Statins and Omega-3 can stabilize carotid plaques. How often and how low does the LDL-C have to go for this to occur?

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Servier
Pierre Fabre

3 Year Follow-up on Intensive Statin Therapy
Thickness 2.1 mm
Area 13.12 mm²
Thickness 2.0 mm
Area 13.06 mm²

3 year Follow-up (No Statin Therapy)
Area 23.7 mm²
Area 71.2 mm²

ACS Hypoechoic Plaque

Intensive Statin Therapy for 3 months
Reconstructed 3D Plaque Volume (mm³)

Fenster et al. Ultrasonics 1998;36:629-33

Effect of Atorvastatin on Plaque Volume (mm³)

Prospective RCT of 38 patients with > 60% ACS to placebo or Atorvastatin 80 mg for 3 months

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Baseline Volume (mm³)</th>
<th>3 months Volume (mm³)</th>
<th>Change in Volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>21</td>
<td>722±473</td>
<td>738±494</td>
<td>16.8</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>17</td>
<td>689±410</td>
<td>599±355</td>
<td>-90.2</td>
</tr>
</tbody>
</table>

p < 0.0001


Inflammation in carotid plaque using 18F-Fluorodeoxyglucose PET + CT

RCT (N = 43) consecutive patients undergoing 18FDG-PET for cancer screening and had uptake in carotid plaques were randomised to:

- Diet n = 22
- Simvastatin n = 21 aiming to reduce LDL-C by 30%

Note: 18FDG is taken up by tumour cells or macrophages

Tahara N et al. J Am Coll Cardiol 2006;48:1825-31

Effect of Simvastatin and Diet on plaque inflammation at 3 months

Tahara N et al. J Am Coll Cardiol 2006;48:1825-31

Effect of Simvastatin and Diet on plaque inflammation at 3 months

Tahara N et al. J Am Coll Cardiol 2006;48:1825-31

What is the Effect of Statins on Plaque Morphology?

Makis GC et al. Atherosclerosis 2010;20:1-8-20
17 prospective studies (9 RCT) reported changes in plaque morphology as a result of statin therapy.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased echogenicity</td>
<td>9</td>
</tr>
<tr>
<td>Decreased lipid core size</td>
<td>9</td>
</tr>
<tr>
<td>Regression or slower progression</td>
<td>7</td>
</tr>
<tr>
<td>Reduction in TCD microemboli</td>
<td>1</td>
</tr>
</tbody>
</table>

The above effects correlate with decrease in LDL rather than intensity of therapy.

Each 10% LDL-C reduction reduces stroke risk by: 15.6% (95% CI 6.7 to 23.6) or 50% LDL-C reduction reduces stroke risk by approximately 50%.

Clinical Efficacy of PCSK9 Inhibitor Evolocumab (N=25,982) The FOURIER Trial (FUP 2.6 years)

Stable CVD (MI, non haemorrhagic stroke or PAD)

<table>
<thead>
<tr>
<th>Statin ± Ezetimibe vs Placebo Evolocumab</th>
<th>LDL C 92 mg/dL vs 30 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any MI</td>
<td>was reduced by 27% vs 25%</td>
</tr>
<tr>
<td>Ischaemic Stroke</td>
<td>was reduced by 27% vs 25%</td>
</tr>
<tr>
<td>Coronary revascularisation</td>
<td>was reduced by 22%</td>
</tr>
</tbody>
</table>

Sabatine MC et al. NEJM 2017;376:1713-22

Effect of PCSK9 Inhibitor Evolocumab on progression of Coronary Disease in Statin-Treated Patients (18 months)

968 patients who on clinically indicated cor. angiography had at least one stenosis > 20% and a target vessel suitable for IVUS

<table>
<thead>
<tr>
<th>Statin ± Ezetimibe vs Placebo Evolocumab</th>
<th>LDL C 93.0 mg/dL vs 36.6 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>% atheroma Volume</td>
<td>No Change vs -0.95% (P &lt;0.001)</td>
</tr>
<tr>
<td>Total atheroma volume</td>
<td>No change vs -5.8 mm² (P &lt; 0.001)</td>
</tr>
<tr>
<td>Patients with regression</td>
<td>47.3%</td>
</tr>
<tr>
<td></td>
<td>64.3% (P &lt; 0.001)</td>
</tr>
</tbody>
</table>

Sabatine MC et al. NEJM 2017;376:1713-22

Effect of Omega-3 Polyunsaturated Fatty Acids (PUFA) on carotid plaque

In a RCT (n=170), EPA and DHA (1.4 g/day) were incorporated into the carotid plaque and
(a) reduced the number of macrophages,
(b) reduced inflammation and
(c) resulted in thicker fibrous caps than controls OR 0.62 (95% CI 0.24 to 0.89)

Note: Only 33% of patients were on statins and total cholesterol was 4.8 mmoll/L in both groups


Effect of Omega-3 Polyunsaturated Fatty Acids (PUFA) on carotid plaque

In a RCT (n=121), EPA and DHA (1.4 g/day) were incorporated into the carotid plaque and
(a) There was lower expression of inflammatory genes
(b) but histologically or morphologically there was no difference between placebo and treatment groups.

Note: 85% of patients were on statins

Cawood A et al. Atherosclerosis 2010;212:252-9
**Early Systematic Reviews and Meta-analyses**

11 RCTs published 1966-1999 (N=15,806 patients with history of MI)
Intake of Omega-3 supplements reduced
(a) overall mortality (RR 0.8; 95% CI 0.7 to 0.9)
(b) MI mortality (RR 0.7; 95% CI 0.6 to 0.8)


14 RCTs
Intake of Omega-3 supplements reduced
(a) overall mortality
(b) Cardiac and sudden death
(c) Possibly stroke


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**Recent Systematic Reviews and Meta-analyses**

61 RCTs published 2002-2015 (Patients with or at risk of CVD)
Intake of Omega-3 supplements does not affect
(a) Major CV events
(b) All cause death
(c) Sudden cardiac death or
(d) stroke


79 RCTs (112,059 patients)
Intake of Omega-3 supplements has little or no effect
(a) Mortality
(b) Cardiovascular health

Abelhamid AS et al. Cochrane Database Syst Rev 2018;7:CD003177

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**Conclusion**

1. Statin treatment to target of LDL < 70 mg/dL:
   (a) Stabilizes plaques and
   (b) Reduces embolic phenomena and CV events including stroke

2. Lowering LDL-C below 50 mg/dL stops plaque progression and is often associated with plaque regression.

3. Diets high in Omega-3 fish oil may be beneficial in healthy populations not on statins

4. Omega-3 supplements have no additional effect on atherosclerotic plaques and no benefit on CV events in patients on modern statin therapy