Intensive lipid-lowering for plaque stabilisation and regression? Implications for surgeons and our patients!

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PSC: CHD mortality vs usual cholesterol

Lancet 2007

2 mmol/L
(77 mg/dL)
~ halves risk
Cholesterol Treatment Trialists’ Collaboration

• 27 trials: 175,000 participants

• Major Vascular Event (MVE) = non-fatal myocardial infarction or coronary death, coronary revascularisation or stroke

• 5-year risk of a MVE evaluated for all participants at time of entry into the studies

• Participants stratified into vascular disease risk groups:

<table>
<thead>
<tr>
<th>5-year risk of a MVE</th>
<th>&lt; 5%</th>
<th>5 to 10%</th>
<th>10 to 20%</th>
<th>20 to 30%</th>
<th>≥ 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24,790</td>
<td>28,503</td>
<td>56,413</td>
<td>42,764</td>
<td>21,679</td>
</tr>
</tbody>
</table>

Lancet 376:1670-81
CTTC: MVEs avoided per 1,000 treated over 5 years

LDL cholesterol reduction (mmol/L) with statin treatment

CTTC: MVEs avoided per 1,000 treated over 5 years

LDL cholesterol reduction (mmol/L) with statin treatment

Lancet 376:1670-81
Absolute effects on MAJOR VASCULAR EVENTS of lowering LDL cholesterol with STATIN therapy

- 33% relative risk reduction per 1.5 mmol/L (since 0.79 x 0.84 = 0.67)
- 21% relative risk reduction per mmol/L
- 16% relative risk reduction per 0.5 mmol/L

Combined evidence: ~40% relative risk reduction per 2.5 mmol/L

Lancet 376:1670-81
High-risk patients need high-dose statins
Could intensive LDL-lowering therapy promote plaque regression?
Intensive statin therapy and coronary atherosclerosis assessed by IVUS: #1

• REVERSAL
• Double-blind RCT
• 654 randomised and 502 assessed with IVUS
• 40mg Pravastatin v 80mg Atorvastatin
• 18 months duration

• Atorvastatin reduced progression of CHD over 18 months (but no regression)
Intensive statin therapy and coronary atherosclerosis assessed by IVUS: #2

- **ASTEROID**
- Non-randomised observational study
- 507 randomised and 349 assessed at 24 months
- All received rosuvastatin 40mg
- Average LDL-C = 60.8mg/dl
ASTEROID Results

- Regression in 64% (Primary) 78% (Secondary) of participants
- 9% reduction in atheroma volume in most diseased segment

<table>
<thead>
<tr>
<th>Primary efficacy parameters</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change</th>
<th>Percent Change</th>
<th>No. (%) With Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent atheroma volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>222 (63.6)</td>
</tr>
<tr>
<td>(n = 349)</td>
<td>Mean (SD)</td>
<td>39.6 (8.5)</td>
<td>38.6 (8.5)</td>
<td>−0.98 (3.15)</td>
<td>NA</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>39.9 (33.8-45.3)</td>
<td>38.5 (32.6-44.3)</td>
<td>−0.79 (−1.21 to −0.53)*†</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Atheroma volume in most diseased 10-mm subsegment, mm³ (n = 319)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>249 (78.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>65.1 (27.0)</td>
<td>59.0 (24.5)</td>
<td>−6.1 (10.1)</td>
<td>−8.5 (13.7)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>65.1 (45.2-82.2)</td>
<td>58.4 (40.6-76.3)</td>
<td>−5.6 (−6.82 to −3.96)*†</td>
<td>−9.1 (−10.83 to −7.23)*†</td>
<td></td>
</tr>
</tbody>
</table>
LDL-lowering with agents other than statins

PCSK-9 Inhibitors
Evolucumab [FOURIER] and Alirocumab [ODYSSEY]

Small interfering RNA particles
Inclisiran [ORION-4]
Lipid biochemistry for surgeons
GLAGOV RCT

• 968 patients undergoing coronary angiography
• Evolocumab (PCSK-9i) v Placebo
• Background statin therapy: 60% intensive LLT
• 18 months duration
• Primary outcome = change in atheroma vol
• LDL-C achieved: 36.6mg/dl v 93.0mg/dl
GLAGOV Results

- Regression seen in around 2/3rds of patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n = 423)</th>
<th>Evolocumab (n = 423)</th>
<th>Between Group Differences, Least Squares Means (95% CI)</th>
<th>P Value for Between Groups$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change From Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent atheroma volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least squares mean (95% CI)</td>
<td>0.05 (-0.32 to 0.42)</td>
<td>-0.95 (-1.33 to -0.58)</td>
<td>-1.0 (-1.8 to -0.64)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>P value for change from baseline</td>
<td>.78</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total atheroma volume, mm$^3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Least squares mean (95% CI)</td>
<td>-0.91 (-3.29 to 1.47)</td>
<td>-5.80 (-8.19 to -3.41)</td>
<td>-4.9 (-7.3 to -2.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>P value for change from baseline</td>
<td>.45</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with regression, % (95% CI)</td>
<td></td>
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</tr>
<tr>
<td>Percent atheroma volume</td>
<td>47.3 (42.5 to 52.0)</td>
<td>64.3 (59.7 to 68.9)</td>
<td>17.0 (10.4 to 23.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total atheroma volume</td>
<td>48.9 (44.2 to 53.7)</td>
<td>61.5 (56.8 to 66.1)</td>
<td>12.5 (5.9 to 19.2)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

$^a$ The P value for comparison between treatments for change from baseline were generated from an analysis of covariance. Primary and secondary end points as evaluated on intravascular ultrasonography at baseline and 78-week follow-up with changes from baseline. Results expressed as mean (SD) and median (95% CI) for continuous variables and percentage for categorical variables at baseline and follow-up.
Post hoc non-randomised analysis...
Achieved LDL-C and % atheroma volume reduction
Epidemiology...
Life-long exposure to risk factors predicting late events
The Prevention Paradox

- “A large number of people exposed to a small risk can create many more cases of harm than a small number exposed to a high risk.”
Start “treatment” much earlier
Does intensive LLT promote plaque regression?

It certainly does prevent many more heart attacks and strokes than moderate statin therapy and should be used much more widely.