An Unorthodox View on the Alzheimer's Pandemic: Are Statins to Blame?

Alex Shnyra, MD, PhD

CONFLICT OF INTEREST

I am not one of them

How USMLE 1 Results Are Presented to You

INFORMATION PROVIDED FOR EXAMINEE USE ONLY

The Performance Profile below is provided solely for the benefit of the examinee.
These profiles are developed as self-assessment tools for examinee only and will not be reported or verified to any third party.

USMLE STEP 1 PERFORMANCE PROFILE

PHYSICIAN TASK	Lower Performance	Borderline Performance	Higher Performance
MK: Applying Foundational Science Concepts			**********
PC: Diagnosis			**********
PC: Management			**********
PBLI: Evidence-Based Medicine			**********

Seeing the USME 1 results of my advisees, I have noticed that their knowledge of "Evidence-Based Medicine" is consistently rated lower than other "Physician Tasks".

What is the Evidence-Based Medicine?

Evidence Based Medicine – New Approaches and Challenges

Izet Masic, Milan Miokovic, Belma Muhamedagic
Faculty of Medicine, University of Sarajevo, B&H

SUMMARY
Evidence based medicine (EBM) is the conscientious, explicit, judicious and reasonable use of modern, best evidence in making decisions about the care of individual patients. EBM integrates clinical experience and patient values with the best available research information. It is a movement which aims to increase the use of high quality clinical research in clinical decision making. EBM requires new skills of the clinician, including efficient literature-searching, and the application of formal rules of evidence in evaluating the clinical literature. The practice of evidence-based medicine is a process of lifelong, self-directed, problem-based learning in which caring for one's own patients creates the need for clinically important information about diagnosis, prognosis, therapy and other clinical and health care issues. It is not "cookbook" with recipes, but its good application brings cost-effective and better health care. The key difference between evidence-based medicine and traditional medicine is not that EBM considers the evidence while the latter does not. Both take evidence into account; however, EBM demands better evidence than has traditionally been used. One of the greatest achievements of evidence-based medicine has been the development of systematic reviews and meta-analyses, methods by which researchers identify multiple studies on a topic, separate the best ones and then critically analyze them to come up with a summary of the best available evidence. The EBM-oriented clinicians of tomorrow have three tasks: a) to use evidence summaries in clinical practice; b) to help develop and update selected systematic reviews or evidence-based guidelines in their area of expertise; and c) to enrol patients in studies of treatment, diagnosis and prognosis on which medical practice is based.
Key words: Evidence Based Medicine, health, patients, decision making

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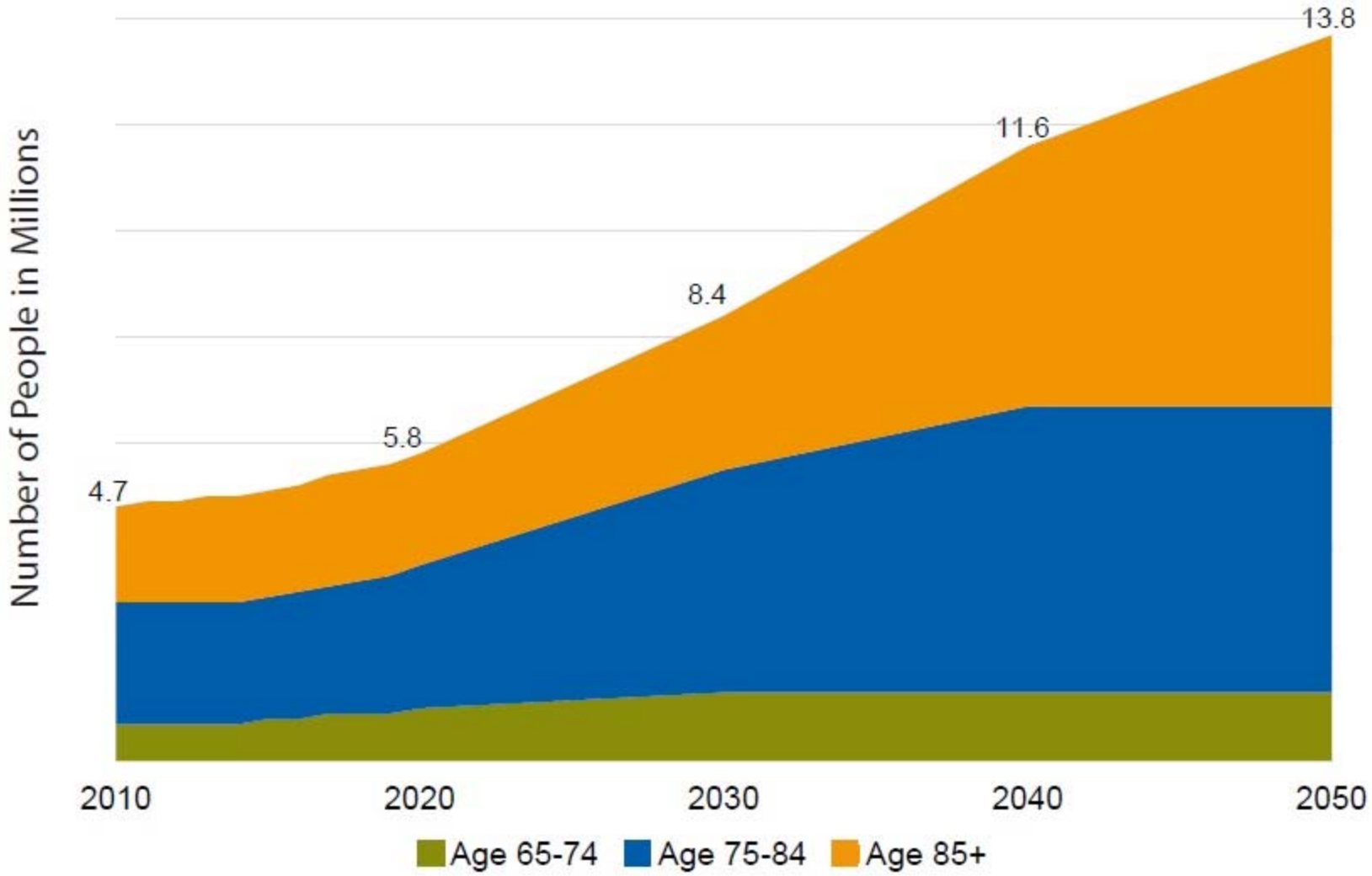
EBM [illegible] individual [illegible] clinical experi[illegible] evidences ob[illegible] search (2). The re[illegible] of ev[illegible] systematic [illegible] which [illegible] best available research evidence with clinical expertise and patient values. Under the individual clinical noticing we thought of the ability, skill that doctors acquired during years of clinical practice, and clinical experience is necessary and indispensable part that makes a good doctor. The best scientific evidence is considered to be a

Definition Of Evidence-Based Medicine

LEARNING OBJECTIVES

After reviewing the relevant reading material and studying the lecture notes students should be able to apply scientific evidence for better understanding the projected pandemic in Alzheimer's Disease.

Projected Number of People Aged 65 or Older With Alzheimer's Disease, by Age Group, United States, 2010-2050



Source: Created from data in Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 Census. *Neurology* 2013;80(19):1778-83.

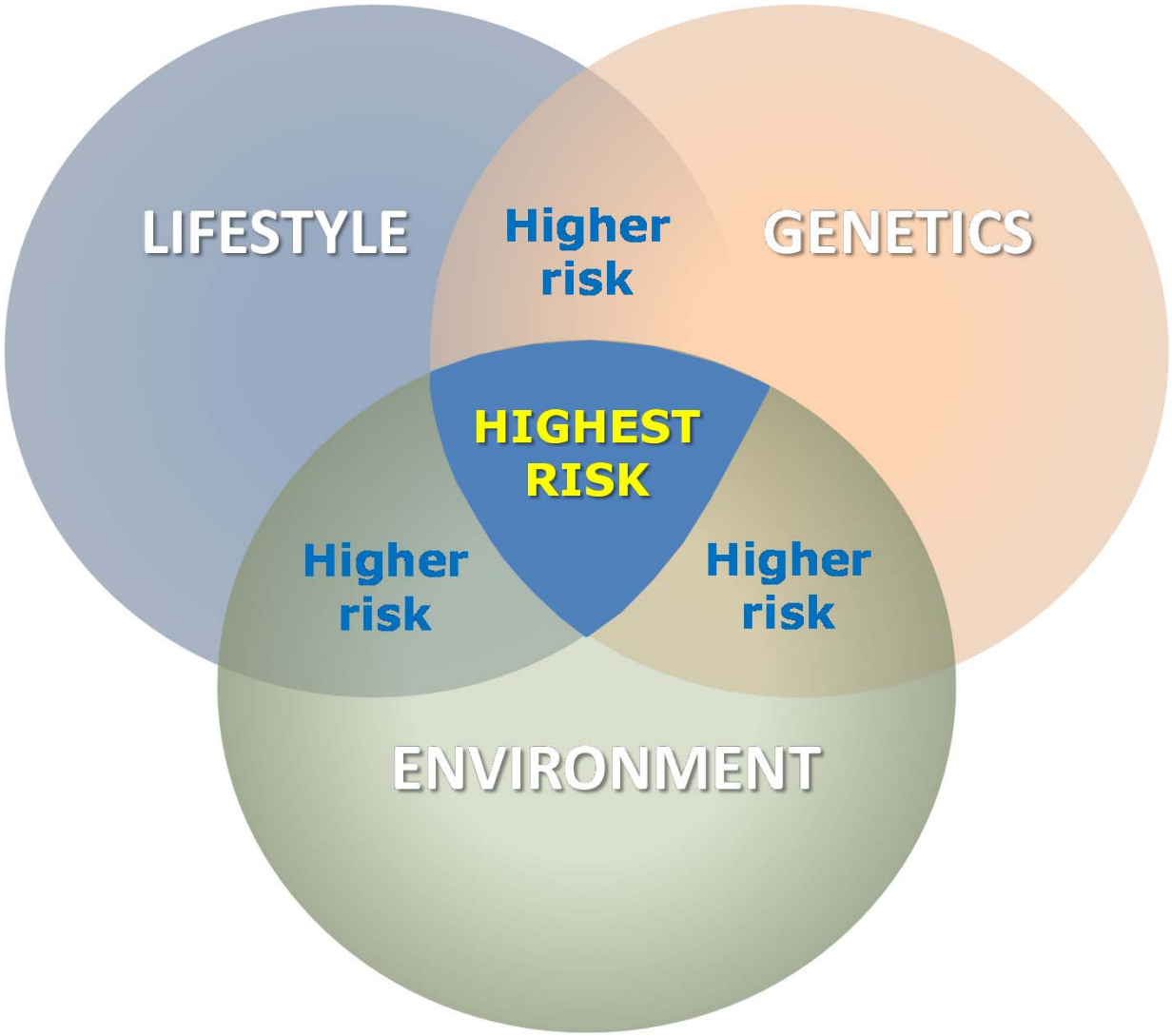
Let’s start with understanding whether Alzheimer’s Disease is Mendelian or Complex disease.

Mendelian & Complex Diseases

Diseases can be put into two categories based on the influence of genes:

- **MENDELIAN DISEASES**, also called single gene disorders, are caused by a variant in a single gene in our DNA code.
  - » Sickle Cell Anemia, Cystic Fibrosis, Huntington's Disease
- **COMPLEX DISEASES** are caused by many genetic variants in many genes, in addition to non-genetic factors, including lifestyle and environment.
  - » Type 1 Diabetes, Coronary Heart Disease, Systemic Lupus

COMPLEX DISEASES



How are diseases classified as Mendelian or Complex?

TWIN STUDIES

- Twin studies offer a special design for estimating the ***relative importance of genetic*** and ***environmental influences***.

- In a twin study, the ***most basic descriptive information*** is whether a twin pair is **CONCORDANT** (both have the disorder) or **DISCORDANT** (only 1 is affected).

- **IDENTICAL TWINS** ***share all of their genes*** whereas dizygotic **NONIDENTICAL TWINS** ***share on average 50%*** of their segregating genes.

- When identical twins are **MORE CONCORDANT** for a disease than nonidentical twins, ***genetic influences are suggested***.

- Evidence for the ***role of the environment*** comes from identical twins pairs who are **DISCORDANT FOR THE DISEASE**.

Let's see how it works!

TWIN STUDIES

CONCORDANT = both twins have a disease
DISCORDANT = one twin has a disease but another doesn't

	CONCORDANCE RATE IN		
Disease	Identical twins	Nonidentical twins	Interpretation
Huntington's disease	100%	50%	Autosomal dominant
Sickle cell anemia	100%	[illegible]	Autosomal recessive
Cystic fibrosis	100%	25%	Autosomal recessive
Type 1 diabetes	30%	6%	Environment + ≥ 1 gene
Coronary heart disease	46%	12%	Environment + ≥ 1 gene
Crohn's disease	40%	4%	Environment + ≥ 1 gene

MENDELIAN DISEASES

COMPLEX DISEASES

Role of Genes and Environments for Explaining Alzheimer Disease

Margaret Gatz, PhD; Chandra A. Reynolds, PhD; Laura Fratiglioni, MD, PhD; Boo Johansson, PhD; James A. Mortimer, PhD; Stig Berg, PhD; Amy Fiske, PhD; Nancy L. Pedersen, PhD

CONCLUSION?

Context: Twin studies using selected samples have shown high heritability for Alzheimer disease (AD).

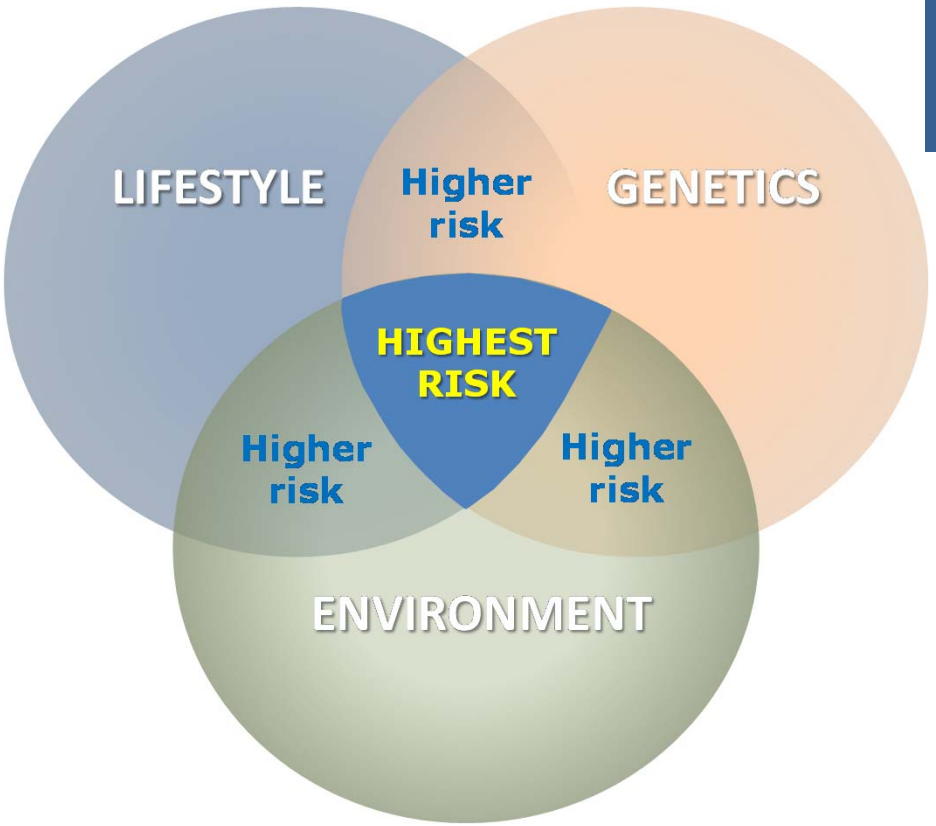
ronmental influences, adjusting for age, were derived from the twin data.

	Identical Men	Identical Women	Nonid. Men	Nonid. Women
Complete pairs, No.*				
Individuals, No.				
Prevalence				
Total dementia, No., %†	68 (	143	94	245
AD, %‡				
Age at onset of dementia, mean ± SD, y	76	7 6	7 2	7 8
Probandwise concordance, %				
Total dementia				
AD	45	61	19	41

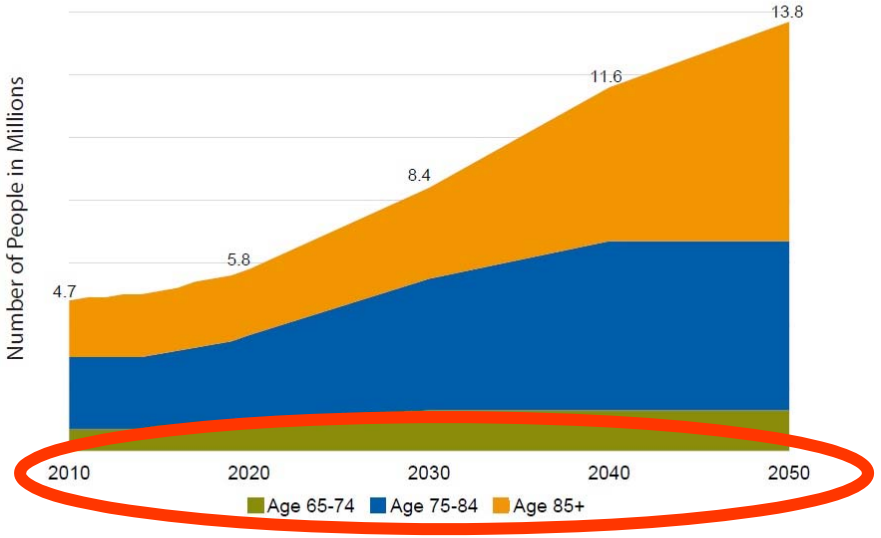
agnostic evaluations for AD. Estimates of heritability, shared environmental influences, and nonshared envi-

Arch Gen Psychiatry. 2006;63:168-174

Alzheimer's Disease Is a COMPLEX DISEASE



If an increase in the rate of AD (complex disease) is projected within 40 years, then it may only be associated with modification of lifestyle or change in environmental , but not GENETICS, for which 40 years is very short time.



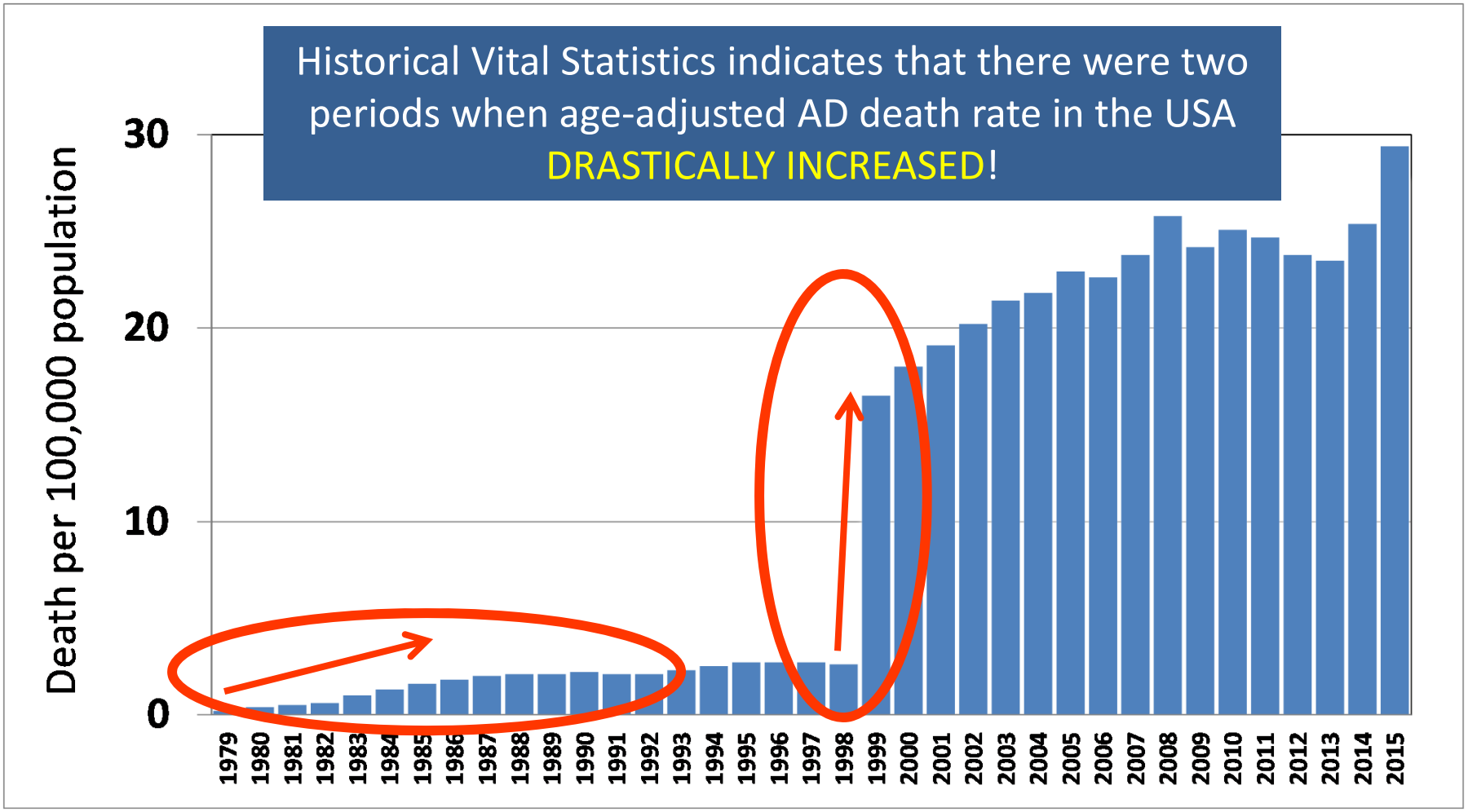
Source: Created from data in Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 Census. *Neurology* 2013;80(19):1778-83.

Age-Adjusted Alzheimer's Disease Death Rate in the USA

Vol. 44, No. 7, Supplement • February 29, 1996
Monthly Vital Statistics Report
Final Data From the CENTERS FOR DISEASE CONTROL AND PREVENTION/National Center for Health Statistics

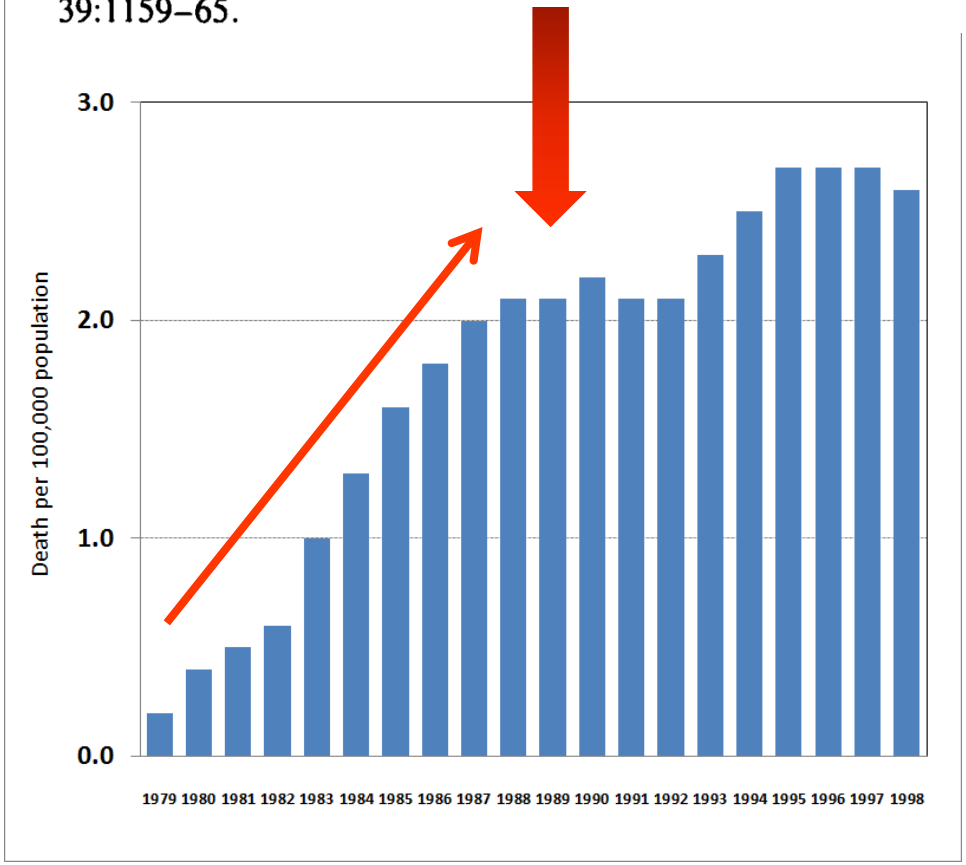
www.mdch.state.mi.us/pha/osr/annuals/Append07.xls *Age-Adjusted AD Death Rates* 1990 - 2007

https://www26.state.nj.us/doh-shad/indicator/complete_profile/AlzDeath.html?ListCategoryFirst=x 2007 to 2014



1979 - 1989

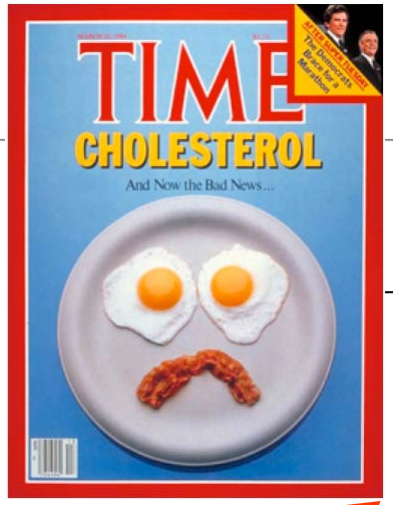
Morris JC, Heyman A, Mohs RC, et al. The consortium to establish a registry for Alzheimer's disease (CERAD): I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989; 39:1159–65.



It was NOT due to the "improved diagnostics" of AD, because the guidelines for clinical and neuropsychological assessment of the disease were introduced in 1989!

In the Seventies-Eighties CHOLESTEROL was identified as a CAUSE of Atherosclerosis

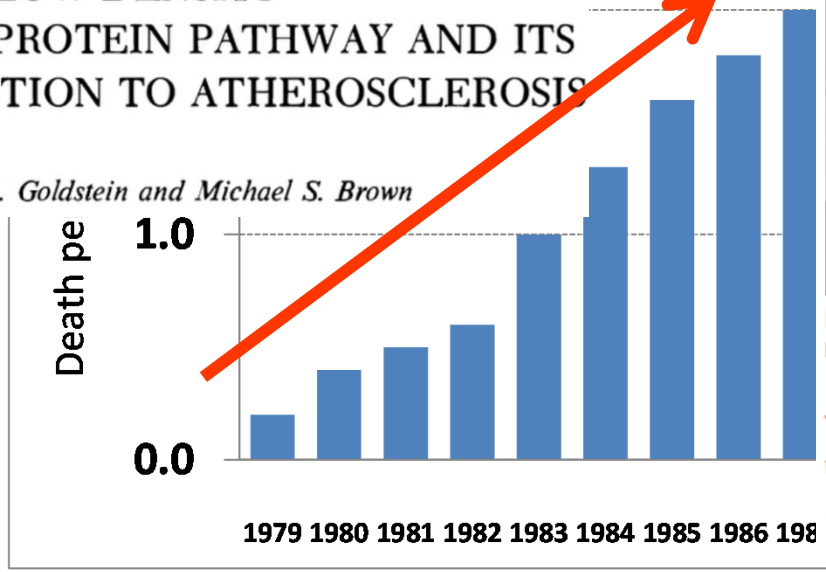
The cover of the March 1984 issue of TIME magazine



Ann. Rev. Biochem. 1977, 46:897

THE LOW-DENSITY LIPOPROTEIN PATHWAY AND ITS RELATION TO ATHEROSCLEROSIS

Joseph L. Goldstein and Michael S. Brown



The Nobel Prize in Physiology or Medicine 1985

Michael S. Brown
Prize share: 1/2

Joseph L. Goldstein
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 1985 was awarded jointly to Michael S. Brown and Joseph L. Goldstein *"for their discoveries concerning the regulation of cholesterol metabolism"*

Alzheimer's Disease Is a COMPLEX DISEASE

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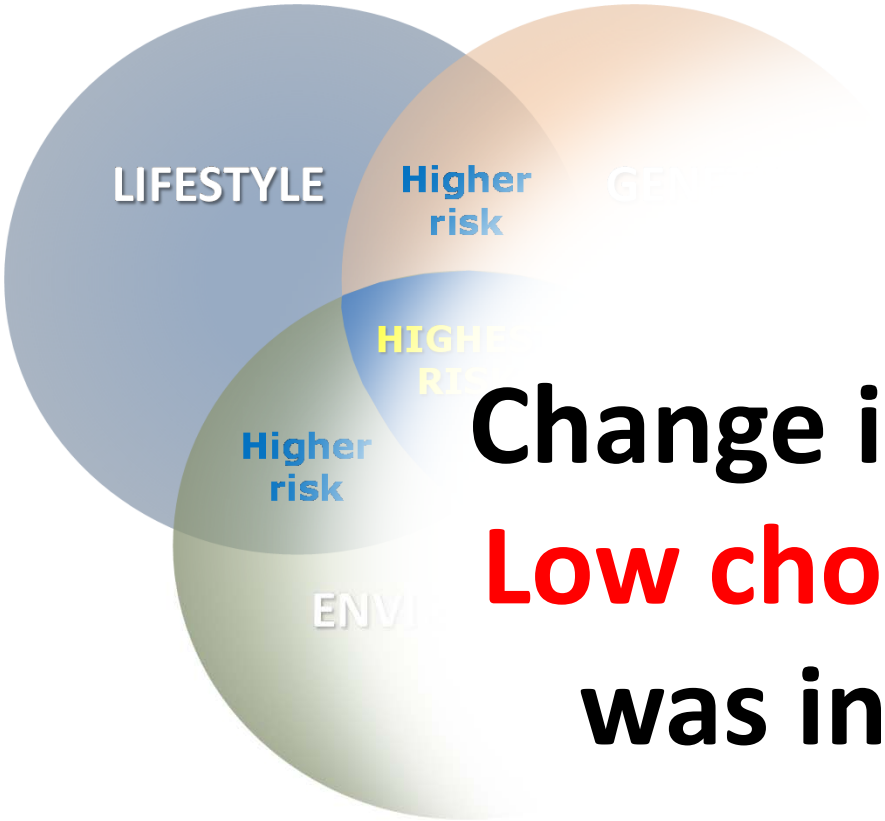
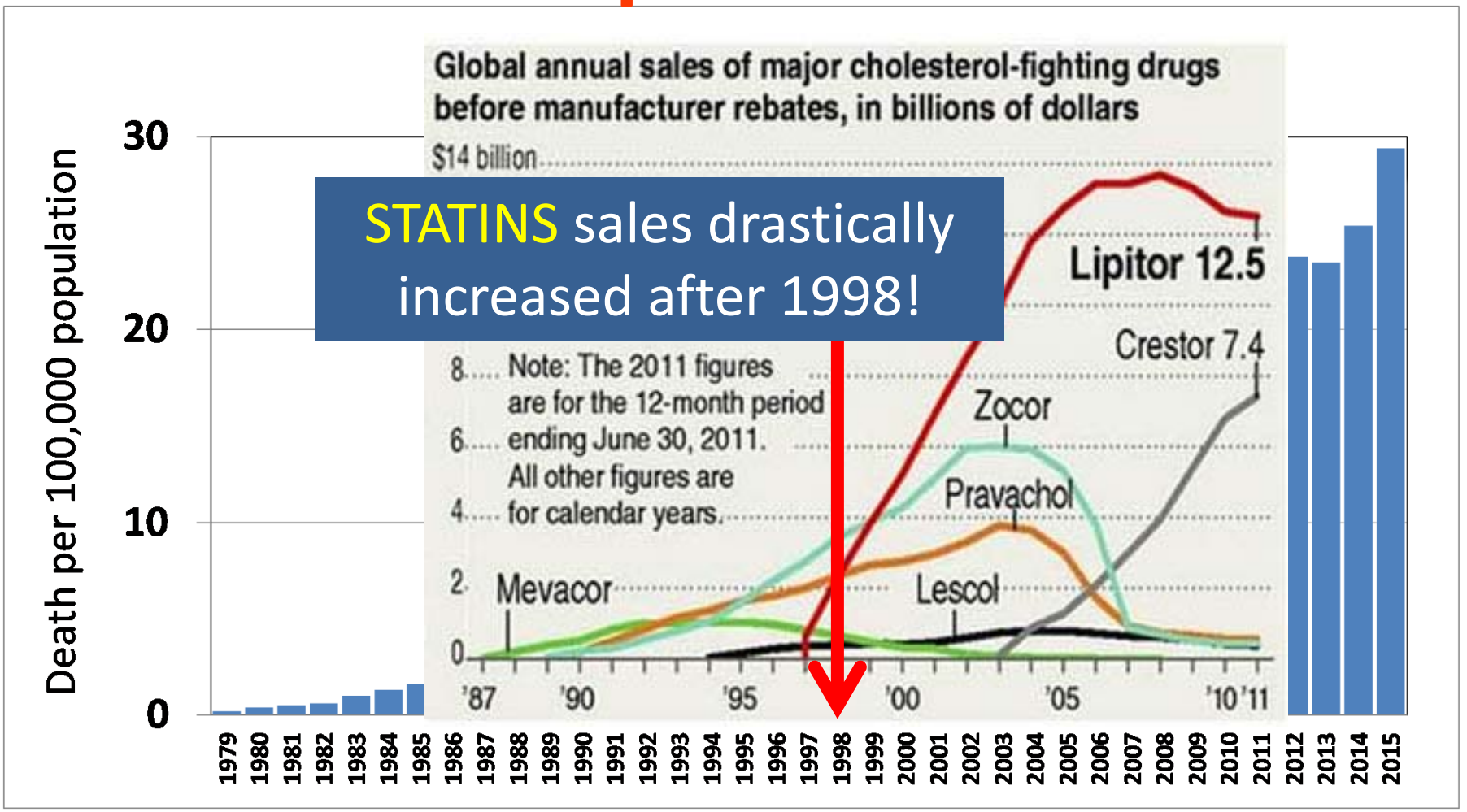


Change in LIFESTYLE:

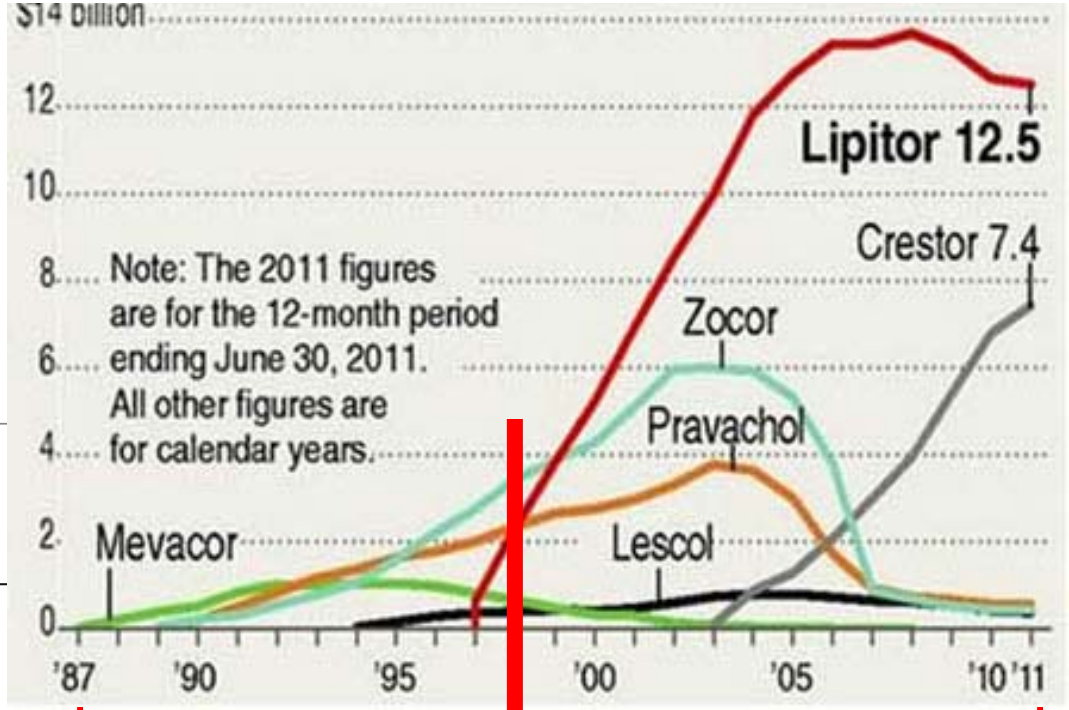
Low cholesterol diet was introduced!

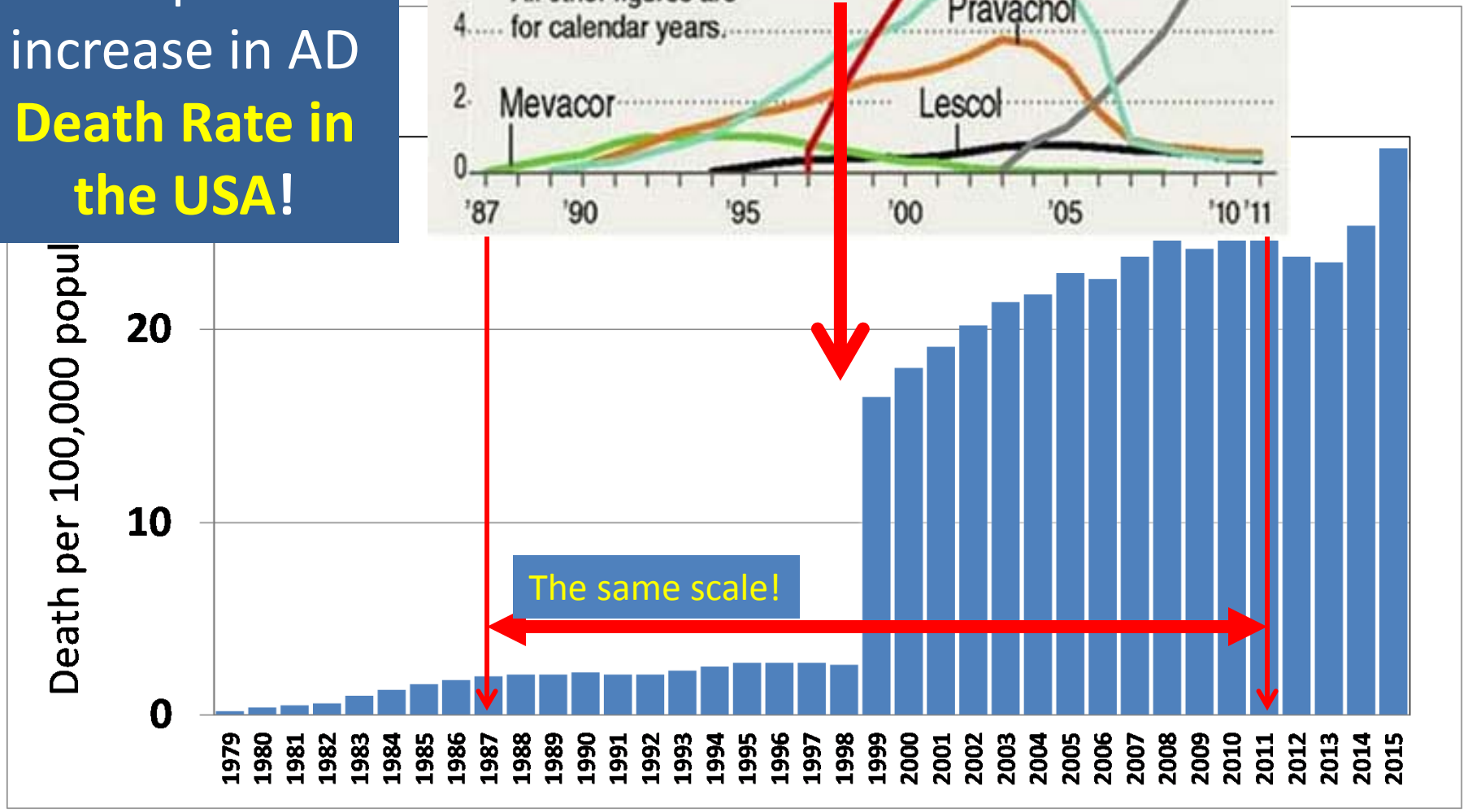
Evans DA. Alzheimer disease in the ... *Neurology* 2013;80(19):1778-83.

The first statin MEVACOR (Upjohn) was approved for treatment of high cholesterol patients in 1987!



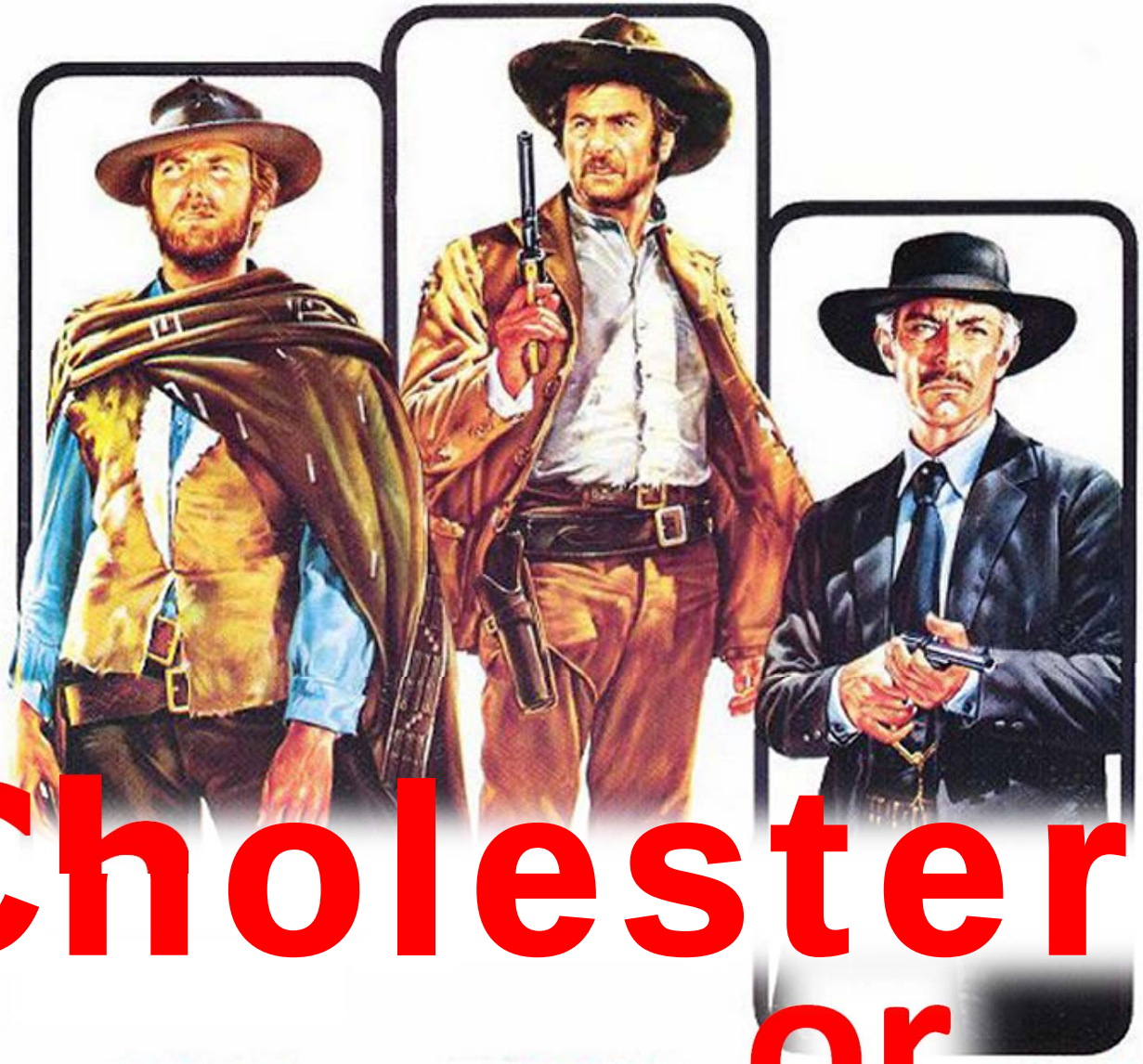
Increased STATINS sales coincided with a stepwise increase in AD **Death Rate in the USA!**





Circumstantial evidence suggest that introduction of both low-cholesterol diet and statins were associated with a stepwise increase in AD death rate…

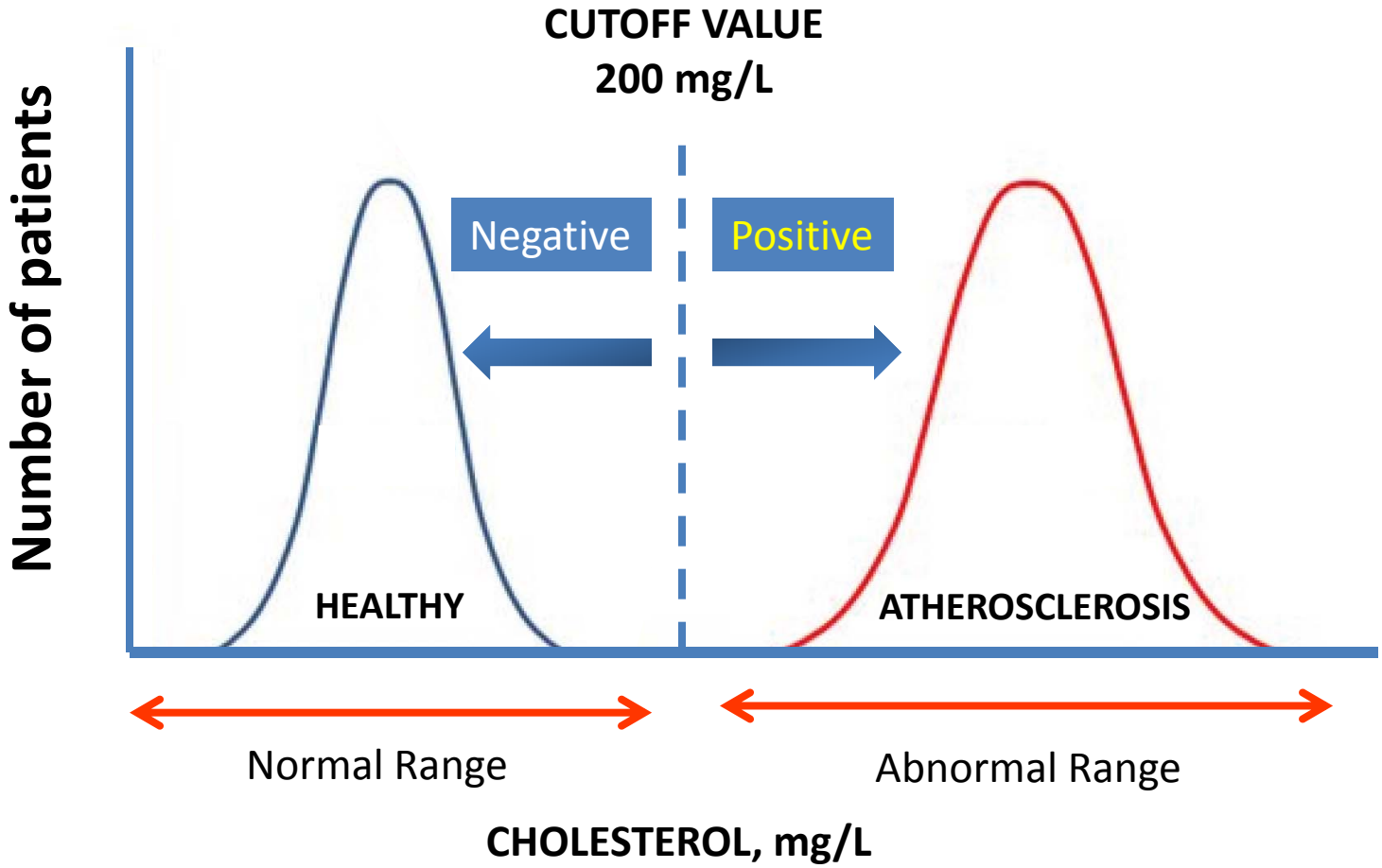
So, it is all about CHOLESTEROL, but…



Is Cholesterol or ?

Cholesterol Is Identified As a RISK FACTOR for Atherosclerosis

That's how an IDEAL risk factor would look like…



Now let's see what the Framingham Study found…

NB!

The first statin **MEVACOR** (Upjohn) was approved for treatment of high cholesterol patients in 1987!

Ann Intern Med. 1979 Jan;90(1):85-91.

Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study.

Kannel WB, Castelli WP, Gordon T.

Abstract

Prospective data at Framingham and elsewhere have shown conclusively that risk of coronary heart disease in persons younger than age 50 is strikingly related to the serum total cholesterol level. Within so-called normal limits risk has been found to mount over a five-fold range. The in ... tal c ... n f ... a ... c ... o ... pertaining to coronary heart disease resided in the serum total cholesterol must be accordingly modified.

In 1948, FHS scientists and participants embarked on an ambitious project to **IDENTIFY RISK FACTORS FOR HEART DISEASE**. Today, the study remains a world-class epicenter for cutting-edge heart, brain, bone, and sleep research.

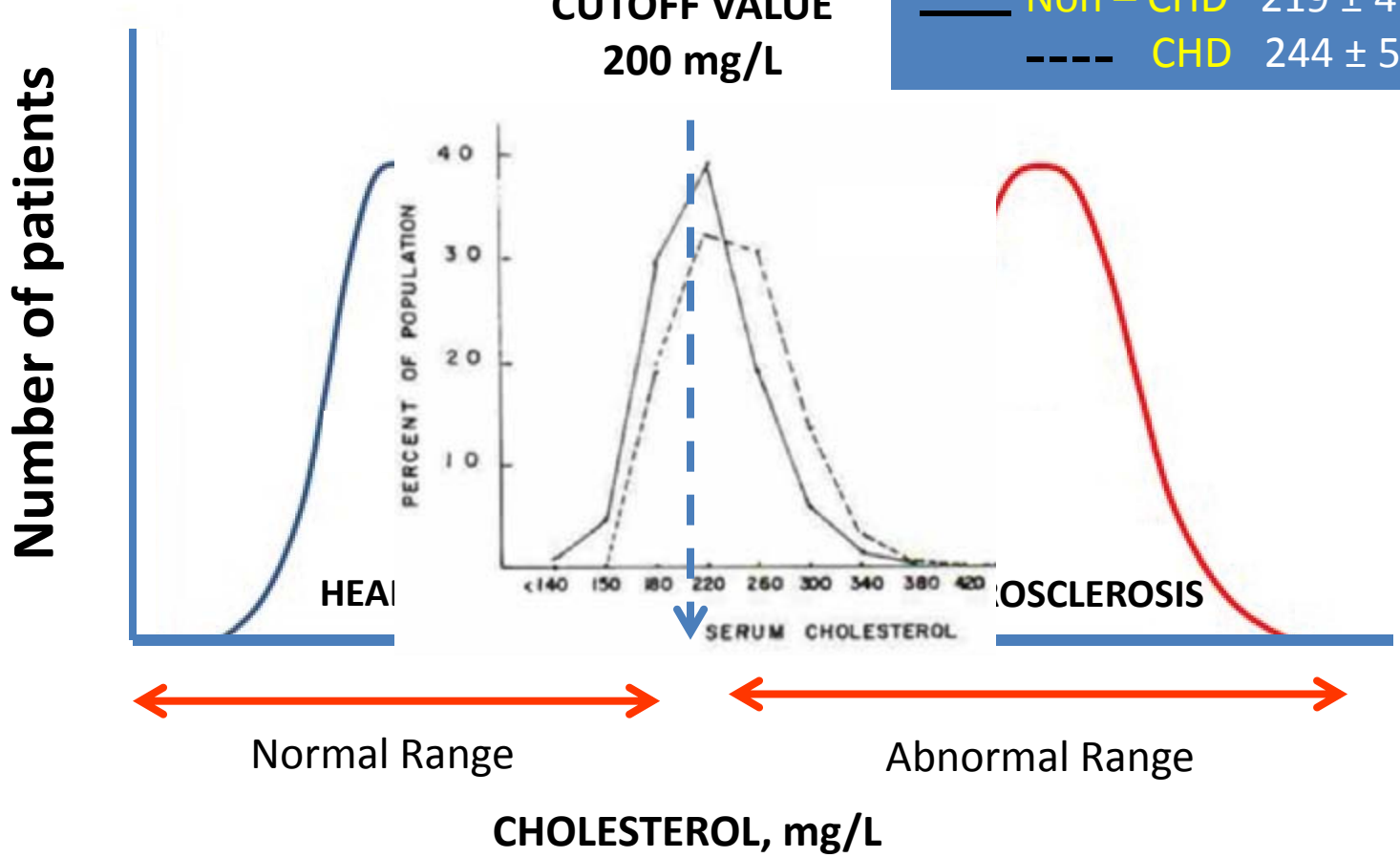
The following data were obtained before introduction of Statins in 1987.

Viewer discretion advised☺!

Framingham Study

CHD - coronary heart disease

		Mean ± SD
———	Non – CHD	219 ± 41.4 mg/L
- - - -	CHD	244 ± 51.4 mg/L



Evidence Based Medicine – New Approaches and Challenges

and then critically analyze them to come up with a summary of the best available evidence. The EBM-oriented clinicians of tomorrow have three tasks: a) to use evidence summaries in clinical practice; b) to help develop and update selected systematic reviews or evidence-based guidelines in their area of expertise; and c) to enrol patients in studies of treatment, diagnosis and prognosis on which medical practice is based.

Key words: Evidence Based Medicine, health, patients, decision making

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the ability, skill that doctors acquired during years of clinical practice, and clinical experience is necessary and indispensable part that makes a good doctor. The best scientific evidence is considered to be a

Based on the Framingham study...

Could CHOLESTEROL be considered as a reliable risk factor for ATHEROSCLEROSIS?

Now let's see how cholesterol levels are associated with relative risk of death…

Report of the Conference on Low Blood Cholesterol: Mortality Associations

Background. A National Heart, Lung, and Blood Institute (NHLBI) Conference was held October 9–10, 1990, to review and discuss existing data on U-shaped relations found between mortality rates and blood total cholesterol levels (TC) in some but not other studies. Presentations were given from 19 cohort studies from the United States, Europe, Israel, and Japan. A representative of each study presented its findings

…to review and discuss the existing data on U-shaped relations found between mortality rates and blood total cholesterol levels…

production and secretion of cholesterol-bearing lipoproteins with liver disease. In this sort of situation, the TC:mortality association found in observational studies may be due to preexisting disease. This was

Presentations were given from 19 cohort studies (total men: 523,737; total women: 124,814) from the United States, Europe, Israel, and Japan.

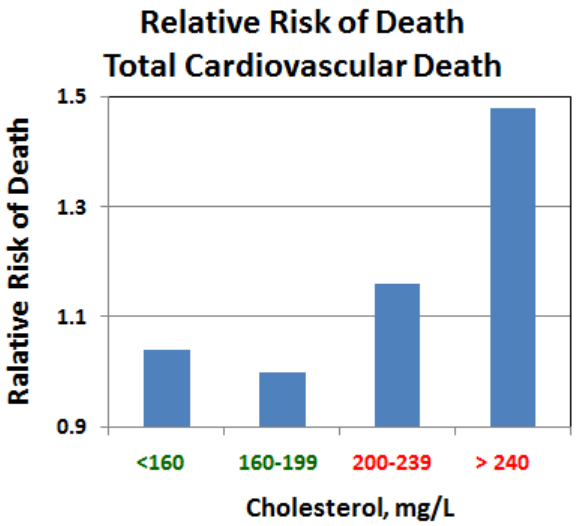
manifestations in specific lipid disorders, and further study of the proposed causal mechanisms linking low TC and hemorrhagic stroke. (*Circulation* 1992;86:1046–1060)

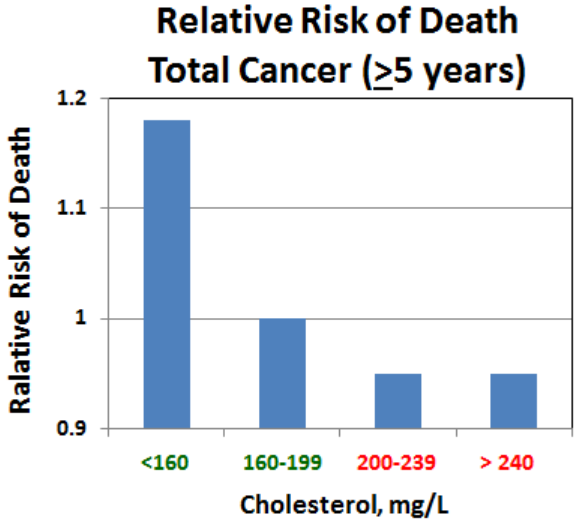
KEY WORDS • cholesterol • mortality

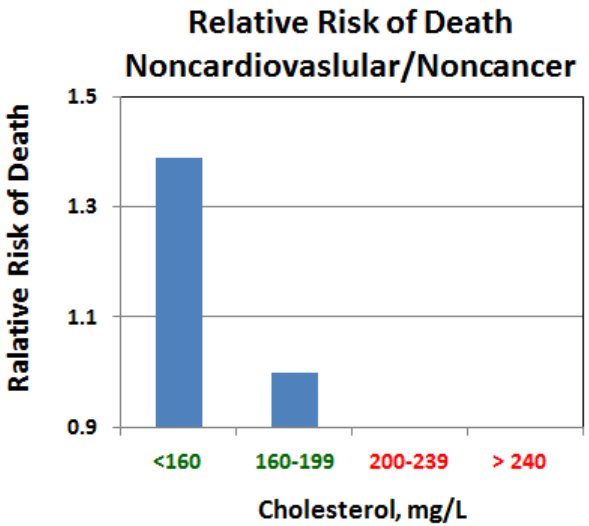
Relative Risk of Death

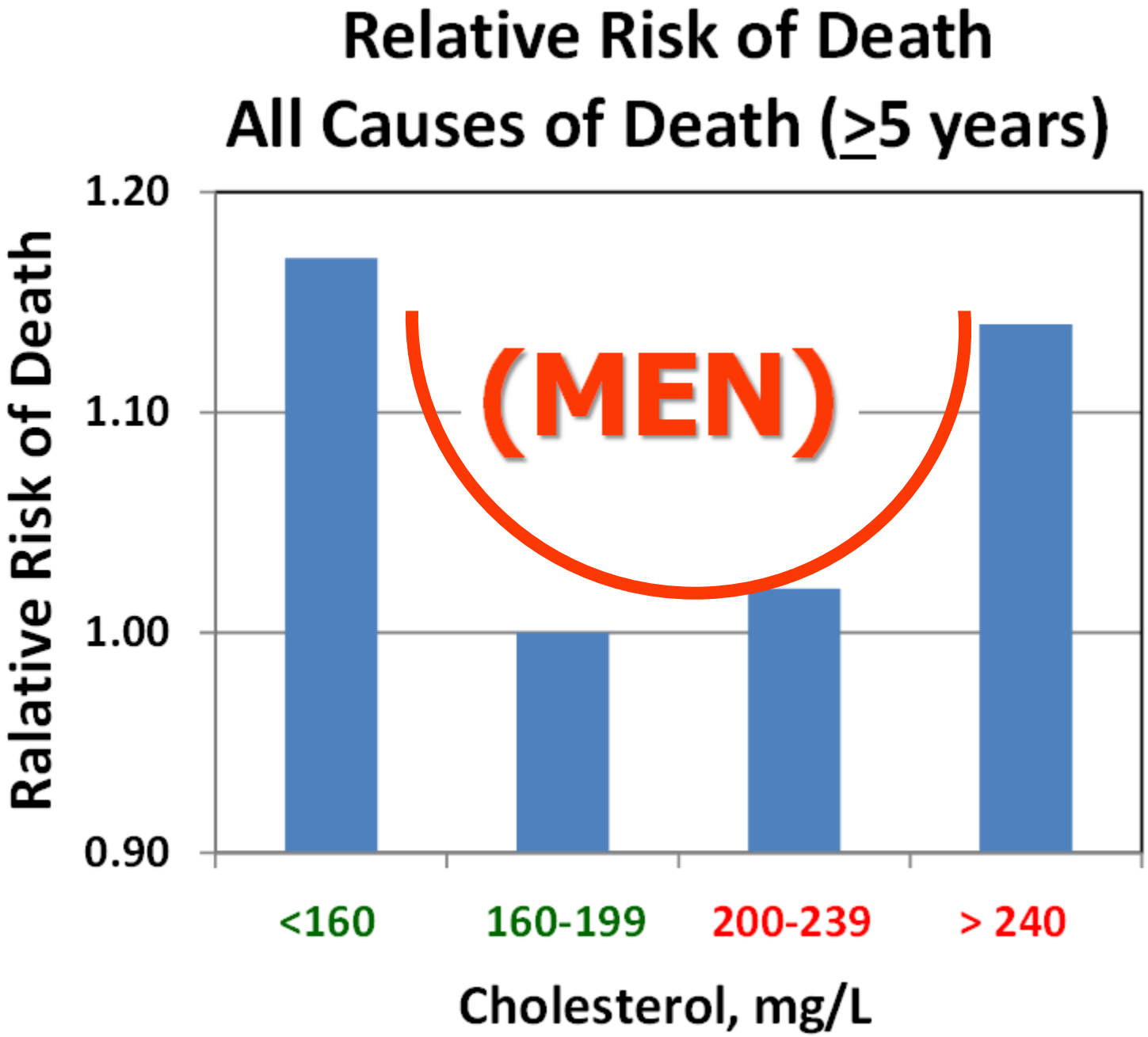
≥ 5 years after study baseline

(MEN)








Relative Risk of Death
All Causes of Death (≥5 years)
Ralative Risk of Death
1.20
1.10
1.00
0.90
(MEN)
<160
160-199
200-239
> 240
Cholesterol, mg/L

Evidence Based Medicine – New Approaches and Challenges

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Based on the Conference report…

Are normal-to-moderately elevated levels of total cholesterol (160-239 mg/dL) associated with reduced relative death rate of all causes in men?

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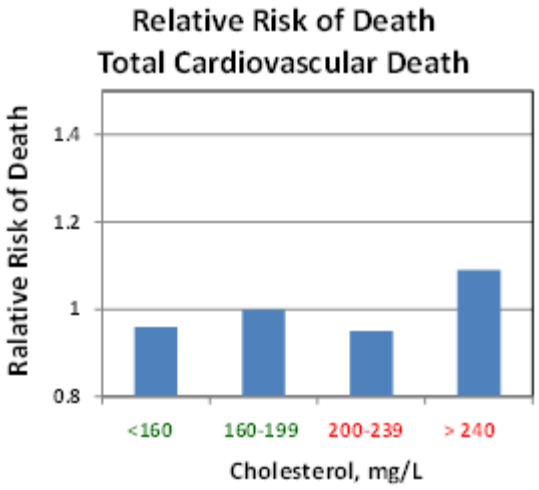

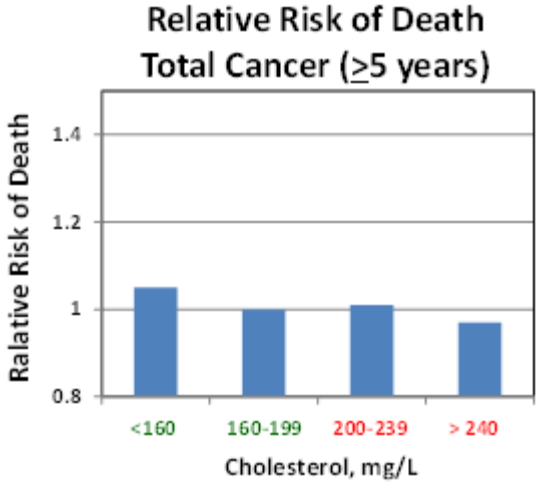

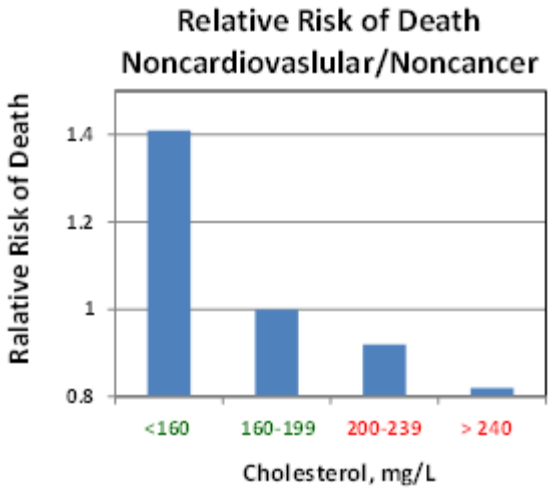

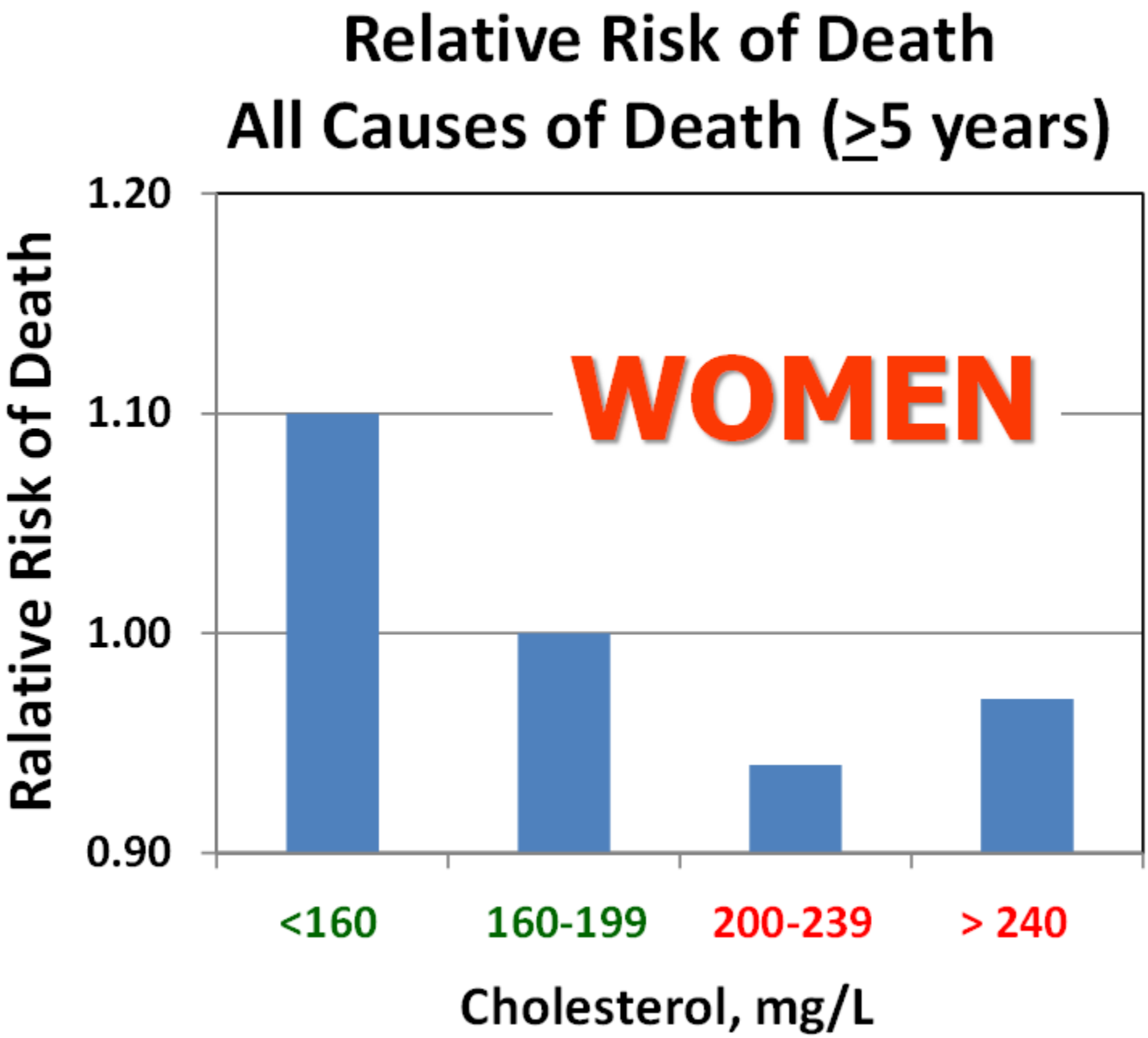
Relative Risk of Death
All Causes of Death (≥5 years)
Ralative Risk of Death
1.20
1.10
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0.90
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<160
160-199
200-239
> 240
Cholesterol, mg/L

PROFESSIONAL PAPER

Evidence Based Medicine – New Approaches and Challenges

Izet Masic, Milan Miokovic, Belma Muhamedagic
Faculty of Medicine, University of Sarajevo, BiH

SUMMARY
Evidence ... moderately ... tes clinical ... movement ... making ... of evidence ... which ... diagnosis ... with ... different ... evidence ... methods ... and those ... The EBM-oriented ... clinical practice; b) to help develop and update selected systematic reviews or evidence-based guidelines in their area of expertise; and c) to enrol patients in studies of treatment, diagnosis and prognosis on which medical practice is based.

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Based on the Conference report...

Are moderately-elevated levels of total cholesterol (200-239 mg/dL) associated with reduced relative death rate of all causes in women ?

Now let's see how cholesterol levels are associated with the risk of heart attack…

Lipid levels in patients hospitalized with coronary artery disease: An analysis of 136,905 hospitalizations in Get With The Guidelines

Amit Sachdeva, MD,[a] Christopher P. Cannon, MD,[b] Prakash C. Deedwania, MD,[c] Kenneth A. LaBresh, MD,[d] Sidney C. Smith, Jr, MD,[e] David Dai, MS,[f] Adrian Hernandez, MD,[f] and Gregg C. Fonarow, MD[a] on behalf of the GWTG Steering Committee and Hospitals *Los Angeles and San Francisco, CA; Boston and Waltham, MA; and Chapel Hill and Durham, NC*

Backgro
well studie
with CAD
Metho
documente
high-densi
assessed
Results
Mean lipi
cholestero
lipoprotei
receiving
hyperlipid
declined
Conclu
More than h
provide further
HDL. (Am Heart J 2009;157:111-7.e2.)

- Analyzed data from **136,905 patients** hospitalized in the US for a **HEART ATTACK** whose lipid levels upon hospital admission were documented.
- Among individuals **without CAD**:
  - **72.1 %** of patients had LDL levels less than **< 130 mg/dL**.
- Among individuals **with CAD**:
  - **50%** of patients had LDL cholesterol **< 100 mg/dL**
  - **17.6 %** of patients had LDL levels **70 mg/dL**

Only 1 in 4 patients hospitalized in the US with heart attack had cholesterol > 130 mg/L

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Based on the above study…

Is CHOLESTEROL a risk factor for heart attack?

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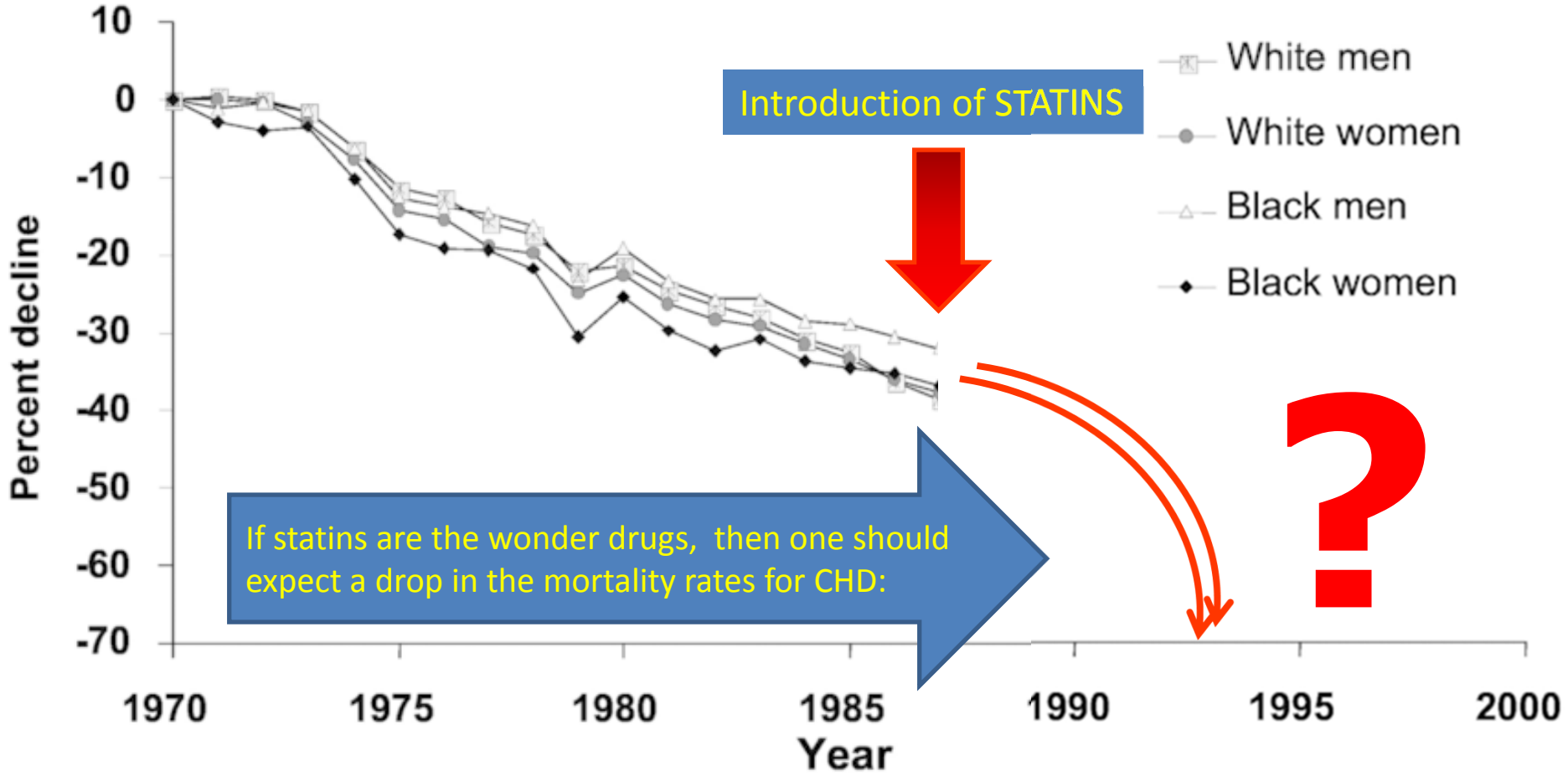
The End of Low-Fat Diet Recommendations

The 2015 U.S. DIETARY GUIDELINES ADVISORY COMMITTEE AT NIH reviewed all the research over 40 years and told us to ***stop worrying about dietary cholesterol***, arguing it is "**NOT A NUTRIENT OF CONCERN**." They also finally lifted any recommendations to restrict dietary fat after 35 years of a steady diet of low-fat recommendations!

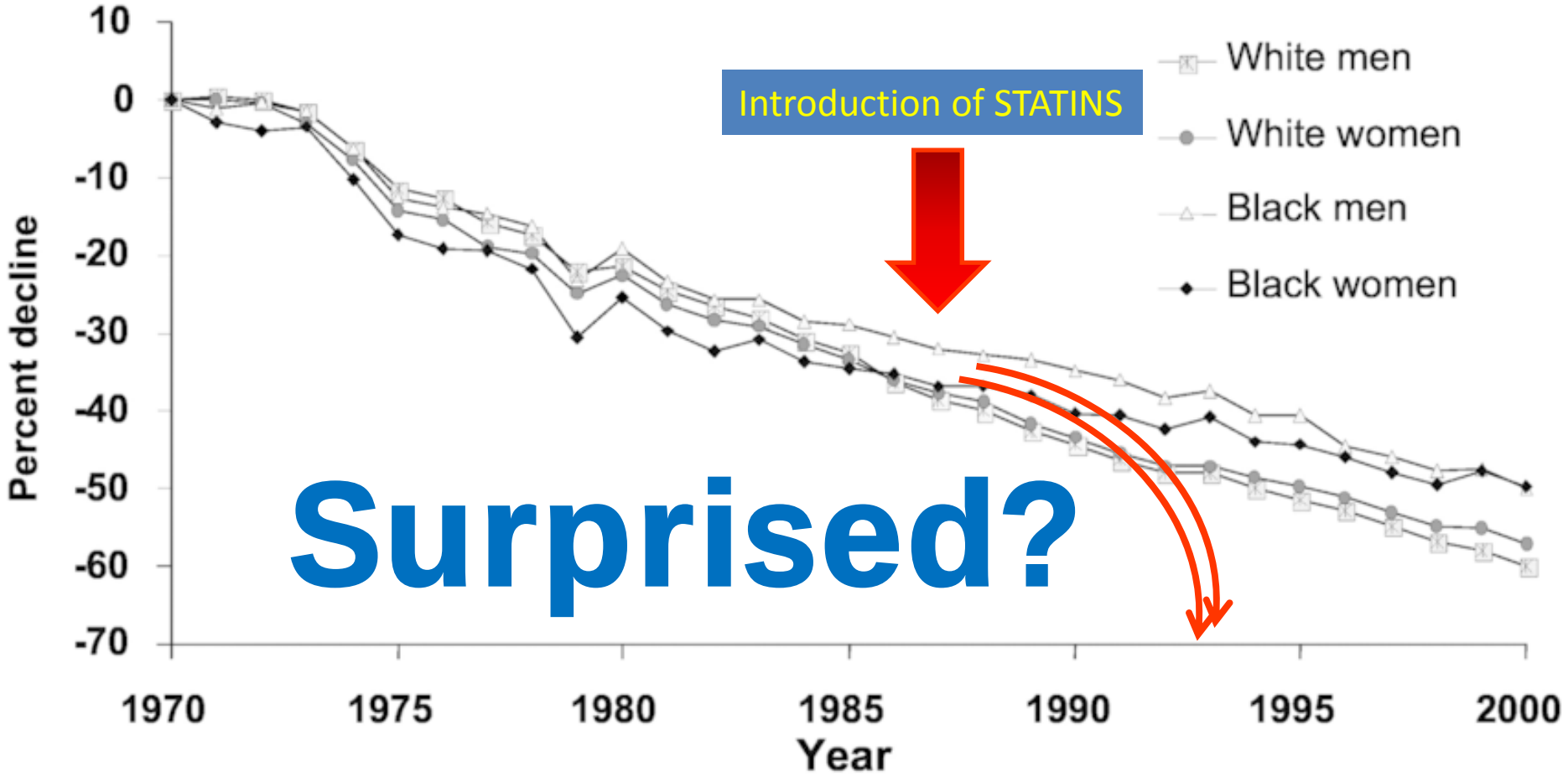
Now let's see how introduction of STATINS affected the mortality caused by CHD.

Percentage Decline in Age-Adjusted Mortality Rates for CHD: United States, 1970 to 2000.

Source: National Heart, Lung, and Blood Institute from Vital Statistics of the United States, National Center for Health Statistics. Death rates are age-adjusted to the 2000 US census population.



STATINS Did NOT Affect the CHD Mortality After 20 Years of Use



Evidence Based Medicine – New Approaches and Challenges

not (1). Family medicine, by its nature, is very complicated discipline which is featured among other things, high proportion of poorly differentiated problems overlapping with the biological, psychological and social factors. EBM - Evidence Based Medicine, which originated in the second half of the 19th Century and earlier, means conscious and reasonable use of current,

Based on NIH statistics...

Was introduction of statins followed by a decline in mortality rates for CHD?

and then critically analyze them to come up with a summary of the best available evidence. The EBM-oriented clinicians of tomorrow have three tasks: a) to use evidence summaries in clinical practice; b) to help develop and update selected systematic reviews or evidence-based guidelines in their area of expertise; and c) to enrol patients in studies of treatment, diagnosis and prognosis on which medical practice is based.

Key words: Evidence Based Medicine, health, patients, decision making

dividual clinical noticing we thought of the ability, skill that doctors acquired during years of clinical practice, and clinical experience is necessary and indispensable part that makes a good doctor. The best scientific evidence is considered to be a

Dr. Shnyra's Problems with STATIN TRIALS

- Oversight by the pharmaceutical company sponsor
- Use of the Relative Risk instead of Absolute Risk
- Combined clinical endpoints instead of mortality

Benjamin Disraeli
(1804–1881)
British Prime Minister

There are three kinds of lies:
lies,
damned lies,
and STATISTICS!

CMAJ • AUG. 17, 2004; 171 (4)

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Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat

Alexandra Barratt, Peter C. Wyer, Rose Hatala, Thomas McGinn, Antonio L. Dans, Sheri Keitz, Virginia Moyer, Gordon Guyatt, for the Evidence-Based Medicine Teaching Tips Working Group

ß See related article page 347

Physicians, patients and policy-makers are influenced not on
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The tips in
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based medicine skills to clinicians.[5,6] A related article, intended for people who teach these concepts to clinicians, is available online at www.cmaj.ca/cgi/content/full/171/4/353/DC1.

event without treatment.

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You can calculate relative and absolute risk reductions using simple mathematical formulas (see Appendix 1). How-

Appendix 1: Formulas for commonly used measures of therapeutic effect

Measure of effect	Formula
Relative risk	(Event rate in intervention group) ÷ (event rate in control group)
Absolute risk reduction	(Event rate in intervention group) – (event rate in control group)

Let's consider that the event rate is

1.9% in drug-treated (intervention) group and

3.0% in placebo (control) group

then, the ABSOLUTE RISK REDUCTION will be 3-1.9 = 1 or

1 of 100 patients benefits from drug use

What would the result be if you calculate the relative risk?

1.9/3 = 0.63 or 63%

Then, the RELATIVE RISK REDUCTION would be staggering (100%-63%) =

36%

The data on the next slide is reproduced from this review.

EXPERT REVIEWS

How statistical deception created the appearance that statins are safe and effective in primary and secondary prevention of cardiovascular disease

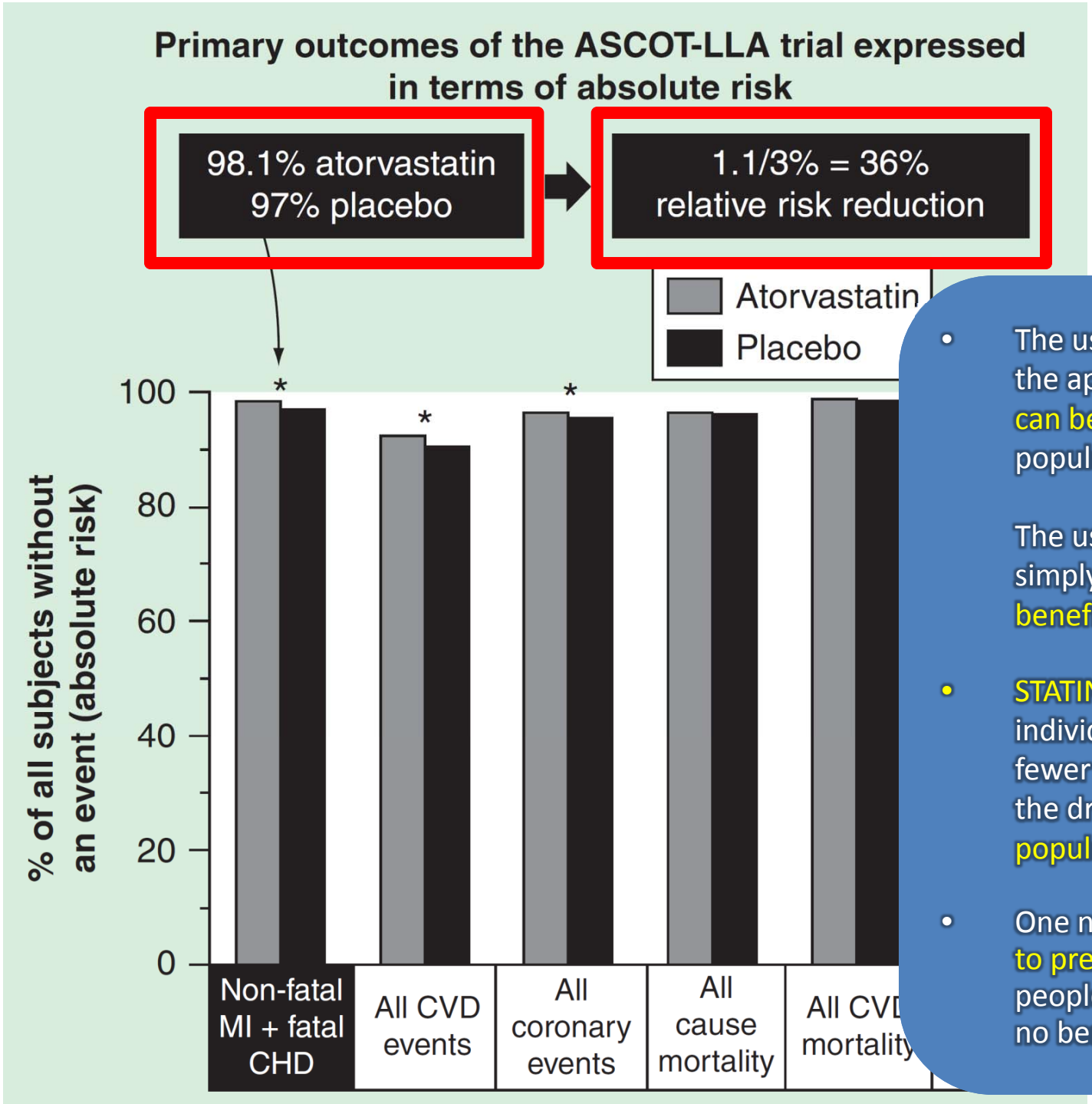
Expert Rev. Clin. Pharmacol. 8(2), 201–210 (2015)

David M Diamond*[1–3] and Uffe Ravnskov[4]

[1]*Medical Research Service, Veterans Hospital, Tampa, 33612 FL, USA*
[2]*Department of Psychology, Center for Preclinical and Clinical Research on PTSD, University of South Florida, Tampa, 33620 FL, USA*
[3]*Department of Molecular Pharmacology and Physiology, Center for Preclinical and Clinical Research on PTSD, University of South Florida, Tampa, 33620 FL, USA*
[4]*Independent Researcher, Magle Stora Kyrkogata 9, 22350 Lund, Sweden*

We have provided a critical assessment of research on the reduction of cholesterol levels by statin treatment to reduce cardiovascular disease. Our opinion is that although statins are effective at reducing cholesterol levels, they have failed to substantially improve cardiovascular outcomes. We have described the deceptive approach statin advocates have deployed to create the appearance that cholesterol reduction results in an impressive reduction in cardiovascular disease outcomes through their use of a statistical tool called relative risk reduction (RRR), a method which amplifies the trivial beneficial effects of statins. We have also described how the directors of the clinical trials have succeeded in minimizing the significance of the numerous adverse effects of statin treatment.

KEYWORDS: absolute risk • adverse effects • cancer • dementia • hypercholesterolemia • myositis • relative risk • statins • trials



- The use "relative risk" creates the appearance that statins can benefit 30% to 50% of the population.

  The use of "relative risk" simply amplifies the trivial beneficial effects of statins.

- STATINS would help 1 of 100 individuals to experience 1 fewer heart attack, meaning the drugs benefit 1% of the population.

- One need to treat 890 people to prevent 1 death - 889 people are taking statins with no benefit.

Are statins safe?

Statins (HMG-CoA reductase inhibitors) are among the best-selling prescription drugs and have been viewed as having a favorable safety profile.

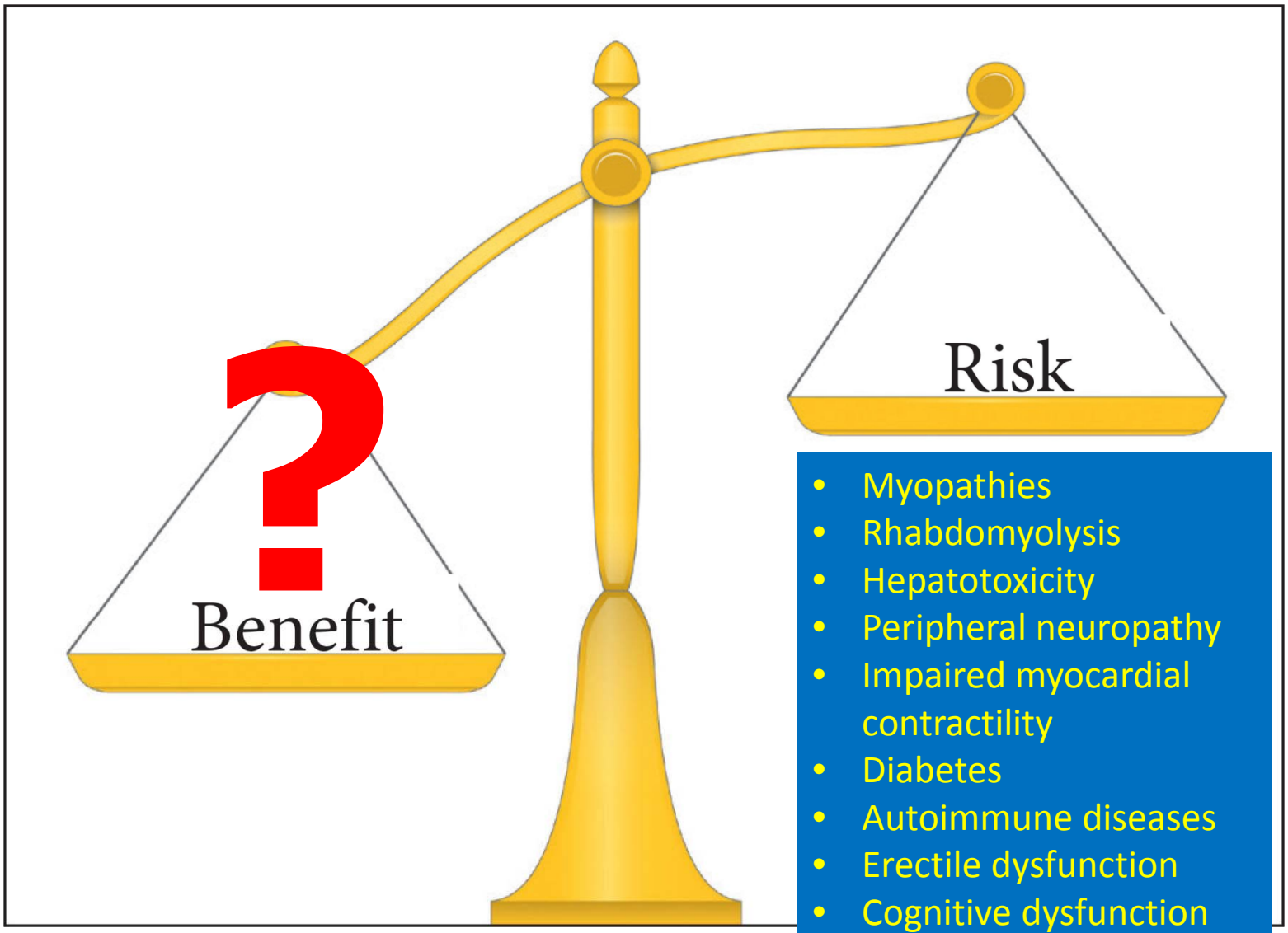
While adverse effects (AEs) are reported to be rare in clinical trials, they are less uncommon in clinical experience.

Scott RS, Lintott CJ, Wilson MJ. Simvastatin and side effects. N Z Med J. 1991;104:493–5.
Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. Cardiovasc Drugs Ther. 2005;19:403–14.

A short analysis at the University of California, San Francisco concluded that 96% of authors with drug company ties declared statins to be safe versus 37% authors with no ties.

Blinznakov E. Coenzyme Q10, lipid-lowering drugs (statins) and cholesterol: a present day Pandora's box. JANA 2002;5: 32-38.

Statins: Risk Versus Benefit



- Myopathies
- Rhabdomyolysis
- Hepatotoxicity
- Peripheral neuropathy
- Impaired myocardial contractility
- Diabetes
- Autoimmune diseases
- Erectile dysfunction
- Cognitive dysfunction

Statins: Risk Versus Benefit

REVIEW ARTICLE

Are statins really wonder drugs?

Harpreet Singh Grover, Shailly Luthra*, Shruti Maroo

Good paper to begin your understanding the side-effects of STATINS

Received 21 January 2013; received in revised form 4 May 2013; accepted 11 May 2013

KEYWORDS
adverse effects;
diabetes;
hepatotoxicity;
myopathy;
neuropathy;
statins

Statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase], are wonder drugs that have reshaped the treatment of hypercholesterolemia and associated cardiovascular diseases. However, evidence from various studies indicates existence of many statin-induced side effects such as myopathies, rhabdomyolysis, hepatotoxicity, peripheral neuropathy, impaired myocardial contractility, diabetes, autoimmune diseases, and erectile dysfunction (ED). Physician awareness of these side effects is reported to be very low even for the adverse effects (AEs) most widely reported by patients. This can lead to incorrect treatment decisions, compromised patient care, and an increase in patient morbidity. Therefore, the aim of this article is to highlight the AEs of statin therapy as well as rational management of these complications to further improve safety of these excellent drugs.
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STATINS SIDE-EFFECTS

MYOPATHY

Randomized, controlled TRIALS report about a 1.5% to 5% incidence of statin-associated myopathy.

The Prediction of Muscular Risk in Observational Conditions (PRIMO) study reported a myopathy rate of 10.5% of patients

US Pharmacist 2012;37(2):55-59

HEPATOTOXICITY

Statins have been observed to cause mild ALT elevations in 10% of recipients, and in 1-3% of patients, the elevations are more than three times the ULN.

Beltowski J, Wojcicka G, Jamroz-Wisniewska A. Adverse effects of statins - mechanisms and consequences. Curr Drug Saf 2009;4:209-228.
Tolman KG. The liver and lovastatin. Am Coll Cardiol Curr J Rev. 2002;11:37

NEPHROTOXICITY

The rates of renal disease and failure found in pravastatin-treated patients were 0.8% and 0.5%, respectively.

The hospitalization due to acute renal failure by statins was 34% more in group received high potency statin compared with the group received low potency statin. High potency statins include rosuvastatin, atorvastatin and simvastatin

Pfeffer MA, Keech A, Sacks FM, Cobbe SM, Tonkin A, Byington RP, et al. Safety and tolerability of pravastatin in long-term clinical trials: prospective Pravastatin Pooling (PPP) Project. Circulation 2002;105:2341-6.
Dormuth CR, Hemmelgarn BR, Paterson JM, James MT, Teare GF, Raymond CB, et al. Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. BMJ. 2013;346:f880.

NEUROLOGIC MANIFESTATIONS

Several epidemiological studies demonstrated two to five times increased risk of peripheral polyneuropathy in statin-treated patients.

Backes JM, Howard PA. Association of HMG-CoA reductase inhibitors with neuropathy. Ann Pharmacother 2003;37:274-8.

Gaist D, Jeppesen U, Andersen M, Garcia Rodriguez LA, Hallas J, Sindrup SH. Statins and risk of polyneuropathy: a case-control study. Neurology 2002;58:1333-7.

CANCER

Breast cancer occurred in 12 of 286 women in the treatment group of the CARE (Cholesterol and Recurrent Events) trial, but only in 1 of 290 in the placebo group (P = .002).

In the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) trial, cancer occurred in 245 of 2,891 patients in the treatment group, but only in 199 of 2,913 in the placebo group (P = .02).

In the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial, cancer occurred in 39 of 944 patients in the treatment group, but only in 23 of 929 in the placebo group (P < .05).

U Ravnskov, PJ Rosch, KS McCully : The statin-low cholesterol-cancer conundrum . QJM: An International Journal of Medicine, 105: 383– 388,2012

ERECTILE DYSFUNCTION

The findings suggest a strong relationship between the taking of statin drugs and erectile dysfunction.

Published data reported on five men with coronary artery disease who developed impotence within one week of starting treatment with simvastatin 10 mg or having the dose increased to 20 mg. Within one week of stopping simvastatin, sexual function was restored. Two patients were re-challenged with simvastatin and impotence recurred.

Rizvi K and others. Do lipid lowering drugs cause erectile dysfunction? A systematic review. Family Practice 19 (1):95-8, 2002.
Jackson G. Simvastatin and impotence. BMJ 315:31, 1997

DIABETES

Statins may significantly increase a person's risk of developing type 2 diabetes. Statin use was associated with greater diabetes with pooled HR (95% CI) for incident diabetes of 1.36 (1.17 to 1.58).

Crandall JP, Mather K, Rajpathak SN on behalf of the Diabetes Prevention Program(DPP) Research Group, et al. Statin use and risk of developing diabetes: results from the Diabete Prevention Program. BMJ Open Diabetes Research and Care 2017;5:e000438. doi: 10.1136/bmjdrc-2017-000438

PROFESSIONAL PAPER

Evidence Based Medicine – New Approaches and Challenges

not (1). Family medicine, by its nature, is very complicated discipline which is featured among other things, high proportion of poorly differentiated problems overlapping with the biological, psychological and social factors. EBM - Evidence Based Medicine, which originated in the second half of the 19th Century and earlier, means conscious and reasonable use of current,

Based on the available data...

Do STATINS benefits

(1 of 100 protected from CHD)

overweight the risks of potential complications caused by their side-effects?

Do safe alternatives of statins exist?

BMJ

BMJ 2013;347:f7267 doi: 10.1136/bmj.f7267 (Publi

UK Deaths in 2013 – 576,458
Statins save 1.63%

9400 lives would be saved if every UK citizen over age 50 took a daily STATIN!

A statin a day keeps the doctor away: comparative proverb assessment modelling study

8500 lives would be saved if every UK citizen over age 50 ate an APPLE a day!

er Scarborough *senior*

adington, Oxford OX3 7LF, UK

Journal of the American College of Cardiology
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Vol. 55, No. 13, 2010
ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2009.10.056

Alcohol Consumption and Cardiovascular Mortality Among U.S. Adults, 1987 to 2002

	Volume of Alcohol Consumption			
	Nondrinkers	Light	Moderate	Heavy
Cardiovascular deaths				530
Person-yrs				143,649
Multivariable-adjusted*		0.7 5)	0.6 77)	0.89 (0.73–1.10)
Multivariable + activity/diet†		0.7 5)	0.6 80)	0.90 (0.73–1.10)
5-yr follow-up‡		0.7 4)	0.6 77)	0.83 (0.66–1.04)
Men		0.7 0)	0.7 81)	0.95 (0.76–1.19)
Women		0.7 3)	0.7 81)	0.88 (0.72–1.07)
White		0.7 4)	0.6 78)	0.90 (0.73–1.10)
Not white		0.8 9)	0.7 94)	0.92 (0.70–1.21)
Age <55 yrs		0.7 7)	0.6 86)	0.91 (0.60–1.40)
Age ≥55 yrs		0.7 6)	0.7 80)	0.89 (0.76–1.06)
Excellent health				0.92 (0.66–1.28)
Not excellent health		0.7 0)	0.6 2)	0.82 (0.65–1.03)
Coronary heart disease deaths	4,	57	53	308
Coronary mortality	1.00	0.75 (0.66–0.84)	0.67 (0.57–0.79)	0.80 (0.61–1.05)
Stroke deaths	1,241	288	135	94
Stroke mortality	1.00	0.80 (0.61–1.05)	0.76 (0.58–0.99)	1.25 (0.92–1.70)

According to baseline volume of alcohol consumption. *Multivariable-adjusted HRs adjusted for age, sex, race, smoking, marital status, education, region, urbanization, smoking, body mass index, and general health status. †Analyses adjusted for covariates in multivariable models; physical activity assessed in 1990, 1991, and 1997 to 2000; and diet assessed in 1987 and 1992. ‡Truncated analyses limited follow-up to 5 years after administration of the respective NHIS.

Abbreviations as in Tables 1 and 2.

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Abbreviations as in Tables 1 and 2.

Do you know that there is a company Nymox Pharmaceutical Corporation that holds Patent Rights to Statins in Alzheimer's?

Recent Studies Support Statin Drug Treatment Potential in Alzheimer's Disease; Nymox Pharmaceutical Corporation Holds Patent Rights to Statins in Alzheimer's

May 29, 2003 01:18 PM Eastern Daylight Time

NEW YORK--(BUSINESS WIRE)--May 29, 2003--The major potential importance of statin drugs in Alzheimer's disease (AD) was bolstered by studies presented at the Fourth Manhattan Alzheimer's Disease Conference in New York on May 27.
At the meeting, Dr. Larry Sparks of the Roberts Laboratory for Neurodegenerative Disease presented data from extensive studies supporting the underlying mechanism for the potential value of statins in the treatment of AD.

"Dr. Sparks presented a very compelling case for statins in Alzheimer's disease"

Tweet this

Nymox Pharmaceutical Corporation (NASDAQ: NYMX) holds a U.S. patent and global rights for the use of statin drugs for the treatment and prevention of Alzheimer's disease.

The current global market for statins is over $17 billion per year. Alzheimer's disease is the leading cause of dementia in the elderly, afflicting an estimated 4 million people in the U.S. alone. The potential benefits of statin drug use in the treatment or prevention of Alzheimer's

The HOLY GRAIL of "Alzheimer's Disease and STAINS" is the following research…

Original Research Article

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2009;28:75–80
DOI: 10.1159/000231980

Accepted: April 27, 2009
Published online: August 4, 2009

Midlife Serum Cholesterol and Increased Risk of Alzheimer's and Vascular Dementia Three Decades Later

Alina Solomon[a, b] Miia Kivipelto[a, b] Benjamin Wolozin[c] Jufen Zhou[d]
Rachel A. Whitmer[d]

[a]Department of Neurology, University of Kuopio, Kuopio, Finland; [b]Aging Research Center, Karolinska Institutet, Stockholm, Sweden; [c]Department of Pharmacology, Boston University School of Medicine, Boston, Mass., and [d]Division of Research, Kaiser Permanente, Oakland, Calif., USA

Key Words
Dementia · Epidemiology · Alzheimer's dementia · Cholesterol · Vascular dementia

Abstract

Aims: To investigate midlife cholesterol in relation to Alzheimer's disease (AD) and vascular dementia (VaD) in a large multiethnic cohort of women and men. ***Methods:*** The Kaiser Permanente Northern California Medical Group (healthcare delivery organization) formed the database for this study. The 9,844 participants underwent detailed health evaluations during 1964–1973 at ages 40–45 years; they were still members of the health plan in 1994. AD and VaD were ascertained by medical records between 1 January 1994 and 1 June 2007. Cox proportional hazards models – adjusted for age, education, race/ethnic group, sex, midlife diabetes, hypertension, BMI and late-life stroke – were conducted. ***Results:*** In total, 469 participants had AD and 127 had VaD. With desirable cholesterol levels (<200 mg/dl) as a reference, hazard ratios (HR) and 95% CI for AD were 1.23 (0.97–1.55) and 1.57 (1.23–2.01) for borderline (200–239 mg/dl) and high cholesterol (≥240 mg/dl), respectively. HR and 95% CI for VaD were 1.50 (1.01–2.23) for borderline and 1.26 (0.82–1.96) for high cholesterol. Further analyses for AD (cholesterol quartiles, 1st quartile reference) indicated that cholesterol levels >220 mg/dl were a significant risk factor: HR were 1.31 (1.01–1.71; 3rd quartile, 221–248 mg/dl) and 1.58 (1.22–2.06; 4th quartile, 249–500 mg/dl). ***Conclusion:*** Midlife serum total cholesterol was associated with an increased risk of AD and VaD. Even moderately elevated cholesterol increased dementia risk. Dementia risk factors need to be addressed as early as midlife, before underlying disease(s) or symptoms appear.

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Introduction

A fully manifest dementia syndrome represents the end stage of underlying disease(s), the most frequent of which are Alzheimer's disease (AD) and cerebrovascular disease. Thus, the best approach implies not only early diagnosis and treatment, but also emphasizes prevention. However, chronic diseases with a long preclinical phase (such as AD) pose inherent difficulties in the identification of their risk factors. Since disease onset cannot be pinpointed, the chances are that true risk relationships (factors increasing the probability of getting the disease) and reverse causality (the effects of the disease itself on various factors) get confused. In later life, any apparently normal population will be a mixture of individuals with-

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Accessible online at:
www.karger.com/dem

Alina Solomon
Department of Neurology, University of Kuopio
PO Box 1627
FI–70211 Kuopio (Finland)
Tel. +46 8 690 5822, Fax +46 8 690 5954, E-Mail alina.solomon@uku.fi

Conclusions:

- Midlife serum ***total cholesterol was associated with an increased risk of AD***.
- NB! ***Even moderately elevated cholesterol*** increased dementia risk.
- Dementia risk factors ***need to be addressed as early as midlife***, before underlying disease(s) or symptoms appear.

I guess this paper made Nymox Pharmaceutical Corporation very happy, but let's see the results…

Table 1. Sociodemographic and clinical characteristics of the study population (n = 9,844)

	No dementia (n = 9,248)	AD (n = 469)	VaD (n = 127)	p values
Age at MHC exam	42.4 ± 1.7	42.8 ± 1.7	42.7 ± 1.5	<0.0001
Age in 1994, years	68.8 ± 2.8	69.9 ± 2.5	69.5 ± 2.5	<0.0001
Sex, male	4,281 (46.3)	188 (40.1)	58 (45.7)	0.03
College 3–4 years	1,297 (14.0)	62 (13.2)	10 (7.9)	
Postgraduate	1,683 (18.2)	77 (16.4)	19 (14.9)	
Race/ethnic group (self-reported)				<0.0001
Asian	598 (6.5)	17 (3.6)	5 (3.9)	
Black	1,387 (15)	109 (23.2)	35 (27.6)	
White	6,863 (74.2)	325 (69.3)	85 (66.9)	
Other	400 (4.3)	18 (3.8)	2 (1.6)	
Cholesterol[1], mg/dl	224.1 ± 41.4	228.5 ± 37.8	226.4 ± 38.4	0.06
Midlife BMI	24.9 ± 3.9	25.1 ± 3.9	26.1 ± 4.6	0.002
Midlife diabetes				.03
Midlife hypertensio				.02
Late-life stroke				.0001

The researchers found a barely statistically significant result that people who were diagnosed with Alzheimer's had higher cholesterol in their 50's than the control group. The mean value for the Alzheimer's patients was 228.5, as against 224.1 for the controls.

Difference < 2 %

Values represent means ± SD or number of participants with percentages in parentheses.
[1] To convert cholesterol to millimoles per liter, multiply by 0.0259.

I wondered how accurate was the assay used to find that difference…

Analytical Imperfection & Total Error in Direct Assay for LDL-Cholesterol

- There were taken 2 standard samples of concentration, a.k.a. 102 and 292 mg/dL of cholesterol.
- The assay was done using 30 replicates of each standard.
- Total error of 2.36-2.46% was calculated as [systemic error (%) + random error (%)].

Table 2. Analytical imprecision and total error of direct assay for LDL-C, using control materials

		Imprecision							
		Intraassay		Intraassay					
	Target value mg/dl	Mean±SD, mg/dl n[e]=30	CV, %	Mean ± SD, mg/dl n[f]=10	CV %	Total CV, %[a]	Systematic error, %[b]	Random error, %[c]	Total error %[d]
PnL	102	100.907±1.45	1.40	103.40±1.62	1.56	1.72	-1.01	3.37	2.36
PpL	292	291.14±2.98	1.02	290.08±2.85	0.98	1.41	-0.30	2.76	2.46

[a] Total CV, % = $(CV_{intraassay} + CV_{interassay})^{1/2}$
[b] Systematic error, % = mean of [(direct assay value-target value)/target value] x 100.
[c] Random error, % = total imprecision x 1.96
[d] Total error, %=systematic error (%) + random error(%).
[e] n, number of replicate
[f] n, number of consecutive days
CV: coefficient of varitaion, LDL-C: low-density lipoprotein cholesterol, PnL: Precinorm L, PpL: Precipath L, SD: standard deviation

How one can reconcile the total error of assay (>2.4%) with difference (<2%) found in the study?

		Imprecision							
		Intraassay		Intraassay					
	Target value mg/dl	Mean±SD, mg/dl n[e]=30	CV, %	Mean ± SD, mg/dl n[f]=10	CV %	Total CV, %[a]	Systematic error, %[b]	Random error, %[c]	Total error %[d]
PnL	102	100.907±1.						37	2.36
PpL	292	291.14±2.9						76	2.46

[a] Total CV, % = (CVintraassay + CVinterassay)[1/2]
[b] Systematic error, % = mean of [(direct assay val
[c] Random error, % = total imprecision x 1.96
[d] Total error, %=systematic error (%) + random error(%).
[e] n, number of replicate
[f] n, number of consecutive days
CV: coefficient of varitaion, LDL-C: low-density lipoprotein cholesterol, PnL: Precinorm L, PpL: Precipa : standard deviation

Error > 2.4%

?

Difference < 2%

Other	400 (4.3)	18 (3.8)	2 (1.6)	
Cholesterol[1], mg/dl	224.1 ± 41.4	228.5 ± 37.8	226.4 ± 38.4	0.06
Midlife BMI	24.9 ± 3.9	25.1 ± 3.9	26.1 ± 4.6	0.002
Midlife diabetes				.03
Midlife hypertensio				.02
Late-life stroke				.0001

Values represent means ± SD or number of participants with percentages in parentheses.
[1] To convert cholesterol to millimoles per liter, multiply by 0.0259.

Despite the “major findings supporting potential use of STATINS for Alzheimer’s Disease”…

the FDA has updated (2012) the recommendation for statins in order to reduce the risk of cognitive adverse effects.

FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs

Safety Announcement
Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary
Lovastatin Dose Limitations
References

Facts about statins

- A class of prescription drugs used together with diet and exercise to reduce blood levels of low-density lipoprotein (LDL) cholesterol ("bad cholesterol")
- Marketed as single-ingredient products, including Lipitor (atorvastatin), Lescol (fluvastatin), Mevacor (lovastatin), Altoprev (lovastatin extended-release), Livalo (pitavastatin), Pravachol (pravastatin), Crestor (rosuvastatin), and Zocor (simvastatin)
- Also marketed as combination products, including Advicor (lovastatin/niacin extended-release), Simcor (simvastatin/niacin extended-release), and Vytorin (simvastatin/ezetimibe)

Safety Announcement

[2-28-2012] The U.S. Food and Drug Administration (FDA) has approved important safety label changes for the class of cholesterol-lowering drugs known as statins. These changes were made to provide the public with more information for the safe and effective use of statins and are based on FDA's comprehensive review of the statin class of drugs (see **Data Summary** below). The changes include the following:

Cognitive adverse events

FDA reviewed the AERS database, the published medical literature (case reports and observational studies),[4-13] and randomized clinical trials to evaluate the effect of statins on cognition.[14-17]

The post-marketing adverse event reports generally described individuals over the age of 50 years who experienced notable, but ill-defined memory loss or impairment that was reversible upon discontinuation of statin therapy. Time to onset of the event was highly variable, ranging from one day to years after statin exposure. The cases did not appear to be associated with fixed or progressive dementia, such as Alzheimer's disease. The review did not reveal an association between the adverse event and the specific statin, the age of the individual, the statin dose, or concomitant medication use.

Cholesterol in the CNS

Review Article

Cholesterol: Its Regulation and Role in Central Nervous System Disorders

Hindawi Publishing Corporation
Cholesterol
Volume 2012, Article ID 292598, 19 pages
doi:10.1155/2012/292598

Matthias Orth[1] and Stefano Bellosta[2]

[1] *Institut für Laboratoriumsmedizin, Vinzenz von Paul Kliniken gGmbH, Adlerstraße 7, Postfach 103163, 70199 Stuttgart, Germany*
[2] *Dipartiment... retti 9, 20133 Milan*

Correspondei

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Cholesterol is ... umerous lipoprotein receptors and ... ior brain cells and is essential for ... f other tissues. Brain cholesterol is ... oprotein cholesterol from the circ... stem diseases such as Smith-Lemli-... t different metabolic pathways (cho... eptors, and signaling molecules). W... n-specific interaction with other pa... l as the effects of the widespread us...

Several levels of evidence indicate a distinct metabolism of CNS cholesterol. The brain does not respond to many control mechanisms operative in maintaining cholesterol homeostasis in the whole organism. The half-life of brain cholesterol in the adult organism is between 6 months and 5 years [25, 26], the half-life of plasma cholesterol, in contrast, is only a few days [27]. In the 1940s, administration of deuterated water into rats led to an incorporation of the label into the unsaponifiable lipids of the brain [28]. Similar findings were observed in unrelated studies employing deuterated cholesterol in dogs [29]. From the current level of knowledge, in the CNS of mammals such as mice, rats, and humans, >95% of cholesterol is synthesized *de novo* from acetate and exchange between plasma lipoprotein cholesterol and brain cholesterol has only very little impact [1, 30–33].

Brain cholesterol in normal and pathological aging

Vanmierlo T, Lütjohann D, Mulder M. Brain cholesterol in normal and pathological aging. *OCL* 2011; 18(4): 214-7.

Tim VANMIERLO[1,2]
Dieter LÜTJOHANN[1]
Monique MULDER[3]

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Abstract: *Aberrations in cerebral cholesterol homeostasis can lead to severe neurological diseases. Recent findings strengthen the link between brain cholesterol metabolism and factors involved in synaptic plasticity, a process essential for learning and memory functions, as well as regeneration, which are affected in Alzheimer's Disease (AD). Cholesterol homeostasis within the brain is independent of that in the rest of the body and*
as

- The BRAIN makes up about 2% of the total body weight, but contains almost 25% of all free cholesterol.
- Aberrations in cerebral cholesterol homeostasis can lead to severe neurological diseases and have recently been linked to Alzheimer's Disease (AD).
- The cholesterol synthesis rate within the brain decreases with age and has been suggested to be associated with an increased decline of memory functions.
- There is evidence indicating that neurons largely shut down their cholesterol synthesis after birth and rely on astrocytes for their cholesterol supply.
- The process of cholesterol supply from astrocytes to neurons may be compromised in AD.
- Neurons require cholesterol for a number of different functions including vesicle transport, neurotransmitter release and the generation of new membranes, a.k.a. the formation of new synapses during a process called synaptic plasticity; the reorganization of synaptic contacts between neuronal axons and dendrites or somata of other neurons which occurs during learning.

Review Article

Cholesterol: Its Regulation and Role in Central Nervous System Disorders

- Differences in BBB permeability coefficients might be a clue to the higher incidence of neurological adverse events of some statins.
- Lovastatin and simvastatin had much higher BBB permeability coefficients than did fluvastatin, pravastatin, or rosuvastatin.
- Transfer of the lipophilic compounds lovastatin and simvastatin across the BBB occurs via passive diffusion.
- Brain cholesterol synthesis in mice is significantly affected by statins.
- The effects of STATINS on brain cholesterol could occur by forming a cholesterol gradient across the BBB which facilitates the efflux of brain cholesterol .
- Numerous reports as well as small trials have suggested that statin therapy causes cognitive impairment, although the true extent of this effect remains under study.

The important role of cholesterol for CNS function is exemplified by a number of rare hereditary diseases caused by mutations in cholesterol-related genes.

SMITH–LEMLI–OPITZ SYNDROME

Smith–Lemli–Opitz syndrome (SLOS) is a rare autosomal recessive disorder caused by mutations in the gene encoding the enzyme 7-dehydrocholesterol reductase (DHCR7). This enzyme catalyzes the last step in the Kandutsch–Russell pathway of cholesterol biosynthesis. SLOS patients present, with different degree of gravity, INTELLECTUAL DISABILITIES, delayed motor and language maturation, affective disorders and sleeping problems. The signs and symptoms may be due to reduced brain cholesterol levels. Severely affected SLOS patients have plasma cholesterol concentrations at 2% of the normal level and low cholesterol content in all tissues, especially in the brain.

RETT SYNDROME

Rett syndrome is an X-linked neurological disorder characterized by DEFECTIVE motor control, cognitive abilities, and social interactions, namely appearance of speech difficulties, stereotypic hand movements, problematic walking, seizures, intellectual disabilities, and autistic behavior. Rett syndrome is caused by mutations in the X-linked mecp2 gene, which encodes a methyl DNA-binding protein that regulates gene expression. Until recently, Rett syndrome was not associated with a defect in cholesterol metabolism. However, a recent study has shown that a suppressing mutation in the sqle gene, encoding for the squalene epoxidase that mediates a dedicated step in cholesterol synthesis, was sufficient to restore function and longevity in Mecp-2 null mice. These data suggest that Mecp-2 may be involved in the transcriptional control of cholesterol metabolism.

Niemann-Pick C disease

Niemann-Pick C disease is an autosomal recessive disorder caused in 95% of the cases by mutations in the npc1 or npc2 genes. The adult form presents psychiatric problems, cerebellar ataxia, and PROGRESSIVE DEMENTIA. Cataplexy, seizures, and dystonia are other common features. At the histological level, neuronal death is the prominent feature, affecting specific cell types, particularly cerebellar Purkinje cells. At the cellular level, NPC1 and NPC2 cooperate to mediate the exit of cholesterol from the endosomal-lysosomal system.

DESMOSTEROLOSIS

Desmosterolosis is a rare, autosomal recessive disease caused by mutations in the dhcr24 gene. The enzyme encoded by this gene catalyzes the reduction of desmosterol to cholesterol, the last step in the Bloch pathway of cholesterol synthesis. Patients with DHCR24 mutations present severe brain defects including microcephalia, hydrocephalia, ventricular enlargement, defects in the corpus callosum, and thinning of white matter and seizures. Disease signs may be attributed to reduced cholesterol levels or to accumulation of desmosterol. Accumulation of desmosterol in the brain was linked to the development of Alzheimer's disease.

ORIGINAL ARTICLE

Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update

© 2004 Blackwell Publishing *Fundamental & Clinical Pharmacology* **19** (2004) 117–125

Michael Schachter

Department of Clinical Pharmacology, National Heart and Lung Institute, Imperial College School of Medicine, St Mary's Hospital, London, W2 4NY, UK

Table II Pharmacokinetic properties of the statins.

	Atorvastatin	Cerivastatin[a]	Fluvastatin	Lovastatin	Pravastatin	Simvastatin	Rosuvastatin	Pitavastatin [Ref. 27]
Optimal time of dosing	Any time of day	Evening [Ref. 74]	Bedtime	With meals morning and evening	Bedtime	Evening	Any time of day	na
Bioavailability (%)	12	60 [Ref. 9]	24	5	18	5	20	~80
Solubility	Lipophilic	Lipophilic [Ref. 24]	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	Hydrophilic	Lipophilic
Effect of food	Bioavailability decreased	No effect	Bioavailability decreased	Bioavailability increased	Bioavailability decreased	No effect	No effect	na
Protein binding (%)	98	>99 [Ref. 9]	>98	>95	~50	95–98	90	96
Active metabolites	✔	✔ [Ref. 9]	×	✔	×	✔	Minor	Minor
Elim…								
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- Studies showed that LIPOPHILIC STATINS cross the BBB and are readily available in the CNS.
- Statins can INHIBIT the autonomous cholesterol synthesis in the brain.
- Since the half-life of brain cholesterol is 6 months-to-5 years, prolonged statin use may result in reduction of brain cholesterol content.
- Accumulated evidence also suggest that the use of statins may well lead to impaired cognitive function.

Original Article J Clin Med Res. 2017;9(7):638-649

Association of Cognitive Impairment in Patients on 3-Hydroxy-3-Methyl-Glutaryl-CoA Reductase Inhibitors

Satyajeet Roy[a, d], Joshua Louis Weinstock[b], Allyse Sachiko Ishino[b], Jefferson Felix Benites[b], Samantha Rachel Pop[b], Christopher David Perez[b], Edvard Adrian Gumbs[b], Jennifer Ann Rosenbaum[b], Mary Kate Roccato[b], Hely Shah[b], Gabriela Contino[b], Krystal Hunter[c]

Abstract

Background: Atherosclerotic cardiovascular diseases are the leading cause of death in the United States. A reduction in cholesterol with 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statin) significantly reduces mortality and morbidity. Statins may be associated with cognitive impairment or dementia. Our aim was to study the association of cognitive impairment or dementia in patients who were on a statin.

Methods: Electronic medical records of 3,500 adult patients in our suburban internal medicine office were reviewed.

Results: There were 720 (20.6%) patients in the statin treatment group. Dementia or cognitive impairment was an associated comorbid condition in 7.9% patients in the statin treatment group compared to 3.1% patients in the non-statin group ($P < 0.001$). Analysis of all of the patients with cognitive impairment or dementia showed that rosuvastatin (12.2%) and pravastatin (8.8%). We found greater odds of dementia or cognitive impairment with each year increase in age (1.3 times), in women (2.2 times), African American race (2.7 times), non-consumption of moderate amount of alcohol (two times), diabetes mellitus (1.6 times), hypothyroidism (1.7 times), cerebrovascular accident (3.2 times), and other rheumatological diseases (1.8 times).

Conclusions: The association of dementia or cognitive impairment was significantly higher in the patients who were on statin therapy compared to the patients who were not on a statin.

Keywords: Cognitive function; Cognitive impairment; Dementia; Statin therapy; HMG-CoA reductase inhibitor therapy

Introduction

World Journal of Diabetes

Submit a Manuscript: http://www.f6publishing.com

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DOI: 10.4239/wjd.v8.i6.286

ISSN 1948-9358 (online)

ORIGINAL ARTICLE

Observational Study

Statin use and cognitive function in middle-aged adults with type 1 diabetes

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CONCLUSION

Statin use was associated with cognitive impairment, particularly affecting memory, in these middle-aged adults with childhood-onset T1D, whom at this age, should not yet manifest age-related memory deficits.

Pharmacotherapy. 2009 Jul;29(7):800-11. doi: 10.1592/phco.29.7.800.

Statin-associated adverse cognitive effects: survey results from 171 patients.

Evans MA[1], Golomb BA.

Author information

Abstract

STUDY OBJECTIVE: To characterize the adverse cognitive effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins).

DESIGN: Patient survey-based analysis.

PATIENTS: One hundred seventy-one patients (age range 34-86 yrs) who self-reported memory or other cognitive problems associated with statin therapy while participating in a previous statin effects study.

MEASUREMENTS AND MAIN RESULTS: Patients completed a survey assessing statin-associated, cognitive-specific adverse drug reaction (ADR) characteristics, relation of the ADR to specific statin and dose (or potency), and time course of symptom onset and recovery. Visual analog scales were used to assess the effect of the cognitive ADRs on seven quality-of-life domains. Demographic and clinical data were also collected. To target cognitive ADRs with a probable or definite causal relationship to statins, the Naranjo adverse drug reaction probability scale was used: 128 patients (75%) experienced cognitive ADRs determined to be probably or definitely related to statin therapy. Of 143 patients (84%) who reported stopping statin therapy, 128 (90%) reported improvement in cognitive problems, sometimes within days of statin discontinuation (median time to first-noted recovery 2.5 wks). Of interest, in some patients, a diagnosis of dementia or Alzheimer's disease reportedly was reversed. Nineteen patients whose symptoms improved or resolved after they discontinued statin therapy and who underwent rechallenge with a statin exhibited cognitive problems again (multiple times in some). Within this vulnerable group, a powerful relationship was observed between potency of the statin and fraction of trials with that agent resulting in cognitive ADRs ($p<0.00001$). Quality of life was significantly adversely affected for each of the seven assessed domains (all $p<0.00000001$).

CONCLUSION: Findings from the survey suggest that cognitive problems associated with statin therapy have variable onset and recovery courses, a clear relation to statin potency, and significant negative impact on quality-of-life. Administration of a patient-targeted questionnaire is a feasible approach that provides a useful complement to other ADR surveillance approaches.

Am J Geriatr Pharmacother. 2012 Oct;10(5):296-302. doi: 10.1016/j.amjopharm.2012.08.002. Epub 2012 Aug 22.

The effect of HMG-CoA reductase inhibitors on cognition in patients with Alzheimer's dementia: a prospective withdrawal and rechallenge pilot study.

Padala KP[1], Padala PR, McNeilly DP, Geske JA, Sullivan DH, Potter JF.

Author information

Abstract

BACKGROUND: Statins are well-known for their cardiovascular benefits. However, the cognitive effects of statins are not well understood. We hypothesized that individuals with preexisting dementia would be more vulnerable to statin-related cognitive effects.

OBJECTIVE: The aim of this study was to evaluate the impact on cognition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (statin) discontinuation and rechallenge in individuals with Alzheimer's dementia (AD) on statins at baseline.

METHODS: A 12-week prospective, open-label study was conducted in a geriatric clinic setting. Eighteen older subjects underwent a 6-week withdrawal phase of statins followed by a 6-week rechallenge. The primary outcome measure was cognition, measured by the Mini-Mental State Examination (MMSE); secondary outcome measures were the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery, Activities of Daily Living (ADL) scale, Instrumental ADL (IADL) scale, and fasting cholesterol. The change in outcome measures was assessed using repeated-measures ANOVA and paired t tests.

RESULTS: At the end of the intervention, there was a significant difference across time for MMSE score ($P = 0.018$), and total cholesterol ($P = 0.0002$) and a trend toward change across time for ADL ($P = 0.07$) and IADL ($P = 0.06$) scale scores. Further analyses using paired t tests indicated improvement in MMSE scores ($\Delta 1.9$ [3.0], $P = 0.014$) with discontinuation of statins and a decrease in MMSE scores ($\Delta 1.9$ [2.7], $P = 0.007$) after rechallenge. Total cholesterol increased with statin discontinuation ($P = 0.0003$) and decreased with rechallenge ($P = 0.0007$). The CERAD score did not show a change across time ($P = 0.31$). There was a trend toward improvement in ADL ($P = 0.07$) and IADL ($P = 0.06$) scale scores with discontinuation of statins, but no change with rechallenge.

CONCLUSIONS: This pilot study found an improvement in cognition with discontinuation of statins and worsening with rechallenge. Statins may adversely affect cognition in patients with dementia.

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Drug Saf - Case Rep (2017) 4:3
DOI 10.1007/s40800-017-0045-0

CASE SERIES

Physicians' Experiences as Patients with Statin Side Effects: A Case Series

Hayley J. Koslik[1] · Athena Hathaway Meskimen[1] · Beatrice Alexandra Golomb[1]

Dr. A, a radiologist in his 50s, stated that he developed marked cognitive problems and also neuropathy shortly after increasing his atorvastatin dose from 40 to 80 mg/day. Effects were new, marked, sustained, and interfered with his work, leading to difficulty understanding case presentations, to radiology reading errors (including right/left errors on readings), and to placement of orders for the wrong patients. These consequences to his professional accuracy led him to fear medicolegal repercussions.

Drug Saf - Case Rep (2017) 4:3
DOI 10.1007/s40800-017-0045-0

CASE SERIES

Physicians' Experiences as Patients with Statin Side Effects: A Case Series

Hayley J. Koslik[1] · Athena Hathaway Meskimen[1] · Beatrice Alexandra Golomb[1]

No suggestion was made by his doctor of a possible statin role, or suggestion for a trial of statin discontinuation, until a medical student commented on the association of neuropathy to statin use. Discontinuation of statins, after 3 years of sustained symptoms, led to rapid and striking improvement in cognitive function. By a week after discontinuation, Dr. A noted dramatic cognitive recovery, which he perceived to be approximately complete. He observed more gradual recovery of neuropathy symptoms, which he characterized as having improved by an estimated 95% at 8 months (improvement having apparently plateaued at that level).

Drug Saf - Case Rep (2017) 4:3
DOI 10.1007/s40800-017-0045-0

CASE SERIES

Physicians' Experiences as Patients with Statin Side Effects: A Case Series

Hayley J. Koslik[1] · Athena Hathaway Meskimen[1] · Beatrice Alexandra Golomb[1]

(1) Shortly after statin initiation, Dr. G developed confusion, disorientation, and short-term memory loss. She asked repetitive questions and had a short attention span. Statins were discontinued, followed by marked improvement in cognitive function. A month after discontinuation, she recalled running into one of her former colleagues in the grocery store and being able to immediately recognize the person (a clear improvement over her prior state). This acquaintance exclaimed that she looked much better than 8 months previously, when they had last interacted

(2) Dr. G's physician dismissed the potential statin connection. Her son stated, "He replied in a condescending tone of disbelief that I 'read too much'"

(3) Dr. G. was referred to a neurologist, and treated with donepezil for a year under the assumption the cognitive problems may be Alzheimer's. Other diagnoses that had been considered included depression and pseudo-dementia

(4) Not known

(5) Disability from statin AEs contributed to retirement

The end