A guided tour round the statin wonderland

by Aidan Goggins

For years official advice on how best to protect yourself from heart disease has been wonderfully simplistic: high levels of 'bad' LDL cholesterol are the major cause, so cut your risk by lowering LDL cholesterol production as much as possible with statin drugs.

Now it turns out that this advice was wrong. Not just according to long-term statin critics but it's admitted by drug companies themselves. (See: "Cholesterol: I've never been wrong so fast or so right" by Dr Malcolm Kendrick.) The impetus for the change is that patents on statins have nearly all expired, drastically lowering drug company income, so a new range of expensive drugs to protect us from heart disease is lining up on the launch pad.

But the reasons given for why you should take them are rather different from the story about heart disease we were spun to explain why we should use statins first time around. And that should make you very suspicious.

Driving down cholesterol is out and instead we have to be worried about quite different factors – the combination of high levels of fats in the blood and low levels of the "good" cholesterol HDL. The challenge for the drug companies is that statins have little effect on either.

As low as you can go

To get them out of this bind they have had to turn to that old favourite of CAM (complementary and alternative medicine) – omega 3 fish oil. Hardly considered a proper medicine until suddenly it is combined with a drug.

This is how it happened

The old view went something like this. Statins, depending on the type and dose, reduce LDL cholesterol 20-50% [1] and for every 1.0 mmol/L (38.6 mg/dL) reduction in LDL cholesterol, there is approximately a one fifth reduction in coronary heart disease [2]. These apparently impressive stats have encouraged medical practitioners to embrace an *"as low as you can go"* approach; to put an increasing number of people on these drugs. If the official formula for calculating your risk defined yours as high then the advice was to aim for an LDL cholesterol of 1.8 mmol/L [3] and if you couldn't reach that on a low dose statin then you should switch to a high dose one.

This result of this protocol was disastrous. Since only 8% of the population hit

that target naturally that means 92% of the population were potentially eligible [3] and once you got over fifty, everyone was automatically in line for a prescription [4] because simply getting older raised your risk rating. Currently 1 in 4 American over the age 45 take a statin, that's a tenfold increase over 14 years. At this point the boundaries between preventative medicine and medicating society have virtually disappeared and mass drugging has become official policy.

If they worked as well as the hype this might just be justified but it has become clear that statins are far from a magic bullet. To begin with this enthusiastic drugging of millions effectively ignored the fact that as many as 20% of people on statins suffered side effects [5].

These include muscle pains, memory loss and confusion, raised liver enzymes, (indicating possible damage) and type 2 diabetes. Doctors often claim that side effects are rare and/or mild but a sign of how distressing they can be is that as few as 25% of those taking statins, who don't have heart disease, are still taking them after two years.

In fact doctors are so cavalier about the side effects that the guidelines say your dose should be doubled if your LDL cholesterol hasn't dropped enough. This will double your risk of side effects but only push your LDL cholesterol down by a further 6-7%

Statins haven't been working

The way side effects are effectively disregarded is one good reason to be wary of official advice. Another is that the explanation we have been given for years about why statins helped to cut the risk of heart disease is now effectively being abandoned.

Mass drugging and a far higher level of side effects are still likely to be part of the brave new statin world but otherwise the picture is changing. The problem with pushing LDL cholesterol as low as it would go was that it didn't actually bring down heart disease too. Thousands of patients were still experiencing adverse coronary events despite having extremely low LDL cholesterol levels- a problem known as 'residual risk'.

So very quietly there was a change of policy and a new set of villains emerged – fatty acids in the blood, otherwise known as triglycerides. These are transported through the blood, like cholesterol, in a container known as a lipoprotein. The triglyceride one is called VLDL and the cholesterol one LDL.

This is why they have been failing

Studies had shown that each 1 mmol/L (88mg/dL) decrease in triglyceride levels reduced coronary heart disease risk by 14% in men and 37% in women

[6]. The reason the drug companies kept this fairly quiet was because statins have very little effect on your triglycerides.

But triglycerides as a risk factor couldn't be ignored any longer because the rising tides of obesity and diabetes means that means that people have been showing up with a different set of risk factors for heart disease. Rather than raised LDL cholesterol, they have a condition called "atherogenic dyslipidemia" This involves three things: high triglycerides, low levels of the "good" HDL cholesterol and a raised level of a particularly harmful type of LDL, made up of small, dense particles.

This new pattern supposedly explained the "residual risk" – all thos patients who despite floor level cholesterol were still having heart attacks. In America a third of the population has elevated triglycerides (>150mg/dl) and 16% are classified as 'high risk' (>200mg/dl). However statins can't effectively bring down triglycerides or push up their HDL, although they do have some effect.

In a desperate attempt to find a solution the companies tried combining statins with two other compounds that can affect both triglycerides and HDL – the B vitamin niacin and an old type of drug called fibrates. Both of these are very effective at lowering triglycerides; 20- 50% in in the case of niacin which also raises HDL cholesterol, and 30-60% with fibrates along with small increases in HDL.

But taking these drugs had no more benefit than popping sugar pills. Big trials in which niacin or fibrates were added to a statin had no effect on the rate of cardiovascular disease. However the adverse events went up further. Reports of skin rashes, gastro-intestinal distress and an increased diagnosis of diabetes [7] in the case of niacin and a worsening of renal function [8] with fibrates.

This new crisis is where we are at the moment and the logic is that drug strategies to reduce heart disease have been aiming at the wrong targets. High triglycerides and LDL, along with low HDL aren't the villains, they are just innocent bystanders, signs that something is wrong. So what's needed is something to target the underlying problem.

Lowering cholesterol is shooting the messenger

Statins are actually part of the solution because even though their ability to lower cholesterol is pretty much irrelevant. That's because the reason they show up as reducing heart disease risk is that they also do other things (so called pleiotropic effects) which do tackle some of the real causes of heart disease. These include bringing down levels of compounds that surround LDL cholesterol (apolipoprotein B), suppressing inflammation and improving the way the lining of the arteries (endothelium) functions.

But this still left stains failing. So Big Pharma needed another new partner for statins to rescue them from this unmitigated disaster. One that could also target underlying factors. Enter omega 3 fish oil, long-time favourite of complementary and alternative practitioners. Like statins it brings down inflammation and improves the way the endothelium works but it also has a number of other heart healthy effects. It makes blood less likely to clot, stabilises the electrical rhythm of the heart and brings down blood pressure.

Eating fish can cut the risk developing heart disease by 14% [10] and giving a 1 gram supplement to patients after a heart attack cuts their risk of death, non-fatal heart attack and non-fatal stroke by about 15% [11]). So fish oil is the new darling of the post-statin world and companies are putting money where their mouth is.

This year alone, a fish oil drug (Vascepa) has been launched in the USA while the pharma giant Astra Zeneca paid out almost half a billion dollars for a fish oil drug that's not even approved yet.

We won't know the evidence based results of the statin/fish oil combo until 2017 when the result of a trial of Vascepa® will be released. We also don't know if lowering cholesterol will be a big selling point even though it is irrelevant. Giving fish oils to patients already on statins lowers combined LDL cholesterol and triglycerides (VLDL cholesterol) by the same about as doubling the drug dosage [9], but without the increase in side-effects

However until 2017 official guidelines, flying in the face of evidence based medicine, will be based on the discredited ideas getting cholesterol as low as possible with statins and even taking niacin and fibrates, despite knowing they are ineffective with nasty side effects. Of course instead you could just take omega 3.

Notes:

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