Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S)

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Summary

Background **The effects of cholesterol-lowering treatment with statins on mortality and risk of cancer beyond the usual 5–6-year trial periods are unknown. We extended post-trial follow-up of participants in the Scandinavian Simvastatin Survival Study (4S) to investigate cause-specific mortality and incidence of cancer 5 years after closure of the trial.**

Methods **4S was a randomised double-blind trial of simvastatin or placebo in patients with coronary heart disease, serum total cholesterol 5·5–8·0 mmol/L, and serum triglycerides 2·5 mmol/L or lower. The double-blind period lasted for a median of 5·4 years (range for survivors 4·9–6·3) and ended in 1994. After the trial, most patients in both groups received open-label lipid-lowering treatment. National registers were used to assess mortality and causes of death and cancer incidence in the original treatment groups for a median total follow-up time of 10·4 years (range for survivors 9·9–11·3). Analysis was by intention to treat.**

Findings **414 patients originally allocated simvastatin and 468 assigned placebo died during the 10·4-year follow-up (relative risk 0·85 [95% CI 0·74–0·97], p=0·02), a difference largely attributable to lower coronary mortality in the simvastatin group (238 *vs* 300 deaths; 0·76 [0·64–0.90], p=0·0018). 85 cancer deaths arose in the simvastatin group versus 100 in the placebo group (0·81 [0·60–1·08], p=0·14), and 227 incident cancers were reported in the simvastin group versus 248 in the placebo group (0·88 [0·73–1·05], p=0·15). Incidence of any specific type of cancer did not rise in the simvastatin group.**

Interpretation **Simvastatin treatment for 5 years in a placebo-controlled trial, followed by open-label statin therapy, was associated with survival benefit over 10 years of follow-up compared with open-label statin therapy for the past 5 years only. No difference was noted in mortality from and incidence of cancer between the original simvastatin group and placebo group.**

Introduction

Publication of the Scandinavian Simvastatin Survival Study (4S) in *The Lancet* in 1994[1] was early trial evidence of the benefits of 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins) in the prevention of coronary events and in the reduction of all-cause mortality. The benefits of statin treatment both in primary and secondary prevention of coronary heart disease and other forms of atherosclerotic disease have since then become well established.[2–12]

In general, the safety profile of statins has been good, but not all concerns have been silenced, particularly with respect to the possible increased risk of cancer associated with pronounced cholesterol lowering.[13,14] This concern originated in the early 1990s from findings of prospective epidemiological studies showing some rise in non-cardiovascular mortality, particularly cancer deaths, in people with low cholesterol concentrations,[15] and from results of early trials of cholesterol lowering.[16] Furthermore, some researchers showed that lipid-lowering drugs, including statins, increase the occurrence of several types of cancer in rodents.[17] Most statin trials, which generally last 5–6 years, have not shown any rise in cancer incidence in statin-treated participants, but in two studies some excess of cancer was reported. In the CARE trial,[3] incidence of female breast cancer rose, and in the PROSPER trial in elderly people,[9] incidence of all cancers increased in patients given pravastatin. However, meta-analyses of data from pravastatin[9] and statin[13] studies, and the large Heart Protection Study with simvastatin,[7] did not show any significant excess of cancers. The average duration of randomised double-blind trials of statin treatment is, however, a fairly short period to study incidence of cancer. Therefore, longer follow-up of participants in statin trials has been called for.[14]

After completion of 4S in 1994, we decided that follow-up of the randomised patients would be extended by 5 years after the end of the double-blind period. Our aim was to investigate cause-specific mortality and cancer incidence in the original simvastatin and placebo groups on the basis of data from national registers in the five participating countries. Here, we report our 10-year follow-up results.

Methods

4S was a randomised, double-blind, placebo-controlled trial of simvastatin treatment in patients with clinically established coronary heart disease undertaken in five Nordic countries (Denmark, Finland, Iceland, Norway,

	Placebo (n=2223)	Simvastatin (n=2221)
Men	1803 (81%)	1814 (82%)
Age ⩾60 years	1126 (51%)	1156 (52%)
Qualifying diagnosis		
Angina only	456 (21%)	462 (21%)
Infarction only	1385 (62%)	1399 (63%)
Both angina and infarction	361 (17%)	360 (16%)
Secondary diagnoses		
Hypertension	584 (26%)	570 (26%)
Claudication	123 (6%)	130 (6%)
Previous CABG or PCI	151 (7%)	189 (9%)
Diabetes	97 (4%)	105 (5%)
Pretrial cancer diagnosis	68 (3%)	62 (3%)
Current smoker	596 (27%)	542 (24%)
Other treatment		
Aspirin	815 (37%)	822 (37%)
β blockers	1266 (57%)	1258 (57%)
Calcium antagonists	668 (30%)	712 (32%)
Serum lipids (mmol/L)		
Total cholesterol	6·75 (0·66)	6·74 (0·67)
HDL cholesterol	1·19 (0·29)	1·18 (0·30)
LDL cholesterol	4·87 (0·65)	4·87 (0·66)
Triglycerides	1·51 (0·52)	1·49 (0·49)

Data are number of patients (%) or mean (SD). CABG=coronary-artery bypass graft. PCI=percutaneous coronary intervention.

Table 1: **Selected baseline characteristics of randomised patients**

and Sweden). The design, organisation, and practical aspects of the trial have been described in detail.[1]

Between May 19, 1988, and Aug 16, 1989, we recruited patients age 35–70 years with previous myocardial infarction or angina pectoris, serum total cholesterol 5·5–8·0 mmol/L, and serum triglycerides 2·5 mmol/L or lower. These participants were randomly allocated either simvastatin or matching placebo. Table 1 shows selected baseline characteristics of the randomised patients. The initial dose of simvastatin was 20 mg daily, which was titrated to 40 mg daily in patients who did not reach the target total cholesterol concentrations of 3·0–5·2 mmol/L after 6–18 weeks (37%) by methods that preserved the double-blind nature of the study.

The trial ended on Aug 1, 1994. Median follow-up during the double-blind phase was 5·4 years (range for survivors 4·9–6·3 years). The primary endpoint of 4S was all-cause mortality, but secondary endpoints included cause-specific mortality, which was classified by an independent endpoint committee with hospital records, death certificates, and, if needed, contact with doctors and relatives.

After the double-blind period had ended, the 4S steering committee advised that all patients should be treated with simvastatin 20 mg daily until the results had been published. Thereafter, the decision about lipid-lowering treatment was made by patients and their doctors.

The results of a 2-year, interim follow-up study (until Aug 1, 1996) of cause-specific mortality have been reported.[18] This study also included a postal questionnaire survey of surviving participants, undertaken 3·4 years after the trial closed, in which we asked about use of lipid-lowering drugs and the latest serum cholesterol measurement. The response rate in this postal survey was 88% in the original placebo group (n=1613) and 89% in the original simvastatin group (1706). Of those responding, 82% originally allocated placebo (1315) and 86% (1458) originally assigned simvastatin reported that they were taking cholesterol-lowering drugs, usually statins. Mean total cholesterol concentrations were 5·16 mmol/L in the original placebo group and 5·11 mmol/L in the original simvastatin group.

The cutoff for the 5-year extension study was Aug 1, 1999. The protocol for the extension was approved by regional or, if applicable, national ethics committees and by data protection authorities in the participating countries. We obtained data from national registers and used the unique social security number of every individual to link study register data with nationwide cause-of-death and cancer register data.[19] These registers are judged to be very reliable, and estimated completeness of follow-up is virtually 100% for deaths and more than 95% for cancer incidence. We did not contact the surviving patients. When records in the cause-of-death and cancer registers were complete at the cutoff date we compared them with the 4S patient register.

Causes of death and diagnoses of incident cancers were categorised with ICD9 (International Classification of Diseases 9th revision) codes. We used data from the registers of the date and cause of death and the date and

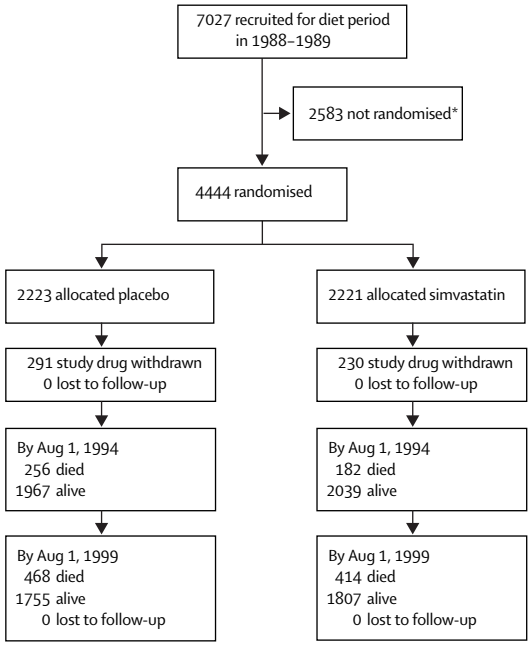


Figure 1: **Outline of 10-year follow-up**
*Most important reasons (not mutually exclusive): cholesterol outside study range in 1300 patients; triglycerides outside study range in 864; unwillingness to participate in 396.

diagnosis code of incident cancer. All diagnosis codes were converted to ICD9 codes if another version (ICD10 in past years) had been used. Codes 390–459 and 798 defined cardiovascular death, within which 410–414 and 798 made up the coronary death subcategory and the remaining codes formed other cardiovascular death. Non-cardiovascular death included all ICD9 codes other than those for cardiovascular deaths. This category was divided into two subsets: the cancer death subcategory consisted of ICD9 codes 140–208 and the remaining codes were other non-cardiovascular deaths. Site-specific subclassification of cancer deaths was based on relevant ICD9 codes.

Two investigators (KP and TES) ascertained cause of death and diagnoses of incident cancers, without any knowledge of treatment allocation, on the basis of information available from the registers. They checked for inconsistencies, which were resolved by consensus and, if needed, by consultation with the country coordinators. Inconsistencies were rare, arose similarly in both groups, and consisted of difficulties in allocation of the primary cause of death or errors and inconsistencies of dates or diagnosis codes in cancer data.

For statistical analyses, we used SAS software version 8.2. Patients originally randomised to placebo and simvastatin were compared by intention to treat. Because some participants were known to have had cancer before randomisation, the following data analyses with respect to cancer incidence were considered before the actual analyses were started: 1) ignoring prerandomisation cancers; 2) excluding as endpoints postrandomisation cancers that were of the same category as prerandomisation cancer; and 3) excluding all patients with prerandomisation cancer. We judged the second approach to be the most appropriate, and two investigators (KP and TES) adjudicated which postrandomisation cancers were similar to those that had been diagnosed prerandomisation. The other approaches were used as sensitivity analyses.

We calculated treatment-group differences, relative risks, and 95% CIs with the Cox proportional-hazards

	Double-blind trial		5-year extension		10-year follow-up	
	Placebo (n=2223)	Simvastatin (n=2221)	Placebo (n=1967)	Simvastatin (n=2039)	Placebo (n=2223)	Simvastatin (n=2221)
All causes						
Number of deaths	256	182	212	232	468	414
Kaplan-Meier estimate (95% CI)*	12·4% (10·8–13·9)	8·7% (7·4–10·0)	10·8% (9·4–12·2)	11·4% (10·0–12·8)	21·3% (19·5–23·0)	19·9% (17·8–22·1)
Relative risk (95% CI)†	1·00	0·70 (0·58–0·84)	1·00	1·03 (0·86–1·24)	1·00	0·85 (0·74–0·97)
p		<0·0001		N/A‡		0·016
All cardiovascular						
Number of deaths	207	136	128	155	335	291
Kaplan-Meier estimate (95% CI)*	10·2% (8·8–11·7)	6·7% (5·5–7·8)	6·6% (5·5–7·8)	7·7% (6·6–8·9)	15·6% (14·0–17·1)	14·6% (12·5–16·7)
Relative risk (95% CI)†	1·00	0·64 (0·52–0·80)	1·00	1·14 (0·90–1·44)	1·00	0·83 (0·71–0·97)
p		<0·0001		N/A		0·023
Coronary						
Number of deaths	189	111	111	127	300	238
Kaplan-Meier estimate (95% CI)*	9·4% (8·0–10·9)	5·5% (4·4–7·3)	5·8% (2·4–4·1)	6·4% (5·3–7·5)	14·1% (12·6–15·6)	12·3% (10·2–14·4)
Relative risk (95% CI)†	1·00	0·57 (0·45–0·73)	1·00	1·08 (0·83–1·39)	1·00	0·76 (0·64–0·90)
p		<0·0001		N/A		0·002
Other cardiovascular						
Number of deaths	18	25	17	28	35	53
Kaplan-Meier estimate (95% CI)*	0·8% (0·5–1·3)	1·2% (0·5–1·3)	0·9% (0·3–1·7)	1·4% (0·9–2·0)	1·7% (1·2–2·3)	2·6% (1·9–3·3)
Relative risk (95% CI)†	1·00	1·37 (0·74–2·51)	1·00	1·53 (0·84–2·80)	1·00	1·45 (0·94–2·22)
p		0·312		N/A		0·088
All non-cardiovascular						
Number of deaths	49	46	84	77	133	123
Kaplan-Meier estimate (95% CI)*	2·4% (1·7–3·1)	2·2% (1·6–2·8)	4·4% (3·5–5·4)	3·9% (3·1–4·8)	6·7% (5·6–7·9)	6·3% (5·2–7·4)
Relative risk (95% CI)†	1·00	0·92 (0·62–1·38)	1·00	0·87 (0·64–1·19)	1·00	0·89 (0·70–1·14)
p		0·692		N/A		0·347
Cancer						
Number of deaths	35	33	65	52	100	85
Kaplan-Meier estimate (95% CI)*	1·7% (1·1–2·2)	1·6% (1·0–2·1)	3·4% (2·6–4·3)	2·7% (2·0–3·4)	5·1% (4·1–6·1)	4·3% (3·4–5·2)
Relative risk (95% CI)†	1·00	0·91 (0·57–1·46)	1·00	0·75 (0·52–1·08)	1·00	0·80 (0·60–1·08)
p		0·696		N/A		0·142
Other non-cardiovascular						
Number of deaths	14	13	19	25	33	38
Kaplan-Meier estimate (95% CI)*	0·7% (0·3–1·2)	0·6% (0·3–0·9)	1·0% (0·6–1·5)	1·3% (0·8–1·8)	1·8% (1·2–2·3)	2·1% (1·4–2·8)
Relative risk (95% CI)†	1·00	0·94 (0·44–1·20)	1·00	1·29 (0·71–2·35)	1·00	1·15 (0·72–1·83)
p		0·871		N/A		0·561

*Estimate for cumulative incidence. †Adjusted for age, sex, hypertension, smoking, myocardial infarction, and diabetes at baseline. ‡Not assessed, because the groups entering 5-year extension were not randomisation-based.

Table 2: **Mortality and causes of death during the double-blind trial, 5-year extension, and 10-year follow-up**

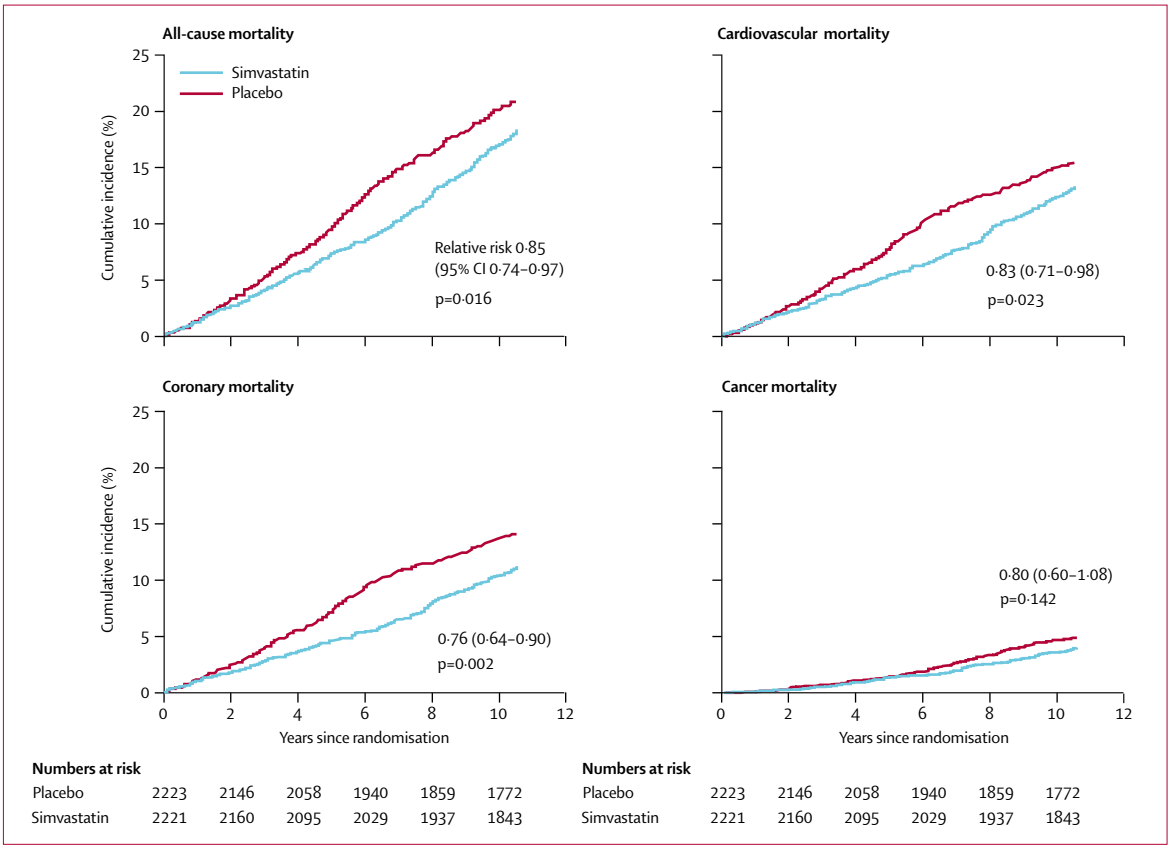


Figure 2: **Kaplan-Meier curves for all-cause mortality, cardiovascular mortality, coronary mortality, and cancer mortality**

regression model. Covariates used in analyses were age, sex, hypertension, smoking, diabetes, and history of myocardial infarction at baseline. Cumulative incidence and 95% CI were calculated with the Kaplan-Meier method. We regarded p<0·05 (two-sided) as significant.

Role of the funding source

The extension study was initiated, planned, and undertaken by the investigators. The sponsor provided technical help in the coordination of data collection and through the contribution of one of the investigators (TJC) in data analysis.

Results

Figure 1 shows an outline of the 4S double-blind trial and the 5-year extension of follow-up. At the end of the double-blind period, 1967 survivors in the placebo group and 2039 in the simvastatin group did not differ with respect to sex and age distribution, smoking status, or baseline diagnoses (previous myocardial infarction, coronary-artery bypass graft or percutaneous coronary intervention, claudication, hypertension, diabetes), but as expected, serum lipid concentrations between patients treated with placebo and simvastatin differed. Mean values for the main lipid fractions (mmol/L) in the placebo versus simvastatin groups were 6·85 (SD 0·98) versus 5·31 (1·02) for total cholesterol, 4·93 (0·93) versus 3·42 (0·95) for LDL cholesterol, 1·21 (0·33) versus 1·27 (0·34) for HDL cholesterol, and 1·59 (0·82) versus 1·37 (0·67) for triglycerides. The proportion of patients who had had a non-fatal major coronary event during the double-blind trial was greater in survivors in the placebo group than in the simvastatin group (436 [20%] *vs* 285 [13%]).

At the cutoff of the 5-year extension of follow-up, 468 (21%) of the 2223 patients originally allocated placebo and 414 (19%) of the 2221 originally assigned simvastatin had died (table 2). Figure 2 shows cumulative incidence curves for all-cause, cardiovascular, coronary, and cancer mortality in the simvastatin and placebo groups over the entire follow-up. During the double-blind trial, simvastatin treatment reduced all-cause mortality by 30%, cardiovascular mortality by 36%, and coronary mortality by 43% (table 2). During the 5-year extension, when more than 80% of patients in both groups were treated with lipid-lowering drugs, relative risks were close to unity. Although the double-blind and 5-year extension periods had very different relative risks, reductions in these mortality categories over the entire 10-year follow-up were 15% in all-cause mortality, 17% in cardiovascular mortality, and 24% in coronary mortality

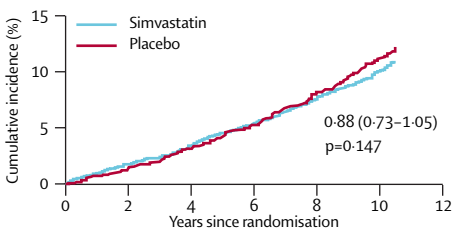
	Placebo (n=2223)	Simvastatin (n=2221)
Cancer type		
Gastrointestinal	57	45
Stomach	7	7
Pancreas	10	9
Colorectal	32	25
Other gastrointestinal	8	4
Lung	31	25
Melanoma	7	9
Non-melanoma skin	28	29
Basal cell	17	20
Other non-melanoma skin	11	9
Female breast	5	7
Cervical	2	0
Endometrial	3	3
Prostate	55	51
Urinary bladder	19	17
Lymphatic or haematopoetic	19	17
Other	22	24
All cancers	248	227
Kaplan-Meier estimate (95% CI)	13·9% (11·7–16.1)	11·7% (9·9–13·6)
Relative risk (95% CI)†	1·00	0·88 (0·73–1·05)
p		0·147

*Excluding cancers in the same category as prerandomisation cancer. †Adjusted for age, sex, hypertension, smoking, myocardial infarction, and diabetes at baseline.

Table 3: **Number of first postrandomisation cancers during 10-year follow-up***

(table 2). Absolute differences between simvastatin and placebo did not change much. The difference between treatment groups for all-cause mortality at median follow-up of the double-blind trial (65 months) was 3·28%, and at 125 months (10·4-year follow-up) it was 2·81%. For cardiovascular mortality, the differences between treatments were 3·19% at 65 months and 2·27% at 125 months, and for coronary mortality they were 3·48% and 3·06%, respectively. During the double-blind trial, 35 patients in the placebo group and 33 in the simvastatin group, and during the entire 10-year follow-up 100 on placebo and 85 on simvastatin, died from cancer (table 2).

Between randomisation and Aug 1, 1999, a diagnosis of cancer was made in 259 patients (12%) in the placebo group and in 237 (11%) in the simvastatin group. 68 allocated placebo and 62 assigned simvastatin had a history of cancer diagnosis (verified by cancer register) before randomisation. Table 3 shows the number of postrandomisation cancers in the simvastatin group and the placebo group during the 10-year follow-up, excluding cancers of the same category as the prerandomisation cancer, and figure 3 shows cumulative incidence curves for cancer in the two groups over the entire follow-up. During the 10-year follow-up, risk of incident cancer was 12% lower in the simvastatin group than in the placebo group (p=0·147; table 3). When non-melanoma skin cancers (mainly basal cell cancers) arising during the 10-year follow-up were excluded, the relative risk of incident cancer (simvastatin *vs* placebo) was 0·86 (95% CI 0·71–1·04, p=0·13). When prerandomisation cancers were ignored the relative risk of incident cancer was 0·88 (0·73–1·04, p=0·141), and when we excluded prerandomisation cancers of any type it was 0·91 (0·75–1·09, p=0·289).



Numbers at risk

Placebo	2223	2123	2013	1877	1770	1661
Simvastatin	2221	2129	2048	1953	1843	1729

Figure 3: **Kaplan-Meier curves for cancer incidence**

Discussion

The main finding of this 10-year follow-up study of the participants of 4S was that the survival benefit of patients allocated simvastatin compared with those allocated placebo that accrued during the double-blind trial period persisted during follow-up. The reduction in the relative risk between the two original treatment groups was not unexpected, because open-label treatment with lipid-lowering drugs (mostly statins) was given to most patients when the trial ended. After 3 years, more than 80% of patients in both groups were using these drugs. Nevertheless, the absolute differences in all-cause, cardiovascular, and coronary mortality achieved during the double-blind trial changed little during the 5-year extension of the follow-up. Another important finding of our study was that during the 10-year follow-up, mortality from and incidence of cancer were slightly, although non-significantly, reduced in the original simvastatin group relative to the original placebo group. Although this finding should be interpreted with caution, the 95% CIs (0·60–1·08 for cancer mortality, 0·73–1·05 for cancer incidence) nevertheless suggest that even if the effect were in the other direction, it would be clinically negligible.

The strength of our study is that we have been able to achieve complete follow-up of the original 4S patient groups with respect to cause-specific mortality and virtually complete follow-up with respect to incident cancer, because we could use, with approval of data protection authorities, the unique social security number of every individual to link study register data with national cause-of-death and cancer register data.

Among statin trials, our study, with its median follow-up period of 10·4 years, is so far the longest follow-up of patients originally randomised to receive statin or placebo. However, it has unavoidable weaknesses, which make interpretation of findings complex. First, during the double-blind period, the simvastatin-treated group became larger than the placebo-treated group, mainly because of a pronounced reduction of coronary deaths in

the simvastatin-treated group. Second, after closure of the double-blind trial, the original placebo group received open-label lipid-lowering drug treatment.

The use of Cox proportional-hazards models as the main method of data analysis can be criticised, because the proportional-hazards assumption does not hold in strict sense over the entire 10-year follow-up. However, as we have shown, the results are essentially similar, if the original simvastatin and placebo groups comparisons are done by comparing Kaplan-Meier point estimates for mortality categories at the end of the double-blind trial and at the end of the entire follow-up. The advantage of Cox-model analyses is that the relative risks can be adjusted for the effect of important covariates.

During the double-blind period of the 4S, the survival curves for all-cause, cardiovascular, and coronary mortality in the simvastatin group and the placebo group began to diverge early and progressively until closure of the trial. Thereafter, during the 5-year extension of the follow-up, the survival curves took a more parallel course. For the reasons mentioned above, interpretation of the evolution of cause-specific mortality during the post-trial follow-up has to be made with caution. However, it is noteworthy that during the 5-year extension the number of cardiovascular deaths, and specifically the number of coronary deaths, was lower in the original placebo group, which could indicate an accruing benefit from lipid-lowering drug treatment in these patients whose cholesterol concentrations had remained in the high-risk range during the trial. On the other hand, in the original simvastatin group some coronary deaths could have been delayed into the follow-up period. These deaths could account for the almost similar coronary mortality in the placebo and simvastatin groups during the 5-year extension.

Competition between cardiovascular and non-cardiovascular causes of death could potentially take place during long-term follow-up of an ageing study population, such as the 4S participants, of whom about half were age 60 years or older at the time of randomisation. The original simvastatin group could be expected to be at an increased risk of non-cardiovascular death during the extended follow-up because their survival improved during the trial through the reduction of cardiovascular deaths. Yet, no increase in non-cardiovascular mortality was recorded in the original simvastatin group during the 5-year extension or the whole 10-year follow-up period. During the 10-year follow-up, mortality from cancer, forming the largest proportion of non-cardiovascular deaths, was actually lower in the original simvastatin group than in the original placebo group, although this difference was not significant.

In accordance with the cancer mortality data, our 10-year follow-up study also showed that the incidence of cancer was similar in the original simvastatin group and in the original placebo group. These findings are reassuring and in accordance with the negative findings on the risk of cancer in the Heart Protection Study[7] and in the meta-analyses of statin trials.[9,13] The effects of statins beyond 10 years remain, so far, unknown. However, we should note in this context that studies of cancer cell biology and animal work have shown mechanisms by which statin drugs might have anticancer effects.[20]

Contributors

All authors contributed to study design; collected, checked, and analysed data; and took part in interpretation of findings and in drafting of the manuscript. K Pyörälä coordinated development of the study design and collection and checking of data. T J Cook did statistical analyses. T E Strandberg and K Pyörälä took main responsibility for writing of the manuscript.

Conflict of interest statement

TES has received honoraria and consulting fees from Merck, Pfizer, AstraZeneca, Schering-Plough, Novartis, and Bristol-Myers Squibb. KP has received honoraria and consulting fees from Merck. TC is an employee and stockholder of Merck. OF is a member of the steering committee of the IDEAL study sponsored by Pfizer. GT has received honoraria from Merck, AstraZeneca, and Novartis. TRP has received honoraria and consulting fees from Merck. JK has received honoraria from Merck and AstraZeneca. LW has no conflict of interest to declare.

Acknowledgments

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References

1 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344:** 1383–89.

2 Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; **333:** 1301–07.

3 Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; **335:** 1001–09.

4 The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; **339:** 1349–57.

5 Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. *JAMA* 1998; **279:** 1615–22.

6 Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effect of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL Study, a randomized controlled trial. *JAMA* 2001; **285:** 1711–18.

7 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360:** 7–22.

8 Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; **287:** 3215–22.

9 Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER); a randomised controlled trial. *Lancet* 2002; **360:** 1623–30.

10 Holdaas H, Fellstrom B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet* 2003; **361:** 2024–31.

11 Sever P, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesteroal concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; **361:** 1149–58.

12 Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease and stroke: systematic review and meta-analysis. *BMJ* 2003; **326:** 1423–27.

13 Bjerre LM, LeLorier J. Do statins cause cancer? A meta-analysis of large randomized clinical trials. *Am J Med* 2001; **110:** 716–23.

14 Guallar E, Goodman SN. Statins and cancer: a case of meta-uncertainty. *Am J Med* 2001; **110:** 738–40.

15 Jacobs D, Blackburn H, Higgins M, et al. Report of the conference on low blood cholesterol: mortality associations. *Circulation* 1992; **86:** 1046–60.

16 Davey-Smith G, Pekkanen J. Should there be a moratorium on the use of cholesterol lowering drugs? *BMJ* 1992; **304:** 431–34.

17 Newman TB, Hulley SB. Carcinogenicity of lipid-lowering drugs. *JAMA* 1996; **275:** 55–60

18 Pedersen TR, Wilhelmsen L, Faergeman O, et al. Follow-up study of patients randomized in the Scandinavian simvastatin survival study (4S) of cholesterol lowering. *Am J Cardiol* 2000; **86:** 257–62.

19 Engeland A, Haldorsen T, Tretli S, et al. Prediction of cancer mortality in the Nordic countries up to the years 2000 and 2010, on the basis of relative survival analysis: a collaborative study of the five Nordic Cancer Registries. *APMIS Suppl* 1995; **45:** 1–161.

20 Bonetti PO, Lerman LO, Napoli C, Lerman A. Statin effect beyond lipid lowering: are they clinically relevant? *Eur Heart J* 2003; **24:** 225–48.