PREVENTION OF CARDIOVASCULAR EVENTS AND DEATH WITH PRAVASTATIN IN PATIENTS WITH CORONARY HEART DISEASE AND A BROAD RANGE OF INITIAL CHOLESTEROL LEVELS

THE LONG-TERM INTERVENTION WITH PRAVASTATIN IN ISCHAEMIC DISEASE (LIPID) STUDY GROUP*

ABSTRACT

Background In patients with coronary heart disease and a broad range of cholesterol levels, cholesterol-lowering therapy reduces the risk of coronary events, but the effects on mortality from coronary heart disease and overall mortality have remained uncertain.

Methods In a double-blind, randomized trial, we compared the effects of pravastatin (40 mg daily) with those of a placebo over a mean follow-up period of 6.1 years in 9014 patients who were 31 to 75 years of age. The patients had a history of myocardial infarction or hospitalization for unstable angina and initial plasma total cholesterol levels of 155 to 271 mg per deciliter. Both groups received advice on following a cholesterol-lowering diet. The primary study outcome was mortality from coronary heart disease.

Results Death from coronary heart disease occurred in 8.3 percent of the patients in the placebo group and 6.4 percent of those in the pravastatin group, a relative reduction in risk of 24 percent (95 percent confidence interval, 12 to 35 percent; $P<0.001$). Overall mortality was 14.1 percent in the placebo group and 11.0 percent in the pravastatin group (relative reduction in risk, 22 percent; 95 percent confidence interval, 13 to 31 percent; $P<0.001$). The incidence of all cardiovascular outcomes was consistently lower among patients assigned to receive pravastatin; these outcomes included myocardial infarction (reduction in risk, 29 percent; $P<0.001$), death from coronary heart disease or nonfatal myocardial infarction (a 24 percent reduction in risk, $P<0.001$), stroke (a 19 percent reduction in risk, $P=0.048$), and coronary revascularization (a 20 percent reduction in risk, $P<0.001$). The effects of treatment were similar for all predefined subgroups. There were no clinically significant adverse effects of treatment with pravastatin.

Conclusions Pravastatin therapy reduced mortality from coronary heart disease and overall mortality, as compared with the rates in the placebo group, as well as the incidence of all prespecified cardiovascular events in patients with a history of myocardial infarction or unstable angina who had a broad range of initial cholesterol levels. (N Engl J Med 1998;339: 1349-57.)

BY the end of the 1980s, there was strong epidemiologic evidence of a continuous association between plasma cholesterol levels and the risk of coronary heart disease (CHD).[1-3] Most patients with CHD have cholesterol levels that are not markedly elevated.[4] However, most randomized, controlled trials of cholesterol-lowering therapy have involved patients with at least moderate hypercholesterolemia, and the treatments used have had limited efficacy in lowering cholesterol. Taken together, those trials have demonstrated a clear reduction in the incidence of coronary events, both among persons with a history of CHD[5] and among those without such a history.[6] However, the reduction in coronary mortality associated with cholesterol-lowering therapy has been small (about 10 percent) and may be partially counterbalanced by a nonsignificant excess of deaths from noncoronary causes.[7] There has therefore been considerable uncertainty about the effects of cholesterol-lowering therapy on overall mortality among patients with high cholesterol levels[8] and about its effects on the risk of coronary events among patients with lower cholesterol levels.

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial was initiated in 1989 to investigate the effects of substantial lowering of cholesterol levels with the 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitor pravastatin on death from CHD among patients with a history of myocardial infarction or unstable angina and a broad range of initial cholesterol levels (155 to 271 mg per deciliter [4.0 to 7.0 mmol per liter]). Since our study began, two other large-scale trials of HMG-CoA reductase inhibitors in patients with CHD have been completed.[9,10] The Scandinavian Simvastatin Survival Study[9] demonstrated a significant reduction in overall mortality with simvastatin therapy among patients with higher initial cholesterol levels than those of our patients (213 to 309 mg per deciliter [5.5 to 8.0 mmol per liter]). The Cholesterol and Recurrent Events (CARE) trial[10] studied patients who had had myocardial infarction and who had cholesterol levels below 240 mg per deciliter (6.2 mmol per liter); it demonstrated a significant re-

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duction in the incidence of the composite outcome of coronary death and nonfatal myocardial infarction with pravastatin therapy. However, the study was not designed to detect a significant effect on overall mortality or mortality from CHD alone. Consequently, the effect of cholesterol-lowering therapy on these outcomes in patients with average cholesterol levels remained uncertain.

METHODS

Study Design and Patients

The design of the study is described in detail elsewhere.[11] We recruited a total of 9014 patients, 31 to 75 years of age, at 87 centers — 67 in Australia and 20 in New Zealand. Patients were eligible if they had had an acute myocardial infarction or had a hospital-discharge diagnosis of unstable angina between 3 and 36 months before study entry. Patients entered an eight-week-long single-blind placebo run-in phase during which they received dietary advice aimed at reducing their fat intake to less than 30 percent of total energy intake. For patients to qualify for the study, the plasma total cholesterol level measured four weeks before randomization was required to be 155 to 271 mg per deciliter and the fasting triglyceride level less than 445 mg per deciliter (5.0 mmol per liter). Exclusion criteria included a clinically significant medical or surgical event within three months before study entry, cardiac failure, renal or hepatic disease, and the current use of any cholesterol-lowering agents.

After stratification according to the qualifying event (myocardial infarction or unstable angina) and clinical center, patients were randomly assigned to receive either 40 mg of pravastatin (Pravachol, Bristol-Myers Squibb) or matching placebo once daily. Both groups continued to receive dietary advice. Plasma cholesterol levels were measured by the core laboratory at randomization, six months later, each year after randomization, and at the end of the study. High-density lipoprotein (HDL) cholesterol and triglyceride levels were measured in blood samples obtained while patients were fasting, at base line, one, three, and five years after randomizaton, and at the end of the study. Low-density lipoprotein (LDL) cholesterol was estimated indirectly, with use of the formula of Friedewald et al.[12] Study personnel and patients remained blinded to the results of the central analyses of lipid levels. The patients' usual care, including the institution of other cholesterol-lowering treatment, continued to be under the direction of their own doctors. The results of the other large-scale trials of HMG-CoA reductase inhibitors[9,10,13] were communicated to both patients and their treating doctors, with the further explanation that if it was considered indicated, open-label cholesterol-lowering therapy could be commenced. Routine visits to the clinic were scheduled every six months after randomization to monitor compliance with the study treatment and to obtain data on hospital admissions, serious adverse events, and study outcomes.

Classification and Review of Outcomes

The primary study outcome was death from CHD. Deaths from CHD were further classified as death due to fatal myocardial infarction, sudden death, death in the hospital after possible myocardial infarction, or death due to heart failure or another coronary cause. Secondary outcomes were death from any cause; death from cardiovascular causes; death from CHD or nonfatal myocardial infarction; myocardial infarction; stroke; nonhemorrhagic stroke; coronary revascularization (coronary angioplasty, coronary-artery bypass surgery, or both); number of days in the hospital; serum lipid levels; and the relation of changes in lipid levels to the occurrence of cardiovascular end points. Each of these analyses was prespecified in the original protocol or in subsequent amendments made without knowledge of the results of any analysis according to treatment assignment.

All deaths, myocardial infarctions, and strokes were reviewed by an outcomes-assessment committee or stroke-adjudication committee whose members had no knowledge of the patient's treatment assignment. Myocardial infarction was diagnosed on the basis of the presence of at least two new pathologic Q waves on the electrocardiogram[11] or two of the following three criteria: at least 15 minutes of ischemic chest pain, evolutionary ST-T wave changes (as previously defined[11]), or elevation of the serum level of creatine kinase or its MB isoenzyme to at least twice the upper limit of normal. A stroke was defined as an acute new disturbance of focal neurologic function resulting in death or lasting more than 24 hours.

An independent data and safety monitoring committee regularly monitored the progress of the study; five formal interim analyses were planned to examine differences in overall mortality or the incidence of serious adverse events associated with pravastatin treatment. Guidelines for stopping the trial early were based on a difference of at least 3 SD ($P<0.003$) between the groups in either of these outcomes.[14] The trial was conceived, managed, and analyzed independently of Bristol-Myers Squibb. All patients gave written informed consent, and the trial was approved by the ethics committee at each participating center.

Statistical Analysis

The study was designed to have 80 percent power to detect a reduction of 18.3 percent in the risk of death due to CHD at five years, with a two-sided P value of <0.05. The trial was planned to continue until 700 deaths from CHD had occurred unless it was stopped early. All analyses were performed on an intention-to-treat basis.

Time-to-event analyses were performed with the log-rank test, with stratification according to the qualifying event.[15] Estimates of the relative reduction in risk associated with pravastatin therapy and 95 percent confidence intervals were derived with use of the Cox proportional-hazards model.[16] Prespecified subgroup analyses evaluated variation in the effect of treatment on the composite outcome of death due to CHD and nonfatal myocardial infarction, on the basis of tests for interaction in the Cox model[16] and with use of continuous variables for age and base-line lipid values. P values were not adjusted for multiple comparisons.

RESULTS

Between June 12, 1990, and December 18, 1992, 9014 patients were randomly assigned to study treatment: 4512 to pravastatin and 4502 to placebo. Of these, 91 patients (1 percent) were subsequently found not to meet all the eligibility criteria (31 did not meet the criteria for myocardial infarction or unstable angina within 3 to 36 months before study entry; 46 underwent coronary revascularization or had unstable angina within 3 months before study entry; 8 were taking cholesterol-lowering drugs; and 6 met other exclusion criteria); these patients were included in all analyses. The two groups were very well balanced in terms of base-line characteristics (Table 1). Twelve percent had both qualifying events and were included in the stratum with myocardial infarction. A total of 42 percent of patients had a qualifying plasma total cholesterol level of less than 213 mg per deciliter (5.5 mmol per liter).

Status at the End of the Study

In May 1997, after the data and safety monitoring committee determined that the prespecified boundary for a difference in overall mortality had been

TABLE 1. BASE-LINE CHARACTERISTICS OF PATIENTS RANDOMLY ASSIGNED TO RECEIVE PRAVASTATIN OR PLACEBO.

CHARACTERISTIC*	PLACEBO (N=4502)	PRAVASTATIN (N=4512)
Age		
<55 yr — no. (%)	1021 (23)	1065 (24)
55–64 yr — no. (%)	1708 (38)	1706 (38)
65–69 yr — no. (%)	1087 (24)	1081 (24)
≥70 yr — no. (%)	686 (15)	660 (15)
Median — yr	62	62
Interquartile range — yr	55–68	55–67
Sex — no. (%)		
Male	3742 (83)	3756 (83)
Female	760 (17)	756 (17)
Qualifying event — no. (%)		
Myocardial infarction	2875 (64)	2879 (64)
Unstable angina	1627 (36)	1633 (36)
Time from qualifying event to randomization — yr		
Median	1.2	1.1
Interquartile range	0.7–2.1	0.6–2.1
Coronary risk factors — no. (%)		
Current smoker	444 (10)	425 (9)
Former smoker	2814 (63)	2923 (65)
History of systemic hypertension	1891 (42)	1867 (41)
Antihypertensive treatment	1711 (38)	1622 (36)
Diabetes mellitus	386 (9)	396 (9)
Obesity†	788 (18)	823 (18)
Other vascular disease — no. (%)		
Claudication	467 (10)	438 (10)
Stroke	198 (4)	171 (4)
Transient ischemic attack	176 (4)	156 (3)
Previous coronary revascularization — no. (%)		
PTCA only	486 (11)	502 (11)
CABG only	1219 (27)	1217 (27)
Both PTCA and CABG	133 (3)	135 (3)
Medication use — no. (%)		
Aspirin	3689 (82)	3726 (83)
Beta-blocker	2152 (48)	2090 (46)
Calcium antagonist	1610 (36)	1563 (35)
ACE inhibitor	719 (16)	720 (16)
Nitrate	1610 (36)	1599 (35)
Diuretic	761 (17)	727 (16)
Insulin	49 (1)	60 (1)
Oral hypoglycemic drug	262 (6)	236 (5)
Lipid levels — mg/dl‡		
Total cholesterol		
Median	218	218
Interquartile range	196–240	196–241
LDL cholesterol		
Median	150	150
Interquartile range	131–170	130–170
HDL cholesterol		
Median	36	36
Interquartile range	31–42	31–41
Triglycerides		
Median	138	142
Interquartile range	105–188	104–196
Total:HDL cholesterol ratio		
Median	6.07	6.11
Interquartile range	5.12–7.14	5.13–7.16

*The interquartile range is that from the 25th to the 75th percentile. PTCA denotes percutaneous transluminal coronary angioplasty, CABG coronary-artery bypass surgery, ACE angiotensin-converting enzyme, LDL low-density lipoprotein, and HDL high-density lipoprotein.

†Obesity was defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) above 30.

‡To convert values for cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.01129. Except for base-line triglyceride levels ($P=0.025$), there were no significant differences between the groups.

crossed, all patients were advised that the study would end. Patients' final follow-up visits took place between July 1 and September 30, 1997, when the mean duration of the study was 6.1 years and vital status was ascertained in all but one patient. After one year, after three years, and at the end of the study, 6 percent, 11 percent, and 19 percent, respectively, of the patients randomly assigned to treatment with pravastatin had permanently stopped taking the study drug, whereas 3 percent, 9 percent, and 24 percent of those assigned to placebo had begun open-label therapy with a cholesterol-lowering drug.

Effects of Treatment on Lipid Levels

Lipid levels, averaged over the first five years of follow-up, were analyzed on an intention-to-treat basis. In the pravastatin group, the plasma total cholesterol level fell by 39 mg per deciliter (1.0 mmol per liter) from the initial level of 218 mg per deciliter (5.6 mmol per liter); the reduction in total cholesterol was 18 percentage points greater than in the placebo group ($P<0.001$). Similarly, the LDL cholesterol level in the pravastatin group, initially 150 mg per deciliter (3.9 mmol per liter), was reduced by 25 percentage points more than in the placebo group; the plasma triglyceride level, initially 142 mg per deciliter (1.6 mmol per liter), was reduced by 11 percentage points more than in the placebo group; and the HDL cholesterol level, initially 36 mg per deciliter (0.9 mmol per liter), increased by 5 percentage points more than in the placebo group ($P<0.001$ for all comparisons). At six months, the total cholesterol level in the pravastatin group was an average of 21 percent lower than that in the placebo group. This difference declined to 13 percent at six years because of the discontinuation of treatment by patients assigned to pravastatin and the commencement of open-label cholesterol-lowering treatment by patients assigned to placebo.

Effects on Outcomes

The effects of treatment on cardiovascular outcomes are shown in Table 2. Among patients assigned to pravastatin, the incidence of the primary study end point of death from CHD was 6.4 percent in the pravastatin group, as compared with 8.3 percent in the placebo group (relative reduction in risk with pravastatin therapy, 24 percent; 95 percent confidence interval, 12 to 35 percent; $P<0.001$) (Fig. 1). Overall mortality was 22 percent lower (95 percent confidence interval, 13 to 31 percent) in the pravastatin group (11.0 percent) than in the placebo group (14.1 percent, $P<0.001$) (Fig. 2). Mortality from cardiovascular causes was 25 percent lower (7.3 percent vs. 9.6 percent, $P<0.001$). There were fewer deaths from cancer and trauma or suicide among patients assigned to pravastatin, but these differences were not significant (Table 3).

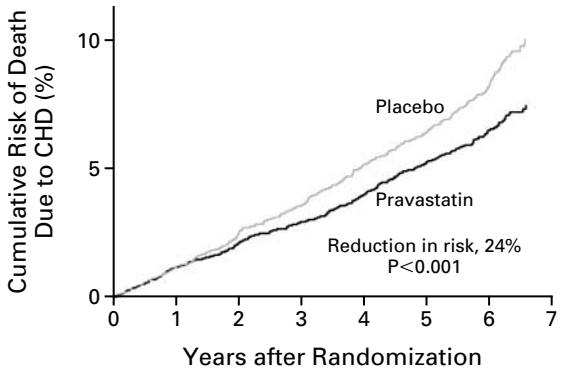
TABLE 2. CARDIOVASCULAR EVENTS ACCORDING TO TREATMENT GROUP.

EVENT*	PLACEBO (N=4502)	PRAVASTATIN (N=4512)	REDUCTION IN RISK (95% CI)†	P VALUE‡
	no. (%)		%	
Death due to CHD	373 (8.3)	287 (6.4)	24 (12–35)	<0.001
Death due to CVD	433 (9.6)	331 (7.3)	25 (13–35)	<0.001
Death from any cause	633 (14.1)	498 (11.0)	22 (13–31)	<0.001
Death due to CHD or nonfatal MI	715 (15.9)	557 (12.3)	24 (15–32)	<0.001
Any MI	463 (10.3)	336 (7.4)	29 (18–38)	<0.001
CABG	520 (11.6)	415 (9.2)	22 (11–31)	<0.001
PTCA	253 (5.6)	210 (4.7)	19 (3–33)	0.024
CABG or PTCA	708 (15.7)	585 (13.0)	20 (10–28)	<0.001
Hospitalization for unstable angina	1106 (24.6)	1005 (22.3)	12 (4–19)	0.005
Any stroke	204 (4.5)	169 (3.7)	19 (0–34)	0.048

*CHD denotes coronary heart disease, CVD cardiovascular disease, MI myocardial infarction, CABG coronary-artery bypass surgery, and PTCA percutaneous transluminal coronary angioplasty.

†Relative reductions in risk are for the pravastatin group as compared with the placebo group and have been estimated on the basis of the hazard ratio in a Cox regression analysis. CI denotes confidence interval.

‡P values were derived with the stratified log-rank test.



NO. AT RISK

Placebo	4502	4431	4338	4253	4134	3786	1766
Pravastatin	4512	4445	4373	4306	4215	3852	1869

Figure 1. Kaplan–Meier Estimates of Mortality Due to Coronary Heart Disease (CHD), the Primary Outcome, in the Pravastatin and Placebo Groups.

The relative reduction in risk with pravastatin therapy was derived from the Cox proportional-hazards model. The P value was based on the log-rank test with stratification according to the qualifying event. On the basis of the differences in the proportions of patients who died of CHD during the entire study period, for every 1000 patients assigned to pravastatin, death from CHD was avoided in 19 patients.

There were also significant reductions in mortality from CHD and overall mortality among patients assigned to pravastatin in each of the two groups defined by qualifying event. In the subgroup with previous myocardial infarction, mortality from CHD was 23 percent lower among those assigned to pravastatin than among those assigned to placebo (P=0.004), and overall mortality was 21 percent lower (P=0.002). In the subgroup of patients who had been hospitalized for unstable angina before randomization, mortality from CHD was 26 percent lower with pravastatin (P=0.036), and overall mortality was 26 percent lower (P=0.004).

With respect to other secondary end points, the incidence of myocardial infarction was 7.4 percent among those assigned to pravastatin, as compared with 10.3 percent in the placebo group (relative reduction in risk, 29 percent; P<0.001), the incidence of stroke was 3.7 percent as compared with 4.5 percent (reduction in risk, 19 percent; P=0.048), the rate of coronary-artery bypass surgery was 9.2 percent as compared with 11.6 percent (reduction in risk, 22 percent; P<0.001), the rate of coronary angioplasty was 4.7 percent as compared with 5.6 percent (reduction in risk, 19 percent; P=0.024), and the rate of hospitalization for unstable angina was 22.3 percent as compared with 24.6 percent (reduction in risk, 12 percent; P=0.005).

Patients in the pravastatin group also spent significantly less time in the hospital (2.9 days less per patient, P<0.001), had fewer hospital admissions, and spent less time in the hospital per admission (0.6 day, or 10 percent, less time per admission; P=0.002).

Prespecified Subgroup Analyses

Table 4 shows the analyses of subgroups with respect to the combined end point of death from CHD and nonfatal myocardial infarction. There was no evidence of significant heterogeneity of the treatment effect in any of these subgroup analyses. The reduction in risk with pravastatin treatment in each subgroup was consistent with the overall 24 percent reduction in risk for the entire cohort. Significant reductions in the risk of coronary events among patients treated with pravastatin were observed both among patients with previous myocardial infarction and among those who had been hospitalized for unstable angina pectoris and also in other large subgroups, such as patients with initial plasma total cholesterol levels below 213 mg per deciliter.

Safety

A total of 403 newly diagnosed primary cancers occurred in 379 patients assigned to receive pravastatin, as compared with 417 cancers in 399 patients assigned to receive placebo (P=0.43). Organ-specific analysis of cancers, including breast cancer (10 invasive cancers in the placebo group, as compared

TABLE 3. CAUSES OF DEATH ACCORDING TO TREATMENT GROUP.

CAUSE OF DEATH*	PLACEBO (N=4502)	PRAVASTATIN (N=4512)
	number (percent)	
CHD	373 (8.3)	287 (6.4)
Definite MI	74	34
Possible MI	15	19
Sudden death	211	182
Cardiac failure	46	36
Other	27	16
CVD other than CHD	60 (1.3)	44 (1.0)
Stroke	27	22
Other	33	22
All CVD	433 (9.6)	331 (7.3)
All causes other than CVD	200 (4.4)	167 (3.7)
Cancer	141	128
Trauma or suicide	11	6
Other	48	33
All causes	633 (14.1)	498 (11.0)

*CHD denotes coronary heart disease, MI myocardial infarction, and CVD cardiovascular disease.

with 9 invasive cancers and 1 carcinoma in situ in the pravastatin group), showed no significant differences. There was also no difference in the incidence of accidents, violence, or attempted suicide (213 patients in the pravastatin group died or were hospitalized for one of these reasons, as compared with 221 in the placebo group). There was no significant increase in the incidence of adverse events that were ultimately attributed to the study medication (3.2 percent vs. 2.7 percent, P=0.16) or of serious adverse events. Among laboratory variables, 2.1 percent of the pravastatin group had a serum alanine aminotransferase level greater than three times the upper limit of normal, as compared with 1.9 percent of the placebo group (P=0.41). There were no significant differences in the proportions of patients with elevated serum creatine kinase levels, myopathy (8 vs. 10 cases), or serious adverse events due to hepatic disease.

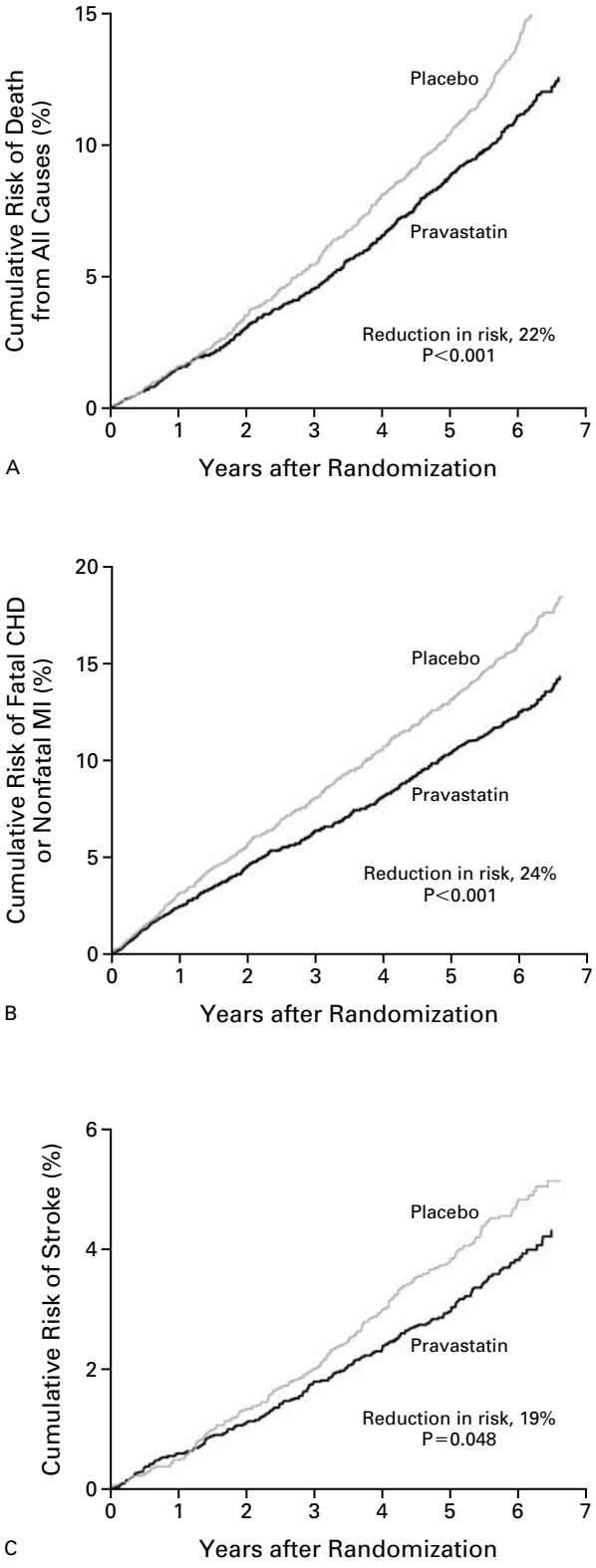


Figure 2. Kaplan–Meier Estimates of the Incidence of Major Secondary Outcomes in the Pravastatin and Placebo Groups.

Panel A shows mortality from all causes, Panel B death due to coronary heart disease (CHD) or nonfatal myocardial infarction (MI), and Panel C stroke of any type. The relative reductions in risk with pravastatin therapy were derived from the Cox proportional-hazards model. The P values were based on the log-rank test, with stratification according to the qualifying event. On the basis of the differences in the proportions of patients with an event during the entire study period, for every 1000 patients assigned to pravastatin, death from any cause was avoided in 30 patients, death due to CHD or nonfatal MI was avoided in 35 patients, and stroke was avoided in 8 patients.

TABLE 4. EFFECTS OF PRAVASTATIN TREATMENT ON DEATH DUE TO CORONARY HEART DISEASE AND NONFATAL MYOCARDIAL INFARCTION WITHIN SUBGROUPS DEFINED IN THE PROTOCOL.*

VARIABLE	TOTAL PATIENTS		PATIENTS WITH EVENT		REDUCTION IN RISK (95% CI)
	PLACEBO	PRAVASTATIN	PLACEBO	PRAVASTATIN	
	no.		no. (%)		%
Sex					
Female	760	756	104 (14)	90 (12)	11 (−18 to 33)
Male	3742	3756	611 (16)	467 (12)	26 (17 to 35)
Qualifying event					
Myocardial infarction	2875	2879	499 (17)	398 (14)	22 (11 to 32)
Hospitalization for unstable angina	1627	1633	216 (13)	159 (10)	29 (12 to 42)
Age					
<55 yr	1021	1065	132 (13)	96 (9)	32 (12 to 48)
55–64 yr	1708	1706	234 (14)	191 (11)	20 (3 to 34)
65–69 yr	1087	1081	203 (19)	151 (14)	28 (11 to 41)
≥70 yr	686	660	146 (21)	119 (18)	15 (−8 to 33)
Hypertension†					
Yes	1891	1867	314 (17)	266 (14)	15 (0 to 28)
No	2609	2644	400 (15)	291 (11)	30 (19 to 40)
Diabetes					
Yes	386	396	88 (23)	76 (19)	19 (−10 to 41)
No	4116	4116	627 (15)	481 (12)	25 (15 to 33)
Smoking					
Current smoker	444	425	92 (21)	66 (16)	27 (0 to 47)
Former smoker	2814	2923	456 (16)	352 (12)	28 (17 to 37)
Nonsmoker	1244	1164	167 (13)	139 (12)	11 (−12 to 29)
Total cholesterol					
<213 mg/dl	1894	1898	271 (14)	223 (12)	19 (4 to 32)
213–250 mg/dl	2003	2010	346 (17)	259 (13)	27 (15 to 38)
≥251 mg/dl	605	604	98 (16)	75 (12)	27 (1 to 46)
LDL cholesterol					
<135 mg/dl	1305	1332	185 (14)	163 (12)	16 (−4 to 32)
135–173 mg/dl	2338	2336	376 (16)	282 (12)	26 (14 to 37)
≥174 mg/dl	859	844	154 (18)	112 (13)	30 (10 to 45)
HDL cholesterol					
<39 mg/dl	2831	2890	487 (17)	388 (13)	24 (13 to 34)
≥39 mg/dl	1671	1622	228 (14)	169 (10)	25 (8 to 38)
Triglycerides					
<133 mg/dl	2022	1951	322 (16)	238 (12)	25 (12 to 37)
133–230 mg/dl	1801	1750	269 (15)	202 (12)	24 (9 to 37)
≥231 mg/dl	679	811	124 (18)	117 (14)	24 (2 to 41)

*Subgroups were defined on the basis of variables assessed before randomization. The lipid levels represent the averages of the values measured four weeks before randomization and those measured at randomization. To convert values for cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.01129. CI denotes confidence interval, LDL low-density lipoprotein, and HDL high-density lipoprotein. Tests for heterogeneity of treatment effect were undertaken across each of the subgroups. In addition, we performed tests for interaction between treatment and the following continuous base-line variables: age; total, LDL, and HDL cholesterol; and triglyceride levels. There was no evidence of significant heterogeneity of treatment effect in any prespecified subgroup ($P \geq 0.08$).

†Data were missing for three patients, two in the placebo group and one in the pravastatin group.

DISCUSSION

Our results provide strong evidence that lowering cholesterol levels with pravastatin in patients with a broad range of initial cholesterol levels and a history of myocardial infarction or unstable angina reduces the risk of death from CHD, cardiovascular disease, and all causes combined. In addition, the risk of myocardial infarction or stroke is significantly reduced. Over a period of 6.1 years, we estimate that 30 deaths, 28 nonfatal myocardial infarctions, and 9 nonfatal strokes were avoided (with allowance for multiple events in each patient) in 48 patients for every 1000 randomly assigned to treatment with pravastatin. Twenty-three episodes of coronary-artery bypass surgery, 20 of coronary angioplasty, and 82 hospital admissions for unstable angina were also avoided. These benefits were not offset by adverse effects. Our results demonstrate that pravastatin re-

duced the risk of all major cardiovascular events in a large group of patients who were representative of those seen in current practice. Indeed, the mean total cholesterol level in our study approximates that in recent epidemiologic studies of patients with CHD.[17,18]

These results extend the findings of the Scandinavian Simvastatin Survival Study,[9] which showed that treatment had benefit in terms of mortality from CHD and overall mortality among patients with CHD who had a mean cholesterol level of 261 mg per deciliter (6.7 mmol per liter) at study entry. Our results demonstrate similar benefits in patients with a mean cholesterol level about 44 mg per deciliter (1.1 mmol per liter) lower than in that study. Our study sample also had a wider range of initial triglyceride levels (some patients had mixed hyperlipidemia), and a much larger proportion of our patients had undergone coronary revascularization (41 percent, as compared with 8 percent in the Scandinavian study) and were receiving aspirin at entry (82 percent vs. 37 percent). Our results also extend the findings of the CARE study,[10] which showed a reduction in the composite outcome of death due to CHD and nonfatal myocardial infarction in patients with CHD and had a similar mean cholesterol level at entry (209 mg per deciliter [5.4 mmol per liter]), by providing clear evidence of benefit in terms of both mortality from CHD and overall mortality.

Our study also extends the evidence of benefit to patients with unstable angina, who were not specifically included in the Scandinavian Simvastatin Survival Study and the CARE trial. Since this condition is now a more frequent cause of hospital admission than myocardial infarction,[19] the demonstration of significant reductions both in major coronary events and in mortality among patients with unstable angina represents an important new finding. Furthermore, the effects of treatment with pravastatin on the incidence of stroke are important, particularly because stroke is now the chief cause of functional impairment in many countries. Our findings with respect to stroke are consistent with those of the other studies.[9,10]

We examined the effects of treatment on coronary events in prespecified subgroups defined by sex, age, initial lipid levels, and the presence or absence of other risk factors. No evidence of significant heterogeneity of treatment effect was detected. Specifically, we found no evidence of a greater relative effect of treatment in women than in men, as had been suggested by the results of the CARE study.[10] However, although the effects of treatment were not significant in some subgroups, such as patients with diabetes and women, the power of our study to determine the effects of treatment reliably in these relatively small subgroups was inadequate. The estimate of the effect of treatment in the study group as a whole nonetheless provides a reasonable indication of the probable relative benefits of treatment in these and other subgroups. Hence, the absolute benefits of treatment are likely to be greater in groups of patients who are at higher absolute risk for a major coronary event, such as those with a lower HDL cholesterol level, a higher LDL cholesterol level, older age, or a history of diabetes or smoking.

Although the relative and absolute effects we observed are clinically important, it is necessary to consider possible biases that may have modified the observed effects. The large number of patients who were assigned to pravastatin but discontinued treatment or who were assigned to placebo but ultimately received cholesterol-lowering therapy outside the study is likely to have reduced the difference in the incidence of events between the treatment groups. Since the rate of crossover from the allocated treatment at the midpoint of the trial was 20 percent (9 percent of the placebo group began nonstudy treatment and 11 percent of the pravastatin group discontinued active treatment), it is possible that the effects of treatment on both the average difference in the cholesterol levels and the relative difference in the incidence of major events were reduced by a similar proportion.

It is also possible that the patients we studied were at lower risk than the general population of patients with myocardial infarction or unstable angina. The rate of death from CHD among the patients assigned to receive placebo was only 1.4 percent per year, as compared with the rate of 2 percent per year that was expected initially.[11] In general, if the rate of events is higher in patients who elect not to enroll in trials, then a greater absolute benefit would be expected, assuming a similar relative effect of treatment. Consequently, the absolute effects of treatment in our study may significantly underestimate the effects of such therapy in broader clinical practice. Conversely, the likely effect of a policy of cholesterol-lowering treatment may be less in a community, where there is poorer adherence to long-term treatment regimens.[20]

Finally, in our study, as in the Scandinavian Simvastatin Survival Study[9] and the CARE trial,[10] at least three months elapsed after the qualifying event before patients were enrolled. Consequently, our data do not clarify the effects of pravastatin early after an acute coronary event but, rather, approximate event rates among patients with stable CHD, to whom it would be reasonable to extrapolate these results.

Treatment with pravastatin was safe and well tolerated. The results of this study confirm those of other large-scale trials[9,10,13] in showing no association between cholesterol-lowering therapy and cancer, deaths due to trauma or suicide, or other serious adverse events. In particular, there was no increase

in the number of newly diagnosed breast cancers among the women assigned to receive pravastatin, suggesting that the excess rate of breast cancer in the CARE study was a chance finding.[10] Further data on long-term safety and outcomes will be obtained from ongoing follow-up of our study cohort.

Because of our results, cholesterol-lowering therapy should now be considered for virtually all patients presenting with CHD. Whether individual patients are treated will also depend on cost-effectiveness analyses, other factors defining individual risk, and coexisting conditions. With respect to other aspects of treatment, our study does not indicate whether a dose of pravastatin lower than that we used (40 mg once daily) would be sufficient, whether treatment should target a particular cholesterol level or aim for a specific reduction, or whether the duration of treatment should be lifelong.

The current low rate of use of cholesterol-lowering therapy among patients with CHD can no longer be accepted. A recent North American study found that only 30 percent of patients who had survived a myocardial infarction were prescribed lipid-lowering drugs.[21] The situation is similar in many European countries[18] and in the Asian–Pacific region,[22] whereas in the United Kingdom only about 10 percent of such patients are receiving treatment.[23] On the basis of the findings reported here, current recommendations for treatment after acute myocardial infarction or hospitalization for unstable angina should be reviewed.

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APPENDIX

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