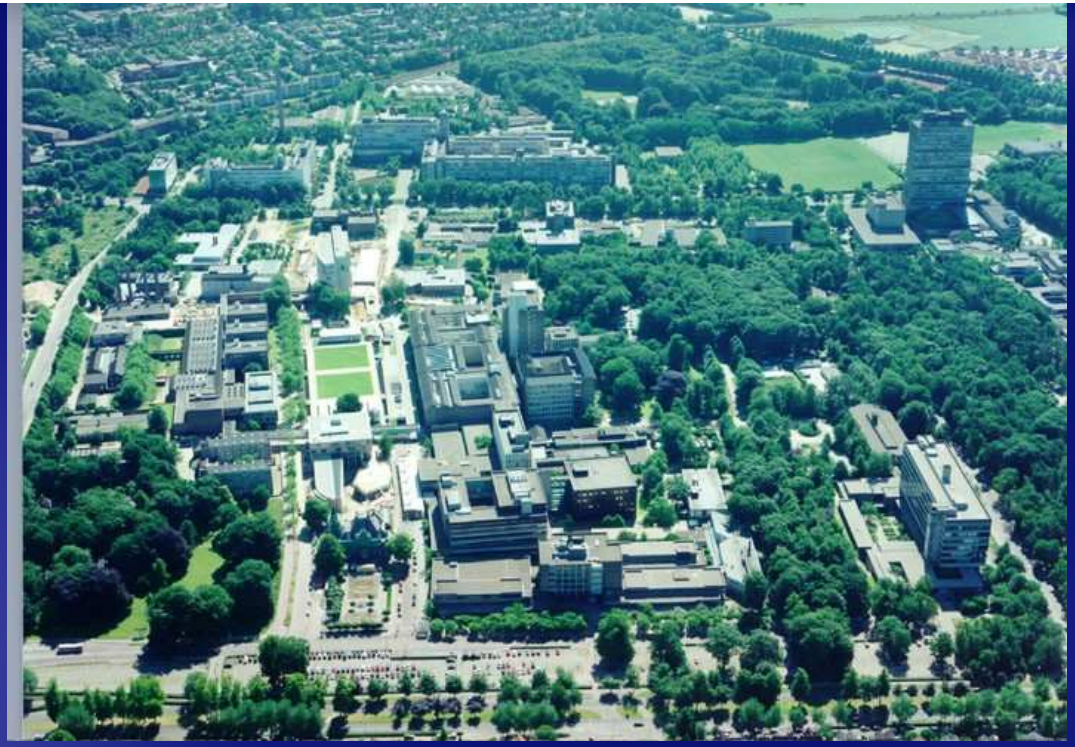


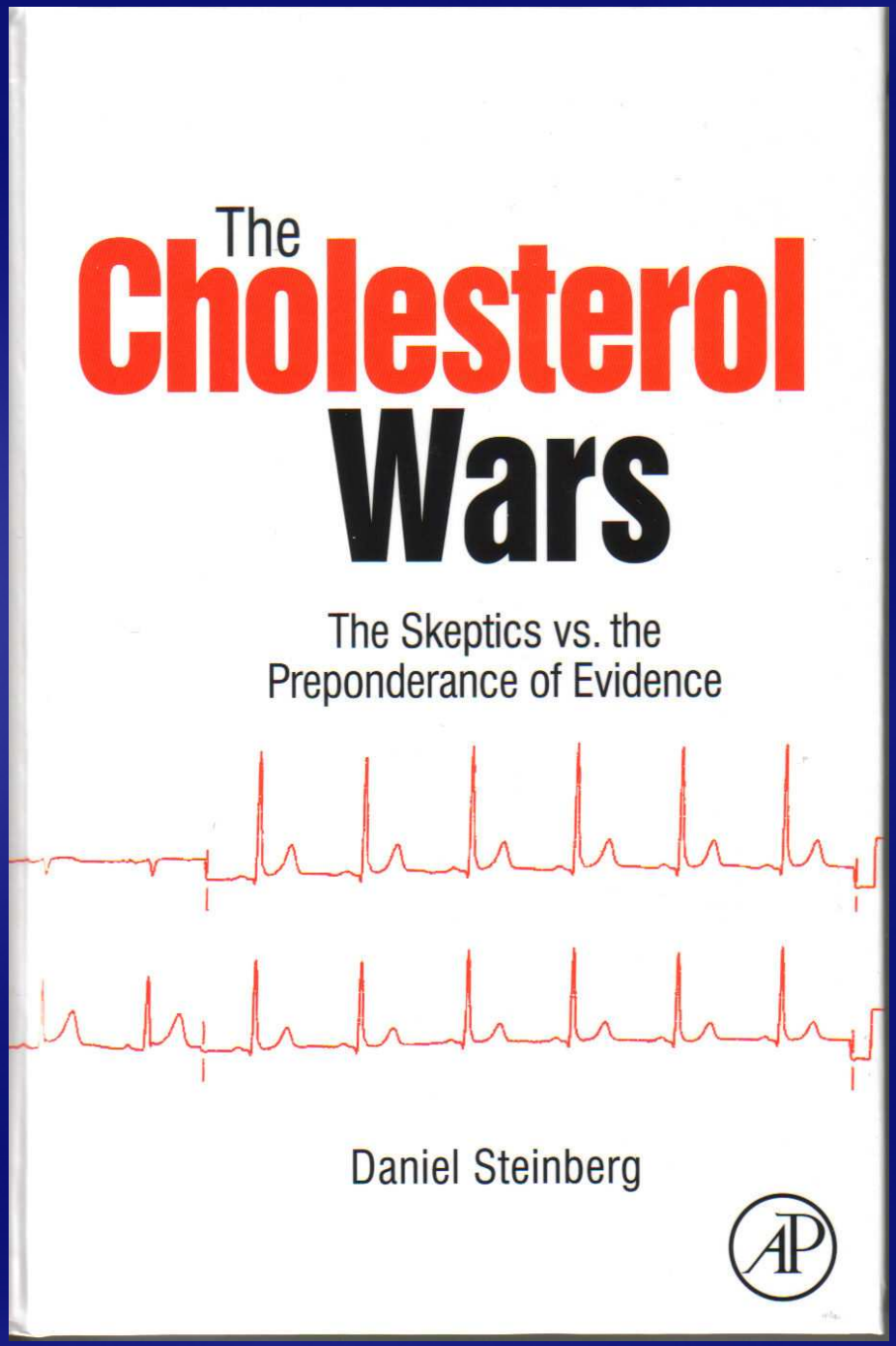
UMC St Radboud

The Cholesterol Controversy: the role of blood cholesterol in cause and complications of heart disease

Prof. Anton Stalenhoef, internist

UMC St Radboud Nijmegen

Satellite Session 9th ISSFAL Conference, Maastricht May 28th, 2010


The
Cholesterol
Wars
The Skeptics vs. the
Preponderance of Evidence
Daniel Steinberg
AP

D.S. S.G.

The Cholesterol Controversy: the role of blood cholesterol in cause and complications of heart disease

History: Pre-statin era

Cholesterol-debate

Introduction of the statins

Present practice

Failures

The Cholesterol Controversy: the role of blood cholesterol in cause and complications of heart disease

History: Pre-statin era

Cholesterol-debate

Introduction of the statins

Present practice

Failures

Milestones on the road to acceptance of the lipid hypothesis

N. Anitschov

1913

Development of atherosclerose after feeding rabbits with cholesterol diet

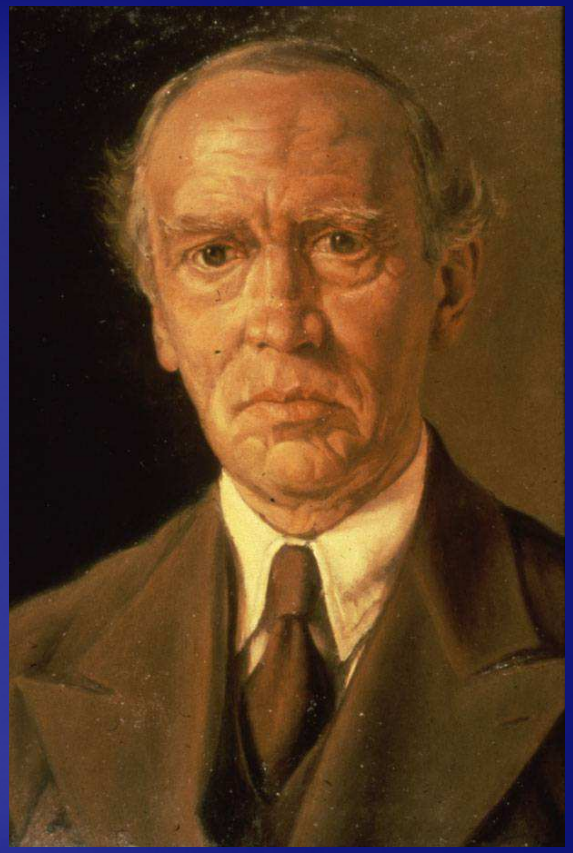
Normal diet

Cholesterol diet

Figure 2. *Dr. Anichkov with his nurse wife-to-be, pictured in 1915.*

Figure 3. *Dr Anichkov in 1945 in the uniform of a Lieutenant General in the Soviet Army.*

Milestones on the road to acceptance of the lipid hypothesis



1913

1943

Prof. C. de Langen: relation cholesterol in diet and blood cholesterol.

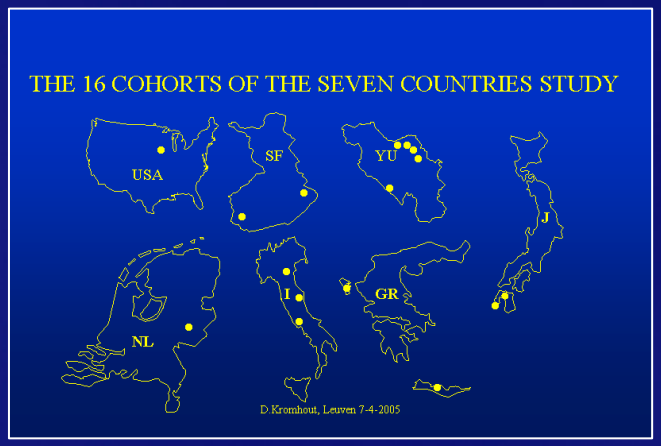
Difference between NL and Indonesia

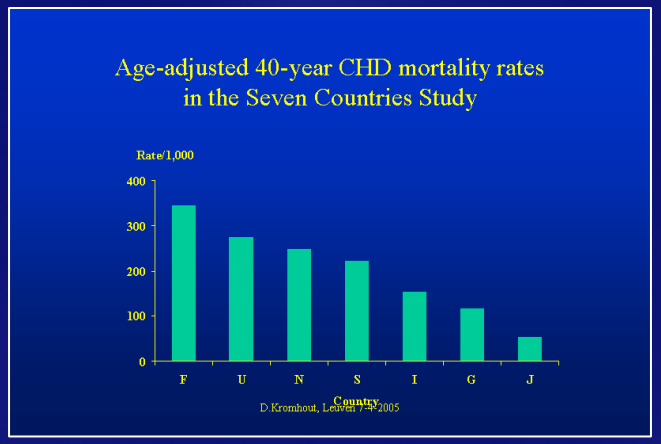
Prof. Snapper, Prof. Groen

Milestones on the road to acceptance of the lipid hypothesis

Seven Countries Study shows linear relation between blood cholesterol and heart disease

Ancel Keys

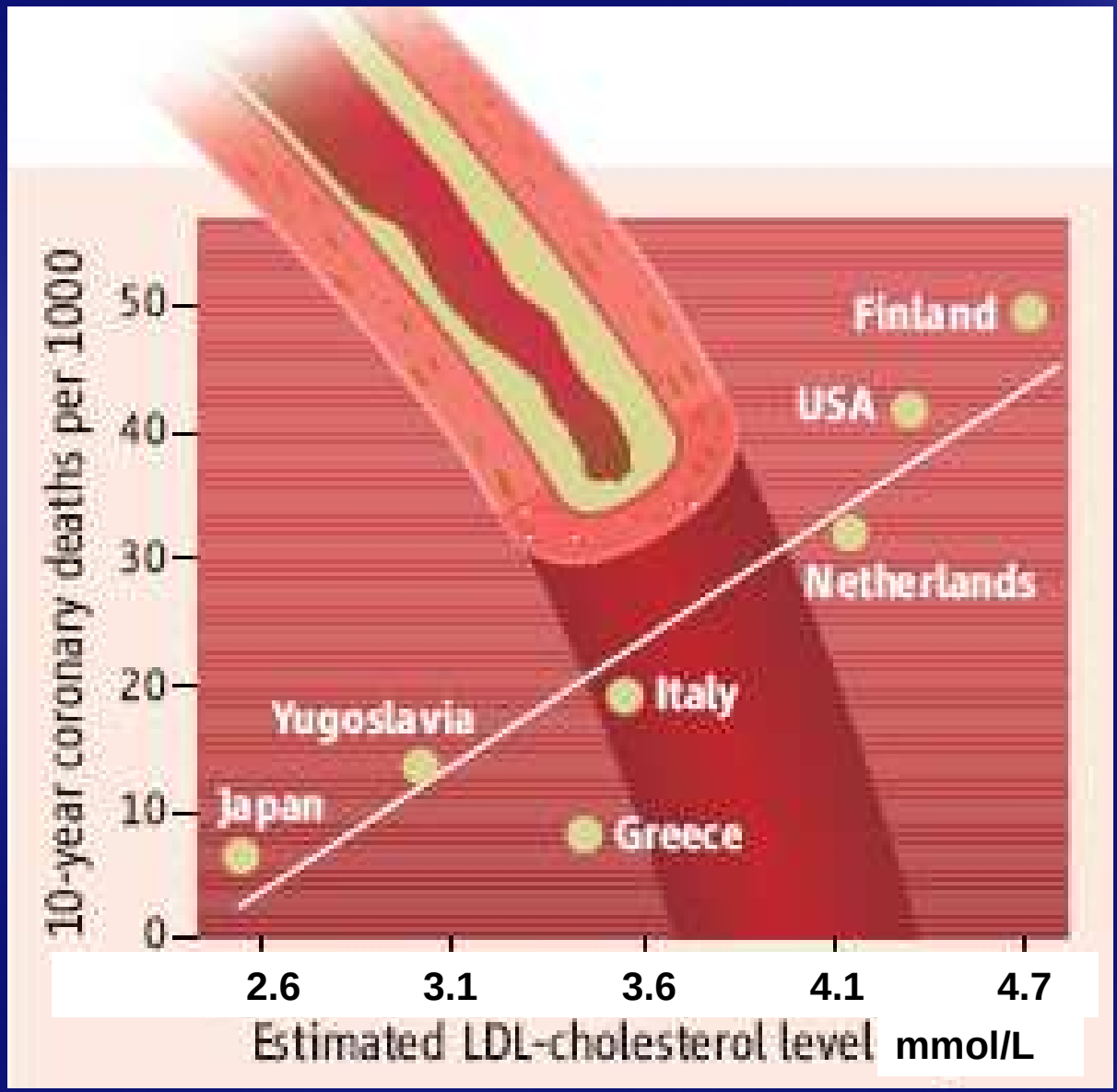




1913

1955

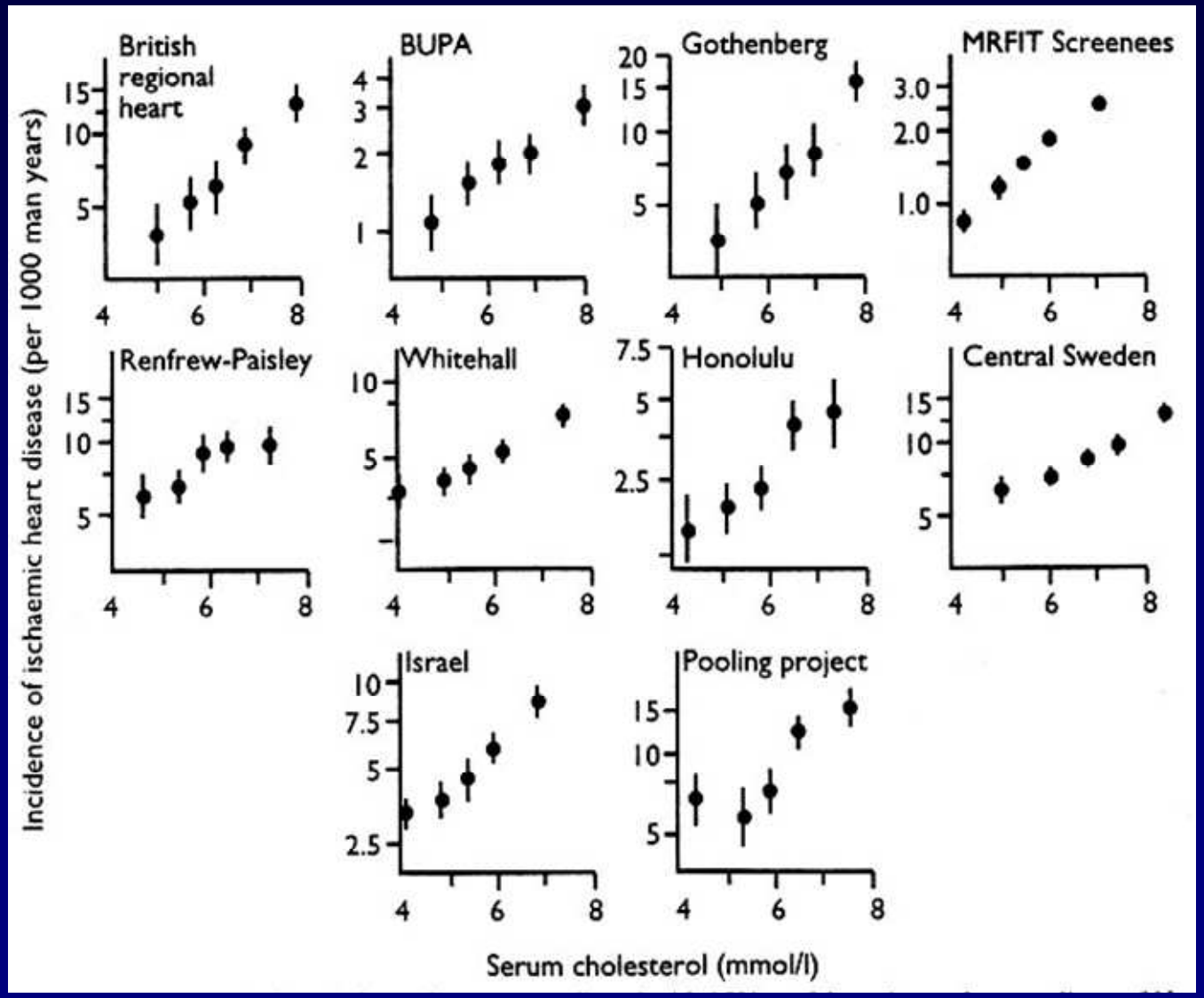
A. Keys, 7 countries study, 1952-1962



Goldstein & Brown, Science 2006

Incidence of CHD by Cholesterol Quintiles

Law MR, Wald NJ, Thompson SG BMJ 1994;308:367



British Heart Journal, 1978, 40, 1069-1118

A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate

Report[1] *from the Committee of Principal Investigators*

SUMMARY A double-blind intervention trial was started in 1965 to test the hypothesis that the incidence of ischaemic heart disease in middle-aged men can be reduced by lowering raised serum cholesterol levels. It was carried out in 3 European centres—Edinburgh, Budapest, and Prague. Serum cholesterol was to be lowered by the drug clofibrate (ethyl chlorophenoxyisobutyrate) which was considered to be free from serious side effects.

[1]*Prepared by*—
M. F. Oliver, J. A. Heady, J. N. Morris, J. Cooper

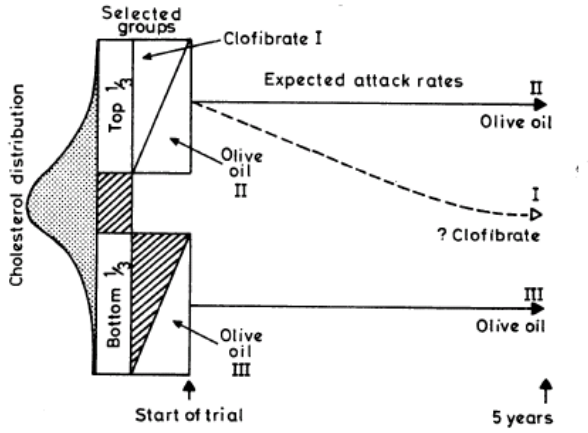


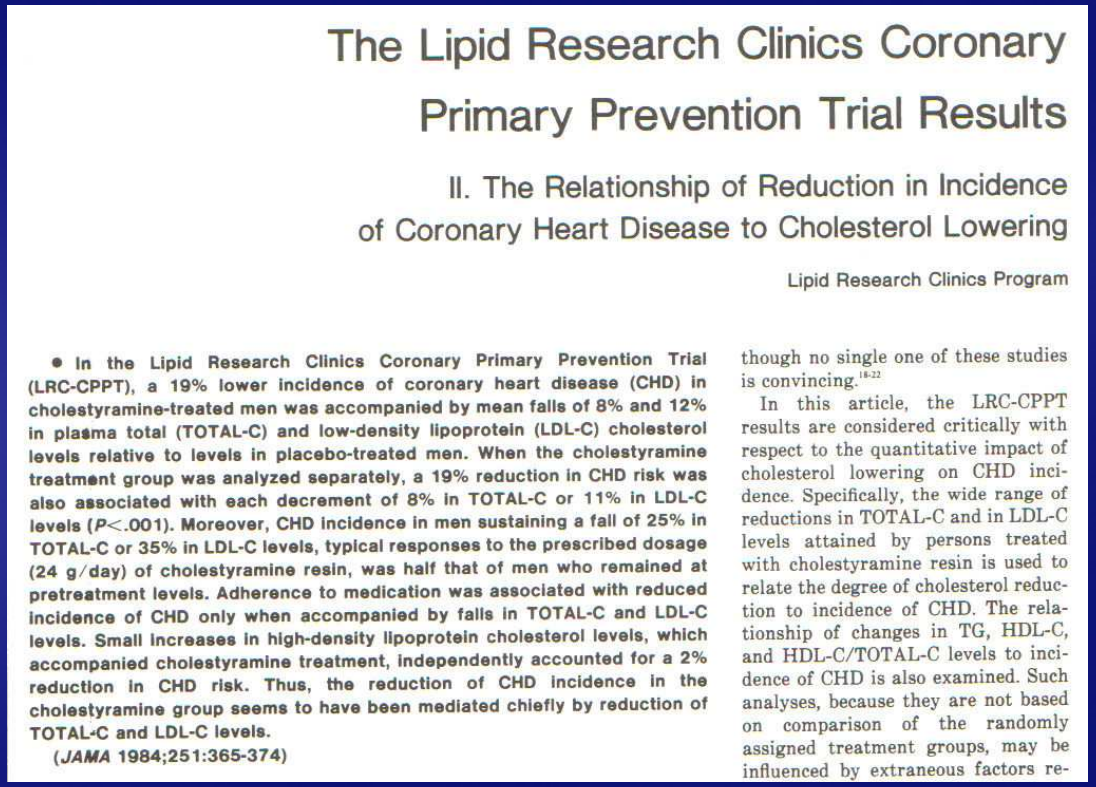
Fig. 1 *Design of the trial (broken line represents hypothetical effect of clofibrate on serum cholesterol and IHD attack rates).*

15.745 men in 3 centres (E, B, P): (WHO sponsored)

Results after 5 years:

- **9% reduction in TC, 20% reduction in IHD rate**
- **Excess total mortality (n=30) in clofibrate group**

Milestones on the road to acceptance of the lipid hypothesis



The Lipid Research Clinics Coronary Primary Prevention Trial Results

II. The Relationship of Reduction in Incidence of Coronary Heart Disease to Cholesterol Lowering

Lipid Research Clinics Program

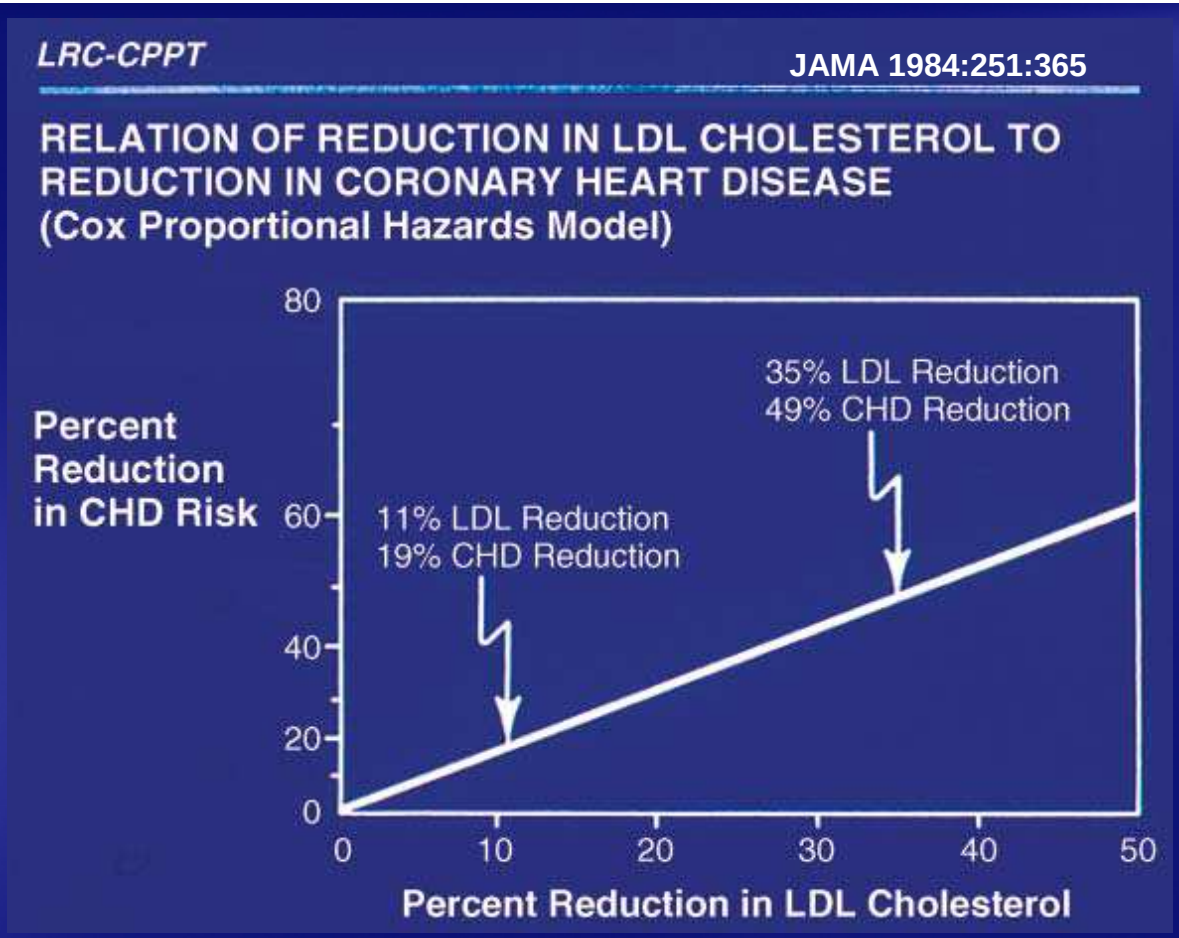
• In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), a 19% lower incidence of coronary heart disease (CHD) in cholestyramine-treated men was accompanied by mean falls of 8% and 12% in plasma total (TOTAL-C) and low-density lipoprotein (LDL-C) cholesterol levels relative to levels in placebo-treated men. When the cholestyramine treatment group was analyzed separately, a 19% reduction in CHD risk was also associated with each decrement of 8% in TOTAL-C or 11% in LDL-C levels ($P<.001$). Moreover, CHD incidence in men sustaining a fall of 25% in TOTAL-C or 35% in LDL-C levels, typical responses to the prescribed dosage (24 g/day) of cholestyramine resin, was half that of men who remained at pretreatment levels. Adherence to medication was associated with reduced incidence of CHD only when accompanied by falls in TOTAL-C and LDL-C levels. Small increases in high-density lipoprotein cholesterol levels, which accompanied cholestyramine treatment, independently accounted for a 2% reduction in CHD risk. Thus, the reduction of CHD incidence in the cholestyramine group seems to have been mediated chiefly by reduction of TOTAL-C and LDL-C levels.

(*JAMA* 1984;251:365-374)

though no single one of these studies is convincing.[18-22]

In this article, the LRC-CPPT results are considered critically with respect to the quantitative impact of cholesterol lowering on CHD incidence. Specifically, the wide range of reductions in TOTAL-C and in LDL-C levels attained by persons treated with cholestyramine resin is used to relate the degree of cholesterol reduction to incidence of CHD. The relationship of changes in TG, HDL-C, and HDL-C/TOTAL-C levels to incidence of CHD is also examined. Such analyses, because they are not based on comparison of the randomly assigned treatment groups, may be influenced by extraneous factors re-

1913 → 1971 → 1984 LRC-CPPT with cholestyramine

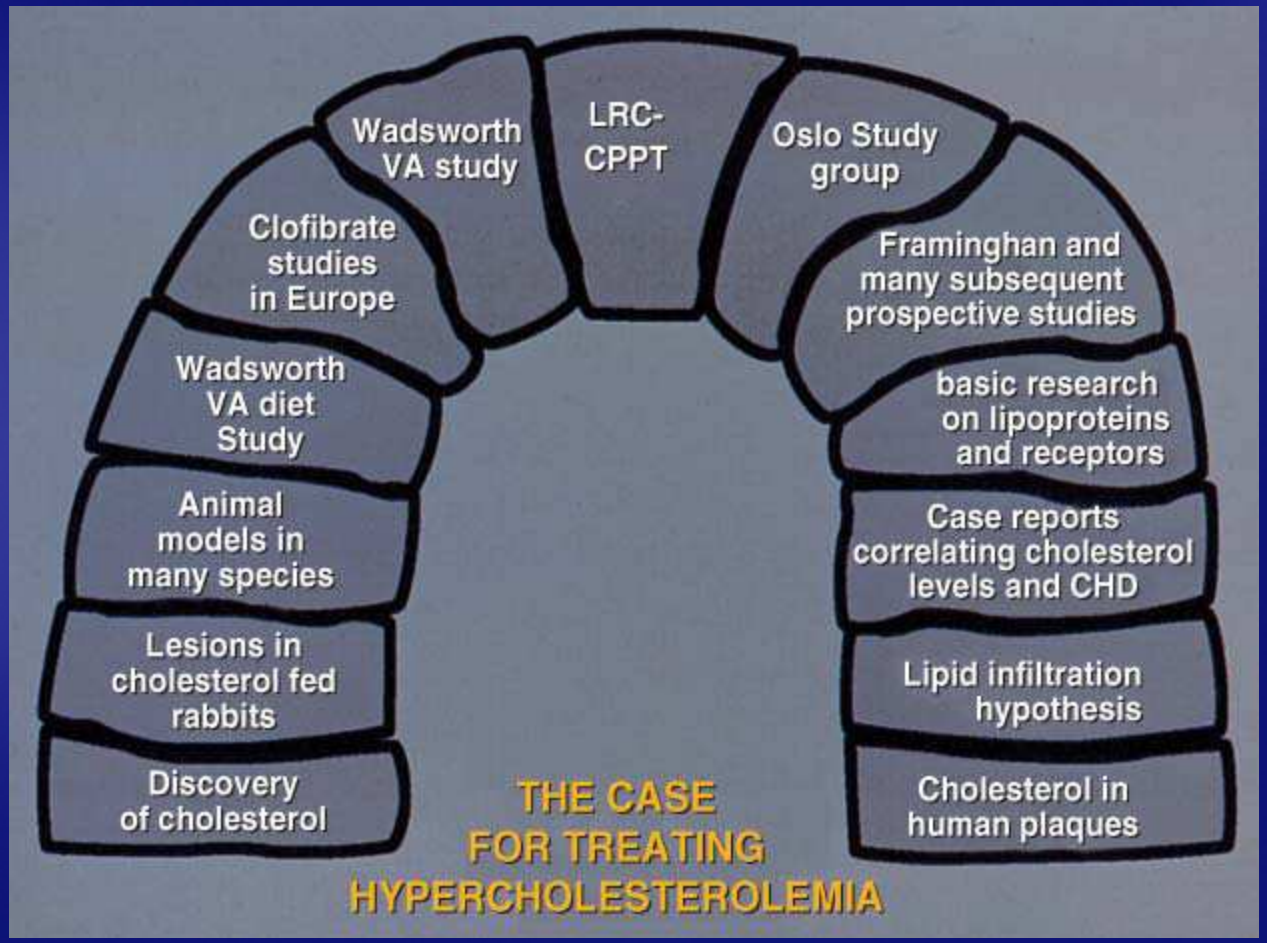


- 1971 – 1984, aver. 7.4 yr
- 24 g cholestyramine
- 3806 men 35-59 yr
- Total cholesterol > 6.9 mmol/L
- 500.000 men screened from 1973-76
- $150 million NIH

Result:

- 13.4% reduction in TC
- 20% reduction in LDL-chol
- 19% reduction PE, $p<0.05$

(one-tailed t-test)


Wadsworth VA study
LRC-CPPT
Oslo Study group
Clofibrate studies in Europe
Framinghan and many subsequent prospective studies
Wadsworth VA diet Study
basic research on lipoproteins and receptors
Animal models in many species
Case reports correlating cholesterol levels and CHD
Lesions in cholesterol fed rabbits
Lipid infiltration hypothesis
Discovery of cholesterol
Cholesterol in human plaques
THE CASE FOR TREATING HYPERCHOLESTEROLEMIA

1985

NIH CONSENSUS CONFERENCE — PANEL'S CONCLUSIONS

"It has been established beyond a reasonable doubt that lowering definitely elevated blood cholesterol levels (specifically, blood levels of low-density lipoprotein [LDL] cholesterol) will reduce the risk of heart attacks caused by coronary heart disease. . ."

From NIH Consensus Development Conference (*JAMA* 1985;253:2080)

Search for inhibitors of cholesterol biosynthesis

1959: **Introduction Triparanol (Wm. S. Merrell Co., Cincinnati, USA)**

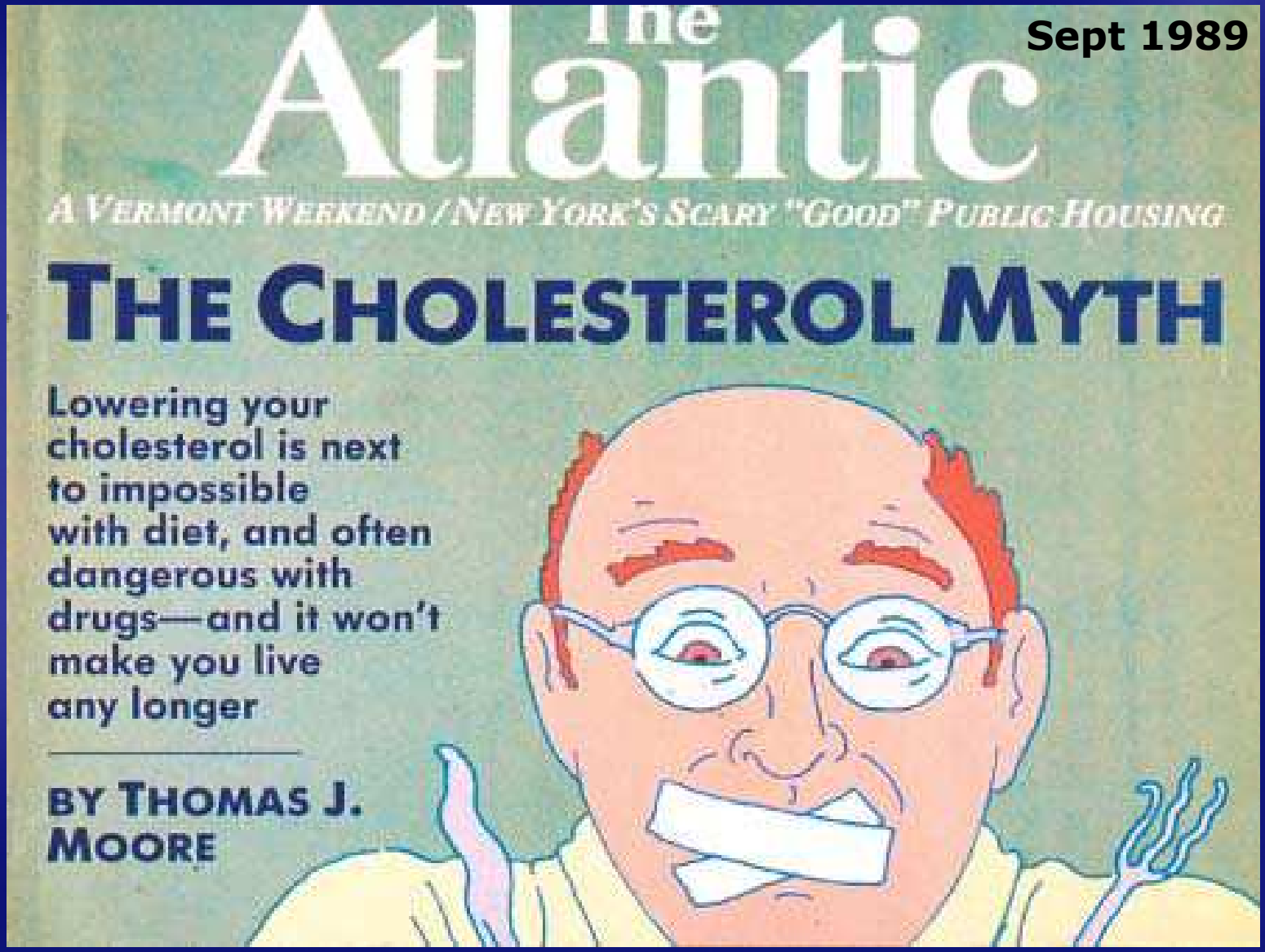
Inhibition latest step conversion desmosterol -> cholesterol
25% reduction cholesterol, but increase atherogenic precursor

Lens cataract, even blindness and hair loss in rats and dogs
(FDA not notified)
Eye abnormalities in patients

1963: **Grand jury criminal indictment; settlement $ 50 million**

Consequence: Abrupt stop in search for inhibitors of cholesterol biosynthesis!

Sept 1989


The Atlantic
A Vermont Weekend / New York's Scary "Good" Public Housing
THE CHOLESTEROL MYTH
Lowering your cholesterol is next to impossible with diet, and often dangerous with drugs—and it won't make you live any longer
BY THOMAS J. MOORE

BMJ

LONDON, SATURDAY 15 FEBRUARY 1992

15 February 1992

Doubts about preventing coronary heart disease

Multiple interventions in middle aged men may do more harm than good

For Debate

Should there be a moratorium on the use of cholesterol lowering drugs?

George Davey Smith, Julia Pekkanen

PAPERS

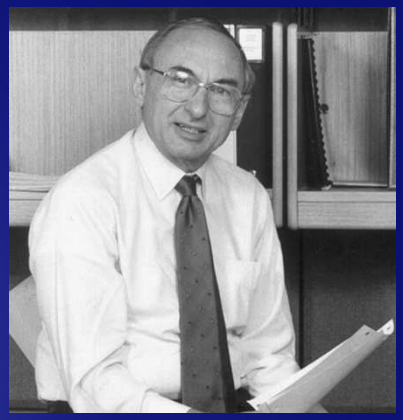
Cholesterol lowering trials in coronary heart disease: frequency of citation and outcome

U Ravnskov

Low serum cholesterol concentration and short term mortality from injuries in men and women

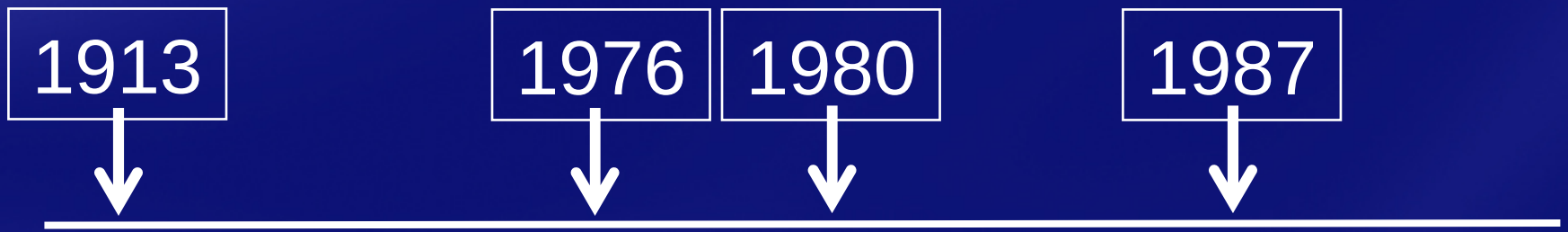
Milestones on the road to acceptance of the lipid hypothesis

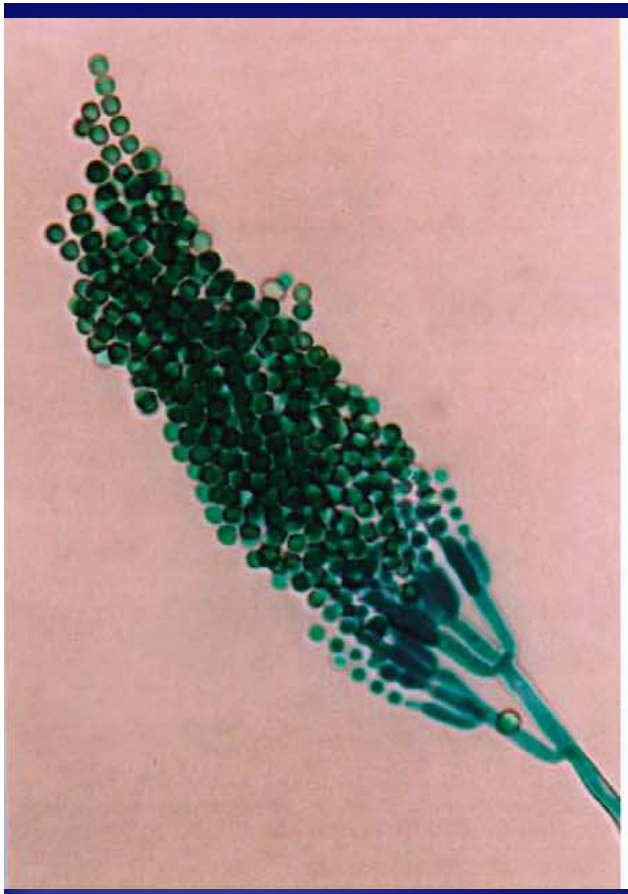
A. Endo
(Sankyo)



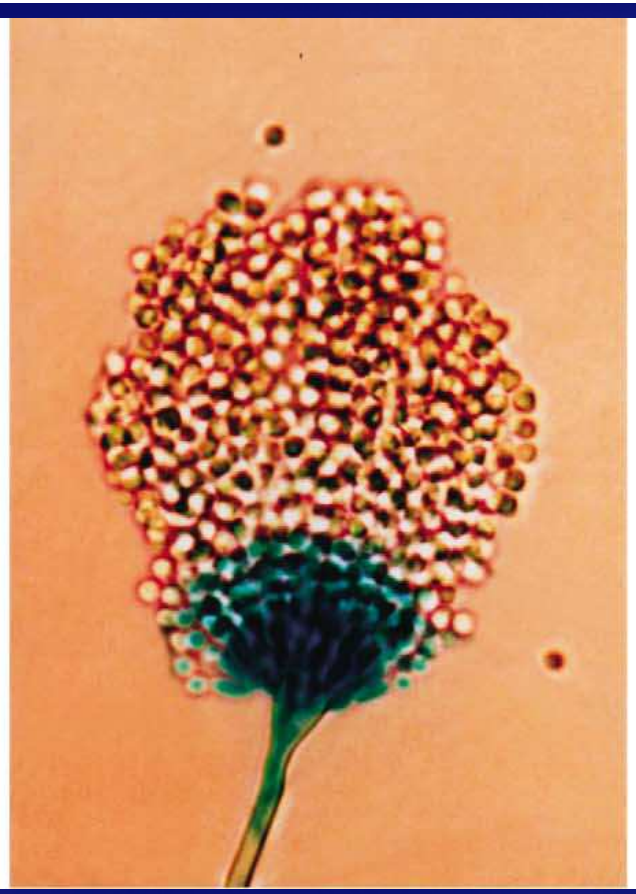
A. Alberts
(Merck)

- 1976: Discovery first statin (compactin) after testing >6000 fungi (A. Endo)
- 1980: 2^{e} statin (mevinolin, lovastatin) (A. Alberts)
- 1987: FDA approval mevinolin (lovastatin)

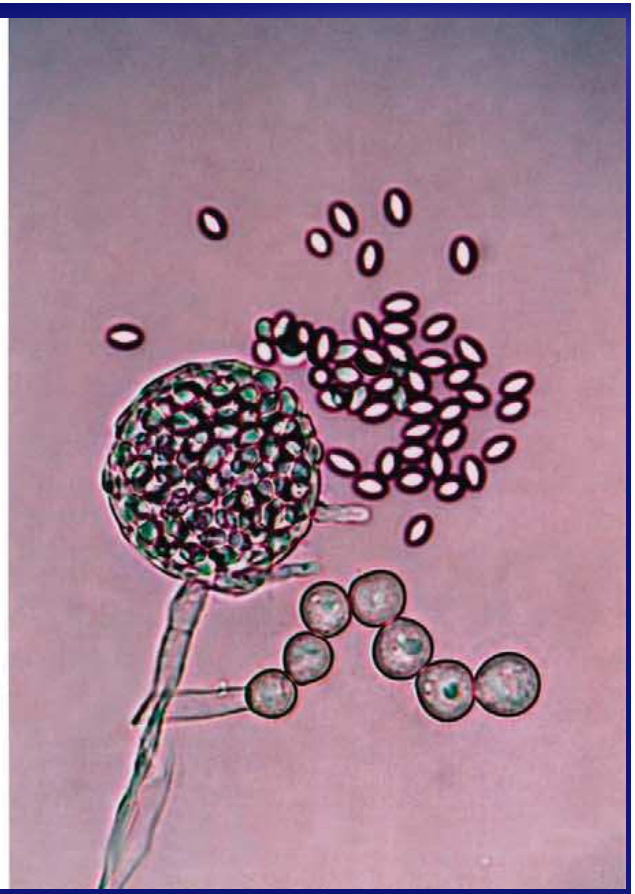




Penicillium citrinum, producer of compactin (mevastatin)



Aspergillus terreus



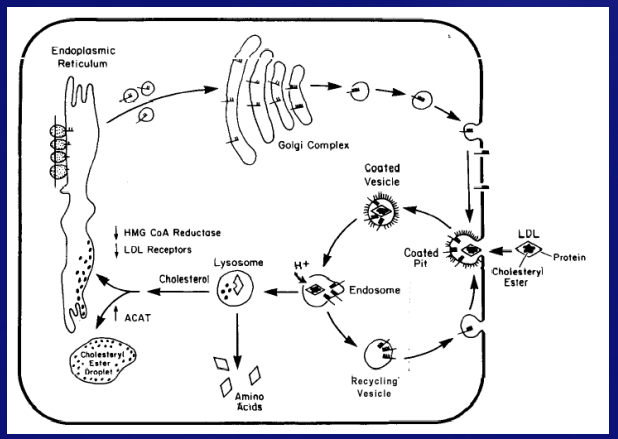
Monascus ruber

producers of mevinolin (lovastatin)

Milestones on the road to acceptance of the lipid hypothesis

Joseph L. Goldstein
Michael S. Brown

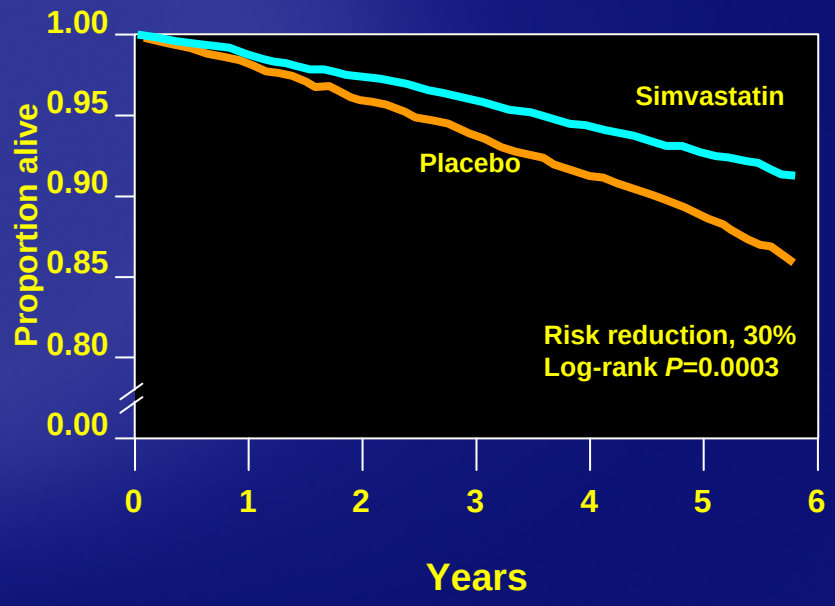
- Discovery LDL receptor and cellular cholesterol regulation
- 1985 Nobel price



1913 → 1974 → 1985

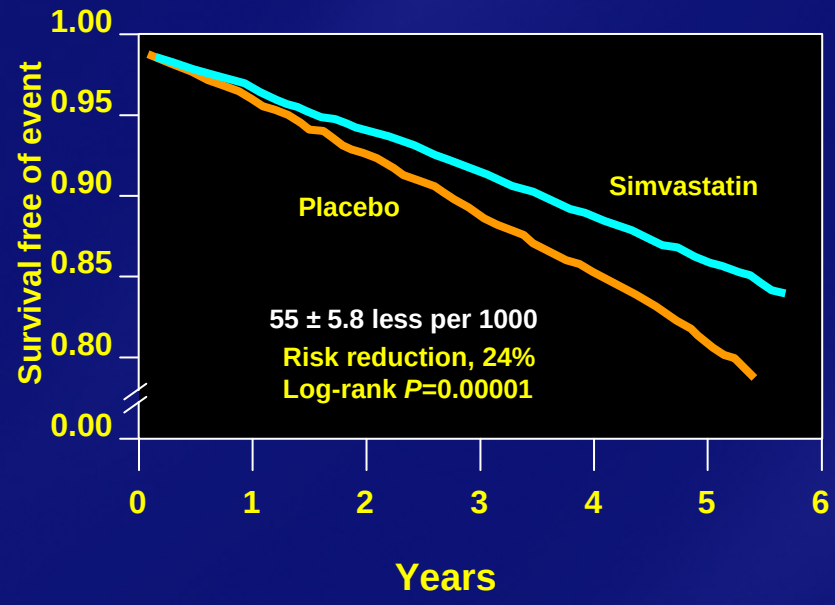
Mortality/Event Reduction in Landmark Trials with Statins

4S



Lancet 1994

HPS



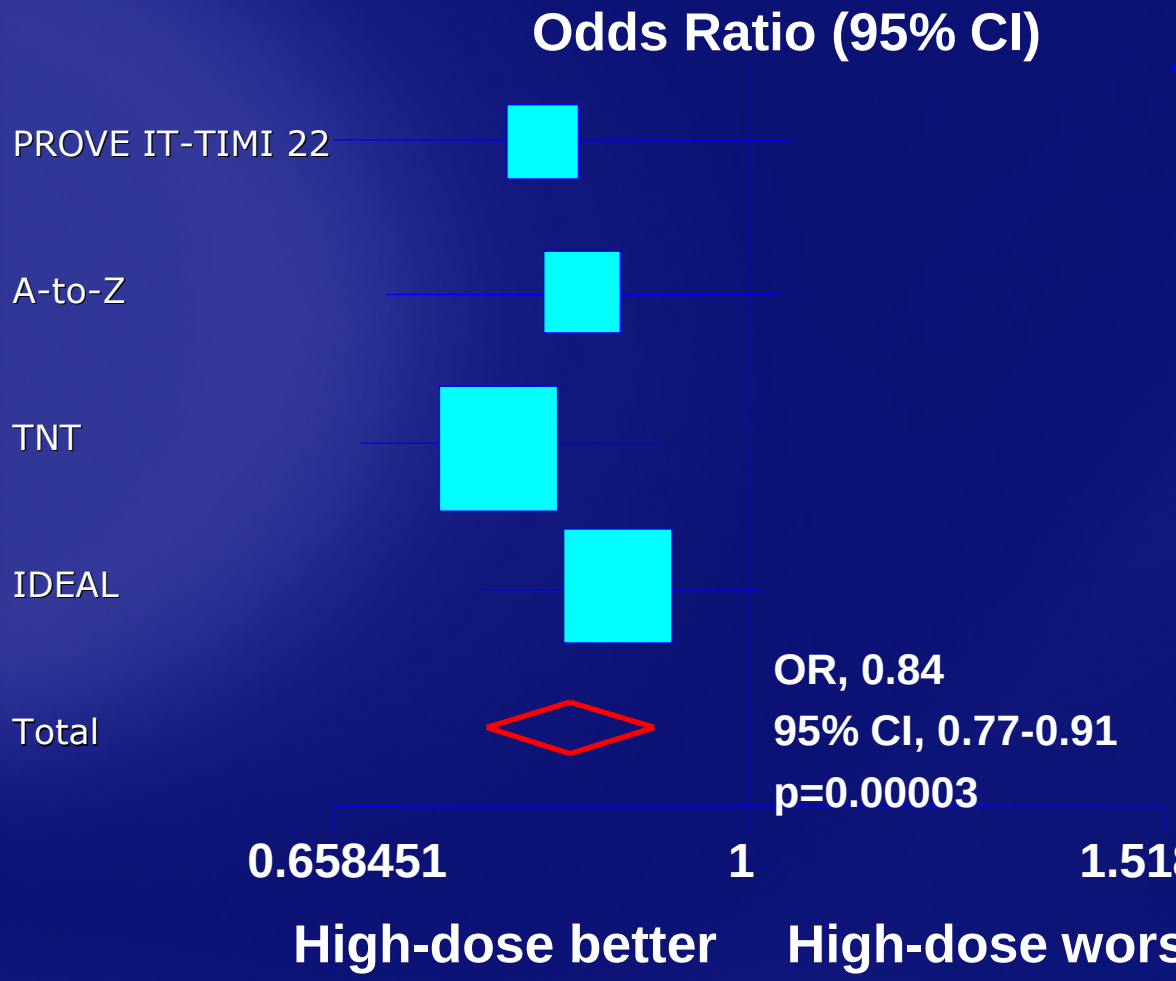
Lancet 2002

Landmark Statin Trials n= >125,000

1994	4S	First 5 Trials Proved RRR In Morbidity And Mortality Vs Placebo
1995	WOSCOPS	
1996	CARE	
1998	AFCAPS/TexCAPS LIPID	
2001	MIRACL	Second Wave Of Trials ▪ Focus on other high-risk groups – ACS, elderly, DM, HTN, ESRD ▪ Comparisons beyond placebo – vs usual care (ALLIANCE, ALL-HAT) – active comparator (PROVE IT, A to Z)
2002	HPS PROSPER ALL-HAT LLT*	
2003	ASCOT-LLA	
2004	PROVE IT ALLIANCE CARDS A to Z, 4 D*	
2005	TNT IDEAL	Intensity Of Statin Treatment In Stable CHD Patients Receiving Contemporary Therapy
2006	SPARCL MEGA	Stroke, intensive treatment Japanese, low risk populations
2007/8	CORONA* JUPITER	Heart Failure

* NS

Meta-Analysis of Intensive Statin Therapy Coronary Death or MI



	Odds Reduction	Event Rates No./Total (%)	
		High Dose	Std Dose
PROVE IT-TIMI 22	-17%	147/2099 (7.0)	172/2063 (8.3)
A-to-Z	-15%	205/2265 (9.1)	235/2232 (10.5)
TNT	-21%	334/4995 (6.7)	418/5006 (8.3)
IDEAL	-12%	411/4439 (9.3)	463/4449 (10.4)
Total	-16%	1097/13798 (8.0)	1288/13750 (9.4)

Cannon CP, et al. JACC 2005; 48: 438 - 445.

IHD Mortality versus total cholesterol

Lancet 2007;370:1829-39

Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths

*Prospective Studies Collaboration**

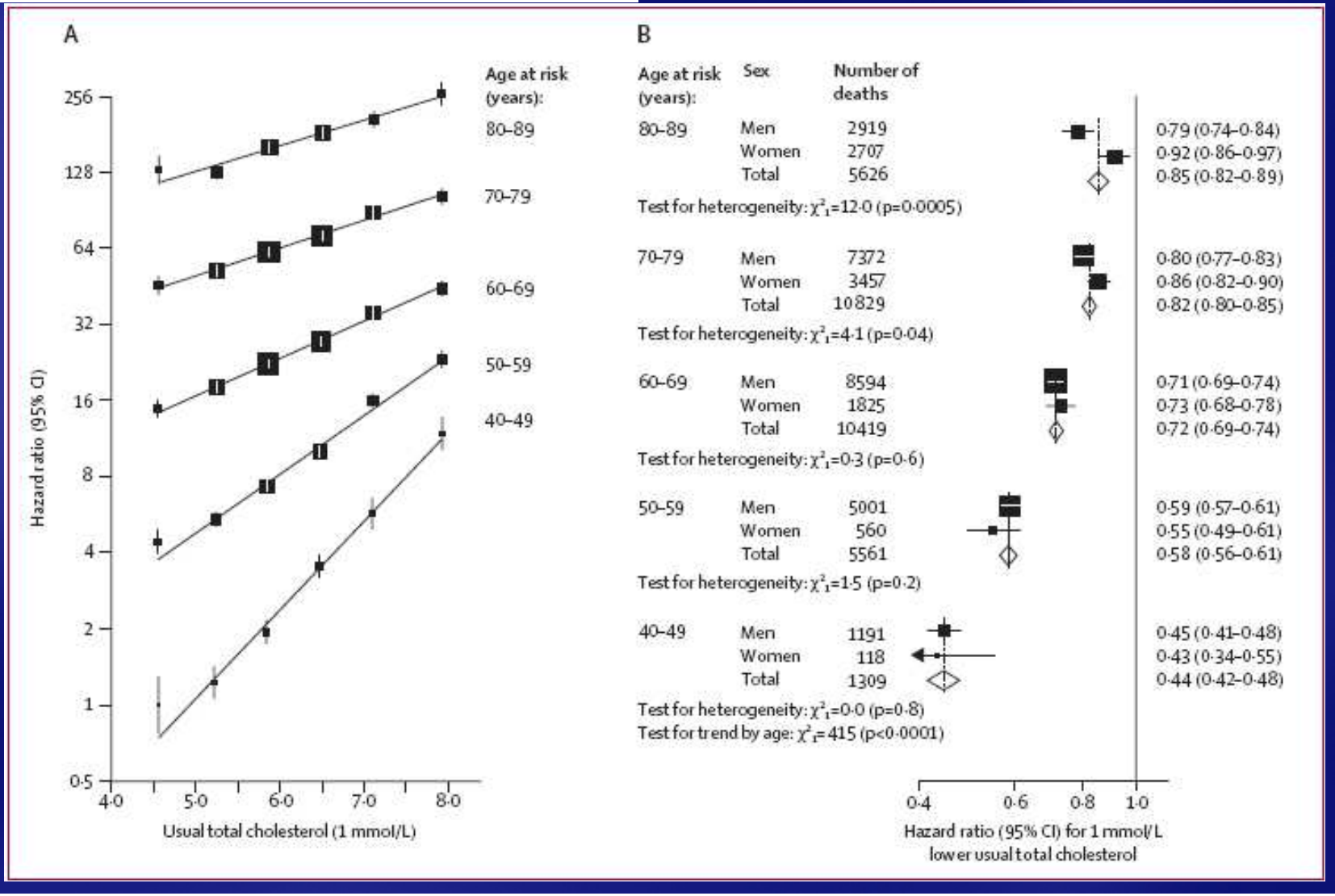
Summary

Background Age, sex, and blood pressure could modify the associations of total cholesterol (and its main two fractions, HDL and LDL cholesterol) with vascular mortality. This meta-analysis combined prospective studies of vascular mortality that recorded both blood pressure and total cholesterol at baseline, to determine the joint relevance of these two risk factors.

Lancet 2007; 370: 1829–39

See Comment page 1803

*Collaborators listed in full at end of paper



IHD Mortality versus (A) HDL-chol and (B) non-HDL-chol

Lancet 2007;370:1829-39

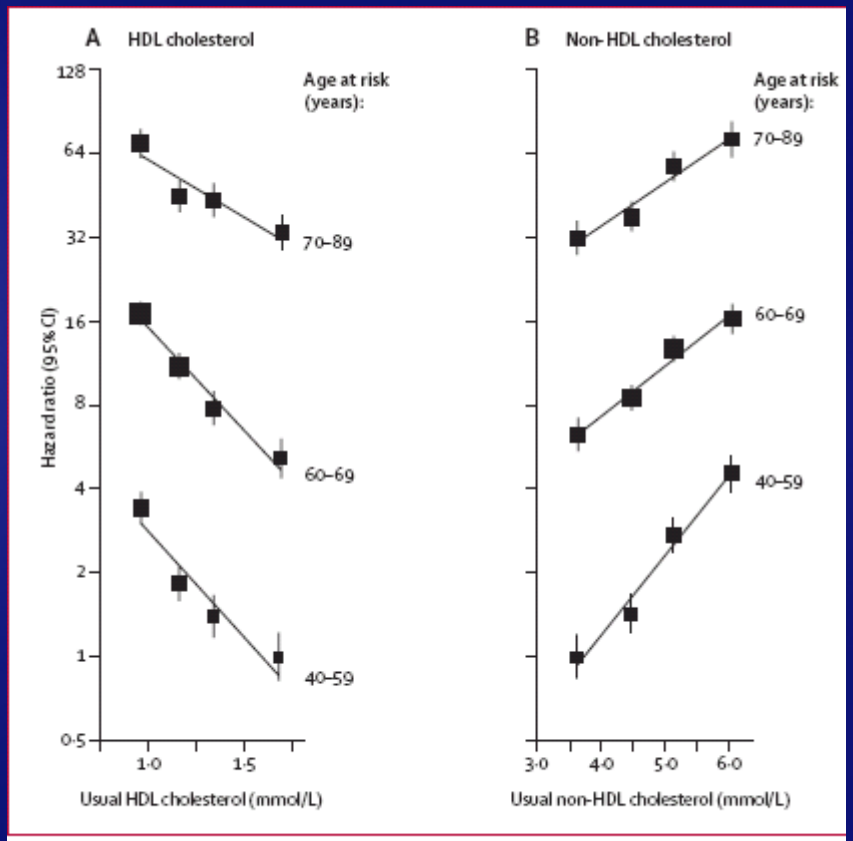
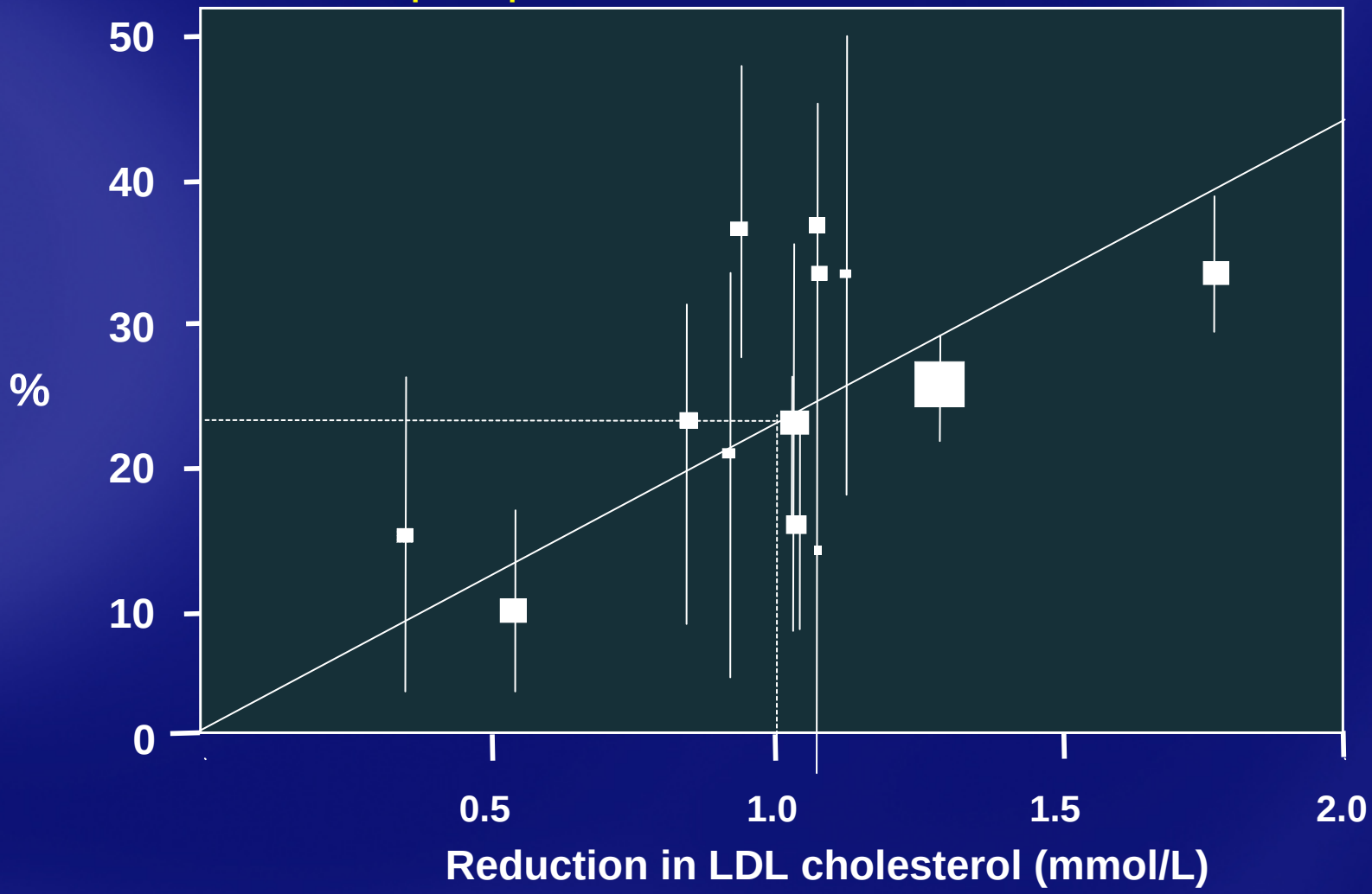


Figure 3: IHD mortality (3020 deaths) versus usual (A) HDL cholesterol; (B) non-HDL cholesterol; ar
Age-specific associations. Conventions as in figure 1. HR denotes the hazard ratio (95% CI) per 1·33 lowe

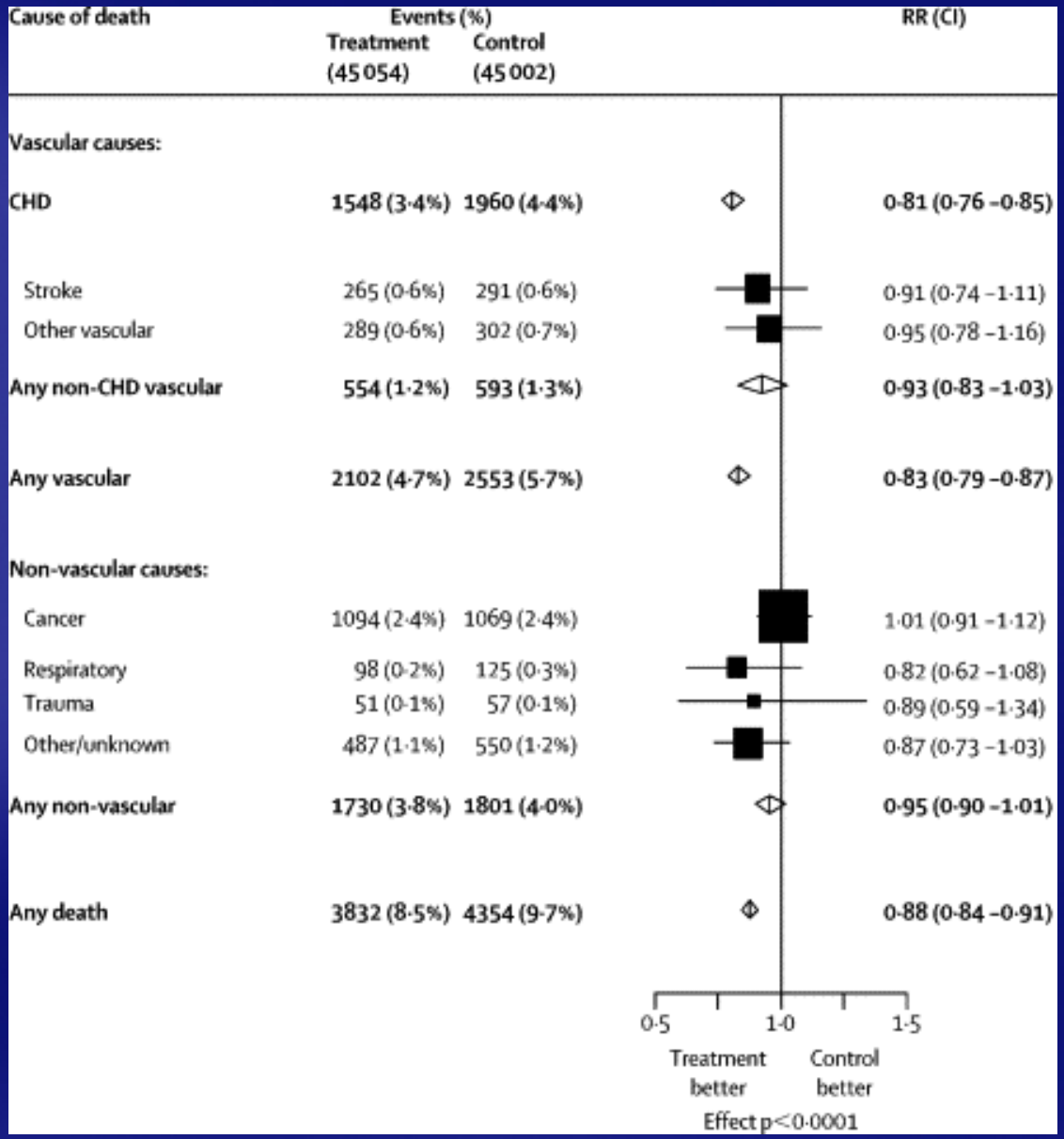
Proportional Reduction in MCE by Mean Reduction in LDL-C

Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins



CTT Collaborators. Lancet 2005;366:1267-78

Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins



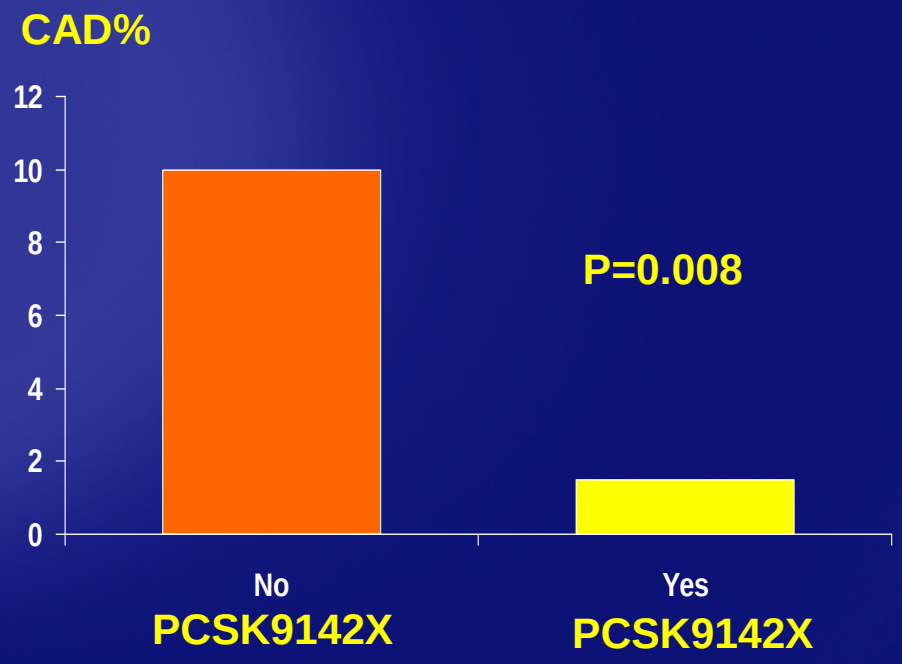
CTT Collaborators,

Lancet 2005; 366:1267

What is the optimal LDL-cholesterol?

CAD incidence in 15 years in ARIC

In those with PCSK9 variants and 28 % LDL reduction CAD risk decreased 88 %



Sequence variation in PCSK9 that decreased LDL 15 %

CHD risk ↓ 47 %
p = 0.003

NEJM 2006; 354:1264.

Lowering LDL only how low

Or for how long ?

BIOMEDICINE

Lowering LDL—Not Only How Low, But How Long?

Michael S. Brown and Joseph L. Goldstein

Brown & Goldstein Science 2006; 311:1721.

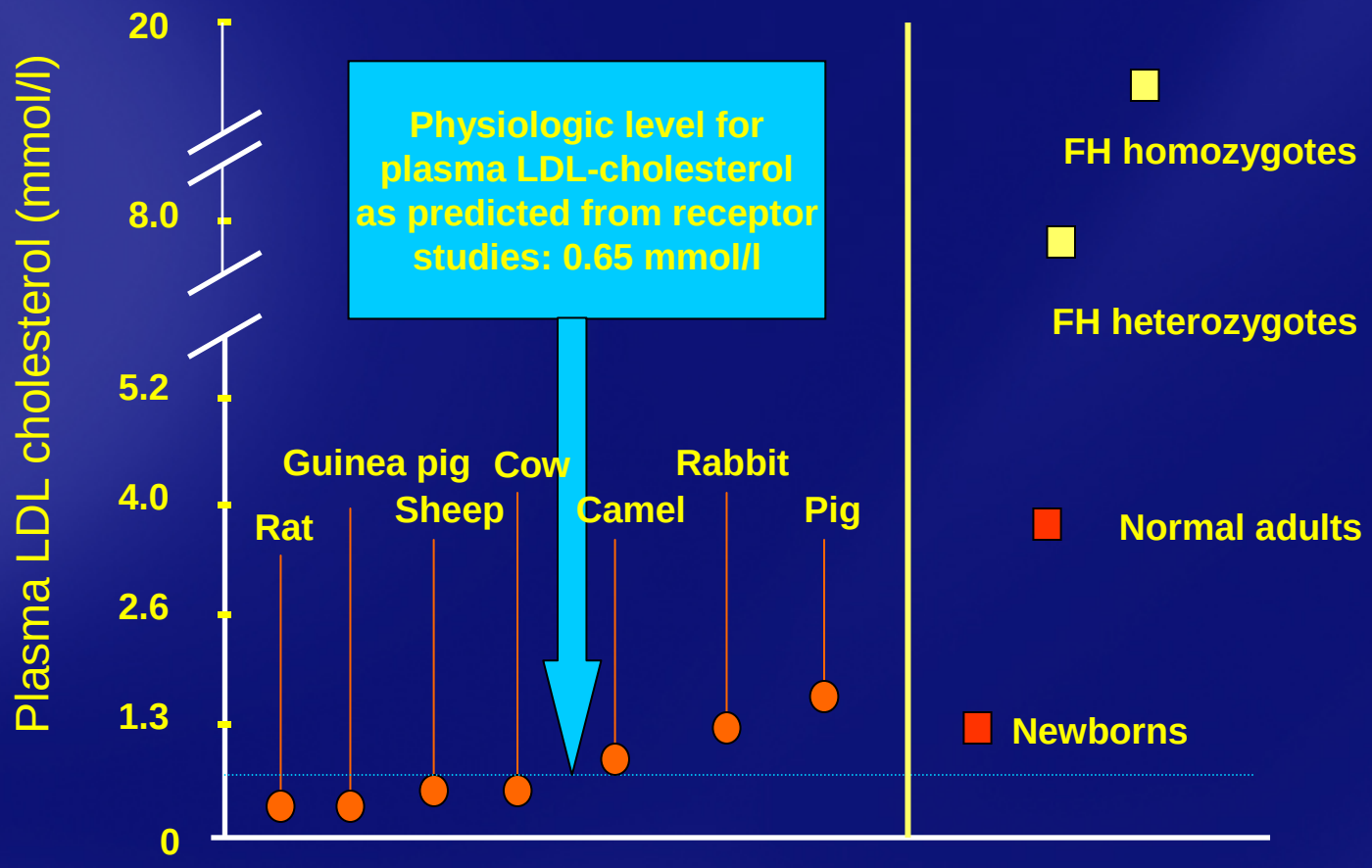
Lipid Levels in 525 Newborns

	(mean)	
• Total cholesterol	72 mg/dl	1.9 mmol/L
• HDL cholesterol	34 mg/dl	0.9 mmol/L
• LDL cholesterol	29 mg/dl	0.8 mmol/L
• Triglycerides	43 mg/dl	0.5 mmol/L
• Apo A1	77 mg/dl	
• Apo B	28 mg/dl	
• Apo B/Apo A1	0.36	

Descamps O, et al. Atherosclerosis 2004;172:287-298

UMC Nijmegen

"Normal" LDL-cholesterol



What are the disadvantages of intensive LDL-cholesterol lowering?

Cerivastatin and Rhabdomyolyis

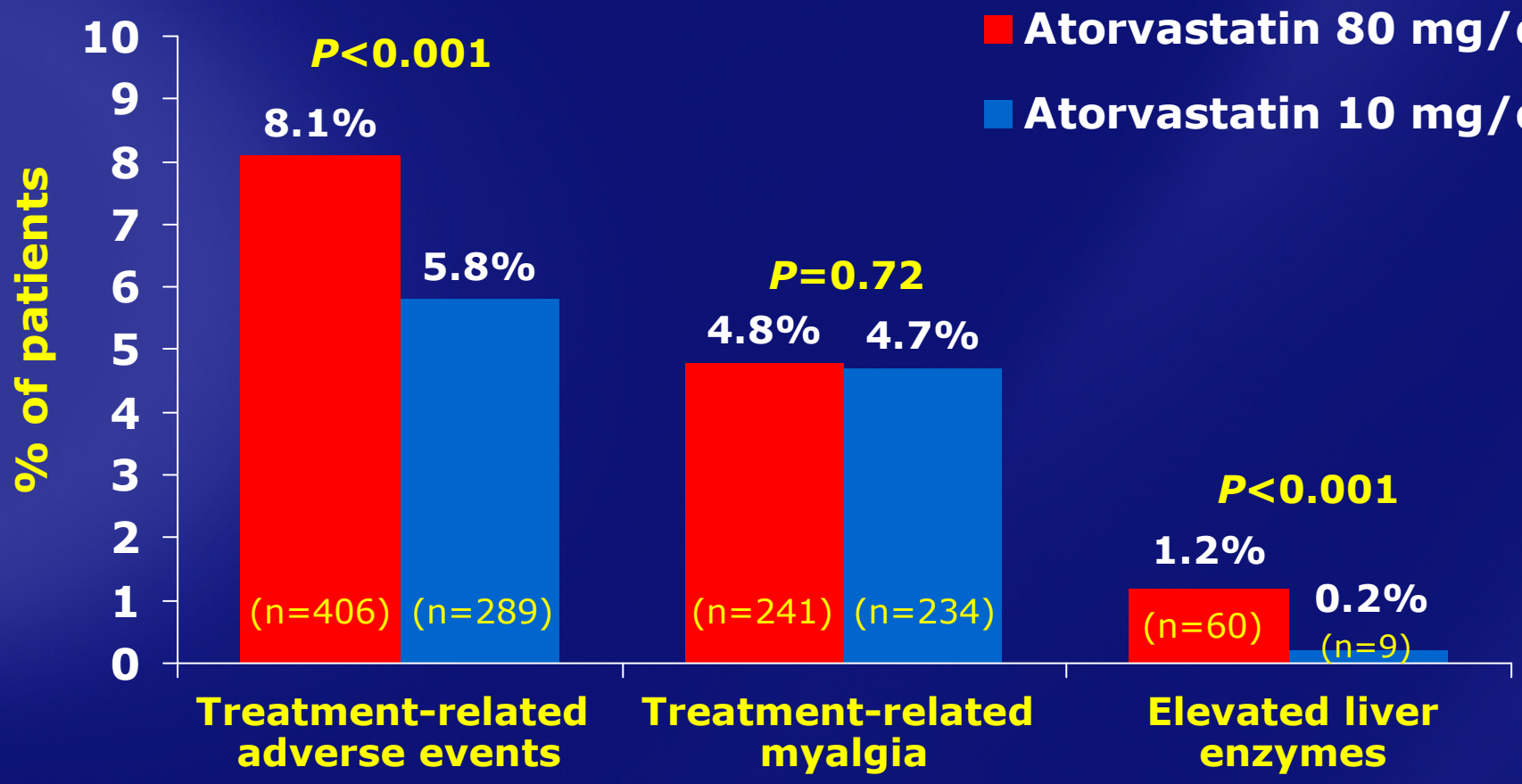
- Cerivastatin introduced in the US in 1997
- 1997 - December 2000
  - 772 cases of Rhabdomyolysis
  - 387 cases using Cerivastatin
  - Mortality
    - 31 patients using Cerivastatin
    - 12 patients using Cerivastatin and Gemfibrozil
    - 52 patients using other statins
    - Before 1997 in total 29 patients
  - Global mortality with Cerivastatin 52 patients (june 30 2001)

IDEAL: Tolerability of treatments

	Simvastatin 20-40 mg (N = 4449)	Atorvastatin 80 mg (N = 4439)	P
Discontinuation	4.2%	9.6%	<0.001
Myalgia	1.1%	2.2%	<0.001
ALT/AST >3x ULN	0.14%	1.38%	<0.001
Rhabdomyolysis	n=3	n=2	
CK > 10 x ULN	0	0	

Pedersen et al. *JAMA* 2005;294:2437

TNT: Safety Profile



TNT=Treating to New Targets.

LaRosa JC et al. *N Engl J Med.* 2005;352:1425-1435.

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine with Simvastatin and Folic Acid/Vitamin B_{12} (SEARCH)

SEARCH: 2 separate randomized treatment comparisons in 12,064 post-MI patients

More versus less LDL-lowering comparison:

Simvastatin 80 mg daily	vs	Simvastatin 20mg daily

Homocysteine-lowering comparison:

Folic acid 2mg plus vitamin B12 1mg daily	vs	Placebo tablets

Mean (SD) duration: 6.7 (1.5) years

SEARCH

Collins, AHA nov 2008

SEARCH: Myopathy rates by SIMVASTATIN comparison

	Simvastatin allocation (per 1000 person-years)	
Years of follow-up	80 mg (6031)	20 mg (6033)
0-1	25 (4.2)	1 (0.2)
2-7	28 (0.8)	2 (0.1)
Total	53	3

Myopathy: New, unexplained muscle pain or weakness plus CK>10x ULN (7 vs 0 developed rhabdomyolysis)

SEARCH

Collins, AHA nov 2008

Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

Naveed Sattar, David Preiss, Heather M Murray, Paul Welsh, Brendan M Buckley, Anton J M de Craen, Sreenivasa Rao Kondapally Seshasai, John J McMurray, Dilys J Freeman, J Wouter Jukema, Peter W Macfarlane, Chris J Packard, David J Stott, Rudi G Westendorp, James Shepherd, Barry R Davis, Sara L Pressel, Roberto Marchioli, Rosa Maria Marfisi, Aldo P Maggioni, Luigi Tavazzi, Gianni Tognoni, John Kjekshus, Terje R Pedersen, Thomas J Cook, Antonio M Gotto, Michael B Clearfield, John R Downs, Haruo Nakamura, Yasuo Ohashi, Kyoichi Mizuno, Kausik K Ray, Ian Ford

Lancet 2010; 375: 735–42
Published Online
February 17, 2010

Summary

Background Trials of statin therapy have had conflicting findings on the risk of development of diabetes mellitus in patients given statins. We aimed to establish by a meta-analysis of published and unpublished data whether any relation exists between statin use and development of diabetes.

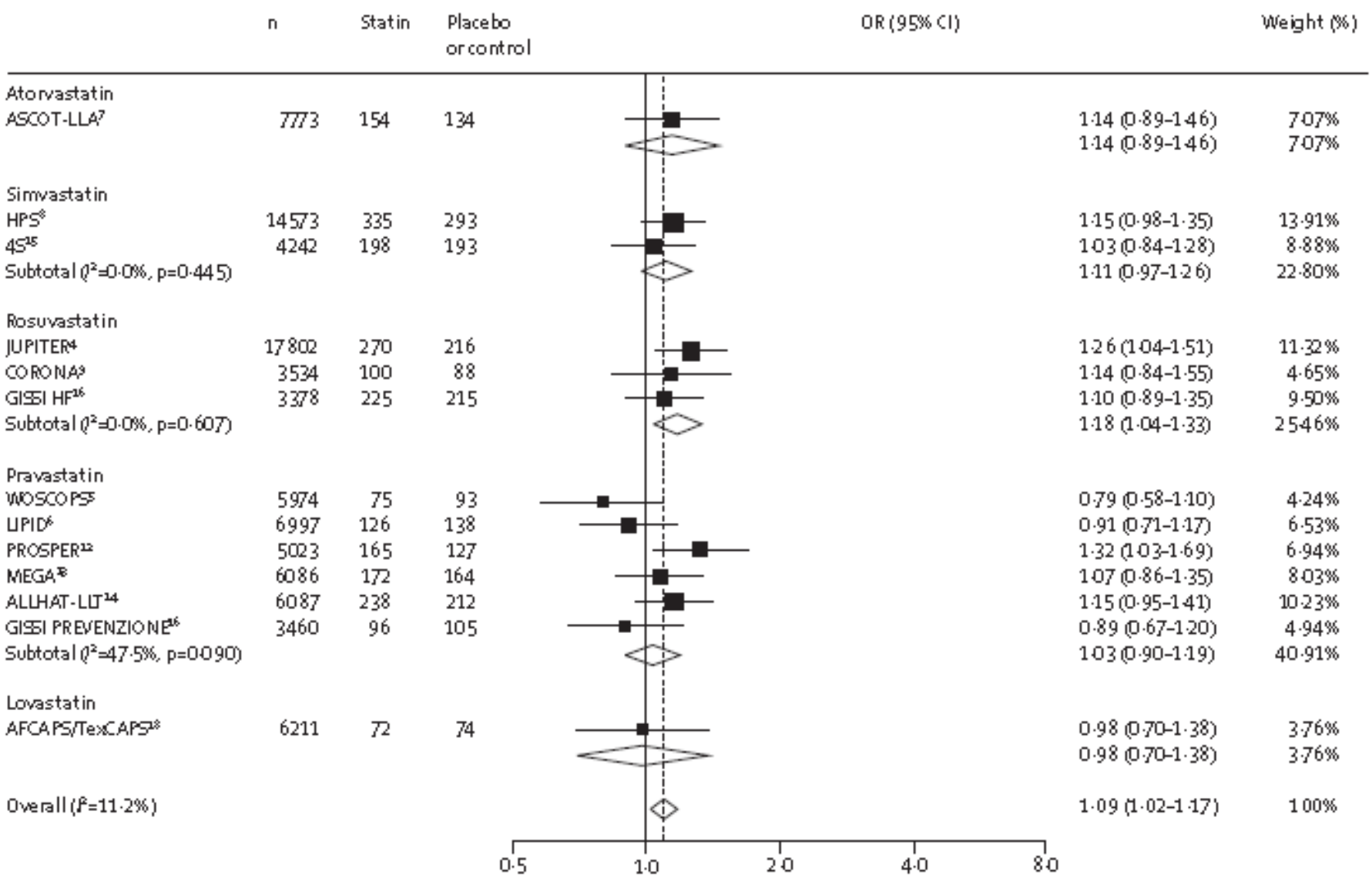


Figure 3: Association between different statins and development of diabetes

Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis

M R Law, N J Wald, A R Rudnicka

BMJ 2003;326:1423

Table 2 Absolute reductions* (mmol/l) (with 95% confidence intervals) and percentage reductions† in serum LDL cholesterol concentration according to statin and daily dose (summary estimates from 164 randomised placebo controlled trials)

	Daily dose (mg)				
Statin	5	10	20	40	80
Atorvastatin	1.51 (1.28 to 1.74), 31%	1.79 (1.62 to 1.97), 37%	2.07 (1.90 to 2.25), 43%	2.36 (2.12 to 2.59), 49%	2.64 (2.31 to 2.96), 55%
Fluvastatin	0.46 (0.18 to 0.75), 10%	0.74 (0.55 to 0.93), 15%	1.02 (0.90 to 1.13), 21%	1.30 (1.19 to 1.41), 27%	1.58 (1.40 to 1.76), 33%
Lovastatin	—	1.02 (0.71 to 1.34), 21%	1.40 (1.21 to 1.59), 29%	1.77 (1.60 to 1.94), 37%	2.15 (1.86 to 2.43), 45%
Pravastatin	0.73 (0.54 to 0.92), 15%	0.95 (0.83 to 1.07), 20%	1.17 (1.10 to 1.23), 24%	1.38 (1.31 to 1.46), 29%	1.60 (1.46 to 1.74), 33%
Rosuvastatin	1.84 (1.74 to 1.94), 38%	2.08 (1.98 to 2.18), 43%	2.32 (2.20 to 2.44), 48%	2.56 (2.42 to 2.70), 53%	2.80 (2.63 to 2.97), 58%
Simvastatin	1.08 (0.93 to 1.22), 23%	1.31 (1.22 to 1.40), 27%	1.54 (1.46 to 1.63), 32%	1.78 (1.66 to 1.90), 37%	2.01 (1.83 to 2.19), 42%

*Absolute reductions are standardised to usual serum LDL cholesterol concentration of 4.8 mmol/l before treatment (mean concentration in trials).
†Percentage reductions are independent of pretreatment LDL cholesterol concentration; 95% confidence intervals on percentage reductions can be derived by dividing those on absolute reductions by 4.8.

Consequence:

-when LDL ≤ 4,0: simva 40

-when LDL > 4,0: atorva 80, rosuva 40

-when LDL > 5,6: target mostly not achieved

Wierema en Stehouwer, Med Contact 2007

Lipid management anno 2010: Insights in developments and innovations

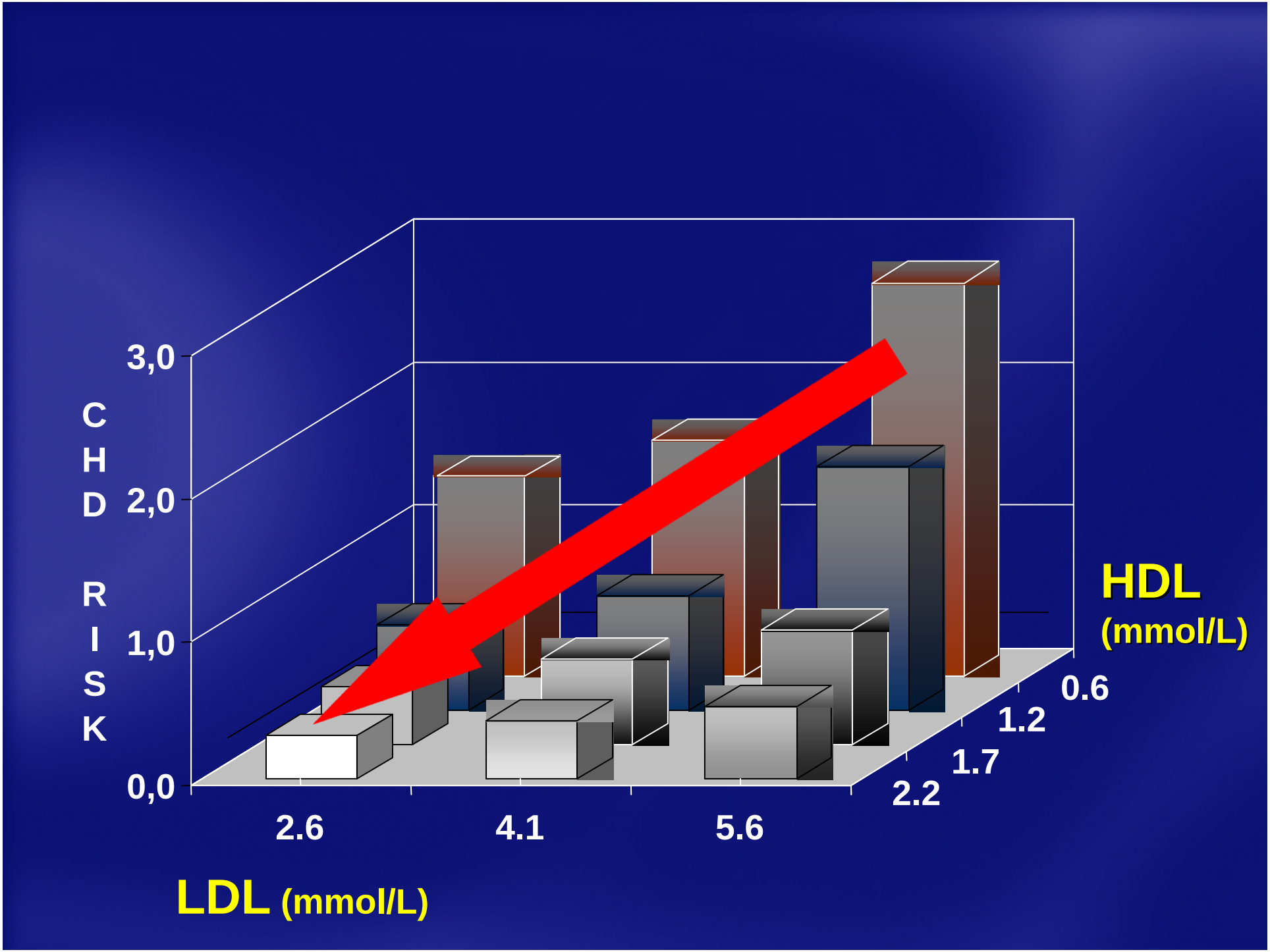
History: Pre-statin era

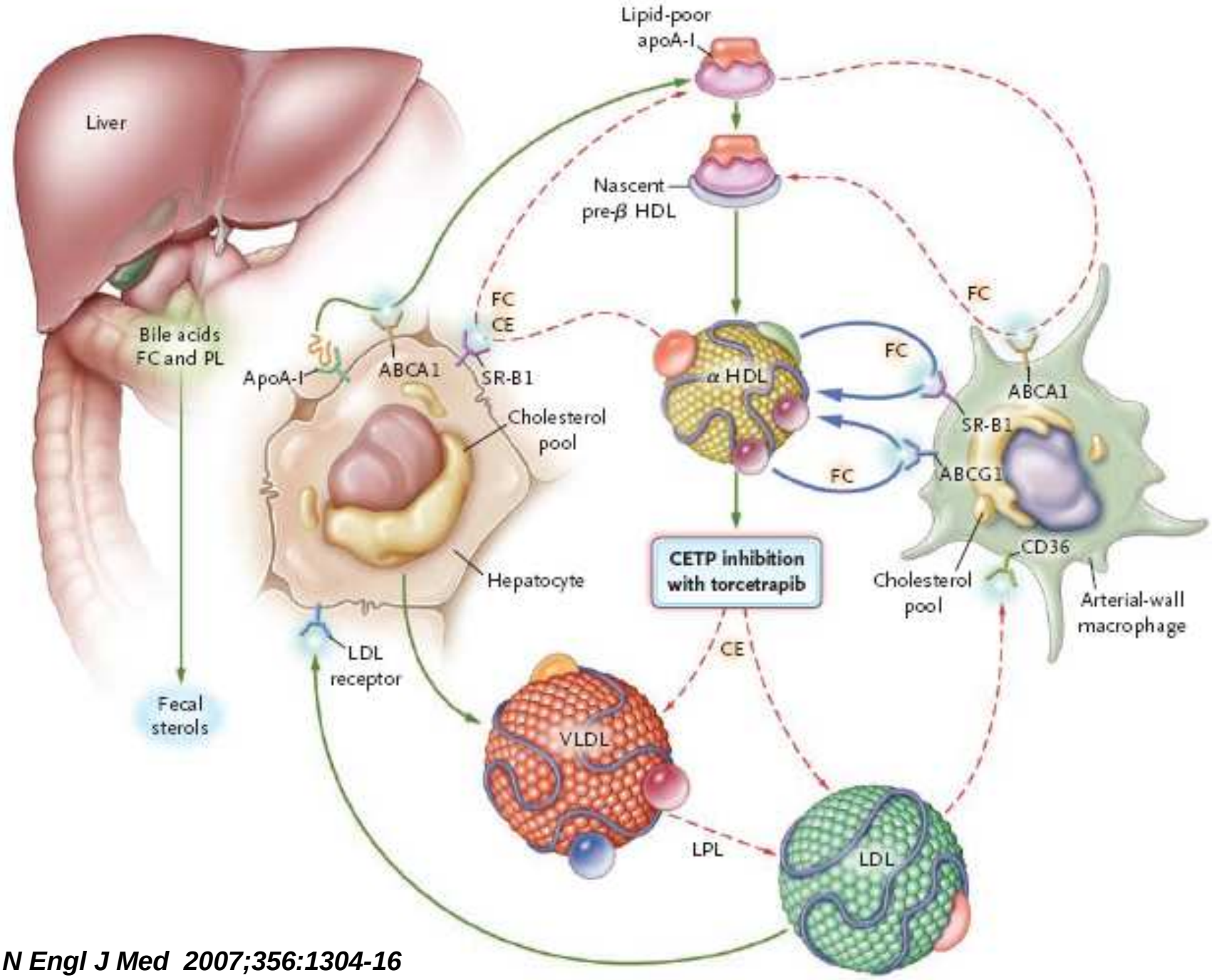
Cholesterol-debate

Introduction of the statins

Present practice

Failures

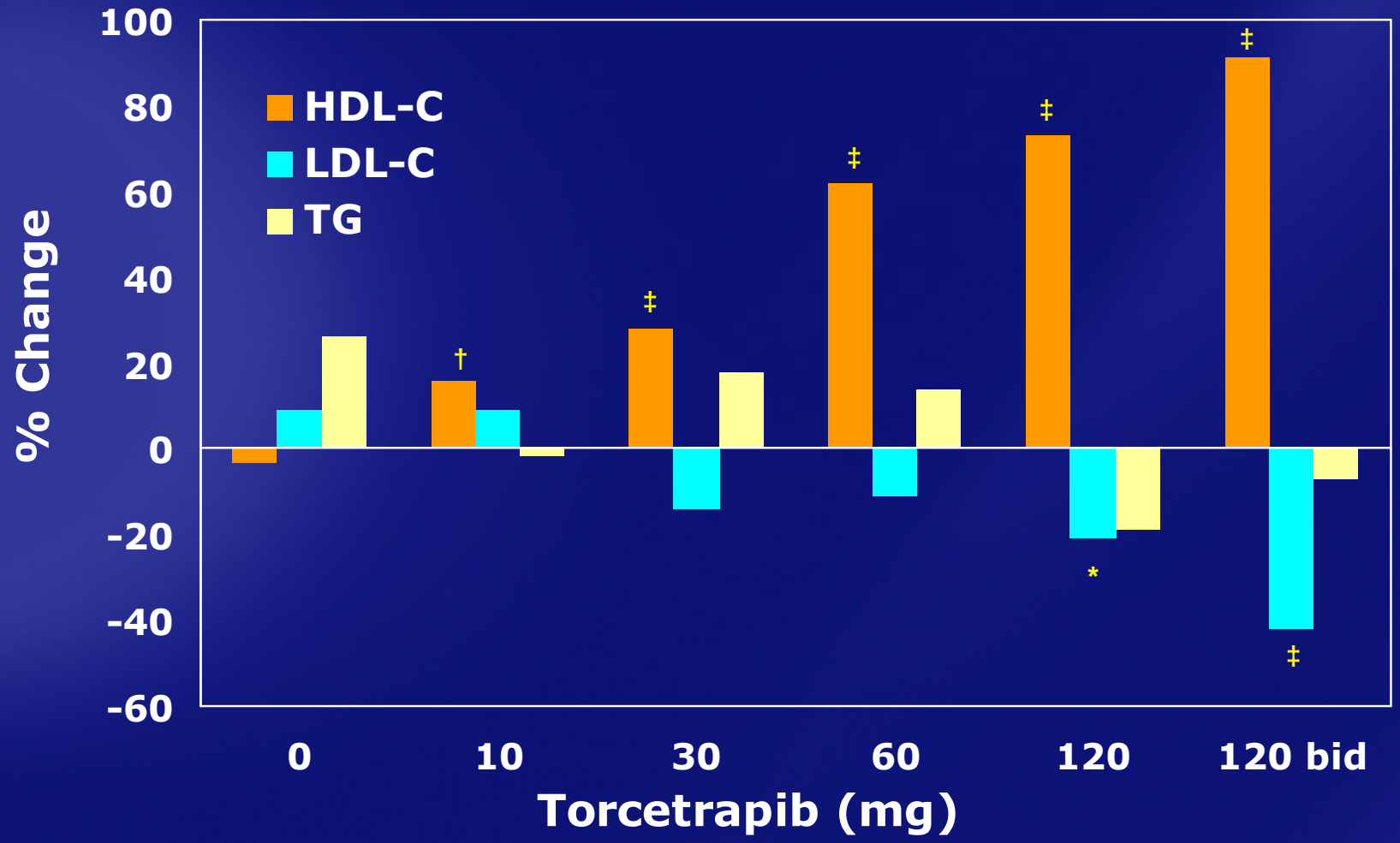

CHD RISK
3,0
2,0
1,0
0,0
2.6
4.1
5.6
LDL (mmol/L)
0.6
1.2
1.7
2.2
HDL
(mmol/L)



N Engl J Med 2007;356:1304-16

Torcetrapib in Healthy Individuals

14 days treatment vs. placebo



*P<0.05, †P<0.01, ‡P<0.001

Clark et al. ATVB 2004, 24:1–9

ILLUMINATE

(n= 15000 pts, high risk)

Torceptrapib 60 mg
+
Atorvastatin

Atorvastatin (10-80 mg)

Terminated prematurely at 1 year due to excessive deaths

93 vs 59

December 4, 2006.

Conclusions

UMC Nijmegen

- Solid relation between CVD & LDL-cholesterol
- Aim for lower LDL-C values in high risk patients: statins crucial (? + ezetimibe)

- 2006:
  - Guidelines NCEP: LDL-C < 2.6 (100 mg/dL)
    Option: 1.8 mmol/L (70mg/dL)
  - 2007:

- Guidelines ESC/EAS:

  - Total C < 4.5 mmol/L (175 mg/dL)
    - Option < 4.0 mmol/L (155 mg/dL)
  - LDL-C < 2.5 mmol/L (100 mg/dL)
    - Option < 2.0 mmol/L (80 mg/dL)

SCIENCE, 10 OCT 2008 VOL 322
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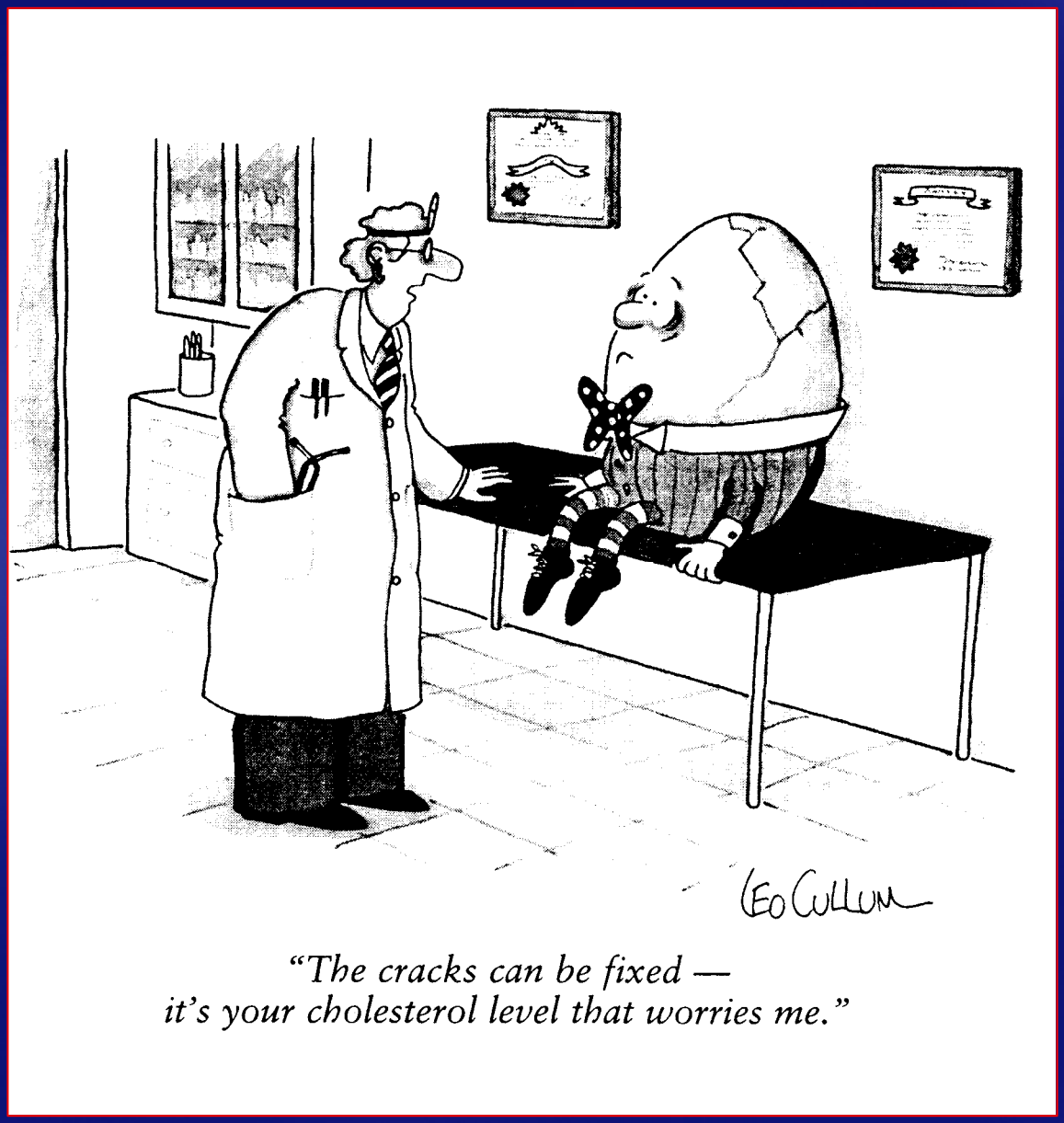
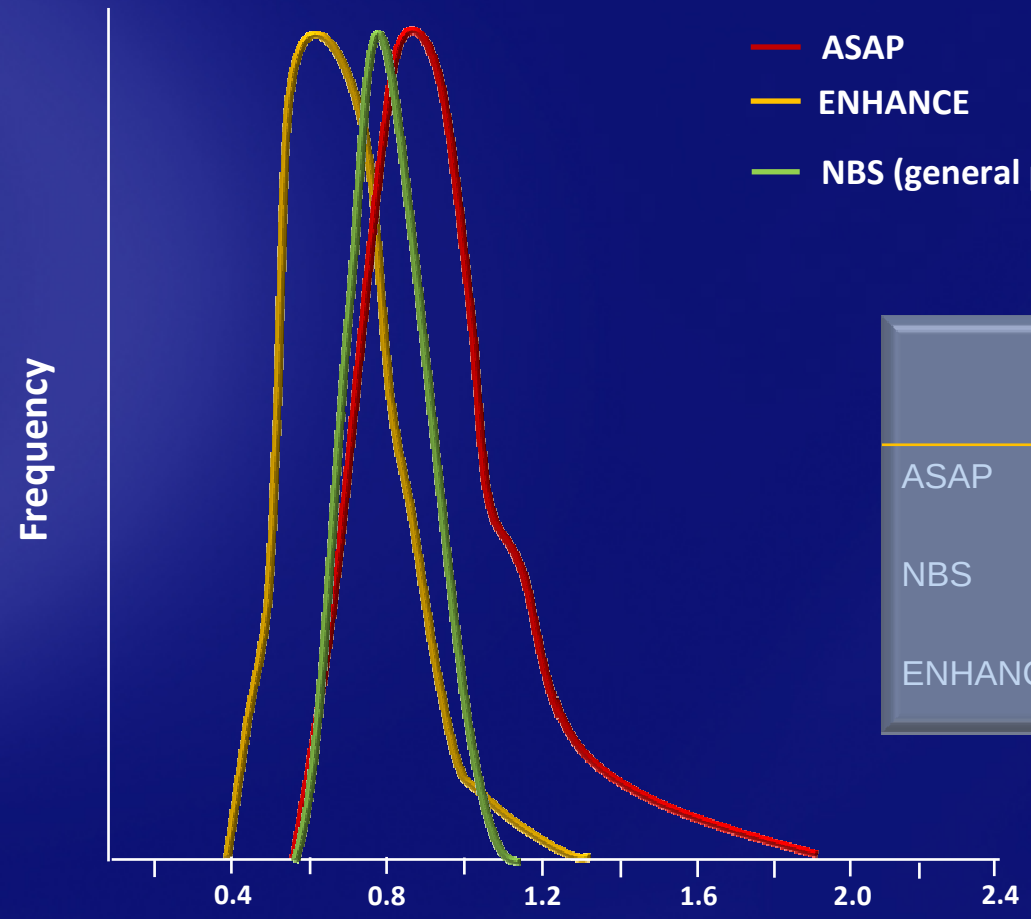


"The cracks can be fixed —
it's your cholesterol level that worries me."

Baseline cIMT in ASAP, ENHANCE and NBS*



	Baseline mean cIMT (mm)
ASAP	0.92±0.20
NBS	0.84 ±0.12
ENHANCE	0.70±0.13

ENHANCE

*Nijmegen Biomedical Study