Cholesterol and total mortality: need for larger trials

EDITOR,—It has been suggested that the current trials of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors can be expected to provide reliable evidence on the effects of lowering blood cholesterol concentration on total mortality.[1] Those trials are, however, designed primarily to assess the effects of lowering cholesterol concentration only on coronary heart disease. Consequently, they have limited ability to detect the sort of effects on total mortality that it is realistic to hope for, except perhaps in the special circumstance of patients who have already suffered a myocardial infarction, among whom nearly all deaths are due to coronary heart disease. But this special circumstance of "secondary" prevention includes only a fraction of the wide range of people who have a moderately raised risk of coronary heart disease and for whom reliable evidence is needed about the efficacy, safety, and overall effects of reducing cholesterol concentration. Moreover, if reducing cholesterol concentration has any real effects on mortality from causes other than coronary heart disease these need to be recognised, as they could be of substantial relevance not only to patients but also to the general population.

In considering total mortality, suppose that in the current trials cholesterol lowering has no material effect on deaths from causes other than coronary heart disease and, as is suggested by previous trials,[2,3] that there is a roughly one to one relation between the percentage reduction in cholesterol concentration and the percentage reduction in deaths from coronary heart disease during a trial lasting five or six years (so that a 20% reduction in cholesterol would lower mortality from coronary heart disease in a five year trial by about 20%). The table shows the numbers of deaths from all causes that would then be expected and the statistical power of the current trials to detect such reductions in total mortality.

Taken separately from each other, even the studies of secondary prevention among patients after myocardial infarction may well fail to show the sort of effects on total mortality that might realistically be expected (table). Combining all their results in a systematic overview (or meta-analysis[4]) should allow such an effect on total mortality to be detected, but there is still a material chance that it might fail to be. And, even if the overall results were significant, there would almost certainly be some major subgroup (for example, men or women, young or old, moderately or extremely raised cholesterol concentration) in which ambiguous results would lead to prolonged dispute—especially since an overview of several results may not be as convincing to some clinicians as a single trial of adequate size.[5,6]

The situation is much worse in the primary prevention of myocardial infarction among people at high risk of coronary heart disease, among whom a larger proportion of deaths are from causes other than coronary heart disease. For even an overview of the studies of primary prevention currently under way may fail to show the expected reductions in fatal coronary heart disease, let alone any effects on total mortality (table). Moreover, for primary as for secondary prevention, the power calculations for the current trials relate only to the overall results: if any subgroups (for example, men or women, middle aged or old) are to be analysed separately to help determine which patients need treatment then the power of the individual trials (and of any overview) is further reduced.

It might have been hoped that the current trials would at least be able to address reliably the suggestion that lowering cholesterol concentration results in an increase in deaths from causes other than coronary heart disease, but this too is uncertain. In assessing any potential hazards of lowering cholesterol concentration the power of the trials depends on the numbers of deaths from causes other than coronary heart disease. Overall in the current trials only about 600 such deaths are expected, of which one third might be from cancer and one sixth from external causes such as accidents, violence, and suicide. Even a meta-analysis of all these studies would have less than a one in three chance of detecting (or excluding) the sort of increases in deaths from all causes other than coronary heart disease (of about 20%), from cancer (of about 30%), and from external causes (of about 50%) suggested by some reviewers of the previous cholesterol lowering trials.[1,7]

There is therefore a substantial risk of false negative results for total mortality from these trials and of equivocal evidence about any effects of lowering cholesterol concentrations on causes of death other than coronary heart disease (such as cancer). This underlines the need for further large studies which, taken together with the results from the current trials, could answer these questions more reliably. Such evidence would not just be relevant to drug treatment for a wide range of people at increased risk of coronary heart disease but also help, indirectly, to resolve the long running controversy about the public health importance of lowering cholesterol concentrations by dietary means.

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Diets that protect against coronary heart disease

EDITOR,—Many tests of the effect of diet in preventing coronary disease are flawed by the assumption that a raised blood cholesterol concentration is in itself a cause of the disease. This has led to the use of cholesterol lowering drugs as well as diet to reduce cholesterol concentrations. This approach is a typical result of the common assumption that association denotes cause. But Ram B Singh and colleagues, who assessed the effect of diet specifically on coronary mortality, avoided this error.[1] Nor did they use cholesterol lowering drugs, which have been suspected of

Expected numbers of deaths and power to detect effects on total mortality in current trials of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors designed to enrol more than 1000 patients

Study	No to be randomised	HMG CoA reductase inhibitor	Estimated 5-6 year average reduction in cholesterol (%)	Estimated No of deaths		Expected No of deaths from all causes*		Power for total mortality (%)*
				From CHD	From non-CHD	Statin group	Control group	
Patients after myocardial infarction								
SSSS	4 500	Simvastatin	23	360	80	197	243	38
LIPID	8 000	Pravastatin	18	700	180	405	475	46
CARE	4 200	Pravastatin	18	260	80	157	183	13
Primary prevention of myocardial infarction								
Post-CABG	1 500	Lovastatin	18	150	25	80	95	7
AFCAPS	8 000	Lovastatin	18	100	150	120	130	2
WOSCOPS	6 500	Pravastatin	18	100	80	85	95	3
Overview of trial results								
All patients after myocardial infarction	16 700	Various	19	1320	340	759	901	85
All primary prevention	16 000	Various	18	350	255	285	320	12

SSSS=Scandinavian simvastatin survival study. LIPID=Long term intervention with pravastatin in ischaemic disease. CARE=Cholesterol and recurrent events study. Post-CABG=Post-coronary artery bypass graft study. AFCAPS=Air force coronary atherosclerosis prevention study. WOSCOPS=West of Scotland coronary prevention study. CHD=Coronary heart disease.
*Expected numbers of deaths are calculated by assuming no effect on deaths from causes other than coronary heart disease and a 1:1 relation between estimated 5-6 year average reduction in cholesterol concentration and percentage reduction in deaths from coronary heart disease; power to detect a difference in total mortality is calculated as probability of achieving $2p<0{\cdot}01$.