Cholesterol lowering after participation in the Scandinavian Simvastatin Survival Study (4S) in Finland

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Background Patient compliance is crucial for the effectiveness of preventive medication. The aim of the study was to investigate changes in serum cholesterol levels and the use of cholesterol lowering drugs one year after the end of the Scandinavian Simvastatin Survival Study (4S), a randomized secondary prevention study of coronary heart disease with simvastatin and placebo.

Methods and results A questionnaire asking the current use of cholesterol lowering drugs, most recent serum cholesterol value and attitudes towards cholesterol lowering was sent to 785 surviving 4S participants in four 4S centres in Finland. The response rate was 94%. The current use of cholesterol lowering drugs and the reported mean serum cholesterol values were similar to the original simvastatin and placebo groups. In all, 74% (n = 546) reported that they had used cholesterol lowering drugs after the study, and 63% (n=467) were currently using them, mostly simvastatin (96%) with an average dose of 14 (SD 5) mg . day⁻¹. Cholesterol lowering was considered to be 'very important' by 53% and 'important' by 37% of the respondents. The most frequent reasons for discontinuation were 'drug costs' (38%) and 'normal cholesterol values' (30%). The reported mean serum cholesterol levels were 5.1 (SD 1.0) and 5.7 (SD 1.1) mmol⁻¹ in the current cholesterol lowering drug users and non-users, respectively (P<0.0001). The in-trial treatment goal of serum cholesterol (≤ 5.2 mmol⁻¹) was not met in 38% of the users and in 68% of the non-users of cholesterol lowering drugs.

Conclusion One year post-trial the original simvastatin and placebo groups of the 4S had become similar with regard to the use of cholesterol lowering drugs and serum cholesterol levels. The adherence to medication, however, still remained relatively high, but there was a shift toward lower doses, and consequently toward higher post-trial serum cholesterol levels.

Key Words: Cholesterol, patient compliance, secondary prevention, simvastatin.

Introduction

The Scandinavian Simvastatin Survival Study (4S) clearly demonstrated the benefit of effective cholesterol lowering in the secondary prevention of coronary heart disease[1]. Over the 5-4 years of median follow-up, simvastatin at the mean dose of 27 mg . day⁻¹, reduced total and low density lipoprotein cholesterol by 25% and 35%, respectively, and increased high density lipoprotein cholesterol by 8%. In the simvastatin group, total mortality risk was reduced by 30% (P=0.0003 vs placebo group) attributable to a 42% reduction in the risk of coronary death. The risk of other major coronary events was also significantly reduced. The recently published results of the Cholesterol and Recurrent Events (CARE) study[2] confirm and extend the value of statin treatment in patients with coronary heart disease. Now the important goal is to convert and implement these results into everyday clinical practice where hyperlipidaemia is still often neglected or treated inefficiently[3,4].

In the 4S, the in-trial drop-out rate was exceptionally low, 11-6% overall and only 8-2% out of 868 randomized patients in the four Finnish centres. At the last visit, the majority of the Finnish 4S patients were recommended to use cholesterol-lowering medication in the future as part of the normal health care. A recent
study from the United States showed that low discontinuation rates of hypolipidaemic drugs in randomized clinical studies did not reflect the discontinuation rates actually observed in primary care. Therefore, it is interesting to know how a motivated trial group of patients, such as the 4S participants, adheres to lipid treatment post-trial. We evaluated this in the Finnish 4S patients.

**Patients and methods**

The details of the 4S have been reported earlier[11]. The study included 4444 coronary patients (19% women) with baseline cholesterol levels between 5.5 and 8.0 mmol·L⁻¹ in five Nordic countries. The patients were randomly allocated into placebo and simvastatin (20 mg·day⁻¹) groups. In the latter, the simvastatin dose was titrated, maintaining the blind to 40 mg·day⁻¹ in one third of patients in order to reduce serum total cholesterol to 3.0–5.2 mmol·L⁻¹. During the median follow-up time of 5.4 years, in the simvastatin group the mean change of total cholesterol was −25%, to around 5.06 mmol·L⁻¹. The 4S formally ended on 1 August 1994, whereafter it was continued in the four Finnish centres as an open label study with simvastatin 20 mg·day⁻¹ offered to all participants for approximately 6 months. Final examinations for serum lipid measurements were performed during the winter of 1995, whereafter participants were referred to the care of their own physicians. At the final visit, investigators were given ‘free hands’ to judge appropriate lipid therapy for the patients; the majority of them were advised to continue lipid-lowering medication, mainly simvastatin. One year later, in winter 1996, we sent a simple structured postal questionnaire to all eligible participants (n = 785) and asked about the current use of cholesterol-lowering drugs, cholesterol levels measured in open care and attitudes toward cholesterol lowering (scale 1 to 4: ‘doesn’t matter’, ‘somewhat important’, ‘important’, ‘very important’). The questionnaire was re-sent after one month to non-respondents.

Statistical analyses were performed with Biomedical Data Processing (BMDP) software. Chi-square test with Yates’ correction was used to compare proportions.

**Results**

The response rate was 94% (n = 741) with only slight differences between the four centres. The current use of lipid lowering medication and post-trial cholesterol values were reported by 737 (94%) and 572 (73%) patients, respectively. The data are shown in Table 1 according to the treatment status during the actual trial. One year post-trial use of cholesterol lowering drugs and serum cholesterol values are similar in the original simvastatin and placebo groups. Cholesterol lowering was considered to be ‘very important’ by 53% and ‘important’ by 37% of the respondents.

**Table 1** Current use of cholesterol-lowering drugs and post-trial serum cholesterol levels according to the original treatment groups during 4S

<table>
<thead>
<tr>
<th>Original treatment group</th>
<th>Currently using cholesterol lowering drug %</th>
<th>Post-trial serum cholesterol, mmol·L⁻¹ (SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, n = 367</td>
<td>62 (25)</td>
<td>5.3 (1.1)</td>
</tr>
<tr>
<td>Simvastatin, n = 370</td>
<td>65 (25)</td>
<td>5.3 (1.1)</td>
</tr>
</tbody>
</table>

*Reported in 289 and 283 patients of the placebo and simvastatin groups, respectively.

**Table 2** Current use of cholesterol-lowering drugs and serum cholesterol levels one year post-trial in former 4S patients

<table>
<thead>
<tr>
<th>Currently using cholesterol lowering drug</th>
<th>Number (%)</th>
<th>Post-trial serum cholesterol, mmol·L⁻¹ (SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>467 (63)</td>
<td>5.1 (1.0)</td>
</tr>
<tr>
<td>No</td>
<td>270 (37)</td>
<td>5.7 (1.1)†</td>
</tr>
<tr>
<td>no drug treatment after final visit</td>
<td>188 (26)</td>
<td>5.7 (1.0)</td>
</tr>
<tr>
<td>discontinued drug during the post-trial year details of discontinuation unknown</td>
<td>79 (11)</td>
<td>5.6 (1.2)‡</td>
</tr>
<tr>
<td>unknown</td>
<td>3 (0.4)</td>
<td></td>
</tr>
</tbody>
</table>

*Reported by 572 patients. †P < 0.0001 vs patients on cholesterol-lowering drugs.

**Table 3** Reported reasons for discontinuation of cholesterol-lowering drugs after 4S trial

<table>
<thead>
<tr>
<th>Reason for discontinuation*</th>
<th>Number (% of all reasons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal serum cholesterol</td>
<td>79 (30)</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>23 (9)</td>
</tr>
<tr>
<td>Drug cost</td>
<td>99 (38)</td>
</tr>
<tr>
<td>Don’t want to use</td>
<td>23 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>40 (15)</td>
</tr>
</tbody>
</table>

*Six patients failed to report their reason for discontinuation.

The reported levels of post-trial serum cholesterol were clearly (P < 0.0001) lower in the current drug users than non-users (Table 2). Altogether, 74% (n = 546) reported that they had used cholesterol-lowering drugs after the study, and 63% (n = 467, 66% of men and 58% of women, P = 0.036) of the respondents were currently using these drugs (Table 2). Simvastatin was the most frequent drug (in 96%) and its average dose was 14 (SD 5) mg·day⁻¹. In the four centres the proportion of users varied between 75% and 51%. The reasons for discontinuation are shown in Table 3. The most frequently reported reasons were ‘drug costs’ (in 38%) and 'normal cholesterol values' (in 30%). Among patients without current cholesterol-lowering medication, adverse
effects were reported as the reason for discontinuation in 9%, which is only 3% of all respondents. The distributions of the reasons for discontinuation were similar in the original placebo and simvastatin groups.

Discussion

The present results showed a continued positive attitude toward cholesterol lowering one year post-trial among former 4S patients. This in accordance with results from final questionnaires in three Finnish 4S centres (480 patients), demonstrating a high degree of patient satisfaction during the actual trial[6]. Furthermore, the adherence to cholesterol medication among motivated patients is high: 86% (467 out of 546) of those who reported having used cholesterol lowering medication after the last visit were continuing this medication one year later. An important finding was that — at least in Finland — one year post-trial the original simvastatin and placebo groups had become similar as regards serum cholesterol levels and the current use of cholesterol lowering drugs. This will probably also dilute post-trial differences in cardiovascular events between the original groups and should be taken into account in future follow-up studies of the 4S. On the other hand, there is a shift toward lower doses of simvastatin, 14 mg · day⁻¹ one year post-trial vs 27 mg · day⁻¹ during the actual trial, and the post-trial serum cholesterol levels appear to be accordingly higher. In fact, the in-trial treatment goal for serum total cholesterol (≤ 5.2 mmol· L⁻¹) was not met one year post-trial in 38% of the users of cholesterol lowering drugs, and, furthermore, 68% of patients without cholesterol lowering medication had cholesterol levels above this goal.

In Finland, the reimbursement of the expenses of cholesterol lowering drugs by the Social Insurance Institution is only 50%, and this explains why drug costs was an important reason for discontinuation (and probably for lower dose) of statin treatment. The second most frequent reason for discontinuation in our patients, 'normal serum cholesterol', seemed to be a wrong concept about 'normal' cholesterol levels because their mean cholesterol level was 5.4 mmol· L⁻¹ (SD 0.76) with a range from 3.5 to 7.3 mmol· L⁻¹. This range clearly overlaps that of cholesterol levels at which patients is high: 86% (467 out of 546) of those who reported having used cholesterol lowering medication after the last visit were continuing this medication one year later. An important finding was that — at least in Finland — one year post-trial the original simvastatin and placebo groups had become similar as regards serum cholesterol levels and the current use of cholesterol lowering drugs. This will probably also dilute post-trial differences in cardiovascular events between the original groups and should be taken into account in future follow-up studies of the 4S. On the other hand, there is a shift toward lower doses of simvastatin, 14 mg · day⁻¹ one year post-trial vs 27 mg · day⁻¹ during the actual trial, and the post-trial serum cholesterol levels appear to be accordingly higher. In fact, the in-trial treatment goal for serum total cholesterol (≤ 5.2 mmol· L⁻¹) was not met one year post-trial in 38% of the users of cholesterol lowering drugs, and, furthermore, 68% of patients without cholesterol lowering medication had cholesterol levels above this goal.

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The 4S Study Group in Finland also includes: T. A. Miettinen, H. Vanhanen, K. Hölttä, H. Luomamäki, T. Pekuri, A. Vuorinen (Helsinki); A. Pasternack, L. Siitonen, R. Rimpi (Tampere); M. Lilja, T. Korhonen, A. Rantala, M. Rantala, M. Savolainen, O. Ukkola, L. Laine, L. Virkkala (Oulu); A. Rantala, H. Miettinen, A. Aartolahti, R. Räsänen (Oulu).

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References


Appendix

The 4S Study Group in Finland also includes: T. A. Miettinen, H. Vanhanen, K. Hölttä, H. Luomamäki, T. Pekuri, A. Vuorinen (Helsinki); A. Pasternack, L. Siitonen, R. Rimpi (Tampere); M. Lilja, T. Korhonen, A. Rantala, M. Rantala, M. Savolainen, O. Ukkola, L. Laine, L. Virkkala (Oulu); A. Rantala, H. Miettinen, A. Aartolahti, R. Räsänen (Oulu).

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