On the other hand, in primary prevention, statin therapy reduces the risks of CHD events for men but not for women, without reducing total mortality for either men or women. Furthermore, there is reason to believe that the beneficial action of statin drugs is mediated in spite of their cholesterol-lowering effects. Indeed, statins have an effect only when patients have a heightened inflammatory state. Finally, it has been shown that low total cholesterol is an independent and robust predictor of future external-cause mortality, and this association could not be explained by other obvious interrelated risk factors.

As Thompson stated, the cholesterol controversy in Britain dates back to 1950. Changing our current practice pattern could take other 50 or more years, but we may one day prescribe cholesterol-raising medications to certain patients.

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History of the cholesterol hypothesis in Britain

Sir,

‘The statins trials resolved the controversy’1 is an error of scientific thought, and it is sad that so many respected clinical scientists such as Prof. G.R. Thompson fail to appreciate this.

Yes, there has been a controversy concerning cholesterol, which is clearly a risk indicator, not for just coronary heart disease (CHD) but for all deaths, but only in men of working age.2,3 We know from Framingham studies that cholesterol is neutral in women and older men4 and we know from other studies that a high blood cholesterol is a survival advantage in elderly people.5,6 The question following the MRFIT2 and Whitehall3 studies is whether the elevated level of cholesterol is a risk indicator on a causative pathway or whether it is a reflection of existing sub-clinical CHD. Subsequent studies have shown that it matches the inflammatory marker C-reactive protein very closely.2,7
The statin trials, initially the Scandinavian Simvastatin Survival Study (4S) and the West of Scotland Coronary Prevention Study (WOSCOPS), were trials of statin therapy. The fundamental point of a scientific experiment is that the factor under investigation is strictly controlled, so that it is found only in the study group and not in the control group. Statin therapy was controlled by successful randomization. The statin trials are trials of statin therapy and that alone.

The trials were not trials of cholesterol lowering as this could not be controlled. Although at the inception of the trials it was felt that the only metabolic effect of statins was reduction of cholesterol (LDL-cholesterol) through inhibition of HMG-CoA reductase, it became clear after analysis of the trials that there were many other unforeseen metabolic effects taking place. It cannot be assumed that the mechanism of benefit of statins was their undoubted cholesterol-lowering action, as this was not the only action. First, there was an elevation of HDL-cholesterol and a reduction of triglyceride in those randomized to pravastatin. This immediately invalidated WOSCOPS as a trial of cholesterol lowering as that was not the only metabolic effect. It was noted in the full data of WOSCOPS that the clinical benefit was greater than the cholesterol hypothesis would predict, and there was not a quantitative relationship between cholesterol lowering and clinical outcome. The authors state that ‘...The influence of pravastatin on CHD risk could not be completely explained by the reduction in LDL-cholesterol. ...Pravastatin may, through pathways not involving lipid-lowering, beneficially affect atherosclerosis.’

Statins are an effective treatment for atherosclerosis, though mechanisms uncertain. We now know that there are several metabolic effects of statins, which have led to reports of many unexpected beneficial consequences. These included reduction of incidence of diabetes, reduction of rejection rate after heart transplantation and renal transplantation, reduced incidence of colon, prostate and lung cancer incidence, improved survival after pneumonia, improved bone density, clinical improvement in rheumatoid arthritis, reduction of lesions in multiple sclerosis, reduction of septic illness and reduction or modulation of inflammatory processes.

The statin trials clearly failed to resolve the cholesterol controversy but they opened up an exciting field of research into statin effects. Of course, cholesterol lowering is the only licensed indication for statins and so the companies that develop them are happy to maintain a belief in the diet-cholesterol-heart hypothesis, flawed as it may be. Oliver was premature in accepting the cholesterol hypothesis following publication of 4S, but at the time he was unaware of the then-unpublished data concerning the uncontrolled and then-unknown effects of statins in the trials.

Thompson’s history comes to a premature end before the arrival of the latest cholesterol-lowering medication, ezetimibe. There is no question that this has a major effect on reduction of serum cholesterol, but it is of no clinical benefit. At the present time, ezetimibe cannot ethically be used as monotherapy for cholesterol lowering and in the clinical trial it was given in addition to simvastatin. It had an additive cholesterol-lowering effect but no additional clinical benefit. We could in fact use the ezetimibe trial as indicating the inadequacy and inconsistency of the cholesterol controversy, which is in fact not a controversy at all. It simply represents the triumph of evangelism over evidence.

Thompson acknowledges the scepticism of Sir John McMichael, Michael Oliver and Tony Mitchell, and I expect that they will ultimately be acknowledged as being correct. But this cannot happen until clinical scientists such as Thompson recognize that cholesterol-lowering and statin therapy are different scientific entities.

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