ORIGINAL ARTICLE

A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke

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ABSTRACT

BACKGROUND

The use of intensive lipid-lowering therapy by means of statin medications is recommended after transient ischemic attack (TIA) and ischemic stroke of atherosclerotic origin. The target level for low-density lipoprotein (LDL) cholesterol to reduce cardiovascular events after stroke has not been well studied.

METHODS

In this parallel-group trial conducted in France and South Korea, we randomly assigned patients with ischemic stroke in the previous 3 months or a TIA within the previous 15 days to a target LDL cholesterol level of less than 70 mg per deciliter (1.8 mmol per liter) (lower-target group) or to a target range of 90 mg to 110 mg per deciliter (2.3 to 2.8 mmol per liter) (higher-target group). All the patients had evidence of cerebrovascular or coronary-artery atherosclerosis and received a statin, ezetimibe, or both. The composite primary end point of major cardiovascular events included ischemic stroke, myocardial infarction, new symptoms leading to urgent coronary or carotid revascularization, or death from cardiovascular causes.

RESULTS

A total of 2860 patients were enrolled and followed for a median of 3.5 years; 1430 were assigned to each LDL cholesterol target group. The mean LDL cholesterol level at baseline was 135 mg per deciliter (3.5 mmol per liter), and the mean achieved LDL cholesterol level was 65 mg per deciliter (1.7 mmol per liter) in the lower-target group and 96 mg per deciliter (2.5 mmol per liter) in the higher-target group. The trial was stopped for administrative reasons after 277 of an anticipated 385 end-point events had occurred. The composite primary end point occurred in 121 patients (8.5%) in the lower-target group and in 156 (10.9%) in the higher-target group (adjusted hazard ratio, 0.78; 95% confidence interval, 0.61 to 0.98; P=0.04). The incidence of intracranial hemorrhage and newly diagnosed diabetes did not differ significantly between the two groups.

CONCLUSIONS

After an ischemic stroke or TIA with evidence of atherosclerosis, patients who had a target LDL cholesterol level of less than 70 mg per deciliter had a lower risk of subsequent cardiovascular events than those who had a target range of 90 mg to 110 mg per deciliter. (Funded by the French Ministry of Health and others; Treat Stroke to Target ClinicalTrials.gov number, NCT01252875.)

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Intensive therapy to lower serum lipid levels with the use of statins is recommended after transient ischemic attack (TIA) or ischemic stroke of atherosclerotic origin.[1] These recommendations are based on the results of the Stroke Prevention by Aggressive Reduction in Cholesterol Level (SPARCL) trial that showed a 16% lower incidence of recurrent stroke with atorvastatin (at a dose of 80 mg per day) than with placebo in patients with stroke and no known coronary heart disease.[2] In the group with carotid stenosis, there was a 33% lower incidence of stroke in the atorvastatin group than in the placebo group.[3] A subsequent analysis of the data from that trial showed that patients who reached a level of low-density lipoprotein (LDL) cholesterol of less than 70 mg per deciliter (1.8 mmol per liter) had a 28% lower relative risk of stroke than those who reached a level of 100 mg per deciliter (2.6 mmol per liter).[4] A meta-regression analysis, including results from the SPARCL trial, showed that the risk of stroke was 20% lower for every reduction of 39 mg per deciliter (1.0 mmol per liter) in the LDL cholesterol level, without any threshold effect.[5]

The current guidelines of the American Heart Association and the American Stroke Association (AHA–ASA) recommend "intense" statin therapy after an ischemic stroke of atherosclerotic origin but do not stipulate a target level of LDL cholesterol because there are limited data on outcomes with different targets for LDL cholesterol.[1] Although physicians typically prescribe high-intensity statin therapy after stroke as recommended, most patients are later prescribed a low or moderate statin dose and have only a moderate reduction in the level of LDL cholesterol. For example, in a multicenter, multinational registry (TIAregistry.org) that enrolled patients with TIA or minor ischemic stroke who were followed in TIA clinics during a 5-year period, 70% of the patients had been prescribed a statin at the time of hospital discharge, and 63% were still taking a statin at 5 years. Among these patients, the mean (±SD) LDL cholesterol level went from 119±41 mg per deciliter (3.1±1.1 mmol per liter) at baseline to 92±32 mg per deciliter (2.4±0.8 mmol per liter) at 5 years.[6]

In the Treat Stroke to Target trial, we tested the hypothesis that a target level of LDL cholesterol of less than 70 mg per deciliter would be superior to a target range of 90 mg to 110 mg per deciliter (2.3 to 2.8 mmol per liter) in reducing overall cardiovascular events after an ischemic stroke or a TIA in patients with evidence of atherosclerosis.

Methods

Trial Design and Oversight

This randomized, parallel-group, event-driven trial was conducted at 61 sites in France and 16 sites in South Korea. The methods of patient recruitment, evaluation, and statistical planning have been described previously.[7] The protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at each trial site. All the patients provided written informed consent.

The trial was funded by the French Ministry of Health and the SOS–Attaque Cérébrale Association, with oversight by the Assistance Publique–Hôpitaux de Paris. The first author and independent academic statisticians at Bichat Hospital, Centre Hospitalier Universitaire de Lille, and Fernand Widal Hospital had full access to the trial databases, analyzed the data, prepared the first draft of the manuscript, and made the decision to submit the manuscript for publication. There were unrestricted grants from Pfizer, AstraZeneca, and Merck for the support of the trial, but there was no industry involvement in the conduct of the trial, in the gathering or analysis of the data, or in the writing of the manuscript. All the authors vouch for the completeness and accuracy of the data and reporting of adverse events and for the fidelity of the trial to the protocol.

For administrative reasons, the trial was registered 9 months after the first patient had been enrolled and after 330 patients had been treated, as described in the Supplementary Appendix, available at NEJM.org. We did not appoint a data and safety monitoring board, since there was no expectation of adverse events related to the LDL target strategies that were evaluated in the trial.

Patients

Patients were eligible for enrollment if they were 18 years of age or older (>20 years of age in South Korea); had an ischemic stroke within the past 3 months, which was followed by a score of 0 to 3 on the modified Rankin scale (which ranges from 0 to 6, with 0 indicating no symptoms, 1 no disability, 2 to 3 needing some help

with daily activities, 4 to 5 dependent or bedridden, and 6 death), once investigators determined that the neurologic deficit was stable; or had a TIA within the previous 15 days that included a motor deficit in at least one arm or leg or a speech disturbance lasting more than 10 minutes. An ischemic stroke was defined as symptoms with a documented ischemic lesion on computed tomography (CT) or magnetic resonance imaging (MRI) in the cerebral regions corresponding to the symptoms, even if the symptoms were transient.[8]

As recommended by the AHA–ASA guidelines,[9] all the patients were screened with the use of noninvasive imaging of the cervical vessels (carotid duplex, CT angiography, and MR angiography) as part of the routine evaluation of patients with suspected TIA or ischemic stroke. In addition, CT angiography or MR angiography of the intracranial vasculature was performed to rule out proximal intracranial stenosis or occlusion, as well as transesophageal echocardiography or CT angiography of the aorta to detect aortic atheroma. All imaging was performed when the responsible clinician determined that knowledge of intracranial steno-occlusive disease or severe aortic atheroma would alter treatment.[9] The choice of cardiovascular tests and the diagnosis of atherosclerotic stenosis were made and judged by the investigators and were not standardized or adjudicated.

To be enrolled in the trial, patients had to have atherosclerotic disease that included stenosis of an extracranial or intracranial cerebral artery, ipsilateral or contralateral to the region of imputed brain ischemia; atherosclerotic plaques of the aortic arch measuring at least 4 mm in thickness; or a known history of coronary artery disease. Patients also had to have an indication for statin treatment on the basis of the recommendations of the AHA–ASA,[1] French Agence Nationale de Sécurité du Médicament,[10] or the Korean Stroke Society.[11] According to these recommendations, patients with ischemic stroke that was presumed to be of atherosclerotic origin should receive statin therapy.[1] The French and Korean guidelines recommend that patients should receive treatment with a target LDL cholesterol level of 100 mg per deciliter or lower. Patients were required to have a directly measured LDL cholesterol level of at least 70 mg per deciliter if they were taking a statin before randomization or at least 100 mg per deciliter if they had not previously received a statin.

RANDOMIZATION AND FOLLOW-UP

Eligible patients were randomly assigned in a 1:1 ratio to a target LDL cholesterol level of less than 70 mg per deciliter (lower-target group) or a target range of 90 mg to 110 mg per deciliter (higher-target group). Investigators, who were allowed to prescribe any type and any dose of statin to reach these targets, were asked to determine the LDL cholesterol level 3 weeks after randomization in order to adjust the statin dose or to add other lipid-lowering agents, including ezetimibe, to reach the assigned LDL cholesterol target.

Patients were followed every 6 months after randomization with measurement of LDL cholesterol. In addition to face-to-face visits with the investigators, a central core of clinical research assistants based at Bichat Hospital contacted patients or their relatives every 6 months to obtain the results of LDL cholesterol measurements at the preceding visit and to collect potential trial end points using a structured questionnaire. If the LDL cholesterol level was above or below the assigned target range, the investigator was contacted in order to adjust the lipid-lowering treatment to the target range. If a potential trial end point was observed, the local investigator was contacted in order to confirm the event clinically and activate the adjudication process. Data regarding levels of triglycerides, high-density lipoprotein cholesterol, blood pressure in the sitting position, fasting glucose, and glycated hemoglobin were collected at the 6-month visits. We recommended that the investigators provide treatment for all patients to maintain blood pressure at a target level of 130/80 mm Hg in those with diabetes and to less than 140/90 mm Hg in all others, to maintain a glycated hemoglobin level of less than 7% in those with diabetes, and to encourage smoking cessation.

END POINTS

The composite primary end point of major cardiovascular events included adjudicated nonfatal cerebral infarction or stroke of undetermined origin, nonfatal myocardial infarction, hospitalization for unstable angina followed by urgent coronary-artery revascularization, TIA treated with urgent carotid revascularization, or cardiovascu-

lar death, including unexplained sudden death. The secondary end points were myocardial infarction or urgent coronary revascularization after the onset of new symptoms; cerebral infarction or urgent revascularization of a carotid or cerebral artery after TIA; cerebral infarction or TIA; any revascularization of a coronary, cerebral, or peripheral artery (either urgent or elective); cardiovascular death; death from any cause; cerebral infarction or intracranial hemorrhage; intracranial hemorrhage; newly diagnosed diabetes; and a composite of the primary end point or intracranial hemorrhage. (The last of these end points was prespecified in the protocol but was inadvertently left out of the statistical analysis plan.) All incident events that were components of these end points were adjudicated by a committee in which the members were unaware of trial-group assignments or LDL cholesterol levels reached.

STATISTICAL ANALYSIS

We estimated that the enrollment of 3786 patients would result in 385 primary end-point events and provide a power of approximately 80% to detect a 25% lower relative risk of major cardiovascular events in the lower-target group than in the higher-target group, as detected during 3 years of follow-up and with an attrition rate of 20%. All the analyses were performed according to the intention-to-treat principle.

We used the Kaplan–Meier method to estimate the cumulative incidence of the primary end point by censoring data for patients who had withdrawn from the trial or been lost to follow-up; data for patients who had died from causes other than cardiovascular disease were censored at the time of death. We used a Cox proportional-hazards regression model to perform the primary efficacy analysis, which included the following covariates (as was done in the SPARCL trial[2]): age, sex, index event (stroke or TIA), and the time since the index event. Missing values for covariates that were included in the Cox model were handled with the use of a multiple-imputation technique (as described in the protocol).

We derived the adjusted hazard ratio for the lower-target group relative to the higher-target group and its 95% confidence interval from this model as the relative measure of effect size. The unadjusted hazard ratio and results of log-rank testing are also reported. The proportional-hazards assumption was checked by examining the plot of scaled Schoenfeld residuals against time and by adding time-dependent covariates to the Cox model. We determined the absolute between-group difference in risk by calculating the rate of events per 100 person-years.

Sensitivity analyses were performed by treating noncardiovascular death as a competing risk with the use of the Fine and Gray model and with inverse probability-of-censoring–weighted log-rank tests.[12] These models were applied to censored data in Cox analyses with and without adjustment for covariates to reduce potential bias from censored data. We performed regression model analyses of prespecified subgroups, as detailed in the protocol.

We used log-rank tests to analyze the secondary end points according to a hierarchical procedure to control for multiple comparisons. In this procedure, we tested each end point for significance in a prespecified order and analyzed the next end point in the hierarchy only if significance was established for the previous one. All statistical testing was performed at a two-tailed alpha level of 0.05. The data were analyzed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

PATIENTS

From March 2010 through December 2018, a total of 2873 patients underwent randomization at the 77 trial sites. Of these patients, 2860 met the inclusion criteria and were included in the primary analysis; 13 patients were excluded because they did not provide written informed consent for participation (Fig. S1 in the Supplementary Appendix).

As a result of slow enrollment, the steering committee extended the enrollment period to allow recruitment until December 31, 2018. All the patients were followed until the end of the trial, with 1-year follow-up planned for the last patient to be enrolled (until December 31, 2019). Patients were followed for incident cardiovascular events until May 26, 2019, when the trial was stopped by the sponsor due to lack of funding, and all the patients were followed for adverse events through the last visit. This report includes all the cardiovascular events that occurred up to May 26, 2019.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Lower-Target Group (N=1430)	Higher-Target Group (N=1430)
Age — yr	66.4±11.3	67.0±11.1
Male sex — no. (%)	971 (67.9)	963 (67.3)
Median body-mass index (IQR)†	25.6 (23.3–28.6)	25.5 (23.2–28.4)
Index event — no./total no. (%)		
Ischemic stroke	1220/1425 (85.6)	1229/1429 (86.0)
Transient ischemic attack	205/1425 (14.4)	200/1429 (14.0)
Median time since index event (IQR) — days	6.0 (4.0–10.0)	6.0 (4.0–11.0)
Medical history — no./total no. (%)		
Hypertension	909/1422 (63.9)	959/1424 (67.3)
Diabetes	328/1420 (23.1)	315/1421 (22.2)
Dyslipidemia	878/1418 (61.9)	862/1420 (60.7)
Smoking history		
Former smoker	349/1420 (24.6)	306/1421 (21.5)
Current smoker	446/1420 (31.4)	413/1421 (29.1)
Stroke or transient ischemic attack	169/1419 (11.9)	153/1420 (10.8)
Coronary artery disease	263/1418 (18.5)	227/1419 (16.0)
No previous use of statin	800/1418 (56.4)	769/1420 (54.2)
Lipids — mg/dl		
Low-density lipoprotein cholesterol	135±37	136±38
High-density lipoprotein cholesterol	50±18	50±18
Total cholesterol	209±47	210±51
Median triglycerides (IQR)	121.0 (89.0–167.0)	123.0 (92.0–165.0)
Blood pressure — mm Hg		
Systolic	140±23	141±21
Diastolic	79±13	80±13
Median glucose (IQR) — mmol/liter	5.6 (5.0–6.6)	5.6 (5.0–6.6)
Glycated hemoglobin — %	6.4±2.7	6.2±1.3

* Plus–minus values are means ±SD. Patients in the lower-target group had a target level of low-density lipoprotein cholesterol of less than 70 mg per deciliter, and those in the higher-target group had a target range of 90 mg to 110 mg per deciliter. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to milligrams per deciliter, divide by 0.05551. IQR denotes interquartile range.

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

The characteristics of the patients at baseline were similar in the two groups (Table 1). The mean LDL cholesterol level was 135 mg per deciliter (3.5 mmol per liter) in each group. The median follow-up was 3.5 years (interquartile range, 2.0 to 6.7) in the lower-target group and 3.6 years (interquartile range, 2.0 to 6.7) in the higher-target group. The median follow-up according to country trial site was 5.3 years (interquartile range, 2.9 to 7.2) in France and 2.0 years (interquartile range, 0.5 to 2.9) in South Korea. (The characteristics of French and Korean patients at baseline are provided in Table S1.)

During the trial, 65.9% of the patients in the lower-target group and 94.0% of those in the higher-target group received only a statin; 33.8% and 5.8% of the patients, respectively, received ezetimibe plus a statin (Table S2). At a median of 2.7 years in the two groups, discontinuation rates were 30.3% and 28.5%, respectively.

EFFECTS ON LIPID LEVELS

At a median follow-up of 3.5 years, the mean LDL cholesterol level was 65 mg per deciliter (1.7 mmol per liter) in the lower-target group and 96 mg per deciliter (2.5 mmol per liter) in the higher-target group (Fig. 1A). The percentage of time that patients spent in the assigned therapeutic range of LDL cholesterol was 52.8% in the lower-target group (53.4% among the French patients and 50.8% among the Korean patients) and 32.2% in the higher-target group (33.1% and 29.1%, respectively, for each country). The median percentage of the average time that patients spent in the assigned therapeutic range of LDL cholesterol at each trial center was 48.8% (interquartile range, 37.5 to 61.0). In the lower-target group, 47.2% of the patients were above the assigned target range, 44.7% were in the range from 50 mg to 70 mg per deciliter, 7.7% were in the range from 30 mg to 49 mg per deciliter, and 0.3% were below 30 mg per deciliter. In the higher-target group, 48.5% were below the target (<90 mg per deciliter), and 16.8% were above the target (>110 mg per deciliter). Doses of statin and ezetimibe that were used in each group are provided in Table S2.

END POINTS

The primary end point occurred in 121 of 1430 patients (8.5%) in the lower-target group (2.27 per 100 person-years) and in 156 of 1430 patients (10.9%) in the higher-target group (2.98 per 100 person-years) (adjusted hazard ratio, 0.78; 95% confidence interval [CI], 0.61 to 0.98; P=0.04) (Table 2 and Fig. 1B). A majority of the end-point events were cerebral infarctions or strokes of undetermined origin.

In sensitivity analyses, results were similar to those for the primary analysis, as calculated by means of inverse probability-of-censoring–weighted method, with models before adjustment (hazard ratio, 0.77; 95% CI, 0.61 to 0.97) and after adjustment (hazard ratio, 0.78; 95% CI, 0.62 to 0.98). On the basis of the prespecified hierarchical testing plan, because the difference between groups for the first composite secondary end point of myocardial infarction or urgent coronary revascularization was not significant, P values are not reported for the remaining secondary end points. The 95% confidence intervals have not been adjusted for multiple comparisons, and no clinical inferences can be made (Table 2).

Figure 1 (facing page). LDL Cholesterol Levels and Major Cardiovascular Events.

Panel A shows the mean levels of low-density lipoprotein (LDL) cholesterol over time in patients assigned to a target range of 90 mg to 110 mg per deciliter (higher-target group) or to a target level of less than 70 mg per deciliter (lower-target group). Under the graph, the row labeled "absolute difference" refers to the difference between the lower-target group and the higher-target group in the LDL cholesterol level, as measured in milligrams per deciliter. Panel B shows the cumulative incidence of the composite primary end point of major cardiovascular events (including ischemic stroke, myocardial infarction, hospitalization for symptoms resulting in urgent coronary or carotid revascularization, or cardiovascular death) in the two groups. The inset shows the same data on an expanded y axis. The I bars indicate 95% confidence intervals. Confidence intervals have not been adjusted for multiple comparisons and cannot be used to infer treatment effects.

The hazard ratios for all secondary end points were generally in the same direction as the hazard ratio for the primary end point, but the confidence intervals all included 1.00, including those for stroke and TIA.

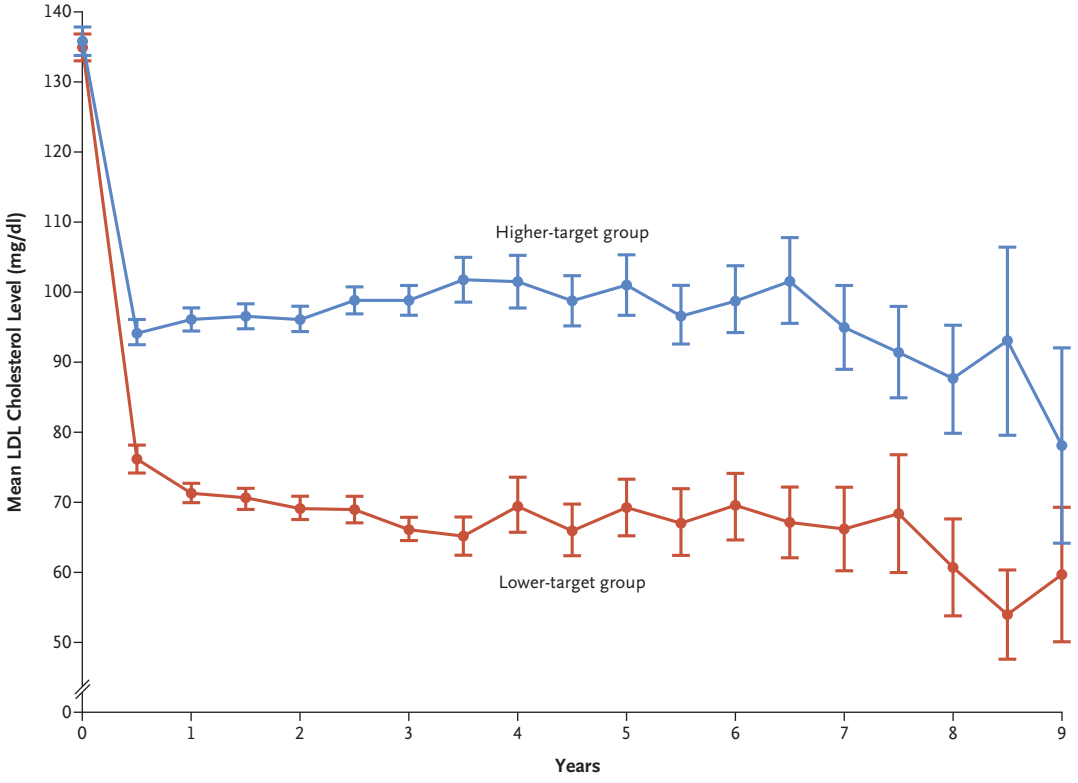
ADVERSE EVENTS

Intracranial hemorrhage occurred in 18 patients (1.3%) in the lower-target group and in 13 (0.9%) in the higher-target group (hazard ratio, 1.38; 95% CI, 0.66 to 2.82). The composite secondary end point consisting of the primary end point or intracranial hemorrhage occurred in 133 patients and 165 patients, respectively (hazard ratio, 0.80; 95% CI, 0.63 to 1.00). Newly diagnosed diabetes (fasting glucose level of ≥7.0 mmol per liter or glycated hemoglobin level of ≥6.5% on two separate occasions) occurred in 103 patients (7.2%) in the lower-target group and in 82 (5.7%) in the higher-target group (hazard ratio, 1.27; 95% CI, 0.95 to 1.70). The results of prespecified subgroup analyses are provided in Figure 2.

DISCUSSION

In our trial involving patients with recent ischemic stroke or TIA and evidence of atherosclerotic disease, those who were assigned to a target LDL cholesterol level of less than 70 mg per deciliter had fewer major cardiovascular events than those assigned to a target range of 90 mg to 110 mg per deciliter. The lowering of the LDL

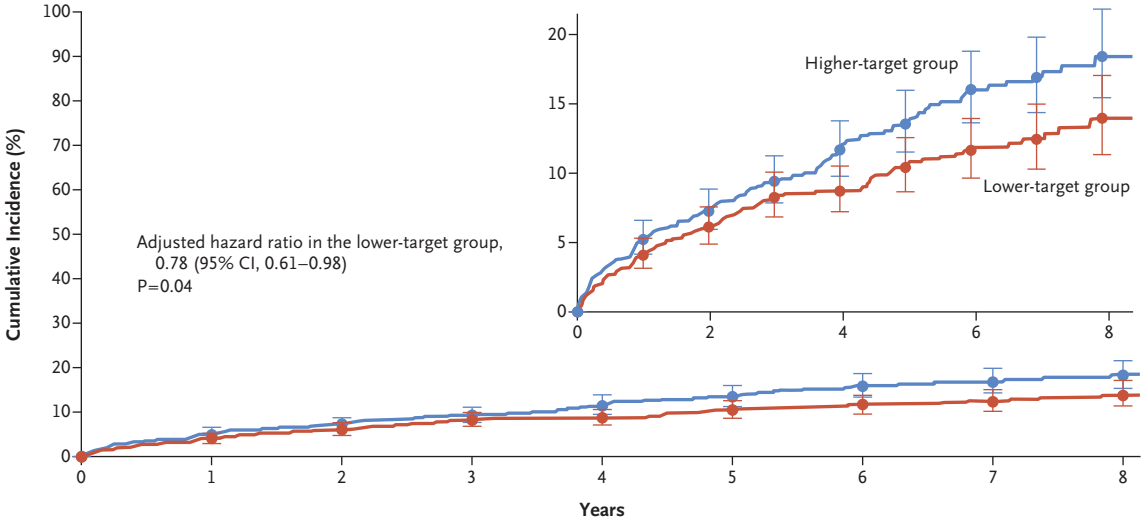
A **LDL Cholesterol Level, According to Target Group**



No. at Risk

Higher target	1420	1115	989	787	792	681	598	292	242	185	164	133	114	80	83	67	31	22	5
Lower target	1414	1102	965	879	774	653	570	277	227	180	169	141	126	81	73	46	26	21	6
Absolute difference	−1.14	−18.3	−24.7	−26.1	−27.1	−29.8	−32.5	−36.6	−32.0	−32.8	−31.9	−29.5	−29.4	−34.6	−29.0	−23.2	−26.9	−39.2	−18.5

B **Primary End Point**



No. at Risk

Higher target	1430	1146	973	730	590	487	392	253	106
Lower target	1430	1128	964	740	586	475	353	238	104

Table 2. Hazard Ratios for Adjudicated Clinical End Points.

End Points	Lower-Target Group (N=1430)	Higher-Target Group (N=1430)	Hazard Ratio (95% CI)	P Value
Primary end point				
Major cardiovascular event — no. (%)	121 (8.5)	156 (10.9)	0.78 (0.61–0.98)*	0.04
Death from cardiovascular causes	17 (1.2)	24 (1.7)	—	
Fatal cerebral infarction or stroke of undetermined origin	3 (0.2)	6 (0.4)	—	
Fatal myocardial infarction	1 (0.1)	1 (0.1)	—	
Other cardiovascular death	7 (0.5)	6 (0.4)	—	
Sudden death of undetermined origin	6 (0.4)	11 (0.8)	—	
Nonfatal cerebral infarction or stroke of undetermined origin	81 (5.7)	100 (7.0)	—	
Nonfatal acute coronary syndrome	15 (1.0)	23 (1.6)	—	
Urgent coronary revascularization	5 (0.3)	6 (0.4)	—	
Urgent carotid revascularization	3 (0.2)	3 (0.2)	—	
Secondary end points				
Myocardial infarction or urgent coronary revascularization — no. (%)	20 (1.4)	31 (2.2)	0.64 (0.37–1.13)	0.12†
Cerebral infarction or urgent revascularization of carotid or cerebral artery — no. (%)	88 (6.2)	109 (7.6)	0.81 (0.61–1.07)	
Cerebral infarction or TIA — no. (%)	120 (8.4)	139 (9.7)	0.87 (0.68–1.11)	
Any revascularization procedure — no./total no. (%)‡	94/1430 (6.6)	99/1430 (6.9)	0.93 (0.70–1.24)	
Carotid artery	17/94 (18)	23/99 (23)	—	
Coronary artery	44/94 (47)	51/99 (52)	—	
Peripheral artery	33/94 (35)	25/99 (25)	—	
Death — no. (%)				
Cardiovascular cause	22 (1.5)	32 (2.2)	0.69 (0.40–1.18)	
Any cause	88 (6.2)	93 (6.5)	0.97 (0.73–1.30)	
Cerebral infarction or intracranial hemorrhage — no. (%)	103 (7.2)	126 (8.8)	0.82 (0.63–1.07)	
Intracranial hemorrhage — no. (%)	18 (1.3)	13 (0.9)	1.38 (0.68–2.82)	
Newly diagnosed diabetes — no. (%)§	103 (7.2)	82 (5.7)	1.27 (0.95–1.70)	

* The hazard ratio for the primary end point was adjusted for the index event (stroke or transient ischemic attack [TIA]), the time since the index event, sex, and age. Missing values for covariates were handled with the use of a multiple-imputation technique in 37 patients (1.3%). The unadjusted hazard ratio was 0.77 (95% confidence interval [CI], 0.61 to 0.97; P=0.03). Confidence intervals have not been adjusted for multiple comparisons and cannot be used to infer treatment effects.

† P values for additional secondary end points were not calculated after there was no significant between-group difference for the first end point on hierarchical testing.

‡ The percentage of patients who underwent each revascularization procedure has been rounded because the overall denominator of patients in each category is less than 100.

§ Patients in whom diabetes had not been diagnosed at baseline were categorized by investigators as having newly diagnosed diabetes if they had at least two measures of fasting glucose of 126 mg per deciliter (7.0 mmol per liter) or more or a glycated hemoglobin value of 6.5% or more at a follow-up visit. This classification was not adjudicated.

cholesterol level was accomplished by adjustment of the statin dose, with the addition of ezetimibe in 33.8% of the patients. In addition to monitoring LDL cholesterol levels, investigators encouraged the targeted treatment of blood pressure and diabetes, along with smoking cessation, with favorable results (Figs. S2, S3, and S4).

According to data in TIAregistry.org, after

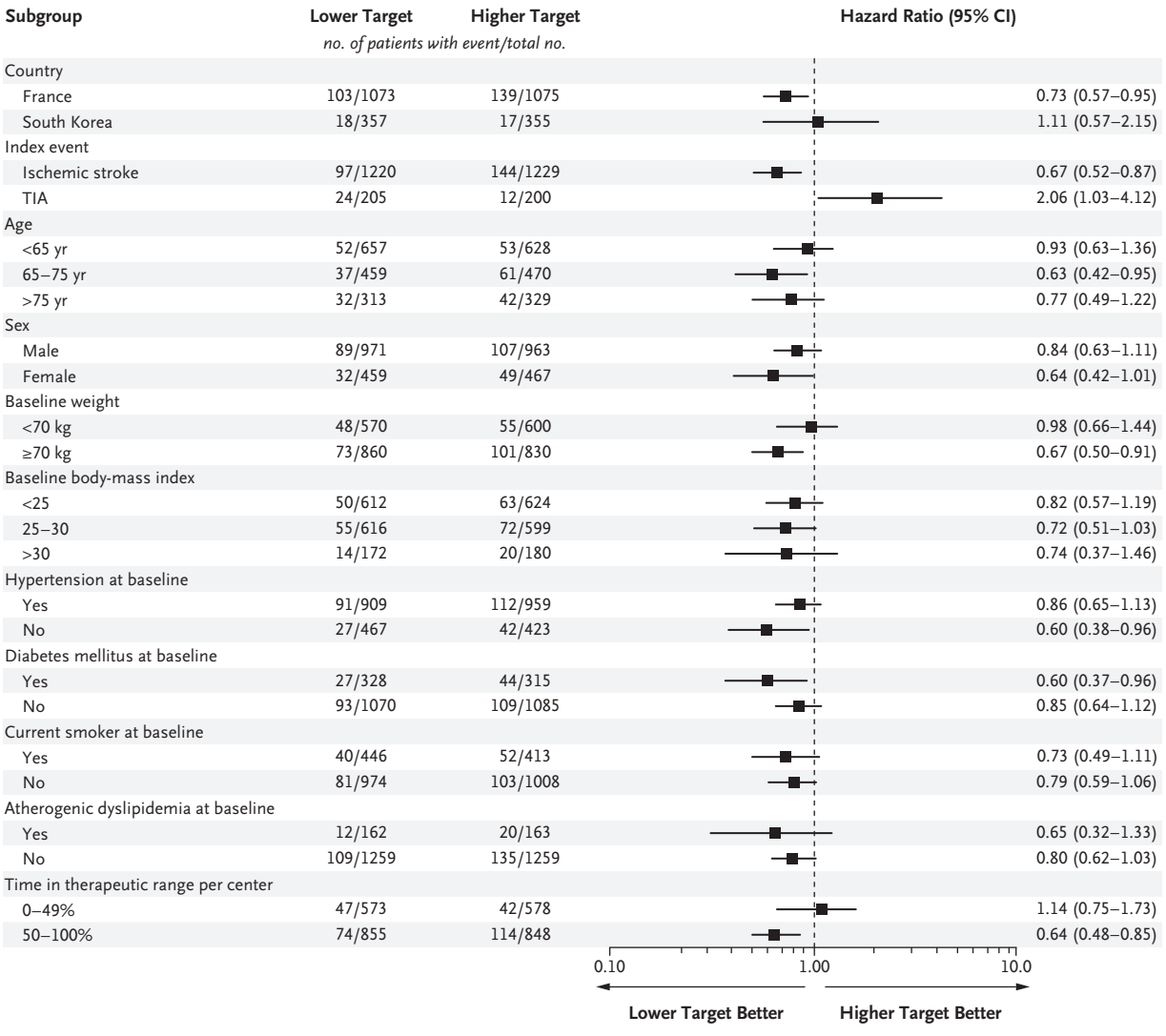


Figure 2. Subgroup Analysis of Major Cardiovascular Events.

Shown is the risk of major cardiovascular events (the primary end point) among patients in the lower-target LDL cholesterol group (<70 mg per deciliter) and in the higher-target group (range of 90 mg to 110 mg per deciliter), according to prespecified subgroups. Confidence intervals have not been adjusted for multiple comparisons and cannot be used to infer treatment effects. TIA denotes transient ischemic attack.

atherothrombotic ischemic stroke or TIA, the mean LDL cholesterol level was 92 mg per deciliter (2.4 mmol per liter), and patients who were included in the registry had a 13% risk of a major cardiovascular event at 5 years, despite being treated to reduce cholesterol levels according to the guidelines.[5] The results of our trial suggest that a target LDL cholesterol level of less than 70 mg per deciliter could provide a further risk reduction.

In our trial, which included French and Korean patients, we found no heterogeneity in the results between these national groups. The average time that patients spent in the assigned therapeutic range of LDL cholesterol was similar in the two groups (53.4% and 50.8%, respectively). Patients in South Korea were recruited later in the trial than French patients, with a median follow-up of 2.0 years, as compared with 5.3 years among the French patients, which may

have produced a lack of power to detect a significant effect in Korean patients. This factor makes it possible that the result of the trial in Korean patients is not generalizable to that population.

Given the established relationship between LDL cholesterol levels and cardiovascular events,[13] our results support the findings from meta-analyses of lipid-lowering trials suggesting that a lower level of LDL cholesterol is associated with better outcomes than higher LDL cholesterol targets.[6,14] Whether reducing the LDL cholesterol level to a target below 50 mg per deciliter is beneficial is not known and could be tested in other studies.

We found a numerically higher number of intracranial hemorrhages in the lower-target group than in the higher-target group, as was observed in the SPARCL trial,[2] in the Heart Protection Study,[15] and in meta-analyses of trials of secondary stroke prevention,[6,14,16] but the 95% confidence interval for the hazard ratio suggested that the between-group difference was not significant in our trial (Table 2). In addition, in the SPARCL trial, incident diabetes was 30% higher in the group assigned to receive atorvastatin (80 mg per day) than in the placebo group,[17] whereas in our trial the between-group difference in incident diabetes was not significant.

Our results should be interpreted with consideration of the premature cessation of the trial. The goal was to reach 385 primary events, and 277 events had occurred when the sponsor stopped the trial early as a result of a shortage of funds after a median follow-up of 3.5 years. Since an average of 30 primary end points occurred per year, at the time of trial cessation, it would have taken 3 additional years for the occurrence of 385 events. The extension of the trial by the sponsor allowed follow-up for every patient until the end of the trial rather than for 3 years, as initially planned. This allowed for the observed 277 events to provide a sufficient power to detect a 25% lower relative risk in the lower-target group, as hypothesized in the original trial design. Although adjudicators were unaware of LDL cholesterol targets and levels, the investigators and the technical and clinical research assistants were aware of the assigned targets. The secondary end points could not be formally tested because of the failure of the hierarchical analysis. The confidence intervals for hazard ratios comparing the two target groups, which were not adjusted for multiple comparisons, all included 1.00, which suggests that they may not be substantially different.

In our trial involving patients with an ischemic stroke or TIA and with evidence of atherosclerotic disease, those who were assigned to a target LDL cholesterol level of less than 70 mg per deciliter with the use of statins and, if required, ezetimibe had a lower risk of a composite end point of major cardiovascular events than those who were assigned to a target range of 90 mg to 110 mg per deciliter.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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