Regression and Progression of Atherosclerosis: Insights from Intravascular Ultrasound

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Disclosure

Consulting: Many companies

Companies are directed to pay any honoraria directly to charity. No personal reimbursement is accepted for directing or participating in clinical trials.
Heart attacks: gone with the century?
Brown MS, Goldstein JL.
Beyond Statins: Is LDL Reduction Enough?

4S Trial

WOSCOPS Trial

CV Death/MI (Number of events)

Placebo
Treated

34% reduction

31% reduction

4S Trial
2° prevention trial with simvastatin

WOSCOPS Trial
1° prevention trial with pravastatin
Deep Fried Mars Bar

‘The World’s Most Atherogenic Food’
Glagov Remodeling Phenomenon

Early Atherosclerosis

Advanced Disease

3.5 mm

3.5 mm
Angiographically Normal Segment of LAD
Donor Atherosclerosis: 17 Year Old Male

Left Anterior Descending

Magnified View
Coronary Atherosclerosis in 262 Heart Transplant Donors

Percent Reaching 0.5 mm Threshold

Mean donor age (years)

- <20: 17%
- 20-29: 37%
- 30-39: 60%
- 40-49: 71%
- ≥50: 85%
654 patients at 34 centers
Symptomatic CAD, coronary angiography with >20% stenosis
LDL 125 to 210 mg/dL after 8 week washout

Intravascular ultrasound with 30 MHz transducer
Motorized pullback at 0.5 mm/sec through >30 mm
length of single “target” coronary artery

pravastatin 40 mg

18 months treatment

78 patients withdrew

249 pravastatin patients

Follow-up IVUS of originally imaged “target” vessel (n=502)

atorvastatin 80 mg

74 patients withdrew

253 atorvastatin patients
Ultrasound Measurement of Atheroma Area

Precise Manual Planimetry of EEM and Lumen Borders
Ultrasound Measurement of Atheroma Volume

Motorized Pullback: Cross-sections Selected at 1 mm Intervals

Cross-section 48
Cross-section 26
Cross-section 10
Final Lipid Values and Percent Change

<table>
<thead>
<tr>
<th>Lipid Value (mg/dL)</th>
<th>Pravastatin (n=249)</th>
<th>Atorvastatin (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>110±26</td>
<td>-25.2</td>
<td>79±30</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>

* ANOVA

Percent Change in Atheroma Volume

Progression ($p=0.001$)

No change ($p=0.98$)

Combined atorvastatin and pravastatin treatment groups

LDL-C Change vs. Atherosclerosis Progression

CRP Change vs. Atherosclerosis Progression

Combined atorvastatin and pravastatin treatment groups

Observational and Pre-Clinical Studies

- Apolipoprotein A1 Milano is a variant derived from 40 subjects in the Italian village of Limone sul Garda.
- Apo A1 Milano carriers exhibit mean HDL levels of 17 mg/dL (0.44 mmol/L) with normal longevity and no atherosclerosis. A cysteine is substituted for arginine at position 173.
- Recombinant Apo A1 Milano has been complexed with phospholipid to produce nascent HDL-like particle. (Esperion)
- Infusions of Apo A1 Milano phospholipid complex in Apo E deficient mice rapidly (48 hours!!) mobilized lipid and reduced macrophage content within atherosclerotic lesions.*

123 patients at 10 centers screened
Recent myocardial infarction or Acute coronary syndrome
>20% stenosis in a non-intervened vessel

 Intravascular ultrasound with 40 MHz transducer
Motorized pullback at 0.5 mm/sec through >30 mm length of single “target” coronary artery

5 weeks

Placebo 12 pts  
1 patients withdrew
Placebo 11 pts

ETC-216 low (23 pts)  
2 patients withdrew
ETC-216 low (21 pts)

ETC-216 high (22 pts)  
7 patients withdrew
ETC-216 high (15 pts)

Follow-up IVUS of originally imaged “target” vessel (n=47)
ApoA1 Milano: Change in Total Atheroma Volume

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Atheroma Volume (mm$^3$)</th>
<th>$P$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-15.1 mm$^3$</td>
<td>0.02</td>
</tr>
<tr>
<td>Low Dose</td>
<td>-12.6 mm$^3$</td>
<td>0.007</td>
</tr>
<tr>
<td>High Dose</td>
<td>-2.9 mm$^3$</td>
<td>0.97</td>
</tr>
<tr>
<td>Combined</td>
<td>-14.1 mm$^3$</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Drano for the Heart

An experimental drug no one expected to work is surprisingly effective at rooting out cholesterol.
Systolic Pressure: All Three Treatment Groups

Nissen et al. JAMA. 2004;292(18); 2217-2226.
Effect of LDL and SBP on Atheroma Progression

\[ p < 0.001 \text{ for trend} \]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent Atheroma Volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C &lt;70 SBP &lt;120</td>
<td>0.15</td>
</tr>
<tr>
<td>LDL-C &lt;70 SBP ≥120</td>
<td>0.3</td>
</tr>
<tr>
<td>LDL-C ≥70 SBP &lt;120</td>
<td>0.51</td>
</tr>
<tr>
<td>LDL-C ≥70 SBP ≥120</td>
<td>0.61</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol 2009:53:1110-52009
Prior Coronary IVUS Progression Trials

Relationship between LDL-C and Progression Rate

Median Change In Percent Atheroma Volume (%)

Mean LDL-C (mg/dL)

Unexplored Region

REVERSAL pravastatin

REVERSAL atorvastatin

CAMELOT placebo

ACTIVATE placebo

A-Plus placebo
## 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</td>
<td>204</td>
<td>133.8</td>
<td>-33.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></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>

* Time-weighted average  
† From least square mean
Dual Primary IVUS Efficacy Parameters

Median Change in Percent Atheroma Volume

Regression $p<0.001^*$

Change In Percent Atheroma Volume (%)

Median Change in Most Diseased Subsegment

Change In Atheroma Volume ($\text{mm}^3$)

Regression $p<0.001^*$

-5.6

*Wilcoxon signed rank test for comparison with baseline
Distribution: Percent Atheroma Volume

- **Regression**: 63.6%
- **Progression**: 36.4%

Change in Percent Atheroma Volume (%)

Number of Patients
**Time Course: Change in HDL-C Levels**

Nissen et al.
Cumulative Histogram: Change in Systolic BP

- Torcetrapib
- Atorvastatin

LS Mean difference: 4.6 mm Hg

Change in Systolic Blood Pressure (mmHg)

Percentage of Subjects (%)
Primary Efficacy Parameter

Change in Percent Atheroma Volume

Change in percent atheroma volume

Atorvastatin monotherapy

Torcetrapib-atorvastatin

$ p = 0.72^{\dagger} $

Nissen et al. 
Change in Percent Atheroma Volume

Atorvastatin 80 mg

Rosuvastatin 40mg

$-0.99$ vs $-1.22$

$p = 0.17$

Impact of LDL-C Lowering on Plaque Progression

LAPLACE-TIMI 57: Reduction in LDL-C

420 mg dose Q 4 weeks compared with placebo

Mean % Change From Baseline in Calculated LDL-C

P < .0001 for weeks 2-12 vs placebo

LDL-C calculated using the Friedewald equation

## Recent and Ongoing IVUS Atherosclerosis Trials

<table>
<thead>
<tr>
<th>Name</th>
<th>Trial Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activate</td>
<td>An ACAT inhibitor</td>
<td>NEJM (April ‘06)</td>
</tr>
<tr>
<td>Asteroid</td>
<td>Rosuvastatin 40 mg for regression</td>
<td>JAMA (April ’06)</td>
</tr>
<tr>
<td>Illustrate</td>
<td>Torcetrapib+statin vs. statin alone</td>
<td>NEJM (March ’07)</td>
</tr>
<tr>
<td>Periscope</td>
<td>Pioglitazone vs. glimepiride</td>
<td>JAMA (April ’08)</td>
</tr>
<tr>
<td>Stradivarius</td>
<td>Rimonabant vs usual care</td>
<td>JAMA (April ’08)</td>
</tr>
<tr>
<td>Aquarius</td>
<td>Aliskerin in normotensive patients</td>
<td>JAMA (2013)</td>
</tr>
<tr>
<td>Glagov</td>
<td>PCSK9 Inhibitor</td>
<td>Completion 2016</td>
</tr>
<tr>
<td>TBD</td>
<td>Apo A1 Milano</td>
<td>Startup 2015</td>
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