Intravascular Ultrasound: Eight Insights for the Clinical Lipidologist

Steven E. Nissen MD MACC

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.

Insight 1:
Coronary Disease is Not a Plumbing Problem
Single Vessel Left Anterior Descending Disease
Intravascular Ultrasound Coronary Imaging

Rotating Transducer
Coronary Atheroma

Glagov Remodeling Phenomenon

Early Atherosclerosis
Advanced Disease

3.5 mm

3.5 mm
Angiographically Normal Segment of LAD
Low Grade Stenoses Cause Most Infarctions

Coronary Stenosis Severity Prior to MI

- 50-70% Stenosis: 18%
- >70% Stenosis: 14%
- <50% Stenosis: 68%

CAD: The Diagnosis Often Comes Too Late

Myocardial infarction (MI) or death as initial presentation of CAD

- Men: 62%
- Women: 46%
Insight 2: Coronary Disease is Ubiquitous and Starts at a Young Age
Transplant Donor: 33 Year Old Male
Left Anterior Descending | Left Circumflex

Donor Atherosclerosis: 17 Year Old Male
Left Anterior Descending | Magnified View
Insight 3: Coronary Disease is Exquisitely Sensitive to LDL-C Levels
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 atorvastatin 80 mg

78 patients withdrew 74 patients withdrew
249 pravastatin patients 253 atorvastatin patients

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

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

1 mm spacing

12.64 mm$^3$
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

Primary Endpoint
Percent Change in Atheroma Volume

Progression (p=0.001*)

No change (p=0.98*)

Wilcoxon signed rank test† ANCOVA of rank transformed results
Insight 4: 
Coronary Disease is an Inflammatory Disorder

LDL-C Change vs. Atherosclerosis Progression

Combined atorvastatin and pravastatin treatment groups

**LDL-C Change vs. Atherosclerosis Progression**

- **Pravastatin 40 mg**
- **Atorvastatin 80 mg**

Change in LDL-cholesterol (mg/dL) vs. Change in Percent Atheroma Volume (%)

**Secondary Endpoint: C-reactive Protein**

Percent reduction in CRP (mean baseline level = 2.9 mg/dL)

- Pravastatin
- Atorvastatin

Percent Change (%)

-5.2% (p < 0.0001*)

-36.4%

*Wilcoxon rank sum test
CRP Change vs. Atherosclerosis Progression

Combined atorvastatin and pravastatin treatment groups

Insight 5:
HDL Matters
(even if we don’t fully understand how)
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.*

ApoA1 Milano: Change in Total Atheroma Volume

-18
-16
-14
-12
-10
-8
-6
-4
-2
0

Total Atheroma Volume (mm$^3$)

Placebo
Low Dose
High Dose
Combined

-2.9 mm$^3$
P = 0.97

-15.1 mm$^3$
P = 0.02

-12.6 mm$^3$
P = 0.007

-14.1 mm$^3$
P < 0.001

Side Branch

EEM area
14.37 mm$^2$

Lumen area
6.27 mm$^2$

Atheroma area - 8.10 mm$^2$

Side Branch

EEM area
11.58 mm$^2$

Lumen area
6.23 mm$^2$

Atheroma area - 5.35 mm$^2$
**Percent Atheroma Volume: LDL-C and HDL-C**

<table>
<thead>
<tr>
<th>Percent Atheroma Volume (%)</th>
<th>LDL-C worse</th>
<th>LDL-C worse</th>
<th>LDL-C better</th>
<th>LDL-C better</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3%</td>
<td>HDL-C worse</td>
<td>HDL-C better</td>
<td>HDL-C worse</td>
<td>HDL-C better</td>
</tr>
<tr>
<td>0.9%</td>
<td>LDL-C worse</td>
<td>LDL-C better</td>
<td>LDL-C worse</td>
<td>LDL-C better</td>
</tr>
<tr>
<td>0.2%</td>
<td>LDL-C worse</td>
<td>LDL-C better</td>
<td>LDL-C worse</td>
<td>LDL-C better</td>
</tr>
</tbody>
</table>

Median LDL-C - 87.5 mg/dL
Median HDL-C change - 7.5%

**P < 0.001**

**Insight 6:**
It’s Not Just Lipids
Blood Pressures Also Matters
1991 patients at 100 centers, North America and Europe
Symptomatic CAD, coronary angiography with >20% stenosis
Diastolic BP $\leq$ 100 mm Hg

Baseline intravascular ultrasound in 428 participants

placebo  
enalapril 20 mg  
amloprine 10 mg

24 months treatment

Intent-to-treat analysis of cardiovascular events (1991 patients)
Repeat intravascular ultrasound examination (274 patients)

Systolic Pressure: All Three Treatment Groups
Comparison: Events Rates and IVUS Progression

Patients with baseline systolic blood pressure $\geq$ mean

Nissen et al. JAMA. 2004;292(18); 2217-2226.

Blood Pressure Classification and Progression

Changes In Atheroma Volume (mm$^3$)

JACC. 2006 15;48(4):833-8
Effect of LDL and SBP on Atheroma Progression

Insight 7:
A Lower LDL-C is Almost Always Better
Rosuvastatin: Percent Change in Lipids (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>

* Time-weighted average † From least square mean

Dual Primary IVUS Efficacy Parameters

Median Change in Percent Atheroma Volume: -0.79, p<0.001*

Median Change in Most Diseased Subsegment: -5.6, p<0.001*

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

- Regression 63.6%
- Progression 36.4%

Number of Patients

Change in Percent Atheroma Volume (%)

Coronary IVUS Regression-Progression Trials

Relationship between LDL-C and Progression Rate

- r² = 0.95
- p < 0.001
Impact of LDL-C Lowering on Plaque Progression

Insight 8:
Many Promising Therapies Don’t Work
1188 patients at 137 centers in North America and Europe
Symptomatic CAD, coronary angiography with >20% stenosis

Intravascular ultrasound with 40 MHz transducer
Motorized pullback at 0.5 mm/sec through >40 mm segment

4-10 week run-in atorvastatin 10-80 mg
to achieve LDL-C of 100±15 mg/dL

Atorvastatin monotherapy
140 patients withdrew
446 atorvastatin patients

Torcetrapib 60mg-atorvastatin
135 patients withdrew
464 torcetrapib patients

24 Month follow-up IVUS of originally imaged “target” vessel (n=910)

Time Course: Change in LDL-C Levels

LDL cholesterol Level (mg/dL)

0 1 3 6 9 12 15 18 21 24

Atorvastatin Monotherapy
Difference 19.9%

Torcetrapib-Atorvastatin
Time Course: Change in HDL-C Levels

- **Torcetrapib-Atorvastatin**
- **Atorvastatin Monotherapy**

Difference 60.8%

Primary Efficacy Parameter

Change in Percent Atheroma Volume

Change in percent atheroma volume

\[ p = 0.72^\dagger \]

- **Atorvastatin monotherapy**
- **Torcetrapib-atorvastatin**

\[ 0.19 \]

\[ 0.12 \]
ACAT Inhibition: Mechanism of Action

Change in Atheroma Volume (mm³)

Placebo Pactimibe

Entire Ultrasound Pullback

Most Diseased 10 mm

Pactimibe vs. Placebo: Atheroma Volume

## A Decade of IVUS Atherosclerosis Trials

<table>
<thead>
<tr>
<th>Name</th>
<th>Trial Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversal</td>
<td>High intensity statins</td>
<td>JAMA (2004)</td>
</tr>
<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>Saturn</td>
<td>Two potent statins</td>
<td>NEJM (2011)</td>
</tr>
<tr>
<td>Aquarius</td>
<td>Aliskerin in normotensive patients</td>
<td>JAMA (2013)</td>
</tr>
<tr>
<td>Assure</td>
<td>Apo A1 inducer (Resverlogix)</td>
<td>Published 2015</td>
</tr>
<tr>
<td>Glagov</td>
<td>PCSK9 Inhibitor</td>
<td>AHA 2016</td>
</tr>
<tr>
<td>Apo A1 Milano</td>
<td>HDL mimetic</td>
<td>Underway 2016</td>
</tr>
</tbody>
</table>
Cumulative Histogram: Change in Systolic BP

- LS Mean difference: 4.6 mm Hg
- Atorvastatin Monotherapy
- Torcetrapib

PERISCOPE: Glycohemoglobin Levels

- Average Difference = 0.19%
- \( P = 0.03 \)
Percentage Changes: Biochemical Parameters

- **HDL-cholesterol**:
  - Glimepiride: 4.1% increase
  - Pioglitazone: 16.0% increase
  - P < 0.001

- **LDL-cholesterol**:
  - Glimepiride: 6.9% increase
  - Pioglitazone: 6.6% increase
  - P = 0.69

- **hs C-reactive Protein**:
  - Glimepiride: -18.0% decrease
  - Pioglitazone: -44.9% decrease
  - P < 0.001

- **Triglycerides**:
  - Glimepiride: 0.6% decrease
  - Pioglitazone: -15.3% decrease
  - P < 0.001

**Primary Efficacy Parameter**

**Change in Percent Atheroma Volume (%)**

- **Glimepiride (n=181)**: Change in PAV = 0.73
  - P < 0.001

- **Pioglitazone (n=179)**: Change in PAV = -0.16
  - P = 0.44
SATURN: Study Design

1385 patients with symptomatic CAD (angiographic stenosis >20%)
LDL-C with (>80 mg/dL) or without (>100 mg/dL) statin use last 4 weeks

Visit:          Week: 1 2 3 4 5 6 7 8 9 10 11
-4 -2 0 13 26 39 52 65 78 91 104

Screening Period

Randomization Period

Primary Efficacy Parameter
Change in Percent Atheroma Volume

<table>
<thead>
<tr>
<th>Change in percent atheroma volume</th>
<th>Atorvastatin 80 mg</th>
<th>Rosuvastatin 40mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>-0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p = 0.17
Correlation with Clinical Outcomes
IVUS Disease Burden and Cardiovascular Events
Death, myocardial infarction and coronary revascularization

Nicholls J Amer Coll Cardiol 2010
Plaque Burden Predicts MACE with High Intensity Statins

Cumulative Incidence of MACE (%)

- Baseline PAV Quartile 1 (14.78-30.73)
- Baseline PAV Quartile 2 (30.80-36.09)
- Baseline PAV Quartile 3 (36.12-41.74)
- Baseline PAV Quartile 4 (41.78-68.75)

Log Rank Test P value = 0.001 for PAV quartile 4 vs. lower quartile

Baseline PAV Quartile 1 (14.78-30.73)
Baseline PAV Quartile 2 (30.80-36.09)
Baseline PAV Quartile 3 (36.12-41.74)
Baseline PAV Quartile 4 (41.78-68.75)

Plaque Burden Predicts MACE with High Intensity Statins

Puri Eur. Heart J 2013
Prior Coronary IVUS Progression Trials

Relationship between LDL-C and Progression Rate

Impact of HDL-C Raising on Plaque Progression

### 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>Saturn</td>
<td>Atorvastatin vs. rosuvastatin</td>
<td>NEJM (2011)</td>
</tr>
<tr>
<td>Glagov</td>
<td>PCSK9 Inhibitor</td>
<td>Coming soon</td>
</tr>
</tbody>
</table>
Torcetrapib Results: Levels of HDL-C Achieved

Percent Atheroma Volume
Primary Efficacy Parameter

Quartile 1
<56 mg/dL

Quartile 2
56 to 69 mg/dL

Quartile 3
69 to 86 mg/dL

Quartile 4
>86 mg/dL

Percent Atheroma Volume (%)

0.70%
0.30%
0.18%
-0.69%

P < 0.001

Serum Potassium: Effect of Torcetrapib

Baseline
Atorvastatin

Follow-up
Torcetrapib-Atorvastatin

P = 0.08
P < 0.001
Correlation Between LDL-C and CRP Change

Atorvastatin 80 mg

Pravastatin 40 mg

\[ r = 0.08 \]
\[ p = 0.17 \]

\[ r = -0.008 \]
\[ p = 0.90 \]