

Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)

Scandinavian Simvastatin Survival Study Group*

Summary

Drug therapy for hypercholesterolaemia has remained controversial mainly because of insufficient clinical trial evidence for improved survival. The present trial was designed to evaluate the effect of cholesterol lowering with simvastatin on mortality and morbidity in patients with coronary heart disease (CHD). 4444 patients with angina pectoris or previous myocardial infarction and serum cholesterol 5.5–8.0 mmol/L on a lipid-lowering diet were randomised to double-blind treatment with simvastatin or placebo.

Over the 5.4 years median follow-up period, simvastatin produced mean changes in total cholesterol, low-density-lipoprotein cholesterol, and high-density-lipoprotein cholesterol of –25%, –35%, and +8%, respectively, with few adverse effects. 256 patients (12%) in the placebo group died, compared with 182 (8%) in the simvastatin group. The relative risk of death in the simvastatin group was 0.70 (95% CI 0.58–0.85, $p=0.0003$). The 6-year probabilities of survival in the placebo and simvastatin groups were 87.6% and 91.3%, respectively. There were 189 coronary deaths in the placebo group and 111 in the simvastatin group (relative risk 0.58, 95% CI 0.46–0.73), while noncardiovascular causes accounted for 49 and 46 deaths, respectively. 622 patients (28%) in the placebo group and 431 (19%) in the simvastatin group had one or more major coronary events. The relative risk was 0.66 (95% CI 0.59–0.75, $p<0.00001$), and the respective probabilities of escaping such events were 70.5% and 79.6%. This risk was also significantly reduced in subgroups consisting of women and patients of both sexes aged 60 or more. Other benefits of treatment included a 37% reduction ($p<0.00001$) in the risk of undergoing myocardial revascularisation procedures.

This study shows that long-term treatment with simvastatin is safe and improves survival in CHD patients.

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Introduction

High serum cholesterol is regarded by many as the main cause of coronary atherosclerosis.¹ Several cholesterol-lowering interventions have reduced coronary heart disease (CHD) events in primary and secondary prevention clinical trials.^{2–9} Expert panels in Europe and the USA have therefore recommended dietary changes and, if necessary, addition of drugs to reduce high cholesterol concentrations—specifically low-density-lipoprotein (LDL) cholesterol^{10–13}—especially in patients with CHD. However, these recommendations have been questioned,^{14,15} mainly because no clinical trial has convincingly shown that lowering of cholesterol prolongs life. Furthermore, overviews of these trials have suggested that survival is not improved, particularly in the absence of established CHD, because the observed reduction of CHD deaths is offset by an apparent increase in non-cardiac mortality, including cancer and violent deaths.^{14–18}

Simvastatin is an inhibitor of hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase, which reduces LDL cholesterol^{19,20} to a greater extent than that achieved in previous diet and drug intervention trials. The Scandinavian Simvastatin Survival Study (4S) was conceived in April, 1987, to test the hypothesis that lowering of cholesterol with simvastatin would improve survival of patients with CHD. Other objectives were to study the effect of simvastatin on the incidence of coronary and other atherosclerotic events, and its long-term safety.

Patients and methods

Organisation

The study design has been published previously.²¹ Patients were recruited at 94 clinical centres in Scandinavia. A steering committee made up of cardiologists, lipidologists, and epidemiologists had scientific responsibility for the study and all reports of the results. One member was the scientific coordinator who worked closely with the study monitors in the Scandinavian subsidiaries of Merck Research Laboratories. Major study events were classified by an independent endpoint classification committee (two experienced cardiologists) without knowledge of treatment allocation. A data and safety monitoring committee performed independent interim analyses of total mortality at prespecified numbers of deaths. The statistician of this committee received information on all deaths directly from the investigators. The study protocol was approved by regional or, if applicable, national ethics committees and by the regulatory agencies in each of the participating Scandinavian countries.

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Recruitment and randomisation

Patient records of men and women aged 35–70 years with a history of angina pectoris or acute myocardial infarction (MI) were systematically screened for study eligibility. The exclusion criteria were: premenopausal women of childbearing potential, secondary hypercholesterolaemia, unstable or Prinzmetal angina, tendon xanthomata, planned coronary artery surgery or angioplasty, MI during the preceding 6 months, antiarrhythmic therapy, congestive heart failure requiring treatment with digitalis, diuretics, or vasodilators, persistent atrial fibrillation, cardiomegaly, haemodynamically important valvular heart disease, history of completed stroke, impaired hepatic function, partial ileal bypass, history of drug or alcohol abuse, poor mental function, other serious disease, current treatment with another investigational drug, or hypersensitivity to HMG-CoA reductase inhibitors. Potentially eligible patients were invited to the clinic for a briefing about the study. If none of the exclusion criteria applied and the patient consented, fasting serum cholesterol and triglyceride were determined by a local laboratory. If serum total cholesterol was >5.5 mmol/L, patients were invited to participate in the study and were given dietary advice.¹¹ After 8 weeks blood was drawn and serum was sent to the central laboratory for analysis of lipid concentrations and a 2-week placebo run-in phase was initiated. If serum cholesterol was 5.5 to 8.0 mmol/L, serum triglyceride was ≤ 2.5 mmol/L, and the patient was compliant and still eligible, final informed consent was obtained and the patient was randomly assigned to treatment with simvastatin 20 mg or placebo, to be taken before the evening meal. Randomisation was stratified for clinical site and previous MI.

Laboratory measurements

The patients visited the clinics every 6 weeks during the first 18 months and every 6 months thereafter for determination of serum aspartate aminotransferase, alanine aminotransferase, and creatine kinase in the local laboratories. Routine haematology and urine examinations were done at baseline and at the final visit. Lipids were measured²¹ at the central laboratory every 6 weeks during the first 6 months and half yearly thereafter. Patients were queried for adverse experiences after 6 weeks, 12 weeks, and 6 months, and every 6 months thereafter. A clinical examination with resting electrocardiogram was performed annually.

Dosage titration

Dosage was adjusted, if necessary, at the 12-week and 6-month visits, on the basis of serum total cholesterol at 6 and 18 weeks. The goal of treatment was to reduce serum total cholesterol to 3.0–5.2 mmol/L. A computer program at the central laboratory issued dosage adjustment messages without revealing lipid levels or treatment allocation. Patients in the simvastatin group whose serum cholesterol was out of range had their dose increased to 40 mg daily, as two 20 mg tablets, or reduced to one 10 mg tablet. To maintain the double-blind, patients in the placebo group were randomly assigned to take matching placebo tablets.

Endpoint definition, ascertainment, and analysis

The primary endpoint of the study was total mortality. The secondary endpoint, analysed by time of first event, was "major coronary events", which comprised coronary deaths, definite or probable hospital-verified non-fatal acute MI, resuscitated cardiac arrest, and definite silent MI verified by electrocardiogram. The tertiary endpoints, also analysed by time of first event, were: (1) any coronary event, ie, the secondary endpoint events plus myocardial revascularisation procedures and hospital admission for acute CHD events without a diagnosis of MI (mainly prolonged chest pain); (2) death or any atherosclerotic event (coronary, cerebrovascular, and peripheral), ie, death from any cause and events included under the first tertiary endpoint, plus hospital-verified non-fatal non-coronary atherosclerotic events; (3) incidence of myocardial

revascularisation procedures, either coronary artery bypass grafting or percutaneous transluminal coronary angioplasty; (4) incidence of hospital admission for acute CHD events without a diagnosis of MI. The fifth and final tertiary endpoint, which relates to health economics, will be addressed in a subsequent report. The protocol specified subgroup analyses of females and of patients aged ≥ 60 years, with recognition that these analyses had less statistical power than those based on the whole population. Whether the patients were alive or not was ascertained half-yearly and at the end of the study by contact with each patient or another member of the household. Cause of death was ascertained from hospital records and death certificates, as well as interviews with physicians and relatives. A summary of these records, and of hospital records of patients with suspected nonfatal endpoint events, was provided to the endpoint classification committee, who then determined and categorised each event for use in the analysis.

Hospital-verified cardiovascular events were classified according to a modification of the WHO MONICA method.^{22,23} Annual electrocardiograms were coded for major Q-wave pattern changes,²⁴ with confirmation by visual overreading. When such a change appeared without a corresponding hospital-verified acute MI, a silent MI was recorded and dated as the midpoint between the two corresponding visits.

The study was planned to have 95% power to detect a 30% reduction in total mortality at $\alpha=0.05$ (two-sided, adjusted for three preplanned interim analyses and one final analysis). To achieve this power the protocol specified 4400 patients to be followed until the occurrence of 440 deaths, unless the trial was stopped early on the basis of an interim analysis. Vital status was monitored throughout the study. Treatment group differences were assessed by the logrank test. Relative risk and 95% confidence intervals were calculated with the Cox regression model.²⁵ Mortality data were also analysed with the same model, with baseline variables that were significantly related to outcome. Two-sided *p* values ≤ 0.05 were regarded as significant and only in the case of the primary endpoint was the significance level adjusted for the three interim analyses. All data were analysed by intention-to-treat.

Results

Of the 7027 patients recruited for the diet period 4444 fulfilled the entry criteria and were randomised between May 19, 1988, and Aug 16, 1989. The main reasons for exclusion were serum total cholesterol after diet outside the 5.5–8.0 mmol/L range ($n=1300$), serum triglyceride >2.5 mmol/L ($n=864$), and unwillingness to participate ($n=396$).

Having completed the third (and final) interim analysis of available endpoint reports, the data safety and monitoring committee advised (on May 27, 1994) that the study should be stopped as soon as was possible. At this analysis the *p* value crossed the boundary of the predefined statistical guideline. After discussion with the chairman of the steering committee, Aug 1, 1994 was selected as the cut-off date at which it was anticipated that the protocol-specified target of 440 deaths would be approximated.

Median follow-up time was 5.4 years (range of those surviving was 4.9–6.3). Confirmation of whether the patients were alive or dead was obtained in every case at the end of the study. The two treatment groups were well matched at baseline (table 1). 288/2223 (13%) patients in the placebo group and 231/2221 (10%) in the simvastatin group stopped taking their tablets. Adverse events were the reason for discontinuing therapy in 129 patients in the placebo group and 126 in the simvastatin group, and patient reluctance to continue accounted for most of the remainder.

	Placebo (n=2223)	Simvastatin (n=2221)
No (%) of patients		
Male	1803 (81)	1814 (82)
Female	420 (19)	407 (18)
Age \geq 60 yr	1126 (51)	1156 (52)
Qualifying diagnosis		
Angina only	456 (21)	462 (21)
Infarction only	1385 (62)	1399 (63)
Both angina and infarction	381 (17)	360 (16)
Time since first diagnosis of angina or infarction		
-1 yr	589 (26)	602 (27)
1-5 yr	961 (43)	929 (42)
\geq 5 yr	673 (30)	690 (31)
Major ECG Q-wave	782 (35)	724 (33)
Secondary diagnoses		
Hypertension	584 (26)	570 (26)
Claudication	123 (6)	130 (6)
Diabetes mellitus	96 (4)	105 (5)
Previous CABG or angioplasty	151 (7)	189 (9)
Non-smokers	562 (25)	558 (25)
Ex-smokers	1065 (48)	1121 (50)
Smokers	596 (27)	542 (24)
Other therapy		
Aspirin	815 (37)	822 (37)
Beta-blockers	1266 (57)	1258 (57)
Calcium antagonists	668 (30)	712 (32)
Isosorbide mono/dinitrate	727 (33)	684 (31)
Thiazides	138 (6)	151 (7)
Warfarin	51 (2)	29 (1)
Fish oil	293 (13)	283 (13)
Mean (SD)		
Age (yr) men	58.1 (7.2)	58.2 (7.3)
Age (yr) women	60.51 (5.7)	60.5 (6.4)
Body mass index (kg/m ²)	26.0 (3.3)	26.0 (3.4)
Heart rate	64.2 (10.1)	63.8 (10.1)
Blood pressure (mm Hg)		
Systolic	139.1 (19.6)	138.5 (19.6)
Diastolic	83.7 (9.5)	83.2 (9.5)
Cholesterol (mmol/L)		
Total	6.75 (0.66)	6.74 (0.67)
HDL	1.19 (0.29)	1.18 (0.30)
LDL	4.87 (0.65)	4.87 (0.66)
Triglycerides (mmol/L)	1.51 (0.52)	1.49 (0.49)

CABG=coronary artery bypass graft; HDL=high-density lipoprotein; LDL=low-density lipoprotein.

Table 1: Baseline characteristics of randomised patients

Changes in serum lipid concentrations

37% of the patients taking simvastatin had their dose raised to 40 mg during the first 6 months after randomisation, while the rest continued to take 20 mg daily, except for 2 patients whose dosage was reduced to 10 mg daily, according to protocol.

Lipid concentrations showed little change in the placebo group, except for an upward drift in serum triglycerides. After 6 weeks of therapy with simvastatin, at which point all patients were still taking 20 mg daily, total cholesterol was reduced on average by 28%, LDL cholesterol by 38%, and triglycerides by 15%, whereas high-density-lipoprotein (HDL) cholesterol rose by 8%. After 1 year, 72% of the simvastatin-treated patients had achieved the total-cholesterol goal (<5.2 mmol/L). In subsequent years there was a small increase in mean total and LDL cholesterol, while HDL cholesterol and triglycerides tended to move in parallel with changes in the placebo group. Over the whole course of the study, in the simvastatin group the mean changes from baseline in total, LDL, and HDL cholesterol, and serum triglycerides, were -25%, -35%, +8% and -10%, respectively. The corresponding values in the placebo group were +1%, +1%, +1%, and +7%, respectively. 35 patients in the placebo group were switched to lipid-

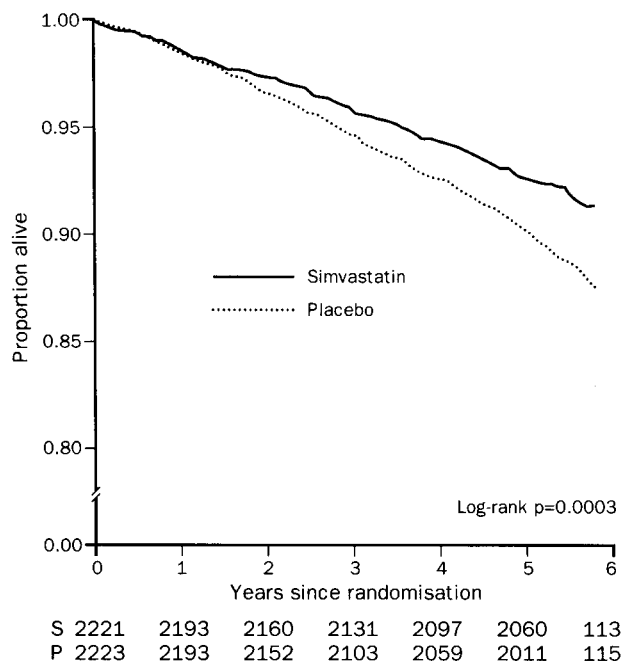


Figure 1: Kaplan-Meier curves for all-cause mortality

Number of patients at risk at the beginning of each year is shown below the horizontal axis.

lowering drugs, either because serum cholesterol rose above the protocol-specified limit of 9.0 mmol/L (16 patients) or because such therapy was initiated by non-study physicians (19 patients).

Mortality

The primary endpoint was total mortality. During the double-blind study period 438 patients died, 256 (12%) in the placebo group and 182 (8%) in the simvastatin group (table 2); the relative risk was 0.70 (95% CI 0.58-0.85, $p=0.0003$) with simvastatin. The Kaplan-Meier 6-year (70 months) probability of survival (figure 1) was 87.7% in the placebo group and 91.3% in the simvastatin group. Adjustment for the baseline covariates made no material difference to the results for survival or the other endpoints. There were 189 coronary deaths in the placebo group (74% of all deaths in this group), compared with 111 in the simvastatin group. The relative risk of coronary death was 0.58 (95% CI 0.46-0.73) with simvastatin. This 42% reduction in the risk of coronary death accounts for the improvement in survival. There was no statistically significant difference between the two groups in the number of deaths from non-cardiovascular causes. There were similar numbers of violent deaths (suicide plus trauma) in the two groups, 7 versus 6. Of the fatal cancers, 12/35 in the placebo group and 9/33 in the simvastatin group arose in the gastrointestinal system. There were similar numbers of cerebrovascular deaths in the two groups, and the difference (6 vs 11) in deaths from other cardiovascular diseases is not significant.

Nonfatal and combined endpoints

The secondary study endpoint was major coronary events: coronary death (table 2), nonfatal definite or probable MI, silent MI, or resuscitated cardiac arrest (table 3). 622 (28%) patients in the placebo group and 431 (19%) in the simvastatin group had one or more secondary endpoint events. The relative risk of a major coronary event in the simvastatin group was 0.66 (95% CI 0.59-0.75, $p<0.00001$). The Kaplan-Meier 6-year

Causes of death	No (%) of patients		
	Placebo (n=2223)	Simvastatin (n=2221)	Relative risk (95% CI)
Definite acute MI	63	30	
Probable acute MI	5	5	
Acute MI not confirmed			
Instantaneous death	39	29	
Death within 1 h*	24	8	
Death within 1-24 h	15	9	
Death >24 h after onset of event	11	10	
Non-witnessed death†	23	13	
Intervention-associated‡	9	7	
All coronary	189 (8.5)	111 (5.0)	0.58 (0.46-0.73)
Cerebrovascular	12	14	
Other cardiovascular	6	11	
All cardiovascular	207 (9.3)	136 (6.1)	0.65 (0.52-0.80)
Cancer	35	33	
Suicide	4	5	
Trauma	3	1	
Other	7	7	
All noncardiovascular	49 (2.2)	46 (2.1)	
All deaths	256 (11.5)	182 (8.2)	0.70 (0.58-0.85)

Relative risk, calculated by Cox regression analysis. MI=myocardial infarction.
 *Following acute chest pain, syncope, pulmonary oedema, or cardiogenic shock.
 †With no likely non-coronary cause. ‡Coronary death within 28 days of any invasive procedure.

Table 2: Mortality and causes of death

probability of escaping such events was 70.5% in the placebo group and 79.6% in the simvastatin group (figure 2A). The relative risk of hospital-verified non-fatal definite or probable acute myocardial infarction was 0.63 (95% CI 0.54-0.73).

Results for the four tertiary endpoints are presented below. The relative risk of having any coronary event in the simvastatin group was 0.73 (95% CI 0.66-0.80, p<0.00001). The 6-year Kaplan-Meier probability of

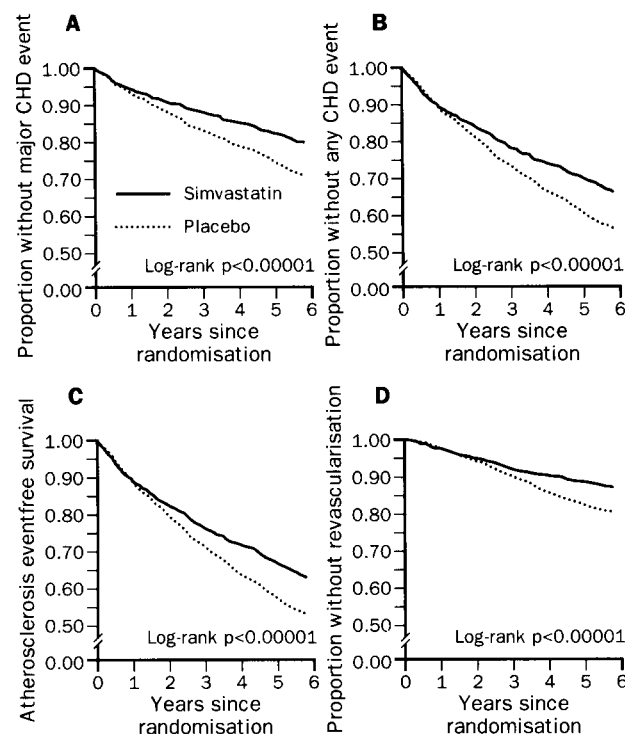


Figure 2: Kaplan-Meier curves for secondary and tertiary endpoints

(A) major coronary events; (B) any coronary event; (C) survival free of any atherosclerotic event; (D) myocardial revascularisation procedures.

Event	No (%) of patients*	
	Placebo (n=2223)	Simvastatin (n=2221)
Major coronary		
Definite acute MI	270 (12.1)	164 (7.4)
Definite or probable acute MI	418 (18.8)	279 (12.6)
Silent MI	110 (4.9)	88 (4.0)
Resuscitated cardiac arrest	0	1
Acute MI, intervention-associated	25	12
Any major coronary*	502 (22.6)	353 (15.9)
Coronary surgery or angioplasty	383 (17.2)	252 (11.3)
Non-MI acute CHD	331 (14.9)	295 (13.3)
Acute non-CHD cardiac	109 (4.9)	109 (4.9)
Cerebrovascular		
Stroke, non-embolic	33	16
Stroke, embolic	16	13
Stroke, haemorrhagic	2	0
Stroke, unclassified	13	15
Stroke, intervention-associated	10	3
Transient ischaemic attack	29	19
Any cerebrovascular*	95 (4.3)	61 (2.7)
Other cardiovascular	33 (1.5)	24 (1.1)

*A patient with 2 or more events of different types will appear more than once in a column but only once in a row.

Table 3: Patients with nonfatal cardiovascular events during follow-up

escaping any coronary event was 56.7% in the placebo group and 66.6% in the simvastatin group (figure 2B). The relative risk of death or having any atherosclerotic cardiovascular event was 0.74 (95% CI 0.67-0.81, p<0.00001). The probability of escaping such events was 53.0% in the placebo group and 62.9% in the simvastatin group (figure 2C). Simvastatin also reduced the patient's risk of undergoing coronary artery bypass surgery or angioplasty (table 3 and figure 2D); the relative risk was 0.63 (95% CI 0.54-0.74, p<0.00001). There was no significant difference between treatment groups with regard to non-MI acute CHD events. A post-hoc analysis was performed on fatal plus nonfatal cerebrovascular events: there were 98 patients with such events in the placebo group and 70 in the simvastatin group, relative risk 0.70 (95% CI 0.52-0.96, p=0.024).

Results in women and patients aged ≥60

The results in the protocol-specified subgroups are presented in table 4. Only 52 of the 827 women died in the trial, 25 (6%) in the placebo group and 27 (7%) in the simvastatin group. Of these deaths 17 and 13, respectively, were the result of CHD. The probability that a woman would escape a major coronary event was 77.7% in the placebo group and 85.1% in the simvastatin group: relative risk was 0.65 (95% CI 0.47-0.90, p=0.010). For both the primary and secondary endpoints, there were no

	No (%) of patients		
	Placebo	Simvastatin	Relative risk* (95% CI)
Death			
Women	25 (6.0)	27 (6.6)	1.12 (0.65-1.93)
Men	231 (12.8)	155 (8.5)	0.66 (0.53-0.80)
Age <60 yr	89 (8.1)	55 (5.2)	0.63 (0.45-0.88)
Age ≥60 yr	167 (14.8)	127 (11.0)	0.73 (0.58-0.92)
Major coronary event			
Women	91 (21.7)	59 (14.5)	0.65 (0.47-0.91)
Men	531 (29.4)	372 (20.5)	0.66 (0.58-0.76)
Age <60 yr	303 (27.6)	188 (17.6)	0.61 (0.51-0.73)
Age ≥60 yr	319 (28.3)	243 (21.0)	0.71 (0.60-0.86)

*Calculated by Cox regression analysis.

Table 4: Endpoints in predefined subgroups

significant interactions between treatment and either sex or age. Although the observed relative risk reductions produced by simvastatin were somewhat less in the patients aged ≥ 60 , they were statistically significant ($p < 0.01$ in both age groups for mortality and $p < 0.0001$ for major coronary events) and the absolute differences between treatment groups were similar in the two age groups.

Adverse experiences

The overall frequency of adverse events was similar in the two groups. As previously noted, 6% of patients in both groups discontinued the study drug because of adverse events. In addition to the cancer deaths reported in table 2, there were 61 nonfatal cases of cancer in the placebo group and 57 in the simvastatin group, of which 14 and 12, respectively, arose in the gastrointestinal system. These totals exclude cases of non-melanoma skin cancer, of which there were 6 in the placebo group and 13 in the simvastatin group. There were no significant differences between the treatment groups for fatal plus nonfatal cancer as a whole or at any particular site. A single case of rhabdomyolysis occurred in a woman taking simvastatin 20 mg daily; she recovered when treatment was stopped. An increase of creatine kinase to more than ten times the upper limit of normal occurred in 1 and 6 patients in the placebo and simvastatin groups, respectively, but in none of the latter was this high level maintained in a repeat sample or accompanied by muscle pain or weakness. Increases of aspartate aminotransferase to more than three times the upper limit of normal occurred in 23 patients in the placebo group and 20 in the simvastatin group. For alanine aminotransferase the corresponding numbers were 33 and 49.

Discussion

As expected in a large study, the groups were well matched at baseline. 79% of patients had a history of MI. Patients were excluded if they had a history of complicated MI with significant myocardial dysfunction, or required drug therapy for heart failure. This was done to avoid excess early mortality from congestive heart failure or arrhythmias, which might dilute the postulated effect of simvastatin on deaths caused by progression of coronary atherosclerosis. These factors resulted in a selection of patients with a lower risk of death in the placebo group than has usually been seen in postinfarction populations.¹¹

The effect of simvastatin on lipids was similar to that observed in other long-term controlled trials with this drug.^{26,27} As often happens in long-term studies analysed by intention-to-treat, there was a slight attenuation of the mean drug effect over time, due at least in part to dilution by patients who stopped treatment but continued to provide blood samples.

Simvastatin produced highly significant reductions in the risk of death and morbidity in patients with CHD followed for a median of 5.4 years, relative to patients receiving standard care. The results in CHD endpoints and in subgroups are internally consistent and very robust. They indicate that addition of simvastatin 20–40 mg daily to the treatment regimens of 100 CHD patients, with characteristics similar to those of our patients, can be expected, on the basis of the corresponding Kaplan-Meier curves, to yield the following approximate benefits over the first 6 years: preservation of the lives of 4 of the 9

patients who otherwise would die from CHD, prevention of nonfatal MI in 7 of an expected 21 patients, and avoidance of myocardial revascularisation procedures in 6 of the 19 anticipated patients.

No previous unifactorial trial of any lipid-lowering therapy has demonstrated reduction of total or even coronary mortality during the planned follow-up period. In the extended follow-up of the first Oslo Diet-Heart study² there was a significant reduction after 11 years in fatal MI. In the niacin arm of the Coronary Drug Project trial there was a significant 11% reduction in total mortality over 15 years.²⁸ Except for the POSCH study,⁹ in which patients with a history of MI underwent partial ileal bypass to reduce mean LDL cholesterol by 38%, none of these trials achieved changes in LDL cholesterol comparable with the 35% average reduction observed in this trial; the reductions in these earlier trials averaged about 10%. The POSCH trial was not large enough to show an effect on total or coronary mortality, but there was a significant 35% reduction over 5 years in CHD deaths plus nonfatal myocardial infarctions, which is in good agreement with our results. Combining the results from twenty-eight cholesterol-lowering trials, Law et al²⁹ estimated that the risk of coronary death plus nonfatal MI was reduced by 7% (95% CI 0–14%) per 0.6 mmol/L reduction in serum total cholesterol concentration in the first 2 years of treatment, and 22% (95% CI 15–28%) in years 3–5. In our study a mean reduction of serum cholesterol of 1.8 mmol/L (25%) was achieved. With the exclusion of silent MI, the risk of coronary death plus nonfatal MI was reduced by 37% over the whole study, by 26% in the first 2 years, and by 46% thereafter. Thus our results are consistent with the estimates of Law et al.

Our study also provided evidence for a beneficial effect of simvastatin on fatal plus nonfatal cerebrovascular events. This finding is consistent with a report³⁰ that lovastatin, a closely related inhibitor of HMG-CoA reductase, can reverse the progression of carotid atherosclerosis. Since it is based on a data-driven post-hoc analysis, prospective trials are needed to confirm this possible additional benefit.

Patient compliance with the demands of the study protocol was generally good and doubtless contributed substantially to the clearcut outcome. Under 1% of placebo patients discontinued study drug to receive open-label cholesterol lowering therapy—an indication that treatment allocation was seldom unblinded by measurement of serum cholesterol outside the study. This reflects in part the contemporary conservative attitude of Scandinavian physicians towards drug treatment of hypercholesterolaemia.

The impact of simvastatin on CHD seems to begin after about 1 year of therapy and increases steadily thereafter. This is consistent with several angiographic studies showing beneficial effects on coronary atherosclerosis within 2 years of effective lipid-lowering therapy.^{31,32} Progression of coronary atherosclerotic lesions clearly predicts subsequent coronary events.³³ Lately the Multicentre Anti-Atheroma Study (MAAS) investigators²⁷ showed by quantitative angiography a retardation of the progression of coronary atheromatous lesions, compared with standard care, at 2 and 4 years after starting treatment with simvastatin in patients similar to those studied in 4S. Significantly fewer new lesions and total occlusions developed in the simvastatin group. Coronary lesions may stabilise as their lipid core shrinks or at least

does not further enlarge; there is thus a drop in risk of plaque rupture, which triggers intramural haemorrhage and intraluminal thrombosis, which in turn may cause coronary events.³¹⁻³⁵ Stabilisation of coronary lesions is most likely the main reason for the improved survival observed in our trial.

Only 19% of the study population were women. In the placebo group mortality rate for women was less than half that for men. With only 52 deaths among women, demonstration of improved survival in women as a separate subgroup was unlikely. Nevertheless, simvastatin did reduce the risk of major coronary events in women to about the same extent as it did in men. It also improved survival in patients aged 60 or more. This is the first trial to show that cholesterol-lowering reduces major coronary events in women and the first to show that it improves survival in older patients.

The improvement in survival produced by simvastatin was achieved without any suggestion of an increase in non-CHD mortality, including deaths due to violence and cancer, which have raised concern in some overviews of cholesterol-lowering trials.¹⁴⁻¹⁸ The overall incidence of fatal plus nonfatal cancer was also similar in the two groups. Simvastatin therapy was well tolerated and the frequencies of adverse events in general, and those associated with drug discontinuation in particular, were similar in the two groups. Rhabdomyolysis, the most important adverse effect of inhibitors of HMG-CoA reductase, occurred in 1 patient who recovered when treatment was stopped. No previously unknown adverse effects were apparent in this trial. Thus the substantial and sustained reduction of total and LDL cholesterol in the simvastatin group was not associated with any serious hazard. The results of the 4S are consistent with the idea that raised LDL cholesterol is an important factor in pathogenesis of CHD.

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