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Effects of Intense Low-Density Lipoprotein Cholesterol Reduction in Patients With Stroke or Transient Ischemic Attack

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

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Background and Purpose—The intention-to-treat analysis of data from the placebo-controlled Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial found 80 mg atorvastatin per day reduced the risk of stroke and major coronary events in patients with recent stroke or transient ischemic attack. This benefit was present despite only a 78% net difference in adherence to randomized treatment over the course of the trial. In this exploratory analysis, our aim was to evaluate the benefit and risks associated with achieving a ≥50% low-density lipoprotein cholesterol (LDL-C) reduction from baseline.

Methods—This post hoc analysis was based on 55 045 LDL-C measurements among the 4731 patients enrolled in SPARCL (average, 11.6 measurements per patient) during a mean follow-up of 4.9 years. At each postrandomization LDL-C assessment, percent change in LDL-C from baseline for each patient was classified as no change or increase from baseline (32.7% of measurements), <50% LDL-C reduction (39.4%), or ≥50% reduction (27.9%).

Results—Compared with no change or an increase in LDL-C, analysis of time-varying LDL-C change showed that patients with ≥50% LDL-C reduction had a 31% reduction in stroke risk (hazard ratio, 0.69, 95% CI, 0.55 to 0.87, $P=0.0016$), a 33% reduction in ischemic stroke ($P=0.0018$), no statistically significant increase in hemorrhagic stroke ($P=0.8864$), and a 37% reduction in major coronary events ($P=0.0323$). There was no increase in the incidence of myalgia or rhabdomyolysis. Persistent liver enzyme elevations were more frequent in the group with ≥50% LDL-C reduction.

Conclusions—As compared with having no change or an increase in LDL-C, achieving a ≥50% lowering was associated with a greater reduction in the risk of stroke and major coronary events with no increase in brain hemorrhages. **(*Stroke*. 2007;38:3198-3204.)**

Key Words: lipids ■ prevention ■ statins ■ stroke

Epidemiological studies[1] do not establish a clear relationship between total cholesterol levels and the risk of incident strokes. Despite this, HMG-CoA reductase inhibitors (statins) reduce the risk of stroke in a number of patient populations, including those with coronary heart disease (CHD), hypertension, diabetes, and the elderly.[2] Meta-analysis of such trials found that low-density lipoprotein cholesterol (LDL-C)-lowering explained between 35% and 80% of the benefit[3]; every 1-mmol decrease in LDL-C was associated with a 17% reduction in fatal and nonfatal stroke.[4] Whether the reduction of stroke risk involves effects of statins other than LDL-C-lowering remains uncertain.[5,6]

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial was a randomized, double-blind, placebo-controlled trial showing that treatment with 80 mg atorvastatin per day reduced the risk of stroke and coronary events in 4731 patients with recent stroke and transient ischemic attack (TIA) and no known CHD.[7] This benefit was found despite only 78% adherence to randomized treatment by the end of the trial. More patients in the placebo group discontinued study treatment and began open-label, nonstudy statin therapy than patients in the atorvastatin group (25.4% versus 11.4%). This could lead to an underestimate of the potential of benefit of treatment.

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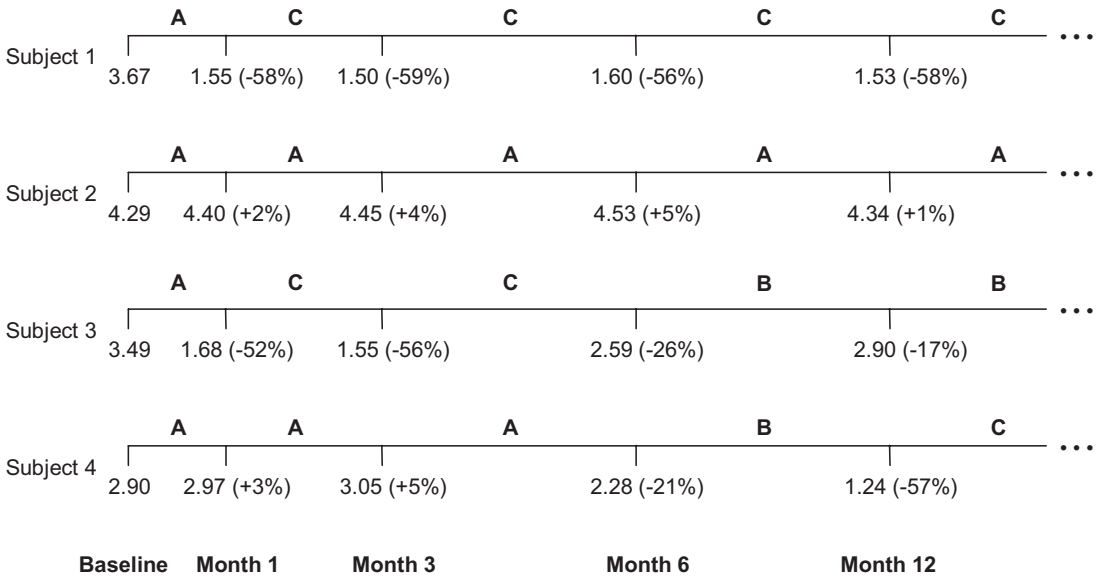

Figure 1. Example subject classifications into LDL-C categories: 4 hypothetical examples of classifications into LDL-C percent change categories. Patients were classified at each laboratory assessment into one of the 3 categories according to magnitude of percent change in LDL-C from their prerandomization, stain-naive baseline. A, No change or increase; (B) <50% decrease; or (C) ≥50% decrease. Follow-up visits were scheduled at 1, 3, and 6 months and then every 6 months with a blinded assessment of LDL-C levels. Subject 1 is a hypothetical patient maintaining a ≥50% reduction in LDL-C over 12 months on 80 mg atorvastatin per day; subject 2 is a hypothetical placebo-treated patient with no reduction in LDL-C; subject 3 could be one who permanently discontinued randomized active treatment and subsequently dropped in to a nonstudy statin or one with incomplete adherence to atorvastatin; subject 4 is a hypothetical placebo-treated patient who then dropped in to 80 mg open-label atorvastatin per day. LDL-C values are given in mmol/L. To convert to mg/dL, multiply by 39.

In this post hoc exploratory analysis of the SPARCL data, we evaluated the benefit and risks associated with achieving a ≥50% reduction in LDL-C from baseline, <50% reduction in LDL-C, or no change or an increase in LDL-C. We hypothesized that those achieving a ≥50% reduction in LDL-C would have the greatest reductions in stroke and other vascular events.

Materials and Methods

The SPARCL methodology has been described in detail previously.[7,8] The study was approved by the local research committee or Institutional Review Board at each participating center (15 of 205 centers excluded otherwise suitable patients with an LDL-C >4.1 mmol/L [160 mg/dL] as required by their Institutional Review Boards) and patients gave written informed consent.

SPARCL Primary Study Hypothesis and Patient Population

The primary hypothesis of the SPARCL trial was that treatment with 80 mg atorvastatin per day would reduce the combined risk of fatal and nonfatal stroke in patients with a recent stroke or TIA. Eligible patients were men and women older than 18 years and having had an ischemic or hemorrhagic stroke or TIA (all diagnosed by a neurologist within 30 days of the event) 1 to 6 months before randomization. Patients with hemorrhagic stroke could be included if they were deemed by the investigator to be at risk for ischemic stroke or CHD. Stroke was defined as focal clinical signs of central nervous system dysfunction of vascular origin lasting ≥24 hours. TIA was defined as an acute loss of cerebral or ocular function lasting <24 hours and presumed to be of atherosclerotic origin. Patients had to be ambulatory (modified Rankin score ≤3; score can range from 0 to 6 with higher scores indicating more severe disability or death) and have a LDL-C level ≥2.6 and ≤4.9 mmol/L (≥100 and ≤190 mg/dL).[7] The exclusion criteria included having atrial fibrillation, mechanical prosthetic heart valves, CHD, or subarachnoid hemorrhage.[7] Patients were enrolled between September 1998 and March 2001.

Study Protocol

Between 1 and 6 months after stroke (within 30 days of the initial screening visit), eligible patients were randomized to double-blind therapy with either 80 mg atorvastatin per day or placebo. Nonstudy statins were not permitted. Those patients who began a nonstudy statin or withdrew from randomized treatment were included in the intention-to-treat analysis.[7] All patients were counseled to follow the National Cholesterol Education Program (NCEP) Step 1 (or similar) diet throughout the study. Visits were scheduled at 1, 3, and 6 months and every 6 months thereafter. Surviving patients had last study visits between March and June 2005.

SPARCL Efficacy Outcomes

The SPARCL primary outcome was the time from randomization to the first occurrence of a nonfatal or fatal stroke. There were 7 prespecified secondary composite outcomes: stroke or TIA; major coronary event (cardiac death, nonfatal myocardial infarction, or resuscitated cardiac arrest); major cardiovascular event (stroke plus any major coronary event); acute coronary event (major coronary event or unstable angina); any CHD event (acute coronary event plus coronary revascularization procedure, unstable angina or angina/ischemia requiring emergent hospitalization); revascularization procedure (coronary, carotid, or peripheral); and any cardiovascular event (any of the former plus clinically significant peripheral vascular disease).[8] Individual components of the composite end points and all-cause mortality were also prespecified secondary outcomes.

Lipid Level Analysis and Safety Assessments

Clinical laboratory assessments were performed at 1, 3, and 6 months and every 6 months thereafter with measurement of blood samples in the same central laboratory. Measurements included LDL-C assessment. If LDL-C was below 1.0 mmol/L (40 mg/dL), the investigator was informed of the result and could lower the dosage of study drug from 80 to 40 mg per day. A second randomly chosen investigator

Table 1. Baseline Characteristics by First Postrandomization Percent Change in LDL-C

	≥50% Decrease	<50% Decrease	≥0% Increase
Baseline characteristic	(n=1645)	(n=1776)	(n=1310)
Age, years	63±11	63±11	63±11
Female	642 (39.0)	723 (40.7)	543 (41.4)
Current smoker	298 (18.1)	349 (19.7)	261 (19.9)
History of diabetes	262 (15.9)	306 (17.2)	226 (17.3)
Systolic blood pressure, mm Hg	142±20	141±19	141±20
Entry event			
Stroke	1154 (70.2)	1216 (68.5)	898 (68.6)
Ischemic	1114 (67.7)	1168 (65.8)	872 (66.6)
Hemorrhagic	27 (1.6)	43 (2.4)	23 (1.8)
Other/not determined	13 (0.8)	5 (0.3)	3 (0.2)
TIA	490 (29.8)	559 (31.5)	411 (31.4)
Unknown	1 (0.1)	1 (0.1)	1 (0.1)
Time since entry event, days	90±48	83 ±47	83±47
Randomized to atorvastatin	1643 (99.9)	614 (34.6)	108 (8.2)
Exposed to study drug ≥6 months	1540 (93.6)	1598 (90.0)	1139 (86.9)
No open-label statin within 6 months of randomization	1635 (99.4)	1736 (97.7)	1276 (97.4)
Concomitant antihypertensive	893 (54.3)	949 (53.4)	682 (52.1)
Concomitant antiplatelet	1462 (88.9)	1574 (88.6)	1142 (87.2)
LDL-C, mmol/L	3.5±0.6	3.5±0.6	3.3±0.6

Values in table are n (%) or mean±SD.

Note: If a subject had no postrandomization LDL-C data, they were placed in the no change or increase group.

for a placebo patient was similarly notified, and LDL-C levels were retested for both patients to maintain the blind. Drug safety was assessed by an evaluation of the type, frequency, severity, and duration of any reported adverse event and by vital signs, physical examinations, and laboratory tests.

Statistical Analysis

For this post hoc analysis, patients were classified at each laboratory assessment into one of the 3 categories according to magnitude of percent change in LDL-C from their prerandomization baseline: no change or increase, <50% decrease, or ≥50% decrease (Figure 1).

A given patient with ≥50% decease in LDL-C from baseline (and related accumulated patient-years of follow-up) remained in the same group until another measurement showed a <50% reduction in LDL-C or no LDL-C reduction or an increase. In that case, the next 6 months (ie, the period until the next measurement) contributed to the analysis of the "<50% decrease" or "no change or increase" group as appropriate (Figure 1). The patient then remained in this group until another measurement showed an LDL-C falling in one of the 2 other categories. For each patient, the patient-years of follow-up were divided into each of the 3 groups proportional to the time actually spent in a given category of LDL-C reduction.

The intention was to attribute to each group the accumulated patient-years of follow-up actually spent by the 4731 patients in each LDL-C category. It was hypothesized that this classification strategy would identify the patients who were adherent to atorvastatin treatment (ie, those with a ≥50 reduction in LDL-C) during the trial and therefore provide an index of an "on-treatment" effect. We also conducted an additional analysis comparing an achieved LDL-C <70 mg/dL versus >70 mg/dL or no change or increase (a <70 mg/dL target has been advocated for patients at high risk with coronary heart disease by NCEP III experts[9]). Thus, the target of <70 mg/dL in patients with stroke is exploratory.

The relationship between LDL-C category and outcome was analyzed as a time-varying covariate in a Cox regression model with adjustment for gender and age at baseline (model 1). The continuous percent change in LDL-C was also evaluated as a time-varying covariate in a Cox regression model with adjustment for gender and age at baseline. To further assess possible confounding by other important risk factors, additional models included the model 1 variables plus time-varying systolic blood pressure (measured at each study visit), baseline smoking, history of diabetes (model 2), all previous variables plus compliance (assessed at each study visit by the question, "In your opinion, has the patient been compliant on the study medication since the last visit?"), and antihypertensive and antiplatelet agents used at randomization (model 3). Wald confidence intervals and 2-sided probability values for the hazard ratios are presented throughout the results. The assumption of proportional hazards could not be tested because all of the models had at least one time-varying covariate.

Role of the Funding Source

Employees of Pfizer (the study sponsor) contributed to the design and conduct of the study; the collection, management, analysis, and interpretation of the data; and review of the manuscript.

Results

Table 1 gives the baseline characteristics by first postrandomization percent change in LDL-C. There were 55 045 LDL-C measurements obtained during the trial (mean of 11.6 measurements per patient); 32.7% of the measurements corresponded to no change or an increase in LDL-C, 39.4% to a

Table 2. Distribution of LDL-C Percent Change and Nominal Value Categories

	Atorvastatin No. of Measurements (patient-years)	Placebo No. of Measurements (patient-years)	Total No. of Measurements (patient-years)
Percent change			
No change or increase	4142 (1275)	13 852 (5297)	17 994 (6572)
<50% decrease	8735 (3953)	12 959 (5585)	21 694 (9538)
≥50% decrease	14 772 (5843)	585 (268)	15 357 (6111)
Nominal value			
≥2.6 mmol/L	6000 (2213)	23 486 (9457)	29 486 (11,670)
≥1.8 to <2.6 mmol/L	5860 (2560)	3305 (1421)	9165 (3981)
<1.8 mmol/L	15 789 (6297)	605 (272)	16 394 (6569)

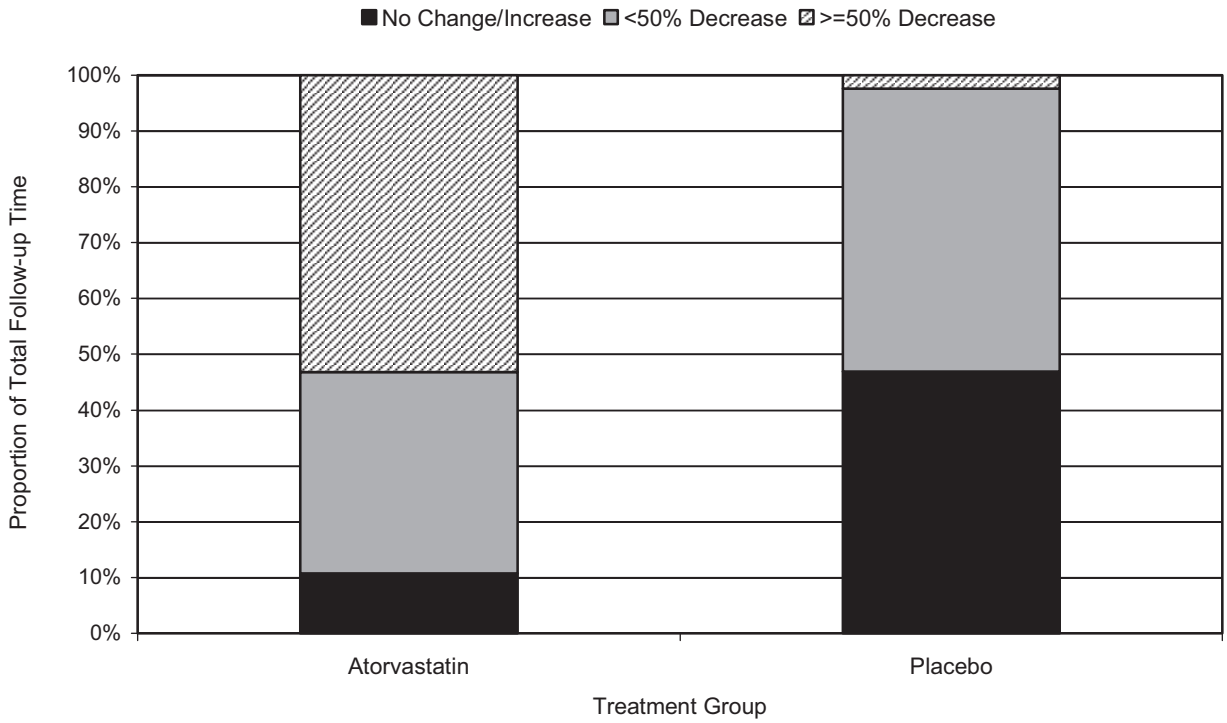

Figure 2. Proportion of total follow-up time in each percent change in LDL-C category.

<50% decrease, and 27.9% to a ≥50% decrease (Table 2). Almost all (96%) of the time points corresponding to a ≥50% decrease in LDL-C were from patients randomized to atorvastatin treatment with 88% of patients randomized to atorvastatin having at least one measurement corresponding to a ≥50% reduction. Figure 2 gives the proportion of total follow-up time spent by patients randomized to atorvastatin or placebo in each of the 3 groups.

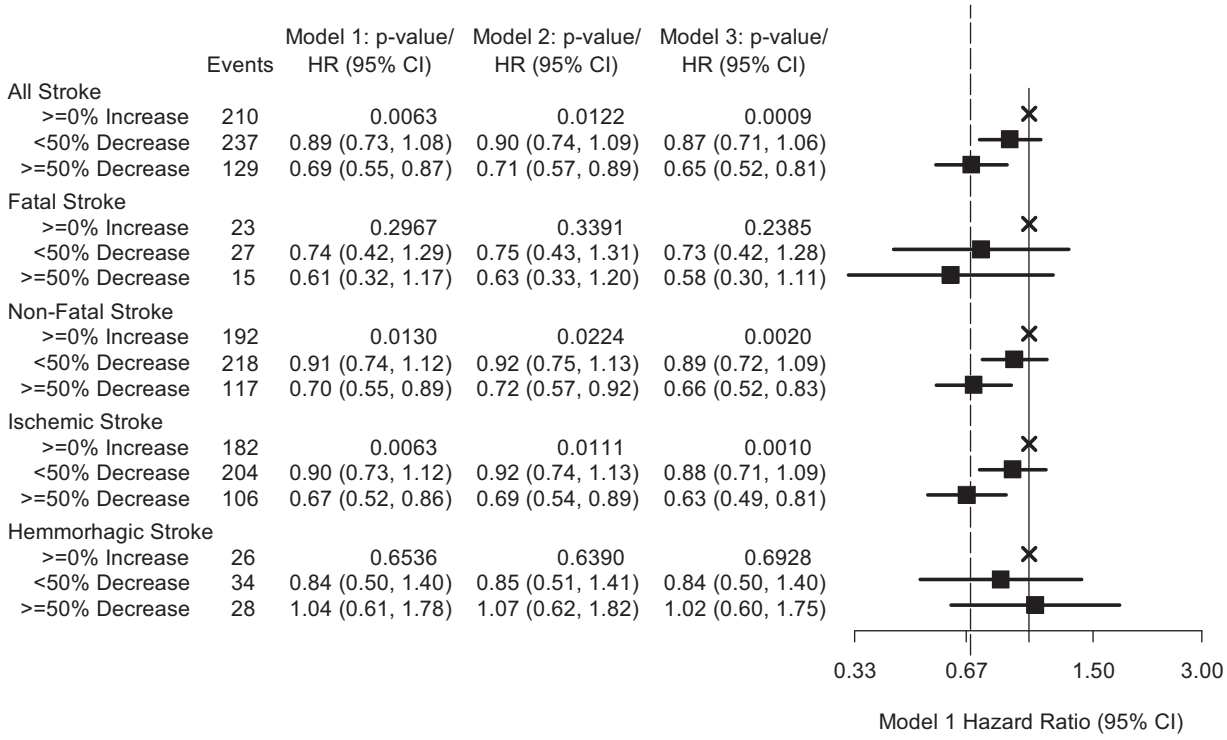

Figure 3. Relationship between change in LDL-C and risk of stroke. Note: Percent change effects from time-varying Cox regression models with adjustment for fixed gender and baseline age with reference group=no change or increase. Model 1: adjustment for gender, baseline age; model 2: adjustment for gender, baseline age, history of diabetes, baseline smoking, time-varying systolic blood pressure; model 3: adjustment for gender, baseline age, history of diabetes, baseline smoking, time-varying systolic blood pressure, time-varying compliance, concomitant antihypertensive use, concomitant antiplatelet use. *P* value is for 3-category percent change comparison.

	Events	Model 1: p-value/ HR (95% CI)	Model 2: p-value/ HR (95% CI)	Model 3: p-value/ HR (95% CI)
Major Coronary				
>=0% Increase	57	0.0017	0.0019	0.0029
<50% Decrease	106	1.25 (0.90, 1.74)	1.27 (0.92, 1.77)	1.29 (0.93, 1.80)
>=50% Decrease	36	0.63 (0.41, 0.96)	0.64 (0.42, 0.98)	0.67 (0.44, 1.03)
Any CHD				
>=0% Increase	101	0.0006	0.0007	0.0011
<50% Decrease	161	1.08 (0.84, 1.39)	1.09 (0.85, 1.40)	1.09 (0.85, 1.40)
>=50% Decrease	63	0.61 (0.45, 0.84)	0.62 (0.45, 0.85)	0.63 (0.46, 0.87)
Major Cardiovascular				
>=0% Increase	256	0.0003	0.0006	<0.0001
<50% Decrease	324	0.97 (0.82, 1.15)	0.99 (0.83, 1.17)	0.96 (0.81, 1.14)
>=50% Decrease	159	0.68 (0.56, 0.84)	0.70 (0.57, 0.86)	0.65 (0.53, 0.80)
Any Revascularization				
>=0% Increase	90	0.0003	0.0003	0.0003
<50% Decrease	124	1.04 (0.78, 1.38)	1.05 (0.79, 1.40)	1.05 (0.79, 1.40)
>=50% Decrease	43	0.52 (0.36, 0.75)	0.53 (0.36, 0.77)	0.52 (0.36, 0.76)
Any Cardiovascular				
>=0% Increase	437	<0.0001	<0.0001	<0.0001
<50% Decrease	521	0.95 (0.83, 1.09)	0.96 (0.84, 1.10)	0.95 (0.83, 1.08)
>=50% Decrease	258	0.66 (0.56, 0.77)	0.67 (0.57, 0.78)	0.64 (0.54, 0.75)
All Cause Death				
>=0% Increase	117	0.1552	0.1723	0.2751
<50% Decrease	204	1.08 (0.86, 1.36)	1.08 (0.86, 1.37)	1.10 (0.87, 1.38)
>=50% Decrease	105	0.86 (0.66, 1.12)	0.87 (0.66, 1.13)	0.90 (0.69, 1.19)
CV Death				
>=0% Increase	49	0.5015	0.5193	0.5065
<50% Decrease	82	1.06 (0.74, 1.52)	1.07 (0.75, 1.53)	1.06 (0.75, 1.53)
>=50% Decrease	44	0.85 (0.57, 1.28)	0.87 (0.57, 1.30)	0.86 (0.57, 1.30)
Cancer Death				
>=0% Increase	31	0.6216	0.6554	0.7424
<50% Decrease	52	1.05 (0.67, 1.65)	1.05 (0.67, 1.65)	1.06 (0.67, 1.67)
>=50% Decrease	27	0.84 (0.50, 1.41)	0.85 (0.50, 1.43)	0.88 (0.52, 1.50)

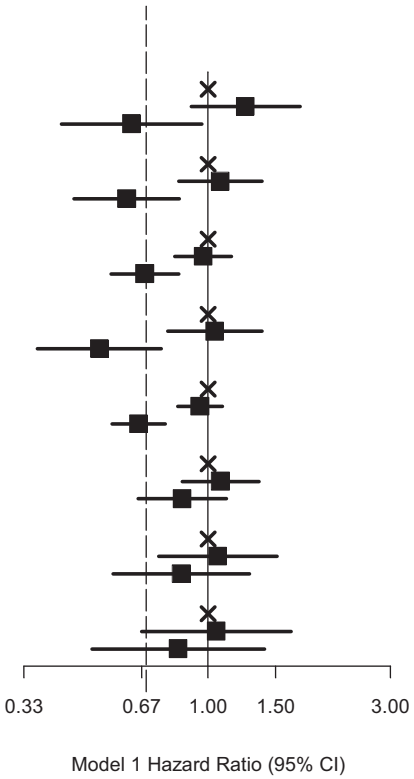

Figure 4. Relationship between change in LDL-C and risk of cardiovascular events and death: Note: Percent change effects from time-varying Cox regression models with adjustment for fixed gender and baseline age with reference group=no change or increase. Model 1: adjustment for gender, baseline age; model 2: adjustment for gender, baseline age, history of diabetes, baseline smoking, time-varying systolic blood pressure; model 3: adjustment for gender, baseline age, history of diabetes, baseline smoking, time-varying systolic blood pressure, time-varying compliance, concomitant antihypertensive use, concomitant antiplatelet use. *P* value is for 3-category percent change comparison.

Time-Varying Percent Low-Density Lipoprotein Cholesterol Reduction

Stroke Risk Reduction

Compared with no change or an increase, patients with ≥50% reductions in LDL-C had a 31% reduction (hazard ratio=0.69; 95% CI, 0.55 to 0.87; $P=0.0016$) in the combined risk of nonfatal and fatal stroke (the SPARCL primary end point), including a 30% reduction in nonfatal stroke (hazard ratio=0.7; 95% CI, 0.55 to 0.89; $P=0.004$; Figure 3). Whereas ischemic strokes were reduced by 33% ($P=0.0018$), there was no increase in hemorrhagic stroke (hazard ratio=1.04; 95% CI, 0.61 to 1.78; $P=0.8864$), although the confidence intervals around the point estimate were wide. Further adjustment for age, gender time-varying systolic blood pressure (taken at each study visit), cigarette smoking, diabetes, compliance to study drug, and antihypertensive and antiplatelet agents use did not modify these findings (Figure 3). The planned analysis, including LDL-C reduction as a continuous variable, could not be performed because the percent change values tended to be clustered around a 50% decrease for the subjects randomized to atorvastatin and no change for the subjects randomized to placebo.

Coronary Heart Disease Event Reduction

After adjustment for age and gender, the risk of a major coronary event was reduced by 37% ($P=0.032$), any CHD event by 39% ($P=0.025$), and any revascularization by 48% ($P=0.0006$) in patients with LDL-C reduction ≥50% (Figure 4). Further adjustments did not modify these findings (Figure 4).

Time-Varying Nominal Value in Low-Density Lipoprotein Cholesterol Results

Table 3 shows effects of achieved LDL-C based on NCEP Adult Treatment Panel III LDL-C goals (<1.8 mmol/L [<70 mg/dL], 1.8 to <2.6 mmol/L [70 to <100 mg/dL], ≥2.6 mmol/L [≥100 mg/dL]) on stroke, coronary events, and mortality. Compared with LDL-C ≥2.6 mmol/L (≥100 mg/dL), achieving an LDL-C level <1.8 mmol/L (<70 mg/dL) was associated with a 28% reduction in the risk of stroke ($P=0.0018$) (Table 3) without an increase in the risk of hemorrhagic stroke ($P=0.3358$). A confirmatory analysis based on a 1.3-mmol/L (50 mg/dL) reduction in LDL-C was consistent with these findings.

All-Cause Death, Cancer, Liver Enzyme, and Muscle End Points

All-cause death and death from cancer were similar in the 3 groups (Figure 4). Persistent elevations in liver enzymes occurred at a rate of 5.7 per 1000 patient-years in the group with an LDL-C reduction ≥50% as compared with 2.0 per 1000 patient-years in the group with a <50% decrease and 1.2 per 1000 patient-years in the group with no change or an increase in LDL-C. The risks of myalgia (0.92 [95% CI, 0.65

Table 3. Time-Varying Nominal Value in LDL-C Results for First Event in Composite

	Events	Hazard Ratio (95% CI)	*P* Value
Stroke			
≥2.6 mmol/L	336	1.00	NA
1.8 to <2.6 mmol/L	104	1.01 (0.81 to 1.27)	0.9076
<1.8 mmol/L	136	0.72 (0.59 to 0.89)	0.0018
Fatal stroke			
≥2.6 mmol/L	40	1.00	NA
1.8 to <2.6 mmol/L	11	1.08 (0.52 to 2.22)	0.8456
<1.8 mmol/L	14	0.63 (0.31 to 1.26)	0.1867
Nonfatal stroke			
≥2.6 mmol/L	308	1.00	NA
1.8 to <2.6 mmol/L	94	1.01 (0.80 to 1.27)	0.9515
<1.8 mmol/L	125	0.74 (0.60 to 0.91)	0.0042
Ischemic stroke			
≥2.6 mmol/L	294	1.00	NA
1.8 to <2.6 mmol/L	88	1.00 (0.79 to 1.27)	0.9941
<1.8 mmol/L	110	0.66 (0.53 to 0.83)	0.0003
Hemorrhagic stroke			
≥2.6 mmol/L	41	1.00	NA
1.8 to <2.6 mmol/L	13	1.06 (0.56 to 2.01)	0.8528
<1.8 mmol/L	34	1.28 (0.78 to 2.09)	0.3358
Major coronary event			
≥2.6 mmol/L	114	1.00	NA
1.8 to <2.6 mmol/L	42	1.11 (0.78 to 1.59)	0.5649
<1.8 mmol/L	43	0.64 (0.45 to 0.91)	0.0120
Any CHD event			
≥2.6 mmol/L	195	1.00	NA
1.8 to <2.6 mmol/L	62	0.98 (0.73 to 1.30)	0.8631
<1.8 mmol/L	68	0.58 (0.44 to 0.77)	0.0001
Major cardiovascular event			
≥2.6 mmol/L	430	1.00	NA
1.8 to <2.6 mmol/L	135	1.02 (0.84 to 1.24)	0.8279
<1.8 mmol/L	174	0.71 (0.60 to 0.85)	0.0002
Any revascularization			
≥2.6 mmol/L	160	1.00	NA
1.8 to <2.6 mmol/L	50	0.99 (0.72 to 1.37)	0.9567
<1.8 mmol/L	47	0.51 (0.37 to 0.71)	<0.0001
Any cardiovascular event			
≥2.6 mmol/L	673	1.00	NA
1.8 to <2.6 mmol/L	272	0.91 (0.78 to 1.07)	0.2494
<1.8 mmol/L	271	0.69 (0.60 to 0.79)	<0.0001
All-cause death			
≥2.6 mmol/L	226	1.00	NA
1.8 to <2.6 mmol/L	79	1.01 (0.78 to 1.30)	0.9554
<1.8 mmol/L	121	0.92 (0.74 to 1.15)	0.4531
Cardiovascular death			
≥2.6 mmol/L	96	1.00	NA
1.8 to <2.6 mmol/L	32	0.99 (0.66 to 1.48)	0.9659
<1.8 mmol/L	47	0.86 (0.61 to 1.22)	0.3988
Cancer death			
≥2.6 mmol/L	63	1.00	NA
1.8 to <2.6 mmol/L	19	0.92 (0.55 to 1.52)	0.7296
<1.8 mmol/L	28	0.75 (0.48 to 1.17)	0.2061

Note: Nominal value effects from Cox regression models with adjustment for gender and baseline age with reference group ≥2.6 mmol/L.

NA indicates not applicable.

to 1.30] in the group ≥50% decrease in LDL-C and 1.03 [95% CI, 0.75 to 1.40] in the group <50% decrease in LDL-C) and rhabdomyolysis (one patient in the group ≥50% decrease in LDL-C, one in the group <50% decrease in LDL-C, and 3 in the group with no change or an increase in LDL-C) were similar in the 3 groups.

Discussion

We performed an exploratory analysis of the occurrence of vascular events based on achieved levels of LDL-C reduction, hypothesizing that those having ≥50% reduction would have the greatest reductions in stroke and other vascular events. In this analysis, periods of follow-up between blinded evaluations of percent change from baseline in LDL-C level in all 4731 patients (and the end points that occurred during these periods) were attributed to one of 3 groups (ie, no change or an increase, <50% decrease, or ≥50% decrease in LDL-C from baseline) based on the 55 045 blinded measurements of LDL-C during the trial (Figure 1). The 31% reduction in the risk of fatal and nonfatal stroke in the group with ≥50% reduction in LDL-C was approximately twice the 16% observed in the prespecified intention-to-treat analysis.[7] Together with the meta-analyses referred to earlier,[3,4] this observation supports using LDL-C as a surrogate therapeutic target to guide the use of statins to reduce the risk of cerebrovascular events. It should be recognized, however, that statin effects other than LDL-C-lowering such as their antiinflammatory properties might explain part of the benefit.[5,6,10]

We found that reaching a ≥50% decrease in LDL-C is a reasonable index of adherence and responsiveness to treatment because 96% of these measurements were in patients randomized to 80 mg atorvastatin per day. Thus, the 31% reduction in stroke in those achieving a ≥50% decrease in LDL-C may also provide an estimate of the potential treatment effect of 80 mg atorvastatin per day among adherent and responsive patients. The planned analysis, including LDL-C reduction as a continuous variable, could not be performed because the percent change values tended to be clustered around a 50% decrease for the subjects randomized to atorvastatin and no change for the subjects randomized to placebo. This point will be best evaluated in a future large

meta-analysis. There was, however, a trend for a "dose–response" in the groups with a less than 50% and more than 50% reduction in LDL-C and the reduction of stroke as shown in Figure 3 (top panel), favoring the hypothesis that a continuous relationship exists between LDL-C reduction and stroke risk reduction.

Accepting the limitations of post hoc analysis, the point estimates for hemorrhagic stroke was 1.04 in the group with ≥50% LDL-C reduction and 1.28 in the group who achieved a <1.8 mmol/L LDL-C levels with a wide confidence interval resulting in a statistically nonsignificant increase in hemorrhagic stroke. The absence of an increase in risk associated with greater reductions in LDL-C is consistent with meta-analyses of more than 90 000 individuals who were included in other statin trials.[3,4] Nevertheless, the power to detect a difference in the risk of brain hemorrhage might have been diminished by our dividing patients among 3 groups. Although we found no LDL-C threshold below which the risk of brain hemorrhage was increased, because of the observed wide confidence intervals, it remains possible that very low LDL-C levels could be harmful in patients with prior stroke because of the lack of statistical power in this analysis. Further analyses are required to explore other potential reasons for the increase in the risk of hemorrhagic stroke in patients treated with atorvastatin in SPARCL.[7]

Intention-to-treat analysis is the only appropriate way to gauge the efficacy of a treatment approach. Consequently, the present analysis should be considered cautiously and can only be viewed as exploratory. One of the major problems inherent to this type of analysis is that it disregards randomization and instead uses a surrogate marker (achieved LDL-C-lowering). This type of analysis can be useful for assessing the theory that guided the study's design (ie, that intense lipid-lowering with atorvastatin would lead to a reduction in stroke in patients with stroke or TIA).

A final observation is that profound reductions in LDL-C were associated with an increase in the number of patients with an elevation of liver enzymes that was in the range of what has been observed in other statin trials. There was no increase in myalgias, myopathy, or rhabdomyolysis despite the lack of a run-in period in a population that was largely statin-naïve, indicating that high-dose atorvastatin was well tolerated.

In conclusion, this exploratory analysis is consistent with the effects of treatment with 80 mg atorvastatin per day in patients with recent stroke or TIA found in the SPARCL intention-to-treat analysis and suggests the greatest benefit is in those with LDL-C lowered more than 50% from baseline.

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Disclosures

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