



Impact of Lower Versus Higher LDL Cholesterol Targets on Cardiovascular Events After Ischemic Stroke in Patients With Diabetes

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After an ischemic stroke with evidence of atherosclerosis, lipid-lowering treatment with a target LDL cholesterol of <70 mg/dL compared with 100 ± 10 mg/dL reduced the risk of subsequent cardiovascular events. In this analysis, we explored the effect in the subgroup of patients with diabetes compared with the subgroup without, as well as in those with newly diagnosed diabetes. Patients with ischemic stroke in the previous 3 months or transient ischemic attack within the previous 15 days and evidence of cerebrovascular or coronary artery atherosclerosis were randomly assigned at a 1:1 ratio to a target LDL cholesterol of <70 mg/dL or 100 ± 10 mg/dL using statin or ezetimibe. The primary outcome was the composite of ischemic stroke, myocardial infarction, new symptoms requiring urgent coronary or carotid revascularization, and death resulting from vascular disease. We performed a prespecified analysis to evaluate the effect in patients with diabetes. Of 2,860 patients enrolled, 643 had diabetes at baseline, with a mean age of 66.2 years and baseline LDL cholesterol of 127 mg/dL, and were followed for a

median of 3 years. The primary composite end point occurred in 27 (8.2%) of 328 patients in the lower-target group and in 44 (14.0%) of 315 patients in the higher-target group (adjusted hazard ratio [HR] 0.56; 95% CI 0.34–0.89; $P = 0.016$). In patients without diabetes, the HR was 0.87 (95% CI 0.66–1.14; $P = 0.31$; interaction $P = 0.15$). In those with diabetes, there were three intracranial hemorrhages in both randomization groups (0.9% vs. 1.0%, respectively). Newly diagnosed diabetes occurred in 98 (9.2%) of 1,070 and in 80 (7.4%) of 1,085 patients in the lower- and higher-target groups, respectively (HR 1.27; 95% CI 0.94–1.71; $P = 0.11$), and baseline higher HbA_{1c} was the unique multivariable predictor. In conclusion, after an ischemic stroke with evidence of atherosclerosis, targeting an LDL cholesterol of <70 mg/dL compared with 100 ± 10 mg/dL consistently reduced the risk of subsequent stroke and other major vascular events in patients with and without diabetes, but the higher risk in those with diabetes yielded a higher absolute risk reduction, with number needed to treat of 17.

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*A complete of the Treat Stroke to Target Investigators can be found in the supplementary material online.

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After a transient ischemic attack (TIA) or an ischemic stroke of atherosclerotic origin, the 2014 American Heart Association/American Stroke Association and 2008 European Stroke Organisation guidelines recommend intensive therapy to lower lipid serum levels without mentioning a specific target level (1,2). Recommendations in patients with stroke are based on the results of the Stroke Prevention by Aggressive Reduction in Cholesterol Level (SPARCL) trial, which found a 16% relative risk reduction with 80 mg atorvastatin per day as compared with placebo in patients with stroke and no known coronary heart disease and a subanalysis of that trial showing a relative risk reduction of 33% in randomly assigned patients with carotid stenosis (3,4). Patients with stroke and diabetes represent 20% of patients with ischemic stroke in Europe and 25% in Asia and up to 38% and 46% in North Africa and the Middle East, respectively (5–7). In patients with diabetes receiving 80 mg atorvastatin per day as compared with placebo in the SPARCL trial, there was a 30% reduction in the 5-year relative risk of stroke recurrence, a 50% reduction in the relative risk of any coronary heart disease event, and a 64% reduction in the relative risk of any revascularization procedure (8). In the SPARCL trial, there was an increase in the 5-year risk of hemorrhagic stroke that did not outweigh the benefit of atorvastatin therapy (9). The other important adverse event was a 30% increase in newly diagnosed diabetes (10).

In the Treat Stroke to Target (TST) trial, patients with ischemic stroke and evidence of atherosclerosis (stenosis of extra- or intracranial artery or aortic arch plaques ≥ 4 mm in thickness or history of symptomatic coronary artery disease) who were assigned a target LDL cholesterol level of <70 mg/dL had a significant major cardiovascular event reduction as compared with patients assigned a target LDL cholesterol level of 100 ± 10 mg/dL (11). We aimed to evaluate, in a prespecified analysis of the TST trial, the risk in patients with diabetes as compared with those without diabetes and the benefit and risk of targeting a LDL cholesterol of <70 mg/dL in patients with stroke and diabetes, as well as to find predictors of newly diagnosed diabetes in those without diabetes at baseline.

RESEARCH DESIGN AND METHODS

Trial

This was a randomized, event-driven trial. The methods of patient recruitment, evaluation, and statistical assumptions have been published (12). The protocol was approved by local institutional review boards. All patients provided written informed consent. The first author and independent academic statisticians at Bichat Hospital, CHU 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 or data gathering or analysis. All authors vouch for the accuracy of the data and all analyses and for the fidelity of the trial to the protocol and reporting of adverse events.

Participants

Patients were eligible for enrollment if they were age ≥ 18 years (>20 years in South Korea), had an ischemic stroke <3 months previously and a modified Rankin scale after stroke of 0 to 3 (scores of 0–6: 0 indicating no symptoms; 1, no disability; 2–3, needing some help; 4–5, dependent or bedridden; and 6, death) at randomization once investigators determined the neurologic deficit was stable, or a TIA within the previous 15 days that included at least arm and leg motor deficit or speech disturbance lasting >10 min. Transient ischemic symptoms with a documented ischemic lesion on computed tomography (CT) or MRI in the cerebral regions corresponding to the symptoms were defined as ischemic strokes. As recommended by the American Heart Association/American Stroke Association guidelines (13), all patients were screened using noninvasive imaging of the cervical vessels (carotid duplex, CT angiography, and magnetic resonance angiography) as part of the routine evaluation for suspected TIA or ischemic stroke, as well as CT angiography or magnetic resonance angiography of the intracranial vasculature to exclude a proximal intracranial stenosis and/or occlusion and transesophageal echocardiography or CT angiography of the aorta to detect aortic atheroma, which were obtained when the responsible clinician determined that knowledge of intracranial steno-occlusive disease or severe aortic atheroma would alter management (13). The choice of vascular test 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 including stenosis of an extra- or intracranial cerebral artery, ipsilateral or contralateral to the region of imputed brain ischemia, or aortic arch atherosclerotic plaques ≥ 4 mm in thickness or a known history of coronary artery disease. Patients also had to have an indication for statin treatment based on American Heart Association/American Stroke Association, French Agence Nationale de Sécurité du Médicament, or South Korean stroke recommendations (1,14,15). According to these recommendations, patients with ischemic stroke presumed to be of atherosclerotic origin should receive statin therapy (1) and, per the French and Korean recommendations, should be treated to a target LDL cholesterol of 100 mg/dL. Patients were required to have a directly measured LDL cholesterol of at least 70 mg/dL (1.8 mmol/L) if they had been receiving statins before randomization or at least 100 mg/dL (2.4 mmol/L) if they had not previously received statins.

Design

Eligible patients were randomly assigned at a 1:1 ratio to a target LDL cholesterol of <70 mg/dL (with no lower LDL threshold limit) or a target LDL cholesterol of 100 ± 10 mg/dL. Investigators could use any type and any dose of statin to reach this target. Investigators were asked to perform a determination of LDL cholesterol 3 weeks after randomization to adjust the statin dose or add other lipid-lowering agents including ezetimibe in order to achieve 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 to collect trial outcomes since the previous visit, a central core of clinical research assistants based at Bichat Hospital called patients or their relatives every 6 months to obtain the results of LDL measurement at the preceding visit and collect potential trial end points using a structured questionnaire. If the LDL cholesterol level was above or below the range assigned at randomization, the investigator was contacted to adjust the lipid-lowering treatment to the target range. If a potential trial outcome was collected, the local investigator was contacted to confirm the event clinically and activate the adjudication process. Triglyceride, HDL cholesterol, blood pressure in the sitting position, fasting glucose, and HbA_{1c} were collected at every 6-month visit.

End Points

The primary outcome was a composite of adjudicated nonfatal cerebral infarction or stroke of undetermined source, nonfatal myocardial infarction, hospitalization for unstable angina followed by urgent coronary artery revascularization, TIA requiring urgent carotid revascularization, or death resulting from cardiovascular disease, including unexplained sudden death. The prespecified secondary composite outcomes were myocardial infarction or urgent coronary revascularization following new symptoms; cerebral infarction or urgent carotid or cerebral artery revascularization following a TIA; cerebral infarction or TIA; any revascularization procedure, whether urgent or elective (coronary, cerebral, or peripheral artery); death resulting from vascular disease; death resulting from any cause; cerebral infarction or intracranial hemorrhage; newly diagnosed diabetes; and composite of primary outcome and intracranial hemorrhage (the last of these was prespecified in the protocol but not included in 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 LDL cholesterol group assignment or LDL level achieved.

Statistical Methods

The cumulative incidence of the primary composite outcome of major cardiovascular events in subgroups with and

without diabetes was estimated using the Kaplan-Meier method, censoring withdrawals and those lost to follow-up at the last available follow-up; patients who died as a result of causes other than vascular disease were censored at the time of death. We estimated the effect of target LDL cholesterol of <70 mg/dL against target LDL cholesterol of 100 ± 10 mg/dL on primary and secondary efficacy outcomes in subgroups with and without diabetes by using a Cox proportional hazards regression model including allocated arm (target LDL cholesterol ≤ 70 mg/dL vs. 100 ± 10 mg/dL), diabetes status at randomization, and interaction term between allocated arm and diabetes status at randomization. Analyses were performed for all randomly assigned patients in their assigned group according to the intention-to-treat principle, and all analyses were adjusted for prespecified covariates, as done in the primary efficacy analysis of the TST trial (age, sex, entry event [stroke or TIA], and time since entry event) (11). Adjusted hazard ratios (HRs) for target LDL cholesterol of <70 mg/dL relative to target LDL cholesterol of 100 ± 10 mg/dL and their 95% CIs were derived from these model as the effect size measure. A sensitivity analysis was conducted for the primary outcome by treating nonvascular death as a competing event using a multivariable Fine and Gray model. Adherence to the intervention was reported as time in therapeutic range (TTR), calculated in the same way the international normalized ratio range of 2 to 3 is determined in the case of warfarin treatment (16).

We assessed predictors of the primary outcome according to diabetes status at randomization by using Cox proportional hazards regression models including the candidate predictor, diabetes status, and the interaction term between the candidate predictor and diabetes status. Effect size (HR) associated with each candidate predictor in subgroups with and without diabetes was derived from these models using linear contrasts. All candidate predictors significantly associated with the primary outcome in either subgroup were introduced into the multivariable Cox proportional hazards regression model, including diabetes status and interaction terms between predictors and diabetes. All Cox regression models were adjusted for allocated arm and included a random center effect (frailty model).

Finally, in the subgroup without diabetes, we assessed predictors of newly diagnosed diabetes using univariable and multivariable Cox proportional hazards regression models. The multivariable analysis was repeated, including in the model smoking cessation and weight gain during follow-up as time-varying covariates.

Before developing multivariable models, we examined the proportional hazards assumption for each variable using the Schoenfeld residual plot and the log-linearity assumption for continuous candidate predictors using martingale residual plots. To avoid case deletion in Cox multivariate analyses resulting from presence of missing

data on candidate predictors, all multivariable analyses were performed after handling missing values by multiple imputation using a regression-switching approach (chained equations with $m = 10$). The imputation procedure was performed under the missing at random assumption using all baseline characteristics and the primary outcome (event status and log of event time), with a predictive mean matching method for continuous variables and logistic regression model for categorical variables. Estimates obtained in the different imputed data sets were combined using Rubin's rules.

Statistical testing was conducted at the two-tailed α level of 0.05. Data were analyzed using SAS software (version 9.3; SAS Institute, Cary, NC).

Data and Resource Availability

Data are available upon reasonable request to the first and corresponding author of this report for research purposes after approval by the steering committee.

RESULTS

Between March 2010 and December 2018, 2,873 patients were enrolled in France and South Korea. Of the 2,860 patients followed for a median of 3.5 years (interquartile range [IQR] 2.0–6.7), 1,430 were assigned an LDL cholesterol target of 100 ± 10 mg/dL (control group) and achieved a mean LDL cholesterol of 96 mg/dL, and 1,430 were assigned an LDL cholesterol target of <70 mg/dL and achieved a mean LDL cholesterol of 65 mg/dL. Of these patients, 643 had diabetes at baseline (328 in the <70 mg/dL group and 315 in the 100 ± 10 mg/dL group).

Baseline characteristics were similar between the two groups (Table 1). The baseline mean LDL cholesterol level in patients with diabetes was 127 mg/dL (3.5 mmol/L) in both groups. During the trial, all patients with diabetes in the <70 mg/dL group received intense or moderate doses of statin, and

Table 1—Baseline characteristics according to LDL cholesterol target groups

Characteristic	Patients with diabetes		Patients without diabetes	
	<70 mg/dL ($n = 328$)	100 ± 10 mg/dL ($n = 315$)	<70 mg/dL ($n = 1070$)	100 ± 10 mg/dL ($n = 1085$)
Age, years	65.3 (10.0)	67.1 (10.4)	66.8 (11.7)	67.0 (11.4)
Male sex	244/328 (74.4)	223/315 (70.8)	704/1070 (65.8)	719/1085 (66.3)
BMI	26.2 (23.7–29.1)	25.5 (23.5–28.4)	25.4 (23.2–28.3)	25.5 (23.2–28.3)
Entry event				
Ischemic stroke	298/328 (90.9)	293/315 (93.0)	894/1067 (83.8)	907/1084 (83.7)
TIA	30/328 (9.1)	22/315 (7.0)	173/1067 (16.2)	177/1084 (16.3)
Time since entry event, days	7 (4–12)	7 (4–14)	6 (4–10)	6 (4–10)
Medical history				
Hypertension	253/321 (78.8)	250/311 (80.4)	644/1042 (61.8)	697/1055 (66.1)
Dyslipidemia	229/310 (73.9)	229/298 (76.9)	639/998 (64.0)	625/992 (63.0)
Former smoker	87/326 (26.7)	76/315 (24.1)	255/1069 (23.9)	227/1081 (21.0)
Current smoker	97/326 (29.8)	82/315 (26.0)	340/1069 (31.8)	319/1081 (29.5)
Stroke or TIA	49/326 (15.0)	46/311 (14.8)	117/1061 (11.0)	105/1067 (9.8)
Coronary artery disease	81/324 (25.0)	63/312 (20.2)	177/1060 (16.7)	160/1063 (15.1)
Statin naive	136/310 (43.9)	126/298 (42.3)	653/998 (65.4)	637/992 (64.2)
Lipids, mg/dL				
LDL cholesterol	127 (38)	127 (40)	137 (37)	138 (35)
HDL cholesterol	45 (15)	46 (17)	52 (19)	51 (18)
Total cholesterol	199 (47)	200 (57)	211 (46)	213 (48)
Triglycerides	137 (105–194)	143 (105–200)	116 (87–159)	119 (89–157)
Atherogenic dyslipidemia*	56/328 (17.1)	55/315 (17.5)	78/1068 (7.3)	74/1081 (6.9)
Atherogenic dyslipidemia†	113/328 (34.5)	119/315 (37.8)	223/1068 (20.9)	227/1081 (21.0)
Systolic blood pressure, mmHg	143 (25)	143 (22)	139 (22)	141 (21)
Diastolic blood pressure, mmHg	79 (14)	79 (12)	79 (13)	80 (13)
Glucose, mmol/L	7.6 (6.2–9.9)	7.5 (6.0–9.5)	5.4 (4.9–5.9)	5.4 (4.9–6.0)
HbA _{1c}	8.2 (4.9)	7.7 (1.8)	5.8 (0.6)	5.8 (0.6)

Data presented as mean (SD), median (IQR), or n /total n (%). *Defined as triglycerides >200 mg/dL and HDL cholesterol ≤ 40 mg/dL for men (≤ 50 mg/dL for women). †Defined as triglycerides >150 mg/dL and HDL cholesterol ≤ 50 mg/dL.

ezetimibe was added to this background in 16.7%, 24.5%, 27.8%, and 27.6% of patients at 6 months, 1 year, 2 years, and 3 years, respectively, as compared with 4.4% to 7.2% in the 100 ± 10 mg/dL group.

In patients with diabetes, the median follow-up was 3.0 years (IQR, 1.4–5.5) in the lower-target group and 2.6 years (IQR, 1.0–5.4) in the higher-target group. The average achieved LDL cholesterol was 63 mg/dL in the lower-target group and 89 mg/dL in the higher-target group (Fig. 1).

Effect on Outcomes

Among 328 patients with diabetes assigned to a target level of <70 mg/dL, the primary end point occurred in 27 (8.2%), as compared with 44 (14.0%) of 315 patients with diabetes who were assigned an LDL cholesterol target of 100 ± 10 mg/dL (crude HR 0.56; 95% CI, 0.34–0.89; P = 0.016) (Fig. 2). After adjustment for covariates, the HR was 0.57 (95% CI 0.36–0.93; P = 0.024).

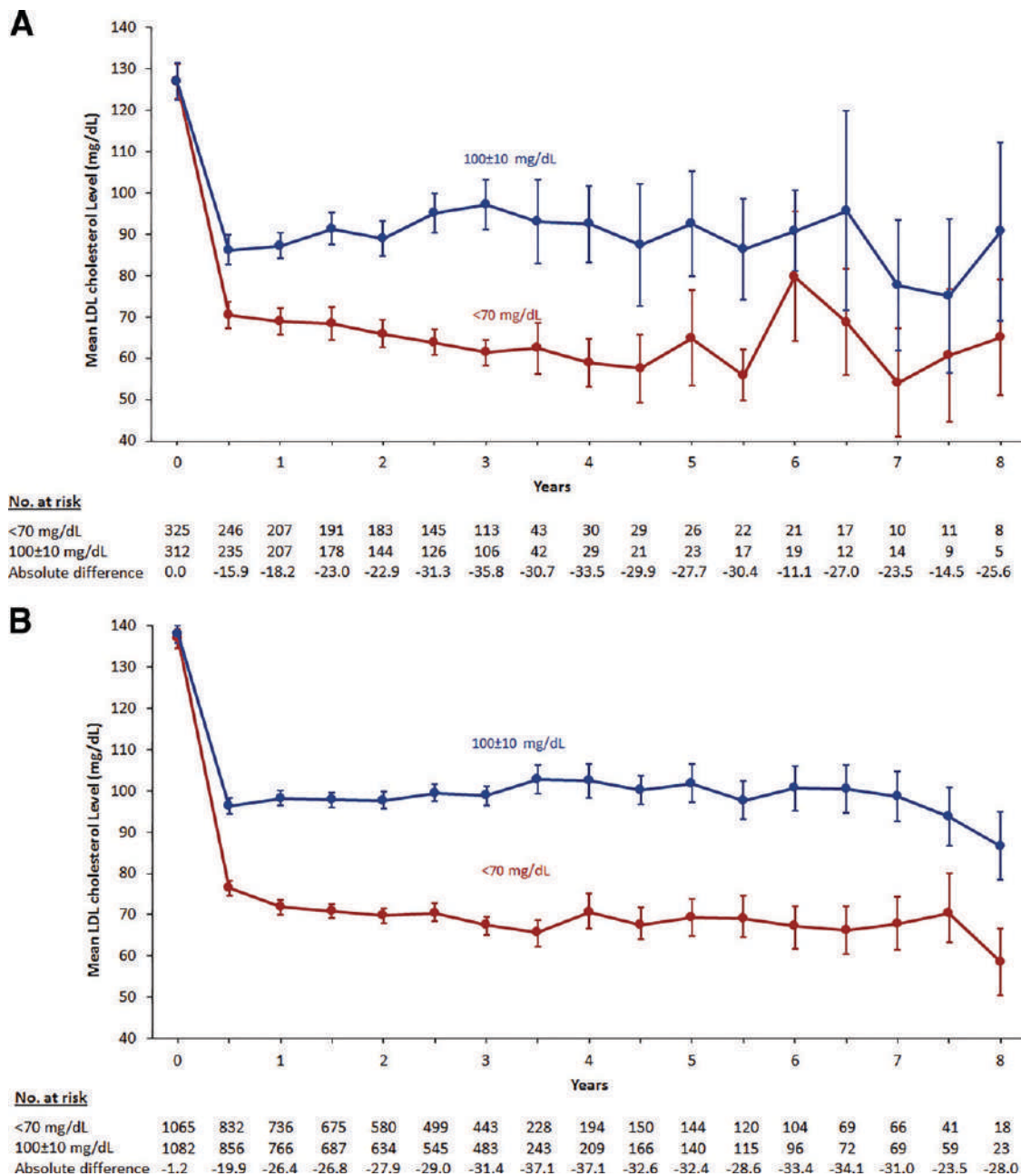


Figure 1—LDL cholesterol levels over time in patients assigned to a target LDL cholesterol level of 100 ± 10 mg/dL (2.4 mmol/L) or 70 mg/dL (1.8 mmol/L) in patients with (A) and without (B); HR adjusted on qualifying event (stroke/TIA), time since qualifying event, and sex and age at baseline (after handling missing covariates [n = 37; 1.3%] by multiple imputation) (B).

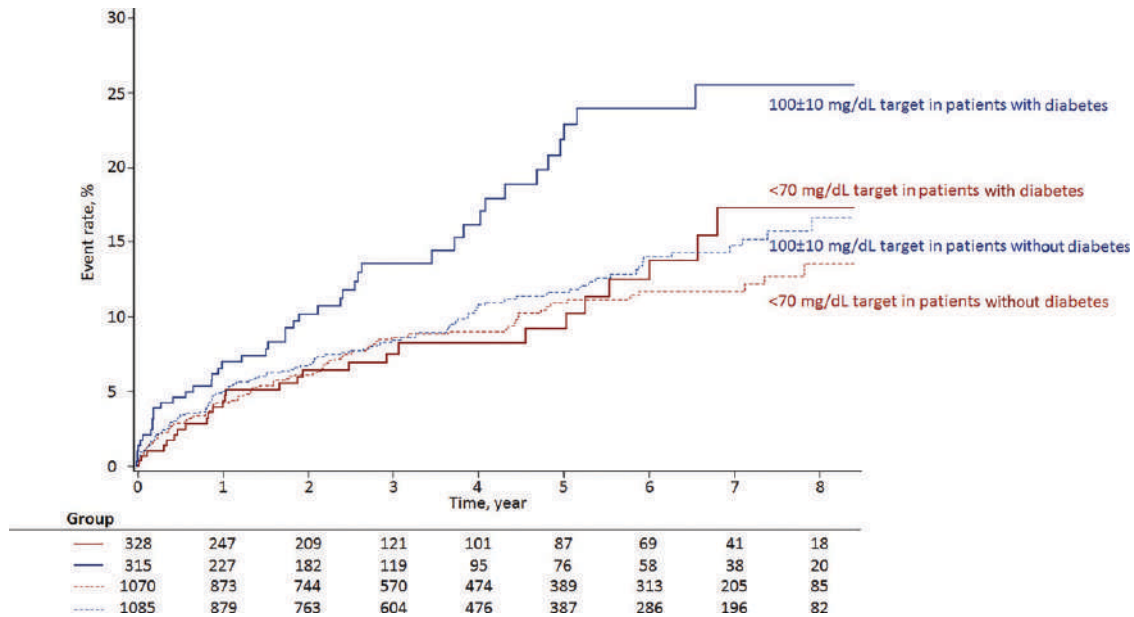


Figure 2—Cumulative incidence of the primary composite outcome (ischemic stroke, myocardial infarction, hospitalization for symptoms requiring urgent coronary or carotid revascularization, death resulting from vascular disease).

In 2,155 patients who did not have diabetes at baseline, the corresponding risks were 8.7% (93 of 1,070) in the lower-target group and 10.1% (109 of 1,085) in the higher-target group (adjusted HR 0.87; 95% CI 0.66–1.14; $P = 0.31$; interaction $P = 0.15$). HRs for adjudicated outcomes in the prespecified subgroup are shown in Fig. 3.

In the subgroup of patients who spent 50% to 100% of their time in the therapeutic range (<70 mg/dL), the primary outcome was observed in 22 of 255, compared with 38 of 228 corresponding patients who were in the higher target group (100 ± 10 mg/dL), who spent less time in the therapeutic range (HR 0.48; 95% CI 0.28–0.81; $P = 0.006$). Patients without diabetes comprised 55 of 367 participants in the subgroup assigned to the <70 mg/dL strategy and 80 of 642 in the subgroup who spent 50% to 100% of their time in the therapeutic range (HR 0.69; 95% CI 0.49–0.97; $P = 0.032$).

Adverse Events

Intracranial hemorrhages occurred in three (0.9%) of 328 (0.9%) patients with diabetes assigned an LDL cholesterol target of <70 mg/dL and in three (1.0%) of 315 patients with diabetes assigned an LDL cholesterol target of 100 ± 10 mg/dL (HR 0.98; 95% CI 0.19–4.63; $P = 0.93$).

The net benefit of the primary outcome or intracranial hemorrhage occurred in 30 (9.2%) of 328 patients in the lower-target group and 46 (14.6%) of 315 in the higher-target group (HR 0.60; 95% CI 0.38–0.95; $P = 0.028$).

Predictors of Primary End Point

After multivariable analysis, independent baseline predictors of the primary end point were coronary artery

disease, older age, and randomization to the lower-target group (<70 mg/dL). Current smoking was also a predictor of the primary end point in patients without diabetes (Supplementary Tables 1 and 2).

Newly Diagnosed Diabetes

Among patients without diabetes at baseline and with at least two measures of fasting glucose ≥ 7 mmol/L or HbA_{1c} $\geq 6.5\%$ during follow-up, newly diagnosed diabetes occurred during follow-up in 98 (9.2%) of 1,070 patients (Kaplan-Meier event rate 23.1%) in the lower-target group and 80 (7.4%) of 1,085 (Kaplan-Meier event rate 13.5%) in the higher-target group (HR 1.27; 95% CI 0.94–1.71; $P = 0.11$). Multivariable analysis showed that baseline predictors of newly diagnosed diabetes included (by order of importance): higher HbA_{1c}, higher BMI, lower HDL cholesterol, hypertension, randomization to the lower-target group (<70 mg/dL), current smoking, and male sex (Supplementary Tables 3 and 4). However, when weight gain and smoking cessation during follow-up were introduced into the model, we found only HbA_{1c} to be an independent predictor of newly diagnosed diabetes (Supplementary Table 5).

DISCUSSION

In this prespecified analysis of the TST trial that enrolled only patients with stroke associated with atherosclerotic stenosis, we found that the absolute risk of subsequent cardiovascular events in patients with diabetes was 1.5 times greater than that in patients without diabetes and that the absolute and relative risk reductions were also

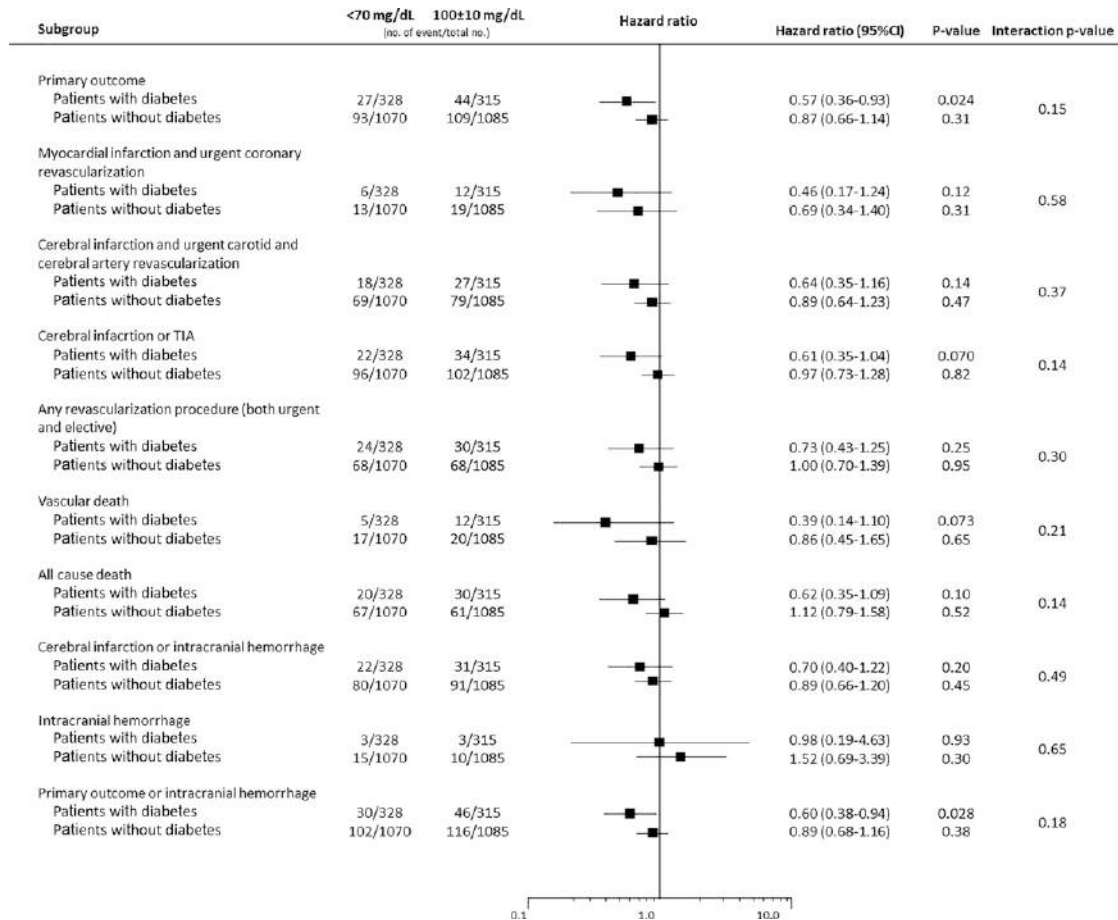


Figure 3—HR (95% CI) for adjudicated clinical outcomes in prespecified subgroups.

greater than those in patients without diabetes (5.8% vs. 1.4% and 42% vs. 13%, respectively), although without heterogeneity. The number needed to treat to avoid one primary outcome was 17 in patients with diabetes and 71 in those without diabetes. These observations concur with the results of previous secondary prevention trials of lipid-lowering agents in patients with diabetes; however, this is the first time that it is shown with a target LDL cholesterol of <70 mg/dL as compared with a target LDL cholesterol of 100 ± 10 mg/dL. Interestingly, the only independent predictors of the primary outcome in patients with diabetes were randomization to the lower-target group (reducing the risk) and older age and coronary artery disease at baseline (both increasing the risk).

The higher absolute benefit of lipid lowering in patients with versus without diabetes despite a lower absolute between-group difference in LDL cholesterol was also observed in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) (17), and the explanation for this remains unclear. The population of patients with diabetes usually has LDL particles of higher density, with well-established atherogenic properties. Although we did not measure particle density or apolipoprotein B, a similar decrease in LDL cholesterol might translate into a higher

decrease in particle number. Furthermore, more patients in the lower-target group received ezetimibe. Other possible explanations for the enhanced benefit in patients with diabetes include inhibition by ezetimibe of the higher levels of platelet aggregation and activation, a reduction in campesterol cholesterol ratio, or other pleiotropic effects of ezetimibe (18).

Secondary prevention trials with statins have shown an increase risk in hemorrhagic stroke (19–21). In this analysis, there was no increase in hemorrhagic stroke in the subgroup with diabetes (HR 0.92; 95% CI 0.19–4.54) or in the group of patients (n = 2148) who were followed for a median of 5.3 years (HR 1.17; 95% CI 0.53–2.62). In SPARCL, the explanation for incident hemorrhagic stroke was mainly uncontrolled hypertension and small vessel disease of hemorrhagic or ischemic type as the etiology of the entry event (9). At variance with the SPARCL trial, the TST trial enrolled only patients with atherosclerotic stenosis (a subgroup with no increase in hemorrhagic stroke in SPARCL), and it may be that the exclusion of patients with small vessel disease in the TST trial partly explains this discrepancy.

In SPARCL, there was a significant 30% increase in newly diagnosed diabetes (10). In the TST trial, although nonsignificant, we did also find a similar increase (HR

1.27; 95% CI 0.95–1.70). Multivariable analysis found higher baseline HbA_{1c}, BMI, lower HDL cholesterol, and hypertension (i.e., all components of the so-called metabolic syndrome); randomization to the lower target group; active smoking; and male sex as predictors of newly diagnosed diabetes, suggesting that these patients had prediabetes at baseline. Interestingly, when we forced into the model weight gain and smoking cessation (which is usually associated with weight gain) during the trial, only higher baseline HbA_{1c} remained an independent predictor; randomization to the lower-target group was no longer a predictor.

Although this study was an analysis of a prespecified subgroup from a large clinical trial, it had limited statistical power, and therefore, the results should be considered with caution.

In conclusion, in patients with stroke in the context of atherosclerotic stenosis, a target LDL cholesterol of <70 mg/dL decreased the risk of subsequent major vascular events as compared with a target LDL cholesterol of 100 ± 10 mg/dL, both in patients with diabetes and those without, without increasing the risk of hemorrhagic stroke at the expense of a slight increase in newly diagnosed diabetes. The higher rate of primary outcome and higher absolute risk reduction in patients with diabetes yielded a number needed to treat of 17, as compared with 71 in those without diabetes.

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Author Contributions. P.A. designed the study, obtained funding, designed the case report form, conducted the study, chaired the steering committee, interpreted the data, and drafted the manuscript. J.L. and H.C. performed the statistical analysis and created tables and figures. E.V. supervised the statistical analysis and methodology of the trial. All other authors revised the manuscript for important intellectual content. P.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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