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Long-Term Follow-up of the West of Scotland Coronary Prevention Study

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ABSTRACT

BACKGROUND

The West of Scotland Coronary Prevention Study was a randomized clinical trial comparing pravastatin with placebo in men with hypercholesterolemia who did not have a history of myocardial infarction, with an average follow-up of approximately 5 years. The combined outcome of death from definite coronary heart disease or definite nonfatal myocardial infarction was reduced from 7.9 to 5.5% ($P<0.001$) in the treatment group. Extended follow-up data were obtained for approximately 10 years after completion of the trial.

METHODS

For the survivors of the trial, all deaths, hospitalizations and deaths due to coronary events and stroke, and incident cancers and deaths from cancer were tracked with the use of a national computerized record-linkage system. The results were analyzed with time-to-event analyses and use of Cox proportional-hazards models.

RESULTS

Five years after the trial ended, 38.7% of the original statin group and 35.2% of the original placebo group were being treated with a statin. In the period approximately 10 years after completion of the trial, the risk of death from coronary heart disease or nonfatal myocardial infarction was 10.3% in the placebo group and 8.6% in the pravastatin group ($P=0.02$); over the entire follow-up period, the rate was 15.5% in the placebo group and 11.8% in the pravastatin group ($P<0.001$). Similar percentage reductions were seen in the combined rate of death from coronary heart disease and hospitalization for coronary events for both periods. The rate of death from cardiovascular causes was reduced ($P=0.01$), as was the rate of death from any cause ($P=0.03$), over the entire follow-up period. There were no excess deaths from noncardiovascular causes or excess fatal or incident cancers.

CONCLUSIONS

In this analysis, 5 years of treatment with pravastatin was associated with a significant reduction in coronary events for a subsequent 10 years in men with hypercholesterolemia who did not have a history of myocardial infarction.

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THE WEST OF SCOTLAND CORONARY PREVENTION Study (WOSCOPS) was a randomized, double-blind, placebo-controlled clinical trial of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor pravastatin (Pravachol, Bristol-Myers Squibb) in middle-aged men without a history of myocardial infarction.¹⁻³ After an average of approximately 5 years, the combined outcome of death from definite coronary heart disease or definite nonfatal myocardial infarction was reduced from 7.9% in the placebo group to 5.5% in the pravastatin group ($P<0.001$), and the risk of death from definite or suspected coronary heart disease was reduced from 1.9% to 1.3% ($P=0.04$). There was a trend toward a reduction in the risk of stroke, and there was no evidence of an increased risk of death from noncardiovascular causes or of an increased risk of incident cancer. Mortality from any cause was 4.1% in the placebo group and 3.2% in the pravastatin group ($P=0.051$, unadjusted for covariants).

The observed benefits of treatment with pravastatin notwithstanding, an extended follow-up study was planned. The goals of long-term follow-up were to monitor the use of cholesterol-lowering therapy for 5 years after the end of the study and to assess ongoing safety and efficacy by collecting data on clinical events for approximately 10 years after the end of the study. We report here the results of this long-term analysis.

METHODS

TRIAL DESIGN

The design and conduct of WOSCOPS have been described elsewhere.^{1,2} In brief, it was a randomized trial comparing pravastatin (40 mg once daily) with placebo in men with no evidence of previous myocardial infarction. To meet the entry criteria, study participants had to have two measurements of low-density lipoprotein (LDL) cholesterol with values of 155 mg per deciliter (4.0 mmol liter) or higher, with at least one value that was 174 mg per deciliter (4.5 mmol per liter) or higher and at least one value that was 232 mg per deciliter (6.0 mmol per liter) or lower. The trial design was approved by the ethics committees of the University of Glasgow and all participating health boards.

Between February 1, 1989, and September 30, 1991, a total of 6595 men meeting the inclusion criteria who gave written informed consent were enrolled and underwent randomization. During the trial, patients were followed for the occur-

rence of end-point events, which were reviewed and classified by an end-points committee.¹ The primary end point was the combined outcome of death from definite coronary heart disease or definite nonfatal myocardial infarction. The average duration of follow-up was 4.9 years (range, 3.5 to 6.1). Final visits occurred between February and May 1995.

POST-TRIAL MANAGEMENT

After the final scheduled trial visits, pravastatin or placebo was withdrawn, and the patients were returned to the care of their primary care physicians. The primary focus of lipid-lowering therapy in general medical practice at this time was on secondary prevention with statins, based on the results of the Scandinavian Simvastatin Survival Study^{4,5} and subsequently on the results of the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial^{6,7} and the Cholesterol and Recurrent Events (CARE) trial.⁸ Principles of lipid lowering for primary prevention had not yet been developed. Therefore, the decision by each patient's primary care physician regarding the use of statin therapy was not based on specific guidelines or established practice.

POST-TRIAL STUDY DESIGN

The post-trial study was a comparison of clinical outcomes of interest for the two original study groups (pravastatin and placebo), regardless of the actual subsequent use of lipid-lowering therapy during the post-trial period. The study was designed by the authors, and the design was approved by the ethics committee of the Royal Infirmary, Glasgow. The staff of the Robertson Centre for Biostatistics, University of Glasgow, collected all post-trial data and conducted all statistical analyses. Dr. Ford wrote the first and subsequent drafts of the manuscript, submitted it for publication after feedback and approval from the other authors, and vouches for the accuracy and completeness of the data and analyses. The funding organizations had no involvement in the collection or analyses of the data or in manuscript preparation.

POST-TRIAL DATA COLLECTION

All survivors were asked to provide written informed consent for a nurse to access their primary care records after 1, 3, and 5 years in order to record their prescribed cholesterol-lowering treatment. Follow-up for clinical events was based en-

tirely on the use of records held by the National Health Service for Scotland. Personal identifiers for the study participants were electronically linked to hospital discharge records (Scottish Morbidity Record 01), the cancer registry (Scottish Morbidity Record 06), and General Register Office death records (held by the Information and Statistical Division of the National Health Service for Scotland) by means of established record-linkage methods.⁹ Data on outcome events for each study participant were extracted from the databases with the use of appropriate *International Classification of Diseases* codes (versions 9 and 10). For deaths and hospital discharge summaries, data were available through December 2004, and for incident cancers through June 2003. Approval for record linkage was given by the Privacy Advisory Committee at the Information and Statistics Division of the National Health Service for Scotland.

For consistency, our analyses of events during the post-trial period are based on these record-linkage data only. Because of differences in definitions of events, differences in ascertainment accuracy between the trial and record-linkage methods, and coding variation, there may be inconsistencies between the numbers of events reported here and those in other WOSCOPS reports. We have previously verified a close correlation between events adjudicated by the trial events committee and those ascertained by record linkage.¹⁰

OUTCOMES

The primary cause of death reported in the death records was used to identify the fatal outcomes of interest. These included death from any cause, death from coronary heart disease, death from cardiovascular or noncardiovascular disease, and death due to cancer.

Composite cardiovascular outcomes analyzed included death from or hospitalization for coronary heart disease, death from coronary heart disease or nonfatal myocardial infarction, and fatal or nonfatal stroke. For the outcomes of myocardial infarction and stroke, any record of myocardial infarction or stroke, whether or not it was the primary reason for hospitalization, was included as an event. For coronary heart disease events, any event that was the primary reason for hospitalization and any nonfatal myocardial infarction were recorded as events. For hospitalizations, the date of admission was used as the date of the event.

Cancer outcomes analyzed included all inci-

dent cancers as well as the most commonly occurring, site-specific cancers (colorectal, lung, prostate, upper gastrointestinal, and urinary tract cancers). Nonmelanoma skin cancer was not included as an event. Any cancer reported on the death form but not recorded in the cancer registry database was included as an event. The date of registration in the database (or the date of death, if that was the time of first identification) was used as the date of the event.

STATISTICAL ANALYSIS

The events during the trial period (average 5 years of follow-up), in the post-trial follow-up period (approximately 10 years), and during the full period of follow-up (approximately 15 years) were tabulated. Cox proportional-hazards models were fitted for the same periods and included the original study-group assignment (pravastatin or placebo) and relevant risk factors for the outcome of interest. Treatment effects (pravastatin as compared with placebo) are expressed as hazard ratios with 95% confidence intervals and corresponding P values. Although we thought it was likely that the proportional-hazards assumption would not be valid for all models fitted over the full period of follow-up, we concluded that the estimated hazard ratios would still reflect an average benefit over the period. For the cardiovascular outcomes, adjustment was made for age, body-mass index, systolic blood pressure, diastolic blood pressure, high-density lipoprotein (HDL) cholesterol level, LDL cholesterol level, log-transformed triglyceride level, nitrate use (yes or no), history of angina (yes or no), history of diabetes (yes or no), history of hypertension (yes or no), smoking status (current smoker, former smoker, or nonsmoker), and social-deprivation score (on a seven-category measure called DEPCAT, in which category 7 represents the greatest deprivation).¹¹ For cancer analyses, adjustments were made for age, body-mass index, smoking status, and social-deprivation score. Time-to-event curves for each of the original randomized study groups were estimated by means of the Kaplan–Meier method.

RESULTS

The participants in the two original study groups were well balanced with respect to major risk factors at study entry.^{2,3} The average age was 55 years. The mean blood pressure and LDL cholesterol level were 135/85 mm Hg and 192 mg per deci-

liter (5.0 mmol per liter), respectively; 44% of the participants were current smokers.

Of the 6345 men who were alive at the completion of the trial, 5778 (91.1%) gave written informed consent for access to their primary care records. The percentages of participants being treated with a statin among those assigned to the original pravastatin and placebo groups were, respectively, 28.6% and 24.3% at 1 year, 33.6% and 29.4% at 3 years, and 38.7% and 35.2% at 5 years. For each of these comparisons, significantly more participants in the original pravastatin

group than in the original placebo group were taking a statin ($P < 0.001$ for all comparisons).

All participants were included in the long-term follow-up for clinical events. For incident cancer, the average follow-up from randomization until the date of the scheduled final visit was 13.2 years (range, 11.8 to 14.4). The corresponding average follow-up for all other outcomes was 14.7 years (range, 13.3 to 15.9).

During the entire follow-up period, 619 study participants originally assigned to pravastatin and 674 assigned to placebo died. The rate of death

Table 1. Mortality Outcomes.*

Cause of Death	Trial Period		Post-Trial Period†		Total Follow-up Period	
	Placebo (N=3293)	Pravastatin (N=3302)	Placebo (N=3158)	Pravastatin (N=3196)	Placebo (N=3293)	Pravastatin (N=3302)
All causes						
Deaths — no. (%)	135 (4.1)	106 (3.2)	539 (17.1)	513 (16.1)	674 (20.5)	619 (18.7)
Hazard ratio (95% CI)	1.00	0.76 (0.59–0.98)	1.00	0.91 (0.81–1.03)	1.00	0.88 (0.79–0.99)
P value		0.04		0.15		0.03
All cardiovascular causes						
Deaths — no. (%)	71 (2.2)	49 (1.5)	226 (7.2)	203 (6.4)	297 (9.0)	252 (7.6)
Hazard ratio (95% CI)	1.00	0.66 (0.46–0.95)	1.00	0.86 (0.71–1.04)	1.00	0.81 (0.68–0.96)
P value		0.03		0.11		0.01
Coronary heart disease						
Deaths — no. (%)	58 (1.8)	40 (1.2)	149 (4.7)	130 (4.1)	207 (6.3)	170 (5.1)
Hazard ratio (95% CI)	1.00	0.66 (0.44–0.98)	1.00	0.83 (0.66–1.05)	1.00	0.78 (0.64–0.96)
P value		0.04		0.12		0.02
Stroke						
Deaths — no. (%)	6 (0.2)	6 (0.2)	31 (1.0)	47 (1.5)	37 (1.1)	53 (1.6)
Hazard ratio (95% CI)	1.00	0.99 (0.32–3.09)	1.00	1.44 (0.92–2.28)	1.00	1.37 (0.90–2.09)
P value		0.99		0.11		0.14
All noncardiovascular causes						
Deaths — no. (%)	64 (1.9)	57 (1.7)	313 (9.9)	310 (9.7)	377 (11.4)	367 (11.1)
Hazard ratio (95% CI)	1.00	0.87 (0.61–1.24)	1.00	0.96 (0.82–1.12)	1.00	0.94 (0.82–1.09)
P value		0.44		0.57		0.43
Cancer‡						
No. of patients with data available	3286	3291	3151	3186	3286	3291
Deaths — no. (%)	49 (1.5)	42 (1.3)	217 (6.9)	224 (7.0)	266 (8.1)	266 (8.1)
Hazard ratio (95% CI)	1.00	0.84 (0.56–1.27)	1.00	1.00 (0.83–1.20)	1.00	0.97 (0.82–1.15)
P value		0.40		1.00		0.73

* Outcomes for cancer were adjusted for age, body-mass index, smoking status (current smoker, former smoker, or nonsmoker), and social-deprivation score. All other outcomes were adjusted for these characteristics as well as for systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol level, low-density lipoprotein cholesterol level, log triglyceride level, nitrate use or nonuse, and presence or absence of a history of angina, diabetes, or hypertension.

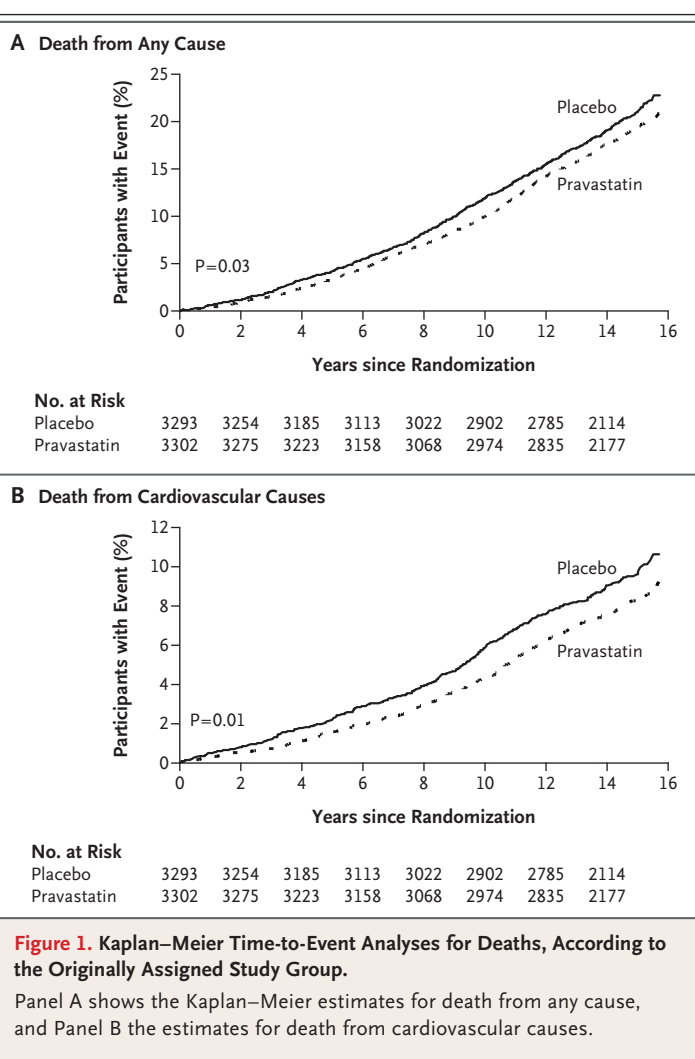
† Participants who died during the trial period were excluded.

‡ Eighteen participants who had cancer within 5 years before randomization were excluded from the analysis.

from any cause was 18.7% for patients originally assigned to pravastatin as compared with 20.5% for patients originally assigned to placebo (hazard ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.99; $P=0.03$). When examined by period, the risk reduction in the pravastatin group was 24% during the trial ($P=0.04$), 9% in the post-trial period ($P=0.15$), and 12% for the overall follow-up period ($P=0.03$) (Table 1 and Fig. 1). For all deaths from cardiovascular causes, the event rate during the entire follow-up period was 7.6% for patients originally assigned to pravastatin as compared with 9.0% for patients originally assigned to placebo (hazard ratio, 0.81; 95% CI, 0.68 to 0.96; $P=0.01$). Assignment to pravastatin was associated with risk reductions of 34% during the trial and 14% during the post-trial period; the risk reduction during the trial was statistically significant, but the post-trial risk reduction was not (Table 1 and Fig. 1). Similar results were obtained for deaths from coronary heart disease. Deaths from stroke were infrequent during the trial, with a trend toward an increased risk in the pravastatin group in the post-trial period and in the overall follow-up period. There was no significant difference between the two study groups in rates of death from noncardiovascular causes or cancer during any period of follow-up.

For the composite cardiovascular end points, there was evidence of a significant ongoing risk reduction in the pravastatin group (Table 2). During the entire follow-up period, the rate of death from coronary heart disease or nonfatal myocardial infarction was 11.8% in the group originally assigned to pravastatin and 15.5% in the group originally assigned to placebo (hazard ratio, 0.73; 95% CI, 0.63 to 0.83; $P<0.001$). Relative risk reductions for death from coronary heart disease or nonfatal myocardial infarction were 40% during the trial and 18% in the post-trial period ($P<0.001$ and $P=0.02$, respectively) (Table 2 and Fig. 2). Similar relative risk reductions were seen for the end point of death from or hospitalization for coronary heart disease (Table 2 and Fig. 2). The trend toward an increase in mortality from stroke in the pravastatin group during the post-trial period was compensated for by a decrease in the rate of nonfatal stroke. However, the overall trend toward a risk reduction (17%) did not quite reach statistical significance ($P=0.06$).

For incident cancers, there was no evidence of an increased risk associated with assignment to



pravastatin at any time in the trial (Table 3). When specific cancer sites were studied, there was no suggestion of treatment-related trends for any cancer site, with the exception of prostate cancer, for which there was a trend toward an increase in risk in the pravastatin group both during and after the trial, with an absolute increase overall from 1.8% to 2.7% ($P=0.03$). This finding was not significant after adjustment for multiple testing (Bonferroni correction).

DISCUSSION

In the original report of our study, we described a significant reduction in the risk of coronary events with the use of pravastatin. We now report that during an extended follow-up period of approximately 10 years after the end of the trial,

Table 2. Coronary Heart Disease and Stroke Outcomes.*

Event	Trial Period		Post-Trial Period†		Total Follow-up Period	
	Placebo	Pravastatin	Placebo	Pravastatin	Placebo	Pravastatin
CHD-related death or nonfatal MI						
No./total no. (%)	199/3293 (6.0)	122/3302 (3.7)	310/3022 (10.3)	268/3115 (8.6)	509/3293 (15.5)	390/3302 (11.8)
Hazard ratio (95% CI)	1.00	0.60 (0.48–0.75)	1.00	0.82 (0.69–0.96)	1.00	0.73 (0.63–0.83)
P value		<0.001		0.02		<0.001
CHD-related death or hospitalization						
No./total no. (%)	295/3293 (9.0)	203/3302 (6.1)	556/2926 (19.0)	473/3038 (15.6)	851/3293 (25.8)	676/3302 (20.5)
Hazard ratio (95% CI)	1.00	0.66 (0.56–0.80)	1.00	0.80 (0.71–0.90)	1.00	0.75 (0.68–0.83)
P value		<0.001		<0.001		<0.001
Fatal or nonfatal stroke						
No./total no. (%)	47/3293 (1.4)	33/3302 (1.0)	176/3122 (5.6)	161/3171 (5.1)	223/3293 (6.8)	194/3302 (5.9)
Hazard ratio (95% CI)	1.00	0.67 (0.43–1.04)	1.00	0.88 (0.71–1.08)	1.00	0.83 (0.68–1.01)
P value		0.08		0.22		0.06

* Data are for the first event. Outcomes were adjusted for age, body-mass index, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol level, low-density lipoprotein cholesterol level, log triglyceride level, nitrate use or nonuse, smoking status (current smoker, former smoker, or nonsmoker), social-deprivation score, and presence or absence of a history of angina, diabetes, or hypertension. CHD denotes coronary heart disease, and MI myocardial infarction.

† Participants who died or had an event of interest during the trial were excluded.

there was evidence of an ongoing reduction in the risk of major coronary events among study participants treated with pravastatin during the trial. This result was presumably due to stabilization of existing plaque and a slowing of the progression of coronary artery disease.^{12–14} A recent uncontrolled study of aggressive cholesterol lowering suggested that over a 2-year period such a regimen can lead to regression of atherosclerosis.¹⁵ It is conceivable that a less intensive regimen over a longer period of time could provide a similar benefit and that some participants may have had regression. However, the primary benefit is most likely due to a slowing of the progression of disease.

There was a small (approximately 4%) excess of participants in the group originally assigned to pravastatin who were being treated with a statin in the first 5 years after the end of the trial, as compared with those assigned to placebo, probably because of a slight preference for continuing active treatment in the pravastatin group after the assigned treatment was revealed.

We do not believe that this small difference can explain the results observed. Five years after the trial, approximately 37% of participants in both groups were taking a statin, arguably reducing the possibility of demonstrating ongoing benefit with respect to the original group assignment. The results do suggest that continuing treatment beyond 5 years may be beneficial. However, the magnitude of such an additional benefit is unclear.

A cost-effectiveness analysis was performed in 1997 to estimate the cost per year of life gained for 5 years of statin treatment as primary prevention on the basis of data from our study.¹⁶ However, this analysis did not incorporate an ongoing benefit with respect to the prevention of nonfatal coronary events after the completion of 5 years of treatment. Using the additional data described here, we found that there was an overall absolute risk reduction of 5.3% for the outcome of death from or hospitalization for coronary heart disease, resulting in the need to initiate treatment in only 19 patients for an average of

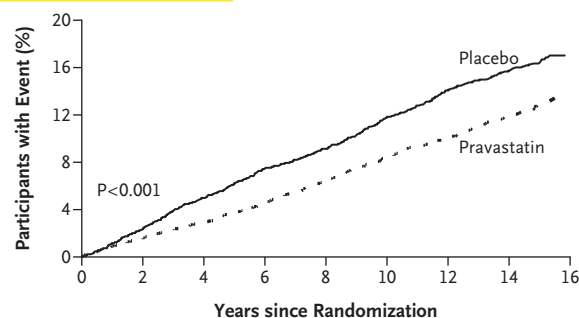
5 years to prevent one such first event over a 15-year period. Work on a revised cost-effectiveness analysis is ongoing.

We observed a trend toward a reduction in the risk of stroke over a period of 15 years (from 6.8% in the group originally assigned to placebo to 5.9% in the group originally assigned to pravastatin). This is the same relative effect as that shown in a recent meta-analysis of statin trials.¹⁷ Hence, it is possible that our failure to demonstrate a significant reduction in the risk of stroke was due to insufficient statistical power. A strong trend toward a reduction in nonfatal strokes was offset in part by an increase in fatal strokes. Despite offering convincing evidence that statins prevent nonfatal strokes, the meta-analysis did not demonstrate a significant reduction in death from stroke (hazard ratio, 0.91; 95% CI, 0.74 to 1.11).¹⁷

The results for mortality from noncardiovascular causes, mortality from cancer, and all incident cancers suggest no evidence of long-term harm for the patients taking pravastatin. The only cancer outcome that occurred with significantly greater frequency in the pravastatin group than in the placebo group was prostate cancer. Taking into account the multiple statistical tests performed, it is arguable that this result was due to chance rather than to a causal relationship. In the meta-analysis of statin trials,¹⁷ data were not reported for prostate cancer as a separate site of cancer. However, there was no excess in the number of genitourinary cancers in that analysis, and the results of an observational case-control study suggest a possible reduction in prostate cancer with statin use.¹⁸ A meta-analysis of the incidence of cancer in statin trials¹⁹ showed no significant difference in the incidence of prostate cancer between the statin and control groups in trials involving a total of 20,063 participants. However, reports on these other studies did not include data on long-term follow-up, and some cancers may have a long latency period.

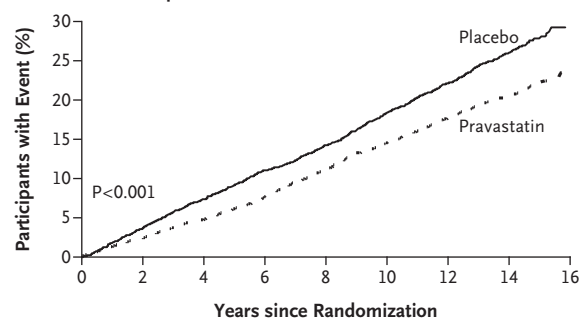
Our results should be compared with those observed in the long-term follow-up of the Scandinavian Simvastatin Survival Study⁵ and the LIPID trial.⁷ Both were secondary prevention studies, and in both studies most participants were treated with open-label cholesterol-lowering drugs at the start of the post-trial follow-up period (84% in the Scandinavian study and 90% in the LIPID study). The Scandinavian group reported on an

A CHD-Related Death or Nonfatal MI



No. at Risk	3293	3199	3071	2953	2841	2691	2549	1903
Placebo								
Pravastatin	3302	3237	3157	3065	2943	2819	2675	2026

B CHD-Related Death or Hospitalization



No. at Risk	3293	3156	2993	2839	2682	2486	2307	1661
Placebo								
Pravastatin	3302	3211	3100	2965	2800	2639	2454	1821

Figure 2. Kaplan–Meier Time-to-Event Analyses for Composite Coronary Outcomes, According to the Originally Assigned Study Group.

Panel A shows the Kaplan–Meier estimates for death from coronary heart disease (CHD) or nonfatal myocardial infarction (MI), and Panel B the estimates for CHD-related death or hospitalization.

extended 5-year follow-up of deaths and incident cancers.⁵ They found no ongoing benefit with respect to a reduction in the rate of death from any cause or from cardiovascular disease in the follow-up period and no evidence of an increase in the incidence of cancer. There were more cases of prostate cancer in the placebo group than in the statin group. The LIPID Study Group reported results⁷ for a 2-year extension. During this period, there was ongoing evidence of a benefit with respect to a reduction in deaths from coronary cause and deaths from any cause. There was no evidence of an excess incidence of cancers of the prostate and testes combined in the group randomly assigned to receive pravastatin. There is no obvious explanation for the apparent dis-

Table 3. Incident Cancers.*

Cancer Type	Trial Period		Post-Trial Period†		Total Follow-up Period	
	Placebo	Pravastatin	Placebo	Pravastatin	Placebo	Pravastatin
All incident cancers						
No./total no. (%)	103/3286 (3.1)	105/3291 (3.2)	301/3102 (9.7)	326/3128 (10.4)	404/3286 (12.3)	431/3291 (13.1)
Hazard ratio (95% CI)	1.00	0.99 (0.76–1.30)	1.00	1.07 (0.91–1.25)	1.00	1.05 (0.92–1.20)
P value		0.96		0.43		0.50
Site-specific incident cancers						
Colorectal						
No./total no. (%)	20/3286 (0.6)	12/3291 (0.4)	46/3138 (1.5)	44/3180 (1.4)	66/3286 (2.0)	56/3291 (1.7)
Hazard ratio (95% CI)	1.00	0.58 (0.28–1.19)	1.00	0.92 (0.61–1.40)	1.00	0.82 (0.58–1.17)
P value		0.14		0.71		0.28
Lung						
No./total no. (%)	26/3286 (0.8)	23/3291 (0.7)	83/3148 (2.6)	79/3183 (2.5)	109/3286 (3.3)	102/3291 (3.1)
Hazard ratio (95% CI)	1.00	0.86 (0.49–1.51)	1.00	0.93 (0.68–1.26)	1.00	0.91 (0.70–1.20)
P value		0.60		0.64		0.50
Prostate						
No./total no. (%)	10/3286 (0.3)	17/3291 (0.5)	49/3143 (1.6)	72/3172 (2.3)	59/3286 (1.8)	89/3291 (2.7)
Hazard ratio (95% CI)	1.00	1.62 (0.74–3.55)	1.00	1.42 (0.99–2.04)	1.00	1.46 (1.05–2.02)
P value		0.22		0.06		0.03
Upper gastrointestinal tract						
No./total no. (%)	10/3286 (0.3)	17/3291 (0.5)	31/3150 (1.0)	37/3178 (1.2)	41/3286 (1.2)	54/3291 (1.6)
Hazard ratio (95% CI)	1.00	1.69 (0.77–3.69)	1.00	1.14 (0.71–1.84)	1.00	1.27 (0.85–1.91)
P value		0.19		0.59		0.25
Urinary tract						
No./total no. (%)	14/3286 (0.4)	13/3291 (0.4)	29/3142 (0.9)	35/3173 (1.1)	43/3286 (1.3)	48/3291 (1.5)
Hazard ratio (95% CI)	1.00	0.93 (0.44–1.98)	1.00	1.18 (0.72–1.92)	1.00	1.10 (0.73–1.66)
P value		0.85		0.52		0.66
Other cancers						
No./total no. (%)	26/3286 (0.8)	31/3291 (0.9)	83/3135 (2.6)	83/3171 (2.6)	95/3286 (2.9)	90/3291 (2.7)
Hazard ratio (95% CI)	1.00	1.10 (0.65–1.85)	1.00	0.97 (0.71–1.31)	1.00	0.92 (0.69–1.22)
P value		0.73		0.83		0.56

* Data are for the first incident cancer. Eighteen participants who had cancer within 5 years before randomization were excluded from the analysis. Outcomes were adjusted for age, body-mass index, smoking status (current smoker, former smoker, or nonsmoker), and social-deprivation score.

† Participants who died or had an event of interest during the trial were excluded.

parity between the two studies with respect to the extended benefit achieved. It is possible that the extended benefit of a period of treatment with a statin will depend on the severity of coronary disease at baseline. In that respect, our study population would rank as having the least severe coronary disease at baseline, and the Scandinavian population as having the most severe disease. Hence, it is not clear that the results achieved during long-term follow-up in our study can be extrapolated to the treatment of patients with established coronary heart disease. In addition, all study participants were middle-aged men, which means that our findings cannot necessarily be extrapolated to any other group.

One important limitation of our study is that we were not able, because of funding constraints, to obtain data on statin use for the entire 10-year follow-up period after completion of the trial. As noted, the rate of statin use during the first 5 years of the extension period was low as compared with the rates in the Scandinavian and LIPID studies, probably because ours was a population largely without evidence of previous coronary disease. With further follow-up, we might have found that statin use increased to a greater degree among patients in whom clinical evidence of coronary disease developed (or in whom other risk factors for coronary disease, such as hypertension or diabetes, developed). Because of the post-

trial use of statins in both randomized groups, it is arguable that our analysis underestimates the likely effect of the initial 5 years of statin use in reducing coronary events.

In conclusion, this study showed that in men with hypercholesterolemia who did not have a history of myocardial infarction, statin treatment for an average of 5 years provided an ongoing reduction in the risk of coronary events for an additional period of up to 10 years. There was no evidence of an overall increase in the risk of death from noncardiovascular causes or cancer or in the incidence of cancer.

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