

High-Dose Atorvastatin after Stroke or Transient Ischemic Attack

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators*

ABSTRACT

BACKGROUND

Statins reduce the incidence of strokes among patients at increased risk for cardiovascular disease; whether they reduce the risk of stroke after a recent stroke or transient ischemic attack (TIA) remains to be established.

METHODS

We randomly assigned 4731 patients who had had a stroke or TIA within one to six months before study entry, had low-density lipoprotein (LDL) cholesterol levels of 100 to 190 mg per deciliter (2.6 to 4.9 mmol per liter), and had no known coronary heart disease to double-blind treatment with 80 mg of atorvastatin per day or placebo. The primary end point was a first nonfatal or fatal stroke.

RESULTS

The mean LDL cholesterol level during the trial was 73 mg per deciliter (1.9 mmol per liter) among patients receiving atorvastatin and 129 mg per deciliter (3.3 mmol per liter) among patients receiving placebo. During a median follow-up of 4.9 years, 265 patients (11.2 percent) receiving atorvastatin and 311 patients (13.1 percent) receiving placebo had a fatal or nonfatal stroke (5-year absolute reduction in risk, 2.2 percent; adjusted hazard ratio, 0.84; 95 percent confidence interval, 0.71 to 0.99; $P=0.03$; unadjusted $P=0.05$). The atorvastatin group had 218 ischemic strokes and 55 hemorrhagic strokes, whereas the placebo group had 274 ischemic strokes and 33 hemorrhagic strokes. The five-year absolute reduction in the risk of major cardiovascular events was 3.5 percent (hazard ratio, 0.80; 95 percent confidence interval, 0.69 to 0.92; $P=0.002$). The overall mortality rate was similar, with 216 deaths in the atorvastatin group and 211 deaths in the placebo group ($P=0.98$), as were the rates of serious adverse events. Elevated liver enzyme values were more common in patients taking atorvastatin.

CONCLUSIONS

In patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke. (ClinicalTrials.gov number, NCT00147602.)

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DESPITE THE EFFICACY OF A VARIETY OF secondary preventive therapies, patients who have had a stroke or transient ischemic attack (TIA) remain at risk for stroke as well as coronary and other cardiovascular events.¹ Therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces the risk of stroke among patients with coronary heart disease and those at increased risk for cardiovascular disease.²⁻⁸ A meta-analysis of 90,000 patients included in these previous statin trials showed that the reduction in the risk of stroke was primarily related to the extent to which low-density lipoprotein (LDL) cholesterol levels were lowered.⁸ No data exist to show that statin treatment decreases the risk of stroke among patients with a history of stroke or TIA.^{9,10} The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial was designed to determine whether a daily dose of 80 mg of atorvastatin would reduce the risk of stroke in patients with no known coronary heart disease who had had a stroke or TIA within the previous six months.

METHODS

The methods of the SPARCL study have been described in detail previously.¹¹ The study was approved by the local research ethics committee or institutional review board at each participating center (15 of 205 centers excluded otherwise suitable patients with an LDL cholesterol level above 160 mg per deciliter [4.1 mmol per liter], as required by their institutional review boards), and all patients gave written informed consent.

STUDY HYPOTHESIS AND PATIENT POPULATION

The primary hypothesis of the study was that treatment with 80 mg of atorvastatin per day would reduce the risk of fatal or nonfatal stroke among patients with a history of stroke or TIA. Eligible patients were men and women over 18 years of age who had had an ischemic or hemorrhagic stroke or a TIA (diagnosed by a neurologist within 30 days after the event) 1 to 6 months before randomization. Patients with hemorrhagic stroke were included if they were deemed by the investigator to be at risk for ischemic stroke or coronary heart disease. Stroke was defined by focal clinical signs of central nervous system dysfunction of vascular origin that lasted for at least 24 hours; TIA was defined by the loss of cerebral or ocular function for less than 24

hours, presumably owing to atherosclerotic causes. Patients had to be ambulatory, with a modified Rankin score of no more than 3 (scores can range from 0 to 6, with higher scores indicating more severe disability or death), and to have an LDL cholesterol level of at least 100 mg per deciliter (2.6 mmol per liter) and no more than 190 mg per deciliter (4.9 mmol per liter).¹² The exclusion criteria, which have been described in detail previously, included atrial fibrillation, other cardiac sources of embolism, and subarachnoid hemorrhage.¹¹ Patients were enrolled between September 1998 and March 2001.

STUDY PROTOCOL

Patients who were taking lipid-altering drugs had to stop these medications 30 days before the screening phase of the study. Within 30 days after the initial screening visit, eligible patients were randomly assigned to double-blind therapy with either 80 mg of atorvastatin per day or placebo. To ensure that investigators remained unaware of a patient's treatment assignment on the basis of changes in LDL cholesterol levels during the study, if LDL cholesterol levels dropped below 40 mg per deciliter (1.0 mmol per liter) in a patient treated with atorvastatin, the investigator for a randomly chosen placebo patient was notified and LDL cholesterol levels were remeasured in both patients. All patients were counseled to follow the National Cholesterol Education Program Step 1 (or similar) diet throughout the study.¹³ Follow-up visits were scheduled one, three, and six months after enrollment and every six months thereafter. Surviving patients made their last study visit between March and June 2005.

EFFICACY OUTCOMES

The primary outcome was the time from randomization to a first nonfatal or fatal stroke. There were seven prespecified secondary composite outcomes: stroke or TIA, major coronary event (death from cardiac causes, nonfatal myocardial infarction, or resuscitation after cardiac arrest), major cardiovascular event (stroke plus any major coronary event), acute coronary event (major coronary event or unstable angina), any coronary event (acute coronary event plus a coronary revascularization procedure, unstable angina, or angina or ischemia requiring emergency hospitalization), revascularization procedure (coronary, carotid, or peripheral), and any cardiovascular event (any of the former plus clin-

ically significant peripheral vascular disease).¹¹ Individual components of the composite end points and death from any cause were also prespecified secondary outcomes.

SAFETY ASSESSMENTS

Full clinical laboratory assessments were performed and electrocardiograms were obtained and subsequently interpreted by a central laboratory at screening, at regular intervals during the study, and on completion of the study. Drug safety was assessed by an evaluation of the type, frequency, severity, and duration of any reported adverse event and on the basis of vital signs, physical examinations, and laboratory tests.

STATISTICAL ANALYSIS

The study was designed to have a statistical power of 90 percent to detect an absolute reduction of 25 percent in the primary end point in the atorvastatin group as compared with the placebo group during a median follow-up of five years with a two-sided significance level of $P < 0.05$. Given the specified statistical power, the enrollment of 4200 patients, and an assumed annual rate of 3.5 percent for the primary end point in the placebo group, the study was designed to continue until 540 primary end points had occurred.

Seven interim analyses of efficacy were performed during the study, with a stopping boundary corresponding to a two-sided significance level of $P = 0.0001$ for the first analysis and $P = 0.001$ thereafter. Because of these interim analyses, the final P value had to be less than 0.048 to indicate a significant difference.

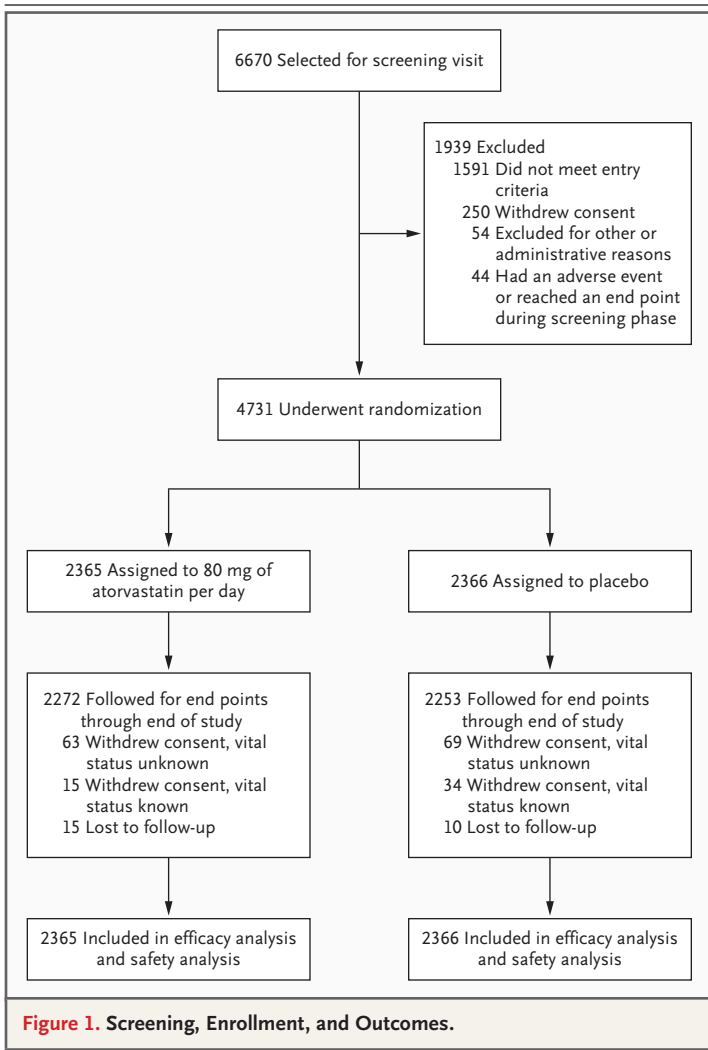
The analysis plan was prespecified and performed on an intention-to-treat basis with the inclusion of all patients who underwent randomization. Efficacy analyses were also performed according to the treatment actually received in a prespecified population consisting of a group of all randomized patients who had an entry event within six months before randomization, were compliant with the study treatment for at least six months after randomization, and did not start statin therapy that was not specified by the study until at least six months after randomization. Initially, the log-rank test was used to compare the time from randomization to the first occurrence of a particular event in the two groups. To account for baseline factors thought to be related to the risk of events, prespecified Cox proportional-haz-

ards models were used to calculate treatment-related hazard ratios, 95 percent confidence intervals, and P values, with adjustment for geographic region, entry event (stroke or TIA), time since entry event (as a continuous variable), sex, and age at baseline (as a continuous variable). Five patients were excluded from the prespecified adjusted analyses because of missing data on the entry event (including one patient in the placebo group who had a nonfatal stroke followed by a fatal stroke). For a given composite outcome, deaths that were not included in the composite were treated as censoring events. Events that occurred after the prespecified end-of-study censoring date for each patient were not included in the analysis; inclusion of these events did not alter the inferences of the data presented. Lipid and lipoprotein levels in patients receiving treatment were determined in linear models with terms for treatment and month of measurement. The absolute reductions in risk and the numbers needed to treat were determined from five-year Kaplan–Meier rates. All P values were two-sided, with no adjustment for multiple testing.

The SPARCL steering committee developed the study protocol with the sponsor and takes responsibility for the data and data analyses. Medpace (Cincinnati) managed all data. Medpace, Charles River Laboratories Clinical Services (Brussels), and the sponsor provided site monitoring throughout the study. Two independent end-point committees (one for neurologic and one for cardiovascular end points) adjudicated all potential end points without knowledge of the patients' treatment status or cholesterol levels. A data and safety monitoring board with independent statistical support performed interim monitoring analyses for safety and efficacy.

RESULTS

Of 6670 screened, eligible patients, 4731 (70.9 percent) fulfilled the inclusion criteria and underwent randomization (Fig. 1). The median duration of follow-up was 4.9 years (range among survivors, 4.0 to 6.6). Among survivors, there was no significant difference in the number of patients in each treatment group lost to follow-up ($P = 0.42$). More patients in the placebo group than in the atorvastatin group withdrew consent after randomization ($P = 0.07$), permanently discontinued study treatment (20.2 percent vs. 15.4 percent of follow-up time for the



primary end point, respectively; $P=0.07$), and began open-label, nonstudy statin therapy (7.5 percent vs. 1.0 percent of follow-up time for the primary end point, respectively; the net difference in statin use between groups was 78.1 percent). During the trial, the treatment assignment of nine patients (three assigned to atorvastatin and six assigned to placebo) was revealed to the study physician.

After randomization, the patients also took aspirin or other antiplatelet drugs (94.1 percent of patients in the placebo group and 93.6 percent of patients in the atorvastatin group); angiotensin-converting-enzyme inhibitors (46.8 percent and 46.9 percent, respectively); dihydropyridine derivatives (29.6 percent and 27.8 percent, respectively); beta-blockers (33.4 percent and 31.5 percent, respectively); angiotensin II-receptor antago-

nists (14.8 percent and 14.1 percent, respectively); vitamin K antagonists, including warfarin (12.4 percent and 12.2 percent, respectively); or open-label statins (25.4 percent and 11.4 percent, respectively). Atorvastatin was the most frequently used nonstudy, open-label statin in both study groups.

The mean (\pm SE) LDL cholesterol levels were similar in the two groups at baseline (Table 1). One month after randomization, the LDL cholesterol level in the atorvastatin group had decreased to 61.3 ± 0.4 mg per deciliter (1.58 ± 0.01 mmol per liter) (a decrease of 53 percent, $P<0.001$) and was unchanged in the placebo group at 133.5 ± 0.5 mg per deciliter (3.45 ± 0.01 mmol per liter) ($P=0.65$). The mean lipid values during the course of the trial were as follows: LDL cholesterol, 72.9 ± 0.5 mg per deciliter (1.89 ± 0.01 mmol per liter) in the atorvastatin group, as compared with 128.5 ± 0.5 mg per deciliter (3.32 ± 0.01 mmol per liter) in the placebo group ($P<0.001$); high-density lipoprotein (HDL) cholesterol, 52.1 ± 0.3 as compared with 51.0 ± 0.3 mg per deciliter (1.35 ± 0.01 vs. 1.32 ± 0.01 mmol per liter), respectively ($P=0.006$); total cholesterol, 147.2 ± 0.6 as compared with 208.4 ± 0.6 mg per deciliter (3.81 ± 0.02 vs. 5.39 ± 0.02 mmol per liter), ($P<0.001$); and triglycerides, 111.5 ± 1.3 as compared with 145.0 ± 1.3 mg per deciliter (1.26 ± 0.01 vs. 1.64 ± 0.01 mmol per liter), respectively ($P<0.001$).

A primary end point (any nonfatal or fatal stroke) occurred in 265 patients in the atorvastatin group and 311 in the placebo group (unadjusted $P=0.05$) (Table 2). The absolute difference in Kaplan–Meier rates at five years was 2.2 percent (95 percent confidence interval, 0.2 to 4.2 percent). A total of 136 patients in the placebo group and 154 patients in the atorvastatin group died from causes other than stroke before they could have a nonfatal stroke. After prespecified adjustment for baseline factors, atorvastatin was associated with a 16.0 percent relative reduction in the risk of nonfatal or fatal stroke (hazard ratio, 0.84; 95 percent confidence interval, 0.71 to 0.99; $P=0.03$) (Table 2 and Fig. 2). Prespecified analysis of 4162 patients according to the protocol showed an 18.0 percent relative reduction in the risk of stroke in the atorvastatin group, as compared with the placebo group (hazard ratio, 0.82; 95 percent confidence interval, 0.69 to 0.98; $P=0.03$).

Analysis of secondary end points showed reductions in the combined risk of stroke and TIA.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Atorvastatin (N=2365)	Placebo (N=2366)
Age — yr	63.0±0.2	62.5±0.2
Male sex — no. (%)	1427 (60.3)	1396 (59.0)
Systolic blood pressure — mm Hg	138.9±0.4	138.4±0.4
Diastolic blood pressure — mm Hg	82.0±0.2	81.4±0.2
Body-mass index†	27.5±0.1	27.4±0.1
Entry event — no. (%)		
Stroke	1655 (70.0)	1613 (68.2)
Ischemic	1595 (67.4)	1559 (65.9)
Hemorrhagic	45 (1.9)	48 (2.0)
Other type or not determined	15 (0.6)	6 (0.3)
TIA	708 (29.9)	752 (31.8)
Unknown	2 (0.1)	1 (<0.1)
Time since entry event — days	87.1±1.0	84.3±1.0
Risk factors — no. (%)		
Current smoker	452 (19.1)	456 (19.3)
Former smoker	963 (40.7)	918 (38.8)
Systemic hypertension	1476 (62.4)	1452 (61.4)
History of diabetes mellitus	395 (16.7)	399 (16.9)
Any prior statin therapy — no. (%)	57 (2.4)	63 (2.7)
Concomitant therapy — no. (%)		
Aspirin or other antiplatelet drug, excluding heparin	2067 (87.4)	2063 (87.2)
ACE inhibitor	683 (28.9)	667 (28.2)
Dihydropyridine derivative	350 (14.8)	359 (15.2)
Beta-blocker	414 (17.5)	422 (17.8)
Angiotensin II–receptor antagonist	110 (4.7)	102 (4.3)
Vitamin K antagonist, including warfarin	139 (5.9)	154 (6.5)
Lipids — mg/dl‡		
LDL cholesterol	132.7±0.5	133.7±0.5
HDL cholesterol	50.0±0.3	50.0±0.3
Total cholesterol	211.4±0.6	212.3±0.6
Triglycerides	144.2±1.9	143.2±1.4
Apolipoprotein A1	149.1±0.6	149.6±0.6
Apolipoprotein B	133.1±0.5	134.1±0.5

* Plus–minus values are means ±SE. ACE denotes angiotensin-converting–enzyme, 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.

‡ 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 risk of cardiovascular events, including major coronary events and revascularization procedures, was reduced substantially (Table 2). There was no significant difference between treatment groups in overall mortality (including cancer-related mortality). Kaplan–Meier estimates for selected com-

ponents of the secondary end points are given in Figure 3.

Post hoc analyses indicated significant differences in the treatment effect (hazard ratios) based on the type of stroke occurring during the trial (ischemic, hemorrhagic, or unclassified stroke)

Table 2. Estimates of the Hazard Ratio for the Primary and Secondary Efficacy Outcome Measures.

Outcome*	Atorvastatin (N=2365)	Placebo (N=2366)	Unadjusted P Value†	Prespecified Adjusted Model‡	
				HR (95% CI)	P Value
	<i>no. (%)</i>				
Primary outcome					
Nonfatal or fatal stroke§	265 (11.2)	311 (13.1)	0.05	0.84 (0.71–0.99)	0.03
Nonfatal stroke	247 (10.4)	280 (11.8)	0.14	0.87 (0.73–1.03)	0.11
Fatal stroke	24 (1.0)	41 (1.7)	0.04	0.57 (0.35–0.95)	0.03
Secondary outcomes					
Stroke or TIA	375 (15.9)	476 (20.1)	<0.001	0.77 (0.67–0.88)	<0.001
TIA	153 (6.5)	208 (8.8)	0.004	0.74 (0.60–0.91)	0.004
Major coronary event§	81 (3.4)	120 (5.1)	0.006	0.65 (0.49–0.87)	0.003
Death from cardiac causes	40 (1.7)	39 (1.6)	0.90	1.00 (0.64–1.56)	1.00
Nonfatal myocardial infarction	43 (1.8)	82 (3.5)	0.001	0.51 (0.35–0.74)	<0.001
Resuscitation after cardiac arrest	1 (<0.1)	1 (<0.1)	—	—	—
Major cardiovascular event	334 (14.1)	407 (17.2)	0.005	0.80 (0.69–0.92)	0.002
Acute coronary event	101 (4.3)	151 (6.4)	0.001	0.65 (0.50–0.84)	0.001
Any coronary event	123 (5.2)	204 (8.6)	<0.001	0.58 (0.46–0.73)	<0.001
Revascularization¶	94 (4.0)	163 (6.9)	<0.001	0.55 (0.43–0.72)	<0.001
Any cardiovascular event	530 (22.4)	687 (29.0)	<0.001	0.74 (0.66–0.83)	<0.001
Death	216 (9.1)	211 (8.9)	0.77	1.00 (0.82–1.21)	0.98
Death from cardiovascular disease	78 (3.3)	98 (4.1)	0.14	0.78 (0.58–1.06)	0.11
Death from cancer	57 (2.4)	53 (2.2)	0.67	1.05 (0.72–1.53)	0.80
Death from infection	26 (1.1)	20 (0.8)	—	—	—
Accidental or violent death	11 (0.5)	6 (0.3)	—	—	—
Death from other causes	23 (1.0)	15 (0.6)	—	—	—
Unclassified deaths	21 (0.9)	19 (0.8)	—	—	—

* Only the first event for each patient is counted.

† Unadjusted P values were calculated by the log-rank test.

‡ Treatment hazard ratios (HRs) and P values are from the Cox regression model with adjustment for geographic region, entry event, time since entry event, sex, and age at baseline. CI denotes confidence interval.

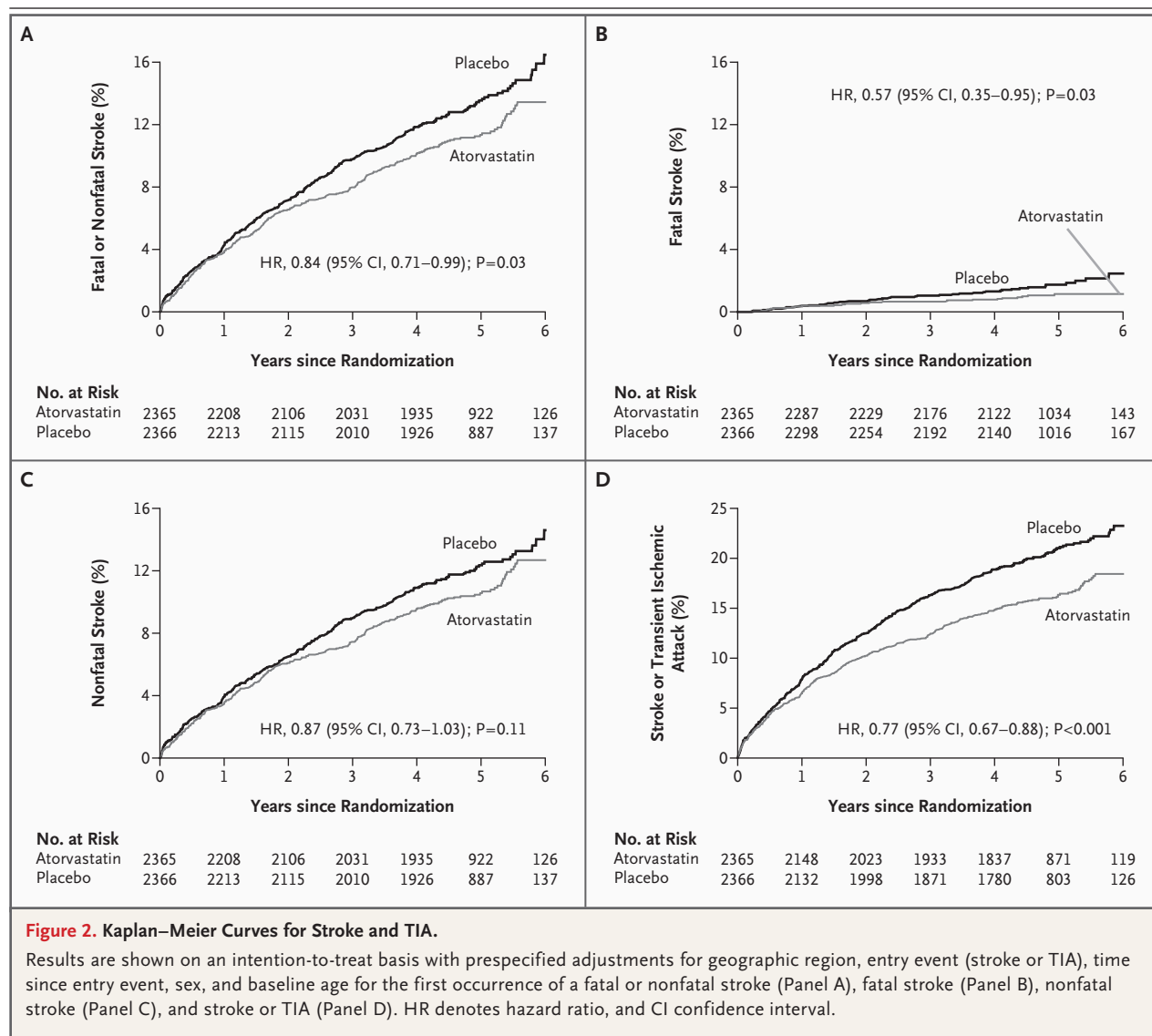
§ Numbers of patients in the outcome subgroups do not total the number for the overall outcome because some patients had multiple events or the outcome could not be subclassified.

¶ Revascularization includes coronary, carotid, and peripheral revascularization.

when the other types were treated as censoring events ($P=0.01$ by the likelihood-ratio test). The cause-specific adjusted hazard ratios in the atorvastatin group, as compared with the placebo group, were 0.78 (95 percent confidence interval, 0.66 to 0.94) for ischemic stroke, 1.66 (95 percent confidence interval, 1.08 to 2.55) for hemorrhagic stroke, and 0.55 (95 percent confidence interval, 0.21 to 1.40) for unclassified stroke. Of the 492 patients who had at least one ischemic stroke, 218 were in the atorvastatin group and 274 were in the placebo group; of the 88 patients who had

at least one hemorrhagic stroke, 55 were in the atorvastatin group and 33 were in the placebo group; and of the 19 patients who had at least one unclassified stroke, 7 were in the atorvastatin group and 12 were in the placebo group. The incidence of fatal hemorrhagic stroke did not differ significantly between the groups (17 in the atorvastatin and 18 in the placebo group).

Safety assessments revealed no significant differences between groups in the incidence of serious adverse events (Table 3). There were five cases of rhabdomyolysis, two in the atorvastatin group



and three in the placebo group. Persistent elevation of alanine or aspartate aminotransferase (>3 times the upper limit of the normal group on two consecutive occasions) was more frequent in the atorvastatin group (51 patients, or 2.2 percent) than in the placebo group (11 patients, or 0.5 percent; $P<0.001$ by the chi-square test). There were no cases of liver failure.

DISCUSSION

This prospective, randomized, placebo-controlled trial demonstrated that treatment with 80 mg of atorvastatin per day reduced the risk of subsequent stroke in patients without known coronary heart

disease and with LDL cholesterol levels of 100 to 190 mg per deciliter who had had a recent stroke or TIA. The study was not powered to assess the effect of treatment on the risk of death from any cause or on fatal and nonfatal stroke separately, but the risk of fatal stroke was significantly reduced. The reduction in the risk of nonfatal stroke was consistent with the treatment effect, but not significant.

Although at enrollment, patients had no known coronary heart disease, the risk of cardiovascular events, including major coronary events and revascularization procedures, was also substantially reduced. On the basis of our data, 46 patients (95 percent confidence interval, 24 to 243)

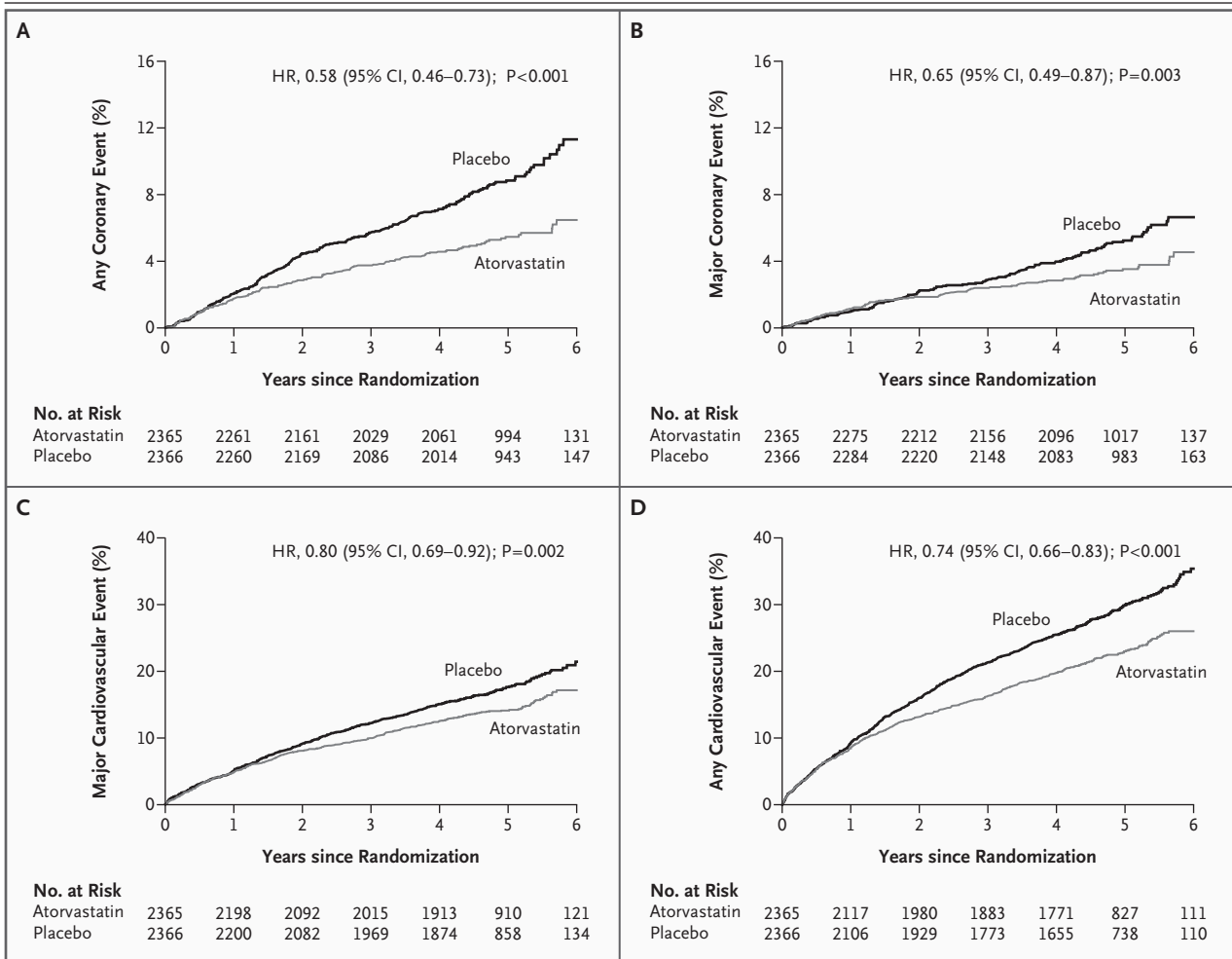


Figure 3. Kaplan–Meier Curves for Coronary and Cardiovascular Events.

Results are shown on an intention-to-treat basis with prespecified adjustments for geographic region, entry event (stroke or TIA), time since entry event, sex, and baseline age for the first occurrence of any coronary event (acute coronary event plus coronary revascularization procedure, unstable angina, or angina or ischemia requiring emergency hospitalization) (Panel A), any major coronary event (death from cardiac causes, nonfatal myocardial infarction, resuscitation after cardiac arrest) (Panel B), any major cardiovascular event (primary event plus any major coronary event) (Panel C), and any cardiovascular event (any of the former plus clinically significant peripheral vascular disease) (Panel D). HR denotes hazard ratio, and CI confidence interval.

would need to be treated for five years to prevent one stroke, 29 patients (95 percent confidence interval, 18 to 75) to prevent one major cardiovascular event, and 32 patients (95 percent confidence interval, 22 to 59) to avoid one revascularization procedure. These benefits were observed despite the increased use of open-label nonstudy statins during the study, a result suggesting that the effect is robust.

As expected, the beneficial effect of statin therapy on the risk of recurrent stroke was due to a reduction in the risk of cerebral infarction, the

mechanism of which largely has been attributed to a reduction in LDL cholesterol levels.⁸ The lower average LDL cholesterol level achieved in the atorvastatin as compared with the placebo group is consistent with this hypothesis. Other putative mechanisms include a variety of possible pleiotropic effects.¹⁴

Our results contrast with those of the Heart Protection Study (HPS), which found no reduction in the risk of stroke among patients with prior cerebrovascular disease (10.4 percent of patients in the statin group had a recurrent stroke, as com-

pared with 10.5 percent of patients in the placebo group).¹⁰ A possible explanation for this difference in results is that patients in the HPS were enrolled an average of 4.3 years after the index event, whereas the risk of recurrence is highest within the first years after stroke.^{10,15,16} Another explanation may be the larger reduction in LDL cholesterol in our study than in the HPS (56 mg per deciliter [1.4 mmol per liter] vs. 39 mg per deciliter [1.0 mmol per liter]).¹⁰ Other differences between the trials have been reviewed previously.⁹

Although patients with known coronary heart disease were excluded at baseline, 9.2 percent (434 patients) had a coronary event or a noncoronary revascularization procedure during the trial. Treatment with atorvastatin reduced the risk of these events. This observation adds to evidence from previous studies involving patients at increased risk for cardiovascular disease showing that statin treatment reduces atherosclerotic complications.²⁻⁷ Our results support the concept that from the standpoint of statin treatment, stroke or TIA should be considered a coronary heart disease risk equivalent.

In our study, the overall benefit in terms of the reduction in the risk of stroke was significant despite an increase in hemorrhagic stroke in the atorvastatin group. Statistical heterogeneity was observed in the effects of atorvastatin on ischemic and hemorrhagic stroke. An increase in the incidence of hemorrhagic stroke among patients with cerebrovascular disease treated with simvastatin (40 mg) was noted in the HPS.¹⁰ Epidemiologic studies have suggested an association between low cholesterol levels and brain hemorrhage.¹⁷⁻¹⁹ Statin trials conducted largely in patients without cerebrovascular disease have reduced LDL cholesterol levels to 70 mg per deciliter (1.8 mmol per liter) or below, with no increase in the incidence of hemorrhagic stroke.²⁰⁻²² The small number of patients with brain hemorrhage at entry in our study precludes any meaningful conclusions regarding the relative risks and benefits of statin treatment in this population. The potential risk of recurrent hemorrhage should be considered when one is deciding whether to administer a statin to patients who have had a hemorrhagic stroke.

In conclusion, in patients with a recent stroke or TIA, treatment with 80 mg of atorvastatin per day decreased the risk of stroke, major coronary events, and revascularization procedures. These

Table 3. Incidence of Adverse Events and Elevated Laboratory Values.*

Variable	Atorvastatin (N = 2365)	Placebo (N = 2366)
	no. (%)	
Adverse event		
Any adverse event	2199 (93.0)	2156 (91.1)
Any serious adverse event	988 (41.8)	975 (41.2)
Any adverse event resulting in discontinuation of study treatment	415 (17.5)	342 (14.5)
Musculoskeletal adverse events		
Myalgia	129 (5.5)	141 (6.0)
Myopathy	7 (0.3)	7 (0.3)
Rhabdomyolysis†	2 (0.1)	3 (0.1)
Adverse events with incidence of ≥10% in either group		
Accidental injury	487 (20.6)	447 (18.9)
Infection	414 (17.5)	439 (18.6)
Hypertension	395 (16.7)	443 (18.7)
Pain	357 (15.1)	388 (16.4)
Depression	296 (12.5)	298 (12.6)
Headache	272 (11.5)	271 (11.5)
Back pain	266 (11.2)	241 (10.2)
Diarrhea	238 (10.1)	187 (7.9)
Laboratory value		
ALT or AST >3× ULN at 2 consecutive measurements	51 (2.2)	11 (0.5)
Creatine kinase >10× ULN at 2 consecutive measurements	2 (0.1)	0

* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.

† There was no preset definition of rhabdomyolysis.

results support the initiation of atorvastatin treatment soon after a stroke or TIA.

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APPENDIX

Participants in the SPARCL Study were as follows: **Steering Committee** — K.M.A. Welch (chair), A. Callahan, III, L.B. Goldstein, J. Zivin, United States; P. Amarengo, France; J. Bogousslavsky, Switzerland; M.G. Hennerici, Germany; H. Sillesen, Denmark; **Publication Subcommittee** — H. Sillesen, Denmark (chair); W. Clark, L.B. Goldstein, J. Zivin, United States; A. Dávalos, Spain; M. Kaste, Finland; L. Leiter, Canada; **Retention Subcommittee** — P. Amarengo (cochair), France; A. Callahan III (cochair), Canada; G. Graham, United States; J. Glahn, Germany; D. Jiménez Hernández, Spain; R. MacWalter, United Kingdom; R. Scott, New Zealand; A. Shuaib, Canada; J. Sivenius, Finland; R. Stipal, Czech Republic; **Safety Committee** — R. Hart (chair), J. Marsh, R. Sacco, United States; B. Norring, Sweden; S. Pocock, United Kingdom; **Cerebrovascular End-Point Committee** — J. Easton (chair), J. Whisnant, United States; M. Brown, United Kingdom; Z. Nagy, Hungary; **Cardiovascular End-Point Committee** — B. O'Neill (chair), Canada; F. Kleber, Germany; J.-M. LaBlanche, France; F. Wely, United States; **Investigators (number of randomized patients in parentheses)** — Australia (167): D. Crimmins, S. Davis, S. Dimmitt, G. Donnan, J. Frayne, D. Freilich, A. Zagami; Austria (87): J. Mikocki, C. Schmidauer, R. Schmidt; Belgium (41): J. De Bleecker, F. Deceuninck, P. Tack, V. Thijs; Brazil (8): J. Gomes Fernandes; Canada (295): M. Beaudry, R. Cote, K. Hoyte, L.-H. Lebrun, A. Mackey, D. Sahlas, D. Selchen, A. Shuaib, J.D. Spence, P. Teal, M. Winger; Chile (10): G. Matamala; Czech Republic (222): R. Gifkova, Z. Kalita, I. Rektor, H. Rosolova, R. Stipal, D. Vaclavik; Denmark (57): G. Boysen, H. Iversen, H. Klingenberg, H. Sillesen; Finland (385): M. Hillbom, M. Kaste, H. Numminen, A. Pilke, A. Salmivaara, J. Sivenius; France (161): S. Alamowitch, P. Amarengo, J. Boulliat, T. De Broucker, F. Chollet, M.-H. Mahagne, L. Milandre, T. Moulin; Germany (284): U. Bogdahn, H.-C. Diener, M. Dichgans, J. Glahn, R. Haberl, L. Harms, M.G. Hennerici, S. Knecht, G. Kroczeck, C. Lichy, D. Sander, D. Schneider; Greece (39): C. Karageorgiou, A. Kazis, I. Milonas, P. Stathis, D. Vogiatzoglou; Israel (61): N. Bornstein, S. Honigman, Y. Lampl, J. Streifler; Italy (75): A. Capurso, G. Comi, C. Ferrarese, C. Gandolfo, M. Poloni, U. Senin; Mexico (9): R. Rangel Guerra; Netherlands (171): A.M. Boon, J.H.A. De Keyser, P.L.M. De Kort, J.A. Haas, D.J. Kamphuis, P.-J. Koudstaal; New Zealand (219): N. Anderson, R. Scott, G. Singh; Poland (249): E. Czlonkowska, W. Drozdowski, Z. Gralewski, W. Kozubski, A. Kuczynska-Zardzewialy, R. Podemski, Z. Stelmasiak; A. Szczudlik; Portugal (102): C. Da Costa Correia, J. Ferro, L. Salgueiro e Cunha; Slovakia (37): J. Lietava, K. Raslova; South Africa (93): J. Carr, J. Gardiner, A. Kruger; Spain (744): J. Alvarez-Sabin, A. Chamorro, E. Diez-Tejedor, O. Fernández, J. Trejo Gabriel y Galán, J. González Marcos, J. Egidio Herrero, M. Jiménez Martínez, A. Lago Martín, E. Mostacero Miguel, J. Vivanco Mora, J. Moltó, J. Viguera Romero, E. Cuartero Rodriguez, F. Rubio, J. Serena; Sweden (121): A.C. Laska, B. Leijd, T. Strand, A. Terent, A. Waegner, T. Wallén; Switzerland (86): R. Baumgartner, J. Bogousslavsky, H. Hungerbühler, P. Lyrer, H. Mattle; United Kingdom (146): P.M. Bath, E.B. Ekpo, A. Freeman, K.R. Lees, M.J. MacLeod, R.S. MacWalter, A.K. Sharma, H.G.M. Shetty; United States (853): G. Albers, I. Altafullah, O. Benavente, D. Book, J. Broderick, C. Calder, A. Callahan III, W. Carlini, S. Chaturvedi, T. Chippendale, W. Clark, B. Coull, P. Davis, T. Devlin, A. Dick, G. Dooneief, R. Duff, N. Estronza, A. Forteza, M. Frankel, J. Frey, G. Friday, J. Goldstein, G. Graham, M. Hammer, W. Harper, J. Harris, B. Hendin, D. Hess, R. Hinton, J. Hollander, R. Hughes, S. Kasner, T. Kent, L. Kim, H. Kirshner, M. LaMonte, L. Ledbetter, P. Lee-Kwen, K. Levin, R. Libman, J. Matlock, P. McDowell, F. McGee Jr., B. Meyer, A. Minagar, M. Moussouttas, R. Munson, M. Nash, A. Nassief, S. Orr, G. Ratinov, V. Salanga, S. Silliman, R. Singer, D. Smith, H. Sullivan, G. Tietjen, D. Thaler, M. Tuchman, D. Uskavitch, P. Verro, R. Vicari, R. Weinstein, J. Wilterdink, R. Zweifler; Venezuela (9): M. De Bastos.

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