29 NOVEMBRE 2013

13:00-13:30 Lettura

IL PUNTO ATTUALE SULLA TERAPIA CON STATINE NELL'ANZIANO

Mario Bo (Torino)

Presiede: Walter De Alfieri (Grosseto)

58°

Congresso Nazionale

Società Italiana di Gerontologia e Geriatria

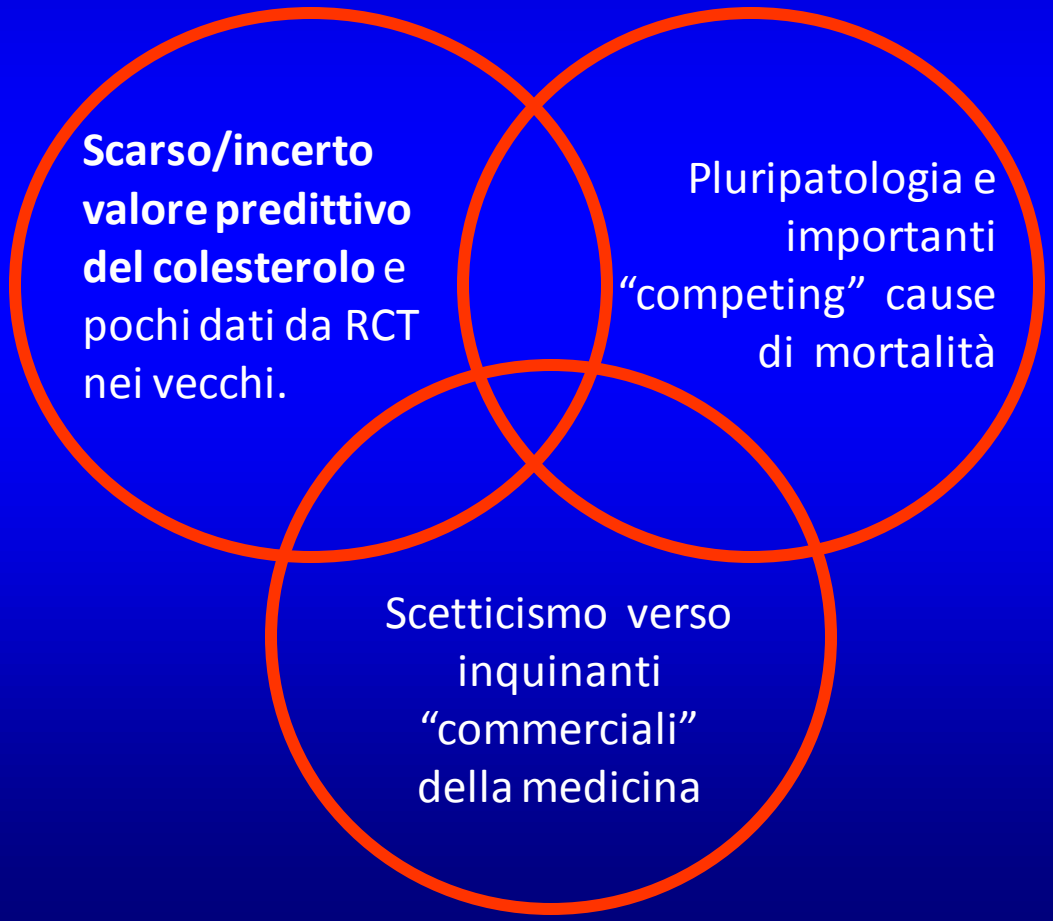
27-30 Novembre 2013 Torino

EDITORIAL

Cholesterol Can be Lowered in Older Persons

Should we care?

JAGS 1990



Age and Ageing 1999; **28:** 313-315

Cholesterol and long-term mortality after acute myocardial infarction in elderly patients

Mario Bo, Umberto Fiandra, Gianfranco Fonte,
Marco Bobbio, Fabrizio Fabris

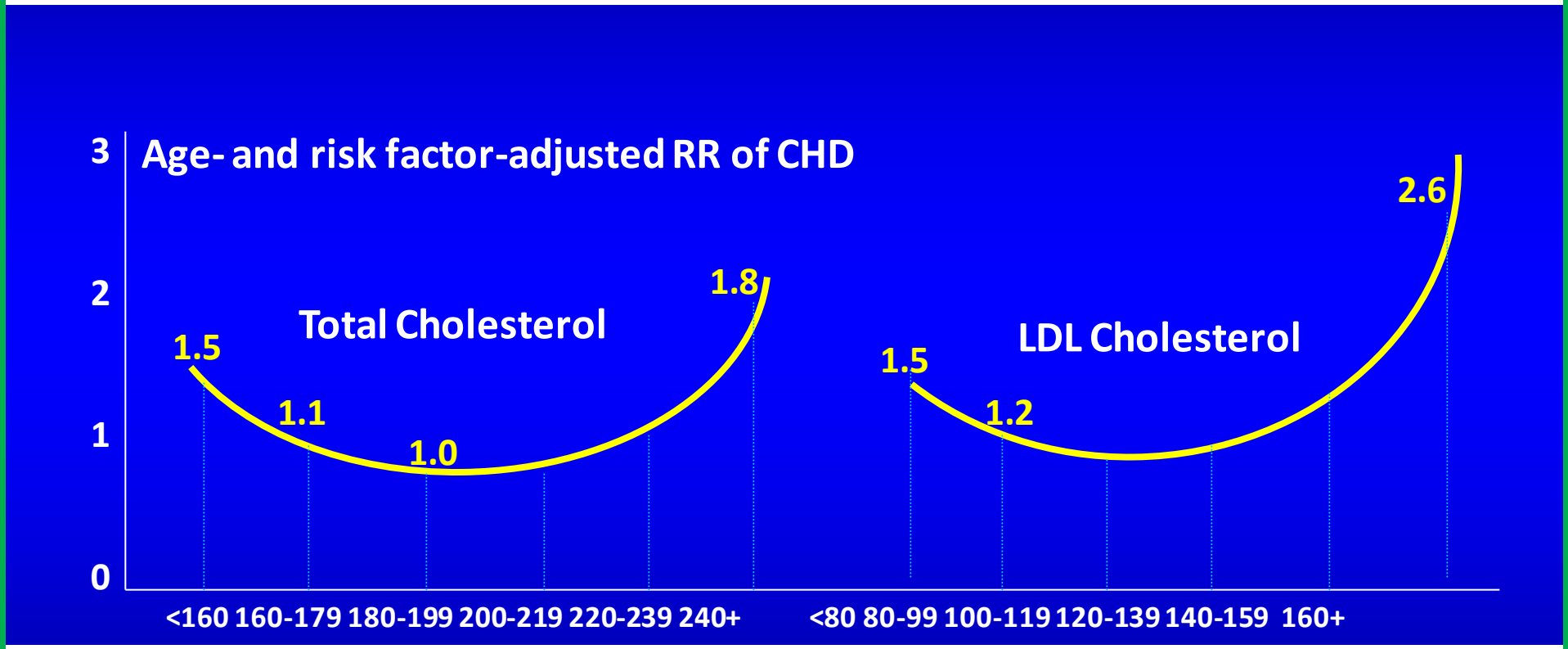
	No. (%) by total cholesterol, mg/dl				Normo/Hyper cholesterolemia		
	<164	165-188	189-220	>220	<230	>=230	p
All-cause mortality	52 (67.5)	54 (72.0)	44 (57.9)	48 (63.2)	114 (69.5)	84 (60.0)	<0.05
CHD mortality	23 (29.9)	26 (34.7)	20 (26.3)	21 (27.6)	53 (34.6)	37 (29.8)	<0.05

304 patients (192 men, mean age 73.3+-5.7 years), mean survival time 1758.1+- 113.8 days

Prospective Association Between Low and High Total and Low-Density Lipoprotein Cholesterol and Coronary Heart Disease in Elderly Men

J.David Curb, MD et al.

J Am Geriatr Soc 52:1975-1980, 2004

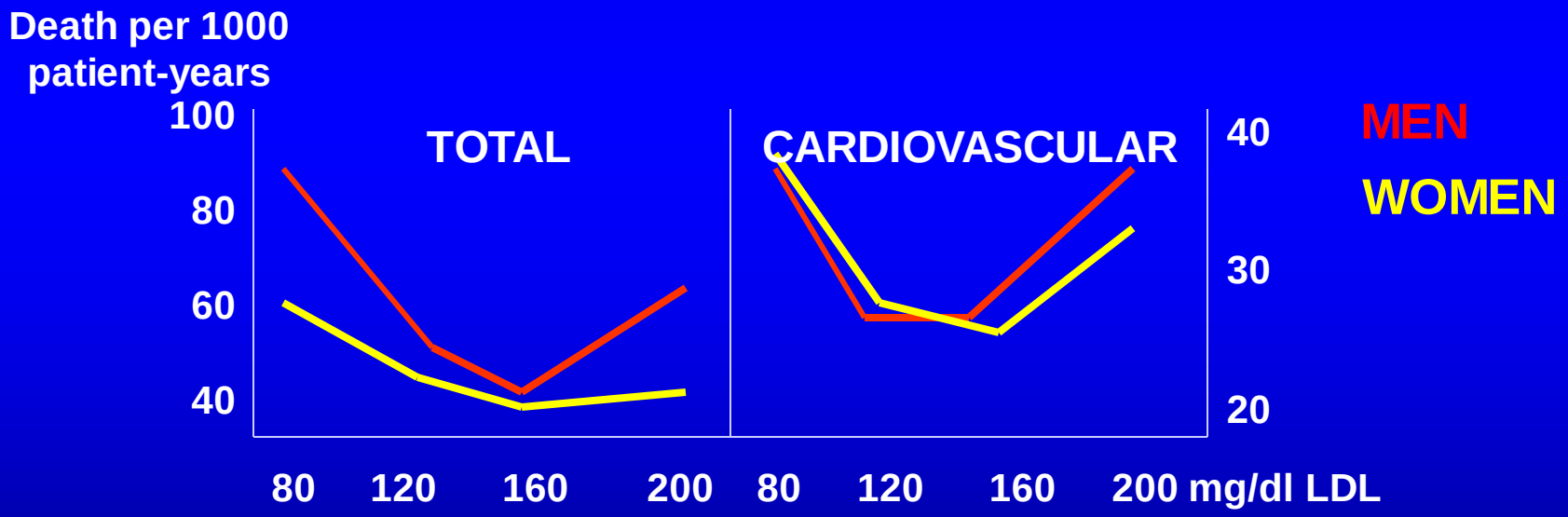


CONCLUSION…the U-shaped associations between TC and LDL-C and CHD imply a complex relationship between lipids and CHD in late life…the results indicate that elevated lipid levels should continue to be treated in healthy elderly individuals, as they are in those who are younger

BRIEF REPORTS

Low-Density Lipoprotein Cholesterol and Mortality in Older People

1887 women and 1223 men 65 years+ (mean age 73.8); mean follow-up 11.1 years



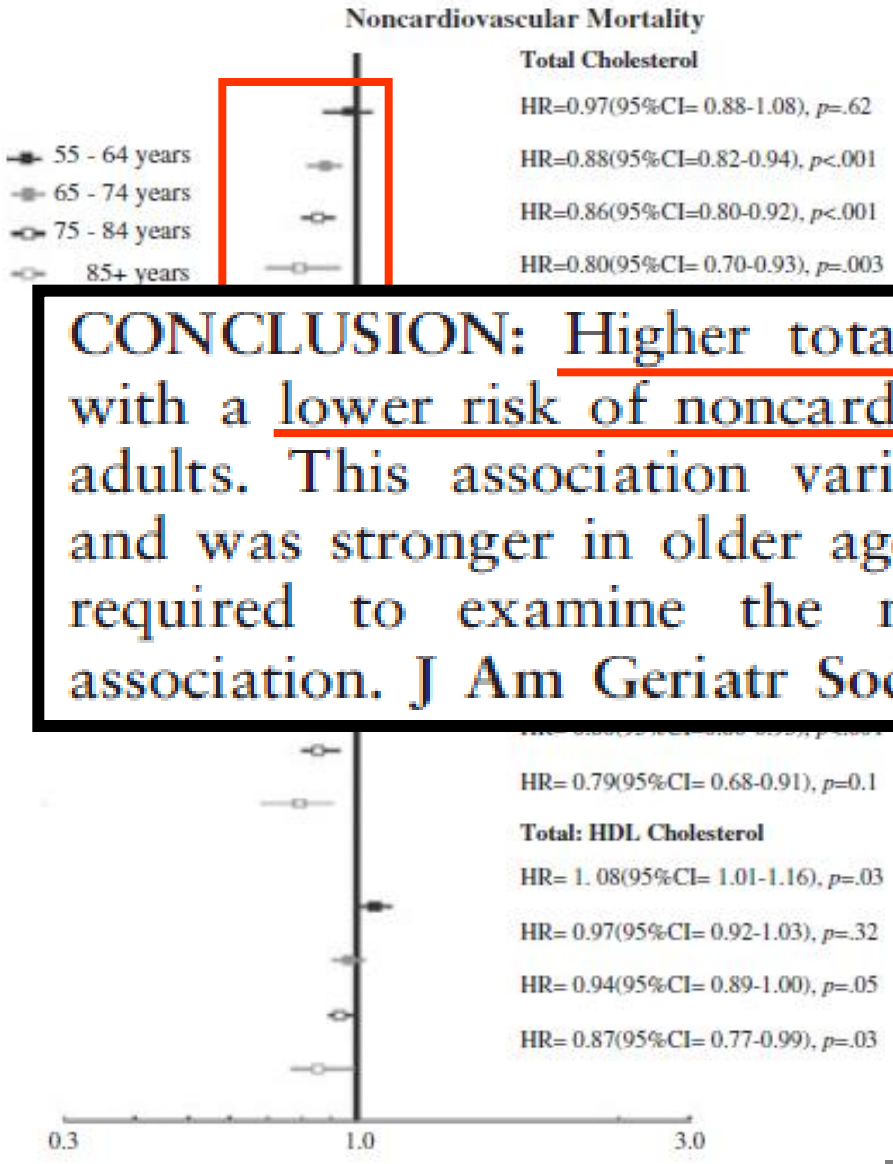
CONCLUSION: This study adds to the uncertainty of the role of elevated levels of LDL-C as a risk factor for mortality in old people.

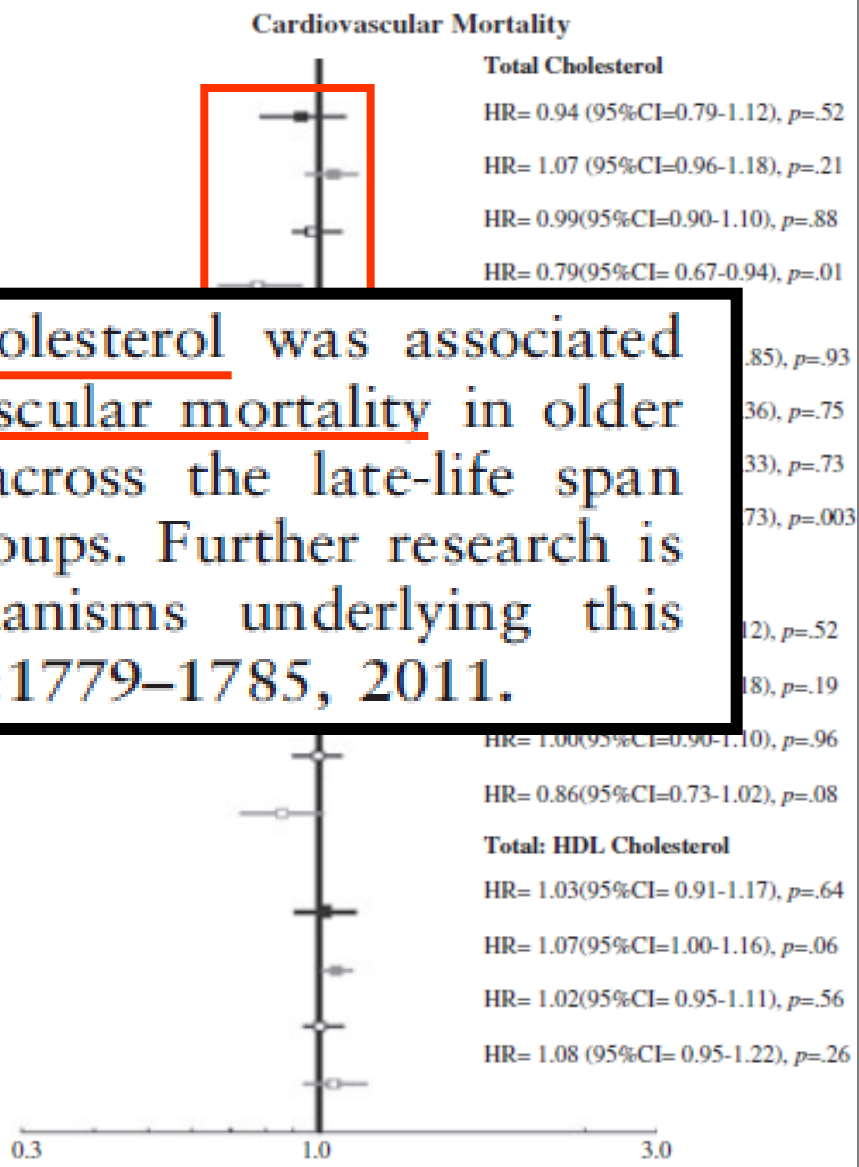
J. Am. Geriatr. Soc. 2005

J Am Geriatr Soc 59:1779–1785, 2011.

Association Between Serum Cholesterol and Noncardiovascular Mortality in Older Age

Prospective population-based cohort study; 5750 adults aged 55 to 99; median follow up 13.9 years





CONCLUSION: Higher total cholesterol was associated with a lower risk of noncardiovascular mortality in older adults. This association varied across the late-life span and was stronger in older age groups. Further research is required to examine the mechanisms underlying this association. J Am Geriatr Soc 59:1779–1785, 2011.

Journal of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci. 2010 May;65A(5):488–494
doi:10.1093/gerona/glq014

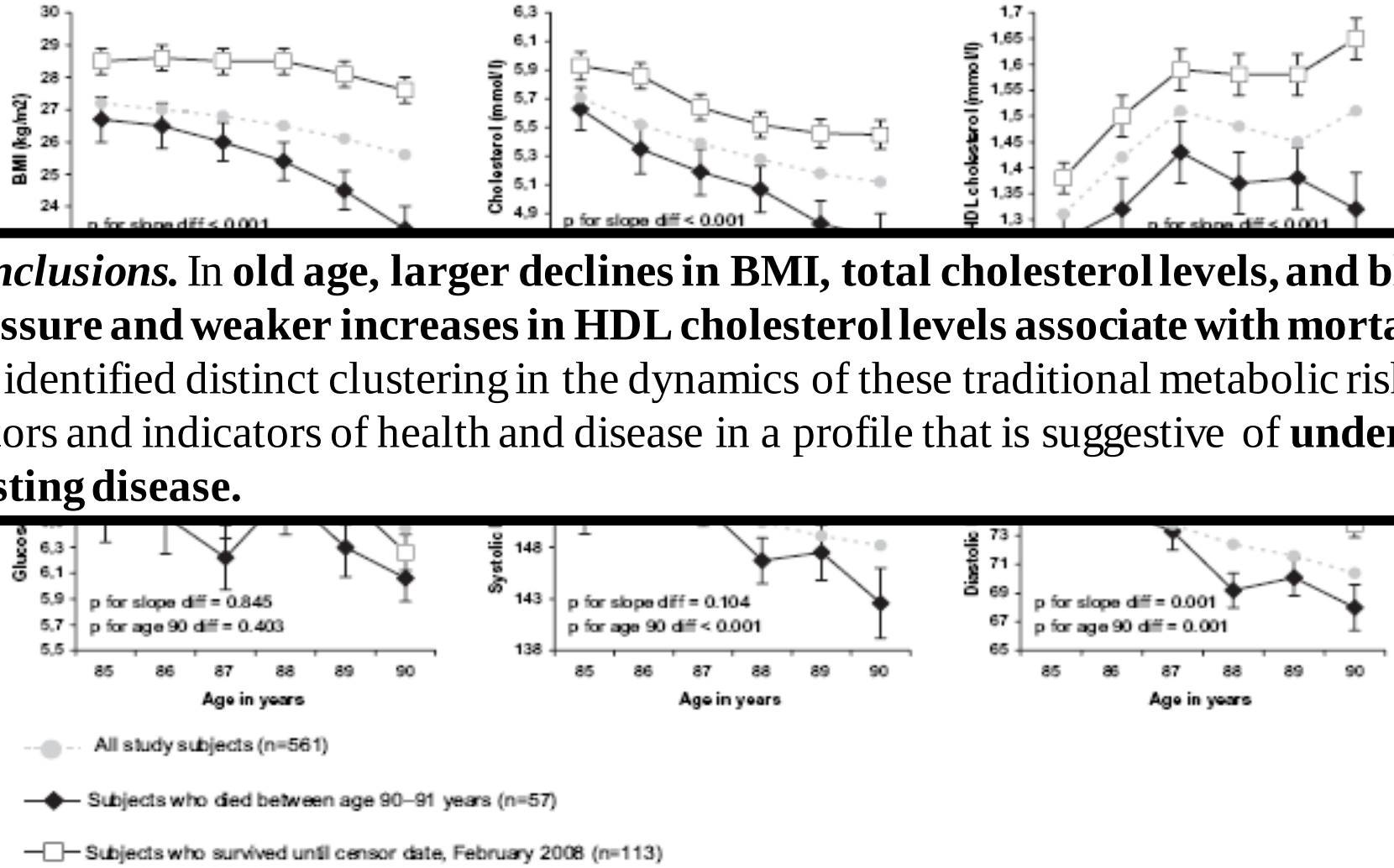
© The Author 2010. Published by Oxford University Press on behalf of The Gerontological Society of America.
All rights reserved. For permissions, please e-mail: journals.permissions@oxfordjournals.org.

Advance Access published on February 12, 2010

Dynamics of Traditional Metabolic Risk Factors Associate With Specific Causes of Death in Old Age

Leiden Plus Study on 599 patients aged >=85 years

Late life annual changes in traditional metabolic risk factors dependent on survival



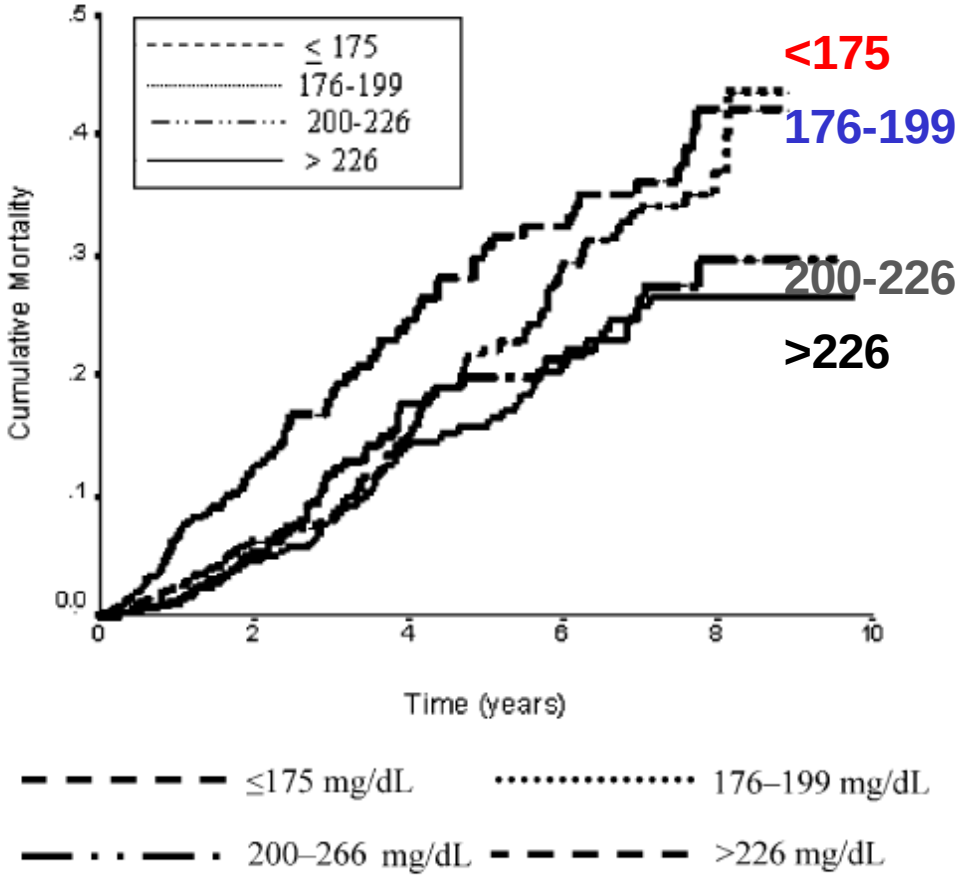
Conclusions. In **old age, larger declines in BMI, total cholesterol levels, and blood pressure and weaker increases in HDL cholesterol levels associate with mortality**. We identified distinct clustering in the dynamics of these traditional metabolic risk factors and indicators of health and disease in a profile that is suggestive of **underlying wasting disease.**

Relationship Between Plasma Lipids and All-Cause Mortality in Nondemented Elderly

JAGS 53:219–226, 2005

SETTIN: Community-based sample of Medicare recipients, aged 65 years and older, residing in northern Manhattan.

PARTICIPANTS: Two thousand two hundred seventy-seven nondemented elderly, aged 65 to 98; 672 (29.5%) white/non-Hispanic, 699 (30.7%) black/non-Hispanic, 876 (38.5%) Hispanic, and 30 (1.3%) other.



<175

176-199

200-226

>226

Figure 2. Risk of death by quartiles of total cholesterol.

CONCLUSION: Low cholesterol level is a robust predictor of mortality in the nondemented elderly and may be a **surrogate of frailty** or **subclinical disease…**

Participants taking lipid-lowering drugs were only one-quarter as likely to die as those not taking drugs

Journal of the American College of Cardiology
© 2004 by the American College of Cardiology Fou
Published by Elsevier Inc.
Vol. 44, No. 5, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.06.022

EDITORIAL COMMENT

Low and Lowered Cholesterol and Total Mortality*

Michael H. Criqui, MD, MPH,†‡
Beatrice A. Golomb, MD, PHD†§
San Diego, California

Lowest levels. Several prospective population studies have suggested that the mortality benefit associated with lower TC plateaus at levels around 180 mg/dl…

Lowered by treatment. ***Lowered TC***, either by behavioral intervention or – much more potently – by ***drug therapy***, ***is a question distinct from naturally low TC***. The evidence that pharmacologic therapy of dyslipidemia in higher risk middle-aged men results in a total mortality benefit is extensive and convincing…. The benefits of statins…appear proportional to the degree of improvement in the TC/HDL ratio, and by far the largest reductions in event rates reported occurred with combination statin and niacin therapy, with the attendant profound lowering of the TC/HDL ratio….Only consideration of HDL cholesterol allows much predictive power at middle or older ages.

Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study)

Lancet 2005; 366: 1773–83

P M Rothwell, A J Coull, L E Silver, J F Fairhead, M F Giles, C E Lovelock, J N E Redgrave, L M Bull, S J V Welch, F C Cuthbertson, L E Binney, S A Gutnikov, P Anslow, A P Banning, D Mant, Z Mehta, for the Oxford Vascular Study

…all individuals presenting with an acute vascular event of any type in any arterial territory irrespective of age in a population of 91106 in Oxfordshire, UK, in 2002-05

…2024 acute vascular events occurred in 1657 individuals: 918 (45%) cerebrovascular (618 stroke, 300 TIA); 856 (42%) coronary vascular (159 STEMI, 316 NSTEMI, 218 UA, 163 SCD); 188 (9%) peripheral vascular (43 aortic, 53 embolic visceral or limb ischemia, 92 critical limb ischemia)…event and incidence rates rose steeply with age in all arterial territories, with 80% cerebrovascular, 73% coronary and 78% peripheral vascular events in 12886 (14%) individuals aged 65 years or older; and 54%, 47% and 56%, respectively, in the 5919 (6%) aged 75 years or older….although case fatality rates increased with age, 47% of non-fatal events occurred at age 75 years or older

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2012;366:321-9.

ORIGINAL ARTICLE

Lifetime Risks of Cardiovascular Disease

Lifetime risks of fatal and nonfatal events according to aggregate burden of risk factors in men and women

Variable	Risk-Factor Status				
	All Risk Factors Optimal	≥1 Risk Factor Not Optimal	≥1 Elevated Risk Factor	1 Major Risk Factor	≥2 Major Risk Factors
	percent (95% confidence interval)				
Risk at 75 yr of age Men					
Fatal coronary heart disease or nonfatal myocardial infarction	9.2 (0–21.8)	12.5 (5.0–20.0)	22.1 (17.1–27.1)	29.3 (25.5–33.0)	34.6 (29.2–40.0)
Fatal or nonfatal stroke		9.1 (5.9–12.3)	10.6 (8.4–12.8)	9.1 (7.7–10.5)	9.6 (7.6–11.6)
Death from cardiovascular disease	20.7 (11.1–30.3)	18.7 (13.9–23.5)	28.1 (24.6–31.6)	32.2 (29.6–34.7)	39.3 (35.8–42.9)
Total events related to atherosclerotic cardiovascular disease	17.5 (3.0–32.0)	22.8 (14.4–31.2)	28.9 (22.7–35.2)	36.1 (31.6–40.5)	38.5 (32.0–45.0)
Risk at 75 yr of age Women					
Fatal coronary heart disease or nonfatal myocardial infarction		10.8 (2.6–19.0)	14.3 (10.5–18.2)	17.3 (14.8–19.9)	27.8 (24.4–31.2)
Fatal or nonfatal stroke		7.8 (4.6–11.1)	10.8 (8.5–13.1)	11.7 (10.3–13.2)	13.7 (11.9–15.5)
Death from cardiovascular disease		19.2 (13.4–25.0)	20.5 (17.4–23.6)	24.3 (22.2–26.3)	33.6 (31.0–36.2)
Total events related to atherosclerotic cardiovascular disease	12.4 (0–25.6)	19.9 (10.9–29.0)	21.8 (16.8–26.8)	29.4 (26.1–32.7)	36.3 (32.2–40.4)

51° CONGRESSO NAZIONALE SIGG

"La longevità del Paese: risorse e problema"

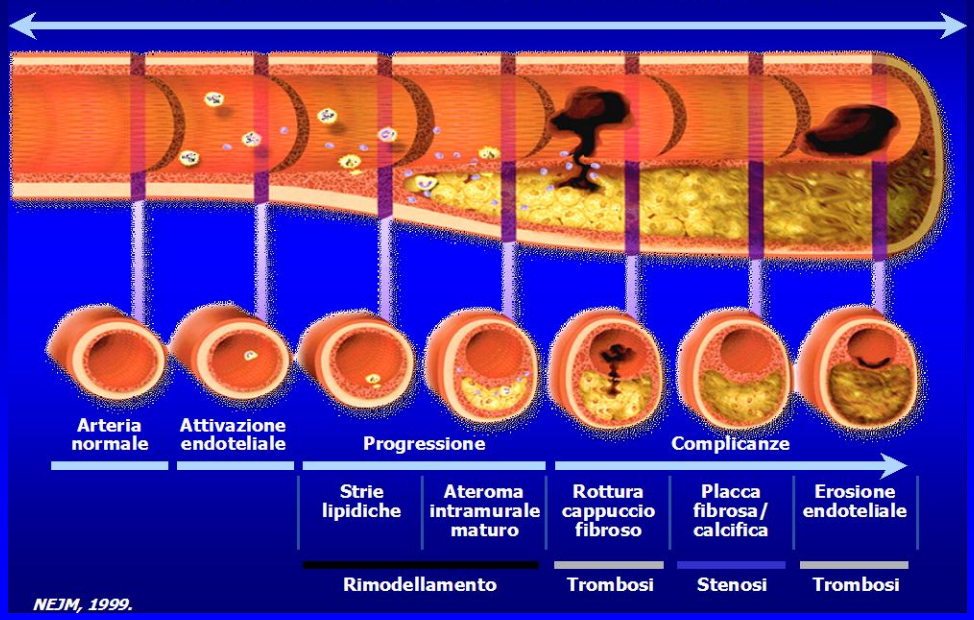
Firenze, 29 novembre-3 dicembre 2006

PAZIENTE ANZIANO E DISLIPIDEMIE: QUALE TRATTAMENTO E' PIU' EFFICACE?

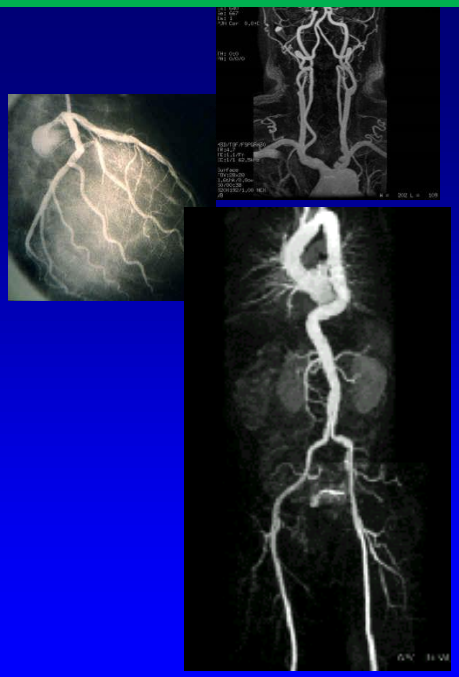
L'evidenza che colesterolo totale ed LDL non sono predittivi di mortalità cardiovascolare e totale nell'insieme dei soggetti anziani non significa necessariamente che non vi sia spazio per i benefici di una terapia ipocolesterolemizzante in questi pazienti. Occorre quindi chiedersi se

Vi sono evidenze che l'intervento ipocolesterolemizzante si associ ad un beneficio in termini di morbilità/mortalità negli anziani?

In caso di risposta affermativa, quali sono le priorità per un trattamento ottimale in questa fascia di età?



DISLIPIDEMIE
FUMO
DIABETE
IPERTENSIONE
ETA'
SESSO
FAMILIARITA'
OBESITA'
SEDENTARIETA'
S.METABOLICA
INFIAMMAZIONE
IPERCOAGULABILITA'…



*…il punto quindi non è tanto l'**ipercolesterolemia** in sé quanto la possibilità della **prevenzione delle manifestazioni cliniche aterosclerotiche** attraverso l'impiego di **farmaci ipocolesterolemizzanti** che hanno dimostrato importanti benefici nei soggetti ad alto rischio CV…occorre quindi valutare se esistano delle evidenze in questo senso e quali siano gli interventi efficaci in questo ambito nell'anziano…*

ORIGINAL INVESTIGATION

Therapy With Hydroxymethylglutaryl Coenzyme A Reductase Inhibitors (Statins) and Associated Risk of Incident Cardiovascular Events in Older Adults

Evidence From the Cardiovascular Health Study

Arch Intern Med. 2002;162:1395-1400

1250 women and 664 men 65 years and older (71.1); mean follow-up 7.3 years; 382 CV events and 362 deaths

Association of drug therapy to lower cholesterol levels with incident CV events

Drug to Lower Cholesterol Levels	Person-years	No. of Events	Unadjusted HR (95% CI)	Adjusted HR (95% CI)†	*P* Value
None	9453	347	1.00	1.00	. . .
Statin	1129	17	0.38 (0.24-0.63)	0.44 (0.27-0.71)	.001
Nonstatin	626	15	0.69 (0.41-1.16)	0.68 (0.40-1.14)	.14
Total	**11 208**	**379**	. . .	. . .	. . .

Association of drug therapy to lower cholesterol levels with mortality

Drug to Lower Cholesterol Levels	Person-Years	No. of Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI)†	*P* Value
		All-Cause Mortality			
None	10 130	325	1.00	1.00	. . .
Statin	1250	21	0.45 (0.29-0.71)	0.56 (0.36-0.88)	.01
Nonstatin	658	8	0.43 (0.21-0.86)	0.43 (0.21-0.88)	.02
Total	**12 038**	**354**	. . .	. . .	. . .
		Cardiovascular Mortality			
None	10 130	141	1.00	1.00	. . .
Statin	1250	9	0.44 (0.22-0.86)	0.54 (0.27-1.08)	.08
Nonstatin	658	4	0.51 (0.19-1.37)	0.50 (0.18-1.36)	.18
Total	**12 038**	**154**	. . .	. . .	. . .

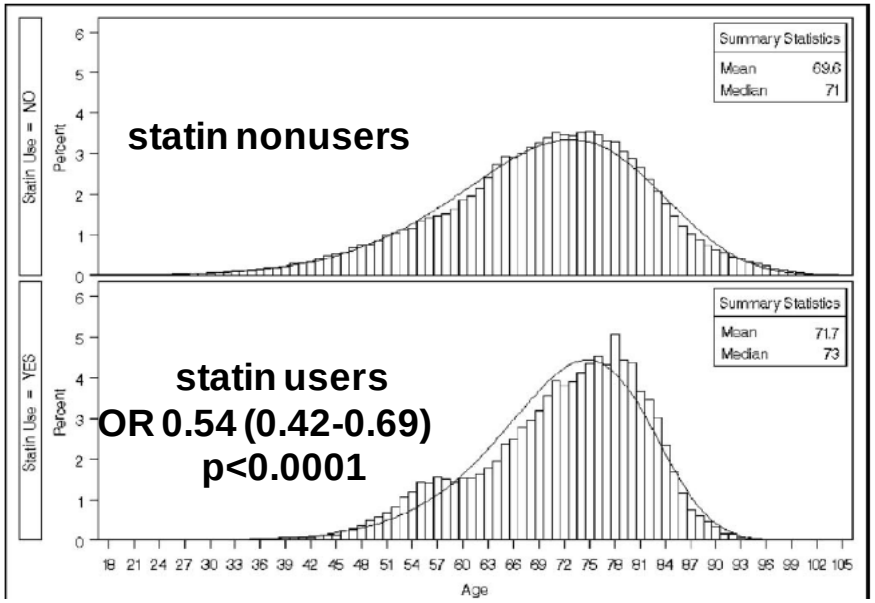
*HR indicates hazard ratio; CI, confidence interval.

…statin use was associated with similar lower risk of incident CV events among **participants 74 years and older** and among participants aged 65 to 73 years…

(Am J Cardiol 2006;98:923–928)

Comparison of Mortality Rates in Statin Users Versus Nonstatin Users in a United States Veteran Population

1.5 million veterans in 10 hospitals

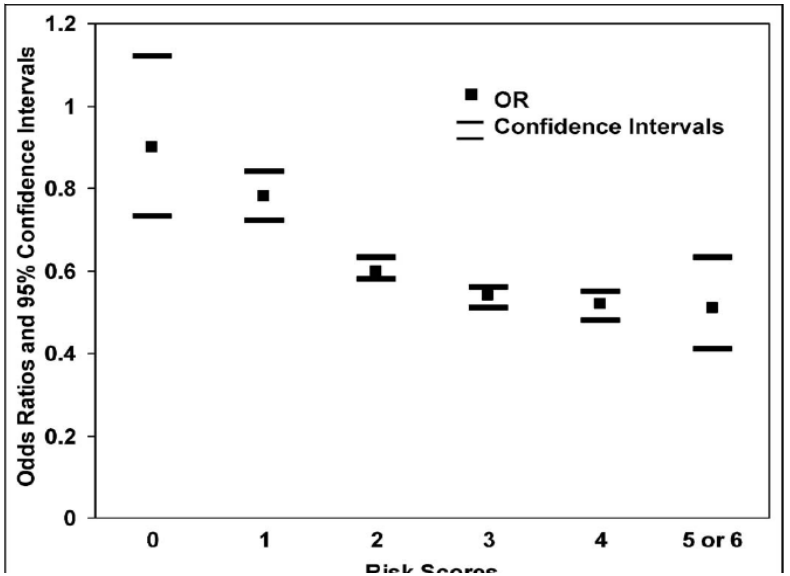


statin nonusers

statin users
OR 0.54 (0.42-0.69)
p<0.0001

Age distribution at death among statin users and nonusers. Age at death was 2.1 years older among statin users (p<0.0001)

Risk score (0-6): age>70; DM; previous MI; hypertension; LDL-C>100 mg/dl; current smoking



Graded relation between risk of death and benefit of statin therapy. For risk scores >1, reduction in death was highly significant

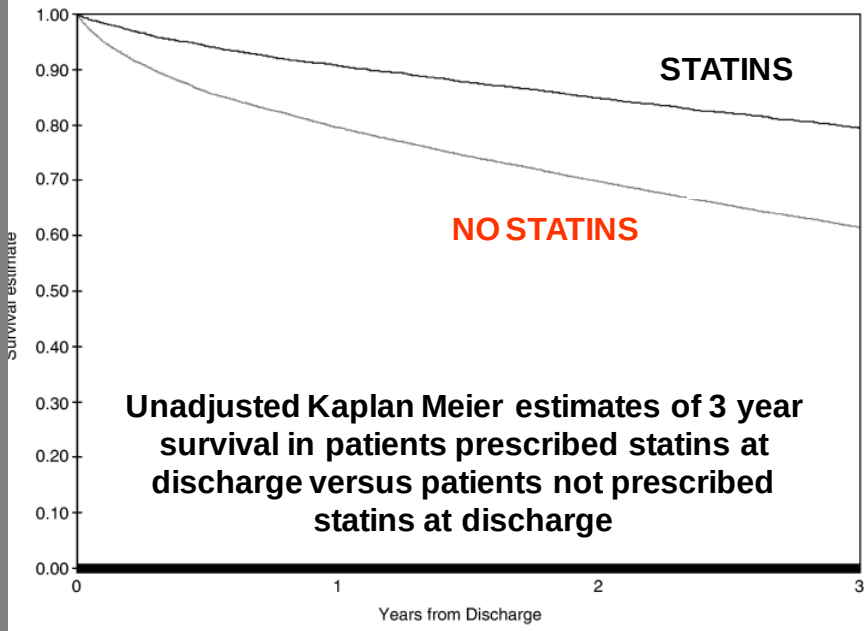
Predictors of death

Statin use	−0.6133 (0.1273)	0.54 (0.42–0.69)	23.2	<0.0001
Age	0.0378 (0.0059)	1.04 (1.03–1.05)	41.5	<0.0001
Diabetes mellitus	0.4283 (0.137)	1.54 (1.19–1.99)	10.5	0.0012
Cancer	0.7699 (0.1235)	2.16 (1.69–2.75)	38.9	<0.0001
β blockers	0.311 (0.1276)	1.37 (1.06–1.75)	5.9	0.0146
ACE inhibitors	0.3579 (0.146)	1.43 (1.07–1.9)	6	0.0142
Calcium channel blockers	0.2599 (0.1249)	1.3 (1.02–1.66)	4.3	0.0374
Body mass index	−0.0578 (0.013)	0.95 (0.92–0.97)	19.9	<0.0001

Hydroxymethylglutaryl-CoA Reductase Inhibitors in Older Persons with Acute Myocardial Infarction: Evidence for an Age–Statin Interaction

JoAnne Micale Foody, MD,†§‖¶ Saif S. Rathore, MPH,* Deron Galusha, MS, MS,† Frederick A. Masoudi, MD, MSPH,‖***†† Edward P. Havranek, MD,‖***‡‡ Martha J. Radford, MD,*‡ and Harlan M. Krumholz, MD*†‡‖¶*

JAGS 54:421–430, 2006



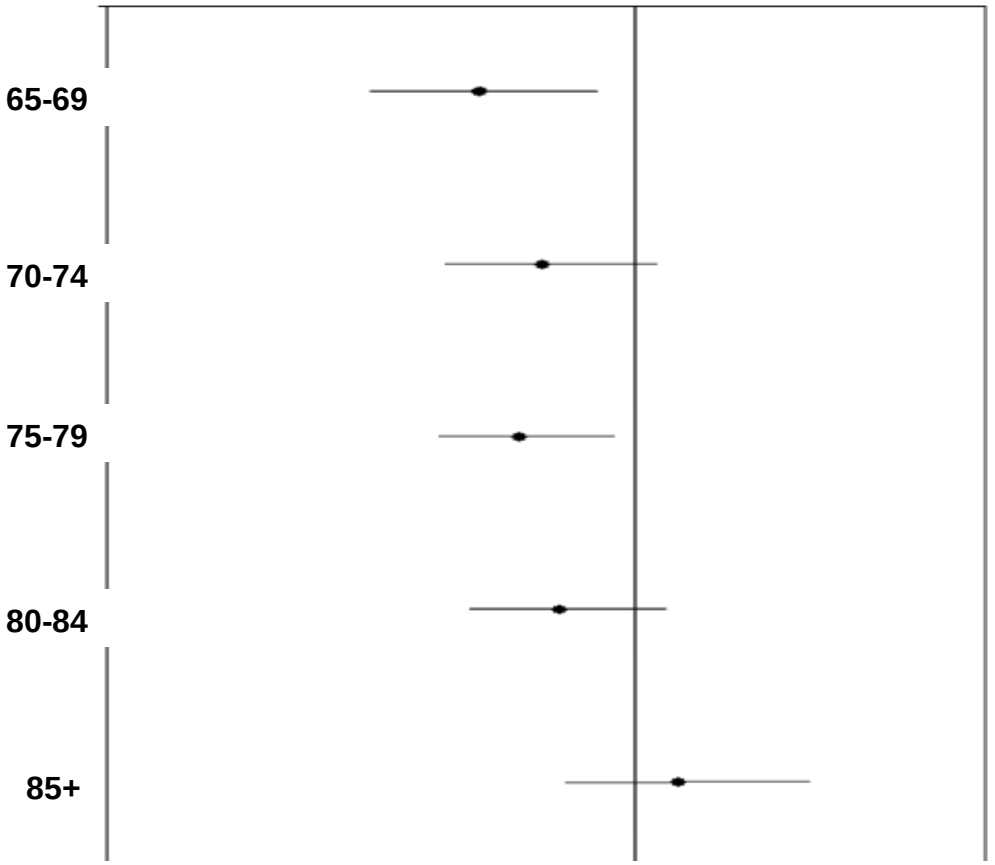
Unadjusted Kaplan Meier estimates of 3 year survival in patients prescribed statins at discharge versus patients not prescribed statins at discharge

Observational study in acute care hospitals in US from april 1998 to june 2001

23013 Medicare patients aged 65 and older who did and did not receive a discharge prescription for statin

8452 of patients (40%) were aged 80 and older

5513/23013 (24%) in the overall sample and 1310/8452 of those aged 80 and older (15.5%) received a statin at discharge



Adjusted hazard ratio (HR) of 3 year mortality for patients prescribed statins at discharge versus patients not prescribed statins at discharge by 5-year age increments.

CONCLUSION-*Statin therapy is associated with lower mortality in older patients with AMI younger than 80 but not in those aged 80 and older, as a group*. This finding questions whether statin efficacy data in younger patients can be broadly applied to the very old and indicated the need for further study of this group.

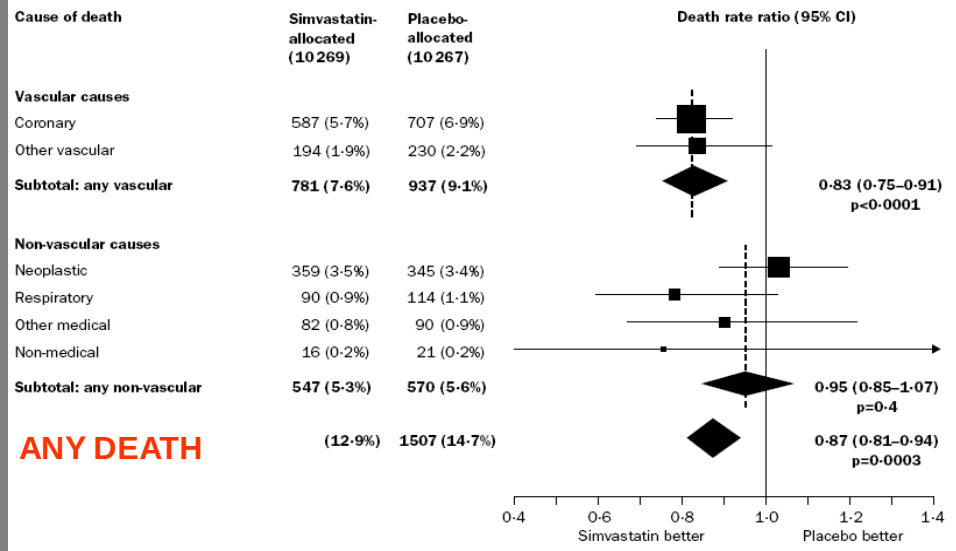
Articles

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial

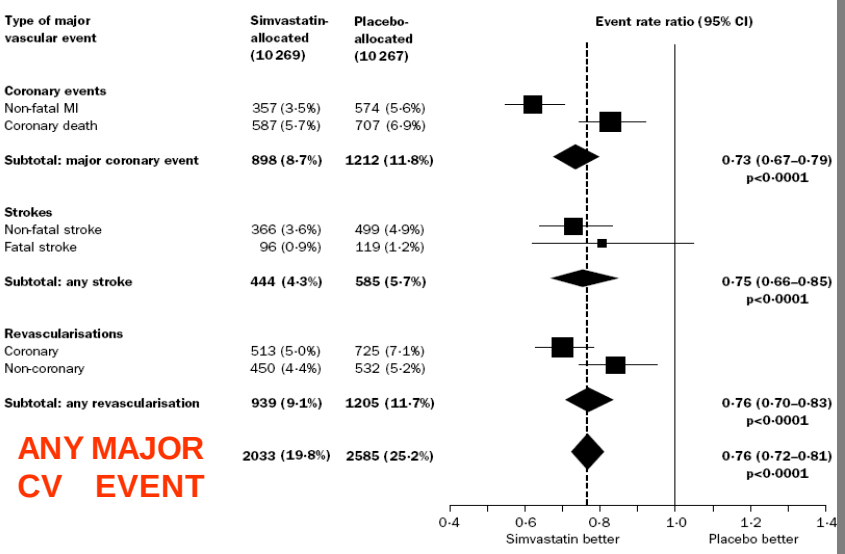
*Heart Protection Study Collaborative Group**

Lancet 2002; **360:** 7–22

20536 pazienti (75% maschi), 40-80 anni (28%>70), col.tot.>134 mg/dl, alto rischio CV: storia di CAD; altre malattie ats ostruttive o precedenti rivascolarizzazioni; DM (tipo 1 e 2); ipertesi se maschi >65 anni



Cause of death	Simvastatin-allocated (10 269)	Placebo-allocated (10 267)
Vascular causes		
Coronary	587 (5·7%)	707 (6·9%)
Other vascular	194 (1·9%)	230 (2·2%)
Subtotal: any vascular	**781 (7·6%)**	**937 (9·1%)**
Non-vascular causes		
Neoplastic	359 (3·5%)	345 (3·4%)
Respiratory	90 (0·9%)	114 (1·1%)
Other medical	82 (0·8%)	90 (0·9%)
Non-medical	16 (0·2%)	21 (0·2%)
Subtotal: any non-vascular	**547 (5·3%)**	**570 (5·6%)**
ANY DEATH	**(12·9%)**	**1507 (14·7%)**



Type of major vascular event	Simvastatin-allocated (10 269)	Placebo-allocated (10 267)
Coronary events		
Non-fatal MI	357 (3·5%)	574 (5·6%)
Coronary death	587 (5·7%)	707 (6·9%)
Subtotal: major coronary event	**898 (8·7%)**	**1212 (11·8%)**
Strokes		
Non-fatal stroke	366 (3·6%)	499 (4·9%)
Fatal stroke	96 (0·9%)	119 (1·2%)
Subtotal: any stroke	**444 (4·3%)**	**585 (5·7%)**
Revascularisations		
Coronary	513 (5·0%)	725 (7·1%)
Non-coronary	450 (4·4%)	532 (5·2%)
Subtotal: any revascularisation	**939 (9·1%)**	**1205 (11·7%)**
ANY MAJOR CV EVENT	**2033 (19·8%)**	**2585 (25·2%)**

Presenting feature	Simvastatin-allocated	Placebo-allocated	Heterogeneity or trend χ^2
Age (years)			
<65	831/4903(16·9%)	1091/4936(22·1%)	0·73
≥65 <70	512/2447(20·9%)	665/2444(27·2%)	
≥70	690/2919(23·6%)	829/2887(28·7%)	

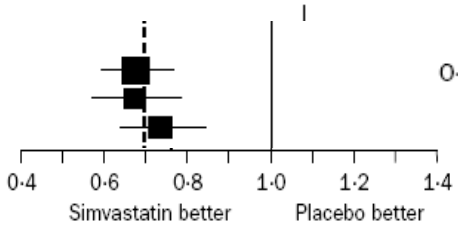


Figure 8: **Effects of simvastatin allocation on first major vascular event in different categories of participant**

Articles

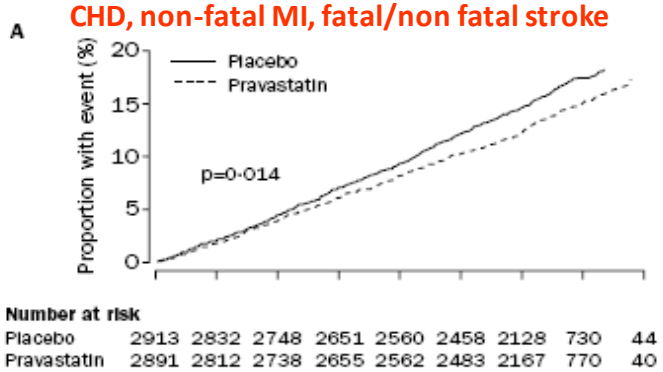
Lancet 2002; **360:** 1623–30. Published online Nov 19, 2002

Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial

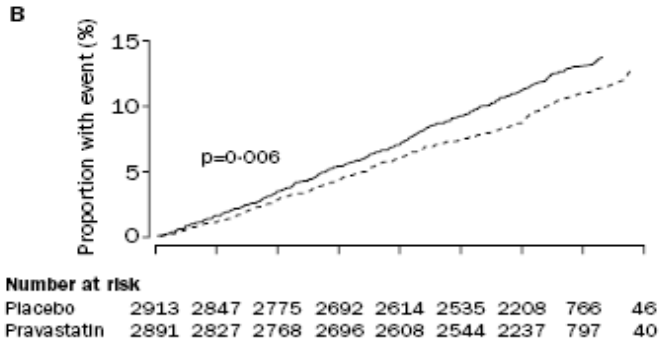
- 5804 patients (2804 men), 70-82 years with history of, or risk factors for, vascular disease
- Pravastatin 40 mg/day vs placebo, follow-up 3.2 years
- Primary end-point: composite of coronary death, non-fatal MI, fatal and non-fatal stroke

	Placebo (2913)	Pravastatin (2891)	Hazard ratio (95%CI)
Primary end-point	473 (16.2%)	408 (14.1%)	0.85 (0.74-0.97)
CHD death or non-fatal MI	356 (12.2%)	292 (10.1%)	0.81 (0.69-0.94)
Fatal/non-fatal stroke	131 (4.5%)	135 (4.7)	1.03 (0.81-1.31)
All CV end-points	523 (18%)	454 (15.7%)	0.85 (0.75-0.97)
CHD deaths	122 (4.2%)	94 (3.3%)	0.76 (0.58-0.99)
Cancer	91 (3.1%)	115 (4%)	1.28 (0.97-1.68)
All-cause mortality	306 (10.5%)	298 (10.3%)	0.97 (0.83-1.14)

CHD, non-fatal MI, fatal/non fatal stroke



CHD death or non-fatal MI



Fatal/non-fatal stroke

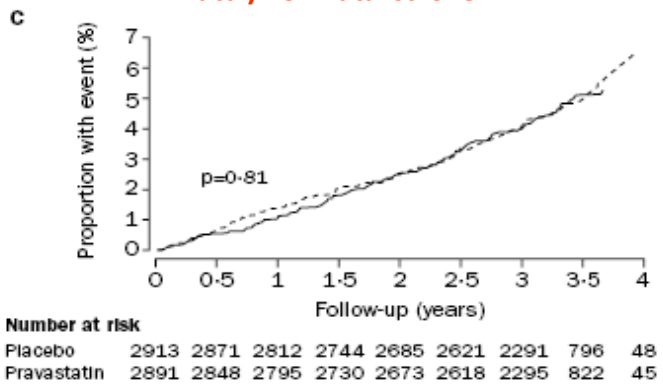


Figure 2: **Kaplan-Meier analysis of time to primary and secondary endpoints**
A=coronary heart disease death, non-fatal myocardial infarction, or fatal or non-fatal stroke. B=coronary heart disease death or non-fatal myocardial infarction. C=fatal or non-fatal stroke.

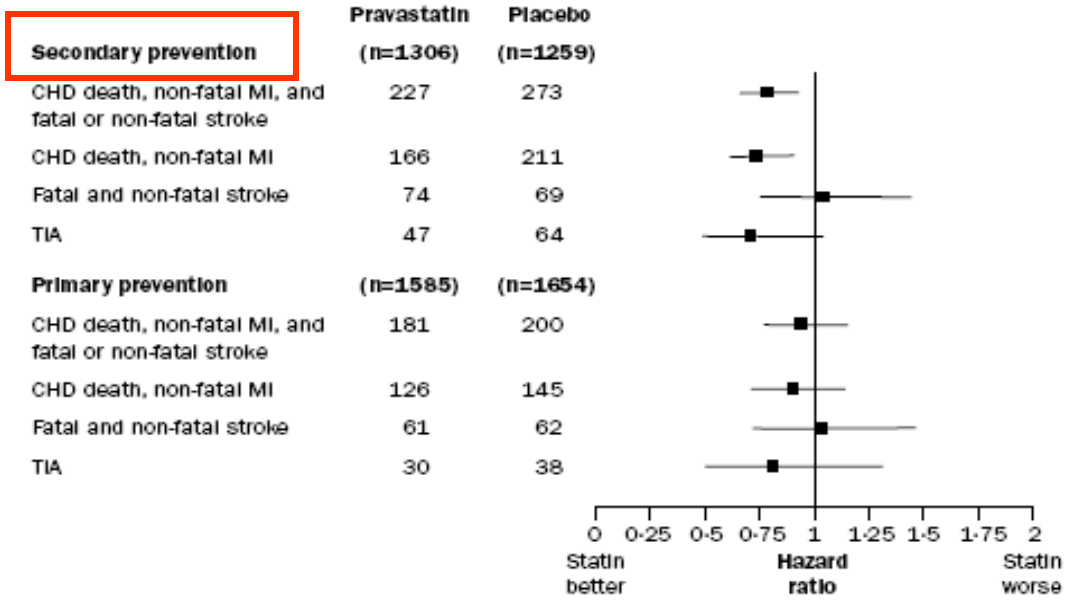


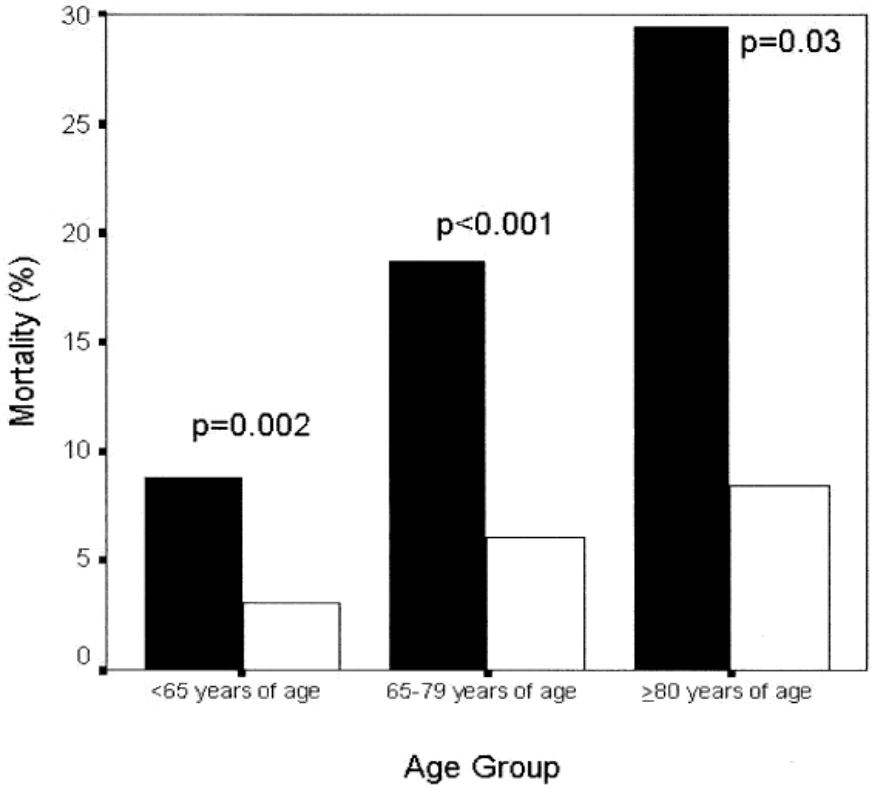
Figure 4: **Major cardiovascular outcomes, according to primary or secondary prevention status of participants**
CHD=coronary heart disease. MI=myocardial infarction. TIA=transient ischaemic attack. The primary endpoint of the study is reproduced for comparative purposes.

Interpretation Pravastatin given for 3 years reduced the risk of coronary disease in elderly individuals. PROSPER therefore extends to elderly individuals the treatment strategy currently used in middle aged people.

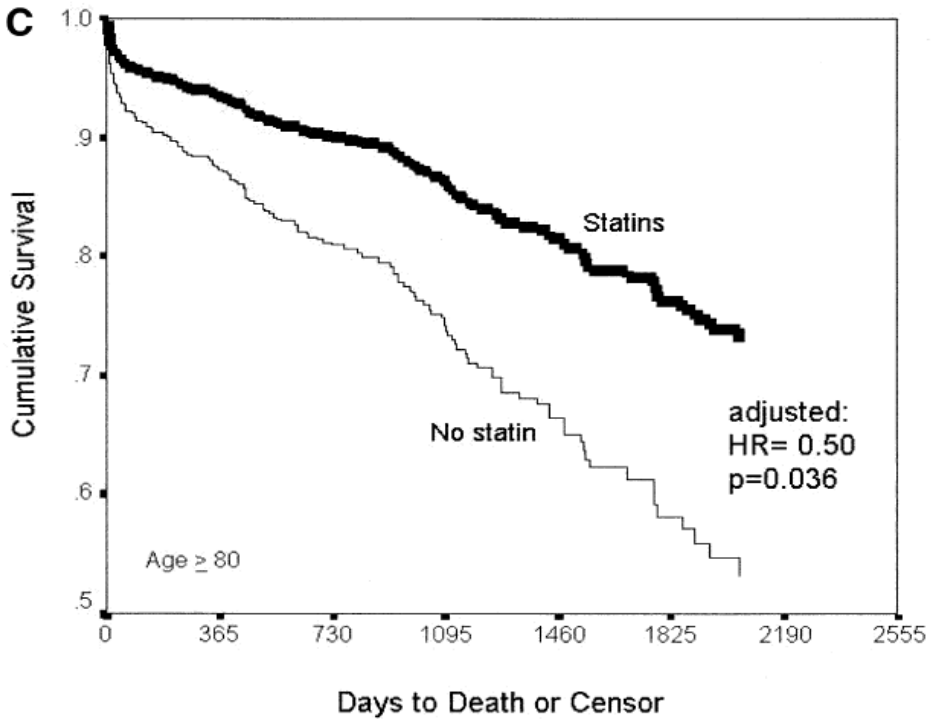
Statin Therapy Is Associated With Reduced Mortality Across All Age Groups of Individuals With Significant Coronary Disease, Including Very Elderly Patients

(J Am Coll Cardiol 2002;40:1777–85)

Studio osservazionale su **7220 pazienti** con CAD definita angiograficamente, seguiti per un periodo di 3.3 anni in relazione all'uso di statine in rapporto all'età



Mortalità in pazienti che **assumevano (colonne bianche)** e **non assumevano (colonne nere) statine**



Analisi **multivariata** dell'effetto delle **statine** sulla **mortalità complessiva** nei pazienti di **80+ anni**

Journal of the American College of Cardiology
© 2008 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 51, No. 1, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.06.063

Lipids and Atherosclerosis

Statins for Secondary Prevention in Elderly Patients

A Hierarchical Bayesian Meta-Analysis

Jonathan Afilalo, MD,* Gustavo Duque, MD, PHD,*† Russell Steele, PHD,‡
J. Wouter Jukema, MD, PHD,§ Anton J. M. de Craen, PHD,‖ Mark J. Eisenberg, MD, MPH*¶

Montreal, Canada; and Leiden, the Netherlands

9 trials, 19569 pazienti, range età basale 65-82 anni

(C)

Study	No. Events/ Total No. of Patients: Statin	Placebo	Posterior Median Relative Risk (95% Credible Interval)
4S	89 / 518	122 / 503	0.75 (0.62 , 0.89)
CARE	41 / 640	57 / 643	0.73 (0.57 , 0.93)
FLARE	5 / 179	9 / 187	0.72 (0.49 , 0.98)
LIPID	110 / 1741	138 / 1773	0.77 (0.64 , 0.93)
LIPS	12 / 324	16 / 299	0.72 (0.51 , 0.97)
PLAC I	2 / 42	6 / 52	0.73 (0.48 , 0.99)
PROSPER	98 / 934	116 / 899	0.78 (0.64 , 0.95)
REGRESS	0 / 75	1 / 63	0.71 (0.43 , 0.97)
Pooled (5 year)	**357 / 4453**	**465 / 4419**	**0.74 (0.60 , 0.89)**

Favors Statin | Favors Placebo

RRR 26%, NNT 28

(D)

Study	No. Events/ Total No. of Patients: Statin	Placebo	Posterior Median Relative Risk (95% Credible Interval)
CARE	29 / 640	47 / 643	0.72 (0.51 , 0.92)
HPS	280 / 5366	390 / 5331	0.73 (0.64 , 0.84)
LIPID	104 / 1741	119 / 1773	0.80 (0.66 , 1.01)
PLAC I	0 / 42	2 / 52	0.72 (0.35 , 1.04)
PROSPER	45 / 934	53 / 899	0.77 (0.60 , 1.02)
Pooled (5 year)	**458 / 8723**	**611 / 8698**	**0.75 (0.56 , 0.94)**

Favors Statin | Favors Placebo

0.0 0.5 1.0 1.5 2.0

RRR 25%, NNT 58

Bayesian Forest Plot for Non-Fatal MI (C)

Bayesian Forest Plot for Stroke (D)

Journal of the American College of Cardiology
© 2008 by the American College of Cardiology Foundation
Published by Elsevier Inc.

EDITORIAL COMMENT

Prevention and Treatment

A Tale of Two Strategies*

George A. Diamond, MD, FACC,
Sanjay Kaul, MD, FACC
Los Angeles, California

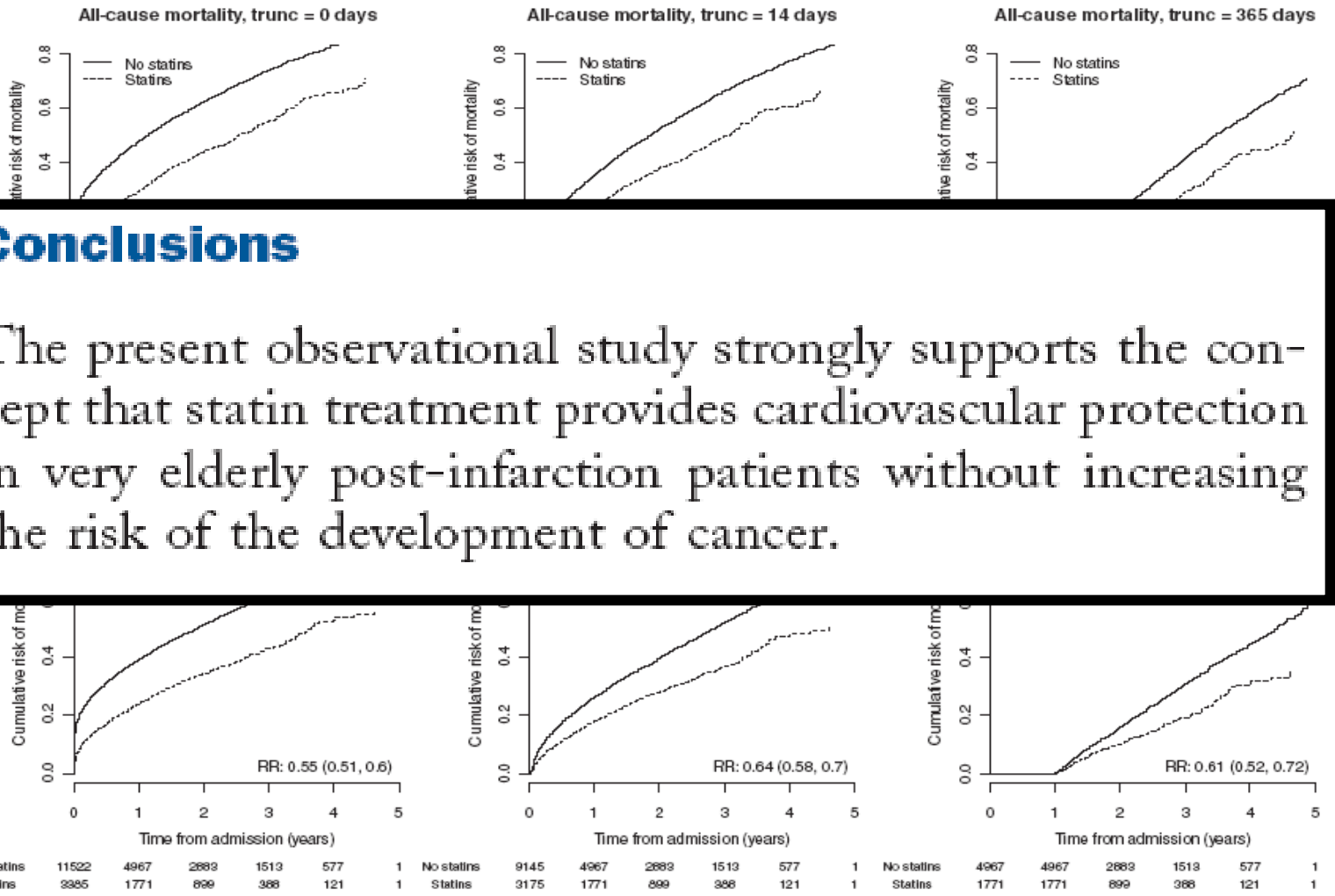
Table 1 Expected Benefit of Statins for Secondary Prevention of Atherosclerotic Events

Age (yrs)	Expected Survival (yrs)	Absolute Annual Mortality (%)	Absolute Mortality Reduction (%)	Absolute Survival Gain (yrs)	Relative Survival Gain (%)
85	2.8	18.8	8.9	2.1	75
70	8.3	5.0	2.2	4.1	49
55	18.8	1.3	0.4	4.3	23

Cardiovascular and Cancer Mortality in Very Elderly Post-Myocardial Infarction Patients Receiving Statin Treatment

Vol. 55, No. 13, 2010
ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2010.01.013

Studio osservazionale su **pazienti >80 anni** con diagnosi di **IMA** tra il 1999 e il 2003. Analisi di sopravvivenza ed eventi in relazione all'uso di statine sul **campione totale** (**popolazione A**, 14907 pazienti) e **dopo aver escluso quelli deceduti entro 14 giorni (popolazione B**) ed **entro un anno (popolazione C**)



Conclusions

The present observational study strongly supports the concept that statin treatment provides cardiovascular protection in very elderly post-infarction patients without increasing the risk of the development of cancer.

Figure 4 Adjusted Cumulative Risk of CVD Mortality Estimated at the Mean of Each Covariate Included in the Model

(J Am Coll Cardiol 2008;52: 1769–81) © 2008
Journal of the American College of Cardiology
© 2008 by the American College of Cardiology Foundation
Published by Elsevier Inc.
Vol. 52, No. 22, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.08.039

Preventive Cardiology

Primary Prevention of Cardiovascular Mortality and Events With Statin Treatments

A Network Meta-Analysis Involving More Than 65,000 Patients

Edward J. Mills, MSc, PhD, LLM,* Beth Rachlis, MSc,§ Ping Wu, MBBS, MSc,‖
Philip J. Devereaux, MD, PhD,*† Paul Arora, MSc,¶ Dan Perri, BScPharm, MD, FRCP(C)†‡
Hamilton and Toronto, Ontario, and Vancouver, British Columbia, Canada; and London, United Kingdom

Conclusions Statins have a clear role in primary prevention of CVD mortality and major events. (J Am Coll Cardiol 2008;52: 1769–81) © 2008 by the American College of Cardiology Foundation

We hope that this newest contribution can put to rest the debate on statin effectiveness for primary prevention and that the debate should now move to better understand the clinical and pharmacoeconomic criteria to delineate when to initiate statins rather than whether to.

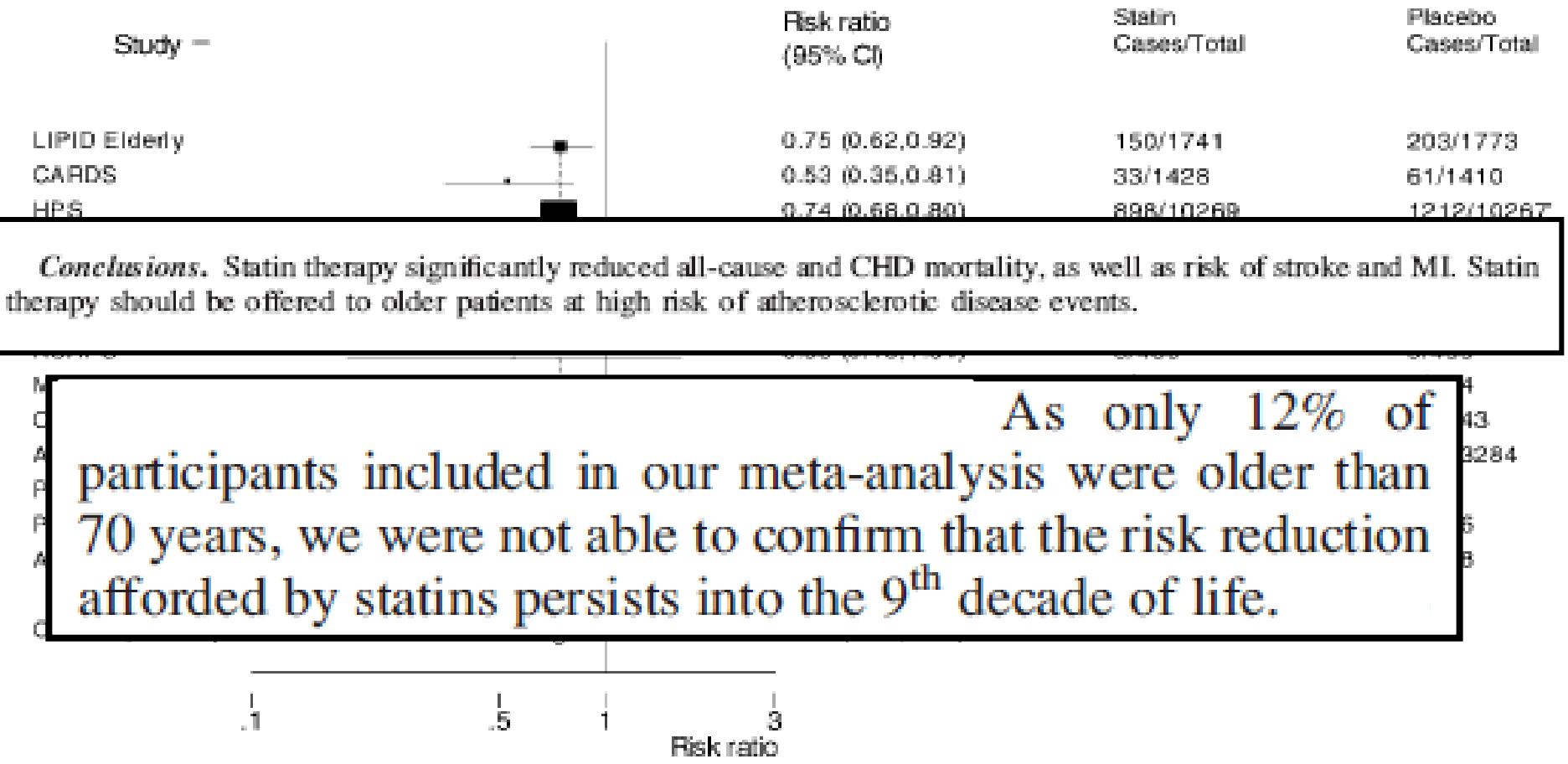
Journal of Gerontology: MEDICAL SCIENCES
2007, Vol. 62A, No. 8, 879–887

Copyright 2007 by The Gerontological Society of America

51351 pazienti **>60 anni** in RCT con statine, prevenzione primaria e secondaria

Efficacy and Safety of Statin Monotherapy in Older Adults: A Meta-Analysis

Caroline G. P. Roberts,[1] Eliseo Guallar,[2] and Annabelle Rodriguez[1]



Conclusions. Statin therapy significantly reduced all-cause and CHD mortality, as well as risk of stroke and MI. Statin therapy should be offered to older patients at high risk of atherosclerotic disease events.

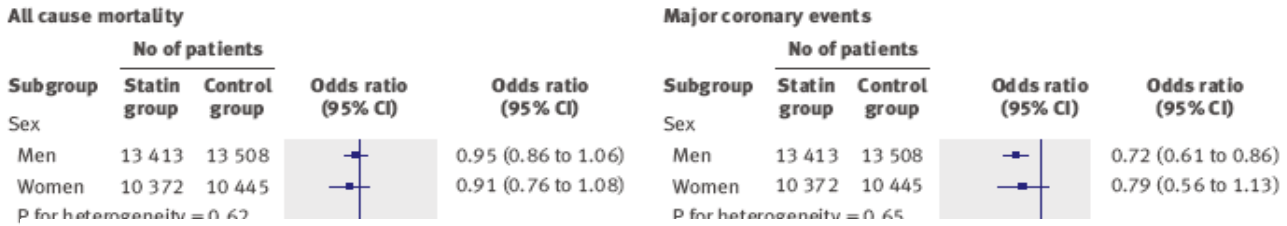
As only 12% of participants included in our meta-analysis were older than 70 years, we were not able to confirm that the risk reduction afforded by statins persists into the 9th decade of life.

Figure 4. Risk ratio for fatal and nonfatal myocardial infarction (MI) from 13 studies.

BMJ

BMJ 2009;338;b2376;

The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials



WHAT IS ALREADY KNOWN ON THIS TOPIC

Statins are effective in patients with established cardiovascular disease (secondary prevention) but whether the benefits apply to primary prevention is unknown

Research has provided ambiguous answers on statin use in people at relatively lower risk

Furthermore, the efficacy of statins in subgroups of people aged more than 65, women, and those with diabetes mellitus is debated

WHAT THIS STUDY ADDS

Statins improve survival and reduce the risk of major cardiovascular and cerebrovascular events in people without established cardiovascular disease

No significant differences in treatment effect of statins were observed in clinically defined groups for age, sex, and diabetes status

People at increased risk for cardiovascular disease should not be denied the relative benefits of long term statin use

Accepted Manuscript

Benefits Of Statins In Elderly Subjects Without Established Cardiovascular Disease. A Meta-Analysis

Gianluigi Savarese, MD Antonio M. Gotto, Stefania Paolillo, MD Carmen D,Amore, MD Teresa Losco, MD Francesca Musella, MD Oriana Scala, MD Caterina Marciano, MD Donatella Ruggiero, MD Fabio Marsico, MD Giuseppe De Luca, MD, PhD Bruno Trimarco, MD, PhD Pasquale Perrone-Filardi, MD, PhD

Methods: Randomized trials comparing statins versus placebo and reporting all-cause and CV mortality, myocardial infarction (MI), stroke, and new cancer onset in elderly (≥65 years old) subjects without established CV disease were included.

Results. Eight trials enrolling 24,674 subjects (42.7% females; mean age 73.0±2.9; mean follow-up 3.5±1.5 years) were included in analyses. Statins, compared to placebo, significantly reduced the risk of MI by 39.4% (relative risk [RR]: 0.606 [95% confidence interval (CI): 0.434 to 0.847]; p=0.003), as well as the risk of stroke by 23.8% (RR: 0.762 [CI: 0.626 to 0.926]; p=0.006). In contrast, the risk of all-cause death (RR: 0.941 [CI: 0.856 to 1.035]; p=0.210) and of CV death (RR: 0.907 [CI: 0.686 to 1.199]; p=0.493) were not significantly reduced. New cancer onset did not differ between statin- compared to placebo-treated subjects (RR: 0.989 [CI: 0.851 to 1.151]; p=0.890).

Conclusions. In elderly subjects at high CV risk without established CV disease, statins significantly reduce the incidence of MI and stroke, but do not significantly prolong survival in the short-term.

CLINICAL PHARMACOLOGY

Statins: established indications and controversial subgroups

J Wouter Jukema,[1,2] Sandrin C Bergheanu[1,2,3]

Heart ONLINE

Table 1 Effect of statin treatment according to the groups of patients

Patients	Overall death	Cardio-vascular death	Cardio-vascular events
High risk with CHD and high baseline cholesterol values	↓	↓	↓
High risk with CHD and average cholesterol values	↓	↓	↓
High risk with high baseline cholesterol values—primary prevention	↓	↓	↓
Heart failure	↔	↔	↓
Chronic kidney disease			
– pre-dialysis	↓	↓	↓
– dialysis	↔	↔	↓
– transplant	↔	↔	↔
– mixed population (pre-dialysis and dialysis)	↔	↓	↓
Elderly with/at risk for CHD	↓	↓	↓

EDITORIAL

Statin Therapy in Older Persons

Pertinent Issues

LDL lowering therapy undoubtedly should be **one therapeutic modality for secondary prevention in older persons with CHD**

The issue of LDL lowering drugs for older persons without CHD is more problematic. LDL lowering drugs should be reserved for persons who are deemed to be at higher risk. In younger elderly (65-75 years) use of statin therapy even in primary prevention is justifiable; in the older persons (>75 years) statins should be used more cautiously

(Grundy S., Arch.Intern. Med. 2002, 162, 1329)

CLINICAL INVESTIGATIONS J Am Geriatr Soc 59:1779–1785, 2011.

Association Between Serum Cholesterol and Noncardiovascular Mortality in Older Age

EDITORIALS

The Cholesterol Conundrum

WHEN SHOULD STATINS BE USED IN OLDER PERSONS?

In persons aged 70 to 80 with documented coronary artery disease, the preponderance of evidence favors the use of statins.

In persons aged 80 and older, there is, for practical purposes, no good evidence to use statins. Based on observational studies, the oldest-old may receive a statin if they have arteriographically documented coronary atherosclerosis. Persons aged 80 and older who are taking a statin should have their LDL size measured, and only if they have a preponderance of small, dense LDL should the statin be continued.

The safety of statins in clinical practice

Jane Armitage

Statins are effective cholesterol-lowering drugs that reduce the risk of cardiovascular disease events (heart attacks, strokes, and the need for arterial revascularisation). Adverse effects from some statins on muscle, such as myopathy and rhabdomyolysis, are rare at standard doses, and on the liver, in increasing levels of transaminases, are unusual. Myopathy—muscle pain or weakness with blood creatine kinase levels more than ten times the upper limit of the normal range—typically occurs in fewer than one in 10 000 patients on standard statin doses. However, this risk varies between statins, and increases with use of higher doses and interacting drugs. Rhabdomyolysis is a rarer and more severe form of myopathy, with myoglobin release into the circulation and risk of renal failure. Stopping statin use reverses these side-effects, usually leading to a full recovery. Asymptomatic increases in concentrations of liver transaminases are recorded with all statins, but are not clearly associated with an increased risk of liver disease. For most people, statins are safe and well-tolerated, and their widespread use has the potential to have a major effect on the global burden of cardiovascular disease.

Lancet 2007; 370: 1781–90

Published Online
June 7, 2007
DOI:10.1016/S0140-6736(07)60716-8

Clinical Trial Service Unit and Epidemiological Studies Unit, Oxford, UK (J Armitage FRCP)

Correspondence to:
Dr Jane Armitage,
Clinical Trial Service Unit and Epidemiological Studies Unit,
Richard Doll Building, University

Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 50, No. 5, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.02.073

Statins and Toxicity

Effect of the Magnitude of Lipid Lowering on Risk of Elevated Liver Enzymes, Rhabdomyolysis, and Cancer

Insights From Large Randomized Statin Trials

Alawi A. Alsheikh-Ali, MD, Prasad V. Maddukuri, MD, Hui Han, MD, Richard H. Karas, MD, PHD
Boston, Massachusetts

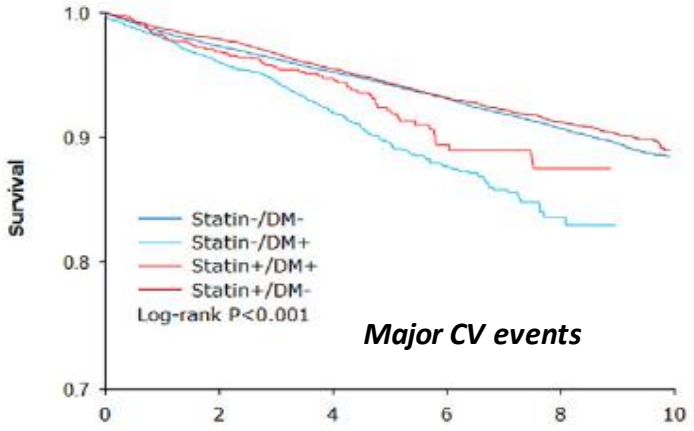
..il rischio di **rabdomiolisi** è principalmente determinato dalla dose di statina piuttosto che dall'entità della riduzione del colesterolo LDL…

.. il **maggior determinante del beneficio** associato all'uso delle statine è **l'entità della riduzione del colesterolo LDL** piuttosto che il tipo o la dose di statina usata… il **maggior determinante della tossicità** (peraltro assai modesta) delle statine non è l'entità della riduzione del colesterolo LDL quanto la **dose di statina usata**… sembra pertanto prudente **non usare dosi di statine superiori a quelle necessarie a raggiungere l'obiettivo LDL desiderato**

..l'insieme delle evidenze rassicura sul fatto che **l'impiego delle statine non è associato ad un maggior rischio di cancro** rispetto al placebo…

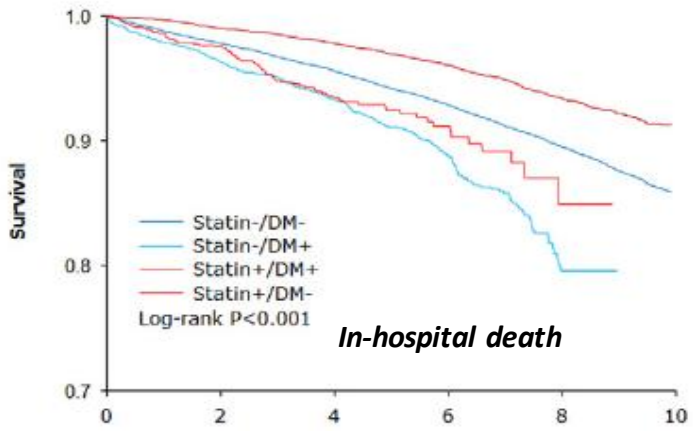
Statins, Risk of Diabetes, and Implications on Outcomes in the General Population

A



Major CV events

B



In-hospital death

Conclusions

Statin use is associated with an increase in diabetes occurrence. However, the benefit of statin treatment overweighs the hazard in high-risk subjects and secondary prevention subjects. The outcomes of those who developed diabetes after statin use are generally favorable in those subgroups.

Therefore, continuous surveillance of signals of dysglycemia should be incorporated into the care program to optimize overall risk management.

Clinical [illegible] netics of STATINS

	Tmax hours	Bio [illegible]			Metab. pathw.	Active metab.	T 1/2 hours	Urinary/ Fecal excret.
ATORVA	2-3	1[illegible]			CYP 3A4	Yes	15-30	2/70
FLUVA	0.5-1	20-30	Yes	>99	CYP 2C9	No	0.5-2	6/90
PRAVA	1-1.5	18	No	43-55	Sulfation	No	1-3	20/71
SIMVA	1-2.5	5	Yes	94-98	CYP 3A4/5	Yes	2-3	13/58
ROSUVA	3	20	No	88	CYP 2C9	Yes (minor)	21	10/90

CYP3A4
Amiodarone
Clarithromicin, Erythromicin
Cyclosporine
Diltiazem, Nifedipine, Verapamile, Lacidipine
Itraconazole, Ketoconazole
Midazolam
Nefazodone
Quinidine
Sildenafil
Warfarin

CYP2C9
Alprenolol
Diclofenac
Fluvastatin
Phenitoin
Tolbutamide
Warfarin

Pharmacol.Ther. 1999, 84, 413-428 J.Clin.Pharmacol. 2002, 42, 963-970

ELDERLY & SAFETY OF STATINS

Patients at highest risk for CHD include **older individuals**, patients after transplantation and patients with hypertension, diabetes or multivessel disease…who are also **the most likely to need multiple medications and thus are at greatest risk for drug-drug interaction**

FACTORS INCREASING THE RISK OF MYOPATHY

- Patient characteristics: **older age; female sex; renal insufficiency; hepatic disease**; hypothyroidism; grapefruit juice; **polypharmacy**
- **Statin properties**: high systemic exposure; **lipophilicity**; high bioavailability; limited protein binding; potential for **drug-drug interactions** metabolized by CYP pathways (CYP3A4)

WHEN PRESCRIBING STATINS CONSIDER:

- Personal characteristics: advanced age (**women and patients >80 years**), **frailty**, **small body frame**, alcohol abuse, muscle disorders, grapefruit juice
- Disease burden: multisystem disease (**chronic RF with diabetes**), **hypothyroidism**, antecedent liver or muscle disease
- High-risk clinical situations: perioperative period
- **Medication burden**

poiché l'anziano è estremamente sensibile e vulnerabile agli effetti avversi delle terapie mediche, la prevenzione cardiovascolare nel vecchio non può prescindere dal

- *Mantenimento e miglioramento dell'autonomia funzionale*
- *Mantenimento della performance psico-cognitiva*
- *Prevenzione del danno iatrogeno*
- *Prevenzione delle cadute*

REVIEW | *Ann Intern Med.* 2013;159:688-697. **Annals of Internal Medicine**

Statins and Cognitive Function

A Systematic Review

Study Selection: Randomized, controlled trials (RCTs) and cohort, case–control, and cross-sectional studies evaluating cognition in patients receiving statins.

Conclusion: Larger and better-designed studies are needed to draw unequivocal conclusions about the effect of statins on cognition. Published data do not suggest an adverse effect of statins on cognition; however, the strength of available evidence is limited, particularly with regard to high-dose statins.

cessing speed, or visuoperception. Examination of the FDA post-marketing surveillance databases revealed a low reporting rate for cognitive-related adverse events with statins that was similar to the rates seen with other commonly prescribed cardiovascular medications.

Statins and Cognitive Decline in Older Adults with Normal Cognition or Mild Cognitive Impairment

JAGS 61:1449–1455, 2013

PARTICIPANTS: Research volunteers with normal cognition at baseline evaluated an average 4.1 times over 3.4 years (1,244 statin users, 2,363 nonusers) and with mild cognitive impairment (MCI) at baseline evaluated an average 3.9 times over 2.8 years (763 users, 917 nonusers).

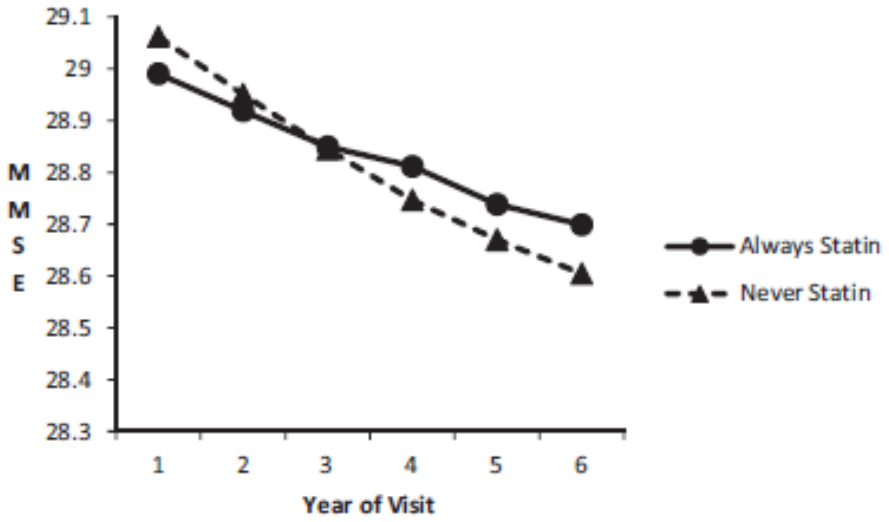


Figure 1. Decline in Mini-Mental State Examination (MMSE) score over annual visits for participants with normal cognition at baseline for statin users and nonusers, from linear regression model.

CONCLUSION: Elderly adults with normal cognition at baseline who used statins had a slower rate of annual worsening in CDR-SOB than nonusers. **J Am Geriatr Soc 61:1449–1455, 2013.**

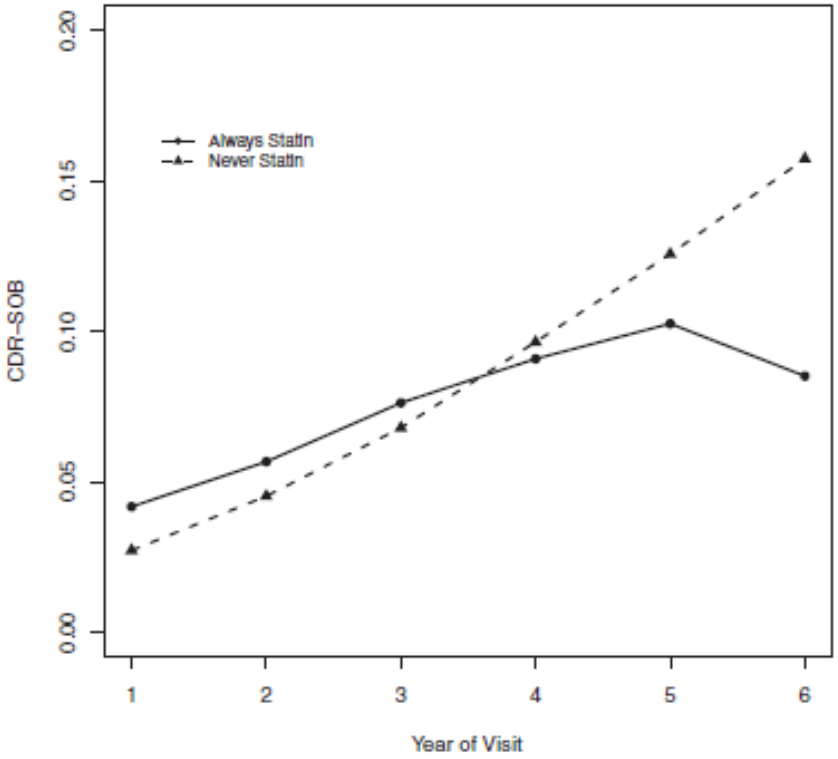


Figure 2. Increase in mean predicted Clinical Dementia Rating Sum of Boxes (CDR-SOB) over annual visits for participants with normal cognition at baseline, statin users vs nonusers, using predicted CDR category from the logistic regression model.

Età estremamente avanzata e/o ridotta spettanza di vita

Dipendenza e non autonomia

Queste condizioni in linea di massima controindicano una prevenzione con statine

Estrema fragilità

Severe comorbilità irreversibili

Valutazione rischio CV globale

Valutazione spettanza di vita, comorbilità e politerapia, stato funzionale e cognitivo, fragilità, tono dell'umore, volontà individuale…

FRAIL /DISABLE

Severità sindromi geriatriche

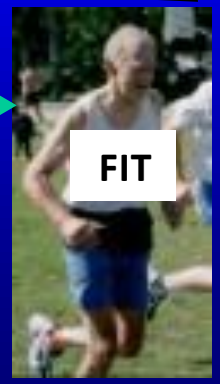
Aggressività prevenzione CV

Isolati fdr dopo i 75 anni

DM e/o plurimi fdr dopo i 75 anni

DM e/o plurimi fdr prima dei 75 anni

Precedenti clinici CV



In sintesi:

- *La **terapia con statine non ha indicazione razionale** negli anziani con **ridotta spettanza di vita, dipendenza funzionale, fragilità** o **severe comorbilità** croniche irreversibili.*

- *Negli **anziani «robusti»** la terapia con statine può essere utile e dovrebbe essere impiegata per ridurre le recidive vascolari **dopo un evento coronarico.***

- *Negli **anziani «robusti» ad alto rischio di ma senza precedenti CV** una terapia con statine già in atto e ben tollerata **può essere continuata fino ai 75 – 80 anni con le più basse dosi efficaci** a condizione che non vi sia rischio di interazioni e tossicità. Non vi sono invece sostanziali evidenze circa l'opportunità di iniziare una prevenzione primaria con statine dopo i 75 anni.*