Benefit of a target LDL cholesterol of less than 70 mg/dL after an ischemic stroke of atherosclerotic origin with 5-year follow-up

Results of the Treat Stroke to Target trial*


*Investigator initiated RCT
Conducted by the Charles Foix Group for Clinical Trial in Stroke (ARO) at Bichat hospital – University of Paris
Supported by the French Neurovascular Society
Funding: PHRC (French government), SOS-ATTAQUE CEERBRALE Association (NPO)
Unrestricted grant: Pfizer Europe, Astra-Zeneca, Merck, Pfizer global (Korea)
Disclosures

• Pierre Amarenco:
  • Honoraria Modest: Amgen, Kowa, Shin Poong, BMS;
  • Honoraria Significant: Bayer, GSK, Fibrogen;
  • Research Grant Significant: Pfizer, AstraZeneca, Sanofi, BMS, Merck, Boston Scientific, French government
Background

• The SPARCL trial\(^1\) found a 16% relative risk reduction in stroke with atorvastatin 80 mg per day during 4.9 years of follow-up as compared to placebo in patients with stroke and no known coronary heart disease.

• In the sub group with carotid stenosis\(^2\) the relative risk reduction was 33%.

• In SPARCL, patients achieving a LDL cholesterol of less than 70 mg/dL (1.8 mmol/L) had a 28% relative risk reduction as compared to patients who achieved 100 mg/dL (2.4 mmol/L) or above\(^3\).

• Current AHA/ASA guidelines\(^4\) recommend “intense” statin therapy after an ischemic stroke of atherosclerotic origin but does not stipulate a target level of LDL cholesterol because there is limited data on outcomes with different LDL-cholesterol lowering targets.

• Therefore, there was uncertainty about the target level of LDL cholesterol is appropriate to reduce cardiovascular events after stroke.

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Patients with ischemic stroke or TIA with evidence of atherosclerosis

1:1

LDL cholesterol $100 \pm 10$ mg/dL (2.5 mmol/L)

Titration of lipid lowering treatment

LDL cholesterol <70 mg/dL (1.8 mmol/L)

≥3 years

Investigators used statin and dose of their choice in monotherapy or in combination with ezetimibe or other drugs

CRAs in the trial unit contacted with patients 3 months before the next visit, making sure they were treated to the assigned target

Patients and investigators were not maintained blinded but the adjudication committee was fully blinded

Primary End-Point

• Composite of:
  • non fatal ischemic stroke or undetermined stroke
  • non fatal MI
  • Unstable angina followed by urgent coronary revascularization
  • TIA (DWI-) followed by urgent carotid revascularization
  • and vascular death including sudden death
Study specifications

• Patients were enrolled between March 15, 2010 to December 31, 2018

• We followed-up the patients until one year after last patients included

• It was an event driven trial until an accrual of 385 primary endpoints

• Follow-up visits occurred every 6 months

• The number of center was 61 in France, 16 in Korea (joined the trial in late 2015)

• Trial was stopped on May 25, 2019 after allocated funds have been used, with 277 primary endpoints accrued

• Median follow-up 3.5 years (5.3 years in France, 2.0 years in Korea)
135 mg/dL (3.5 mmol/L)

136 mg/dL (3.5 mmol/L)

65 mg/dL (1.7 mmol/L)

96 mg/dL (2.4 mmol/L)
**PRIMARY OUTCOME**

Ischemic stroke or undetermined stroke, myocardial infarction, urgent coronary revascularization following unstable angina, urgent carotid revascularization following TIA, vascular death

**PRE SPECIFIED COVARIATES ADJUSTMENTS**
- Age
- Sex
- Entry event (ischemic stroke vs. TIA)
- Time from symptom onset to randomization
- Geographical region (France vs Korea) (SPARCL trial adjustment)

Adjusted HR = 0.78 [95% CI: 0.61 to 0.98; P value = 0.036]

Non adjusted HR = 0.77 [95% CI: 0.61-0.97; P value = 0.029]

Median follow-up 3.5 years

A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke

## Key subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>&lt;70 mg/dL</th>
<th>100±10 mg/dL</th>
<th>Hazard ratio (95%CI)</th>
<th>Hazard ratio (95%CI)</th>
<th>Nominal interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>France</td>
<td>103/1073</td>
<td>139/1075</td>
<td>0.73 (0.57-0.95)</td>
<td>0.73 (0.57-0.95)</td>
<td>0.26</td>
</tr>
<tr>
<td>South Korea</td>
<td>18/357</td>
<td>17/355</td>
<td>1.11 (0.57-2.15)</td>
<td>1.11 (0.57-2.15)</td>
<td></td>
</tr>
</tbody>
</table>

- F/U was 5.3 years in France and 2.0 years in Korea
- Exposure time drives the benefit of lipid lowering therapy\(^1\)
- SPARCL trial lasted 4.9 years

Randomized (n=2873)

- Korean center (n=715)
- French center (n=2158)

Allocation

Assigned to LDL-c<70mg/dL target (n=1081)
- Did not meet the inclusion criteria (n=23)

Followed for endpoints through end of the study (n=786)
- Lost to follow-up (n=62)
- No signed consent (n=8)
- Withdrawn consent (n=121)
- Other reasons (n=104)
  - Serious adverse event (n=2)
  - Investigator's decision (n=102)

Analyzed (n=1073)
- Excluded (n=8 no signed consent)

Primary Analysis

Assigned to LDL-C 100±10 mg/dL target (n=1077)
- Did not meet the inclusion criteria (n=21)

Followed for endpoints through end of the study (n=806)
- Lost to follow-up (n=49)
- No signed consent (n=2)
- Withdrawn consent (n=108)
- Other reasons (n=112)
  - Serious adverse event (n=3)
  - Investigator's decision (n=109)

Analyzed (n=1075)
- Excluded (n=2 no signed consent)
## Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LDL-c &lt;70 mg/dL (N=1073)</th>
<th>LDLc 100±10 mg/dL (N=1075)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67.2 (11.2)</td>
<td>67.6 (11.0)</td>
</tr>
<tr>
<td>Male sex, no/total no, (%)</td>
<td>727/1073 (67.8)</td>
<td>741/1075 (68.9)</td>
</tr>
<tr>
<td>Body-mass index, median (IQR)</td>
<td>26.2 (23.7-29.1)</td>
<td>26.3 (23.8-29.1)</td>
</tr>
<tr>
<td>Entry event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>881/1068 (82.5)</td>
<td>896/1074 (83.4)</td>
</tr>
<tr>
<td>TIA (DWI- or CT-)</td>
<td>187/1068 (17.5)</td>
<td>178/1074 (16.6)</td>
</tr>
<tr>
<td>Time since entry event, days, median (IQR)</td>
<td>6.0 (3.0-9.0)</td>
<td>6.0 (3.0-9.0)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, no/total no, (%)</td>
<td>693/1070 (64.8)</td>
<td>727/1073 (67.8)</td>
</tr>
<tr>
<td>Diabetes, no/total no, (%)</td>
<td>198/1069 (18.5)</td>
<td>188/1070 (17.6)</td>
</tr>
<tr>
<td>Dyslipidemia, no/total no, (%)</td>
<td>674/1069 (63.0)</td>
<td>647/1070 (60.5)</td>
</tr>
<tr>
<td>Former smoker, no/total no, (%)</td>
<td>276/1068 (25.8)</td>
<td>241/1071 (22.5)</td>
</tr>
<tr>
<td>Current smoker, no/total no, (%)</td>
<td>333/1068 (31.2)</td>
<td>315/1071 (29.4)</td>
</tr>
<tr>
<td>Stroke or TIA, no/total no, (%)</td>
<td>123/1068 (11.5)</td>
<td>115/1073 (10.7)</td>
</tr>
<tr>
<td>Coronary artery disease, no/total no, (%)</td>
<td>225/1070 (21.0)</td>
<td>194/1073 (18.1)</td>
</tr>
<tr>
<td>Statin naïve (%)</td>
<td>645/1069 (60.3)</td>
<td>624/1070 (58.3)</td>
</tr>
</tbody>
</table>
Statin only 94%
Statin+Ezetimibe 5%

137 mg/dL (3.5 mmol/L)

Statin only 66%
Statin+Ezetimibe 33%

47% > 70 mg/dL
45% 50-70 mg/dL
8% < 50 mg/dL
66 mg/dL (1.7 mmol/L)

Université de Paris
Achievement of prevention targets in the two treatment arms

**Blood pressure lowering**
- Systolic: 143 mm Hg to 135 mm Hg
- Diastolic: 80 mm Hg to 75 mm Hg

**Diabetes control**
- Hb A1C: 8.3% to 8.1% to 7.0%

**Active smokers**
- Smoking cessation: -83%

**Diabetes control**
- 18% Diabetics
PRIMARY OUTCOME
Ischemic stroke or undetermined stroke, myocardial infarction, urgent coronary revascularization following unstable angina, urgent carotid revascularization following TIA, vascular death

PRE SPECIFIED COVARIATES ADJUSTMENTS
- Age
- Sex
- Entry event (ischemic stroke vs. TIA)
- Time from symptom onset to randomization
- Geographical region (France vs Korea) (SPARCL trial adjustment)

Median follow-up 5.3 years

Adjusted HR = 0.74 [95% CI : 0.57 to 0.95; P value = 0.019]

Non adjusted HR = 0.73 [95% CI; 0.57-0.94; P value = 0.015]
<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>LDL &lt;70 mg/dL (N=1073)</th>
<th>LDL 100±10 mg/dL (N=1430)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>myocardial infarction and urgent coronary revascularization</td>
<td>18/1073 (1.7)</td>
<td>27/1075 (2.5)</td>
<td>0.66 (0.67-1.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cerebral infarction or urgent carotid and cerebral artery revascularization</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>following a TIA DWI</td>
<td>72/1073 (6.7)</td>
<td>98/1075 (9.1)</td>
<td>0.73 (0.54-0.99)</td>
<td>0.046</td>
<td>42</td>
</tr>
<tr>
<td>cerebral infarction or TIA</td>
<td>103/1073 (9.6)</td>
<td>125/1075 (11.6)</td>
<td>0.83 (0.64-1.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>any revascularization procedure (both urgent and elective)</td>
<td>90/1073 (8.4)</td>
<td>87/1075 (8.0)</td>
<td>1.01 (0.75-1.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid</td>
<td>17/90</td>
<td>22/87</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Coronary</td>
<td>41/90</td>
<td>41/87</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral</td>
<td>32/90</td>
<td>24/87</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vascular death</td>
<td>22/1073 (2.1)</td>
<td>29/1075 (2.7)</td>
<td>0.76 (0.44-1.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>all cause death</td>
<td>86/1073 (8.0)</td>
<td>86/1075 (8.0)</td>
<td>1.00 (0.74-1.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction or intracranial hemorrhage</td>
<td>80/1073 (7.5)</td>
<td>112/1075 (10.4)</td>
<td>0.72 (0.54-0.96)</td>
<td>0.023</td>
<td>35</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>13/1073 (1.2)</td>
<td>11/1075 (1.0)</td>
<td>1.17 (0.53-2.62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed diabetes</td>
<td>87/1073 (8.1)</td>
<td>66/1075 (6.1)</td>
<td>1.33 (0.97-1.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome or intracranial hemorrhange</td>
<td>111/1073 (10.3)</td>
<td>146/1075 (13.6)</td>
<td>0.75 (0.58-0.96)</td>
<td>0.021</td>
<td>30</td>
</tr>
</tbody>
</table>
# Key subgroups

<table>
<thead>
<tr>
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<th>100±10 mg/dL</th>
<th>Hazard ratio</th>
<th>Hazard ratio (95%CI)</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic of index event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>82/881</td>
<td>128/896</td>
<td>0.63</td>
<td>0.48-0.83</td>
<td>0.005</td>
</tr>
<tr>
<td>TIA</td>
<td>21/187</td>
<td>11/178</td>
<td>1.94</td>
<td>0.94-4.03</td>
<td></td>
</tr>
<tr>
<td>Diabete mellitus at baseline</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20/198</td>
<td>33/188</td>
<td>0.58</td>
<td>0.33-1.00</td>
<td>0.31</td>
</tr>
<tr>
<td>No</td>
<td>82/849</td>
<td>103/861</td>
<td>0.80</td>
<td>0.60-1.06</td>
<td></td>
</tr>
<tr>
<td>Time in therapeutic range</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>0%-49%</td>
<td>38/384</td>
<td>36/389</td>
<td>1.07</td>
<td>0.68-1.68</td>
<td>0.007</td>
</tr>
<tr>
<td>50%-100%</td>
<td>65/687</td>
<td>103/682</td>
<td>0.60</td>
<td>0.42-0.84</td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSIONS

• In patients with ischemic stroke associated with atherosclerotic disease

• As compared to a target LDL of 100 mg/dL (2.4 mmol/L)

• Targeting a LDL cholesterol of less than 70 mg/dL (1.8 mmol/L) during 5.3 years avoided
  • 1 subsequent major vascular event in 4
  • 1 ischemic stroke or intracranial hemorrhage in 4
  • without increasing the risk of intracranial hemorrhage
  • with a number needed to treat of 30
  • With no harm (intracerebral hemorrhage)
Benefit of Targeting a LDL (Low-Density Lipoprotein) Cholesterol <70 mg/dL During 5 Years After Ischemic Stroke

Pierre Amarenco, MD; Jong S. Kim, MD; Julien Labreuche, BST; Hugo Charles, BST; Maurice Giroud, MD; Byung-Chul Lee, MD; Marie-Hélène Mahagne, MD; Norbert Nighoghossian, MD; Philippe Gabriel Steg, MD; Éric Vicaud, MD; Éric Bruckert, MD; on behalf of the Treat Stroke to Target Investigators*

Background and Purpose—The TST trial (Treat Stroke to Target) evaluated the benefit of targeting a LDL (low-density lipoprotein) cholesterol of <70 mg/dL to reduce the risk of cardiovascular events in 2860 patients with ischemic stroke with atherosclerotic stenosis of cerebral vasculature or aortic arch plaque >4 mm, in a French and Korean population. The follow-up lasted a median of 5.3 years in French patients (similar to the median follow-up time in the SPARCL trial [Stroke Prevention by Aggressive Reduction in Cholesterol Level]) and 2.0 years in Korean patients. Exposure duration to statin is a well-known driver for cardiovascular risk reduction. We report here the TST results in the French cohort.

Methods—One thousand seventy-three French patients were assigned to <70 mg/dL (1.8 mmol/L) and 1075 to 100±10 mg/dL (90–110 mg/dL, 2.3–2.8 mmol/L). To achieve these goals, investigators used the statin and dosage of their choice and added ezetimibe on top if needed. The primary outcome was the composite of ischemic stroke, myocardial infarction, new symptoms requiring urgent coronary or carotid revascularization and vascular death.

Results—After a median follow-up of 5.3 years, the achieved LDL cholesterol was 66 (1.69 mmol/L) and 96 mg/dL (2.46 mmol/L) on average, respectively. The primary end point occurred in 9.6% and 12.9% of patients, respectively (HR, 0.74 [95% CI, 0.57–0.94]; P=0.019). Cerebral infarction or urgent carotid revascularization following transient ischemic attack was reduced by 27% (P=0.046). Cerebral infarction or intracranial hemorrhage was reduced by 28% (P=0.023). The primary outcome or intracranial hemorrhage was reduced by 25% (P=0.021). Intracranial hemorrhages occurred in 13 and 11 patients, respectively (HR, 1.17 [95% CI, 0.53–2.62]; P=0.70).

Conclusions—After an ischemic stroke of documented atherosclerotic origin, targeting a LDL cholesterol of <70 mg/dL during 5.3 years avoided 1 subsequent major vascular event in 4 (number needed to treat of 30) and no increase in intracranial hemorrhage.

Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT01252875. (Stroke. 2020;51:00-00. DOI: 10.1161/STROKEAHA.119.028718.)