

WDDTY

Cholesterol lowering - The statin 'wonder' drugs

Statins are the new wonder drugs now used to prevent everything from heart disease to Alzheimer's. But new evidence from a Finnish doctor shows that statins don't lower cholesterol which, in any case, isn't the real culprit

In the late 1980s, the pharmaceutical companies introduced a new type of cholesterol lowering drug called the 'statins'. These drugs inhibit the body's production of many important substances, one of which is cholesterol.

Sold as Zocor (Zocord in the US), Mevacor, Pravachol, Lescol and Lipitor, these new drugs have received wide acclaim because of the substantial cholesterol reduction they achieve, without serious side effects. Whereas the earlier drugs could lower cholesterol by 15-20 per cent at most, the statins can lower cholesterol by 30-40 per cent or more.

As of January 2000, the results of five large scale, controlled, randomised, double blind studies involving more than 30,000 study participants and numerous angiographic trials have been published.

The 4S trial

In 1994, the results of a large multicentre trial, The Scandinavian Simvastatin Survival Study (4S) trial, were published (Lancet, 1994; 344: 1383-9). The results were noteworthy indeed. For the first time, a trial had succeeded in significantly lowering the risk of both fatal and non fatal coronary heart disease (CHD), and even total mortality.

The British Medical Journal proclaimed: "Lower patients' cholesterol now! There is no longer any doubt about the benefit and safety of treating hypercholesterolaemia in patients who have had a myocardial infarction" (BMJ, 1995; 310: 1280-1).

The results of the 4S trial were published in The Lancet on November 19 and, on the same day, presented at a press conference arranged by the manufacturer of simvastatin Merck Sharpe & Dohme. In the vigorous marketing that followed, simvastatin was heralded as "the missing link".

The study was performed in cooperation with 94 Scandinavian medical departments. The steering committee and monitoring staff also included employees from Merck, as they were the sponsors of the trial.

Altogether, 4444 men and women who had had a previous heart attack were treated-half with simvastatin and half with

a placebo. After 5.4 years, 8.5

per cent had died from a heart attack in the control group compared with 5 per cent in the treatment group. This improvement included men only; the number of women who had died from a heart attack was the same in both groups.

But there were other benefits. The number of non-fatal heart attacks had been lower-even more-from 22.6 per cent in the control group to

15.9 per cent in the simvastatin group, a gain of 6.7 per cent. Furthermore, the number of strokes was reduced significantly-from 4.3 per cent to

2.7 per cent.

LIPID

The most recent statin trial, cleverly named the Long-term Intervention with Pravastatin in Ischemic Disease study, or LIPID, included patients who had previous CHD with all stages of cholesterol levels. This was a logical approach because, if the statins can prevent cardiovascular disease whether cholesterol is high or low, then there is no reason to look at cholesterol levels at all.

This trial was conducted

by members of the National Health and Medical Research Council Clinical Trials Centre

at the University of Sydney, Australia, along with a team of

63 other researchers. Three of the co-workers came from the drug company Bristol-Myers Squibb, the makers of the trial drug.

After six years, total mortality was lowered significantly-by 14 per cent in the controls compared with 11 per cent in the treatment group. CHD mortality was lowered by 8.3 per cent in the controls and by 6.2 per cent in the treatment group. These effects were again more pronounced in men. In fact, the benefit to women

was much lower and not statistically significant.

In addition, although an effect was seen regardless of

the initial total or low-density lipoprotein (LDL) cholesterol levels, the effect in patients with LDL cholesterol levels below 135 mg/dL was not

statistically significant (N Engl

J Med, 1998; 339: 1349-57).

The wrong culprit

In their reports, the directors

of these trials cited LDL chol-esterol as an important risk

factor in CHD. But what these trials actually provide, in spite of the glowing reports they re-ceived in the press, is strong evidence that cholesterol levels do not matter.

In some trials, the statins were almost as effective in women as they were in men. Indeed, in the CARE trial (see box on p 4), the effects were more pronounced in the fe-male sex, although almost all studies have shown that high cholesterol is not a risk factor

in women.

Second, the elderly were protected as much as younger individuals, although all studies have shown that high cho-lesterol is only a weak risk factor, if at all, in men over 50.

Third, the number of strokes was reduced after statin treatment, although all studies have shown that high cholesterol is, at best, a weak risk factor for stroke.

Fourth, patients who had suffered a heart attack were protected, even though most studies have shown that high cholesterol is a weak risk factor, if at all, in those who have already had a heart attack (Am J Med Sci, 1964; 247: 145-55).

Furthermore, the statins protected against CHD whether cholesterol was high or low, even though most studies have shown that normal or low cholesterol is not a risk factor for CHD.

Most important, there was no association between the degree of cholesterol lowering and the outcome. The risk of having a heart attack was reduced by the same degree regardless of whether the cholesterol level was lowered by a large or small amount.

This phenomenon is called 'lack of exposure response' and is a strong indication that the factor under investigation is not the true cause, but secondary to the real cause.

So, why are the statins effective in individuals for whom cholesterol is not a risk factor? And why is it that the effect of the statins does not depend on how much they lower blood cholesterol? If the cholesterol level is not a risk factor

for CHD in these people, why should a reduction of that cholesterol improve their chances of avoiding a heart attack? If the level of our blood cholesterol is as important as we have been told it is for so many years, then why doesn't it matter whether we lower it by large or small amounts?

The only reasonable explanation is that the statins do more than just lower cholesterol. There is strong evidence to show exactly that.

The statins inhibit the body's production of a substance called mevalonate, a precursor of cholesterol. When the production of mevalonate goes down, less cholesterol is produced by the cells, and blood cholesterol goes down as well.

But mevalonate is a precursor of other substances as well, substances that have important biological functions (Toxicol Lett, 1992; 64/65: 1-15). Although the metabolic pathways are not known in all of its details, reduced amounts of mevalonate may explain why simvastatin makes smooth muscle cells less active (Atherosclerosis, 1992; 95: 87-94) and platelets less inclined to produce thromboxane (Circulation, 1992; 85: 1792-8). One of the first steps

in the process of atherosclerosis is the growth and migration of smooth muscle cells inside the artery walls, and thromboxane is a substance that is necessary for blood to clot.

By blocking the function of smooth muscle cells and platelets, simvastatin may benefit cardiovascular disease by at least two mechanisms, both of which are independent of cholesterol levels. In one experiment by Japanese researcher Dr Yusuke Hidaka and his team, the inhibitory effect of simvastatin on muscle cells could not be abolished by adding LDL cholesterol to the test tubes (Atherosclerosis, 1992; 95: 87-94) and, in experiments that compared the statins with several different cholesterol-lowering agents, thromboxane production was inhibited only by the statins, indicating that the effect was not due to cholesterol reduction itself, but to something else (Circulation, 1992; 1792-8).

The protective effects of simvastatin were also demonstrated in animal experiments. In one such study by Dr B.M. Meiser and colleagues in Munich, Germany, hearts were transplanted into rats (Transpl Proc, 1993; 25: 2077-9). Normally, the function of such grafts gradually deteriorates because the coronary vessels become narrowed by an increased growth of smooth muscle cells in the vessel walls. This condition is called graft vessel disease, a condition with many similarities to early atherosclerosis.

In Dr Meiser's experiment, however, rats that received simvastatin had considerably less graft vessel disease than control rats, which did not receive simvastatin, and this was not

due to cholesterol reduction because simvastatin has been shown not to lower cholesterol in rats. In fact, LDL cholesterol was highest in the rats that received simvastatin.

In another experiment, Dr Maurizio Soma and his colleagues in Milan, Italy, placed a flexible collar around one of the carotid arteries in rabbits (Atherosclerosis, 1993; 25: 2077-9). After two weeks, the arteries with collars were narrowed, but less so if the rabbits had received simvastatin. Again, the effect was not related to the rabbits' cholesterol levels.

Thus, the statins in some way protect against cardiovascular disease, but their effect is not due to cholesterol reduction. The proponents of the cholesterol hypothesis have simply had incredible luck in finding a substance that prevents cardiovascular disease and, at the same time, lowers cholesterol.

Statistical manipulation

But why bother about pharmacological mechanisms. Isn't it wonderful that the statins work? Should we all be taking statins?

To answer that question, it is necessary to look at the figures from the

trials. Coronary mortality in these studies was lowered by 19 per cent to 41

per cent-most in the 4S trial and least

in the CARE trial. These are the so-called relative risk figures, used by most doctors and by the drug companies in their ads, which reflect the probability or

likelihood of death due to CHD.

But let's also look at the absolute figures, the 'percentage points', the actual numbers of people who die because of CHD. In this case, it is evident that death from a heart attack was prevented in only a small number of treated individuals. This figure was highest in the trials that included patients with CHD, but was only a trivial 0.12 per cent in the AFCAPS/TexCAPS trial, which included healthy individuals with normal cholesterol levels.

Put another way, the chances of not dying from a heart attack over four to six years for patients with CHD and high cholesterol is about 92 per cent without treatment and increases to 95 per cent with statin treatment.

For healthy individuals, the figures are even less impressive. In the WOSCOP trial, for instance, the chances of not dying from a heart attack during the five years of the study was 98.4 per cent without treatment and 98.8 with treatment. In the AFCAPS/TexCAPS trial, the chances of surviving was 99.55 per cent without treatment and 99.67 with treatment.

Let's compare these figures with another kind of treatment-for instance, treatment of urinary tract infections. Nine out of ten patients with a urinary tract infection will recover immediately if treated with an antibiotic for a few days and at the cost of a few dollars for each treatment. But, in the 4S trials, 289 patients had to be treated for five

years to prevent one fatal heart attack.

So, while one of the patients benefited from the treatment, the others took the drug in vain because they would have survived anyway. To prevent one fatal heart attack in healthy people, 235 individuals with high cholesterol and 826 with normal cholesterol would have to take a statin drug for four to five years.

The implications of such reasoning is that, to add as many years as possible to longevity, more than half of mankind should be taking a statin drug every day from an early age to the end of life.

Statin and cancer

In 1996, Drs Thomas Newman and Stephen Hulley, from San Francisco, published the results of a meticulous review of what we currently know about cancer and cholesterol-lowering drugs. They found that clofibrate, gem-fibrozil and all the statins stimulate cancer growth in rodents (JAMA, 1996; 275: 55-60).

Newman and Hulley asked themselves how it was that these drugs had been approved by the Food and Drug Administration at all. The answer was that the dosages used in the animal experiments were much higher than those recommended for clinical use. But, as Newman and Hulley commented, it is more relevant to compare blood levels of the drug. Their review showed that the blood levels that caused cancer in rodents were close to those seen in patients taking the statin drugs.

Because the latent period between exposure to a carcinogen and the incidence of clinical cancer in humans may be 20 years or more, the absence of any controlled trials of this duration means that we do not know whether statin treatment will lead to an increased rate of cancer in the coming decades.

Thus, millions of healthy people

are being treated with medications, the ultimate effects of which are not yet known. Newman and Hulley therefore recommended that the new statins be used only for patients at very high risk of CHD and avoided for those with life expectancies of more than 10-20 years. Healthy people with high cholesterol as their only risk factor belong to the latter category. Yet, these are the very people targeted for cholesterol-lowering drugs.

In the CARE study, breast cancer was indeed more common among those who took the drug than in the control group. In the treatment group, 12 women developed breast cancer during the trial whereas there was only one case in the control group, a difference that is highly statistically significant.

The authors of the CARE report were eager to explain away the increased

frequency of breast cancer, terming it

an 'anomaly'. It is possible that they are right, since the expected number of breast cancer cases, as calculated from the frequency normally seen in the general population, should have been five cases. Nevertheless, 12 is more than twice as many as five.

The gain in the numbers of fatal heart attacks was 1.1 per cent whereas the loss in numbers of breast cancers was 4.2

per cent. Calculated in the way that trial directors usually do-as relative, rather than absolute, risk-the difference was even more striking, with 12 per cent fewer attacks, but 1500 per cent more breast cancer. (However, side-effects are never calculated in this way-only positive effects.)

The number of side-effects has tremendous importance when it comes to assessing preventative treatment as the number of patients experiencing side-effects easily exceeds the number of prevented heart attacks. Unfortunately, this fact is often ignored or-worse-hidden by using the concept of relative risk to make positive effects seem larger than they are while

citing side-effects in absolute numbers.

The cholesterol myth

and where it came from

In 1953, Ancel Keys, director of the Laboratory of Physiological Hygiene at the University of Minnesota, published a paper that served as an early kickoff for the cholesterol campaign. According to Dr Keys, high-fat food was the culprit. His proof was a diagram, published in 1953, which showed a close correlation between the total intake of fat and the death rates from CHD in six countries. But why did Dr Keys limit his data to a mere six countries when, at that time, information was available from 22 countries?

The reason is that, if all of the countries were included, the association became rather weak. The death rate from CHD in Finland, for instance, was seven times that of Mexico, although fat consumption in the two nations was almost the same.

To prove his idea about dietary fat, Dr Keys organised a study of CHD

in seven countries (Circulation, 1970; suppl 1: 1-211). He selected 16 local populations in the Netherlands, Yugoslavia, Finland, Japan, Greece, Italy

and the US. The conclusion drawn from this gigantic project was that the factor most likely to predict the number of heart attacks in a country was the amount of animal fat consumed by the people of that country. Yet, no association was found with the total fat consumption, in striking contrast to Keys' previous study.

But within the individual countries, the number of heart attacks showed no correlation with diet. For instance, two districts of Finland had strikingly different heart disease and death rates, but virtually identical diets.

Other population studies have the same flaws. In the US, CHD mortality increased about 10 times between 1930 and 1960, levelled off during the 1960s and has since decreased slowly. During the decline of CHD mortality, the consumption of animal fat declined also but, during the 30 years of sharply rising CHD mortality, the consumption of animal fat decreased (Am J Clin Nutr, 1964; 14: 169-78).

In the town of Framingham, Massachusetts, the number of fatal heart attacks went down during the decline of animal fat consumption, but the number of non-fatal heart attacks increased during the same period (N Engl J Med, 1990; 322: 1635-41).

In England, the intake of animal fat has been relatively stable since at least 1910, whereas the number of heart attacks increased 10 times between 1930 and 1970 (Lancet, 1957; ii: 155-62).

The most we can say for the many studies that have been performed to test the diet-heart hypothesis is that there is a weak association between

the CHD mortality in various countries and the amount of fat available for them to eat, but no difference between the amount of fat eaten by coronary patients and by healthy individuals.

Such discrepancies clearly indicate that fat is not a causal factor. Usually, the common denominator in countries where people eat lots of high-fat food

is prosperity. In prosperous countries, high-fat foods are abundant, but so

are stress-provoking factors. Also, more people smoke, fewer people perform manual labour, industrial pollution of the environment is often worse and the ability to diagnose CHD is

better.

In Framingham, a small town near Boston, a large number of citizens have taken part in a study since the early 1950s surveying all the factors that may play a role in the development of atherosclerosis and heart disease. Among other things, their blood cholesterol levels have been measured frequently.

After five years, the researchers observed what has become one of the cornerstones of the diet-heart connection. When they divided the participants into three groups of low, medium and high cholesterol values, they observed that, in the

lattermost group, more had died from a heart attack than in the two other groups. This must mean, they reasoned, that high cholesterol is a risk factor for CHD.

In the study, they showed that, on average, one per cent of all men with high cholesterol died each year during the 30 years of follow-up. During the first 10 years, about a quarter of one per cent of

the total died each year. Women with low cholesterol died equally as often as did women with high cholesterol. Among those with the lowest cholesterol values, only half as many died.

But these figures covered all causes of death. The researchers said nothing about death from heart disease. And heart mortality was the main issue of the project.

Furthermore, for men above age 47, cholesterol levels made no difference. Those who had low cholesterol at the age of 48 died just as often as those with high cholesterol. Blood cholesterol is usually at its highest at about age 50. It is after this age that heart attacks usually appear, increasing in frequency year by year. But few die from a heart attack before age 48, and most of those who do are diabetics or have a rare genetic component. More than 95 per cent of all heart attacks occur in people over 48. If cholesterol has no correlation with heart disease after 48, it cannot be associated with heart attacks in the majority.

Even more damning, the study showed that low cholesterol levels were associated with greater mortality and that people with low cholesterol levels were dying of other diseases.

The Framingham findings are not

a rare exception. High cholesterol has no importance in Australian men over 74, according to an Australian study (*Atherosclerosis*, 1995; 117: 107-18). A New York study also found that neither total

nor LDL cholesterol predicted the risk of

a heart attack or any other cardiovascular diseases in very old men (*Arteriosclerosis*, 1992; 12: 416-23). Indeed, in the elderly, high cholesterol may even be protective. In one New York study, about twice as many individuals with low cholesterol had

a heart attack or died from one compared with those with the highest cholesterol levels (*JAMA*, 1994; 272: 1335-40).

In France, a team of researchers found that old women with very high cholesterol live the longest. The death rate was more than five times higher for women who had very low cholesterol, and the report actually warned against lowering cholesterol in elderly women (*Lancet*, 1989; i: 868-70).

Blood cholesterol is also apparently not important in men who've already had a heart attack. A Canadian study of 120 men 10 years after recovery from a heart attack showed

that those with low cholesterol had a second coronary as often as those with high cholesterol (Can Med Assoc J, 1970; 103: 927-31). In Russia, low cholesterol is associated with an increased risk of CHD (Circulation, 1993; 88: 846-53).

According to the data, high cholesterol is dangerous for Americans, but not for Canadians, Stockholmers, Russians or Maoris. It's dangerous for men but not women, for healthy men but not coronary patients, and for men of 30 but not over 48. Such discrepancies indicate that the association between high cholesterol and CHD is not due to simple cause and effect. The most likely interpretation is that high cholesterol is not dangerous in itself, but a marker for something else.

One study might be illuminating. A study of CHD in Japanese immigrants found that high cholesterol increased their risk of CHD but, if they maintained their cultural traditions, they were protected against heart attacks. Indeed, those who adopted an American way of life, but preferred lean Japanese food, had coronary disease twice as often as those who maintained Japanese traditions, but consumed a high-fat diet. According to the study, there is something in the Japanese lifestyle that

protects against CHD, and it's not

the food.

The study postulated that certain factors in traditional Japanese culture are protective: the Japanese place great emphasis on group cohesion, group achievement and social stability. Members of the stable Japanese society enjoy the support of other members and, thus, are protected from the emotional and social stress that could be a more important cause of heart disease than diet. The Japanese tradition of togetherness contrasts dramatically with the typical Western emphasis on social and geographic mobility, individualism and striving ambition.

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Dr Ravnskov has published nearly 40 papers disproving the cholesterol myth. This article has been adapted from his book, *The Cholesterol Myths: Exposing the Fallacy That Saturated Fat and Cholesterol Cause Heart Disease*

(\$20; Washington, DC: New Trends Publishing, 2000). To order a copy, ring 001 877 707 1776

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Published: 01/12/2000 00:00:00 GMT

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