SYNOPSIS

Statin drugs: do the results of trials stand up to scrutiny?

'The case for statin drugs, especially for primary prevention, has not been made.'

This is the opinion of Andrew Thompson and Norman J Temple, writing in the *Journal of the Royal Society of Medicine*.[1] They have reviewed the major trials of statin drugs, and express concerns regarding the methodology, interpretation of endpoints, presentation of trial data and cost-effectiveness of the agents.

The comparison group

'The control groups of all the trials have been given placebo pills.' A more strenuous test, say the writers, would be that of the best current prophylactic, diagnostic and therapeutic methods, which would, in the case of statins, not be a placebo or another drug, but the modification of lifestyle. The decision to add drug therapy to a regimen should be made 'only after vigorous efforts at dietary treatment have not proven sufficient,' according to the US National Cholesterol Education Program in 1988. 'Vigorous efforts' are defined as a minimum of 6 months of intensive dietary counselling. In all of the trials, the researchers waited a few weeks and then, if the desired blood cholesterol concentrations were not reached, enrolled the subjects into the drug arm of the study.

End-points

The writers suggest an inconsistency in the criteria used to measure success. Single-criterion end-points are found in some of the trials, but not in others, and there is an increasing list of items placed in varying combinations with each other. All-cause mortality, the only measure not prone to diagnostic variance, is not popular. Combinations are often used, such as death, myocardial infarction (MI) and stroke, and only the first event is counted. Some of the studies add a treatment such as revascularisation – a clinician-driven event – not morbidity.

With regard to data on deaths, the most important end-point is all-cause mortality. This is of primary concern to the recipients of the treatment – are they less likely to die soon, whatever the reason, if they take this drug? For morbidity items, we need to have clear information on the patient's quality of life. We need to focus on these two end-points and they should be kept separate. Unfortunately, designating all-cause mortality and overall quality of life as the primary end-points is not 'usual practice' in the medical research world.

Presentation of trial data

The statin trials found absolute differences from less than 1% to a maximum of 3.3% in all-cause mortality between the control and treatment groups, and from 1.1% to 4.7% in the most standard combined event, fatal and non-fatal MI. These are not impressive results, but there is a way of making them look impressive: by expressing the results as a relative difference rather than as absolute difference. Take, for example, the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial where the difference in deaths between the statin group and the placebo group was 3.1% (14.1% in the placebo group, and 11% in the statin group). The impact of these results can be magnified by expressing them as relative differences: 'The statin drug lowered the risk of death by 22%' (11 is 22% lower than 14.1).

Another problem is that the reader is often not told the number needed to treat (NNT) for 1 patient to benefit. The NNTs range from around 30 in the Scandinavian Simvastatin Survival Study (4S) and LIPID trials to over 100 in the primary prevention trials. This is not the information that patients are likely to be given. They are told that they will reduce their risk of death by about 30%.

The situation in the primary prevention trials is completely different from that in the secondary prevention trials. Here, the participants have one or more risk factors for coronary heart disease (CHD) and are at increased risk for the disease. However, their risk of death from CHD is still much lower than that of participants in secondary trials. The NNT for such patients is much higher. The doctor is unlikely to say, 'Mr Smith, if you take the statins, then in 7 years' time, there is a 1 chance in about 120 that your death will have been prevented'. More likely, he will say, 'Mr Smith, if you take statins this will reduce your risk of dying from heart disease by about 30%'. The writers argue that the former is a more honest version of the clinical reality.

Cost-effectiveness

Using the NNTs of the secondary trials (NNT = 30) and a conservative estimate of the cost of statin drugs of about $500 per year, the cost of postponing one death is about $85 500. The figure becomes much higher when the NNTs of the primary trials are used (> 100); the cost of statins rises to over $300 000 to prevent one major CHD event.

In an accompanying editorial,[2] mention is made of complicating factors such as the metabolic processes involved in the anti-inflammatory actions of statins, the fact that statin therapy tends to reduce the risk of MI more than would be predicted from the reduction in cholesterol achieved, the results of trials on diabetic patients, and the influence of some common dietary components (like folic acid, vitamins B_6 and B_{12}) on nitric oxide synthase (and thus endothelial function) and homocysteine.

Some of these issues are being addressed in trials currently under way, such as the SEARCH study.[3] The main message, say the writers of the editorial, is that if we are to make the best of what common micronutrients and statins can offer against vascular disease, we need to know much more about their mechanisms of action.

1. Thompson A, Temple N J. *J Roy Soc Med* 2004; **97:** 461-464.
2. McKee M, *et al*. *J Roy Soc Med* 2004; **97:** 459-460.
3. SEARCH (Study for Evaluation of Additional Reductions in Cholesterol and Homocysteine), **www.ctsu.ox.ac.uk**

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