Pravastatin Decreases Wall Shear Stress and Blood Velocity in the Internal Carotid Artery Without Affecting Flow Volume
Results From the PROSPER MRI Study

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Background and Purpose—Despite speculations, it is unknown whether statins affect wall shear stress (WSS). Therefore, the effect of pravastatin on WSS was investigated.

Methods—In 355 elderly individuals participating in the PROSPER study (follow up after 3 years), the effect of 40 mg pravastatin on WSS was assessed in the internal carotid artery using magnetic resonance imaging.

Results—WSS and blood velocity decreased both in the pravastatin group and in the placebo group but decreased faster in the pravastatin group ($P<0.04$, $P<0.02$). Blood volume flow did not differ between the groups.

Conclusions—In elderly subjects, the WSS and blood velocity of the internal carotid artery declines significantly over time and this decline is more pronounced in subjects treated with 40 mg pravastatin compared with the placebo group. (Stroke. 2007;38:1374-1376.)

Key Words: blood flow ■ blood flow velocity ■ computer-assisted ■ image processing ■ magnetic resonance imaging ■ statins

Aterial vessel areas with low or oscillating wall shear stress (WSS) are most prone to develop atherosclerotic plaques.1 Statins have been shown to be important clinical pharmacological tools to prevent atherosclerosis and have other favorable effects, eg, increasing nitric oxide availability and reducing blood viscosity.2–4

To date, the possible effects of statins on WSS are unknown. An increase in WSS will decrease atherosclerotic plaques and increase nitric oxide availability, whereas a decrease in blood viscosity will reduce WSS.1,5 We examined the effect of 40 mg pravastatin per day on WSS in the internal carotid artery in subjects participating in the nested magnetic resonance imaging (MRI) study of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER).6

Methods

The PROSPER is a double-blind, randomized, placebo-controlled trial aimed at assessing the effect of therapy with 40 mg pravastatin on vascular events in 5804 men and women, aged 70 to 82 years, with vascular disease or at risk for vascular disease.6 Three hundred fifty-five Dutch participants of the PROSPER study had two successive MRIs of the internal carotid artery, allowing the assessment of WSS. The first MRI was acquired during the lead-in period and the second MRI after an average follow up of 33 (SD=1.4) months.

Flow measurements were performed on a 1.5 T-MR system (Philips Medical Systems) in a plane perpendicular to the internal carotid artery 4 cm distal to the bifurcation. We used a gradient echo phase-contrast technique with retrospective gating with peripheral pulse unit; repetition time/echo time 16/9 ms; flip angle 7.5°; slice thickness 5 mm, scan matrix 256×154, field of view 250×188 mm, velocity encoding 100 cm/s, and 1 number of signal averages.

For a parabolic velocity profile the flow volume (Flow), the maximum velocity in the vessel cross section (Vmax), the diameter (Diam), and WSS have the following relations5,7:

\[
Diam = \sqrt{\frac{8 \times \text{Flow}}{\text{Vmax}}} \quad (1)
\]

and

\[
WSS = \frac{4 \times \mu \times \text{max/Diam}}{\pi} \quad (2)
\]

The viscosity ($\mu$) was taken as 3.39 mPa/s at baseline and 3.32 mPa/s at follow up.4 The cardiac cycle was divided into 16 time phases. To segment the image, a parabolic velocity profile was fitted to the measured data (Figure).7 Parameters during systole and diastole were assessed by averaging the three consecutive phases with highest and lowest Flow, respectively. For calculation of the probability values, we used the linear mixed model corrected for smoking behavior.
Results
Baseline characteristics for the 355 participants are presented in Table 1. In the pravastatin group, low-density lipoprotein decreased from 3.9±0.8 mmol/L to 2.5±0.5 mmol/L and high-density lipoprotein increased from 1.2±0.3 mmol/L to 1.3±0.4 mmol/L at follow up; cholesterol in the placebo group remained unaltered. This was similar to the entire PROSPER study group.6 We found no significant differences in blood pressure between the two groups. Errors in data conversion and positioning of the scan plane left 328 vessels in the pravastatin group and 334 vessels in the placebo group for analysis. WSS, Flow, Vmax, and Diam data are presented in Table 2. At baseline, there were no significant differences in these parameters between the groups. At follow up, WSS and Vmax-M showed a significant decrease in both groups. However, in the pravastatin group, the decrease in WSS and Vmax and the increase in Diam was larger than in the control group (P<0.05).

Discussion
Our study indicates that WSS decreases faster over time in elderly individuals treated with pravastatin than in those treated with placebo. This finding is surprising because it can be expected that because of its reducing effect on atherosclerosis, pravastatin would lead to less decrease of WSS over time.

We confirmed WSS decline with age measured by Gnasso et al in both groups.5 A decrease in Flow or Vmax, in the paraboloid model, gives a WSS decrease and a diameter increase gives a WSS decrease. The faster WSS decrease in the pravastatin group is probably caused by the fast decrease in Vmax. Because blood velocity increases in the presence of a stenosis,8 a relative decrease in Vmax might reflect a decrease of stenoses.

As a result of the limited resolution of our MRI protocol, the diameter could not be measured directly. An increase in diameter for the pravastatin group is in agreement with Stroes et al.9 However, a faster decay of Vmax compared with Flow would give a wrong impression of diameter increase (Equation 1).
TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=178)</th>
<th>Pravastatin (n=177)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean±SEM</td>
<td>75.0±3.23</td>
<td>74.9±3.07</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>110 (61.8)</td>
<td>95 (53.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg, mean±SEM</td>
<td>156±20.4</td>
<td>157±21.7</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg, mean±SEM</td>
<td>86±10.7</td>
<td>85±11.3</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L, mean±SEM</td>
<td>5.7±0.91</td>
<td>5.8±0.85</td>
<td>NS</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mmol/L, mean±SEM</td>
<td>3.9±0.77</td>
<td>3.9±0.75</td>
<td>NS</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mmol/L, mean±SEM</td>
<td>1.3±0.32</td>
<td>1.2±0.34</td>
<td>NS</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>51 (28.7)</td>
<td>28 (15.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>30 (16.9)</td>
<td>24 (13.6)</td>
<td>NS</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>102 (57.3)</td>
<td>119 (67.2)</td>
<td>NS</td>
</tr>
<tr>
<td>History of myocardial infarction, n (%)</td>
<td>26 (14.6)</td>
<td>21 (11.9)</td>
<td>NS</td>
</tr>
<tr>
<td>History of stroke or transient ischemic attack, n (%)</td>
<td>37 (20.8)</td>
<td>24 (13.6)</td>
<td>NS</td>
</tr>
<tr>
<td>History of any vascular disease, n (%)</td>
<td>83 (46.6)</td>
<td>78 (44.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS indicates not significant.

Summary

In elderly subjects, the WSS and Vmax of the internal carotid artery declines significantly over time and this decline is more pronounced in subjects treated with 40 mg pravastatin compared with the placebo group.

Appendix


Table 1: WSS and Related Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n=178)</th>
<th>Pravastatin (n=177)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>WSS-M</td>
<td>0.63±0.16</td>
<td>0.54±0.16</td>
<td>4.69±10</td>
</tr>
<tr>
<td>WSS-D</td>
<td>0.46±0.12</td>
<td>0.39±0.12</td>
<td>5.31±10</td>
</tr>
<tr>
<td>Flow-M</td>
<td>194±45</td>
<td>189±45</td>
<td>0.129</td>
</tr>
<tr>
<td>Flow-D</td>
<td>121±35</td>
<td>117±35</td>
<td>0.098</td>
</tr>
<tr>
<td>Flow-S</td>
<td>300.3±82</td>
<td>299±80</td>
<td>0.503</td>
</tr>
<tr>
<td>Vmax-M</td>
<td>260±49</td>
<td>244±46</td>
<td>4.56±10</td>
</tr>
<tr>
<td>Vmax-D</td>
<td>179±38</td>
<td>167±36</td>
<td>6.30±10</td>
</tr>
<tr>
<td>Vmax-S</td>
<td>385±84</td>
<td>366±81</td>
<td>3.96±10</td>
</tr>
<tr>
<td>Diam-M</td>
<td>4.37±0.48</td>
<td>4.44±0.48</td>
<td>0.067</td>
</tr>
<tr>
<td>Diam-D</td>
<td>4.14±0.48</td>
<td>4.19±0.48</td>
<td>0.209</td>
</tr>
<tr>
<td>Diam-S</td>
<td>4.49±0.53</td>
<td>4.57±0.55</td>
<td>0.051</td>
</tr>
</tbody>
</table>

The results are: Flow in mL/min, Vmax in mm/s, Diam in mm, and WSS in Pa with± the SD. M, S, and D refer to mean values over the cardiac cycle, systole, and end-diastole, respectively. There was no significant difference at the baseline between the groups for all parameters. The difference at follow up is given in the column “Diff Pravastatin–Placebo.” P<0.05 is indicated with asterisks (*).


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Disclosures

None.

References

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