Statins

Statins are one of the most widely prescribed drugs. They include simvastatin, atorvastatin, pravastatin and rosuvastatin. Statins reduce cholesterol and are used for both treat and prevent heart disease.

They've received much publicity, both good and bad. But what is the truth? **But how much benefit will they really give?**

SUMMARY

If you take any drug you want to know the **benefits** and the **downsides** before taking a drug

The benefits of statins are they reduce the risk of heart disease, at least in men, but only by a surprisingly small amount.

For patients without heart disease taking statins 98% of patients will get no benefit and for those with heart disease, 96% will get no benefit. The average increase in life expectancy for those without heart disease taking statins for over 4 years is 3 days and for those with heart disease it is 4 days.

What are the downsides? These include an increased risk of **cataract, diabetes, heart failure, impotence,** a variety of neurological disease such as **Parkinson's disease, peripheral neuropathy and motor neurone disease** and an increased risk of **cancer**, notably breast cancer (see below for more details).

So in my opinion, for most people, the benefits are outweighed by the risks.

Given the widespread promotion of statins, the information I found surprised me and may surprise you.

To understand the headlines it's worth understanding a bit about medical trials.

Perhaps the best known trial of statins is called the **4S trial,** the study first brought statins into the limelight. This was a study of Swedish patients who had all had previous heart attacks. They were given statins or placebo. The headlines were that statins reduced deaths from heart attacks in men by 40% (this is called **relative risk**). There was no benefit for women.

Now 40% sounds very impressive but how big a benefit is it? Well, it's a surprisingly small one. For the men who didn't take the statin their chances of **not** dying from a heart attack over five and a half years was 92%, if they took the drug it was 95%. **It was an absolute risk reduction of 3%.** (For the difference between relative and absolute risk see below.)

In other words for the great majority of patients statins made no difference. Put another way **151 of the men had to be treated for 1 year to prevent one death from a heart attack (or death from all causes)**. The other 150 didn't really need the drug and were at risk from side effects. Welcome to the complex world of medical statistics.

SECONDARY PREVENTION
(Those who already have heart disease)

Giving drugs to someone who has had a heart attack is called **secondary prevention**. **The 4S trial gave unusually good results.** To get a more realistic idea of the benefits it's worth pooling three secondary prevention trials, in this case 4S, CARE and LIPID.

The figures work for these combined trials work out that 209 people would need to take the drug for one year to prevent one death. **In other words if you've had a heart attack then taking statins would give you an approximately 1 in 200 chance of avoiding death** (in reality delaying death for approximately 3 months)**.** The odds aren't that good but the odds of getting adverse effects are unfortunately far greater.

In other words there is a marginal benefit in taking statins after a heart attack but this needs to be weighed against the chance of adverse effects.

PRIMARY PREVENTION
(Those without heart disease)

Primary Prevention (High Risk)

But what if you have not had a heart attack but are simply at high risk of having one. The WOSCOPS trial was set up to give the answer, (they were high risk as 80% were smokers and most had high cholesterol).

This showed an absolute risk reduction of 0.8%. What does this mean? The data showed that for those taking a statin there was a **91.4% of living without a heart attack for or 5 years** compared to **90.6% without a statin**. This means that 100 men would have to use the drug for 5 and half years to prevent just one death from heart disease. **But the overall death rate (called all-cause mortality) was exactly the same in both groups. *A preventative drug with no survival benefit has no value to a patient.***

And taking these drug needs to be carefully weighed against adverse effects (see later).

Primary Prevention (Average Risk)

This is the most common situation for a patient to be prescribed a statin. The AFCAPS/TexCAPS trial studied this group with an average risk. The results of the trial were that **100 people would have to take the drug for 25 years to prevent one death from a heart attack.** (99.55% survived for 5 years without having a fatal heart attack on no treatment and 99.67% with treatment) **Here the benefits look vanishingly small.**

Again the overall mortality was not reduced. In other words in the group taking the statins one death from heart disease was prevented but this was counterbalanced by an extra death from another cause. **Put another way taking a statin would alter what was written on the death certificate but not the date on it.**

Researchers from the University of Columbia have reviewed **all primary prevention trials and found no overall effect on mortality**. The independent Cochrane Collaborative came to the same conclusion and said they **could not recommend statins for primary prevention**. A meta-analysis of 11 trials of statins for primary prevention by Professor Ray, published in 2010 found no benefit in terms of mortality.

It is therefore difficult to justify giving statins to patients without heart disease given their doubtful benefit and their potential for side effects.

Will I Live Longer if I take a Statin?

Another way of looking at the benefits of statins is to **estimate how much longer you will live if taking one**. This was done in the study below by combining 11 different statin trials all including at least 1000 people. What they found was surprising.

For those with pre-existing heart disease, taking a statin for four and half years increased life-expectancy by 4.1 days. For those without a heart condition it added an extra 3.2 days.
See http://dx.doi.org/10.1136/bmjopen-2014-007118 for further information.

Numbers Needed to Treat (NNT)

This is the number of people who would need to take a drug for one person to benefit. There is a medical website which details of the NNTs for the most widely used drugs and medical procedures and it is worth a visit. It is www.thennt.com. If you look at statins for heart disease prevention (without prior heart disease) it will list

the benefits and harms. For a person who takes a statin for 5 years the listed benefits are: no lives would be saved, 1 person in 104 would be saved from a heart attack and 1 in 154 would be saved from having a stroke. The Harms listed are in in 50 would develop diabetes and 1 in 10 would get muscle pain.

Estimating Risk

Despite the absence of good evidence that primary prevention with statins doesn't work, doctors often do give them for this purpose. They use a system called QRisk to estimate risk. Those who have a greater than 10% risk of heart disease are often recommended to have statins. Unfortunately QRisk can overestimate the risk five-fold. **In addition it estimates nearly all men over 63 and nearly all women over 70 to be designated high risk** (because age is the biggest factor) and therefore in need of statins.

This is a cavalier policy as these older patients are helped least by statins (see below) and are most vulnerable to their adverse effects.

Three Key Nutrients Blocked by Statins

1) **Co-enzyme Q10** is essential for muscle and heart function. Statins reduce this vital nutrient by about 20%.
2) **Squalene** is a little known nutrient with some powerful properties. It is anti-inflammatory, it blocks tumours, it stops thromboses. It is antimicrobial, antioxidant and antifungal. Statins block its production.
3) **Vitamin K2.** This vitamin stops calcification in the arteries and helps prevent osteoporosis. It is vital for good heart function. It is in perilously short supply in the modern diet. (See osteoporosis leaflet for more information). Again it is blocked by statins.

Adverse Effects

These include **peripheral neuropathy** (26 times more common on statins and can be irreversible - a concern for patients with diabetes who are at greater risk of this problem), memory loss (including the severe memory form of loss called global amnesia), sexual difficulties (impotence in 1 in 5 taking statins), irritability and aggression, myalgia (muscle pain), dizziness, **cataracts** (57% increase), pancreatitis, higher risk of Parkinson's disease, higher risk of cancer (see below) and reduction of Co-enzyme Q10 (essential for muscle, heart and brain function).

An adverse effect which surprises most people is the **higher risk of heart failure**. This is because statins reduce co-enzyme Q10 by about 20% which can impair muscle function especially heart muscle. Texas cardiologist Dr Peter Langsjoen stated that he has seen a frightening increase in cardiomyopathy secondary to statin usage.

Another important adverse affect is an increased risk of diabetes. **For every 255 patients treated with statins for four years there will be one extra case of diabetes**. This may not sound a lot but with seven million people taking statins in the UK this amounts to **27,450 extra cases of diabetes**. In the USA statin prescriptions come with a warning label about the risk of diabetes.

Adverse effects with statins typically come on very slowly after many months and often disappear slowly on stopping them.

Muscle pain occurs in one in four patients who take statins and exercise regularly. This is not a minor problem because it often stops people from exercising. Exercise is the one of the best methods of preventing heart disease (and cancer). For most people the side effect they notice most is **lack of energy**. Co-enzyme Q10 is necessary for energy production in the mitochondria in all cells.

A study of 1000 patients in San Diego found **40% of the group on statins complained of fatigue** and this was more common in women.

One statin had to be withdrawn because of the high incidence of deaths from rhabdomyolsis –a condition where muscle breaks down and causes kidney failure. The commonly prescribed statin, simvastatin, is thought to have caused over **600 deaths worldwide**.

Another serious problem with muscles is **immune-mediated necrotising myositis (MNR).** This is a serious and often progressive muscle disease causing weakness of muscles, reduced mobility and sometimes difficulty swallowing. **Of particular concern is that it can continue to progress after stopping statins.** It is associated with auto-antibodies, raised CK and may need treatment with immunosuppressive drugs.

Statins and a very nasty disease

Statins are known to increase the incidence of motor neurone disease. Depending on the type of statin, they increase the risk between nine-fold and twenty-three-fold. Malcolm Kendrick, author of Statin Nation, has estimated this will lead to an extra 23,750 cases per year cases in the UK and USA combined. The headlines

may claim "statins save lives" but let's not forget they sometimes contribute to a grisly death.

New Trials show Minimal Benefits

In 2005 the guidelines on clinical trials were tightened (a little). The implication is that many trials before that time were flawed. The only statin trials available since 2005 have been done on rosuvastatin.

These were extensively investigated by Michel de Lorgil and Mikael Rabaeus in 2015 (Beyond Confusion and Controversy, can we evaluate the Real Efficacy and safety of Cholesterol-Lowering with Statins?)

They found that the trials "showed unambiguously that statins have no benefit in secondary prevention (those with heart disease) and their use in primary prevention was highly debatable".

There has been one trial on patients who had heart attacks (CORONA) and one on patients who either had heart attacks or severe heart disease (GISSF-HF). Neither showed any mortality benefit from statins in these high-risk patients. There was one trial on primary prevention (JUPITER) and this trial showed no cardiac benefit but a minimal benefit in total mortality.

High Dose or Low Dose?

Something else of real importance came out of this analysis. It is common policy to give high doses of statins. These typically causes more side-effects. Is there any justification for this?

Three trials have compared high and low doses of statins. **Only one of these trials (SEARCH) was done after the regulations changed.** The results were unequivocal. There **was no difference in cardiac events, cardiac mortality or total mortality** in those taking simvastatin 80mg compared to those taking simvastatin 20mg. What the trial did show was a seven-fold increase in rhabdomyolysis, a potentially fatal condition, in those given a high dose statin.

The A-Z trial also looked at patients put on different dosages of simvastatin. Different doses produced big differences in cholesterol and LDL levels as expected but made **no difference in mortality or to cardiovascular events. This lack of correlation between cholesterol lowering and outcome** has been noted before.

A third trial (PROVE-IT-TIMI) confusingly compared 2 different statins: one which produced big drops in cholesterol to those producing moderate drops (atorvastatin 80mg against pravastatin 40mg). It was reported as showing a 28% improvement

in cardiac mortality and a 30% improvement in total mortality. The truth was less impressive - a difference was of just 4 deaths in 1600 patients over 2 years, a miniscule benefit.

What about adverse effects with high doses of statins. A recent paper in the Lancet (2024) found the **risk of new-onset diabetes was much higher with high dose statins.** They looked at the risk of diabetes over a 4.4 year period. This period was used because a previous paper had found 77 patients would need to take a statin for 4.4 years to prevent one case of myocardial infarction MI).

However, these patients would also be put at high risk of diabetes. To be precise, if 240 patients took a low or moderate dose taking statins for 4.4 years there would be one case of new-onset diabetes. But if only 21 patients took a high dose stain for 4.4 years there would be one case of new onset diabetes. **Put another way, for every case of MI prevented on a high dose statin there would be three or four cases of new-onset diabetes.** This seems to me to a rsik that is hard to justify.

See https://**doi.org/10.1016/S2213-8587(24)00217-1** for details.

This data strongly implies the lowest dose of statin should be used whenever possible.

Statins and Diabetes

There was a further discovery after trial guidelines were tightened in 2005. It came from analysis of three trials (CARD, ASPEN and 4D). These showed no mortality benefit for diabetics taking statins and in one trial an increase in strokes in diabetics taking statins.

This is important as it is standard practice to give all diabetics statins for heart protection. However statins can themselves provoke diabetes. They can also cause cataracts and peripheral neuropathy which are already commoner in diabetes. This makes the present policy of giving all diabetics statins highly questionable.

Statins and Women

Most of these trials have been done on middle aged men but **what about women?**

There have been three trials of women who already had heart disease. Two showed that risk of recurrent heart disease was reduced but there was no difference in mortality. The third showed no benefit. For **primary prevention in women the** University of Columbia **pooled data from all trials and found no benefit**.

This lack of effect of statins in women is something acknowledged but skirted over in the guidelines. In fact the large Heart Protection Study included 5000 women, many in the high risk group, but there was **no difference in overall mortality** between those on statins and those not on them.

It is sadly typical of the pharmaceutical industry that this crucial information on mortality was absent from the original publication.

As statins have no overall mortality benefit for women there is, in my opinion, no justification for their use in women.

Statins and Age

What about age? The PROSPER trial, looked at **high risk men between the ages of 70 and 82.** In those without heart disease statins **did not reduce their risk of developing heart disease or strokes**. It did however significantly **increase their risk of cancer**. The risk increased each year and by the fourth year there was one extra case of cancer per year for every 100 people taking the drug. In addition a meta-analysis of twelve trials of men over 80 with heart disease or at high risk of heart disease found insufficient evidence to recommend the use of statins.

The ALLHAT was a huge trial of 10,000 patients that looked at men and women **over 55** who were at high risk of heart disease and were given statins. There study showed **no benefit** in those given statins except for a small subgroup of African Americans.

A review by the BMJ found no benefit of statins in those over 75 and a JAMA review of 2900 patients over 65 found **no benefit in those over 65 taking statins** and those over 75 were more likely to die if on statins.

It is interesting that the manufacturer's leaflet on atorvastatin suggests consulting your doctor before starting this drug if you are over 70 (because of the higher risk).

Statins and Cancer

At least thirty separate studies have shown that people with low cholesterol have a greater risk of getting cancer. Three studies have demonstrated the **link between low LDL** (sometimes called bad cholesterol) and increased **cancer** incidence. People with familial hypercholesterolaemia (who have gene for high cholesterol) are known to have a low risk of cancer. Statins lower cholesterol and LDL.

The CARE trial also showed a **twelve-fold increased incidence of breast cancer** in those taking statins. The 4S and HPS trials showed higher incidence of **skin cancers**. Animal studies

have shown statins are carcinogenic at doses not much above that given to patients.

A Japanese trial of simvastatin showed the highest cancer risk was in those with the greatest reduction in cholesterol which tallies exactly with what we know about cholesterol being a cancer-protective substance.

A study by McDougall in 2013 found women who had used statins for 10 years or longer had an 83% higher risk of invasive ductal cancer of the breast and a 97% increased risk of invasive lobar carcinoma of the breast. **The importance of this study is that it was long-term and shows a large increased risk.** Note that industry studies follow-up is only for 5 years at a maximum.

Cholesterol is Good for the Brain

Researchers at Boston University have studied the link between brain function and cholesterol in 789 men and 1105 women who performed tests on brain function every 6 years. They found that **as cholesterol went up every aspect of brain function improved**. They found subjects with "desirable levels" of cholesterol performing less well than those with high cholesterol whilst those with the lowest cholesterol performed the worst.

Those with cholesterol levels **below 4.4 show a decline in mental function** in another study.

I have personally seen people thought to be developing dementia who changed personalities on stopping statins.

Statins and Pregnancy

Statins are known to cause severe malformations in pregnant women and these are as bad as those with thalidomide. The likely reason is that cholesterol is a critically important substance for the body and especially for the brain. Breast milk and eggs are very high in cholesterol for just this reason.

Other Interesting Facts:

No Link between Cholesterol and Heart Disease

The link between raised cholesterol and heart disease doesn't hold water. Switzerland has the highest average level of cholesterol in Europe and has one of the lowest rates of heart disease (one third of that of the UK). The Maoris have one of the highest rates of heart disease in the world – fifteen to thirty times higher than the UK. They have one of the lowest average levels of cholesterol.

Russia has the second lowest average cholesterol level in Europe and the second highest rate of coronary heart disease.

The Japanese have increased their intake of saturated fat 2-300% in the last 50 years with an increase of average cholesterol from 4.0 to 5.2 (23% increase).And yet heart attacks have gone down by 60% with a 7 fold reduction in strokes. The UK has four times the incidence of heart disease as that in France but similar cholesterol levels.

Between 1994 and 2006 there was no change in mortality from heart disease in the UK but cholesterol levels dropped by 40%.

Diet and the Heart

A major study, the Lyon Heart Study, found that eating a Mediterranean diet (for four years) gave a 70% reduced risk of heart disease and a 45% reduction in mortality. This is a relative risk reduction but is over twice the best ever results seen for statins. Interestingly those on the diet had no change in their cholesterol or LDL levels.

However perhaps the most remarkable studies I ever came across are those on drinking water. **Drinking water beats drugs hands down.** A study of 20,000 men and women who drank 5-6 glasses of water daily had 50% less heart attacks than those taking 2 or less glasses.

A whole range of other foods substantially reduce the risk of heart disease, including nuts (by 50%), oily fish and fruit (see separate leaflet)

Dangers of Low Cholesterol

Low cholesterol is dangerous. This is well documented but receives little publicity. A study published in a major medical journal in 2007 of men between 60 and 85 found those with a cholesterol of over 5.5 had a 24% reduction in mortality **and those with a cholesterol of less than 4.4 had a 60% increase in mortality.** A huge Austrian study of 149,650 men & women found that **low cholesterol over the age of 50 was significantly associated with all cause mortality.** A British study published in 1995 found cholesterol levels of below 4.8 was associated with the highest all cause mortality, largely due to a significant increase in cancer deaths.

It has also been shown that low cholesterol is more hazardous as you get older. A study of elderly women found those with cholesterol of 4.0 had 5 times the mortality of those with a cholesterol level of over 7.0. A study of 15,000 healthy people

found those with low cholesterol and especially low LDL had a greater number of hospital admissions for infections.

A large American study of 137,000 patients admitted with heart attacks found average cholesterol was lower than normal (4.46 and LDL was also lower than normal). This is the opposite to what most people (and most doctors) would expect.

Eighteen separate studies have noted a link between raised cholesterol and longevity in the elderly. Sadly, in spite of good data, the link between low cholesterol and increased mortality is not known by many doctors.

And LDL, often known as **bad cholesterol,** may not be so bad as we get older. A review of 17 studies in 2016 in the BMJ Open involving 68,000 people over 60 found that **80% of people living the longest had the highest levels of LDL and** were less likely to develop cancer, respiratory, gastro-intestinal disease and heart disease.

Summary

Doctors can give widely different opinions on cholesterol and statins and I fully acknowledge that it is extremely difficult, even for doctors, to get to the truth behind these studies. So I have kept as closely to the raw data as possible. To summarise: there is a definite but **very small benefit from using statins in men who already have heart disease**.

However the data give no support for the use of statins to prevent heart disease in older men or in men at moderate risk of heart disease. For women there is no evidence to recommend them. Lifestyle measures such as diet and exercise have benefits which often vastly exceed those of drugs but rarely get the same publicity.

Relative and Absolute Risk

Why are the two risks so different?

*Let's look at the 4S trial where 95% of patients given statins survived and 5% died over 5 years. In those given a placebo 92% survived and 8% died. The **absolute risk** is 8% minus 5% –which works out as 3%. This means that you are 3% more likely to survive, in real terms, if you take the drug.*

*The **relative risk** is an estimate of how much greater the chance of surviving with the drug as compared with not taking it. Here there is an 8% chance of dying without the drug reducing to 5% with it which is about **30% better** chance of surviving.*

Typically pharmaceutical companies publicise the benefits in terms of relative risk and the adverse effects are given as absolute risk.

See Food, Lifestyle and the Heart leaflet for more information on lifestyle measures which reduce the risk of heart disease.