CORRESPONDENCE

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MRC/BHF Heart Protection Study

Sir—The Heart Protection Study (HPS, July 6, p 7)[1] reported that therapy with simvastatin significantly reduced the composite primary endpoint of coronary heart disease (CHD) death and the secondary endpoints of non-fatal myocardial infarction, stroke, and revascularisation procedures in seemingly all categories of patients at high risk of a vascular event. The results seem at variance, however, with those of other large placebo-controlled trials, which have found that there are limitations to statin therapy, notably in individuals with lower concentrations of LDL cholesterol,[2–5] and in those with high LDL cholesterol concentrations but low rates of hepatic cholesterol synthesis.[4]

One possible explanation for the difference between HPS and other statin trials involves the inclusion of revascularisations as a component of a major vascular disease endpoint. Is it possible that the results of HPS might be different and not as uniformly positive for the benefit of statin therapy if reinterpreted without the inclusion of revascularisations as a major endpoint? In a clinical trial with a combined endpoint and time-to-event analysis by log-rank statistics, the first endpoint to occur is counted as the incident endpoint. What, then, is the implication of a reduction with therapy of possibly a different vascular endpoint in different subgroups of patients or at different concentrations of LDL cholesterol in a population in which all vascular endpoints may not necessarily have the same pathological basis, have the same clinical importance, or can be equally supported by criteria that can be formally adjudicated?

Overall, revascularisations, or more precisely the need for revascularisations, accounted for 40% of the "major vascular events" in HPS. Unlike other statin trials, this category of events included not just coronary revascularisations but carotid and peripheral vascular disease surgery that accounted for almost half of the revascularisation procedures. Since the premise for all the statin trials is that CHD risk and risk reduction are related to cholesterol, does a need for revascularisation (especially because amputations were even included in this category) have the same curvilinear relation to LDL cholesterol as do myocardial infarction and CHD death, which traditionally have constituted the epidemiological basis for cholesterol-lowering therapy? More particularly, one might ask, is a reduction in the need for revascularisation procedures proportional to a reduction in LDL cholesterol values or, alternatively, to some other favourable vascular properties of statins that result in a decrease in angina, transient ischaemic attacks, or claudication that frequently lead to a revascularisation?

HPS was undertaken with the premise that there is no threshold of cholesterol at which the risk of CHD cannot be made lower by reducing cholesterol to the very low levels normally present in certain Asian populations. However, observational studies, which form the basis for this premise, have tracked only the incidence of CHD death. What is the epidemiological evidence that justifies including a need for revascularisations as an endpoint that is either positively related to cholesterol or has the equivalent clinical implications of myocardial infarction, stroke, or CHD death?

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1 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360:** 7–22.

2 Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; **335:** 1001–09.

3 The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; **339:** 1349–57.

4 Miettinen TA, Gylling H, Strandberg T, et al. Baseline serum cholestanol as predictor of recurrent coronary events in subgroup of Scandinavian Simvastatin Survival Study. *BMJ* 1998; **316:** 1127–30.

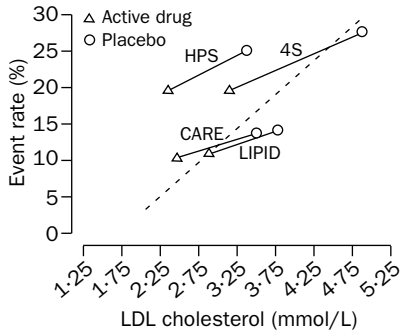
5 Ridker PM, Rifai N, Cleafield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001; **344:** 1959–65.

Sir—One unresolved issue of HPS[1] is whether there is a true and sustained linear relation between LDL cholesterol lowering and event reduction over a wide range of LDL cholesterol concentrations. The HPS investigators suggest that a threshold LDL cholesterol concentration does not exist, and call for aggressive LDL cholesterol lowering.

Indeed, others have also suggested that lower is better by extrapolating data from the placebo and treated groups in other secondary prevention trials. Before HPS, interpretations of trial data, such as that represented in the figure by the dashed line, have been used to support the dogma that lower is better.[2] Versions of the figure (minus the HPS data points) have been widely promulgated by proponents in lectures at international symposia. We suggest that, taken together with previous statin studies, HPS may not in fact support the lower is better concept. The overall event rates in the treated groups in HPS and 4S[3] are similar, yet the lower absolute LDL cholesterol concentration in HPS did not translate into reduced events when compared with 4S (figure). This result cannot be explained by major baseline differences between the groups because the placebo groups in both trials had roughly the same major event rate.

Additionally, the proportional reductions in risk did not seem to be associated with pretreatment LDL cholesterol concentrations in HPS.[1] If lower is better, the change in LDL cholesterol should have the highest effect in those with the highest baseline LDL cholesterol concentrations, and in those with the greatest LDL cholesterol reduction. The CARE study[4] also indicates that lower may not be better, and suggests a threshold LDL cholesterol concentration below which benefit is not apparent.

Statin trials mainly show that the treatment with active medication results in clinical benefit. Mechanistic



Relation between on-treatment LDL-cholesterol concentrations and fatal plus non-fatal coronary events in secondary prevention studies of statin treatment

explanations of this finding, including that of cholesterol lowering, remain inferential. In aggregate, data from statin trials also support the existence of a set benefit, possibly drug-specific, that is largely dissociated from the degree to which LDL cholesterol is lowered. This set benefit in HPS amounted to about 25% reduction in event rate and is in keeping with other large secondary prevention studies. We await an analysis of HPS to examine the relation between LDL cholesterol decrease and risk reduction similar to that provided for the CARE[4] and WOSCOPS[5] trials.

Trials currently in progress directly address whether therapy should pursue the lowest achievable LDL cholesterol concentration. Until they report, it would seem prudent to treat patients with a statin in the categories for which benefit has been shown in HPS, even at LDL cholesterol concentrations of below 3·0 mmol/L, without necessarily forcing titration of LDL cholesterol to the lowest achievable level.

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1 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360:** 7–22.
2 Kastelein JJP. The future of best practice. *Atherosclerosis* 1999; **143:** S17–21.
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4 Sacks FM, Pfeffer MA, Moye LA, et al, for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; **335:** 1001–09.
5 West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation* 1998; **97:** 1440–45.

Sir—The results of HPS[1] show that the effect of simvastatin increases with increasing duration of treatment, but results are shown only in respect to all major vascular events in combination. Could the Collaborative Group provide a tabulation of major coronary events (coronary death and non-fatal myocardial infarction) alone, showing the numbers of events in the simvastatin and placebo groups and the event rate ratio for each year of follow-up?

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1 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360:** 7–22.

Sir—I should be grateful if the authors of HPS[1] could provide clarification of three issues raised by their findings.

First, they state that to be eligible for the trial, participants must have had a past history of coronary disease, occlusive disease of non-coronary arteries, diabetes mellitus, or treated hypertension. However, by looking at the results, many participants must have fallen into more than one category. This is particularly germaine to the issue of primary prevention of CHD and stroke in diabetes mellitus. There were 4625 people with type 1 or 2 diabetes and no previous CHD in the trial. However, many of them must have had cerebral or peripheral vascular disease, and thus prevention of CHD in these individuals was not truly primary. The vascular event rate in the placebo diabetic group without CHD, which was 3·7% annually, also suggests that they were not a true primary prevention group. So, what was the outcome of primary prevention in diabetes?

Second, it was good to see that some patients with triglyceride concentrations greater than 4 mmol/L were randomised. For the benefit of those of us with lipid clinics, what was the median triglyceride concentration in this group?

Third, the laboratory method used in the study seems to have underestimated LDL cholesterol concentrations by about 0·4 mmol/L. The total serum cholesterol concentration was on average 5·9 mmol/L, HDL cholesterol 1·06 mmol/L, and triglycerides 2·1 mmol/L, and these are likely to be accurate. The triglyceride concentration indicates that the VLDL cholesterol concentration would be around 1 mmol/L. So the mean LDL cholesterol measurement of 3·4 mmol/L would suggest that about 0·4 mmol/L of LDL cholesterol is missing. The important point here is that, if this underestimation is not consistent throughout the range of LDL cholesterol values encountered, misleading conclusions about the effect of initial levels and of responses to therapy could be drawn. It would therefore be helpful to know the effect on outcome of pretreatment serum apolipoprotein B (the main protein component of LDL and VLDL) concentration and of its response to treatment.[2,3]

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1 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk patients: a randomised placebo-controlled trial. *Lancet* 2002; **360:** 7–22.
2 Miremadi S, Sniderman A, Frohlich J. Can measurement of serum apolipoprotein B replace the lipid profile monitoring of patients with lipoprotein disorders? *Clin Chem* 2002; **48:** 484–88.
3 Durrington PN. Can measurement of apolipoprotein B replace the lipid profile in the follow-up of patients with lipoprotein disorders? *Clin Chem* 2002; **48:** 401–02.

Sir—One of the conclusions of the HPS Collaborative Group (July 6, p 23),[1] namely that "the lower risks of vascular disease and cancer found in observational studies among people with higher intake of [these] antioxidant vitamins must have been largely or wholly artefactual", seems to go beyond the data.

All the participants, including those subsequently randomised to the placebo group, received a 10-week supply of vitamins in the prerandomisation "run-in" phase.[1] This amount was equivalent to about an 8-month supply of vitamin C, 140 months of vitamin E, and 24 months of carotene, at median UK intakes.[2] There was no wash-out period before the main trial. Nutrients, especially fat-soluble ones, are usually retained within the body for longer periods than most drugs, and wash-out periods are typically much longer. I also suspect that many of the non-vitamin group may have taken over-the-counter