

CORRESPONDENCE

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Comments on the MRC/BHF Heart Protection Study

Sir—The Heart Protection Study (HPS) Collaborative Group (June 14, p 2005)¹ reports an impressive amount of data, but does not present numbers for overall mortality.

The endpoint of major coronary events includes a broad clinical range, from angina with raised troponins to death.² Rates of deaths due to coronary artery disease have not been specified.

When considering a medical intervention, we should know 1) its effect on mortality, and 2) its effect on quality of life, or morbidity. Endpoints should be graded accordingly.

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- 1 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; **361**: 2005–16.
- 2 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—In the HPS,¹ in people with diabetes only the difference in coronary death rates between the simvastatin group and the placebo group are mentioned; the authors do not provide the difference in rates of all-cause, vascular (including those related to stroke), and non-vascular mortality between groups. This information was reported in the original article published in 2002, which provided details on the whole study population. Provision of such data for patients with diabetes would be interesting, since they might respond differently to the study population as a whole.

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- 1 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; **361**: 2005–16.

Sir—The re-elaboration of data from the HPS¹ seems to indicate a specific benefit of cholesterol reduction in individuals with diabetes; a conclusion supported by the accompanying Commentary by L Lindholm (June 14, p 2000).²

However, the data do not back up this conclusion. Participants with diabetes in the placebo group do have a higher frequency of major coronary events and stroke than those without diabetes, however, they also have a greatly reduced rate of revascularisation, and overall major cardiovascular events are just slightly reduced. This finding does not, therefore, justify any special emphasis on the specificity of patients with diabetes versus other patients with a high cardiovascular risk, and it casts doubt on the frequently expressed notion that diabetes is a coronary event equivalent.

An important contribution of the MRC/BHF study is its assessment of cholesterol reduction in patients with an extraordinarily high cardiovascular risk. In the 5-year follow-up, one patient in four had an event, versus one in five in the 4S study,³ and far lower risks in other intervention studies with statins or fibrates. In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm study,⁴ the global cardiovascular risk was 2.5-fold lower than in the MRC/BHF study, possibly because of the unexpected selection of patients with high HDL cholesterolaemia. Conversely, the HPS reproduces, 30 years on, the conditions of the Mental Hospital Study in Finland,⁵ in which again a cholesterol reduction by diet alone led to a similar reduction in risk. In the case of patients with a fairly low risk or a risk already well covered by other interventions, the benefit of cholesterol reduction might be less evident.

Cholesterol reduction is justified for individuals with a high cardiovascular risk and the benefit is proportional to baseline risk, easily calculated with widely available computer programs. Diabetes is one component of the risk analysis, but I do not agree, as suggested in the Commentary,² that “all patients with type 2 diabetes should be given a statin regardless of their cholesterol value”.

Cesare R Sirtori

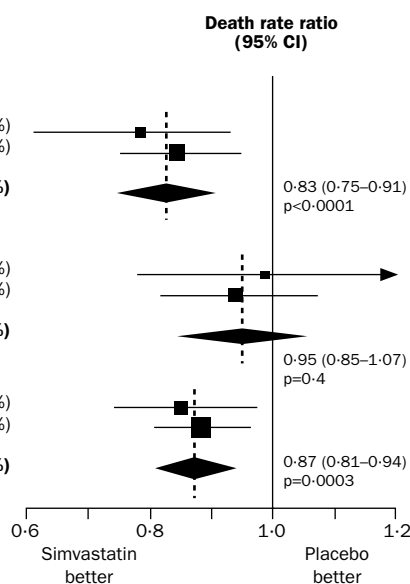
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- 1 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; **361**: 2005–16.
- 2 Lindholm LH. Major benefits from cholesterol-lowering in patients with diabetes. *Lancet* 2003; **361**: 2000–01.
- 3 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**: 1383–89.
- 4 Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; **361**: 1149–58.
- 5 Miettinen M, Turpeinen O, Karvonen MJ, Elosuo R, Paavilainen E. Effect of cholesterol lowering diet on mortality from coronary heart disease and other causes. *Lancet* 1972; **2**: 835–38.

Authors' reply

Sir—We reported that allocation to simvastatin in HPS produced a 20% (95% CI 4–34) reduction in coronary mortality (193 [6.5%] simvastatin *vs* 239 [8.0%] placebo; *p*=0.02) among the 5963 participants with diabetes, as well as a 37% (20–50) reduction in first non-fatal myocardial infarction (105 [3.5%] *vs* 164 [5.5%]; *p*=0.0002). We prespecified that assessments in different subcategories would be based not on mortality but on first major coronary event (defined as non-fatal myocardial infarction or death from coronary disease; but not, as stated by Christoph Pechlaner, angina) and, particularly, on the even larger numbers of first major vascular events (ie, major coronary events, strokes, or revascularisation procedures). These analyses showed that an average reduction in LDL cholesterol of 1 mmol/L significantly reduced the risks of coronary and other vascular events by about a quarter in the

| Cause of death and prior disease group | Simvastatin-allocated (10 269) | Placebo-allocated (10 267) |
|--|--------------------------------|----------------------------|
| Vascular causes | | |
| Diabetes | 242 (8.1%) | 304 (10.2%) |
| No diabetes | 539 (7.4%) | 633 (8.7%) |
| Subtotal: vascular | 781 (7.6%) | 937 (9.1%) |
| Non-vascular causes | | |
| Diabetes | 142 (4.8%) | 142 (4.8%) |
| No diabetes | 405 (5.6%) | 428 (5.9%) |
| Subtotal: non-vascular | 547 (5.3%) | 570 (5.6%) |
| All causes | | |
| Diabetes | 384 (12.9%) | 446 (14.9%) |
| No diabetes | 944 (12.9%) | 1061 (14.6%) |
| Any death | 1328 (12.9%) | 1507 (14.7%) |



Effects of simvastatin allocation on cause-specific mortality in participants presenting with or without diabetes

diabetic participants—which was similar to the reduction seen among the non-diabetic participants—irrespective of any pre-existing occlusive arterial disease or their presenting age, sex, blood lipid concentrations, or glycaemic control.

Overall, allocation to simvastatin in HPS produced a significant 17% (95% CI 9–25; $p<0.0001$) proportional reduction in the death rate from vascular causes (figure). Among the diabetic participants there was a significant 21% (7–33; $p=0.006$) reduction in vascular deaths, which was similar to the 15% (5–25; $p=0.004$) reduction among the other high-risk individuals studied (heterogeneity $p=0.5$). No significant differences in non-vascular deaths were seen between the treatment groups, either overall or among the diabetic and non-diabetic participants considered separately. Because most of the deaths were vascular, these results translated into reductions in all-cause mortality of 15% (SE 6; $p=0.02$) among the diabetic participants and of 12% (SE 4; $p=0.006$) among the other participants. The cause-specific analyses of mortality are, however, likely to be most informative about the effects of treatment on survival. For, they provide more reliable estimates about not only the beneficial effects on vascular mortality but also about the lack of adverse effects on non-vascular mortality, which are more readily generalisable to different circumstances in which the proportions of deaths from particular causes differ from those in the present study.¹

With respect to Cesare Sirtori's comments, the non-diabetic participants

in HPS were generally older than the diabetic participants (mean age at entry: 64.7 vs 62.1 years), and were more likely to have prior myocardial infarction (51 vs 19%) or other occlusive arterial disease (48 vs 32%). These differences probably explain the similar absolute risks of vascular events in participants with or without diabetes, since pre-existing disease was the chief determinant of absolute risk. For example, the 5-year rates of a first major vascular event in the placebo group ranged from 13% for those with diabetes but no previously diagnosed occlusive arterial disease to 36% for those with both diabetes and prior vascular disease, with intermediate rates of 25% in those with vascular disease but no diabetes. After making allowance for non-compliance, 40 mg simvastatin daily would probably reduce these rates by about a third. Hence, 5 years of treatment would be expected to prevent major vascular events among about 45 per 1000 diabetic individuals without occlusive arterial disease compared to about 120 per 1000 with both diabetes and arterial disease. The results of HPS also show that continued treatment reduces the rate not just of the first occurrence of such events but also of subsequent events. Consequently, about 70 first or subsequent major vascular events would be avoided among the 45 diabetic participants without pre-existing vascular disease per 1000 who avoid at least one major vascular event during 5 years of treatment. Given the size of these benefits (and the low risk of side-effects), it would seem appropriate for such statin therapy to be considered routinely for all diabetic

participants at sufficiently high risk of major vascular events, irrespective of their initial blood cholesterol concentrations or pre-existing vascular disease.

The Clinical Trial Service Unit has a staff policy of not accepting honoraria or other payments from the pharmaceutical industry, except for the reimbursement of costs to participate in scientific meetings. R Collins, J Armitage, S Parish, and R Peto have, therefore, only had such costs reimbursed, and P Sleight has received honoraria as well as such reimbursement of costs.

Rory Collins, Jane Armitage, Sarah Parish, Peter Sleight, Richard Peto, on behalf of the MRC/BHF Heart Protection Study Collaborative Group

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- Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. *Lancet* 2001; 357: 373–80.

Sir—The HPS Collaborative Group¹ concludes that “cholesterol-lowering therapy is beneficial for people with diabetes even if they do not already have manifest coronary disease or high cholesterol concentrations”, and that “40 mg simvastatin daily is safe and well tolerated”. The headline on *The Lancet's* website reads, “The UK Heart Protection study . . . concludes statins should be used for routine therapy for people with diabetes”.

A closer look at the data, however, indicates this conclusion is not justified. What was the effect of simvastatin on diabetic patients' overall mortality, serious adverse events, and hospital admission rates? Though not stated, the answers to these questions are available in data reported previously by the group and should be taken into account.

If these concerns seem far-fetched, we have only to look back to clofibrate, the blockbuster cholesterol-lowering drug of the 1970s, to remind ourselves of their importance. Just like simvastatin in the HPS, clofibrate decreased the risk of coronary heart disease by 20%.² However, the WHO's cooperative trial,³ showed there is more to improving health than the reduction of cardiovascular disease; based on more than 200 000 person-years of observation, the study indicated that, despite the cardiovascular benefit, patients taking clofibrate had an excess overall mortality of 47%.

Might statins similarly decrease cardiovascular complications in diabetics with normal cholesterol concentrations yet produce no overall benefit? The results of the lipid-lowering trial component of the Antihypertensive and Lipid-Lowering Treatment to