Statin Cholesterol Notes

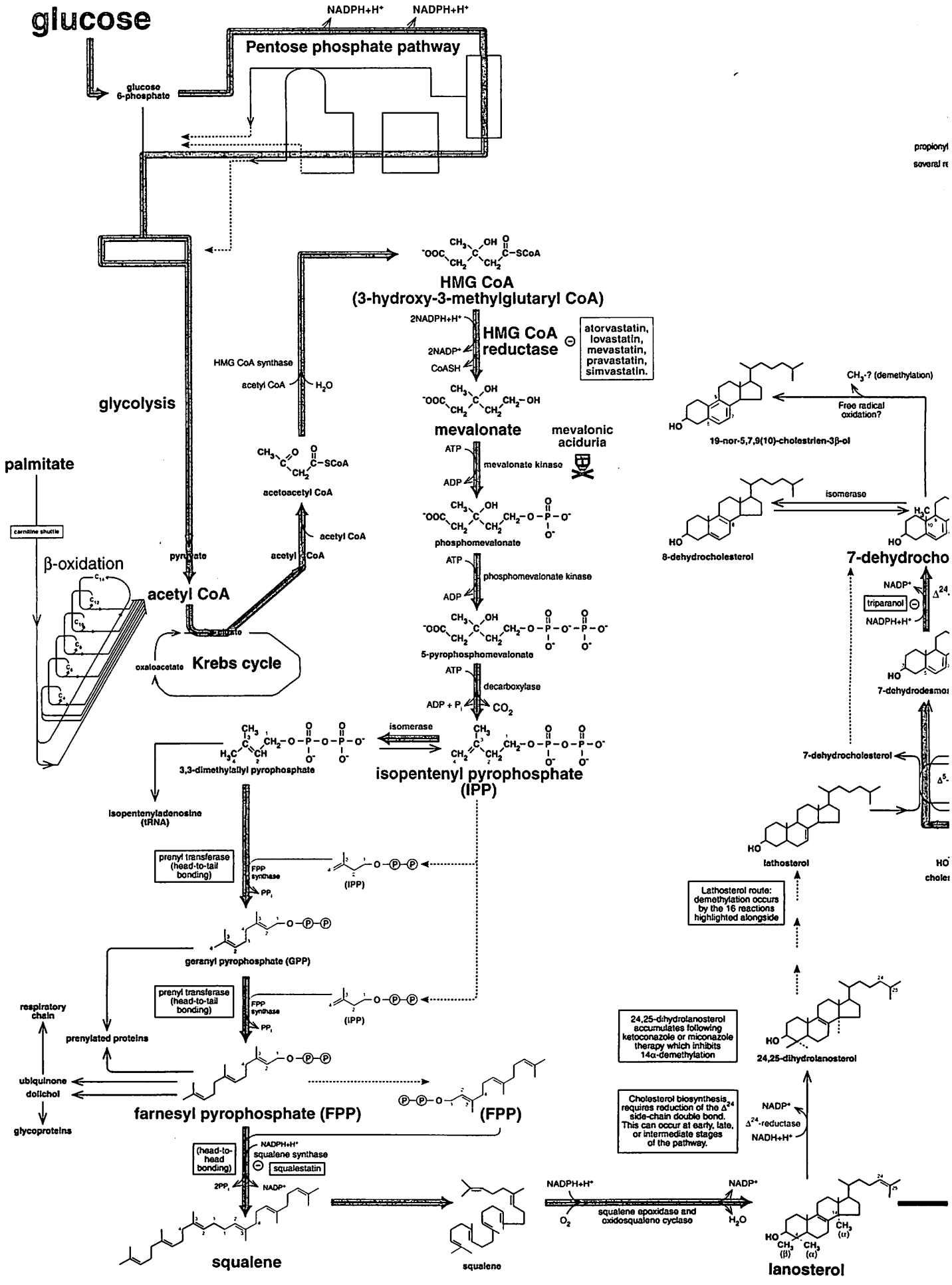
2011

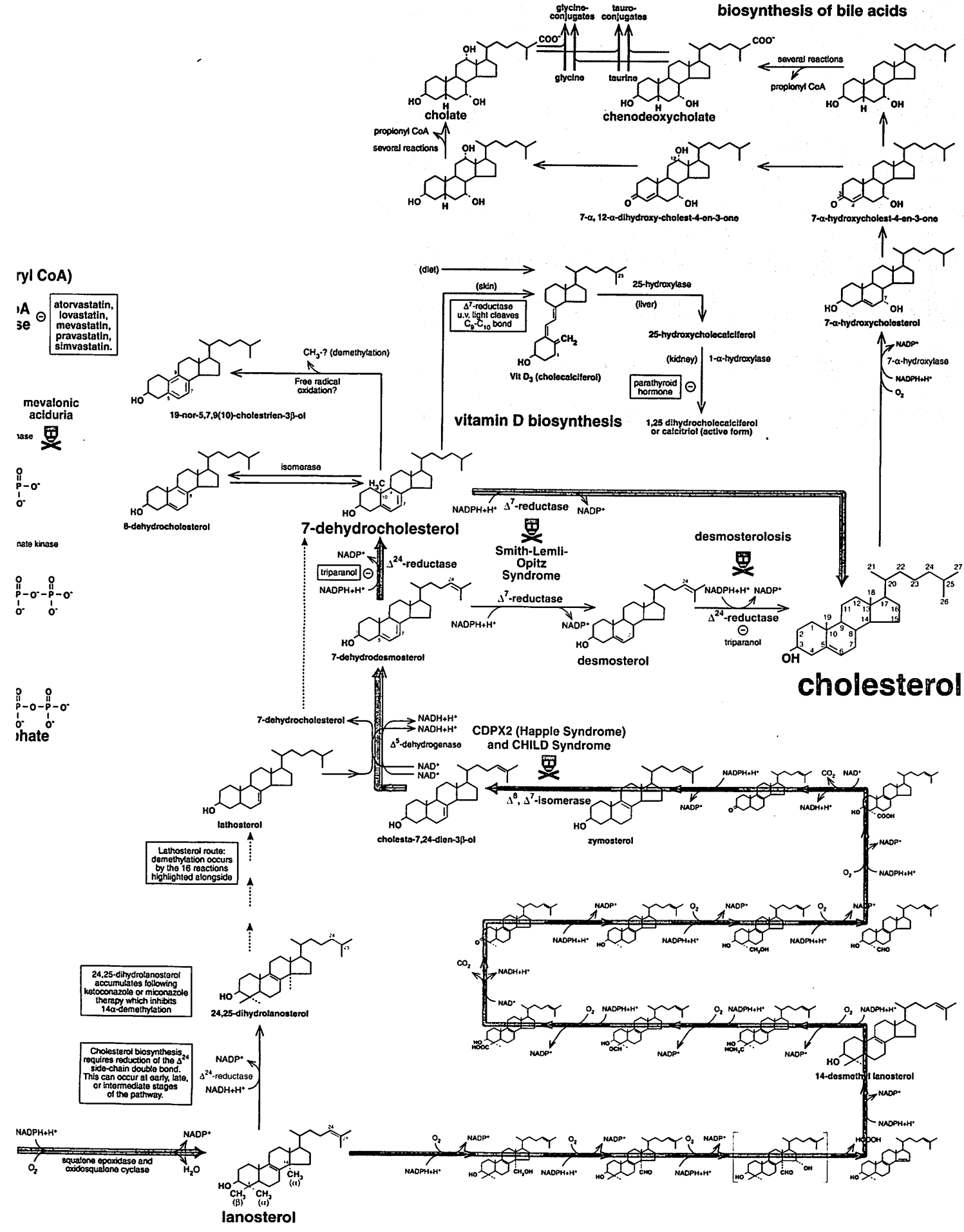
STATIN DRUGS SIDE EFFECTS
and the Misguided War on Cholesterol

By
Duane Graveline, M.D.

2006

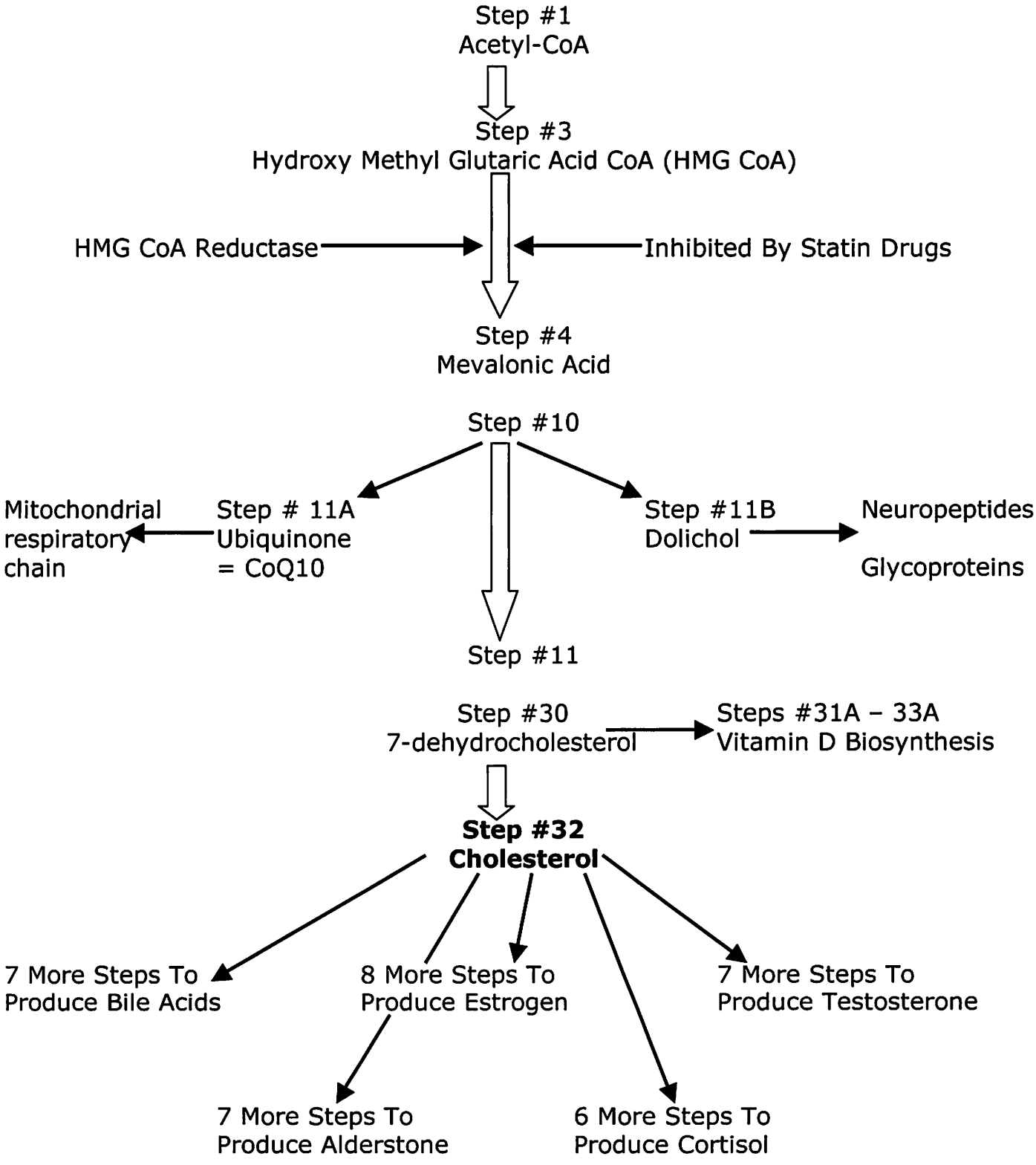
www.spacedoc.net


glucose
NADPH+H+
NADPH+H+
Pentose phosphate pathway
glucose 6-phosphate
glycolysis
HMG CoA synthase
acetyl CoA
H2O
HMG CoA
(3-hydroxy-3-methylglutaryl CoA)
2NADPH+H+
HMG CoA reductase
2NADP+
CoASH
atorvastatin, lovastatin, mevastatin, pravastatin, simvastatin.
mevalonate
mevalonic aciduria
ATP
ADP
mevalonate kinase
phosphomevalonate
phosphomevalonate kinase
5-pyrophosphomevalonate
decarboxylase
ADP + Pi
CO2
isomerase
3,3-dimethylallyl pyrophosphate
isopentenyl pyrophosphate (IPP)
acetoacetyl CoA
acetyl CoA
palmitate
carnitine shuttle
β-oxidation
pyruvate
acetyl CoA
oxaloacetate
Krebs cycle
isopentenyladenosine (tRNA)
prenyl transferase (head-to-tail bonding)
FPP synthase
PPi
(IPP)
geranyl pyrophosphate (GPP)
respiratory chain
prenylated proteins
ubiquinone
dolichol
glycoproteins
farnesyl pyrophosphate (FPP)
(FPP)
(head-to-head bonding)
NADPH+H+
squalene synthase
squalestatin
2PPi
NADP+
squalene
squalene epoxidase and oxidosqualene cyclase
O2
H2O
lanosterol
CH3-? (demethylation)
Free radical oxidation?
19-nor-5,7,9(10)-cholestrien-3β-ol
8-dehydrocholesterol
7-dehydrocho
triparanol
7-dehydrocholesterol
lathosterol
Lathosterol route: demethylation occurs by the 16 reactions highlighted alongside
24,25-dihydrolanosterol accumulates following ketoconazole or miconazole therapy which inhibits 14α-demethylation
24,25-dihydrolanosterol
Cholesterol biosynthesis requires reduction of the Δ24 side-chain double bond. This can occur at early, late, or intermediate stages of the pathway.
Δ24-reductase
NADP+
NADH+H+


biosynthesis of bile acids
glycine-conjugates
tauro-conjugates
glycine
taurine
cholate
chenodeoxycholate
several reactions
propionyl CoA
7-α, 12-α-dihydroxy-cholest-4-en-3-one
7-α-hydroxycholest-4-en-3-one
7-α-hydroxycholesterol
7-α-hydroxylase
NADPH+H+
O2
(diet)
(skin)
Δ7-reductase u.v. light cleaves C9-C10 bond
25-hydroxylase
(liver)
25-hydroxycholecalciferol
Vit D3 (cholecalciferol)
(kidney) 1-α-hydroxylase
parathyroid hormone
1,25 dihydrocholecalciferol or calcitriol (active form)
vitamin D biosynthesis
CH3-? (demethylation)
Free radical oxidation?
19-nor-5,7,9(10)-cholestrien-3β-ol
isomerase
8-dehydrocholesterol
7-dehydrocholesterol
NADPH+H+ Δ7-reductase NADP+
Smith-Lemli-Opitz Syndrome
desmosterolosis
NADP+
triparanol
Δ24-reductase
NADPH+H+
7-dehydrodesmosterol
Δ7-reductase
desmosterol
Δ24-reductase
triparanol
cholesterol
7-dehydrocholesterol
NADH+H+
Δ5-dehydrogenase
NAD+
CDPX2 (Happle Syndrome) and CHILD Syndrome
cholesta-7,24-dien-3β-ol
Δ8, Δ7-isomerase
zymosterol
lathosterol
Lathosterol route: demethylation occurs by the 16 reactions highlighted alongside
24,25-dihydrolanosterol accumulates following ketoconazole or miconazole therapy which inhibits 14α-demethylation
24,25-dihydrolanosterol
Cholesterol biosynthesis requires reduction of the Δ24 side-chain double bond. This can occur at early, late, or intermediate stages of the pathway.
NADP+
Δ24-reductase
NADH+H+
squalene epoxidase and oxidosqualene cyclase
lanosterol
14-desmethyl lanosterol
ryl CoA)
atorvastatin, lovastatin, mevastatin, pravastatin, simvastatin.
mevalonic aciduria

Metabolism At A Glance

By J. G. Salway
Blackwell Publishing
2004
Chapter 32: "Cholesterol, Bile Acids, Vitamin D, and the Steroid Hormones"



What We Have Learned About Vitamin D Dosing?

Integrative Medicine
Vol. 9, No. 1, Feb/Mar 2010

Joseph Pizzorno, ND, Editor in Chief

BACKGROUND FROM DAN MURPHY

The world standard uses nmol/l, while US standard uses mg/dl.

For vitamin D, to convert mg/dl to nmol/l, divide the mg/dl by 2.5.

For vitamin D, to convert nmol/l to mg/dl, just multiply by 2.5.

KEY POINTS FROM THIS ARTICLE:

1) "Over the past several years, the surprising prevalence of vitamin D deficiency has become broadly recognized."

2) Vitamin D deficiency is linked to:
Osteoporosis
Cardiovascular disease
Cancer
Autoimmune diseases
Multiple sclerosis
Pain
Loss of Cognitive function
Decreased strength
Increased rate of all-cause mortality

3) "Deficiency of vitamin D is now recognized as a pandemic, with more than half of the world's population at risk."

4) Approximately 50% of the healthy North American population and more than 80% of those with chronic diseases are vitamin D deficient.

5) 80% of healthy Caucasian infants are vitamin D deficient. [And the rate of vitamin D deficiency tends to be greater in African American and Hispanic children].

6) Those with vitamin D deficiency experience 39% higher annual healthcare costs than those with normal levels of vitamin D.

7) Suggested levels of vitamin D as measured by 25(OH)D3 is:

Caucasians	125 – 175 nmol/l	=	50 - 70 mg/dl
Hispanics	100 – 150 nmol/l	=	40 - 60 mg/dl
African Americans	80 – 120 nmol/l	=	32- 48 mg/dl

8) The minimum blood levels of vitamin D [25(OH)D3] is 80 nmol/l (32 mg/dl).

9) Prolonged intake of 10,000 IU of supplemental vitamin D3 "is likely to pose no risk of adverse effects in almost all individuals."

10) The maximum safe levels for vitamin 25(OH)D3 in the blood is 275 nmol/l (100 mg/dl).

11) Sarcoidosis patients (and other granulomatous diseases) should not supplement with vitamin D because it increases granuloma production increasing the risk of hypercalcemia.

12) A loading dose of supplemental vitamin D3 of 10,000 IU/day for 3 months and maintenance dose of 5,000 IU/day "is not enough for most people in northern climes."

13) The loading dose of supplemental vitamin D3 should be about 20,000 IU/day for 3 – 6 months with a maintenance dose of 5,000 IU/day. Those taking this amount of supplemental vitamin D3 should periodically have their serum 25(OH)D3 levels measured.

COMMENTS FROM DAN MURPHY

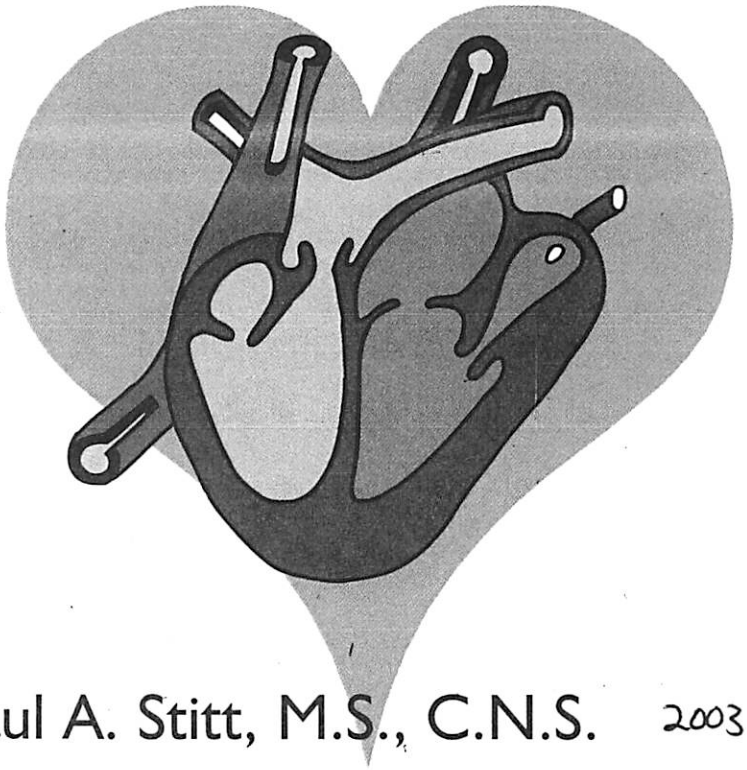
The lab we use to test blood vitamin D3 [25(OH)D3] uses a finger prick analysis:
ZRT Laboratory
8605 SW Creekside Pl
Beaverton, OR 97008
866-600-1636
www.zrtlab.com
Vitamin D Testing Finger prick

The vitamin D3 my family takes is ***Complete Hi D3***, from Nutri-West (5,000 IU):
800-443-3333
The primary researcher on this product was Don Bellgrau, PhD. Dr. Bellgrau is a tenured Professor of Immunology and Medicine at the University of Colorado, Denver, where he is a Program Leader in Immunology and Immunotherapy at the Cancer Center on vitamin D3 supplementation. Dr. Bellgrau has conducted experiments with nutrients/vitamin D and immune cells. He has published in over 100 peer-reviewed articles, including the Journal of Neurooncology, Nature, Clinical Immunology, Cancer Research, Cancer Immunology and Immunotherapy, and Cell Transplantation.

The *Real* cause of

HEART DISEASE

Is NOT Cholesterol!



by: Paul A. Stitt, M.S., C.N.S. 2003

Health Myths Exposed

Learn How to Avoid Deadly Health Myths-Add 10 Years to Your Life

by

Shane Ellison M.Sc.

2005

authorHOUSE

1663 Liberty Drive, Suite 200
Bloomington, Indiana 47403
(800) 839-8640
www.AuthorHouse.com

Table of Contents

WHAT YOU MUST KNOW ABOUT STATIN DRUGS & THEIR NATURAL ALTERNATIVES

Jay S. Cohen, MD

2005

SQUAREONE PUBLISHERS

Good Calories, BAD CALORIES

Fats, Carbs, and the Controversial Science of Diet and Health

GARY TAUBES

2008

ANCHOR BOOKS
A DIVISION OF RANDOM HOUSE, INC.
NEW YORK

Cholesterol

Dr. Michael DeBakey (d. 2008, age 99 years) was a world-renowned American cardiac surgeon, innovator, scientist, medical educator, and international medical statesman.

DeBakey was the chancellor emeritus at Baylor College of Medicine in Houston, Texas and director of The Methodist DeBakey Heart & Vascular Center and senior attending surgeon of The Methodist Hospital in Houston.

DeBakey helped develop the mobile army surgical hospital (MASH) units during the Korean War.

DeBakey was chairman of the President's Commission on Heart Disease, Cancer and Stroke during the Johnson Administration.

He was appointed to a three-year membership on the National Advisory Heart and Lung Council of the National Institutes of Health.

DeBakey postulated in 1939 a strong link between smoking and lung cancer.

DeBakey was one of the first to perform coronary artery bypass surgery, and in 1953 he performed the first successful carotid endarterectomy.

A pioneer in the development of an artificial heart, DeBakey was the first to use an external heart pump successfully in a patient.

Internationally acclaimed for his trailblazing efforts in the treatment of cardiovascular diseases, Dr. DeBakey received the prestigious Albert Lasker Clinical Research Award in 1963 for developing the fundamental concept of arterial disease.

In 1949, DeBakey successfully initiated the movement to establish the National Library of Medicine [the Pubmed Database], which is now the world's largest and most prestigious repository of medical archives, housing more than 3.8 million books, journals, technical reports, manuscripts, microfilms, and pictorial materials. He served on the first Board of Regents of the Library and has since been the Chairman.

DeBakey authored more than 1,600 medical articles, chapters, and books on various aspects of surgery, medicine, health, medical research, and medical education, as well as ethical, socioeconomic, and philosophic discussions.

DeBakey received more than 50 honorary degrees from prestigious colleges and universities, as well as innumerable national and international accolades and awards from educational institutions, professional and civic organizations, and governments.

DeBakey practiced medicine until the day he died at age 99 in 2008. His contributions to the field of medicine spanned the better part of 75 years. DeBakey operated on more than 50,000 patients, including several heads of state.

The Paleolithic Prescription

S. Boyd Eaton, MD
1988

"In 1984 a National Institute of Health (NIH) Consensus Conference concluded that 'elevation of blood cholesterol is a major cause of coronary artery disease' and that lowering blood cholesterol levels would reduce the risk of heart attacks caused by coronary artery disease. But in 1987 heart surgeon Michael De Bakey was quoted as saying that cholesterol is *not* the main cause of coronary atherosclerosis, that cholesterol levels do *not* appear related to the rates of the disease's progression, and that some people with *low* cholesterol levels were as likely as people with higher levels to develop atherosclerotic plaques. Dr. DeBakey also claimed that about a third of patients with heart attacks had "perfectly normal" cholesterol levels." pg. 274

"Dietary cholesterol, by itself, has a relatively limited influence on serum cholesterol levels." Pg. 115

Bernadine Healy, M.D.

Dr. Bernadine Healy was born August 4, 1944:

- Harvard and Johns Hopkins educated physician and cardiologist.
- Former head of the National Institutes of Health (NIH).
- Former professor of medicine at Johns Hopkins.
- Former professor and dean of the College of Medicine and Public Health at Ohio State University.
- Served as president of the American Red Cross.
- Former President of the American Heart Association.
- Currently she is health editor and columnist for U.S. News & World Report. She has become a well-known commentator in the media on health issues.

A medical-industrial complex

PRESIDENT DWIGHT EISENHOWER'S 10-minute farewell address to the nation in 1961 is well remembered for its warning about the "military-industrial complex." His parting admonition has fresh meaning for today's "medical-industrial complex." Look no further than the current collision between the National Institutes of Health's National Cholesterol Education Program and a watchdog group, the Center for Science in the Public Interest.

The case in point is the NCEP call, through its new guidelines, for lowering America's cholesterol levels. The new target would only be achieved by tripling the current number of people taking the cholesterol-lowering drugs called statins—a bonanza for drug companies. Unlike earlier guidelines for people with known heart disease, the new ones focus on the healthy and their future heart risk. If followed, 36 million American adults—close to 1 in 5—will be popping statins or a similar drug for the rest of their lives.

But this debate goes way beyond cholesterol. So-called evidence-based guidelines are becoming codes of medical practice. Doctors will be using them to direct everyday care, and woe to those who dare not follow new rules that carry the imprimatur of medicine's research elite.

CSPI took on the experts and petitioned NIH to take another look at the guidelines, particularly those relating to women and those over age 70. The response was quick and negative. But the issue stays alive because eight of the nine experts on the panel had financial ties to companies that would benefit grandly from expanding the ranks of lifetime statin takers. It's been ugly. In a heartbeat, the panel members, a distinguished group called upon to do a hard job (after disclosing their financial interests to NIH), have had their motives questioned. This is neither fair to them nor good for the well-regarded NCEP. And it is awful for doctors and patients who are left wondering what to do.

If only we had remembered Eisenhower's less famous second warning: that "public policy could itself become the captive of a scientific-technological elite" in which the "power of money is ever present." He feared elites would dominate the nation's scholars by virtue of their federal employment or their control over large research grants. Eisenhower was thinking about the solitary tinkerer overrun by task forces of scientists, but his instincts were prescient.

Inspired by Ike. With Eisenhower-inspired wisdom, we could prevent messes like the cholesterol debacle. How about medical grand juries made up of public and private medical scholars to oversee, analyze, and give final approval to guidelines emerging from expert task forces? These "jurists" would be screened ahead of time, as judges are, for expertise, independence, and judicial temperament: compassion, decisiveness, open-mindedness, and the ability to see patients holistically. Their freedom from financial influence goes without saying. Disclosure of a conflict of interest is not enough: Such a conflict would designate an individual as technically nonindependent and thus ineligible to serve on the overarching panel that delivers the final verdict or reviews appeals. Those with conflicts would be eligible to be part of the groups that develop proposed options.

Some claim you can't find experts available these days who don't have industry ties. That is nonsense, based on my own experience running the NIH and elsewhere. Plenty of independent clinicians and scientists are up to this duty, highly skilled in analyzing medical data and wise in the ways of patients. There are also younger experts who have not yet attained the national reputation that would make industry seek them out, and an older group, just retired from active academic life or practice but steeped in wisdom and experience. These people are known and respected in every community and in every medical school in the country, even if they have not achieved national visibility in government or research.

NIH and the Centers for Disease Control and Prevention, whose work drives the evolution of medical practice, could together create a center to enable such a process, as long as the center itself is independent of other agency forces. Great Britain fashioned something along these lines in 1999, charmingly called NICE: the National Institute for Clinical Excellence. Wouldn't it be nice if Americans could have one, too? ●

How about medical grand juries to oversee, analyze, and approve the experts' health guidelines?

WARREN K. LEFFLER FOR USN&WR

PARTING WORDS. Eisenhower at his 1961 farewell address, in which he warned about a military-industrial complex

medical

THE PRIMAL BLUEPRINT

2009

MARK SISSON

The Primal Blueprint

Mark Sisson
2009

Lipitor, the world's best-selling drug with nearly $13 billion in sales in 2005, is a statin medication taken for 'high' cholesterol that can cause muscle and liver problems, deplete CoQ10 (coenzyme Q10; a natural antioxidant and cofactor that is critical to cellular energy metabolism).

Statins also produce serious side effects, mainly by blocking the production and flow of CoQ10 into cell mitochondria. This disturbance of mitochondria hampers the body's ability to generate normal amounts of energy (hence the common statin user complaint, "I feel tired and weak"), as well as fight free radicals and moderate inflammation.

Statins do not affect triglyceride (blood fat) levels or LDL, the so-called bad cholesterol.

Statins do not they decrease risk of death in any women, in men over 65, or in men under 65 who have not had a heart attack.

More important causes of heart disease are inflammation and oxidation, driven primarily by poor food choices, excessive insulin production and all forms of stress in excess.

Among the most notable research refuting the cholesterol story is the highly respected Framingham Heart Study. The study has followed the dietary habits of 15,000 participants for over three generations. It is regarded as the longest (beginning in 1948), most comprehensive epidemiological assessment in medical history. It has led to the publication of more than 1,200 research articles. Study director Dr. William Castelli summarized the issue unequivocally when he said,

"Serum cholesterol is not a strong risk factor for coronary heart disease"

Among the study's highlights are these:

- **There is no correlation** between dietary cholesterol intake and blood cholesterol levels.

- Framingham residents who ate the most cholesterol, saturated fat, and total calories actually weighed the least and were the most physically active.

A group called the International Network of Cholesterol Skeptics is populated by dozens of leading M.D.'s and Ph.D.'s from across the globe. Their research now shows that atherosclerosis is caused mainly by the excessive oxidation (and the ensuing inflammation) of a certain type of cholesterol that constitutes a small fraction of the mostly good stuff flowing through your bloodstream. Ironically, it

appears that this oxidation might be made worse by consuming the very (cholesterol-free) polyunsaturated fats in vegetable and grain oils that the medical establishment led us to believe were healthier than animal fats! The millions who use statin drugs daily incur a significant expense and endure disappointing side effects. For nearly all users, there is little or no demonstrable reduction in heart disease risk.

Cholesterol is one of the most important substances in the human body. Every cell membrane has cholesterol as a critical structural and functional component. Brain cells need cholesterol to make synapses (connections) with other brain cells. Cholesterol is the precursor molecule for important hormones such as testosterone, estrogen, DHEA, Cortisol, and pregnenolone. Cholesterol is needed for making the bile acids that allow us to digest and absorb fats. Bottom line is that you can't live without cholesterol, which is why your liver actually makes up to 1,400 milligrams a day regardless of how much food-borne cholesterol you consume—or how much you avoid it like the plague—in your diet.

Excessive carbohydrate consumption causes excessive insulin production. This insulin drives the conversion of the carbohydrates into triglycerides. Consuming too many carbs leads to high triglycerides. High triglycerides increase LDLs become stuck in the spaces between the cells lining the artery. Once the LDLs become stuck, they become oxidized. This oxidative damage causes inflammation and begins the process of atherosclerosis.

Statins do slightly reduce the risk of additional heart attacks among men under the age of 65 who have had a prior heart attack. However, many doctors now believe that these benefits are independent of their "cholesterol-lowering" properties and instead come from an anti-inflammatory effect that addresses the more proximate cause of heart disease. A cheaper and more effective anti-inflammatory effect can be achieved by eating foods high in omega-3, taking fish oil supplements, or popping a small dose of aspirin daily.

In the case of statins, known side effects include muscle pain, weakness and numbness, chronic fatigue, tendon problems, cognitive problems, impotence, and blood glucose elevations. These side effects are believed to be due in large part to statins' interference with the normal production of a critical micronutrient known as coenzyme Q10 (CoQ10). CoQ10 is essential to healthy mitochondrial function and defending our cells against free radical damage. Statin therapy is believed to lower CoQ10 levels by up to 50%. Ironically, CoQ10 plays a particularly important role in the healthy function of the cardiovascular system, and heart attack patients show depressed levels of CoQ10! Some researchers suggest that statins' depletion of CoQ10 may nullify any potential benefits of statin therapy.

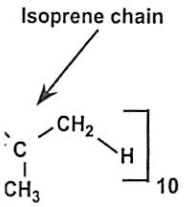
Oxidative Stress, Disease and Cancer

Edited by Keshav K. Singh

Roswell Park Cancer Institute,
New York, USA

2006

Imperial College Press



) (ubiquinone).

n the side chain, hence the
contains nine units and in
:vels vary in the body, with
highest metabolic rates such
inish with advancing age.[2]
Table 1). CoQ_{10} is abundant
ibrane where it is an essen-
ydrogenase (Complex 1) to
(Complex 2) to cytochrome
oxidoreductase) by transfer-
proton-motive Q cycle within
s found as a semiquinone in
H_2) or oxidized (ubiquinone,
brane proton gradient across
reduction of oxygen to water
imately drives ATP synthase

TP-generating capacity after
rabbit hearts pretreated with
oved post-ischemic preserva-
uced creatine phosphokinase
al.[6] showed that CoQ_{10} pre-
high-energy phosphates and
preventing calcium overload
recent study, also using an
oQ_{10} pretreatment improved

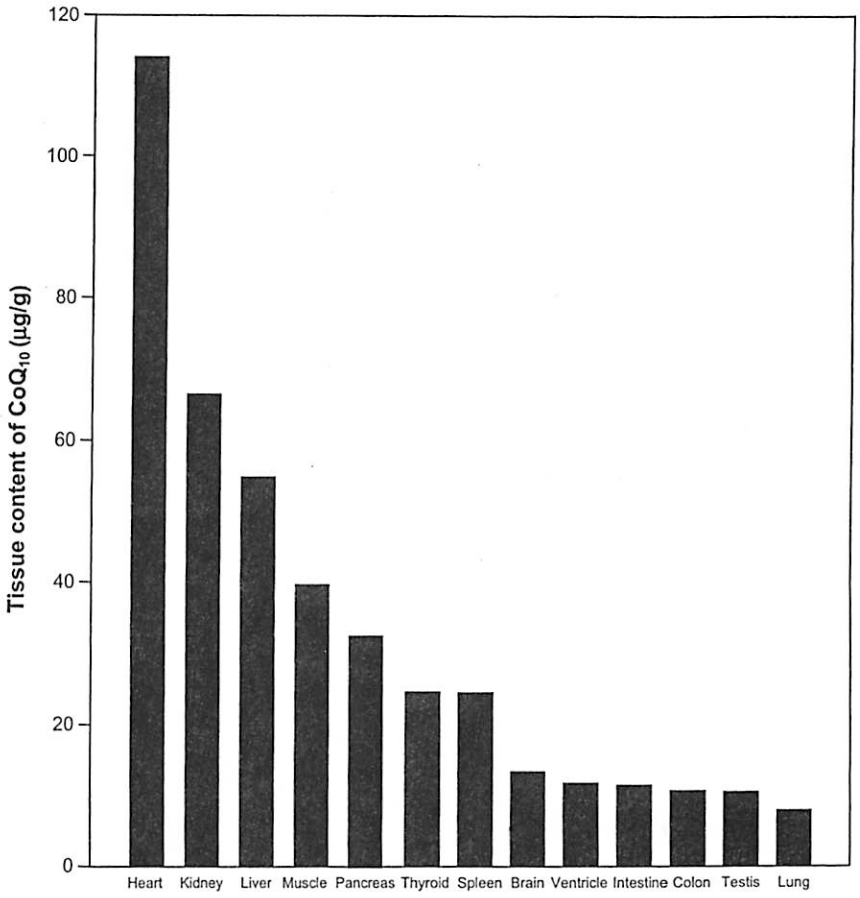


Fig. 2. Human organ tissue content of coenzyme Q_{10}.[1]

Table 1. Functions of coenzyme Q_{10}.[4]

Participation as electron carrier in the mitochondrial respiratory chain
Participation in extra-mitochondrial electron transport
Endogenously synthesized, lipid-soluble antioxidant
Regulation of mitochondrial permeability transition pore
Required for activation of mitochondrial uncoupling proteins
Regulation of the physiochemical properties of membranes
Modulation of the amount of β_2-integrins on the surface of blood monocytes
Improvement of endothelial dysfunction

Oxidative Stress, Disease and Cancer

Edited by Keshav K. Singh
Roswell Park Cancer Institute, New York, USA
Imperial College Press
2006

CoQ10 controls these functions:

- Participation as electron carrier in the mitochondrial respiratory chain
- Participation in extra-mitochondrial electron transport
- Endogenously synthesized, lipid-soluble antioxidant
- Regulation of mitochondrial permeability transition pore
- Activation of mitochondrial uncoupling proteins
- Regulation of the physiochemical properties of membranes
- Improvement of endothelial dysfunction

Organ systems require varying amount of CoQ10 for optimal function, in this order: (micrograms/gram of tissue)

Heart	about	120
Kidney	about	65
Liver	about	60
Muscle	about	40
Pancreas	about	40
Thyroid and Spleen	about	30
Brain, Ventricles, Intestine, Colon, Testis, Lung,	less than	20

"The commonly used cholesterol lowering drugs, the statins, inhibit HMG-CoA reductase [the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase]. Thus, the statins not only reduce the synthesis of cholesterol but also of CoQ10 and dolichol." p. 970

Based upon clinical trials and meta-analysis, "it is not unreasonable to recommend to patients with symptomatic heart failure despite conventional therapy or those who are experiencing side effects of conventional therapy, to take 150-300 mg of CoQ10 daily."

"Statins cause CoQ10 Deficiency"

"The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors or 'statins' are at present one of the most widely prescribed drugs in the Western world. These drugs lower cholesterol by inhibiting the enzyme HMG CoA reductase, a key enzyme in the synthetic pathway for cholesterol and also for CoQ10."

Studies show that statins effect CoQ10 metabolism. Studies indicate that statin-treated patients have mitochondrial dysfunction, "most likely induced by CoQ10 depletion."

Statin-induced CoQ10 depletion causes a depression in cardiac function, reversible by CoQ10 supplementation.

"Statins, especially the lipid-soluble types such as simvastatin [Zocor], deplete body CoQ10 levels. This depletion may be particularly important in the elderly where CoQ10 levels are generally low. Adverse effects of statin-induced CoQ10 have been observed at a mitochondrial level and a clinical level and these effects can be corrected by concurrent administration of CoQ10." Pp. 977-978

Carcinogenicity of Lipid-lowering Drugs

Journal of the American Medical Association
January 3, 1996;275(1):55-60

Newman TB, Hulley SB.
Department of Laboratory Medicine, School of Medicine, University of California, San Francisco, USA.

BACKGROUND INFORMATION:
Fibrates:
Bezafibrate (e.g. Bezalip)
Ciprofibrate (e.g. Modalim)
Gemfibrozil (e.g. Lopid)
Fenofibrate (e.g. TriCor)

Statin	**Brand name**	**Derivation**
Atorvastatin	Lipitor, Torvast	Synthetic
Fluvastatin	Lescol	Synthetic
Lovastatin	Mevacor, Altocor, Altoprev	Fermentation-derived
Mevastatin		Naturally-occurring, found in red yeast rice
Pitavastatin	Livalo, Pitava	Synthetic
Pravastatin	Pravachol, Selektine, Lipostat	Fermentation-derived
Rosuvastatin	Crestor	Synthetic
Simvastatin	Zocor, Lipex	Fermentation-derived
Simvastatin+Ezetimibe	Vytorin	Combination therapy
Lovastatin+Niacin	Advicor	Combination therapy
Simvastatin+Niacin	Simcor	Combination therapy

OBJECTIVE
To review the findings and implications of studies of rodent carcinogenicity of lipid-lowering drugs.

DATA SOURCES
Summaries of carcinogenicity studies published in the 1992 and 1994 Physicians' Desk Reference (PDR), additional information obtained from the US Food and Drug Administration, and published articles identified by computer searching, bibliographies, and consultation with experts.

STUDY SAMPLE
We tabulated rodent carcinogenicity data from the 1994 PDR for all drugs listed as "hypolipidemics." For comparison, we selected a stratified random sample of antihypertensive drugs. We also reviewed methods and interpretation of carcinogenicity studies in rodents and results of clinical trials in humans.

DATA SYNTHESIS
All members of the two most popular classes of lipid-lowering drugs (the fibrates and the statins) cause cancer in rodents, in some cases at levels of animal exposure close to those prescribed to humans.

In contrast, few of the antihypertensive drugs have been found to be carcinogenic in rodents.

Evidence of carcinogenicity of lipid-lowering drugs from clinical trials in humans is inconclusive because of inconsistent results and insufficient duration of follow-up.

CONCLUSIONS
Extrapolation of this evidence of carcinogenesis from rodents to humans is an uncertain process. Longer-term clinical trials and careful post-marketing surveillance during the next several decades are needed to determine whether cholesterol-lowering drugs cause cancer in humans.

In the meantime, the results of experiments in animals and humans suggest that lipid-lowering drug treatment, especially with the fibrates and statins, should be avoided except in patients at high short-term risk of coronary heart disease.

THESE AUTHORS ALSO NOTE:

In the past decade (1985 – 1995) there has been a greater than 10-fold increase in the prescription of lipid-lowering drugs because they are being aggressively promoted by their manufacturers.

Lipid-lowering drugs may be taken for 30 years or more, yet the FDA approved these drugs based upon clinical trial that lasted only a fraction of this time.

"Thus, millions of asymptomatic people are being treated with medications, the ultimate effects of which are not yet known."

"Meta-analyses of randomized clinical trials have suggested that cholesterol-lowering drugs may increase noncardiovascular mortality."

"Drug companies are required to submit data from rodent carcinogenicity studies to the FDA. These studies are not generally published in scientific journals but are summarized in the *Physicians' Desk Reference* (PDR)." These authors evaluated the results of these carcinogenicity rodent studies in the PDR and compared them to other classes of drugs.

RESULTS

"The product information for lipid-lowering drugs indicates that all the fibric acid derivatives and statins caused cancer in rodents."

"In most cases the rodent exposure at which carcinogenicity was observed was of the same order of magnitude as that observed with the maximum dose recommended for humans."

"Unlike the lipid-lowering drugs, most drugs for lowering blood pressure do not cause cancer."

"Almost all known human carcinogens have been found to be carcinogenic in mice and rats."

"Why Were These Drugs Approved?"

These authors reviewed the minutes of the approval committee meeting, and found that representatives of the makers of these drugs downplayed the importance of the rodent carcinogenicity studies. Additionally, for gemfibrozil, "only three of the nine members of the advisory committee believed that the potential benefit of using gemfibrozil, for the prevention of coronary heart disease outweighed the potential risks associated with such use."

Sadly, such votes are only advisory, and the FDA approved gemfibrozil, when all of the following criteria are met:

1) Low high-density lipoprotein cholesterol.
2) Elevated low-density lipoprotein cholesterol.
3) Elevated triglycerides.
4) Inadequate response to weight loss, diet, and exercise.

"Unfortunately, the subsequent popularity of gemfibrozil suggests that its use has not been restricted to this small group."

"For patients not at high short-term risk of CHD death, especially patients with life expectancies of more than 10 to 20 years, pharmacologic treatment probably should be avoided."

It is possible that these drugs are not carcinogenic, but rather that it is the lower cholesterol levels they cause being responsible for the adverse effects. "Persons with low cholesterol levels have higher cancer death rates in cohort studies."

"It seems prudent to reserve the statins for people at high short-term risk of heart disease and to be wary about their long-term use."

CONCLUSION

"Most cholesterol-lowering drugs cause or promote cancer."

"Patients to whom these drugs are prescribed are exposed throughout many years to doses approaching those shown to be carcinogenic in animals."

Use of cholesterol-lowering drugs should be restricted to those at high risk of short-term CHD death, such as those with prior CHD, in whom the short-term benefits of treatment are most likely to justify the long-term risks.

KEY POINTS FROM DAN MURPHY

1) "Drug companies are required to submit data from rodent carcinogenicity studies to the FDA. These studies are not generally published in scientific journals but are summarized in the *Physicians' Desk Reference* (PDR)." These authors evaluated the results of these carcinogenicity rodent studies in the PDR and compared them to other classes of drugs.

2) "The results of experiments in animals and humans suggest that lipid-lowering drug treatment, especially with the fibrates and statins, should be avoided except in patients at high short-term risk of coronary heart disease."

3) Lipid-lowering drugs may be taken for 30 years or more, yet the FDA approved these drugs based upon clinical trials that lasted only a fraction of this time.

4) "Millions of asymptomatic people are being treated with medications [lipid-lowering drugs], the ultimate effects of which are not yet known."

5) "Meta-analyses of randomized clinical trials have suggested that cholesterol-lowering drugs may increase noncardiovascular mortality."

6) "The product information for lipid-lowering drugs indicates that all the fibric acid derivatives and statins caused cancer in rodents."

7) "In most cases the rodent exposure at which carcinogenicity was observed was of the same order of magnitude as that observed with the maximum dose recommended for humans."

8) "Almost all known human carcinogens have been found to be carcinogenic in mice and rats."

9) "For patients not at high short-term risk of CHD death, especially patients with life expectancies of more than 10 to 20 years, pharmacologic treatment [with lipid-lowering drugs] probably should be avoided."

10) It is possible that these drugs are not carcinogenic, but rather that it is the lower cholesterol levels they cause being responsible for the adverse effects. "Persons with low cholesterol levels have higher cancer death rates in cohort studies."

11) "It seems prudent to reserve the statins for people at high short-term risk of heart disease and to be wary about their long-term use."

12) "Most cholesterol-lowering drugs cause or promote cancer."

13) "All members of the two most popular classes of lipid-lowering drugs (the fibrates and the statins) cause cancer in rodents, in some cases at levels of animal exposure close to those prescribed to humans."

14) "Patients to whom these drugs are prescribed are exposed throughout many years to doses approaching those shown to be carcinogenic in animals."

15) Use of cholesterol-lowering drugs should be restricted to those at high risk of short-term CHD death, such as those with prior CHD, in whom the short-term benefits of treatment are most likely to justify the long-term risks.

Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study

The Lancet
Volume 358, Issue 9279, August 4, 2001, pp. 351-355

Irwin J Schatz MD, Kamal Masaki MD, Katsuhiko Yano MD, Randi Chen MS, Beatriz L Rodriguez MD and J David Curb MD

FROM ABSTRACT
Background
A generally held belief is that cholesterol concentrations should be kept low to lessen the risk of cardiovascular disease. However, studies of the relation between serum cholesterol and all-cause mortality in elderly people have shown contrasting results. To investigate these discrepancies, we did a longitudinal assessment of changes in both lipid and serum cholesterol concentrations over 20 years, and compared them with mortality.

Methods
Lipid and serum cholesterol concentrations were measured in 3,572 Japanese/American men (aged 71–93 years) as part of the Honolulu Heart Program. We compared changes in these concentrations over 20 years with all-cause mortality using three different Cox proportional hazards models.

Findings
Mean cholesterol fell significantly with increasing age.

Only the group with low cholesterol concentration at both examinations [20 years apart] had a significant association with mortality [an increased risk of mortality by 64%].

Interpretation
We have been unable to explain our results.
These data cast doubt on the scientific justification for lowering cholesterol to very low concentrations in elderly people.

THESE AUTHORS ALSO NOTE:

Researchers have been unable to conclusively show high concentrations of total serum cholesterol to be directly related to mortality in people older than age 65.

"Results of several studies have shown an inverse relation, or no relation, between total cholesterol concentration and risk of death in elderly people."

These authors assessed changes in lipid concentrations over 20 years, from 1972 to 1992, and correlated them with all-cause mortality in a large cohort of Japanese/American men who were followed up in the Honolulu Heart Program.

RESULTS

Higher cholesterol concentrations were associated with:
1) Higher body mass index [they were less frail]
2) Higher HDL [good] cholesterol
3) Higher hemoglobin
4) Better hand-grip strength

"Kaplan-Meier survival curves showed lowest survival rates for those with the lowest serum cholesterol concentrations."

DISCUSSION

"Our data accord with previous findings of increased mortality in elderly people with low serum cholesterol, and show that long-term persistence of low cholesterol concentration actually increases risk of death."

"Thus, the earlier that patients start to have lower cholesterol concentrations, the greater the risk of death."

"Our results lend support to previous findings that low serum cholesterol imparts a poor outlook when compared with higher concentrations of cholesterol in elderly people, our data also suggest that those individuals with a low serum cholesterol maintained over a 20-year period will have the worst outlook for all-cause mortality."

"Is this low/low effect unique to individuals of Japanese ethnic extraction? There is no evidence to support such a contention. Risk factors for atherosclerosis in Japanese are much the same as those for whites."

These authors believe that there is no scientific justification to lower cholesterol to concentrations below 4·65 mmol/L (180 mg/dL) in elderly people.

KEY POINTS FROM DAN MURPHY:

1) These authors note that the relationship between cholesterol levels and mortality in elderly people (aged >65) have not been adequately assessed in studies. Consequently, they measured serum cholesterol concentrations in 3,572 Japanese/American men (aged 71–93 years) over 20 years and compared them with all-cause mortality.

2) "Only the group with low cholesterol concentration at both examinations [20 years apart] had a significant association with mortality," which was an increased risk of mortality by 64%.

3) These authors state:
A)) "We have been unable to explain our results."
B)) "These data cast doubt on the scientific justification for lowering cholesterol to very low concentrations in elderly people."

4) "Results of several studies have shown an inverse relation, or no relation, between total cholesterol concentration and risk of death in elderly people."

5) This study "showed lowest survival rates for those with the lowest serum cholesterol concentrations." [Again, these patients were elderly, between 71-93 years of age].

6) "Our data accord with previous findings of increased mortality in elderly people with low serum cholesterol, and show that long-term persistence of low cholesterol concentration actually increases risk of death."

7) "The earlier that patients start to have lower cholesterol concentrations, the greater the risk of death."

8) "Low serum cholesterol imparts a poor outlook when compared with higher concentrations of cholesterol in elderly people, our data also suggest that those individuals with a low serum cholesterol maintained over a 20-year period will have the worst outlook for all-cause mortality."

9) These authors believe that there is no scientific justification to lower cholesterol to concentrations below 4·65 mmol/L (180 mg/dL) in elderly people.

NOTE:
Canada and the UK measure cholesterol in mmol/L, which is millimoles per liter.
Americans use mg/dL, which is milligrams per deciliter.
The conversion from mmo/L to mg/dL is X38.6596.

Statins and risk of polyneuropathy: a case-control study.

Neurology 2002 May 14;58(9):1333-7

Gaist D, Jeppesen U, Andersen M, Garcia Rodriguez LA, Hallas J, Sindrup SH.

FROM ABSTRACT

BACKGROUND:
Several case reports and a single epidemiologic study indicate that use of statins occasionally may have a deleterious effect on the peripheral nervous system.

The authors therefore performed a population-based study to estimate the relative risk of idiopathic polyneuropathy in users of statins.

METHOD:
The authors used a population-based patient registry to identify first-time-ever cases of idiopathic polyneuropathy registered in the 5-year period 1994 to 1998.

For each case, validated according to predefined criteria, 25 control subjects were randomly selected among subjects from the background population matched for age, sex, and calendar time.

The authors used a prescription register to assess exposure to drugs and estimated the odds ratio of use of statins (ever and current use) in cases of idiopathic polyneuropathy compared with control subjects.

RESULTS:
The authors verified a diagnosis of idiopathic polyneuropathy in 166 cases. The cases were classified as definite (35), probable (54), or possible (77).

The odds ratio linking idiopathic polyneuropathy with statin use was 3.7 (1.8 to 7.6) for all cases and 14.2 (5.3 to 38.0) for definite cases.

The corresponding odds ratios in current users were 4.6 (2.1 to 10.0) for all cases and 16.1 (5.7 to 45.4) for definite cases.

For patients treated with statins for 2 or more years the odds ratio of definite idiopathic polyneuropathy was 26.4 (7.8 to 45.4).

CONCLUSIONS:
Long-term exposure to statins may substantially increase the risk of polyneuropathy.

THESE AUTHORS ALSO NOTE:

Statins drugs are lipid-lowering drugs.

"An ever-growing number of patients are receiving long-term treatment with statins."

The relative safety of long-term use of statins drugs in unselected populations of patients may reveal unrecognized problems.

One of these complications is polyneuropathy.

This study is the only published epidemiologic study to date on this topic.

The clinical criteria for a diagnosis of polyneuropathy were distal symmetric sensory symptoms or symmetric motor symptoms and no upper motor neuron signs, or both.

The neurophysiologic criteria were abnormal conduction velocity in two or more peripheral nerves.

The median duration of statin use in the cases was 2.8 years (range 1.9 to 3.0).

DISCUSSION

"Users of statins were at a 4 to 14-fold increased risk of developing idiopathic polyneuropathy compared with the background population, and that this adverse effect may primarily occur after long-term treatment with statins."

The results of this study are in line with several other studies that indicate an association between statin use and polyneuropathy.

This study and previous studies "strongly suggest a toxic effect of statins on peripheral nerves."

Interference with cholesterol synthesis by statin drugs "may alter nerve membrane function because cholesterol is a ubiquitous component of human cell membranes."

"Statins also inhibit the synthesis of the key mitochondrial respiratory chain enzyme, ubiquinone, which may disturb neuron energy utilization and thereby induce neuropathy."

Long-term exposure to statins cause structural and functional changes of the neurons.

"Polyneuropathy as a side effect to statin use is not mentioned in the Danish physicians drug reference book, and this potential side effect received little attention in the international medical literature during the study period."

Because of the protective effect of statin drugs have on coronary artery disease, the authors believe that their benefits outweighs the risks.

However, they note if peripheral neuropathy complaints arise in statin drug users, that the physician should reconsider continuous treatment with these drugs.

THIS ARTICLE GENERATED THE FOLLOWING EDITORIAL

Assessing the risk of drug-induced neurologic disorders: Statins and Neuropathy

Neurology. 2002 May 14;58(9):1321-2.

Michael Donaghy

"Clinicians are familiar with the myopathy induced by the statin class of cholesterol-lowering drugs that are now in common use."

This case-control study by shows that statins can also cause polyneuropathy.

"Medications are responsible for a huge range of neurologic disorders, but for most such drugs we have little useful concept of risk."

If one suspects a drug side effect, stopping the drug may not reverse the damage the structure or physiology of the nervous system.

Statins are connected to "polyneuropathy with a relative risk of 16.1 (5.7 to 45.4) for definite cases. The risk was increased by the duration of statin use and cumulative dose. It seems a fairly conclusive association."

"In the case of statin-induced myopathy, the daily dosage predicts the risk of muscle damage."

"The polyneuropathy in question has electrophysiologic features predominantly of axonal degeneration, and usually presents with pain, paraesthesias, and numbness; muscle stretch reflexes were absent in half."
[This could easily be many chiropractic patients.]

KEY POINTS FROM DAN MURPHY

(1) Statin drugs are lipid-lowering drugs.

(2) Nerve cell membrane function depends upon cholesterol.

(3) "Long-term [2 – 3 years] exposure to statins may substantially increase the risk of polyneuropathy."

(4) Many patients are receiving long-term treatment with statin drugs.

(5) Statin drugs raise a person's risk of polyneuropathy nerve damage by about 16%, and some groups may have an increased risk of 45%.

(6) Statin drugs are also known to cause myopathy.

(7) The toxic structural and functional changes of the neurons from use of statin drugs on peripheral nerves may be permanent.

(8) Statin drugs also inhibit mitochondrial respiratory energy production.

COMENTS FROM DAN MURPHY

The nerve damage of polyneuropathy is characterized by extremity weakness, tingling, difficulty walking, and weakness.

Statin drugs raise a person's risk of polyneuropathy nerve damage by about 16%, and some groups may have an increased risk of 45%.

Currently, about 16 million Americans are taking statin drugs, and about 36 million Americans have blood lipid levels high enough to warrant them taking these drugs.

These numbers will skyrocket as baby boomers age. Sales of statin drugs are projected to rise by 20% per year.

Statin drugs are already the most profitable drug ever. Lipitor, the best selling of the statin drugs, had $7 billion in sales last year, and is projected to have $10 billion in sales this year.

Every chiropractor has patients taking statin drugs. These drugs may be responsible for the signs and symptoms that we are treating the patient for.

The case for statins: has it really been made?

Journal of the Royal Society of Medicine

October 2004; Volume 97, Number 10, pp. 461-464

Andrew Thompson PhD and Norman J Temple PhD

FROM ABSTRACT

Statin drugs are a modern success story. They are the medical treatment for coronary disease and the star of the pharmaceutical industry. Worldwide, sales of statins are running at about $19 billion a year and growing quickly.

This success profits not only the pharmaceutical industry but also all those whose finances and careers are furthered by the research and the sales. But to what extent is it also a success for the general public?

To answer this we will look at the major long-term (five to six year) clinical trials of statins. We start with the treatment offered to the participants, then look at the endpoints that were selected, and continue with a look at how the results have been reported.

We conclude with a discussion of the cost-effectiveness of statins for people at different levels of risk of coronary heart disease (CHD).

THESE AUTHORS ALSO NOTE:

> In 1988, the US National Cholesterol Education Program stated:
>
> "Drug therapy is likely to continue for many years, or for a lifetime. Hence, the decision to add drug therapy to the regimen should be made only after vigorous efforts at dietary treatment have not proven sufficient."

"Vigorous" dietary efforts are defined as a minimum of 6 months of intensive dietary counseling before starting statin drug therapy.

Although all of the statin drug cholesterol trials were initiated after the publication of these guidelines, none of the trials adhered to the 6 month dietary protocols prior to putting subjects on statin drugs.

"Why were these guidelines not followed?" If all statin drug trial participants had been given dietary intervention before starting statins, "it would have much reduced the differences in deaths from CHD and all-cause mortality in the trials." In other words, the statins would have appeared to be less effective in reducing deaths from CHD and other causes of mortality.

In performing a clinical trial of a drug, "all-cause mortality" is the only endpoint measure not prone to diagnostic variance, and is therefore not popular with the drug company studies. Most statin drug trials do not even look at all-cause mortality because of the probability that taking the drugs do not alter all-cause mortality.

Drug company study designers search for endpoints that are most apt to yield a positive result. "This would not be the scientific approach but would make sense if the aim was to make the study appear highly successful."

"With respect to data on deaths the most important endpoint is all-cause mortality. This can be manipulated only by fraud and is the one primary concern to the recipients of the treatment—are they less likely to die soon, whatever the reason, if they take this drug?"

"If a drug or other intervention neither extends life nor improves its overall quality, then it is of no value."

"There is no rigorous reporting of all-cause morbidity, nor of measurement of changes in overall quality of life, in any of the [statin drug] studies."

Statin drug trials show absolute differences of less than 1% to a maximum of 3.3% in all-cause mortality between the control and treatment groups. "These are not impressive results."

However, drug companies make statin drug results look impressive "by expressing the results as relative difference rather than as absolute difference." In a statin drug trial of patients with existing CHD, the difference in deaths between the statin group and the placebo group was 3.1% (14.1% of the placebo group died and 11% of the statin group). The benefit of such results can appear to be magnified by expressing them as relative differences, which would be 11/14.1 = 22%: "The statin drug lowered the risk of death by 22% (11 is 22% lower than 14.1)."

Another serious problem is that the study does not state the number needed to treat (NNT) for one patient to benefit, which is over 100 in primary prevention trials. This means that more than 100 patients would have to take the drugs for one patient to actually receive any benefit.

In a study where 100 patients take statins drugs, 2 will have a fatal heart attack. In 100 patients taking a placebo, 3 will have a fatal heart attack. The absolute risk reduction of a fatal heart attach is 1%. Yet the drug company spins the pathetic results by dividing 2/3 and publish the relative risk, which is a 33% reduction of a fatal heart attack. This is dishonest. These authors claim an honest disclosure would be to state "if you take statins, then in seven years' time there is a one chance in about 120 that your death will have been prevented."

Using current available NNT data and assuming the cost of a year of statin drugs is $500, the cost of postponing one death by using statin drugs is $85,500 for patients with the highest risk, to more than $300,000 for those with the lowest risk.

"It is arguable that statins are cost-effective for the small minority of people at especially high risk of CHD."

CONCLUSIONS

The design of the statin drug trials has not involved the testing of the value of statin drugs relative to that of guideline-recommended promotion of lifestyle changes.

The small differences favouring statin drugs in published studies "have been magnified by the manner of presentation of results, most notably by the use of relative differences between statins and placebo groups rather than absolute differences."

"Lowering the threshold to make much larger numbers of people eligible for drug therapy has the effect of making statins an extremely expensive means of preventing heart disease. The case for statin drugs, especially for primary prevention, has not been made."

KEY POINTS FROM DAN MURPHY

1) Because statin drug therapy is likely to continue for many years, or for a lifetime, the official written position of the National Cholesterol Education Program of the National Institutes of Health state "the decision to add drug therapy to the regimen should be made only after vigorous efforts at dietary treatment have not proven sufficient." "Vigorous" dietary efforts are defined as a minimum of 6 months of intensive dietary counseling before starting statin drug therapy.

2) Statin drug trials are not preceded by vigorous dietary efforts because to do so would help people and render statin drug therapy less effective in reducing deaths from CHD and other causes of mortality.

3) In performing a clinical trial of a drug, "all-cause mortality" is the only endpoint measure not prone to diagnostic variance, and is therefore not popular with the drug company studies. Most statin drug trials do not even look at all-cause mortality because of the probability that taking the drugs do not alter all-cause mortality.

4) Drug company study designers search for endpoints that are most apt to yield a positive result. "This would not be the scientific approach but would make sense if the aim was to make the study appear highly successful."

5) "If a drug or other intervention neither extends life nor improves its overall quality, then it is of no value."

6) "There is no rigorous reporting of all-cause morbidity, nor of measurement of changes in overall quality of life, in any of the [statin drug] studies."

7) Statin drug trials show absolute differences of less than 1% to a maximum of 3.3% in all-cause mortality between the control and treatment groups. "These are not impressive results."

8) However, drug companies make statin drug results look impressive "by expressing the results as relative difference rather than as absolute difference." In a statin drug trial of patients with existing CHD, the difference in deaths between the statin group and the placebo group was 3.1% (14.1% of the placebo group died and 11% of the statin group). The benefit of such results can appear to be magnified by expressing them as relative differences, which would be 11/14.1 = 22%: "The statin drug lowered the risk of death by 22% (11 is 22% lower than 14.1)."

9) The small differences favouring statin drugs in published studies "have been magnified by the manner of presentation of results, most notably by the use of relative differences between statins and placebo groups rather than absolute differences."

10) Another serious problem is that the study does not state the number needed to treat (NNT) for one patient to benefit, which is over 100 in primary prevention trials. This means that more than 100 patients would have to take the drugs for one patient to actually receive any benefit.

11) In a study where 100 patients take statins drugs, 2 will have a fatal heart attack. In 100 patients taking a placebo, 3 will have a fatal heart attack. The absolute risk reduction of a fatal heart attach is 1%. Yet the drug company spins the pathetic results by dividing 2/3 and publish the relative risk, which is a 33% reduction of a fatal heart attack. This is dishonest. These authors claim an honest disclosure would be to state "if you take statins, then in seven years' time there is a one chance in about 120 that your death will have been prevented."

12) Using current available number needed to treat (NNT) data and assuming the cost of a year of statin drugs is $500, the cost of postponing one death by using statin drugs is $85,500 for patients with the highest risk, to more than $300,000 for those with the lowest risk.

13) "It is arguable that statins are cost-effective for the small minority of people at especially high risk of CHD."

14) "Lowering the threshold to make much larger numbers of people eligible for drug therapy has the effect of making statins an extremely expensive means of preventing heart disease. The case for statin drugs, especially for primary prevention, has not been made."

Do Cholesterol Drugs Do Any Good?
Research suggests that, except among high-risk heart patients, the benefits of statins such as Lipitor are overstated

Cover Story, BusinessWeek

January 28, 2008

by John Carey
John Carey is a senior correspondent for BusinessWeek in Washington.

Cholesterol-lowering drugs called a statins are the "best-selling medicines in history, used by more than 13 million Americans and an additional 12 million patients around the world, producing $27.8 billion in sales in 2006. Half of that went to Pfizer for its leading statin, Lipitor."

However, critical review of the evidence for the benefits of statin drugs show that they can be life-saving in patients who already have suffered heart attacks, somewhat reducing the chances of a recurrence that could lead to an early death. But for the majority of patients who don't have heart disease, statin drugs offer "no benefit in people over the age of 65, no matter how much their cholesterol declines, and no benefit in women of any age."

The reduction in the number of heart attacks for middle-aged men taking statins in clinical trials is small. "But even for these men, there was no overall reduction in total deaths or illnesses requiring hospitalization—despite big reductions in 'bad' cholesterol."

Most people taking statin drugs have no chance of benefit and a risk of harm.

"Americans are bombarded with the message from doctors, [drug] companies, and the media that high levels of bad cholesterol are the ticket to an early grave and must be brought down. Statins, the message continues, are the most potent weapons in that struggle. The drugs are thought to be so essential that, according to the official government guidelines from the National Cholesterol Education Program (NCEP), 40 million Americans should be taking them. Some researchers have even suggested that the medications should be put in the water supply, like fluoride for teeth."

Statins are sold by:

Merck	Mevacor and Zocor
AstraZeneca	Crestor
Bristol-Myers Squibb	Pravachol
Pfizer	Lipitor

Many researchers harbor doubts about the need to drive down cholesterol levels.

On January 14, 2008, statin drug makers Merck and Schering-Plough revealed results of a trial in which a two-drug combination succeeded in forcing down patients' cholesterol further than with just the statin alone, "but even with two years of treatment, the further reductions brought no health benefit."

When Lipitor ads claim a dramatic 36% reduction in heart attacks, it means that "3% of patients taking a sugar pill or placebo had a heart attack compared to 2% of patients taking Lipitor."

In the Lipitor study, for every 100 people in the 3 1/3 year-long study, three people on placebos and two people on Lipitor had heart attacks.

This means there was one fewer heart attack per 100 people over a period of 3 1/3 years. "So to spare one person a heart attack, 100 people had to take Lipitor for more than three years. The other 99 (99%) got no measurable benefit."

This useful statistic is known as the **Number Needed to Treat (or NNT)**. To benefit one person, Lipitor had to be taken by 100 people for 3 1/3 years. This NNT, 100, is exceedingly high.

The NNT for antibiotic therapy to eradicate ulcer-causing stomach bacteria H. pylori is 1.1. Give the drugs to 11 people, and 10 will be cured. This is a low NNT.

There are reasons to believe the overall benefit for many patients taking statin drugs is even less than what the NNT score of 100 suggests. This is due to potential biases that were determined in a drug industry-sponsored trial, which carefully selected patients with multiple risk factors, including high blood pressure or smoking. "The only large clinical trial funded by the government, rather than [drug] companies, found no statistically significant benefit at all."

Experts claim that an "NNT of 50 is worse than a lottery ticket."

"Several recent scientific papers peg the NNT for statins at 250 and up for lower-risk patients, even if they take it for five years or more."

"What if you put 250 people in a room and told them they would each pay $1,000 a year for a drug they would have to take every day, that many would get diarrhea and muscle pain, and that 249 would have no benefit? And that they could do just as well by exercising? How many would take that?"

Statins have been in use now for 20 years, and the NNT does not decrease the longer people take the drug.

The statin trials of people without existing heart disease showed no reduction in deaths or serious health events.

"We should tell patients that the reduced cardiovascular risk will be replaced by other serious illnesses," says Dr. John Abramson, clinical instructor at Harvard Medical School and author of Overdosed America.

10% to 15% of statin users suffer side effects, such as muscle pain, cognitive impairments, and sexual dysfunction, and they cost billions of dollars per year.

"What would work better? Perhaps urging people to switch to a Mediterranean diet or simply to eat more fish. In several studies, both lifestyle changes brought greater declines in heart attacks than statins."

"The things that really work are lifestyle, exercise, diet, and weight reduction." Their cost is much less than drugs and they have benefits for quality of life.

"Difficult risk-benefit questions surround most drugs, not just statins. One dirty little secret of modern medicine is that many drugs work only in a minority of people."

"Beta-blockers are seen as essential in treating congestive heart failure. Yet studies show that an average of 24 people must take the drugs for seven months to prevent one hospitalization from heart failure (thus, an NNT of 24). And 40 people must take it to prevent one death (NNT of 40)."

The diabetes drug Avandia, increases the risk of heart attacks and does not prevent heart disease, strokes, and kidney failure in diabetic patients. "Its NNT is close to infinite." Yet it sells $2.6 billion per year.

"Many drugs are most effective in relatively small subgroups of sufferers. With statins, these are the patients who already have heart disease. But that's not a blockbuster market. So companies have every incentive to market their drugs as being essential for wider groups of people, for whom the benefits are, by definition, smaller. What the shrewd marketing people at Pfizer and the other companies did was spin it to make everyone with high cholesterol think they really need to reduce cholesterol. It was pseudo-science, never telling you the bottom-line truth, which is that the drugs don't help unless you have pre-existing cardiovascular disease."

Drug companies "make sure that the researchers and doctors who extol the benefits of medications are well compensated." "It's almost impossible to find someone who believes strongly in statins who does not get a lot of money from the industry."

"The National Cholesterol Education Program's 2004 guideline update garnered headlines by recommending lower targets for bad cholesterol, which would put more Americans on the drugs. But there was also a heated controversy in the medical community over the fact that 8 of the 9 experts on the panel had financial ties to the industry. Thirty-five experts sent a petition of protest to the National Institutes of Health, saying the evidence [for the benefit of lowering cholesterol with statins] was weak and the panel members were biased by their ties to [statin drug] companies."

Dr. Howard Brody, professor of family medicine at the University of Texas Medical Branch at Galveston states "I now see it as myth that everyone should have their cholesterol checked."

Cholesterol is just one of the risk factors for coronary disease. Spaniards have cholesterol levels similar to Americans', but less than half the rate of heart disease. The Swiss have higher cholesterol levels than Americans, but their rates of heart disease are lower. Australian aborigines have low cholesterol but high rates of heart disease.

Cholesterol-lowering medications other than statins do not prevent heart attacks or strokes, indicating that statins do not work because they lower cholesterol. Recent evidence indicates that statins probably work (as poorly as they do] because they reduce inflammation in arteries called Rho-kinase.

Experts conclude "Cholesterol lowering is not the reason for the benefit of statins."

"For anyone worried about heart disease, the first step should always be a better diet and increased physical activity."

"If the drugs were used more rationally, drugmakers would take a hit. But the nation's health and pocketbook might be better off."

"The way our health-care system runs, it is not based on data, it is based on what makes money."

KEY POINTS FROM DAN MURPHY

Statins are sold by:

Merck	Mevacor and Zocor
AstraZeneca	Crestor
Bristol-Myers Squibb	Pravachol
Pfizer	Lipitor

1) Cholesterol-lowering drugs called statins are the "best-selling medicines in history, used by more than 13 million Americans and an additional 12 million patients around the world, producing $27.8 billion in sales in 2006. Half of that went to Pfizer for its leading statin, Lipitor."

2) Statin drugs offer "no benefit in people over the age of 65, no matter how much their cholesterol declines, and no benefit in women of any age."

3) The reduction in the number of heart attacks for middle-aged men taking statins in clinical trials is small. "But even for these men, there was no overall reduction in total deaths or illnesses requiring hospitalization—despite big reductions in 'bad' cholesterol."

4) Most people taking statin drugs have no chance of benefit and a risk of harm.

5) Statin drugs are thought to be so essential that the official government guidelines from the National Cholesterol Education Program, claim that 40 million Americans should be taking them and they "should be put in the water supply, like fluoride for teeth."

6) When Lipitor ads claim a dramatic 36% reduction in heart attacks, it means that "3% of patients taking a sugar pill or placebo had a heart attack compared to 2% of patients taking Lipitor," and this occurred over a period of 3 1/3 years. This means there was one fewer heart attack per 100 people over a period of 3 1/3 years. "So to spare one person a heart attack, 100 people had to take Lipitor for more than three years. The other 99 (99%) got no measurable benefit."

7) This useful statistic is known as the **Number Needed to Treat (or NNT)**. To benefit one person, Lipitor had to be taken by 100 people for 3 1/3 years. This is a very high NNT, 100.

8) There are reasons to believe the overall benefit for many patients taking statin drugs is even less than what the NNT score of 100 suggests. This is due to potential biases that were determined in a drug industry-sponsored trial, which carefully selected patients with multiple risk factors, including high blood pressure or smoking. "The only large clinical trial funded by the government, rather than [drug] companies, found no statistically significant benefit at all."

9) Experts claim that an "NNT of 50 is worse than a lottery ticket."

10) "Several recent scientific papers peg the NNT for statins at 250 and up for lower-risk patients, even if they take it for five years or more."

11) The statin trials of people without existing heart disease showed no reduction in deaths or serious health events.

12) 10% to 15% of statin users suffer side effects, such as muscle pain, cognitive impairments, and sexual dysfunction, and they cost billions of dollars per year.

13) "What would work better? Perhaps urging people to switch to a Mediterranean diet or simply to eat more fish. In several studies, both lifestyle changes brought greater declines in heart attacks than statins."

14) "The things that really work are lifestyle, exercise, diet, and weight reduction." Their cost is much less than drugs and they have benefits for quality of life.

15) "Difficult risk-benefit questions surround most drugs, not just statins. One dirty little secret of modern medicine is that many drugs work only in a minority of people."

16) "Many drugs are most effective in relatively small subgroups of sufferers. With statins, these are the patients who already have heart disease. But that's not a blockbuster market. So companies have every incentive to market their drugs as being essential for wider groups of people, for whom the benefits are, by definition, smaller. What the shrewd marketing people at Pfizer and the other companies did was spin it to make everyone with high cholesterol think they really need to reduce cholesterol. It was pseudo-science, never telling you the bottom-line truth, which is that the drugs don't help unless you have pre-existing cardiovascular disease."

17) Drug companies "make sure that the researchers and doctors who extol the benefits of medications are well compensated." "It's almost impossible to find someone who believes strongly in statins who does not get a lot of money from the [drug] industry."

18) "The National Cholesterol Education Program's 2004 guideline update garnered headlines by recommending lower targets for bad cholesterol, which would put more Americans on the drugs. But there was also a heated controversy in the medical community over the fact that 8 of the 9 experts on the panel had financial ties to the [drug] industry. Thirty-five experts sent a petition of protest to the National Institutes of Health, saying the evidence [for the benefit of lowering cholesterol with statins] was weak and the panel members were biased by their ties to [statin drug] companies."

19) Cholesterol-lowering medications other than statins do not prevent heart attacks or strokes, indicating that statins do not work because they lower cholesterol. Statins probably work (as poorly as they do] because they reduce inflammation in arteries called Rho-kinase. "Cholesterol lowering is not the reason for the benefit of statins."

20) "For anyone worried about heart disease, the first step should always be a better diet and increased physical activity."

21) "If the drugs were used more rationally, drugmakers would take a hit. But the nation's health and pocketbook might be better off."

22) "The way our health-care system runs, it is not based on data, it is based on what makes money."

Statins and All-Cause Mortality in High-Risk Primary Prevention: A Meta-analysis of 11 Randomized Controlled Trials Involving 65,229 Participants

Archives of Internal Medicine
June 29, 2010, Vol. 170, No. 12, pp. 1024-1031

Kausik K. Ray, MD; Sreenivasa Rao Kondapally Seshasai, MD; Sebhat Erqou, MD, PhD; Peter Sever, PhD; J. Wouter Jukema, MD, PhD; Ian Ford, PhD; Naveed Sattar:
The authors are from University of Cambridge
FROM ABSTRACT:

Background: Statins have been shown to reduce the risk of all-cause mortality among individuals with clinical history of coronary heart disease. However, it remains uncertain whether statins have similar mortality benefit in a high-risk primary prevention setting.

Notably, all systematic reviews to date included trials that in part incorporated participants with prior cardiovascular disease (CVD) at baseline. Our objective was to reliably determine if statin therapy reduces all-cause mortality among intermediate to high-risk individuals without a history of CVD.

Data Sources: Trials were identified through computerized literature searches of MEDLINE and Cochrane databases (January 1970-May 2009) using terms related to statins, clinical trials, and cardiovascular end points and through bibliographies of retrieved studies.

Study Selection: Prospective, randomized controlled trials of statin therapy performed in individuals free from CVD at baseline and that reported details, or could supply data, on all-cause mortality.

Data Extraction: Relevant data including the number of patients randomized, mean duration of follow-up, and the number of incident deaths were obtained from the principal publication or by correspondence with the investigators.

Data Synthesis: Data were combined from 11 studies and effect estimates were pooled using a random-effects model meta-analysis, with heterogeneity assessed with the I2 statistic. Data were available on 65,229 participants followed for approximately 244,000 person-years, during which 2,793 deaths occurred.

The use of statins in this high-risk primary prevention setting was not associated with a statistically significant reduction in the risk of all-cause mortality.

Conclusion: This literature-based meta-analysis did not find evidence for the benefit of statin therapy on all-cause mortality in a high-risk primary prevention set-up.

BACKGROUND FROM DAN MURPHY:

LDL-C means low density lipoprotein cholesterol. This is the "bad" cholesterol because it can plaque on the arterial wall. Ideally, it should measure less then 100 mg/dL. High is over 130 mg/dL.

In 2007, the *New England Journal of Medicine* published the JUPITER study. This study claimed that individuals with low cholesterol but high levels of inflammation [high sensitivity C-Reactive protein {hs-CRP}] could "significantly reduce all-cause mortality by 20%" by taking statin drugs. However, other studies have "questioned these findings as a chance or exaggerated observation."
[Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207].

Therefore, these authors analyzed 11 randomized controlled trials involving a total of 65,229 participants to provide the most robust information to assess whether statins reduce all-cause mortality. All of the participants had high cholesterol, but **none** of them had cardiovascular disease. The study represented about 244,000 person-years of follow-up.

Statin drugs are commonly prescribed for two groups of patients:

Group I	**Group II**
Those that have established cardiovascular disease	**Those that do not have cardiovascular disease, but do have high cholesterol levels**
It is thought that statins for this group will prevent atherosclerosis and subsequent heart attack	**It is thought that statins for this group will prevent cardiovascular disease and heart attack**

KEY POINTS FROM DAN MURPHY

1) Some researchers have questioned the benefits of statins among individuals without cardiovascular disease, noting there is little evidence for reductions of all-cause mortality, and the potential to cause "serious unrecognized harm."

2) These authors assessed the effect of statin therapy (compared with placebo) on all-cause mortality in individuals who did **not** have cardiovascular disease. They used 65,229 subjects and a follow-up period of 3.7 years:

Placebo Group	**Statin Group**
# of participants: 32,606	# of participants: 32,623
# of deaths: 1,447	# of deaths: 1,346
LDL Cholesterol level: 134 mg/dL	LDL Cholesterol level with statins: 94 mg/dL
Death rate: 4.44%	Death rate: 4.13%

3) Taking statin drugs lowered LDL-C by 40 mg/dL compared to the placebo group. This lowered the death rate by .31% (4.44% - 4.13%). The authors considered such a small reduction in death to be nonsignificant.

4) "This literature-based meta-analysis of 11 clinical trials involving 65,229 participants with approximately 244,000 person-years of follow-up and 2,793 deaths provides more reliable evidence than previously available on the impact of statin therapy on all-cause mortality among high-risk individuals without prior CVD. These data indicate that over an average treatment period of 3.7 years, the use of statin therapy did not result in reduction in all-cause mortality."

5) "There were on average an estimated 7 fewer deaths for every 10,000 person-years of treatment" with statin drugs.

6) "Our meta-analysis was based on data from only those individuals without clinically manifest CVD, including previously unpublished data, thus providing the most reliable effect estimates about the effect of statins in this population."

7) "The present data suggest that the all-cause mortality reduction of 20% reported in JUPITER is likely to be an extreme and exaggerated finding as often occurs when trials are stopped early, hence, indicating that more liberal use of potent statin regimens, particularly in the setting of lower risk primary prevention subjects, is unlikely, at least in the short term, to have a major impact on all-cause mortality reduction."

8) Fibrates are drugs that primarily lower triglyceride levels. A 2007 meta-analysis of randomized controlled trials published in the *American Heart Journal* "showed that despite a significant reduction in nonfatal myocardial infarction, all-cause mortality was approximately 7% higher among individuals randomized to a fibrate."

9) "In conclusion, based on aggregate data on 65,229 men and women from 11 studies, yielding approximately 244,000 person-years of follow-up and 2,793 deaths, we observed that statin therapy for an average period of 3.7 years had no benefit on all-cause mortality in a high-risk primary prevention population."

10) "There is no evidence that prescribing cholesterol-lowering drugs known as statins to patients at risk of heart disease reduces their chances of premature death in the short term."

11) "There is little evidence that statins reduce the risk of dying from any cause in individuals without heart disease."

12) People taking statin drugs may have higher risks of liver dysfunction, kidney failure, muscle weakness and cataracts.

13) "While low-density lipoprotein (LDL), or 'bad' cholesterol levels, were higher among those taking placebo than those taking statins (134 milligrams per deciliter versus 94 milligrams per deciliter), this had no effect on the risk of premature death."

COMMENTS FROM DAN MURPHY

The number needed to treat (NNT) is an epidemiological measure used to assess the effectiveness of a health-care intervention. The NNT is the number of patients who need to be treated in order to prevent one additional bad outcome. The ideal NNT is 1, where everyone improves with treatment and no one improves with placebo or in the control group. The higher the NNT, the less effective is the treatment.

NNT values are time-specific. A study's NNT would be multiplied by the number of years of the study. For example, if a study ran for 3.7 years and it was found that the NNT was 321 during this 3.7-year period, in one year the NNT would have to be multiplied by 3.7 to correctly assume the right NNT for only the one-year period (in the example the one year NNT would be 1,188).

Even though NNT is an important measure in a clinical trial, it is infrequently included in medical journal articles reporting the results of clinical trials.

In this study, the Number Needed to Treat (NNT) was 321 over a period of 3.7 years. The one-year NNT was 1,188:

1) This means for a period of 3.7 years for every 321 people taking a statin drug only one is benefited, and 320 are not benefited, although they are spending about $1000/year on the drugs, and often experiencing numerous side effects.

2) This means for a period of 1 year for every 1,188 people taking a statin drug only one is benefited, and 1,187 are not benefited.

One can calculate the NNT using a calculator, or there are web pages that will do it for you by plugging in the numbers, such as www.graphpad.com, or just Googling "Number Needed to Treat" or "NNT."

In the end, the consumer is paying for all of this, either through taxes (the government pays), or health insurance premiums, or cash.

Cholesterol Lowering, Cardiovascular Diseases, and the Rosuvastatin-JUPITER Controversy: A Critical Reappraisal

Archives of Internal Medicine
June 28, 2010, Volume 170, Number 12, pp. 1032-1036

Michel de Lorgeril, MD; Patricia Salen, BSc; John Abramson, MD; Sylvie Dodin, MD; Tomohito Hamazaki, PhD; Willy Kostucki, MD; Harumi Okuyama, PhD; Bruno Pavy, MD; Mikael Rabaeus, MD

FROM ABSTRACT:

Background: Among the recently reported cholesterol lowering drug trials, the JUPITER (Justification for the Use of Statins in Primary Prevention) trial is unique: it reports a substantial decrease in the risk of cardiovascular diseases among patients without coronary heart disease and with normal or low cholesterol levels.

Methods: Careful review of both results and methods used in the trial and comparison with expected data.

Results: The trial was flawed. It was discontinued (according to pre-specified rules) after fewer than 2 years of follow-up, with no differences between the 2 groups on the most objective criteria.

Clinical data showed a major discrepancy between significant reduction of nonfatal stroke and myocardial infarction but no effect on mortality from stroke and myocardial infarction.

The possibility that bias entered the trial is particularly concerning because of the strong commercial interest in the study.

Conclusion: The results of the trial do not support the use of statin treatment for primary prevention of cardiovascular diseases and raise troubling questions concerning the role of commercial sponsors.

BACKGROUND FROM DAN MURPHY

Most (maybe 80-90%) of the cholesterol in the blood is made by one's own liver. The liver makes cholesterol from glucose (sugar). The number of separate enzymatic steps required to convert sugar into cholesterol is 32 (my count from a biochemistry text). Statin drugs block the process by inhibiting the enzyme between the third and fourth steps. Consequently, statin drugs have become the most popular drug for lowering blood cholesterol levels.

C-reactive protein is an enzyme found in the blood. It is a non-specific marker for inflammation. Elevated levels of C-reactive protein have been have been linked to

increased risk of heart disease. Dr. Paul Ridker has been the leading advocate of having one's C-reactive protein checked.

The JUPITER (Justification for the Use of Statins in Primary Prevention) study was published in the New England Journal of Medicine in November 2008. In this study, patients with high C-reactive protein levels but with no heart disease and with normal levels of cholesterol showed a substantial decrease in the risk of cardiovascular disease if they took the statin drug Rosuvastatin [Crestor].

Because of the JUPITER study, physicians have been putting thousands of patients on statin drugs when they have normal cholesterol levels but high levels of C-reactive protein.

Paul Ridker, MD, is the primary author of the JUPITER study. Paul Ridker is also the co-holder of the patent on the test for C-reactive protein, apparently making money each time the test is performed.

Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195-2207.

These authors critically review the JUPITER study and its controversies.

THESE AUTHORS ALSO NOTE:

1) Nine recent studies do NOT show that taking statin drugs reduce morbidity or mortality from coronary heart disease.

2) The JUPITER (Justification for the Use of Statins in Primary Prevention) study is the one exception study that shows that taking a statin drug will reduce cardiovascular disease, even if cholesterol levels are normal.

3) The JUPITER study has "undoubtedly propelled many healthy persons without elevated cholesterol levels onto long-term statin treatment."

4) In the March 2008, meeting of the American College of Cardiology, the JUPITER study authors announced that they were prematurely discontinuing the study because of its excellent results. The drug companies immediately began a marketing blitz of the JUPITER outcomes to enhance sales. (AstraZeneca is the drug company that makes Crestor).

5) The JUPITER trial was inappropriately prematurely terminated because the authors did not follow the well-accepted early stopping rules for clinical trials.

6) The chairman of the board for the early termination of the JUPITER study is heavily financially supported by the statin drug industry, "raising issues of conflict of interest."

7) There was no difference in the incidence of serious adverse events (total hospitalizations, prolongations of hospitalizations, cancer, and permanent disability) between the 2 groups. (JUPITER group and placebo group)

8) "A close examination of the all-cause mortality curves shows that the curves were actually converging when the trial was ended, suggesting that the borderline significant difference between groups may have disappeared in case of a slightly longer follow-up. Strangely, in a subsequent article [written solely by Paul Ridker] that was apparently written to defuse the controversy, the all-cause mortality curves were truncated so that the previous converging portion was no longer displayed."

9) The "unequivocal reduction in cardiovascular mortality" was announced in March 2008 as the main justification for the premature trial termination, the "absence of cardiovascular mortality data in the published article is striking."

10) Numerous clinical inconsistencies in JUPITER "suggests a major flaw in the study."

11) One figure in JUPITER implies that the use of rosuvastatin [Crestor] tripled the case-fatality rate.

12) Sudden cardiac death (death occurring within 1 hour after the first symptoms of heart attack) is the simplest and most reliable diagnosis in cardiology; it usually represents about 65% to 70% of total cardiac mortality. Yet, the JUPITER trial did not report on sudden cardiac death. "The way sudden cardiac death is reported—or not reported—may be a good indicator of the quality of the methods used in a trial."

13) "There is no significant difference in cardiovascular mortality between the 2 groups in the JUPITER trial."

14) The JUPITER data appears to be biased; three other trials involving rosuvastatin (Crestor) therapy in high-risk patients did not show any cardiac protection. "The authors of the JUPITER study fail to comment on these negative trials."

15) The significant increase in new diagnoses of diabetes among patients taking rosuvastatin was barely mentioned by the JUPITER authors.

16) "The JUPITER trial involved multiple conflicts of interest. It was conducted by a sponsor with obvious commercial interests."

17) Nine of 14 authors of the JUPITER article have financial ties to the sponsor (AstraZeneca).

18) The principal investigator of the JUPITER study has a personal conflict of interest as a co-holder of the patent for the C-reactive protein test.

19) The JUPITER study sponsor's [AstraZeneca] own investigators controlled and managed the raw data, which is suspect and inappropriate.

20) "The results of the JUPITER trial are clinically inconsistent and therefore should not change medical practice or clinical guidelines."

21) "The results of the JUPITER trial support concerns that commercially sponsored clinical trials are at risk of poor quality and bias."

22) "Documentation of the failure of the JUPITER trial to demonstrate a protective effect of rosuvastatin is all the more important as it occurred in the context of the failure of more than 12 other cholesterol-lowering trials published in recent years and in various clinical settings. None of these trials provided significant evidence of protection against CHD complications—especially fatal complications—by cholesterol lowering." "These failures strongly suggest that the presumed preventive effects of cholesterol lowering drugs have been considerably exaggerated."

23) "The time has come for a critical reappraisal of cholesterol-lowering and statin treatments for the prevention of CHD complications."

24) "The emphasis on pharmaceuticals for the prevention of CHD diverts individual and public health attention away from the proven efficacy of adopting a healthy lifestyle, including regular physical activity, not smoking, and a Mediterranean-style diet."

25) These authors conclude that JUPITER is "flawed" as it was discontinued after fewer than 2 years of follow-up, and there was no difference between the 2 groups on the most objective criteria. Clinical data showed no effect on mortality from stroke and myocardial infarction between the 2 groups.

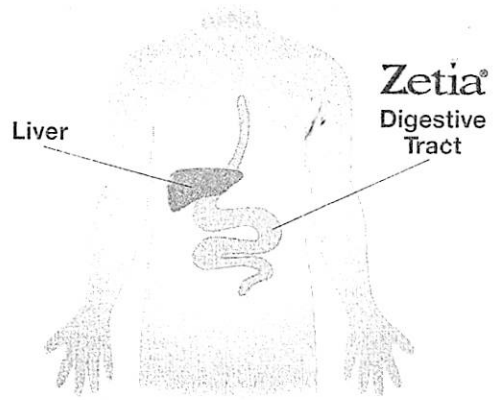
26) "The possibility that bias entered the trial is particularly concerning because of the strong commercial interest in the study."

27) "The results of the trial do not support the use of statin treatment for primary prevention of cardiovascular diseases and raise troubling questions concerning the role of commercial sponsors."

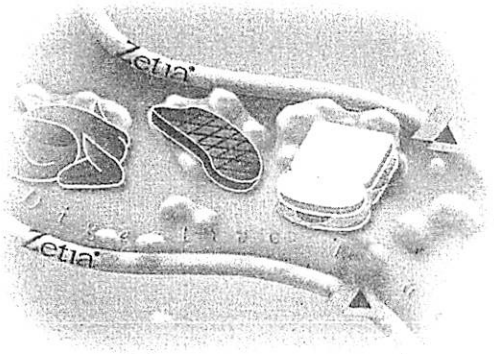
NEWSWEEK 7-21-08

GET THE STORY ON A DIFFERENT WAY TO LOWER CHOLESTEROL.

The most common cholesterol-lowering medicines, statins, are a good option. ZETIA is different.



Statins work mainly with the liver. ZETIA works in the digestive tract, as do some other cholesterol-lowering medicines.



But ZETIA is unique in the way it helps block the absorption of cholesterol that comes from food. Unlike some statins, ZETIA has not been shown to prevent heart disease or heart attacks.

A healthy diet and exercise are important, but sometimes they're not enough to get your cholesterol where it needs to be. Ask your doctor if ZETIA is right for you.

Important Risk Information About ZETIA: ZETIA is a prescription medicine and should not be taken by people who are allergic to any of its ingredients. If you have ever had liver problems, are nursing or pregnant or may become pregnant, a doctor will decide if ZETIA alone is right for you.

Unexplained muscle pain or weakness could be a sign of a rare but serious side effect and should be reported to your doctor right away. Common side effects included stomach pain and feeling tired. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please read the Patient Product Information on the adjacent page.

Zetia®
(ezetimibe) Tablets
A different way to help fight cholesterol

Merck/Schering-Plough Patient Assistance Program
To find out if you qualify, call 1-800-347-7503.

MERCK / Schering-Plough Pharmaceuticals

For more information, call 1-800-98-ZETIA or visit zetia.com.

IF YOU HAVE HIGH CHOLESTEROL,

YOU MAY BE AT RISK FOR ATHEROSCLEROSIS.

Atherosclerosis is the progressive buildup of plaque in arteries over time.

FOR ILLUSTRATIVE PURPOSES ONLY

Time
10-20-08

Talk to your doctor about high cholesterol and the risk for plaque buildup in your arteries.

These three important facts may help start the conversation.

- Plaque buildup in arteries is a progressive disease called atherosclerosis that can start in early adulthood
- High cholesterol, family history of early heart disease, diabetes, and high blood pressure may play a role in the buildup of plaque
- CRESTOR® (rosuvastatin calcium), along with diet, ▼ lowers bad cholesterol and ▲ raises the good. And CRESTOR is approved to slow the progression of atherosclerosis in adults as part of a treatment plan to lower cholesterol to goal

Talk to your doctor – and find out if it's time for CRESTOR.

Important Safety Information about CRESTOR:
In adults, CRESTOR is prescribed along with diet for lowering high cholesterol. CRESTOR is also prescribed along with diet to slow the progression of atherosclerosis (the buildup of plaque in arteries) as part of a treatment plan to lower cholesterol to goal. CRESTOR has not been determined to prevent heart disease, heart attacks, or strokes.

CRESTOR is not right for everyone, including anyone who has previously had an allergic reaction to CRESTOR, anyone with liver problems, or women who are nursing, pregnant, or who may become pregnant. Your doctor will do blood tests before and during treatment with CRESTOR to monitor your liver function. Unexplained muscle pain and weakness could be a sign of a rare but serious side effect and should be reported to your doctor right away. The 40-mg dose of CRESTOR is only for patients who do not reach goal on 20 mg. Be sure to tell your doctor if you are taking any medications. Side effects occur infrequently and include headache, muscle aches, abdominal pain, weakness, and nausea.

Please read the important product information about CRESTOR on the adjacent page.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

If you can't afford your medication, AstraZeneca may be able to help.

IT'S TIME.™

800-CRESTOR CRESTOR.COM

CRESTOR® rosuvastatin calcium

AstraZeneca

Effect of Different Antilipidemic Agents and Diets on Mortality
A Systematic Review

Archives of Internal Medicine
April 11, 2005; pp. 725-730

Marco Studer, MD; Matthias Briel, MD; Bernd Leimenstoll, MD; Tracy R. Glass, MSc; Heiner C. Bucher, MD, MPH

[Statins, interrupt the formation of cholesterol in blood: Lipitor, Lescol, Mevacor, Pravachol, Crestor, Zocor]
[Fibrates, cholesterol-lowering drugs that primarily lower triglycerides: Lopid, Tricor]
[Resins, increase the disposal of cholesterol in intestines: Questran, Prevalite, Lo-Cholest, Colestid, Wel Chol]
FROM ABSTRACT:

Background:
We aimed to assess efficacy and safety of different lipid-lowering interventions based on mortality data.

Methods:
We conducted a systematic search of randomized controlled trials published up to June 2003, comparing any lipid-lowering intervention with placebo or usual diet with respect to mortality.

Outcome measures were mortality from all, cardiac, and noncardiovascular causes.

Results:
A total of 97 studies met eligibility criteria, with 137,140 individuals in intervention and 138,976 individuals in control groups.

KEY POINTS FROM DAN MURPHY:

1) This article found all randomized controlled trials through June 2003 that evaluated the effect on mortality by lowering blood lipids by various methods. A total of 97 studies were used with 137,140 individuals in intervention and 138,976 individuals in control groups. Consequently, this study has harvested the best available evidence on the topic and should be taken seriously.

2) Ironically, omega-3 essential fatty acids did the worse job at reducing blood cholesterol (mean of only 2% reduction), yet they did the best job at reducing death from all causes (mean of 23% reduction) and death from heart problems (mean of 32% reduction).

3) Statin drugs did the best job at lowering cholesterol levels (mean of 20% reduction). Statin drugs were 10 times more effective in lowering blood cholesterol

than were omega-3 fatty acids (20% v. 2% reduction). Yet, omega-3 fatty acids were 44% more effective than statin drugs in reducing death from cardiac events and 32% more effective than statin drugs in reducing death from all reasons.

4) Statin drugs reduced cardiac deaths by a mean of 22%.
Omega-3 fatty acids reduced cardiac deaths by a mean of 32%.

5) Statin drugs reduced all deaths by a mean of 13%.
Omega-3 fatty acids reduced cardiac deaths by a mean of 23%.

6) Omega-3 fatty acids lower cholesterol levels to a very small extent, which indicates that their beneficial effects are mediated by other means, such as their antiarrhythmic properties, their membrane stabilizing effects, as well as their antithrombotic and anti-inflammatory properties.

COMMENTS FROM DAN MURPHY

This study offers the best proof in history that the problem is not cholesterol. Omega-3 fatty acids proved to be significantly more effective at reducing all deaths and in particular cardiac deaths, yet they reduced cholesterol very little. Statin drugs make tens of billions of dollars for drug companies yearly, are very expensive for the consumer and for the government (taxpayers) beginning in 2006, and are associated with numerous serious side effects. Omega-3 fatty acids work significantly better than statin drugs (proved by this article), are significantly less expensive, and have no side effects. Plus, we have seen numerous articles that prove that omega-3s benefit the brain, the immune system, and the joints.

According to Ray Moynihan, in Selling Sickness, How the World's Biggest Pharmaceutical Companies are Turning us all into Patients, Nation Books, 2005, page 1, cholesterol-lowering drugs "generate revenues of more than $25 billion a year for their manufacturers."