PRAVASTATIN THERAPY AND THE RISK OF STROKE

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ABSTRACT

Background   Several epidemiologic studies have concluded that there is no relation between total cholesterol levels and the risk of stroke. In some studies that classified strokes according to cause, there was an association between increasing cholesterol levels and the risk of ischemic stroke and a possible association between low cholesterol levels and the risk of hemorrhagic stroke. Recent reviews of trials of 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors have suggested that these agents may reduce the risk of stroke.

Methods   In a double-blind trial (the Long-Term Intervention with Pravastatin in Ischaemic Disease study), we compared the effects of pravastatin on mortality due to coronary heart disease (the primary end point) with the effects of placebo among 9014 patients with a history of myocardial infarction or unstable angina and a total cholesterol level of 155 to 271 mg per deciliter (4.0 to 7.0 mmol per liter). Our goal in the present study was to assess effects on stroke from any cause and nonhemorrhagic stroke, which were secondary end points.

Results   There were 419 strokes among 373 patients over a follow-up period of six years. A total of 309 strokes were classified as ischemic, 31 as hemorrhagic, and 79 as of unknown type. Among the patients given placebo, the risk of stroke was 4.5 percent, as compared with 3.7 percent among those given pravastatin (relative reduction in risk, 19 percent; 95 percent confidence interval, 0 to 34 percent; P=0.05). Nonhemorrhagic stroke occurred in 4.4 percent of the patients given placebo, as compared with 3.4 percent of those given pravastatin (reduction in risk, 23 percent; 95 percent confidence interval, 5 to 38 percent; P= 0.02). Pravastatin had no effect on hemorrhagic stroke (incidence, 0.2 percent in the placebo group vs. 0.4 percent in the pravastatin group; P=0.28).

Conclusions   Pravastatin has a moderate effect in reducing the risk of stroke from any cause and the risk of nonhemorrhagic stroke in patients with previous myocardial infarction or unstable angina. (N Engl J Med 2000;343:317-26.)
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CEREBROVASCULAR disease is the second leading cause of death worldwide[1,2] and the leading cause of long-term disability in developed countries.[3,4] There has been controversy about whether there is an association between cholesterol levels and the risk of stroke; a meta-analysis found no clear evidence of such an association.[5] Most of the studies made no distinction between ischemic and hemorrhagic strokes, which have different pathophysiologic mechanisms. A positive association between increasing cholesterol levels and ischemic stroke due to atherothrombosis in a large artery may be offset by a possible association between low cholesterol levels and hemorrhagic stroke.

Studies of the relation between cholesterol levels at base line and ischemic stroke have reported a positive association.[2,6] The Multiple Risk Factor Intervention Trial found a positive, continuous relation between cholesterol levels and the risk of ischemic stroke. However, the risk of intracerebral hemorrhage was greater at low levels of cholesterol than at high levels, and this risk was associated with hypertension.[6] A meta-analysis of the incidence of stroke in Asian populations showed a positive relation between increasing cholesterol levels and the incidence of nonhemorrhagic stroke.[2]

In trials of diet, clofibrate, niacin, colestipol, cholestyramine, gemfibrozil, or partial ileal-bypass surgery, cholesterol was lowered by 6 to 23 percent, but no trial identified a significant reduction in rates of stroke. Meta-analysis also showed no effect of these treatments on rates of stroke, as compared with placebo or no treatment (relative risk, 1.0; 95 percent confidence interval, 0.8 to 1.6).[7]

Several trials of 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors (statins) have reported reductions of 25 to 30 percent in the rate of stroke.[8-11] However, many of these trials were limited by the small number of strokes (reducing the precision of the estimates) and by failure to classify the types of stroke.

In the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, we randomly assigned patients with previous myocardial infarction or unstable angina to receive pravastatin or placebo. Data on the primary end point, death due to

coronary heart disease, were published previously.[12] Here we present the findings on the overall incidence of stroke and the incidence of various types of stroke, which were secondary end points.

METHODS

Study Design and Patients

The design of the LIPID study has been described previously.[12,13] A total of 9014 patients, 31 to 75 years of age, were recruited in Australia and New Zealand between June 1990 and December 1992. Patients were eligible for the study if they had had a myocardial infarction or unstable angina pectoris during the previous 3 to 36 months. For patients to proceed to randomization, the total cholesterol level had to be 155 to 271 mg per deciliter (4.0 to 7.0 mmol per liter) and the fasting triglyceride level had to be less than 445 mg per deciliter (5.0 mmol per liter). Exclusion criteria included a clinically significant medical or surgical event during the previous three months, cardiac failure, or a left ventricular ejection fraction known to be less than 25 percent.

After stratification according to qualifying diagnosis (myocardial infarction or unstable angina pectoris) and clinical center, patients were randomly assigned in a double-blind manner to receive either 40 mg of pravastatin (Pravachol, Bristol-Myers Squibb) or a matching placebo once daily. The sample size was calculated on the assumption that there would be 700 deaths from coronary heart disease. Five interim analyses were planned to examine differences between the study groups in overall mortality and the rate of adverse events. The study was to be stopped, on the recommendation of the data and safety monitoring board, if the prespecified boundary for a difference between the groups in overall mortality (3 SD, P<0.003) was crossed. All the patients gave written informed consent, and the study was approved by the ethics committee at each participating center.

The primary end point of the LIPID study was death due to coronary heart disease. Prespecified secondary end points included stroke from any cause (total stroke), subtypes of nonhemorrhagic stroke, and hemorrhagic stroke.

Assessment of Stroke

All events reported as strokes were reviewed by a Stroke Assessment Committee made up of three neurologists and two Management Committee members. The reviewers were blinded with respect to study-group assignment. Confirmation that a stroke had occurred and classification of the stroke required agreement between at least two of the three neurologists or the consensus of the entire Stroke Assessment Committee.

Definitions

Stroke was defined as an acute new disturbance of focal neurologic function resulting in death or lasting longer than 24 hours and thought to be due to intracranial hemorrhage or ischemia. Each stroke was first classified as ischemic, hemorrhagic, or of unknown type.

Ischemic stroke was defined as a stroke accompanied by a computed tomographic (CT) or magnetic resonance imaging (MRI) scan within three weeks after onset that either was normal or showed an infarct in the expected area on the basis of the clinical findings or a stroke for which there was evidence of cerebral infarction at autopsy. Each ischemic stroke was classified as one of the following: a cerebral infarct in a large artery (with evidence on clinical examination, duplex ultrasonography, MRI, or angiography of disease in an extracranial or intracranial large artery, but with no cardioembolic source); a cerebral infarct in a small artery (with preservation of consciousness and higher cerebral function, a lacunar syndrome, and a CT or MRI scan that was normal or showed a small infarct in the basal ganglia, internal capsule, or brain stem); a cerebral infarct of cardioembolic cause (with a major cardioembolic source but no definite evidence of occlusive disease in a large artery); a retinal infarct[14]; or a cerebral infarct of unknown or un-

certain origin. Each hemorrhagic stroke was classified as due to either a subarachnoid hemorrhage or an intracerebral hemorrhage (on the basis of evidence obtained on CT or MRI scanning or at autopsy), excluding hemorrhagic conversion of infarction.

A stroke was considered to be of unknown type if there was no information available from CT or MRI scanning or from autopsy findings. In addition, each stroke was classified according to whether it occurred within seven days after enrollment and whether it was related to coronary angiography, angioplasty, bypass surgery, or other similar procedures.

Disability

Patients' functional status was assessed at hospital discharge or 30 days after the event, whichever came first. Disability was clas-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

VARIABLE	PLACEBO (N=4502)	PRAVASTATIN (N=4512)
Median age (yr)	62	62
Sex (%)		
Male	83	83
Female	17	17
Qualifying event (%)		
Myocardial infarction	64	64
Unstable angina pectoris	36	36
Median time from event to randomization (yr)	1.2	1.1
Coronary risk factors (%)		
Current smoking	10	9
Former smoking	63	65
History of hypertension	42	41
Antihypertensive medication	38	36
Diabetes mellitus	9	9
Obesity†	18	18
Other vascular disease (%)		
Claudication	10	10
Stroke	4	4
Transient ischemic attack	4	3
Atrial fibrillation (%)	1.3	1.4
Coronary revascularization (%)		
Angioplasty only	11	11
Coronary bypass only	27	27
Both angioplasty and coronary bypass	3	3
Medications (%)‡		
Aspirin	82	82
Other antiplatelet agent	3	3
Warfarin	2	2
Beta-blocker	48	46
Calcium antagonist	35	34
Angiotensin-converting–enzyme inhibitor	16	16
Nitrate	30	30
Diuretic	16	15
Insulin	1	1
Oral hypoglycemic agent	5	4
Median lipid levels§		
Total cholesterol (mg/dl)	218	218
HDL cholesterol (mg/dl)	36	36
LDL cholesterol (mg/dl)	150	150
Triglycerides (mg/dl)	138	142
Total:HDL cholesterol ratio	6	6

*Except for base-line triglyceride levels (P=0.02), there were no significant differences between the groups.

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

‡The percentage of patients receiving medication is marginally lower than previously reported,[12] after correction for the use of multiple drugs in each class of drugs.

§HDL denotes high-density lipoprotein, and LDL low-density lipoprotein. 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.

sified as severe (inability to live independently), moderate (substantial limitations), or minor (functional status unchanged). The need for additional care at home was also assessed.

Statistical Analysis

All analyses were performed on an intention-to-treat basis, and P values were two-sided. Reductions in risk and 95 percent confidence intervals were estimated with use of the Cox proportional-hazards model and relate to the number of patients, not the number of strokes or other events.[15] The times to events were analyzed by the log-rank test, with stratification according to the event that had qualified the patient for enrollment (previous myocardial infarction or unstable angina pectoris).[16] Assessment of variation in the effects of treatment among subgroups defined according to variables assessed before randomization was based on tests for interaction in the Cox model. The effect of nonfatal coronary events on the time to stroke was assessed with the use of Cox regression analysis, in which the coronary event was a time-dependent, binary covariate that switched value when a nonfatal coronary event occurred. The effects of treatment on measurements of lipids and blood pressure in the two study groups were expressed as group means and compared with the use of t-tests. P values for comparisons between subgroups were unadjusted for multiple comparisons.

Base-line risk factors for stroke from any cause were identified by backward selection in the Cox proportional-hazards model.[15] Relative risks were based on estimates of the hazard ratios, with 95 percent confidence intervals. Similar analysis was also performed with nonhemorrhagic stroke as an outcome.

RESULTS

Base-Line Characteristics

Table 1 lists the base-line characteristics of the 9014 enrolled patients, 4512 of whom were randomly assigned to receive pravastatin and 4502 to receive placebo. The two groups were well matched; the only significant difference was a slightly higher level of plasma triglycerides in the pravastatin group. The median age of the patients was 62 years, and 39 percent were 65 years of age or older. Forty-two percent had a total cholesterol level of less than 213 mg per deciliter (5.5 mmol per liter) at base line. Eighty-two percent of each group were taking aspirin, and 2 percent of each group were taking warfarin.

Four percent of the patients in each group had a history of stroke. On average, these patients were four years older than the patients without a history of stroke and were more likely to have a history of hypertension, diabetes, peripheral vascular disease, transient ischemic attack, or atrial fibrillation (P<0.001 for all comparisons).

Effect of Pravastatin as Compared with Placebo

The mean duration of treatment and follow-up was six years. In the pravastatin group, during the first five years, the total cholesterol level decreased from 218 mg per deciliter (5.6 mmol per liter) to 179 mg per deciliter (4.6 mmol per liter), a reduction of 18 percent (a reduction 18 percentage points greater than the reduction in the placebo group). The low-density lipoprotein (LDL) cholesterol level in the pravastatin group, initially 150 mg per deciliter (3.9 mmol per liter), decreased by 27 percent (a reduction 25 percentage points greater than that in the placebo group); the plasma triglyceride level, initially 142 mg per deciliter (1.6 mmol per liter) decreased by 6 percent (a change 11 percentage points different from that in the placebo group); and the high-density lipoprotein (HDL) cholesterol level, initially 36 mg per deciliter, increased by 4 percent (a change 5 percentage points different from that in the placebo group) (P<0.001 for all comparisons).

In the pravastatin group, there was a 24 percent relative reduction in the risk of death due to coronary heart disease (6.4 percent, vs. 8.3 percent in the placebo group; P<0.001), and a 22 percent relative reduction in the risk of death from all causes (11 percent vs. 14.1 percent, P<0.001).[13]
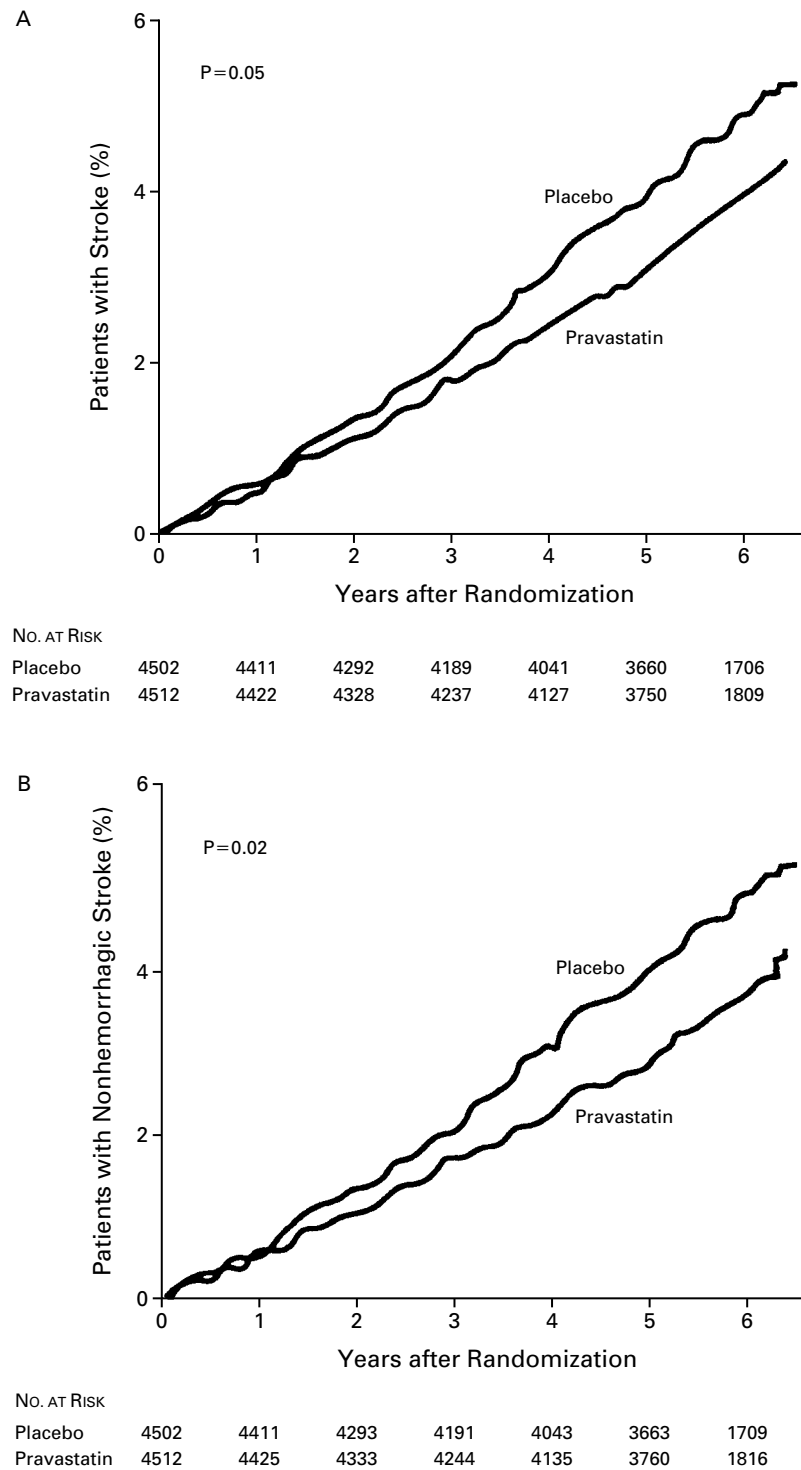
All 471 events reported as strokes were reviewed, and 419 were confirmed. CT or MRI was performed for 82 percent of the strokes. Imaging was not performed in 45 patients in the placebo group and 31 patients in the pravastatin group. In the placebo group, 231 strokes occurred in 204 of the 4502 patients (4.5 percent), and in the pravastatin group, 188 strokes occurred in 169 of the 4512 patients (3.7 percent), a relative reduction in risk of 19 percent (95 percent confidence interval, 0 to 34 percent; P=0.05) (Table 2 and Fig. 1A). This risk reduction corresponds to the occurrence of strokes in

TABLE 2. INCIDENCE OF STROKE ACCORDING TO STUDY GROUP.

VARIABLE	PLACEBO (N=4502)	PRAVASTATIN (N=4512)	TOTAL (N=9014)	REDUCTION IN RISK WITH PRAVASTATIN (95% CI)*
	no.		no. (%)	%
Patients with stroke	204	169	373	19 (0 to 34)
Patients with a single stroke	179	153	332 (89)†	16 (−4 to 32)
Patients with multiple strokes	25	16	41 (11)†	37 (−19 to 66)
Total strokes	231	188	419	

*CI denotes confidence interval. Negative numbers indicate an increase in risk.

†Percentages are of the total number of patients with stroke.

A

P=0.05

Placebo

Pravastatin

Years after Randomization

NO. AT RISK

Placebo	4502	4411	4292	4189	4041	3660	1706
Pravastatin	4512	4422	4328	4237	4127	3750	1809

B

P=0.02

Placebo

Pravastatin

Years after Randomization

NO. AT RISK

Placebo	4502	4411	4293	4191	4043	3663	1709
Pravastatin	4512	4425	4333	4244	4135	3760	1816

Figure 1. Kaplan–Meier Estimates of the Incidence of Stroke from Any Cause (Panel A) and Nonhemorrhagic Stroke (Panel B), According to Study Group.

The P values were calculated by the log-rank test.

8 fewer patients for every 1000 patients treated with pravastatin instead of placebo for six years. Nonhemorrhagic strokes occurred in 4.4 percent of the patients assigned to placebo and in 3.4 percent of those assigned to pravastatin, a relative reduction in risk of 23 percent (95 percent confidence interval, 5 to 38 percent; P=0.02) (Fig. 1B). This risk reduction corresponds to the occurrence of nonhemorrhagic stroke in 9 fewer patients for every 1000 patients treated with pravastatin for six years.

Table 2 shows the reduction in the risk of stroke in the two treatment groups, and Figure 2 shows the risk of particular types of stroke. Sensitivity analysis that excluded retinal infarctions (five in the pravastatin group and one in the placebo group) did not change the results. There was no significant difference between the two groups in the incidence of hemorrhagic stroke (0.2 percent in the placebo group and 0.4 percent in the pravastatin group, P=0.28).
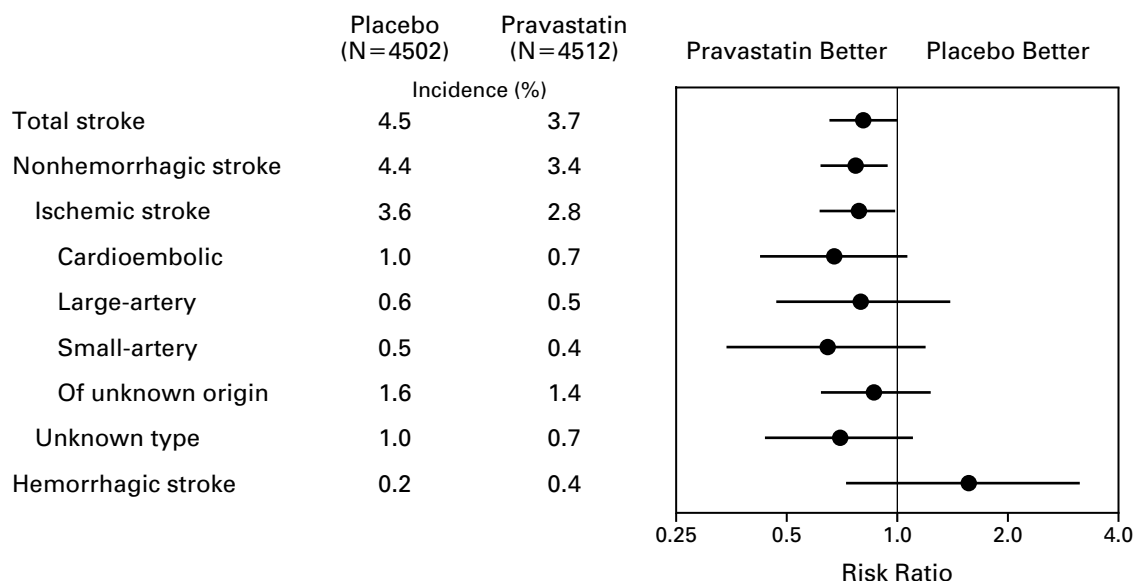
At the completion of the study, the percentages of patients using aspirin (84 percent of the placebo group and 83 percent of the pravastatin group) or warfarin (7 percent of the placebo group and 6 percent of the pravastatin group) were similar in the two groups. In both groups, blood pressure increased during the study (from 133/79 at base line to 135/80 mm Hg in the placebo group and from 133/79 to 135/81 mm Hg in the pravastatin group; P=0.73 for the comparison of systolic pressure and P=0.63 for the comparison of diastolic pressure).

Table 3 shows the overall incidence of stroke in various subgroups of the patients. Similar reductions in risk were seen in most subgroups. There was a greater relative reduction in the risk of stroke among patients with low HDL cholesterol levels than among those with high HDL cholesterol levels, but there was no statistical evidence of heterogeneity of the effect of treatment on the risk of stroke when all of the subgroups were considered together (P=0.75).

Relation between Events during the Study and Stroke

In both the placebo group and the pravastatin group, more strokes occurred among the patients in whom unstable angina or myocardial infarction developed during the study than among those in whom these conditions did not develop (Table 4). Stroke without a previous event occurred in 4.6 percent of the placebo group and 3.6 percent of the pravastatin group. The rates of stroke after any nonfatal coronary event were 13.9 and 12.9 per 1000 person-years in the placebo and pravastatin groups, respectively. Among the patients who had not had a coronary event, the rates of stroke were 6.9 and 5.5 per 1000 person-years in the placebo and pravastatin groups, respectively. The reduction in risk did not differ significantly between the periods before and after a nonfatal coronary event (P>0.48 for all comparisons). The relative reduction in risk associated with pravastatin after adjustment for all nonfatal coronary events was 17 percent (95 percent confidence interval, −2 to 32 percent [the negative value indicates an increase in risk]), similar to the reduction in risk before adjustment. Atrial fibrillation was present at the beginning of the study in 5.6 percent of the patients who

	Placebo (N=4502)	Pravastatin (N=4512)	
	Incidence (%)		
Total stroke	4.5	3.7	
Nonhemorrhagic stroke	4.4	3.4	
Ischemic stroke	3.6	2.8	
Cardioembolic	1.0	0.7	
Large-artery	0.6	0.5	
Small-artery	0.5	0.4	
Of unknown origin	1.6	1.4	
Unknown type	1.0	0.7	
Hemorrhagic stroke	0.2	0.4	

Figure 2. Risk Ratios for Stroke from Any Cause (Total Stroke) and Various Types of Stroke, According to Study Group.
The horizontal lines indicate 95 percent confidence intervals. The scale for risk ratios is logarithmic. Because of rounding, values for subcategories do not necessarily sum to the category totals.

TABLE 3. EFFECTS OF TREATMENT ON THE OVERALL RISK OF STROKE IN SUBGROUPS OF PATIENTS DEFINED ACCORDING TO BASE-LINE CHARACTERISTICS.*

VARIABLE†	PLACEBO (N=4502)		PRAVASTATIN (N=4512)		REDUCTION IN RISK WITH PRAVASTATIN (95% CI)‡	P VALUE FOR HETEROGENEITY§
	NO. OF PATIENTS	NO. OF PATIENTS WITH STROKE (%)	NO. OF PATIENTS	NO. OF PATIENTS WITH STROKE (%)	%	
Sex						
Female	760	27 (3.6)	756	33 (4.4)	−26 (−110 to 24)	0.09
Male	3742	177 (4.7)	3756	136 (3.6)	25 (6 to 40)	
Qualifying event						
Myocardial infarction	2875	120 (4.2)	2879	98 (3.4)	20 (−5 to 39)	0.88
Unstable angina	1627	84 (5.2)	1633	71 (4.3)	17 (−14 to 39)	
Age						
<55 yr	1021	17 (1.7)	1065	17 (1.6)	4 (−87 to 51)	0.22
55–64 yr	1708	68 (4.0)	1706	48 (2.8)	31 (0 to 52)	
65–69 yr	1087	79 (7.3)	1081	58 (5.4)	28 (−1 to 49)	
≥70 yr	686	40 (5.8)	660	46 (7.0)	−21 (−85 to 21)	
Hypertension						
Yes	1891	107 (5.7)	1867	100 (5.4)	7 (−22 to 29)	0.28
No	2609	96 (3.7)	2644	69 (2.6)	30 (4 to 49)	
Diabetes						
Yes	386	40 (10.4)	396	31 (7.8)	27 (−17 to 54)	0.64
No	4116	164 (4.0)	4116	138 (3.4)	17 (−4 to 34)	
Smoking						
Current	444	26 (5.9)	425	18 (4.2)	30 (−28 to 61)	0.88
Former	2814	120 (4.3)	2923	106 (3.6)	16 (−9 to 35)	
None	1244	58 (4.7)	1164	45 (3.9)	18 (−21 to 44)	
Atrial fibrillation						
Yes	59	12 (20.3)	64	9 (14.1)	31 (−63 to 71)	0.61
No	4443	192 (4.3)	4448	160 (3.6)	18 (−1 to 34)	
Previous stroke						
Yes	198	25 (12.6)	171	18 (10.5)	25 (−39 to 60)	0.96
No	4303	179 (4.2)	4341	151 (3.5)	17 (−3 to 33)	
Transient ischemic attack						
Yes	176	13 (7.4)	156	13 (8.3)	−11 (−139 to 49)	0.41
No	4325	191 (4.4)	4351	156 (3.6)	20 (1 to 35)	
Total cholesterol						
<213 mg/dl	1894	96 (5.1)	1898	77 (4.1)	21 (−7 to 41)	0.84
213–250 mg/dl	2003	83 (4.1)	2010	68 (3.4)	20 (−10 to 42)	
≥251 mg/dl	605	25 (4.1)	604	24 (4.0)	5 (−66 to 46)	
LDL cholesterol						
<135 mg/dl	1305	66 (5.1)	1332	49 (3.7)	28 (−4 to 50)	0.61
135–173 mg/dl	2338	107 (4.6)	2336	90 (3.9)	17 (−10 to 37)	
≥174 mg/dl	859	31 (3.6)	844	30 (3.6)	4 (−59 to 42)	
HDL cholesterol						
<39 mg/dl	2831	139 (4.9)	2890	100 (3.5)	31 (10 to 46)	0.04
≥39 mg/dl	1671	65 (3.9)	1622	69 (4.3)	−8 (−52 to 23)	
Triglycerides						
<133 mg/dl	2022	92 (4.5)	1951	83 (4.3)	8 (−24 to 31)	0.40
133–220 mg/dl	1801	72 (4.0)	1750	55 (3.1)	22 (−10 to 45)	
≥221 mg/dl	679	40 (5.9)	811	31 (3.8)	37 (−1 to 61)	
Aspirin use						
Yes	3684	166 (4.5)	3718	126 (3.4)	26 (7 to 41)	0.08
No	611	29 (4.7)	592	34 (5.7)	−20 (−97 to 27)	

*Because base-line data were missing for some patients, the numbers of patients do not always total 4502 in the placebo group and 4512 in the pravastatin group.

†LDL denotes low-density lipoprotein, and HDL high-density lipoprotein. 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. Negative values indicate an increase in risk.

§The global test for interaction (with all subgroups considered together) did not indicate a statistically significant result.

TABLE 4. EVENTS DURING THE STUDY BEFORE STROKE AND THE INCIDENCE OF STROKE, ACCORDING TO STUDY GROUP.

CORONARY EVENTS BEFORE STROKE	INCIDENCE OF STROKE		RELATIVE RISK (95% CI)*
	PLACEBO (N=4502)	PRAVASTATIN (N=4512)	
	no./1000 person-yr		
Nonfatal myocardial infarction			
No	7.6	6.2	1.0
Yes	22.5	22.4	3.1 (2.3–4.3)
Unstable angina			
No	7.4	5.9	1.0
Yes	13.7	12.8	1.9 (1.5–2.4)
Coronary-artery bypass grafting			
No	8.0	6.6	1.0
Yes	14.9	11.0	1.6 (1.0–2.6)
Angioplasty			
No	7.8	6.4	1.0
Yes	15.7	11.6	1.8 (1.3–2.5)
Any nonfatal coronary event†			
No	6.9	5.5	1.0
Yes	13.9	12.9	2.0 (1.6–2.6)

*Relative risks refer to the placebo group and were based on the hazard ratio in a time-dependent Cox model. CI denotes confidence interval.

†Nonfatal coronary events included nonfatal myocardial infarction, unstable angina, coronary-artery bypass grafting, and angioplasty.

had a stroke, as compared with 1.2 percent of the patients who did not have a stroke (P<0.001). Atrial fibrillation developed for the first time during the study in 2.2 percent of the placebo group and 2.9 percent of the pravastatin group (P=0.06). There was no significant difference between the pravastatin and placebo groups in mortality after stroke (13.0 percent and 13.2 percent, respectively) or in the severity of disability associated with stroke.

Relation between Base-Line Characteristics and the Incidence of Stroke

Table 5 shows the base-line predictors of stroke from any cause according to the multivariate model and the univariate model for each predictor. The risk increased with older age and increasing systolic blood pressure, and it was higher among patients with a history of hypertension, diabetes, a history of stroke, current smoking, or the presence of atrial fibrillation. The risk was higher in patients in whom unstable angina pectoris was the qualifying event than in those with myocardial infarction as a qualifying event and was higher in patients with previous anterior myocardial infarction than in those with other types of myocardial infarction. Lipid levels at base line were not significant predictors of the occurrence of stroke in either the total cohort or the placebo group.

Except for sex, all the predictors of overall stroke in the multivariate analysis were also predictors of nonhemorrhagic stroke in this analysis. Body-mass index was also a predictor. Base-line lipid levels were

not significant predictors of the risk of nonhemorrhagic stroke either in the total study population or in the placebo group. The change in the LDL cholesterol level during the first year after enrollment was not a significant predictor of overall stroke or of nonhemorrhagic stroke in either the pravastatin group or the total study population (P>0.1 for all comparisons). After adjustment for significant base-line factors, treatment with pravastatin was associated with a reduction of 16 percent in the overall risk of stroke (95 percent confidence interval, −3 to 31 percent; P=0.10) and a reduction of 21 percent in the risk of nonhemorrhagic stroke (95 percent confidence interval, 3 to 36 percent; P=0.03).

DISCUSSION

This study shows that lipid-lowering therapy with pravastatin reduces the risk of stroke in patients with known coronary heart disease. The benefits of pravastatin were achieved without adverse effects and without an increase in the rate of hemorrhagic stroke. Aspirin given for secondary prevention reduces the risk of stroke by 25 percent,[17] and in this study the benefits of pravastatin were achieved in a population in which the rate of aspirin use was high. Analysis according to total and LDL cholesterol levels at base line revealed no evidence of differences in the treatment effect.

Previous studies reported that lowering lipid levels with non-statin therapies as compared with placebo or control therapy reduced the rate of coronary events

TABLE 5. RISK FACTORS FOR STROKE FROM ANY CAUSE.*

VARIABLE†	NO. OF PATIENTS	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
		RELATIVE RISK (95% CI)	P VALUE	RELATIVE RISK (95% CI)	P VALUE
Treatment with pravastatin		0.81 (0.66–1.00)	0.048	0.84 (0.69–1.03)	0.10
Age			<0.001		<0.001
<55 yr‡	2086	1.00		1.00	
55–64 yr	3411	2.16 (1.47–3.17)		1.89 (1.28–2.78)	
65–69 yr	2167	4.27 (2.93–6.21)		3.56 (2.43–5.23)	
≥70 yr	1346	4.45 (2.99–6.62)		3.56 (2.37–5.37)	
Male sex	7494	1.06 (0.80–1.40)	0.69	1.34 (1.01–1.78)	0.045
Qualifying event			0.002		0.014
Anterior myocardial infarction‡	2253	1.00		1.00	
Other myocardial infarction	3499	0.70 (0.53–0.91)		0.69 (0.53–0.91)	
Unstable angina pectoris	3258	1.05 (0.82–1.35)		0.93 (0.73–1.20)	
Stroke before randomization	369	3.33 (2.42–4.57)	<0.001	2.25 (1.63–3.11)	<0.001
Smoking status			0.241		0.002
Never smoked‡	2408	1.00		1.00	
Former smoker	5734	0.93 (0.74–1.18)		0.94 (0.74–1.20)	
Current smoker	868	1.23 (0.86–1.75)		1.70 (1.18–2.43)	
Systolic blood pressure			<0.001		0.001
≤125 mm Hg‡	3145	1.00		1.00	
126–140 mm Hg	3286	1.73 (1.31–2.28)		1.48 (1.12–1.95)	
>140 mm Hg	2579	2.47 (1.88–3.25)		1.72 (1.29–2.29)	
Hypertension	3758	1.79 (1.46–2.20)	<0.001	1.39 (1.12–1.72)	0.003
Diabetes	782	2.69 (2.08–3.48)	<0.001	2.23 (1.71–2.89)	<0.001
Atrial fibrillation	123	5.00 (3.22–7.77)	<0.001	3.18 (2.04–4.97)	<0.001
Total cholesterol		0.94 (0.82–1.08)	0.388		
LDL cholesterol		1.14 (0.73–1.76)	0.563		
HDL cholesterol		0.91 (0.79–1.06)	0.245		

*Because data were missing for four patients in the multivariate analysis, the numbers of patients total 9010 rather than 9014. CI denotes confidence interval, LDL low-density lipoprotein, and HDL high-density lipoprotein.

†Lipid levels (total, LDL, and HDL cholesterol) were assessed as continuous variables and were not significant risk factors in either univariate or multivariate analysis.

‡Patients with this characteristic served as the reference group.

but not the rate of stroke.[18] The discrepancy between their results and ours could have been due to the lower absolute rate of strokes than of coronary events, the diverse causes of stroke, the relatively young age of the patients in those studies (most of which excluded patients over the age of 70 years, a subgroup that constituted 15 percent of the population in our study), the small overall reduction in cholesterol levels (10 to 11 percent, as compared with approximately 18 percent in our study), and the small number of strokes.

Post hoc analysis of the Scandinavian Simvastatin Survival Study showed that simvastatin, as compared with placebo, was associated with a lower incidence of the combined end point of stroke and transient ischemic attack (28 percent relative reduction [3.4 percent vs. 4.6 percent], P=0.03) over a period of 5.4 years in patients with coronary heart disease (mean age, 58.1 years) and with cholesterol levels of 213 to 309 mg per deciliter (5.5 to 8.0 mmol per liter).[19,20] The incidence of stroke alone was nonsignificantly lower with simvastatin (reduction in risk, 22 percent; 95 percent confidence interval, −9 to 44 per-

cent), and the rate of aspirin use was low (37 percent of patients at base line and 55 percent at the completion of the study). In a prespecified analysis of the Cholesterol and Recurrent Events (CARE) Study, 132 patients had strokes, and pravastatin reduced the incidence of stroke by 32 percent over a period of five years as compared with placebo (2.6 percent vs. 3.8 percent, P<0.03) in patients who had had an infarction (mean age, 59 years) and who had average plasma total cholesterol levels at base line of less than 240 mg per deciliter (6.2 mmol per liter). Eighty-three percent of the patients in the CARE Study were taking aspirin at base line.[11,21]

The results of several meta-analyses of trials of statins, in which there were a total of 454 strokes, have been reported.[10,18,22,23] Use of statins was associated with a significantly lower rate of stroke (24 to 32 percent lower) in secondary-prevention trials[18,22] and a nonsignificantly lower rate (15 to 20 percent lower)[18,22] in primary-prevention trials.

In the LIPID study, there were 419 confirmed strokes, and the strokes were prospectively classified according to type. The reduction in the rate of strokes

was consistent among the categories of ischemic stroke, including lacunar infarcts. The number of patients with hemorrhagic stroke was small (28), and thus no conclusions with respect to this type of stroke can be drawn from our data.

Atheroma of the carotid arteries[24] and aortic arch[25] is a potent independent risk factor for stroke. The pathophysiology of disease is less well defined in these vascular territories than in the coronary circulation. However, histologic lesions in the carotid arteries similar to those that characterize unstable plaque in the coronary circulation have been described.[26]

It has been reported that total and LDL cholesterol levels may be associated with thickening of the intima–media layer of the carotid artery, as determined by B-mode ultrasonography of the carotid artery,[27,28] and indeed, lipid-lowering therapy has been shown to reduce the progression of carotid intima–media thickening.[22,29-35] In a substudy of the LIPID study, pravastatin reduced the development of carotid-wall thickening over a four-year follow-up period.[35] The effect of treatment was similar among subgroups of patients defined according to cholesterol level at base line.

The incidence of cardioembolic stroke in the pravastatin group in our study may have been lowered by the 29 percent reduction in the rate of myocardial infarction, with its associated complications of left ventricular mural thrombosis, heart failure, and atrial fibrillation, that was observed with pravastatin. The presence of atrial fibrillation at base line was a strong predictor of overall stroke; the risk of stroke in patients with atrial fibrillation was more than three times that in other patients. Although new atrial fibrillation occurred in similar percentages of patients in the placebo and pravastatin groups, the number of patients in whom paroxysmal atrial fibrillation developed is not known.

Angioplasty and coronary-artery bypass surgery were performed less frequently in the pravastatin group than in the placebo group. The rates of stroke associated with these procedures were similar in the two groups. The reduction in the rate of overall stroke cannot be explained by the reduction in the rate of nonfatal coronary events associated with pravastatin, since the estimated treatment effect was at least as great after adjustment for these events.

Cholesterol levels at base line were not correlated with the risk of overall stroke or the risk of nonhemorrhagic stroke. There was a greater relative reduction in risk with pravastatin in patients with low HDL cholesterol levels. This finding conflicts with the results of the CARE Study,[11] which showed a trend in the opposite direction, and in both studies these were probably chance findings. Similar relative reductions in risk were seen in other subgroups defined according to variables assessed at base line. The change in LDL cholesterol from base line to one year was also not a predictor of the likelihood of subsequent stroke.

The benefits of pravastatin may be due to a number of mechanisms other than a lowering of lipid levels. Statins have other effects and may reduce the incidence of clinical events by influencing endothelial function,[36,37] the inflammatory response,[38] plaque stability,[39] and thrombus formation.[40] Our data do not allow us to comment on the extent to which local effects on atheroma of the carotid artery or aortic arch or effects other than a reduction in the LDL cholesterol level may have contributed to our findings.

The decrease in the risk of stroke that was associated with pravastatin was observed in patients with previous myocardial infarction or unstable angina. It is not known whether similar effects would be observed in patients with previous stroke or transient ischemic attack or whether stroke would be prevented in patients without manifest atherosclerosis.

The incidence of stroke is increasing as the population ages. The costs of acute hospital care and nursing home care for patients with stroke are considerable.[41] The most common cause of death among patients who have had a stroke is coronary heart disease.[42] Our results show that lipid-lowering therapy with pravastatin can reduce both the rate of coronary heart disease and the rate of stroke, two of the three major public health problems in industrialized countries, as judged by the burden of disease as measured in disability-adjusted life years.[1] Recognition of these two beneficial effects should lead to more widespread use of lipid-lowering therapy. It is also possible that discussion of stroke prevention with patients may reduce noncompliance with lipid-lowering therapy, a major impediment to the clinical implementation of the results of large-scale trials such as this one in the community.

APPENDIX

The Stroke Assessment Committee of the LIPID study consisted of the following (asterisks indicate previous members): H. White (chair), N. Anderson, G. Hankey, J. Simes, J. Watson, and S. Simes (secretary); the Management Committee consisted of A. Tonkin (chair), J. Shaw* (previous chair) (deceased), P. Aylward, D. Colquhoun, P. Glasziou, P. Harris, D. Hunt, A. Keech, S. MacMahon, P. Nestel,* D. Newell,* N. Sharpe, J. Simes, P. Thompson, A. Thomson, M. West, and H. White; Bristol-Myers Squibb nominees (nonvoting members) ex officio were M. Ablett, M. MacAskill, and R. Turner*; and National Heart Foundation of Australia nominees were P. Magnus* and P. Wallace.

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