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# The problem with cholesterol

*No light at the end of this tunnel?*

Lowering the cholesterol concentration undoubtedly reduces the prevalence of fatal and non-fatal myocardial infarction,[1] but three concerns remain. firstly, meta-analyses of both primary and secondary trials show a significant excess of non-coronary mortality in patients randomised to cholesterol lowering interventions; the end result is no effect on all cause mortality.[2,3]. The excess non-coronary mortality does not arise from a single cause but includes a significant increase in deaths from accidents, violence, and suicide.[3]

Secondly, within the time scale of a randomised controlled trial the achievable reduction in the risk of a cardiovascular event is small for the individual participant, particularly in primary prevention trials.[4] And, thirdly, evidence exists of an association between low serum cholesterol concentration and increased non-cardiovascular morbidity and mortality.[5,6]

The British Hyperlipidaemia Association recently organised a symposium to discuss these issues. Reviewing the proceedings of the American conference "Low blood cholesterol: mortality associations," based on a meta-analysis of deaths of 524 000 men and 125 000 women, Jacobs *et al* concluded that serum cholesterol concentrations below 4 mmol/l are associated with an increased risk of death from cancer, respiratory disease, trauma, and digestive diseases.[5] For some associations, increased risk extends above this low cut off point. Adjusting for important confounding variables —such as occult cancer, alcoholism, smoking, body mass index, and blood pressure—does not remove the association. By contrast, the smaller Whitehall study concluded that lower socioeconomic class and poor health status among subjects with low cholesterol concentrations at the time of sampling largely accounted for the association between cholesterol concentration and non-cardiovascular mortality.[6] The biological basis for any cause and effect relation remains obscure.

The meta-analysis also found no significant relation between serum cholesterol concentration within the range $<4$ to $\geq 6$ mmol/l and all cause and cardiovascular mortality in women. For cardiovascular mortality this is partly because of a negative association between serum cholesterol concentration and death from haemorrhagic stroke, which counterbalances a positive association between serum cholesterol concentration and death from coronary heart disease. These findings suggest that attempting to lower the cholesterol concentration of the whole population by dietary means may be inappropriate for people whose concentration places them on the left hand limb of the shallow U shaped curve relating cholesterol concentration and cardiovascular mortality.[7] The lack of association between cholesterol concentration and cardiovascular mortality in women raises doubts about screening for or treating raised serum cholesterol concentrations in women except those at substantially increased risk of death from coronary heart disease. It also reinforces doubts about the wisdom of extrapolating results derived from high risk middle aged men to the female population.

At the symposium Richard Peto and Rory Collins said that meta-analyses of randomised controlled trials that used an end point that combined morbidity and mortality from coronary heart disease suggested favourable results for lipid lowering interventions.[1] They considered that subdividing this hypothesis driven end point may generate significant differences of dubious biological possibility. Ingar Holme's meta-analysis of primary and secondary prevention trials failed to show a significant effect on all cause mortality, and he attributed this to the lack of statistical power inherent in small studies and the small reductions in cholesterol concentration achieved in many trials.[8]

A different interpretation of essentially the same evidence from randomised controlled trials, published in this issue of the journal (p 1367),[9] was presented by George Davey Smith. A stratified meta-analysis of 35 randomised controlled trials showed a highly significant relation between a favourable reduction in all cause mortality in the treatment arm of each trial and annual mortality from coronary heart disease in the control arm. Benefit in terms of reduced all cause mortality in treated compared with control patients occurred only in trials with high mortality from coronary heart disease in the control arm (exceeding 3% a year). These death rates greatly exceed those in asymptomatic patients aged under 65 with primary hypercholesterolaemia. The findings refine previous observations that trends in all cause mortality are neutral or modestly favourable in secondary prevention trials and often unfavourable in primary prevention trials. They conflict with the view that excess deaths from causes other than coronary heart disease in randomised controlled trials can be dismissed as a statistical artefact and add weight to the author's previous claim that these deaths occur in drug intervention trials but not in dietary trials.[10]

The concluding discussion reviewed the British Hyperlipidaemia Association's revised guidelines for treating hyperlipidaemia.[11] The prudent "Mediterranean" diet remains the preferred option for patients with moderate hyperlipidaemia, with lipid lowering drugs being reserved for "high risk" patients who do not respond to diet. The unresolved problem

lies in defining high risk. There was general agreement that patients with established coronary heart disease and hyperlipidaemia (cholesterol concentration >6.5 mmol/l), asymptomatic patients with familial hyperlipidaemia (>7.8 mmol/l) and a strong family history of premature death under 60, and asymptomatic middle aged men and women with multiple risk factors and a similarly malign family history are strong candidates for lipid lowering drugs.

The association's guidelines also recommended lipid lowering drugs for patients with established coronary heart disease and a serum cholesterol concentration exceeding 5.2 mmol/l (the great majority), for asymptomatic men with hypercholesterolaemia (>7.8 mmol/l) as their only risk factor, and for asymptomatic women with hypercholesterolaemia (7.8 mmol/l) and a low ratio (<0.2) of high density to low density lipoprotein but no other risk factors. Given the doubts about the costs and benefits of lowering cholesterol concentration, these indications for starting patients on lifelong treatment are debatable. How many numerate participants in the primary prevention trials of cholestyramine and gemfibrozil would contemplate lifelong drug treatment with equanimity if informed that these drugs had reduced the incidence of cardiovascular events by only 1.7% and 1.4% respectively when the treatment groups were compared with the control groups.[2] Among control subjects 90.2% in the cholestyramine trial and 95.9% in the gemfibrozil trial did not suffer a cardiovascular event. Participants might also be deterred by being told that their risk of dying had not been significantly reduced over the duration of the trial and that information on mortality beyond the trial period was unavailable or, in the case of gemfibrozil, the subject of controversy.[12]

The use of lipid lowering drugs is increasing rapidly in most developed countries, driven mainly by promotional techniques and advertising literature that concentrate on the modification of surrogate biochemical end points.[13,14] The epidemiological content of promotional literature is often inadequate or unbalanced, promoting drugs that either have not been the subject of randomised controlled trials or, as in the case of the statins, are currently being studied in randomised controlled trials whose results are unknown. Unfortunately, the sample sizes of current trials of the statins may lack the statistical power necessary for mortality to be evaluated as an end point.[15]

The larger "mega" drug and diet intervention trial proposed by Peto and colleagues would therefore be valuable and cost effective.[15] Some 20 000 participants with an anticipated 2000 deaths from all causes over five years would ensure sufficient statistical power to evaluate all cause mortality in high risk patients with established vascular disease. This trial, however, will not address the risks and benefits of treating most asymptomatic patients aged under 65 with primary hypercholesterolaemia as the annual all cause mortality in the control arms of the three largest primary prevention trials was less than a quarter of that expected in the proposed "mega" trial. About 80 000 trialists would be required to evaluate all cause mortality in this class of patient with a trial of comparable statistical power. The likelihood of such a trial being carried out is extremely small.

Without definite data an all cause mortality and with current unresolved concerns about excess deaths from non-cardiac causes in randomised controlled trials, decisions to embark on lifelong lipid lowering drug treatment in most patients with primary hypercholesterolaemia depend on the doctor's interpretation of available evidence. As in other situations in which certainty is illusory, this varies from evangelical enthusiasm for lowering lipid concentrations to therapeutic nihilism. Most doctors pursue a somewhat uncertain middle way, which attempts to balance putative risks and benefits for the individual patient. Further clarification may prove elusive in the foreseeable future.

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# The GMC: size and public accountability

## *Shrink it drastically but increase lay members as a proportion*

One of the problems of the General Medical Council (GMC) is its size. Another problem is the perception that it has insufficient lay representation and hence is not sufficiently accountable to the public. These two problems come together in proposals to reconstitute the council, which will be debated at its meeting next week.

The GMC started with 24 members but now has 102. Organisational psychologists think that the optimum size of a group that takes decisions rather than debates and rubber stamps them is about eight. Inevitably, as the GMC's size has grown the influence of the full council has declined. This problem is seen in many organisations as they try to balance representativeness against effective decision making, and many don't get it right. They end up with large, expensive, ineffective talking shops, and the real decisions are made elsewhere by often unelected cabals. Doctors may be particularly at risk of ending up with councils that are too large because of their suspicions of those who try to lead. Many members of the GMC would like to see a smaller council, but most are reluctant to give up their own seats.

The belief that the council ought to have more lay members has been growing for a long time both in the broader community and within the council. This is because the lay members are much appreciated and are being worked harder