

LE Magazine November 2004

REPORT

Novel Dietary Supplement Shows Dramatic Effects in Lowering Cholesterol, LDL, and Triglycerides

By Jim English

According to the federal Centers for Disease Control and Prevention, 61 million Americans currently suffer from cardiovascular disease. Cardiovascular disease covers a broad spectrum of disorders, including high blood pressure, coronary heart disease (heart attack and chest pain), stroke, congestive heart failure, and birth defects of the heart and blood vessels.

Every year, heart attacks and stroke cause more than 930,000 deaths in the US, accounting for 40% of deaths from all causes and making cardiovascular disease the nation's number-one killer. While cardiovascular disease primarily kills people aged 65 and older, the incidence of sudden death from heart disease is rising in people aged 15 to 34.¹

Reducing serum cholesterol levels—especially low-density lipoprotein (LDL)—is an effective, well-established strategy for preventing cardiovascular disease and reducing coronary events and mortality.^{2,3} Unfortunately, a recent report in the journal *Circulation* found that between 1988 and 2000, average total serum cholesterol concentrations in the US population declined by only 1%.⁴ And while 91% of those surveyed by the American Heart Association (AHA) felt it was “important to them personally to have a healthy cholesterol level,” fewer than 50% knew their own cholesterol levels, and 53% either did not know or overestimated the recommended cholesterol levels for a healthy adult.⁵

Compounding the problem, only a fraction of those at risk for cardiovascular disease are using pharmaceutical and nutritional strategies known to reduce cholesterol levels. According to estimates based on data gathered from the National Health and Nutrition Examination Survey III (NHANES III), only 6.6% of the 21.1 million Americans eligible for cholesterol-lowering drug therapy under National Cholesterol Education Program (NCEP) guidelines were using such therapy.⁶ When researchers examined responses gathered from 13,990 patients, they discovered that fewer than 4% of those diagnosed with hypercholesterolemia (elevated cholesterol) were taking vitamins or supplements known to reduce cholesterol.⁷

Concerned with the persistent failure of conventional strategies to significantly improve cholesterol profiles and reduce the incidence of cardiovascular disease, a broad coalition of medical researchers and scientists is now calling for a massive increase in the use of cholesterol-lowering drugs, particularly the family of pharmaceuticals known as statins.⁸

Unfortunately, the statin drugs, while very effective, also have side effects that understandably compromise patient compliance. Additionally, statin drugs are expensive to use; depending on the drug and dosage, the cost of statin therapy ranges from \$63 to \$228 a month.⁹

A newly available, all-natural supplement has been shown in human studies to significantly lower cholesterol levels—particularly of LDL, triglycerides, and apolipoprotein B—thus helping to reduce the risk of developing cardiovascular disease. This supplement, called Sytrinol™, is an important option for health-conscious people seeking a safe, effective, and convenient way to lower cholesterol levels without the side effects and expense of drugs.

Cholesterol and Human Health

Cholesterol is a fatty (lipid) component found in virtually all cell membranes. In addition to supporting cellular integrity, cholesterol is also required for the transport of phospholipids and the biosynthesis of mineralocorticoids (aldosterone), glucocorticoids (cortisol), and sex hormones (progesterone, pregnenolone, testosterone, and estradiol). Far from endangering health, cholesterol is essential to life. In fact, Italian researchers have shown that when serum cholesterol levels are too low (less than 160 mg/dL), mortality in older adults actually increases.^{10,11}

LDL, popularly known as “bad cholesterol,” is the primary transporter of cholesterol in the blood. In atherosclerosis, LDL is taken up in lesions in endothelial cells lining the inner walls of blood vessels, forming deposits in the arterial walls. The deposited LDL undergoes modification, as free radicals oxidize LDL to form foam cells that create a thick, hard plaque.

Over time, plaque accumulation can constrict vessels, inhibiting blood flow and reducing the supply of oxygen reaching the heart,



brain, and other organs.¹² If a clot (thrombus) blocks an artery already restricted by plaque, blood and oxygen flow can be cut off entirely, leading to a heart attack (if the occlusion occurs in the heart) or a stroke (if it occurs in the brain).

HDL is commonly referred to as “good” cholesterol because it helps remove excess cholesterol from atherosclerotic deposits and retard the growth of new plaque. Low HDL levels have been shown to be an additional risk factor for increased mortality from coronary artery disease and strokes in the elderly.¹³

How the Body Manages Cholesterol Levels

While cholesterol levels can be modestly influenced by dietary modification about 80% of cholesterol does not come from dietary sources, but is synthesized by the liver.² The rate-limiting enzyme HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase controls the biosynthesis of cholesterol.

Normally, the liver regulates cholesterol levels via a biochemical feedback loop. When cholesterol levels are low, liver production of HMG-CoA reductase increases to speed biosynthesis of cholesterol. Conversely, when cholesterol levels are too high, the liver limits HMG-CoA reductase production to reduce cholesterol production. Proper functioning of this feedback mechanism is vital for the maintenance of healthy cholesterol levels.

Unfortunately, modern dietary habits (such as excess intake of saturated and trans fatty acids) and lifestyle contribute to the disruption of this system, leading to elevated cholesterol levels and increased risks for developing cardiovascular disease. Additionally, certain genetic disorders, such as familial hypercholesterolemia and autosomal recessive hypercholesterolemia, are known to increase LDL levels and risk for developing cardiovascular disease.¹⁴



Not All LDL Is Created Equal

To bind with other molecules for transport through the circulatory system, lipids rely on a specialized class of structural proteins, called apoproteins. LDL exists in two versions, differentiated by their protein components. The first, apolipoprotein A, consists of a large, “fluffy” protein called apoprotein A that is cardioprotective when bound to LDL. The second, apolipoprotein B, consists of a small, dense protein called apoprotein B that plays a major role in cardiovascular disease when bound to LDL. Apolipoprotein-B particles enable cholesterol to penetrate and lodge in vascular walls, an important step in initiating the formation of atherosclerotic plaque.¹⁵ Apo-lipoprotein B is the predominant form of apolipoprotein, and over 90% of all LDL cholesterol particles in the blood carry apolipoprotein B, making it an especially accurate (and convenient) marker for measuring the cholesterol-depositing capacity of blood.¹⁶⁻¹⁸

The importance of apolipoprotein B was highlighted in a report published in 2001 in the British medical journal *The Lancet*. In the AMORIS study, researchers evaluated cardiovascular markers in over 175,000 men and women over a period of five and a half years. In addition to conventional lipid markers, such as triglycerides, total cholesterol, and LDL:HDL ratios, the researchers also measured apolipoprotein-B levels. Their findings revealed that those with the highest ratios of apolipoprotein B to apolipoprotein A were at the greatest risk of dying from a heart attack.¹⁹

These findings were supported by a second study, published in 2003 in the journal *Circulation*. In the IRAS study, researchers again measured apolipoprotein-B levels in 1,522 individuals and compared them with an array of standard lipid markers (such as C-reactive protein, fibrinogen, and carotid artery intima-media thickness) to assess cardiovascular disease risks. They found that elevated apolipoprotein-B levels were strongly associated with cardiovascular disease, and concluded that apolipoprotein-B levels are a better predictor of vascular risk than are LDL levels.²⁰

Given the well-documented link between apolipoprotein B and cardiovascular disease, measuring apolipoprotein-B levels offers clinicians and patients a new, highly specific marker for assessing the precise level of LDL in serum and determining individual risk for developing cardiovascular disease.

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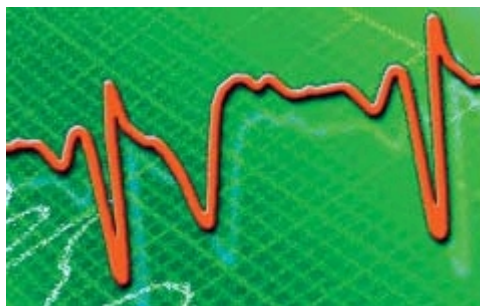
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Statin Drugs: the New Aspirin?

Due to the failure of previous public health programs to substantially lower cholesterol levels in the general population, medical researchers and health experts are seeking a new approach to better manage the problem. For the last decade, physicians and patients have relied on cholesterol guidelines published by the AHA. According to the AHA, a total cholesterol level of 200 mg/dL or less is considered optimal. Levels of 200-239 mg/dL are considered borderline high risk, and levels above 240 mg/dL are considered high risk.

In May 2001, the National Institutes of Health published new federal guidelines calling for aggressive expansion of the use of statin drugs to treat cholesterol.²¹ Statin drugs such as atorvastatin (Lipitor®), lovastatin (Mevacor®), pravastatin (Pravachol®), and simvastatin (Zocor®) are among the most potent lipid-lowering agents currently available.



Statins lower cholesterol levels by inhibiting the production of HMG-CoA reductase, resulting in a decrease in cholesterol synthesis in the liver. To compensate for the resulting reduction of cholesterol production, the liver begins to remove LDL circulating in the blood, further reducing overall LDL levels. Statin therapy has been proven to contribute to a decrease in cardiovascular disease morbidity and mortality in recent years, as documented in a number of controlled clinical trials.²² In addition to improvements in lipid profile, statins also appear to confer other benefits, including improved endothelial function, decreased platelet thrombus formation, improved fibrinolytic activity, and reduced frequency of transient myocardial ischemia.²³

Although statin therapy was initially used to treat patients suffering from severe hypercholesterolemia, health experts are now pushing to expand statin use to patients with only moderately elevated cholesterol. Moreover, health authorities have called for the use of statins to treat conditions such as diabetes, high blood pressure, high serum triglycerides, and low HDL, as well as for those with a strong family history of heart disease.

Most recently, in July 2004, the journal *Circulation* published an updated version of the NCEP guidelines, encouraging physicians to aggressively increase the use of statin drugs to lower cholesterol levels. In particular, the report recommends that target LDL levels be reduced from the current 100 mg/dL to 70 mg/dL in patients considered at high risk for a heart attack or death from cardiovascular disease. Additionally, patients at only moderate risk of a heart attack—those with heart disease, diabetes, or other risk factors—are now being encouraged to reduce their cholesterol levels by 30-40%.²⁴

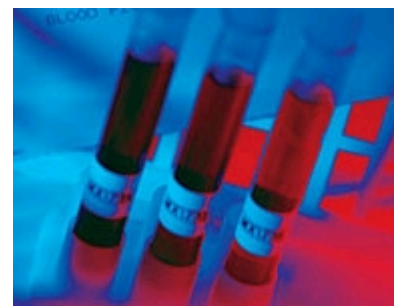
Not surprisingly, the new guidelines could dramatically increase the number of patients on statin drugs to as many as 50 million.²⁵ In an embarrassing oversight, the same government panel drafting the new guidelines failed to mention in its report that most of its panelists are linked to pharmaceutical companies that manufacture statin drugs. Six of the nine panelists had either received grants from or were paid consulting or speakers' fees by the companies that make some of the most popular statins, including Pfizer's Lipitor®, Bristol-Myers Squibb's Pravachol®, Merck's Mevacor®, and AstraZeneca's Crestor®.²⁶

Statins and Side Effects

While statin drugs effectively lower LDL, they also produce serious side effects. In 1990, Folkers theorized that inhibition of HMG-CoA reductase would also inhibit intrinsic biosynthesis of coenzyme Q10 (CoQ10), a central compound in the mitochondrial respiratory chain. Dr. Folkers' researchers stated, "If lovastatin were to reduce levels of CoQ10, this reduction would constitute a new risk of cardiac disease, since it is established that CoQ10 is indispensable for cardiac function."

When the researchers examined five hospitalized patients aged 43 to 72, they found that lovastatin did in fact cause CoQ10 levels to drop. Furthermore, the patients showed evidence of increased cardiac distress, a potentially life-threatening situation for patients hospitalized with class IV cardiomyopathy. The researchers concluded, "Although a successful drug, lovastatin does have side effects, particularly including liver dysfunction, which presumably can be caused by the lovastatin-induced deficiency of CoQ10."²⁷ Taking supplemental CoQ10 may potentially offset this side effect, but other, more serious side effects cannot be so easily resolved.

For example, rhabdomyolysis is a rare but potentially deadly condition that occurs when large numbers of skeletal muscle cells die. As the rapidly dying cells deteriorate, they release large quantities of muscle proteins into the bloodstream, quickly overwhelming the kidneys. An analysis of the Food and Drug Administration's side-effect registry, conducted in 2001 by the consumer watchdog group Public Citizen, discovered that statin drugs were linked to 72 fatal and 772 non-fatal cases of rhabdomyolysis between October 1997 and December 2000. In August 2001, pharmaceutical giant Bayer AG was forced to remove its statin drug Baycol® (cerivastatin) from the market after it was found to be responsible for killing at least 31 people.²⁸



More recently, an article in the June 26, 2004, issue of *The Lancet* raised concerns about the FDA's approval of one of the newest statin drugs, Crestor®, citing pre-approval evidence that the drug caused rhabdomyolysis. According to the author, Dr. Sidney Wolfe, director of Public Citizen's Health Research Group, Crestor® was approved despite an FDA claim that new cholesterol drugs would be approved only if they presented a comparable or lower risk of rhabdomyolysis than drugs already on the market.

According to Wolfe, patients taking Crestor® experienced severe muscle deterioration at higher rates than patients taking other cholesterol-lowering drugs. In fact, the incidence of post-marketing reports of rhabdomyolysis for Crestor® appears to exceed that of all other currently marketed statins. From its approval in August 2003 to mid-April 2004,¹⁸ patients using Crestor®, including 11 in the US, suffered severe muscle deterioration. In addition, eight cases of acute kidney failure and four cases of kidney insufficiency related to the use of Crestor® have been reported.²⁹

Unknown Long-Term Effects

While the cardioprotective benefits of statin drugs outweigh the known side effects, the most recent NCEP recommendations may result in tens of millions of new patients taking statins for a period of decades, and possibly for a lifetime. Unfortunately, data on the long-term use of statins are scant. In one paper published in the *Journal of the American Medical Association* in 1996, researchers set off a furious round of debate by raising the possibility of long-term statin use causing cancer. In the original paper, authors Newman and Hulley pointed out that all statin drugs have been shown to induce cancer in experimental lab rodents, and in some cases, the amount of statins causing cancer in the animals matched dosages being prescribed to humans. While conceding that extrapolating the incidence of cancer in rodents to humans is "an uncertain process," the authors wrote 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."³⁰ Interestingly, more recent studies indicate that statin drugs might actually reduce the incidence of certain cancers.³¹⁻³⁷

Another potentially serious long-term problem appeared in a case study initiated after several reports and a single epidemiological study suggested that statins cause damage to the peripheral nervous system. After reviewing patient records from 1994 to 1998, the authors verified diagnosis of idiopathic polyneuropathy in 166 patients receiving statin therapy for at least two years, concluding in their 2002 paper that "long-term exposure to statins may substantially increase the risk of polyneuropathy."³⁸

Healthy Options for Lowering Cholesterol

In their enthusiasm to reduce premature deaths from heart attack and strokes, the authors of the new cholesterol guidelines are recommending that millions of Americans start taking statin drugs. This recommendation ignores the danger of potential side effects from the long-term use of statins. Would informed health consumers willingly choose to lower their risk of cardiovascular disease if it meant substantially increasing their chances of developing health problems after a decade or two?

In a recent opinion piece published in the *Washington Post*, Dean Ornish, MD, clinical professor of medicine at the University of California, San Francisco, and president of the nonprofit Preventive Medicine Research Institute, wrote, "As tens of millions of people begin taking these medications for decades, more long-term side effects are likely to become apparent." Dr. Ornish also questioned why the panel failed to recommend other options, such as diet and lifestyle changes, that for most people "can be a safe and effective alternative to a lifetime of cholesterol-lowering drugs."³⁹

One of the newest and most effective alternatives to statin drugs is a patented, proprietary formula comprising citrus and palm fruit extracts that contain polymethoxylated flavones and tocotrienols. It has been shown in human trials to significantly reduce total cholesterol, LDL, and triglycerides. Additionally, the powerful antioxidant and anti-inflammatory properties of the extracts in this natural formulation (trademarked under the name Sytrinol™) are known to contribute to managing additional cardiovascular disease risk factors.

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Safety and Effects of Sytrinol™

Sytrinol™ was developed after 12 years of extensive research on the cardiovascular effects of polymethoxylated flavonoids and tocotrienols. The health benefits of Sytrinol™ have been demonstrated in in-vitro, in-vivo, and human clinical studies. Animal toxicity studies have shown that Sytrinol™ is well tolerated, with no toxic effects following consumption of polymethoxylated flavones in amounts of up to 1% of total dietary intake, or the equivalent of a 150-pound individual consuming almost 14 grams per day.



The cholesterol-lowering effects of Sytrinol™ were documented in a recent animal study published in the May 2004 issue of the *Journal of Agricultural and Food Chemistry*.

Canadian researchers first induced high blood levels of cholesterol in hamsters. The animals were then treated with either polymethoxylated flavonoids (tangeretin) or a combination of flavones (hesperidin and naringin). While the flavones were shown to lower cholesterol levels, the tangeretin formulation proved to be almost three times as effective. In hamsters receiving the tangeretin formula, total cholesterol declined by up to 27% and LDL was reduced by 40%. While HDL levels were unchanged, the net result was a significant improvement in the LDL:HDL ratio.⁷⁰

The cardioprotective and cholesterol-lowering claims for Sytrinol™ are also supported by human studies. Two early trials, each using 10 subjects, measured the effects of Sytrinol™ in men and women diagnosed with hypercholesterolemia and screened to eliminate thyroid disorders, kidney disorders, and diabetes. Subjects were instructed to maintain normal dietary habits and discontinue using vitamins, supplements, and cholesterol-lowering medications for at least six weeks before and during the study. Fasting blood samples were drawn at the onset and at the end of each four-week trial, and plasma lipid profiles and other metabolic parameters were analyzed using standard methods.

The results from the first trial (Table 1) show that four weeks of treatment with 300 mg of Sytrinol™ daily significantly reduced levels of total cholesterol (-25%), LDL (-19%), and triglycerides (-24%). HDL levels were unchanged and body mass remained relatively stable.

In the second trial, subjects with elevated cholesterol again benefited after only four weeks of treatment with 300 mg per day of Sytrinol™. As shown in Table 2, treatment with Sytrinol™ substantially cut levels of plasma total cholesterol (-20%), LDL (-22%), apolipoprotein B (-21%), and triglycerides (-28%). Additionally, subjects in the second trial benefited from a significant 5% increase in apolipoprotein A1, an important structural protein of HDL.

Sytrinol™ is currently being tested in a long-term, double-blind, crossover randomized study involving 120 men and women with moderately elevated cholesterol levels (total cholesterol above 230 mg/dL and LDL greater than 155 mg/dL). For 12 weeks, subjects will receive either 300 mg per day of Sytrinol™ or placebo, followed by a washout period of four weeks and another 12 weeks during which the groups receiving the active compound or placebo will be crossed over.

Only the first 12 weeks (phase 1) of the long-term study have been completed, yet already the results are compelling. As shown in Table 3, compared to placebo, the Sytrinol™ subjects saw reductions of 30% in total cholesterol, 27% in LDL, and 34% in total triglycerides. In addition, HDL levels increased 4%, resulting in a significant 29% reduction in the LDL:HDL ratio.

Table 1: Sytrinol™ Clinical Study I Results

Measured Endpoints	Treatment Group	Sytrinol™ Clinical Study I % Change at 4 weeks
Total Cholesterol	Sytrinol™	-25% ^b
LDL	Sytrinol™	-19% ^b
Triglycerides	Sytrinol™	-24% ^b
HDL	Sytrinol™	no change

Means ± SEM. Statistical analysis by ANOVA plus post test by Dunnett's method
b – Significantly different within same group, P ≤ 0.05 **Source:** SourceOne Global Partner

Table 2: Sytrinol™ Clinical Study II Results

Measured Endpoints	Treatment Group	Sytrinol™ Clinical Study II % Change at 4 weeks
Total Cholesterol	Sytrinol™	-20% ^b
LDL	Sytrinol™	-22% ^b
Triglycerides	Sytrinol™	-28% ^b
HDL	Sytrinol™	+3% ^b
Apolipoprotein A	Sytrinol™	+5% ^b
Apolipoprotein B	Sytrinol™	-21% ^b

Means ± SEM. Statistical analysis by ANOVA plus post test by Dunnett's method
b – Significantly different within same group, P ≤ 0.05 **Source:** SourceOne Global Partner

Table 3: Sytrinol™ Clinical Study III Results

Measured Endpoints	Treatment Group	Sytrinol™ Clinical Study III % Change at 4 weeks
Total Cholesterol	Sytrinol™	-30% ^b
LDL	Sytrinol™	-27% ^b
Triglycerides	Sytrinol™	-34% ^b
HDL	Sytrinol™	+4% ^b
LDL: HDL Ratio	Sytrinol™	-29% ^b

Means ± SEM. Statistical analysis by ANOVA plus post test by Dunnett's method
b – Significantly different within same group, P ≤ 0.05 **Source:** SourceOne Global Partner

Conclusion

Cholesterol management is a well-established means of maintaining health and preventing premature death from cardiovascular disease. Many people can maintain desirable cholesterol profiles by natural means, including lifestyle modifications, exercise, dietary strategies, and natural hormone replacement protocols. For those in need of additional cholesterol-lowering strategies, Sytrinol™ is an important new option that can help achieve substantial reductions in total cholesterol, LDL, and triglyceride levels, while improving the LDL:HDL ratio. Its lack of the side effects associated with statin drugs makes Sytrinol™ an especially attractive therapy for maintaining healthy cholesterol levels.

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