High-dose statins prior to carotid interventions

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Cardiothoracic Department
University of Pisa, Italy
Conflicts of interest

I do not have any potential conflict of interest
Statins and carotid artery disease

1. Excellent evidence (multiple large RCTs) of the benefits of statins for **primary and secondary prevention of stroke** in patients with cardiovascular disease

2. Some evidence (large retrospective studies) that **being on statins BEFORE CEA** reduces peri-operative risk of death, MI and stroke

3. Very little evidence (few retrospective studies) that **being on statins BEFORE CAS** reduces peri-procedural risk of stroke
Statins and carotid artery disease

4. Some evidence (small prospective studies) that short-term (≤ 6 months) statin treatment in patients with carotid stenosis positively modifies carotid plaque morphology.

5. Good evidence (multiple RCTs) that very short-term high-dose statin treatment BEFORE PCI reduces peri-procedural MI.

6. Almost no evidence on high-dose statins pre-treatment before either CEA or CAS.
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2. Some evidence (large retrospective studies) that being on statins BEFORE CEA reduces peri-operative risk of death, MI and stroke.

3. Very little evidence (low-quality retrospective studies) that being on statins BEFORE CAS reduces peri-procedural risk of stroke.
<table>
<thead>
<tr>
<th>10% LDL reduction:</th>
<th>relative risk reduction 7.5% (2.3–12.5) overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>relative risk reduction 13.5% (7.7–18.8) for primary prevention of stroke</td>
</tr>
<tr>
<td>1 mmol/L LDL reduction</td>
<td>relative risk reduction 21.1% (6.3–33.5) overall</td>
</tr>
<tr>
<td></td>
<td>relative risk reduction 35.9% (21.7–47.6) for primary prevention of stroke</td>
</tr>
<tr>
<td>Recommendations</td>
<td>Class&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level ≥10%) the LDL-C goal is &lt;1.8 mmol/L (less than ~70 mg/dL) and/or ≥50% LDL-C reduction when target level cannot be reached.</td>
<td>I</td>
</tr>
</tbody>
</table>
### ESC Guidelines on PAD

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class (^a)</th>
<th>Level (^b)</th>
<th>Ref (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with PAD who smoke should be advised to stop smoking.</td>
<td>I</td>
<td>B</td>
<td>48</td>
</tr>
<tr>
<td>All patients with PAD should have their LDL cholesterol lowered to &lt; 2.5 mmol/L (100 mg/dL), and optimally to &lt; 1.8 mmol/L (70 mg/dL), or ≥ 50% when the target level cannot be reached.</td>
<td>I</td>
<td>C(^d)</td>
<td>-</td>
</tr>
</tbody>
</table>

ESC Guidelines on PAD. Eur Heart J 2011, in press
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Benefits of statin pre-treatment on perioperative stroke in CEA

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Statin pre-treatment before CAS reduces procedural complications

Retrospective registry of 180 pts undergoing CAS for symptomatic carotid stenosis:

- 127 patients not pre-treated with statins
- 53 patients pre-treated with statins (mainly atorvastatin) for ≥1 week

Baseline LDL-C was 115 ± 37 vs. 129 ± 42mg/dL (P>0.2)

Groeschel K. Radiol 2008;240:145-51
Statin pre-treatment before CAS reduces procedural complications

<table>
<thead>
<tr>
<th>Event</th>
<th>With Preprocedural Statin Therapy (n = 53)</th>
<th>Without Preprocedural Statin Therapy (n = 127)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor stroke</td>
<td>2 (4)</td>
<td>14 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Major stroke</td>
<td>0</td>
<td>1 (0.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>2 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>2 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>2 (4)</td>
<td>19 (15)</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Groeschel K. Radiol 2008;240:145-51
Clinical benefit of statin treatment before CAS

- Retrospective evaluation of 1083 CAS patients:
  - 465 (43%) on statins before and after CAS
  - 618 (57%) not on statins before CAS (no information on statins after CAS)
- Statin patients were significantly younger, had more frequently CAD and dyslipidaemia, and were more often on clopidogrel

Clinical benefit of statin treatment before CAS

Procedural results

<table>
<thead>
<tr>
<th></th>
<th>No statins (n = 618)</th>
<th>Statins (n = 465)</th>
<th>OR</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/death</td>
<td>25 (4%)</td>
<td>6 (1.3%)</td>
<td>0.31</td>
<td>0.126-0.762</td>
</tr>
<tr>
<td>Stroke</td>
<td>25 (4%)</td>
<td>6 (1.3%)</td>
<td>0.31</td>
<td>0.126-0.762</td>
</tr>
<tr>
<td>Death</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>11 (1.8%)</td>
<td>1 (0.2%)</td>
<td>0.11</td>
<td>0.015-1.924</td>
</tr>
<tr>
<td>TIA</td>
<td>26 (4.2%)</td>
<td>13 (2.7%)</td>
<td>0.65</td>
<td>0.333-1.289</td>
</tr>
<tr>
<td>MI</td>
<td>2 (0.3%)</td>
<td>1 (0.2%)</td>
<td>0.66</td>
<td>0.060-7.343</td>
</tr>
<tr>
<td>MACE</td>
<td>29 (4.7%)</td>
<td>7 (1.5%)</td>
<td>0.31</td>
<td>0.135-0.715</td>
</tr>
<tr>
<td>Hematoma</td>
<td>6 (0.9%)</td>
<td>9 (1.9%)</td>
<td>2.01</td>
<td>0.712-5.696</td>
</tr>
<tr>
<td>Conversion to CEA</td>
<td>3 (0.5%)</td>
<td>1 (0.2%)</td>
<td>0.44</td>
<td>0.046-4.261</td>
</tr>
</tbody>
</table>

Clinical benefit of statin treatment before CAS

Statins and carotid artery disease

4. Some evidence (small prospective studies) that short-term (≤ 6 months) statin treatment in patients with carotid stenosis positively modifies carotid plaque morphology.

5. Good evidence (multiple RCTs) that very short-term high-dose statin treatment BEFORE PCI reduces peri-procedural MI.

6. Almost no evidence on high-dose statins pre-treatment before either CEA or CAS.
Pravastatin before CEA stabilizes carotid plaques

24 pts scheduled for CEA randomized to either:
• 40 mg/day of pravastatin (n=11)
• Placebo (n=13)

Time from randomization to surgery: 3 months

Crisby M. Circulation 2001;103:926-33
Pravastatin before CEA stabilizes carotid plaques

**TABLE 3. Lipid Content in Carotid Lesions**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Oil Red O</th>
<th>P</th>
<th>ApoB</th>
<th>P</th>
<th>NA 59</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=13)</td>
<td></td>
<td></td>
<td>19.1±6.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin (n=11)</td>
<td>&lt;0.05</td>
<td>21.5±13.1</td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

NA59 is oxidized LDL. Values represent percentage positive-stained lesional area; data are mean±SD.

**TABLE 4. T-Cell, Macrophage, SMC, and TUNEL Positivity in Carotid Lesions**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>CD3</th>
<th>P</th>
<th>CD68</th>
<th>P</th>
<th>HHF35</th>
<th>P</th>
<th>TUNEL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>&lt;0.05</td>
<td></td>
<td>&lt;0.05</td>
<td></td>
<td>16.9±3.5</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CD3 is T cells; CD68, macrophages; HHF35, SMCs; and TUNEL, apoptotic cells. Values represent percentage positive cells; data are mean±SD.

Crisby M. Circulation 2001;103:926-33
Intensive atorvastatin treatment modifies plaque morphology

- Prospective study on 113 patients with bilateral carotid stenosis:
  - 46 patients underwent CAS on the most severe stenosis
  - 67 patients with low-grade bilateral carotid stenosis did not undergo revascularisation
- All patients received atorvastatin (10-80 mg/day) to target LDL-C <100 mg/dL
- Follow-up with DUS of the low-grade carotid stenosis after 6 months

Kadoglu N. EJVES 2010;39:e258-65
Intensive atorvastatin treatment modifies plaque morphology

Kadoglu N. EJVES 2010;39:e258-65
Atorvastatin reduces carotid plaque inflammation before CEA

60 pts scheduled for CEA randomized to either:

- 10 mg/day of atorvastatin (n=20)
- 80 mg/day of atorvastatin (n=20)
- 8 g/day cholestyramine + 2.5 g/day sitosterol (n=20)

Time from randomization to surgery: 3 months

Puato M. Stroke 2010;41:1163-1168
Atorvastatin reduces carotid plaque inflammation before CEA

Puato M. Stroke 2010;41:1163-1168
Atorvastatin reduces carotid plaque inflammation before CEA

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High-dose statins before PCI

• Patient-level meta-analysis of 13 RCTs on high-dose statin pre-treatment before PCI:
  – high-dose statin (n=1692)
  – no statin/low-dose statin (n=1649)

• All patients receiving statin therapy after PCI

• End points:
  – periprocedural myocardial infarction
  – 30-day MACE (death, MI, TVR)

Patti G. Circulation 2011;123:1622-1632
High-dose statins before PCI

Log-rank $P < 0.00001$
High-dose statins before PCI

Odds ratio for periprocedural myocardial infarction

<table>
<thead>
<tr>
<th>Category</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>Interaction P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 y</td>
<td>0.39</td>
<td>(0.27-0.56)</td>
<td>0.0001</td>
<td>0.01</td>
</tr>
<tr>
<td>Age &lt;65 y</td>
<td>0.76</td>
<td>(0.53-1.08)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.56</td>
<td>(0.42-0.75)</td>
<td>0.0001</td>
<td>0.64</td>
</tr>
<tr>
<td>Women</td>
<td>0.49</td>
<td>(0.30-0.80)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.53</td>
<td>(0.34-0.82)</td>
<td>0.004</td>
<td>0.91</td>
</tr>
<tr>
<td>No diabetes mellitus</td>
<td>0.54</td>
<td>(0.40-0.74)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>0.64</td>
<td>(0.40-1.02)</td>
<td>0.06</td>
<td>0.43</td>
</tr>
<tr>
<td>Stable angina</td>
<td>0.52</td>
<td>(0.41-0.66)</td>
<td>0.00001</td>
<td></td>
</tr>
<tr>
<td>Multivessel PCI</td>
<td>0.52</td>
<td>(0.25-1.06)</td>
<td>0.07</td>
<td>0.94</td>
</tr>
<tr>
<td>Single vessel PCI</td>
<td>0.53</td>
<td>(0.40-0.71)</td>
<td>0.00001</td>
<td></td>
</tr>
<tr>
<td>IIb/IIIa inhibitors</td>
<td>0.71</td>
<td>(0.45-1.12)</td>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>No IIb/IIIa inhibitors</td>
<td>0.49</td>
<td>(0.36-0.66)</td>
<td>0.00001</td>
<td></td>
</tr>
</tbody>
</table>

Patti G. Circulation 2011;123:1622-1632
High-dose statins before PCI

31% RRR
$P = 0.021$

68% RRR
$P < 0.001$

Periprocedural myocardial infarction (%)

<table>
<thead>
<tr>
<th></th>
<th>High-dose statin</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CRP</td>
<td>7.8</td>
<td>10.9</td>
</tr>
<tr>
<td>High CRP</td>
<td>4.3</td>
<td>12.3</td>
</tr>
</tbody>
</table>

N=946 N=915

N=369 N=365

Patti G. Circulation 2011;123:1622-1632
High-dose statins before PCI

- The mechanisms of early protection from statins are unclear, but not due to LDL-C lowering effects (median pretreatment 0.5 days)
- Early lipid-independent effects of statins:
  - antithrombotic action
  - vasodilation of coronary microvessels
  - rapid (<12 hours) improvement of endothelial function
- Patients with high inflammatory status derived most benefits from high-dose statin pretreatment

Patti G. Circulation 2011;123:1622-1632
• Why should all these consideration not apply to carotid artery revascularization, particularly in symptomatic patients?
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Embolization during CAS

- 188 consecutive patients undergoing CAS were prospectively enrolled
- After CAS, the filter was examined to assess the amount of distal embolization
- Embolization was classified by visual inspection:
  - "SCARCE EMBOLIZATION" (no debris or hardly visible debris) N=148
  - "RELEVANT EMBOLIZATION" (visible embolic debris) N=40
Embolization rate according to baseline LDL-C and CRP levels

- LDL>120: P<0.0001
- LDL<120: P<0.0001
- CRP>4
- CRP<4

De Carlo M. ESC congress 2011
<table>
<thead>
<tr>
<th>Procedure &amp; Outcome</th>
<th>Scarce Embolization</th>
<th>Relevant Embolization</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural success</td>
<td>148 (100%)</td>
<td>40 (100%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Distal filter</td>
<td>124 (84.4%)</td>
<td>36 (90.0%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Open-cell-design stent</td>
<td>77 (52.0%)</td>
<td>22 (55.0%)</td>
<td>0.74</td>
</tr>
<tr>
<td>30-day death</td>
<td>0 (0%)</td>
<td>2 (5.0%)</td>
<td>0.04</td>
</tr>
<tr>
<td>30-day stroke</td>
<td>0 (0%)</td>
<td>4 (10.0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>30-day TIA</td>
<td>0 (0%)</td>
<td>8 (20.0%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

De Carlo M. ESC congress 2011
RCT of high-dose rosuvastatin before CAS to reduce embolization

Candidate to elective CAS

LDL>120 mg/dL
and/or CRP>4 mg/dL

Randomize 1:1

Rosuvastatin 40mg for 6 w

CAS with embolic protection

Assessment of embolic debris

1- and 6-month follow-up

LDL≤120 mg/dL
and CRP≤4 mg/dL

Exclude from trial

Placebo
Conclusions

1. Current **Guidelines** recommend intensive statin **treatment** (LDL<70 mg/dL) for all patients with carotid artery stenosis (independent of the indication to revascularization)

2. A few small-sized studies demonstrated that **short-term (≤6 months)** statin treatment is able to induce a more stable **carotid plaque phenotype**

3. This might reduce the propensity of **carotid plaque to fragmentation** during manipulation (CEA) or stenting (CAS)
Conclusions

4. **Properly designed prospective studies are warranted** to verify whether pre-treatment with high-dose statins can improve the operative results of CEA and CAS.

5. However, such studies are maybe outdated before they begin, since I currently see **no reason not to treat all carotid stenosis patients with high-dose statins from the very moment of diagnosis**.