The New England Journal of Medicine

VOLUME 335 OCTOBER 3, 1996 NUMBER 14

THE EFFECT OF PRAVASTATIN ON CORONARY EVENTS AFTER MYOCARDIAL INFARCTION IN PATIENTS WITH AVERAGE CHOLESTEROL LEVELS

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ABSTRACT

Background In patients with high cholesterol levels, lowering the cholesterol level reduces the risk of coronary events, but the effect of lowering cholesterol levels in the majority of patients with coronary disease, who have average levels, is less clear.

Methods In a double-blind trial lasting five years, we administered either 40 mg of pravastatin per day or placebo to 4159 patients (3583 men and 576 women) with myocardial infarction who had plasma total cholesterol levels below 240 mg per deciliter (mean, 209) and low-density lipoprotein (LDL) cholesterol levels of 115 to 174 mg per deciliter (mean, 139). The primary end point was a fatal coronary event or a nonfatal myocardial infarction.

Results The frequency of the primary end point was 10.2 percent in the pravastatin group and 13.2 percent in the placebo group, an absolute difference of 3 percentage points and a 24 percent reduction in risk (95 percent confidence interval, 9 to 36 percent; P = 0.003). Coronary bypass surgery was needed in 7.5 percent of the patients in the pravastatin group and 10 percent of those in the placebo group, a 26 percent reduction (P = 0.005), and coronary angioplasty was needed in 8.3 percent of the pravastatin group and 10.5 percent of the placebo group, a 23 percent reduction (P = 0.01). The frequency of stroke was reduced by 31 percent (P = 0.03). There were no significant differences in overall mortality or mortality from noncardiovascular causes. Pravastatin lowered the rate of coronary events more among women than among men. The reduction in coronary events was also greater in patients with higher pretreatment levels of LDL cholesterol.

Conclusions These results demonstrate that the benefit of cholesterol-lowering therapy extends to the majority of patients with coronary disease who have average cholesterol levels. (N Engl J Med 1996; 335:1001-9.)

THE plasma levels of total cholesterol and low-density lipoprotein (LDL) cholesterol are important risk factors for coronary heart disease.[1-4] However, the relation between plasma cholesterol and coronary events appears to be stronger if levels are at elevated, rather than average, values.[1-4] Angiography in clinical trials has demonstrated that lowering cholesterol levels slows the progression and promotes the regression of coronary atherosclerosis.[5] These beneficial changes are also directly related to the pretreatment level of LDL cholesterol,[5,6] with little benefit occurring in patients with average base-line levels.[7] Clinical trials have shown that lowering elevated LDL cholesterol levels prevents both first and recurrent coronary events.[8-11] However, it has not been clear whether coronary events can be prevented by cholesterol-lowering therapy in patients who do not have hypercholesterolemia. This issue is of importance because the large majority of patients with coronary disease have cholesterol levels that are, like those of the general population,[12] in the average, not the elevated, range.[13-16]

The Cholesterol and Recurrent Events (CARE)

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*Participants in the Cholesterol and Recurrent Events trial are listed in the Appendix.

TABLE 1. BASE-LINE CHARACTERISTICS OF PATIENTS IN THE PLACEBO AND PRAVASTATIN GROUPS.*

CHARACTERISTIC	PLACEBO (N = 2078)	PRAVASTATIN (N = 2081)
General		
Age (yr)	59±9	59±9
Sex (%)		
Female	14	14
Male	86	86
Race (%)		
White	92	93
Other	8	7
Country of residence (%)		
United States	66	66
Canada	34	34
Hypertension (%)	43	42
Current smoker (%)	21	21
Diabetes (%)	15	14
Body-mass index†	28±4	28±4
Blood pressure (mm Hg)		
Systolic	129±18	129±18
Diastolic	79±10	79±10
Cardiovascular status		
Months from myocardial infarction to randomization	10±5	10±5
Type of myocardial infarction (%)		
Q wave	61	61
Other	38	38
Angina (%)	20	21
Congestive heart failure (%)	4	4
CABG (%)	28	26
PTCA (%)	32	34
CABG or PTCA (%)	54	54
Thrombolysis (%)	40	42
Ejection fraction (%)	53±12	53±12
Medication use		
Aspirin (%)	83	83
Beta-blocker (%)	39	41
Nitrate (%)	33	32
Calcium-channel blocker (%)	38	40
ACE inhibitor (%)	14	15
Diuretic agent (%)	11	11
Insulin (%)	2.6	2.4
Oral hypoglycemic agent (%)	7	5‡
Estrogen (% of women)	10.3	8.4
Plasma lipids§		
Cholesterol (mg/dl)		
Total	209±17	209±17
VLDL	27±16	27±16
LDL	139±15	139±15
HDL	39±9	39±9
Triglycerides (mg/dl)	155±61	156±61

*Plus–minus values are means ±SD. Except for the use of oral hypoglycemic agents, differences between the groups were not significant. CABG denotes coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty, ACE angiotensin-converting enzyme, VLDL very-low-density lipoprotein, LDL low-density lipoprotein, and HDL high-density lipoprotein.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡$P<0.05$ for the comparison with the placebo group.

§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.

trial and its entry criteria (a plasma total cholesterol level of less than 240 mg per deciliter [6.2 mmol per liter] and an LDL cholesterol level of 115 to 174 mg per deciliter [3.0 to 4.5 mmol per liter]) were designed specifically to study the effectiveness in a typical population of lowering LDL cholesterol levels to prevent coronary events after myocardial infarction.

METHODS

Study Design and Patients

The design of the CARE trial has been described in detail elsewhere.[17] Patients were recruited from 80 participating centers, 13 in Canada and 67 in the United States. Men and postmenopausal women were eligible if they had had an acute myocardial infarction between 3 and 20 months before randomization, were 21 to 75 years of age, and had plasma total cholesterol levels of less than 240 mg per deciliter, LDL cholesterol levels of 115 to 174 mg per deciliter, fasting triglyceride levels of less than 350 mg per deciliter (4.0 mmol per liter), fasting glucose levels of no more than 220 mg per deciliter (12.2 mmol per liter), left ventricular ejection fractions of no less than 25 percent, and no symptomatic congestive heart failure. Criteria for a qualifying myocardial infarction included typical symptoms and an elevated serum level of creatine kinase.[17] The lipid levels, as measured at two or three specified visits to the clinic at least eight weeks after hospitalization for myocardial infarction and after four weeks of treatment with the National Cholesterol Education Program (NCEP) Step 1 diet,[18] were averaged for eligibility. After stratification according to clinical center, we randomly assigned the eligible patients to receive either 40 mg of pravastatin (Pravachol, Bristol-Myers Squibb) once daily, or a matching placebo, by means of a telephone call to the data center. After randomization, visits to the clinic took place quarterly. Patients continued to take all prescribed medication, for cardiac and other conditions, that they had been receiving at base line (Table 1).

Plasma total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured by the core laboratory at base line, at 6 and 12 weeks after randomization, at the end of each quarter during the first year, and semiannually thereafter. LDL cholesterol levels were calculated.[19] For any patient in either group with an LDL cholesterol level of 175 mg per deciliter (4.5 mmol per liter) or more, intensified (NCEP Step 2) dietary counseling was initiated.[18] If the LDL level remained at 175 mg per deciliter or more, cholestyramine was prescribed, in a daily dose of 8 to 16 g, as needed, to decrease the level to less than 175 mg per deciliter. To maintain blinded conditions, a patient in the other treatment group who was matched for age and sex and had an LDL cholesterol level in the highest decile was provided with parallel dietary counseling and cholestyramine treatment. If counseling and treatment were unsuccessful, the patient with a persistently elevated LDL cholesterol level was referred to his or her physician for treatment. The primary end point of the trial was death from coronary heart disease (including fatal myocardial infarction, either definite or probable; sudden death; death during a coronary intervention; and death from other coronary causes) or a symptomatic (unless during noncardiac surgery) nonfatal myocardial infarction confirmed by serum creatine kinase measurements. In each group, we measured the time elapsed to the primary end point. Deaths were reviewed by the end-points committee without knowledge of the patient's treatment assignment or plasma lipid levels.

The protocol was approved by the Safety and Data Monitoring Committee and the institutional review boards of all participating centers.

Statistical Analysis

The size of the sample was designed to provide an 80 percent power to detect a 20 percent reduction in the number of primary

TABLE 2. CARDIOVASCULAR EVENTS ACCORDING TO STUDY GROUP.*

EVENT	PLACEBO (N=2078)		PRAVASTATIN (N=2081)		RISK REDUCTION WITH PRAVASTATIN (95% CI)	P VALUE
	NO. OF PATIENTS	INCIDENCE (%)	NO. OF PATIENTS	INCIDENCE (%)		
					percent	
Death from CHD or nonfatal MI†	274	13.2	212	10.2	24 (9 to 36)	0.003
Death from CHD	119	5.7	96	4.6	20 (−5 to 39)	0.10
Nonfatal MI	173	8.3	135	6.5	23 (4 to 39)	0.02
Fatal MI	38	1.8	24	1.2	37 (−5 to 62)	0.07
Fatal MI or confirmed nonfatal MI	207	10.0	157	7.5	25 (8 to 39)	0.006
Clinical nonfatal MI‡	231	11.1	182	8.7	23 (6 to 36)	0.01
CABG	207	10.0	156	7.5	26 (8 to 40)	0.005
PTCA	219	10.5	172	8.3	23 (6 to 37)	0.01
CABG or PTCA	391	18.8	294	14.1	27 (15 to 37)	<0.001
Unstable angina	359	17.3	317	15.2	13 (−1 to 25)	0.07
Stroke	78	3.8	54	2.6	31 (3 to 52)	0.03

*Risk reductions and P values were based on Cox proportional-hazards analysis; P values are identical to those derived by log-rank analysis. Patient-specific data were used to compute P values and confidence intervals (CI). CHD denotes coronary heart disease, MI myocardial infarction, CABG coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

†This combined variable was the specified primary end point. Nonfatal myocardial infarctions were confirmed by the core laboratory.

‡This variable comprises all nonfatal myocardial infarctions reported by investigators.

events with pravastatin. All analyses were performed on an intention-to-treat basis, and P values were two-sided. The effect of therapy on the rate of the primary end point of the trial was assessed with use of log-rank P values.[20] All other hypothesis tests and all reductions in risk were assessed with a Cox proportional-hazards model.[21] The size of the trial did not provide adequate power to assess therapeutic efficacy against the primary end point within subgroups. Therefore, treatment effects were analyzed in several prespecified subgroups with a more broadly defined end point: major coronary events (including fatal coronary heart disease, nonfatal myocardial infarction, bypass surgery, and angioplasty).

RESULTS

Between December 4, 1989, and December 31, 1991, 4159 patients were randomly assigned to study groups, 2078 to the placebo group and 2081 to the pravastatin group. The characteristics of the patients before randomization were similar in the two groups (Table 1). In the last year of follow-up, 86 percent of the placebo group and 94 percent of the treatment group were taking their study medication. This included the 6 percent of patients in each treatment group who were taking cholestyramine according to the protocol. Of the patients, 8 percent in the placebo group and 2 percent in the treatment group discontinued the study medication and started treatment to lower lipid levels with open-label drug therapy, as prescribed by their personal physicians. The final study visit was between January 1 and February 14, 1996, at which time the median duration of follow-up was 5.0 years (range, 4.0 to 6.2). Data were obtained to classify myocardial infarctions as confirmed or unconfirmed for all patients in whom a myocardial infarction was reported. Vital status was ascertained for the first four years for all patients and, at the end, for all but one patient.

Pravastatin therapy lowered the mean LDL cholesterol level of 139 mg per deciliter (3.6 mmol per liter) by 32 percent and maintained mean levels of 97 to 98 mg per deciliter (2.5 mmol per liter) throughout the five-year follow-up. During follow-up, the LDL cholesterol level was 28 percent lower in the pravastatin group than in the placebo group, the total cholesterol level was 20 percent lower, the HDL cholesterol level was 5 percent higher, and the triglyceride level was 14 percent lower ($P<0.001$ for all comparisons).

Patients treated with pravastatin had a 24 percent lower incidence of the primary end point, fatal coronary heart disease or confirmed myocardial infarction, than patients in the placebo group (95 percent confidence interval, 9 to 36 percent; $P=0.003$) (Table 2 and Fig. 1). Two hundred seventy-four patients (13.2 percent) had a primary event in the placebo group, as compared with 212 (10.2 percent) in the pravastatin group. One hundred seventy-three

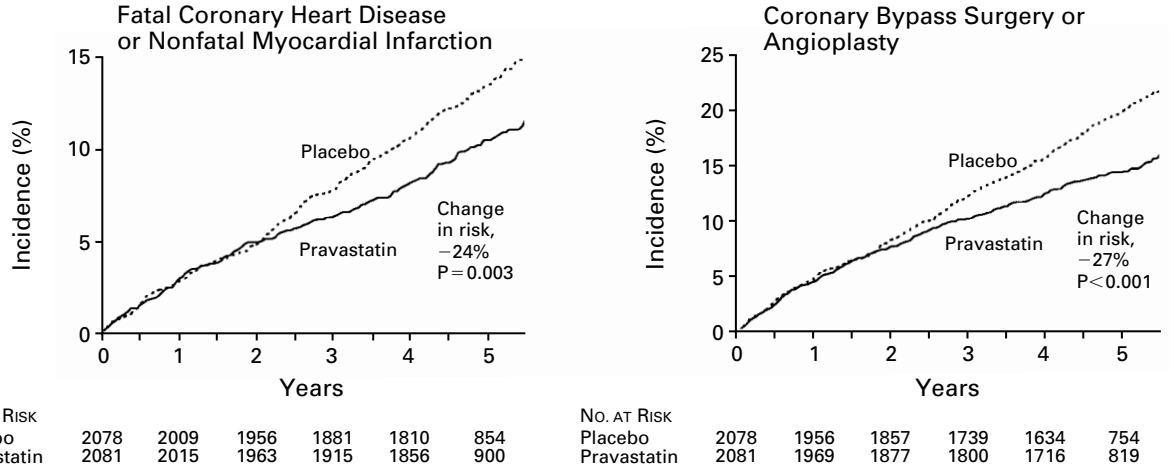

Figure 1. Kaplan–Meier Estimates of the Incidence of Coronary Events in the Pravastatin and Placebo Groups.
The left-hand panel shows data for the primary end point — fatal coronary heart disease or nonfatal myocardial infarction. The right-hand panel shows data for coronary bypass surgery or angioplasty. Changes in risk are those attributable to pravastatin. P values and changes in risk are based on Cox proportional-hazards analysis.

patients had a nonfatal myocardial infarction in the placebo group, as compared with 135 in the pravastatin group, a 23 percent reduction in risk (P=0.02) (Table 2). In the placebo group, 119 patients died from coronary heart disease, as compared with only 96 in the pravastatin group, for a 20 percent decrease in risk (P=0.10) (Table 2). Patients who had nonfatal myocardial infarctions during the trial and subsequently died from a coronary event (18 in the placebo group and 19 in the pravastatin group) were counted as having had only one primary end point; this explains why the reduction in risk for the primary end point exceeded that for coronary death or nonfatal myocardial infarction considered separately. The rate of fatal myocardial infarction was 37 percent lower in the pravastatin group than in the placebo group (P=0.07), and that of total myocardial infarction, fatal or confirmed nonfatal, was 25 percent lower (P=0.006) (Table 2). The pravastatin group had a 26 percent lower rate of coronary bypass surgery than the placebo group (P=0.005), a 23 percent lower rate of angioplasty (P=0.01), and a 27 percent lower rate of either procedure (P<0.001) (Table 2 and Fig. 1). The pravastatin group had a 31 percent lower incidence of stroke (P=0.03) (Table 2).

As compared with patients given placebo, both men and women treated with pravastatin had significantly lower rates of major coronary events (46 percent lower for women [P=0.001] and 20 percent lower for men [P=0.001]) (Table 3). The effect of pravastatin was greater among women than among men (P=0.05 for the interaction between the patient's sex and treatment). The effect of pravastatin on the rate of major coronary events was not substantially altered by the patient's age at base line (60 to 75 or 24 to 59 years of age), the presence of hypertension or diabetes, smoking status, or the patient's left ventricular ejection fraction (25 to 40 percent or more than 40 percent) (Table 3). The lower rate of major coronary events among the patients treated with pravastatin was similar whether their pretreatment plasma lipid levels were above or below the median (Table 3). This pattern of results in the subgroup analysis was qualitatively similar if the primary end point (fatal coronary heart disease or nonfatal myocardial infarction) was examined, rather than the more broadly defined end point, major coronary events.

The reduction in the rate of coronary events with pravastatin was influenced by the pretreatment level of LDL cholesterol. The patients with base-line LDL cholesterol levels above 150 mg per deciliter (3.9 mmol per liter; n=953) had a 35 percent reduction in major coronary events, as compared with a 26 percent reduction in those with base-line levels of 125 to 150 mg per deciliter (3.2 to 3.9 mmol per liter; n=2355) and a 3 percent increase in those with base-line levels below 125 mg per deciliter (n=851) (P=0.03 for the interaction between base-line LDL cholesterol level and risk reduction) (Table 3 and Fig. 2). For patients with base-line LDL cholesterol levels below the median, the lower the value was, the smaller the reduction, if any, in risk. The rate of major coronary events was 23 percent lower in the pravastatin group than in the placebo group for patients with base-line LDL cholesterol levels below the median (median, 137.5 mg per deciliter [3.55 mmol per liter]), but only 15 percent lower in patients with values in the lowest third (no more than 130 mg per

TABLE 3. MAJOR CORONARY EVENTS IN SUBGROUPS DEFINED BY BASE-LINE VARIABLES.*

VARIABLE†	NO. OF PATIENTS		NO. (%) OF PATIENTS WITH EVENT		RISK REDUCTION (95% CI)	P VALUE
	PLACEBO	PRAVASTATIN	PLACEBO	PRAVASTATIN		
					percent	
Sex						
Female	290	286	80 (28)	46 (16)	46 (22 to 62)	0.001
Male	1788	1795	469 (26)	384 (21)	20 (8 to 30)	0.001
Age						
<60 yr	1003	1027	258 (26)	217 (21)	20 (4 to 33)	0.02
≥60 yr	1075	1054	291 (27)	213 (20)	27 (12 to 38)	<0.001
Hypertension						
Present	899	875	263 (29)	200 (23)	23 (8 to 36)	0.005
Absent	1179	1206	286 (24)	230 (19)	24 (9 to 36)	0.002
Diabetes						
Present	304	282	112 (37)	81 (29)	25 (0 to 43)	0.05
Absent	1774	1799	437 (25)	349 (19)	23 (11 to 33)	<0.001
Smoking						
Current	334	337	111 (33)	81 (24)	33 (11 to 50)	0.006
Other	1744	1744	437 (25)	349 (20)	22 (10 to 33)	<0.001
Left ventricular ejection fraction						
≤40%	353	353	112 (32)	84 (24)	28 (4 to 45)	0.02
>40%	1725	1728	436 (25)	346 (20)	23 (11 to 33)	<0.001
Previous CABG						
Yes	564	527	116 (21)	88 (17)	22 (−3 to 41)	0.08
No	1514	1554	433 (29)	342 (22)	25 (13 to 35)	<0.001
Previous PTCA						
Yes	668	701	188 (28)	153 (22)	25 (7 to 39)	0.009
No	1410	1380	361 (26)	277 (20)	23 (10 to 34)	<0.001
Previous CABG or PTCA						
Yes	1118	1127	269 (24)	218 (19)	22 (7 to 35)	0.006
No	960	954	280 (29)	212 (22)	25 (10 to 37)	0.002
Type of MI‡						
Q wave	1277	1279	334 (26)	251 (20)	27 (14 to 38)	<0.001
Other	799	801	215 (27)	179 (22)	19 (1 to 34)	0.04
Total cholesterol						
≤209 mg/dl	1040	1032	260 (25)	211 (20)	19 (3 to 33)	0.02
>209 mg/dl	1038	1049	289 (28)	219 (21)	27 (13 to 39)	<0.001
LDL cholesterol						
≤137 mg/dl	1048	1042	269 (26)	210 (20)	23 (8 to 36)	0.004
>137 mg/dl	1030	1039	280 (27)	220 (21)	24 (10 to 36)	0.002
LDL cholesterol						
<125 mg/dl	441	410	93 (21)	89 (22)	−3 (−38 to 23)	0.85
125–150 mg/dl	1172	1183	311 (27)	239 (20)	26 (13 to 38)	<0.001
>150–175 mg/dl	465	488	145 (31)	102 (21)	35 (17 to 50)	0.008
HDL cholesterol						
≤37 mg/dl	1025	1033	290 (28)	236 (23)	21 (6 to 33)	0.008
>37 mg/dl	1053	1048	259 (25)	194 (19)	27 (12 to 39)	<0.001
LDL:HDL ratio						
<3.7	1043	1036	251 (24)	190 (18)	26 (11 to 39)	0.002
≥3.7	1035	1045	298 (29)	240 (23)	21 (7 to 34)	0.006
Triglycerides						
<144 mg/dl	1049	1031	281 (27)	195 (19)	32 (18 to 43)	<0.001
≥144 mg/dl	1029	1050	268 (26)	235 (22)	15 (−1 to 29)	0.07

*Major coronary events were the primary end point (death from coronary heart disease or nonfatal myocardial infarction [MI]), coronary-artery bypass grafting (CABG), or percutaneous transluminal coronary angioplasty (PTCA). P values for the interaction between subgroup and treatment were >0.10 except for sex (P=0.05), LDL cholesterol level (<125, 125–150, and >150 mg per deciliter; P=0.03), and triglyceride level (P=0.08). LDL denotes low-density lipoprotein, and HDL high-density lipoprotein.

†The median values for all 4159 patients were as follows: total cholesterol, 209 mg per deciliter; LDL cholesterol, 137 mg per deciliter; HDL cholesterol, 37 mg per deciliter; LDL:HDL ratio, 3.7; and triglycerides, 144 mg per deciliter. 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.

‡The type of myocardial infarction could not be determined for three patients.

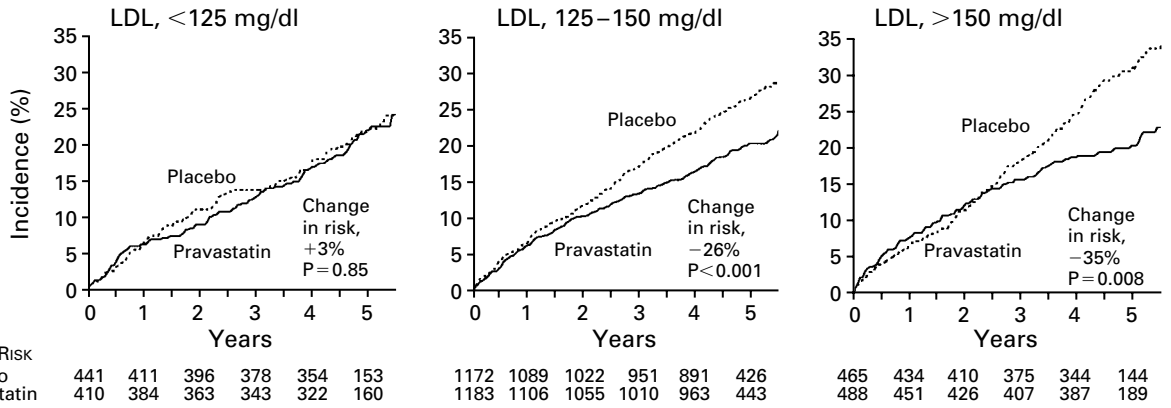

Figure 2. Kaplan–Meier Estimates of the Incidence of Fatal Coronary Heart Disease, Nonfatal Myocardial Infarction, Coronary Bypass Surgery, or Angioplasty in the Study Groups, According to Base-Line LDL Cholesterol Level.

Changes in risk are those attributable to pravastatin. P=0.03 for the interaction between base-line LDL cholesterol level and treatment, by Cox proportional-hazards analysis.

deciliter [3.36 mmol per liter]), 10 percent lower in the lowest quartile (less than 127 mg per deciliter [3.28 mmol per liter]), and 3 percent higher in the lowest quintile (less than 125 mg per deciliter).

In all, 196 patients in the placebo group died, as compared with 180 in the pravastatin group (9 percent reduction in the risk of death; 95 percent confidence interval, −12 to 26 percent; P=0.37). Seventy-five patients in the placebo group and 84 in the pravastatin group died from noncoronary causes. There were 11 deaths due to cardiovascular but noncoronary causes in the placebo group and 16 in the pravastatin group; 45 due to cancer in the placebo group and 49 in the pravastatin group; 4 violent deaths in the placebo group and 8 in the pravastatin group; and 15 due to other causes in the placebo group and 11 in the pravastatin group, with no significant differences between the groups. The cause of death could not be determined for two patients in the placebo group.

Seventy-four patients in the placebo group (3.6 percent) discontinued the study medication because of an adverse event, as compared with 45 (2.2 percent) in the pravastatin group (P=0.007). Elevated serum aminotransferase levels were found in 73 patients given placebo and 66 given pravastatin, elevated serum creatine kinase in 7 given placebo and 12 given pravastatin, and myositis in 4 given placebo and none given pravastatin, with no significant differences between the groups. There were 161 fatal or nonfatal primary cancers in the placebo group and 172 in the pravastatin group. These included colorectal cancer (21 in the placebo group and 12 in the pravastatin group), gastrointestinal cancer other than colorectal cancer (15 and 14), liver cancer (1 and 0), lymphoma or leukemia (10 and 8), and melanoma (3 and 4). Breast cancer occurred in 1 patient in the placebo group and 12 in the pravastatin group (P=0.002). Of the 12 cases in the pravastatin group, all were nonfatal; 3 occurred in patients who had previously had breast cancer, 1 was ductal carcinoma in situ, and 1 occurred in a patient who took pravastatin for only six weeks. The one instance of breast cancer in the placebo group was a fatal case in a woman who had previously had breast cancer. There were no other significant differences between the groups in the site-specific incidence of cancer.

DISCUSSION

Previous trials tested the effect of lowering cholesterol levels in patients with hypercholesterolemia. This approach was logical, since the relation between blood cholesterol levels and coronary events is stronger, and rates of coronary events are greater, in patients with elevated, rather than average, values.[1-4] This research firmly established that treatment of hypercholesterolemia lowers the rate of coronary events.[8-11] The purpose of the CARE trial was to investigate whether the benefit achieved by lowering the LDL cholesterol levels of patients who have hypercholesterolemia could be extended to the more typical patient with coronary disease, who has an average LDL cholesterol level. The results of the CARE trial show that reducing LDL cholesterol with pravastatin from average to low levels (from a mean of 139 mg per deciliter to a mean of 97 mg per deciliter) significantly reduces the number of recurrent coronary events. The magnitude of the reduction in risk was consistent for the major end points of myocardial infarction, death from coronary causes, bypass surgery, and angioplasty. However, there was no significant reduction in overall mortality. Patients 60 years old or older, women, and those

with impaired left ventricular ejection, in all of whom the efficacy of lowering cholesterol levels had been questioned, had a reduction in risk. These results demonstrate that for patients with coronary disease in North America, the average cholesterol level is too high and can contribute to the recurrence of cardiovascular events.

These results also suggest that the pretreatment LDL cholesterol level, at least within the CARE trial's eligibility range of 115 to 174 mg per deciliter, has an influence on the success of cholesterol-lowering therapy in preventing coronary events. In the upper part of the range, >150 to 175 mg per deciliter, the reduction in risk (35 percent) was similar to that achieved with reductase inhibitors in patients with hypercholesterolemia.[8-10] In the middle of the range, 125 to 150 mg per deciliter, the risk reduction remained substantial (26 percent); this range is at the center of the distribution of LDL cholesterol values in contemporary populations with coronary heart disease.[13-16] However, there was no reduction in coronary events among patients with base-line LDL cholesterol levels below 125 mg per deciliter. These results are consistent with those of epidemiologic studies that show a stronger relation between LDL cholesterol levels and coronary events at hypercholesterolemic, as compared with average, levels,[1-4] as well as those of angiographic studies that show that improvement in coronary-artery stenosis in patients receiving lipid-lowering therapy is proportional to the base-line LDL cholesterol level.[5-7] Although our finding cannot be considered definitive and requires confirmation, it suggests that an LDL cholesterol level of 125 mg per deciliter may be an approximate lower boundary for a clinically important influence of the LDL cholesterol level on coronary heart disease.

Stroke, a specified end point in the CARE trial,[17] was reduced significantly (by 31 percent) in the pravastatin group. A reduction in cerebrovascular end points was found in post hoc analyses of data from several previous trials conducted in hypercholesterolemic populations.[8,10,22,23] A meta-analysis of trials of pravastatin in patients with atherosclerosis showed a significant, 62 percent reduction in stroke.[10] Dietary therapy that replaced saturated fat with polyunsaturated fat reduced the incidence of stroke by 45 percent ($P = 0.055$).[22] The incidence of stroke and transient ischemic attacks considered together was lowered significantly (by 24 percent) by nicotinic acid[23] and lowered by 30 percent by simvastatin.[8] Ultrasound measurements of carotid atherosclerosis demonstrated slowing of the progression of disease by treatment with pravastatin[24,25] and lovastatin.[26] This evidence from clinical trials therefore suggests that high plasma LDL cholesterol levels are a treatable cause of cerebrovascular atherosclerosis and clinical cerebrovascular events. The potential for benefit from cholesterol-lowering treatment should continue to be evaluated in patients with coronary disease, as well as in other groups of patients at high risk for stroke, such as those with a history of stroke, transient ischemic attack, carotid-artery bruit, or hypertension.

The overall incidence of fatal or nonfatal cancer was not increased in the pravastatin group as compared with the placebo group. The incidence of gastrointestinal, liver, and lymphatic cancers was also not increased, thus providing no confirmation in humans of findings from testing in animals.[27] The increased incidence of breast cancer in patients given pravastatin was surprising; it has not been reported in previous or ongoing trials with pravastatin or other related drugs, and testing in animals has not identified breast cancer as one that is increased by such therapy. There is also no known potential biologic basis, such as an increase in estrogen levels,[28] to suggest a causal link. In evaluating this finding, it should be noted that although there was one case of breast cancer among the women given placebo, five cases would have been expected on the basis of the rate of breast cancer in the general population for women of similar race and age.[29] Importantly, interim results of the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial,[30] from four years of treatment of 1508 women, show no increase in breast cancer (Barter P, Safety and Data Monitoring Committee, LIPID study: personal communication). The totality of evidence suggests that these findings in the CARE trial could be an anomaly and may be best interpreted in the context of the trial's very low event rates and statistical testing of many adverse events.

The Scandinavian Simvastatin Survival Study was a study of secondary prevention in patients with hypercholesterolemia and coronary disease in which the reduction in coronary events was 37 percent.[8] In the 544 CARE patients who, on the basis of lipid levels and other characteristics, would have been eligible for the Scandinavian study, the reduction in coronary events (as defined in that study) was 43 percent in the pravastatin group as compared with the placebo group ($P = 0.048$). Therefore, we conclude that the difference in overall risk reduction in the two trials was caused mainly by the difference in the base-line LDL cholesterol levels of the two groups of subjects, although other characteristics, such as a greater use of aspirin by the CARE patients, may also have contributed. The results of the CARE trial should be considered representative of what can be achieved by lipid-lowering treatment, over and above other strategies currently employed in the modern, comprehensive treatment of patients with a history of myocardial infarction and average cholesterol levels.

We calculated the overall clinical benefit that could

TABLE 4. EXPECTED NUMBER OF CARDIOVASCULAR EVENTS PREVENTABLE BY TREATING 1000 PATIENTS WITH PRAVASTATIN FOR FIVE YEARS.*

EVENT	UNSELECTED PATIENTS	PATIENTS ≥60 YR OF AGE	WOMEN
		number	
Fatal coronary heart disease	11	27	10
Clinical nonfatal myocardial infarction	26	46	83
Coronary-artery bypass grafting	25	32	34
Percutaneous transluminal coronary angioplasty	37	20	66
Stroke or transient ischemic attack	13	25	28
Other cardiovascular event	38	57	7
All cardiovascular events	150	207	228
Patients with ≥1 event prevented	51	71	97

*We assumed that pravastatin was given to three hypothetical groups of patients with a history of myocardial infarction and a total cholesterol level of less than 240 mg per deciliter: 1000 otherwise unselected patients, 1000 patients 60 or older, and 1000 female patients.

be expected from treating 1000 patients with a documented history of myocardial infarction and a total cholesterol level of less than 240 mg per deciliter with pravastatin for five years (Table 4). Overall, in a general population of such patients, 150 cardiovascular events could be prevented and 51 patients would be spared from having at least one such event. If the 1000 patients were all at higher risk (e.g., patients 60 years of age or older) or women, the absolute benefits would be greater (Table 4). In conclusion, the CARE trial demonstrates that treatment with pravastatin can substantially reduce the burden of cardiovascular disease in patients with a history of myocardial infarction. The study gives new importance to cholesterol-lowering therapy by demonstrating a significant reduction in the incidence of coronary events in patients with cholesterol levels of less than 240 mg per deciliter. This group includes the majority of survivors of myocardial infarction.

Supported by a grant from the Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, N.J.

We are indebted to the patients for their long-term commitment to the study and to Margot J. Mellies, M.D., Mark E. McGovern, M.D., and Stephen T. Mosley, Ph.D., at Bristol-Myers Squibb.

APPENDIX

The following investigators participated in the CARE trial. A complete list of the staff of the trial organization and the clinical and coordinating center has been published previously.[31] Principal investigators are indicated by asterisks. In Canada — **London, Ont.:** L. Melendez, P. Nichol, J. Brown, J. McGillen, P. Squires, M. Calhoun; **Vancouver, B.C.:** V. Bernstein,* S. Mooney, K. Ilott, H. Mizgala,* G. Larsen; **Winnipeg, Man.:** T. Cuddy,* P. Courcelles, B. Hotson; **Ottawa, Ont.:** R. Davies,* G. Ewart, S. Hatfield; **Montreal:** T. Huynh,* J. McCans, E. Marcotte, A. Serpa, F. Sestier,* J. Lenis, N. Kandalaft, H. Bedard, L. Quenneville, P. Carmichael, J. Levesque, S. Foucher; **Halifax, N.S.:** D. Johnstone,* W. Sheridan, S. Barnhill, J. Cossett; **Sherbrooke, Que.:** S. LePage,* C. Maranda, A. Fradet, J. Bedard, R. Dupuis, G. Robert, M. Xhignesse, C. Lavoie; **Ste.-Foy, Que.:** J. Rouleau,* F. DeLage, C. Nadeau, M. Poulin, N. Bilodeau, P. Banville, G. Houde; **St. John's, Newf.:** B. Sussex,* B. Josephson, J. Cole, J. Sanger; **Calgary, Alta.:** A. White, D. Meldrum, D. Woelke, B. Smith, J. Grant, M. Romanosky. In the United States — **Appleton, Wis.:** P. Ackell,* M. Noble; **Birmingham, Ala.:** R. Allman,* L. Jones; **Philadelphia:** B. Berger,* D. Palazzo, D. Wiener,* D. Madonna; **Chicago:** D. Berkson,* J. Berkson, M. Davidson,* S. Torri; **Madison, Wis.:** N. Bittar,* M. Spatola, D. Farnham,* M. Miller; **Las Vegas:** J. Bowers,* A. Tammen; **Omaha, Nebr.:** J. Campbell,* D. Meyers,* J. Coleman; **Miami Beach, Fla.:** M. Canossa-Terris,* M. Goodison; **St. Louis:** J. Cohen,* J. Ostdiek; **Petoskey, Mich.:** H. Colfer,* M. Antonishen; **Reno, Nev.:** S. Daugherty,* J. Frey; **Mobile, Ala.:** A. Davis,* J. Clark; **Takoma Park, Md.:** R. DiBianco,* R. Costello; **Little Rock, Ark.:** H. Dinh,* P. Gordon; **Newark, Del.:** A. Doorey,* T. Hanna; **Dallas:** C. East,* S. Nawab; **Brooklyn, N.Y.:** N. El-Sherif,* B. Caref; **Columbia, Mo.:** G. Flaker,* R. Webel, K. Belew; **Stony Brook, N.Y.:** I. Freeman,* E. Brown, G. Mallis, L. Teplitz, L. Blanz, J. Eaton; **Bronx, N.Y.:** W. Frishman,* S. Furia; **Springfield, Mass.:** R. Gianelly,* D. Tomaszewski; **Tampa, Fla.:** S. Glasser,* T. West; **Miami:** R. Goldberg,* A. Saenz; **Tucson, Ariz.:** S. Goldman,* S. Bigda, J. Ohm, J. Felicetta, D. Caroll; **Bethesda, Md.:** R. Goldstein,* G. Bolling; **Minneapolis:** R. Grimm,* M. Segal,* T. Wilt, J. Levin; **Portland, Oreg.:** J. Grover,* D. Towery, S. Lewis,* J. Mitchell; **Durham, N.C.:** J. Guyton,* C. Gundersdorff; **Boston:** H. Hartley,* L. Bishop, R. Pasternak,* P. Joyce, R. Zusman,* B. Buczynski; **Washington, D.C.:** W. Howard,* B. Howard,* N. Plotsky, V. Papademetriou,* B. Gregory; **Houston:** W. Insull, Jr.,* B. Wilson; **Eugene, Oreg.:** K. Jacobson,* J. McCormick; **Long Beach, Calif.:** M. Kashyap,* N. Downey; **Portland, Me.:** L. Keilson,* K. Curtis; **Seattle:** W. Kennedy,* R. Letterer; **Buffalo, N.Y.:** R. Kohn,* M. Bonora; **Tulsa, Okla.:** J. Durham, W. Leimbach*; **Gainesville, Fla.:** M. Limacher,* G. Ruby; **Oklahoma City:** C. Manion,* E. Wilson; **Loma Linda, Calif.:** G. Marais,* P. Eakes; **Danville and Wilkes-Barre, Pa.:** F. Menapace,* M. Kleman; **Syracuse, N.Y.:** D. Feury; **Kansas City, Mo.:** J. O'Keefe, Jr.,* J. Nelson; **Providence, R.I.:** A. Parisi,* B. Staples; **York, Me.:** L. Petrovich,* S. Russell; **Wynnewood, Pa.:** E. Pickering,* M. Feldman; **Lebanon, N.H.:** C. Moriarty, J. Plehn*; **Valhalla, N.Y.:** A. Pucillo,* A. Kanakaraj; **Richmond, Va.:** D. Romhilt,* C. Chaffin; **Albany, N.Y.:** J. Rodgers,* K. Zolezzi; **Manhasset, N.Y.:** P. Samuel,* L. Markowski; **Atlanta:** R. Schlant,* V. Jeffries; **Farmington, Conn.:** P. Schulman,* L. Kearney; **Baltimore:** R. Sherwin,* K. Yeager; **Cincinnati:** D. Sprecher,* K. Freudemann, E. Stein,* K. Dudley; **Royal Oak, Mich.:** G. Timmis,* D. Davey; **Ann Arbor, Mich.:** R. Vanden Belt,* M. McClain; **Des Moines, Iowa:** W. Wickemeyer,* D. French, M. Polich; **East Lansing, Mich.:** P. Willis, III,* E. Worden. **Safety and Data Monitoring Committee:** A. Gotto (chair), J. Breslow, J. Cairns, C. Furberg, R. Kronmal, P. Meier.

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