CORRESPONDENCE

Comments on the MRC/BHF Heart Protection Study

Sir—The Heart Protection Study (HPS) Collaborative Group (June 14, p 2005) 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. 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.

Christoph Pechlaner
Department of General Internal Medicine, Innsbruck University Hospital, A-6020 Innsbruck, Austria (e-mail: christoph.pechlaner@uibk.ac.at)


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.

Nasser Mikhail
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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 global cardiovascular risk, and it casts doubt on the frequently expressed notion that diabetes is a coronary event equivalent.

Cesare R Sirtori
University Centre for Hyperlipidaemias, Niguarda Hospital, University of Milano, Via Balzaretti 9, 20133 Milan, Italy (e-mail: cesare.sirtori@unimi.it)


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...
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 irrespectively of any pre-existing occlusive arterial disease or their presenting age, sex, blood lipid concentrations, or glycemic 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.  

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 Sleigh 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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CORRESPONDENCE

<table>
<thead>
<tr>
<th>Cause of death and prior disease group</th>
<th>Simvastatin-allocated (10 269)</th>
<th>Placebo-allocated (10 267)</th>
<th>Death rate ratio (95% CI)</th>
<th>Placebo better</th>
<th>Simvastatin better</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular causes</strong></td>
<td></td>
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<tr>
<td>Diabetes</td>
<td>242 (8.1%)</td>
<td>304 (10.2%)</td>
<td>0.83 (0.75–0.91)</td>
<td>0.87 (0.81–0.94)</td>
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<tr>
<td>No diabetes</td>
<td>539 (7.4%)</td>
<td>633 (8.7%)</td>
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<td><strong>Subtotal: vascular</strong></td>
<td>781 (7.6%)</td>
<td>937 (9.1%)</td>
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<tr>
<td><strong>Non-vascular causes</strong></td>
<td></td>
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<tr>
<td>Diabetes</td>
<td>142 (4.8%)</td>
<td>142 (4.8%)</td>
<td>0.95 (0.85–1.07)</td>
<td>0.87 (0.81–0.94)</td>
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<td>No diabetes</td>
<td>405 (5.6%)</td>
<td>428 (5.9%)</td>
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<tr>
<td><strong>Subtotal: non-vascular</strong></td>
<td>547 (5.3%)</td>
<td>570 (5.6%)</td>
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<td><strong>All causes</strong></td>
<td>384 (12.9%)</td>
<td>446 (14.9%)</td>
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<tr>
<td>No diabetes</td>
<td>944 (12.9%)</td>
<td>1061 (14.6%)</td>
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<tr>
<td><strong>Any death</strong></td>
<td>1328 (12.9%)</td>
<td>1507 (14.7%)</td>
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</tr>
</tbody>
</table>

**Death rate ratio**

0-6 0-8 1-0 1-2