Statins - all the same?

Dr Mike Schachter, Department of Clinical Pharmacology, Imperial College, St Mary’s Hospital, London

Although there have been no very large clinical trials published in the last couple of years there has been no reduction in the interest in statins.

In fact, as my colleague Professor Robert Elkeles observed in a letter to a national newspaper, we are flooded with huge amounts of information which is sometimes contradictory. Often this information is more opinion than hard fact. However, we can be reasonably sure of some crucial points. These drugs do reduce the risk of heart disease and probably of stroke, and the greater the risk for a particular individual the greater the benefit of treatment - more of this later. We also have confirmation that statins are very safe drugs. They also seem to have potential for treating conditions other than the ones for which they were designed. We now have 5 types of statins available in the UK: simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin. How different are these drugs from one another? And does it matter? Are all statins really the same?

As always with good questions the answer is: yes and no. All statins do the same thing. They lower the concentration of cholesterol in the blood, especially the “bad” low-density cholesterol (LDL). They all do this in the same way. They stop the cells in the liver from making cholesterol by blocking a key step in the series of reactions needed to make cholesterol in the cells. As a result, these cells sense this “deficit” and suck in cholesterol from the blood, in the form of LDL, thereby reducing the amount present in the circulation. But remember, some cholesterol is absolutely essential for all cells in the body because it is needed to make the membrane which forms the outer wall of any cell. The end result of the removal of some of the LDL is that there is a lower amount present in the blood circulation, which reduces the risk of fatty deposits building up in the arteries, causing heart attacks and of death from coronary disease.

But there are some important questions which arise from this. Do we know this is true for all the statins? If so, are there differences in how well they can achieve this effect? Are there differences in the way that statins can interact with other drugs? And, surely at the forefront of the thoughts of many patients who might be taking these drugs over many years, are they all equally safe?

Let’s start with the last point; the crucial area of safety. The record of these drugs is extremely good. They have been in clinical use for well over a decade and most of the clinical trials, which have involved tens of thousands of patients, continued for 5 years or more. There have been few serious problems and the overall safety of statins have very recently been confirmed by an comprehensive analysis of all the available information. The most serious side-effects concern muscles, which, in a very small percentage of cases, can be damaged by statins. Extremely rarely, the damage is serious enough to be life-threatening.

There seems to be little difference between the drugs currently available in terms of the risk, although there has been one exception. In 2001, another statin called cerivastatin was withdrawn because it caused this muscular problem far more frequently; at least 10 times as often as the drugs still in use. This led to dozens of deaths, especially in the US where particularly high doses were used. This drug differed from the other statins in a number of ways and there has been nothing since to suggest that others are anything like as dangerous. Of the remaining ones, it is possible that pravastatin is the least likely to cause this problem, though this is controversial. There are even rarer problems of potential liver damage associated with statins interacting with other drugs. This is certainly less likely with pravastatin, fluvastatin and rosuvastatin than with the others due to the way that the body breaks these statins down.
How well do the different statins work? For an identical dose, atorvastatin and rosuvastatin lower LDL the most, while at the moment the strongest direct clinical evidence relates to pravastatin, simvastatin and atorvastatin. These have been tested on many thousands of patients and the benefits are clear. Less is known so far about the long-term benefits of fluvastatin and rosuvastatin. One very topical issue is the “more is better” debate. So far the big clinical trials have reduced LDL by roughly a third and the risk of serious heart problems by a similar amount. If we reduce LDL by say 60% or even more will this provide more benefits for patients?

Some studies more recently suggest that this may be so, and the recommended targets for LDL cholesterol are falling, especially in the United States but increasingly also in Europe. If we accept this, then the most powerful drugs, like atorvastatin and rosuvastatin may be preferred since they can produce the largest LDL reductions at the lowest doses. These are also the drugs which act for the longest time from a single dose, which partly explains why they are so effective. This also means, incidentally, that they can be taken at any time of day: the other statins, which act only for a few hours should usually be taken at bedtime since most of the cholesterol in the liver is produced at night.

So we can see that these drugs do differ from one another in several ways:

- How much they lower LDL for a particular dose
- How long each dose works
- How the body breaks down each drug
- How safe they are - though all the existing statins are very similar in this respect

One issue specific to the UK at the moment, is switching patients from one statin to another. Simvastatin and pravastatin are now made by generic manufacturers, are much cheaper than they used to be and much cheaper than any of the other statins. Therefore, there has been an increasing trend to switch patients from other statins to these drugs, especially simvastatin. In some patients this is entirely reasonable and will not lead to increased cholesterol levels in the blood. But in some circumstances cholesterol levels may rise, so each case should be carefully considered in the overall clinical setting.

Do we need more statins? Most clinicians think not, though at least one more is still in clinical development. The key issue is to make the best use of the ones we already have.