TURIN, 22ND NOVEMBER 2008

GREAT INNOVATIONS IN CARDIOLOGY

1ST JOINT MEETING WITH MAYO CLINIC UNDER 35

M. Andriani (Torino)

Le statine nell'acuto

LE STATINE NELL'ACUTO

JMMC UNDER 35

Torino, 22 Novembre 2008

Dr.ssa M. Andriani

S.C. CARDIOLOGIA 2
A.0. SAN GIOVANNI BATTISTA - TORINO

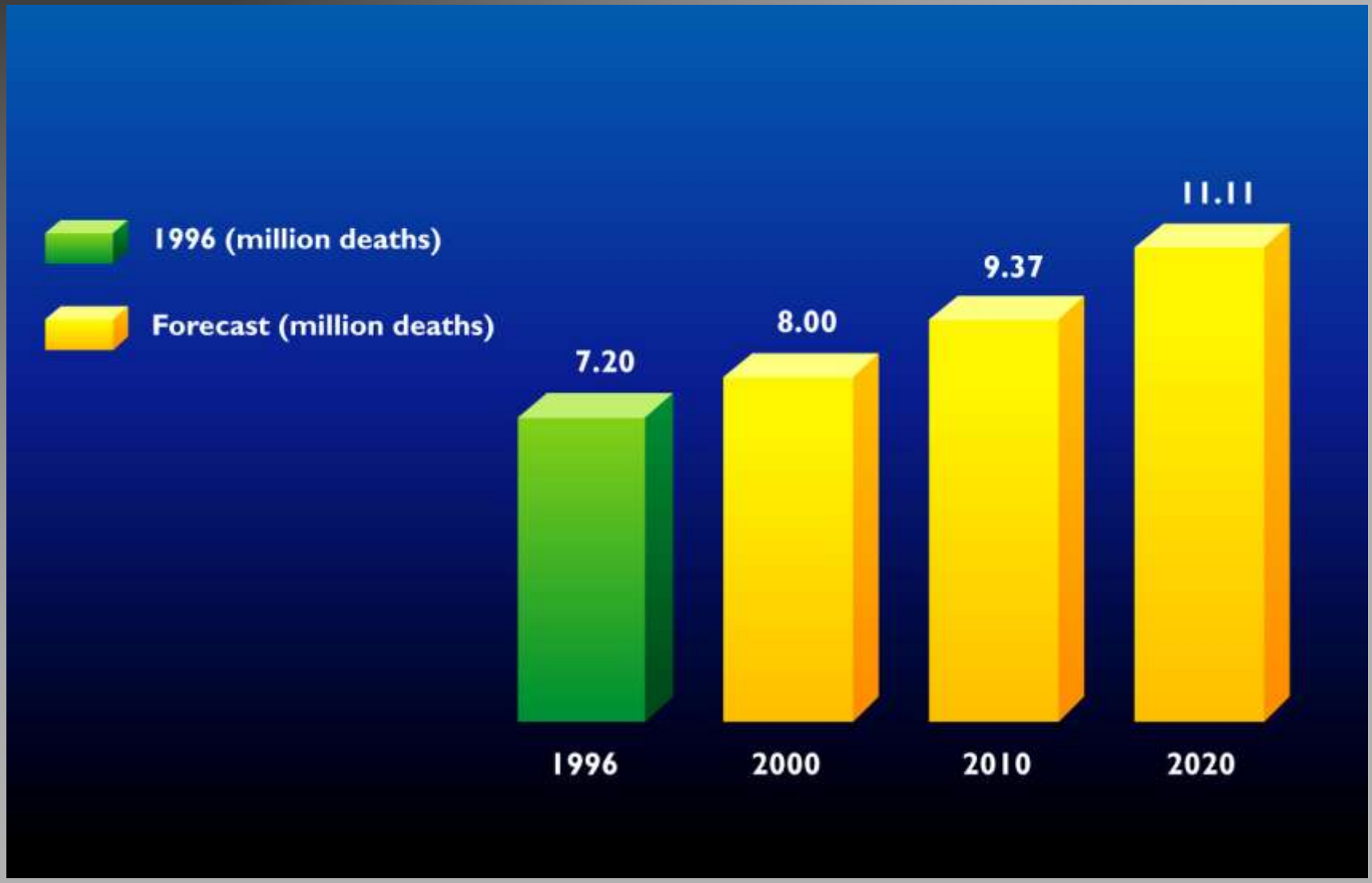
JMMC
4TH JOINT MEETING WITH MAYO CLINIC

Struttura Complessa di Cardiologia Ospedaliera
Azienda Ospedaliera S.G. Battista, Molinette di Torino

INCIDENZA ANNUALE DI MALATTIE CARDIOVASCOLARI NEL MONDO

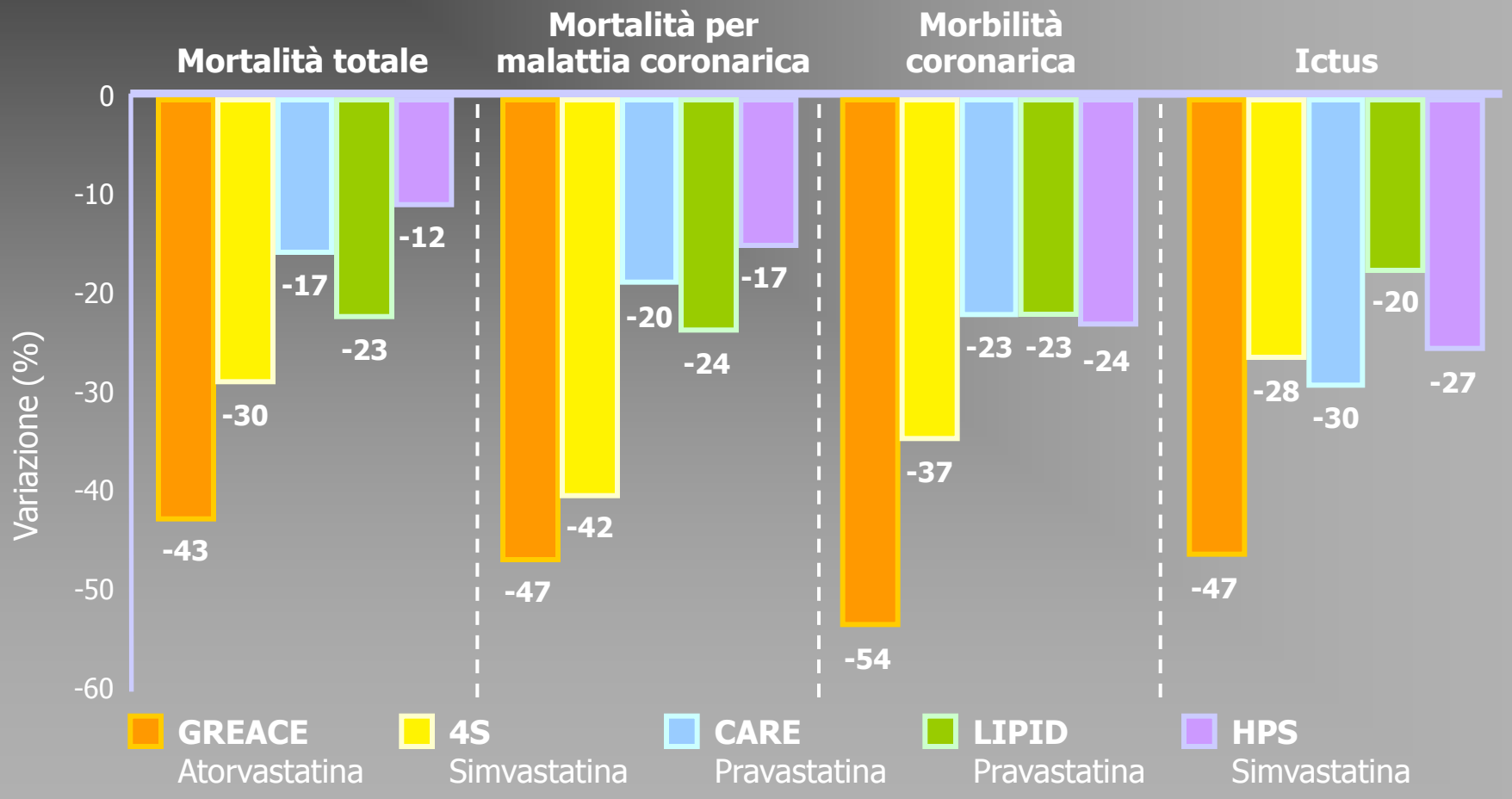
Incidenza basata su dati del 1995 (AHA)

Mortalità per coronaropatia



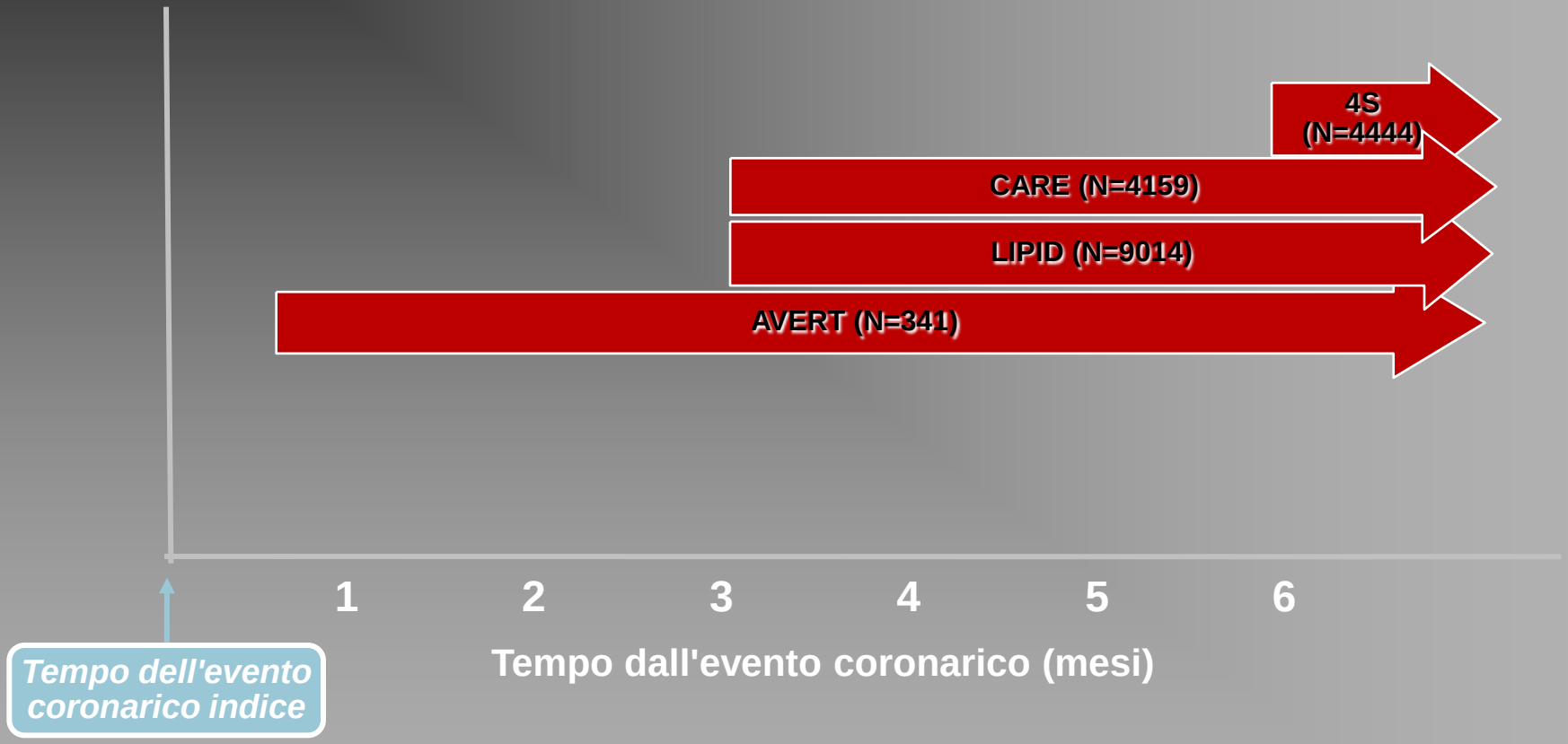
LE STATINE RIDUCONO LA MORTALITA' E LA MORBILITA' NEL CORONAROPATICO CRONICO

GREACE, 4S, CARE, LIPID, HPS



Athyros VG GREACE Study, Poster presentato al 73rd EAS Congress: Salzburg, Austria, July 2002

I PRIMI STUDI IMPORTANTI SULLE STATINE ESCLUDEVANO I PAZIENTI CON SCA



4S=Scandinavian Simvastatin Survival Study; CARE=Cholesterol and Recurrent Events; LIPID=Long-Term Intervention with Pravastatin in Ischaemic Disease; AVERT=Atorvastatin VErsus Revascularization Treatments.

Scandinavian Simvastatin Survival Study Group. Lancet. 1994;344:1383-1389. Lewis SJ et al. Ann Intern Med. 1998;129:681-689; LIPID Study Group. N Engl J Med. 1998;339:1349-1357; McCormick LS et al. Am J Cardiol. 1997;80:1130-1133.

PRESUPPOSTI PER L'UTILIZZO DI STATINE NELLA FASE ACUTA DELLA SINDROME CORONARICA

EFFETTO PLEIOTROPICO

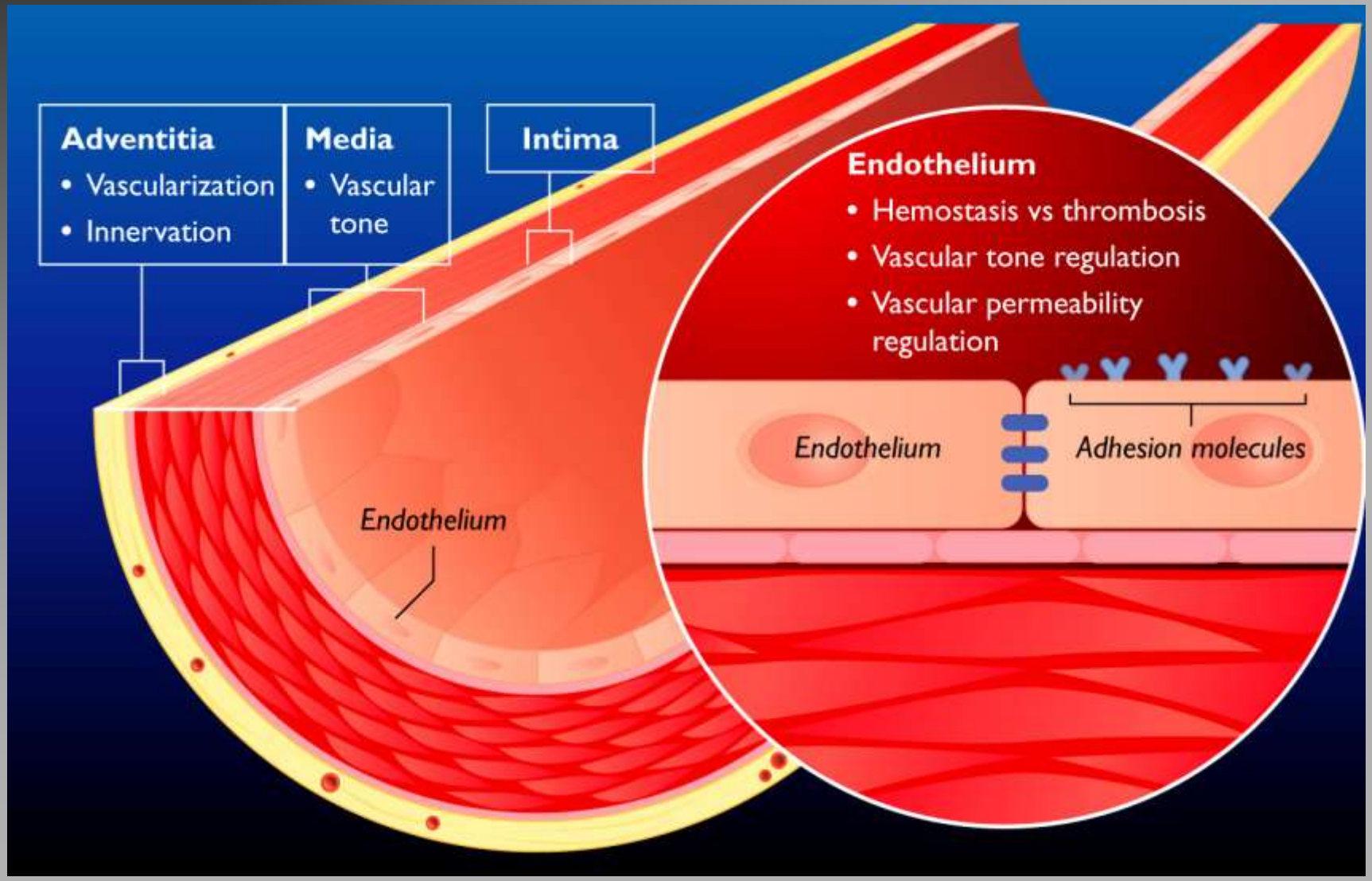
STUDI OSSERVAZIONALI

REGISTRI

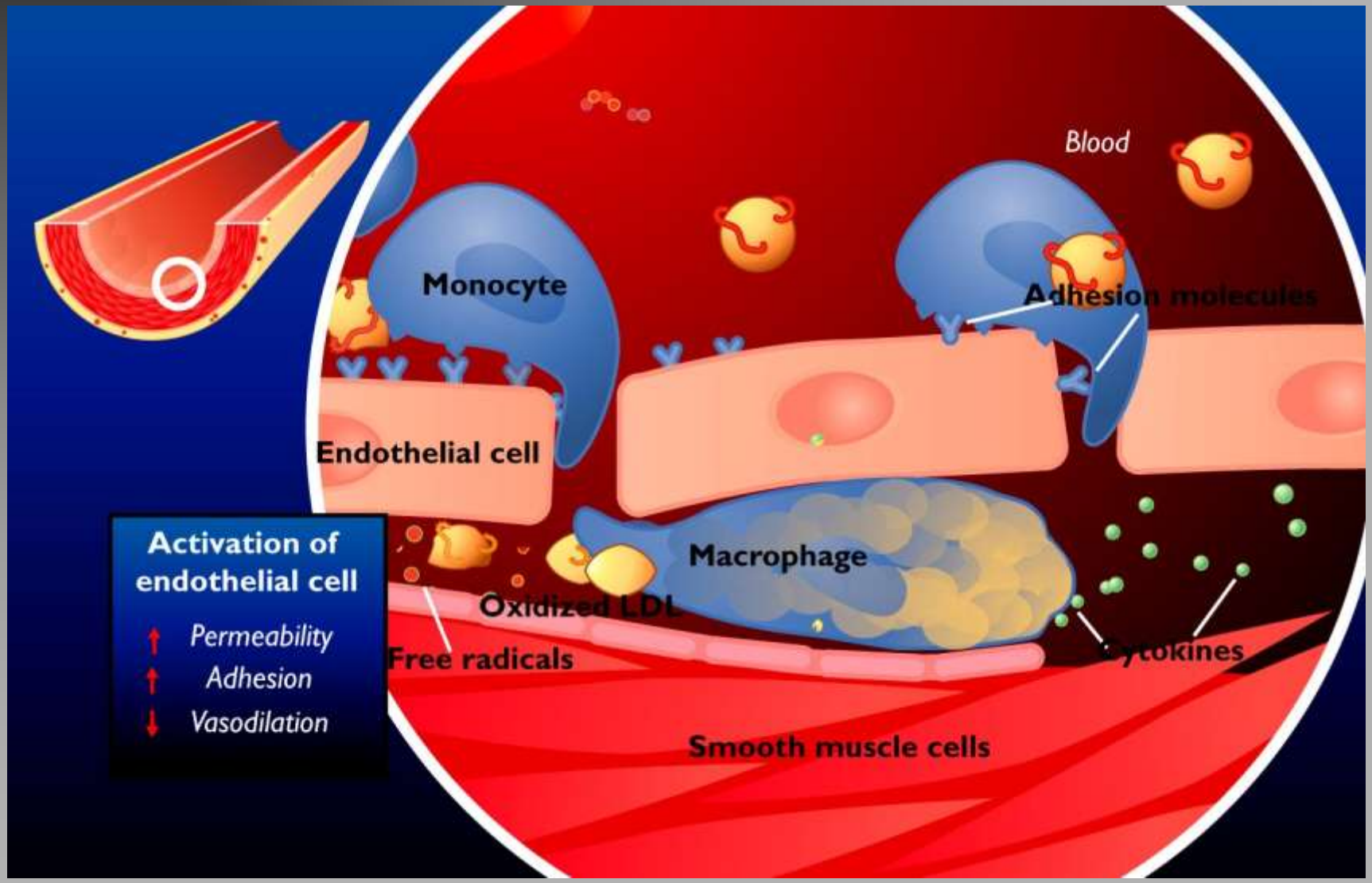
TRIALS

METANALISI

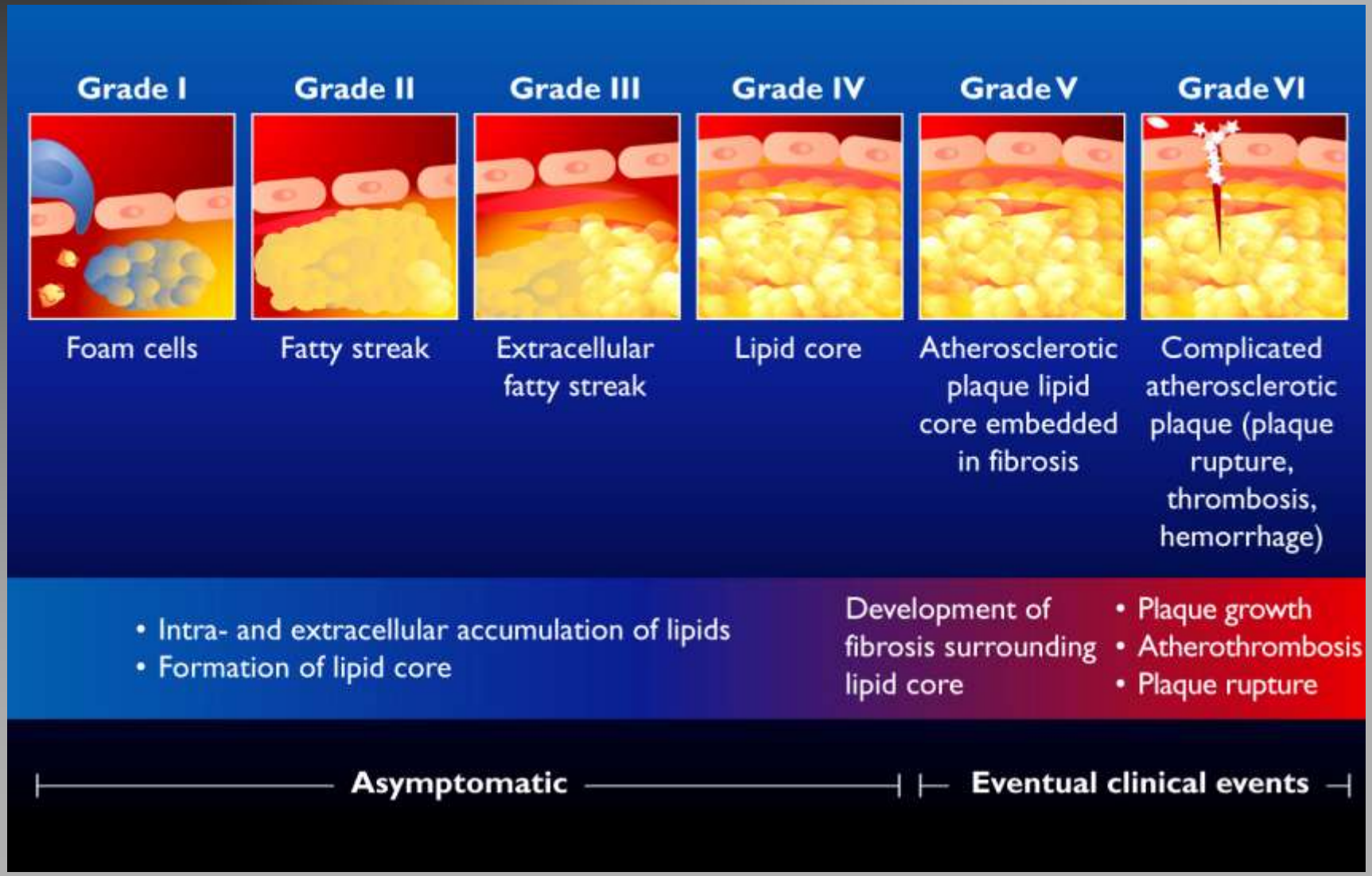
Parete arteriosa: struttura e funzione



Alterazioni endoteliali nell'aterosclerosi



Differenti stadi di sviluppo della placca aterosclerotica

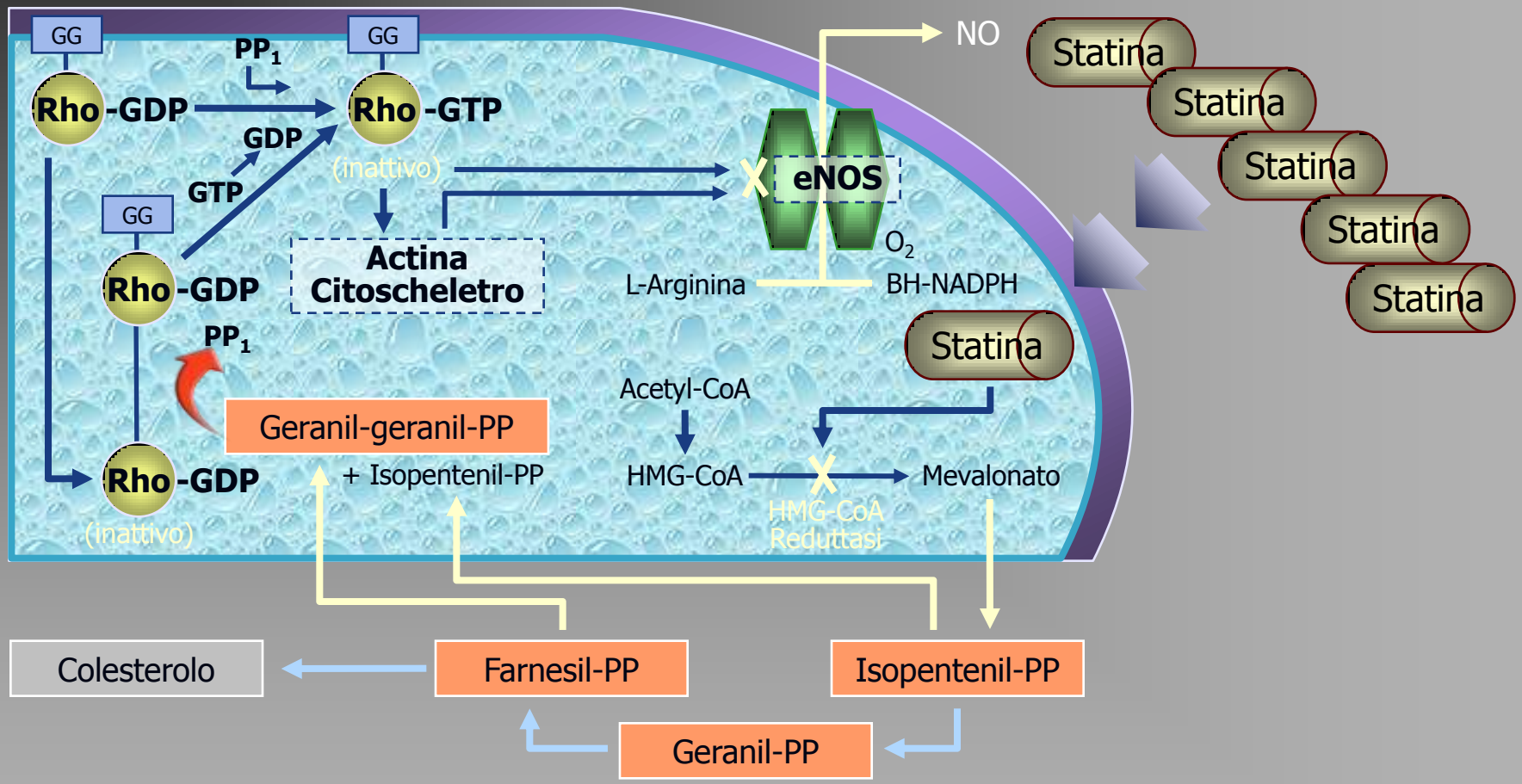


PLEIOTROPISMO

PLEIOTROPISMO: EFFETTI BENEFICI DI UN FARMACO NON CORRELATI AL PRINCIPALE EFFETTO DEL FARMACO STESSO.

NEL CASO DELLE STATINE SONO DA CONSIDERARE GLI EFFETTI NON DERIVABILI DIRETTAMENTE DALLA DIMINUIZIONE DEL COLESTEROLO

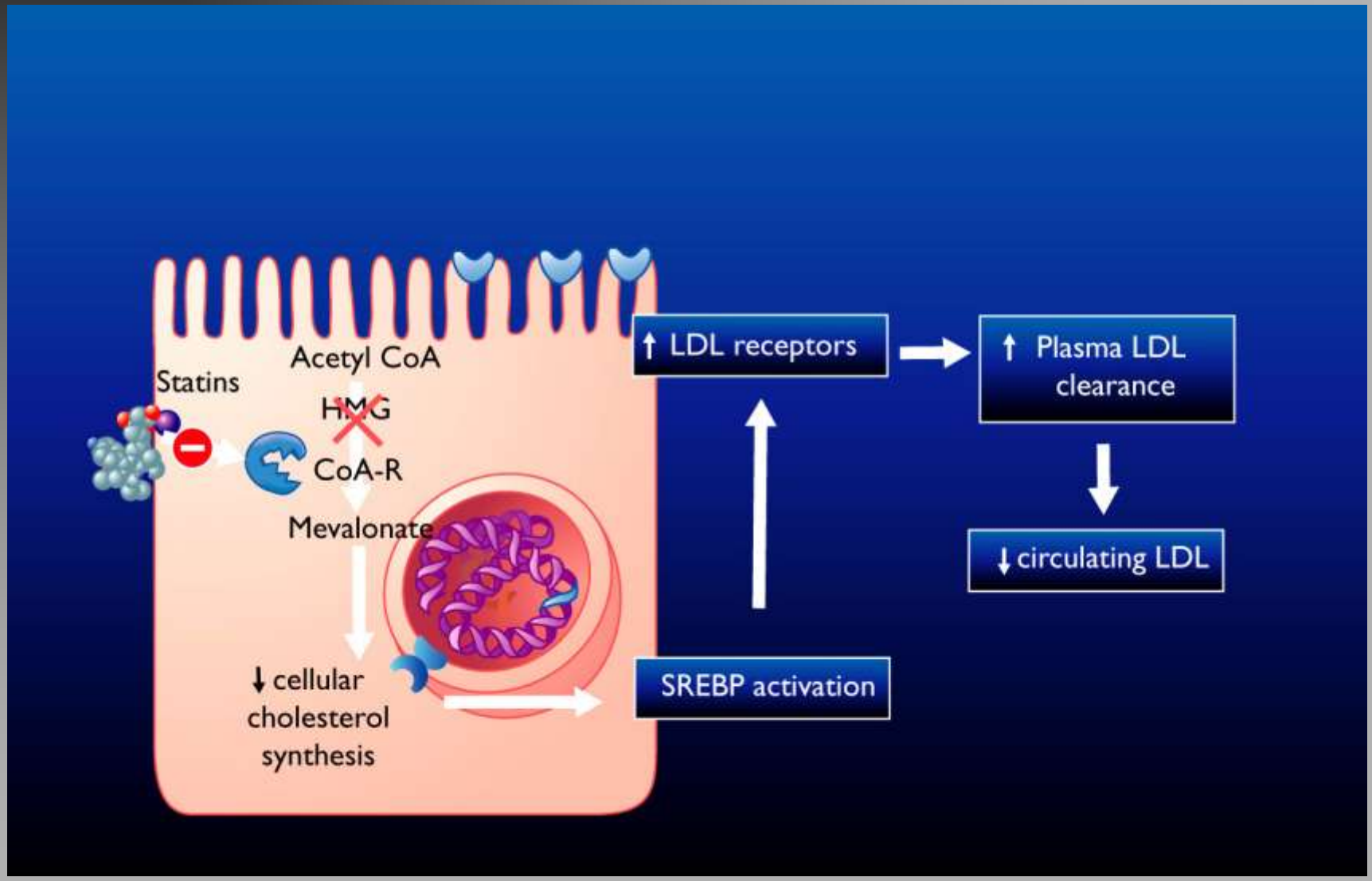
Meccanismo d'azione delle statine



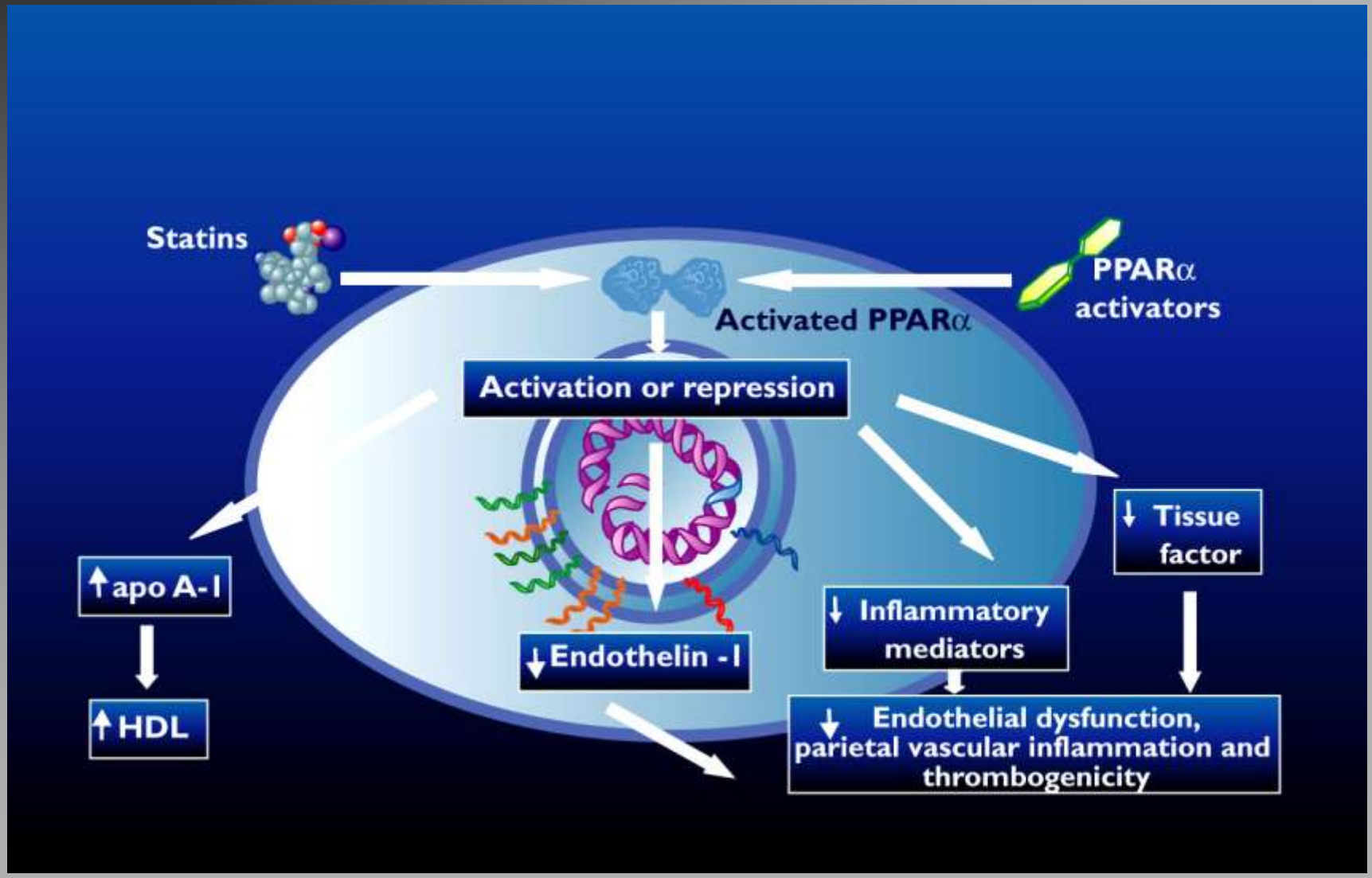
Le statine determinano un'up-regulation dell'eNOS. Le statine bloccano la biosintesi degli isoprenoidi e di colesterolo. L'isoprenoide geranil-geranil-pirofosfato (GG-PP) è importante per la traslocazione sulla membrana e la funzione del fattore Rho.
Il fattore Rho, a sua volta, regola negativamente l'espressione di eNOS agendo sull'actina del citoscheletro.

James K, Liao, Statins and ischemic stroke, Atherosclerosis 2002; Supplements 3:21-25

SREBP feedback control



Parietal vascular effects



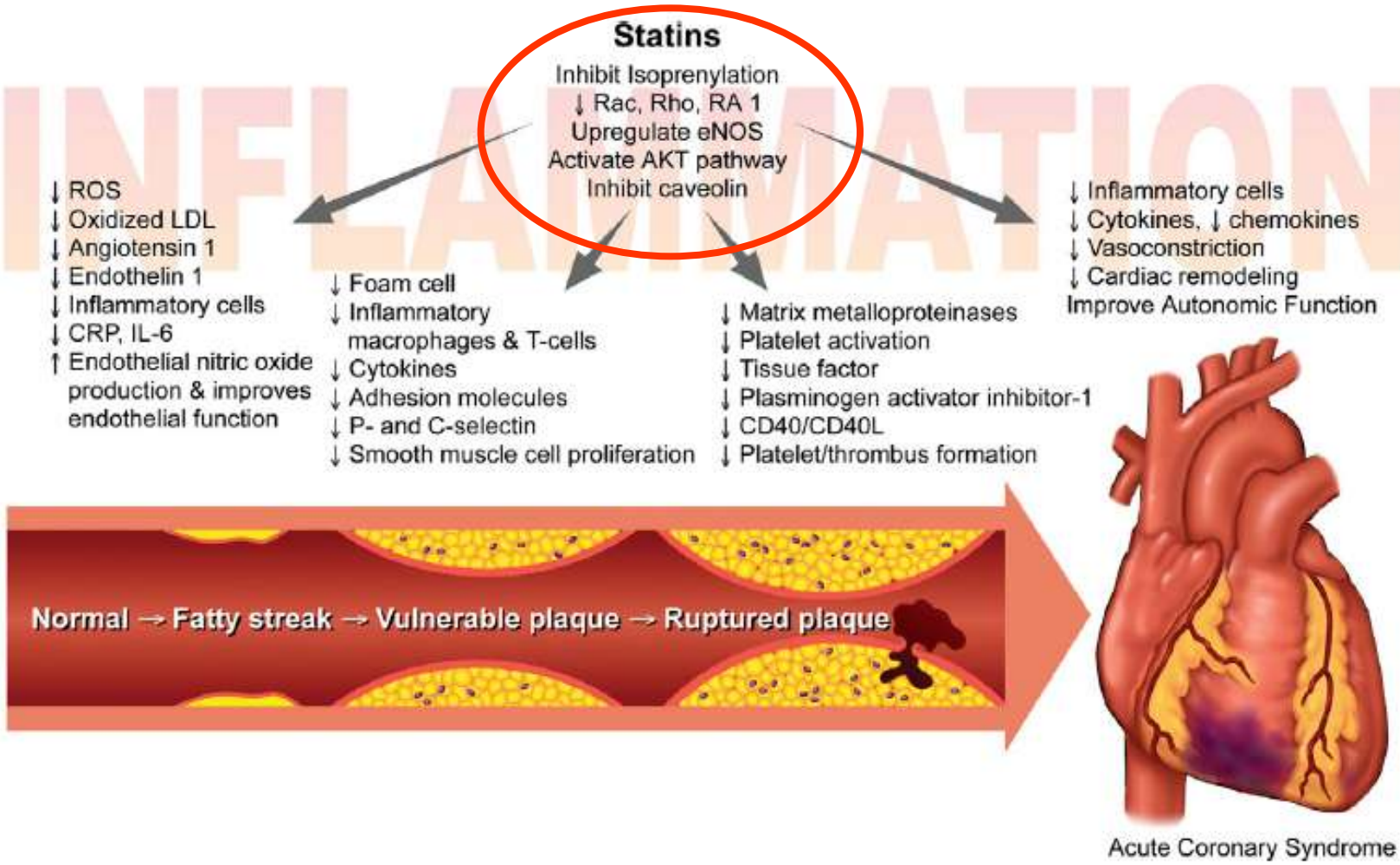
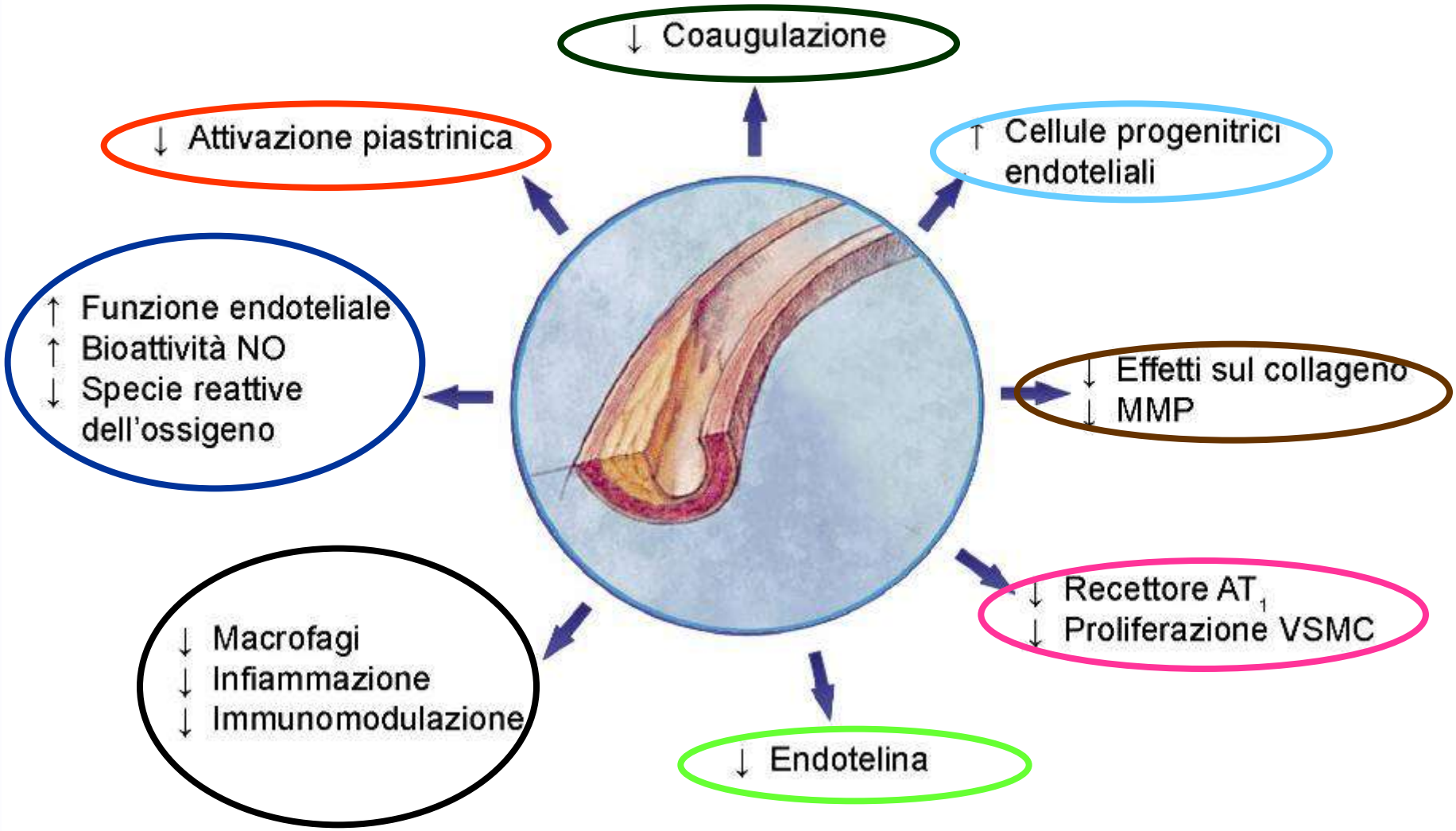


Figure 2 The role inflammation in the pathogenesis of coronary artery disease and ACSs. RAC and Rho, G-protein subunits; RA 1, Rap-activated 1; eNOS, endothelial nitric oxide synthase; ROS, reactive oxygen species; CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6.

T. Patel et al. E.Heart J 2007;28:664

Effetti pleiotropici delle statine



Liao JK. Am J Cardiol. 2005;96(suppl 1):24F-33F.

PRESUPPOSTI PER L'UTILIZZO DI STATINE NELLA FASE ACUTA DELLA SINDROME CORONARICA

EFFETTO PLEIOTROPICO

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STUDI OSSERVAZIONALI SUGGERISCONO BENEFICI POTENZIALI DELLA TERAPIA IPOLIPEMIZZANTE IN SCA

Studio	Pazienti (N)	Pazienti in terapia ipolipidemizzante (%)	Riduzione del rischio osservata con terapia ipolipidemizzante
GRACE	15,481*	38†	Durante ospedalizzazioneOR 0.87, *P*> .05
NRMI 4	148,106*	14.8†	Durante ospedalizzazione OR 0.23, *P*<.001
PRISM	1616	23†	30-giorni OR 0.49, *P*=.004
SYMPHONY & SYMPHONY II	12,365	47†	90-giorni HR 1.08, mortalità 1-anno HR 0.99
PURSUIT/ GUSTO IIb	20,809	18‡	6-mesi OR 0.48, *P*<.0001
OPUS-TIMI 16	10,288	38†	1-anno OR 0.58, *P*<.0001
Swedish Register (RIKS-HIA)	19,599	28†	1-anno OR 0.75, *P*=.001

GRACE=Global Registry of Acute Coronary Events; NRMI=National Registry of Myocardial Infarction; PRISM=Platelet Receptor Inhibition in Ischemic Management; SYMPHONY=Sibrafiban vs Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes; PURSUIT=Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; GUSTO=Global Use of Streptokinase or t-PA for Occluded Coronary Arteries; OPUS-TIMI=Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes; RIKS-HIA=Register of Information and Knowledge About Swedish Heart Intensive Care Administration.
*Pazienti precedentemente non trattati con statine; †Solo terapia con statine; ‡qualsiasi terapia di riduzione dei lipidi;; OR=odds ratio; HR=hazard ratio.

Stenestrand U et al. JAMA. 2001;285:430-436; Cannon CP et al. J Am Coll Cardiol. 2001;35:334A; Heeschen C et al. Circulation. 2002;105:1446-1452; Newby LK et al. JAMA. 2002;287:3087-3095; Aronow HD et al. Lancet. 2001;357:1063-1068; Spencer FA et al. Ann Intern Med. 2004;140:857-866; Fonarow GC et al. Am J Cardiol. 2005;96:611-616.

PRESUPPOSTI PER L'UTILIZZO DI STATINE NELLA FASE ACUTA DELLA SINDROME CORONARICA

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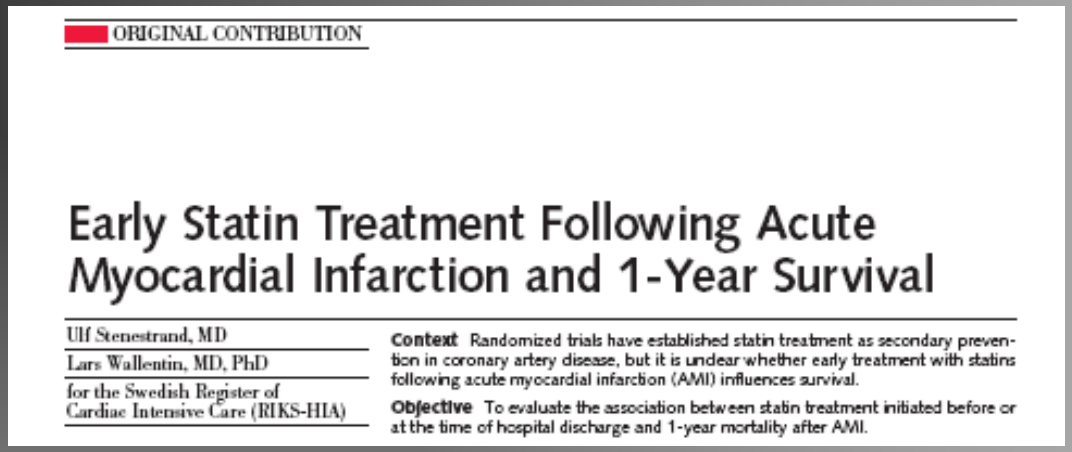
ESPERIENZE - REGISTRI



ORIGINAL CONTRIBUTION

Early Statin Treatment Following Acute Myocardial Infarction and 1-Year Survival

Ulf Stenestrand, MD
Lars Wallentin, MD, PhD
for the Swedish Register of Cardiac Intensive Care (RIKS-HIA)

Context Randomized trials have established statin treatment as secondary prevention in coronary artery disease, but it is unclear whether early treatment with statins following acute myocardial infarction (AMI) influences survival.

Objective To evaluate the association between statin treatment initiated before or at the time of hospital discharge and 1-year mortality after AMI.

DATI SWEDISH REGISTER OF CARDIAC INTENSIVE CARE

1995 -1998

58 OSPEDALI SVEDESI

19599 PAZIENTI

5528 TRATTATI CON STATINA

14071 NON TRATTATI

U. Stenestrand et al. JAMA 2001;285:430-36

ESPERIENZE - REGISTRI

END POINT – MORTALITA' AD 1 ANNO

GRUPPO NO STATINA: 1307/14071 – 9.3%

GRUPPO STATINA : 219/5528 - 4.0%

Relative risk 0.75, 95% C.I. P = 0.001

LIMITI: bias trattamento (pazienti più giovani, miglior classe funzionale, minor numero diabetici)

U. Stenestrand et al. JAMA 2001;285:430-36

ESPERIENZE - REGISTRI

Effect of Statin Use Within the First 24 Hours of Admission for Acute Myocardial Infarction on Early Morbidity and Mortality†

Gregg C. Fonarow, MD[a,*], R. Scott Wright, MD[c], Frederick A. Spencer, MD[d], Paul D. Fredrick, MPH, MBA[e], Wei Dong, MD, PhD[g], Nathan Every, MD, PhD[f], and William J. French, MD[b], for the National Registry of Myocardial Infarction 4 Investigators

NATIONAL REGISTRY of MYOCARDIAL INFARCTION 4
LUGLIO 2000 – GENNAIO 2002
1230 OSPEDALI U.S.A.

300.823 PAZIENTI (ANALISI PER 174.635 pt)

END POINT PRIMARIO: MORTE INTRAOSPEDALIERA
END POOINT SECONDARIO: EVENTI IN OSPEDALE

G. Fonarow et al. Am JCardiol 2005;96:611–616

ESPERIENZE - REGISTRI

4 GRUPPI

1. Pts che già assumevano statina al ricovero = 17.118 Y/Y
2. Pts che l'hanno iniziata entro 24 h dal ricovero = 21.978 N/Y
3. Pts che non hanno ricevuto statine nel ricovero = 126.128 N/N
4. Pts che assumevano statina sospesa nel ricovero= 9.411 Y/N

NATIONAL REGISTRY of MYOCARDIAL INFARCTION 4
LUGLIO 2000 – GENNAIO 2002

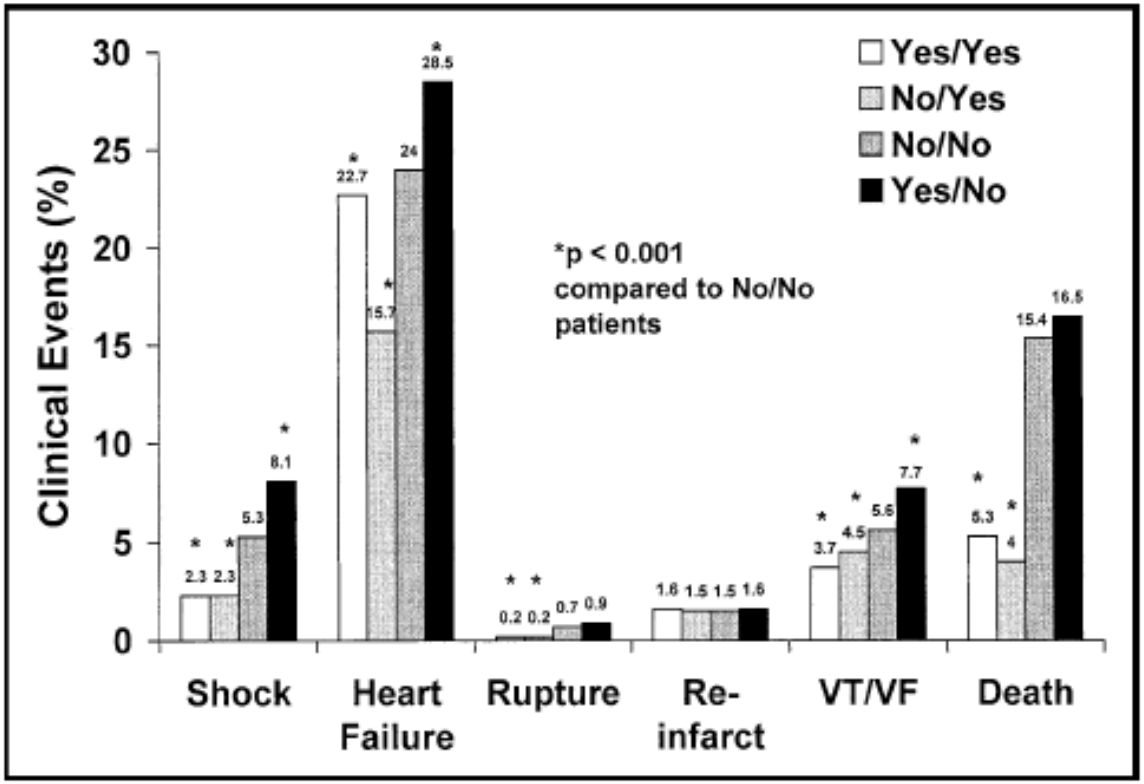


Figure 1. Clinical events by statin use before hospitalization and within the first 24 hours after hospitalization (unadjusted). VT/VF = ventricular tachycardia/ventricular fibrillation.

G. Fonarow et al. Am. J. Cardol. 2005;96:611-16

PRESUPPOSTI PER L'UTILIZZO DI STATINE NELLA FASE ACUTA DELLA SINDROME CORONARICA

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PROVE IT	AMI – UA 4162 pz	10 GG	**Atorvastatina 80 mg vs Pravastatina 40 mg**	18-36 mesi	**P =0.05**
MIRACLE	AMI – UA 3086 pz	1-4 GG	**Atorvastatina 80 mg vs placebo**	4 mesi	**p = 0.048**
PACT	AMI – UA 3048 pz	1 g	**Pravastatina 20 o 40 mg vs placebo**	1	**p = n.s.**
A to Z	AMI – UA 4497 pz	1	**Simvastatina 40 » 80 mg vs placebo » Simvastatina 20 mg**	24	**p = 0.14**
ARMYDA-ACS	NSTE ACS 191 pz	Prima di PCI	**Atorvastatina 80 mg (il giorno prima di PCi) » Atorvastatina 40 mg (4-6 ore prima di PCI) vs placebo**	1	**P = 0.01**
FLORIDA	STEMI 540 pz	1	**Fluvastatina 40 mg b.i.d.vs placebo**	12	**P = n.s.**

MIRACL: disegno dello studio

Caratteristiche pazienti

- Uomini e donne ≥18 anni
- UA o AMI
- TC ≤270 mg/dL
- Escluse le rivascolarizzazioni coronariche pianificate/anticipate

3086 pazienti

24-96 ore
(mediana 63 ore)

- Atorvastatina 80 mg (n=1538)
- Placebo (n=1548)

16 settimane

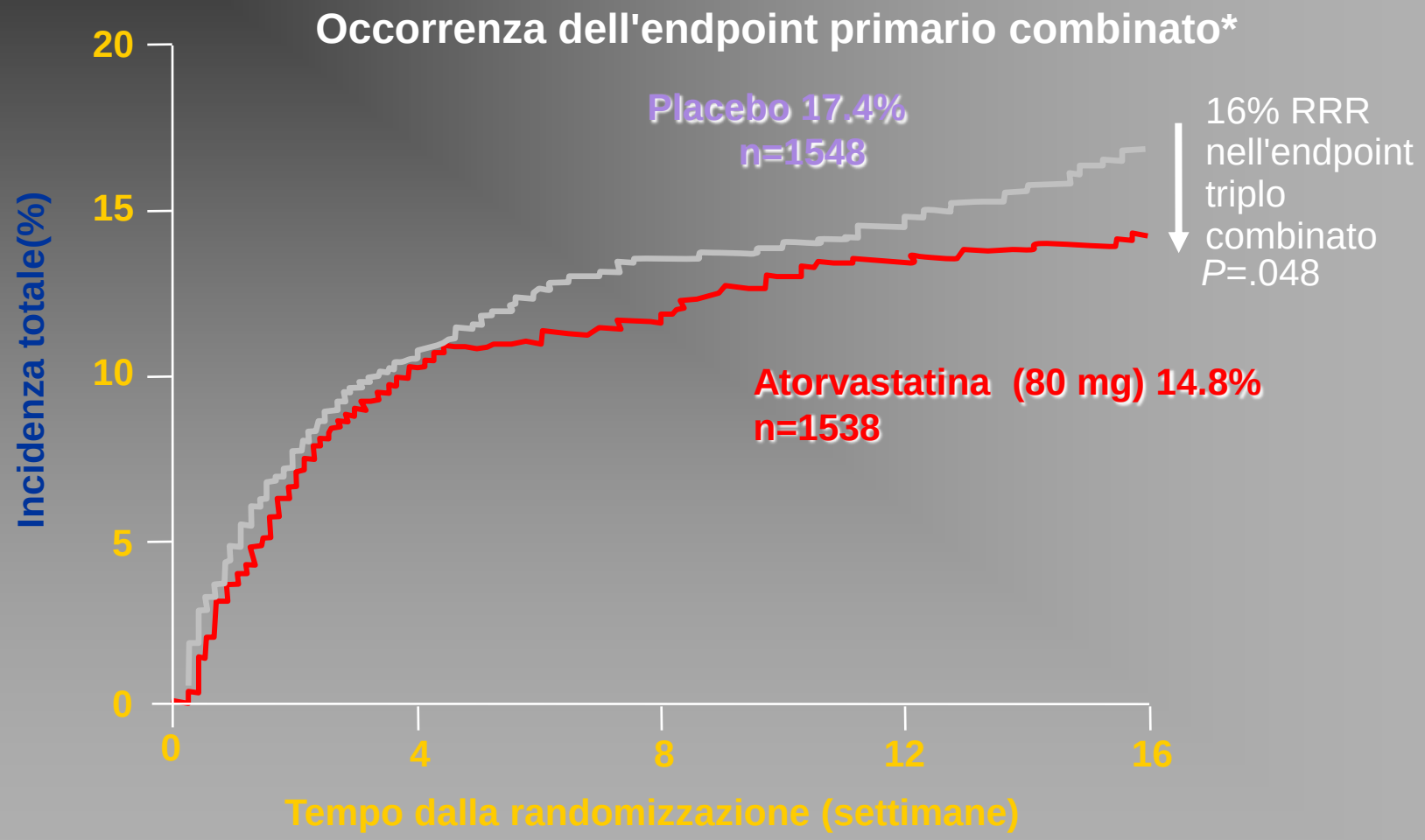
Endpoint principale di efficacia

- Composto di morte, AMI non fatale, arresto cardiaco con rianimazione, o ischemia del miocardio sintomatica ricorrente con ricovero

TC=colesterolo totale

Schwartz GG et al. JAMA. 2001;285:1711-1718.

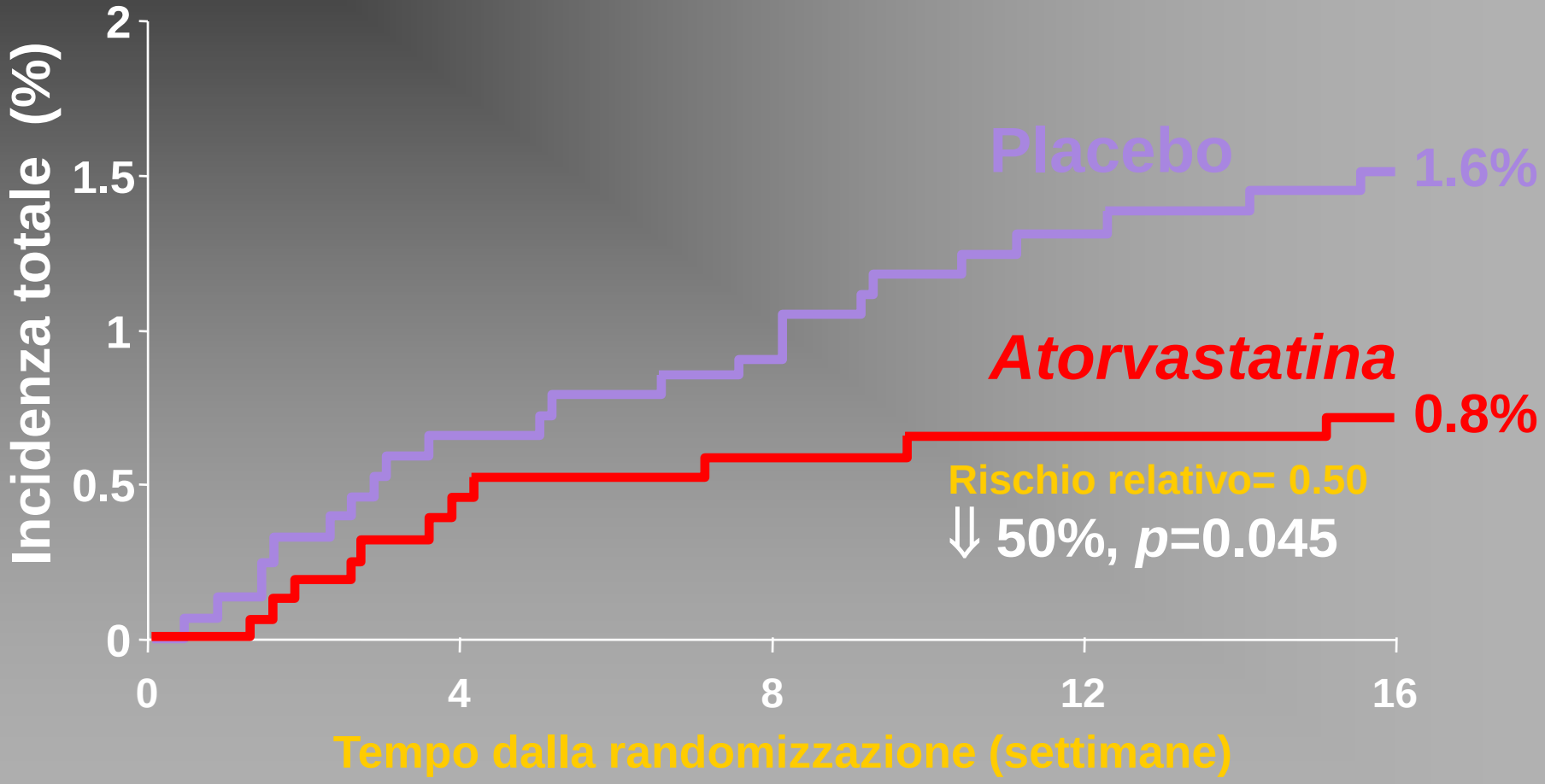
MIRACL: In pazienti con SCA Atorvastatina riduce la ricorrenza di eventi ischemici in maniera significativa



*End poin primario combinato=morte, AMI non fatale, arresto cardiaco con rianimazione, o ischemia ricorrente sintomatica del miocardio con ricovero d'urgenza.
RRR=riduzione del rischio relativo.

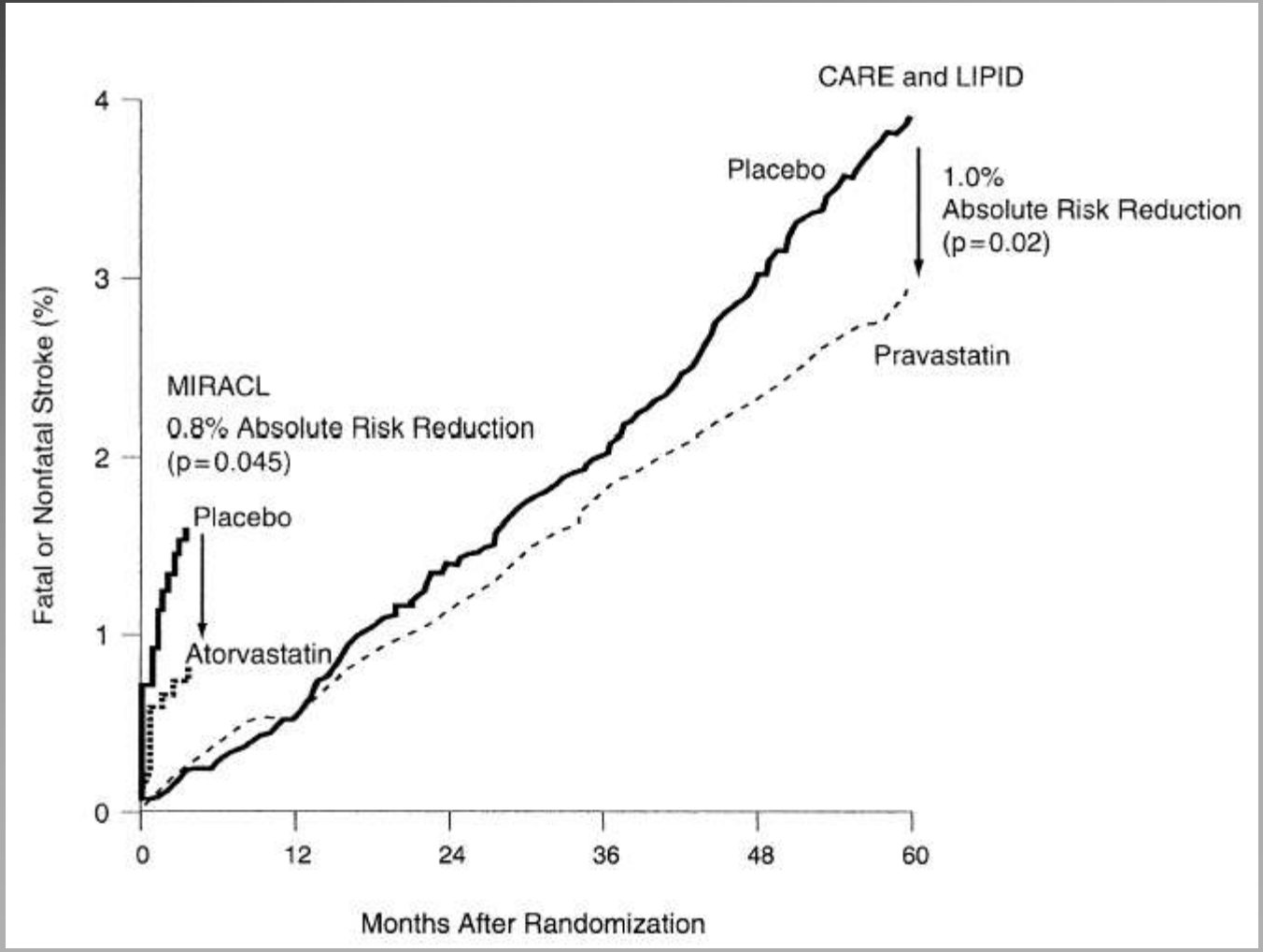
Adapted from Schwartz GG et al. JAMA. 2001;285:1711-1718.

MIRACL: ictus fatali e non fatali



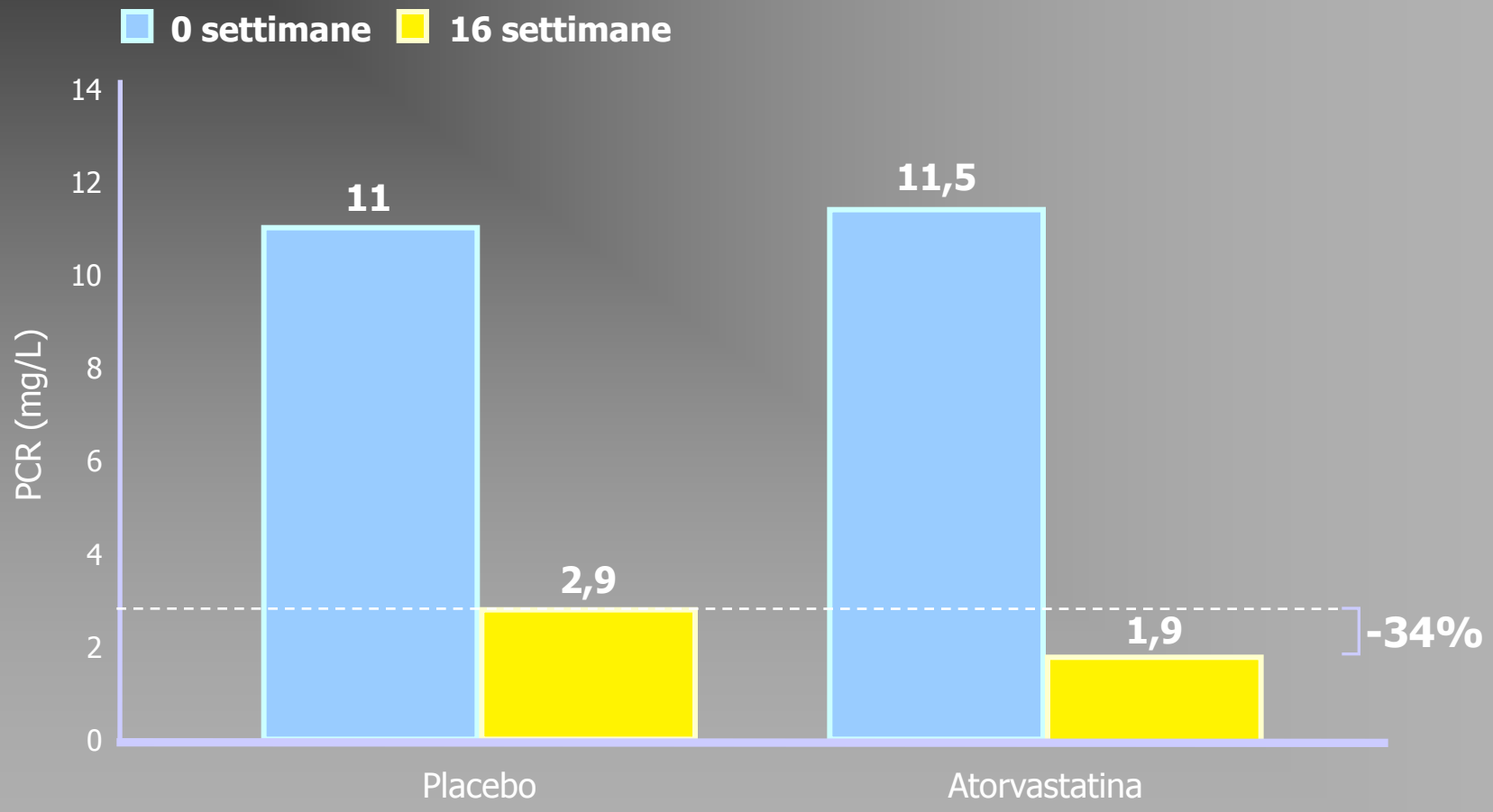
Schwartz GG et al. JAMA. 2001;285:1711-1718.

MIRACL: La riduzione assoluta nel numero degli ictus raggiunta durante 16 settimane dello studio MIRACL è simile alla riduzione raggiunta dopo circa 5 anni negli studi CARE e LIPID



Adapted from Schwartz GG et al. Am J. Cardiol. 2005; 96(Suppl.): 45F-53F

MIRACL
Risultati sui marker infiammatori

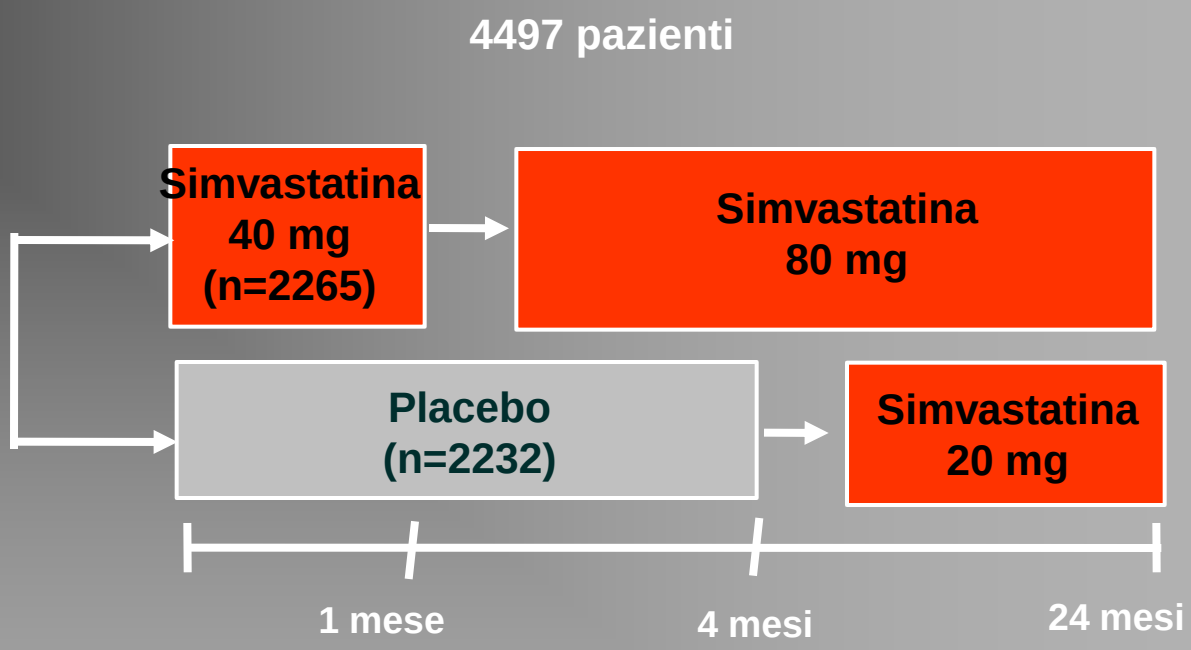


Kinlay S et al., ACC 51st Scientific Sessions 2002;822-823

Fase Z dello studio A to Z: disegno dello studio

Caratteristiche pazienti

- Uomini e donne 21-80 anni
- ACS, MI
- TC ≤250 mg/dL
- Rispondenti ai criteri stabilità
- Almeno 1 fattore di alto rischio per CVD + aumento biomarker cardiaci



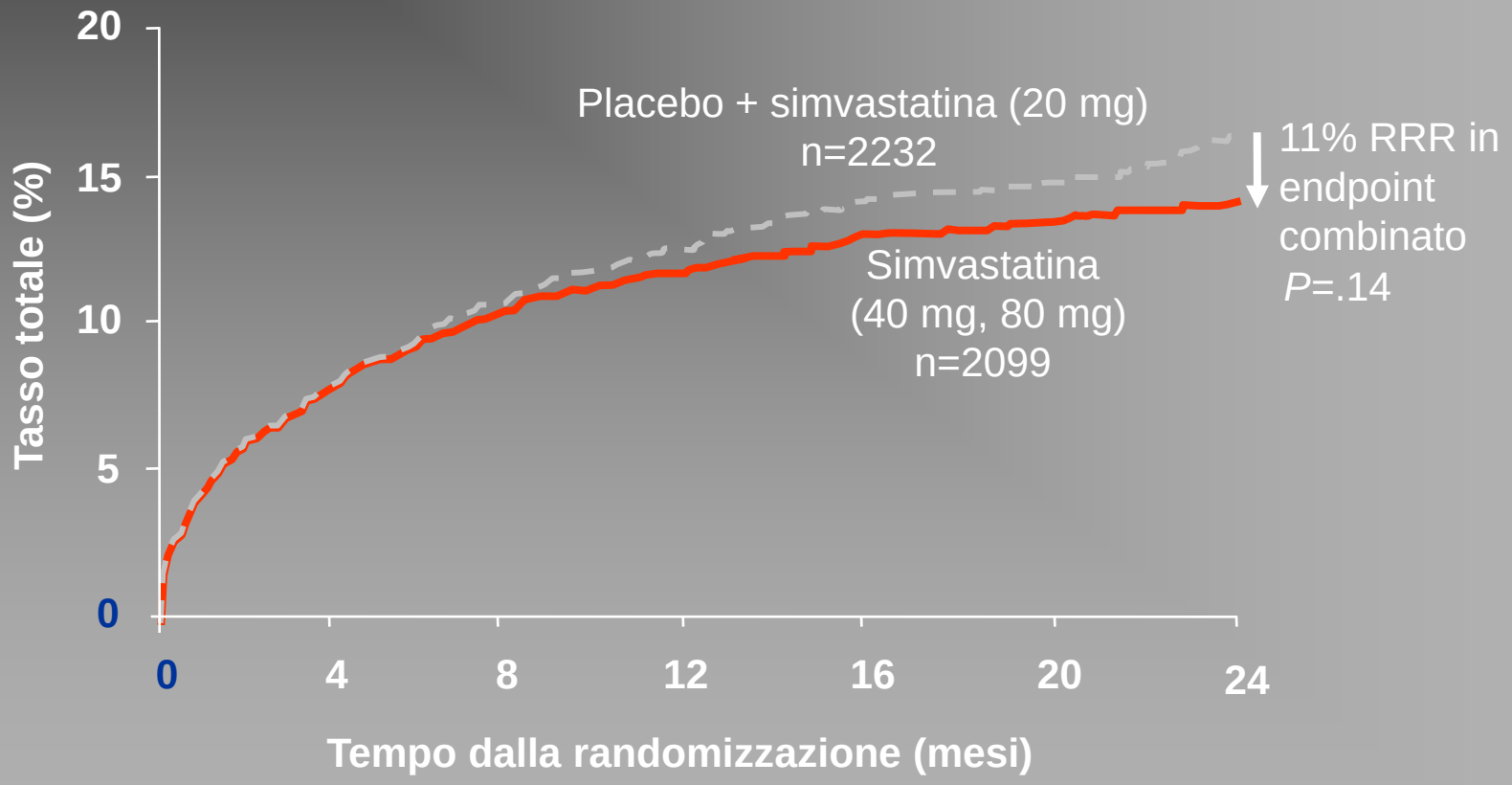
Endpoint principale di efficacia

- Composto di morte CV, MI non fatale, riammissione per ACS, e ictus

de Lemos JA et al. JAMA. 2004;292:1307-1316.

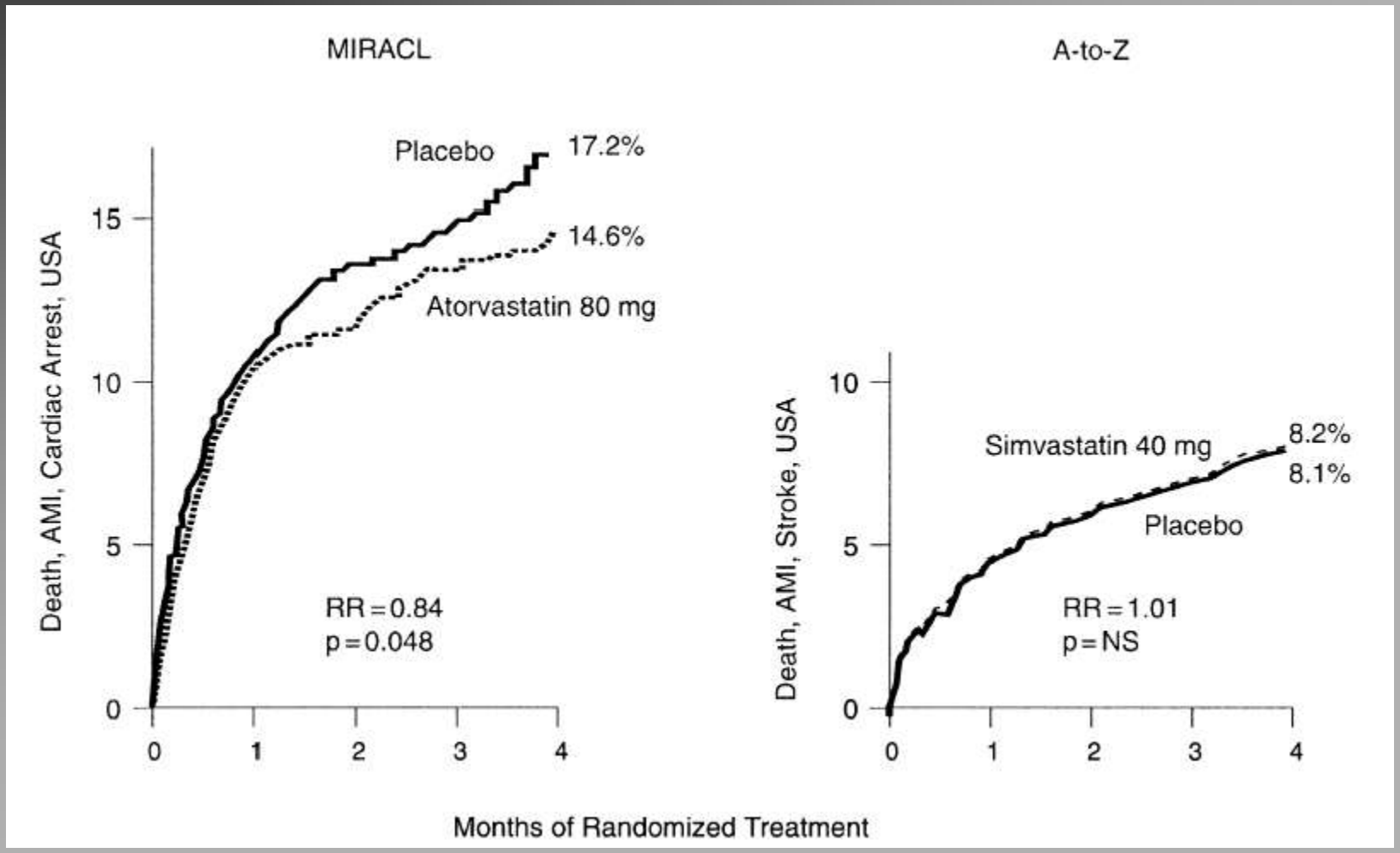
A to Z: Nessuna riduzione significativa dell'endpoint principale in pazienti con SCA trattati con Simvastatina

Occorrenza dell'endpoint principale combinato
(morte cardiovascolare, IM non fatale, riammissione per SCA, e ictus)



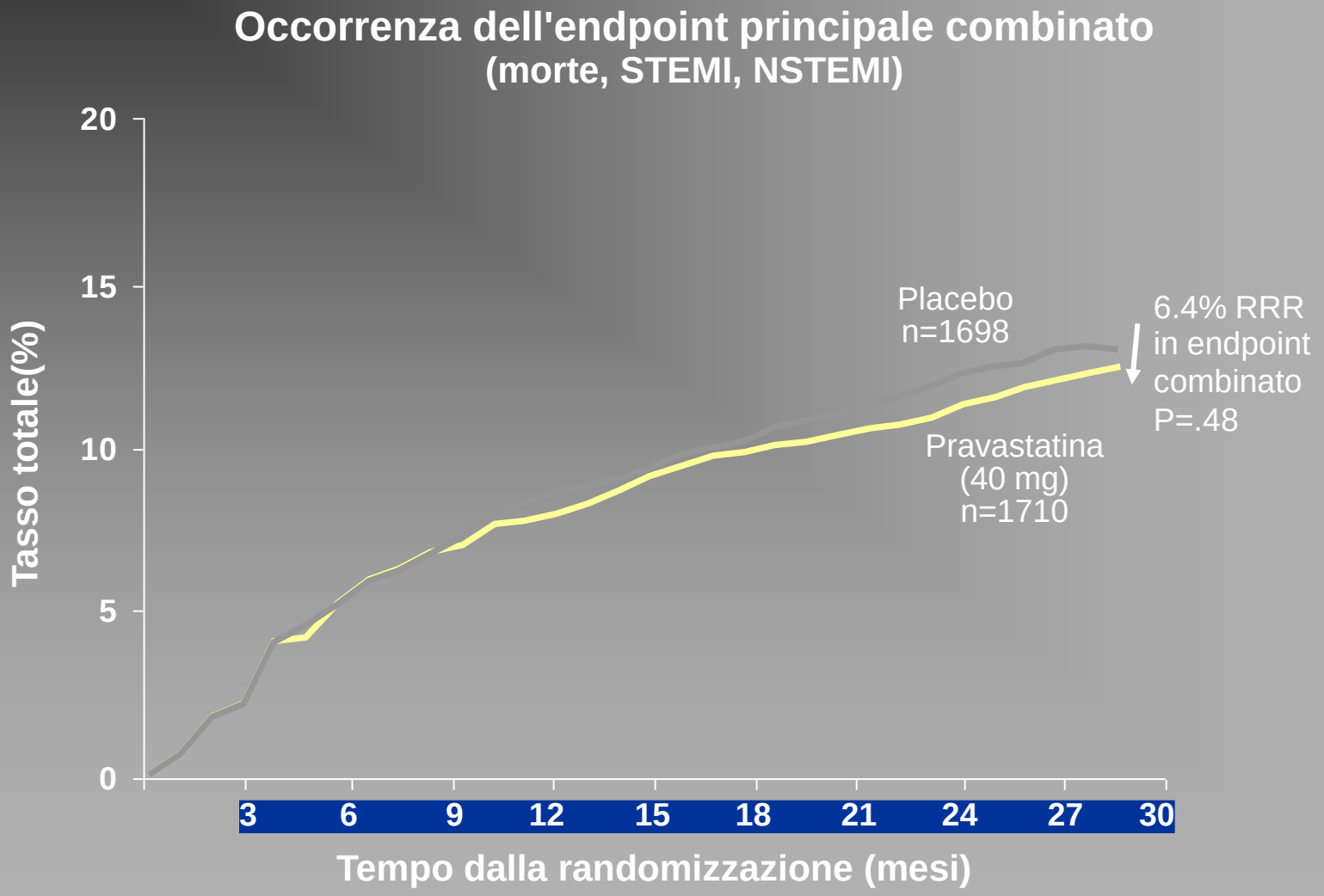
Adattato da de Lemos JA et al. JAMA. 2004;292:1307-1316.

A to Z vs. MIRACL: Il trattamento intensivo a base di statine, ma non quello moderato, riduce il numero di eventi ischemici precoci ricorrenti dopo la sindrome coronarica acuta



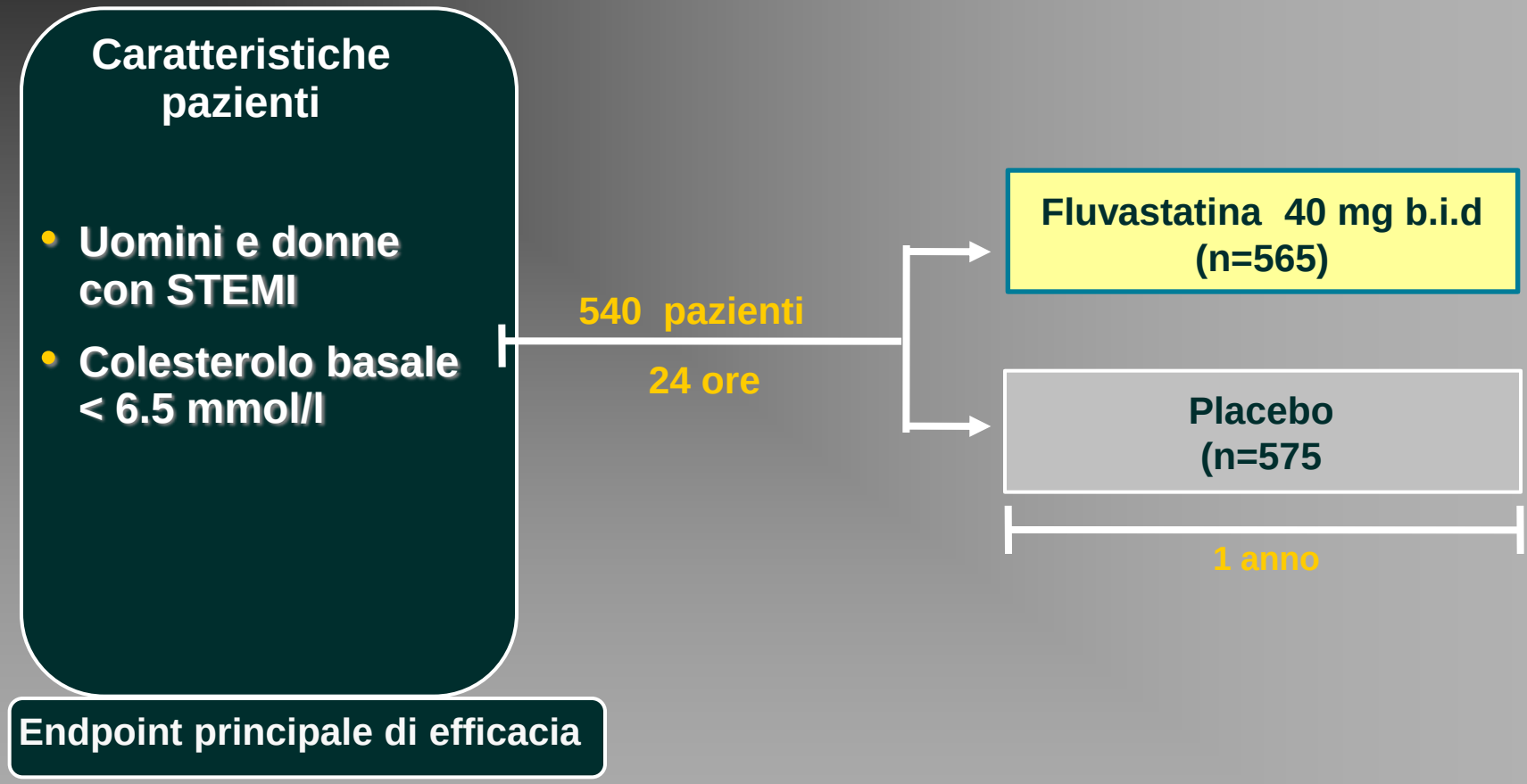
Adapted from Schwartz GG et al. Am J. Cardiol. 2005; 96(Suppl.): 45F-53F

PACT: nessuna significativa riduzione negli esiti è stata evidenziata con Pravastatina



Adattato da Thompson PL et al. Am Heart J. 2004;148:e2

FLORIDA: disegno dello studio



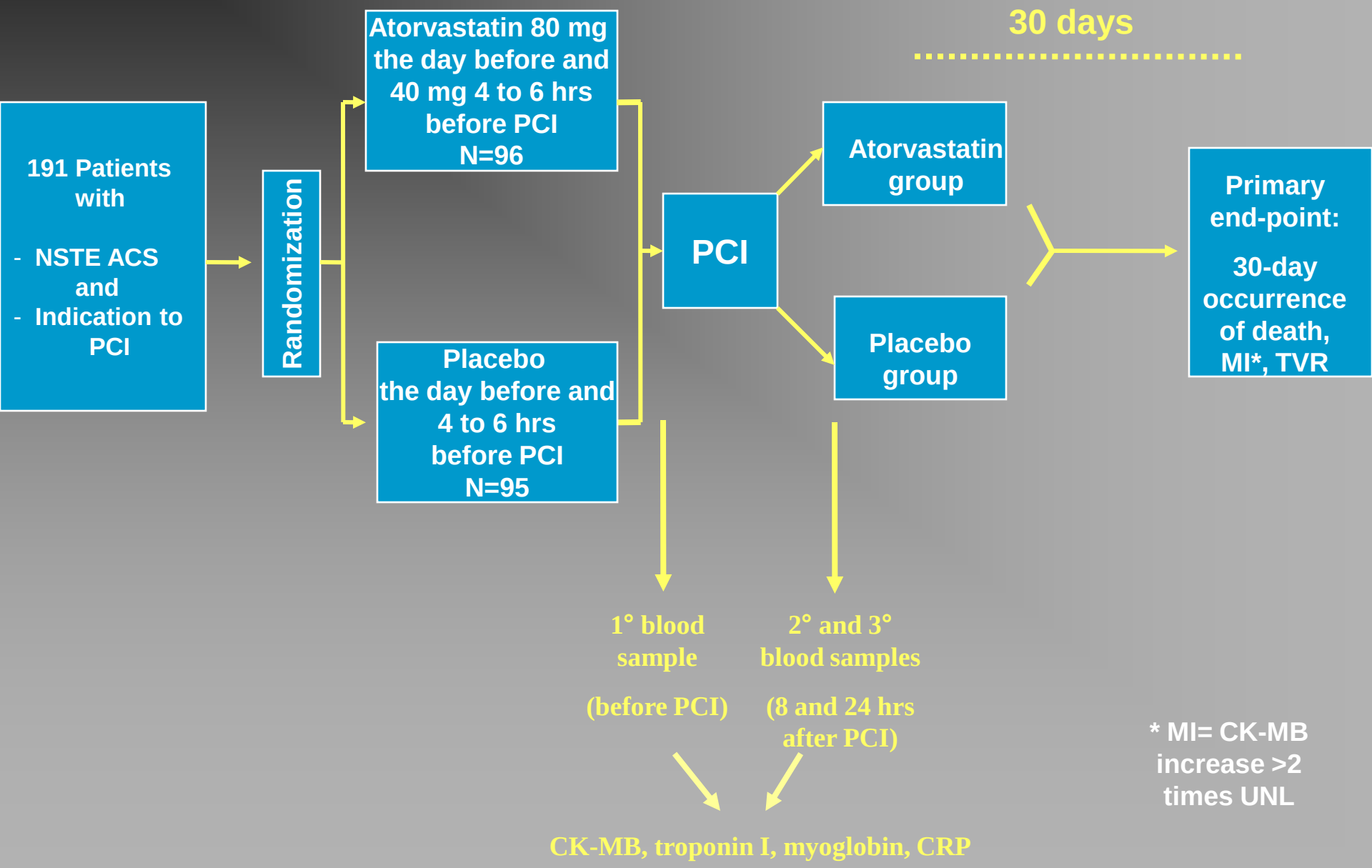
- Composto da ischemia rilevata con AECG di 48 ore, morte per qualsiasi causa o MACE dopo 6 settimane ed 1 anno dopo la randomizzazione

FLORIDA

RISULTATO

NESSUN EFFETTO STATISTICAMENTE SIGNIFICATIVO DELLA FLUVASTATINA NELLA RIDUZIONE DI ISCHEMIA VALUTATA CON E.C.G. AMBULATORIALE DI 48 ORE NE' NELLA RIDUZIONE DI END POINT COMPOSITO DI MORTALITA' E DI MACE.

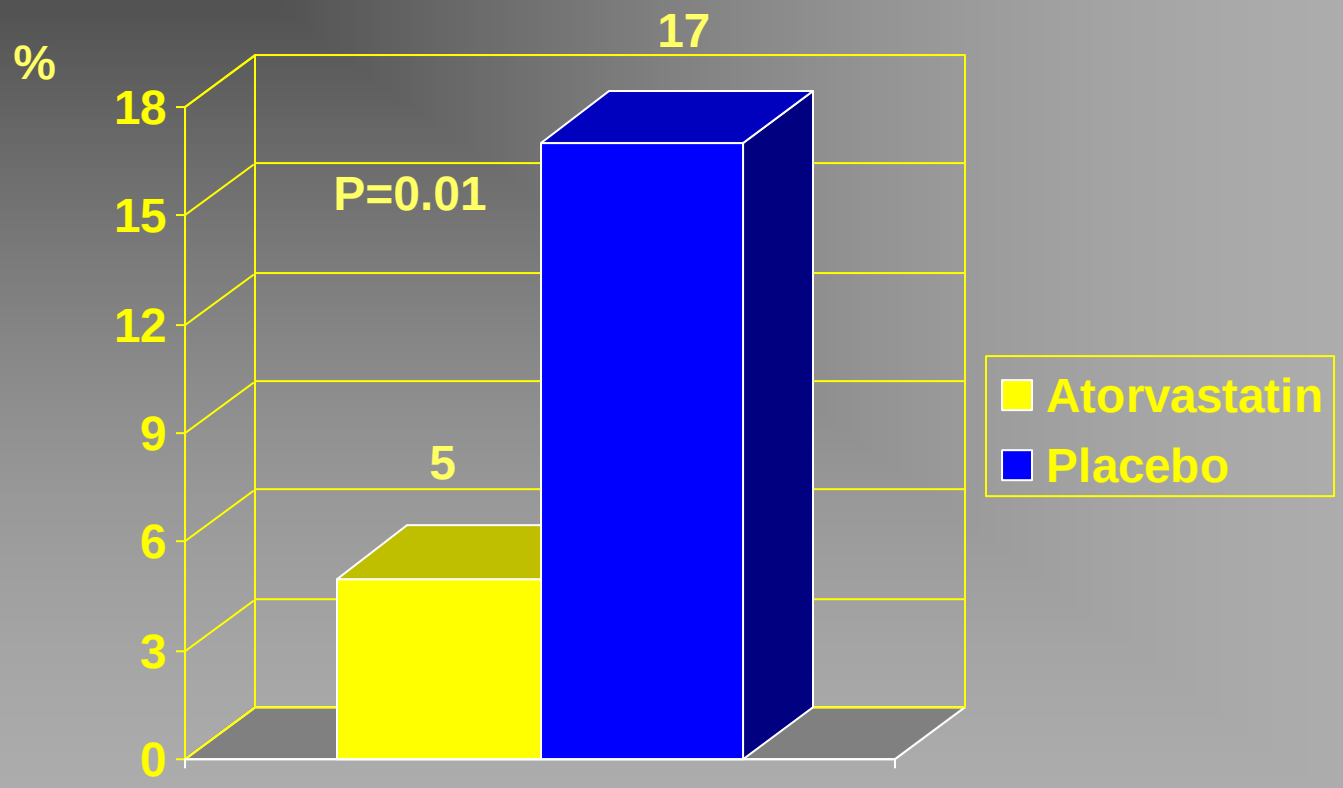
ARMYDA-ACS Trial



* MI= CK-MB increase >2 times UNL

ARMYDA-ACS trial

Composite primary end-point (30-day death, MI, TVR)



Primary end-point entirely due to procedural MI in both arms

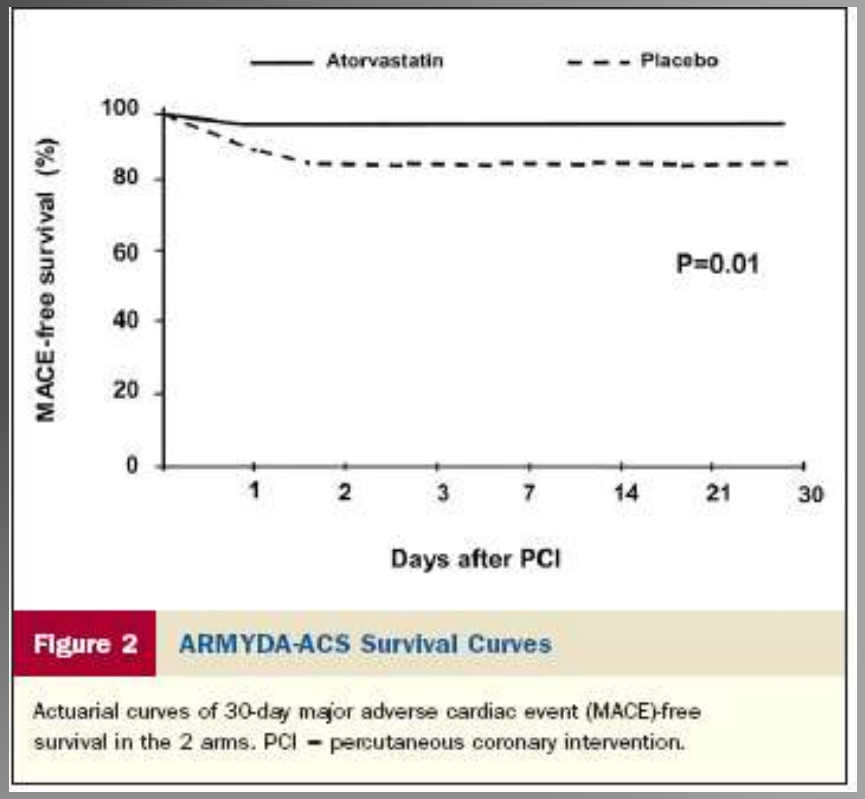


Figure 2 ARMYDA-ACS Survival Curves

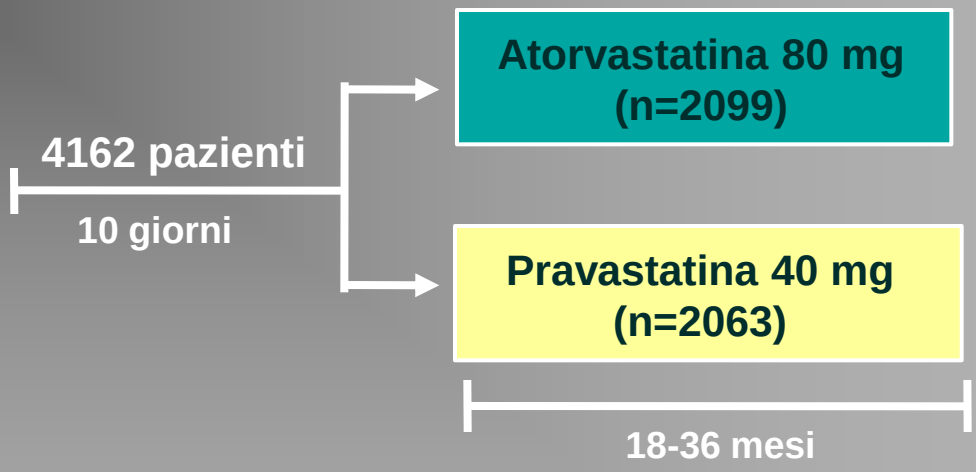
Actuarial curves of 30-day major adverse cardiac event (MACE)-free survival in the 2 arms. PCI = percutaneous coronary intervention.

In conclusion, the present trial shows that a short-term atorvastatin pretreatment before PCI improves clinical outcomes in patients with unstable angina and non–STsegment elevation myocardial infarction. If confirmed by larger additional randomized studies, these findings may
support the indication of "upstream" administration of high-dose statins in patients with acute coronary syndromes treated with an early invasive strategy.

PROVE IT: disegno dello studio

Caratteristiche pazienti

- Uomini e donne ≥18 anni
- Ricoverati con AMI o UA ad alto rischio
- TC ≤240 mg/dL
- Condizioni stabili, arruolati dopo PCI, se pianificato

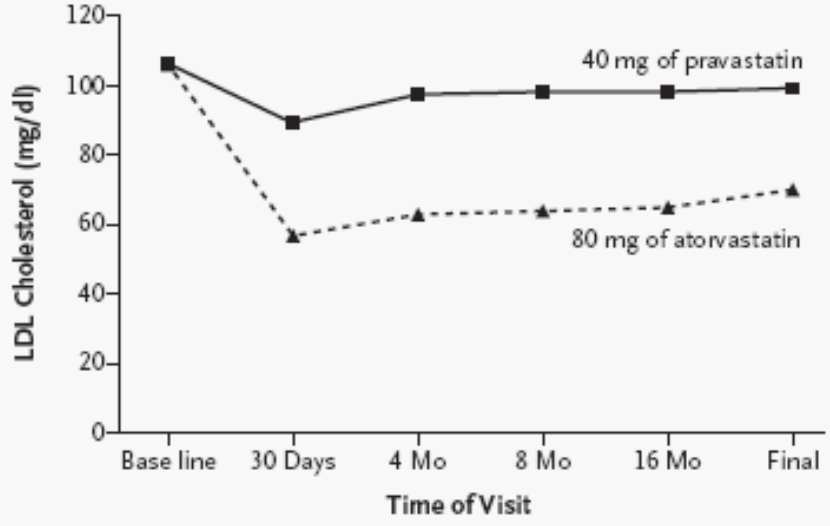


Endpoint principale di efficacia

- Composto di morte per qualsiasi causa, MI, UA documentato con ricovero, rivascolarizzazione, e ictus

Cannon CP et al. N Engl J Med. 2004;350:1495-1504.

PROVE - IT TIMI 22

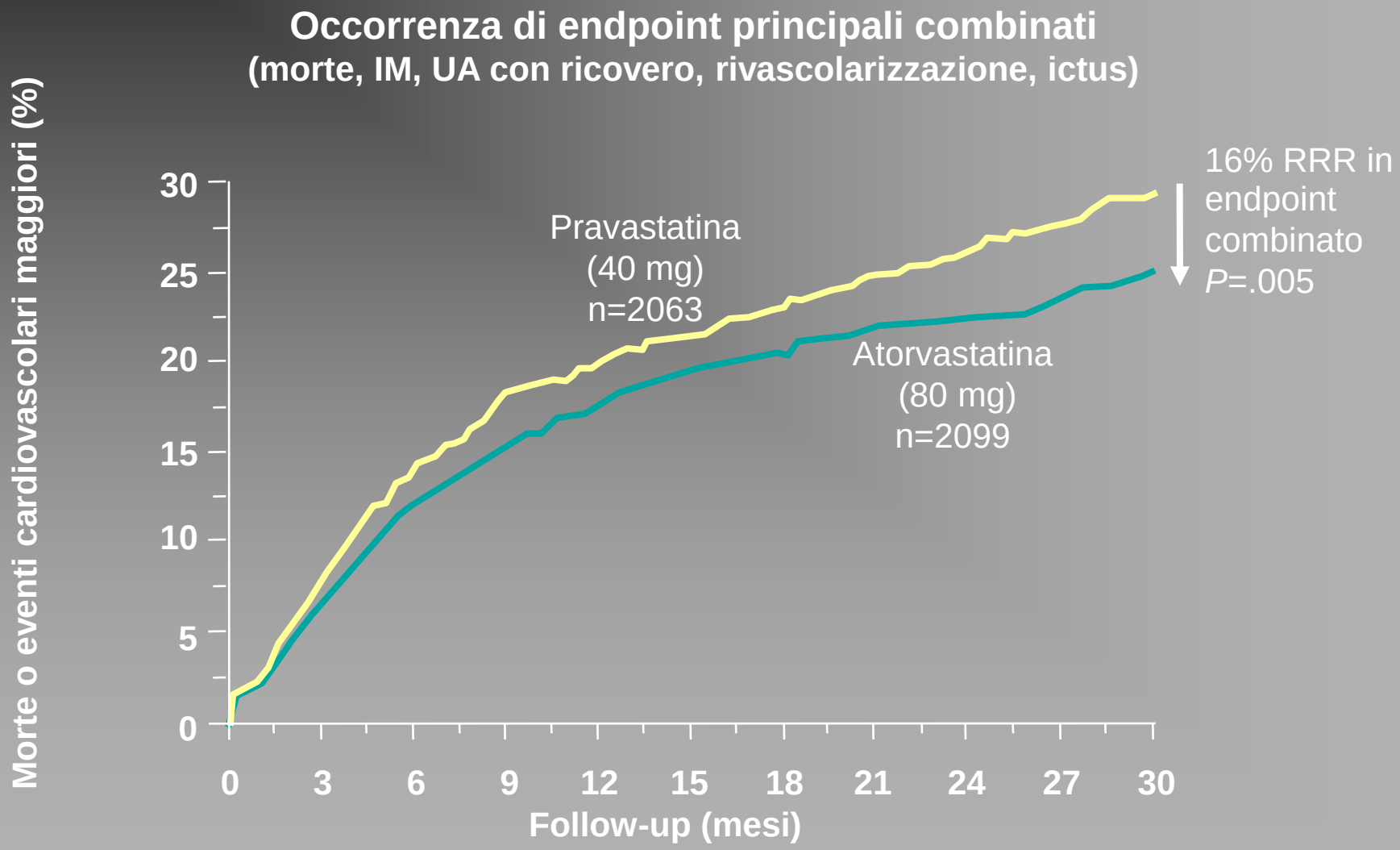


No. of Patients						
Pravastatin	1973	1844	1761	1647	1445	1883
Atorvastatin	2003	1856	1758	1645	1461	1910

Figure 1. Median Low-Density Lipoprotein (LDL) Cholesterol Levels during the Study.

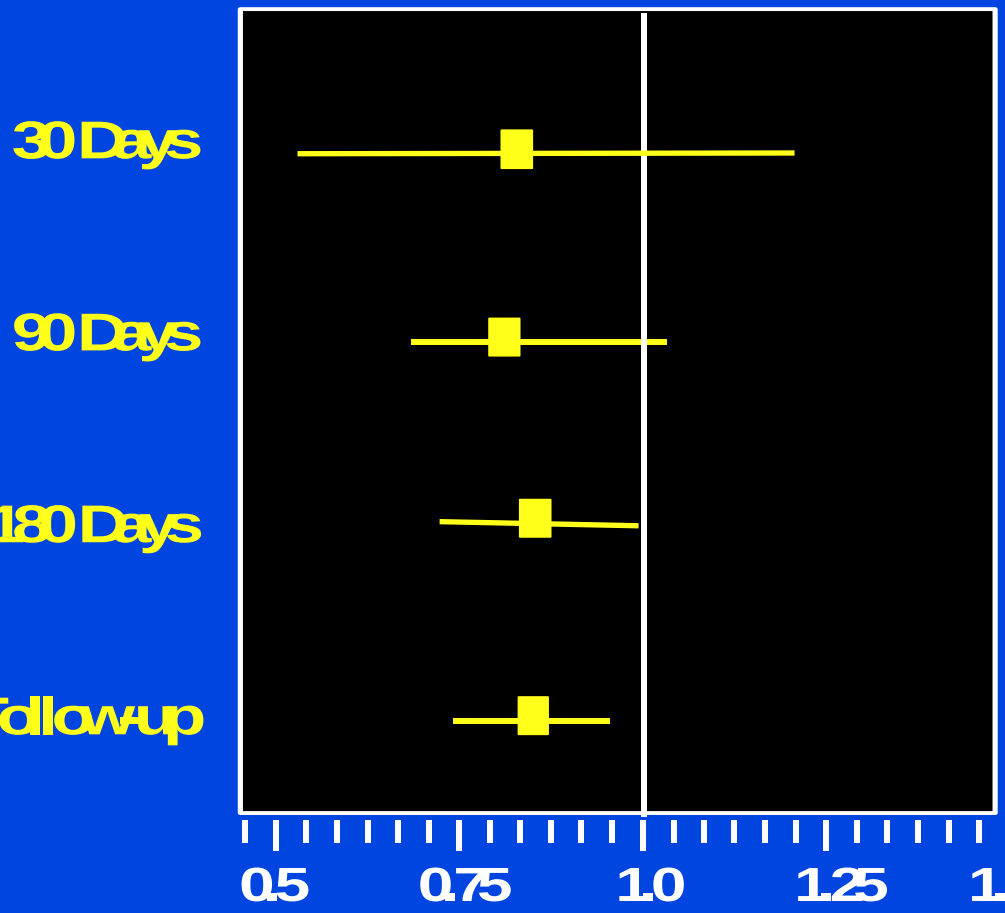
To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

PROVE IT: benefici precoci e consistenti di Atorvastatina rispetto a Pravastatina



Adattato da Cannon CP et al. N Engl J Med. 2004;350:1495-1504.

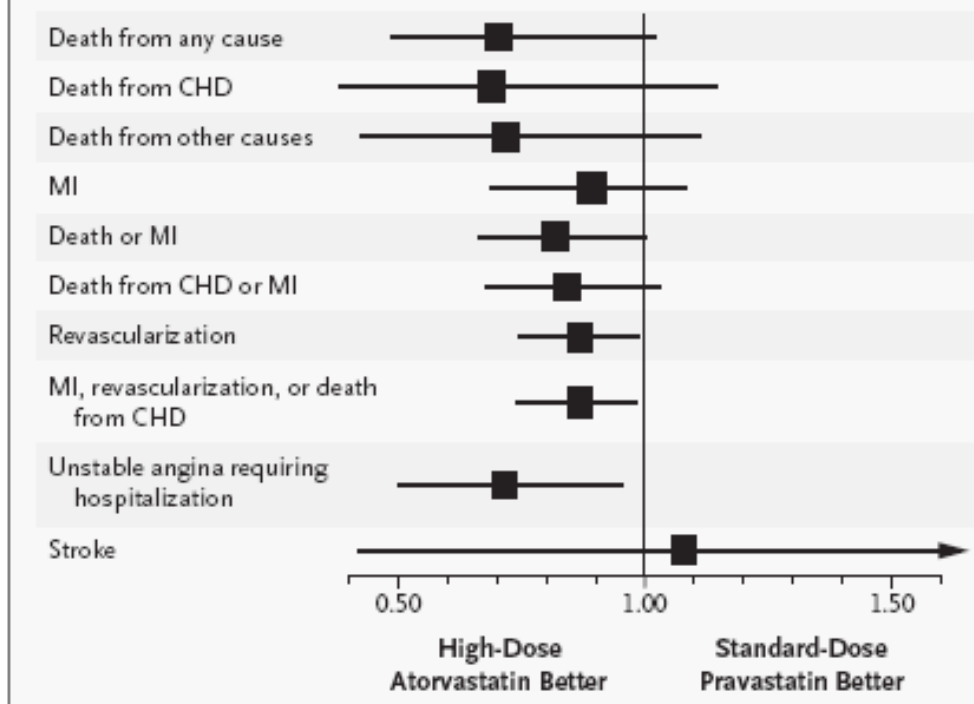
Primary Endpoint Over Time



	Events Rates		
	RR	Atorva 80	Prava 40
30 Days	17%	1.9%	2.2%
90 Days	18%	6.3%	7.7%
180 Days	14%	12.2%	14.1%
End of Follow-up	16%	22.4%*	26.3%*

*2-year event rates

PROVE – IT TIMI 22



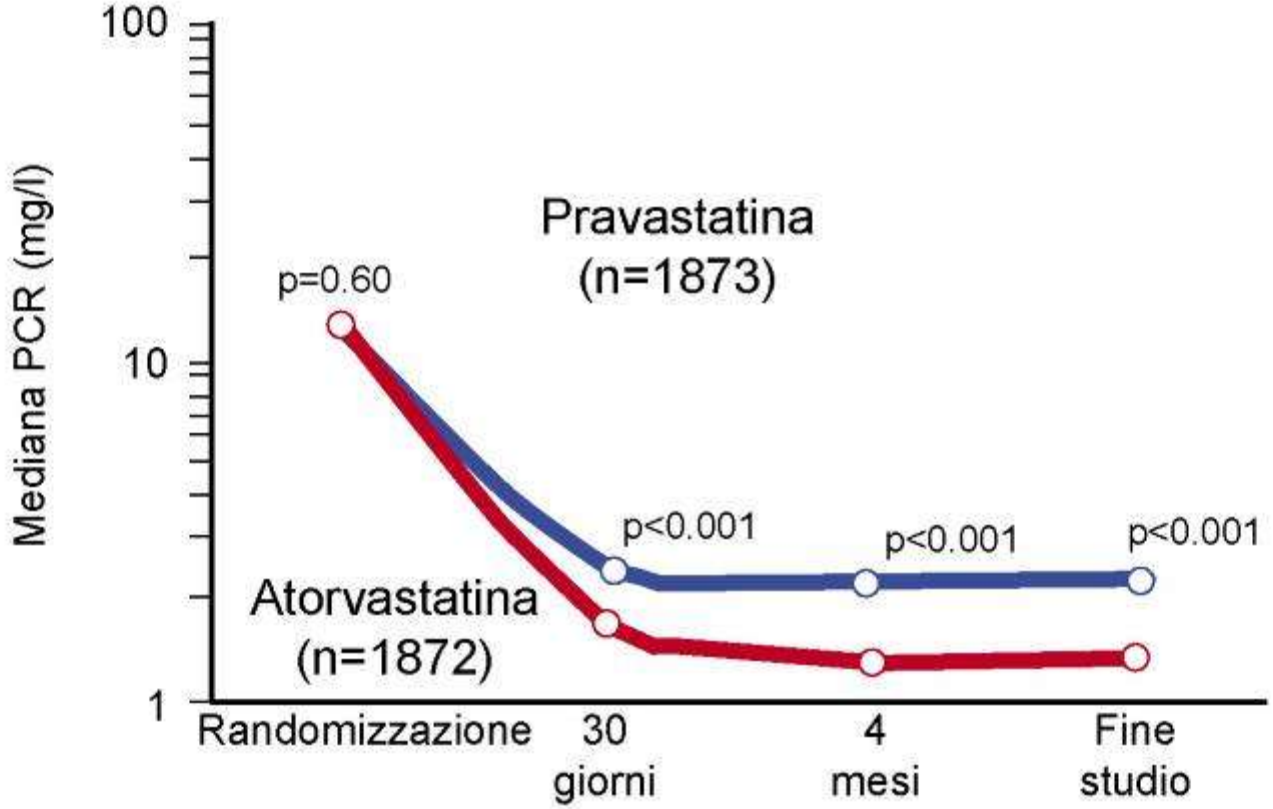
End Point	Risk Reduction	2-Yr Event Rates	
		Atorvastatin	Pravastatin
		percent	
Death from any cause	28	2.2	3.2
Death from CHD	30	1.1	1.4
Death from other causes	27	1.2	1.8
MI	13	6.6	7.4
Death or MI	18	8.3	10.0
Death from CHD or MI	16	7.2	8.3
Revascularization	14	16.3	18.8
MI, revascularization, or death from CHD	14	19.7	22.3
Unstable angina requiring hospitalization	29	3.8	5.1
Stroke	–9	1.0	1.0

Figure 4. Estimates of the Hazard Ratio for the Secondary End Points and the Individual Components of the Primary End Point in the High-Dose Atorvastatin Group, as Compared with the Standard-Dose Pravastatin Group.

CI denotes confidence interval, CHD coronary heart disease, and MI myocardial infarction. Revascularization was performed at least 30 days after randomization.

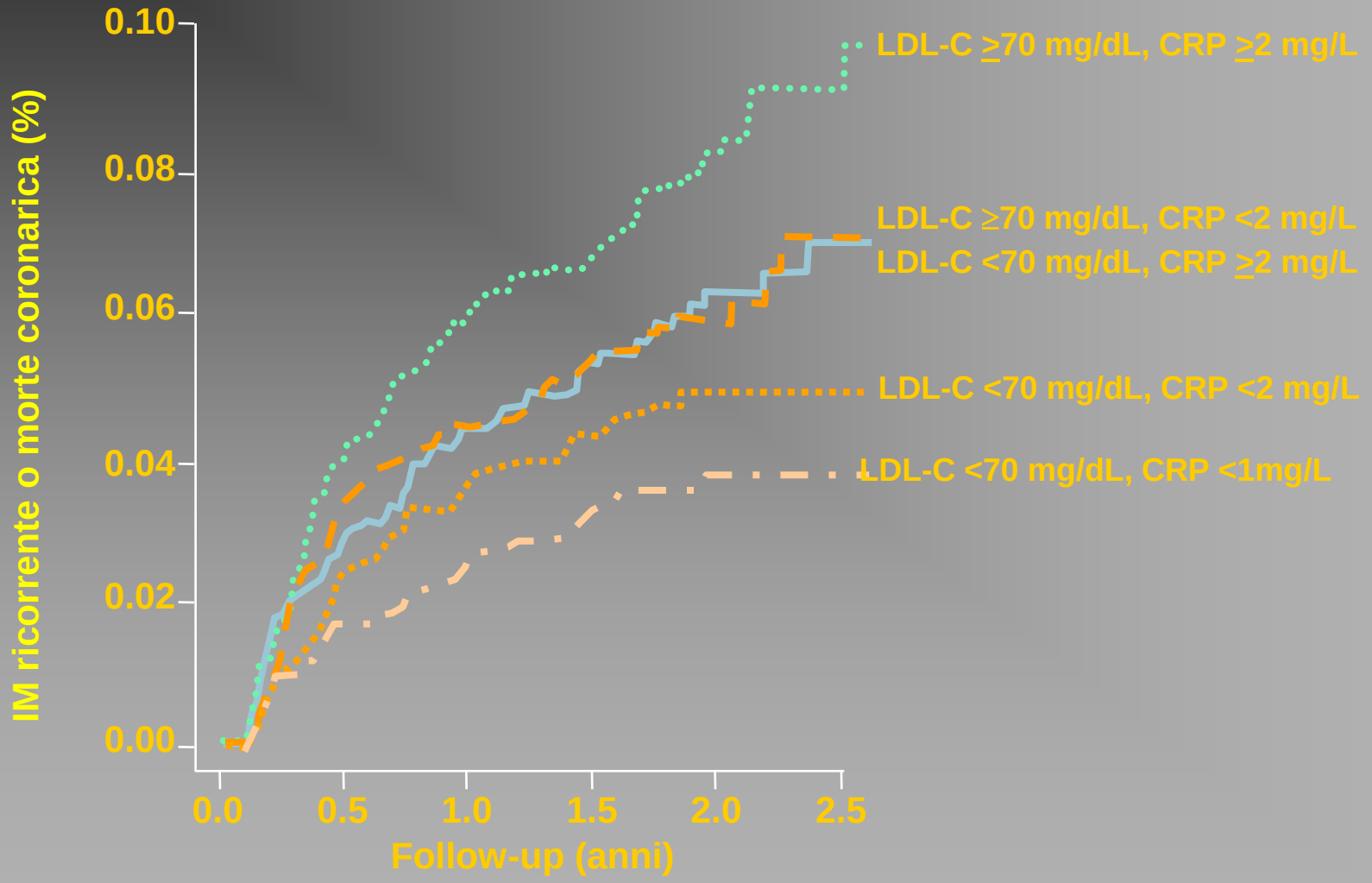
PROVE IT-TIMI 22: evidenza della rapida riduzione dei marker di infiammazione (PCR)

PRavastatin Or AtorVastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22
n = 4.162 con SCA



Ridker PM. N Engl J Med. 2005;352:20-8.

PROVE IT sottoanalisi: i pazienti con livelli più bassi di LDL-C e CRP hanno meno eventi ricorrenti



Adapted from Ridker PM *et al. N Engl J Med. 2005;352:20-28; Ridker PM et al. Presented at AHA Scientific Sessions; 2004.*

ATORVASTATINA ALTE DOSI IN PAZIENTI CON CORONAROPATIA END STAGE

Effects of *Atorvastatin* 80 mg Daily Early After Onset of Unstable Angina Pectoris or Non–Q-Wave Myocardial Infarction

Furio Colivicchi, MD, Vincenzo Guido, MD, Marco Tubaro, MD, Fabrizio Ammirati, MD, Nicola Montefoschi, MD, Antonio Varveri, MD, and Massimo Santini, MD

Angiographic evidence of severe and diffuse coronary artery disease, that was not amenable to direct revascularization by coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, as determined by a cardiac surgeon and an interventional cardiologist during the index admission;

Objective evidence of symptomatic reversible myocardial ischemia (0.1 mV ST-segment depression on the electrocardiogram) at a low exercise workload (4 METs) while receiving medical treatment (2 antianginal medications at maximal tolerated doses), as assessed by treadmill ergometry (Bruce's protocol) before discharge.

Colivicchi et al., Am. Journal Cardiol.2002;90:872

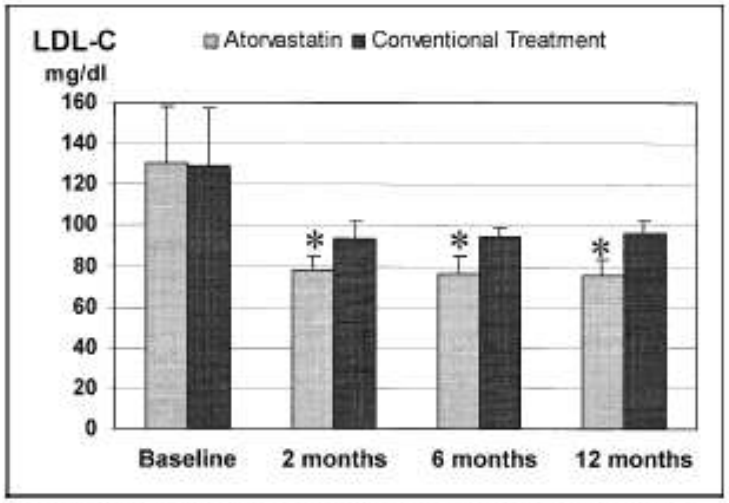


FIGURE 2. Low-density lipoprotein cholesterol (LDL-C) levels during the study in the conventional treatment arm and in the atorvastatin arm. *p <0.0001.

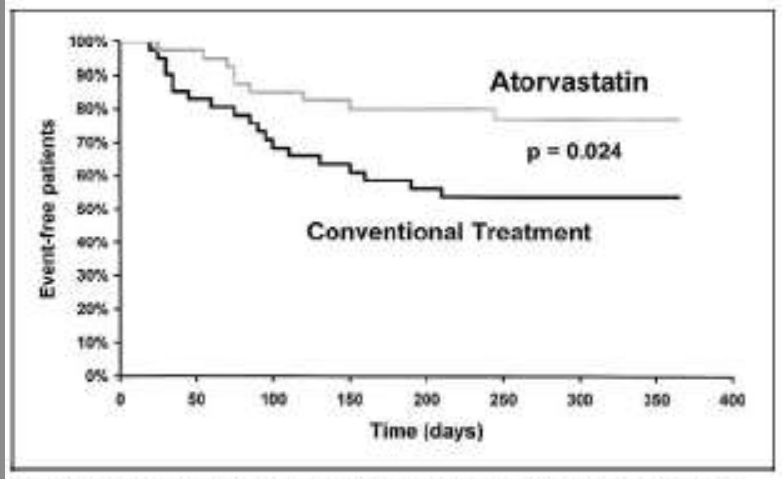


FIGURE 1. Kaplan-Meier estimates of probability of remaining free of ischemic recurrences in 41 patients in the conventional treatment arm and in 40 patients in the atorvastatin arm in the intention-to-treat analysis.

In conclusion, this trial provides evidence that adding early, aggressive, **lipid-lowering treatment in addition to optimal combination therapy significantly reduces cardiac ischemic recurrences after an acute coronary syndrome in patients with endstage coronary artery disease.** In our opinion, this result is clinically relevant, because the number of such high-risk patients is expected to further increase in the near future.

Colivicchi et al., Am. Journal Cardiol.2002;90:872

TRIAL ONGOING

A MULTICENTER , DOUBLE–BIND, RANDOMIZED STUDY TO ESTABLISH THE CLINICAL BENEFIT AND SAFETY OF VYTORIN (EZETIMIBE/SIMVASTATIN TABLET) vs SIMVASTATIN MONOTHERAPY IN HIGH-RISK SUJECTS PRESENTING WITH ACUTE CORONARY SYNDROME.

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (P04103)

IMPROVE-IT

Popolazione in studio :

- 3 Tipologie di pazienti affetti da ACS stabilizzata ad alto rischio e con livelli di LDL-C, misurati entro 24 dalla presentazione al Centro, ≥ 50mg/dL ≤ 125mg/dL (o ≤ 100mg/dL se in trattamento cronico con statine);

- Randomizzazione entro 10 giorni dall'ospedalizzazione.

Obiettivo Primario

- valutare il beneficio clinico del trattamento su:
  - morte da evento cardiovascolare,
  - eventi coronarici maggiori (dopo almeno 30 gg dalla randomizzazione - IMA non fatale , riospedalizzazione per angina, rivascolarizzazione))
  - Ictus in pazienti affetti da Sindrome Coronarica Acuta(ACS) sia con Infarto del Miocardio Acuto (IMA) che con angina instabile.

TRIAL ONGOING

FACS

- FLUVASTATINA 80 mg vs PLACEBO
- 1000 PTS
- S.C.A STEMI/NSTEMI
- FOLLOW UP: 30 GIORNI
- END POINT COMPOSITO MACCE

Ostadal et al. Curr Contrl Trials Cardiovasc 2005 ;6:5

PRESUPPOSTI PER L'UTILIZZO DI STATINE NELLA FASE ACUTA DELLA SINDROME CORONARICA

EFFETTO PLEIOTROPICO

STUDI OSSERVAZONALI

REGISTRI

TRIALS

METANALISI

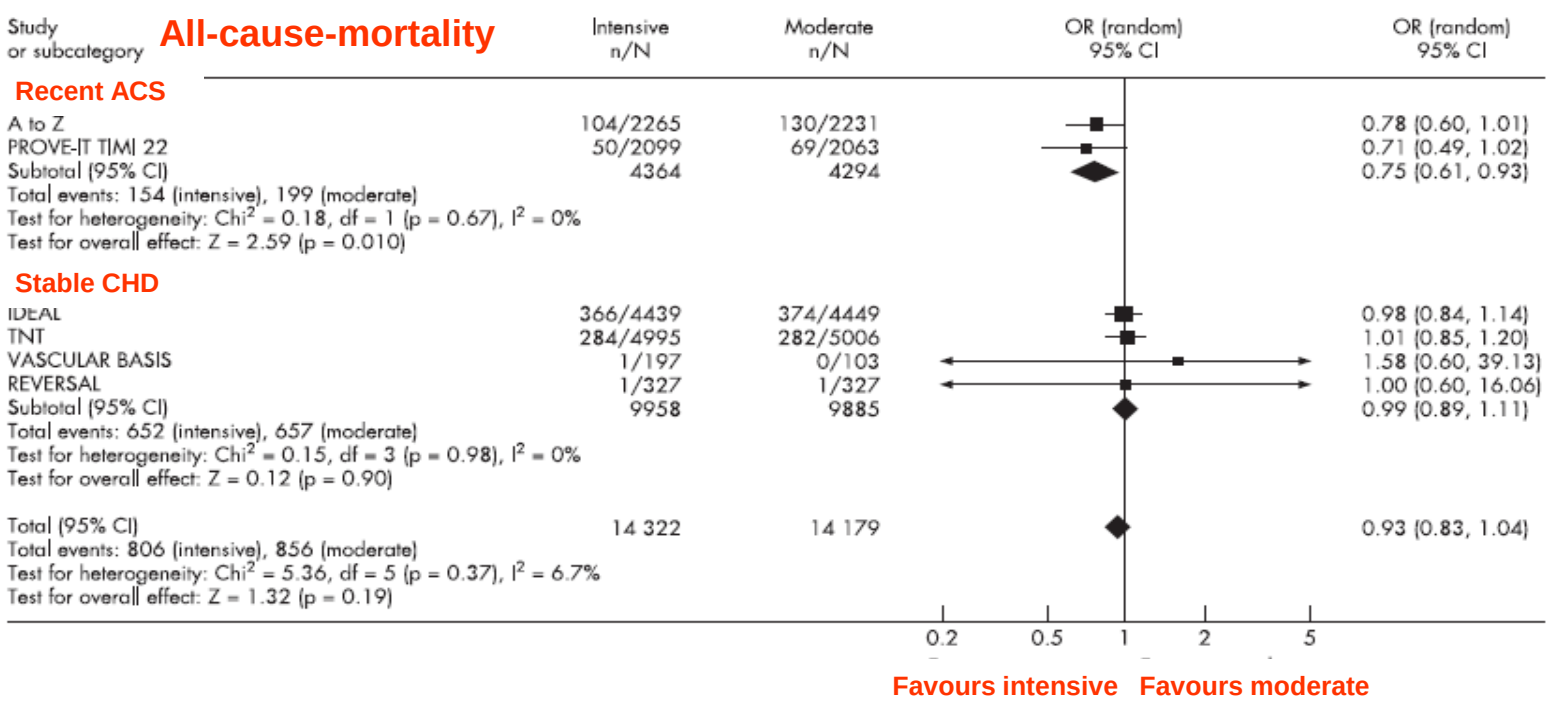
METANALISI

SYSTEMATIC REVIEW

Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials

Jonathan Afilalo, Agnieska A Majdan, Mark J Eisenberg

Heart 2007;**93**:914–921. doi: 10.1136/hrt.2006.112508



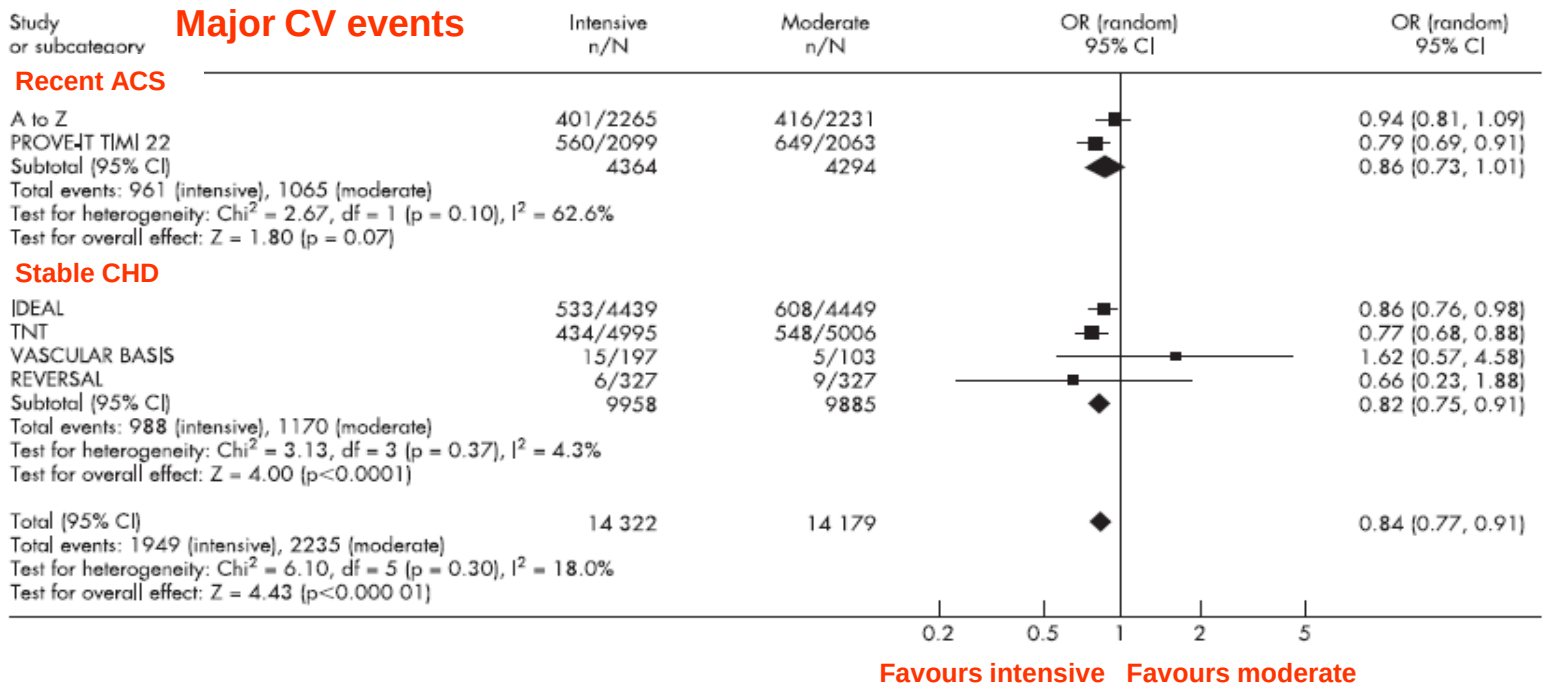


Figure 3 Forest plot for major adverse cardiovascular events.

METANALISI

13 STUDI

17963 PAZIENTI

INIZIO STATINE < 14 GIORNI DA OSPEDALIZZAZIONE

FOLLOW UP MEDIO 22 MESI

E. P. COMBINATO:

MORTE, RECIDIVA ISCHEMICA, REOSPEDALIZZAZIONE

E.Hulten et al. Arch. Intern. Med. 2006;166:1814-21

TRIAL	PAESI	N° Pts	TRATTAMENTO	INIZIO	GIORNI F.U.
PROVE – IT TIMI 22 (2004)	EUROPA U.S.A	4162	ATORVA 80 PRAVA 40	10	30,90,120,730
PAIS (2001)	OLANDA	699	PRAVA 40 PLACEBO	2	90
A to Z (2004)	INTERNAZ.	4497	SIMVA40/80 PLACEBO/SIMVA20	5	30,120,240,730
FLORIDA (2002)	OLANDA	540	FLUVA 80 PLACEBO	14	42, 365
MIRACL (2001)	INTERNAZ.	3086	ATORVA 80 PLACEBO	4	112
PACT (2004)	AUSTRALIA	3408	PRAVA 20/40 PLACEBO	1	30
L – CAD (2000)	GERMANIA	135	PRAVA 20/40 PLACEBO	1	730
LAMIL (1937)	BELGIO	69	PRAVA 10/20 PLACEBO	2	180
ESTABLISH (2004)	GIAPPONE	70	PCI + ATORVA 20 TERAPIA STANDARD	1	180
PTT (2002)	TURCHIA	77	PRAVA 40 PLACEBO	1	180
COLIVICCHI (2002)	ITALIA	83	ATORVA 80 TERAPIA STANDARD	12	360
LIPS (2002)	INTERNAZ	1677	FLUVA 80 PLACEBO	2	1460
RECIFE (2005)	CANADA	60	PRAVA 40 PLACEBO	10	42

SAFETY

EVENTI SU 17963 PAZIENTI

- **RABDOMIOLISI:** 3 (0.01%) A to Z (SIMVASTATINA 80 mg)
  2 (0.04%) TNT (ATORVA 80 mg)
- **EPATITI:** 3 (0.01%) MIRACLE (ATORVA 80 mg)
- ↑ ALT/AST: 3.3% vs 1.1% PROVE - IT
  2.5% vs 0.6% MIRACLE

E.Hulten et al. Arch. Intern. Med. 2006;166:1814-21

Safety of Atorvastatin *80 mg versus 10 mg*

Comparative Safety of *Atorvastatin* 80 mg Versus 10 mg Derived from Analysis of 49 Completed Trials in 14,236 Patients

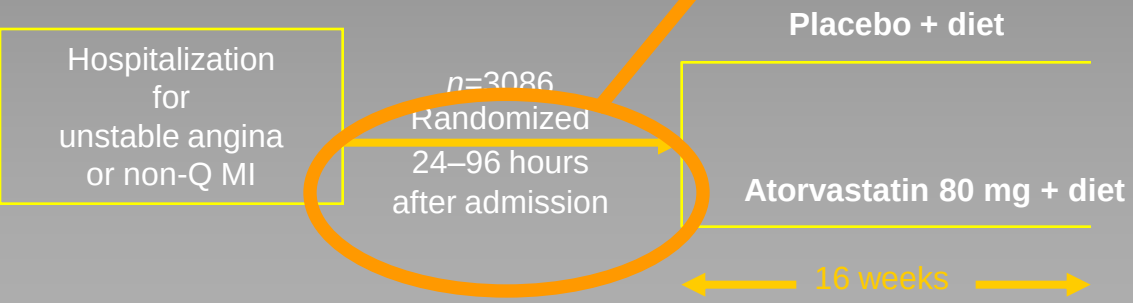
Connie Newman, MD*, John Tsai, MD, Michael Szarek, MS, Don Luo, PhD, and Eric Gibson, PhD

Atorvastatin has been shown to reduce coronary events and revascularization procedures in patients with multiple risk factors for coronary heart disease. Recent studies with atorvastatin 80 mg support the overall safety of this dose during long-term treatment. However, physicians appear reluctant to use high doses of statins. A retrospective analysis of pooled data from 49 clinical trials of atorvastatin in 14,236 patients treated for an average period of 2 weeks to 52 months was conducted. The study compared the safety of atorvastatin 10 mg (n = 7,258), atorvastatin 80 mg (n = 4,798), and placebo (n = 2,180) and included analyses on treatment-associated adverse events; nonserious and serious adverse events related to the musculoskeletal, hepatic, and renal systems; the incidence of elevations of creatine kinase >10 times the upper limit of normal (ULN); and hepatic transaminases >3 times ULN. Percentages of patients experiencing ≥1 adverse event were similar across all 3 groups. Withdrawals due to treatment-related adverse events were observed in 2.4%, 1.8%, and 1.2% of patients in the atorvastatin 10 mg, atorvastatin 80 mg, and placebo groups, respectively. Serious adverse events were rare and seldom led to treatment withdrawal with any dose. Treatment-associated myalgia was observed in 1.4%, 1.5%, and 0.7% of patients in the atorvastatin 10 mg, atorvastatin 80 mg, and placebo groups, respectively. No cases of rhabdomyolysis were reported in any group. Persistent elevations in hepatic transaminases >3 times ULN were observed in 0.1%, 0.6%, and 0.2% of patients in the atorvastatin 10 mg, atorvastatin 80 mg, and placebo groups, respectively. The incidence of treatment-associated adverse events for atorvastatin 80 mg was similar to that of atorvastatin 10 mg and placebo. In conclusion, the results of this analysis support the positive safety profile of atorvastatin at the highest dose. (Am J Cardiol 2006;97:61–67)

Recommendations for lipid-lowering therapy

- **Statins are recommended for all NSTE-ACS patients (in the absence of contraindications), irrespective of cholesterol levels, initiated early (within 1-4 days) after admission, with the aim of achieving LDLc levels <100 mg/dl (<2.6 mmol/L) (I-B).**
- **Intensive lipid-lowering therapy with target LDLc levels <70 mg/dl (<1.81 mmol/L) initiated within 10 days after admission is advisable (IIa-B).**

European Heart Journal, Guidelines for the diagnosis and treatment on Non-ST Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology, June , 14 - 2007



Schwartz GG *et al. Am J Cardiol* 1998;**81**:578–581.

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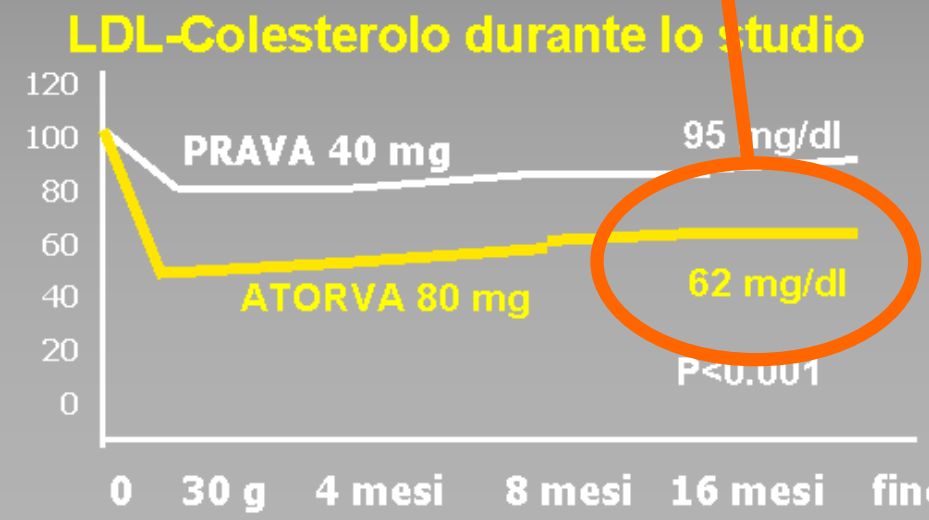


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Eugene Braunwald, M.D. et al for the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators

4162 pazienti (58 anni) con SCA <10 giorni
Studio di non-inferiorità PRAVA 40 mg vs ATORVA 80 mg
End-point primario: morte, IMA, riospedalizzazione per angina instabile, rivascolarizzazione, stroke
Follow-up 18-36 mesi (media 24)

N ENGL J MED 350;15, APRIL 8, 2004

Incremental Benefit and Cost-Effectiveness of High-Dose Statin Therapy in High-Risk Patients With Coronary Artery Disease

Paul S. Chan, MD, MSc; Brahmajee K. Nallamothu, MD, MPH; Hitinder S. Gurm, MD; Rodney A. Hayward, MD; Sandeep Vijan, MD, MSc

Background—Recent clinical trials found that high-dose statin therapy, compared with conventional-dose statin therapy, reduces the risk of cardiovascular events in patients with acute coronary syndromes (ACS) and stable coronary artery disease (CAD). However, the actual benefit and cost-effectiveness of high-dose statin therapy are unknown.

Methods and Results—We designed a Markov model to compare daily high-dose with conventional-dose statin therapy for hypothetical 60-year-old cohorts with ACS and stable CAD over patient lifetime. Pooled estimates for major clinical end points (all-cause mortality, myocardial infarction, stroke, rehospitalization, and revascularization) from relevant clinical trials were incorporated. Incremental benefit was quantified as quality-adjusted life-years (QALYs). Threshold analyses determined at what price difference high-dose statins would yield incremental cost-effective ratios below $50 000, $100 000, and $150 000 per QALY gained. In ACS patients, a high-dose versus conventional-dose statin strategy resulted in a gain of 0.35 QALYs. In threshold analyses, a high-dose statin strategy consistently yielded incremental cost-effective ratios below $30 000 per QALY even under conservative model assumptions. In stable CAD patients, a high-dose statin strategy yielded a gain of only 0.10 QALYs and was sensitive to model assumptions about statin efficacy. The daily cost difference between a high- and conventional-dose statin would need to be <$1.70, $2.65, and $3.55 to yield incremental cost-effective ratios below $50 000, $100 000, and $150 000 per QALY.

Conclusions—High-dose statin therapy is potentially highly effective and cost-effective in patients with ACS. In patients with stable CAD, however, the cost-effectiveness of high-dose statin therapy is highly sensitive to model assumptions about statin efficacy and cost. Use of high-dose statins can be supported on health economic grounds in patients with ACS, but the case is less clear for patients with stable CAD. (***Circulation*. 2007;115:2398-2409.**)

Key Words: cholesterol ■ coronary disease ■ cost-benefit analysis ■ drugs ■ statins

ESPERIENZE DELL'UTILIZZO DELLE STATINE NELLE S.C.A.

CONCLUSIONI - I

- EVIDENZA DI **EFFICACIA (RIDUZIONE DELLA MORTALITA' PER OGNI CAUSA)** A BREVE TERMINE NEI PAZIENTI SOTTOPOSTI A RIVASCOLARIZZAZIONE INTERVENTISTICA CON BENEFICIO ANCHE IN PAZIENTI NON RIVASCOLARIZZATI
- EVIDENZA DI **MANTENIMENTO DELL'EFFICACIA** E DELLA SICUREZZA NEL LUNGO TERMINE
- EVIDENZA DI **SICUREZZA**
- SUGGESTIONE DI **BLOCCO DI PROGRESSIONE DELL'ATEROMA**

ESPERIENZE DELL'UTILIZZO DELLE STATINE NELLE S.C.A.

CONCLUSIONI - II

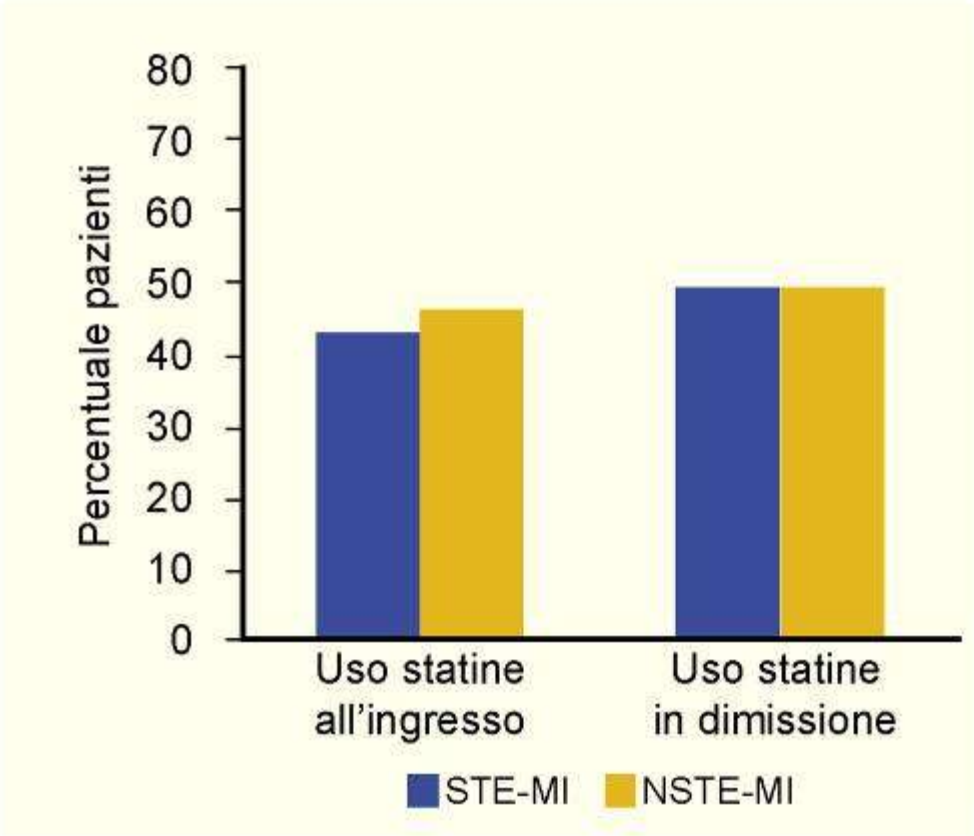
- INDICAZIONE ALLA **PRECOCE SOMMINISTRAZIONE** ("AL MOMENTO DEL RICOVERO" O COMUNQUE PREDIMISSIONE)
- INDICAZIONE AD **ALTO DOSAGGIO INIZIALE** ED EVENTUALE DOWN TITRATION
- INDICAZIONE A "**NUOVI TARGET**" CON PRECOCE INIZIO DI TRATTAMENTO
- POTENZIALE **RAPPORTO COSTO/EFFICACIA FAVOREVOLE**

Ma…

- A che punto siamo?
- E soprattutto a chi e per quanto tempo somministriamo alte dosi di statine?

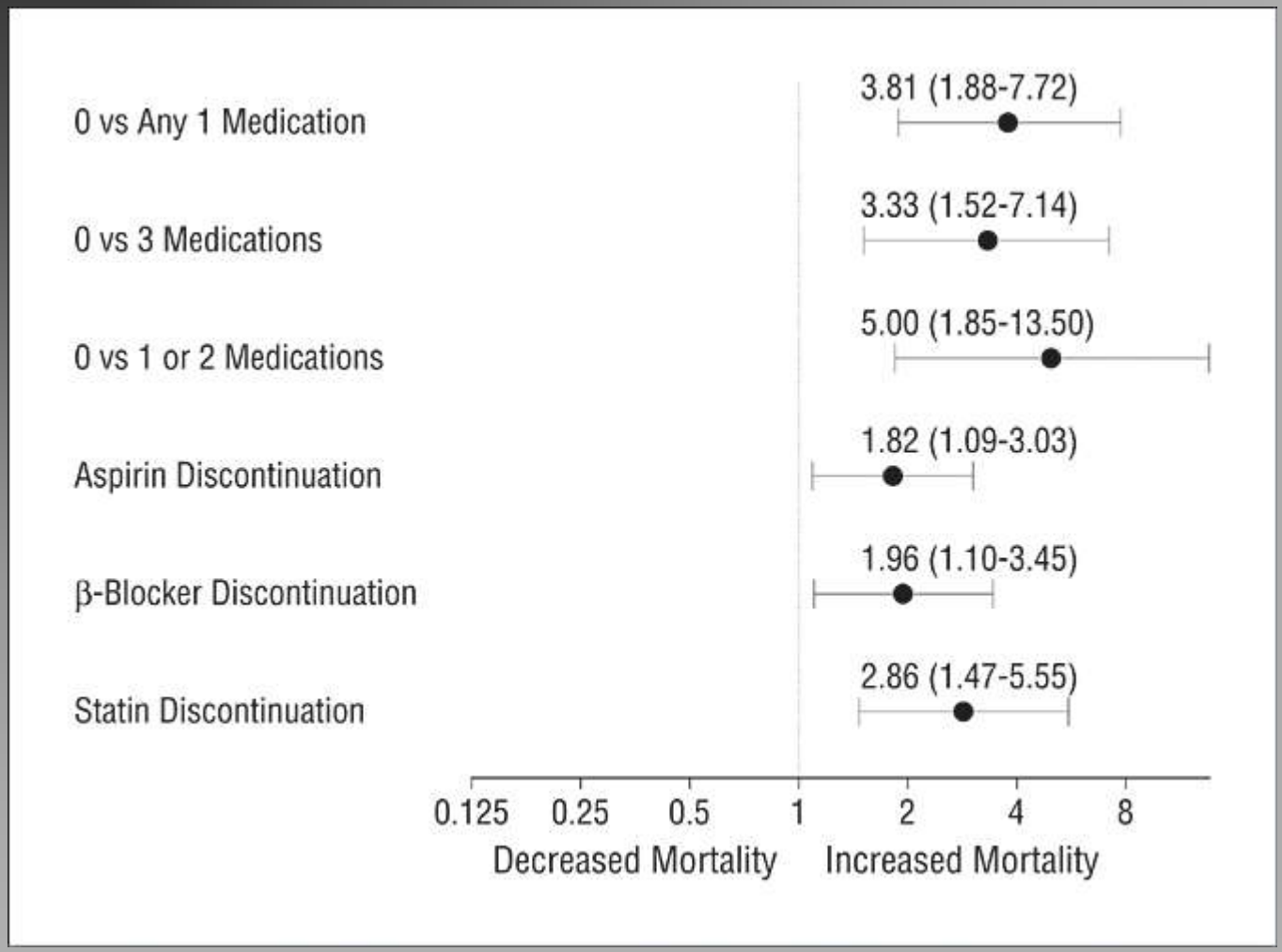
Situazione in Cardiologia: studio Blitz

- 1.954 pazienti con IMA
- 296 UTIC
- Età media 67 anni
- 70% maschi

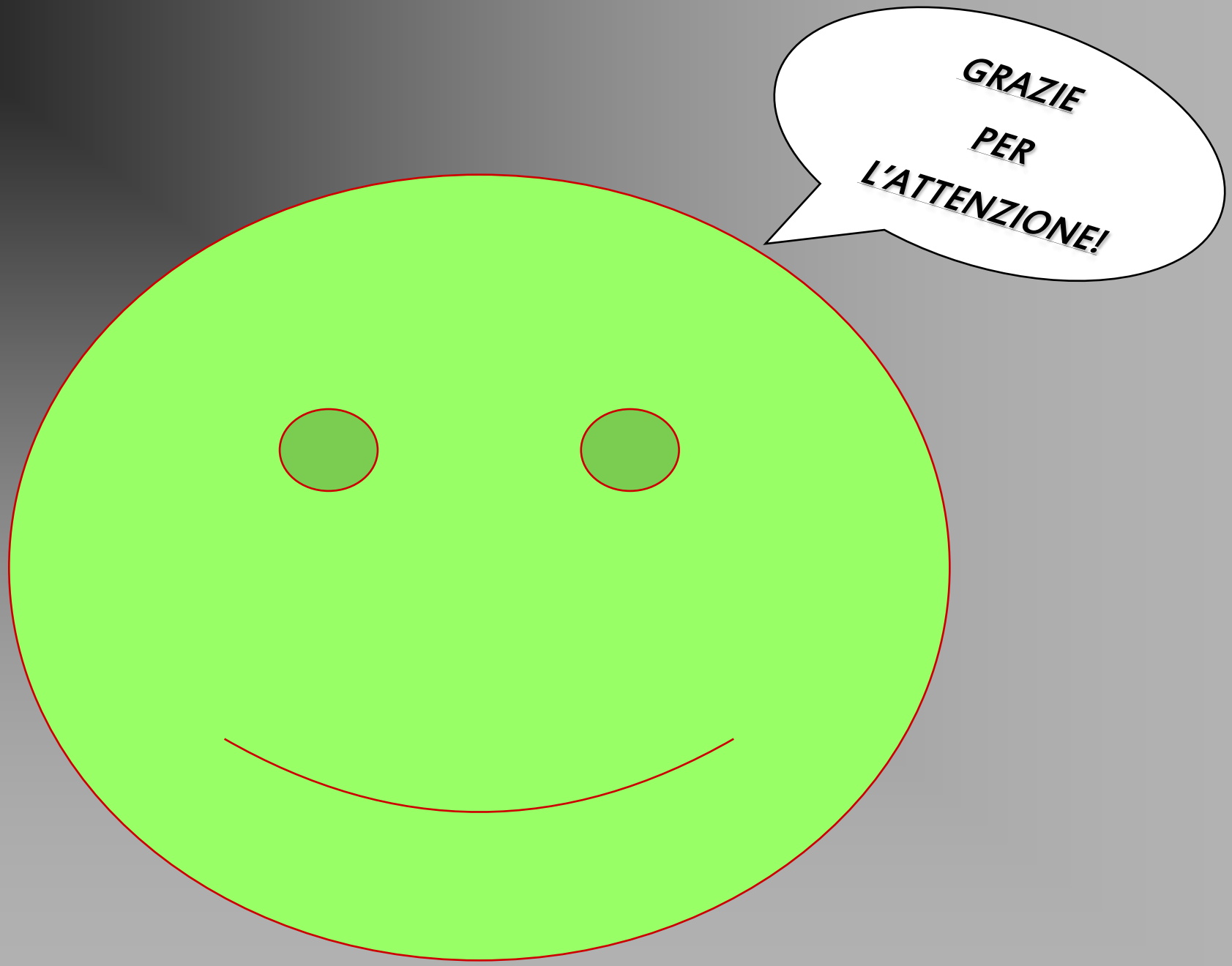


Di Chiara A. Eur Heart J 2003; 24: 1616-1629

Attenzione alla sospensione!!!



P.Michael HO et al., Arch Intern Med. 2006; 166: 1842-1847


GRAZIE
PER
L'ATTENZIONE!