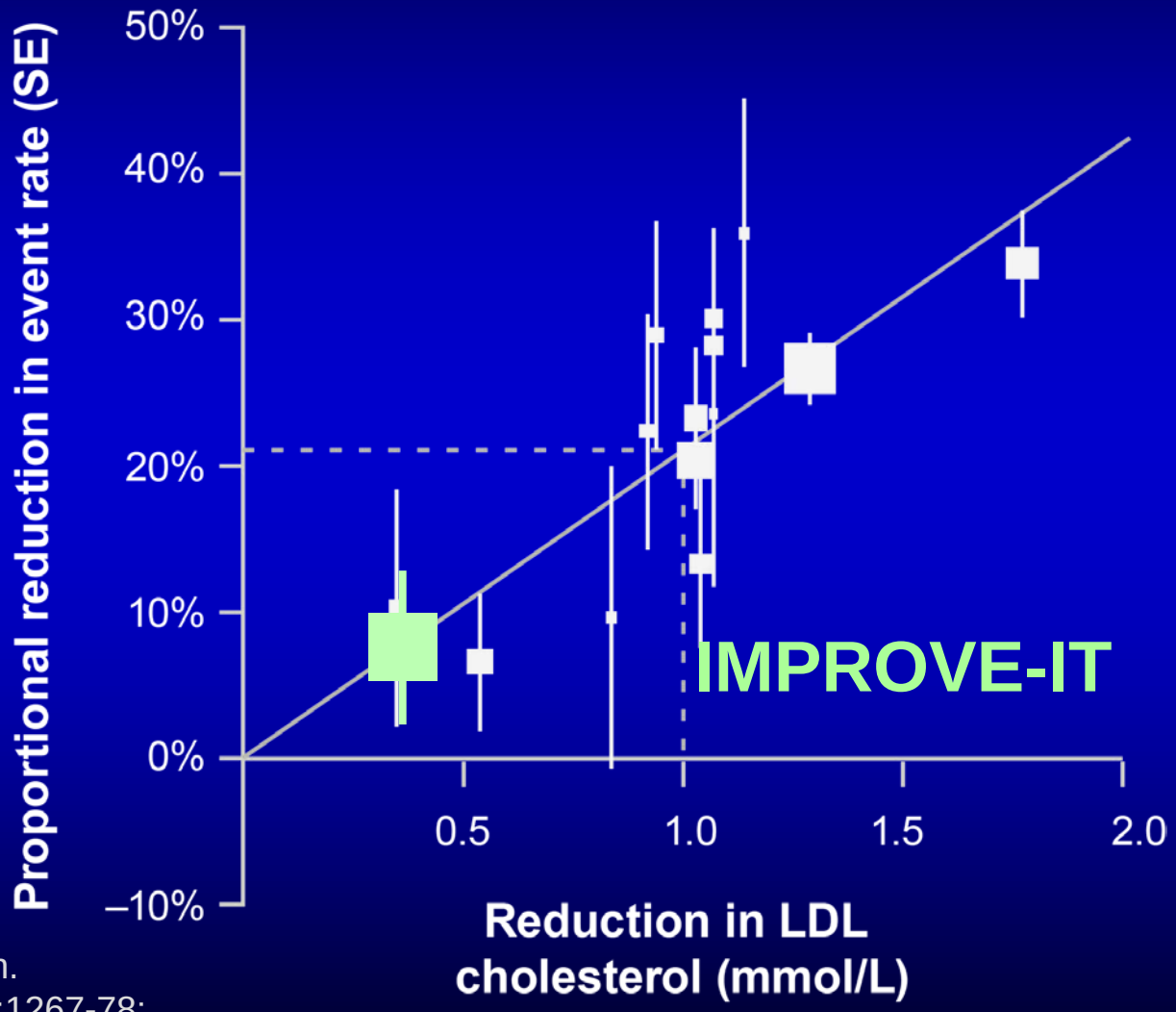


	Simva†	EZ/Simva†
Male	34.9	33.3
Female	34.0	31.0
Age < 65 years	30.8	29.9
Age ≥ 65 years	39.9	36.4
No diabetes	30.8	30.2
Diabetes	45.5	40.0
Prior LLT	43.4	40.7
No prior LLT	30.0	28.6
LDL-C > 95 mg/dl	31.2	29.6
LDL-C ≤ 95 mg/dl	38.4	36.0

†*7-year event rates*

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

IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit



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

Safety — ITT

- **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

Conclusions

- **IMPROVE-IT: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:**
  - **YES: *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events**
  - **YES: Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)**
  - **YES: Confirms ezetimibe safety profile**

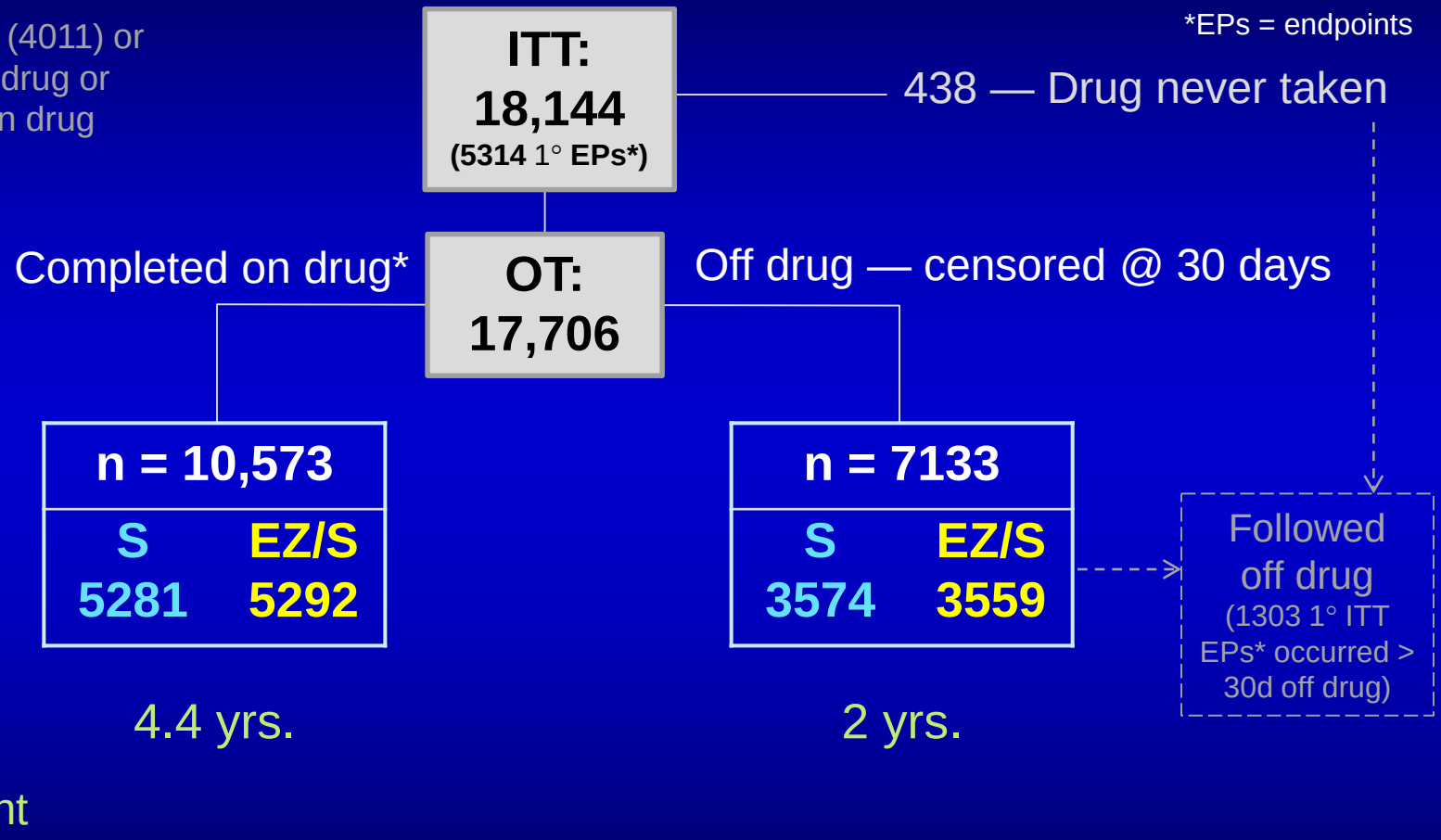
- **Reaffirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events**
- **Results could be considered for future guidelines**

DATI AGGIUNTIVI

Participant Disposition for 1° Endpoint — OT Population

*1° event on drug (4011) or non-CV death on drug or full assessment on drug during closeout

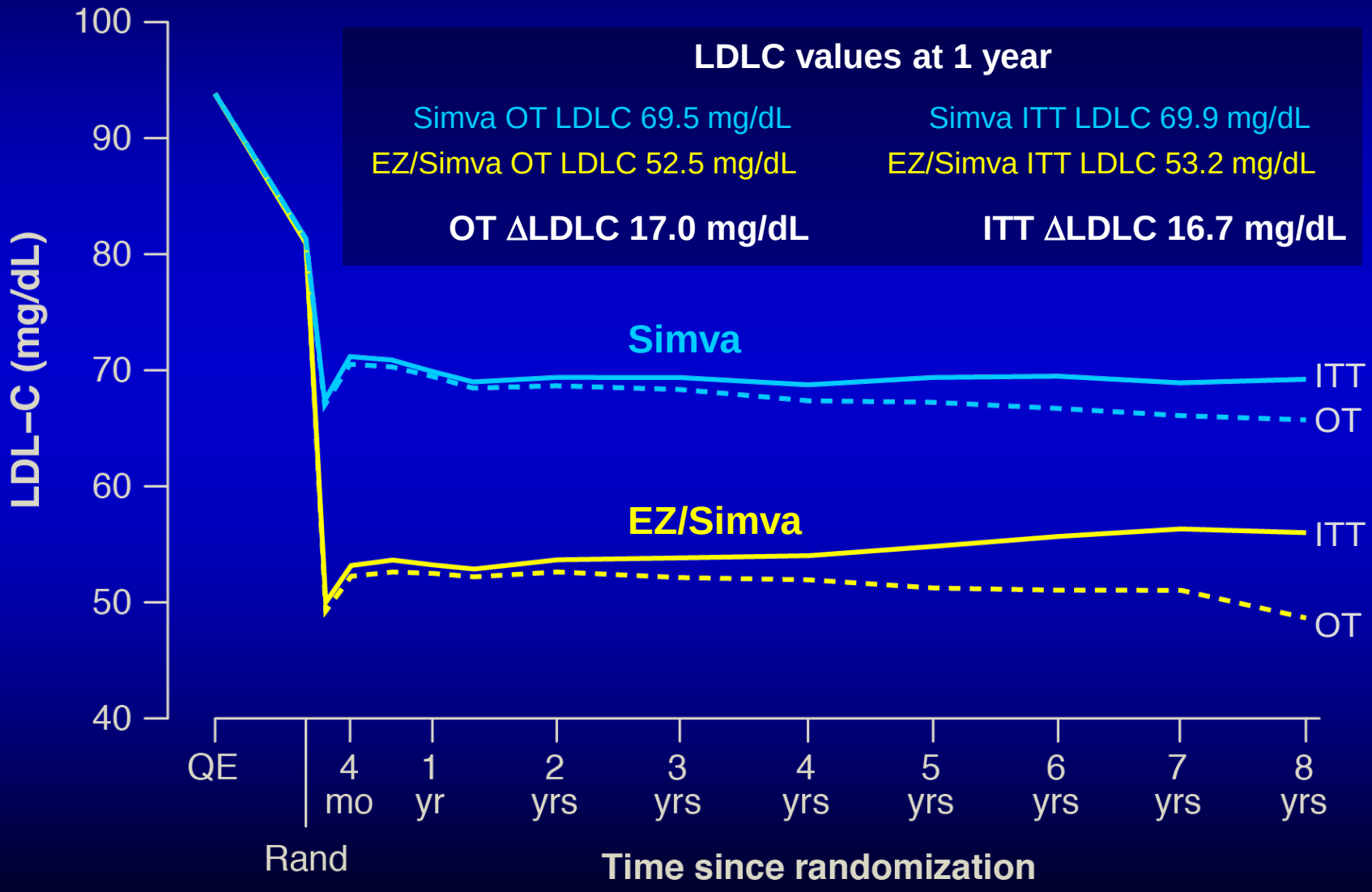
*EPs = endpoints



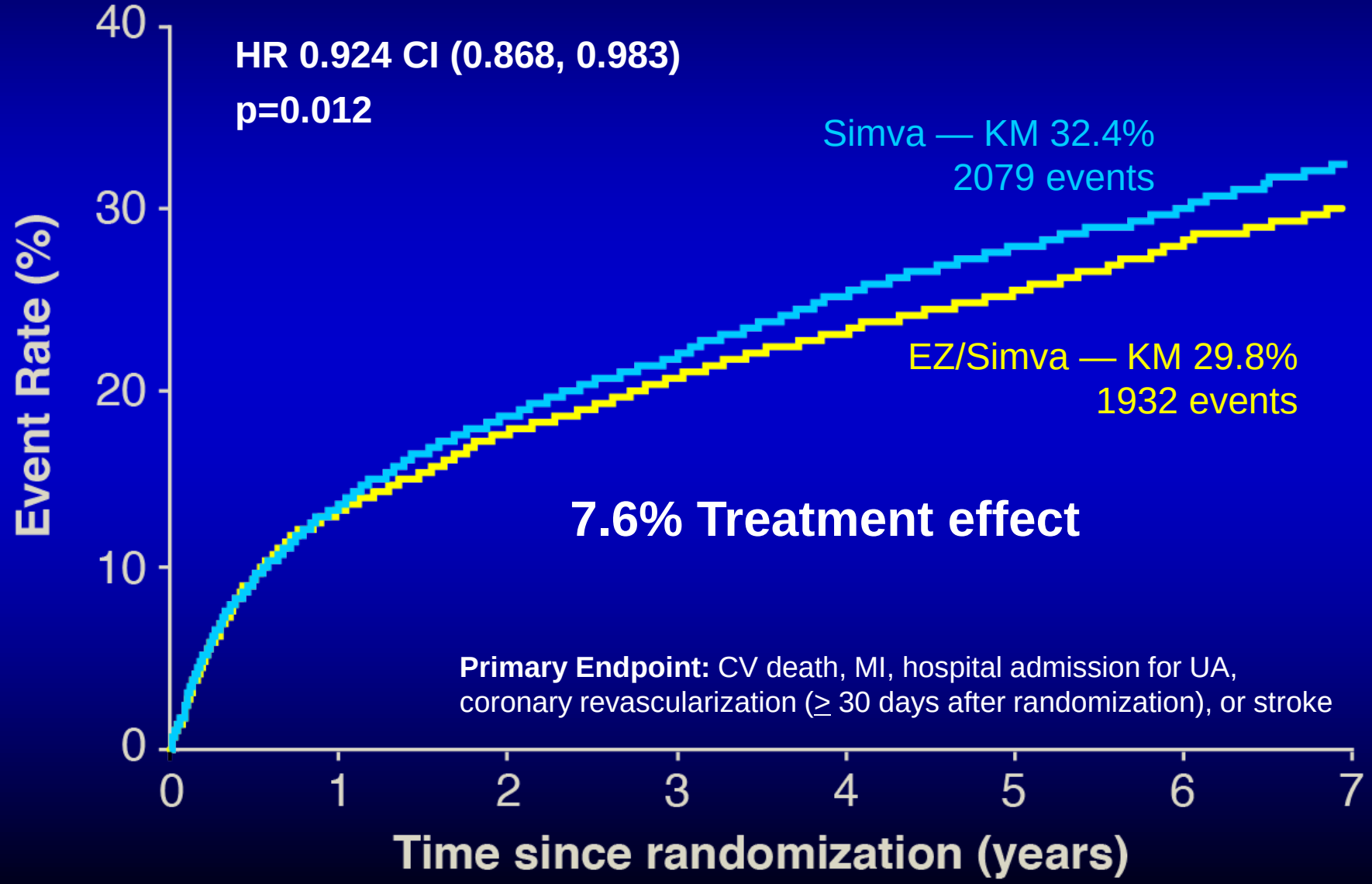
= 60,298 total patient-years of F/U OT

80,286 patient years follow up for primary endpoint in ITT

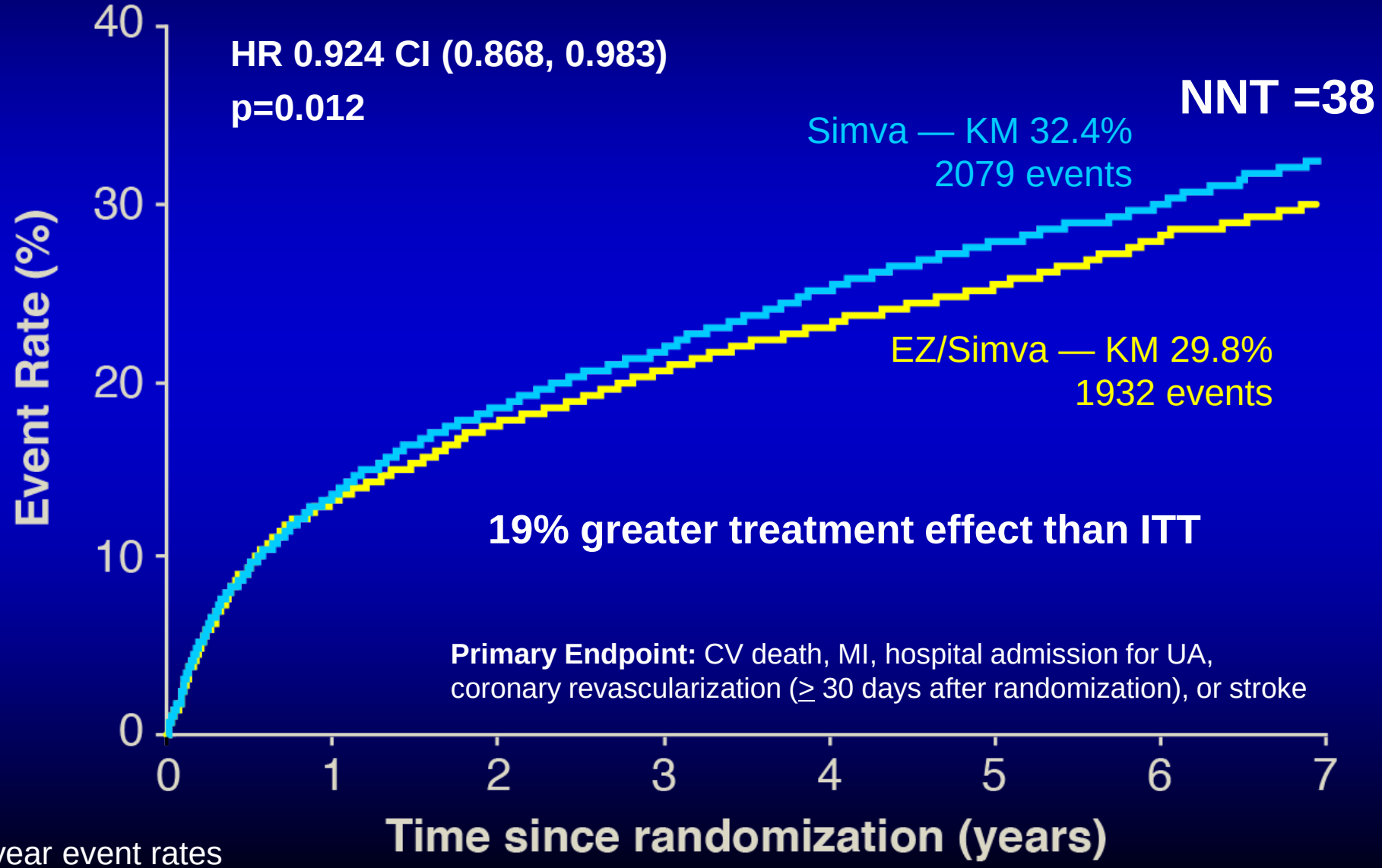
Mean LDL-C at 1 Year
OT & ITT



Primary Endpoint On-Treatment

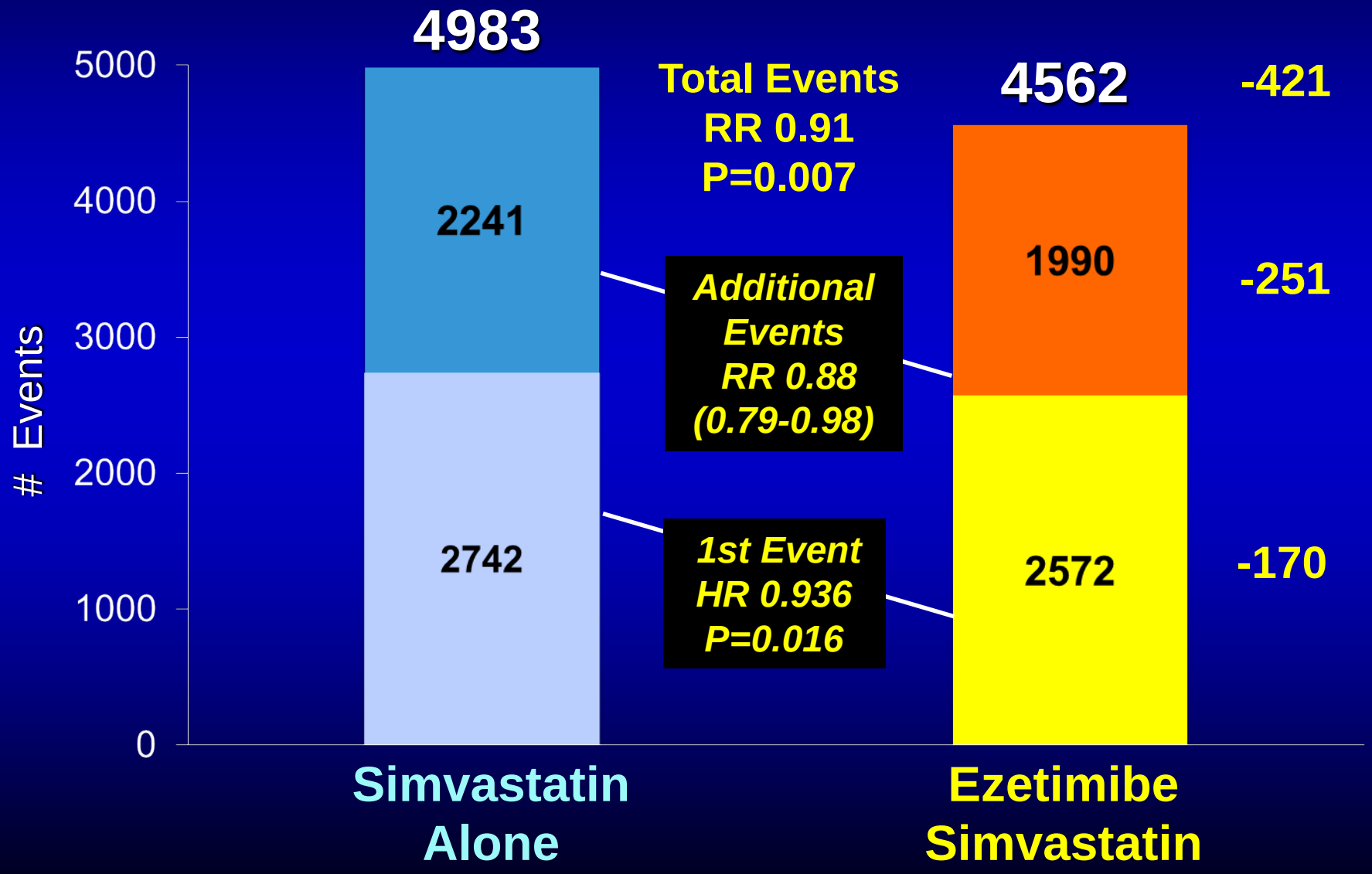


Primary Endpoint On Treatment

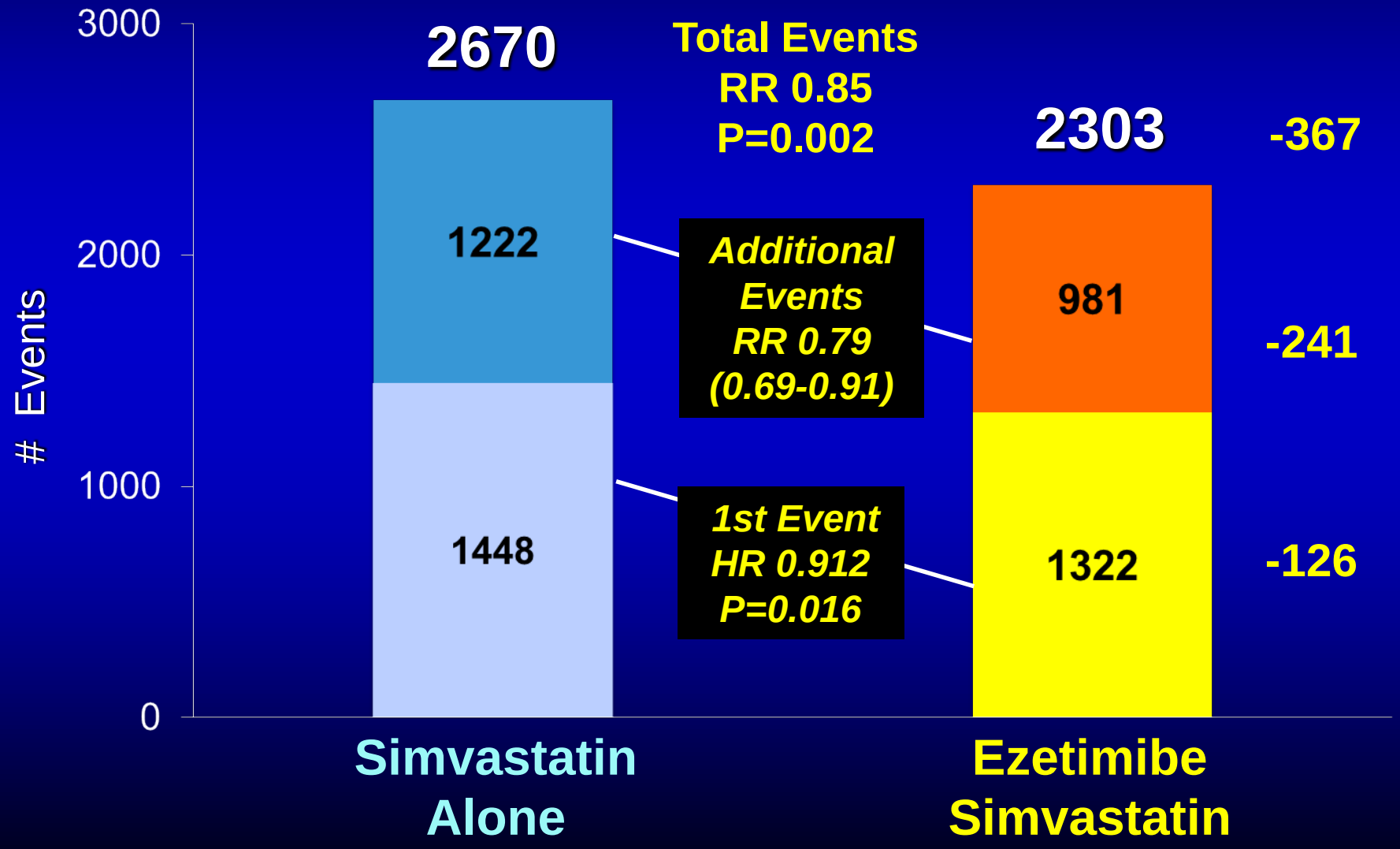


7 year event rates

Total Primary Endpoint Events



Secondary EP: CHD death, MI, urgent revascularization Events



The NEW ENGLAND JOURNAL of MEDICINE

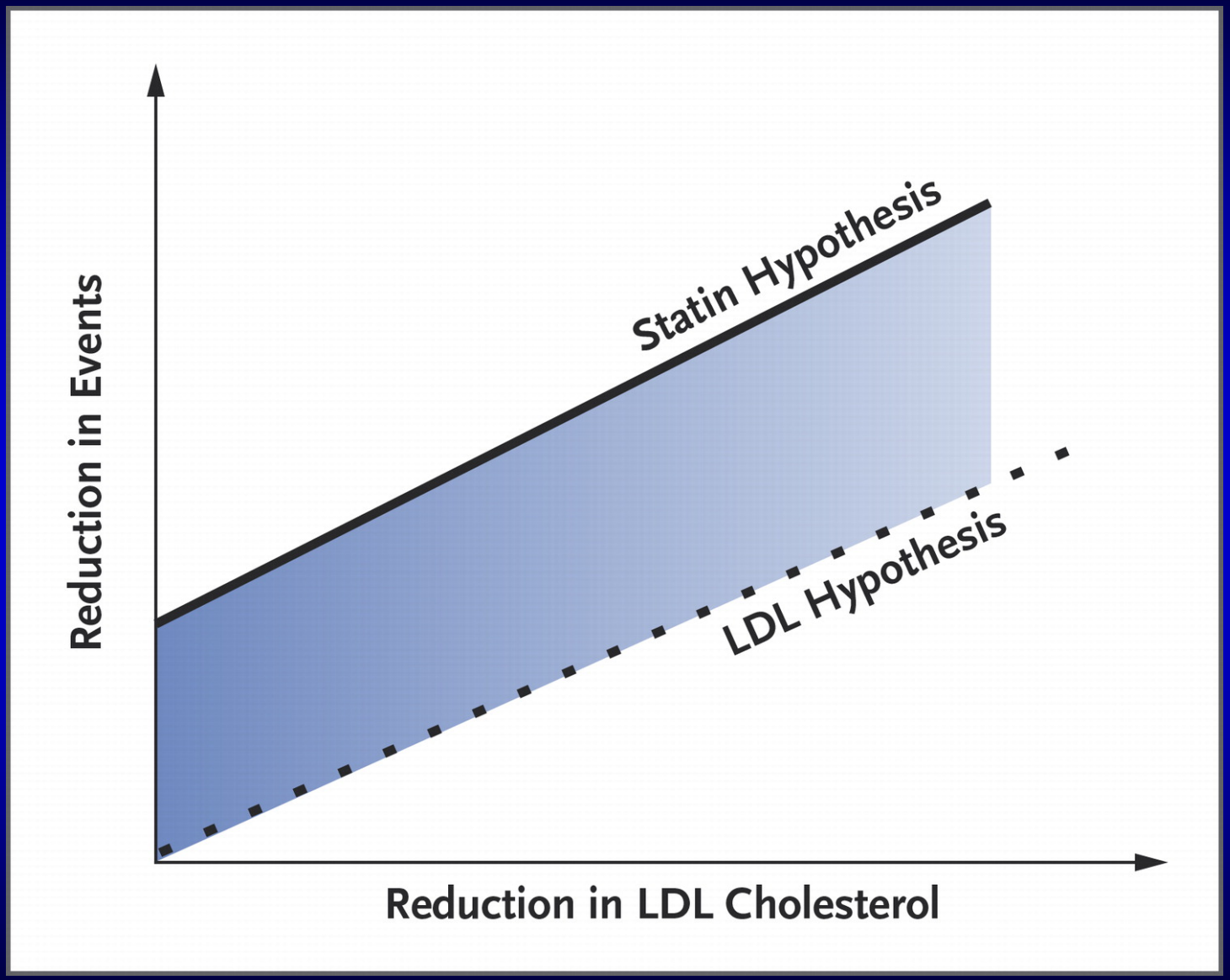
EDITORIAL

Proof That Lower Is Better — LDL Cholesterol and IMPROVE-IT

John A. Jarcho, M.D., and John F. Keaney, Jr., M.D.

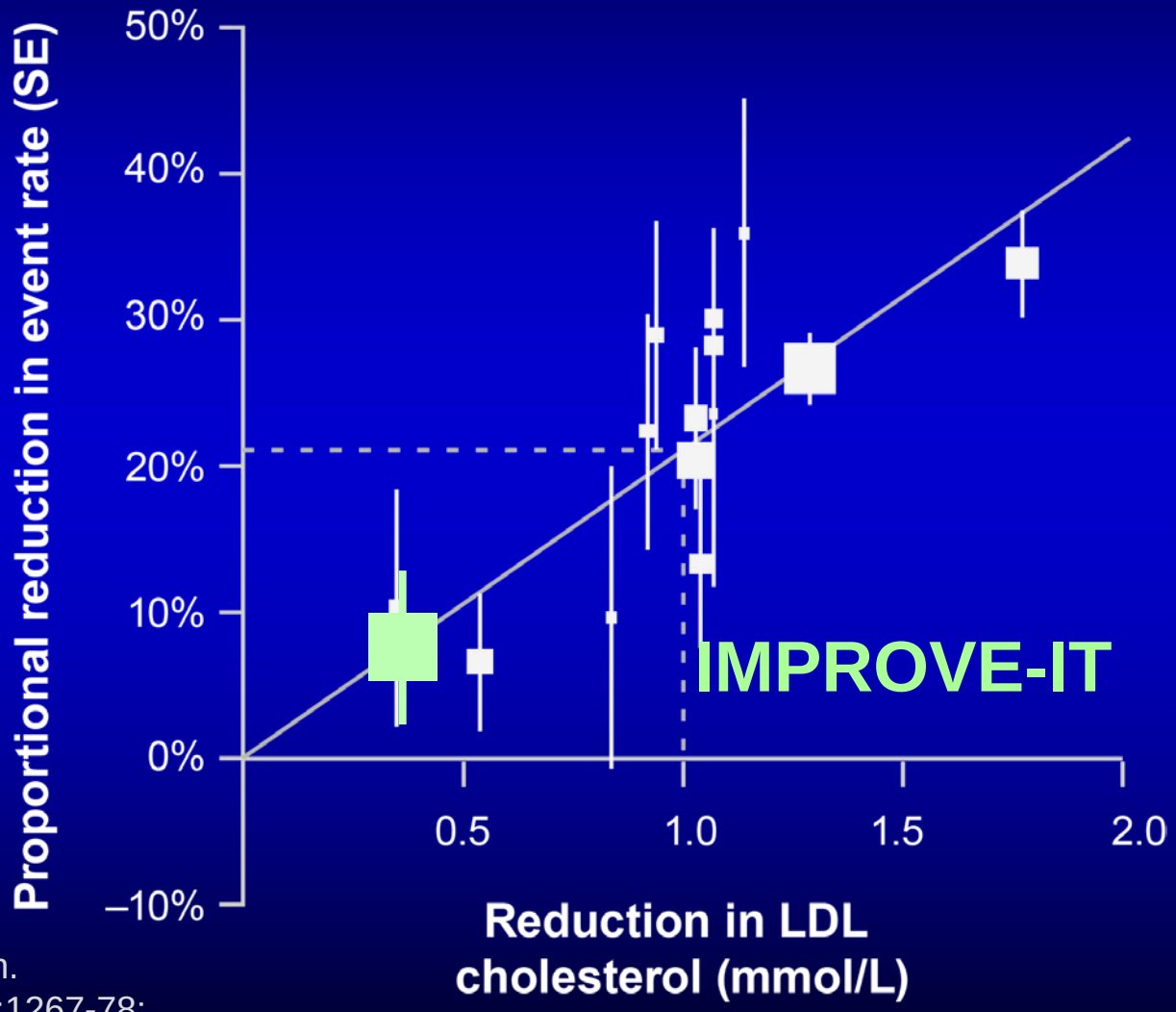
N ENGL J MED 372;25 NEJM.ORG JUNE 18, 2015

Schematic Depiction of the Statin Hypothesis



Jarcho JA, Keaney JF Jr. N Engl J Med 2015;372:2448-2450

IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit



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

"IMPROVE-IT is a landmark study in that it is the first clinical trial to show a benefit of adding a nonstatin lipid-modifying agent to statin therapy."

Jarcho JA, Keaney JF Jr. N Engl J Med 2015;372:2448-2450

"The results of IMPROVE-IT should, at a minimum, reinforce the recommendation of adding of a nonstatin agent..."

Jarcho JA, Keaney JF Jr. N Engl J Med 2015;372:2448-2450

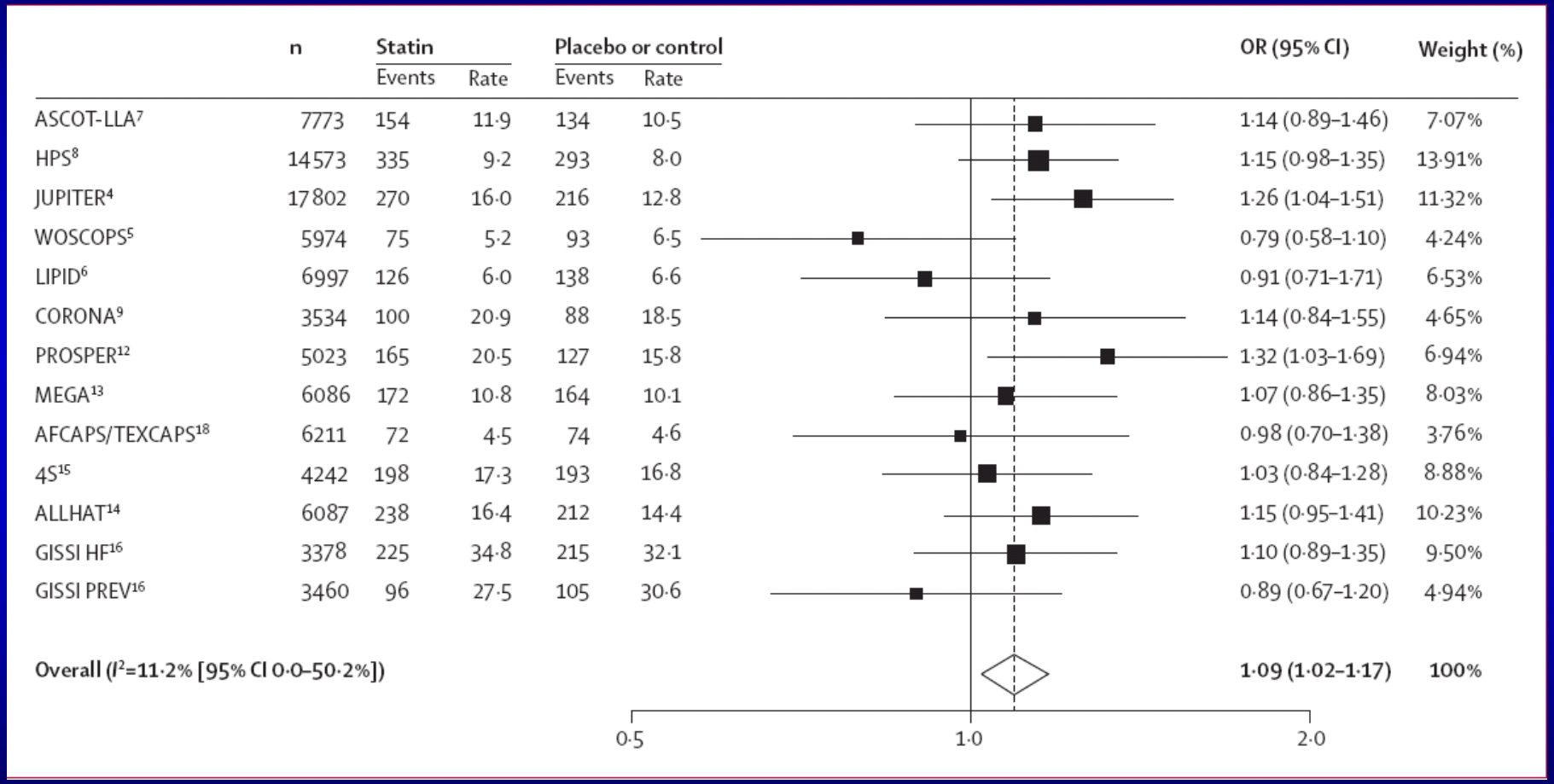
.....the LDL hypothesis should now be considered the "LDL principle."

Jarcho JA, Keaney JF Jr. N Engl J Med 2015;372:2448-2450

Focus sul diabete

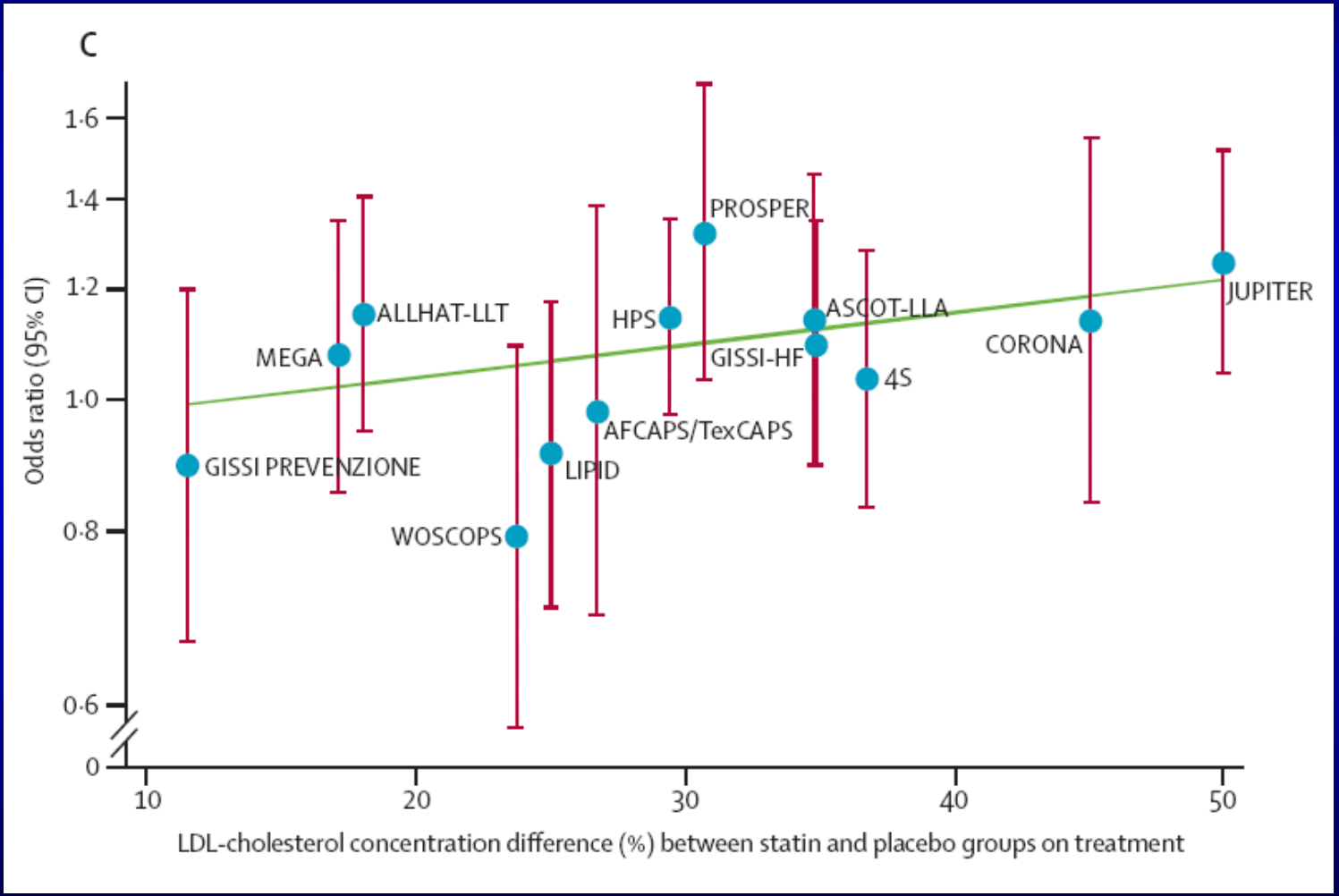
Il mondo si sta Boterizzando

Association between statin therapy and incident diabetes in 13 major cardiovascular trials



Sattar N, et al. Lancet 2010;375:735-42

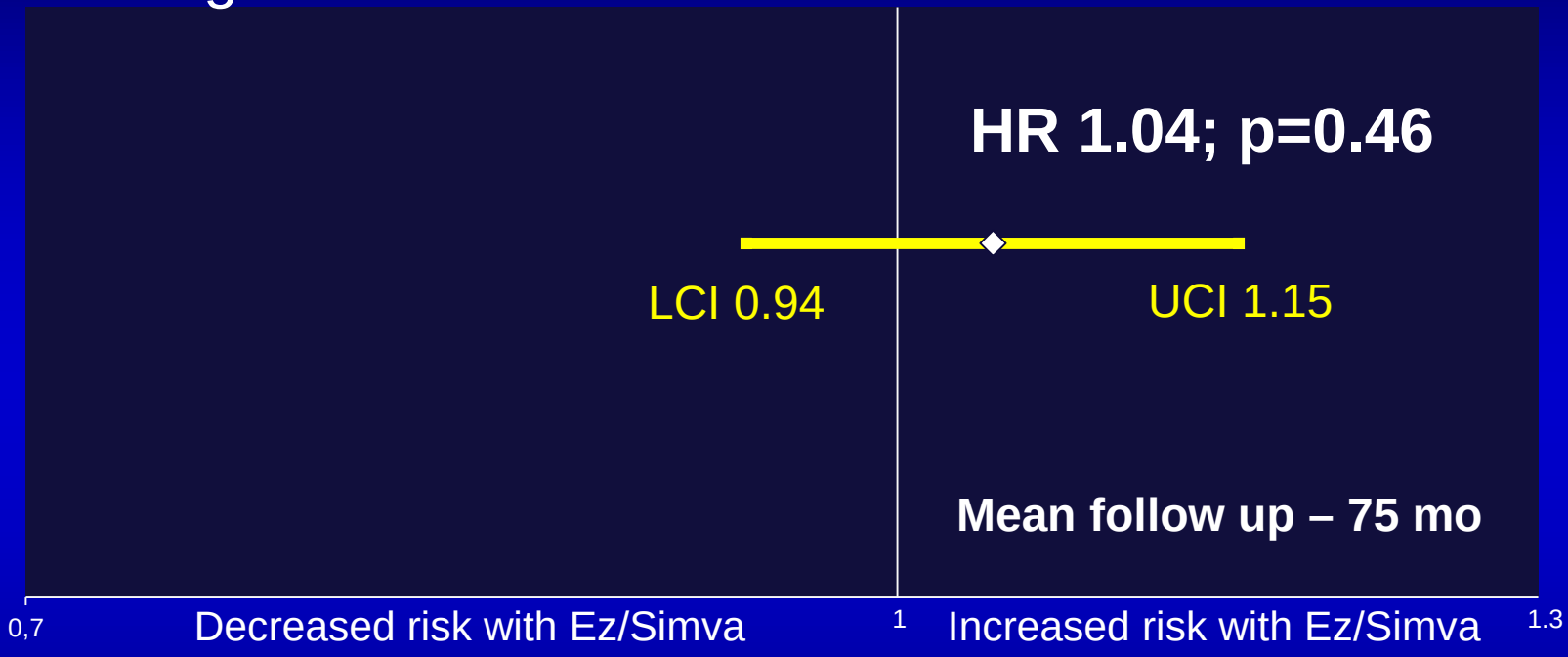
Meta-regression of on-treatment percentage reduction in LDL-cholesterol concentration for incident diabetes



Sattar N, et al. Lancet 2010;375:735-42

Primary outcome - NODM

Magnified view



1,414 (13.3%) patients with NODM

EZ/S = 720 **S = 694**

NODM = antihyperglycemic med and/or 2 fasting glucoses ≥ 7 mmol/L

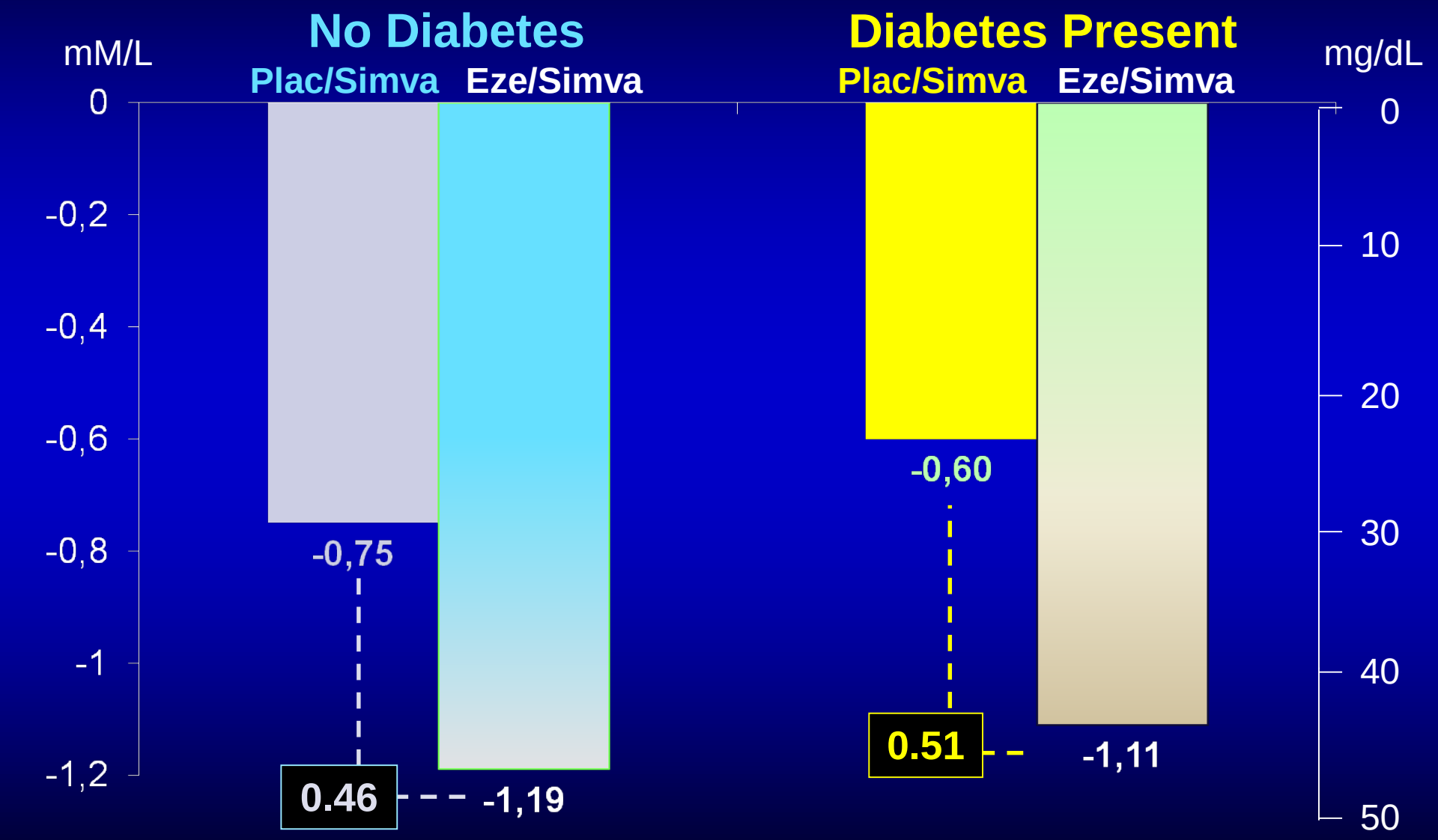
Baseline Characteristics

	No DM (N=13,202)	DM (N=4933)
Age (years)	64	65
Female	23	29
Body mass index (Kg/M^2)	27	29
MI prior to index ACS	19	26
PCI / CABG prior to index ACS	18 / 8	24 / 14
Hypertension	55	78
Aspirin prior to index ACS	38	54
Statin prior to index ACS	30	47
B-blocker / RAA inhibitor prior	31 / 34	44 / 60
Current smoker	36	24
ST-Elevation MI	32	21

Data shown are % unless otherwise indicated

P < 0.001 for each No DM vs DM comparison;
P=NS for comparisons by randomized Rx, stratified by DM

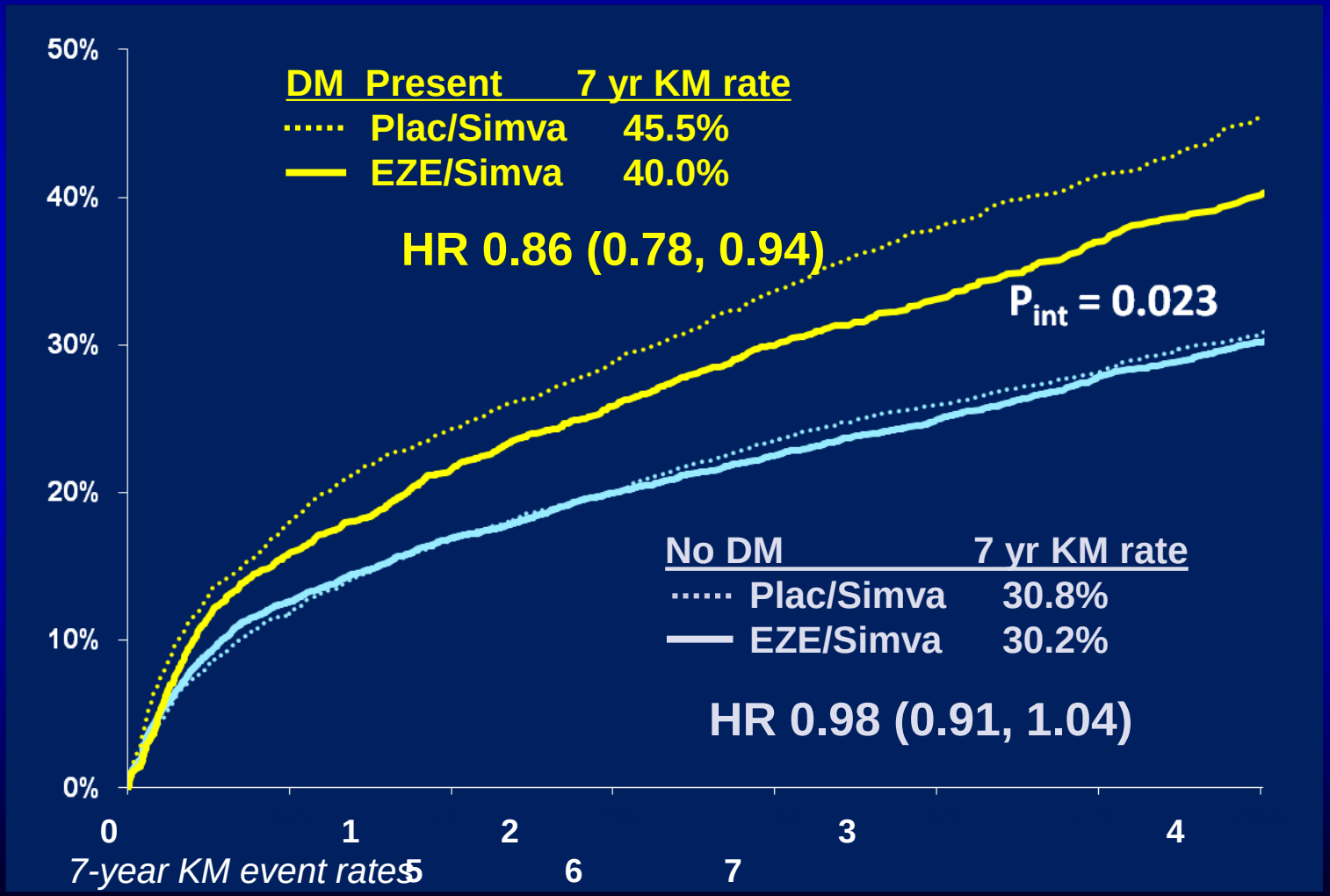
Decreases in LDL-C from Admission to Year 1



Giugliano RP, ESC Congress 2015, London, 8/30/2015

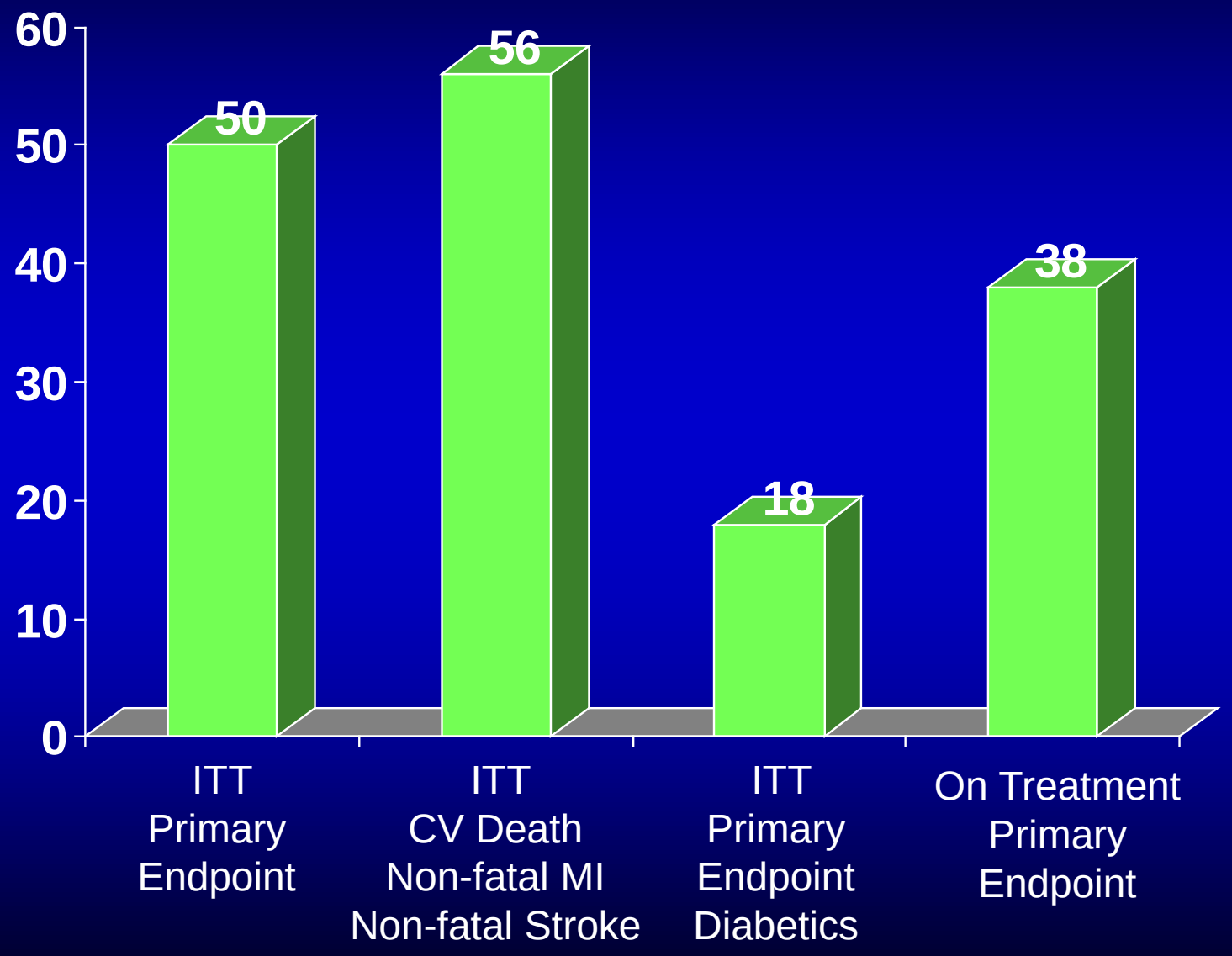
Primary Endpoint — ITT

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



Giugliano RP, ESC Congress 2015,

NNT per Prevenire Evento



Median Lab Values at Admission

	No DM (N=13,202)	DM (N=4933)
LDL-C (mM/L)	2.5	2.3
HDL-C (mM/L)	1.1	1.0
Triglycerides (mM/L)	1.3	1.5
High-sensitivity CRP* (mg/L)	5.0	5.6
Creatinine clearance (ml/min)	84	86

*measured at randomization

P < 0.001 for each, except CrCl P=0.03

P=NS for all comparisons by randomized treatment within each DM subgroup

Treatment Differences in Lipids and hs-CRP During the Trial

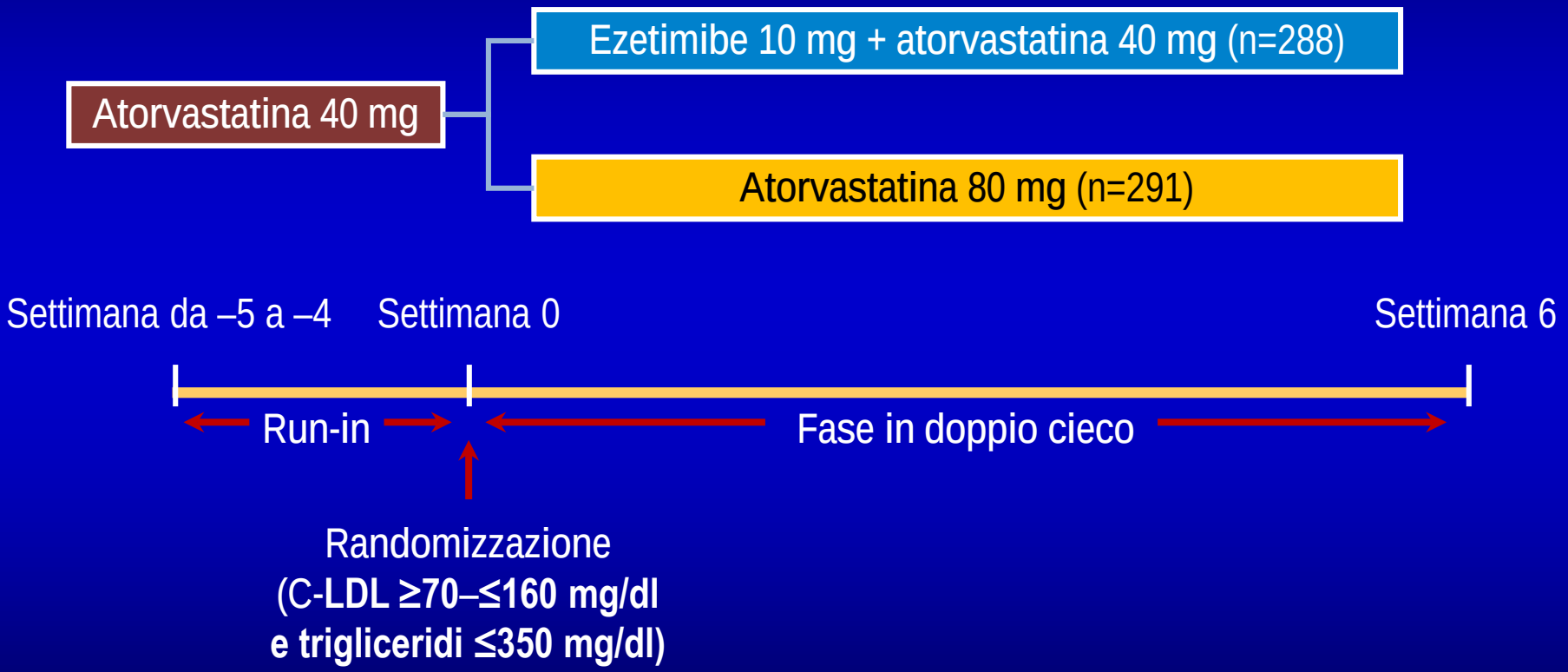
Placebo-adjusted differences between treatments in the changes from baseline* to the time-weighted average during the trial†

Parameter	No Diabetes (ΔE/S – ΔP/S)	DM Present (ΔE/S – ΔP/S)	P_{int}
LDL-C	**-0.37 mM/L**	**-0.43 mM/L**	**0.03**
Triglycerides	-0.09 mM/L	-0.13 mM/L	0.59
HDL-C	+0.013 mM/L	+0.008 mM/L	0.30
hs-CRP*	**-0.05 mg/L**	**-1.09 mg/L**	**0.03**

* baseline hs-CRP at randomization; baseline lipids obtained at admission
† from month 1 to end of trial

Tolleranza Zero agli Eccessi di LDL

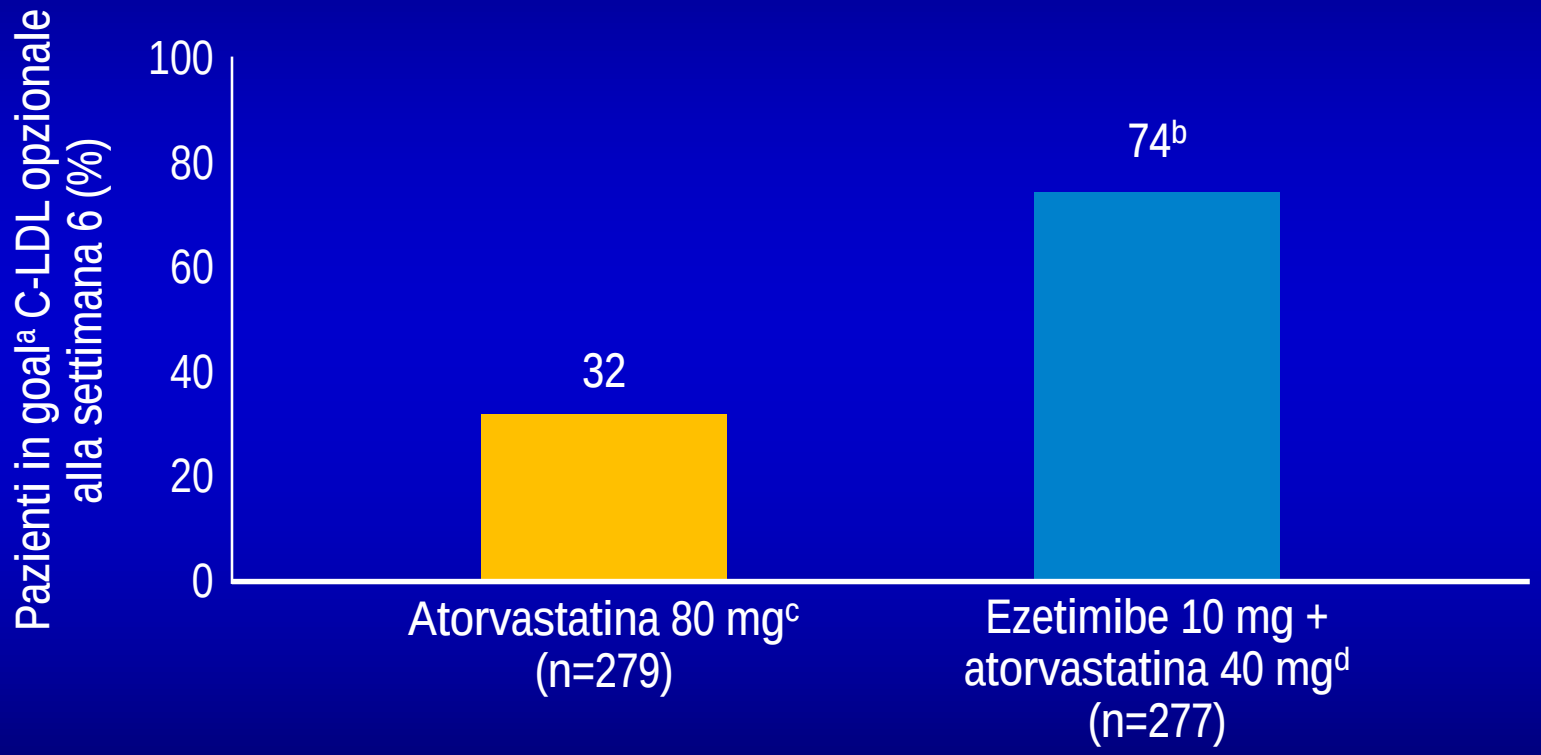
Disegno dello Studio EZ-PATH



Leiter et al. Am J Cardiol 2008;102:1495-1501

Studio EZ-PATH

Confronto tra raddoppio di atorvastatina e aggiunta di ezetimibe nel raggiungere l'obiettivo di C-LDL<70 mg/dl



[a]<70 mg/dl (<1,8 mmol/l); [b]p <0,001 vs atorvastatina 80 mg; [c]C-LDL basale = 90 mg/dl; [e]C-LDL basale = 89 mg/dl

Leiter et al. Am J Cardiol 2008;102:1495-1501

The even lower the even better

Q & A