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## PREVENTION OF CORONARY HEART DISEASE WITH PRAVASTATIN IN MEN WITH HYPERCHOLESTEROLEMIA

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**Abstract Background.** Lowering the blood cholesterol level may reduce the risk of coronary heart disease. This double-blind study was designed to determine whether the administration of pravastatin to men with hypercholesterolemia and no history of myocardial infarction reduced the combined incidence of nonfatal myocardial infarction and death from coronary heart disease.

**Methods.** We randomly assigned 6595 men, 45 to 64 years of age, with a mean ( $\pm$ SD) plasma cholesterol level of  $272 \pm 23$  mg per deciliter ( $7.0 \pm 0.6$  mmol per liter) to receive pravastatin (40 mg each evening) or placebo. The average follow-up period was 4.9 years. Medical records, electrocardiographic recordings, and the national death registry were used to determine the clinical end points.

**Results.** Pravastatin lowered plasma cholesterol levels by 20 percent and low-density lipoprotein cholesterol levels by 26 percent, whereas there was no change with placebo. There were 248 definite coronary events (specified as nonfatal myocardial infarction or death from coronary

heart disease) in the placebo group, and 174 in the pravastatin group (relative reduction in risk with pravastatin, 31 percent; 95 percent confidence interval, 17 to 43 percent;  $P < 0.001$ ). There were similar reductions in the risk of definite nonfatal myocardial infarctions (31 percent reduction,  $P < 0.001$ ), death from coronary heart disease (definite cases alone: 28 percent reduction,  $P = 0.13$ ; definite plus suspected cases: 33 percent reduction,  $P = 0.042$ ), and death from all cardiovascular causes (32 percent reduction,  $P = 0.033$ ). There was no excess of deaths from noncardiovascular causes in the pravastatin group. We observed a 22 percent reduction in the risk of death from any cause in the pravastatin group (95 percent confidence interval, 0 to 40 percent;  $P = 0.051$ ).

**Conclusions.** Treatment with pravastatin significantly reduced the incidence of myocardial infarction and death from cardiovascular causes without adversely affecting the risk of death from noncardiovascular causes in men with moderate hypercholesterolemia and no history of myocardial infarction. (N Engl J Med 1995;333:1301-7.)

EARLIER trials of lipid-lowering drugs in the primary prevention of coronary heart disease have demonstrated that lowering cholesterol levels in middle-aged men with hypercholesterolemia reduces the incidence of myocardial infarction.<sup>1-4</sup> However, these studies, because of their design and low rates of observed events, were unable to show a clear effect of therapy on the risk of death from coronary heart disease or death from any cause. A meta-analysis of the trials provided support for the likelihood that therapy lowered the risk of death from coronary heart disease, but it also aroused concern that the risk of death from noncardiovascular causes might be increased by treat-

ment.<sup>5-8</sup> Whether this latter association was due to chance, to the reduction in cholesterol itself, or to an adverse effect of the drugs is not clear.

Recently, a new class of lipid-lowering drug, the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, has been introduced into clinical practice. These drugs block endogenous synthesis of cholesterol and reduce the levels of low-density lipoprotein (LDL) cholesterol. They slow the progression of coronary disease and reduce the incidence of death from coronary causes and death from any cause in men with manifest coronary heart disease.<sup>9-15</sup> The present study was designed to evaluate the effectiveness of a reductase inhibitor, pravastatin (Pravachol), in preventing coronary events in men with moderate hypercholesterolemia and no history of myocardial infarction.

## METHODS

### Design

The objective was to enroll approximately 6000 middle-aged men, randomly assigned in a double-blind fashion to receive either pravastatin (40 mg each evening) or placebo and to record their clinical progress over a period of five years. The details of the study design,

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including the definitions of the end points, have been described previously.<sup>16</sup> Briefly, the primary end point of the study was the occurrence of nonfatal myocardial infarction or death from coronary heart disease as a first event; these two categories were combined. Other principal end points were the occurrence of death from coronary heart disease and nonfatal myocardial infarction. In all categories, the events were classified as either definite or suspected. In addition to the main end points, the effect of treatment on death from cardiovascular causes, death from any cause, and the frequency of coronary revascularization procedures was analyzed.

All subjects provided written informed consent. The study was approved by the ethics committees of the University of Glasgow and all participating health boards.

### Recruitment and Follow-up

Coronary screening clinics were established in primary medical care facilities throughout the West of Scotland district. Approximately 160,000 men ranging in age from 45 to 64 years were invited to attend the clinics to assess their coronary risk factors. A total of 81,161 appeared for the first visit, and those whose nonfasting plasma cholesterol level was at least 252 mg per deciliter (6.5 mmol per liter) but who had no history of myocardial infarction were given lipid-lowering dietary advice<sup>17</sup> and asked to return four weeks later. A total of 20,914 men returned for the second visit, at which time a lipoprotein profile was obtained that measured plasma cholesterol, the cholesterol content of LDL and high-density lipoprotein (HDL), and plasma triglycerides while the subjects were fasting. If on this occasion the LDL cholesterol level was at least 155 mg per deciliter (4.0 mmol per liter) and the subject had no exclusion criteria,<sup>16</sup> he was advised to stay on the lipid-lowering diet for a further four weeks and then to return for a third visit (13,654 attended), at which time a second lipoprotein profile and a 12-lead electrocardiogram (ECG) were obtained. On the fourth visit the patients underwent randomization if they met the following criteria: fasting LDL cholesterol level of at least 155 mg per deciliter during the second and third visits, with at least one value of 174 mg per deciliter or above (4.5 mmol per liter) and one value of 232 mg per deciliter or below (6.0 mmol per liter); no serious ECG abnormalities according to Minnesota code<sup>18</sup> 1 (pathologic Q waves), 4-1, 5-1, or 7-1-1 or arrhythmia such as atrial fibrillation; and no history of myocardial infarction or other serious illness, although men with stable angina who had not been hospitalized within the previous 12 months were eligible. Further details of the inclusion and exclusion criteria were described previously.<sup>16</sup>

The subjects were seen at three-month intervals, and dietary advice was reinforced on each occasion. A fasting lipoprotein profile was obtained every six months, and an ECG was recorded annually or as required clinically. The subjects received a full medical examination by a physician each year.

### Laboratory Analyses

The cholesterol measurement during the first visit was performed on a Reflotron bench-top analyzer (Boehringer-Mannheim, Lewes, Kent, United Kingdom). All subsequent laboratory analyses, including biochemical, hematologic, and lipoprotein profiles, were conducted at the central laboratory at the Glasgow Royal Infirmary. Lipoprotein profiles were determined according to the Lipid Research Clinics protocol<sup>19</sup> with enzymatic cholesterol and triglyceride assays. The laboratory was certified through the Lipid Standardization Program of the Centers for Disease Control and Prevention in Atlanta. Abnormalities in the results of blood tests were identified with the use of published reference ranges.<sup>16</sup>

Siemens Sicard 440 electrocardiographs were used to record the 12-lead ECGs, and the data were transmitted by telephone to the ECG core laboratory at the Glasgow Royal Infirmary for storage on a central Mingocare data base (Siemens Elema, Stockholm, Sweden) and subsequent automated classification according to the Minnesota code, including serial comparisons.<sup>18,20-22</sup> All ECG results were verified by visual inspection.

### Identification and Classification of End Points

At each follow-up visit, adverse events were documented on the basis of the subjects' recall, and if appropriate, further information was

obtained from hospital records. All data on randomized subjects were flagged electronically on national computer data bases so that the numbers of deaths, incident cancers, hospitalizations, and cardiac surgeries could be monitored according to previously described methods.<sup>23</sup> Potential end points were reviewed and classified according to predefined criteria<sup>16</sup> by the End-Points Committee, whereas non-coronary heart disease events were reviewed and classified by the Adverse-Events Committee. The progress and conduct of the study were monitored regularly by the independent, unblinded Data and Safety Monitoring Committee. Except for the trial statistician and his assistant, all trial personnel remained unaware of the subjects' treatment assignments throughout the study.

### Statistical Analysis

All data were analyzed according to the intention-to-treat principle. The results of the two fasting lipoprotein profiles obtained during visits 2 and 3 were averaged to produce base-line values. The LDL cholesterol results were analyzed according to both the treatment actually received and the intention-to-treat principle. The analysis based on actual treatment used only the measured lipid levels in subjects who had attended the previous scheduled visit and who had been issued with trial medication at that visit. For the intention-to-treat analysis, all recorded levels were included, without reference to the subjects' degree of compliance at previous visits. In addition, in cases in which no lipid value was available for a scheduled visit and no medication had been issued at the previous visit, the subject's base-line level was used. For each end-point category, the lengths of time to a first event were compared with use of the log-rank test, and the relative reduction in risk resulting from pravastatin treatment, with 95 percent confidence intervals, was calculated with the Cox proportional-hazards model.<sup>24</sup> In addition, Kaplan-Meier time-to-event curves were used to estimate the absolute risk of each event at five years for each treatment group. When a silent myocardial infarction was detected on the basis of serial comparison of ECGs, the event was con-

Table 1. Base-Line Characteristics of the Randomized Subjects, According to Treatment Group.\*

CHARACTERISTIC	PLACEBO (N = 3293)	PRAVASTATIN (N = 3302)
<b>Continuous variables</b>		
Age — yr	55.1 ± 5.5	55.3 ± 5.5
Body-mass index†	26.0 ± 3.1	26.0 ± 3.2
Blood pressure — mm Hg		
Systolic	136 ± 17	135 ± 18
Diastolic	84 ± 10	84 ± 11
Cholesterol — mg/dl		
Total	272 ± 22	272 ± 23
LDL	192 ± 17	192 ± 17
HDL	44 ± 10	44 ± 9
Triglycerides — mg/dl	164 ± 68	162 ± 70
Alcohol consumption — units/wk‡	11 ± 13	12 ± 14
<b>Categorical variables — no. of subjects (%)</b>		
Angina§	174 (5)	164 (5)
Intermittent claudication§	96 (3)	97 (3)
Diabetes	35 (1)	41 (1)
Hypertension (self-reported)	506 (15)	531 (16)
Minor ECG abnormality	259 (8)	275 (8)
Smoking status		
Never smoked	705 (21)	717 (22)
Exsmoker	1127 (34)	1138 (34)
Current smoker	1460 (44)	1445 (44)
Employment status		
Employed	2324 (71)	2330 (71)
Unemployed	459 (14)	430 (13)
Retired	338 (10)	330 (10)
Disabled	171 (5)	210 (6)

\*Plus-minus values are means ± SD. To convert values for cholesterol to millimoles per liter, multiply by 0.026, and to convert values for triglycerides to millimoles per liter, multiply by 0.011.

†The weight in kilograms divided by the square of the height in meters.

‡A unit was defined as 1 measure (60 ml) of liquor, 1 glass (170 ml) of wine, or a half pint (300 ml) of beer.

§As indicated by positive responses on the Rose questionnaire.

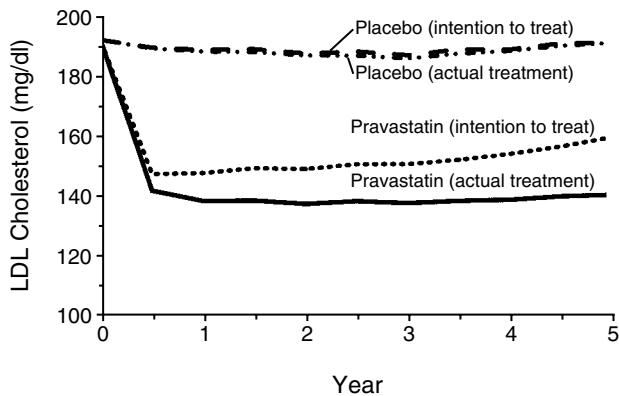


Figure 1. Effects of Pravastatin Therapy on Plasma LDL Cholesterol Levels.

To convert values for cholesterol to millimoles per liter, multiply by 0.026.

sidered to have occurred midway between the first diagnostic ECG and the previous ECG. Two-tailed P values were used throughout.

For the primary end point, an analysis was performed for predefined subgroups<sup>16</sup> characterized at base line according to age (<55 years or  $\geq 55$  years), smoking status (smoker or nonsmoker of cigarettes, cigars, or pipes), and whether at least two of the following risk factors were present: smoking, hypertension, a history of chest pain or intermittent claudication (as indicated by positive responses on the Rose questionnaire), diabetes, and a minor ECG abnormality associated with coronary heart disease (Minnesota code 4-2, 4-3, 5-2, or 5-3).

In addition, the effect of treatment was examined in a subgroup with and a subgroup without vascular disease at base line. Vascular disease was considered to be present if there was evidence of angina, intermittent claudication, stroke, transient ischemic attack, and ECG abnormalities according to the Minnesota code. Finally, the influence of base-line lipid levels on the effect of treatment was assessed by dividing the randomized population according to the median plasma cholesterol, LDL or HDL cholesterol, or plasma triglyceride concentration.

The Data and Safety Monitoring Committee conducted annual reviews of the main end points according to the O'Brien and Fleming criteria for stopping the trial prematurely.<sup>25</sup> The overall P value indicating statistical significance was set at 0.01.

## RESULTS

A total of 6595 subjects underwent randomization. The clinical characteristics of the subjects who were screened and those who were randomized have been described previously.<sup>26</sup> The first patient was enrolled on February 1, 1989, and recruitment was completed by September 30, 1991. The final visits were made between February and May 1995, by which time the study population had accrued 32,216 subject-years of follow-up (an average of 4.9 years per subject). At the end of the study, the vital and clinical status of all randomized subjects was ascertained.

The base-line characteristics of the pravastatin and placebo groups are summarized in Table 1. As expected in a trial of this size, the groups were well balanced. For the study population as a whole, the average ( $\pm$ SD) plasma cholesterol level was  $272 \pm 23$  mg per deciliter ( $7.0 \pm 0.6$  mmol per liter), the LDL cholesterol level was  $192 \pm 17$  mg per deciliter ( $5.0 \pm 0.5$  mmol per liter), and the HDL cholesterol level was  $44 \pm 9$  mg per deciliter ( $1.14 \pm 0.26$  mmol per liter). On the basis of positive responses on the Rose questionnaire, evidence of angina was present in 5 percent of the men, whereas 8 percent had ECG ST-T wave changes (Minnesota codes 4-2, 4-3, 5-2, and 5-3). The prevalence of self-reported diabetes mellitus was 1 percent, and that of hypertension was 16 percent; 44 percent of the subjects were current smokers.

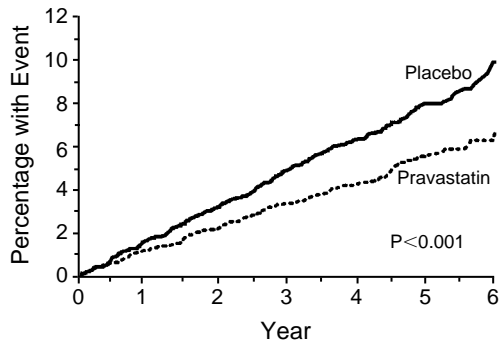
## Withdrawals

The cumulative rates of withdrawal from treatment in the placebo and pravastatin groups were 14.9 percent and 15.5 percent, respectively, at year 1, 19.1 percent and 19.4 percent at year 2, 22.5 percent and 22.7 percent at year 3, 25.2 percent and 24.7 percent at year 4, and 30.8 percent and 29.6 percent at year 5. There was no significant difference in the withdrawal rates between the two groups at any time. The disproportionate increase from year 4 to year 5 can be attributed to the withdrawal from the study of some subjects who had

Table 2. End Points of the Study.\*

VARIABLE	PLACEBO	PRAVASTATIN	P VALUE	RISK REDUCTION WITH
	(N = 3293)	(N = 3302)		PRAVASTATIN (95% CI)
	no. of events (absolute % risk at 5 yr)			%
<b>Definite coronary events</b>				
Nonfatal MI or death from CHD	248 (7.9)	174 (5.5)	<0.001	31 (17 to 43)
Nonfatal MI (silent MIs omitted) or death from CHD	218 (7.0)	150 (4.7)	<0.001	33 (17 to 45)
Nonfatal MI	204 (6.5)	143 (4.6)	<0.001	31 (15 to 45)
Death from CHD	52 (1.7)	38 (1.2)	0.13	28 (-10 to 52)
<b>Definite + suspected coronary events</b>				
Nonfatal MI or death from CHD	295 (9.3)	215 (6.8)	<0.001	29 (15 to 40)
Nonfatal MI (silent MIs omitted) or death from CHD	240 (7.6)	166 (5.3)	<0.001	32 (17 to 44)
Nonfatal MI	246 (7.8)	182 (5.8)	0.001	27 (12 to 40)
Death from CHD	61 (1.9)	41 (1.3)	0.042	33 (1 to 55)
<b>Other events</b>				
Coronary angiography	128 (4.2)	90 (2.8)	0.007	31 (10 to 47)
PTCA or CABG	80 (2.5)	51 (1.7)	0.009	37 (11 to 56)
Fatal or nonfatal stroke	51 (1.6)	46 (1.6)	0.57	11 (-33 to 40)
Incident cancer	106 (3.3)	116 (3.7)	0.55	-8 (-41 to 17)
<b>Death from other causes</b>				
Other cardiovascular causes (including stroke)	12	9	—	—
Suicide	1	2	—	—
Trauma	5	3	—	—
Cancer	49 (1.5)	44 (1.3)	0.56	11 (-33 to 41)
All other causes	7	7	—	—
<b>Death from all cardiovascular causes</b>	73 (2.3)	50 (1.6)	0.033	32 (3 to 53)
<b>Death from noncardiovascular causes</b>	62 (1.9)	56 (1.7)	0.54	11 (-28 to 38)
<b>Death from any cause</b>	135 (4.1)	106 (3.2)	0.051	22 (0 to 40)

\*The P values are based on the log-rank test. No formal analysis was carried out for events with a low incidence. CI denotes confidence interval, CHD coronary heart disease, MI myocardial infarction, PTCA percutaneous transluminal coronary angioplasty, and CABG coronary-artery bypass graft.



Placebo							
Cumulative events	0	55	105	159	205	240	248
No. at risk	3293	3230	3167	3099	2714	1241	83
Pravastatin							
Cumulative events	0	40	72	109	138	167	174
No. at risk	3302	3256	3215	3162	2807	1330	99

Figure 2. Kaplan–Meier Analysis of the Time to a Definite Nonfatal Myocardial Infarction or Death from Coronary Heart Disease, According to Treatment Group.

completed the five years of follow-up and who could have proceeded further but did not wish to do so.

#### Reduction in Lipid Levels

When the data were analyzed according to the treatment actually received, pravastatin was found to have lowered plasma levels of cholesterol by 20 percent, LDL cholesterol by 26 percent (Fig. 1), and triglycerides by 12 percent, whereas HDL cholesterol was increased by 5 percent. There were no such changes with placebo. When the data were analyzed according to the intention-to-treat principle, because such analysis includes subjects who withdrew and noncompliant subjects,

there was an apparent reduction in the observed difference in LDL cholesterol levels between treatment groups over time. This result is in contrast to that based on actual treatment, which showed that the difference was maintained.

#### End Points

As compared with placebo, pravastatin produced a significant reduction in the risk of the combined primary end point of definite nonfatal myocardial infarction and death from coronary heart disease (reduction, 31 percent; 95 percent confidence interval, 17 to 43 percent;  $P < 0.001$ ; absolute difference in the risk at five years, 2.4 percentage points) (Table 2 and Fig. 2). The effects of pravastatin on other principal end points are given in Table 2 and Figure 3. The reduction in the risk of nonfatal myocardial infarction was significant ( $P \leq 0.001$ ) whether the definite cases of myocardial infarction were considered alone or in combination with suspected cases. Excluding silent myocardial infarctions from the analysis of the primary end point did not affect the outcome (Table 2). For the end point of death from coronary heart disease, there was a significant treatment effect in the analysis of both definite and suspected cases (risk reduction, 33 percent; 95 percent confidence interval, 1 to 55 percent;  $P = 0.042$ ), but not in the analysis of definite cases alone, probably because of the smaller number of events in this group. However, there was a similar reduction in risk (28 percent). When the effect of treatment with pravastatin on death from all cardiovascular causes was analyzed, a 32 percent reduction in risk (95 percent confidence interval, 3 to 53 percent;  $P = 0.033$ ) was observed. Treatment with pravastatin was associated with similar reductions in the frequency of coronary angiography (31 percent; 95 percent confidence interval, 10 to 47 percent;  $P = 0.007$ )

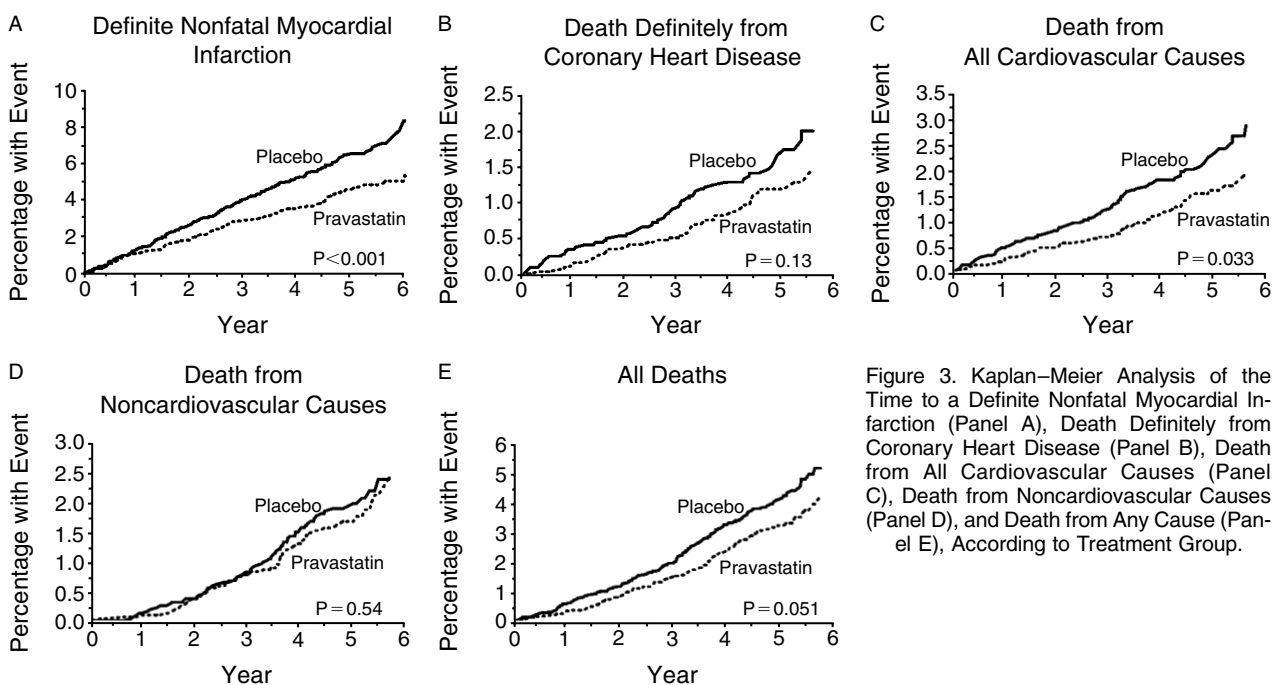


Figure 3. Kaplan–Meier Analysis of the Time to a Definite Nonfatal Myocardial Infarction (Panel A), Death Definitely from Coronary Heart Disease (Panel B), Death from All Cardiovascular Causes (Panel C), Death from Noncardiovascular Causes (Panel D), and Death from Any Cause (Panel E), According to Treatment Group.

and revascularization procedures (37 percent; 95 percent confidence interval, 11 to 56 percent;  $P=0.009$ ).

There were 56 deaths from noncardiovascular causes in the pravastatin group and 62 in the placebo group ( $P=0.54$ ). There was no significant difference between treatment groups in the numbers of deaths from cancer, suicide, or trauma. There were 46 strokes (6 of which were fatal) in the pravastatin group and 51 (4 fatal) in the placebo group. In the pravastatin group, the reduction in the number of deaths from cardiovascular causes in the absence of any increase in the number of deaths from noncardiovascular causes resulted in a 22 percent reduction in the overall risk of death (95 percent confidence interval, 0 to 40 percent;  $P=0.051$ ).

The beneficial effects of pravastatin in therapy were evident in all subgroups (Table 3). The numbers of subjects in the subgroups with either multiple risk factors at base line or vascular disease at base line were too small to show a statistically significant effect.

#### Other Adverse Events

In the pravastatin group 116 subjects had incident (fatal or nonfatal) cancers, as compared with 106 in the placebo group ( $P=0.55$ ). These figures include cases of malignant melanoma but not minor skin cancers. For the placebo and pravastatin groups, respectively, there were 30 and 31 gastrointestinal cancers, 26 and 32 genitourinary cancers, 28 and 27 respiratory tract cancers, and 22 and 26 other cancers. **Twenty subjects in the pravastatin group reported myalgia, and 97 muscle aches. The corresponding numbers in the placebo group were 19 and 102 ( $P$  not significant).** Four subjects (three in the pravastatin group and one in the placebo group) had asymptomatic episodes of elevated creatine kinase concentrations ( $>10$  times the upper reference limit). Elevations in aspartate aminotransferase and alanine aminotransferase values ( $>3$  times the upper reference limits) were recorded for 26 and 16 subjects, respectively, in the pravastatin group, as compared with 20 and 12 subjects in the placebo group ( $P$  not significant).

#### DISCUSSION

As compared with placebo, pravastatin reduced the risk of fatal or nonfatal coronary events in middle-aged men with hypercholesterolemia and no history of myocardial infarction by approximately 30 percent. The beneficial effects of treatment were remarkably consistent across a variety of coronary end points. In contrast to the results of studies using resins, fibrates, or other

Table 3. Incidence of the Primary End Point, According to Subgroup.

VARIABLE	SUBGROUP	NO. OF SUBJECTS	no. of events (absolute % risk at 5 yr)		P VALUE*	RISK REDUCTION WITH PRAVASTATIN (95% CI)
			PLACEBO	PRAVASTATIN		%
Age	<55 yr	3225	96 (6.1)	57 (3.5)	0.0024	40 (16 to 56)
	≥55 yr	3370	152 (9.8)	117 (7.3)	0.0089	27 (8 to 43)
Current smoking status	Nonsmoker	3687	104 (6.0)	74 (4.3)	0.016	31 (6 to 48)
	Smoker	2905	144 (10.4)	100 (7.0)	0.0035	31 (12 to 47)
Multiple risk factors†	Absent	5401	178 (6.9)	114 (4.4)	<0.001	37 (20 to 50)
	Present	1194	70 (12.7)	60 (10.2)	0.20	20 (−13 to 43)
Cholesterol level‡	<269 mg/dl	3192	122 (8.1)	80 (5.4)	0.0019	36 (15 to 51)
	≥269 mg/dl	3403	126 (7.8)	94 (5.6)	0.021	27 (4 to 44)
LDL cholesterol level‡	<189 mg/dl	3211	110 (7.6)	71 (4.9)	0.0025	37 (15 to 53)
	≥189 mg/dl	3384	138 (8.3)	103 (6.1)	0.016	27 (6 to 43)
HDL cholesterol level‡	≥43 mg/dl	3304	99 (6.2)	66 (4.3)	0.011	33 (9 to 51)
	<43 mg/dl	3291	149 (9.7)	108 (6.7)	0.0035	31 (11 to 46)
Triglyceride level§	<148 mg/dl	3239	98 (6.3)	72 (4.4)	0.024	29 (4 to 48)
	≥148 mg/dl	3356	150 (9.4)	102 (6.6)	0.0025	32 (12 to 47)
Prior vascular disease	Absent	5529	183 (7.0)	125 (4.7)	<0.001	33 (15 to 46)
	Present	1066	65 (12.8)	49 (9.6)	0.075	29 (−4 to 51)

\*The P values are based on the log-rank test.

†The presence of two or more of the following risk factors: smoking, hypertension, a history of chest pain or intermittent claudication (as indicated by positive responses on the Rose questionnaire), diabetes, and a minor ECG abnormality associated with coronary heart disease (Minnesota code 4-2, 4-3, 5-2, or 5-3).

‡To convert values for cholesterol to millimoles per liter, multiply by 0.026.

§To convert values for triglycerides to millimoles per liter, multiply by 0.011.

3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors,<sup>1-4,9</sup> the time-to-event curves began to diverge within six months of the initiation of treatment and continued to do so at the same rate throughout the trial. The frequency of the need for coronary angiography and revascularization procedures was significantly lower in the pravastatin group than in the placebo group.

The subjects in this study were representative of the general population in terms of socioeconomic status and risk factors (Table 1). Their plasma cholesterol levels were in the highest quartile of the range found in the British population.<sup>27</sup> A number had evidence of minor vascular disease, and in order to make the findings of the trial applicable to typical middle-aged men with hypercholesterolemia, they were not excluded.

In line with accepted guidelines,<sup>28</sup> the LDL cholesterol level was used as a criterion for entry into the study. As compared with placebo, pravastatin produced a major reduction in this lipoprotein fraction (Fig. 1) and moderate decreases in plasma triglycerides, as well as an increase in HDL cholesterol. These changes are in line with the expected response to pravastatin,<sup>29</sup> and all could potentially result in clinical benefit. The changes in the LDL cholesterol level are more substantial than those observed in earlier primary prevention studies.<sup>1-4</sup>

When the subjects were divided into two groups according to their lipid levels at base line, we found that coronary risk was related to higher plasma LDL cholesterol and triglyceride levels (i.e., levels above the median values) and lower HDL cholesterol levels (i.e., levels below the median value) (Table 3). The plasma cholesterol level was not a significant factor, principally because of the narrow range of cholesterol values used as a criterion for entry into the study. The relative reduc-

tion in risk with pravastatin therapy was statistically significant and of a similar magnitude in subjects with lipid values above and below the median.

The relative reductions in risk attributable to pravastatin therapy were not affected by age (<55 years vs.  $\geq$ 55 years) or smoking status. Furthermore, a significant treatment effect was seen in the subgroup without multiple risk factors and the subgroup without preexisting vascular disease. Thus, it is possible to conclude that in the subjects who might be considered to fall strictly into the primary-prevention category, pravastatin therapy produced a significant reduction in the relative risk of a coronary event.

Pravastatin therapy was well tolerated and resulted in no more study withdrawals than placebo. In particular, as in an earlier study,<sup>15</sup> there was no evidence that pravastatin adversely affected liver function or caused myopathy. Our results support those of a recent secondary-prevention trial<sup>9</sup> that found that lipid lowering with a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor is not associated with an increased risk of death from noncardiovascular causes. As in that earlier trial,<sup>9</sup> a comparison of the treatment and placebo groups showed no significant increase in the incidence of fatal or incident cancers or deaths due to suicide or trauma. More data on the adverse-event profile of this class of drugs will become available as the results of other prevention trials are published. In the current study, the benefit of pravastatin therapy with respect to fatal coronary events and the absence of any increase in the number of deaths from other causes led to a 22 percent reduction in the relative risk of death from any cause ( $P=0.051$ ).

From the data in Table 2, it can be estimated that treating 1000 middle-aged men with hypercholesterolemia and no evidence of a previous myocardial infarction with pravastatin for five years will result in 14 fewer coronary angiograms, 8 fewer revascularization procedures, 20 fewer nonfatal myocardial infarctions, 7 fewer deaths from cardiovascular causes, and 2 fewer deaths from other causes than would be expected in the absence of treatment. Since these figures are based on an intention-to-treat analysis, the magnitude of the benefit in fully compliant subjects is likely to be greater. These findings can be compared favorably with the results of the Medical Research Council trial<sup>30,31</sup> of the treatment of mild hypertension in middle-aged subjects. In that study, it was estimated that five years of active treatment of 1000 men ranging in age from 35 to 64 years would result in six fewer strokes and two fewer cardiovascular events than would be expected. Thus, our results indicate that reducing cholesterol levels with pravastatin reduces the risk of coronary events in asymptomatic subjects with hypercholesterolemia.

#### APPENDIX

The members of the West of Scotland Coronary Prevention Study are as follows: *Executive Committee (Voting Members)* — J. Shepherd (chairman), S.M. Cobbe, A.R. Lorimer, J.H. McKillop, I. Ford, C.J. Packard, P.W. Macfarlane, and G.C. Isles; *Data and Safety Monitoring*

*Committee* — M.F. Oliver (chairman), A.F. Lever, B.W. Brown, J.G.G. Ledingham, S.J. Pocock, and B.M. Rifkind; *End-Points Committee* — S.M. Cobbe, B.D. Vallance, P.W. Macfarlane; *Adverse-Events Committee* — A.R. Lorimer, J.H. McKillop, and D. Ballantyne; *Data-Center Staff* — L. Anderson, D. Duncan, J. McGrath, S. Kean, A. Lawrence, V. Montgomery, and J. Norrie; *Population Screening* — M. Percy; *Clinical Coordination, Monitoring, and Administration* — E. Pomphrey, A. Whitehouse, P. Cameron, P. Parker, F. Porteous, L. Fletcher, and C. Kilday; *Computerized ECG Analysis* — D. Shoit (deceased), S. Latif, and J. Kennedy; *Laboratory Operations* — M.A. Bell and R. Birrell; and *Company Liaison and General Support* — M. Mellies, J. Meyer, and W. Campbell.

#### REFERENCES

1. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate: report from the Committee of Principal Investigators. *Br Heart J* 1978;40:1069-118.
2. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;251:351-64.
3. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA* 1984;251:365-74.
4. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237-45.
5. Oliver MF. Might treatment of hypercholesterolaemia increase non-cardiac mortality? *Lancet* 1991;337:1529-31.
6. Hulley SB, Walsh JMB, Newman TB. Health policy on blood cholesterol: time to change directions. *Circulation* 1992;86:1026-9.
7. Davey Smith G, Pekkanen J. Should there be a moratorium on the use of cholesterol lowering drugs? *BMJ* 1992;304:431-4.
8. LaRosa JC, Hunninghake D, Bush D, et al. The cholesterol facts: a summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease: a joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute. *Circulation* 1990;81:1721-33.
9. The 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;344:1383-9.
10. MAAS Investigators. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994;344:633-8. [Erratum, *Lancet* 1994;344:762.]
11. Furberg CD, Adams HP Jr, Applegate WB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation* 1994;90:1679-87.
12. Jukema JW, Brusckhe AVG, van Boven AJ, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels: the Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 1995;91:2528-40.
13. Crouse JR III, Byington RP, Bond MG, et al. Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *Am J Cardiol* 1995;75:455-9. [Erratum, *Am J Cardiol* 1995;75:862.]
14. Pitt B, Mancini GBJ, Ellis SG, Rosman HS, Park J-SP, McGovern ME. Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I): reduction in atherosclerosis progression and clinical events. *J Am Coll Cardiol* (in press).
15. The Pravastatin Multinational Study Group for Cardiac Risk Patients. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. *Am J Cardiol* 1993;72:1031-7.
16. West of Scotland Coronary Prevention Study Group. A coronary primary prevention study of Scottish men age 45-64 years: trial design. *J Clin Epidemiol* 1992;45:849-60.
17. EAS Task Force for Prevention of Coronary Heart Disease. Prevention of coronary heart disease: scientific background and new clinical guidelines. *Nutr Metab Cardiovasc Dis* 1992;2:113-56.
18. Prineas RJ, Crow RS, Blackburn H. The Minnesota code manual of electrocardiographic findings: standards and procedures for measurement and classification. Boston: John Wright, PSG, 1982.
19. Lipid Research Clinics manual of laboratory operations, 1975. Washington, D.C.: Government Printing Office, 1975. (DHEW publication no. (NIH) 85-268.)
20. Crow RS, Prineas RJ, Jacobs DR Jr, Blackburn H. A new epidemiologic classification system for interim myocardial infarction from serial electrocardiographic changes. *Am J Cardiol* 1989;64:454-61.

21. Macfarlane PW, Devine B, Latif S, McLaughlin S, Shoat DB, Watts MP. Methodology of ECG interpretation in the Glasgow program. *Methods Inf Med* 1990;29:354-61.
  22. Macfarlane PW, Latif S, Shoat DS, Cobbe SM. Automated serial ECG comparison using the Minnesota Code. *Eur Heart J* 1990;11:Suppl:411. abstract.
  23. West of Scotland Coronary Prevention Study Group. Computerised record linkage: compared with traditional follow-up methods in clinical trials and illustrated in a prospective epidemiologic study. *J Clin Epidemiol* (in press).
  24. Collett D. Modelling survival data in medical research. London: Chapman & Hall, 1994.
  25. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
  26. West of Scotland Coronary Prevention Study Group. Screening experience and baseline characteristics in the West of Scotland Coronary Prevention Study. *Am J Cardiol* 1995;76:485-91.
  27. Mann JI, Lewis B, Shepherd J, et al. Blood lipid concentrations and other cardiovascular risk factors: distribution, prevalence, and detection in Britain. *BMJ* 1988;296:1702-6.
  28. Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). *JAMA* 1993;269:3015-23.
  29. Jones PH, Farmer JA, Cressman MD, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol* 1991;14:146-51.
  30. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *BMJ* 1985;291:97-104.
  31. Miall WE, Greenberg G. Mild hypertension: is there pressure to treat? An account of the MRC trial. Cambridge, United Kingdom: Cambridge University Press, 1987.
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