Arterial Wall Remodeling in Response to Atheroma Regression with Very Intensive Lipid Lowering

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Pathobiology
  • plaque composition
  • arterial wall remodeling

Vessel Wall Imaging
  • ultrasound
  • newer techniques

Effects of therapy
  • LDL-C
  • newer targets?
Pathobiology

Vessel wall Imaging

Effects of Statins
Severity of Coronary Plaques before MI

Arterial Remodeling

Arterial Remodeling

Arterial Remodeling

Arterial Remodeling

Pathobiology

Vessel Wall Imaging

Effects of Statins
IVUS: Coronary Imaging

Fibrous Plaque

“Soft” Plaque
Positive Remodeling by IVUS

Newer Imaging modalities

[Images of medical imaging modalities: Ex-vivo PDW, Ex-vivo T1w, Ex-vivo T2w, CME]

QuickTime? and a TIFF (Uncompressed) decompressor are needed to see this picture.
- Pathobiology
- Vessel Wall Imaging
- Effects of Statins
Effects of Statins: carotid IMT

Taylor AJ et al. *Circulation* 2002;106:2055-60
Primary hypothesis
- Rosuvastatin 40 mg will regress carotid IMT

Objective
- Reduction in carotid IMT detected by repeated studies over 2 years, in a low risk cohort 10 yr risk <10%.

Null hypothesis
- Treatment will progress or not change carotid IMT

**Reversal Study**

**REVERSAL - Final Lipid Values**

<table>
<thead>
<tr>
<th>Lipid Value (mg/dL)</th>
<th>pravastatin 40 mg (n=249)</th>
<th>atorvastatin 80 mg (n=253)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Final value</td>
<td>Change (%)</td>
<td>Final value</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>188±32</td>
<td>-18.4</td>
<td>151±39</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td><strong>110±26</strong></td>
<td>-25.2</td>
<td><strong>79±30</strong></td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>45±11</td>
<td>+5.6</td>
<td>43±11</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>166±92</td>
<td>-6.8</td>
<td>148±95</td>
</tr>
</tbody>
</table>

Nissen SE et al. *JAMA* 2004;291:1071-80
Reversal Study

Percent Change in Atheroma Volume

Change in atheroma volume (%)

- Progression (P=0.001) 2.7%
- No change (P=0.98)
- Change in atheroma volume (P=0.02)

Correlation Change CRP v Plaque

Change in C-Reactive Protein (mg/L)

Change in Percent Atheroma Volume (%)

Correlation Change LDL vs Plaque

-90 -80 -70 -60 -50 -40 -30 -20 -10 0
Change in Percent Atheroma Volume (%)

Change in LDL-cholesterol (mg/dL)

Pravastatin 40 mg

Atorvastatin 80 mg

The LDL “gap”
Asteroid Study

◆ Primary hypothesis
  ◆ 24 months rosuvastatin 40 mg will regress coronary AT

◆ Objective
  ◆ Reduction in coronary AT detected by separate IVUS studies

◆ Null hypothesis
  ◆ Treatment will progress or not change coronary AT
Asteroid Study

1183 patients screened and 507 patients treated at 53 centers in US, Canada, Europe and Australia

Intravascular ultrasound with 40 MHz transducer motorised pullback at 0.5mm/sec through >40mm length of single “target” coronary artery

Rosuvastatin 40 mg for 24 months treatment

158 patients withdrew or did not have an evaluable final IVUS

Follow-up IVUS of originally imaged “target” vessel (n=349)
## Atherosclerosis and Statins

### Lipid Values and Percent Change (n=349)

<table>
<thead>
<tr>
<th></th>
<th>Mean Baseline</th>
<th>During treatment*</th>
<th>Percent change†</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>204</td>
<td>133.8</td>
<td>-33.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>130.4</td>
<td>60.8</td>
<td>-53.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>43.1</td>
<td>49.0</td>
<td>+14.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>152.2</td>
<td>121.2</td>
<td>-14.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C/HDL-C ratio</td>
<td>3.2</td>
<td>1.3</td>
<td>-58.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Rosuvastatin is not indicated for atherosclerosis regression

Atherosclerosis and Statins

Mean LDL-C and change in % atheroma volume

Rosuvastatin is not indicated for atherosclerosis regression
Atherosclerosis and Statins

Predictors of Atheroma Regression

- 1,455 patients / 4 trials

- Multivariate correlates of Regression
  - LDL chol reduction (<87.5mg/dL)
  - HDL chol increase (>7.5%)

### Table 6. Relationship Between the Combination of Level of Low-Density Lipoprotein Cholesterol During Treatment and Change in High-Density Lipoprotein Cholesterol With Atheroma Progression or Regression

<table>
<thead>
<tr>
<th>No. of participants</th>
<th>LDL-C Level During Treatment, mg/dL</th>
<th>% Change in HDL-C Level</th>
<th>Change in PAV, Mean (SD) [Median], %</th>
<th>Change in TAV, Mean (SD) [Median], mm³</th>
<th>MI, %</th>
<th>Stroke, %</th>
<th>Revascularization, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>276</td>
<td>&lt;87.5</td>
<td>&gt;7.5</td>
<td>-0.4 (3.4) [-0.5]</td>
<td>-8.8 (21.5) [-7.9]</td>
<td>2.1</td>
<td>0.6</td>
<td>32.5</td>
</tr>
<tr>
<td>329</td>
<td>&lt;87.5</td>
<td>&lt;7.5</td>
<td>0.2 (3.8) [0]</td>
<td>-2.8 (22.7) [-4.0]</td>
<td>1.2</td>
<td>0</td>
<td>28.1</td>
</tr>
<tr>
<td>226</td>
<td>&gt;87.5</td>
<td>&gt;7.5</td>
<td>0.9 (3.9) [0.3]</td>
<td>0.3 (23.0) [-2.0]</td>
<td>0.7</td>
<td>0.3</td>
<td>21.4</td>
</tr>
<tr>
<td>309</td>
<td>&gt;87.5</td>
<td>&lt;7.5</td>
<td>1.3 (4.2) [1.1]</td>
<td>2.1 (25.2) [1.6]</td>
<td>2.1</td>
<td>0</td>
<td>28.1</td>
</tr>
<tr>
<td>P value*</td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.36</td>
<td>.13</td>
<td>.07</td>
</tr>
</tbody>
</table>

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAV, percent atheroma volume; TAV, total atheroma volume.

SI conversion factor: To convert low-density cholesterol to mmol/L, multiply by 0.0259.

*Comparison between all groups using analysis of covariance after controlling for any differences in baseline atheroma volume between groups.
Benefit of Combination HDL Raising and LDL Lowering with Statins


LDL-C

Delta HDL-C

<87.5  <87.5  >87.5  >87.5

>7.5%  <7.5%  >7.5%  <7.5%

P<0.001 for trend

“Man lives with arteriosclerosis, and dies of the complicating thrombosis”