J) Statins – all the same?

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Although there have been no very large clinical trials published in the last couple of years there most certainly 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 sometimes contradictory information. Often this is more opinion than hard fact. But 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 these 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 of these drugs available in the UK: in order of introduction, 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 or 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 from very simple chemicals in the cell. As a result, these cells sense this "deficit" and suck in cholesterol from the blood, in the form of LDL, so reducing the amount 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 not only a lowered amount, as measured in the blood but, and this of course is the clinical point, a considerable reduction in the risk of 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?

To 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 thousand of patients, continued for 5 years or more. There have been few serious problems and the overall safety of the statins have very recently been confirmed by an analysis of all the available information. Much the most serious side-effects concerns 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 currently available drugs in terms of the risk but there has been one exception. In 2001, another statin called cerivastatin was withdrawn because it caused this problem far more frequently, at least 10 times as often as the drugs still in use . This lead 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 with statins as regards interactions with other drugs, this is certainly less likely with pravastatin, fluvastatin and rosuvastatin than with the others because of the way that the body breaks them down.

(continued overleaf...)

J) Statins – all the same? contunued...

How well do the different statins work? For an identical dose, atorvastatin and rosuvastatin lower LDL 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 very 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 the 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

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 and are much cheaper than they used to be and much cheaper than the other statins. Therefore, there has been an increasing trend to switch patients to these drugs, especially simvastatin, from the other statins. 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.