Diabetes and Dyslipidemia

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Lipid Abnormalities Associated with Type 2 Diabetes

**Quantitative**

- Upward: Triglycerides
- Downward: HDL-Cholesterol
- Asterisk: LDL-Cholesterol (Hyper-Apo B)
- Upward: LP (a)

**Qualitative**

- Remnant-particle accumulation
- Small dense LDL
- Cholesterol-enriched VLDL
- Triglyceride-enriched HDL
  - Upward: cholesterol-ester transfer protein (CETP) activity
- Glycosylated apoproteins and phospholipids
Lipopid Levels in Men With and Without Diabetes: Framingham Offspring Study

*P<0.01.

Lipid Levels in Women With and Without Diabetes: Framingham Offspring Study

*P<0.001.

Management Challenges in Diabetic Dyslipidemia

- What is the goal for LDL-cholesterol?
- How aggressive should we be in raising HDL-C and lowering TG?
- Should we measure Apo-B?
- In patients with LDL-C at goal, when to consider combination drug-therapy?
- Do postprandial Triglyceride levels contribute in risk assessment?
HDL Metabolism as a Therapeutic Target: Potential Strategies

- Increase apo A-I production
- Promote reverse cholesterol transport
- Delay catabolism of HDL
HDL Metabolism and Reverse Cholesterol Transport

ABC1 = ATP-binding cassette protein 1; A-I = apolipoprotein A-I; CE = cholesteryl ester; FC = free cholesterol; LCAT = lecithin:cholesterol acyltransferase; SR-BI = scavenger receptor class BI.
Effect of Niaspan on Lipids and Glycemic Control in Patients with Diabetes Mellitus: The Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT)
All changes in the Niaspan group vs. placebo, week 16

P < 0.05 vs. placebo
TRIGLYCERIDES

% Change from Baseline

Placebo
1000 mg
1500 mg

week
481216

*P < 0.05 vs. placebo
†P < 0.05 vs. 1500 mg
ADVENT

% Change from Baseline

Placebo  1000 gm  1500 mg

week

LDL-C

4 8 12 16

-10 -5 0 5 10

0 4.5 2.6 4.2 5.5 3.7 5.3 5.2 8.5 5.2

-6 -4.1 -9 -6.7 -20

4 8 12 16

*P < 0.05 vs. placebo      †P < 0.05 vs. 1500 mg

1000 gm

1500 mg

Placebo
<table>
<thead>
<tr>
<th></th>
<th>Placebo N = 49</th>
<th>1000 mg N = 47</th>
<th>1500 mg N = 52</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Completing Study</td>
<td>86%</td>
<td>87%</td>
<td>81%</td>
<td>NS</td>
</tr>
<tr>
<td>Global Assessment *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved or Same</td>
<td>88%</td>
<td>80%</td>
<td>71%</td>
<td>NS</td>
</tr>
<tr>
<td>Worse</td>
<td>12%</td>
<td>18%</td>
<td>29%</td>
<td>NS</td>
</tr>
<tr>
<td>Added Drug or ↑ Dose</td>
<td>16%</td>
<td>24%</td>
<td>29%</td>
<td>NS</td>
</tr>
</tbody>
</table>

*of diabetes status (by investigator)
Combination Therapy in Mixed Hyperlipidemia:

Evidence from Clinical Trials
HDL Atherosclerosis Treatment Study (HATS)

RANDOMIZED TREATMENT ASSIGNMENT
(double-dummy technique):

1. Niacin (2-4 grams/day) + Simvastatin (10-20 mg/day)

2. Niacin (2-4 grams/day) + Simvastatin (10-20mg/day) plus Antioxidant Vitamins

3. Antioxidant Vitamins

4. Double placebos

Antioxidant Vitamins = Vitamin E 800 IU, Vitamin C 1,000 mg, Beta Carotene 25 mg, Selenium 100 mcg
HDL Atherosclerosis Treatment Study (HATS)

BASELINE CHARACTERISTICS

LDL-C 126 mg/dl
HDL-C 31 mg/dl
Triglycerides 212 mg/dl

15% with Diabetes Mellitus (DM)
10% with Impaired Glucose Tolerance (IGT)
85% men/15% women
50% prior MI
HDL Atherosclerosis Treatment Study (HATS)

CHANGE IN LIPOPROTEINS with NIACIN/SIMVASTATIN

- LDL-C: -35
- HDL-C: +30
- TG: -34
HDL Atherosclerosis Treatment Study (HATS)

CORONARY ANGIOGRAPHIC CHANGE: Randomized Treatment Assignment

% Change

-10 0 10 20 30 40

34 15 7

PBO  Antioxidant Vitamins  Niacin/simvastatin + Vitamins  Niacin/simvastatin alone

*p<0.01
HDL Atherosclerosis Treatment Study (HATS)

CLINICAL EVENTS

- No Antioxidants
- Includes Antioxidants

* p<0.01

- Placebo
- Niacin/simvastatin
- Placebo ± vitamins
- Niacin/simvastatin ± vitamins
# Drug-Therapy in Combined Hyperlipidemia in Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin</th>
<th>Fenofibrate</th>
<th>Atorva+ Feno</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL</td>
<td>% δ</td>
<td>BL</td>
</tr>
<tr>
<td><strong>LDL-C</strong></td>
<td>161</td>
<td>-40</td>
<td>163</td>
</tr>
<tr>
<td><strong>Trig.</strong></td>
<td>278</td>
<td>-30</td>
<td>281</td>
</tr>
<tr>
<td><strong>HDL-C</strong></td>
<td>35</td>
<td>+9</td>
<td>35</td>
</tr>
<tr>
<td><strong>Fibrinogen</strong></td>
<td>379</td>
<td>-3</td>
<td>382</td>
</tr>
</tbody>
</table>

n= 40 in each group (M+F) x 24 wk ; Atorva 20mg, Fenofibrate 200 mg/d

Athyros, VG et el Diabetes Care 2002; 25: 1198-1202
## % of Patients reaching ADA Lipid Targets and probability of MI

<table>
<thead>
<tr>
<th>n</th>
<th>Baseline</th>
<th>Atorva</th>
<th>Feno</th>
<th>A+F</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>0</td>
<td>80</td>
<td>5</td>
<td>97.5</td>
</tr>
<tr>
<td>40</td>
<td>75</td>
<td>92.5</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>17.5</td>
<td>30</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>21.6</td>
<td>7.5</td>
<td>10.9</td>
<td>4.2</td>
<td></td>
</tr>
</tbody>
</table>

Athyros, VG et al. Diabetes Care 2002; 25: 1198-1202
Newer Agents in Lipid Management

- Rosuvastatin (Crestor)
- Niaspan+Lovastatin (Advicor)
- Cholesterol Absorption Inhibitors:
  - Plant Stanol Margarine (Benecol)
  - Colesevelam (Welchol)
  - Ezitimibe (Zetia) - Approved 10/02
Clinical Studies for ZETIA™ (ezetimibe) – Monotherapy

Pooled Results From 2 Multicenter, Double-Blind, Placebo-Controlled, 12-Week Studies in 1,719 Patients With Primary Hypercholesterolemia

- LDL-C
- TG (median)
- HDL-C

<table>
<thead>
<tr>
<th>Mean % Change From Untreated Baseline</th>
<th>LDL-C</th>
<th>TG (median)</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=431)</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>ZETIA 10 mg (n=1,288)</td>
<td>-18%*</td>
<td>-8%*</td>
<td>-2%</td>
</tr>
</tbody>
</table>

Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of ZETIA

*P ≤ 0.01 vs placebo.
## Some On-going Lipid Trials

<table>
<thead>
<tr>
<th>n</th>
<th>Drugs</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNT</td>
<td>&gt;10,000</td>
<td>Atorva 10 or 80 mg</td>
</tr>
<tr>
<td>SEARCH</td>
<td>~ 12,000</td>
<td>Simva 20 or 80 +/- B12+ folate</td>
</tr>
<tr>
<td>IDEAL</td>
<td>7600</td>
<td>Atorva 80 or Simva 20-40</td>
</tr>
<tr>
<td>HPS II</td>
<td>10,000</td>
<td>Simva 20 –40 or Atorva 80 +/- B12 +folate</td>
</tr>
<tr>
<td>ACCORD</td>
<td>~5000</td>
<td>Simva 20 +/- Fenofibrate</td>
</tr>
</tbody>
</table>

TNT: Treat to New Targets; SEARCH : Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine; IDEAL : Incremental decrease in Endpoints through Aggressive Lipid Lowering; ACCORD : Action to Control Cardiovascular Risk in Diabetes