High-dose atorvastatin after stroke or transient ischemic attack

Study Type: POEM
Purpose: Does high-dose atorvastatin reduce the risk of stroke in patients who have had a TIA?
Study Duration: 5 year trial, n = 4731
Trial Design: double-blinded, placebo-controlled, intention-to-treat, multicenter, multi-country
Drug: atorvastatin 80 mg versus placebo
Patients: 6670 patients screened, 4731 were included, mean age ~63, ~40% female, BP = ~138/82, BMI = 27.5, stroke rate was 70% (66% was ischemic), TIA was 30%, most had their event within 90 days, only 2.5% had prior statin, Baseline LDL = 133, HDL = 50, TC = 212, TG = 144, LPa = 149, ApoB = 133
Risk factors: 19% smokers, 17% diabetics, 62% hypertension
Other medications: ASA 87%, ACEI 28%, dihydropyridines, beta-blockers, warfarin, ARBs
Inclusion: age > 18, patients with ischemic stroke, or hemorrhagic stroke or TIA 1 to 6 months before randomization, stroke assessment score was in the moderate severity range, they had to have an LDL of at least 100, but no more than 190
Exclusion: atrial fibrillation, cardiac sources of embolism, subarachnoid hemorrhage
Outcomes: Primary end point: time to first nonfatal or fatal stroke
Secondary measures: see chart below

1. Are the results valid?
   - randomized? yes
   - double-blinded? yes
   - were groups similar? yes
   - allocation concealment? yes
   - all patients accounted for? yes

2. What were the results?
   - p = <.048 due to multiple interim analyses

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Atorvastatin 80 mg</th>
<th>Placebo</th>
<th>p-value**</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal/Nonfatal stroke</td>
<td>11.2%</td>
<td>13.1%</td>
<td>.03</td>
<td>1.9%</td>
<td>53</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>10.4%</td>
<td>11.8%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>1.0%</td>
<td>1.7%</td>
<td>.03</td>
<td>0.7%</td>
<td>143</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or TIA</td>
<td>15.9%</td>
<td>20.1%</td>
<td>&lt;.001</td>
<td>4.2%</td>
<td>24</td>
</tr>
<tr>
<td>TIA</td>
<td>6.5%</td>
<td>8.8%</td>
<td>.004</td>
<td>2.3%</td>
<td>43</td>
</tr>
<tr>
<td>Major Coronary event</td>
<td>3.4%</td>
<td>5.1%</td>
<td>.003</td>
<td>1.7%</td>
<td>59</td>
</tr>
<tr>
<td>Acute Coronary event</td>
<td>4.3%</td>
<td>6.4%</td>
<td>.001</td>
<td>2.1%</td>
<td>48</td>
</tr>
<tr>
<td>Revascularization</td>
<td>4.0%</td>
<td>6.9%</td>
<td>&lt;.001</td>
<td>2.9%</td>
<td>34</td>
</tr>
<tr>
<td>All death</td>
<td>9.1%</td>
<td>8.9%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p-value** statistic is from a prespecified adjusted model which adjust for geographic region, entry event, time since event, sex, age.
The primary outcome was not significant when the model was unadjusted (p = .05, significance level is p < .048)

Adverse Effects
   - 2 cases of rhabdomyolysis in atorvastatin group and 3 cases in placebo group
   - LFT’s at three times normal was more prevalent in the atorvastatin group (ARI = 1.7%, NNH = 59)
   - No cases of liver failure.

3. Will the results help me?
   - The best effect on stroke might be the early use of the statin after a stroke or TIA. Other statin trial enroll patients later. For example, HPS trial enrolled patients 4.3 yrs after the index stroke event, results were poor at preventing events.
   - Takes ~ 3 years to see the best stroke event reduction.
   - Increase risk of hemorrhagic stroke in patients on atorvastatin – there were 55 in the atorvastatin group verses 33 in the placebo group. This has also been seen in other trials. There is a suggestion of the association between low LDL and the increase risk of hemorrhagic stroke.

Conclusion: For every 1000 patients with stroke or TIA treated with atorvastatin 80 mg within one to six months after the first event, 19 second fatal or nonfatal strokes would be prevented over a 5 year period. No deaths from all-causes would be different between the groups. The authors call this reduction substantial, I call it modest, especially when cost to society for 1000 patients for 5 years would be $6.4 million. Could there be another medical or non-medical area where $6.4 million dollars would save more lives. If you treated 1 million people with the drug, ~19,000 strokes would be prevented at a cost of $6.4 trillion dollars. Wow!

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