The Japan Statin Treatment Against Recurrent Stroke (J-STARS): a multicenter, randomized, open-label, parallel-group study

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12)Federation of National Public Service Personnel Mutual Aid Associations Tachikawa Hospital, Tokyo, Japan
Disclosures

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Age-adjusted and sex-adjusted stroke mortality rates. Rates are highest in eastern Europe, north Asia, central Africa, and the south Pacific.
Cardio- and Cerebrovascular Event Rate in patients with atherothrombosis –REACH registry–

Adjusted with sex and age.
MI: myocardial infarction

Cerebral Hemorrhage Event Rate in Aspirin Clinical Study

- Aspirin (81-325mg)
- Aspirin (50mg) + Dipyridamole

*Data of Intracranial Hemorrhage instead of Cerebral Hemorrhage

2) Bhatt DL et al. *NEJM.* 2006; 354: 1706-17
4) Benavente O, Presented at International Stroke Conference 2012 (New Orleans))
In Japan, it is still unclear if hyperlipidemia is a risk factor of recurrent stroke or not in the ischemic stroke patients without coronary heart disease (CHD), though inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase could decrease the incidence of cardiovascular diseases including CHD and ischemic stroke in this population (Management of Elevated cholesterol in the primary prevention Group of Adult Japanese, MEGA).

High dose of atorvastatin (80mg per day) was shown to decrease the overall incidence of strokes in the patients with stroke or TIA (Stroke Prevention by Aggressive Reduction in Cholesterol Levels, SPARCL).

The neuroprotective mechanism beyond cholesterol-lowering effects could be expected to attenuate cerebrovascular inflammation and atherosclerosis.

The present study hypothesizes if treatment with low dose of pravastatin (10mg per day) prevents recurrent stroke in Japanese patients with ischemic stroke with safety.
## Pre-specified and Post-hoc Analyses in SPARCL

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin 80mg N (%)</th>
<th>Placebo N (%)</th>
<th>HR, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-specified</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>265 (11.2)</td>
<td>311 (13.1)</td>
<td>0.84, 0.03</td>
</tr>
<tr>
<td>Fatal Stroke</td>
<td>24 (1.0)</td>
<td>41 (1.7)</td>
<td>0.57, 0.03</td>
</tr>
<tr>
<td>Non-Fatal Stroke</td>
<td>247 (10.4)</td>
<td>280 (11.8)</td>
<td>0.87, 0.11</td>
</tr>
<tr>
<td><strong>Post-hoc</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>218 (9.2)</td>
<td>274 (11.6)</td>
<td>0.78, 0.01</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>55 (2.3)</td>
<td>33 (1.4)</td>
<td>1.66, 0.02</td>
</tr>
<tr>
<td>(Fatal Case)</td>
<td>17 (0.7)</td>
<td>18 (0.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

In Japan, it is still unclear if hyperlipidemia is a risk factor of recurrent stroke or not in the ischemic stroke patients without coronary heart disease (CHD), though inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase could decrease the incidence of cardiovascular diseases including CHD and ischemic stroke in this population (Management of Elevated cholesterol in the primary prevention Group of Adult Japanese, MEGA).

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Background & Aims

■ Although statin therapy is beneficial for preventing first strokes, the benefit for recurrent stroke and its subtypes remains to be determined in Asian population.

■ This study examined whether treatments with low-dose pravastatin prevent recurrence in ischemic stroke patients.
**Pravastatin**

Selective and competitive inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, that can decrease cholesterol biosynthesis in the liver.

**Design**

A multi-center, prospective, randomized, open labeled, blinded-endpoint, active controlled, parallel group trial.
Population studied

- Any patients age 45-80 years old with ischemic stroke after 1 month to 3 years from onset.

- Diagnosed as hyperlipidemia with the total cholesterol concentration of 180-240mg/dl under no prescription of statin in the recent 30 days.

- Exclusion criteria includes,
  (1) cardiogenic embolism and ischemic stroke of other determined or undetermined cause according to the TOAST classification,
  (2) ischemic heart disease to require statins,
  (3) hemorrhagic disorders,
  (4) liver or renal disorders,
  (5) cancer, and (6) scheduled operation.

- The above enrollment criteria were determined by a preliminary study called J-STARS-C (J-STARS-Cross-sectional).
Design of J-STARS

Randomized Controlled Trial
PROBE method

Enrollment Criteria
- Ischemic Stroke
  1 month ~ 3 yrs ago
- TC 180 ~ 240 mg/dl
- >45 yrs, <80 yrs

Exclusion Criteria
- Cardioembolic Stroke

A total of 1578 patients were enrolled and completed follow-up. (originally this study was designed to recruit 3000 patients).
Outcome Measures

**Primary endpoints**
Any cerebrovascular events, including TIA

**Secondary endpoints**
1. Events of ischemic stroke or hemorrhagic stroke
2. Myocardial infarction
3. Any cardiovascular events
4. Any cerebrovascular and cardiovascular events
5. Death of stroke
6. Death of cardiovascular events
7. Death of all causes
8. Admission to the hospital
9. Activity of daily living by modified Rankin scale score and Barthel index
10. Dementia and cognitive impairment.
J-STARS has started since March 2004.
A total of 1,578 patients were recruited from 123 centers by 2009.
1589 patients randomized

4 patients excluded from analysis
2 overlapped registration
2 exclusion criteria violation

Intended-to-treat analysis set (n=1578) 793 patients

13 patients did not take pravastatin

Safety analysis set (n=1565) 780 patients

11 patients had no evaluation of primary endpoint

Full analysis set (n=1547) 769 patients

143 patients had less than 1/4 adherence to pravastatin during observation period

Per protocol set (n=1300) 626 patients

7 patients excluded from analysis
2 overlapped registration
5 exclusion criteria violation

785 patients

7 patients had no evaluation of primary endpoint

778 patients

104 patients had any statin

674 patients

ITT analysis
Pravastatin group (n=793)
Control group (n=785)
## Baseline characteristics I

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pravastatin n=793</th>
<th>Control n=785</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66.1±8.4</td>
<td>66.4±8.6</td>
<td>0.53</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>545 (68.7)</td>
<td>542 (69.0)</td>
<td>0.89</td>
</tr>
<tr>
<td>Height, cm</td>
<td>160.4±8.8</td>
<td>160.1±8.6</td>
<td>0.43</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>61.5±10.2</td>
<td>60.7±10.1</td>
<td>0.11</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.8±3.1</td>
<td>23.6±3.0</td>
<td>0.17</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>513 (64.7)</td>
<td>515 (65.6)</td>
<td>0.70</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>185 (23.3)</td>
<td>184 (23.4)</td>
<td>0.96</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>37 (4.7)</td>
<td>44 (5.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>Smoking habit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>426 (53.7)</td>
<td>420 (53.5)</td>
<td>0.98</td>
</tr>
</tbody>
</table>
## Baseline characteristics II

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pravastatin n=793</th>
<th>Control n=785</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.45±0.62</td>
<td>5.42±0.64</td>
<td>0.40</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.39±0.41</td>
<td>1.37±0.41</td>
<td>0.47</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.35±0.63</td>
<td>3.35±0.64</td>
<td>0.96</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.61±0.85</td>
<td>1.60±0.82</td>
<td>0.91</td>
</tr>
<tr>
<td>Ischemic stroke subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic infarction, n (%)</td>
<td>195 (24.6)</td>
<td>206 (26.2)</td>
<td></td>
</tr>
<tr>
<td>Lacunar infarction, n (%)</td>
<td>502 (63.3)</td>
<td>504 (64.2)</td>
<td>0.67</td>
</tr>
<tr>
<td>Infarction of undetermined etiology, n (%)</td>
<td>96 (12.1)</td>
<td>75 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Use of antiplatelet agents, n (%)</td>
<td>723 (91.2)</td>
<td>715 (91.1)</td>
<td>0.98</td>
</tr>
</tbody>
</table>
Changes in the lipid profile

A. Total cholesterol

B. LDL cholesterol

C. Triglyceride

D. HDL cholesterol

- Pravastatin
- Control

p<0.001

p<0.001

p=0.006

p=0.004
Kaplan-Meier curves for the primary endpoints.

A. Stroke and TIA

- Pravastatin: 2.56%/year
- Control: 2.65%/year
- adjusted HR 0.97 (95%CI 0.73 to 1.29)*

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>793</td>
<td>724</td>
<td>687</td>
<td>642</td>
<td>596</td>
<td>528</td>
<td>44</td>
</tr>
<tr>
<td>Control</td>
<td>785</td>
<td>739</td>
<td>683</td>
<td>633</td>
<td>601</td>
<td>534</td>
<td>68</td>
</tr>
</tbody>
</table>

* adjusted with the subtype of stroke, elevated blood pressure, and diabetes mellitus
Kaplan-Meier curves for the primary and secondary endpoints.

<table>
<thead>
<tr>
<th>A. Stroke and TIA</th>
<th>B. Atherothrombotic infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>0.21%/year</td>
</tr>
<tr>
<td>Control</td>
<td>0.65%/year</td>
</tr>
<tr>
<td>adjusted HR</td>
<td>0.33 (95%CI 0.15 to 0.74)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
</tr>
<tr>
<td>Control</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Lacunar infarction</th>
<th>D. Hemorrhagic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>0.31%/year</td>
</tr>
<tr>
<td>Control</td>
<td>0.31%/year</td>
</tr>
<tr>
<td>adjusted HR</td>
<td>1.00 (95%CI 0.45 to 2.22)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
</tr>
<tr>
<td>Control</td>
</tr>
</tbody>
</table>

* adjusted with the subtype of stroke, elevated blood pressure, and diabetes mellitus
Kaplan-Meier curves for the primary and secondary endpoints.

**Pravastatin:** 3.23%/year  
**Control:** 3.81%/year  
adjusted HR 0.85  
(95%CI 0.66 to 1.09)*

**Pravastatin:** 0.90%/year  
**Control:** 1.11%/year  
adjusted HR 1.23  
(95%CI 0.79 to 1.93)*

*adjusted with the subtype of stroke, elevated blood pressure, and diabetes mellitus
Changes in the stroke-related outcomes.

- **A. Modified Rankin Scale**
  - p=0.69

- **B. Barthel index**
  - p=0.88

- **C. Clinical dementia rating**
  - p=0.53

- **D. Mini-mental state examination**
  - p=0.18

Analyzed using mixed-effects model with repeated measurements (MMRM).
<table>
<thead>
<tr>
<th></th>
<th>J-STDARS (N=1,578)</th>
<th>CSPS II (N=2,757)</th>
<th>SPARCL (N=4,731)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days from onset to enrollment (mean±SD)</td>
<td>314.2±308.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age (years, mean±SD)</td>
<td>66.2±8.5</td>
<td>63.5±9.2</td>
<td>63.4±9.0</td>
</tr>
<tr>
<td>Gender (male, %)</td>
<td>68.8</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg, mean±SD)</td>
<td>137.1±17.8</td>
<td>140.0±19.1</td>
<td>139.6±18.4</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg, mean±SD)</td>
<td>79.3±11.3</td>
<td>81.5±11.9</td>
<td>81.2±12.1</td>
</tr>
<tr>
<td>BMI</td>
<td>23.7±3.08</td>
<td>24.0±3.1</td>
<td>23.9±3.1</td>
</tr>
</tbody>
</table>
Discussions (1):

- Although the sample size was initially set to be 3000, the target was not achieved and 1589 patients were recruited for this study, largely due to the narrower window of patient eligibility. Randomization was successfully conducted and both group patients demonstrated similarly well controlled cardiovascular risk factor profiles at enrollment.

- Although the dose of pravastatin (10 mg/day) was much lower than used in previous studies from the western countries, levels of total cholesterol and LDL cholesterol were substantially reduced and kept in the normal ranges in the prevastatin group and levels of HDL cholesterol were slightly but significantly higher in the prevastatin group, which could have exerted favorable impact on arteries in this group of patients.

- Blood pressure level was similarly well controlled in both groups, making it unlikely that the level exerted significant influence on the recurrence of stroke in either group.
Discussions (2):

- Incidence of recurrent stroke (approximately 2.6%/year in both groups) was roughly half of our assumption (5%/year) at sample size calculation, but it turned out to be similar to the recent study from our country (i.e., CSPS 2).

- Most notably, although total stroke recurrence was similar between the two groups, onset of atherothrombotic infarction was less frequent in the pravastatin group, whereas no significant difference was found for other stroke subtypes. This finding may be reasonable, if pravastatin exerted atheroprotective effects on the carotid and major cerebral arteries. However, reduction of LDL cholesterol was only 20% in this study, compared to the baseline, and other mechanisms such as pleiotropic effects of statins, including atheromatosus plaque stabilization and anti-inflammation could also play pivotal roles for stroke prevention. These mechanisms were explored by concurrent sub-studies focusing on chronic inflammation (NCT00361699) and carotid atherosclerosis (NCT00361530).
Discussions (3):

- The incidence of lacunar infarction was similar between the two groups and pravastatin is not likely to suppress the stroke of small arterial pathologies, as generally referred to “small vessel disease”. Although statin treatment could increase the risk of intracranial hemorrhage, the occurrence was virtually the same between two groups. In the current study, LDL cholesterol level in the pravastatin group was only “moderately low (2.68 mmol/L)” and was substantially higher than in SPARCL trial (1.89 mmol/L) in which risk of intracranial hemorrhage was increased.
Conclusions:

- Low-dose pravastatin treatment significantly suppressed the occurrence of atherothrombotic infarction in patients experiencing non-cardioembolic ischemic stroke.
- However, this treatment did not alter the incidence of other stroke subtypes.
- Suggesting the necessity of stroke risk assessment based on the subtypes due to heterogeneity of stroke.
- These results may help refine preventive strategies for stroke recurrence.
Acknowledgements:

- Patients and Families
- Enrolling Centers (123 centers in Japan)
- All of the investigators (630 in total), including members of several committees and the late Dr Hideo Tohgi for his invaluable advice on conceptualization of the study protocol and the late Dr Takeshi Shima for his great help as a member of regional promotion committee.
- We would also like to show our appreciation for Mr Tatsuo Kagimura, Mr Hideki Kohno and Ms Yoko Nakagawa for their statistical assistance.
Thank you!