Atorvastatin at 80 mg/d reduced cerebrovascular events more than atorvastatin at 10 mg/d in stable coronary heart disease


**Clinical impact ratings:** Cardiology ★★★★★★☆ Endocrinology ★★★★★★☆ Neurology ★★★★★★☆

**Question**
In patients with stable coronary heart disease (CHD), is intensive atorvastatin therapy more effective than moderate atorvastatin therapy for reducing cerebrovascular events?

**Methods**
Design: Randomized controlled trial.
Allocation: (Concealed)†.*
Blinding: Blinded (clinicians, patients, and endpoints adjudication committee).*
Follow-up period: Median 4.9 years.
Setting: 256 sites in 14 countries across 4 continents.
Patients: 10,001 patients 35 to 75 years of age (mean age 61 y, 81% men) who had clinically evident CHD (defined as previous myocardial infarction or coronary revascularization, or previous or current angina with objective evidence of CHD), low-density lipoprotein cholesterol (LDL-C) level 130 to 250 mg/dL (3.4 to 6.5 mmol/L), and triglyceride level ≤ 600 mg/dL (6.8 mmol/L). LDL-C level was required to be < 130 mg/dL (3.4 mmol/L) during an 8-week run-in period with atorvastatin, 10 mg/d.

Intervention: Atorvastatin, 80 mg/d (n = 4995), or atorvastatin, 10 mg/d (n = 5006), with target mean LDL-C levels at 75 mg/dL (1.9 mmol/L) and 100 mg/dL (2.6 mmol/L), respectively.

Outcomes: Cerebrovascular events, including fatal or nonfatal stroke and transient ischemic attack (TIA) (predefined secondary outcome).

Patient follow-up: 99% (intention-to-treat analysis).

**Main results**
Mean LDL-C levels were 77 mg/dL (2.0 mmol/L) in the 80-mg group and 101 mg/dL (2.6 mmol/L) in the 10-mg group. Risk for both a cerebrovascular event and stroke was lower in the 80-mg group than in the 10-mg group (Table). Groups did not differ for TIA (Table). At 3 months, risks for hemorrhagic stroke were similar in the 2 groups and across quintiles of LDL-C levels. Treatment-related adverse events were more frequent in the 80-mg group (Table).

**Conclusion**
In patients with stable coronary heart disease, intensive atorvastatin therapy (80 mg/d) was more effective than moderate atorvastatin therapy (10 mg/d) for reducing cerebrovascular events.

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*See Glossary.
†Information provided by author.

**Adverse events**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Atorvastatin 80 mg/d</th>
<th>Atorvastatin 10 mg/d</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular event</td>
<td>3.9%</td>
<td>5.0%</td>
<td>23% (7 to 35)</td>
<td>89 (57 to 293)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.3%</td>
<td>3.1%</td>
<td>25% (14 to 41)</td>
<td>131 (80 to 234)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1.7%</td>
<td>2.2%</td>
<td>21% (~5 to 40)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

**Commentary**
The study by Waters and colleagues, a prespecified secondary endpoint analysis of the Treating to New Targets (TNT) trial, showed that among patients with known CHD, high-dose atorvastatin further reduced the 5-year risk for cerebrovascular events more than low-dose atorvastatin by an absolute value of about 1%, without increasing the risk for hemorrhagic stroke. However, high-dose atorvastatin was associated with a 6-fold increase in consecutive abnormal liver function test results (1.2% vs 0.2%).

Although it is well recognized that lipid lowering with statins reduces the risk for stroke, it is not known what degree of lipid lowering is necessary for optimum risk reduction or whether aggressive lowering of LDL-C increases the risk for hemorrhagic stroke. The study by Waters and colleagues sheds important light on these unanswered questions. The lack of increased risk for hemorrhagic stroke is consistent with other safety data for statins (1).

The study was well done, and we can certainly trust the validity of the findings: a small but real reduction in cerebrovascular events without increased risk for hemorrhagic stroke at the cost of a small increase in the absolute risk for elevated hepatic enzymes. Caveats include whether these results are generalizable to other populations (patients in the TNT trial were predominantly Caucasian, at high risk for cardiovascular disease, and able to achieve an LDL-C level < 130 mg/dL on 10 mg of atorvas-}

**References**