Treat stroke to target trial design: First trial comparing two LDL targets in patients with atherothrombotic strokes

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Abstract

Background: In patients with non-cardio-embolic stroke, atorvastatin 80 mg/day reduced the relative risk of recurrent stroke by 16%, and a post hoc analysis showed that achieving an LDL-c of less than 70 mg/dL reduced the relative risk by 28% as compared to an on-treatment LDL of 100 mg/dL or more. Current guidelines from the French drug agency recommend treating with a statin after an ischaemic stroke to a target of less than 100 mg/dL, but no study directly tested LDL-c targets. The Treat Stroke to Target (TST) trial will compare the efficacy of achieving an LDL-c of less than 70 mg/dL versus an achieved LDL-c of 100 ± 10 mg/dL for secondary prevention in patients with recent ischaemic stroke of atherosclerotic origin.

Main hypothesis: An achieved on-treatment LDL-c of less than 70 mg/dL will reduce by 25% the risk of recurrent ischaemic stroke, myocardial infarction, urgent coronary or carotid revascularisation following new symptoms requiring hospitalisation, and vascular death compared with on-treatment LDL-c of 100 ± 10 mg/dL.

Design: Patients are randomised to either LDL-c levels, and the investigator who is not blinded can use the lipid-lowering agent of his/her choice available on the market (including statins and ezetimibe), in order to achieve the assigned LDL-c level. To be eligible for enrolment, patients have a recent ischaemic stroke or TIA of atherosclerotic origin with at least one arterial stenosis of a cerebral artery, enrolled between acute phase of the qualifying stroke (once the neurological deficit is stabilised) and three months. The initial planned sample size of 3760 participants followed three years was amended to allow follow-up of all enrolled patients until 385 primary efficacy outcome events have occurred, and no later than 31 December 2019. Patients will be recruited in 76 sites in two countries (France and South Korea) between March 2010 and December 2018 (last included patient followed up to one year). Safety outcomes will include haemorrhagic strokes and new onset diabetes. All primary endpoints will be adjudicated by an endpoint committee, blinded to the assigned LDL-c level. Two sub-studies assess (I) the relative effect of assigned LDL-c levels on occurrence of new atherosclerotic plaque as detected by carotid ultrasound during follow-up, using M'ATH software for

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repositioning and (2) the genetic and biomarker drivers of recurrent primary endpoints according to assigned LDL-c lowering arm, in atherosclerotic strokes.

Summary: The TST trial is evaluating the benefits of achieving an LDL-c less than 70 mg/dL for secondary stroke prevention in ischaemic stroke patients of atherosclerotic origin. Main results are anticipated in 2020 or earlier (ClinicalTrials.gov NCT01252875).

Keywords

Stroke, statin, LDL cholesterol, stroke prevention

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During the last 40 years, cholesterol level was not a target for secondary stroke prevention, contrary to myocardial infarction, because of the lack of a clear demonstration of a relationship between hypercholesterolemia and incident ischaemic stroke in epidemiological studies.^{1,2} Hence, lipid-lowering treatment has received relatively less attention by neurologists than cardiologists.

Statin mega trials performed in patients with coronary artery disease, hypertension or with diabetes, or in patients at high vascular risk, have shown a 20% relative risk reduction of stroke and TIA in these populations that was entirely driven by the magnitude of LDL-lowering (Figure 1).^{3–5} This decrease in stroke and TIA incidence was also observed after a coronary artery disease events with intensive LDL lowering as compared to less intensive LDL lowering with a standard dosage of statin (Figure 2(a) and (b)).⁵

Only one trial evaluated the efficacy/tolerability of long-term secondary prevention of statins after a stroke/TIA (the SPARCL trial). In that trial, atorvastatin 80 mg/d was tested against placebo during a five-year period in patients with a non-cardio-embolic stroke and with no known coronary artery disease.⁶ The relative risk reduction with atorvastatin was 16% for stroke (primary end-point), 42% for any coronary artery end-points and 45% for revascularisation procedures.⁶

These results were obtained and analysed with the intention-to-treat rule, in spite of the fact that 25% of patients randomised to placebo dropped-in, by receiving an open-label non-study statin. A post hoc analysis from the SPARCL data set used LDL-c levels measured at each study visit, taken as a marker of drug compliance. This analysis was made possible because all investigators and patients were maintained blinded from LDL-c levels evaluated at each six-month visit. Hence, the analysis concerned 55,000 measures of LDL-c (with a mean of 11.6 measures per patients, with blood drawn every six month) and showed that

a 50% LDL-c level reduction from baseline or achieved LDL-c levels <70 mg/dL was associated with a 31% and a 28% relative risk reduction of stroke incidence, respectively, which was almost twice greater than the overall reduction observed in the trial.⁷

Translation in practice of the SPARCL trial results has proved to be difficult because most physicians (and patients) are reluctant in long-term prescription of high-dose statins, worrying about adverse effects such as muscle pain and myopathy, fatigue or cognitive impairment, although these adverse effects were not observed in the experimental condition of the SPARCL trial and were relatively marginal in the CTT meta-analysis.⁸ Hence, in practice, most physicians do prescribe a statin after a stroke/TIA, but usually at a lower dosage than that used in SPARCL trial. However, if the clinical benefit of statin is linked to the magnitude of LDL-lowering, then under-treated patients are unlikely to derive the benefits observed in the SPARCL trial with atorvastatin 80 mg/day.

On the other hand, it is possible that decrease in LDL cholesterol is a mere (and the best) biological marker for the positive (pleiotropic) effects of statins on the risk of stroke (and other vascular events). It is possible that these effects are not directly due to LDL-lowering but to other biologic effects on inflammation proteins, cytokines, haemorheology, haemostasis (both fibrinolysis and platelet function), a blood pressure lowering effect, endothelial dysfunction (neuroprotective effect via up-regulation of nitric oxide), or a mere reduction in thrombo-embolic complications after a myocardial infarction by reducing the incidence of myocardial infarction.^{2,9,10}

However, meta-analyses and sub-analyses from HPS trial have shown that any reduction in LDL-c levels, even small, were associated with reduced incidence of any vascular event (including stroke), regardless of baseline LDL-c levels, without any lower threshold effect.^{4,11} Hence, the CTT collaboration recommended statin treatment at any dosage and at any baseline

Figure 1. Relationship between LDL lowering (in percent from baseline) and decrease risk in stroke/TIA in statin treatment (meta-regression analysis) (modified from Amarenco and Labreuche, 2009;8:453).

SPARCL-CS: SPARCL patients without carotid stenosis; SPARCL-CS+: SPARCL patients with carotid stenosis.

Figure 2. Statin trials following cardiac event, intensive LDL lowering versus standard dosage of statin with less LDL lowering, with or without SPARCL subgroup with baseline carotid stenosis with more versus less LDL lowering): effect on stroke incidence (Panel a), effect on a composite of stroke, MI, vascular death (Panel b).

LDL-c levels, even without monitoring on-treatment LDL-c levels.

Currently, the Agence Nationale de Sécurité du Médicament (ANSM, the French drug agency) recommends that, after a stroke/TIA, LDL-C is lowered to 100 mg/dL (2.4 mmol/L).¹² This level is usually easy to reach after a stroke/TIA with a moderate or low dose of statin considering the 124 mg/dL mean baseline LDL-C after a stroke/TIA.¹³ Optionally, ANSM recommends that LDL-C is lowered to less than 70 mg/dL (1.6 mmol/L) in case of “high vascular risk”, such as in patients with acute coronary syndrome. The efficacy of these target strategies has not yet been compared in patients with ischaemic stroke.

It is thus important to evaluate different strategies of LDL-c lowering after a stroke/TIA, e.g., a target LDL-C of 100 mg/dL (± 10 mg/dL) vs. < 70 mg/dL. Indeed, in practice, primary care physicians (PCP) need a validated therapeutic target. Such a target is also useful to judge patient adherence or observance to the therapy. This target can be reached by titration of the statin, so the PCP can find the right dosage for the right patient, and not necessarily use very high dosage if the target is achieved by a lower statin dosage, which would be cost saving and may reduce occurrence of adverse events.

Finally, in a SPARCL pre-specified sub-analysis, performed in 1080 patients with carotid stenosis (on either side) at randomisation ($n = 1080$), patients on atorvastatin 80 mg/day had a significant 33% relative risk reduction of stroke recurrence which was double of what was observed overall in the trial and the KM curves had an early divergence and remained divergent throughout the trial, suggesting that this group of patients likely benefited most, and sooner, from high-dose statins.¹⁴

Therefore, in the proposed evaluation of the relative efficacy of reaching two levels of LDL-C, we will use the group of stroke/TIA associated with atherosclerotic disease that is easy to identify clinically from a PCP, investigator and regulator perspectives, in order to reduce the sample size and study duration.

Design

Overview

TST (Clinicaltrials.gov. NCT01252875) is an international, bi-national (France and South Korea), randomised open label trial comparing an on-treatment achieved LDL-c of less than 70 mg/dL with achieved LDL-c of 100 mg/dL ± 10 mg/dL, using any lipid-lowering agent available on the market (e.g. statin, ezetimibe) (Figure 1). The primary hypothesis is that achieving an LDL-c of less than 70 mg/dL is superior to 100 ± 10 mg/dL in reducing the risk of recurrent

ischaemic stroke, myocardial infarction, urgent revascularisation following new symptoms and vascular death (primary efficacy outcome). The choice of the statin prescribed (with or without other lipid-lowering agents, e.g. ezetimibe) and its dosage will be up to the investigator according to the baseline level of LDL-c and the target LDL-c assigned by randomisation, within the usual care procedures. The patient will buy the statin at its own pharmacy and be reimbursed by the social security system of her/his country. Over the course of the 12 to 116 months of follow-up, at every six-month visit, the statin dosage will be titrated according to the LDL-c level and the allocated therapeutic target assigned by randomisation to maintain on-treatment LDL-c either between 90 and 110 mg/dL or less than 70 mg/dL. If the target is not achieved by the highest dosage of statin, investigators will be allowed to use in addition, intestinal blockers of cholesterol absorption (ezetimibe).

Trial hypothesis and sample size

Three thousand seven hundred sixty patients will be enrolled to detect a $\geq 25\%$ reduction in primary efficacy outcome events with 90% power by assignment to an LDL-c of less than 70 mg/dL on an estimated rate of 4.5% per year among LDL-c of 100 ± 10 mg/dL assigned patients. Anticipated attrition rate will be 20%. Participants will be randomised between the acute phase (once the neurological deficit is stabilised) and three months following the qualifying ischaemic stroke at 76 sites in 2 countries (61 sites in France and 15 sites in South Korea).

Timelines

Patient enrollment began in March 2010 and is anticipated to finish in December 2018. Mean patient follow-up is expected to be about three years, but the study will continue until at least 385 participants have experienced a primary efficacy outcome event. The main results are anticipated to be available in 2020.

Study population

Screening ischaemic stroke patients for participation is based on key eligibility criteria as summarised in Table 1. In short, patients > 18 (in France) ≥ 20 (in South Korea) year-old with an ischaemic stroke or a TIA and a documented arterial stenosis ipsilateral to the cerebral ischaemic area for whom most current guidelines recommend statin treatment for secondary prevention. After the qualifying stroke, patients should undergo at least one vascular imaging, i.e. carotid duplex, CTA, MRA, X-ray angiography. Transesophageal echocardiography or CT angiography

Table 1. Inclusion criteria, patients must have the following:

Patient with:

- a. recent (less than three months) documented cerebral infarction (CI) once the neurologic deficit is stabilised (investigator judgement)
- b. or recent (less than 15 days) transient ischaemic attack with at least arm of leg motor deficit or speech disturbance lasting more than 10 min
- c. or a TIA with documented ischaemic lesion (MRI or CT) in the appropriate area corresponding to the symptoms occurred less than three months before

And documented atherosclerotic disease:

- a. presence of carotid atherosclerotic disease (on the basis of carotid duplex, CTA, MRA, XRA – only the report will be required to document atherosclerotic stenosis)
- b. or presence of atherosclerotic disease of the aortic arch ≥ 4 mm (detected by transesophageal echocardiography or CT angiography)
- c. or presence of atherosclerotic disease of another cerebral artery (documented vertebral artery stenosis, basilar artery stenosis, other intracranial artery stenosis)
- d. or past-history of symptomatic coronary artery disease (based on known history of myocardial infarction, revascularisation procedure or known documented coronary artery disease by coronary angiography) tumor, arteritis, dissection, migraine/vasospasm, cerebral venous thrombosis, drug abuse)

Rankin score less than 5

A clear indication of statin treatment following AHA/ASA, ANSM or South Korean recommendations

Age >18 years (France) ≥ 20 years (South Korea)

Under contraception in case of childbearing potential

Fully informed, ability and willingness to provide written informed consent

of the aorta is optionally performed. Only the report will be required to document atherosclerotic disease of extra- or intracranial arteries or aortic arch (Table 1). Patients with carotid or intracranial artery atherosclerotic plaques causing $>50\%$ or $\leq 50\%$ stenosis or aortic arch plaque ≥ 4 mm in thickness are eligible regardless of ulceration or other features.

Exclusion criteria include CI/TIA due to arterial dissection (as documented following the judgment of the investigator) or due to cardiac source of embolism without documented atherosclerotic disease (e.g. mitral stenosis or endomyocardial fibrosis, endocarditis) [a patient with atrial fibrillation, or with a history of myocardial infarction, or with calcified aortic stenosis will be eligible if the above inclusion criteria are also met]; Symptomatic haemorrhagic stroke (the mere presence of asymptomatic cerebral microbleeding on gradient echo imaging is not an exclusion criteria); Uncontrolled hypertension (investigator judgement); Baseline LDL-C less than 100 mg/dL in statin naïve patient [a patient with baseline LDL-C equal to

Table 2. Key exclusion criteria.

1. Cerebral infarction/TIA due to arterial dissection (as documented following the judgment of the investigator) or due to cardiac source of embolism without documented atherosclerotic disease (e.g. mitral stenosis or endomyocardial fibrosis, endocarditis) a patient with atrial fibrillation, or with a history of myocardial infarction, or with calcified aortic stenosis will be eligible if the above inclusion criteria are also met]
2. Symptomatic haemorrhagic stroke (the mere presence of asymptomatic cerebral microbleeding on gradient echo imaging is not an exclusion criteria)
3. Uncontrolled hypertension (investigator judgement)
4. Baseline LDL-C less than 100 mg/dL while not taking statin [a patient with baseline LDL-C equal to 65 mg/dL, while on statin treatment can be randomised, and, if he is randomised in the 100 ± 10 mg/dL arm, statin treatment will be down-titrated to reach this target level], or patient for whom intensification of treatment is not feasible [e.g. patients with a baseline LDL-C above 100 mg/dL while on maximum dosage of the more potent statin, such as atorvastatin 80 mg/day or rosuvastatin 20 mg/day].
5. Follow-up visit impossible or anticipated bad compliance.
6. Concurrent disease that may interfere with evaluation of the primary end-point or that may prevent follow-up study visits.
7. Participation to another clinical trial

65 mg/dL, while on statin treatment can be randomised, and, if he or she is randomised in the 100 ± 10 mg/dL arm, statin treatment will be down-titrated to reach this target level], or patient for whom intensification of treatment is not feasible [e.g. patients with a baseline LDL-C above 100 mg/dL while on maximum dosage of the more potent statin, such as atorvastatin 80 mg/day or rosuvastatin 20 mg/day]. (Table 2).

Patients will be considered randomised once a therapeutic arm has been assigned and notified to investigators by CW system; the patient is then definitively considered included in the allocated therapeutic arm, even if the target LDL-C assigned has not been achieved. In the TST trial, randomisation will be stratified by centers, with a 1:1 ratio for therapeutic strategy: LDL-C < 70 mg/dL or LDL-C 100 ± 10 mg/dL.

Follow-up

Participants return for outpatient office visits at 6, and 12 months and then every 6 months until a common end-study date. LDL-C will be measured every six month, as part of usual care, immediately before the scheduled follow-up visit. At every visit, investigator will evaluate occurrence of an end-point since last visit, collect biologic data (recent fasting glucose, HbA1C, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride), verify that the target

LDL-C has been obtained, and if not will titrate statin dosage or add ezetimibe, and obtain a new LDL-C determination after 15 days of titration to verify that the target level has been achieved, then finally will prescribe a new set of blood sampling (same as above) to be performed just before the next visit (M12 to M116). Blood pressure will be measured electronically at every visit, in a seating position after a 10-min rest, and target blood pressure will be <140/90 mm Hg (<130/80 mm Hg in diabetic patients); in all patients, regardless of blood pressure control status (whether they will be considered to have a controlled blood pressure or they have no high blood pressure at baseline), it will be recommended to obtain a further 10 mm Hg reduction for SBP and 5 mm Hg reduction for DBP, using the blood pressure lowering drugs chosen by the investigator (as recommended by international and country guidelines). Fasting glucose and haemoglobin A1C will be recorded in the CRF, in diabetic as well as in non-diabetic patient. Smoking status will be recorded.

In addition, all participants will be regularly contacted by telephone by a central CRA team to remind them: to not forget the visit appointments every six month, and the preceding blood sampling. CRAs will also collect by telephone the results of interim dosage of LDL-C performed (and inform the investigator of the results, so he can contact the patient and send him a new prescription to adapt the treatment), will question about potential primary endpoint following a structured questionnaire, and will contact primary care physicians in case of patient being lost-to follow-up to retrieve information on endpoint, blood pressure and LDL-C cholesterol.

Outcome events

The primary efficacy outcome is time to recurrent ischaemic stroke or stroke of undetermined origin (documented haemorrhagic stroke is in the safety endpoint), including TIAs with positive neuroimaging, myocardial infarction, urgent revascularisation following new symptoms requiring hospitalisation, vascular death. Secondary efficacy outcomes are outlined in Table 3. As for safety outcome, we are not expecting unknown safety outcome following LDL lowering in this pragmatic trial performed under usual care. We will, however, record occurrence of haemorrhagic strokes, new onset diabetes, and, as a substudy in South Korea, fatigue (using the Fatigue Severity Scale), depression/dysthymia (using Mini International Neuropsychiatric Interview – MINI, Hospital Anxiety and Depression Scale – HADS), cognitive dysfunction (using Mini Mental State Examination – MMSE and Global Deterioration Scale – GDS), myopathy (using the following definitions

Table 3. Trial outcome events.

Occurrence of any of the following primary or secondary end-points events.
PRIMARY END-POINTS:
<i>A composite of: recurrent nonfatal stroke, nonfatal myocardial infarction, urgent revascularisation of coronary or carotid artery following new symptoms requiring hospitalisation, or vascular death</i>
SECONDARY END-POINTS:
<ul style="list-style-type: none"> • Recurrent stroke • Myocardial infarction • Vascular death • Recurrent ischaemic stroke • Recurrent ischaemic stroke or TIA • Any major coronary events (including fatal and nonfatal myocardial infarction) • Any coronary heart disease end-point (myocardial infarction, hospitalisation for acute coronary symptoms, coronary revascularization procedure) • Any revascularisation procedure (coronary, carotid, or peripheral artery) • Carotid artery revascularisation procedure • Vascular death • All causes deaths • New onset diabetes

for myalgia: muscle ache or weakness without CK elevation; and for myositis: muscle symptoms –muscle pain or soreness – with CK elevation – >10 times upper normal limit) and insomnia according to DSM IV criteria (see Case report form, supplemental file). In addition, all serious adverse events (SAEs) will be reported within 48 h. SEAs are adverse events causing death, or life-threatening, or leading to hospitalisation, or prolonged hospitalisation, or leading to disability or significant, durable impairment.

Statistical analysis plan

Baseline characteristics will be described for both strategies. Qualitative variable will be described by their proportion and quantitative variable by their proportion, mean and standard deviation.

The primary efficacy analyses will be based on the intent-to-treat population and evaluated per 100 person-years of follow-up. LDL-c < 70 mg/dL assigned patients will be compared with the LDL-c 100 ± 10 mg/dL assigned control group using a log-rank test. Kaplan–Meier estimates will be used to plot the cumulative incidence risk over time. Risk reduction will be estimated with the Cox proportional hazards model. Secondary efficacy outcomes will be analysed using similar methods as for the primary efficacy analysis (Table 3). The statistical analysis plan includes several pre-specified subgroup analyses based on age, sex, global region, time in therapeutic range of assigned LDL-c target, percent reduction in LDL-c

from baseline (>50%, 30–50%, 0–30%, increase), and patients who achieved assigned target <70 mg/dL or who had more than 50% LDL-c reduction from baseline. Per protocol analysis restricted to patients who actually achieved the target LDL-c level assigned by randomisation will also be performed.

Interim analysis

No interim analysis was initially planned since the two strategies are currently considered as usual care. However, in 2017, the steering committee decided to amend the plan, by introducing an intermediate analysis when 65% of the primary endpoints are reached. This decision was driven by two facts: (1) the study was originally designed to last four years (one year for accrual and three more years for follow-up), but it was rapidly obvious that accrual will be longer and the study protocol was amended to allow accrual of patients until 31 December 2018, with the last patient included followed one year, and all patients enrolled will be followed the entire duration of the study; therefore, the long duration of the study leads us to perform a futility analysis; (2) the results of the recent lipid-lowering trials using ezetimibe and PCSK9 inhibitors on top of moderate to intense statin treatment (Figure 1), that showed a beneficial effect of these additions, with a potential higher effect than that of the 25% relative risk reduction as hypothesised in the TST trial.^{15,16,17} For futility, the trial steering committee fixed a conditional power threshold value of 30%, and for efficacy (superiority) a nominal *p* value of 0.0076 (O'Brien Fleming) for the intermediate analysis and equal to 0.0476 for the final analysis. Intermediate analysis will occur in 2018 when 65% of events have occurred.

Study development and committees

The trial co-principal investigators (PA, EB) designed the study. The *Steering Committee* is responsible for the scientific leadership and consists of the national leaders (*n* = 6) of each participating country, the co-principal investigators, one cardiologist, one methodologist and one biostatistician experts in clinical trials. The *Publications Committee* is formed by the steering committee members and approves all manuscripts prior to submission. Outcome event verification is overseen by a central *Adjudication Committee* that will assess whether reported outcome events meet study criteria.

Since the study is performed under usual care, using drugs available on the market, and that we did not expect unknown safety outcomes following LDL-c lowering, we did not appoint an independent *Data*

Monitoring Committee. However, since we decided to perform an originally unplanned intermediate analysis in 2019, an independent review committee was appointed, including one lipidologist and one cardiologist, both highly experienced in clinical trials of lipid-lowering strategies.

Two substudies

The primary objective of the TST – Plaque Ultrasound (PL.U.S) substudy is to determine the effect of achieving an LDL-c less than 70 mg/dL versus 100 ± 10 mg/dL on incident new carotid plaque. Secondary objectives are (1) to compare the progression of common carotid artery (CCA) intima media thickness (IMT) in both therapeutic arms; (2) to evaluate the predictive value of CCA-IMT progression on incident new carotid plaque; (3) to test the correlation between reduction in clinical primary outcome events and reduction in the occurrence of new carotid plaque. New ultrasound methods of carotid arteries examination (CCA and internal carotid artery – ICA) and a software (M'ATHTM) allowing a semi-automated measure of IMT, plaque thickness, and plaque surface, now permit rigorous longitudinal study of progression of carotid atherosclerosis. The software has a high inter and intra-observer reproducibility, and allows exact repositioning of the probe using a mask drawn and saved for every patient. All six images (both CCA, both carotid bulbs, and both ICA origin) are saved online on www.iimt.fr, for central measurement. All measures will be performed by a central core lab (Intelligence in Medical Technology, IMT company) once the carotid ultrasound images are up-loaded, by experts unaware of treatment assignment.

The ASAP trial, that used the preceding version of the M'ATHTM software (EUREQATM), has shown that patients on atorvastatin 80 mg/day had less progression of CCA-IMT than patients on simvastatin in 325 patients with familial hypercholesterolemia. Two consensus conferences (the European Mannheim and the North American consensus) have defined IMT and plaque. Hence, evaluation of occurrence of new carotid plaque is now possible in multicentre trials. The EVA study has shown that the higher tertile of CCA-IMT was strongly associated with occurrence of new carotid plaque at the bifurcation or ICA origin. Based on EVA study, our hypotheses are that the incidence of new carotid artery plaque will be 25% at three years in the group of patients assigned to an LDL-c of 100 ± 10 mg/dL and that the incidence will be reduced by 25% in the group of patients assigned to an LDL-c < 70 mg/dL. Second hypothesis is that CCA-IMT will increase by 0.258 (SD 0.068) in the 100 ± 10 mg/dL group and this progression will be reduced by 30% in

the <70 mg/dL group. With a power of 90%, alpha at 5%, we calculated a sample size of 800 patients. Results will be adjusted on age, sex, and blood pressure. To be selected, each center, and each ultrasound investigator will have to be certified by the core lab, by up-loading three full carotid ultrasound examinations on www.iimt.com and have a quality index >0.5 in all exams. This is therefore a verification and (harmonisation) of the quality of image acquisition, image up-loading, image quality for plaque thickness and surface and CCA-IMT for off-line measurements. Ultrasound visits will occur at baseline, six months, two years, three years, five years (the five-year visit has been added after an amendment to the protocol, to take advantage of the longer duration of the trial overall, and compensate possible smaller sample size than expected).

The biomarker pharmaco-genetic study TST-PGS will collect plasma and DNA samples from TST participants for exploratory analyses aimed at establishing correlation between genetic loci and intensity of LDL lowering. We will evaluate the incidence of the primary outcome and secondary outcome in carriers and non-carriers of 719Arg polymorphism of *KIF-6 gene* and of *PCSK-9 gene mutations*. The substudy will integrate biomarker information, comprehensive genomics characterisation and gene expression data, as well as inflammation (US-CRP), Lp(a) and explore prediction of outcome events, and test for assigned LDL-c subgroup-by-biomarker interaction.

Description of drugs used during the trial

Statins. HMG-Co-A (hydroxy-3-méthylglutaryl coenzyme A) reductase inhibitors approved by the country authorities where the research is being conducted: Simvastatin (Zocor® and Lodalas® with doses from 5 to 40 mg/day), pravastatin (Elisor® or Vasten® with doses from 10 to 40 mg/day), fluvastatin (Fractal® and Lescor® with doses from 20 to 80 mg/day), atorvastatin (Tahor® and Lipitor® with doses from 10 to 80 mg/day), rosuvastatin (Crestor® 5, 10 or 20 mg).

Ezetimibe. Ezetimibe (Ezetrol® Zetia® 10 and 20 mg/day [ezetimibe only] or Inegy® Vitoryn® [fix association with simvastatin]) is a blocker of intestinal absorption of cholesterol. It can be associated with statin to reduce further LDL-C in case the highest dose of statin cannot reduce LDL-C to, or below the target level despite good observance, appropriate dosage and diet.

Colestyramin. (Questran®) decreases LDL-C at a dosage of 4 to 24 g/day.

Discussion

Although statin treatment is universally recommended worldwide by national and international guidelines, the exact threshold level of LDL-c to achieve after a stroke or a TIA, as well as after a coronary event remains unclear. There have been several trials in post-acute or chronic coronary artery disease showing that intense LDL-c lowering was better than less intense, but these trials did not define a threshold LDL-c level to achieve. They observed that, with the highest dosage of statin or with adding ezetimibe, patients achieved on average a LDL-c of less than 70 mg and did better than the control group, and they deducted from this observation that this was the level to target. None of these studies titrate statin dosage to achieve that specific target.

In practice, most patients after a stroke or a TIA are treated with statin but at a low or moderate dose of statin, with an achieved LDL-c around 100 mg/dL. TST is a pragmatic trial that aims to define whether achieving an LDL-c of less than 70 mg/dL is better than 100 mg/dL, using titration and therefore the minimal dosage of statin to achieve that goal. To ensure that patients are maintained to their assigned LDL-c target, a central core with CRAs calling all participants has been set-up. During the trial, patients are regularly called to ensure that they did their LDL-c measurements, to collect the results, and to transmit them to the investigator in order to modify the dosage accordingly. CRAs also make sure that the patients will not miss the visit, and whether they did experience an outcome event in-between.

The TST trial will also be an opportunity to evaluate the incidence of haemorrhagic strokes and explore whether it is or not dependent of a low LDL cholesterol, as suggested by some epidemiological studies, but never confirmed by previous statin trials, including the SPARCL trial, meta-analyses of these trials, and the recent PCSK9 inhibitors trials that achieved an unprecedented low level of LDL cholesterol (a mean of 25 mg/dL in the FOURRIER trial) without evidence of a higher risk of haemorrhagic stroke. Finally, the TST trial is closely monitoring new onset diabetes, which has been a concern in the SPARCL trial with a relative of 30% increase.

The TST trial is to be a trial that could change guidelines recommendations for using lipid-lowering agents after a stroke or a TIA of atherosclerotic origin, and could prompt future trials of lipid-lowering agents that reduce further down LDL-c to unprecedented low levels.

Committees

Steering Committee: Pierre Amarenco (Chair), Eric Bruckert (Co-Chair), Maurice Giroud, Jong S Kim

(Korean principal investigator), Julien Labreuche (Senior Biostatistician), Marie-Hélène Mahagne, Norbert Nighoghossian, Philippe Gabriel Steg (Cardiologist), Pierre-Jean Touboul, Eric Vicaud (Methodologist).

TST-PL.U.S.: Pierre Amarenco, Pierre-Jean Touboul.

TST-PGS (Pharmacogenetic study): Pierre Amarenco, Tabassome Simon.

Adjudication committee

Didier Leys (Chair), Yannick Béjot, Philippa C Lavallée, Fernando Pico, Emmanuel Touzé (neurologists), Philippe Gabriel Steg, Gregory Ducrocq, Olivier Varenne, Jeremy Abran (cardiologists).

Independent review committee (interim analysis)

Nicolas Danchin, Michel Farnier.

Monitoring

Pharmacoepidemiology center of the APHP (CEPHEPI) (Nessima Yelles, Sofia Zemouri, Salim Kerai) and the Délégation à la Recherche Clinique et à l'Innovation (Yannick Vacher).

Academic research organisation

Charles Foix Group for clinical trials in stroke (Pierre Amarenco, Julien Labreuche, Pierre-Jean Touboul, Eric Vicaud).

Academic research organisation (South Korea)

ASAN Academic Research Office, Clinical Trial Center, Asan Medical Center (Jong S Kim, YunJeong In).

Conduct of the study

The study was overseen by the Charles Foix Group for Clinical Trial in Stroke (academic research organisation), in collaboration with ASAN Clinical Trial Center (academic research organisation) for South Korean Sites, and the monitoring was performed by the Pharmacoepidemiology center of the APHP (CEPHEPI) at Bichat hospital (2010–2016) and Pitié-Salpêtrière since 2016.

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Inform consent and ethical approval

All participants (or their relatives in case of impossibility) provided written informed consent. The study protocol was approved by the local institutional review board.

Contributorship

PA conceived and designed the study together with the steering committee, wrote the protocols, found the funding, directed and conducted the study, chaired the steering committee, wrote this paper. JSK coordinated the Korean centers. JL is the biostatistician. MG, B-CL, MHM, NN, PGS were steering committee members and reviewed the manuscript for important intellectual content. TS co-chaired the TST-PGS substudy. PJT co-chaired the TST-PL.U.S. substudy. EV is the methodologist. NY is study coordinator. EB is co-chair of the TST trial. All reviewed the manuscript for important intellectual content.

Guarantor

Pierre Amarenco.

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