Stroke

CLINICAL AND POPULATION SCIENCES

Intracranial Hemorrhage in the TST Trial

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BACKGROUND AND PURPOSE: Although statins are effective in secondary prevention of ischemic stroke, they are also associated with an increase risk of intracranial hemorrhage (ICH) in certain conditions. In the TST trial (Treat Stroke to Target), we prespecified an exploration of the predictors of incident ICH.

METHODS: 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 in a 1:1 ratio to a target LDL (low-density lipoprotein) cholesterol of <70 mg/dL or 100±10 mg/dL, using statin or ezetimibe.

RESULTS: Among 2860 patients enrolled, 31 incident ICH occurred over a median follow-up of 3 years (18 and 13 in the lower and higher target group, 3.21/1000 patient-years [95% CI, 2.38–4.04] and 2.32/1000 patient-years [95% CI, 1.61–3.03], respectively). While there were no baseline predictors of ICH, uncontrolled hypertension (HR, 2.51 [95% CI, 1.01–6.31], *P*=0.041) and being on anticoagulant (HR, 2.36 [95% CI, 1.00–5.62], *P*=0.047)] during the trial were significant predictors. On-treatment low LDL cholesterol was not a predictor of ICH.

CONCLUSIONS: Targeting an LDL cholesterol of <70 mg/dL compared with 100±10 mg/dL in patients with atherosclerotic ischemic stroke nonsignificantly increased the risk of ICH. Incident ICHs were not associated with low LDL cholesterol. Uncontrolled hypertension and anticoagulant therapy were associated with ICH which has important clinical implications.

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Although meta-analyses of statin trials have shown no significant increase in intracranial hemorrhages (ICH),[1,2] incident ICH in patients on statin remains a concern in the medical community. In the Cholesterol Trialist Collaboration, lowering LDL cholesterol by 2 mmol/L (78 mg/dL) in 10 000 patients with previous symptomatic vascular disease would prevent 1000 major vascular events and cause 5 to 10 ICH.[3] Trials in secondary prevention of stroke showed a 1.7-fold relative increase in ICH compared with placebo.[1,4,5]

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After a transient ischemic attack or an ischemic stroke of atherosclerotic origin, the 2014 AHA/ASA and 2008 European Stroke Organization guidelines recommend intensive therapy to lower lipid serum levels without mentioning a specific target level.[6,7] Recommendations in patients with stroke are based on the results of the

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*A list of all Treat Stroke to Target Investigators is given in the Supplemental Material.

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Nonstandard Abbreviations and Acronyms

HDL	high-density lipoprotein
ICH	intracranial hemorrhage
LDL	low-density lipoprotein
PCSK 9	proprotein convertase subtilisin/kexin type 9
SPARCL	Stroke Prevention by Aggressive Reduction of Cholesterol Levels
TST	Treat Stroke to Target

SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Level) that found a 16% relative risk reduction with atorvastatin 80 mg per day as compared with placebo in patients with stroke and no known coronary heart disease, and on a sub-analysis of that trial showing a relative risk reduction of 33% in patients randomized with carotid stenosis.[4,8] 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] Predictors of incident ICH over the 5 years of the follow-up were age, male sex, uncontrolled hypertension during the trial, and atorvastatin therapy.[9] On-treatment LDL cholesterol levels were not predictors of ICH, even very low levels.[9]

In the TST trial (Treat Stroke to Target),[10] 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. In a prespecified analysis of the TST trial, we aimed to evaluate the baseline and on-treatment predictors of incident ICH.

METHODS

Trial Design

This was a randomized, event-driven trial. The methods of patient recruitment, evaluation, and statistical assumptions have been published.[11] The protocol was approved by local institutional review boards. All patients gave written informed consent. The first author and independent academic statisticians at Bichat hospital, Centre Hospitalier Regional Universitaire of Lille and Fernand Widal Hospital had full access to the trial databases, analyzed the data, prepared the first draft of the article, and made decision to submit the article for publication. Data are available to other researcher based on reasonable request. The trial was funded by the French government and SOS-ATTAQUE CEREBRALE Association (a not-for-profit stroke survivors association), and 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.

Trial Participants

Patients were eligible for enrollment if they were 18 years or older (>20 years in South Korea), had recent ischemic stroke <3 months, and once the investigators determined the neurological deficit was stable with a modified Rankin Scale after stroke of 0 to 3 (modified Rankin Scale scores of 0 to 6, 0 indicating no symptoms, 1 no disability, 2–3 needing some help, 4–5 dependent or bedridden, and 6 death) at randomization, or a transient ischemic attack within the previous 15 days that included at least arm and leg motor deficit or speech disturbance lasting >10 minutes. Transient ischemic symptoms with a documented ischemic lesion on CT or MRI corresponding to the symptoms were defined as ischemic strokes. 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 stroke AHA/ASA, French Agence Nationale de Sécurité du Médicament, or South Korean recommendations.[6,12,13] According to these recommendations, patients with ischemic stroke presumed to be of atherosclerotic origin should receive statin therapy,[6] and for the French and Korean recommendations should be treated to a target LDL cholesterol of 100 mg/dL.[12,13] Enrolled patients were required to have a directly measured LDL cholesterol of at least 70 mg/dL (1.8 mmol per liter) if they were on statin before randomization, or at least 100 mg/dL (2.4 mmol per liter) if they had not previously received statins.

Trial Design

Eligible patients were randomly assigned in a 1:1 ratio to a target LDL cholesterol of <70 mg/dL or a target LDL cholesterol of 100±10 mg/dL. Investigators could use any type and any dose of statin to reach these targets. Investigators were asked to perform a determination of LDL cholesterol 3 weeks after randomization to adjust the statin dose, or to add other lipid lowering agents including ezetimibe, to achieve the assigned LDL cholesterol target. Patients were followed every 6 months after randomization with measurement of LDL cholesterol, electronic measure of blood pressure in seating position with a target blood pressure of <140/90 mm Hg (<130/80 mm Hg in diabetics) with recommendation, in case of controlled blood pressure or no high blood pressure at baseline, to obtain a further 10 mm Hg systolic and 5 mm Hg diastolic blood pressure reduction using blood pressure lowering drugs at investigator's choice, according to international and country guidelines. In addition to face-to-face visits with the investigators to collect trial outcomes at every visit, a central core of clinical research assistants based at Bichat Hospital called patients or their relatives every 6 months to acquire the results of LDL measurement 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 range assigned by randomization, the investigator was contacted to adjust the lipid lowering treatment to the target range. If a potential trial outcome was

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collected, the local investigator was contacted to confirm the event clinically and activate the adjudication process.

Outcomes

The primary outcome of the overall trial 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, transient ischemic attack requiring urgent carotid revascularization, or cardiovascular death including unexplained sudden death. ICH was a prespecified, adjudicated safety outcome. For the purpose of this analysis, the outcome of interest was ICH. All these events were adjudicated by a committee in which the members were unaware of LDL cholesterol group assignments or LDL levels achieved.

Statistical Methods

Quantitative variables were expressed as means (±SD) in case of normal distribution or median (interquartile range) otherwise. Categorical variables were expressed as counts (percentage).

Association of patient's characteristics at randomization (including TST allocated arm) with the occurrence of ICH during follow-up were assessed using univariable Cox proportional hazard regression models. Proportional hazard assumptions for each characteristics were checked using Schoenfeld residual plots and the log-linearity assumption for quantitative characteristics were assessed using the martingale residual plots. We also examined the association of key factors varying during follow-up (treatment LDL cholesterol and blood pressure levels achieved, and antithrombotic treatment [antiplatelet and anticoagulant therapy] during trials collected at every 6-month visits) with ICH risk by including time varying variables into univariable Cox proportional hazard regression models.

Statistical testing was conducted at the 2-tailed α-level of 0.05. Data were analyzed using SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Between March 2010 and December 2018, 2873 patients were enrolled in France and South Korea. Among 2860 patients who were followed for a median of 3.5 years (IQR, 2.0–6.7), 1430 were assigned a LDL cholesterol of 100±10 mg/dL (the control group) who achieved a mean LDL cholesterol of 96 mg/dL, and 1430 were assigned a LDL cholesterol of <70 mg/dL, who achieved a mean LDL cholesterol of 65 mg/dL. Figure 1 shows the study flow chart. Incident ICHs were observed in 31 patients (2.77/1000 patient-years [95% CI, 1.68–3.86]), including 18 (3.21/1000 patient-years

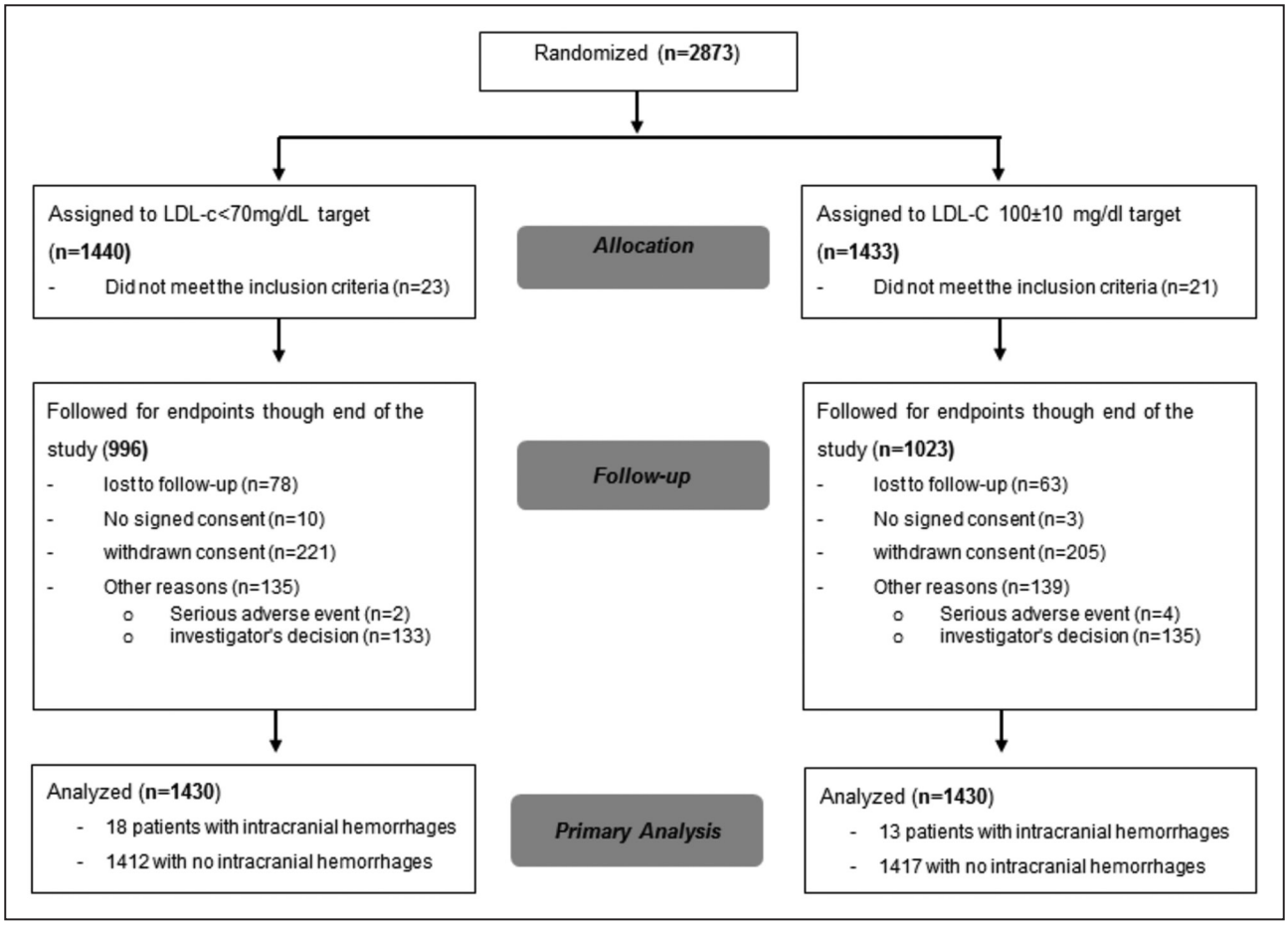

Figure 1. Study flow chart.
LDL-c indicates low-density lipoprotein cholesterol.

[95% CI, 2.38–4.04]) and 13 (2.32/1000 patient-years [95% CI, 1.61-3.03]) in the lower and higher target group (Figure S1), respectively (hazard ratio, 1.38 [95% CI, 0.68–2.82]).

Baseline characteristics of patients with and without ICH are presented in the Table S1. The baseline mean LDL cholesterol level was 130±33 mg/dL (3.5 mmol per liter) in the ICH group and 135±38 mg/dL in the non-ICH group. Treatment during the trial in both groups are shown in Table S2. Table 1 shows hazard ratios of baseline predictors. None of them were significant.

Regarding the factors varying during the course of the trial, only on-treatment uncontrolled hypertension (hazard ratio, 2.51 [95% CI, 1.01–6.31], *P*=0.041) and being on anticoagulant therapy (hazard ratio, 2.36 [95% CI, 1.00–5.62], *P*=0.047]) were significant predictors of incident ICH (Table 2). However, on-treatment achieved LDL cholesterol was not a significant predictor, including very low levels of LDL cholesterol (Table 2). Figure 2 shows the wide distribution of LDL cholesterol levels achieved at the trial visit immediately preceding the ICH event for all individual ICH cases, demonstrating that ICH occurred at any levels of LDL cholesterol, including high levels. The mean difference between baseline LDL and LDL levels at the visit preceding ICH was 28.8 mg/dL, while the difference between baseline LDL and mean LDL levels achieved in patient with no ICH was 50.9 mg/dL (*P*=0.002), with a higher LDL cholesterol at the time of ICH. Figure S2 shows blood pressure achieved in ICH and non-ICH groups over the 3 years of the trial.

Table 1. Univariate Analysis of Baseline Characteristics (at Time of Randomization) With Occurrence of Intracranial Hemorrhage During Trial

Characteristics	HR (95% CI)	*P* value
Age, per 10 y increase	1.31 (0.94–1.82)	0.11
Male sex	1.57 (0.68–3.64)	0.30
Country		0.24
France	0.59 (0.24–1.42)	
Korea	1.70 (0.70–4.13)	
Body-mass index, per 5 kg/m² increase	0.94 (0.69–1.29)	0.71
Ischemic stroke as entry event	1.25 (0.44–3.59)	0.67
Time since entry event to randomization, days	1.01 (0.99–1.03)	0.41
Medical history		
Hypertension	1.34 (0.62–2.90)	0.47
Diabetes	0.96 (0.39–2.33)	0.92
Dyslipidemia	0.98 (0.47–2.01)	0.95
Former smoker	1.58 (0.74–3.35)	0.23
Current smoker	1.10 (0.52–2.33)	0.81
Stroke or TIA	1.24 (0.44–3.55)	0.69
Coronary artery disease	1.64 (0.73–3.66)	0.23
Lipids at randomization		
LDL-c, per 39 mg/dL decrease	1.21 (0.83–1.78)	0.32
HDL-c, per 39 mg/dL increase	0.51 (0.19–1.35)	0.17
Total cholesterol, per 39 mg/dL decrease	1.21 (0.88–1.67)	0.24
Triglycerides, per 114 mg/dL decrease	1.14 (0.70–1.86)	0.61
Systolic blood pressure, per 10 mm Hg	1.11 (0.96–1.28)	0.17
Diastolic blood pressure, per 5 mm Hg	1.07 (0.94–1.21)	0.34
Glucose, per 1 mmol/L	0.97 (0.82–1.15)	0.76
Hemoglobin A1c, per 1%	1.06 (0.82–1.36)	0.66
TST-allocated arm (<70 mg/dL strategy)	1.38 (0.68–2.82)	0.38

HDL-C indicates high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; TIA, transient ischemic attack; and TST, Treat Stroke to Target.

DISCUSSION

In this prespecified analysis of the TST trial that enrolled only patients with stroke associated with atherosclerotic stenosis, we found that 31 patients had an ICH over the course of the trial (absolute risk of incident ICH 1.08%). None of the baseline characteristics were significantly associated with incident ICH. Only patients with uncontrolled hypertension during the trial (JNC7 definition, systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg) and being treated with oral anticoagulant were significant predictors of ICH with an almost 3-fold increase in risk. It is remarkable that achieved LDL cholesterol levels, and particularly low or very low LDL cholesterol levels were not associated with ICH increase. Similar observations had been made in post ACS patients treated with a PCSK 9 (proprotein convertase subtilisin/kexin type 9) inhibitor with mean LDL cholesterol levels achieved as low as 30 mg/dL, where there was no increase in the risk of ICH, and furthermore no relation between low LDL on treatment and incidence of ICH in the PCSK 9 inhibitor group.[14,15]

In the placebo-controlled SPARCL trial, the same analysis found that age, male sex, atorvastatin 80 mg, and randomization with a previous brain hemorrhage were the only baseline characteristics associated with

Table 2. Hazard Ratio for On-Treatment Variables in Relation With Intracranial Hemorrhages Over 5 Years (Univariate Analysis)

Characteristics	HR (95% CI)	*P* Value
Anticoagulant therapy	2.36 (1.00–5.62)	0.047
Dual antiplatelet therapy	1.12 (0.33–3.72)	0.86
Prehypertension	0.72 (0.33–1.58)	0.41
Stage 1 hypertension	1.45 (0.65–3.24)	0.36
Stage 2 hypertension	2.51 (1.01–6.31)	0.041
LDL-c		
≥90 mg/dL	1.00 (ref)	…
70–89 mg/dL	0.81 (0.28–2.30)	0.69
<70 mg/dL	0.84 (0.31–2.25)	0.73

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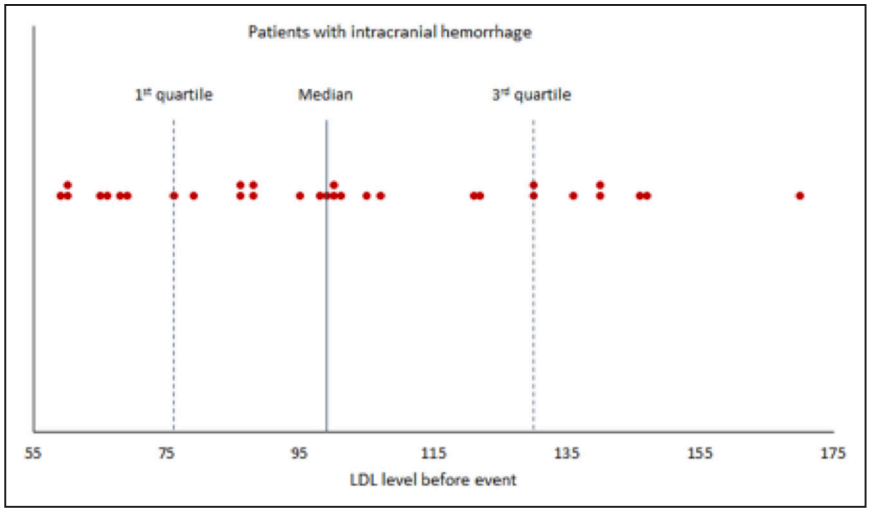

Figure 2. LDL (low-density lipoprotein) level at the visit before hemorrhage outcome.

incident ICH, and that patients with uncontrolled hypertension during the trial were 6 times more likely to develop an ICH.[9] Again, SPARCL analysis found that achieved LDL cholesterol levels, including very low levels were not predictors of ICH, as compared with placebo group. In SPARCL, anticoagulant treatment was not a predictor of ICH.[9] In SPARCL, patients randomized with small vessel disease (either small vessel disease of hemorrhagic type or small vessel disease of ischemic type, taken together) were significantly associated with ICH (data not shown). At variance with the SPARCL trial in which only 1000 among 4732 patients had carotid atherosclerosis, the TST trial only enrolled patients with proven atherosclerotic disease, a subgroup in SPARCL with no increase in ICH.[9] Exclusion of patients with small vessel disease in TST trial may have partly influenced the differences in results of these TST and SPARCL analyses.

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. We did no formal power calculation, and we cannot exclude that some differences have been overlooked. Also, the control group in the TST trial was a target LDL cholesterol 90 to 110 mg/dL using statin treatment. Since in the SPARCL trial analysis atorvastatin staid in the model predicting ICH,[9] it is possible that the mere prescription of a statin in the higher target group in the TST trial was associated with ICH. However, we again showed that ICH was not predicted by the reduction of LDL cholesterol and by achieved very low levels of LDL cholesterol. In many studies, the link between ICH and cholesterol refers to total cholesterol with possibly a role of HDL (high-density lipoprotein; which is usually low when total cholesterol is low),[16] we have also tested total cholesterol and ICH and found no relationship. Although we found numerically less ICH in France (13 and 11 ICH in the lower and higher target group, respectively) than in Korea (5 and 2 ICH, respectively), the difference was not statistically significant, a result that could also be obtained du to limited statistical power.

In conclusions, in patients with stroke in the context of atherosclerotic stenosis, a target LDL cholesterol <70 mg/dL as compared with a target LDL cholesterol 100±10 mg/dL did not significantly increase the risk of ICH and the predictors of ICH were uncontrolled hypertension and anticoagulant treatment but not LDL cholesterol levels achieved.

ARTICLE INFORMATION

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Supplemental Material

Appendix: TST committees and investigator centers
Tables S1–S2
Figures S1–S2

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