Differences in the treatment of coronary heart disease between countries as revealed in the Scandinavian Simvastatin Survival Study (4S)

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Aim To assess differences in treatment of ischaemic heart disease in the Scandinavian countries.

Methods and Results The Scandinavian Simvastatin Survival Study (4S) lasted 5-4 years and showed that death rates in 4444 patients with coronary heart disease were 30% lower in those treated with simvastatin to lower serum cholesterol than in those given placebo. Apart from this main result, the 4S provided detailed information on rates of death and other manifestations of coronary heart disease, as well as on use of non-lipid forms of therapy. There were substantial differences in 4S placebo group rates of mortality, coronary deaths and major coronary events between countries. Surgical and medical therapy varied importantly between countries.

Conclusions Major inter-country differences in rates of death and myocardial infarction in patients with coronary heart disease were likely to be due to a composite of differences in baseline characteristics including smoking. They occurred in a setting of very uneven exploitation of the potential for improving survival of patients with ischaemic heart disease.

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Key Words: Coronary heart disease, cholesterol, medical technology, smoking, beta-blockade, calcium channel blockers, revascularization.

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Introduction

Results of clinical trials and other forms of evidence justify consensus statements[1] that should leave physicians in little doubt about ways of reducing the risk of recurrent acute myocardial infarctions and coronary deaths in survivors of acute myocardial infarction. To varying degrees, such guidelines are, nevertheless, not followed[2,3].

The Scandinavian Simvastatin Survival Study[4] provided definitive evidence to justify recommendations, since it demonstrated that risk of death was reduced by 30% if serum cholesterol was lowered with simvastatin over a period of 5 to 6 years. Apart from this main result, the study also provided detailed information on modes of non-lipid treatment of patients with ischaemic heart disease in the five Nordic countries in which the study was conducted. The data, collected in a standardized manner, show that important differences in prognosis between countries occur in a setting of substantial inter-country differences in treatment of ischaemic heart disease.

Methods

The design, organisation, practical aspects and major findings of the '45' have been published[4,5]. Briefly, it was a randomized clinical trial designed to test the hypothesis that lowering of cholesterol with simvastatin would improve survival of patients with coronary heart disease. Patients had either had a myocardial
infarction (79%) at least 6 months previously, or they had angina pectoris (21%). About 20% of infarction survivors also had angina. Entry criteria of serum cholesterol between 5.5 and 8.0 mmol l⁻¹ and triglycerides less than 2.5 mmol l⁻¹ were fulfilled by 4444 patients, who were randomized to treatment with either placebo (n=2223) or simvastatin (n=2221) 20 to 40 mg daily.

The primary study end-point was death. After a median follow-up of 5-4 years, 11.5% of placebo patients had died compared to 8.2% of simvastatin patients. In relative terms, deaths were reduced by 30% (P <0.0003). The improvement in survival was due to a reduction in coronary deaths of 8.5% in the placebo group and 5.0% in the simvastatin group. There was no difference in non-cardiovascular deaths between the groups. The secondary end-point was ‘major coronary events’, a composite measure of coronary deaths + non-fatal myocardial infarctions and resuscitated cardiac arrests. Major coronary events were reduced by 44%.

For the characteristics given in the Table, the following pairwise differences between countries were significant (<0.05):
- Family history: Denmark vs Finland, Denmark vs Norway, Denmark vs Sweden, Finland vs Norway, Finland vs Sweden.
- Women: Finland vs Norway, Finland vs Sweden.
- Hypertension: Finland vs Norway, Norway vs Sweden.
- Claudication: Iceland vs Norway.
- Diabetes: Finland vs Norway.
- Current smoker: Denmark vs Finland, Denmark vs Iceland, Denmark vs Norway, Denmark vs Sweden, Norway vs Sweden.
- Q-wave: Denmark vs Finland, Finland vs Norway, Finland vs Sweden, Iceland vs Norway.
- <2 years since AMI or onset of angina pectoris: Denmark vs Finland, Denmark vs Iceland, Denmark vs Norway, Denmark vs Sweden, Iceland vs Norway, Iceland vs Sweden.

Table 1 Percentage of placebo patients with on-trial events by country

<table>
<thead>
<tr>
<th></th>
<th>Denmark</th>
<th>Finland</th>
<th>Iceland</th>
<th>Norway</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>All deaths</td>
<td>15·8 (14·6)</td>
<td>7·6 (8·8)</td>
<td>8·9 (9·8)</td>
<td>12·9 (13·2)</td>
<td>11·1 (10·7)</td>
</tr>
<tr>
<td>CHD deaths</td>
<td>12·7 (11·9)</td>
<td>4·4 (5·2)</td>
<td>6·3 (7·5)</td>
<td>10·2 (10·5)</td>
<td>8·1 (7·9)</td>
</tr>
<tr>
<td>Major CHD event</td>
<td>31·0 (28·5)</td>
<td>21·0 (21·3)</td>
<td>27·9 (28·7)</td>
<td>29·9 (28·8)</td>
<td>29·1 (27·6)</td>
</tr>
<tr>
<td>CABG or PTCA</td>
<td>10·1 (9·7)</td>
<td>13·4 (12·0)</td>
<td>24·1 (21·4)</td>
<td>19·2 (18·0)</td>
<td>20·4 (19·3)</td>
</tr>
</tbody>
</table>

Percentages adjusted for sex, age, etc., are given in parentheses so that they apply to a theoretical, medium-risk, non-smoking, male acute myocardial infarction survivor of 60 years without diabetes, hypertension or claudication. The following pairwise comparisons between countries were significant (P <0.05):
- All deaths: Denmark vs Finland (only for unadjusted values).
- Coronary heart disease (CHD) deaths: Denmark vs Finland, Finland vs Norway (for both unadjusted and adjusted values).
- Major coronary heart disease events: Denmark vs Finland, Finland vs Norway, Finland vs Sweden, (only for unadjusted values).
- Revascularizations: Denmark vs Iceland, Denmark vs Norway, Denmark vs Sweden, Finland vs Sweden (for both unadjusted and adjusted values).

Table 2 Baseline characteristics of patients by country

<table>
<thead>
<tr>
<th></th>
<th>Denmark</th>
<th>Finland</th>
<th>Iceland</th>
<th>Norway</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>Simvastatin group</td>
<td>358</td>
<td>435</td>
<td>78</td>
<td>514</td>
</tr>
<tr>
<td></td>
<td>Placebo group</td>
<td>355</td>
<td>433</td>
<td>79</td>
<td>511</td>
</tr>
<tr>
<td>% patients</td>
<td>Family history of CHD</td>
<td>60</td>
<td>83</td>
<td>75</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>19</td>
<td>29</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>21</td>
<td>31</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Claudication</td>
<td>7</td>
<td>6</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>3</td>
<td>7</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Current smokers</td>
<td>42</td>
<td>20</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Q-wave</td>
<td>34</td>
<td>22</td>
<td>27</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>&lt;2 years since AMI or onset of angina pectoris</td>
<td>35</td>
<td>21</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Angina pectoris only</td>
<td>11</td>
<td>36</td>
<td>43</td>
<td>15</td>
</tr>
</tbody>
</table>

For the characteristics given in the Table, the following pairwise differences between countries were significant (<0.05):
- Family history: Denmark vs Finland, Denmark vs Norway, Denmark vs Sweden, Finland vs Norway, Finland vs Sweden.
- Women: Finland vs Norway, Finland vs Sweden.
- Hypertension: Finland vs Norway, Norway vs Sweden.
- Claudication: Iceland vs Norway.
- Diabetes: Finland vs Norway.
- Current smoker: Denmark vs Finland, Denmark vs Iceland, Denmark vs Norway, Denmark vs Sweden, Norway vs Sweden.
- Q-wave: Denmark vs Finland, Finland vs Norway, Finland vs Sweden, Iceland vs Norway.
- <2 years since diagnosis: Denmark vs Finland, Denmark vs Iceland, Denmark vs Norway, Denmark vs Sweden, Finland vs Norway, Iceland vs Norway.
- Angina only: Denmark vs Finland, Denmark vs Iceland, Denmark vs Sweden, Finland vs Norway, Finland vs Sweden, Iceland vs Norway, Iceland vs Sweden.
of tertiary end-points included need of myocardial revascularization, which was reduced by 37%.

All drugs used by the patients were recorded at the clinic visits performed at 6-week intervals during the first half year and semi-annually thereafter. Event rates were analysed using logistic regression. The significance levels for the pairwise differences between countries were adjusted for multiplicity using a step-down procedure [6].

Results

There were appreciable between-country differences in event rates in the placebo group (Table 1). There were no important differences in average age (range 58·0 to 59·4 years) or average total cholesterol (range 6·63 to 6·91 mmoles l$^{-1}$) at entry into the study. These and selected other baseline characteristics of the two treatment groups are given in Table 2.

Some characteristics that worsened patient prognosis within the study differed between countries. These included smoking and the percentage of patients with myocardial infarction as a criterion for entry into the study. The event rates were therefore adjusted so that they applied to a theoretical medium risk non-smoking man of 60 years without diabetes, hypertension or claudication. Adjustments slightly reduced differences in event rates between countries (figures in parentheses in Table 1), and some of the between-country differences in rates of major coronary events could be explained by adjusting for age, sex, smoking, hypertension, diabetes and claudication, as indicated in Table 1. Event rates were calculated in the same way for placebo patients with myocardial infarction as criterion for inclusion into the study (Table 3).

After adjustments, substantial inter-country differences in event rates remained, which in part could be due to differences in time elapsed since the qualifying myocardial infarction. Other possible explanations pertain to the forms of treatment that patients were given apart from simvastatin or simvastatin placebo.

The percentage of patients who had had myocardial revascularization procedures at baseline differed markedly between countries (Denmark 3%, Finland 5%, Iceland 27%, Norway 10% and Sweden 7%). Figure 1(a) shows that revascularization rates during the study in medium risk patients by country were unrelated to major coronary events. The relationship to total mortality tended to be inverse, but it was not a significant finding (Fig. 1(b)).

Several forms of concomitant medical treatment for ischaemic heart disease at baseline and throughout the study also differed markedly (Fig. 2). Use of aspirin increased in all countries during the study as evidence of

Table 3 Percentage of placebo acute myocardial infarction survivors with on-trial events by country

<table>
<thead>
<tr>
<th></th>
<th>Denmark</th>
<th>Finland</th>
<th>Iceland</th>
<th>Norway</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>314</td>
<td>275</td>
<td>46</td>
<td>439</td>
<td>694</td>
</tr>
<tr>
<td>All deaths</td>
<td>16·6 (14·3)</td>
<td>9·8 (9·0)</td>
<td>10·9 (9·8)</td>
<td>13·9 (13·2)</td>
<td>12·2 (10·6)</td>
</tr>
<tr>
<td>CHD deaths</td>
<td>13·7 (12·3)</td>
<td>5·8 (5·4)</td>
<td>10·9 (10·3)</td>
<td>10·7 (10·3)</td>
<td>8·9 (8·0)</td>
</tr>
<tr>
<td>Major CHD events</td>
<td>32·2 (28·2)</td>
<td>24·7 (21·4)</td>
<td>30·4 (26·8)</td>
<td>31·9 (29·5)</td>
<td>31·1 (27·7)</td>
</tr>
<tr>
<td>CABG/PTCA</td>
<td>9·9 (9·3)</td>
<td>13·5 (12·0)</td>
<td>15·2 (13·8)</td>
<td>19·6 (18·4)</td>
<td>18·9 (17·5)</td>
</tr>
</tbody>
</table>

Percentages adjusted for sex, age, etc., are given in parentheses so that they apply to a theoretical medium risk non-smoking man of 60 years without diabetes, hypertension or claudication.
its beneficial effects became more generally known, but Norwegian patients continued to be given less aspirin than, in particular, Danish patients. In contrast, use of beta-blockers, calcium channel blockers, long acting nitrates and thiazides were stable throughout the study. Use of beta blockers in Danish patients was, in almost all cases, less than half of that in the other countries. Use of calcium channel blockers in Finnish and Icelandic patients was, in most cases, more than twice as common as that in Norwegian patients, and long acting nitrates were given at much higher rates in Finland than in the other countries. Thiazides were rarely given in Norway.
and fairly commonly used in Denmark and Iceland. Warfarin or other coumarins were rarely used at baseline in any country, but use increased over time. At the end of the study, about 7% of Norwegian patients, but only 1% of Danish patients, were treated with warfarin-like drugs. In contrast, the increase in use of inhibitors of the angiotensin converting enzyme (ACE) was fairly uniform throughout the Nordic countries. The reader should note the amplification of the y-axis in the panels of Fig. 2 depicting use of thiazides, warfarin and ACE inhibitors.

The analyses of the pairwise country differences in total mortality, coronary mortality and major coronary events indicated in Table 1 did not change when adjusted for baseline therapy with the drugs discussed above. These differences therefore cannot alone be ascribed to differences in concomitant drug therapy.

The percentage of current smokers was high, especially in Norway and Denmark (Table 2), and they remained high throughout the study, especially in Norway and Denmark (Fig. 2(h)). Conversely, the frequency of ex-smokers at the end of the trial was 36% in Denmark, 44% in Finland, 64% in Iceland, 54% in Norway and 56% in Sweden (Fig. 3).

In the trial as a whole, the percentage of patients experiencing a major coronary event was reduced by simvastatin, irrespective of baseline treatment with other drugs. The data given in Table 4 expand those previously published. With the exception of total mortality in simvastatin patients also on warfarin, there was no significant interaction of concomitant therapy at baseline with investigational treatment.

**Discussion**

Rates of death and major coronary events varied markedly between countries. Could this be due to differences either in the selection of patients for the trial or in the concomitant treatment of patients with ischaemic heart disease?

Patients with angina pectoris are at lower risk than survivors of myocardial infarction, and event rates were in fact lowest in Finland and Iceland (Table 1), where angina pectoris was more often an entry criterion than in the three other countries (Table 2). A adjustment for this and other differences (Tables 1 and 3) as well as outright exclusion of patients with angina pectoris as criterion for inclusion into the study (Table 3) attenuated, but did not remove, the marked event rate differences between countries.

In randomized clinical trials, aspirin, beta-blockers, warfarin and, in patients with left ventricular dysfunction, ACE inhibitors reduce rates of deaths and major coronary events after myocardial infarction. In contrast, calcium antagonists have, in general, not been shown to reduce events. Danish patients received much less beta-blocker therapy than did...
patients in the other Nordic countries, and similarly, patients in Norway were given less aspirin than patients in other countries. These differences in therapy could not, however, in formal analysis explain the differences in clinical outcome between countries. The differences in clinical outcome are probably due to a composite of differences in medical and surgical practice and differences in baseline attributes, including smoking habits[13]. Rates of current smoking were lowest in Sweden and highest in Denmark. Conversely, the frequency of ex-smokers was lowest in Denmark and highest in Iceland, suggesting differences in the degrees of success in reducing smoking.

The data on total mortality and major coronary events (Table 4) show only that simvastatin reduced event rates irrespective of almost all forms of concomitant therapy[5]. They do not reflect the effects of the concomitant therapy per se on clinical events, because they are not results of randomized trials of these various agents. For example, in contrast to results of clinical trials of aspirin, death rates in simvastatin patients given aspirin were actually a little higher than in simvastatin patients not given aspirin. This is likely to be due to more frequent use of aspirin in higher risk patients after a recent myocardial infarction or reinfarction.

Mortality was high in patients given both warfarin and simvastatin. Since less than 2% of patients were on warfarin at baseline, however, these results are based on small numbers and are very likely to be spurious. Moreover, although warfarin use was highest in Norwegian patients (Fig. 2(f)), the reduction in relative risk of dying in the simvastatin group was a little greater (34%) in Norwegian patients than in the whole study cohort (30%).

Differences in baseline patient characteristics, for example history of hypertension, probably explain some of the differences in the use of drugs such as beta-blockers and calcium blockers. The long acting nitrates were similarly used more often in Finnish and Icelandic patients, many of whom qualified for entry into the study because of angina pectoris (Table 2). In contrast, the difference in use of aspirin and perhaps of warfarin can only be ascribed to differences in medical tradition, and possibly practice guidelines between countries. The same consideration probably applies to thiazide drugs, which were used more than four times more frequently in Danish than in Norwegian patients, even though the frequencies of history of hypertension were the same, and congestive heart failure was an exclusion criterion in all countries. National medical tradition and practice guidelines can, of course, be affected by whether the country has hosted a randomized clinical trial of the drug in question.

Implementation or abandonment of forms of treatment and prevention, the effects of which have been studied in randomized clinical trials, varies geographically and over time[14,15]. The 4S, performed in patients all fulfilling rigid criteria for inclusion into a large clinical trial, provides an example, within the same trial, of such geographical and temporal variation in medical and non-medical treatment of patients with coronary heart disease. We could not ascribe inter-country differences in disease events and deaths to any particular difference in treatment, but such differences in clinical outcome occurred in a setting of very uneven exploitation of the potential for improving survival of patients with ischaemic heart disease.

References


