

Follow-Up Study of Patients Randomized in the Scandinavian Simvastatin Survival Study (4S) of Cholesterol Lowering

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The Scandinavian Simvastatin Survival Study (4S) and other randomized clinical trials have demonstrated that cholesterol-lowering treatment with statins improves prognosis in patients with coronary atherosclerosis compared with placebo. The effect of therapy with statins beyond the typical 5 to 6 years' duration of the trials, in particular regarding the risk of cancer, has not been investigated. This study examines the long-term effects of simvastatin for up to 8 years on cause-specific mortality in patients with coronary heart disease (CHD). We performed an observational, government registry-based study of mortality in the groups originally randomized to simvastatin or placebo in the 4S over an additional 2-year follow-up period, so that the median total follow-up period was 7.4 years (range 6.9 to 8.3 in surviving patients). Randomization took place at outpatient clinics at 94 clinical centers in Denmark, Finland, Iceland, Norway, and Sweden from 1988 to 1989. Of 4,444 patients with CHD, 2,223 and 2,221 were randomized to treatment with placebo or simvastatin therapy, respectively. Patients received treatment with simvastatin, starting at 20 mg/day, with titration to 40 mg/day at 12 or 24 weeks if total cholesterol was >5.2

mmol/L (200 mg/dl), or placebo. After the double-blind period, most patients in both treatment groups received simvastatin as open-label prescription. Of the 1,967 patients originally treated with placebo and surviving the double-blind period, 97 (4.9%) died during the following 2 years. In the group randomized to simvastatin the corresponding number was 74 of the 2,039 survivors (3.6%). Adding these deaths to those occurring during the original trial, the total was 353 (15.9%) and 256 (11.5%) deaths in the groups originally randomized to placebo and simvastatin, respectively. The relative risk was 0.70 (95% confidence interval 0.60 to 0.82, $p = 0.00002$). The total number of cancer deaths was 68 (3.1%) in the placebo group and 52 (2.3%) in the simvastatin group (relative risk 0.73, 95% confidence interval 0.51 to 0.05, $p = 0.087$), and the numbers of noncardiovascular and other deaths were similar in both groups. We therefore conclude that treatment with simvastatin for up to 8 years in patients with CHD is safe and yields continued survival benefit. ©2000 by Excerpta Medica, Inc.

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Several randomized controlled trials have now demonstrated that long-term treatment with certain hydroxy-methyl-glutaryl-coenzyme A reductase

inhibitors (statins) to lower serum cholesterol can reduce the incidence of cardiovascular events.¹⁻⁶ The trials have had a duration of 5 to 6 years, and the Kaplan-Meier curves for coronary heart disease (CHD) events have started to separate after 1 to 2 years. No trial has found increased risk of cancer or any other life-threatening adverse effects of statin treatment for up to 6 years. Nevertheless, there is still some concern that cholesterol-lowering treatment for longer periods may increase the risk of noncardiovascular mortality including cancer and thereby offset the beneficial effects on CHD.⁷⁻¹⁰ After completion of the Scandinavian Simvastatin Survival Study (4S),¹ in which the median duration of follow-up was 5.4 years, patients were followed for an additional 2 years, with treatment at the discretion of the patient's physician. Because appreciable separation of the Kaplan-Meier survival curves representing the simvastatin and placebo groups was not seen until about 2 years after randomization, we hypothesized that continued sur-

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vival benefit, expressed as maintenance or further widening of the gap between the 2 mortality curves, would be observed regardless of the proportion of patients in the 2 treatment groups receiving simvastatin or other lipid-lowering therapy. In this report, we document the mortality risk reduction attributable to simvastatin therapy after up to 8.3 years of follow-up (median 7.4 years).

METHODS

Double-blind period: The design and results of the original study have been published previously.¹ In brief, this was a randomized, double-blind, placebo-controlled trial performed in 94 clinical centers throughout the 5 Nordic countries: Denmark, Finland, Iceland, Norway, and Sweden. Men and women aged 35 to 70 years with a history of myocardial infarction or angina pectoris and serum total cholesterol in the range 5.5 to 8.0 mmol/L (212 to 309 mg/dl) and triglycerides ≤ 2.5 mmol/L (221 mg/dl) and no exclusion criteria were randomized to treatment with simvastatin 20 mg/day or placebo. Patients in the simvastatin group with serum total cholesterol >5.2 mmol/L after 6 or 18 weeks had their dosage increased to 40 mg (37% of patients required titration, 72% reached the goal of 5.2 mmol/L at 12 months follow-up).

The primary end point was total mortality, but secondary end points included cause-specific mortality, which was classified by an independent end point classification committee using hospital records, death certificates, and, if necessary, through contacts with physicians and relatives.

Extended follow-up: After the cutoff date of the double-blind study, August 1, 1994, surviving patients returned to the clinic for an interview and physical examination. The steering committee advised that all patients should be treated with simvastatin 20 mg/day until the study results had been published. After publication on November 19, 1994, patients were invited to attend a briefing on the results of the study. Further treatment was left to the discretion of each patient's doctor.

The cutoff date of the extended follow-up was set to August 1, 1996, 2 years after the cutoff date of the base study. One year later, when governmental records of vital status were complete as of the cutoff date, a comparison of these records and the 4S patient register was made. Patients reported to be alive at this comparison were sent letters 3.4 years after completion of the double-blind period, informing them about the follow-up study and asking them to complete an enclosed questionnaire about the use of cholesterol-lowering drugs and their latest cholesterol level. The 4S patient registers were compared with the national death by cause registers, which are derived from death certificate information. The comparison was made 2 years after the completion of the extended follow-up to allow for updating and completion of the registers. Cause of deaths occurring in the 2-year extension period was ascertained by 2 of the investigators (TRP and LW) without knowledge of treatment allocation in

the original double-blind period, based on the death certificate information in the registries. The study protocol with its extension was approved by regional, or if applicable, national ethics committees and by the regulatory agencies in each of the participating Scandinavian countries.

Statistical analyses: A pilot study comparing cause of death in the original study as determined by the End point Classification Committee with that recorded on death certificates had revealed inconsistencies, mainly in the cause of death subcategories. For this reason deaths were categorized into only 4 classes, which in the pilot study reduced the error rate to 2.7%. The groups originally randomized to placebo and simvastatin were compared according to the intention-to-treat principle. Treatment group differences, relative risk, and 95% confidence intervals (CIs) were calculated using the Cox proportional-hazards regression model. Covariates used in these analyses were sex, age, hypertension, and history of myocardial infarction, smoking, and diabetes. Two-sided *p* values ≤ 0.05 were regarded as significant.

RESULTS

Four thousand forty-four patients with CHD were randomized in 1988 and 1989 (Figure 1). The placebo and simvastatin treatment groups were well matched at baseline (Table I). Median follow-up at the completion of the double-blind period was 5.4 years (range of those surviving 4.9 to 6.3). In this period, 13% of the patients in the placebo group and 10% in the simvastatin group stopped taking their study medication. Adverse events were the reported reason in 6% of the randomized patients in both groups. Over the entire double-blind duration of the study, mean changes from baseline in the simvastatin group in total, low-density lipoprotein (LDL) and high-density lipoprotein cholesterol, and triglycerides were -25% , -35% , $+8\%$, and -10% , respectively. The corresponding changes in the placebo group were $+1\%$, $+1\%$, $+1\%$, and $+7\%$, respectively. These changes are by intention-to-treat analysis, including patients who stopped taking the study drug but continued to contribute with blood samples.

Open-label lipid-lowering treatment: Questionnaires were sent to 3,731 patients reported to be alive in the autumn of 1997, 1,824 in the group originally randomized to placebo and 1,907 in the original simvastatin group. The response rate was 88.4% in the original placebo group and 89.4% in the original simvastatin group. Of those responding, 81.5% in the original placebo group reported that they were taking cholesterol-lowering drugs, versus 85.5% of the former simvastatin group ($p = 0.002$) (Table II). Of those taking cholesterol-lowering drugs, simvastatin was used by 96.4% in the former placebo group and 96.3% in the former simvastatin group. The mean extension values for serum cholesterol in all patients reporting such data were 5.16 and 5.11 mmol/L in the groups originally randomized to placebo and simvastatin, respectively. The drug reimbursement rules of governments differ among the participating countries.

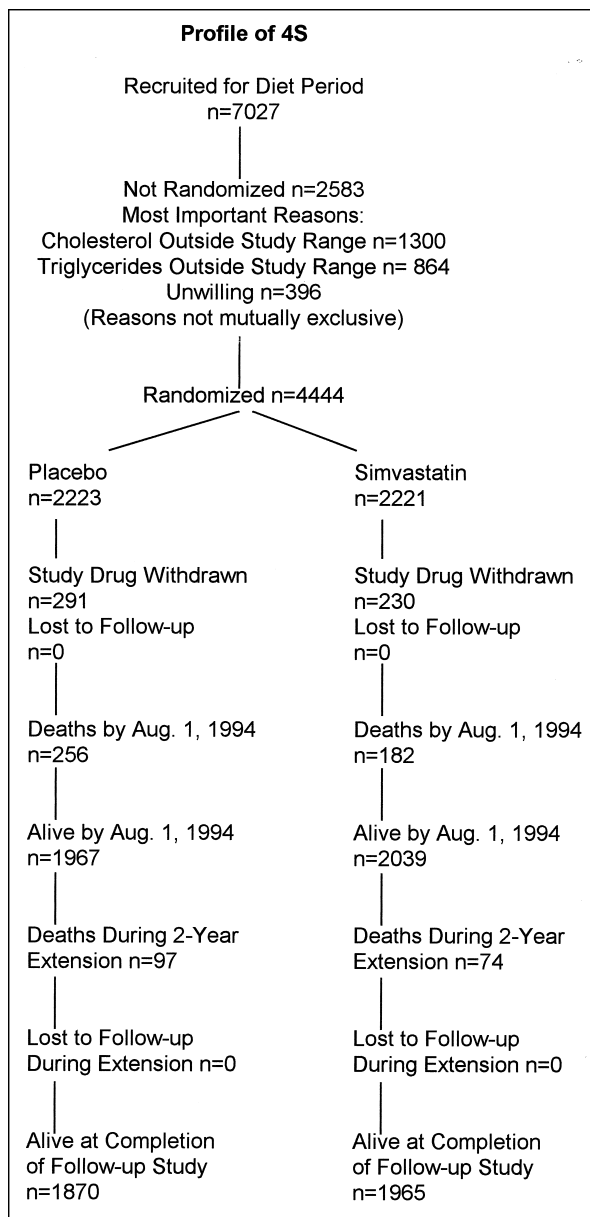


FIGURE 1. Profile of 4S.

Mainly for this reason, open-label prescription of simvastatin occurred less frequently in Denmark and Finland than in the other countries.

Median follow-up time for the double-blind plus the extension period was 7.4 years (range of those surviving 6.9 to 8.3 years). Vital status was confirmed in all randomized patients and cause of death was classified in all cases.

Mortality: During the double-blind period, 256 of the patients (11.5%) in the placebo group and 182 (8.2%) in the simvastatin group died (Table III). The relative risk in the simvastatin group was 0.70 (95% CI 0.58 to 0.85, $p = 0.0003$) due to a 42% risk reduction in coronary deaths. The numbers of deaths from cerebrovascular and other cardiovascular causes were similar, as were numbers for deaths caused by cancer, suicide, and violence.

TABLE I Selected Baseline Characteristics of Randomized Patients

Baseline Characteristics	Placebo (n = 2,223)	Simvastatin (n = 2,221)
No (%) of patients		
Men	1,803 (81)	1,814 (82)
Women	420 (19)	407 (18)
Age ≥ 65 years	503 (23)	518 (23)
LDL cholesterol 3.0–4.5 mmol/L	628 (28)	651 (29)
Qualifying diagnosis (%)		
Angina only	456 (21)	462 (21)
Myocardial infarction	1,767 (79)	1,759 (79)
Secondary diagnoses (%)		
Systemic hypertension	584 (26)	570 (26)
Claudication	123 (6)	130 (6)
Diabetes mellitus	97 (4)	105 (5)
Cholesterol (mmol/L) Mean (SD)		
Total	6.75 (0.66)	6.74 (0.67)
High-density lipoprotein	1.19 (0.29)	1.18 (0.30)
Low-density lipoprotein	4.87 (0.65)	4.87 (0.66)
Triglycerides (mmol/L)	1.51 (0.52)	1.49 (0.49)

TABLE II Use of Cholesterol-Lowering Drugs 3.4 Years After Completion of Double-Blind Study Among Patients' Returning Questionnaires

Drugs Used	Previous Placebo Group (n = 1,824)	Previous Simvastatin Group (n = 1,907)	p Value
Simvastatin	1,268 (78.6)*	1,404 (82.2)*	0.005
Other statin	89 (5.5)	68 (4.0)	0.046
Fibrate	6 (0.4)	11 (0.6)	0.261
Resin	6 (0.4)	12 (0.7)	0.186
Other	5 (0.3)	7 (0.4)	0.616
No drug	298 (18.5)	248 (14.5)	0.004
Unknown	211 (11.6) [†]	201 (10.5) [†]	0.317

*Percentage of patients responding to the questionnaire.

[†]Percentage of those that were sent questionnaires.

Patients could be counted under >1 drug.

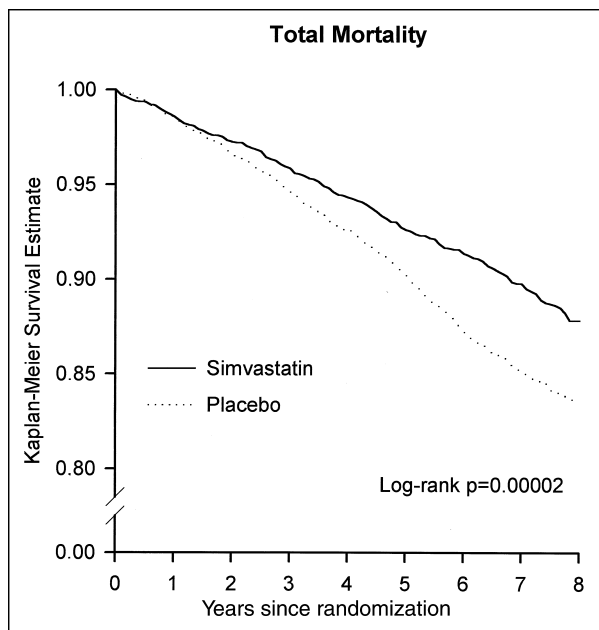
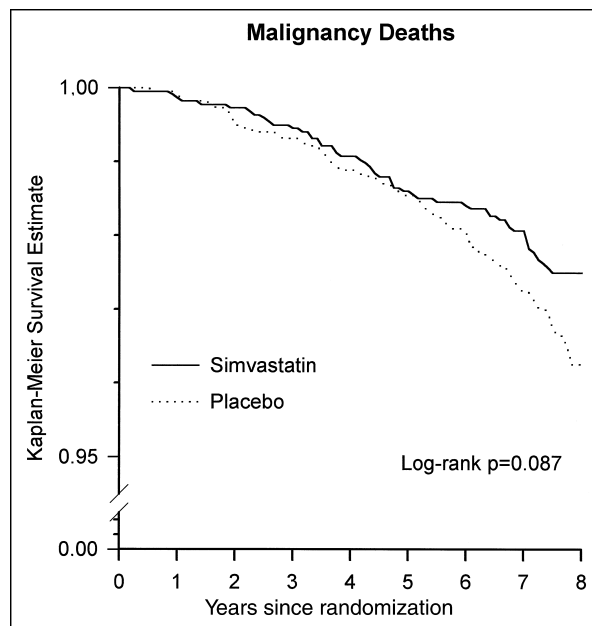
Values are expressed as number (%) of patients.

For the extended follow-up, the vital status of all patients randomized to placebo or simvastatin treatment was confirmed as of August 1, 1996. At this date, 97 patients (4.9%) of the 1967 originally treated with placebo and surviving the double-blind study period had died. In the group randomized to simvastatin the corresponding number was 74 of the 2,039 survivors (3.6%). Adding these deaths to those occurring during the double-blind study period, there were 353 deaths (15.9%) in the group originally randomized to placebo and 256 (11.5%) in the original simvastatin group (Table III). The relative risk was 0.70 (95% CI 0.60 to 0.82, $p = 0.00002$). The Kaplan-Meier 8-year (96 months) survival rate (Figure 2) was 0.84 in the original placebo group and 0.88 in the original simvastatin group. The increase in the absolute difference was due not only in fewer coronary deaths in the simvastatin group, but also in less cancer deaths (Table III), although the cancer death difference did not reach conventional levels of statistical significance ($p = 0.087$) (Figure 3.). Given the observed difference in favor of simvastatin, the proba-

TABLE III Mortality and Causes of Death

Causes of Death	Placebo (n = 2,223)			Simvastatin (n = 2,221)			Relative Risk* (95% CI)
	In-Trial	Extension	Total	In-Trial	Extension	Total	
All coronary	189	50	239 (10.8)	111	42	153 (6.9)	0.62 (0.51–0.76)
Other cardiovascular	18	10	28	25	7	32	
All cardiovascular	207	59	267 (12.0)	136	49	185 (8.3)	0.67 (0.56–0.81)
Malignancy	35	33	68 (3.1)	33	19	52 (2.3)	0.73 (0.51–1.05)
Other noncardiovascular	14	4	18 (0.8)	13	6	19 (0.9)	
All noncardiovascular	49	37	86 (3.9)	46	25	71 (3.2)	0.80 (0.58–1.09)
All deaths	256	97	353 (15.9)	182	74	256 (11.5)	0.70 (0.60–0.82)

*Relative risk calculated by Cox regression analysis.
Values are expressed as number (%) of patients.

**FIGURE 2.** Kaplan-Meier curves for all-cause mortality.**FIGURE 3.** Kaplan-Meier curves for cancer mortality.

bility that simvastatin increases the risk of cancer within the time frame of the study by $\geq 10\%$ is very small ($< 5\%$). For other cardiovascular and noncardiovascular deaths the numbers were similar for the 2 groups.

Mortality was analyzed separately for patients aged ≥ 65 years at the time of randomization and for patients with baseline serum LDL cholesterol < 4.5 mmol/L (174 mg/dl), because these are categories of patients for which there is still some debate about the survival benefit of cholesterol-lowering therapy. In patients ≥ 65 years at randomization, the number of deaths during the entire 8-year follow-up was 120 in the placebo group (23.9%) and 92 in the simvastatin group (17.8%); the relative risk was 0.72 (95% CI 0.55 to 0.94, $p = 0.02$) (Figure 4). In patients with LDL cholesterol less than the median value of 4.5 mmol/L, the number of deaths during 8 years was 96 (15.3%) and 72 (11.1%) in the placebo and simvastatin groups, respectively (relative risk 0.70, 95% CI 0.52 to 0.96, $p = 0.02$) (Figure 5).

During the double-blind part of the trial, patients who stopped taking study medication were infre-

quently treated with nonstudy cholesterol-lowering drugs after discontinuation (35 of 291 patients in the placebo group, and 2 of 230 patients in the simvastatin group). The mortality in the simvastatin group during the trial was about twice as high for withdrawn patients than for those not withdrawn from study therapy (Table IV). In the extension period, patients not withdrawn from the simvastatin group continued to have a much lower mortality than those withdrawn; this was also the case in the placebo group.

DISCUSSION

The 4S with the 2-year extension represents the longest clinical trial experience to date in a large cohort of patients taking statins. Although nonfatal events could not be studied after completion of the double-blind trial, mortality is the ultimate test of long-term safety. With no suggestion of harmful effects, the study provides reassuring evidence of the long-term safety of the drug. In particular, there were fewer cancer deaths with long-term simvastatin therapy, although the difference was not significant. This

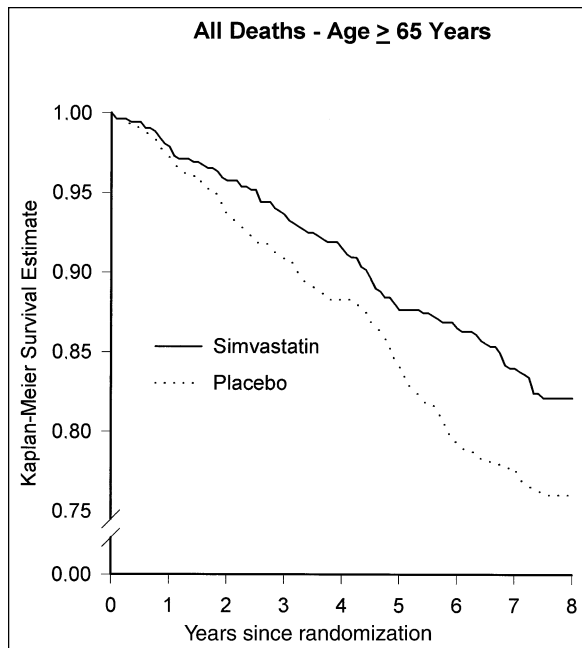


FIGURE 4. Kaplan-Meier curves for mortality in patients aged ≥ 65 years at baseline.

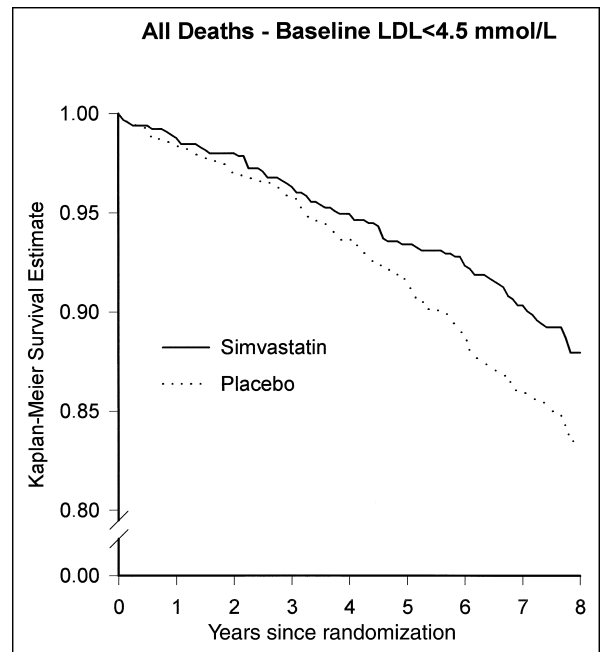


FIGURE 5. Kaplan-Meier curves for mortality in patients with LDL cholesterol <4.5 mmol/L at baseline.

result is in contrast to that of the extended follow-up of the Helsinki Heart Study^{9,10}; after a total observation period of 8.5 years, there was a trend to a higher mortality rate in the gemfibrozil group (101 deaths) than in the placebo group (83 deaths). This was attributable mainly to more cancer deaths in the gemfibrozil group (30 vs 18 in the placebo group, $p = 0.08$).

Reduction in all-cause mortality was demonstrated in patients with relatively low LDL cholesterol levels, <4.5 mmol/L (174 mg/dl) ($n = 1,279$) at baseline. Patients in the simvastatin group experienced a 33% mean reduction in LDL cholesterol from a mean baseline level of 4.10 mmol/L at baseline to a mean level of 2.73 mmol/L at year 1. As in the entire study population, there was a 30% risk reduction ($p = 0.024$) by the end of the extension period. Reducing cholesterol to low levels therefore does not seem to introduce any long-term risk. Patients aged 65 to 70 years at baseline ($n = 1,021$) also had increased survival with simvastatin therapy (28% relative risk reduction, $p = 0.016$). These patients were aged 73 to 78 years at the completion of the extended follow-up, and were thus at an age when cancer is becoming more prevalent. There were no signs of excess risk of cancer or other causes of mortality in this subgroup either.

Patients withdrawn from double-blind therapy had a much higher mortality rate than those adhering to the study regimen. Possibly, development of disease tended to cause withdrawal. The deaths among these patients accounted for 22% of the deaths in the simvastatin group and 25% in the placebo group during the extension. These patients were unlikely to be given statins after the double-blind trial, although information about the use of statins by patients who had died was unavailable. However, the use of simvastatin

TABLE IV Mortality Among Patients Withdrawn from Study Medication and Those Not Withdrawn

	Placebo	Simvastatin
Patients withdrawn	$n = 291$	$n = 230$
Deaths in trial*	50 (17.2)	39 (17.0)
Deaths in extension	24 (10.0) [†]	16 (8.4) [†]
Total deaths	74 (25.4)	55 (23.9)
Patients not withdrawn	$n = 1,932$	$n = 1,991$
Deaths in trial [‡]	206 (10.7)	143 (7.2)
Deaths in extension	73 (4.2) [‡]	58 (3.1) [‡]
Total deaths	279 (14.4)	201 (10.1)

*Deaths occurring after >28 days after withdrawal.
[†]Denominator is number of patients living at the end of the original study.
[‡]Deaths occurring while on study medication or within 28 days of withdrawal.
 Values are expressed as number (%) of patients.

or other statins was probably more widespread among patients not withdrawn from the original simvastatin group. The low mortality in these patients during the extension adds further evidence to the safety and long-term protective effect of simvastatin. (A statistical comparison of mortality in patients withdrawn from the placebo and simvastatin groups would not be a randomized comparison, and would therefore be problematic.)

The absolute mortality difference increased from 3.3% to 4.4%, maintaining the 30% reduction in the mortality risk in the simvastatin group recorded at the end of the base study. Post hoc analysis of the relation between simvastatin-induced changes in serum lipoprotein concentrations and the subsequent risk of CHD during the double-blind trial indicated that reduction in LDL cholesterol by simvastatin could explain most of the effect,¹¹ with some contribution from

raising HDL cholesterol. A meta-analysis by Law et al¹² of several large cohort studies showed that a decrease in serum cholesterol concentration of 0.6 mmol/L (23 mg/dl) (approximately 10%) was associated with a decrease in the incidence of ischemic heart disease, ranging from 54% at the age of 40 years to 19% at 80 years. This suggests that even greater preventive effects could be obtained if treatment were started earlier in life in patients at risk of developing atherosclerotic disease compared with the benefits achieved in randomized trials. Because of the evidence for the long-term safety of simvastatin derived from 4S¹³ and 10 years of postmarketing surveillance, this approach is not unreasonable.

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