Necessita un trattamento ipocolesterolemizzante il grande anziano?

Prof. Alberto Corsini

Università degli Studi di Milano

Young-old (65-74 years)

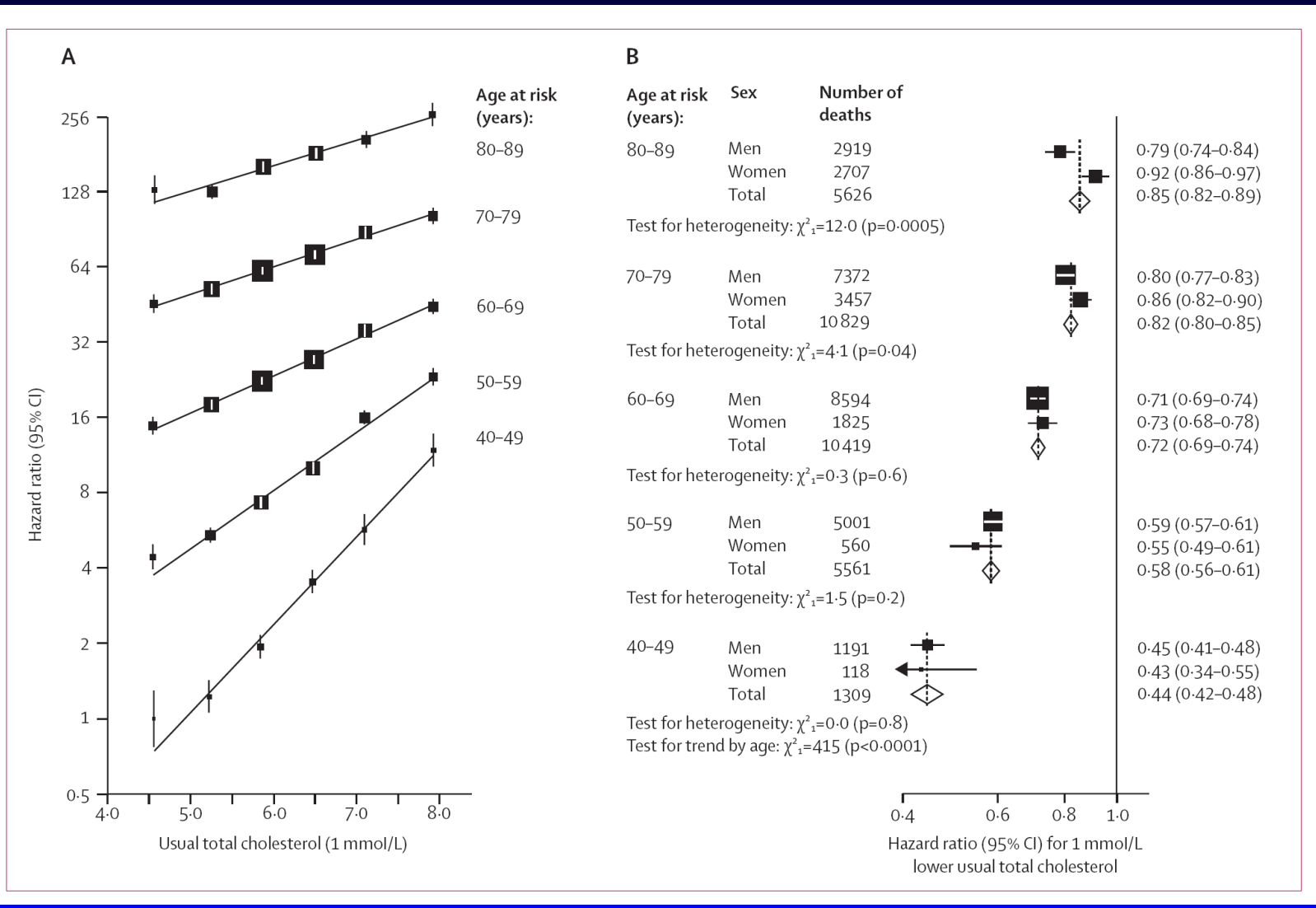
Middle-old (74-84 years)

Old-old (greater than 85 years)

Outline of the presentation

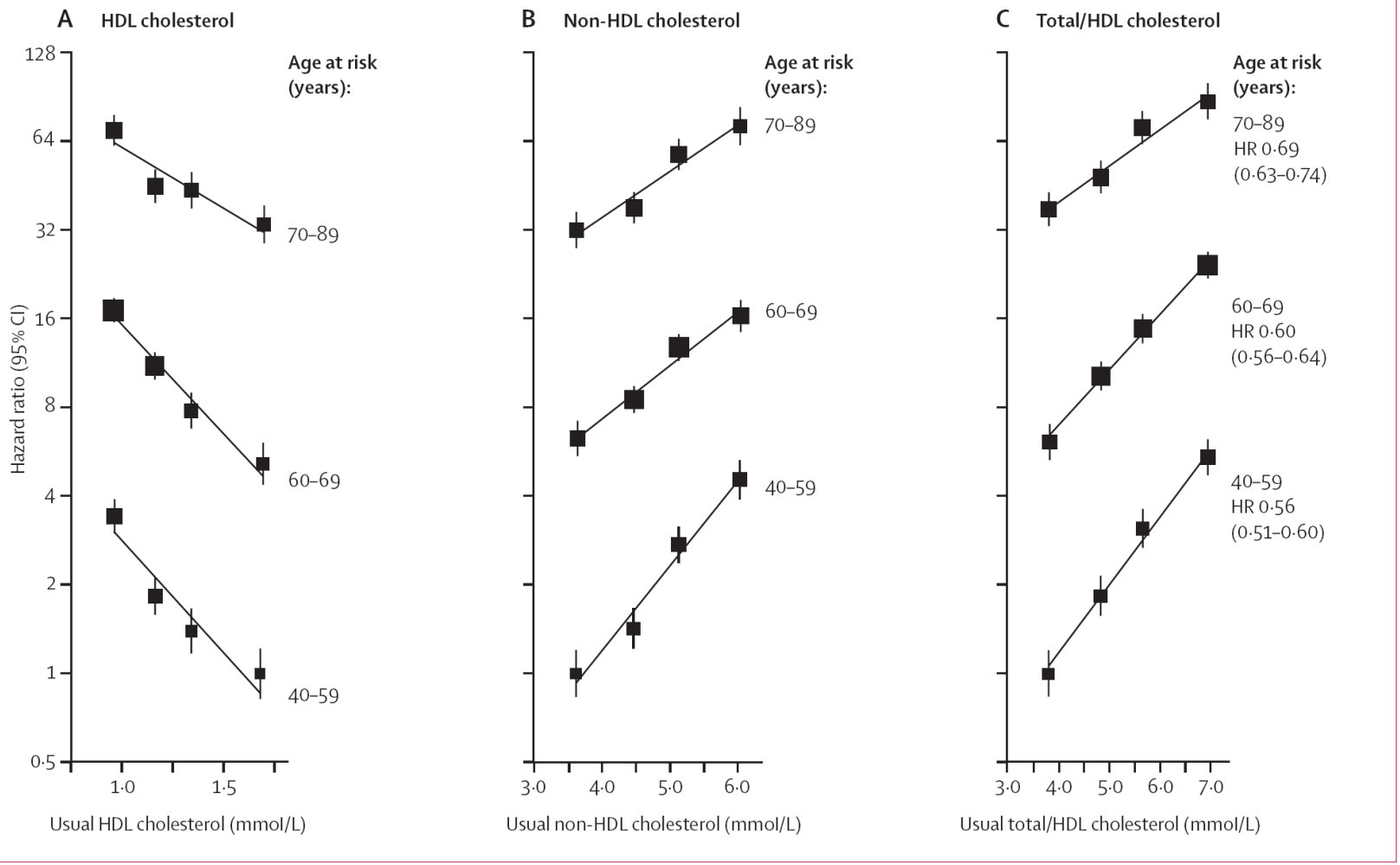
- **Epidemiologia**
- Statine e anziano: evidenze cliniche
- Statine e anziano: raccomandazioni

IHD mortality (33 744 deaths) versus total cholesterol



Prospective Studies Collaboration Lancet 2007; 370: 1829–39

IHD mortality (3020 deaths) versus (A) HDL cholesterol; (B) non-HDL cholesterol; and (C) total/HDL cholesterol



Prospective Studies Collaboration Lancet 2007; 370: 1829–39

Annals of Internal Medicine | ARTICLE

Nonoptimal Lipids Commonly Present in Young Adults and Coronary Calcium Later in Life: The CARDIA (Coronary Artery Risk Development in Young Adults) Study

Mark J. Pletcher, MD, MPH; Kirsten Bibbins-Domingo, PhD, MD; Kiang Liu, PhD; Steve Sidney, MD, MPH; Feng Lin, MS; Eric Vittinghoff, PhD; and Stephen B. Hulley, MD, MPH

Ann Intern Med. 2010;153:137-146

Participants: 3258 participants from the 5115 black and white men and women recruited at age 18 to 30 years in 1985 to 1986 for the CARDIA (Coronary Artery Risk Development in Young Adults) study.

Measurements: Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, triglycerides, and coronary calcium. Time-averaged cumulative exposures to lipids between age 20 and 35 years were estimated by using repeated serum lipid measurements over 20 years in the CARDIA study; these measurements were then related to coronary calcium scores assessed later in life (45 years [SD, 4]).

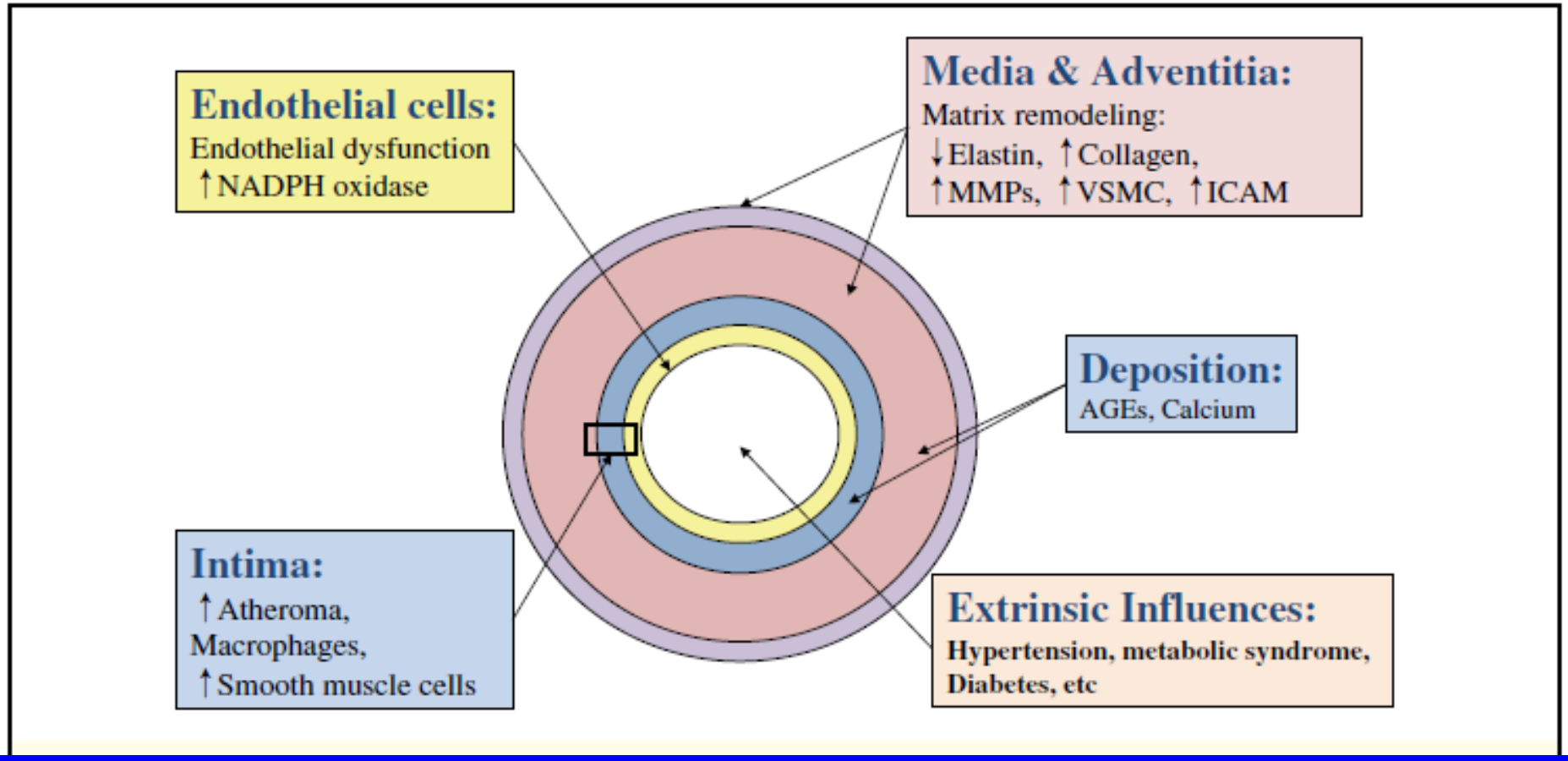
Ann Intern Med. 2010;153:137-146

Table 2. **Average Exposure to Lipids Before Age 35 Years and Coronary Calcium***

Average Exposure to Lipids Between Age 20 and 35 y	Participants, *n*	Proportion With Coronary Calcium	OR (95% CI) for Participants With Coronary Calcium				Adjusted Prevalence, %†
			Unadjusted	*P* Value‡	Adjusted§	*P* Value‡	
Overall	3258	17	–	NA	–	NA	17
Lipid exposure category‖							
Normal	434	7	1.0 (reference)	<0.001	1.0 (reference)	0.031	7
Borderline	2443	17	2.6 (1.8–3.9)		1.6 (1.0–2.5)		11
Abnormal	381	30	5.7 (3.7–8.7)		1.9 (1.1–3.3)		13
Time-averaged LDL cholesterol level							
<1.81 mmol/L (<70 mg/dL)	116	8	1.0 (reference)	<0.001	1.0 (reference)	<0.001	8
1.81–2.56 mmol/L (70–99 mg/dL)	1030	10	1.3 (0.7–2.7)		1.5 (0.7–3.3)		12
2.59–3.34 mmol/L (100–129 mg/dL)	1412	17	2.4 (1.2–4.9)		2.4 (1.1–5.3)		17
3.37–4.12 mmol/L (130–159 mg/dL)	577	26	4.2 (2.1–8.6)		3.3 (1.3–7.8)		22
≥4.14 mmol/L (≥160 mg/dL)	123	44	9.3 (4.3–20)		5.6 (2.0–16)		33
Time-averaged HDL cholesterol level							
<1.04 mmol/L (<40 mg/dL)	273	25	2.6 (1.7–4.1)	<0.001	1.4 (0.6–3.0)	0.25	24
1.04–1.27 mmol/L (40–49 mg/dL)	997	24	2.5 (1.7–3.6)		1.5 (0.8–2.9)		24
1.30–1.53 mmol/L (50–59 mg/dL)	1101	14	1.3 (0.9–1.9)		1.1 (0.6–1.9)		14
1.55–1.79 mmol/L (60–69 mg/dL)	591	10	0.9 (0.5–1.3)		1.0 (0.6–1.6)		10
≥1.81 mmol/L (≥70 mg/dL)	296	11	1.0 (reference)		1.0 (reference)		11
Time-averaged triglyceride level¶							
<0.57 mmol/L (<50 mg/dL)	592	10	1.0 (reference)	<0.001	1.0 (reference)	0.48	10
0.57–1.12 mmol/L (50–99 mg/dL)	2230	17	1.9 (1.4–2.5)		1.1 (0.8–1.6)		11
1.13–1.68 mmol/L (100–149 mg/dL)	354	28	3.6 (2.5–5.2)		1.2 (0.7–2.0)		12
1.70–2.25 mmol/L (150–199 mg/dL)	58	36	5.3 (2.9–10)		1.4 (0.6–3.1)		13
≥2.26 mmol/L (≥200 mg/dL)	24	38	5.6 (2.4–13)		1.4 (0.5–4.3)		13

Ann Intern Med. 2010;153:137-146

Causes of arterial aging



Lee HY and Oh BH *Circ J* 2010; **74:** 2257 – 2262

Outline of the presentation

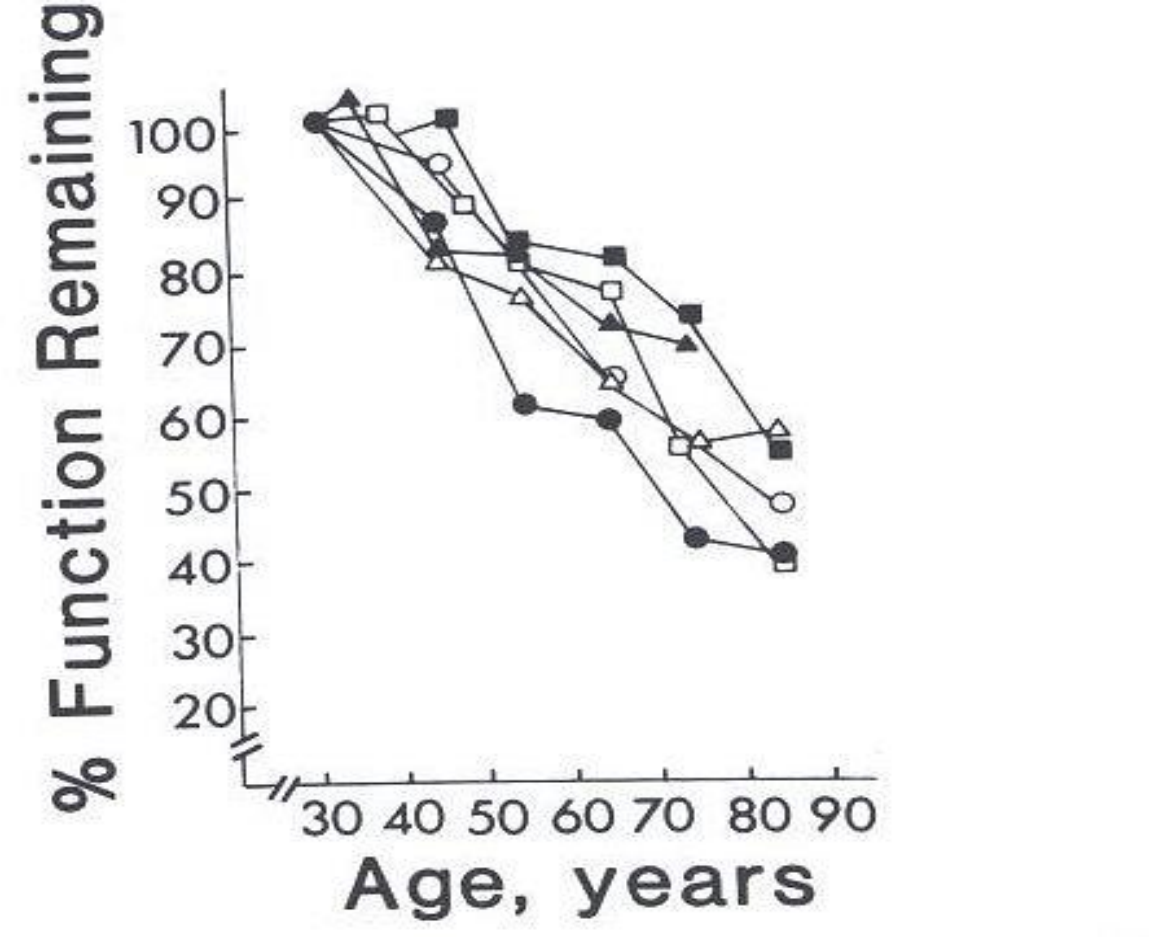
- **Epidemiologia**
- **Statine e anziano: evidenze cliniche**
- Statine e anziano: raccomandazioni

Statine e Anziano

- **Farmacocinetica**

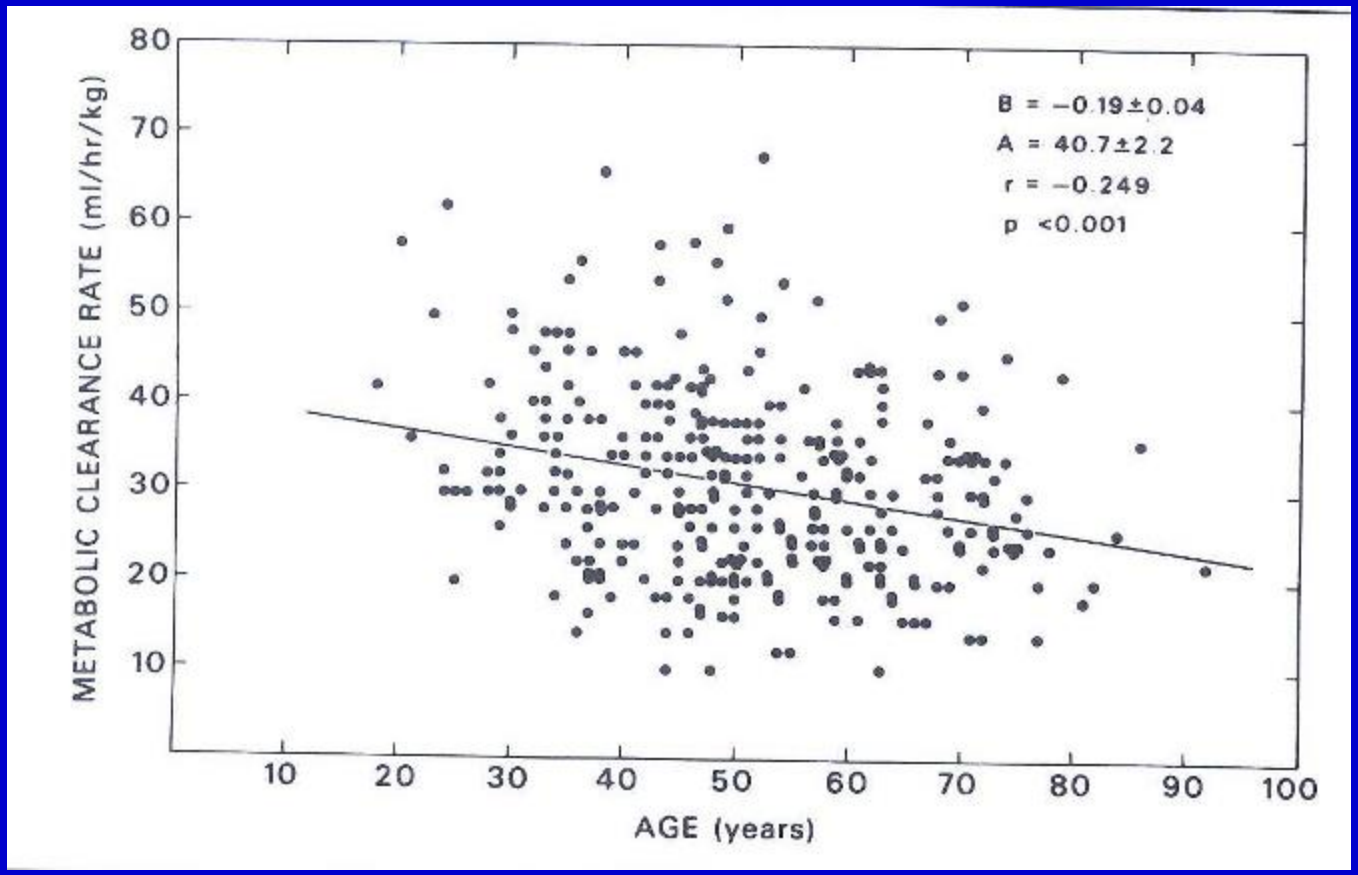
- **Effetti**
  - **sui lipidi**
  - **Non-lipidici**
- Dimostrazione di benefici a lungo termine sulla salute e sulla sicurezza

Percentuale dei parametri fisiologici riscontrabili, in media, in relazione all'età



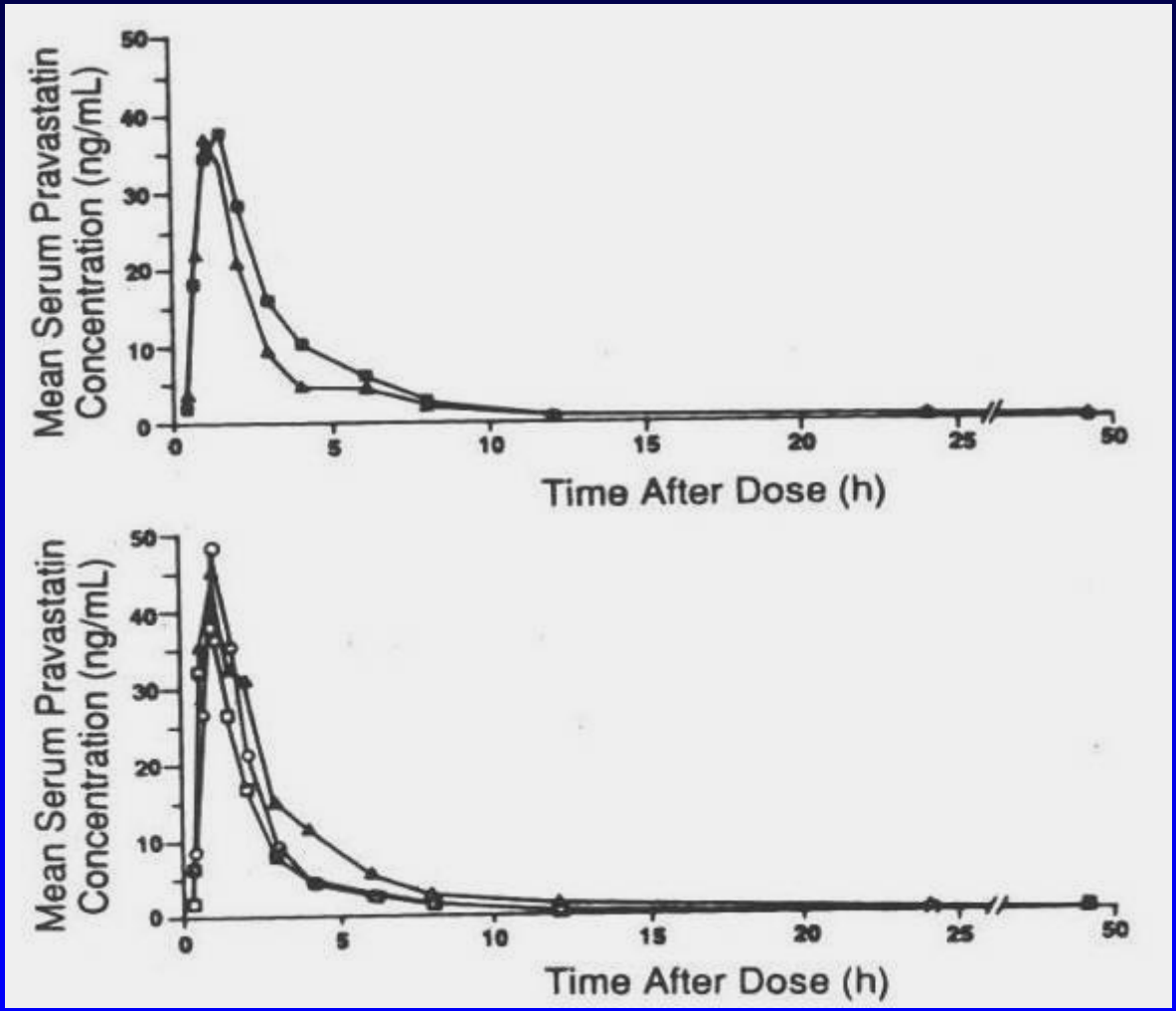
maximal breathing capacity (●); renal plasma flow by para-amino hippurate clearance (□); renal plasma flow by diodrast clearance (○); vital capacity (△); glomerular filtration rate by inulin clearance (■); cardiac index (▲).

Clearance (antipyrine) in funzione dell'età in 307 volontari sani (uomini 18/92 anni)



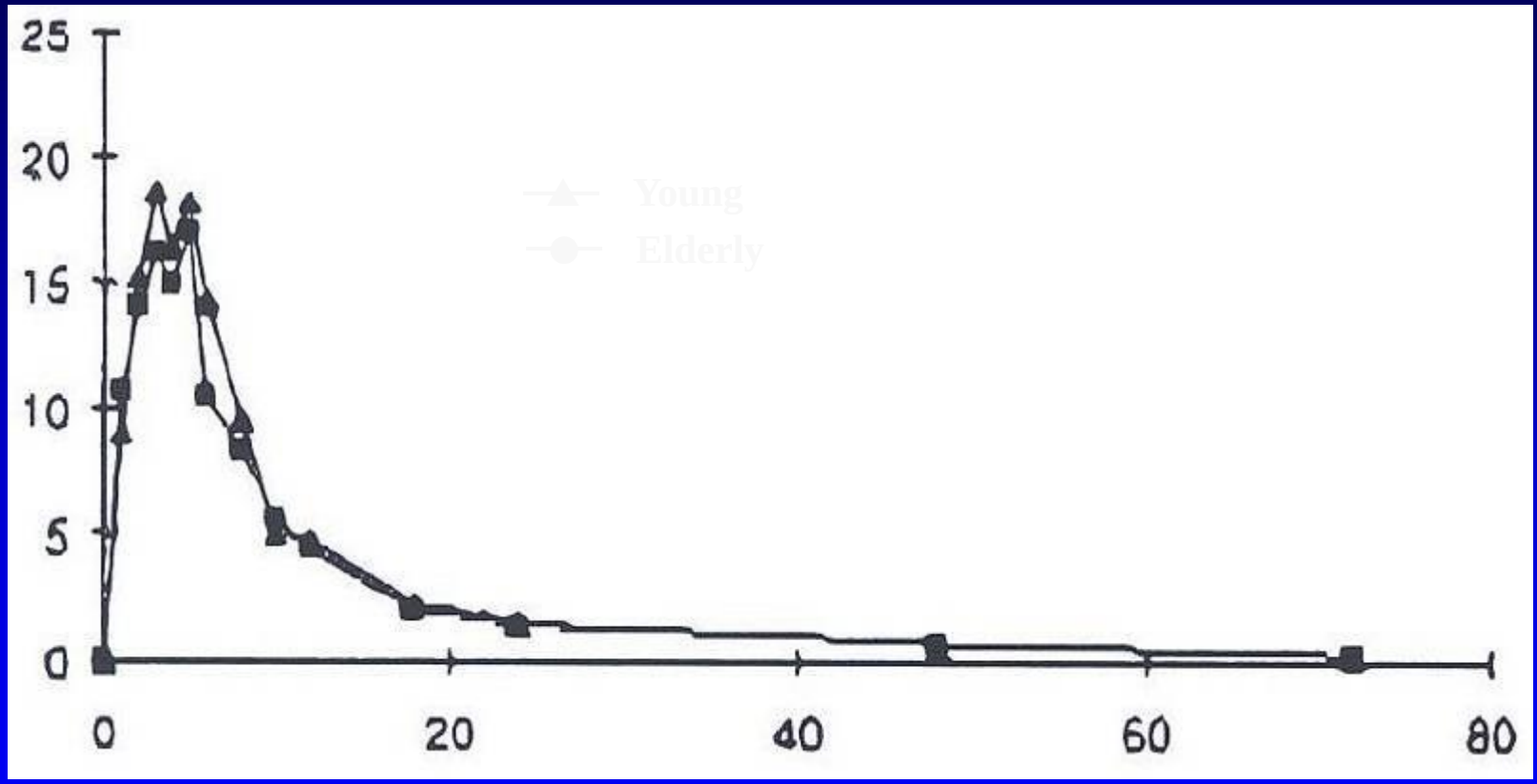
Mayersohn MB, 1994

Mean serum concentration of pravastatin 0-48 hours after a single 20-mg dose in elderly and young men (top), and in elderly women



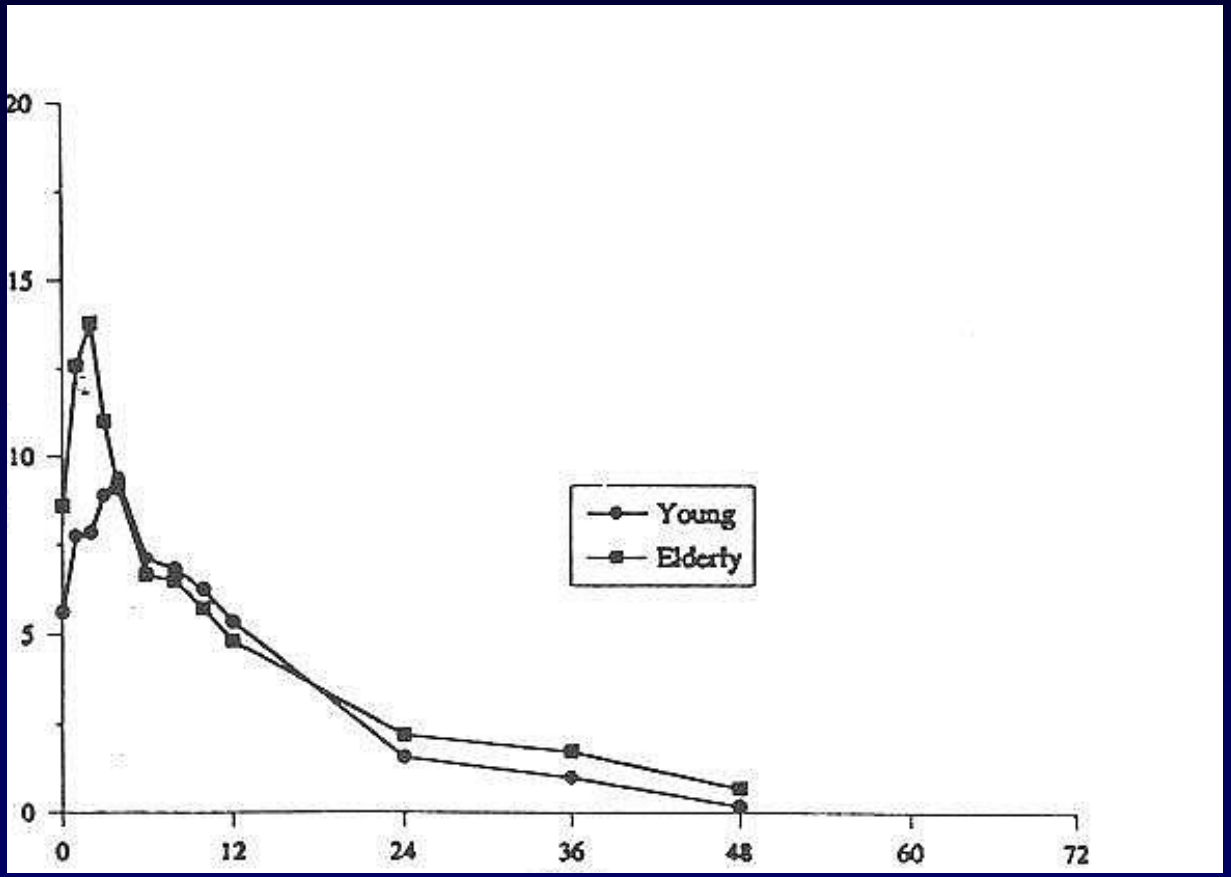
Henry Y. Pan et al., The Annals of Pharmacotherapy, 1993;27:1029-1033

Plasma concentrations of rosuvastatin (40mg) by age



Martin PD et al., Journal of Clinical Pharmacology, 2002;42:1116-1121

Concentration-time profiles of atorvastatin in healthy young and elderly participants after 20-mg atorvastatin



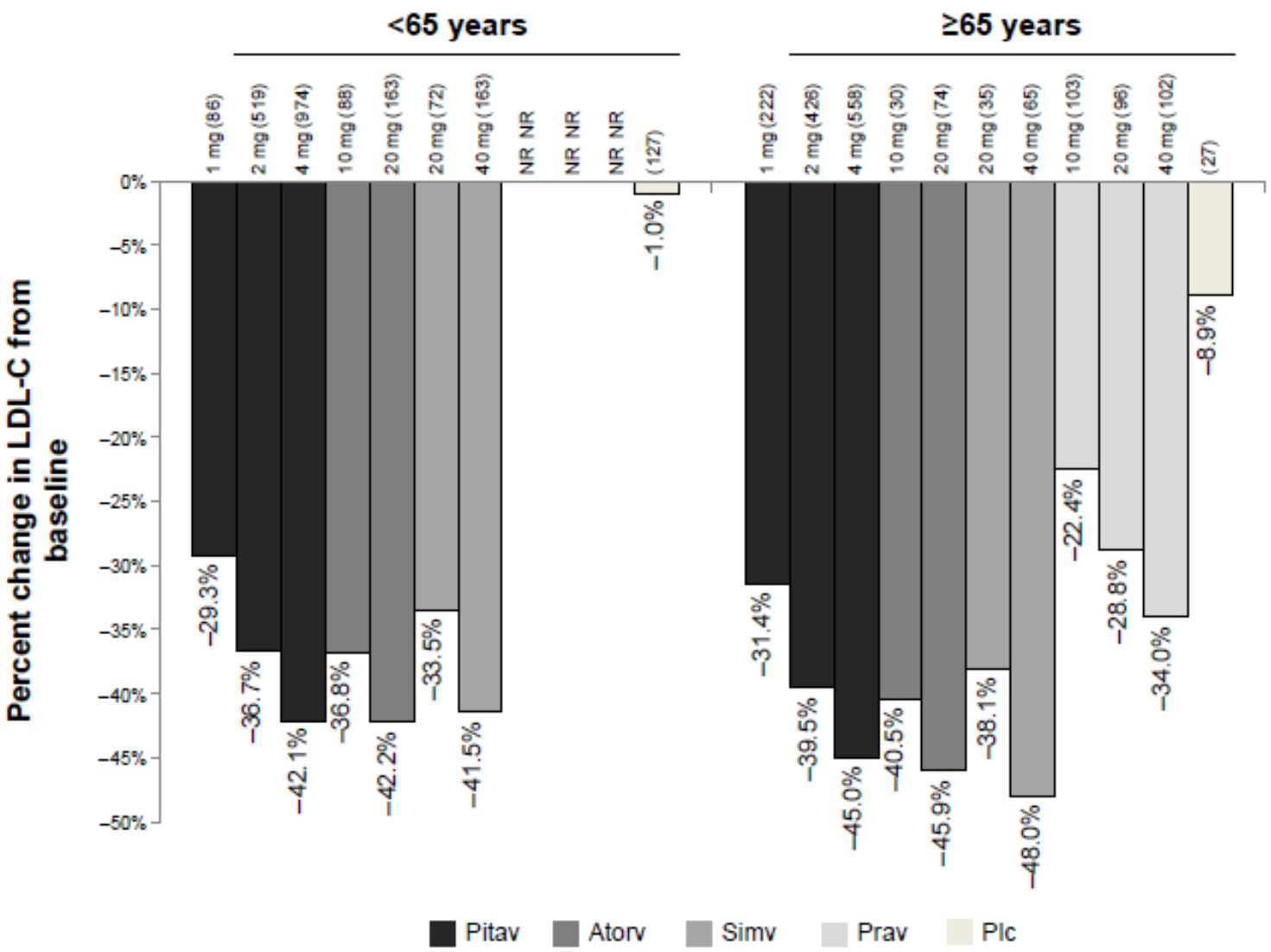
Donald M. Gibson et al., J Clin Pharmacol 1996;36:242-246

LDL Cholesterol: Adjusted Mean Percent Change From Baseline Characteristics Showing Treatment Group Interactions

	Adjusted mean percent change from baseline ±SEM: lovastatin (mg/day)				
Patient characteristic: (probability value)	**Placebo [% (SEM)]**	**20 qpm [% (SEM)]**	**40 qpm [% (SEM)]**	**20 bid [% (SEM)]**	**40 bid [% (SEM)]**
Sex/age intercation (*p*=0.019, df=4)					
Men					
45 years old	+0.3 (0.5)	-22.8 (0.5)	-29.0 (0.5)	-33.2 (0.5)	-39.3 (0.5)
65 years old	-0.1 (0.5)	-25.2 (0.5)	-31.1 (0.5)	-34.0 (0.5)	-40.9 (0.5)
Women					
45 years old	-0.3 (0.9)	-22.0 (0.8)	-28.8 (0.9)	-30.7 (0.9)	-38.4 (0.8)
65 years old	+0.6 (0.6)	-25.5 (0.6)	-32.7 (0.5)	-36.1 (0.6)	-42.8 (0.6)

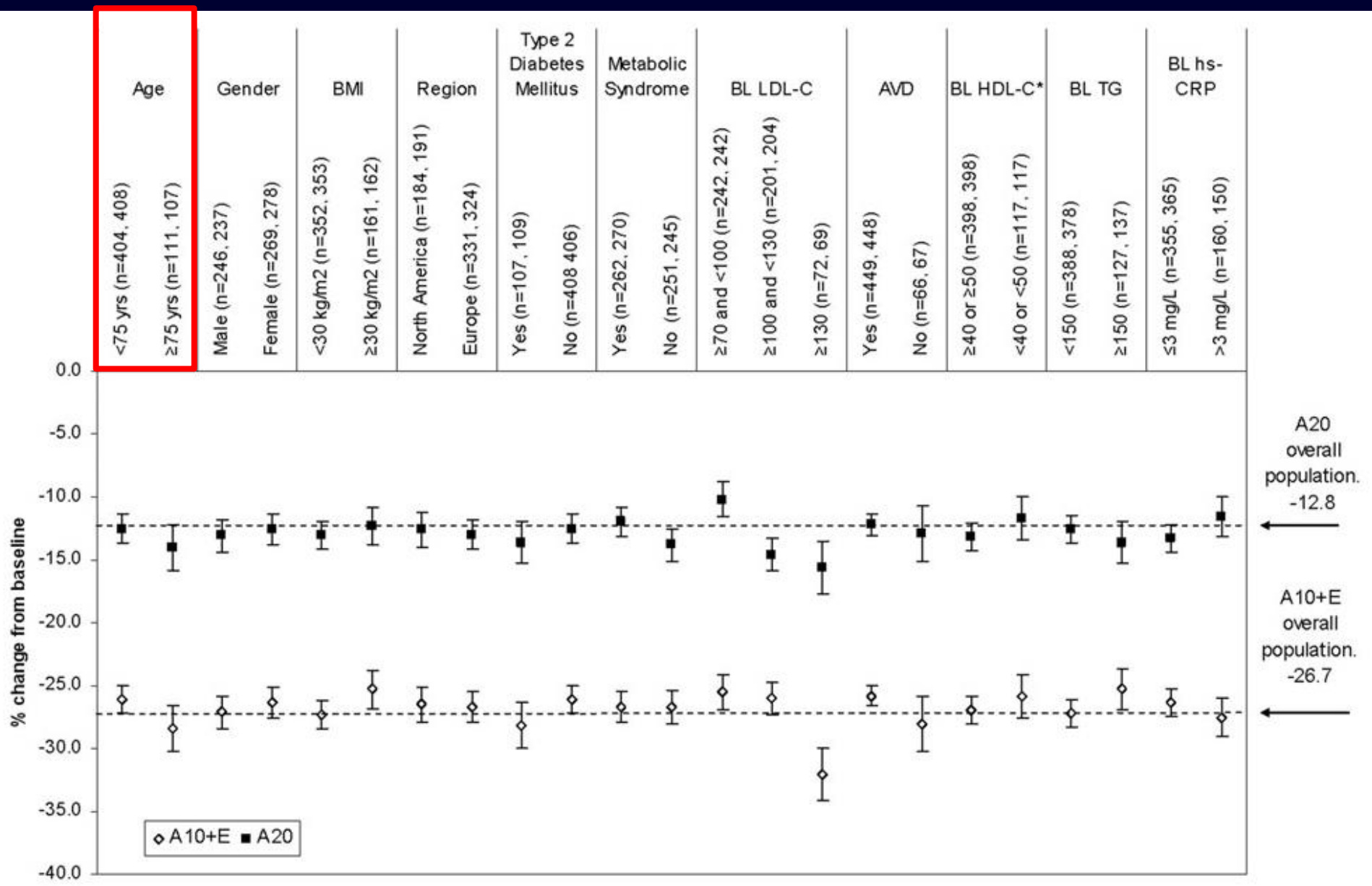
Charles L. Shear et al., Circulation 1992;85:1293-1303

Mean percent LDL-C lowering ability of statins by age



Chamberlin W and L Baker Clinical Interventions in Aging 2015:10

% of change from treated baseline in LDL cholesterol



Pearson T et al. Am J Cardiol 2010;105:656–663

Findings in Older Subjects in Clinical Trials of Lipid-Modifying Drug Therapy

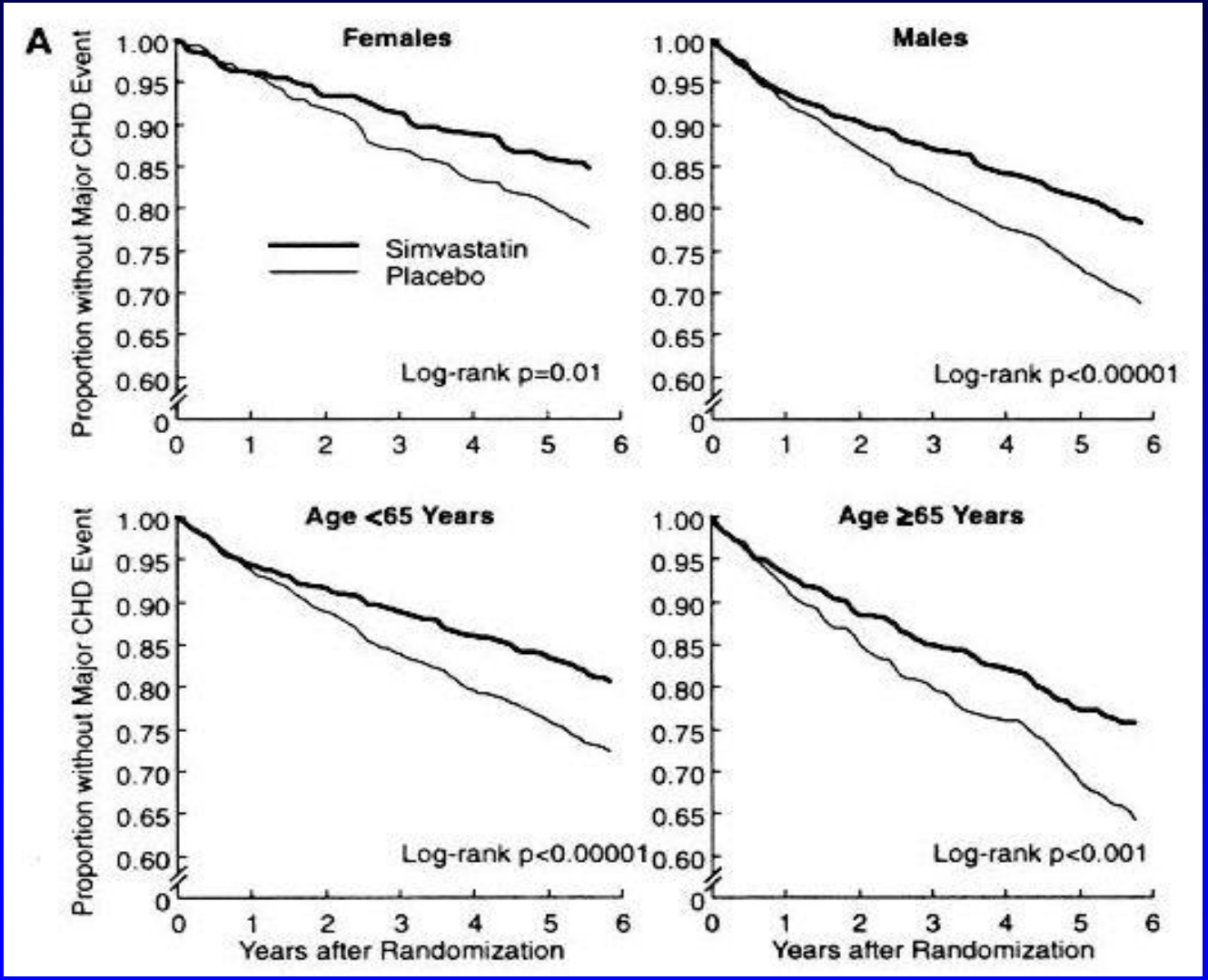
Trial (Agent)	Age at Entry	N (%)	% RRR With Drug Therapy CHD	CHD Death
Secondary prevention				
4S (simvastatin)	65-70	1021 (23)	34	43
CARE (pravastatin)	65-75	1283 (31)	32	45
LIPID (pravastatin)	65-69	2168 (24)	28	—
	70-75	1346 (15)	15	—
VA-HIT (gemfibrozil)	66-73	1266 (50)	26*	—
HPS† (simvastatin)	≥65-<70	4891 (24)	23	—
	≥70	5806 (28)	18	—
PROSPER (pravastatin)	70-82	5804 (100)	15‡	24
Primary prevention				
WOSCOPS (pravastatin)	55-64	3370 (51)	27	—
AFCAPS/TexCAPS (lovastatin)	Age above median§	3180 (48)	30	—
ASCOT-LLA (atorvastatin)	>60	6570 (64)	36	—

Note: RRR= relative risk reduction. See text for full names of trials

* RRR for combined secondary end point of CHD death, nonfatal MI, and confirmed stroke.
† The HPS enrolled many types of high-risk patients, 35% of whom had not experienced a prior coronary event.
‡ RRR for combined primary end point of CHD death, nonfatal MI, and fatal and nonfatal stroke.
§ 57M, 62F; upper limit 73.

"Rationale for control of dyslipidemia": the ILIB Lipid Handbook for Clinical Practice; Dislipidemia and Coronary Heart 3rd Edition

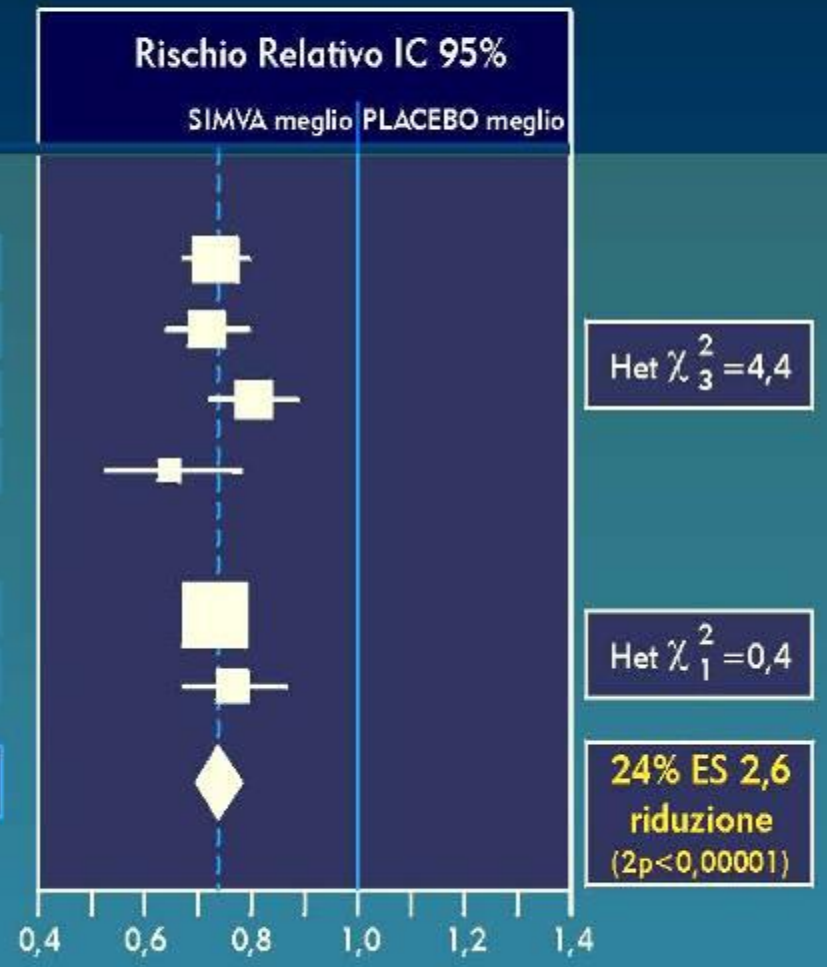
Kaplan-Meier survival curves for women, men, patients age ≥65 years of age, and patients age <65 years of age for the proportion of patients remaining free of any major coronary event



Tatu A. Miettinen et al., Circulation 1997;96:4211-4218

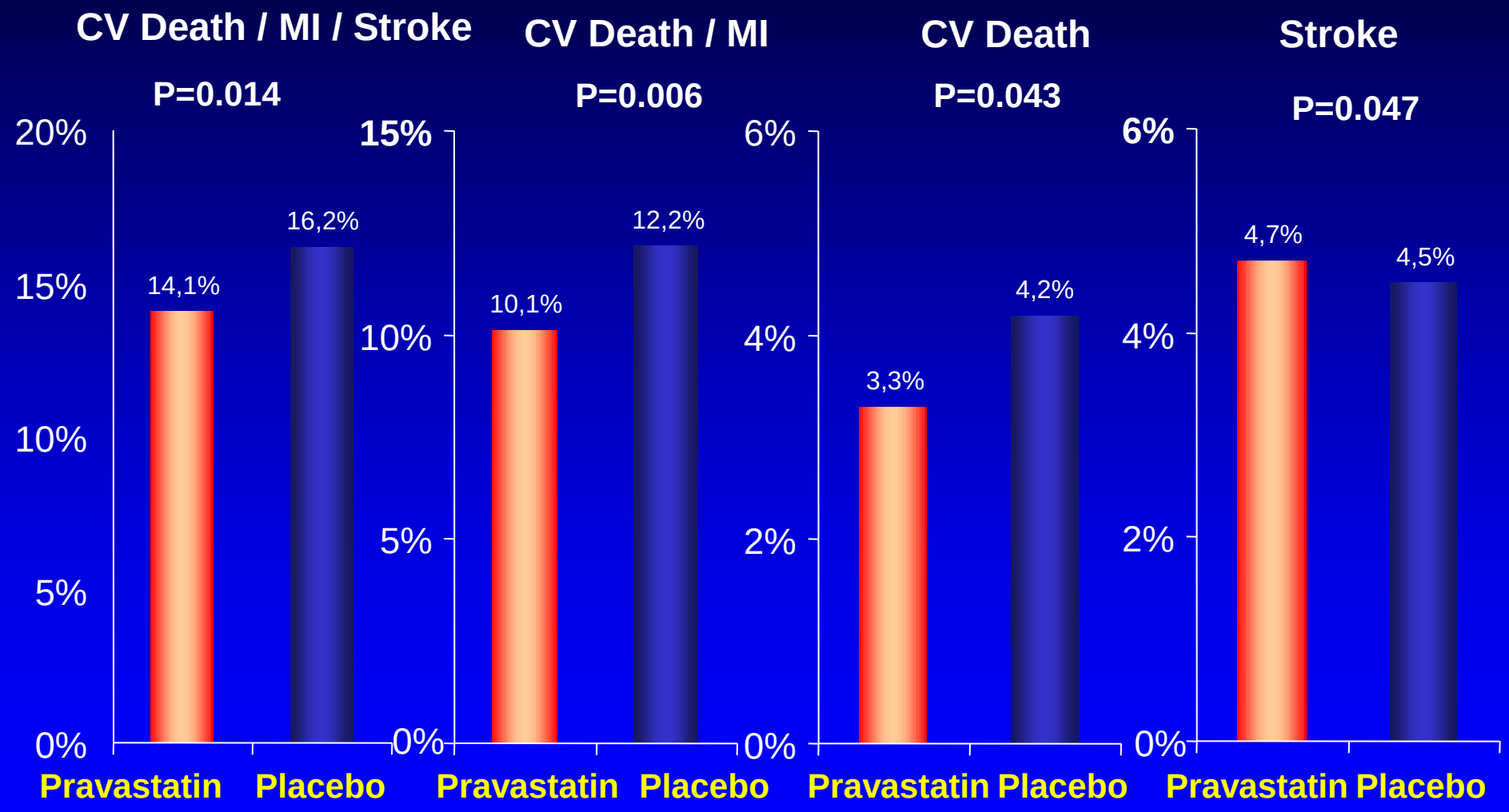
LO STUDIO HPS: EVENTI VASCOLARI PER ETA' E SESSO

Caratteristiche al Basale	Simvastatina (10.269)	Placebo (10.267)
Gruppi per età (anni)		
< 65	838	1.093
65 - 69	516	677
70 - 74	550	628
>75	138	208
Sesso		
Maschi	1.676	2.148
Femmine	366	458
Tutti i pazienti	2.042 (19,9%)	2.606 (25,4%)



Lo Studio HPS, 2001

PROSPER: Clinical Events*



* Mean follow-up = 3.2 years

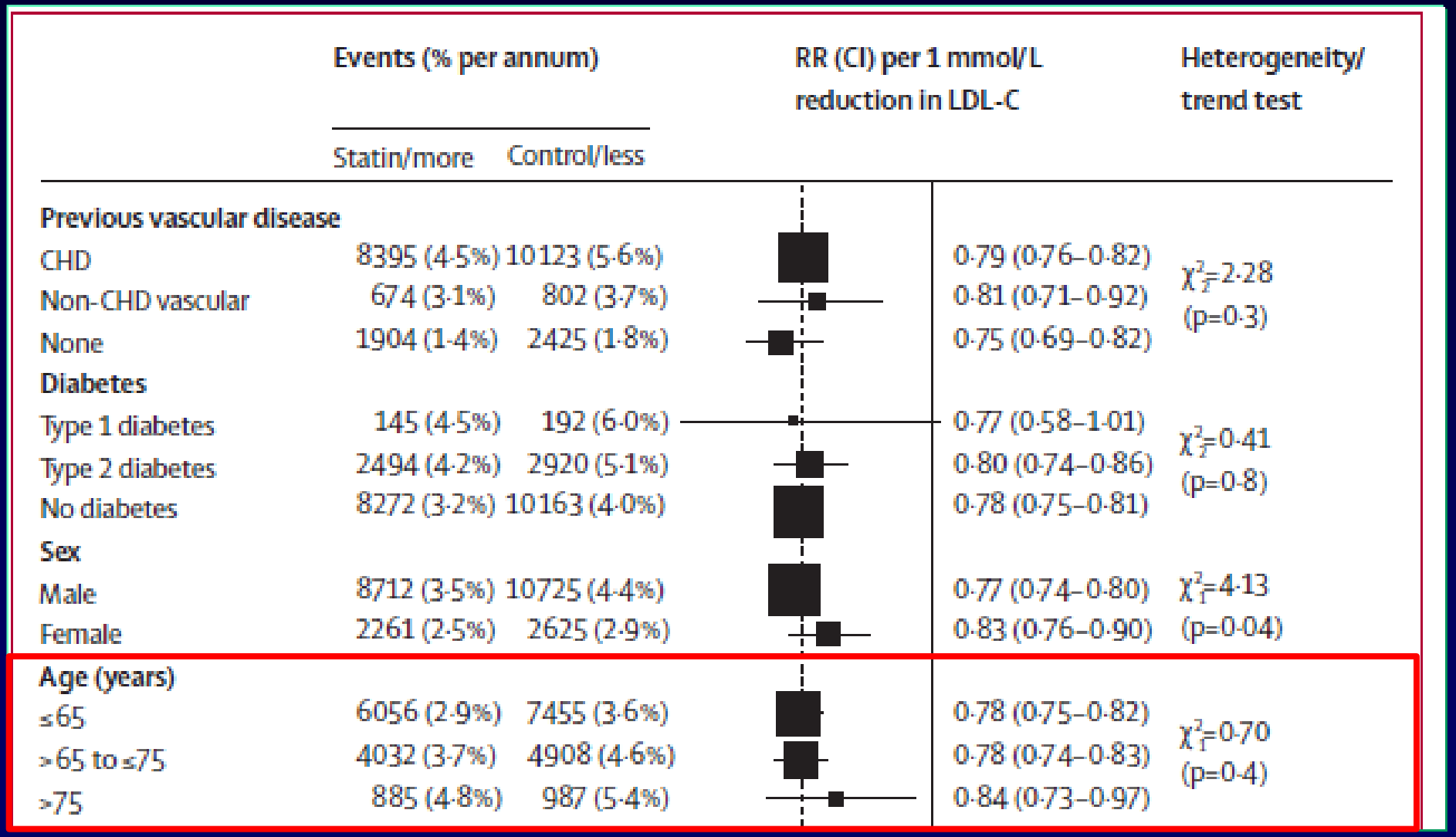
Lancet 2002; 360: 1623–30

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

Cholesterol Treatment Trialists' (CTT) Collaboration

Lancet, November 9th, 2010; 6736(10) 61545-0

Effects on major vascular events per 1·0 mmol/L reduction in LDL cholesterol, by baseline prognostic factors



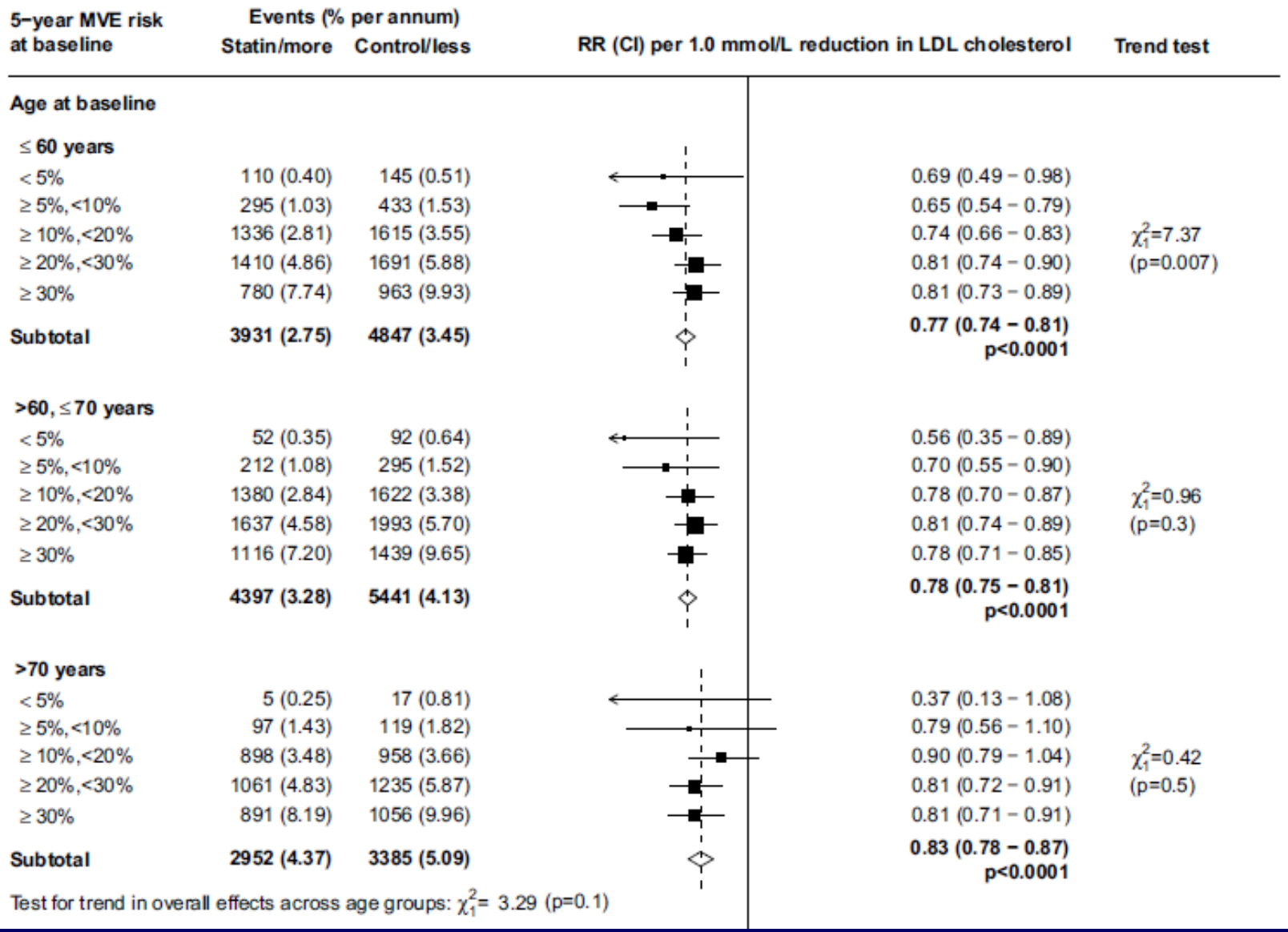
Cholesterol Treatment Trialists' (CTT) Collaboration Lancet, November 9th, 2010

The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaborators**

The Lancet May 17 2012; 673: 60367-5

Webfigure 1: Effects on major vascular events per 1.0 mmol/L reduction in LDL cholesterol at different levels of risk, by baseline age and gender



The Lancet May 17 2012; 673: 60367-5

Pharmacological Research 81 (2014) 64–73

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/yphrs

Long-term efficacy and safety of statin treatment beyond six years: A meta-analysis of randomized controlled trials with extended follow-up

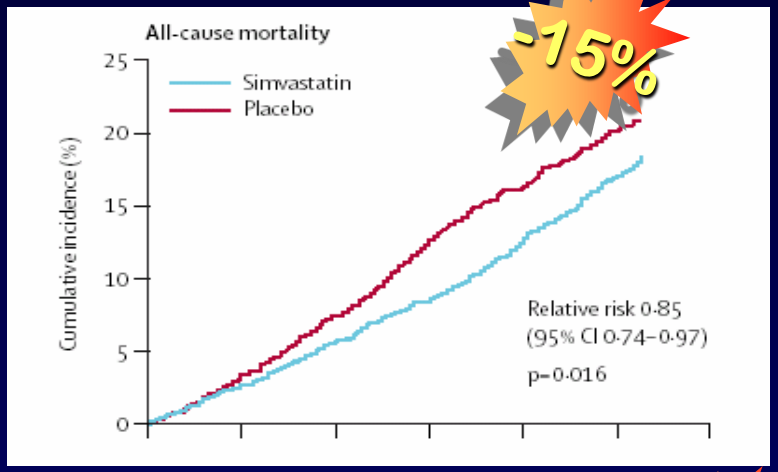
Han-lu Lv[a,1], Dong-mei Jin[b,1], Mo Liu[c,1], Ying-mei Liu[a], Jing-feng Wang[a], Deng-feng Geng[a,*]

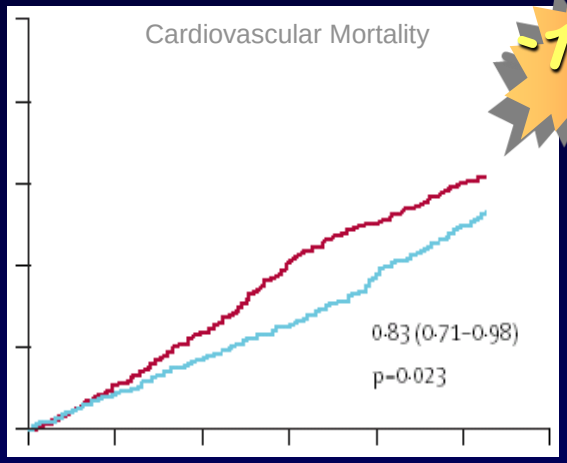
Table 4
Effect of statin treatment on deaths from cancer and incidence of cancer during the total follow-up period. Values are relative risks (95% confidence intervals).

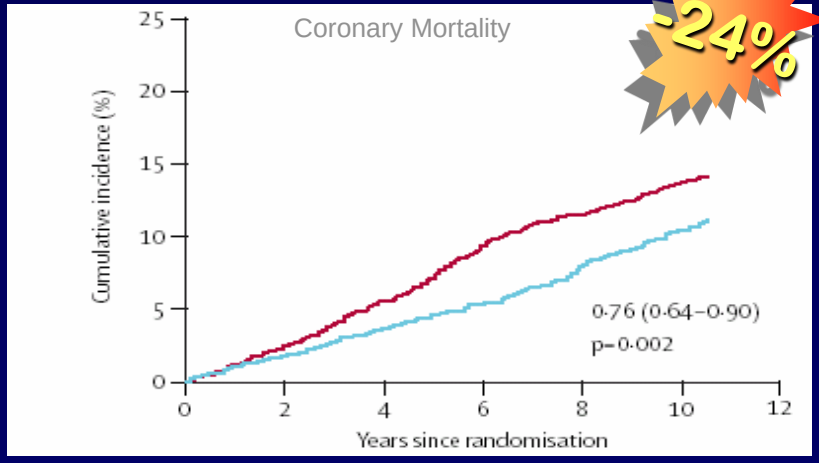
Source	Deaths from cancer	Incidence of cancer
ALERT	1.11 (0.75, 1.63)	NR
ASCOT[a]	0.94 (0.78, 1.13)	NR
WOSCOPS	1.00 (0.85, 1.18)	1.07 (0.94, 1.21)
4S	0.85 (0.64, 1.13)	0.90 (0.75, 1.08)
HPS	1.03 (0.94, 1.13)	1.00 (0.94, 1.07)
LIPID	NR	0.95 (0.84, 1.06)
All trials[b]	1.00 (0.93, 1.07)[c]	0.99 (0.95, 1.04)[c]

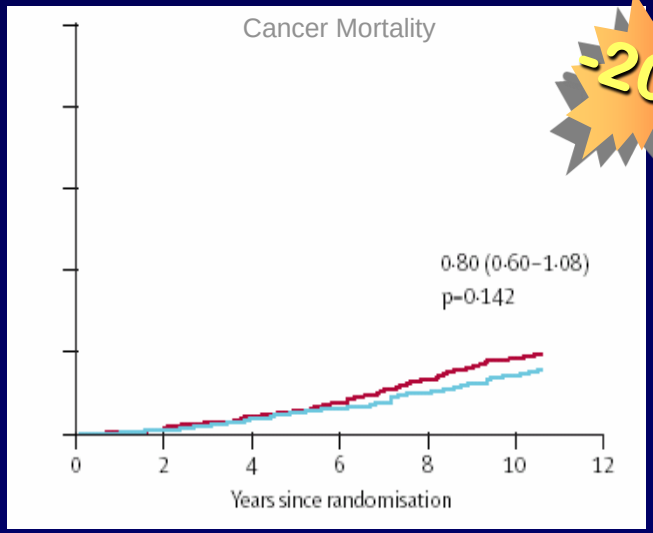
4S Study : 10-year follow-up
Clinical benefits manteined over time

The survival benefits that pts allocated to simvastatin accrued during the double-blind period of the 4S study are still persisting during the long-term follow-up (10.4 years)





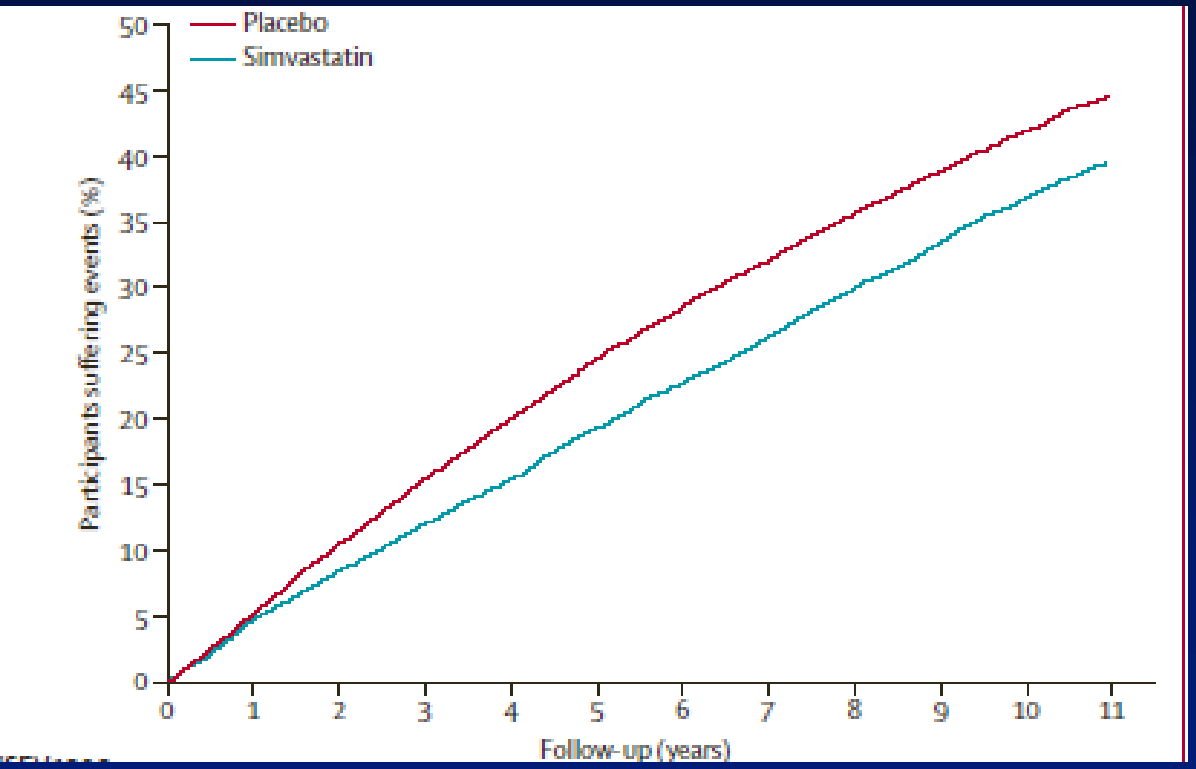




T.E.. Strandeberg et al. For the 4S Group "Mortality and Incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S)" THE LANCET 2004; 364: 771-777

Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial

*Heart Protection Study Collaborative Group**



First major vascular event during total follow-up period

Interpretation More prolonged LDL-lowering statin treatment produces larger absolute reductions in vascular events. Moreover, even after study treatment stopped in HPS, benefits persisted for at least 5 years without any evidence of emerging hazards. These findings provide further support for the prompt initiation and long-term continuation of statin treatment.

Lancet **2011; 378: 2013–20**

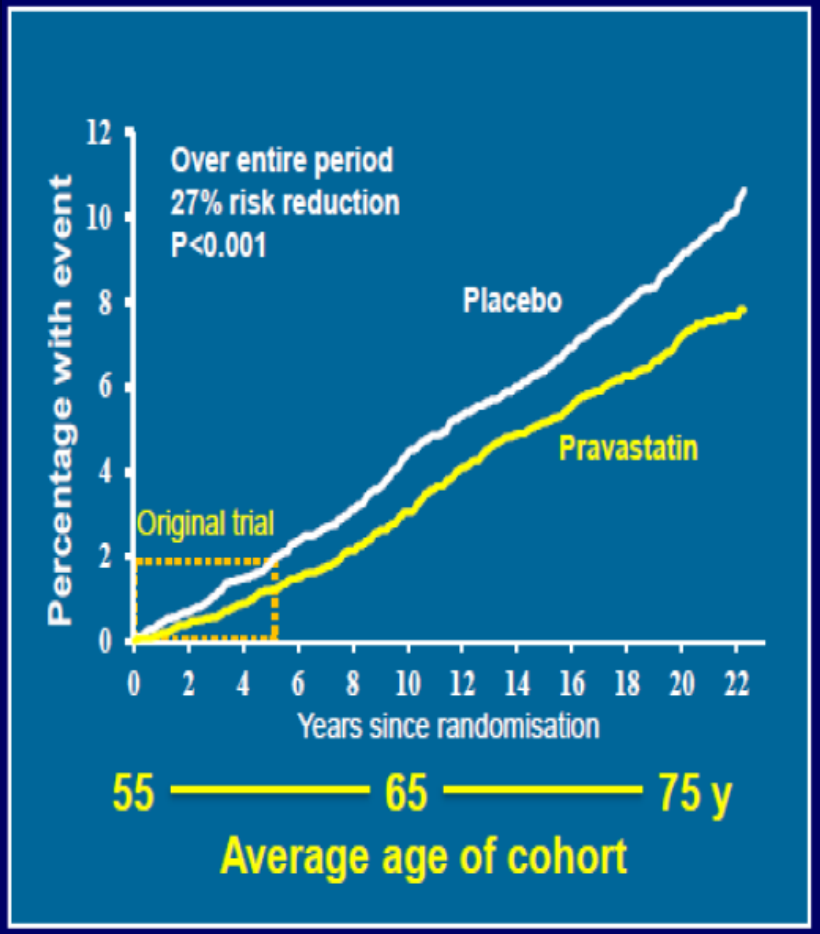
- Long-term (lifetime) clinical and economic benefits of statin-based LDL lowering

- 20 years of follow up (WOSCOPS)

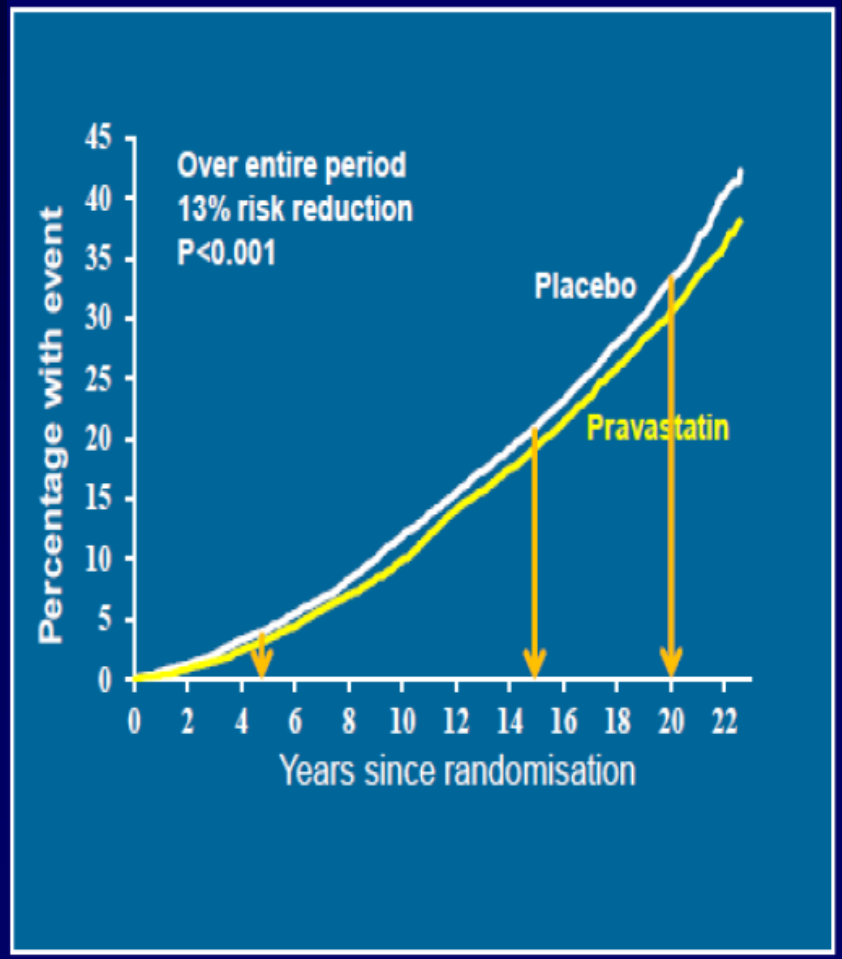
  - Chris J Packard, Ian Ford, Heather Murray, Colin McCowan
  - University of Glasgow

Long term follow up in statin studies
WOSCOPS experience

CHD mortality

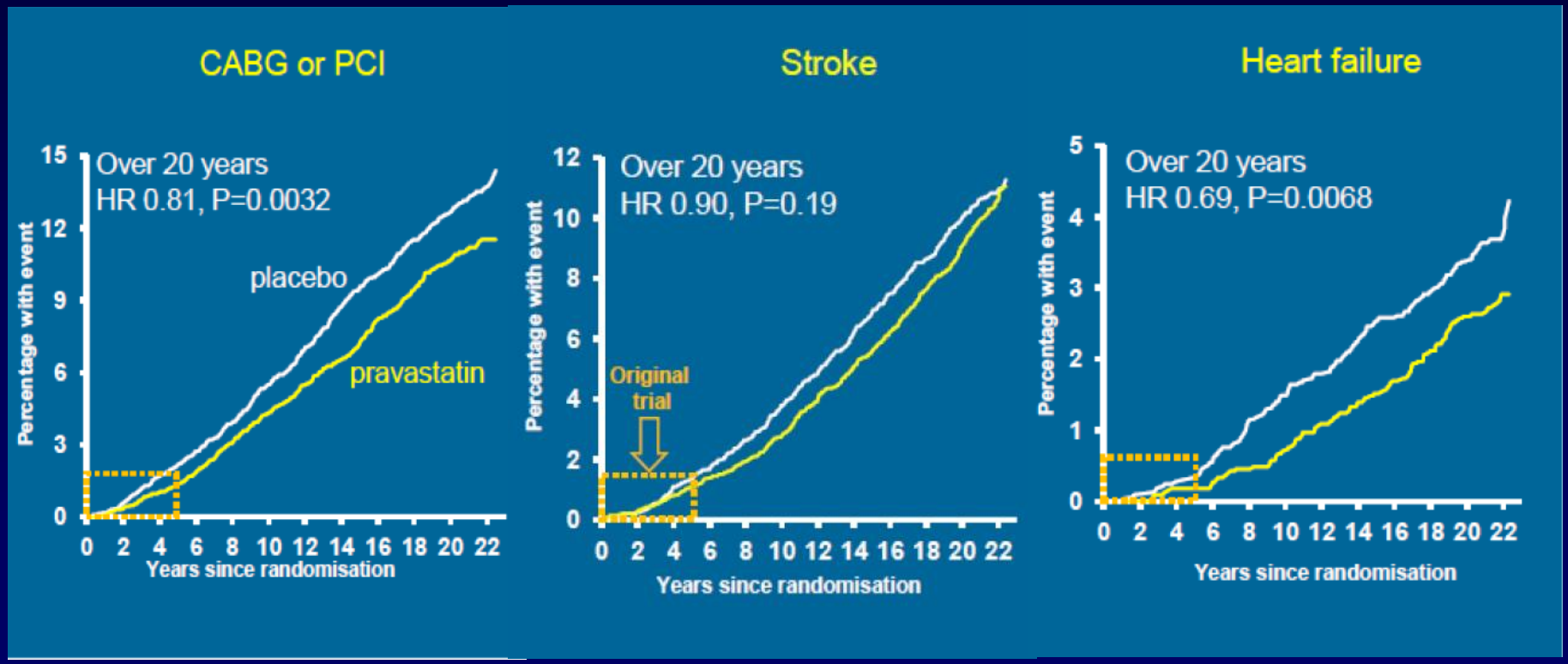


All cause mortality



Assessing long term (lifetime) benefits of LDL lowering

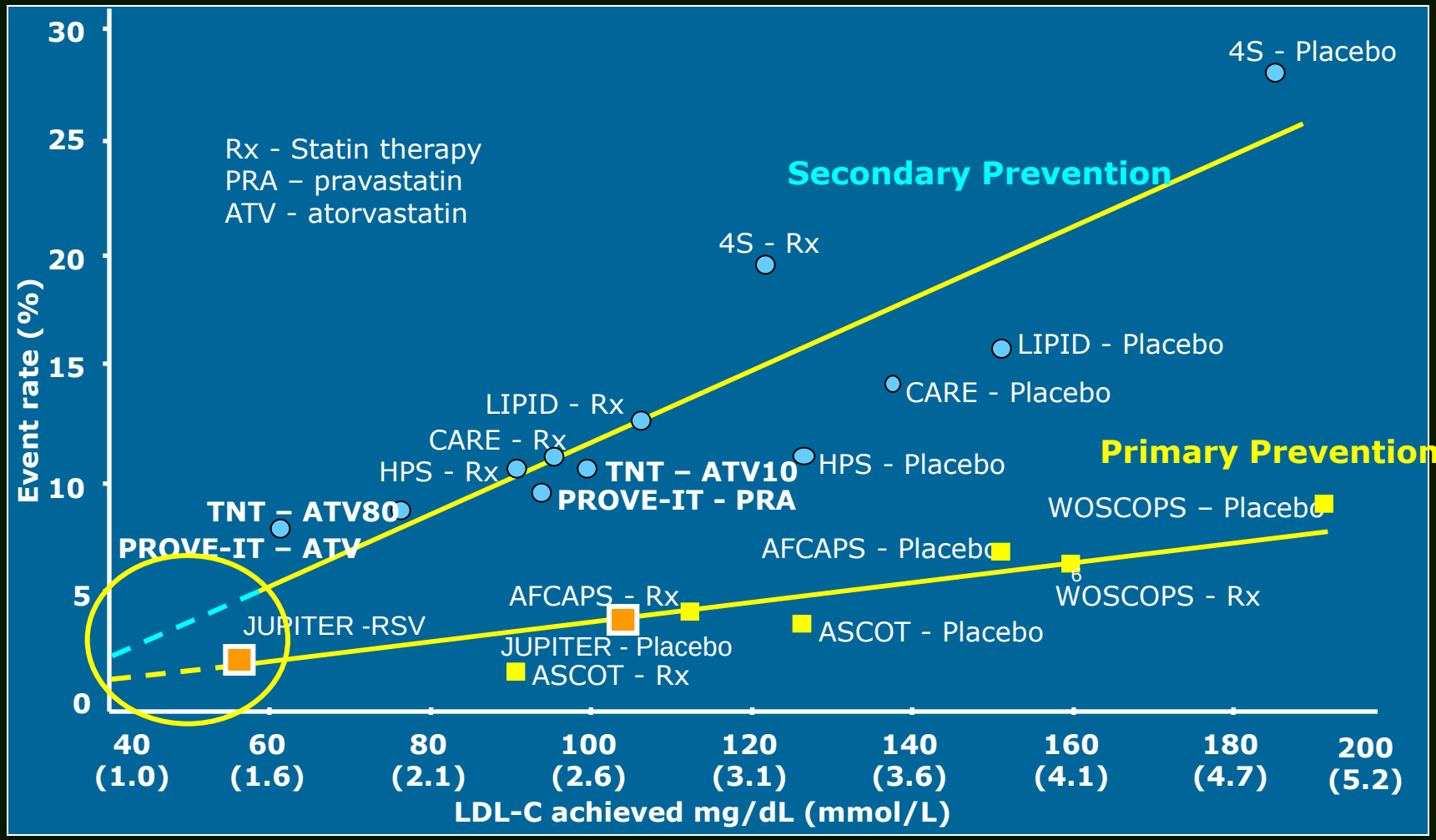
Hospitalization rates for key CVD outcomes



Outline of the presentation

- Epidemiologia
- Statine e anziano: evidenze cliniche
- Statine e anziano: raccomandazioni

LDL cholesterol lowering and benefit in clinical trials



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

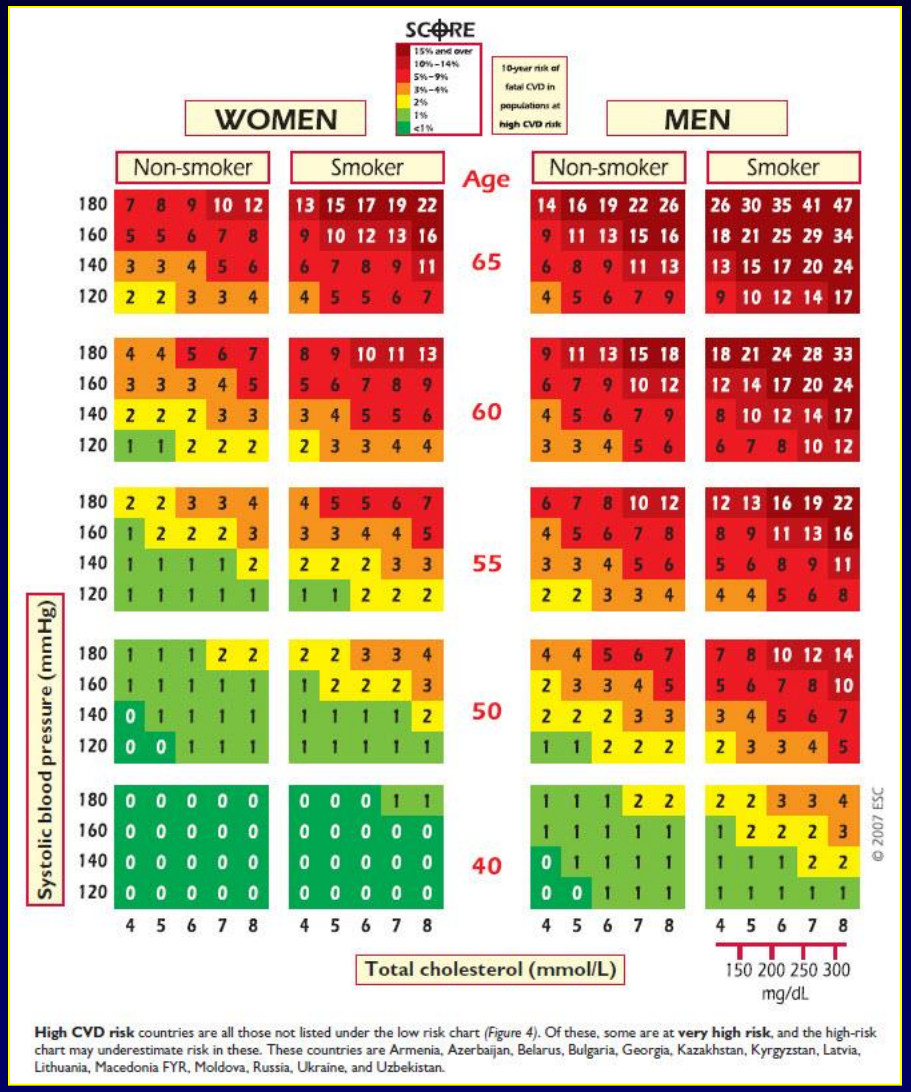
New EAS/ESC Guidelines

- New and more aggressive LDL levels

- New CV risk classification, more patients are now candidates to LDL<70mg/dl

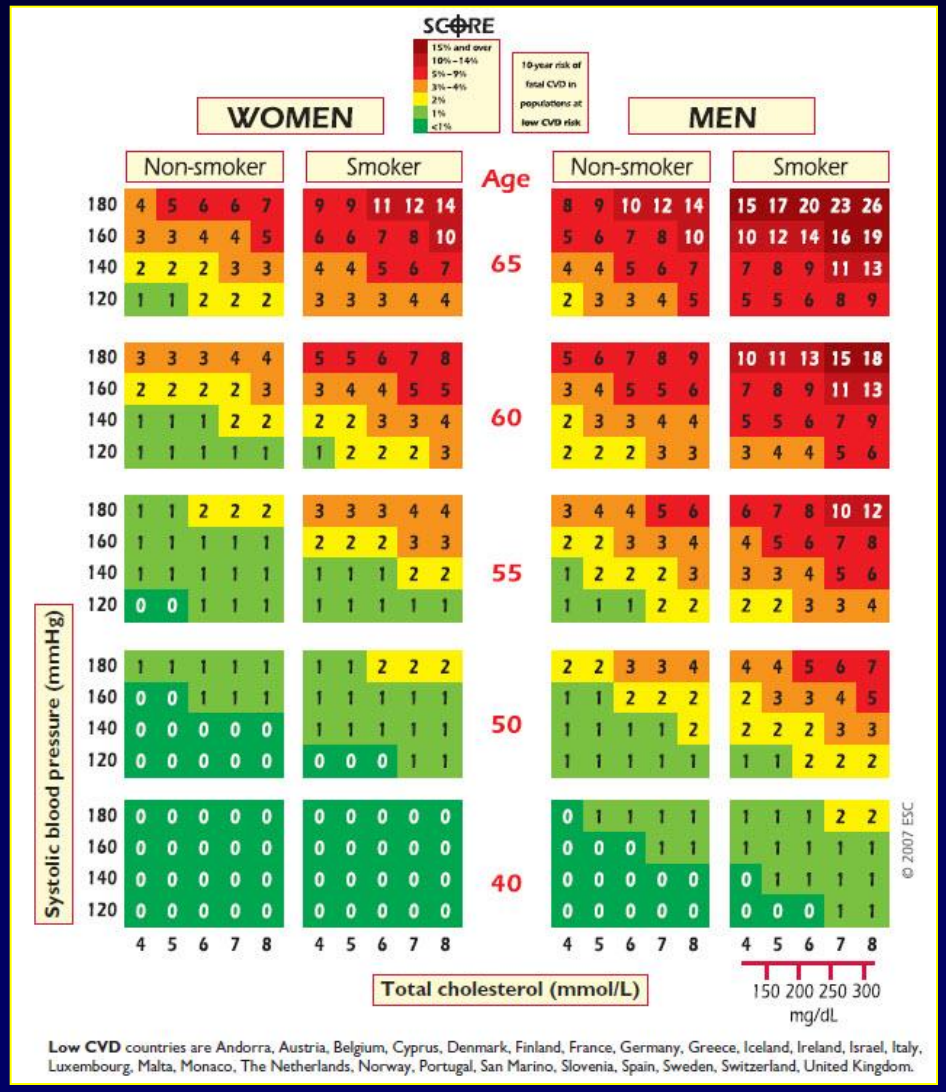
SCORE chart: 10-year risk of fatal cardiovascular disease (CVD)

in countries at high CVD risk



High CVD risk countries are all those not listed under the low risk chart (*Figure 4*). Of these, some are at **very high risk**, and the high-risk chart may underestimate risk in these. These countries are Armenia, Azerbaijan, Belarus, Bulgaria, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Macedonia FYR, Moldova, Russia, Ukraine, and Uzbekistan.

in countries at low CVD risk



Low CVD countries are Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, The Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom.

European Heart Journal 2012;33:1635–1701

Recommendations for treatment of dyslipidaemia in the elderly

Recommendations	Class[a]	Level[b]	Ref[c]
Treatment with statins is recommended for elderly patients with established CVD in the same way as for younger patients.	I	B	15, 16
Since elderly people often have comorbidities and have altered pharmacokinetics, it is recommended to start lipid-lowering medication at a low dose and then titrate with caution to achieve target lipid levels which are the same as in the younger subjects.	I	C	-
Statin therapy may be considered in elderly subjects free of CVD, particularly in the presence of at least one other CV risk factor besides age.	IIb	B	20, 167

Reiner Z et al. Eur H J (2011) 32, 1769–1818

The elderly

Side effects and interactions

The safety and side effects of statins are a matter of special concern

- co-morbidities
- multiple medications
- altered pharmacokinetics and pharmacodynamics.

Statin–drug interactions are a concern primarily because of their potential to increase statin-associated side effects such as myopathy

Adherence

Cost, adverse effects, coronary events occurring despite being on lipid-lowering agents, and the perception that the drug is not beneficial may be the reasons for non-compliance.

Improving patient understanding of CV risk and potential benefits of persistence with statin therapy may further enhance compliance.

Reiner Z et al. Eur H J (2011) 32, 1769–1818

The elderly

Evidence for treatment above the age of 80–85 years is very limited, and clinical judgement should guide decisions in the very old

Reiner Z et al. Eur H J (2011) 32, 1769–1818

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

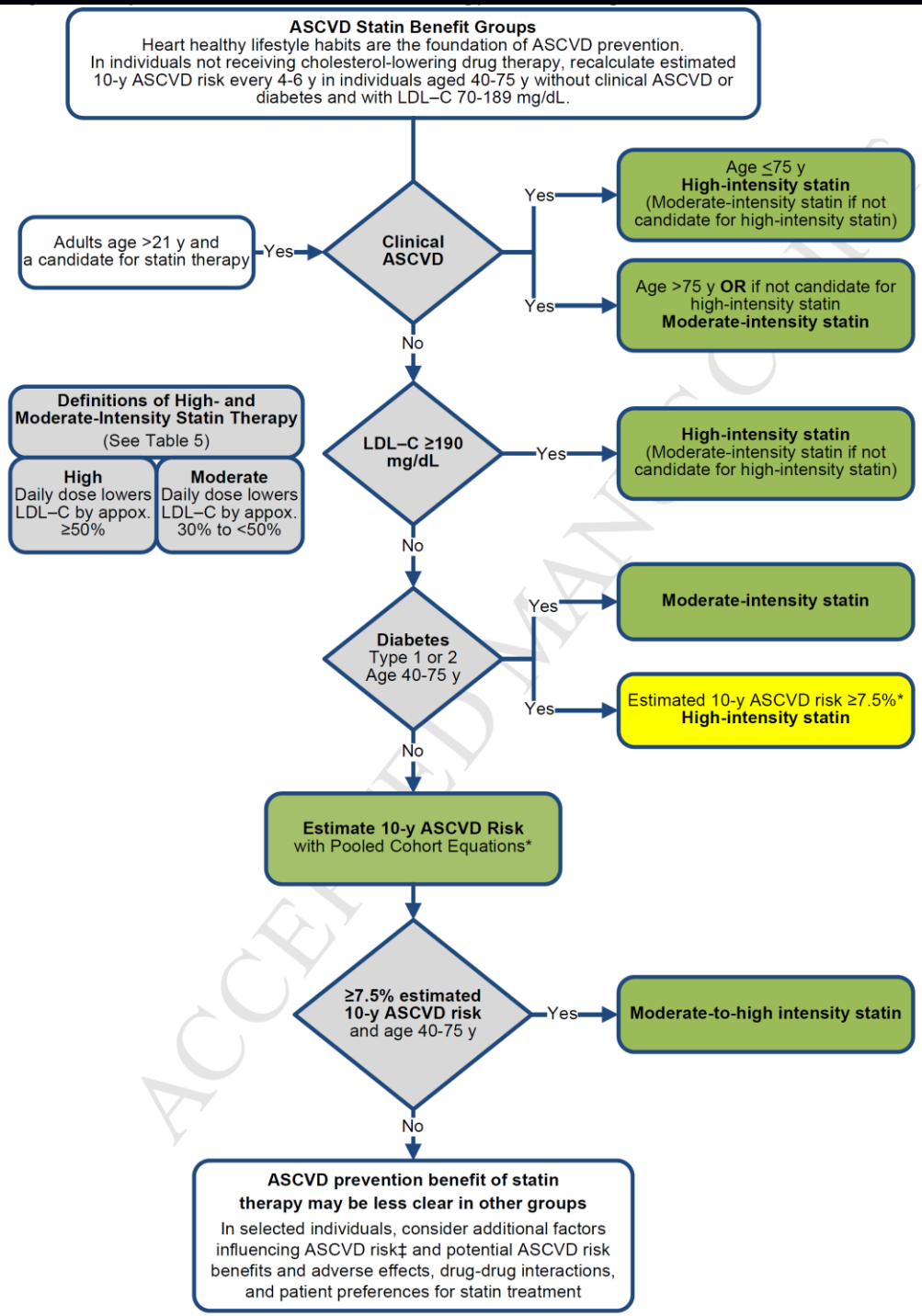
American Heart Association

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

CORE CONCEPTS (1)

- **Value of the Art of Medicine**. The new guidelines allow room for individualizing primary prevention on the basis of shared decision making between the patient and clinician. Encouraging patient-clinician dialogue is a virtue of this guidelines. Finding time for these risk discussions will be challenging.
- **Statins as First-Line Pharmacological Therapy.** Based on trial data from more than 170 000 patients**. Identifies 4 statin benefit groups**
- **Expanding the Scope of Prevention.** From CHD to atherosclerotic CV, adding stroke to the risk calculator.

***Circulation* November 12, 2013**



Major recommendations for statin therapy for ASCVD prevention

In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions
and
to consider patient preferences when initiating a moderate- or high-intensity statin.
It is reasonable to continue statin therapy in those who are tolerating it.

Stone NJ, et al.
jacc.2013.11.002

AGENZIA ITALIANA DEL FARMACO

DETERMINA 19 giugno 2014

Modifica alla Nota 13 di cui alla determina del 26 marzo 2013. (Determina n. 617/2014). (14A05079)

(GU n.156 del 8-7-2014)

Particolari categorie di pazienti

Pazienti di età >65 anni.

In accordo alle raccomandazioni delle linee guida, in considerazione dei risultati dello studio PROSPER, nonché delle metanalisi in cui è stata valutata l'efficacia delle statine nei pazienti anziani, il trattamento con farmaci ipolipemizzanti nei pazienti con eta' >65 anni con aumentato rischio cardiovascolare è da considerarsi rimborsabile dal SSN. La rimborsabilità si intende estesa, in prevenzione primaria, fino agli 80 anni. Oltre tale età, invece, non esistono evidenze sufficienti a sostegno dell'opportunità del trattamento. Nei pazienti con eta' >65 anni ma con evidenza di malattia coronarica, vascolare o diabete mellito la rimborsabilita' dei farmaci ipolipemizzanti è a carico del SSN per definizione, dovendosi considerare questi pazienti in prevenzione secondaria.

Adherence With Statin Therapy in Elderly Patients With and Without Acute Coronary Syndromes

Cynthia A. Jackevicius et al., JAMA 2002;288:462-467

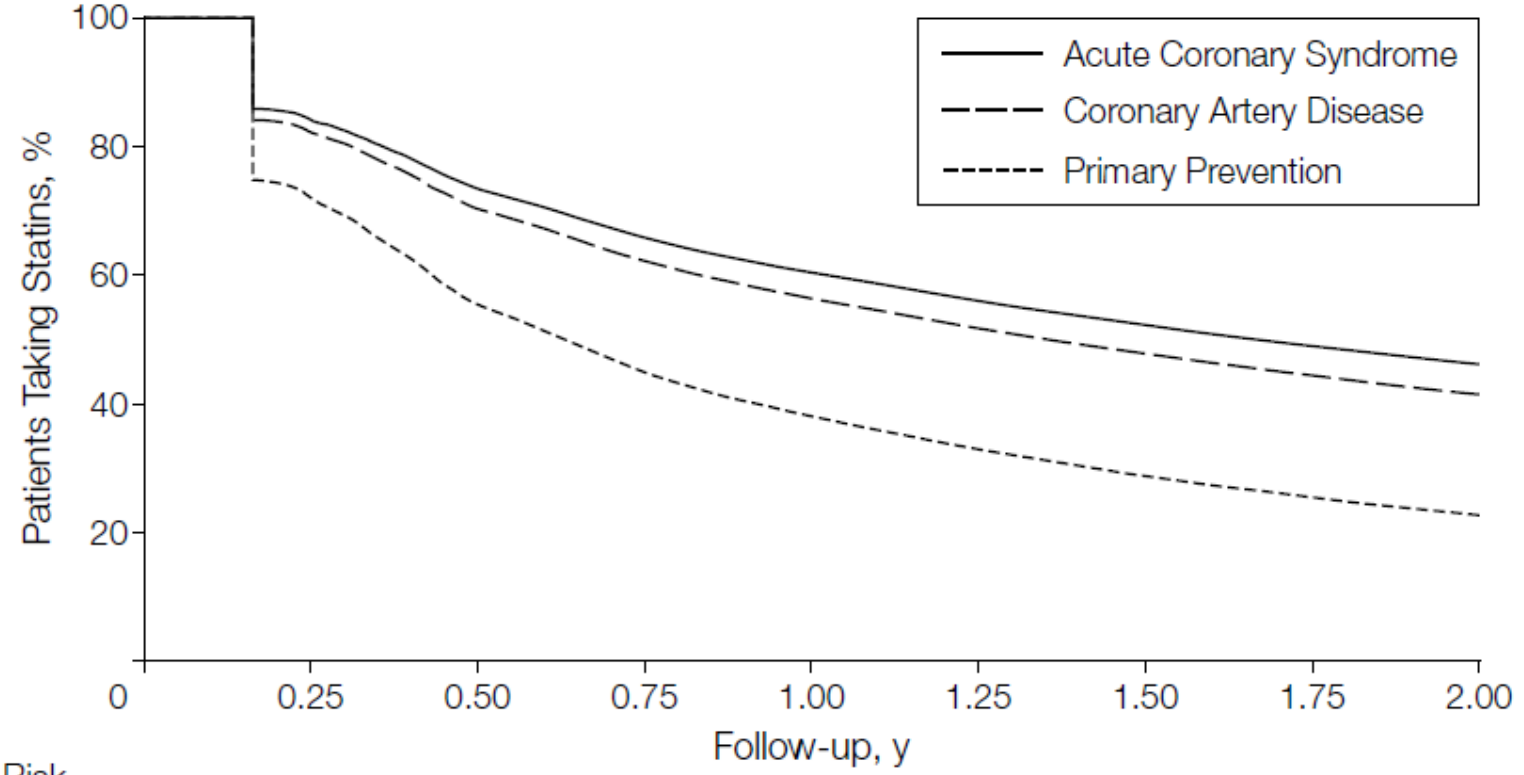
Baseline patient characteristics

Characteristic	Cohort, No. (%)†		
	Acute Coronary Syndrome (n = 22 379)	Coronary Artery Disease (n = 36 106)	Primary Prevention (n = 85 020)
Age, mean (SD), y	72.5 (5.0)	72.4 (4.9)	71.5 (4.6)
Age, ≥75 y	7000 (31.3)	10 963 (30.4)	19 599 (23.1)
Women	9305 (41.6)	16 420 (45.5)	52 074 (61.3)
Diabetes	5543 (24.8)	7395 (20.5)	12 447 (14.6)
Prior CABG	3523 (15.7)	2971 (8.2)	0
Prior PTCA	2061 (9.2)	1010 (2.8)	0
No. of medications in prior year			
Mean (SD)	12.8 (6.8)	11.4 (6.3)	7.9 (5.4)
Median (IQR)	12 (8-16)	10 (7-14)	7 (4-10)
No. of different physicians			
Mean (SD)	11.2 (6.3)	8.9 (5.1)	6.7 (4.0)
Median (IQR)	10 (7-14)	8 (5-11)	6 (4-9)
No. of physician visits in prior year			
Mean (SD)	27.3 (19.3)	20.8 (16.4)	15.1 (12.7)
Median (IQR)	23 (14-35)	17 (10-26)	12 (7-19)

*CABG indicates coronary artery bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty; and IQR, interquartile range.
†$P<.001$ for trend for all comparisons.

Cynthia A. Jackevicius et al., JAMA 2002;288:462-467

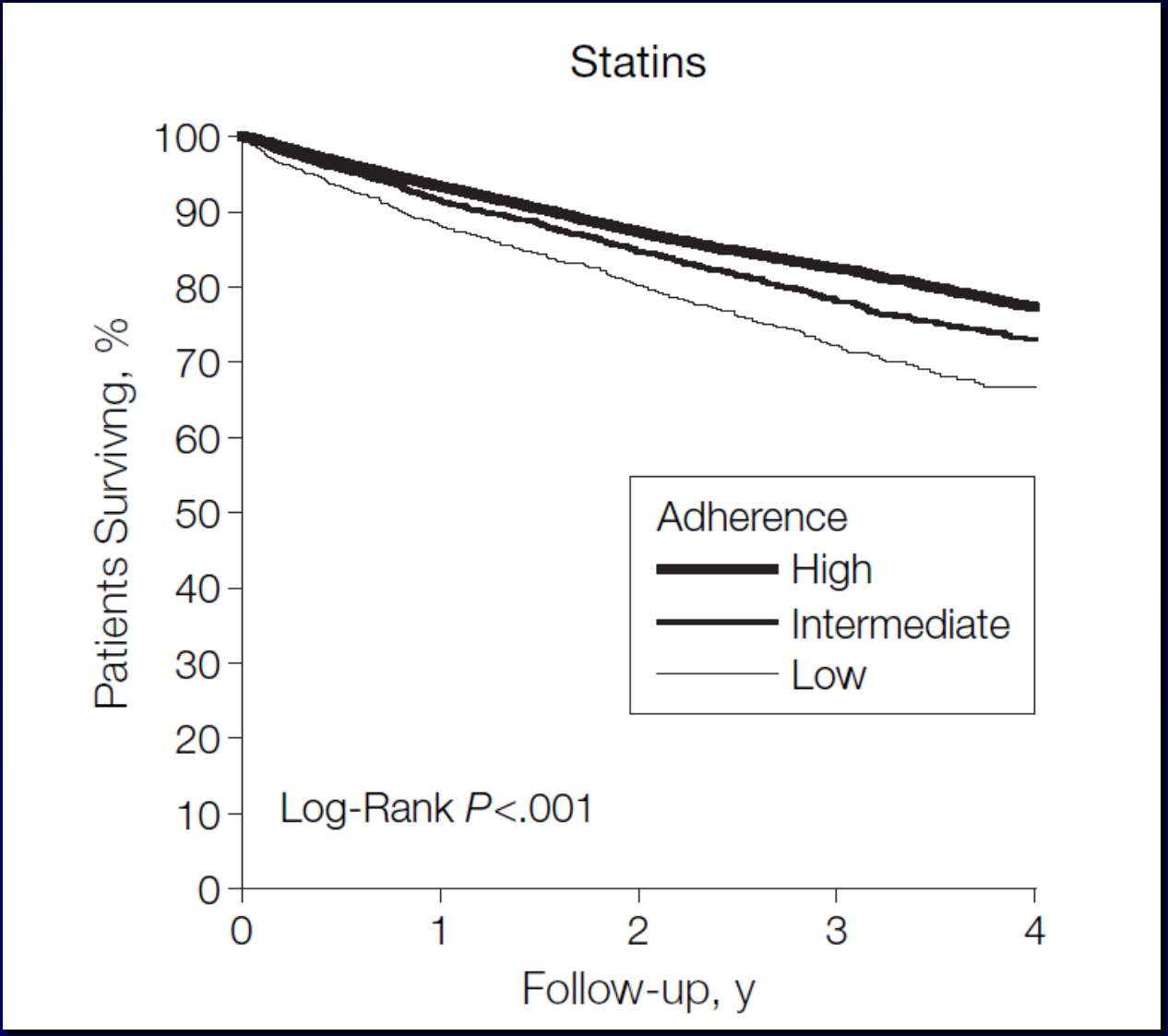
Survival curves for adherence with statins in 3 cohorts



No. at Risk					
Acute Coronary Syndrome	22379	16312	12901	10662	8977
Coronary Artery Disease	36106	25416	19558	15823	13094
Primary Prevention	85020	47685	33564	26401	21602

Cynthia A. Jackevicius et al., JAMA 2002;288:462-467

Estimates of Time to Death for Statin Users According to Adherence Level



Rasmussen JN et al. JAMA. 2007;297:177-186

Factors affecting the response to statins

Extrinsic factors (extraneous influences)

poor compliance
background diet
dose and uptitration of drug
concomitant drug therapy

Intrinsic factors (genetically-determined)

LDL-receptor gene mutations
apo-B-100 gene mutations
rate of cholesterol biosynthesis
rate of cholesterol absorption
CYP/transporter polymorphism
apoE polymorphism

Discontinuation of statin therapy due to muscular side effects: A survey in real life

D. Rosenbaum [a,b,*], J. Dallongeville [c], P. Sabouret [d], E. Bruckert [a,b]

Muscular symptoms were reported in 10% of statin treated patients and led to discontinuation in 30% of the symptomatic patients

Nutrition, Metabolism & Cardiovascular Diseases 1-5, 2012 in press

Risk Factors for Myopathy/Myalgia

- Increasing dose
- Increasing concentration:
  - **Increasing age**, female
  - CYP450 interactions (pharmacokinetic)
- Clinical conditions:
  - **Poly-therapy**
  - **Transplanted**
  - Diabetes
  - Hypothyroidism
  - History of muscular symptoms after LLT

European Heart Journal Advance Access published February 18, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv043

REVIEW

Clinical update

Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management

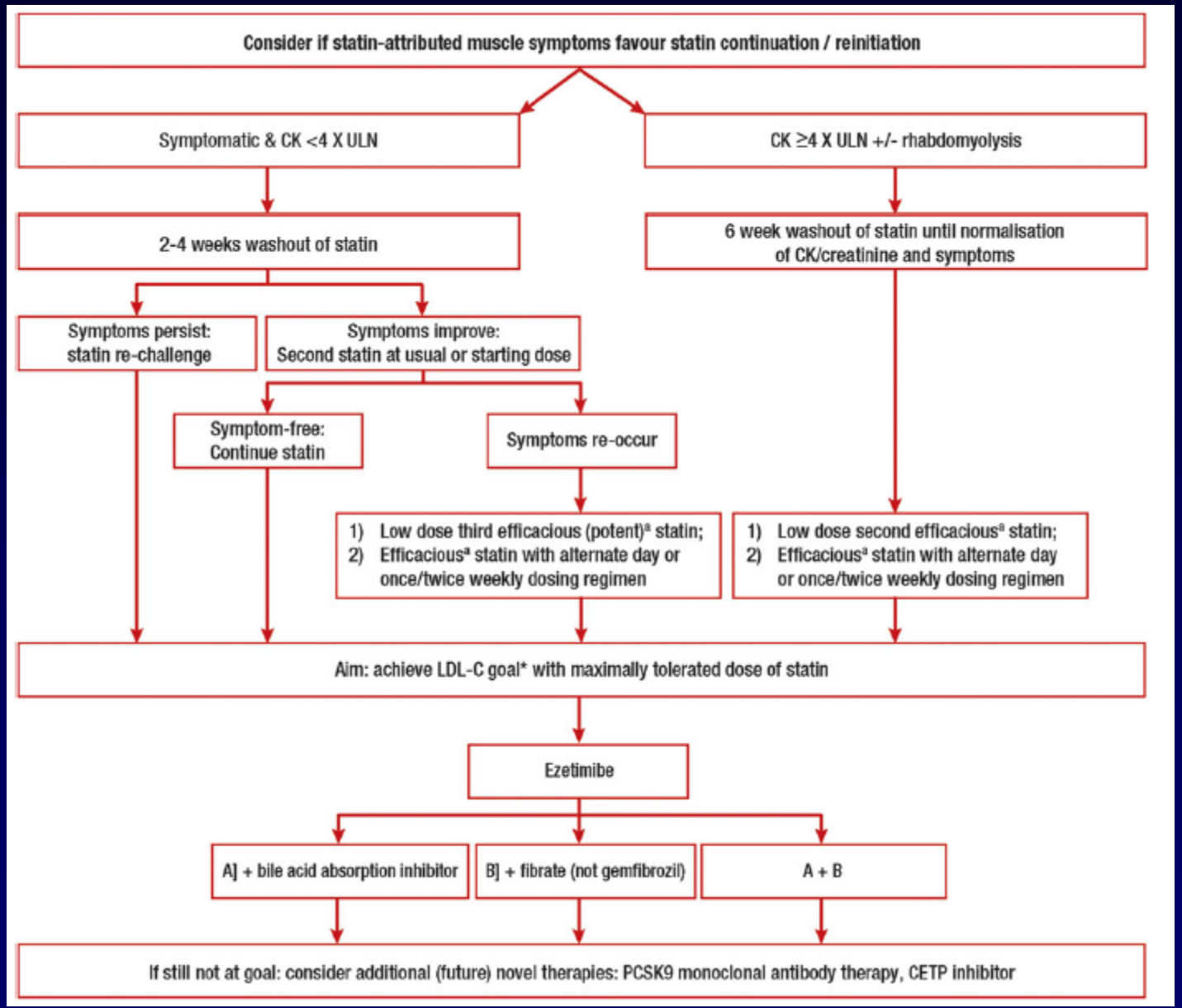
Erik S. Stroes[1*], Paul D. Thompson[2], Alberto Corsini[3], Georgirene D. Vladutiu[4], Frederick J. Raal[5], Kausik K. Ray[6], Michael Roden[7], Evan Stein[8], Lale Tokgözoğlu[9], Børge G. Nordestgaard[10], Eric Bruckert[11], Guy De Backer[12], Ronald M. Krauss[13], Ulrich Laufs[14], Raul D. Santos[15], Robert A. Hegele[16], G. Kees Hovingh[17], Lawrence A. Leiter[18], Francois Mach[19], Winfried März[20], Connie B. Newman[21], Olov Wiklund[22], Terry A. Jacobson[23], Alberico L. Catapano[3], M. John Chapman[24], and Henry N. Ginsberg[25], European Atherosclerosis Society Consensus Panel[†]

Box 1 Risk factors for statin-associated muscle symptoms. Adapted from Mancini *et al.*[9]

Anthropometric	• Age >80 years old (general caution advised for age >75) • Female • Low body mass index • Asian descent
Concurrent conditions	• Acute infection • Hypothyroidism (untreated or undertreated) • Impaired renal (chronic kidney disease classification 3, 4, and 5) or hepatic function • Biliary tree obstruction • Organ transplant recipients • Severe trauma • Human immunodeficiency virus • Diabetes mellitus • Vitamin D deficiency
Surgery	• Surgery with high metabolic demands. The American Heart Association recommends temporary cessation of statins prior to major surgery[120]
Related history	• History of creatine kinase elevation, especially >10× the upper limit of the normal range • History of pre-existing/unexplained muscle/joint/tendon pain • Inflammatory or inherited metabolic, neuromuscular/muscle defects (e.g. McArdle disease, carnitine palmitoyl transferase II deficiency, myoadenylate deaminase deficiency, and malignant hyperthermia) • Previous statin-induced myotoxicity • History of myopathy while receiving another lipid-lowering therapy
Genetics	• Genetic factors such as polymorphisms in genes encoding cytochrome P450 isoenzymes or drug transporters
Other risk factors	• High level of physical activity • Dietary effects (excessive grapefruit or cranberry juice) • Excess alcohol • Drug abuse (cocaine, amphetamines, heroin)

Eur Heart J. 2015 Feb 18.

Therapeutic flow-chart for management of patients with statin-associated muscle symptoms



Eur Heart J. 2015 Feb 18.

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12687

Myopathy in older people receiving statin therapy: a systematic review and meta-analysis

Roli B. Iwere[1] & Jonathan Hewitt[2]

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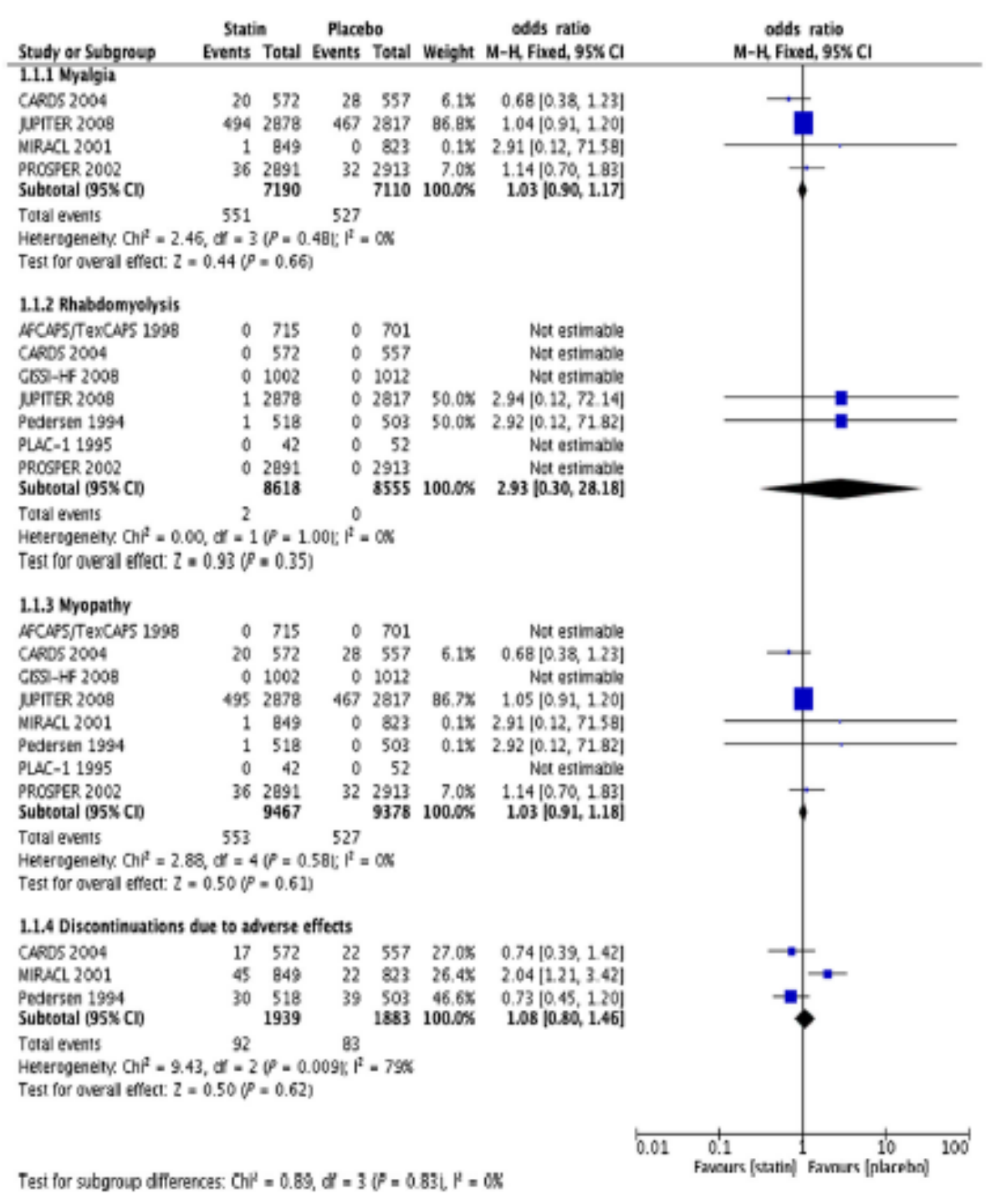
Keywords
adverse effects, aged, elderly, myalgia, myopathy, statin

Received
1 February 2015
Accepted
22 May 2015
Accepted Article Published Online
29 May 2015

Study	Country	Statin	Duration (years)	Age range (years)	Mean age years(SD)	Participants (*N*)	Statin (*N*)	Placebo (*N*)	Gender (% male)	Race (% white)
AFCAPS/TexCAPS 1998 [18]	USA	L†	5.2	65–75	NR	1416	715	701	75	NR
CARDS 2004 [19]	UK/Ireland	A†	3.9*	65–76	69 (NR)	1129	572	557	69	96
GISSI-HF 2008 [20]	Italy	R‡	3.9*	≥70	NR	2014	1002	1012	NR	NR
JUPITER 2008 [21]	26 countries across North/South America, Europe and Africa	R‡	1.9	70–97	74 (72–77)*	5695	2878	2817	49	70
MIRACL 2001 [22]	Europe, North America, South Africa, Australia	A†	0.3	≥65	74 (6.0)	1672	849	823	59	90
Pedersen (4S) 1994 [23]	Nordic countries	S†	5.4*	≥65	67 (1.4)	1021	518	503	76	NR
PLAC I 1995 [24]	USA	P‡	3.0	NR	NR	94	42	52	NR	NR
PROSPER 2002 [12]	Scotland, Ireland, the Netherlands	P‡	3.2	70–82	75 (3.3)	5804	2891	2913	48	NR

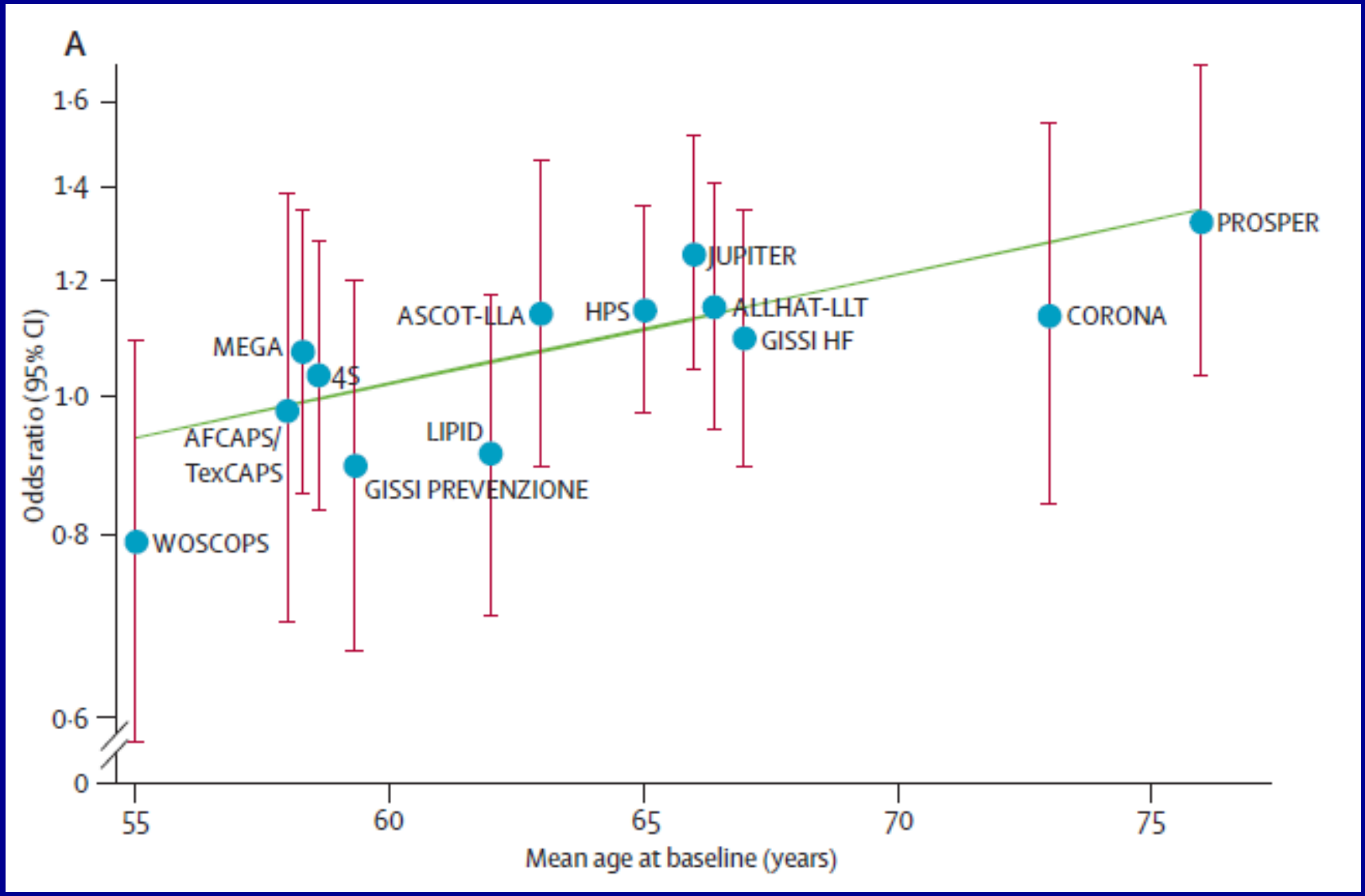


Primary and secondary analysis

- Increases in blood sugar levels (hyperglycemia) have been reported with statin use.
- Patients being treated with statins may have a small increased risk of increased blood sugar levels and of being diagnosed with type 2 diabetes mellitus.

Feb 28, 2012

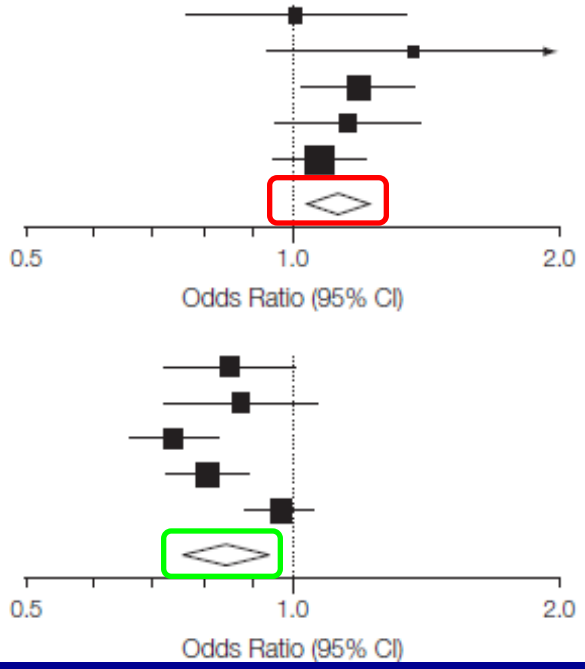
Risk greater with increasing age



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

Meta-analysis of New-Onset Diabetes and First Major CV Events in 5 Large Trials Comparing Intensive- to Moderate-Dose Statin Therapy

	Cases/Total, No. (%)		
	Intensive Dose	Moderate Dose	OR (95% CI)
Incident Diabetes			
PROVE IT–TIMI 22,[18] 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z,[17] 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT,[15] 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL,[16] 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH,[5] 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	1449/16 408 (8.8)	1300/16 344 (8.0)	1.12 (1.04-1.22)
Heterogeneity: $I^2=0\%$; $P=.60$			
Incident CVD			
PROVE IT–TIMI 22,[18] 2004	315/1707 (18.4)	355/1688 (21.0)	0.85 (0.72-1.01)
A to Z,[17] 2004	212/1768 (12.0)	234/1736 (13.5)	0.87 (0.72-1.07)
TNT,[15] 2005	647/3798 (17.0)	830/3797 (21.9)	0.73 (0.65-0.82)
IDEAL,[16] 2005	776/3737 (20.8)	917/3724 (24.6)	0.80 (0.72-0.89)
SEARCH,[5] 2010	1184/5398 (21.9)	1214/5399 (22.5)	0.97 (0.88-1.06)
Pooled odds ratio	3134/16 408 (19.1)	3550/16 344 (21.7)	0.84 (0.75-0.94)
Heterogeneity: $I^2=74\%$; $P=.004$			



NTT/yr **155 for CV events**
NNH/yr **498 for new-onset diabetes**

Preiss et al. JAMA 2011; 305: 2556-64

Numero di farmaci utilizzati dagli anziani in alcuni paesi europei

Numero medio di farmaci/persona (età media 74.7 ± 6 anni)

- Svezia **7.6** (SD ± 2.9)
- Danimarca **6.8** (SD ± 2.3)
- Germania **7.5** (SD ± 2.7)
- Portogallo **6.5** (SD ± 2.0)
- Irlanda del Nord **6.2** (SD ± 2.0)
- EIRE **6.6** (SD ± 2.2)

Journals of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci
doi:10.1093/gerona/glt118

High Prevalence of Poor Quality Drug Prescribing in Older Individuals: A Nationwide Report From the Italian Medicines Agency (AIFA)

Graziano Onder,[1] Stefano Bonassi,[2] Angela M. Abbatecola,[3] Pietro Folino-Gallo,[4] Francesco Lapi,[5] Niccolò Marchionni,[6] Luca Pani,[4] Sergio Pecorelli,[4] Daniele Sancarlo,[7] Angelo Scuteri,[8] Gianluca Trifirò,[9] Cristiana Vitale,[2] Stefano Maria Zuccaro,[10] Roberto Bernabei,[1] and Massimo Fini[2]; on behalf of the Geriatrics Working Group of the Italian Medicines Agency (AIFA)

Table 2. Prevalence of Quality Indicators in the Italian Elderly Population

Quality Indicator	All Age Groups (≥65 y), n = 12,301,537 (%)	65–74 y, n = 6,154,421 (%)	75–84 y, n = 4,474,887 (%)	≥85 y, n = 1,672,229 (%)
1. Polypharmacy				
5–9 drugs	6,024,383 (49.0)	2,681,639 (43.6)	2,462,378 (55.0)	880,366 (52.6)
≥10 drugs	1,389,591 (11.3)	529,506 (8.6)	629,043 (14.1)	231,042 (13.8)
2. Low adherence to antidepressant drug treatment*	201,290 (63.9)	83,110 (62.6)	82,623 (63.0)	35,557 (69.6)
3. Low adherence to antihypertensive drug treatment*	179,975 (46.4)	84,983 (43.2)	65,450 (47.2)	29,542 (56.1)
4. Low adherence to hypoglycemic drug treatment*	92,017 (63.0)	44,227 (63.0)	35,497 (64.7)	12,293 (70.1)
5. Low adherence to antiosteoporotic drug treatment*	56,621 (52.4)	24,424 (48.7)	24,351 (53.4)	7,846 (64.0)
6. Use of anti-Parkinson and antipsychotic drugs	25,949 (0.2)	10,200 (0.2)	10,625 (0.2)	5,124 (0.3)
7. Underutilization of statins in diabetic patients (as % of the whole elderly population)	918,662 (7.5)	418,257 (6.8)	366,813 (8.2)	133,592 (8.0)
As % of the elderly population on hypoglycemic drugs†	53.4	48.3	54.4	73.1
8. Concomitant use of drugs increasing the risk of bleeding				
Warfarin + traditional NSAIDs/COX-2 inhibitors	178,458 (1.5)	64,939 (1.1)	90,580 (2.0)	22,939 (1.4)
Warfarin + aspirin/antiplatelets	100,236 (0.8)	38,953 (0.6)	49,736 (1.1)	11,547 (0.7)
Warfarin + NSAIDs/COX-2 inhibitors + aspirin/antiplatelets	22,174 (0.2)	8,574 (0.1)	11,135 (0.2)	2,465 (0.1)
9. Concomitant use of drugs increasing the risk of renal failure and/or hyperkalemia (ACE inhibitors/ARB + aldosterone antagonists + NSAIDs/COX-2 inhibitors)	85,412 (0.7)	28,860 (0.5)	40,665 (0.9)	15,887 (1.0)
10. Concomitant use of ≥2 QT prolonging drugs‡	36,359 (0.3)	13,580 (0.2)	15,903 (0.4)	6,876 (0.4)
11. Use of antihypertensive drugs with unfavorable risk–benefit profile (doxazosin, clonidine, or methyldopa as monotherapy or any use of short-acting calcium antagonists; as % of the whole elderly population)	196,690 (1.6)	88,069 (1.4)	78,826 (1.8)	29,795 (1.8)
As % of the elderly population on antihypertensive drugs¶	2.5	2.3	2.5	2.8
12. Use of high dosage of digoxin (>0.125 mg/d)	47,314 (0.4)	16,323 (0.3)	22,488 (0.5)	8,503 (1.3)
13. Use of oral hypoglycemic agents associated with high risk of hypoglycemia (chlorpropamide or glibenclamide; as % of the whole elderly population)	87,755 (0.7)	35,786 (0.6)	37,626 (0.8)	14,343 (0.9)
As % of the elderly population on hypoglycemic drugs†	5.1	4.1	5.6	7.8

Notes: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; COX-2 inhibitors = cyclooxygenase-2 inhibitors; NSAIDs = nonsteroidal anti-inflammatory drugs.

*Prevalence has been calculated for newly treated participants only (Indicator 2: n = 315,015; Indicator 3: n = 388,079; Indicator 4: n = 146,094; Indicator 5: n = 108,037). Low adherence is defined as proportion of days covered < 40%.

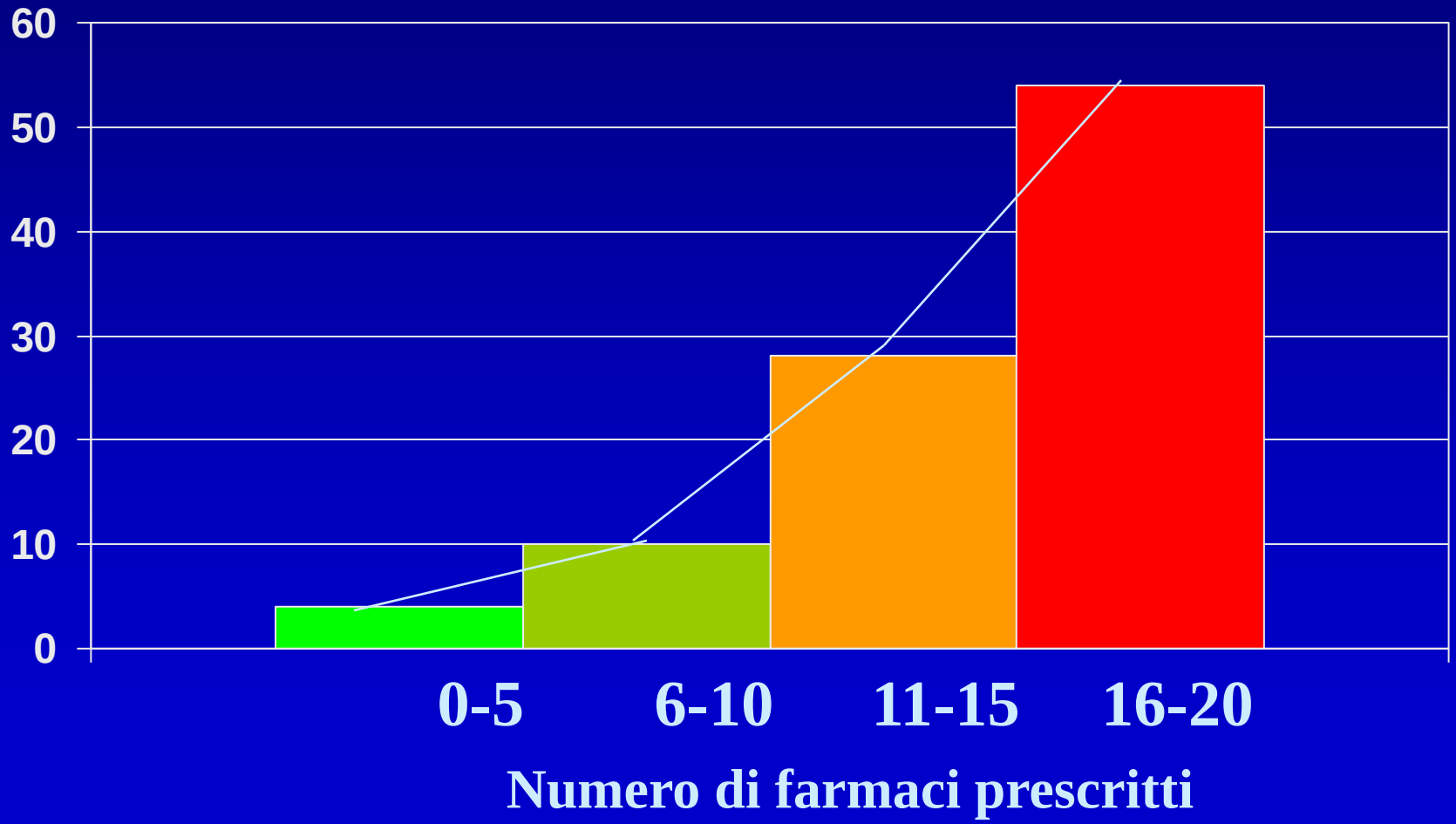
†n = 1,721,767.

‡List of drugs that are well known to carry a risk of Torsades de Pointes, as reported in Arizona Cert list (available at http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm, accessed January 2012).

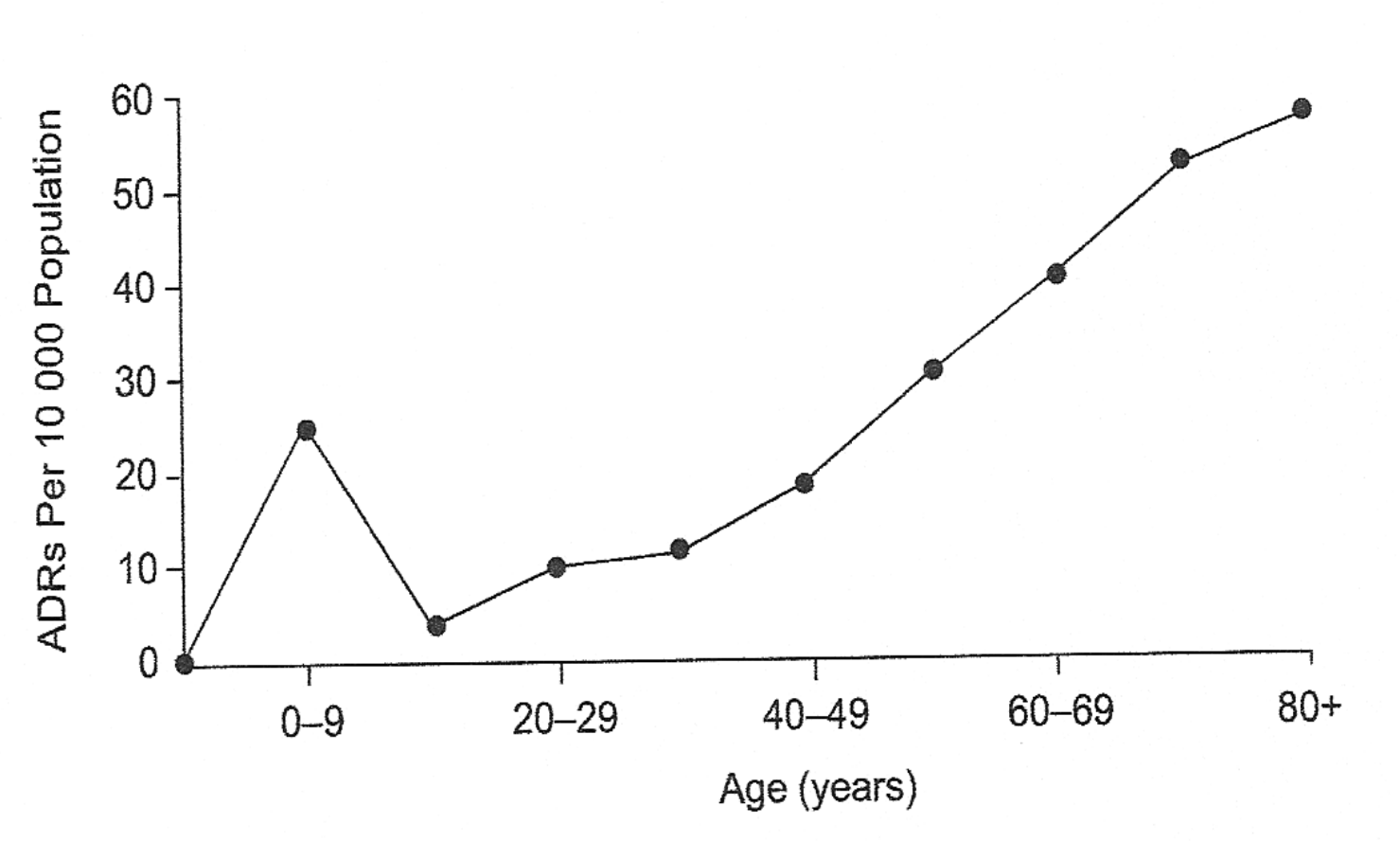
¶n = 7,999,099.

INCIDENZA DI ADR IN RELAZIONE AL NUMERO DI FARMACI PRESCRITTI

May FE et al. Clin Pharmacol Ther 1977; 22: 322



ADVERSE DRUG REACTIONS AS A FUNCTION OF INCREASING AGE



Brandt N, Adv Stud Med, 6(4): 182-188, 2006

Statins Pharmacokinetic Properties

	Fermentation-derived		Synthetic				
Properties	**Simva**	**Prava**	**Fluva**	**Atorva**		**Rosuva**	**Pita**
Absorption (%)	**60-80**	**34**	**98**	**30**		**50**	**75**
Bioavailability (%)	**5**	**18**	**19-29**	**12**		**20**	**51**
Half-life (h)	**2-3**	**1.3-2.8**	**0.5-2.3**	**15-30**		**20.8**	**13**
Protein Binding (%)	**94-98**	**43-55**	**>99**	**80-90**		**88**	**>99**
Metabolic Clearance	**3A4**	**multiple**	**2C9**	**3A4**		**2C9, 2C19 biliar**	**2C9,2C8 biliar**

Corsini A, Bellosta S. *Exp Rev Clin Pharmacol 2008;*
Corsini A and Ceska R Cur Med Res & Op 27: 1551–1562;; 2011

Human Cytochrome P450 Isoenzymes Known to Oxidize Clinically Used Drugs

CYP2C9	CYP2C19	CYP2D6	CYP3A4
Alprenolol	Diazepan	Amitriptyline	Amiodarone
Diclofenac	Ibobrufen	Bufaralol	Atorvastatin
Fluvastatin	Mephenytoin	Codeine	Cerivastatin
Hexobarbital	Methylphenobarbital	Debrisoquine	Clarithromycin
N-desmethyldiazepan	Omeprazol	Dextromethorphan	Cyclosporine A
Tolbutamide	Proguanyl	Encainide	Diltiazem
Warfarin	Phenytoin	Flecainide	Erythromycin
Rosuvastatin	Rosuvastatin	Imipramine	Ketoconazole
Pitavastatin		Metoprolol	Itraconazole
(also CYP2C8)		Mibefradil	Lovastatin
		Nortriptyline	MIbefradil
		Perhexiline	Midazolam
		Perphenazine	Nefazodone
		Propafenone	Nifedipine
		Propanolol	Protease inhibitors
		Sparteine	Quinidine
		Thioridazine	Sildefanil
		Timolol	Simvastatin
			Terbinafine
			Verapamil
			Warfarin

Modified from: Brower et al., In: Evans W.E. (Ed). Applied Pharmacokinetics. Principles of Therapeutic Drug Monitoring, 3rd ed., 1992

Selected Drugs That May Increase Risk of Myopathy and Rhabdomyolysis When Used Concomitantly With Statins

CYP3A4 Inhibitors/Substrates	Others
Cyclosporine, tacrolimus, sirolimus	Digoxin
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Fibrates (gemfibrozil)
	Niacin
Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole)	
Calcium antagonists (mibefradil, diltiazem, verapamil)	
Nefazodone	
HIV protease inhibitors (amprenavir, atanazavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir)	
Hepatitis C drugs (boceprevir, telaprevir)	
Danazol	
Amiodarone	
Grapefruit juice	
Sildenafil	
Warfarin	

Bellosta S and Corsini A Expert Opin Drug Saf. 2012 Nov;11(6):933-46

Annals of Internal Medicine ORIGINAL RESEARCH

Cost-Effectiveness and Population Impact of Statins for Primary Prevention in Adults Aged 75 Years or Older in the United States

Michelle C. Odden, PhD; Mark J. Pletcher, MD, MPH; Pamela G. Coxson, PhD; Divya Thekkethala, BS; David Guzman, MS; David Heller, MD; Lee Goldman, MD, MPH; and Kirsten Bibbins-Domingo, MD, PhD

Results of Sensitivity Analysis: An increased relative risk for functional limitation or mild cognitive impairment of 1.10 to 1.29 could offset the cardiovascular benefits.

Limitation: Limited trial evidence targeting primary prevention in adults aged 75 years or older.

Conclusion: At effectiveness similar to that in trials, statins are projected to be cost-effective for primary prevention; however, even a small increase in geriatric-specific adverse effects could offset the cardiovascular benefit. Improved data on the potential benefits and harms of statins are needed to inform decision making.

Ann Intern Med. 2015;162:533-541

CONTROVERSIES IN GERIATRICS AND GERONTOLOGYS

Statins in Very Elderly Adults (Debate)

Neil J. Stone, MD, MACP, FACC, Sunny Intwala, MD, and Dan Katz, BA

Most experienced clinicians will also want to put in the balance a consideration of harms of any therapy in those 85 and older. Concerns about adding another medication and nonadherence should be considered, and a discussion of metabolic (diabetes mellitus), musculoskeletal (myalgia, myositis, and the very rare rhabdomyolysis), medication interactions, major organ effects (liver and kidney), and memory concerns should ensue.

J Am Geriatr Soc. 2014 May;62(5):943-5

New clinical trials are required to understand whether older adults should take statins to prevent heart attacks and related problems

Meanwhile, for clinicians and patients, the decision to start statins for primary prevention of vascular disease in people over 75 continues to be based on sound clinical judgment after consideration of each person's predicted vascular risk without and with statins, the predicted risk of adverse effects of statins (against a backdrop of increasing comorbidities, polypharmacy, and other safety considerations), and the patient's own priorities and preferences for treatment.

Hankey GJ*BMJ* 2015;350:h2568