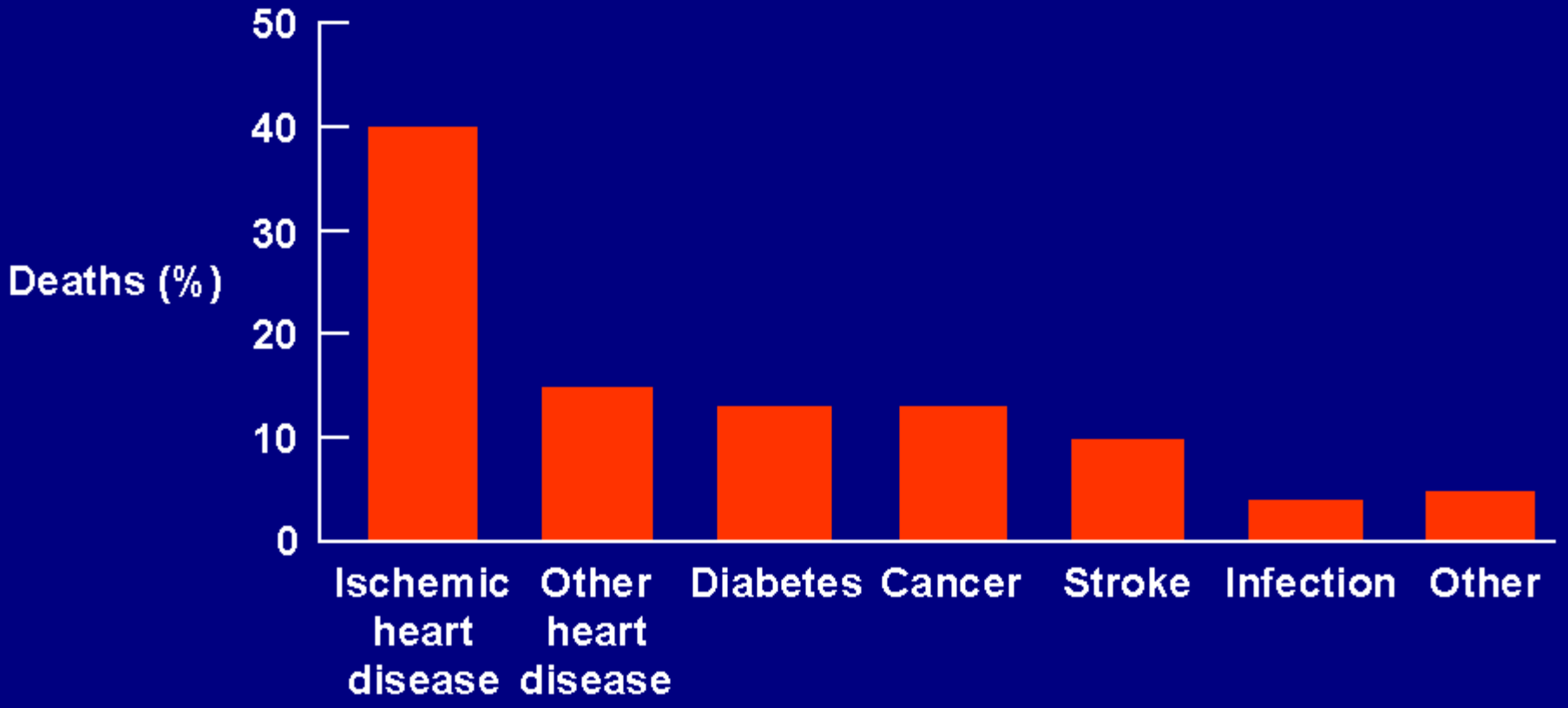
IL PAZIENTE DISLIPIDEMICO AD ALTO RISCHIO CARDIOVASCOLARE

Federico Baldi

Direttore S.C. Endocrinologia e Diabetologia A.S.L. Vercelli

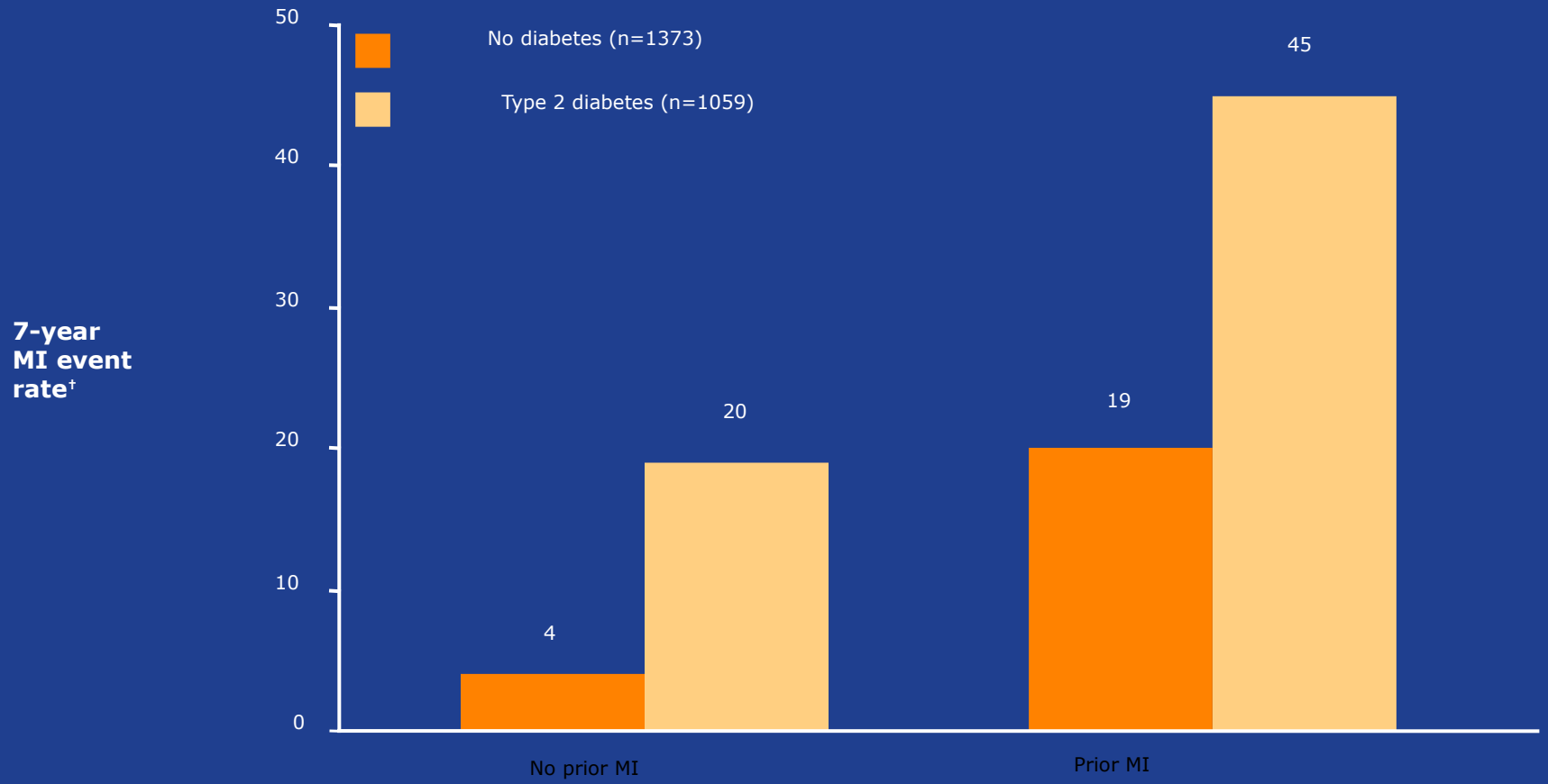
Cause di morte in pazienti con diabete



Data from death certificates.

Geiss LS et al. In: *Diabetes in America*. 2nd ed. 1995; chap 11.

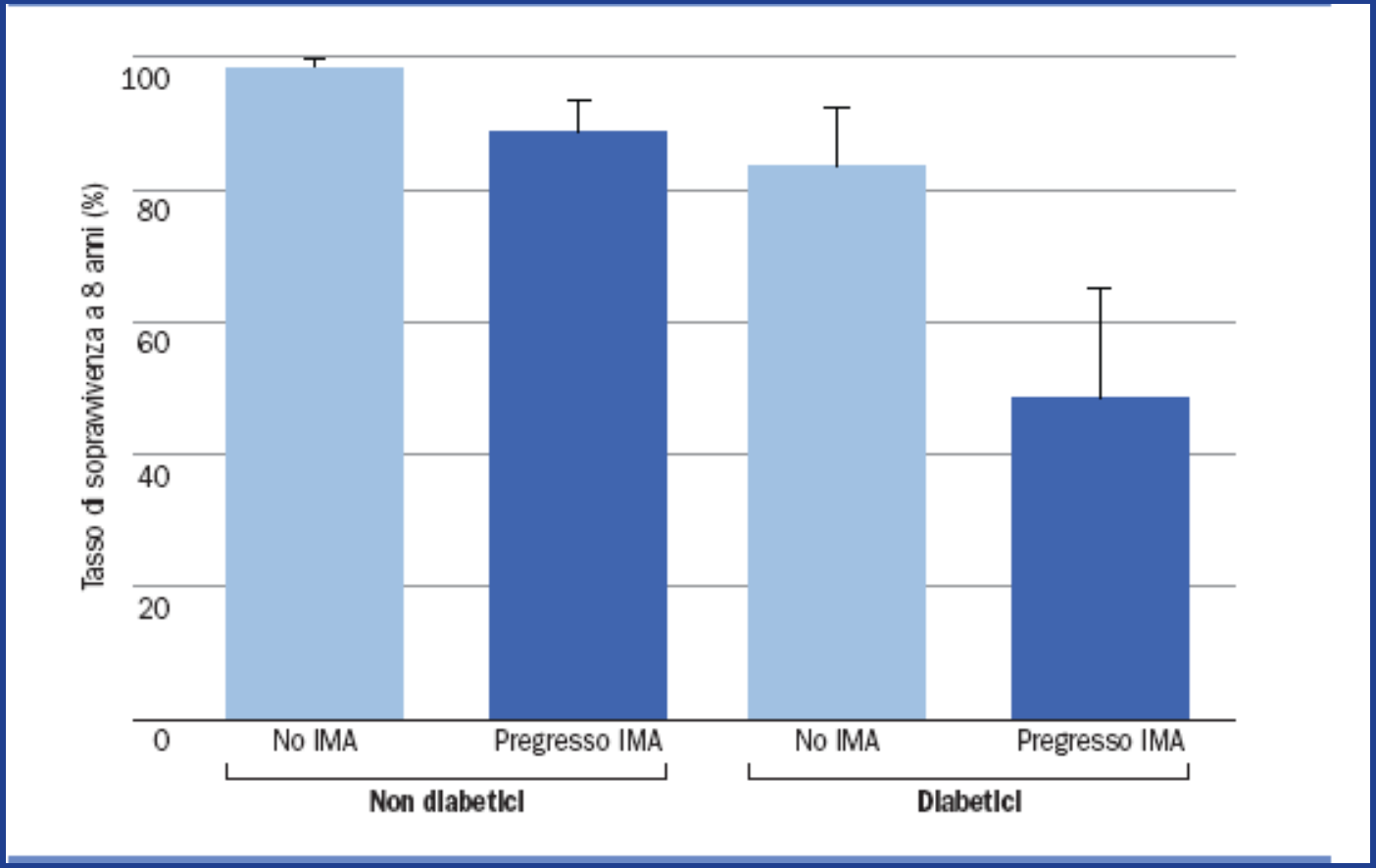
Rischio aumentato per CHD in pazienti con diabete tipo 2



CHD=coronary heart disease; MI=myocardial infarction
†Events/100 person-years

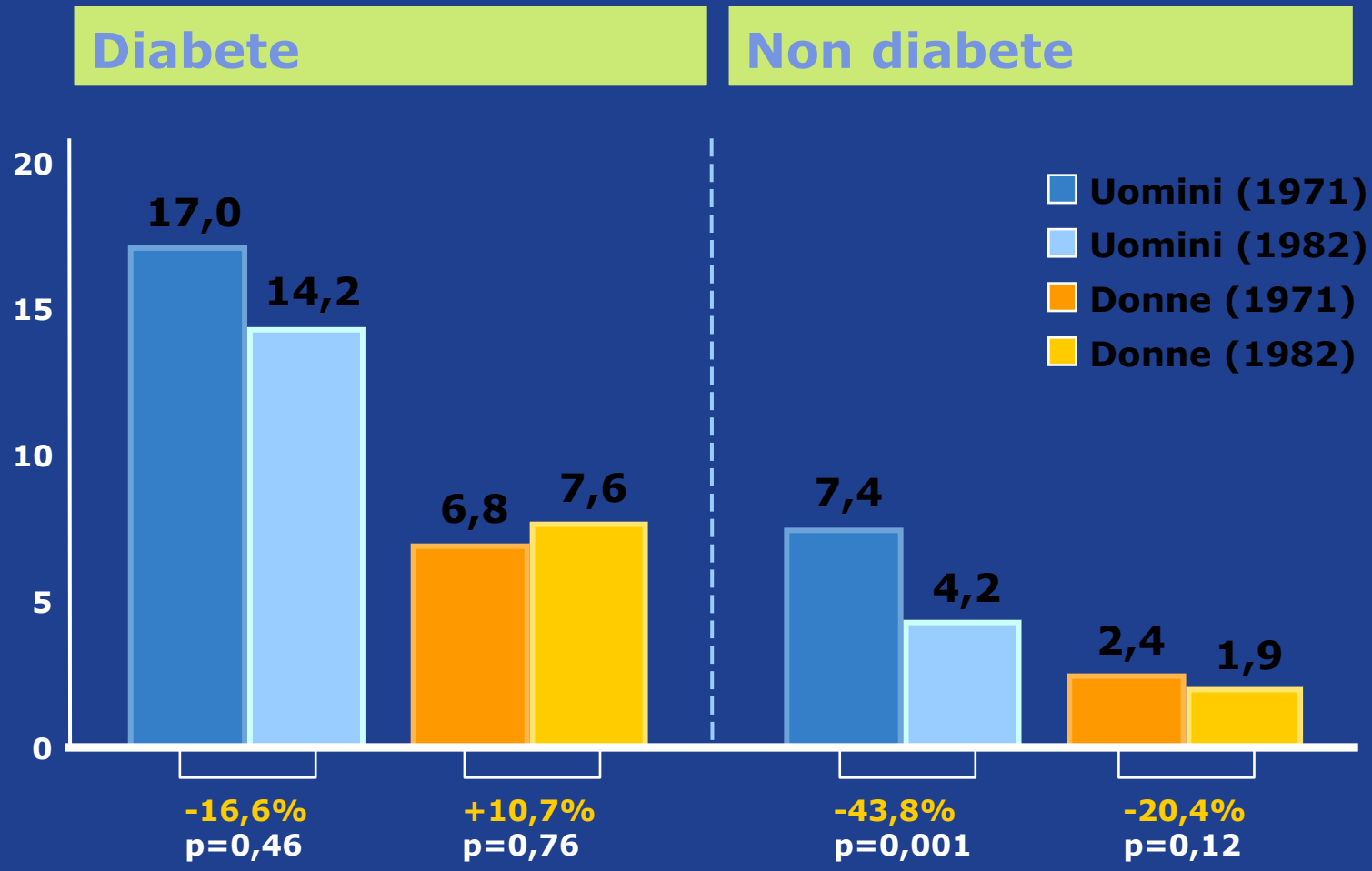
Haffner SM et al. *N Engl J Med* 1998; 339: 229–234

MORTALITA' NEI PZ DIABETICI RISPETTO AI NON DIABETICI, DOPO INFARTO MIOCARDICO ACUTO



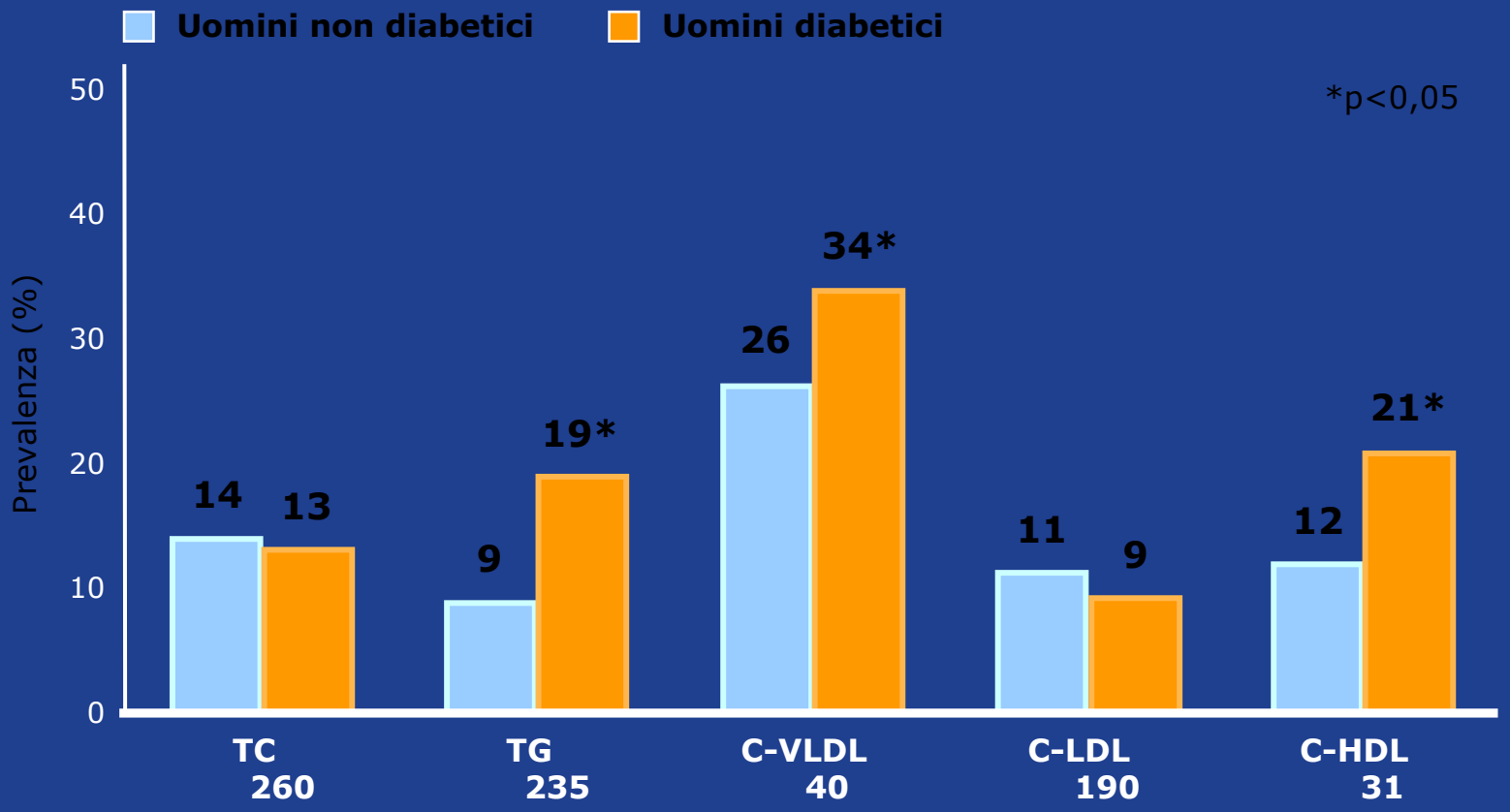
Modificata da Haffner SM, Lethes, Ronnemaa T. et al. N Engl J Med 1998; 339:229-34

Tassi di mortalità per cardiopatia ischemica in pazienti con e senza diabete*



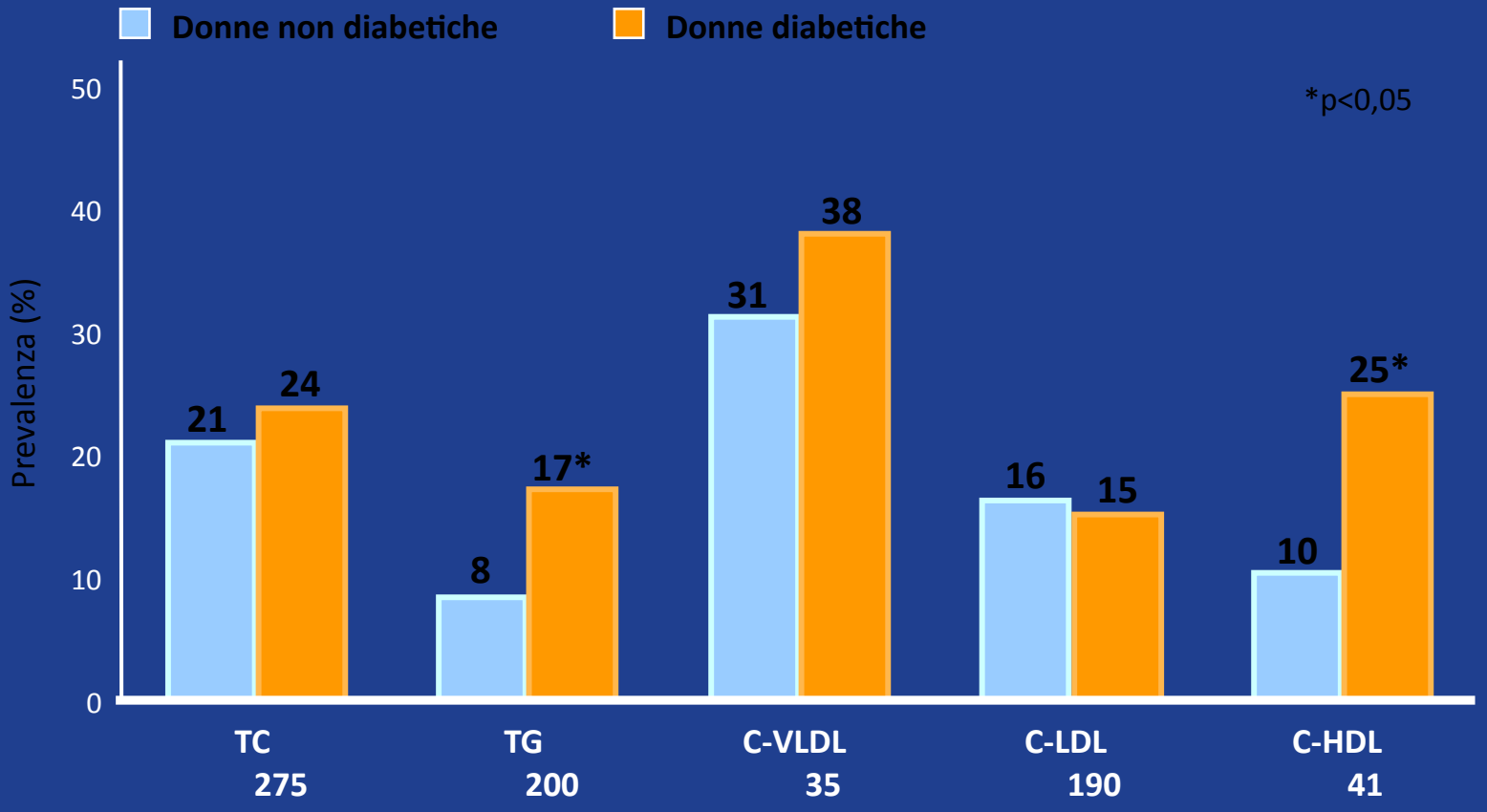
* In campioni nazionali di adulti in NHANES I (1971-75)
Gu K et al., *JAMA* 1999; 281:1291-1297

Livelli lipidici anomali in uomini con diabete di tipo 2



Adattato da Garg A, Grundy SM, *Diabetes Care* 1990; 13:153-169

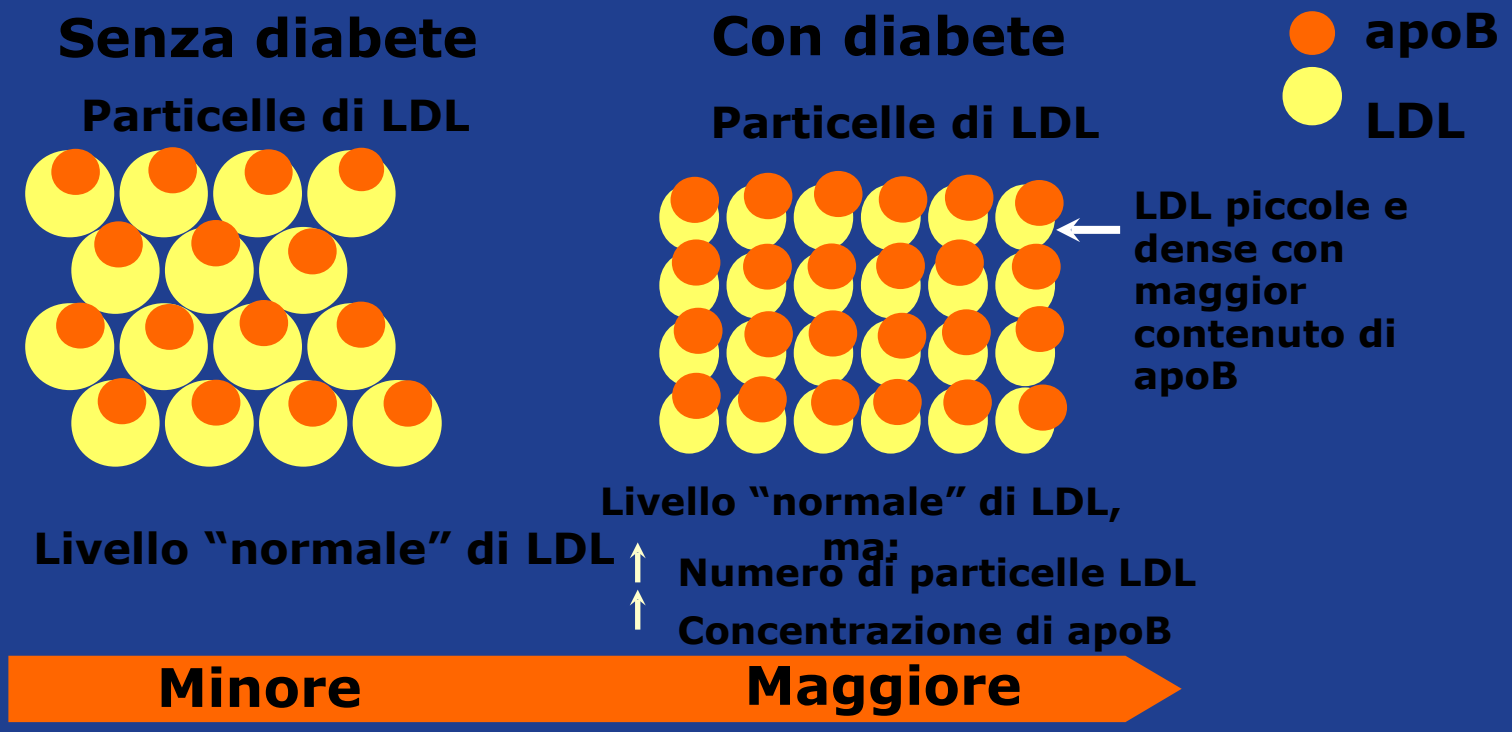
Livelli lipidici anomali in donne con diabete di tipo 2



Adattato da Garg A, Grundy SM, *Diabetes Care* 1990; 13:153-169

Livelli "normali" di LDL nei diabetici possono ingannare...

Particelle di LDL piccole e dense sono più aterogene



Adattato da : Austin MA, Edwards KL *Curr Opin Lipidol* 1996;7:167-171; Austin MA et al *JAMA* 1988;260:1917-1921; Sniderman AD et al *Diabetes Care* 2002;25:579-582.

Nello studio UKPDS
Il colesterolo LDL si è rivelato il miglior predittore del rischio di malattia coronarica nei diabetici

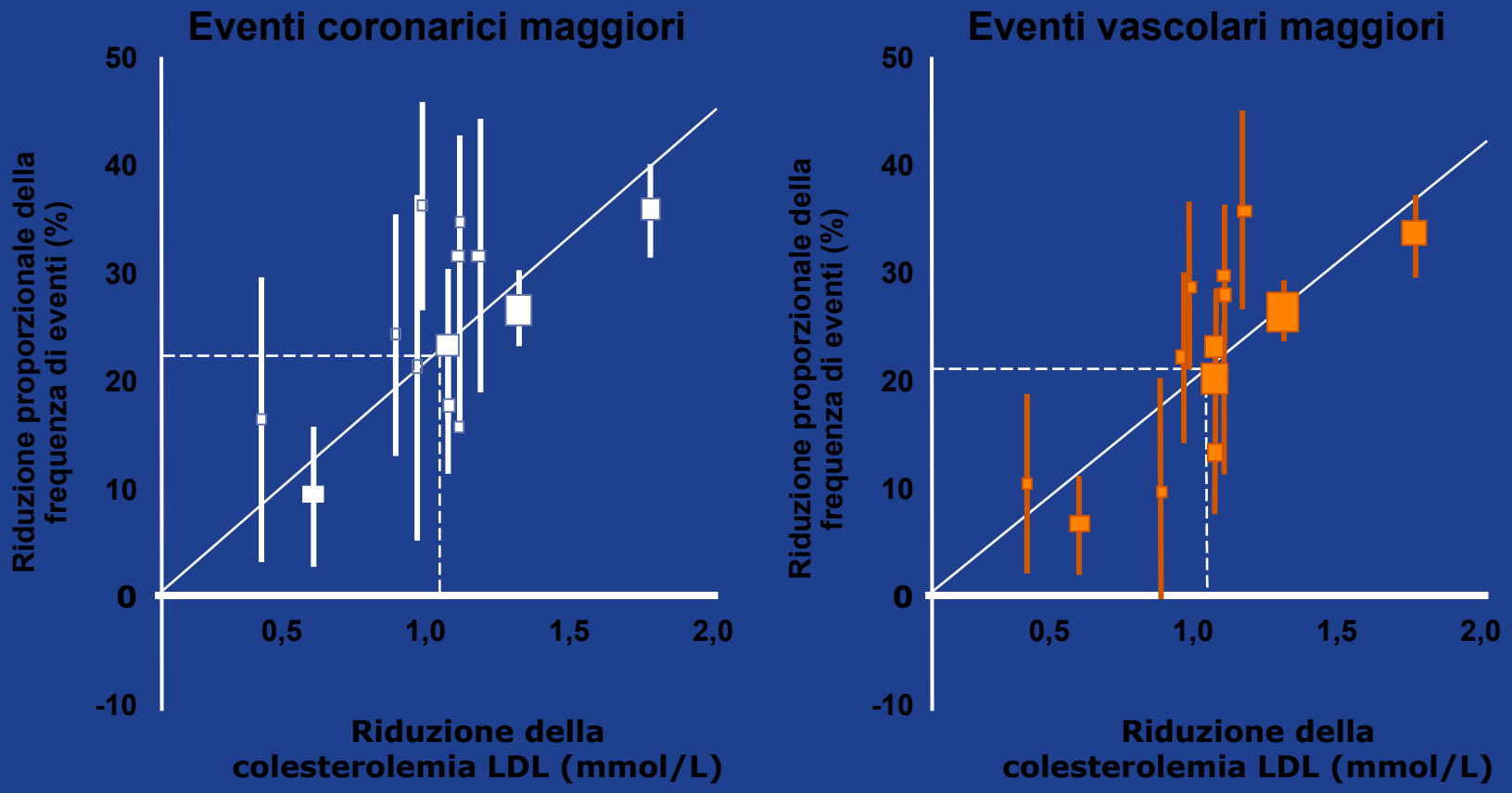
		Aumento % del rischio CHD
LDL	pari a 1 mmol/L	57
HDL	pari a 0.1 mmol/L	–15
Pressione arteriosa sistolica	pari a 10 mmHg	15
Livello di HbA_{1c}	pari a 1%	11

Il fumo è un altro importante fattore di rischio CHD

Questi dati dimostrano l'importanza di ridurre i livelli di LDL per diminuire il rischio di cardiopatia coronarica (CHD) nei diabetici. Il controllo della glicemia è altrettanto importante per ridurre il rischio di complicanze microvascolari.

Adattato da : Turner RC et al *BMJ* 1998;316:823-828.

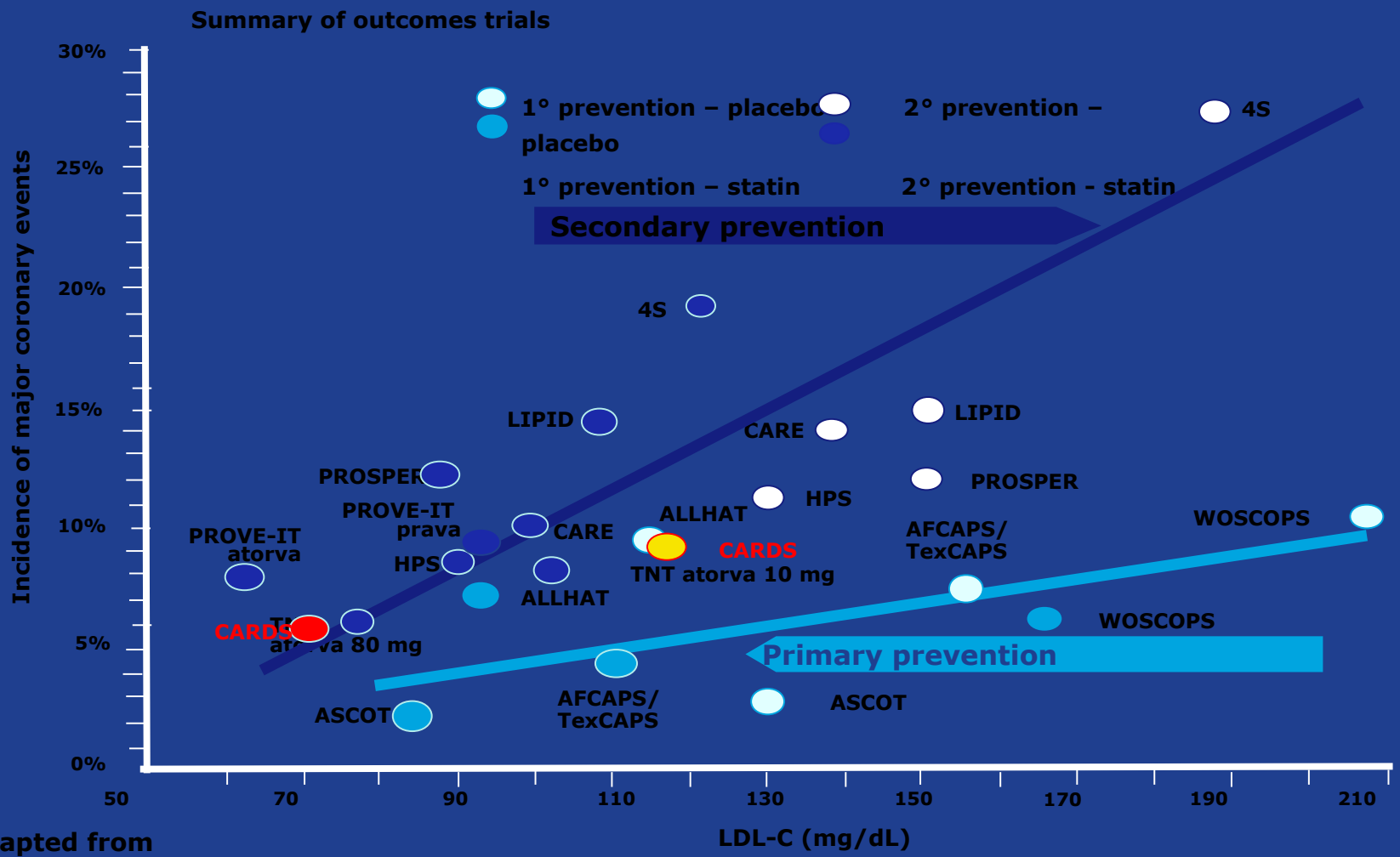
Relazione tra riduzione proporzionale dell'incidenza di eventi coronarici maggiori ed eventi vascolari maggiori e riduzione media assoluta di colesterolemia LDL



I quadrati rappresentano un singolo studio confrontato verso la riduzione media assoluta di colesterolemia LDL ad 1 anno, con le linee verticali sopra e sotto che corrispondono ad un ES della riduzione non pesata della frequenza di eventi.
Per ogni esito, la linea di regressione (che è forzata per passare dall'origine) rappresenta la riduzione pesata della frequenza di eventi per mmol/L di riduzione di colesterolemia LDL.

Baigent C et al. Lancet 2005; 366:1267-1278

STUDIO CARDS (prevenzione primaria in pazienti con diabete tipo 2) e prevenzione secondaria



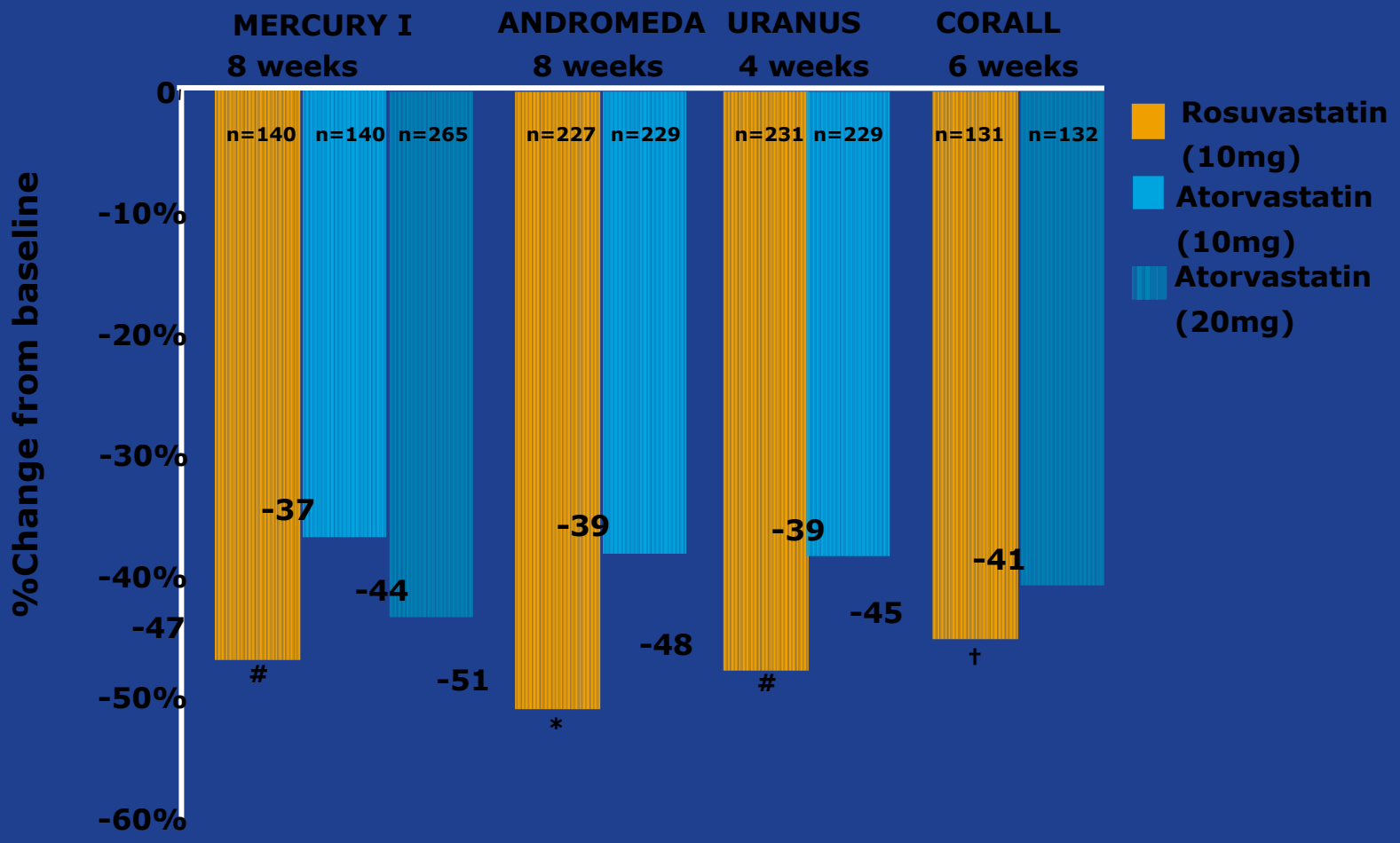
Adapted from

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

LaRosa JC *et al. N Engl J Med* 2005;352:e-version.

Colhoun, HM et al. *Lancet* 2004; 364:685-96

Statine: riduzione del C-LDL in pazienti con diabete tipo 2



#p<0.0001 vs atorvastatin 10 mg *P<0.001 vs atorvastatin 10 mg †P<0.05 vs atorvastatin 20 mg

Berne C, Siewert-Delle A. *Atherosclerosis Supplements* 2004; 5:107, Abs M.463.

Franken A, Wolffenbuttel B, Vincent H. *Atherosclerosis Supplements* 2004;

Betteridge D, Gibson M. *Atherosclerosis Supplements* 2004; 5:107, Abs M.464. 5:118, Abs M.513. 1036–43.

Schuster H *et al. Diabetalogia 2004;* 47 (suppl), AW09; 1146

VOYAGER

- Meta-analysis (of 32 258 patients)
- Review of individual patient data from comparative randomised studies comparing rosuvastatin with either atorvastatin or simvastatin in high-risk populations
- Comprehensive literature search (MEDLINE, EMBASE, Citeline Trialtrove™ and PLANET [AZ database of published literature on AZ's products])
- 37 randomised comparative studies >4 weeks duration were identified as suitable for inclusion in the VOYAGER database, in which baseline and on-treatment lipids were recorded for each patient, as well as lab methods for determining these parameters
- Integrated database of >30 000 patients

The VOYAGER population

Whole population
n=32 258

Nicholls S et al. *Am J Cardiol* 2009 (in press)

(38 199 patient exposures†)

High-risk population
n=21 656

Nicholls S et al. *Am J Cardiol* 2009 (in press)

(26 647 patient exposures†)

Patients with diabetes and/or atherogenic dyslipidaemia and/or atherosclerotic disease

Diabetes
n=8859

Nicholls S, et al. *Atheroscler Suppl* 2009; 10: 965 (abstract)

(11 042 patient exposures†)
Two fasting glucose measurements >126 mg/dL (7.0 mmol/L)
Glycosylated haemoglobin 6%
Use of antidiabetic agents
Presence of diabetic complications

Atherogenic dyslipidaemia
n=6061

(7673 patient exposures†)
Major components of metabolic syndrome
Recognised clinically
by elevated TG (150 mg/dL)
and low HDL-C levels
(<40 mg/dL)

Atherosclerotic disease
n=15 498

Nicholls S, et al. *Atheroscler Suppl* 2009; 10: 964 (abstract)

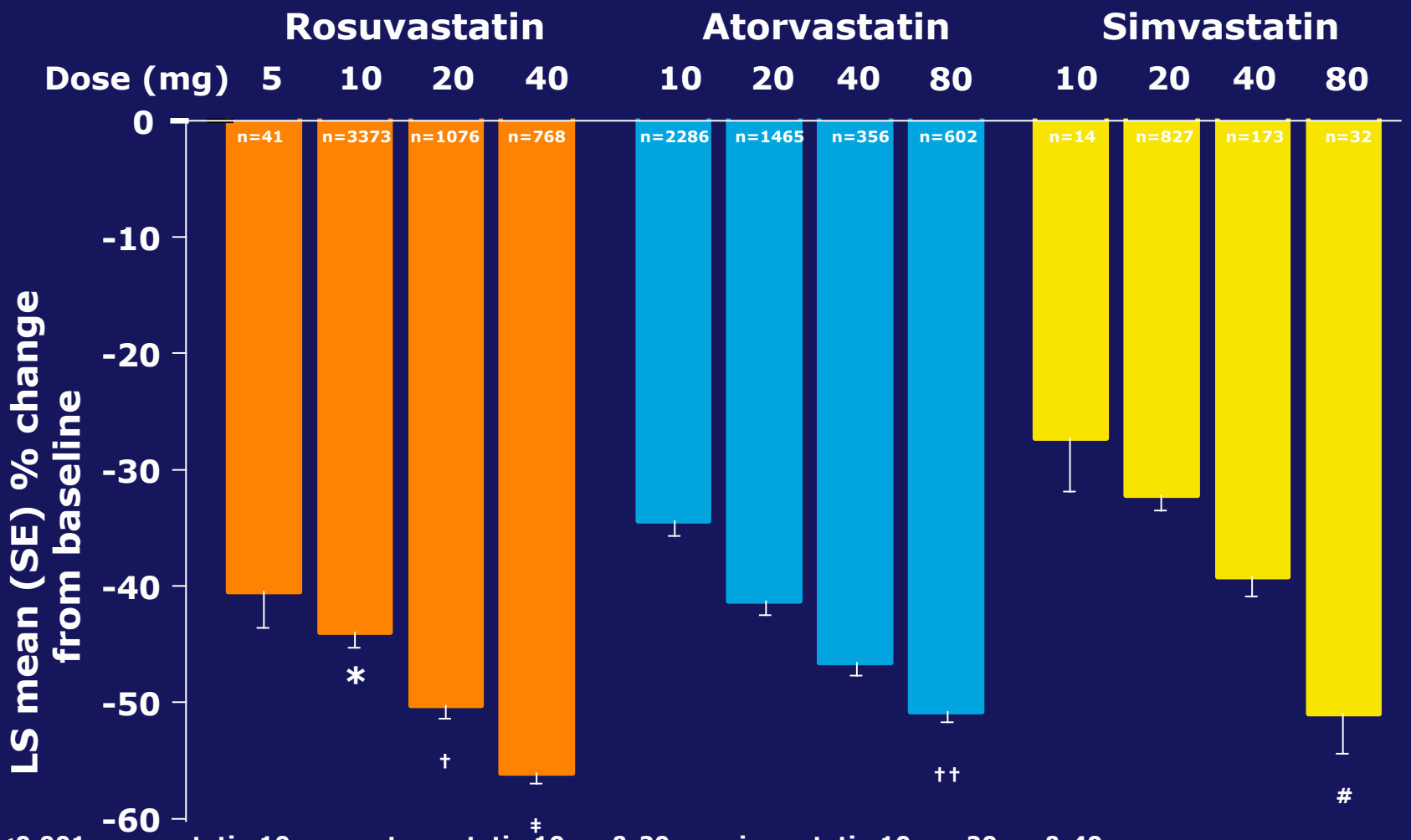
(19 437 patient exposures†)
Coronary heart disease (CHD)
Chronic stable or unstable angina, prior MI, prior coronary angioplasty or stent, prior CABG
Documented peripheral arterial disease (PAD)
Intermittent claudication or prior angioplasty for PAD
Documented carotid artery disease
Prior cerebrovascular accident, prior transient ischaemic attack, carotid angioplasty carotid endarterectomy
carotid stenosis 50%
Abdominal aortic aneurysm

†Studies involving forced-titration to higher statin doses meant that there was a greater number of 'exposures' to individual doses of statins than there were patients within the overall VOYAGER population

CABG=coronary artery bypass graft; HDL-C=high-density lipoprotein cholesterol; MI=myocardial infarction; TG=triglyceride

Variazioni di C-LDL nel sottogruppo pazienti diabetici

Risultati da VOYAGER metanalisi dei dati individuali dei pazienti

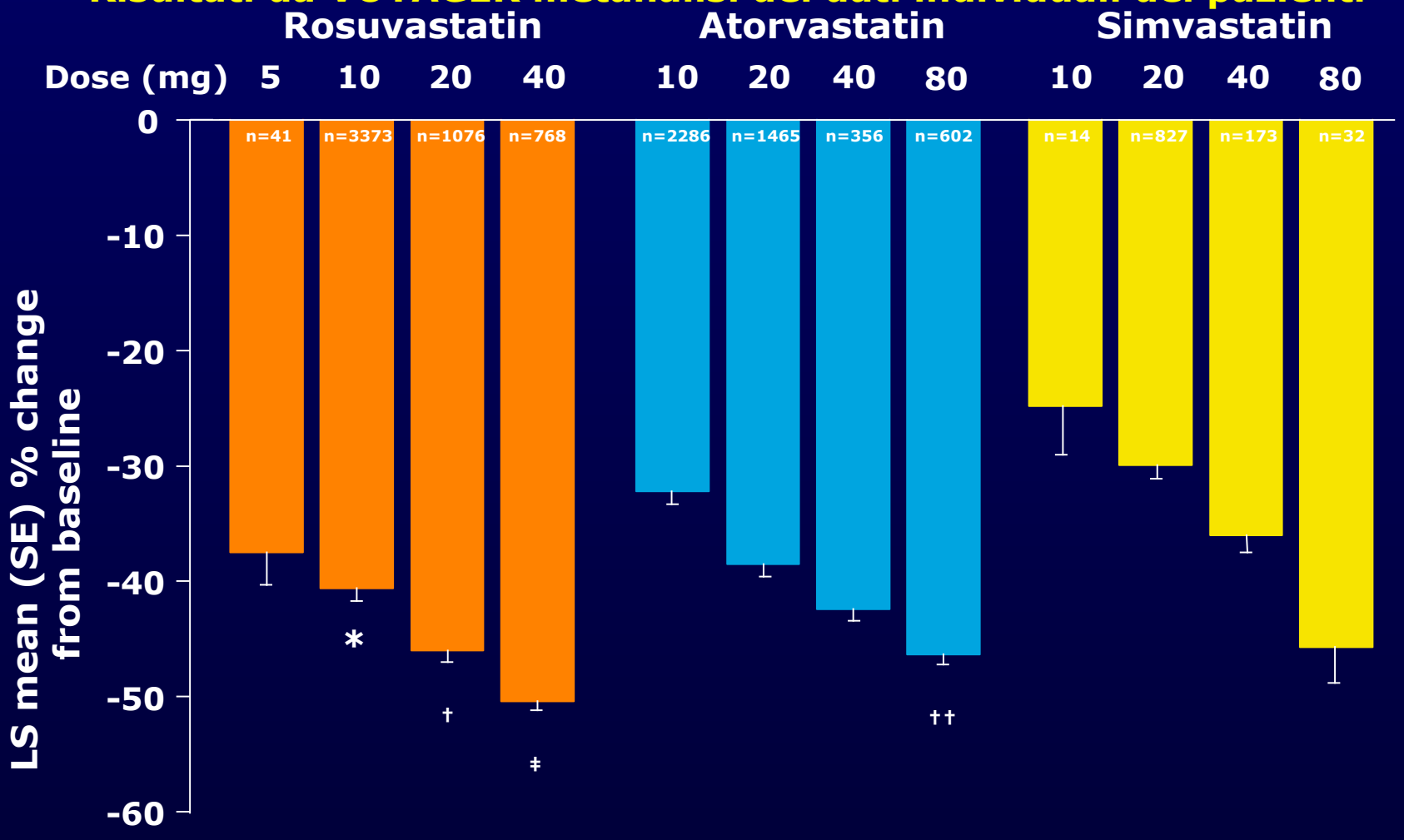


*p≤0.001 rosuvastatin 10mg vs atorvastatin 10mg & 20mg; simvastatin 10mg, 20mg & 40mg;
†p≤0.003 rosuvastatin 20mg vs atorvastatin 20mg & 40mg; simvastatin 20mg & 40mg;
‡p≤0.001 rosuvastatin 40mg vs atorvastatin 40mg & 80mg; simvastatin 40mg;
††p<0.003 atorvastatin 80mg vs rosuvastatin 5mg, 10mg; #p=0.027 simvastatin 80mg vs rosuvastatin 5mg

Nicholls S, Brandrup-Wognsen G, Palmer M et al. Am J Cardiol 2010; 105:69-76

Variazioni di non C-HDL-C nel sottogruppo pazienti diabetici

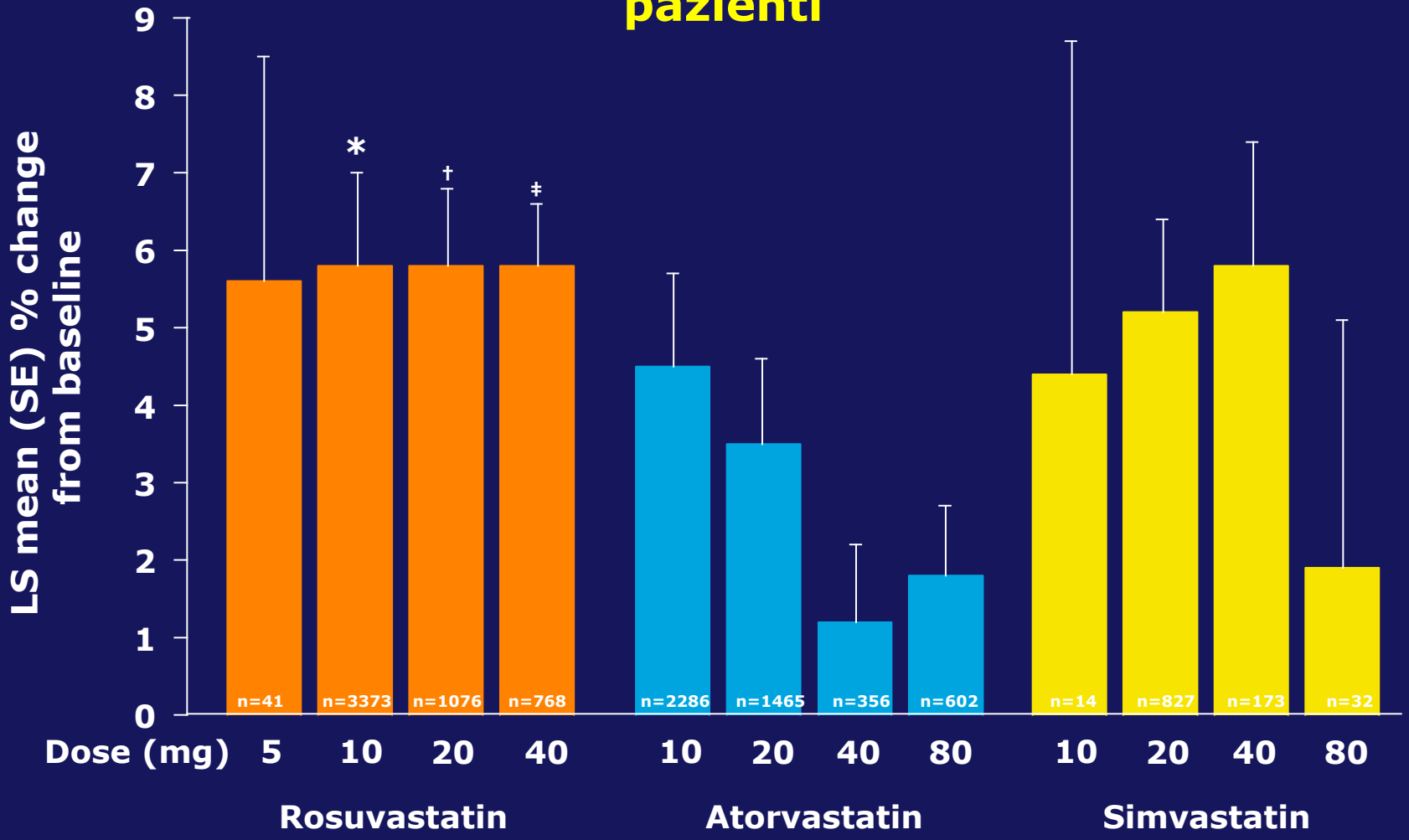
Risultati da VOYAGER metanalisi dei dati individuali dei pazienti



*p≤0.001 vs atorvastatin 10mg & 20mg; simvastatin 10mg, 20mg & 40mg;
†p≤0.003 vs atorvastatin 20mg & 40mg; simvastatin 20mg & 40mg;
‡p≤0.001 vs atorvastatin 40mg & 80mg; simvastatin 40mg;
††p<0.003 atorvastatin 80mg vs rosuvastatin 5mg, 10mg;

Nicholls S, Brandrup-Wognsen G, Palmer M et al. Am J Cardiol 2010; 105:69-76

Variazioni di C-HDL nel sottogruppo di pazienti diabetici Risultati da VOYAGER metanalisi dei dati individuali dei pazienti



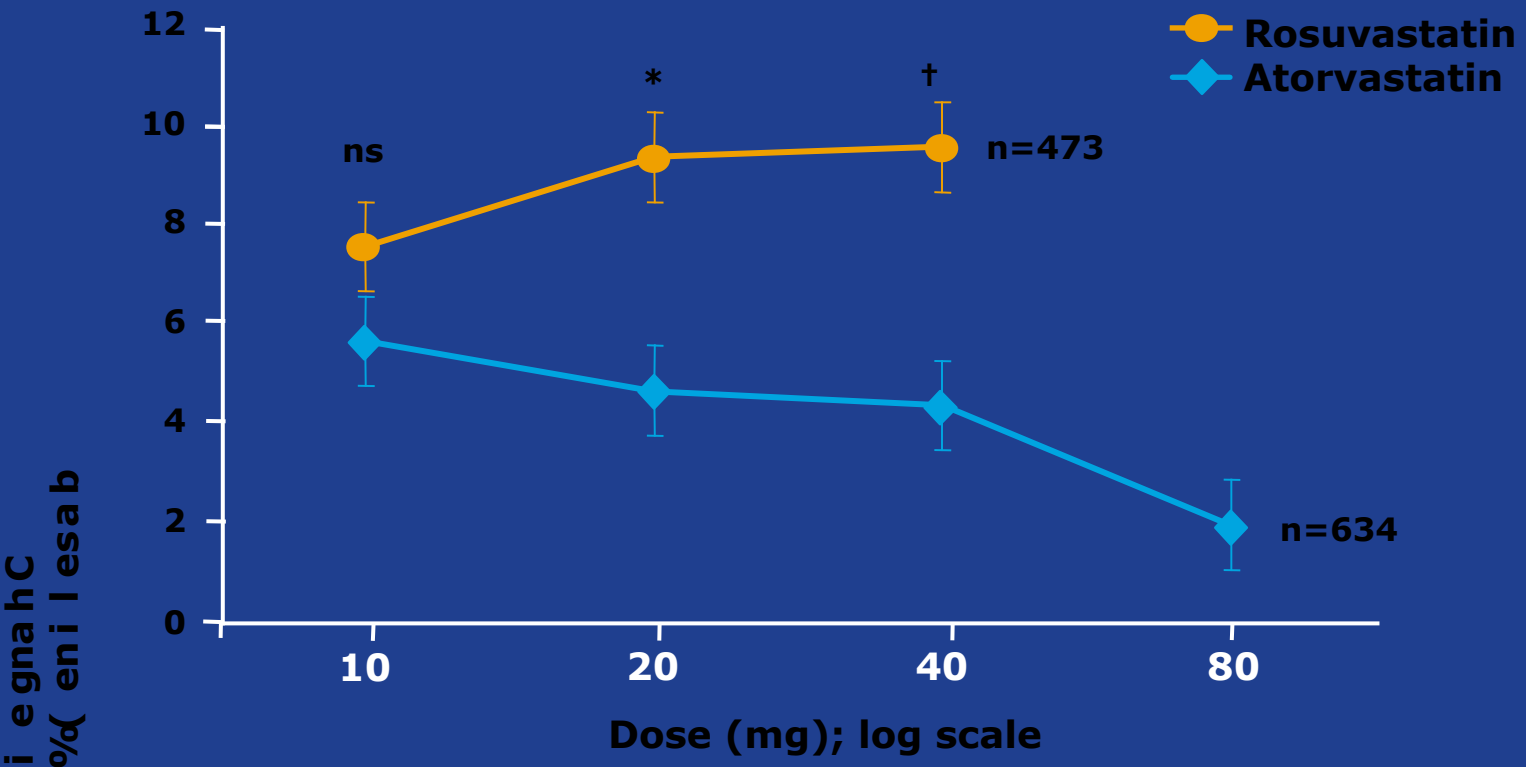
*p≤0.005 rosuvastatin 10mg vs atorvastatin 10mg, 20mg, 40mg and p=0.012 vs atorvastatin 80mg;
†p≤0.005 rosuvastatin 20mg vs atorvastatin 20mg, 40mg & 80mg;
‡p<0.001 rosuvastatin 40mg vs atorvastatin 40mg & 80mg;

Nicholls S, Brandrup-Wognsen G, Palmer M et al. Am J Cardiol 2010; 105:69-76

Relazione tra livelli di LDL-C e HDL-C nel RCV

Third Report of the NCEP Expert Panel. NIH Publication No. 01-3670 2001.
http://hin.nhlbi.nih.gov/ncep_slds/menu.htm

Efficacia comparata su C-HDL
Studio STELLAR

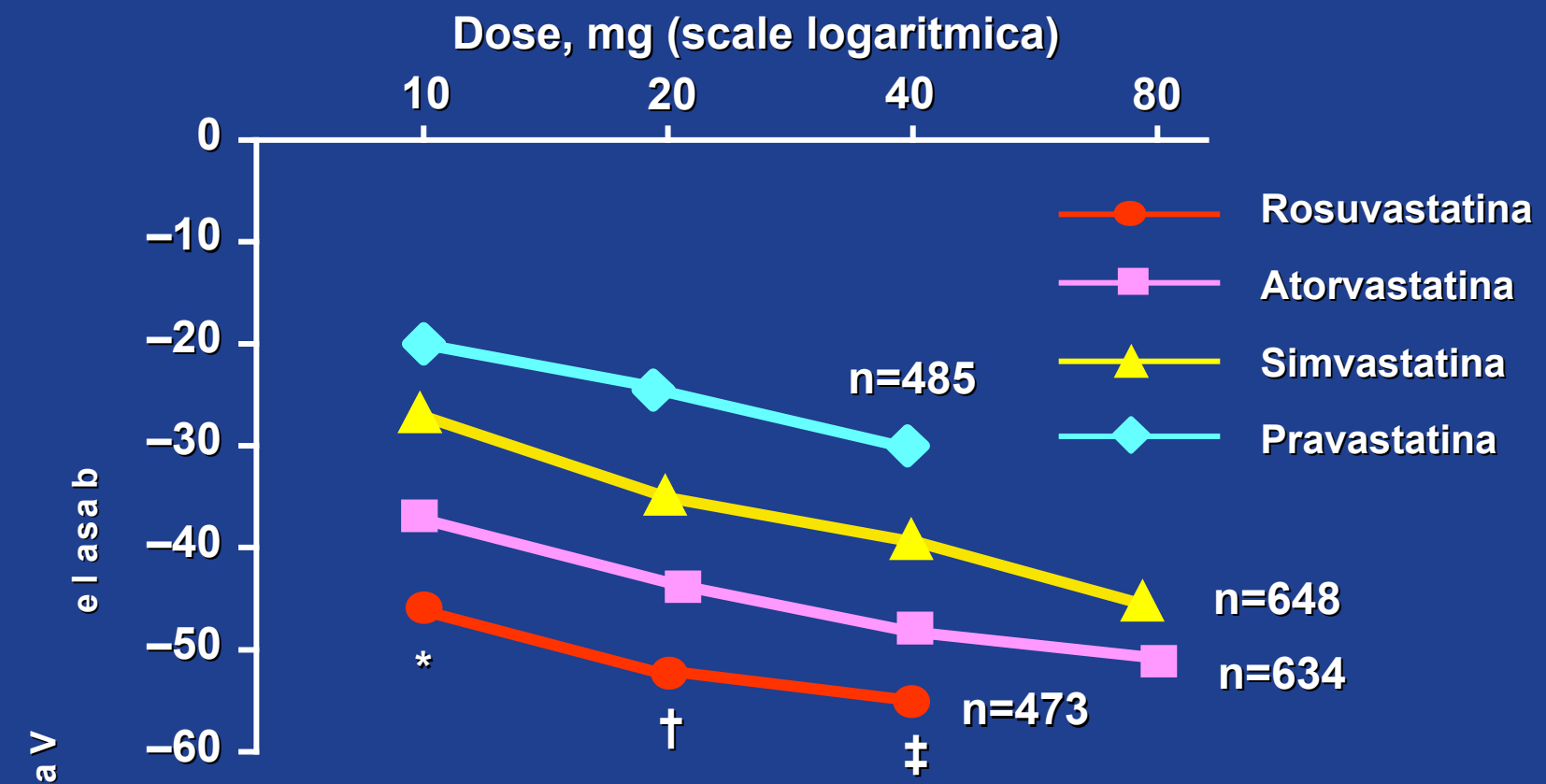


*p<0.002 vs atorvastatin 20, 40 and 80 mg
†p<0.002 vs atorvastatin 40 and 80 mg

Adapted from Jones PH et al. *Am J Cardiol* 2003;92:152–160

Studio Stellar

Confronto tra statine: efficacia sulla colesterolemia LDL a diversi dosaggi

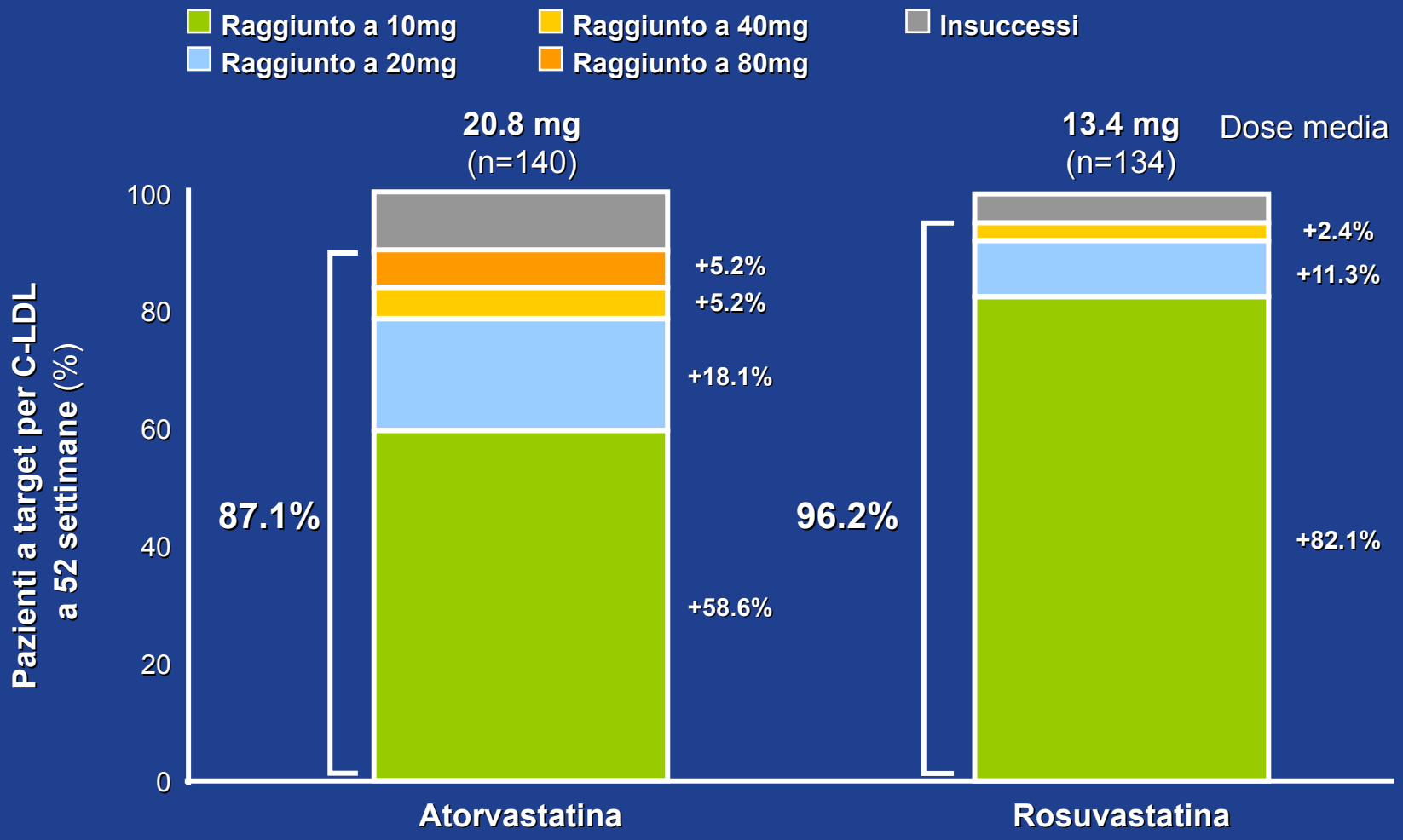


*p<0.002 vs atorvastatina 10 mg; simvastatina 10, 20, 40 mg; pravastatina 10, 20, 40 mg
†p<0.002 vs atorvastatina 20, 40 mg; simvastatina 20, 40, 80 mg; pravastatina 20, 40 mg
‡p<0.002 vs atorvastatina 40 mg; simvastatina 40, 80 mg; pravastatina 40 mg

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

Studio Stellar

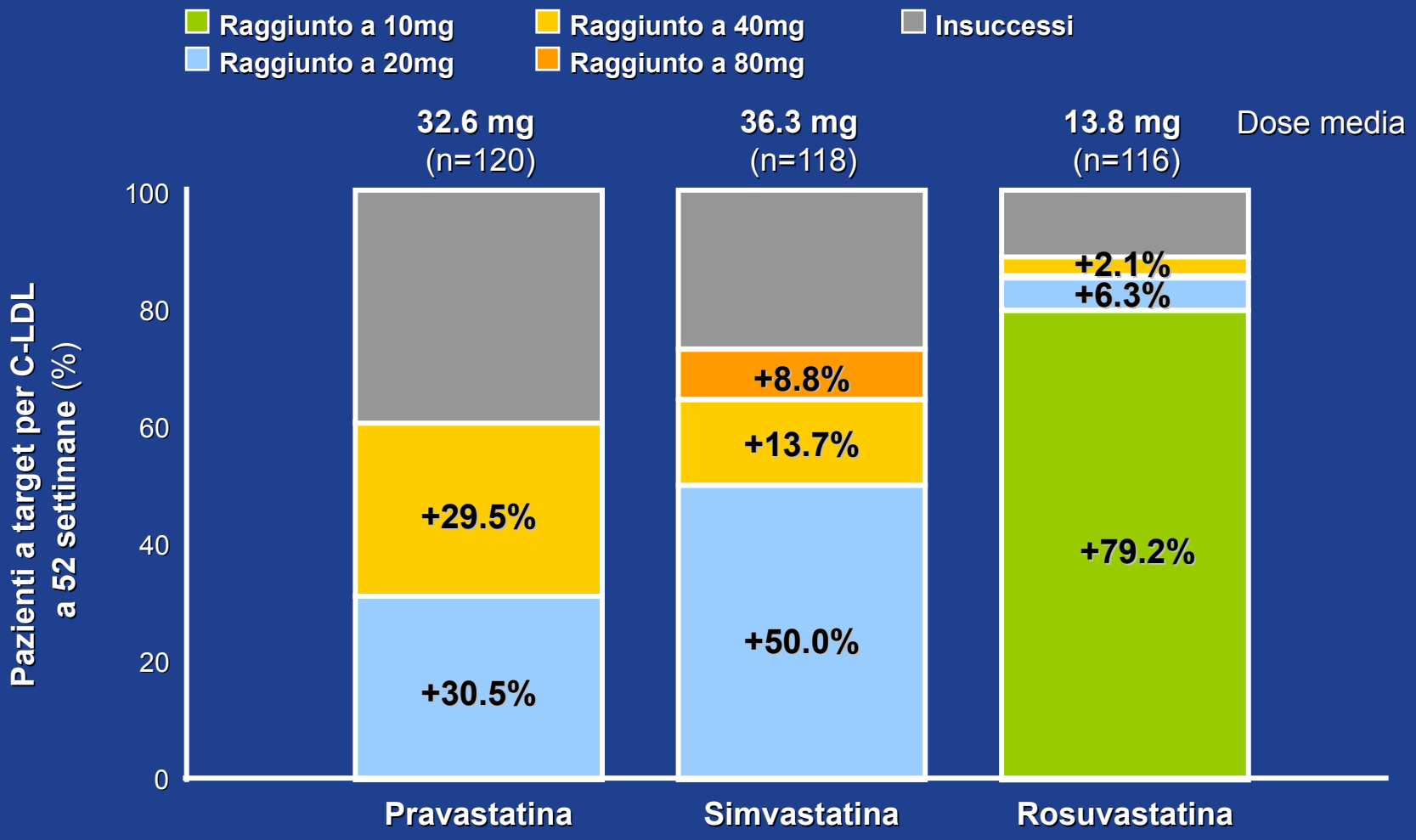
Percentuale di pazienti che raggiungono il target per le C-LDL raccomandato dalle Linee Guida



Olsson AG, Am Heart J 2002; 144:1044-1051

Studio Stellar

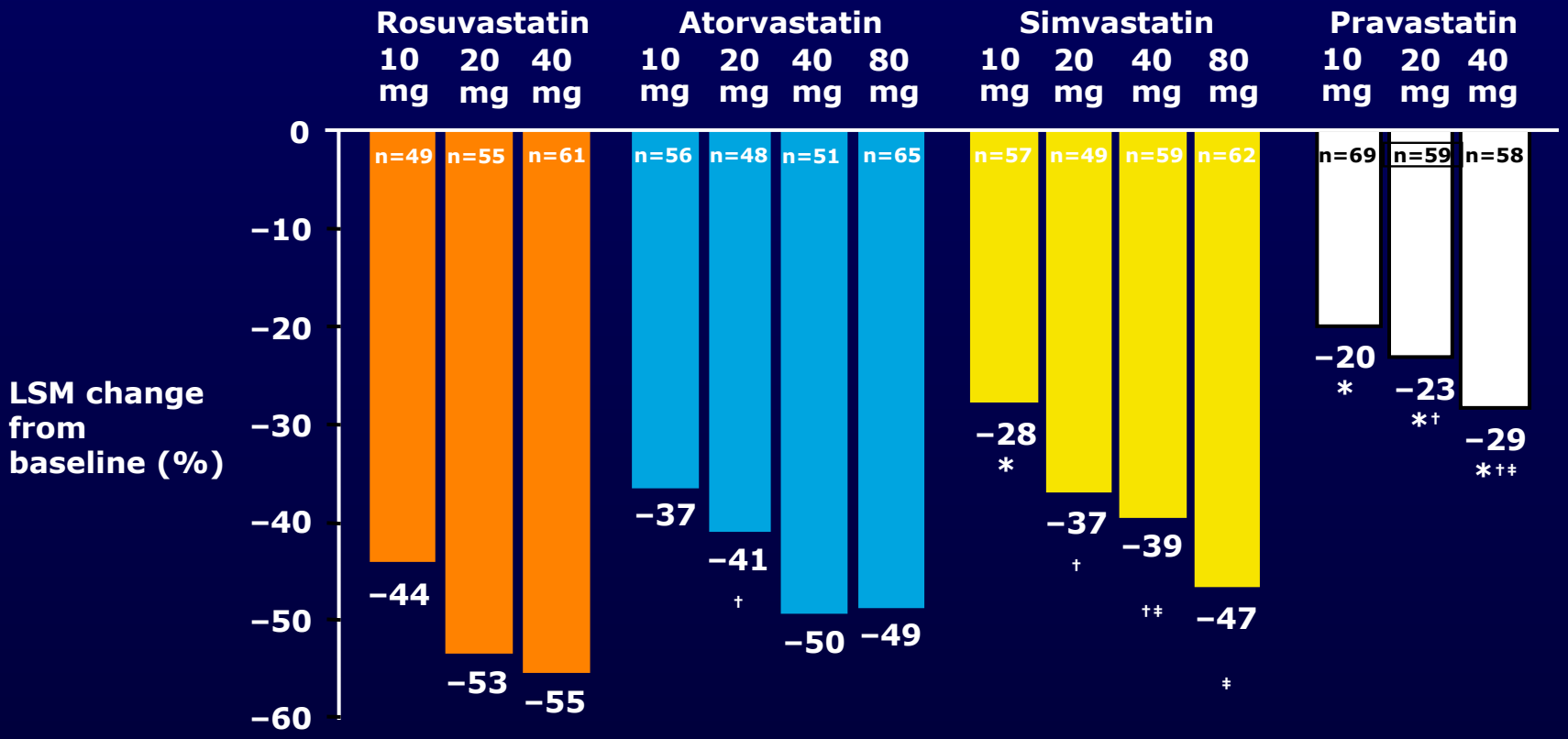
Percentuale di pazienti che raggiungono il target per le colesterolemia LDL raccomandato dalle Linee Guida



Brown VW, Am Heart J 2002; 144:1036-1043

Efficacia comparata riduzione del C-LDL in pazienti con Sindrome Metabolica

Studio STELLAR



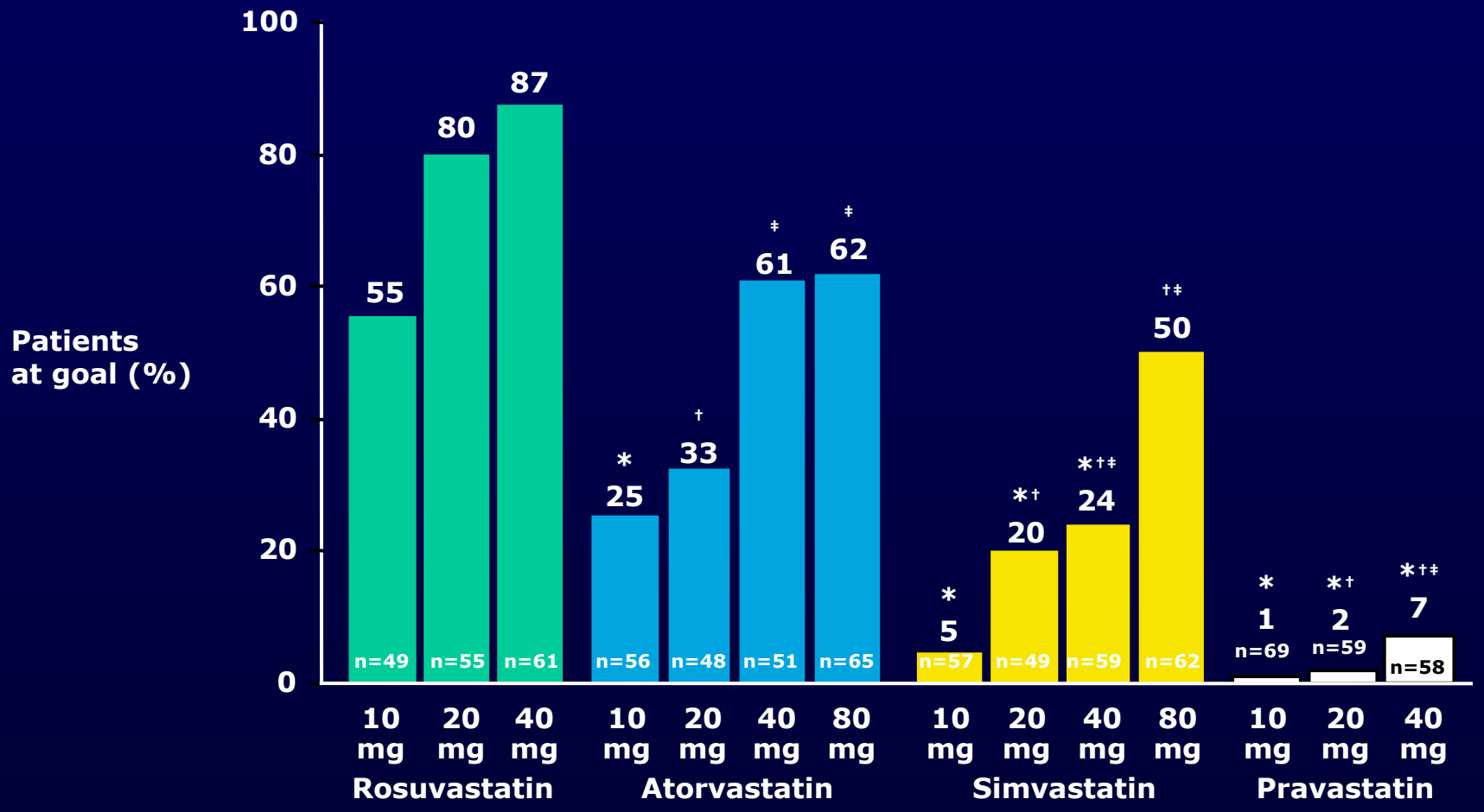
STELLAR=Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin; LDL-C=low-density lipoprotein cholesterol; LSM=least-squares mean

*p<0.002 vs rosuvastatin 10 mg; †p<0.002 vs rosuvastatin 20 mg; ‡p<0.002 vs rosuvastatin 40 mg

Deedwania P et al. *Am J Cardiol* 2005; 95: 360–366

Raggiungimento del target di C–LDL <100 mg/dL in pazienti con Sindrome Metabolica

Studio STELLAR



STELLAR=Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin;
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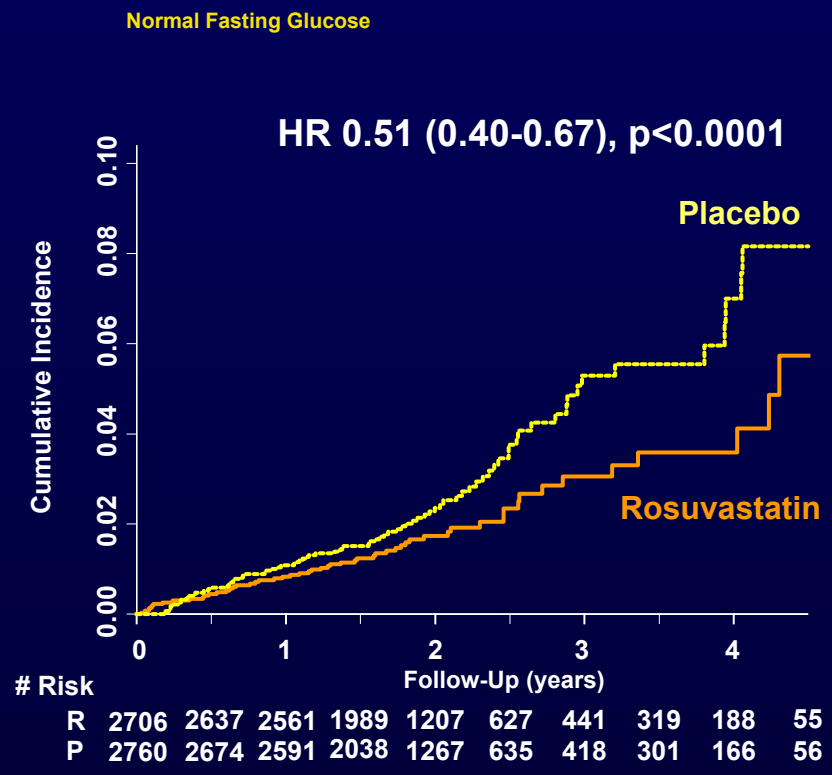
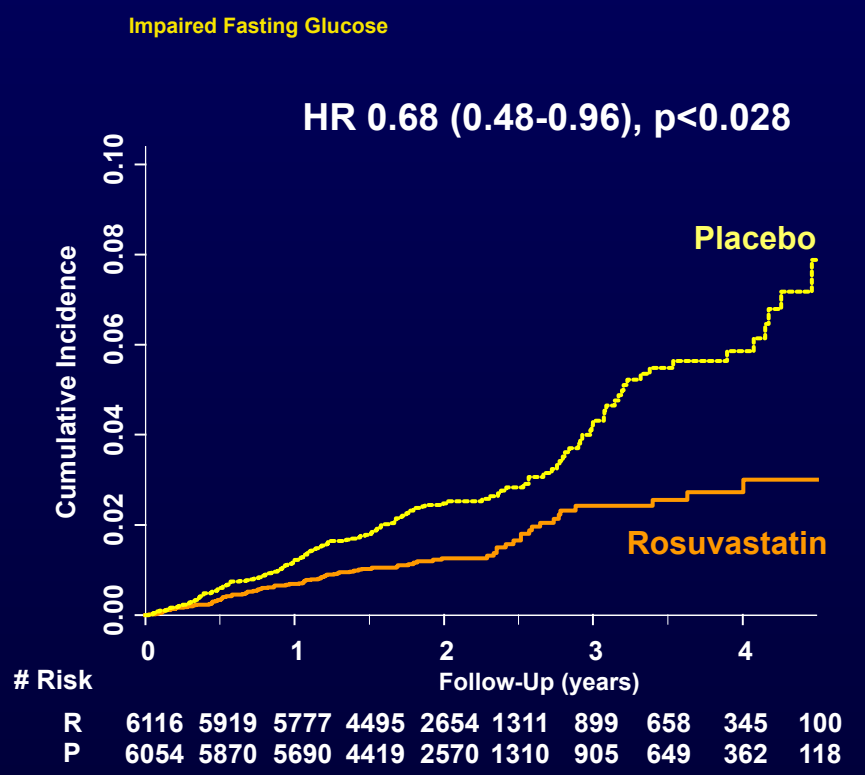
*p<0.002 vs rosuvastatin 10 mg; †p<0.002 vs rosuvastatin 20 mg; ‡p<0.002 vs rosuvastatin 40 mg
Deedwania P et al. *Am J Cardiol* 2005; 95: 360–366

JUPITER – Impaired Fasting Glucose (IFG) Subgroup Data

Cumulative Incidence of the Primary Endpoint According to Baseline IFG Status





Pradhan A *et al*. Circulation 2009; 120 (Suppl): S500; Abs 1425

JUPITER

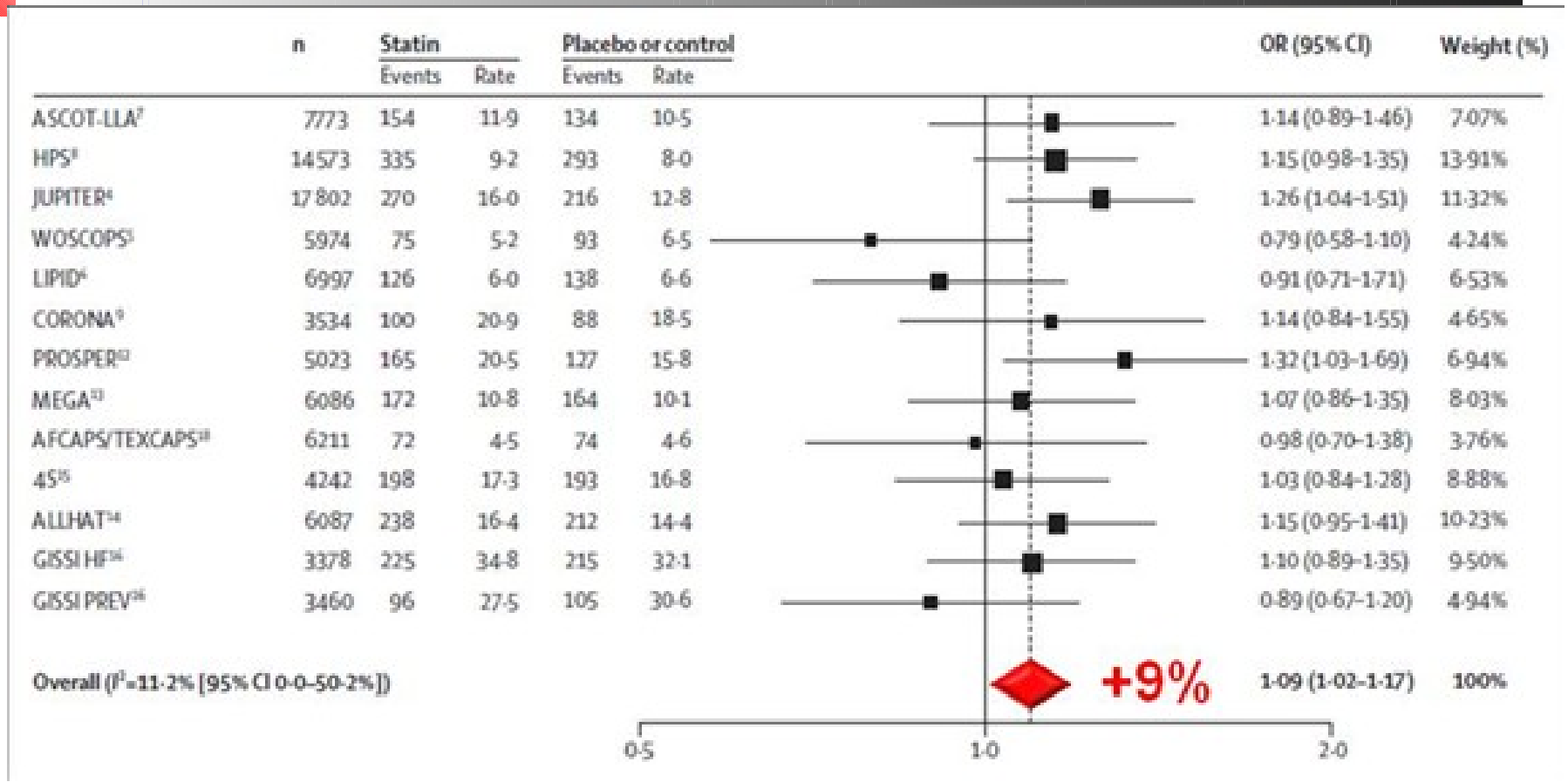
Tolerability and safety data

[n=8901]	Placebo [n=8901]	Rosuvastatin	p-value
Adverse Events, (%)			
Any serious adverse event	15.5	15.2	0.60
Muscle weakness, stiffness, pain	15.4	16.0	0.34
Myopathy	0.1	0.1	0.82
Rhabdomyolysis	0.0	<0.1*	----
Newly diagnosed cancer	3.5	3.4	0.51
Death from cancer	0.7	0.4	0.02
Gastrointestinal disorders	19.2	19.7	0.43
Renal disorders	5.4	6.0	0.08
Bleeding	3.1	2.9	0.45
Hepatic disorders	2.1	2.4	0.13
Other events, (%)			
Newly diagnosed diabetes**	2.4	3.0	0.01
Haemorrhagic stroke	0.1	0.1	0.44

*Occurred after trial completion; **physician reported newly diagnosed diabetes

Ridker P *et al. N Eng J Med* 2008;**359**: 2195-2207

Statins and risk of diabetes: 13 statins trials, 91.140 pts→ 4278 new diabetes pts



Sattar N et al : Lancet 2010; 375: 735-742

Statins and risk of diabetes: 13 statins trials, 91.140 pts→ 4278 new diabetes pts

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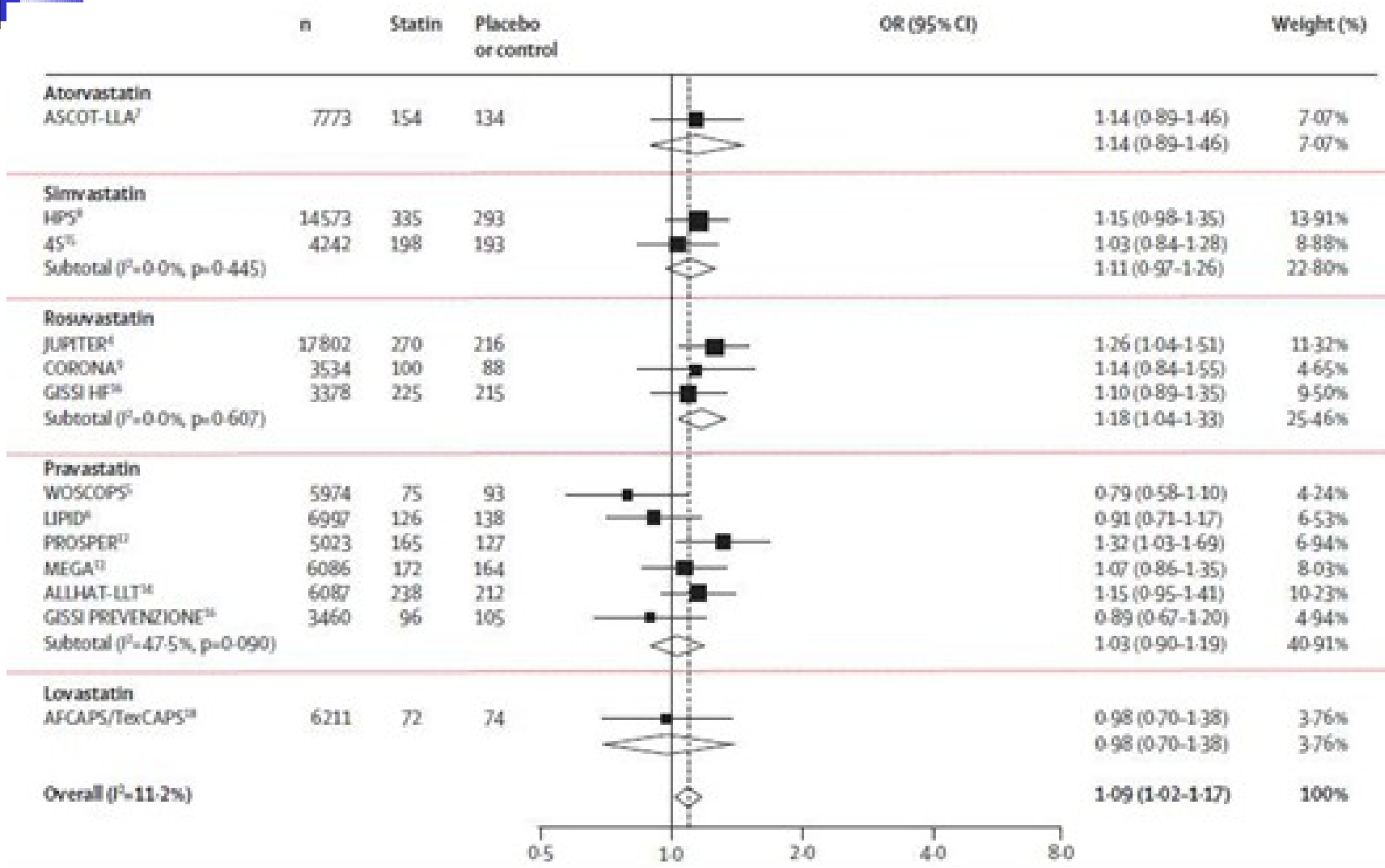


L'insorgenza di nuovi casi di diabete è un effetto di classe della terapia con statine già dimostrato nello studio Lancet (2010;375:735– 42)

studio che dimostra come il trattamento di 255 pazienti con 4 diverse statine (Atorva, Simva, Rosuva, Prava e Lova) per 4 anni determina l'insorgenza di un solo nuovo caso di diabete mellito conportando

"risparmio di 9 casi di patologie o decessi sugli stessi 255 soggetti trattati".

Statina	***N di pazienti***	***Odds ratio***	***95% CI***
Atorvastatina	7.773	1,14	0,89-1,46
Simvastatina	18.815	1,11	0,97-1,26
Rosuvastatina	24.714	1,18	1,04-1,33
Pravastatina	33.627	1,03	0,90-1,19
Lovastatina	6.211	0,98	0,70-1,38
Molecole lipofile *(atorvastatina, simvastatina, lovastatina)*		*1,10*	*0,99-1,22*
Molecole idrofile *(rosuvastatina, pravastatina)*		*1,08*	*0,98-1,20*
Totale	**91.140**	**1,09**	**1,02-1,17**

Higher incidence of physician-reported diabetes mellitus in women on Rosuvastatin

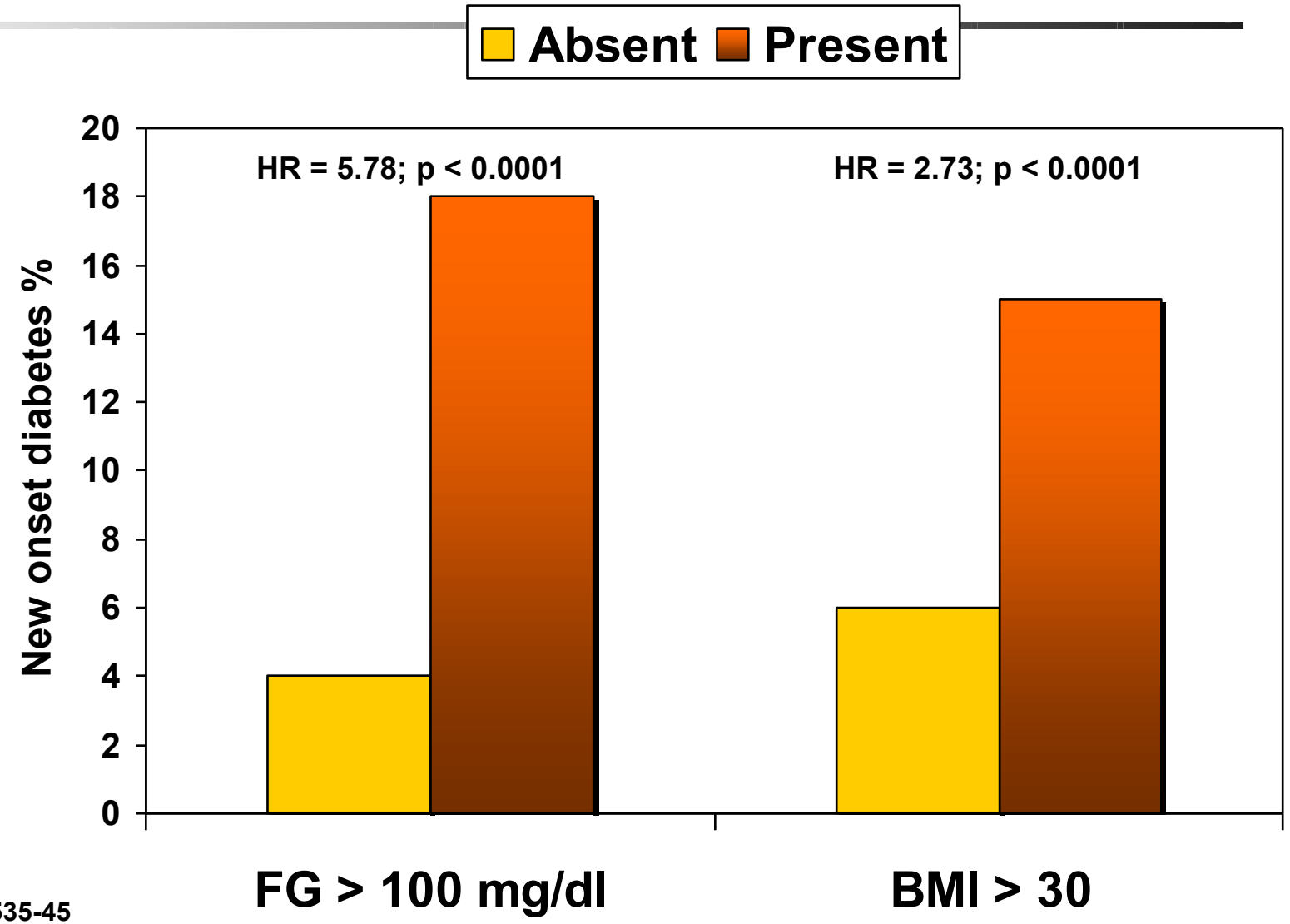
	Women			Men		
	Rosuvastatin (n=3426)	Placebo (n=3375)	*P*	Rosuvastatin (n=5475)	Placebo (n=5526)	*P*
Monitored adverse events, n						
Any serious adverse event						
Muscular weakness, stiffness, or pain						
Myopathy						
Rhabdomyolysis						
Newly diagnosed cancer						
Death resulting from cancer						
Gastrointestinal disorder						
Renal disorder						
Bleeding						
Hepatic disorder						
Laboratory values						
Creatinine, >100% increase from baseline, n						
Glomerular filtration rate at 12 mo, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$						
Alanine aminotransferase >3× ULN on consecutive visits, n						
HbA_{1c} at 24 mo, %	5.9 (5.7–6.2)	5.9 (5.6–6.1)	<0.0001	5.9 (5.6–6.1)	5.8 (5.6–6.0)	<0.0001
Glucose at 24 mo, mg/dL	96 (89–104)	95 (88–104)	0.37	99 (92–107)	99 (91–108)	0.18
Other events						
Newly diagnosed diabetes (physician reported), n	108 (1.5)	71 (1.0)	0.008	162 (1.4)	145 (1.2)	0.29
Hemorrhagic stroke, n	3 (0.04)	3 (0.04)	0.99	3 (0.02)	6 (0.05)	0.32

♀ 1.53 vs 1.03 x 100 pts/y ;
HR = 1.49 (CI 1.11 to 2.01)
p = 0.008

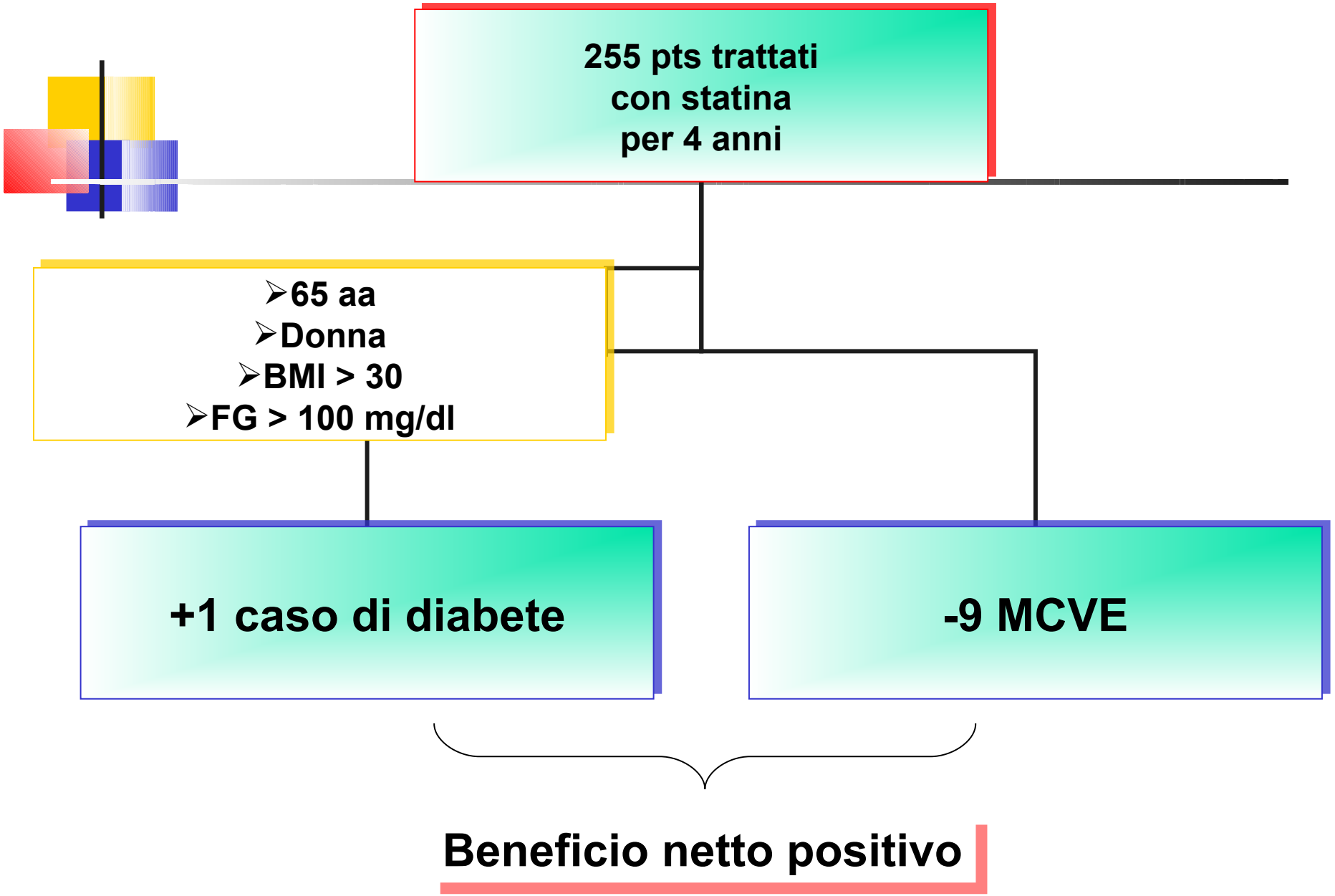
♂ 1.36 vs 1.20 x 100 pts/y ;
HR = 1.14 (CI 0.91 to 1.43)
p = 0.24

S Mora . Circulation 2010; 121: 1069-1077

TNT : +10% IDEAL : + 19% SPARCL : +37%



JACC 2011 ; 57: 1535-45



JACC 2011 ; 57: 1535-45

Meta-Analysis of Impact of Different Types and Doses of Statins on New-Onset Diabetes Mellitus

Eliano Pio Navarese, MD, PhD[a,*], Antonino Buffon, MD[d], Felicita Andreotti, MD, PhD[d], Marek Kozinski, MD, PhD[a], Nicky Welton, PhD[f], Tomasz Fabiszak, MD[a], Salvatore Caputo, MD[e], Grzegorz Grzesk, MD, PhD[a,b], Aldona Kubica, PhD[c], Iwona Swiatkiewicz, MD, PhD[a], Adam Sukiennik, MD, PhD[a], Malte Kelm, MD[g], Stefano De Servi, MD[h], and Jacek Kubica, MD, PhD[a]

In conclusion, different types and doses of statins show different potential to increase the incidence of DM. (Am J Cardiol 2013;111:1123–1130)

Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial

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Findings Trial participants with one or more major diabetes risk factor (n=11 508) were at higher risk of developing diabetes than were those without a major risk factor (n=6095). In individuals with one or more risk factors, statin allocation was associated with a 39% reduction in the primary endpoint (hazard ratio [HR] 0·61, 95% CI 0·47–0·79, p=0·0001), a 36% reduction in venous thromboembolism (0·64, 0·39–1·06, p=0·08), a 17% reduction in total mortality (0·83, 0·64–1·07, p=0·15), and a 28% increase in diabetes (1·28, 1·07–1·54, p=0·01). Thus, for those with diabetes risk factors, a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed. For trial participants with no major diabetes risk factors, statin allocation was associated with a 52% reduction in the primary endpoint (HR 0·48, 95% CI 0·33–0·68, p=0·0001), a 53% reduction in venous thromboembolism (0·47, 0·21–1·03, p=0·05), a 22% reduction in total mortality (0·78, 0·59–1·03, p=0·08), and no increase in diabetes (0·99, 0·45–2·21, p=0·99). For such individuals, a total of 86 vascular events or deaths were avoided with no new cases of diabetes diagnosed. In analysis limited to the 486 participants who developed diabetes during follow-up (270 on rosuvastatin *vs* 216 on placebo; HR 1·25, 95% CI 1·05–1·49, p=0·01), the point estimate of cardiovascular risk reduction associated with statin therapy (HR 0·63, 95% CI 0·25–1·60) was consistent with that for the trial as a whole (0·56, 0·46–0·69). By comparison with placebo, statins accelerated the average time to diagnosis of diabetes by 5·4 weeks (84·3 [SD 47·8] weeks on rosuvastatin *vs* 89·7 [50·4] weeks on placebo).

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Cardiovascular Event Reduction Versus New-Onset Diabetes During Atorvastatin Therapy

Effect of Baseline Risk Factors for Diabetes

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Results Among 8,825 patients with 0 to 1 of the aforementioned NOD risk factors at baseline, NOD developed in 142 of 4,407 patients in the atorvastatin 80 mg group and in 148 of 4,418 in the atorvastatin 10 mg and simvastatin 20 to 40 mg groups (3.22% vs. 3.35%; hazard ratio [HR]: 0.97; 95% confidence intervals [CI]: 0.77 to 1.22). Among the remaining 6,231 patients with 2 to 4 NOD risk factors, NOD developed in 448 of 3,128 in the atorvastatin 80 mg group and in 368 of 3,103 in the lower-dose groups (14.3% vs. 11.9%; HR: 1.24; 95% CI: 1.08 to 1.42; p = 0.0027). The number of CV events was significantly reduced with atorvastatin 80 mg in both NOD risk groups.

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CONCLUSIONI

- **Nelle popolazioni a basso rischio CV, valutare la possibilita' di NOD (diabete di nuova insorgenza).**

- **In tutti gli altri casi il rapporto tra rischio NOD e rischio CV è chiaramente spostato a favore di un trattamento con statine.**

- **Non sembrano esistere classifiche di statine a maggiore o minore rischio di NOD, ma POPOLAZIONI con differenti rischi di sviluppare diabete.**